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Scientific paper

Combustion Synthesis of Nano Fe_2O_3 and its Utilization as a Catalyst for the Synthesis of N^{α}-Protected Acyl Thioureas and Study of Anti-bacterial Activities

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Dedicated to Dr. Sree Sree Sree Shivakumara Mahaswamiji, Siddaganga Matt, Tumakuru, Karnataka, India

Abstract

A simple and eco-friendly nano Fe_2O_3 heterogeneous catalytic system is described for the synthesis of acyl thiourea derivatives from corresponding *in situ* generated acyl isothiocyanates and amino acid esters in acetone obtained in good yields. The structures of synthesized acyl thioureas were confimed by ^{1}H NMR, ^{13}C NMR, mass, and FTIR analysis. Fe_2O_3 NPs has been prepared *via* a solution combustion route using ascorbic acid as the reducing agent and ferric nitrate as the source of iron. The prepared nano material has been characterized by XRD, SEM, UV-Visible, and FTIR analysis. More prominently, the Fe_2O_3 and other impurities are removed though a simple work-up and the material prepared shows to be effective in catalyzing the conversion of reactants to products in good yields. Further, some of the synthesized acyl thioureas were evaluated for *in vitro* antibacterial activity against *Staphylococcus aureus* and *Escherichia coli.*

Keywords: *N*-protected acyl thioureas; *in vitro* antibacterial activity; Fe_2O_3 nanoparticles; solution combustion.

1. Introduction

Many acyl thiourea derivatives are well known to possess a diverse range of biological activities such as anticancer,[1] antiviral,[2] fungicidal,[3] anti-microbial,[4] antimycobacterial,[5] antitumor,[6] anti-inflammatory,[7] herbicidal,[8] anti-aggregating,[9] analgesic, and are often employed as local anesthetic, and antihyperlipidemic.[10] Therefore, the acyl thiourea linkage has received greater attention because of its potent biological as well as structural aspects. The ability to provide a hydrogen bond donor and acceptor point makes it an efficient anion receptor and enables it to play a key role in some epoxy resin curing agents containing amino functional groups and to act as chelating agents in catalysis.[11–13] Aroylthiourea ligands are an important class of compounds in the field of coordination chemistry and catalysis.[14–16] Thiourea and its derivatives have long been studied for their use against the corrosion of a wide range of metals in various corrosion environments.[17–18] Also the thiourea and its derivatives have found wide range of applications in agriculture, medicine, and analytical chemistry.[19–20]

In the past, Benjawan and his group synthesized and evaluated the acyl thiourea derivatives for the *in vitro* evaluation of activity against *Mycobacterium tuberculosis* showing promising results.[21] Substituted thioureas are an important

class of sulphur-containing organic compounds or intermediates in the synthesis of a variety of heterocyclic compounds such as 2-imino-1,3-thiazolines, imidazole-2-thiones, (benzothiazolyl)-4-quinazolinones. Pyrimidine-2-thiones *N*-(substituted phenyl)-*N*-phenylthioureas have been developed as calixarenes containing thioureas as neutral receptors towards α,α-dicarboxylate anions, anion-binding sites in a hydrogen-bonding receptor, and *N*-4-substituted-benzyl-*N*-*tert*-butylbenzyl thioureas as antagonists in rate DRG neurons and vanilloid receptor ligands.[22–28]

There are several works demonstrating the synthesis of acyl thiourea derivatives including: (a) reaction of functionalized diisothiocyanate with various benzenamines in the presence of PEG-400,[29] (b) difluoromethyl pyrazole acyl thiourea derivatives were successfully synthesized using PEG-600 as a phase transfer catalyst,[30] (c) The application of benzoyl / carbethoxy isothiocyanate towards the synthesis of substituted-3-benzoyl/carbethoxy thioureas in the presence of nucleophile such as amine and NH_4SCN was investigated,[31] (d) reaction of acid chloride with potassium thiocyanate to obtain acyl isothiocyanate intermediate, this is coupled with the amines employing TBAB as an organic catalyst to afford *N*-(*o*-fluorophenoxyacetyl) thioureas derivatives,[32] (e) Zhong *et al.* synthesized three different acyl thiourea derivatives of chitosan and their antimicrobial behavior against four species of bacteria were investigated.[33] Therefore, the application of nano Fe_2O_3 for the synthesis of N^{α}-protected acyl thioureas is, according to the literature survey, not established yet. Hence, herein we report a simple and efficient route for the synthesis of biologically active acyl thioureas employing nano Fe_2O_3. Furthermore, the synthesized compounds were screened for *in vitro* activity in anti-bacterial studies.

