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Synthesis of new pyridine derivatives using $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs as efficient organometallic nanocatalyst

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Abstract: In this study a new and procedure was reported for the synthesis of $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs as a new heterogeneous organometallic catalyst. XRD, FESEM, EDX and TEM analysis were used for confirming the structure of synthesized nanocatalyst. The $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs as a high performance catalyst was employed for the preparation of a new family of functionalized spiropyridine via the one-pot condensation reactions of enamine, isatin, malononitrile and electron deficient acetylenic compounds in water at room temperature.

Keywords: Spiropyridine, Antioxidant activity, Antimicrobial activity.

Introduction

Among the heterocyclic compounds, pyridine and their analogues are the most interesting structural units due to their broad spectrum of applications [1] in natural products [2] pharmaceutical [3] agrochemical [4] and material science [5, 6]. Many of the fused pyridine compounds have been confirmed as valuable candidates possessing anti-bacterial [7], anti-fungal [8], anti-microbial [9], anti-oxidant [10, 11], anti-cancer [12, 13], anti-psychotic [14], anti-inflammatory [15, 16], anti-leishmanial [17], anti-viral [18], antihypersensitive [19], anti-convulsants [20], anti-malarial [21], potassium channel openers [22], anti-diabetic [23] and anti-tumor activities [24]. Spiro compounds having cyclic structures fused at a central carbon are of interest due to their interesting conformational features and their structural implications on biological systems [25].

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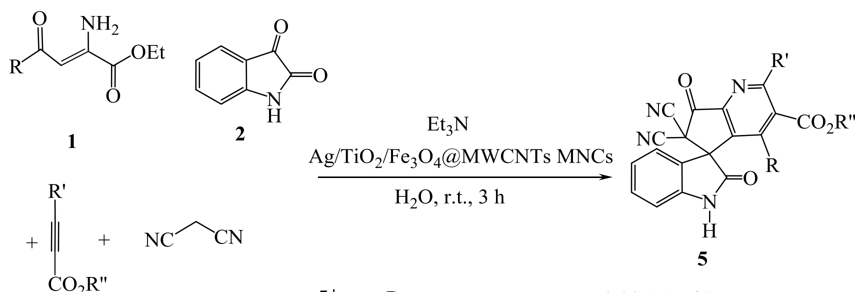
The asymmetric characteristic of the molecule due to the chiral spiro carbon is one of the important criteria of the biological activities. The presence of the sterically constrained spiro structure in various natural products also adds to the interest in the investigations of spiro compounds [26]. TiO_2 because of having appropriate band gap, strong oxidizing ability, long-term stability against photocorrosion and chemical corrosion, low cost and facile preparation. [27-31] is one of the most promising materials for solar energy conversion. Transition metal oxides nanostructures due to their unique features such as high specific surface area, chemical stability and electrochemical activity at nanoscale with promising applications in applied science and technology [32] have been broadly utilized. MWCNTs due to having many convenient properties such as large surface area and high adsorption capacity [33] have been widely investigated. TiO_2 has attracted increasing attention due to excellent chemical stability, nontoxicity and low cost [34-38]. The coupling of CNTs and TiO_2-

NPs has been proved to enhance it performance [39]. The size of TiO2 is so small that it is difficult to be separate from reaction media, which easily causes secondary pollution.[40-41] Magnetic separation is a quicker and more effective technique than traditional separation technology including centrifugation and filtration which helps to separation of nano-sized materials [42-44]. To date, Fe_3O_4 magnetic nanoparticles (MNPs) due to their high surface reactivity and facile recovery and recycling have attracted considerable interest. In this work, the our purpose is finding out new procedures for synthesis of significant organic compounds [45-55], we investigated a procedure for the preparation of some spiropyridine derivatives **7** *via* the multicomponent reactions of enamines **1**, isatin **2**, electron deficient acetylenic **3** and malononitrile **4** in the presence of catalytic amount of Ag/TiO_2/Fe_3O_4@MWCNTs MNCs and Et_3N in water at room temperature with excellent yields (Scheme **1**).



