Green Chemistry

Cite this: *Green Chem.*, 2011, **13**, 2135

www.rsc.org/greenchem

PAPER

Step-economic, efficient, ZnS nanoparticle-catalyzed synthesis of spirooxindole derivatives in aqueous medium *via* Knoevenagel condensation followed by Michael addition†

Anshu Dandia,*[a] Vijay Parewa,[a] Anuj Kumar Jain[a] and Kuldeep S. Rathore[b]

Received 6th March 2011, Accepted 10th May 2011
DOI: 10.1039/c1gc15244k

An environmentally friendly, one-pot, three-component ZnS nanoparticle-mediated synthesis of biologically important spirooxindole derivatives in water under ultrasonic irradiation is described herein. ZnS nanoparticles were synthesized by aqueous chemical method. The advantages of this method lies in its simplicity, cost effectiveness, environment friendliness, easier scaling up for large scale synthesis without using high pressure, temperature and toxic chemicals. Greenness of the process was well instituted as water was exploited both as reaction media as well as medium for synthesis of catalyst (ZnS nanoparticles). The particle size was determined by transmission electron microscopy (TEM) and XRD. Compared with other methods for synthesis of spirooxindole derivatives, satisfactory results were obtained with high yields, short reaction time, with simple experimental procedure. After reaction course, the ZnS NPs can be recycled and reused without any apparent loss of activity.

1. Introduction

A "strong marriage" between nanotechnology and the principles and practices of green chemistry[1] holds the key to build an environmentally sustainable society. Nanotechnology potentially is a doubly green dream. It offers us the opportunity to make products and processes green from the beginning. The development of green processes and pollution abatement catalysts has acquired great importance. Catalysis lies at the heart of countless chemical protocols. The presence of a catalyst is mainly required by both modern organic syntheses, and in fine chemical industries. Thus, the chemical nature and the existing form of the catalyst are of vital importance for the reaction. A new generation of nanocatalysts will replace the conventional ones. Cutting-edge catalytic processes based on such nanocatalysts will be simpler, more economically efficient and more environmentally friendly, constituting "green chemistry" that produces only the most desirable products. Recently, metal-based nanoparticles in the form of nanocatalysts have emerged as viable alternatives to conventional materials in various fields of chemistry and attracted the interest of chemists. Metal-based nanoparticles are known to be promising materials for heterogeneous catalysts in a variety of organic transformations.[2] Metal-based nanoparticles have wide applications in electronic, magnetic, optical, biological and mechanical materials because of their notable differences compared to the bulk metals.[3]

The indole ring system is probably the most ubiquitous heterocycle in nature. Because of the great structural diversity of biologically active indoles, it is not surprising that the indole ring system has become an important structural component in many pharmaceutical agents.[4] Furthermore, indole substituted with heterocyclic rings at the 3-position have been found in a fascinating array of bioactive natural products and pharmaceutical compounds (Fig. 1). New indole alkaloids with a broad spectrum of biological properties are being discovered rapidly as marine invertebrate metabolites.[5,6]

On the other hand, spirooxindole derivatives occupy a special place in organic and medicinal chemistry because these compounds are well-known as microtubule assembly inhibitors (spirotryprostatin A and B),[7] Muscarinic M1, and serotonin receptor modulators (pteropodine and isopteropodine)[8] and nonpeptidyl growth-hormone secretagogues (MK-0677).[9] Considerable attention has been focused on the development of new methodologies to synthesize many kinds of spirooxindole ring systems because of their interesting biological and pharmacological properties, such as vasodilatory, hypoglycemic, anti-inflammatory, analgesic, and antipyretic activities.[10]

In context of this program, we have previously reported the synthesis of spirooxindole derivatives by a multi-step process catalyzed by Et_3N in ethanol under refluxing.[11–13] Recently two papers[14,15] describing three-component synthesis of

[a]*Centre of Advanced Studies, Department of Chemistry, University of Rajasthan, Jaipur, 302004, India*
[b]*Amity School of Engineering and Technology, Amity University Rajasthan, Jaipur, India. E-mail: dranshudandia@yahoo.co.in*
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c1gc15244k

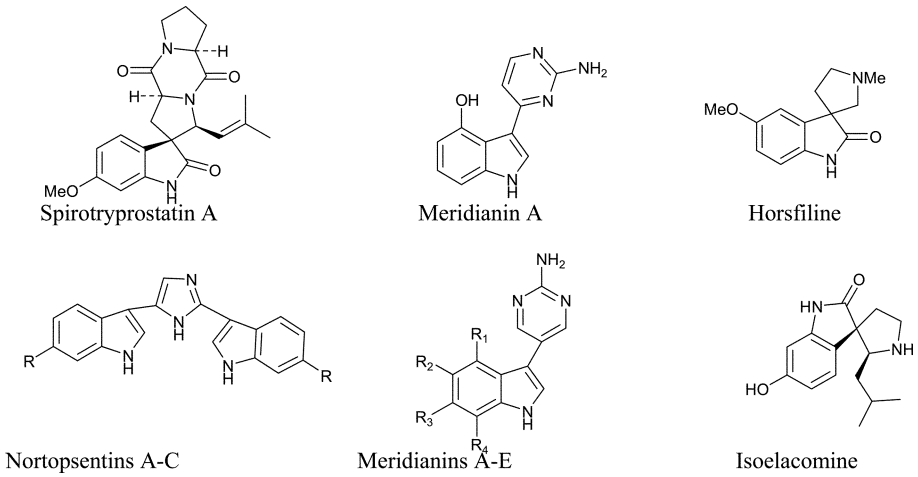


Fig. 1 Representatives of spirooxindole-containing compounds.

spirooxindole derivatives in aqueous medium with surfactants or solvent free, catalyzed by $InCl_3$ with microwave assistance, appeared in the literature. These methods display an important disadvantage in generating mixtures of pyrans and unsaturated nitriles. Microwave assistance is not necessary in pyran synthesis because the reactions are slightly exothermic. Pyrans were also prepared by electrochemical methods that suffer from technical intricacy.[16,17] However, some of the newer reported methods also suffer from drawbacks such as unsatisfactory yields, cumbersome product isolation procedures, and environmental pollution. Moreover, the main disadvantage of almost all existing methods is that the catalysts are destroyed in the workup procedure and cannot be recovered or reused. Therefore, there is still need for versatile, simple, and environmentally friendly processes.

Zinc-based nanoparticles[18] have great potential to be used as a catalysts for a variety of organic and inorganic reactions due to their high surface-to-volume ratio.[19] Since, these nanoparticles are often recovered easily by simple workup, which prevents contamination of products, they may be considered as a promising safe and reusable catalysts as well as greener compared to traditional catalysts. An increasing number of examples are available in the literature where zinc-based nanoparticles alone have been used as a catalyst during organic transformations.[20–22]

Considering the above points and in continuation of our quest for developing green protocols for heterocyclic frameworks[23] and nanoparticle synthesis,[24] herein we employ ZnS NPs as an efficient and heterogeneous catalyst for synthesis of spirooxindole derivatives through one-pot, three-component reactions in water under ultrasonic irradiation

2. Results and discussion

Firstly we prepared ZnS NPs through the wet chemical precipitation method,[25] which is a promising technique for synthesizing ZnS nanoparticles with excellent catalytic properties and high stability. The nanostructure of the ZnS nanoparticles has been studied at room temperature by using X-ray diffraction pattern. Fig. 2 shows the XRD patterns of ZnS nanoparticles. The obtained peak positions correspond to zinc blende type patterns

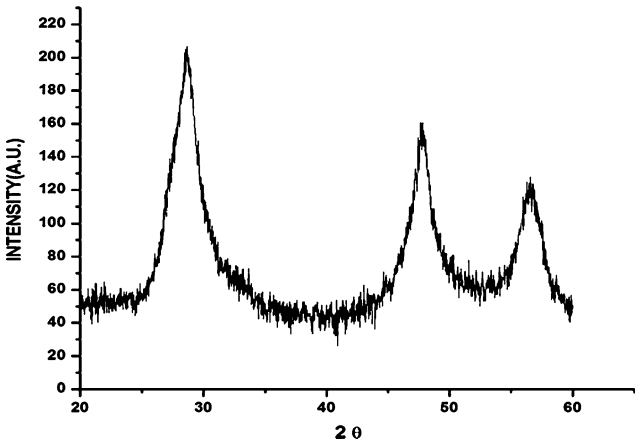


Fig. 2 XRD patterns of ZnS nanoparticles.

for the sample. The observed broad peaks corresponds to the Bragg angle for the (111), (220) and (311) planes of the cubic crystalline ZnS. The average particle size was calculated from the width of the XRD peaks, assuming that they are free from non-uniform strains, using the Scherrer formula.