Nowadays, nano metaloxide semiconductors have attracted a lot of attention, as their properties can be controlled by changing the crystallite size, shape, surface-to-volume ratio, temperature and also by synthetic routes.[34–35] From the view point of the basic research purpose Fe_2O_3 is an important semiconductor for the study of magnetic properties, and polymorphism and structural phase transitions of nanoparticles.[36,37] In the last decades, nanostructured iron oxides such as α-Fe_2O_3, γ-Fe_2O_3, β-Fe_2O_3 and Fe_2O_3, have received remarkable interest from both theoretical and experimental viewpoints because of their potential applications in sensing devices and biomedical applications, such as magnetic resonance imaging, biosensors, hyperthermia, and drug delivery in cancer therapy, and detoxification and also in industrial applications.[38–41] At the same time there is an increased interest in using iron oxide NPs for the removal of various pollutants (As^{5+}, Cr^{6+}, dyes) from wastewaters.[42–45]

Several synthetic methods have been developed for the preparation of Fe_2O_3 nanoparticles due to its inherent biocompatible nature, magnetic properties as well its stability towards oxidation.[46–49] There are many methods available to prepare nano Fe_2O_3 including: co-precipitation, plasma chemical synthesis, micro emulsions, thermal decomposition, sol-gel, and flame spray pyrolysis etc.[50–57] Some of these are expensive and time consuming. Here, we have prepared Fe_2O_3 nanopowder by eco-friendly simple low-cost solution combustion method using ascorbic acid as the reducing agent.[58] Although the synthesis of Fe_2O_3 nanoparticles has seen substantial progress, the preparation of pure, large surface area nano Fe_2O_3 powders is still one of the top goals in the field.

2. Experimental Section

2. 1. General

All the chemicals were purchased from Sigma-Aldrich and Merck and used without purification. The pathogenic bacterial strains were purchased from National Chemical Laboratory Pune, India. IR spectra were recorded on Bruker Alpha-II FTIR spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker AMX 400 MHz spectrometer using TMS as the internal standard and DMSO as the solvent. Mass spectra were recorded on a Micromass Q-ToF Micro Mass Spectrometer. Powder XRD data were recorded on Shimadzu X-ray diffractometer (PXRD-7000) using Cu-Kα radiation of wavelength λ = 1.541 Å. IR spectra were recorded on Bruker Alpha-T FTIR spectrometer (KBr windows, 2 cm^{-1} resolution). The absorption spectrum and band gap were measured using Lambda-35 (Perkin Elmer) spectrophotometer in the wavelength range 200–800 nm diffused reflectance mode. Morphological features were studied by using Hitachi-7000 Scanning Electron Microscopy.

2. 2. Solution Combustion Synthesis of Nano Fe_2O_3

1 g of $Fe(NO_3)_3 \cdot 9H_2O$ (acting as oxidizing agent) and 0.6 g of ascorbic acid (acting as reducing agent) were mixed and stirred in 10 mL distilled H_2O to get homogeneous solution. This solution was poured into silica crucible and kept in a preheated muffle furnace at 500 °C. The homogeneous solution first undergoes dehydration, then decomposition and large amounts of gases were released during the process. Fe_2O_3 NPs were formed within 5 minutes. In continuation of our interest a facile protocol for the nano Fe_2O_3 catalyzed synthesis of acyl thioureidopeptides was developed in peptide chemistry.

2. 3. Reusability and Recyclability of Nano Fe_2O_3

Catalyst was reused and recycled without any loss of activity and product yield. The nano Fe_2O_3 can be recycled by a simple protocol after the completion of the reaction. The catalyst was removed by filtration, washed with methanol and dried. The recovered catalyst was reused for the

second, third and fourth consecutive cycles without any significant loss in catalytic activity.

2. 4. General Procedure for the Synthesis of N^{α}-Protected Acyl Thioureas

To the protected amino acid (1 mmol) dissolved in CH_2Cl_2 (5 mL), $SOCl_2$ (1.5 mmol) was added and the mixture was sonicated at rt for about 40–50 min and monitored through TLC. The excess of CH_2Cl_2 and $SOCl_2$ were carefully eliminated by rotary distillation and the residue was precipitated after the addition of hexane (5 mL) and then filtered and dried to get pure acid chlorides. To the formed acid chloride were added ammonium thiocyanate and acetone, this reaction mixture was refluxed for 1 h and the solvent was removed on a rotary evaporator to obtain a crude product of acyl isothiocyanates. This intermediate was dissolved in CH_2Cl_2 (30 mL), then subjected to H_2O and brine wash and dried over anhydrous Na_2SO_4. The organic phase containing acyl isothiocyanate intermediate was coupled with neutralized amino acid esters followed by the addition of nano Fe_2O_3 (0.5 mmol). The reaction mixture was stirred for 4–6 h at rt and monitored by TLC. After the completion of the reaction, Fe_2O_3 was removed by filtration and the organic phase was washed with 5% HCl (20 mL), 5% Na_2CO_3 (20 mL), H_2O, and brine and dried over anhydrous Na_2SO_4 to get crude product of acyl thioureas; then, it was purified by the trituration with hexane–diethyl ether system to afford analytically pure products.

3. Results and Discussion

3. 1. Characterization of Fe_2O_3 NPs

3. 1. 1. Powder X-Ray Diffraction Technique

Figure 1 shows the XRD pattern of Fe_2O_3 NPs calcined at 500 °C. The diffraction peaks observed at 24.18, 33.34, 35.68, 40.85, 49.63, 54.28, 62.55 and 64.22 could be indexed to the (012), (104), (022) (202), (103), and (123) planes respectively, consistent with the standard XRD data of Fe_2O_3 (JCPDS no. 72-1191). The average crystallite size of the prepared sample was calculated by Debye–Scherrer equation (Equation 1) and it was observed to be 30 nm.