5	R	R'	R''	Yield (%) of **5**
a	4-MeO-C_6H_4	CO_2Me	Me	95
b	4-Me-C_6H_4	CO_2Me	Me	95
c	4-Et-C_6H_4	CO_2Me	Me	92
d	4-Me-C_6H_4	CO_2Et	Et	90
e	4-Me-C_6H_4	H	Me	90
f	4-MeO-C_6H_4	H	Me	92

Scheme 1: Synthesis of functionalized spiropyridines

Result and Discussion

In this research, the new spiropyridine derivatives **5** have been generated in high yields using four component reactions of enamines **1**, isatin **2**, electron deficient acetylenic **3** and malononitrile **4** in the presence of catalytic amount of Ag/TiO_2/Fe_3O_4@MWCNTs MNCs and Et_3N in water at room temperature (Scheme **1**).

For confirmation the structure of novel Ag/TiO_2/Fe_3O_4@MWCNTs MNCs, we utilized SEM, XRD, EDX, VSM and TEM analysis. For determination and confirmation the construction of novel Ag/TiO_2/Fe_3O_4@MWCNTs MNCs, we employed the scanning electron microscopy images (SEM) (Figure **1**). Figure **2** shows the SEM images of Ag/TiO_2/Fe_3O_4@MWCNTs MNCs mircospheres. The XRD analysis of Ag/TiO_2/Fe_3O_4@MWCNTs MNCs is exhibited in the Figure **3** for confirmation the particle size (Figure **2**).

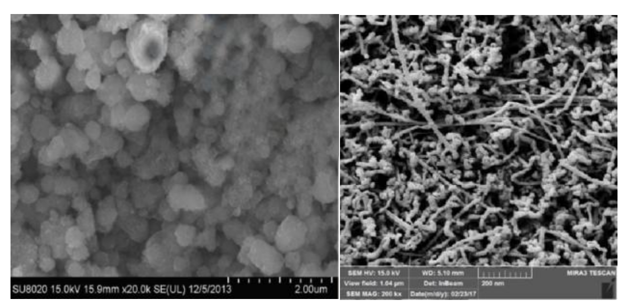


Figure 1: The SEM image of (a) Ag/TiO_2/Fe_3O_4 MNCs and (b) Ag/TiO_2/Fe_3O_4@MWCNTs MNCs

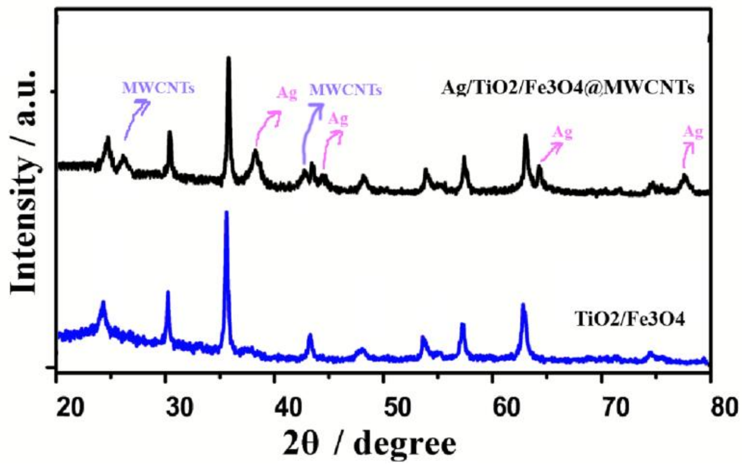


Figure 2: X-ray diffraction spectra of $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs

RD measurements were carried out to investigate the crystal identity of $Ag/TiO_2/Fe_3O_4$ MNCs and $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs (Figure 2). The diffraction peaks at 2θ = 25.2°, 38.0°, 48.2°, 54.2°, 55.1°, 63.0°, 69.0° and 75.3° are determined the presence of TiO_2 nanoparticles in the anatase phase (JCPDS, No. 21-1272). The diffraction peaks at 2θ = 35.0°, 44.0°, 54.2°, 57.2° and 63.0° indicate the presence of Fe_3O_4 MNPs (JCPDS No. 19-629). The peaks at 2θ=38.3 and 46.2° correspond to (1 1 1) and (2 0 0) planes of face-centered cubic (fcc) lattice of metallic Ag (JCPDS file no. 04-0783) which can indicate that the Ag NPs do exist in the composites. A broad crystalline peak of MWNTs around 26.0^o and 43.5^o was observed, which represents the characteristic peak of MWNTs (JCPDS No. 41-1487).

The average crystallite size (D) of catalyst is estimated using Scherrer's equation:

$$D = k\lambda/\beta \cos\theta$$

Where crystallite size (nm) and crystallite shape factor (0.90) was shown by D and k respectively. X-ray wavelength for CuKα (0.15418 nm), the full-width-half-maximum (FWHM) of the peak and Bragg angle was shown by λ, β and θ respectively. The crystallite size was achieved 25 nm according to Scherrer's equation for the peak at 35.0∘.

To further examine the morphology of the $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs, the samples were considered by TEM, as displayed in Figure 3. It can be seen that $Ag/TiO_2/Fe_3O_4$MNCs are supported on the MWCNTs.

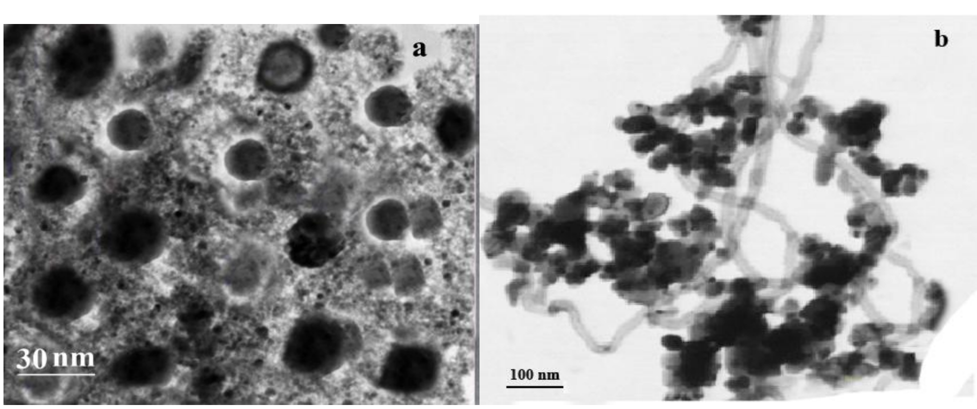


Figure 3: TEM image of the a) $Ag/TiO_2/Fe_3O_4$ MNCs b) $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs

The elemental composition of $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs was investigated by the Energy dispersive X-ray spectroscopy (EDS) spectrum. It was confirmed that $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs were consisted of C, Ti, Ag, Fe and oxygen (Figure 4).

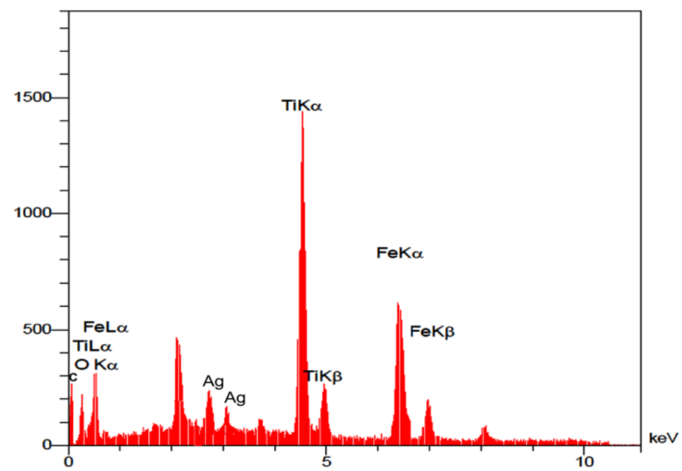


Figure 4; The EDS image of $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs

Figure 5 shows the saturation magnetization (Ms) values of the magnetic $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs and pure Fe_3O_4 NPs. Both of two catalysts displayed superparamagnetic property with a negligible of coercivity and remanence. As exhibited in Figure 5 the Ms of the $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs (24.3 emu/g) was weakened to a large extent compared to that of pure Fe_3O_4 MNPs (67.5 emu/g). The magnetic Ag, Fe_3O_4 MNPs and TiO_2 NPs on carbon nanotubes can cause to the decreasing of the magnetic property. However, this value is high enough for the separation of nanocomposite by an external magnet from the aqueous solution.

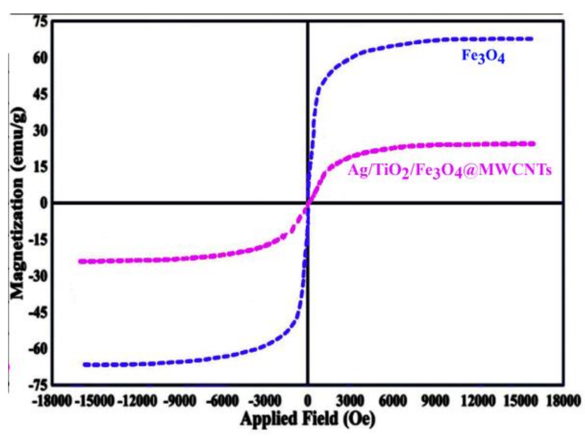


Figure 5: VSM analysis of the $Ag/Fe_3O_4/TiO_2$@MWNTs MNCs

Catalytic properties of Ag/TiO$_2$/Fe$_3$O$_4$@MWCNTs MNCs:

We also evaluated the catalytic activities of the Ag/TiO_2/Fe_3O_4@MWCNTs MNCs through the synthesis of spiropyridine derivatives in the presence Ag/TiO_2/Fe_3O_4@MWCNTs MNCs. The important section in this research is optimization of reaction condition. For this reason, initially, the reaction of enamine **1a**, isatin **2**, dimethyl acetylenedicarboxylate **3a** and malononitrile **4** was utilized as a sample reaction (Table **1**). This reaction have low yield without catalyst even after 8 h in the presence of Et_3N (10 mol%) (entry 1, 2, Table 1). For this reason, ZnO NRs (10 mol%) was added as sample catalyst to the mixture of reaction. The yield of 7**a** was achieved 45% after 5 h (entry 3, Table 1). Another catalyst such as pyridine, K_2CO_3, Ag/TiO_2 NPs, ZnO NRs, Pyridine, Ag/Fe_3O_4 MNPs and Ag/TiO_2/Fe_3O_4 MNCs, are evaluated in the sample reaction for more investigation the effect of catalyst. As a result, these outcomes exhibited the Ag/TiO_2/Fe_3O_4@MWCNTs MNCs are the best catalyst for this reaction.

Table 1. Investigation of solvent, catalyst and temperature effect on the condensation reaction of compound **5a**

Entry	Catalyst	Catalyst amount (mol%)	Solvent^a	Temp.^{b}	Time^c	Yield (%)^d
1	-	-	-	r.t.	12	trace
2	-	-	EtOH	100	12	trace
3	Et_3N	10	EtOH	r.t.	5	15
4	Et_3N	15	EtOH	r.t.	4	15
5	Et_3N	20	EtOH	100	4	20
6	Et_3N	20	H_2O	r.t.	3	20
7	Et_3N	20	CH_3CN	r.t.	3	25
8	Pyridine	10	H_2O	r.t.	3	15
9	Pyridine	10	CH_3CN	r.t.	3	20
10	K_2CO_3	10	H_2O	r.t.	6	30
11	K_2CO_3	10	CH_3CN	r.t.	5	30
12	K_2CO_3	10	EtOH	r.t.	5	25
13	Ag/TiO_2 NPs	10	H_2O	r.t.	4	65
14	Ag/Fe_3O_4 MNPs	10	CH_3CN	r.t.	4	70
15	Ag/TiO_2 NPs	10	EtOH	r.t.	4	60
16	Ag/TiO_2/Fe_3O_4	10	H_2O	r.t.	4	75