$$D = 0.94\lambda/\beta\cos\theta \quad (1)$$

where D is the average particle size perpendicular to the reflecting planes, λ is the X-ray wavelength, β is the full width at half maximum (FWHM), and θ is the diffraction angle. To eliminate additional instrumental broadening, the FWHM was corrected, using the FWHM from a large grained Si sample.

$$\beta_{\text{corrected}} = (\text{FWHM}^2{}_{\text{sample}} - \text{FWHM}^2{}_{\text{si}})^{1/2} \quad (2)$$

This modified formula is valid only when the crystallite size is smaller than 100 nm. The average size of the particles obtained from the XRD is about 1.4 nm, using the Scherrer formula Fig. 3a shows the TEM image of ZnS nanoparticles. It shows abundance of spherical particles, whose size distribution is given by the histogram as shown in Fig. 3b. The size of the particle of ZnS estimated through TEM is found to be ~2.4 nm. The particle sizes obtained from TEM are slightly larger than that

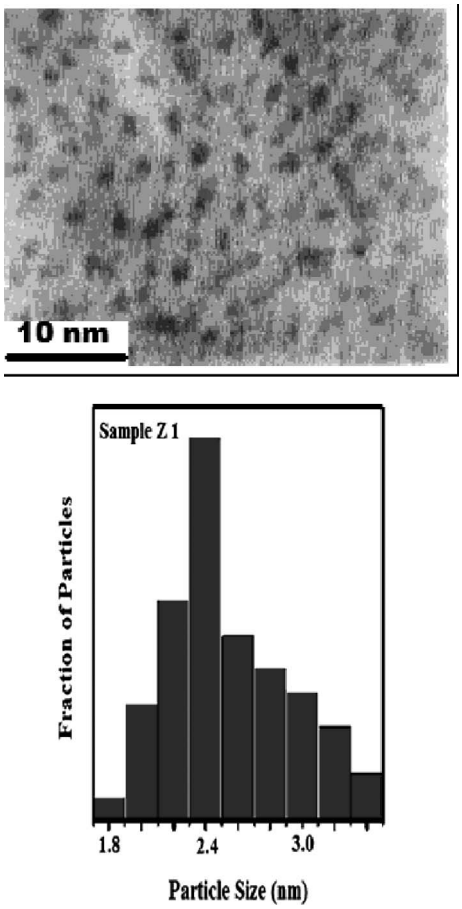
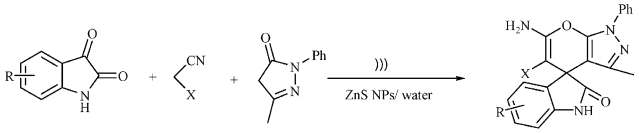


Fig. 3 (a) TEM image of ZnS nanoparticles. (b) Histogram of pure ZnS nanoparticles.

estimated through XRD results. The slight discrepancy is due to the intrinsic defects like twining and dislocations present in the lattice of these samples. No impurities were involved in the synthesized ZnS NPs sample. The synthesis of ZnS nanoparticles was carried out by aqueous chemical method using zinc sulfate and sodium sulfide as source materials. The entire process was carried out in distilled water for its inherent advantages as it is simple, cost effective, environment friendly, easily scaled up for large scale synthesis and in this method there is no need to use high pressure, temperature and toxic chemicals.

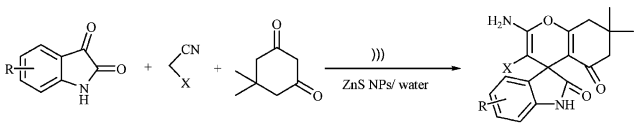
ZnS nanoparticles were used in water as obtained by the wet chemical method. Additionally, water served as a suitable solvent[26] for the currently probed transformation as well, based on the solubility difference of the product from the starting materials, leading to separation of product from the reaction mixture upon completion, thereby facilitating easy isolation of solid product from the reaction mixture simply by filtration. As part of our program aimed at developing new and environmentally benign synthetic methodologies with ZnS nanoparticles, the reaction of isatin, ethyl-cynoacetate and 3-methyl-1-phenyl-2-pyrazolin-5-one was examined in the presence of catalytic amount of ZnS NPs (10 mol%) in water under ultrasonic irradiation (Scheme 1). To delineate this approach, this methodology was evaluated by using different isatin and activated methylene reagent (Table 1). To further explore the potential of this protocol for heterocyclic synthesis, we investigated one-pot



R= H, 5-CH_3, 5-Cl, 5-Br, 5-NO_2, 5,7-diCH_3
X=CN, COOEt

Scheme 1 Synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazole] derivatives.

reactions involving 5,5-dimethylcyclohexane-1,3-dione instead of 3-methyl-1-phenyl-2-pyrazoline-5-one (Scheme 2). To our delight, under the above optimized conditions, the reaction proceeded smoothly and a variety of the desired spirooxindole derivatives were obtained in excellent yields (Table 2). The structures of the synthesized products were deduced from spectral data.



R= H, 5-CH_3, 5-Cl, 5-Br, 5-NO_2, 5,7-diCH_3
X=CN, COOEt

Scheme 2 Synthesis of spiro[chromene-4,3′-indoline] derivatives.

In order to confirm the effective involvement of ZnS nanoparticles during this transformation, we carried out the model reaction without any catalyst. In the absence of ZnS nanoparticles, the reaction was incomplete even after 81 min of sonication, though formation of a small amount of 5a (31%) was observed. In evaluating the effects of catalyst concentration, the best yields were found in the presence of 10 mol% ZnS NPs. A higher amount of catalyst did not improve the results to an appreciable extent.

A conceivable mechanism for the formation of the product would be as follows. The ZnS NPs facilitate the Knoevenagel-type coupling through Lewis acid sites (Zn^{2+}) coordinated to the oxygen of carbonyl groups. On the other hand, ZnS NPs can activate methylene compounds so that deprotonation of the C–H bond occurs in the presence of Lewis basic sites (S^{2-}). As a result the formation of spirooxindole derivatives proceeds by activation of reactants through both Lewis acid and basic sites of ZnS NPs.

The catalyst could be recycled easily simply by solvent extraction of the product from the reaction mixture. For this, ethyl acetate was used, the aqueous layer containing the ZnS nanoparticles could be reused for the next cycle. The catalyst retained optimum activity till three cycles after which drop in yield was observed (Fig. 4). Further, the EDAX pattern of ZnS nanoparticles (after using as a catalyst) shows that there is no peak of oxygen, which deny the possibility that there was any ZnS nanoparticles converted into ZnO (Fig. 5)

A comparison of efficiency of catalytic activity of ZnS NPs with several methods is presented in Table 3. ZnS NPs exhibit higher TOF value than other catalyst in this reaction. These result shows that this method is superior to the other methods in terms of yield and reaction time. Further the analysis of the final product by ICP-AES showed that there was no nanocatalyst present in the final product.

Table 1 Synthesis of spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]derivatives

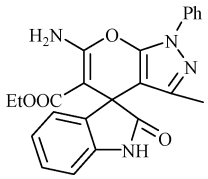
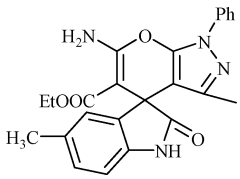
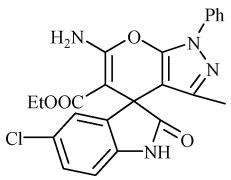
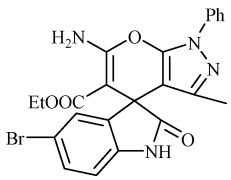
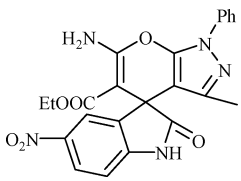
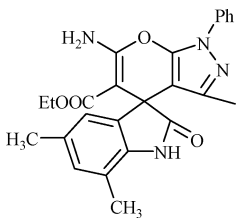
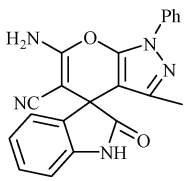
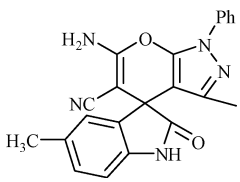
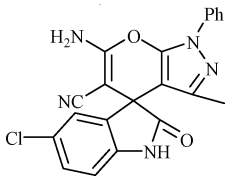
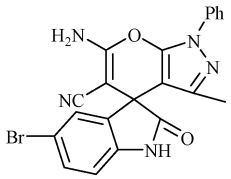
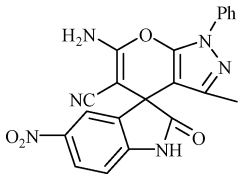
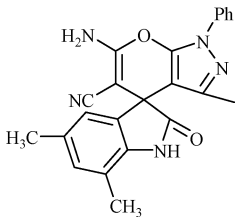
Entry	R	X	Time (min)	Product	Yield (%)[a]	Mp (°C)	Ref.
5a	H	COOEt	15		97	236–237	
5b	5-CH_3	COOEt	15		94	229–231	
5c	5-Cl	COOEt	14		93	241–242	
5d	5-Br	COOEt	15		95	251–253	
5e	5-NO_2	COOEt	15		94	265–266	
5f	5,7-diCH_3	COOEt	14		94	259–261	
5g	H	CN	13		96	237–238	16
5h	5-CH_3	CN	12		97	288–289	16

Table 1 *(Contd.)*

Entry	R	X	Time (min)	Product	Yield (%)[a]	Mp (°C)	Ref.
5i	5-Cl	CN	12		96	230–231	11
5j	5-Br	CN	12		94	241–243	
5k	5-NO_2	CN	14		95	226–228	11
5l	5,7-diCH_3	CN	13		95	218–221	11

[a] Isolated yield.