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

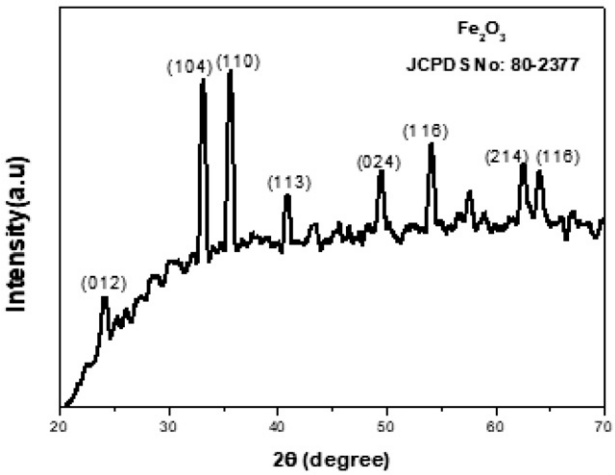


Figure 1. XRD patterns of the Fe_2O_3 NPs.

3. 1. 2. Fourier Transform Infrared Spectroscopy

From Figure 2 the two peaks at 442 and 530 cm^{-1} are observed in the FTIR spectrum of the Fe_2O_3 NPs. In comparison with the literature, we conclude that these peaks were assigned to the stretching and bending modes of the Fe–O bond. The absorption peaks around 1587 and 1383 cm^{-1} are due to the asymmetric and symmetric bending vibration of C=O.

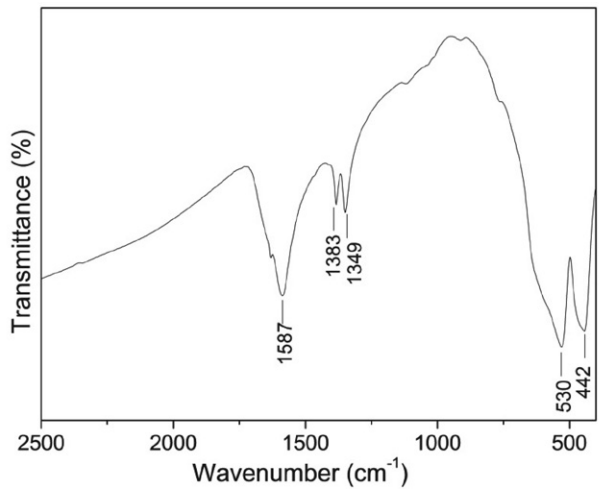


Figure 2. FTIR spectrum of Fe_2O_3 NPs.

3. 1. 3. Scanning Electron Microscopy Analysis

Figure 3 shows the SEM image of the prepared nano Fe_2O_3 which clearly shows that the particles have roughly irregular spongy cave like structure. The size and the shape of the Fe_2O_3 strongly depend on the preparation technique.

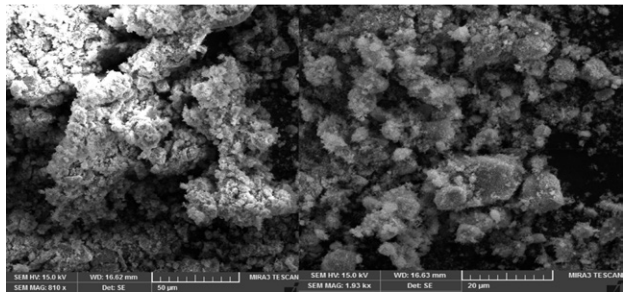


Figure 3. SEM images of Fe_2O_3 NPs.

3. 1. 4. UV-Visible Analysis

The optical properties of nano Fe_2O_3 were studied by UV-visible DRS spectroscopy. The spectrum was recorded in the wavelength region between 200 to 1200 nm at rt. The band gap energy of the samples can be evaluated from the E_g measurements using Kubelka–Munk model and the $F(R)$ was estimated using the equation 2

$$F(R) = \frac{(1-R)^2}{2R} \quad (2)$$

where $F(R)$ is the remission or Kubelka–Munk fuction, and R is the reflectance. A graph was plotted between $[F(R)h\nu]^2$ and hν, the intercept value is the band gap energy of the Fe_2O_3 NPs. From the Figure 4a it was observed that Fe_2O_3 NPs show strong reflectance peak at 510 nm wavelength. From Figure 4b the estimated band gap of nano Fe_2O_3 was found to be 2.5 eV which was higher when compared with the reported value for the bulk Fe_2O_3 (2.1 eV) owing to the quantum confinement effect exerted by the nanostructured materials. Thus there is a blue shift of the band edge of Fe_2O_3 NPs with respect to the bulk Fe_2O_3.

3. 1. 5. Application of Nano Fe_2O_3 as the Catalyst for the Synthesis of N^{α}-Protected Acyl Thioureas of *N*-Protected Amino Acids

To avoid the restrictions, such as cost of synthesis, prolonged reaction conditions, and low yields, the studies were made to develop a well-organized method with higher yields for the synthesis of acyl thioureas in the presence of nano Fe_2O_3. Therefore, we described the synthesis of acyl thiourea derivatives of protected amino acids bearing different side chains employing Fe_2O_3 nano powder under mild reaction conditions. The protocol is based on a three-step strategy, a direct chlorination of the carbonyl group of the protected amino acid with a thionyl chloride followed by the nucleophilic substitution reaction with ammonium thiocyanate in acetone under reflux condition to form acyl isothiocyanates as key intermediates, further being coupled with amino acid esters employing nano Fe_2O_3 as the catalyst leading to the desired acyl thioureas **5a**–**m** in good yields (Scheme 1, Table 1). Basically, acyl thiourea in its basic structure has one sulfur atom, which has six valence electrons. It is believed that the present protocol provides a greater flexibility of amino acids at our convenience and is