17	**$Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs**	10	**H_2O**	**r.t.**	**3**	**95**
18	**$Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs**	10	CH_3CN	r.t.	3	90
19	**$Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs**	15	CH_3CN	r.t.	3	93
20	**$Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs**	10	EtOH	r.t.	3	85
21	ZnO (NRs)	10	H_2O	r.t.	3	65
22	ZnO (NRs)	10	CH_3CN	r.t.	3	65

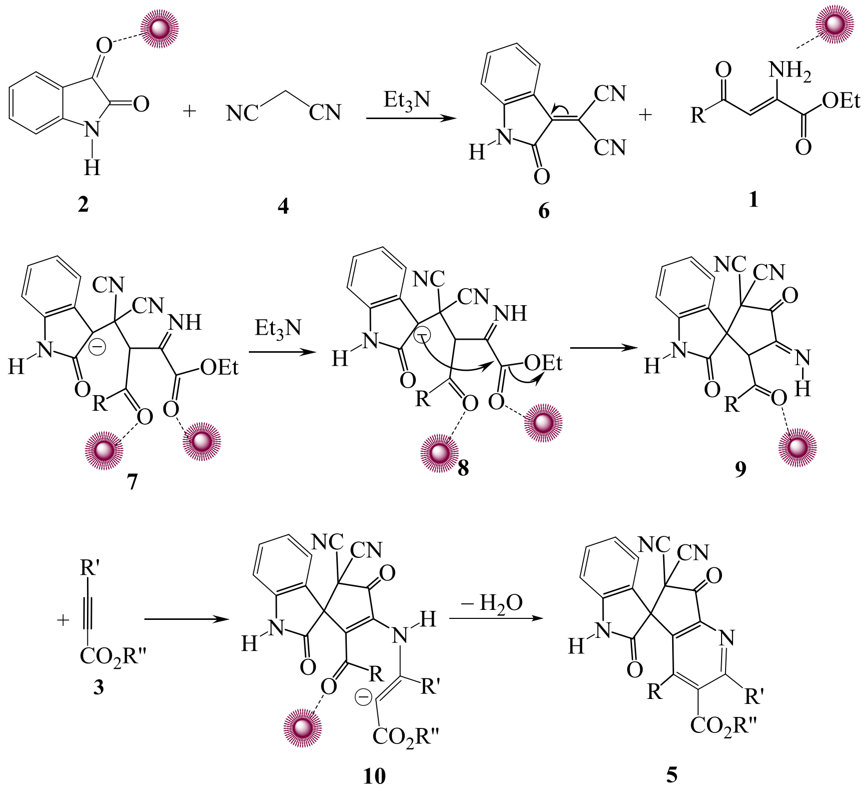
[a]The amount of solvent was 5 mL.
[b]Temperature (^oC) for reaction conditions
[c]Time (h) for reaction conditions
[d]Isolated yield

When Ag/TiO_2 NPs and Ag/Fe_3O_4 MNPs were used as a separate catalyst, the yields were lower than $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs (Table 1, entry 13 and 14). As shown in outcomes, different amounts of catalyst $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs (10-20 mol%) were utilized for the discovering the best amounts of catalyst. The results of investigation displayed that 10 mol% is the best amounts of catalyst for this reaction. By increasing the amount of catalyst from 10 mol%, didn't seen any significant variation in the yields of reaction (entry 18, 19, Table 1). Also, by raising the reaction temperature to 100 ^oC the yield of **5a** was not altered (entry 4, 5, Table 1). Obviously, the yield of product **5a** was obtained in 95 % yield after 3 h (entry 17, Table 1) in the best conditions. As shown in Table 1, the $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs (10 mol%) as catalyst, H_2O as and room temperature are the best conditions for preparation of 5**a**. The outcomes in Table 2 displayed the $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs were employed five times in sample reaction (the preparation of spiropyridine **5a**) without any significant variations in the yield of **5a**. The catalyst was separated after each run, washed with water, dried at environment temperature and used again in model reaction for confirmation the reusability of catalyst.