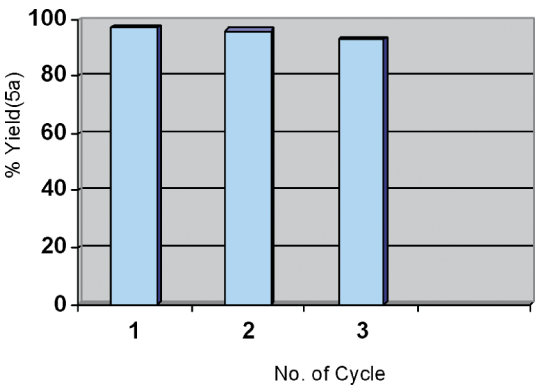


Fig. 4 Recyclability of ZnS nanoparticles.

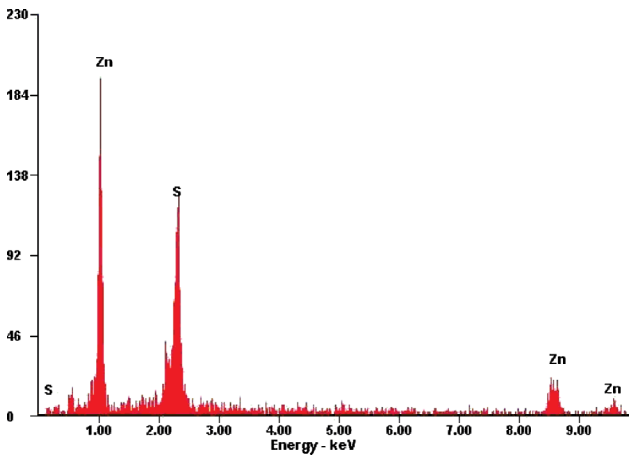


Fig. 5 EDAX pattern of ZnS nanoparticles (after use as catalyst).

3. Experimental

3.1 General

All the chemicals used were of research grade and were used without further purification. IR spectra were recorded on a Shimadzu FT IR- 8400S spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard on a Bruker spectrophotometer at 300 and 75 MHz respectively. Mass spectrum of representative compound was recorded on JEOL SX-102 spectrometer at 70 eV. Elemental microanalyses were carried out on a Carlo-Erba 1108 CHN analyzer. The reactions were carried out using an ultrasonic processor probe (Processor SONOPROS PR-1000 MP, OSCAR ULTRASONICS with power input 230V, 50 Hz, 4Amps and power variac 0-230V and 3Amps) operating at 20 kHz, 750 W with 6mm/12 mm tip diameter probes.

Table 2 Synthesis of spiro[chromene-4,3′-indoline]derivatives

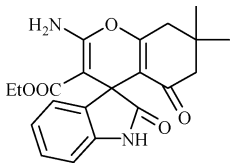
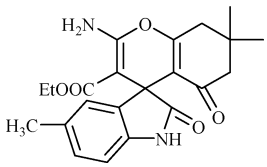
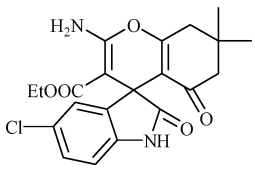
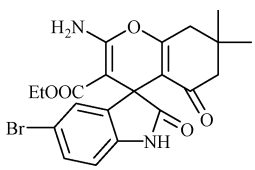
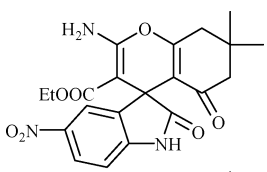
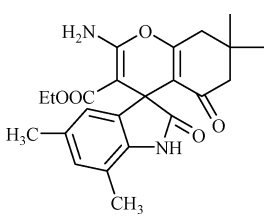
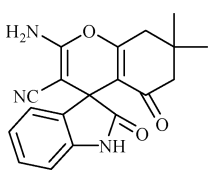
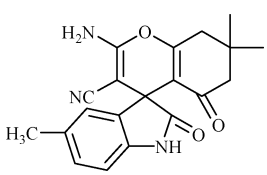
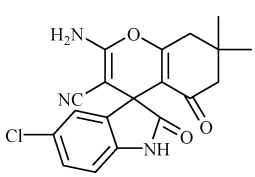
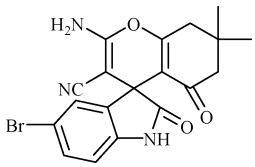
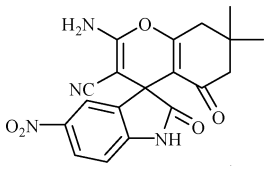
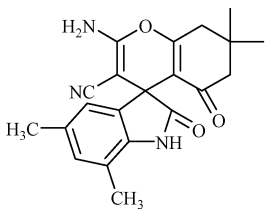
Entry	R	X	Time (min)	Product	Yield (%)[a]	Mp (°C)	Ref.
7a	H	COOEt	14		96	276–278	27
7b	5-CH_3	COOEt	13		95	281–282	
7c	5-Cl	COOEt	13		93	290–292	
7d	5-Br	COOEt	14		95	294–296	
7e	5-NO_2	COOEt	15		93	278–280	
7f	5,7-diCH_3	COOEt	14		92	279–281	
7g	H	CN	11		95	290–292	14
7h	5-CH_3	CN	13		92	278–280	14
7i	5-Cl	CN	12		93	291–293	

Table 2 *(Contd.)*

Entry	R	X	Time (min)	Product	Yield (%)[a]	Mp (°C)	Ref.
7j	5-Br	CN	14		94	305–307	17
7k	5-NO_2	CN	15		95	302–304	
7l	5,7-diCH_3	CN	12		96	>360	

[a] Isolated yield

Table 3 comparison of catalytic activity of ZnS NPs with other catalysts

Entry	Condition	Yield (%)[a]	TOF (h^{-1})
1	PTSA, H_2O, US, 90 min.	85%	172
2	L-Proline, H_2O, US, 58 min.	82%	257
3	Sulfamic acid, H_2O, US, 60 min.	87%	264
4	Et_3N, EtOH, US, 40 min.	79%	359
5	ZnS NPs, H_2O, US, 14 min.	94%	1221

Reactants used: 5,7-dimethyl isatin, ethylcynoacetate, 3-methyl-1-phenyl-2-pyrazolin-5-one and catalyst.[a] Isolated yield.

Melting points were recorded on a Toshniwal apparatus and are uncorrected.

3.2 Catalyst characterization

The wide angle X-ray diffraction pattern of the sample was obtained using Bragg-Brentanno geometry on Panalytical X'pert Pro differactometer in 2θ range of 15–85° with Cu-Kα radiation source ($\lambda = 1.5406$ Å). The X-ray tube was operated at 45 kv and 40 mA. TEM measurements of the sample were carried out using a JEOL transmission electron microscope. Sample for the TEM was prepared by making a clear dispersion of nanoparticles in dimethyl formaldehyde and putting a drop of it on a carbon-coated copper grid. The EDAX measurements of the synthesized nanoparticles were performed to confirm the copper doping using a FEI Quanta 200 F SEM fitted with an EDAX.

3.3 Preparation of ZnS nanoparticles

Nanoparticles of ZnS were prepared at 300 K by dropping simultaneously 50 ml of 1 M solution of $ZnSO_4$ and 50 ml of 1 M solution of Na_2S into 200 ml of distilled water containing 50 ml of 0.1 M solution of EDTA, which was vigorously stirred using a magnetic stirrer under Ar atmosphere. The high insolubility of ZnS formed out of the chemical reaction caused the formation of a number of new nuclei while preventing the growth of already existing ones, thus limiting the particle size. The role of EDTA was to stabilize the particle against aggregation which may lead to an increase in the particle size. The precipitate was separated from the reaction mixture and was dried at room temperature. After sufficient drying, the precipitate was crushed to fine powder with the help of mortar and pestle.