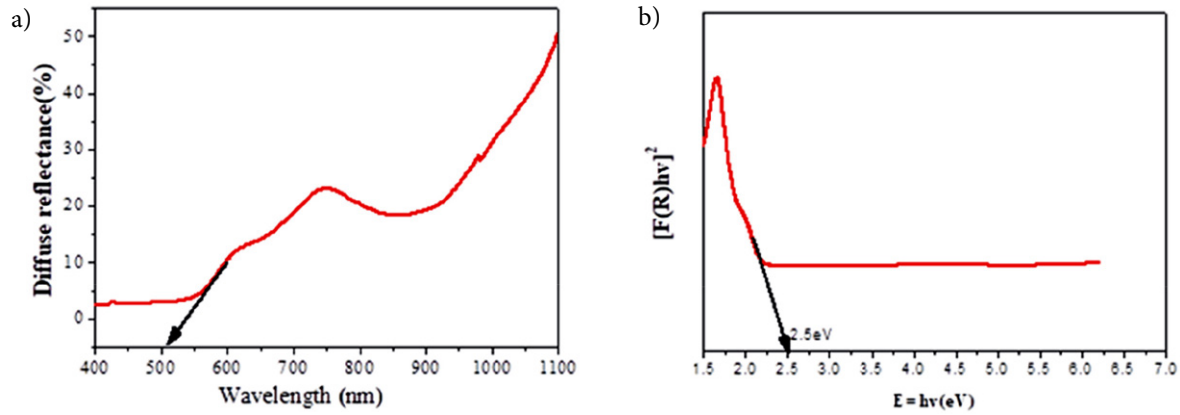
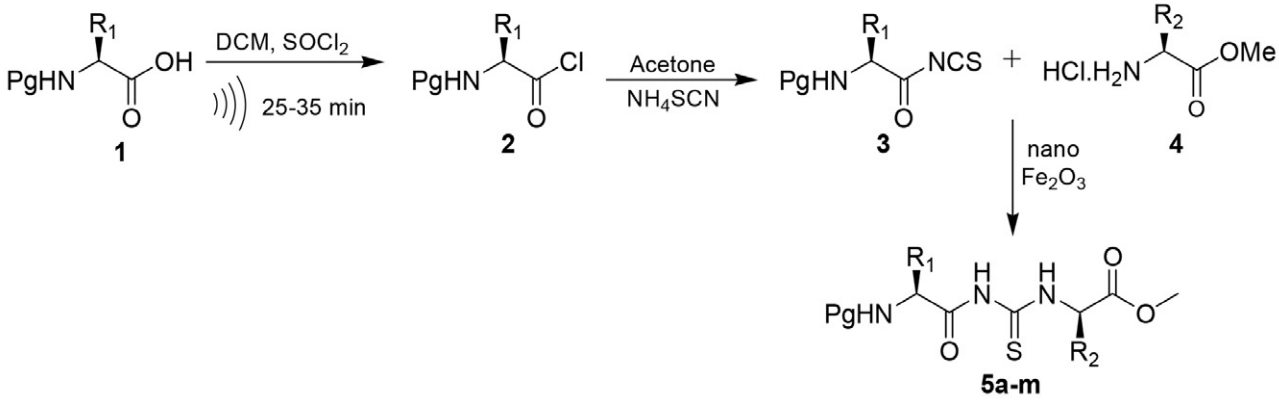


Figure 4. (a) DRS spectrum; **(b)** Energy band gap plot of Fe_2O_3 NPs.



R_1, R_2: H, alkyl, aryl groups
Pg (Protecting group): Fmoc (fluorenylmethyloxycarbonyl), Cbz (benzyloxycarbonyl).

Scheme 1. Synthesis of acyl thioureas employing nano Fe_2O_3

Table 1. List of N^{α}-protected acyl thioureas synthesized *via* scheme 1

Entry	Acyl thioureas	Yield (%)	M.p. (°C)	$[\alpha]_D^{25}$ in degrees
5a	Fmoc-Val-ψ[CONHCSNH]-Ala-OMe	80	184	–55.45
5b	Fmoc-Phe-ψ[CONHCSNH]-Ser-OMe	81	170	–50.91
5c	Cbz-Val-ψ[CONHCSNH]-Gly-OMe	85	165	–9.09
5d	Cbz-Met-ψ[NHCONH]-Phe-OMe	86	180	–16.82
5e	Boc-Ala-ψ[CONHCSNH]-Ser-OMe	81	*Gum*	–22.39
5f	Boc-Leu-ψ[CONHCSNH]-Ala-OMe	79	*Gum*	–18.43
5g	Fmoc-Phe-ψ[CONHCSNH]-Ala-OMe	83	185	–24.56
5h	Fmoc-Leu-ψ[CONHCSNH]-Ile-OMe	84	91	–20.62
5i	Fmoc-Ala-ψ[CONHCSNH]-Val-OMe:	90	180	–17.27
5j	Fmoc-Try-ψ[CONHCSNH]-Ala-OMe	87	205	–12.73
5k	Boc-Val-ψ[CONHCSNH]-Ala-OMe	75	*Gum*	–23.18
5l	Fmoc-Ile-ψ[CONHCSNH]-Val-OMe	86	159	–9.09
5m	Cbz-Thr-ψ[CONHCSNH]-Val-OMe	90	165	–11.10