3.4 General procedure for the synthesis of spirooxindoles derivatives

An equimolar mixture of isatin (1 m mol, 0.147 g), ethyl cynoacetate (1 m mol, 0.113 g), 3-methyl-1-phenyl-2-pyrazolin-5-one (1 m mol, 0.174 g) and 10% mol ZnS nanoparticles in 5 ml water was introduced in a 20 mL heavy walled pear-shaped two-necked flask with non-standard tapered outer joint. The flask was attached to a 12 mm tip diameter probe and the reaction mixture was sonicated at ambient temperature for the specified period at 50% power of the processor and in a 4 s pulse mode till a solid product separates out. Completion of the reaction was monitored by TLC using n-hexane : ethyl acetate (7 : 3) as the eluant. All the reactions were invariably complete in 10–15 min. Upon completion of the reaction, the solid product was filtered washed with water, dried and recrystallised from ethanol. Spirooxindole derivatives were obtained as identified by their spectral data.

3.5 General procedure for the recyclability of the catalyst

After completion of the reaction, 10 ml of ethyl acetate were added to the reaction mixture. The reaction mixture was sonicated until complete dissolution of spirooxindole derivatives in ethyl acetate was observed. The two layers were then separated. The aqueous layer was sonicated for 5–10 min and reused for the same experiment for over three cycles.

3.6 Spectral data

Ethyl 6′-amino-3′-methyl-2-oxo-1′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carboxylate (**5a**). White crystalline solid (yield: 97%); mp: 238–240 °C ν_{max} (KBr): 3392, 3230, 3172, 1716, 1652, 1600, 1554, 1160 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.72 (t, 3H, CH_3), 1.57 (s, 3H, CH_3), 3.91 (q, J = 9.60 Hz, 2H, CH_2), 6.85–6.95 (m, 3H), 7.16 (t, J = 7.20 Hz,1H), 7.33 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 10.2 Hz, 2H), 7.76 (d, J = 8.10 Hz, 2H), 8.18 (br s, 2H, NH_2, D_2O exchangeable), 10.54 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 11.9, 13.3, 59.4, 75.1, 98.3,109.2, 120.3, 122.1, 123.4, 126.7, 128.1, 129.7, 135.9, 137.4, 142.3, 144.2,144.5,161.5, 168.2,179.7. MS (m/z): 417 $[M+H]^+$. Anal. calcd for $C_{23}H_{20}N_4O_4$: C, 66.34; H, 4.84; N, 13.45%. Found: C, 66.30; H, 4.81; N, 13.38%.

Ethyl 6′-amino-3′,5-dimethyl-2-oxo-1′-phenyl-1′*H*-spiro-[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carboxylate (**5b**). White crystalline solid (yield: 94%); mp: 230–232 °C ν_{max} (KBr): 3400, 3236, 3168, 1710, 1652, 1612, 1546, 1158 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.76 (t, 3H, CH_3), 1.59 (s, 3H, CH_3), 2.16 (s, 3H, CH_3), 3.74 (q, J = 6.90 Hz, 2H, CH_2), 6.73–6.77 (m, 2H), 6.97 (d, J = 7.8 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 2H), 7.80 (d, J = 8.1 Hz, 2H), 8.19 (br s, 2H, NH_2, D_2O exchangeable), 10.42 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 11.8, 13.2, 20.7, 47.6, 59.2, 74.8, 98.4, 108.7, 120.0, 123.8, 126.4, 128.1, 129.5, 130.7, 135.9, 137.4, 139.8, 144.0, 144.4, 161.4, 168.0, 179.4. MS (m/z): 431 $[M+H]^+$. Anal. calcd for $C_{24}H_{22}N_4O_4$: C, 66.97; H, 5.15; N, 13.02%. Found: C, 66.92; H, 5.11; N, 13.05%.

Ethyl 6′-amino-5-chloro-3′-methyl-2-oxo-1′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carboxylate (**5c**). White crystalline solid (yield: 93%); mp: 246–248 °C ν_{max} (KBr): 3396, 3228, 3172, 1698, 1644, 1608, 1566, 1160 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.77 (t, 3H, CH_3), 1.61 (s, 3H, CH_3), 3.75 (q, J = 6.6 Hz, 2H, CH_2), 6.89 (d, J = 8.4 Hz, 1H), 7.08 (s, 1H), 7.23 (d, J = 8.1 Hz, 1H), 7.33 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.80 (d, J = 8.1 Hz, 2H), 8.25 (br s, 2H, NH_2, D_2O exchangeable), 10.68 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 11.8, 13.2, 47.8 59.2, 74.1, 97.6, 110.4, 120.2, 123.5, 125.9, 126.5, 127.7, 129.5, 137.3, 137.9, 141.1, 144.1, 161.5, 167.8, 179.2. MS (m/z): 451 $[M+H]^+$. Anal. calcd for $C_{23}H_{19}ClN_4O_4$: C, 61.27; H, 4.25; N, 12.43%. Found: C, 61.30; H, 4.31; N, 12.42%.

Ethyl 6′-amino-5-bromo-3′-methyl-2-oxo-1′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carboxylate (**5d**). White crystalline solid (yield: 95%); mp: 252–254 °C ν_{max} (KBr): 3408, 3232, 3168, 1702, 1652, 1610, 1546,1156 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.78 (t, 3H, CH_3), 1.62 (s, 3H, CH_3), 3.74 (q, J = 6.6 Hz, 2H, CH_2), 6.85 (d, J = 7.8 Hz, 1H), 7.20 (s, 1H), 7.36 (d, J = 6.3 Hz, 1H), 7.50 (d, J = 6.9 Hz, 1H), 7.64 (t, J = 7.8 Hz, 2H), 7.80 (d, J = 7.20 Hz, 2H), 8.25 (br s, 2H, NH_2, D_2O exchangeable), 10.69 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 11.8, 13.2, 47.8, 59.2, 74.2, 97.6, 111.0, 113.6, 120.2, 126.2, 126.5, 129.0, 129.5, 130.6, 137.3, 138.3, 141.5, 144.1, 161.5, 167.8, 179.1. MS (m/z): 496 $[M+H]^+$. Anal. calcd for $C_{23}H_{19}BrN_4O_4$: C, 55.77; H, 3.87; N, 11.31%. Found: C, 55.71; H, 3.88; N, 11.29%.

Ethyl 6′-amino-3′-methyl-5-nitro-2-oxo-1′-phenyl-1′*H*-spiro-[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carboxylate (**5e**). White crystalline solid (yield: 94%); mp: 268–270 °C ν_{max} (KBr): 3424, 3236, 3173, 1700, 1652, 1608, 1586, 1170 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.76 (t, 3H, CH_3), 1.62 (s, 3H, CH_3), 3.75 (q, J = 6.9 Hz, 2H, CH_2), 7.76– 7.84 (m, 3H), 7.86 (t, J = 7.8 Hz, 1H), 7.94 (t, J = 7.6 Hz, 2H), 8.18 (d, J = 7.8 Hz, 2H), 8.26 (br s, 2H, NH_2, D_2O exchangeable), 11.49 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 12.1, 13.5, 48.9, 60.1, 75.9, 98.7, 110.2, 120.5, 122.9, 124.5, 126.9, 129.8, 129.95, 139.5, 144.5, 144.7, 144.9, 147.2,162.8, 169.7, 180.2. MS (m/z): 462 $[M+H]^+$. Anal. calcd for $C_{23}H_{19}N_5O_6$: C, 59.87; H, 4.15; N, 15.18%. Found: C, 59.78; H, 4.11; N, 15.21%.

Ethyl 6′-amino-3′,5,7-trimethyl-2-oxo-1′-phenyl-1′*H*-spiro-[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carboxylate (**5f**). White crystalline solid (yield: 94%); mp: 260–262 °C ν_{max} (KBr): 3398, 3228, 3170, 1702, 1648, 1611, 1570,1168 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.75 (t, 3H, CH_3), 1.58 (s, 3H, CH_3), 2.12 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.73 (q, J = 6.90 Hz, 2H, CH_2), 6.57 (s, 1H), 6.78 (s, 1H), 7.32 (t, J = 7.2 Hz, 1H), 7.50 (t, J = 7.8 Hz, 2H), 7.80 (d, J = 7.8 Hz, 2H), 8.17 (br s, 2H, NH_2, D_2O exchangeable), 10.47 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 11.8, 12.9, 16.3, 18.6, 20.6, 47.8, 56.2, 59.2, 75.0, 98.6, 117.9, 120.0, 121.2, 126.4, 129.4, 129.5,130.6, 135.5, 137.4, 138.3, 144.0, 144.4, 161.3, 168.1, 179.9. MS (m/z): 445 $[M+H]^+$. Anal. calcd for $C_{25}H_{24}N_4O_4$: C, 67.55; H, 5.44; N, 12.60%. Found: C, 67.49; H, 5.39; N, 12.63%.

6′-Amino-3′-methyl-2-oxo-1′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5g**). White crystalline solid (yield: 96%); mp: 237–238 °C. ν_{max} (KBr): 3412, 3280, 3174, 2200, 1692, 1650, 1526, 1132 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 1.55 (s, 3H, CH_3), 6.94 (d, J = 7.4 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H),7.18 (d, J = 7.2 Hz, 1H), 7.28 (t, J = 7.5 Hz,1H), 7.36 (t, J = 7.6 Hz,1H), 7.52 (t, J = 7.8 Hz, 2H), 7.58 (br s, 2H, NH_2, D_2O exchangeable), 7.79 (d, J = 7.9 Hz, 2H), 10.76 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 12.3, 48.3, 56.6, 96.9, 110.4, 118.6, 120.7, 123.2, 125.4, 127.1, 129.8, 130.8, 132.6, 138.2, 142.1, 144.5, 145.5, 162.3, 178.8. MS (m/z): 370 $[M+H]^+$. Anal. calcd for $C_{21}H_{15}N_5O_2$: C, 68.28; H, 4.09; N, 18.96%. Found: C, 68.26; H, 4.04; N, 18.88%.

6′-Amino-3′,5-dimethyl-2-oxo-1′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5h**). White crystalline solid (yield: 97%); mp: 288–290 °C. ν_{max} (KBr): 3426, 3269, 3178, 2192, 1696, 1650, 1576, 1174 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz):δ 1.56 (s, 3H, CH_3), 2.26 (s, 3H, CH_3), 6.84 (d, J = 7.8 Hz, 1H), 7.08 (s, 1H), 7.12 (d, J = 7.6 Hz, 1H), 7.35 (t, J = 8 Hz, 1H),7.52 (t, J = 8.4 Hz, 2H), 7.55 (br s, 2H, NH_2, D_2O exchangeable), 7.78 (d, J = 8.3 Hz, 2H), 10.64 (s, 1H, NH, D_2O exchangeable). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 11.9, 20.4, 48.2, 56.7, 96.6, 110.1, 118.4, 119.9, 125.3, 126.8, 129.9, 130.5, 131.9, 132.6, 137.4, 139.8, 144.3, 145.7, 161.2, 177. MS (m/z): 384 $[M+H]^+$. Anal. calcd for $C_{22}H_{17}N_5O_2$:

C, 68.92; H, 4.47; N, 18.27%. Found: C, 68.82; H, 4.51; N, 18.11%.

6′-Amino-5-chloro-3′-methyl-2-oxo-1′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5i**). White crystalline solid (yield: 96%); mp: 232–234 °C. ν_{max} (KBr): 3440, 3264,3172, 2196, 1698, 1652, 1576, 1174 cm^{-1}. ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 1.58 (s, 3H, CH$_3$), 6.96 (d, J = 8.4 Hz, 1H), 7.34–7.42 (3H, m), 7.52 (t, J = 8.2 Hz, 2H), 7.63 (br s, 2H, NH$_2$, D$_2$O exchangeable), 7.78 (d, J = 8 Hz, 2H), 10.89 (s, 1H, NH, D$_2$O exchangeable). ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 11.8, 47.9, 56.4, 96.5, 109.6, 118.1, 120.2, 125.4, 126.6, 129.5, 129.6, 131.7, 132.3, 137.3, 139.2, 144.1, 145.0, 161.0, 177.5. MS (m/z): 404 [M+H]$^+$. Anal. calcd for $C_{21}H_{14}ClN_5O_2$: C, 62.46; H, 3.49; N, 17.34%. Found: C, 62.48; H, 3.47; N, 17.35%.

6′-Amino-5-bromo-3′-methyl-2-oxo-1′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5j**). White crystalline solid (yield: 94%); mp: 242–244 °C. ν_{max} (KBr): 3436, 3269, 3168, 2198, 1706, 1650, 1576, 1168 cm^{-1}. ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 1.58 (s, 3H, CH$_3$), 6.91 (d, J = 7.6 Hz, 1H), 7.42–7.54 (4H, m), 7.28 (t, J = 7.9 Hz, 1H), 7.64 (br s, 2H, NH$_2$, D$_2$O exchangeable), 7.79 (d, J = 7.8 Hz, 2H), 10.90 (s, 1H, NH, D$_2$O exchangeable). ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 12.1, 47.9, 56.4, 96.7,110.6, 118.2, 120.9, 125.8, 126.6, 129.5, 129.6, 131.7, 132.3, 137.3, 139.2, 144.1, 145.0, 161.0, 178. MS (m/z): 448 [M+H]$^+$. Anal. calcd for $C_{21}H_{14}BrN_5O_2$: C, 56.27; H, 3.15; N, 15.62%. Found: C, 56.17; H, 3.21; N, 15.60%.

6′-Amino-3′-methyl-5-nitro-2-oxo-1′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5k**). White crystalline solid (yield: 95%); mp: 226–228 °C. ν_{max} (KBr): 3446, 3269, 3176, 2208, 1710, 1650, 1576, 1178 cm^{-1}. ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 1.59 (s, 3H, CH$_3$), 7.12 (d, J = 8.4 Hz, 1H), 7.38–7.55 (m, 3H), 7.68 (br s, 2H, NH$_2$, D$_2$O exchangeable), 7.78 (m, 2H), 7.98 (d, J = 6.8 Hz, 2H), 11.44 (s, 1H, NH, D$_2$O exchangeable). ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 12.3, 47.9, 56.4, 96.5, 109.6, 118.1, 120.2, 125.4, 126.6, 132.0, 132.6, 131.7, 134.3, 137.3, 139.2, 144.9, 145.0, 161.2, 178.8. MS (m/z): 415 [M+H]$^+$. Anal. calcd for $C_{21}H_{14}N_6O_4$: C, 60.87; H, 3.41; N, 20.28%. Found: C, 60.76; H, 3.47; N, 20.29%.

6′-Amino-3′,5,7-trimethyl-2-oxo-1′-phenyl-1′*H*-spiro[indoline-3,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (**5l**). White crystalline solid, (yield 95%); 218–220 °C ν_{max} (KBr): 3428, 3264, 3171, 2198, 1700, 1652, 1564, 1155 cm^{-1}. ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 1.57 (s, 3H, CH$_3$), 2.24 (s, 3H, CH$_3$), 2.33 (s, 3H, CH$_3$), 6.84 (s, 1H), 7.02 (s, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.58 (br s, 2H, NH$_2$, D$_2$O exchangeable), 7.64 (d, J = 7.6 Hz, 2H), 10.68 (s, 1H, NH, D$_2$O exchangeable). ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 11.9, 19.2, 20.6, 47.9, 56.8, 96.3, 109.6, 118.4, 120.2, 125.4, 126.6, 129.5, 129.8, 131.6, 132.3, 137.3, 139.7, 143.9, 145.0, 161.0, 177. MS (m/z): 398[M+H]$^+$. Anal. calcd for $C_{23}H_{19}N_5O_2$: C, 69.51; H, 4.82; N, 17.62%. Found: C, 69.47; H, 4.80; N, 17.56%.

Ethyl 2-amino-7,7-dimethyl-2′,5-dioxo-5, 6,7, 8-tetrahydrospiro[chromene-4,3-indoline]-3-carboxylate (**7a**). White crystalline solid (yield: 96%); mp: 278–280 °C. ν_{max} (KBr): 3398, 3276, 3212, 2925, 1698, 1652, 1610, 1221 cm^{-1}. ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 0.82 (t, J = 7.2 Hz, 3H, CH$_3$), 0.98 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 2.04 (d, J = 16.2 Hz, 1H, CH), 2.18 (d, J = 16.2 Hz, 1H, CH), 2.55 (d, J = 6.2 Hz, 2H, CH$_2$), 3.69 (q, J = 7.2 Hz, 2H, CH$_2$), 6.65 (d, J = 7.5 Hz, 1H), 6.76 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 6.9 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.72 (br s, 2H, NH$_2$, D$_2$O exchangeable) 10.19 (s, 1H, NH, D$_2$O exchangeable). ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 13.5, 27.1, 28.2, 32.3, 47.1, 51.1, 59.3, 76.7, 108.6, 113.5, 120.9, 122.6, 127.5, 136.7, 144.3, 159.1, 160.8, 162.8, 168.1, 180.4, 195.3. MS (m/z): 383 [M+H]$^+$. Anal. calcd for $C_{21}H_{22}N_2O_5$: C, 65.96; H, 5.80; N, 7.33%. Found: C, 65.72; H, 6.01; N, 7.47%.