superior to the other methods. N^{α}-Protected amino acid was dissolved in CH_2Cl_2 (dichloromethane), thionyl chloride was added and the mixture was sonicated at rt for about 40–50 minutes yielding acyl chlorides **2**. Then, the carbonyl group in **2** (in the form of acyl chloride) was modified by the nucleophilic substitution reaction. To the acyl chlorides **2** ammonium isothiocyanate was added, yielding acyl isothiocyanates **3** under reflux condition. The formed acyl isothiocyanate intermediates **3** were trapped with amino acid esters **4** employing nano Fe_2O_3 as an efficient, eco-friendly catalyst to form the final product acyl thioureas **5a–m** as monitored by TLC. The reaction was complete in about 6 h and all the compounds were isolated, after a simple work-up, and purified by hexane-diethyl ether system and their structures were confirmed by mass, ^{1}H NMR, ^{13}C NMR, and FTIR spectroscopy techniques.

3. 1. 6. Spectral Data of the Synthesized Compounds 5a–m

(*S*)-Methyl 2-(3-((*S*)-2-(((9*H*-Fluoren-9-yl)methoxy) carbonyl)-3-methylbutanoyl)thioureido)propanoate (*Fmoc-Val-ψ[CONHCSNH]-Ala-OMe*) (5a). Yield 80%, m.p. 184 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.01 (d, J = 12.0 Hz, 6H), 1.30 (d, J = 8.0 Hz, 3H), 2.0 (br, 1H), 2.70 (m, 1H), 3.60 (m, 1H), 3.70 (s, 3H), 4.45–4.70 (m, 4H), 6.0 (br, 2H), 7.20–7.90 (m, 8H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.0, 17.80, 32.0, 47.0, 52.30, 54.0, 61.0, 68.0, 126.0, 128.0, 128.40, 129.0, 140.0, 143.80, 156.0, 170.0, 175.0, 187.0. MS: Calcd. for $C_{25}H_{29}N_3O_5S$: *m/z* 506.1726 (M + Na^+), found: 506.1060.

(*S*)-Methyl 2-(3-((*S*)-2-(((9*H*-Fluoren-9-yl)methoxy) carbonyl)-3-phenylpropanoyl)thioureido)-3-hydroxypropanoate (*Fmoc-Phe-ψ[CONHCSNH]-Ser-OMe*) (5b). Yield 81%, m.p. 170 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.10 (s, 1H), 2.90 (*d*, J = 6.0 Hz, 2H), 3.50 (t, J = 10.0 Hz, 1H), 3.70 (s, 3H), 4.40–4.90 (m, 6H), 6.0 (br, 2H), 7.10–7.90 (m, 13H), 8.0 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 38.0, 46.50, 51.20, 53.0, 62.0, 68.70, 126.0, 127.0, 127.80, 128.0, 128.40, 128.70, 129.0, 140.0, 141.0, 143.0, 156.0, 176.0, 187.10. MS: Calcd. for $C_{29}H_{29}N_3O_6S$: *m/z* 570.1675 (M + Na^+), found: 570.2275.

(*S*)-Methyl 2-(3-(2-(Benzyloxycarbonyl)-3-methylbutanoyl)thioureido)acetate (*Cbz-Val-ψ[CONHCSNH]-Gly-OMe*) (5c). Yield 85%, m.p. 165 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.0 (d, J = 8.0 Hz, 6H), 2.70 (m, 1H), 3.70 (s, 3H), 4.40–4.50 (m, 3H), 5.30 (s, 2H), 6.10 (br, 2H), 7.10–7.30 (m, 5H), 8.0 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.89, 21.67, 46.67, 56.18, 64.93, 65.26, 126.98, 127.51, 127.54, 129.08, 129.14, 129.28, 129.38, 129.44. MS: Calcd. for $C_{17}H_{23}N_3O_5S$: *m/z* 404.1256 (M + Na^+), found: 404.2250.

(*S*)-Methyl 2-(3-((*S*)-2-(Benzyloxycarbonyl)-4-(methylthio)butanoyl)thioureido)-3-phenylpropanoate (*Cbz-Met-ψ[NHCONH]-Phe-OMe*)(5d). Yield 86%, m.p. 180 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.0 (s, 3H), 2.30–2.50 (m, 4H), 3.30–3.50 (m, 4H), 3.70 (s, 3H), 5.30 (s, 2H), 6.10 (br, 2H), 7.10–7.30 (m, 10H), 8.01 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.10, 29.0, 32.0, 38.0, 52.0, 54.50, 60.0, 66.0, 126.0, 127.40, 127.60, 127.90, 128.50, 129.0, 139.0, 141.0, 156.0, 171.0, 175.50, 187.0. MS: Calcd. for $C_{24}H_{29}N_3O_5S_2$: *m/z* 526.1446 (M + Na^+), found: 526.2130.