Ethyl 2-amino-5′,7,7-trimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3 indoline]-3-carboxylate (**7b**). White crystalline solid (yield: 95%); mp: 282–284 °C. ν_{max} (KBr): 3402, 3280, 3209, 2930, 1696, 1652, 1614, 1220 cm^{-1}. ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 0.82 (t, J = 7.2 Hz, 3H, CH$_3$), 0.99 (s, 3H, CH$_3$), 1.02 (s, 3H, CH$_3$), 2.04 (d, J = 16.2 Hz, 1H, CH), 2.19 (d, J = 16.2 Hz, 1H, CH), 2.2 (s, 3H, CH$_3$), 2.56 (d, J = 6.2 Hz, 2H, CH$_2$), 3.68 (q, J = 7.2 Hz, 2H, CH$_2$), 6.66 (d, J = 7.6 Hz, 1H), 6.75 (s, 1H), 6.84 (d, 1H, J = 6.9 Hz), 7.74 (br s, 2H, NH$_2$, D$_2$O exchangeable) 10.21 (s, 1H, NH, D$_2$O exchangeable). ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 13.5, 27.2, 21.1, 28.5, 32.3, 47.2, 51.4, 59.2, 76.8, 108.6, 113.7, 121.1, 122.6, 127.5, 136.7, 144.4, 159.2, 160.8, 162.8, 168.8, 180.5, 195.4. MS (m/z): 397 [M+H]$^+$. Anal. calcd for $C_{22}H_{24}N_2O_5$: C, 66.65; H, 6.10; N, 7.07%. Found: C, 66.82; H, 6.01; N, 7.27%.

Ethyl 2-amino-5′-chloro-7,7-trimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3-indoline]-3-carboxylate (**7c**). White crystalline solid (yield: 93%); mp: 292–294 °C. ν_{max} (KBr): 3401, 3284, 3218, 2935, 1698, 1658, 1610, 1226 cm^{-1}. ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 0.82 (t, J = 7.2 Hz, 3H, CH$_3$), 0.98 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 2.07 (d, J = 16.4 Hz, 1H, CH), 2.2 (d, J = 16.4 Hz, 1H, CH), 2.56 (d, J = 6.2 Hz, 2H, CH$_2$), 3.67 (q, J = 7.4 Hz, 2H, CH$_2$), 6.68 (d, J = 7.4 Hz, 1H), 6.76 (s, 1H), 6.85 (d, J = 7.2 Hz, 1H), 7.74 (br s, 2H, NH$_2$, D$_2$O exchangeable) 10.19 (s, 1H, NH, D$_2$O exchangeable) ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 13.6, 27.2, 28.5, 32.3, 47.2, 51.4, 59.2, 76.8, 108.6, 113.7, 116.9, 121.9, 128.4, 136.9, 145.8, 159.2, 160.4, 162.8, 168.7, 180.6, 195.3. MS (m/z): 417 [M+H]$^+$. Anal. calcd for $C_{21}H_{21}ClN_2O_5$: C, 60.51; H, 5.08; N, 6.72%. Found: C, 60.72; H, 5.01; N, 6.55%.

Ethyl 2-amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3-indoline]-3-carboxylate (**7d**). White crystalline solid (yield: 98%); mp: 296– 298 °C. ν_{max} (KBr): 3398, 3282, 3209, 2934, 1700, 1662, 1612, 1223 cm^{-1}. ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 0.82 (t, J = 7.2 Hz, 3H, CH$_3$), 0.99 (s, 3H, CH$_3$), 1.01 (s, 3H, CH$_3$), 2.06 (d, J = 16.4 Hz, 1H, CH), 2.2 (d, J = 16.4 Hz, 1H, CH), 2.54 (d, J = 6.2 Hz, 2H, CH$_2$), 3.68 (q, J = 7.2 Hz, 2H, CH$_2$), 6.67 (d, J = 7.2 Hz, 1H), 6.76 (s, 1H), 6.86 (d, J = 7.4 Hz, 1H), 7.72 (br s, 2H, NH$_2$, D$_2$O exchangeable) 10.20 (s, 1H, NH, D$_2$O exchangeable) ^{13}C NMR (DMSO-d$_6$, 75 MHz): δ 13.3, 27.4, 28.5, 32.6, 47.2, 51.5, 59.2, 76.3, 108.6, 111.7, 118.9, 121.9, 128.5, 136.9, 145.8, 159.7, 161.4, 161.9, 168.7, 181.1, 195.6. MS (m/z): 462 [M+H]$^+$. Anal. calcd for $C_{21}H_{21}BrN_2O_5$: C, 54.68; H, 4.59; N, 6.07%. Found: C, 54.85; H, 4.48; N, 5.92%.

Ethyl 2-amino-7,7-dimethyl-5′-nitro-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3-indoline]-3-carboxylate (**7e**). White crystalline solid, (Yield: 93%); mp: 276– 278 °C. ν_{max} (KBr): 3406, 3288, 3212, 2935, 1702, 1662, 1618, 1225 cm^{-1}. ^{1}H NMR (DMSO-d$_6$, 300 MHz): δ 0.83 (t, J = 7.4 Hz, 3H, CH$_3$), 0.99 (s, 3H, CH$_3$), 1.02 (s, 3H, CH$_3$), 2.07 (d, J = 16.2 Hz, 1H, CH), 2.2 (d, J = 16.2 Hz, 1H, CH), 2.58 (d, J = 6.8 Hz, 2H, CH$_2$), 3.71

(q, J = 7.6, 2H, CH_2), 6.86 (d, J = 7.6 Hz, 1H), 6.98 (s, 1H), 7.27 (d, J = 7.6 Hz, 1H), 7.78 (br s, 2H, NH_2, D_2O exchangeable) 11.39 (s, 1H, NH, D_2O exchangeable) ^{13}C NMR (DMSO-d_6, 75 MHz): δ 13.5, 27.8, 28.6, 32.4, 47.6, 51.9, 59.2, 76.3, 108.6, 112.8, 121.9, 123.9, 132.5, 138.9, 148.8, 159.9, 163.4, 164.1, 168.7, 181.4, 195.7. MS (m/z): 428 $[M+H]^+$. Anal. calcd for $C_{21}H_{21}N_3O_7$: C, 59.01; H, 4.95; N, 9.83%. Found: C, 58.85; H, 4.82; N, 9.92%.

Ethyl 2-amino-5′,7′,7,7-tetramethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3-indoline]-3-carboxylate (**7f**). White crystalline solid (yield: 92%); mp: 280–282 °C. ν_{max} (KBr): 3398, 3282, 3210, 2934, 1698, 1652,1615,1223 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.82 (t, J = 7.2 Hz, 3H, CH_3), 0.99 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.03 (d, J = 16.2 Hz, 1H, CH), 2.18 (d, J = 16.2 Hz, 1H, CH), 2.24 (s, 3H, CH_3), 2.32 (s, 3H, CH_3), 2.57 (d, J = 6.2 Hz, 2H, CH_2), 3.69 (q, J = 7.4 Hz, 2H, CH_2), 6.64 (s, 1H), 6.72 (s, 1H), 7.74 (br s, 2H, NH_2, D_2O exchangeable) 10.20 (s, 1H, NH, D_2O exchangeable) ^{13}C NMR (DMSO-d_6, 75 MHz): δ 13.4, 21.2, 22.7, 27.2, 28.5, 32.4, 47.5, 51.5, 59.2, 76.6, 108.6, 113.7, 121.4, 122.7, 127.3, 136.9, 144.8, 159.7, 160.8, 162.8, 168.6, 180.7, 195.4. MS (m/z): 411 $[M+H]^+$. Anal. calcd for $C_{23}H_{26}N_2O_5$: C, 67.30; H, 6.38; N, 6.82%. Found: C, 67.52; H, 6.31; N, 7.07%.

2-Amino-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro-[chromene-4,3-indoline]-3-carbonitrile (**7g**). White crystalline solid (yield: 95%); mp: 290–292 °C. ν_{max} (KBr): 3412, 3280, 3114, 2200, 1692, 1650, 1526, 1132 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.97 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.06 (d, J = 16.2 Hz, 1H, CH) 2.15 (d, J = 16.2 Hz, 1H, CH) 2.47 (s, 2H, CH_2) 6.75 (d, J = 7.5 Hz, 1H), 6.84 (t, J = 7.5 Hz, 1H), 6.94 (d, J = 6.9 Hz, 1H), 7.09 (t, J = 7.5 Hz, 1H), 7.22 (br s, 2H, NH_2, D_2O exchangeable) 10.39 (s, 1H, NH, D_2O exchangeable) ^{13}C NMR (DMSO-d_6, 75 MHz): δ 27.3, 27.9, 32.3, 47.1, 50.3, 57.7, 109.6, 111.1, 117.7, 122.1, 123.4, 128.5, 134.7, 142.3, 159.1, 164.5, 178.4, 195.3. MS (m/z): 336 $[M+H]^+$. Anal. calcd for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53%. Found: C, 68.24; H, 5.21; N, 12.64%.

2-Amino-5′,7,7-trimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3-indoline]-3-carbonitrile (**7h**). White crystalline solid (yield: 92%); mp: 278–280 °C. ν_{max} (KBr): 3410, 3286, 3122, 2195, 1692, 1648, 1526, 1128 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.98 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.11 (s, 2H, CH_2) 2.17 (s, 3H, CH_3), 2.50 (d, J = 14.70 Hz, 2H, CH_2) 6.63 (d, J = 7.80 Hz, 1H), 6.75 (s, 1H), 6.90 (d, J = 7.80 Hz, 1H), 7.21 (br s, 2H, NH_2, D_2O exchangeable) 10.29 (s, 1H, NH, D_2O exchangeable) ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.0, 27.5, 27.8, 32.3, 47.3, 50.3, 57.8, 109.3, 111.1, 117.8, 123.9, 128.8, 130.8, 134.8, 139.9, 159.0, 164.4, 178.4, 195.3. MS (m/z): 350$[M+H]^+$. Anal. calcd for $C_{20}H_{19}N_3O_3$: C, 68.75; H, 5.48; N, 12.03%. Found: C, 68.91; H, 5.56; N, 12.10%.

2-Amino-5′-chloro-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3-indoline]-3-carbonitrile (**7i**). White crystalline solid (yield: 93%); mp: 294–296 °C. ν_{max} (KBr): 3416, 3268, 3118, 2202, 1692, 1650, 1528, 1132 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.97 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.12–2.18 (m, 2H, CH_2) 2.48–2.60 (m, 2H, CH_2), 6.80 (d, J = 8.40 Hz, 1H), 7.10 (s, 1H), 7.18 (d, J = 8.40 Hz, 1H), 7.30 (br s, 2H, NH_2, D_2O exchangeable) 10.52 (s, 1H, NH, D_2O exchangeable) ^{13}C NMR (DMSO-d_6, 75 MHz): δ 27.7, 27.9, 32.4, 47.5, 50.4, 57.2, 110.3, 111.1, 117.6, 123.7, 126.2, 128.6, 137.1, 141.6, 141.9, 159.3, 165.4, 178.3, 195.5. MS (m/z): 370$[M+H]^+$. Anal. calcd for $C_{19}H_{16}ClN_3O_3$: C, 61.71; H, 4.36; N, 11.36%. Found: C, 61.84; H, 4.50; N, 11.58%.

2-Amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3-indoline]-3-carbonitrile (**7j**). White crystalline solid (yield: 94%); mp: 306–308 °C. ν_{max} (KBr): 3408, 3280, 3133, 2206, 1690, 1658, 1520, 1128 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.97 (s, 3H, CH_3), 1.00 (s, 3H, CH_3), 2.09–2.16 (m, 2H, CH_2) 2.41–2.55 (m, 2H, CH_2), 6.76 (d, J = 8.40 Hz, 1H), 7.16 (s, 1H), 7.29 (d, J = 8.40 Hz, 1H), 7.30 (br s, 2H, NH_2, D_2O exchangeable) 10.53 (s, 1H, NH, D_2O exchangeable) ^{13}C NMR (DMSO-d_6, 75 MHz): δ 27.7, 27.9, 32.4, 47.5, 50.4, 57.2, 110.3, 111.1, 117.6, 123.7, 126.2, 128.6, 137.1, 141.6, 141.9, 159.3, 165.4, 178.3, 195.5. MS (m/z): 414 $[M+H]^+$. Anal. calcd for $C_{19}H_{16}BrN_3O_3$: C, 55.09; H, 3.89; N, 10.14%. Found: C, 55.32; H, 3.97; N, 10.22%.

2-Amino-7,7-dimethyl-5′-nitro-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3-indoline]-3-carbonitrile (**7k**). White crystalline solid (yield: 95%); mp: 302–304 °C. ν_{max} (KBr): 3422, 3290, 3139, 2202, 1698, 1660, 1520, 1132 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.99 (s, 3H, CH_3), 1.02 (s, 3H, CH_3), 2.23–2.35 (m, 2H, CH_2) 2.68–2.81 (m, 2H, CH_2), 7.30 (d, J = 8.60 Hz, 1H), 8.20– 8.29 (m, 1H), 8.34– 8.42 (m, 1H), 7.78 (br s, 2H, NH_2, D_2O exchangeable) 11.32 (s, 1H, NH, D_2O exchangeable) ^{13}C NMR (DMSO-d_6, 75 MHz): δ 27.9, 28.4, 33.4, 48.8, 50.9, 58.8, 112.3, 113.8, 118.6, 124.7, 126.9, 129.4,138.6, 142.4, 143.2, 160.8, 167.2, 179.3, 196.1. MS (m/z): 381 $[M+H]^+$. Anal. calcd for $C_{19}H_{16}N_4O_5$: C, 60.0; H, 4.24; N, 14.73%. Found: C, 60.26; H, 4.35; N, 14.64%.

2-Amino-5′,7′,7,7-tetramethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3-indoline]-3-carbonitrile (**7l**). White crystalline solid (yield: 96%); mp: >360 °C. ν_{max} (KBr): 3412, 3286, 3116, 2195, 1692, 1648, 1526, 1128 cm^{-1}. ^1H NMR (DMSO-d_6, 300 MHz): δ 0.98 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.12 (s, 2H, CH_2) 2.17 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 2.47 (d, J = 14.8 Hz, 2H, CH_2) 6.61 (s, 1H), 6.78 (s, 1H), 7.18 (br s, 2H, NH_2, D_2O exchangeable) 10.26 (s, 1H, NH, D_2O exchangeable) ^{13}C NMR (DMSO-d_6, 75 MHz): δ 21.2, 22.7, 27.5, 27.8, 32.3, 47.3, 50.3, 57.8, 109.3, 111.1, 117.8, 123.9, 128.8, 130.8, 134.8, 139.9, 159.0, 164.4, 178.4, 195.4. MS (m/z): 364 $[M+H]^+$. Anal. calcd for $C_{21}H_{21}N_3O_3$: C, 69.41; H, 5.82; N, 11.56%. Found: C, 69.60; H, 5.66; N, 11.40%.

4. Conclusion

In conclusion, we have described a novel and highly efficient protocol for the synthesis of structurally complex and diverse spirooxindole derivatives catalyzed effectively by ZnS nanoparticles in aqueous medium. ZnS nanoparticles were well characterized by TEM and XRD techniques. This method offers several advantages including high yield, short reaction time, a simple work-up procedure, ease of separation and recyclability of the catalyst, as well as the ability to tolerate a wide variety of substitutions in the components. The application of this new catalyst in organic synthesis will be further expanded. This work is under way in our laboratory

Acknowledgements

Financial assistance from the CSIR (01/2248/08/EMR-II) New Delhi is gratefully acknowledged. We are also thankful to the Central Drug Research Institute (CDRI), Lucknow, for the elemental and spectral analyses.