(*S*)-Methyl 2-(3-((*S*)-2-(*tert*-Butoxycarbonyl)propanoyl) thioureido)-3-hydroxypropanoate (*Boc-Ala-ψ[CONHCSNH]-Ser-OMe*) (5e). Yield 81%, Gum. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.29 (s, 9H), 1.50–1.59 (d, J = 6.0 Hz, 3H), 2.0 (br, 1H), 3.40–3.55 (m, 1H), 3.78 (s, 3H), 4.10–4.25 (t, J = 10.0 Hz, 2H), 4.60–4.75 (m, 1H), 6.45 (br, 1H), 8.01 (br, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.0, 28.0, 50.0, 51.80, 61.0, 80.0, 155.0, 172.0, 176.20, 188.0. MS: Calcd. for $C_{13}H_{23}N_3O_6S$: *m/z* 372.1205 (M + Na^+), found: 372.3041.

(*S*)-Methyl 2-(3-((*S*)-2-(*tert*-Butoxycarbonyl)-4-methylpentanoyl)thioureido)propanoate (*Boc-Leu-ψ[CONHCSNH]-Ala-OMe*) (5f). Yield 79%, Gum. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.0 (d, *J* = 10.0 Hz, 6H), 1.25 (d, *J* = 8.0 Hz, 3H), 1.50 (s, 9H), 1.70–1.85 (m, 3H), 3.60 (m, 1H), 3.70 (s, 3H), 4.50 (t, *J* = 4.0 Hz, 1H), 6.20 (br, 2H), 8.0 br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.0, 22.0, 22.7, 28.40, 41.20, 51.0, 52.10, 55.20, 80.0, 155.0, 171.40, 175.50, 188.0. MS: Calcd. for $C_{16}H_{29}N3O_5S$: *m/z* 398.1726 (M + Na^+), found: 398.2230.

(*S*)-Methyl 2-(3-((*S*)-2-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-3-phenylpropanoyl)thioureido)propanoate (*Fmoc-Phe-ψ[CONHCSNH]-Ala-OMe*) (5g). Yield 83%, m.p. 185 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.30 (d, *J* = 8.0 Hz, 3H), 2.90 (d, *J* = 10.0 Hz, 2H), 3.60 (s, 3H), 3.70 (m, 1H), 4.40–4.90 (m, 4H), 6.02 (br, 2H), 7.10–7.90 (m, 13H), 8.0 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.0, 37.60, 47.10, 52.0, 54.60, 55.0, 67.0, 126.0, 126.60, 128.0, 128.40, 128.70, 129.0, 140.0, 141.0, 143.0, 156.20, 176.60, 171.0, 187.0. MS: Calcd. for $C_{29}H_{29}N_3O_5S$: *m/z* 554.1726 (M + Na^+), found: 554.5204.

(2*S*,3*S*)-Methyl 2-(3-((*S*)-2-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-4-methylpentanoyl)thioureido)-3-methylpentanoate (*Fmoc-Leu-ψ[CONHCSNH]-Ile-OMe*) (5h). Yield 84%, m.p. 91 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.0–1.30 (m, 14H), 1.70–1.85 (m, 3H), 2.50 (m, 1H), 3.40 (d, *J* = 6.0 Hz, 1H), 3.68 (s, 3H), 4.40–4.70 (m, 4H), 6.20 (br, 2H), 7.22–7.84 (m, 8H), 8.0 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.69. 22.30, 22.92, 28.17, 28.25, 37.69, 38.68, 47.85, 50.02, 55.81, 59.63, 78.09, 126.45, 126.61, 128.06, 128.18, 128.25, 138.05, 144.30, 145.25, 155.59, 170.79. MS: Calcd. for $C_{29}H_{37}N_3O_5S$: *m/z* 562.2352 $[M+Na]^+$, found: 562.3050.

(*S*)-Methyl 2-(3-((*S*)-2-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)propanoyl)thioureido)-3-methylbutanoate (*Fmoc-Ala-ψ[CONHCSNH]-Val-OMe*) (5i). Yield 90%, m.p. 180 °C. IR (KBr): 3455, 2062, 1640, 1434, 1275, 706 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.10–1.20 (d, *J* = 10.0 Hz, 6H), 1.50–1.57 (d, *J* = 8.0 Hz, 3H), 2.70–2.94 (m, 1H), 3.40–3.50 (t, *J* = 6.0 Hz, 1H), 3.75 (s, 3H), 4.48–4.75 (m, 4H), 6.38–6.47 (br, 2H), 7.16–7.50 (m, 8H), 7.98 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.92, 21.32, 21.69, 46.67, 54.81, 56.16, 64.93, 65.29, 126.03, 126.98, 127.51, 127.55, 128.47, 129.08, 140.66, 143.76, 156.57, 157.26. MS: Calcd. for $C_{25}H_{29}N_3O_5S$: *m/z* 506.1726 $[M+Na]^+$, found: 506.2440.

(*S*)-Methyl 2-(3-((*S*)-2-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-3-(1*H*-indol-3-yl)propanoyl)thioureido)propanoate (*Fmoc-Try-ψ[CONHCSNH]-Ala-OMe*) (5j). Yield 87%, m.p. 205 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.27–1.34 (d, *J* = 8.0 Hz, 3H), 2.0 (br, 1H), 3.05–3.12 (d, *J* = 6.0 Hz, 2H), 3.30–3.59 (m, 1H), 3.80 (s, 3H), 4.40–4.80 (m, 4H), 6.0 (br, 1H), 6.30 (s, 1H), 7.12–7.98 (m, 12H), 8.12 (br, 1H), 8.85 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 14.62, 37.61, 47.75, 49.93, 55.73, 59.53, 77.97, 125.97, 126.15, 126.36, 126.53, 127.97, 128.10, 128.17, 128.53, 129.25, 137.94, 138.01, 144.25, 144.46, 145.19, 155.17, 155.48, 156.23, 170.69. MS: Calcd. for $C_{31}H_{30}N4O_5S$: *m/z* 593.1835 $[M+Na]^+$, found: 593.3030.

(*S*)-Methyl 2-(3-((*S*)-2-(*tert*-Butoxycarbonyl)-3-methylbutanoyl)thioureido)propanoate (*Boc-Val-ψ[CONHCSNH]-Ala-OMe*) (5k). Yield 75%, Gum. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.0–1.28 (m, 9H), 1.50 (s, 9H), 2.60 (m, 1H), 3.60 (m, 1H), 3.70 (s, 3H), 6.0 (br, 2H), 8.0 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 17.0, 17.40, 28.40, 32.0, 52.0, 55.0, 60.0, 80.0, 156.0, 172.0, 177.0, 187.0. MS: Calcd. for $C_{15}H_{27}N_3O_5S$: *m/z* 384.1569 $[M+Na]^+$, found: 384.2060.

(*S*)-Methyl 2-(3-((2*S*,3*S*)-2-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-3-methylpentanoyl)thioureido)-3-methylbutanoate (*Fmoc-Ile-ψ[CONHCSNH]-Val-OMe*) (5l). Yield 86%, m.p. 159 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 1.20–1.46 (m, 12H), 1.65–1.90 (m, 2H), 2.70–2.92 (m, 2H), 3.33–3.46 (d, *J* = 6.0 Hz, 1H), 3.60 (s, 3H), 4.60–4.79 (m, 4H), 6.10–6.21 (br, 2H), 7.17–7.65 (m, 8H), 8.06–8.18 (br, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 10.0, 15.0, 18.20, 24.80, 30.0, 37.10, 47.0, 52.0, 57.80, 62.70, 67.0, 126.60, 128.40, 128.60, 129.0, 141.0, 143.40, 156.0, 171.40, 175.50, 187.0. MS: Calcd. for $C_{28}H_{35}N_3O_5S$: *m/z* 548.2195 $[M+Na]^+$, found: 548.3090.

(*S*)-Methyl 2-(3-((2*S*,3*S*)-2-(Benzyloxycarbonyl)-3-hydroxybutanoyl)thioureido)-3-methylbutanoate (*Cbz-Thr-ψ[CONHCSNH]-Val-OMe*) (5m). Yield 74%, Gum. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.0 (d, *J* = 6.0 Hz, 6H), 1.20 (d, *J* = 8.0 Hz, 3H), 2.0 (s, 2H), 2.75 (m, 1H), 3.40 (d, *J* = 4.0 Hz, 1H), 3.70 (s, 3H), 4.20–4.60 (m, 2H), 5.40 (s, 2H), 6.0 (br, 2H), 7.20–7.40 (m, 5H). ^{13}C NMR (100 MHz, DMSO-d_6): δ 18.0, 19.0, 30.0, 51.4, 60.0, 62.40, 65.0, 67.60, 127.2, 127.9, 129.0, 140.0, 156.10, 172.0, 175.7, 188.0. MS: Calcd. for $C_{19}H_{27}N_3O_6S$: *m/z* 448.1518 $[M+Na]^+$, found: 448.2024.

3. 2. *In vitro* Anti-bacterial Activity

3. 2. 1. Determination of Zone of Inhibition by Agar Well Diffusion Method

Finally, the synthesized acyl thioureas were tested for the antibacterial activity by agar well diffusion method. For this, the synthesized acyl thiourea samples **5a–j** were subjected for the antibacterial activities against two Gram positive bacteria: *Escherichia coli* (MTCC1692) and *Staphylococcus aureus* (MTCC 3160) employing agar well diffusion method.[59,60] The bacterial pathogens were cultured on Mueller–Hinton broth agar for 24 h at 37 °C.[61] The inoculums were prepared by allowing bacteria

to grow on media containing nutrient broth at 37 °C with permanent stirring at 250 rpm for overnight. After obtaining 24 h fresh culture, Mueller–Hinton agar plates were prepared, strains of *S. aureus*, and *E. coli* were swabbed uniformly on individual plates using sterile cotton swabs. Wells of approximately 6 mm diameter were made on MH agar plates using gel puncture. Synthesized samples, approximately 200 mg were dissolved in 2 mL of DMSO. With a concentration of 500 µg/µL were used to measure the activity of the synthesized molecules and streptomycin sulphate (50 mg/2 mL) was used as the standard antibiotic. To each well, a volume of 50 µL of streptomycin sulphate standard (**S**) and 100 µL respective samples were added to individual plates. The plates were incubated at 37 °C for 24 h and inhibition zones obtained were measured. Antibacterial activity was evaluated in terms of the diameters of growth inhibition zones (mm). If the growth inhibition zones were less than 10 mm in diameter, confluent growth over the plates were scored as the absence of antibacterial activity, zones of 10–15 mm as weak activity, zones of 15–20 mm as moderate-marked activity, and greater than 20 mm as marked activity. Results are summarized and analyzed in Table 2 and Figures 5 and 6.