References

1 (*a*) D. Astruc, F. Lu and J. R. Aranzaes, *Angew. Chem., Int. Ed.*, 2005, **44**, 7852; (*b*) I. P. Beletskaya and A. V. Cheprakov, *Chem. Rev.*, 2000, **100**, 3009.
2 (*a*) D. Astruc, *Inorg. Chem.*, 2007, **46**, 1884; (*b*) D. Astruc, F. Lu and J. R. Aranzaes, *Angew. Chem., Int. Ed.*, 2005, **44**, 7852; (*c*) V. Polshettiwar, B. Baruwati and R. S. Varma, *Green Chem.*, 2009, **11**, 127; (*d*) M. T. Reetz and E. Westermann, *Angew. Chem., Int. Ed.*, 2000, **39**, 165.
3 (*a*) T. M. Whitney, J. S. Jiang, P. C. Searson and C. L. Chien, *Science*, 1993, **261**, 1316; (*b*) M. Green and P. O'Brien, *Chem. Commun.*, 1999, 2235; (*c*) L. Lu, M. L. Sui and K. Lu, *Science*, 2000, **287**, 1463; (*d*) N. Grobert, W. K. Hsu, Y. Q. Zhu, J. P. Hare, H. W. Kroto and D. R. M. Walton, *Appl. Phys. Lett.*, 1999, **75**, 3363; (*e*) A. K. Salem, P. C. Searson and K. W. Leong, *Nat. Mater.*, 2003, **2**, 668; (*f*) Y. M. Wang, M. W. Chen, F. H. Zhou and E. Ma, *Nature*, 2002, **419**, 912; (*g*) K. S. Kumar, H. V. Swygenhoven and S. Suresh, *Acta Mater.*, 2003, **51**, 5743; (*h*) G. Liu, Y. Lin, V. Ostatńa and J. Wang, *Chem. Commun.*, 2005, 3481; (*i*) K. M. Yeo, C. J. Gao, K. H. Ahn and I. S. Lee, *Chem. Commun.*, 2008, 4622; (*j*) W. Zhou, N. Yao, G. Yao, C. Deng, X. Zhang and P. Yang, *Chem. Commun.*, 2008, 5577; (*k*) S. Singh and S. B. Krupanidhi, *Dalton Trans.*, 2008, 4708.
4 (*a*) R. J. Sundberg, *The Chemistry of Indoles*, Academic Press, New York, 1970; (*b*) R. J. Sundberg, Pyrroles and Their Benzoderivatives: Synthesis and Applications, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon, Oxford, U.K., 1984, vol. 4, pp. 313–376.
5 (*a*) A. Casapullo, G. Bifulco, I. Bruno and R. Riccio, *J. Nat. Prod.*, 2000, **63**, 447; (*b*) B. Bao, Q. Sun, X. Yao, J. Hong, C. O. Lee, C. J. Sim, K. S. Im and J. H. Jung, *J. Nat. Prod.*, 2005, **68**, 711.
6 (*a*) L. Gupta, A. Talwar, N. S. Palne, S. Gupta and P. M. S. Chauhan, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4075; (*b*) K. Kaniwa, M. A. Arai, X. Li and M. Ishibashi, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4254.
7 (*a*) M. M. Khafagy, A. H. El-Wahas, F. A. Eid and A. M. El-Agrody, *Farmaco*, 2002, **57**, 715; (*b*) P. R. Sebahar and R. M. Williams, *J. Am. Chem. Soc.*, 2000, **122**, 5666.
8 T. H. Kang, K. Matsumoto, Y. Murakami, H. Takayama, M. Kitajima, N. Aimi and H. Watanabe, *Eur. J. Pharmacol.*, 2002, **444**, 39.
9 (*a*) P. E. Maligres, I. Houpis, K. Rossen, A. Molina, J. Sager, V. Upadhyay, K. M. Wells, R. A. Reamer, J. E. Lynch, D. Askin, R. P. Volante and P. J. Reider, *Tetrahedron*, 1997, **53**, 10983; (*b*) B. L. Palucki, S. D. Feighner, S. S. Pong, K. K. McKee, D. L. Hrenuik, C. Tan, A. D. Howard, L. H. Y. Vander Ploeg, A. A. Patchett and R. P. Nargund, *Bioorg. Med. Chem. Lett.*, 2001, **11**, 1955.
10 (*a*) R. Gein Stein, J. H. Biel and T. Singh, *J. Med. Chem.*, 1970, **13**, 153; (*b*) A. M. Farghaly, N. S. Habib, M. A. Khalil and O. A. El-Sayed, *Alexandria J. Pharm. Sci.*, 1989, **3**, 90; (*c*) F. Gatta, M. Pomponi and M. Marta, *J. Heterocycl. Chem.*, 1991, **28**, 1301; (*d*) T. Kohara, K. Fukunaga, M. Fujimura, T. Hanano and H. Okabe, *U. S. Pat.*, 0052822, 2004.
11 A. Dandia, K. Arya, M. Sati and R. Sharma, *Heterocycl. Commun.*, 2003, **9**, 415.
12 A. Dandia, R. Singh, H. Sachdeva, R. Gupta and S. Paul, *J. Chin. Chem. Soc.*, 2003, **50**, 273.
13 K. C. Joshi, A. Dandia, S. Baweja and A. Joshi, *J. Heterocycl. Chem.*, 1989, **26**, 1097.
14 S. L. Zhu, S. J. Ji and Y. Zhang, *Tetrahedron*, 2007, **63**, 9365.
15 G. Shanthi, G. Subbulakshmi and P. T. Perumal, *Tetrahedron*, 2007, **63**, 2057.
16 M. N. Elinson, A. S. Dorofeev, F. M. Miloserdov and G. I. Nikishin, *Mol. Diversity*, 2008, **13**, 47.
17 M. N. Elinson, A. L. Ilovaisky, A. S. Dorofeev, V. M. Merkulova, N. O. Stepanov, F. M. Miloserdov, Y. N. Ogibin and G. I. Nikishin, *Tetrahedron*, 2007, **63**, 10543.
18 (*a*) R. Paula, P. Kumbhakara and A. K. Mitra, *J. Exp. Nanosci.*, 2010, **5**, 363; (*b*) A. L. Stroyuk, A. E. Raevskaya, A. V. Korzhak and S. Y. Kuchmii, *J. Nanopart. Res.*, 2006, **9**, 1027; (*c*) D. U. Saenger, G. Jung and M. Mennig, *J. Sol-Gel Sci. Technol.*, 1998, **13**, 635; (*d*) J. Yang, J. J. Peng, R. Zou, F. Peng, H. Wang, H. Yu and J. Y. Lee, *Nanotechnology*, 2008, **19**, 255603; (*e*) A. A. Revina, E. V. Oksentyuk and A. A. Fenin, *Prot. Met.*, 2007, **43**, 554; (*f*) W. Q. Peng, G. W. Cong, S. C. Qu and Z. G. Wang, *Opt. Mater.*, 2006, **29**, 313.
19 R. Narayanan and M. A. El-Sayed, *J. Phys. Chem. B*, 2005, **109**, 12663.
20 M. Hosseini-Sarvari and S. Etemad, *Tetrahedron*, 2008, **64**, 5519.
21 M. Hosseini-Sarvari, H. Sharghi and S. Etemad, *Helv. Chim. Acta*, 2008, **91**, 715.
22 Z. Mirjafary, H. Saeidian, A. Sadeghi and M. F. Matloubi, *Catal. Commun.*, 2008, **9**, 299.
23 (*a*) A. Dandia, R. Singh and S. Bhaskaran, *Ultrason. Sonochem.*, 2010, **17**, 399; (*b*) A. Dandia, M. Sati, K. Arya and A. Loupy, *Green Chem.*, 2002, **4**, 599; (*c*) A. Dandia, R. Singh and S. Khaturia, *Bioorg. Med. Chem.*, 2006, **14**, 1303; (*d*) A. Dandia and K. Arya, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 114; (*e*) A. Dandia, S. Gautam and A. Jain, *J. Fluorine Chem.*, 2007, **128**, 1454; (*f*) A. Dandia, K. Arya, M. Sati and S. Gautam, *Tetrahedron*, 2004, **60**, 5253.
24 K. S. Rathore, Y. Janu, Deepika, N. S. Saxena and K. Sharma, *Optoelectron. Adv. Mater., Rapid Commun.*, 2009, **3**, 313.
25 (*a*) B. S. Rema Devi, R. Raveendran and A. V. Vaidyan, *Pramana*, 2007, **68**, 679; (*b*) G. Murugadoss, B. Rajamannan and U. Madhusudhanan, *Chalcogenide Lett.*, 2009, **6**, 197; (*c*) R. John and S. S. Florence, *Chalcogenide Lett.*, 2010, **7**, 269; (*d*) H. Zhang, B. Gilbert, F. Huang and J. F. Banfield, *Nature*, 2003, **424**, 1025; (*e*) A. K. Yashar and K. Ali, *Phys. Status Solidi A*, 2010, **207**, 2144.
26 (*a*) V. Polshettiwar and R. S. Varma, *Green Chem.*, 2010, **12**, 743; (*b*) V. Polshettiwar and R. S. Varma, *Chem. Soc. Rev.*, 2008, **37**, 1546; (*c*) V. Polshettiwar and R. S. Varma, *Chem.–Eur. J.*, 2009, **15**, 1582; (*d*) V. Polshettiwar, B. Baruwati and R. S. Varma, *Chem. Commun.*, 2009, 1837; (*e*) V. Polshettiwar and R. S. Varma, *Tetrahedron*, 2010, **66**, 1091; (*f*) C. J. Li and L. Chen, *Chem. Soc. Rev.*, 2006, **35**, 68.
27 M. Dabiri, M. Bahramnejad and M. Babhbanzadeh, *Tetrahedron*, 2009, **65**, 9443.