Table 2. Antibacterial activity of acyl thioureas **5a–j** against *E. coli* and *S. aureus*

Compound	Treatment (concentration in µg/µL)	*E. coli*	*S. aureus*
S	50	14.55 ± 0.88	12.67 ± 0.33
5a	100	14.67 ± 0.67	13.67 ± 0.88
5b	100	16.00 ± 0.58	10.33 ± 0.67
5c	100	15.67 ± 0.88	10.00 ± 1.0
5d	100	16.67 ± 0.88	12.67 ± 0.33
5e	100	12.67 ± 0.33	13.67 ± 0.88
5f	100	13.66 ± 0.88	11.33 ± 0.88
5g	100	10.67 ± 0.88	10.67 ± 1.2
5h	100	14.67 ± 0.67	12.33 ± 0.33
5i	100	13.67 ± 0.88	13.33 ± 1.2
5j	100	17.33 ± 0.33	31.00 ± 1.2

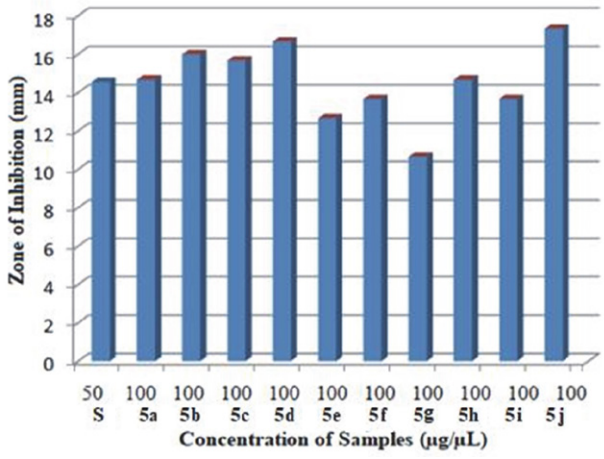


Figure 5. Antibacterial activity of acyl thioureas against *E. coli*

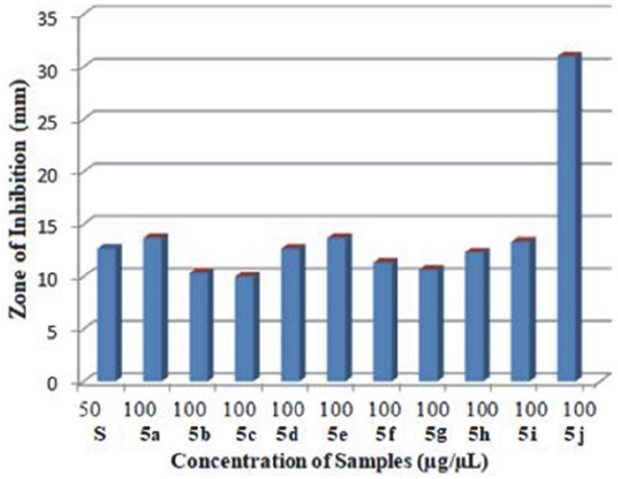


Figure 6. Antibacterial activity of acyl thioureas against *S. aureus.*

4. Conclusions

We have developed a highly convenient and effective protocol for the synthesis of substituted acyl thiourea derivatives from the carboxyl group of N^{α}-amino acids and organic acids by nano Fe_2O_3-catalysed coupling of acyl isothiocyanates and amino acid esters at room temperature in very good yields. Some of the synthesized acyl thiourea derivatives showed promising anti-bacterial activity against two bacterial pathogens, possibly due to the presence of pharmacologically active keto-thiourea group. The presented protocol underlines the potential applicability of nano Fe_2O_3 as inexpensive, user friendly and efficient catalyst prepared *via* solution combustion method using ascorbic acid as a novel reducing agent. This work can be considered as a very good step towards the emerging trend of heterogeneous and environmentally friendly synthesis of acyl thiourea derivatives from N^{α}-amino acids.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Povzetek

Opisujemo enostaven in okolju prijazen heterogeni katalitski sistem, temelječ na Fe_2O_3 nanodelcih, uporaben za sintezo acil tiosečninskih derivatov iz ustreznih *in situ* pripravljenih acil izotiocianatov in estrov aminokislin. Sinteza poteka v acetonu in daje produkte z dobrimi izkoristki. Strukture pripravljenih acil tiosečnin smo potrdili z ^{1}H NMR, ^{13}C NMR, masno in FTIR analizo. Nanodelce Fe_2O_3 smo pripravili s pomočjo sežiga raztopine, z uporabo askorbinske kisline kot reducenta ter **železovega**(III) nitrata kot vira **železovih** ionov. Pripravljen nanomaterial smo okarakterizirali z XRD, SEM, UV-vidno in FTIR analizami. Pomembno je, da lahko Fe_2O_3 in ostale nečistoče po sintezi enostavno odstranimo. Katalitski sistem je učinkovit in katalizira pretvorbe reaktantov v produkte z dobrimi izkoristki. Za nekatere izmed pripravljenih acil tiosečnin smo določili *in vitro* antibakterijske aktivnosti proti *Staphylococcus aureus* in *Escherichia coli.*