Table 2: Reusability of $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs in the synthesis of compound **5a**

Run	**1**	**2**	**3**	**4**	**5**	**6**
Compound 6a yield (%)	95	95	95	90	90	85

IR, ^1H NMR, ^{13}C NMR, and mass spectral data are used for investigation and confirmation the structures of spiropyridines **5**. For instance, the ^1H NMR spectrum of **5a** displayed three singlets at δ= 3.78, 3.83 and 3.87 ppm for methoxy protons, one singlet at 10.32 ppm for NH proton along with signals for aromatic protones at 6.98-8.22 ppm. The carbonyl group resonance of **5a** was detected at δ 164.2, 165.2, 167.3 and 187.2 ppm in the ^{13}C NMR spectrum. The characteristic C=O bands was shown in IR spectrum of **5a** and the mass spectrum of **5a** was displayed the molecular ion peak at m/z = 522. Although there aren't any records for the details of reaction mechanism, the suggested mechanism for these reactions is investigated in Scheme **2**. It is supposable that the reaction begins with the reaction of enamin **1** with addition product of isatin **2** and malononitrile **4** in the presence of $Ag/TiO_2/Fe_3O_4$@MWCNTs MNCs as catalyst and Et_3N. The intermolecular cyclization of **7** produced **9** that react with activated acetylenic compounds **3** and produce intermediate **10** that by intermolecular cyclization along with elimination of water produce compounds **5**.



Scheme 2: Plausible mechanism for the production of **5.**

Conclusions

The Ag/TiO_2/Fe_3O_4@MWCNTs MNCs as a new heterogeneous nanocatalyst was prepared and characterized using XRD, FESEM, EDX and TEM analyses. The performance of nanocatalyst was tested by carry out the one-pot synthesis of a new family of substituted spiropyridines via the condensation reactions of enamin, isatin, malononitrile and dimethyl acetylenedicarboxylate in the presence of Et_3N and synthesized catalyst in water at room temperature. The advantages of this procedure are: the one-pot operation, excellent yields of product in short reaction time, abundant and eco-friendly of catalyst. High atom economy and yield, mild and clean reaction condition, low catalyst loading, and short reaction time are some advantages of this procedure for synthesis of spiropyridines.

Experimental

General

All materials employed in this work were purchased from Fluka and Merck with no further purification. The structure of Ag/TiO_2/Fe_3O_4@MWCNTs MNCs was confirmed by XRD, SEM, EDX and. X-ray diffraction patterns (XRD) was performed for calculating of the size of prepared Ag/TiO_2/Fe_3O_4@MWCNTs MNCs. The Scherrer's formula; $D= 0.9\lambda/\beta \cos\theta$ used for calculating the average crystallite size of Ag/TiO_2/Fe_3O_4@MWCNTs MNCs, where D is the diameter of the nanoparticles, λ (CuK_α) =1.5406 Å and β is the full-width at half-maximum of the diffraction lines. FT-IR spectra were recorded by a Shimadzu IR-460 spectrophtometer for synthesized compounds. Also, the ^1H and ^{13}C NMR spectra are used for confirmation the structure of synthesized compounds by BRUKER DRX-500 AVANCE spectrometer at 500.1 and 125.8 MHz respectively using TMS as the internal standard or 85% H_3PO_4 as the external standard for solution in $CDCl_3$. A FINNIGAN-MAT 8430 spectrometer with an ionization potential of 70 eV utilized for Mass spectra. The elemental analysis C, H, and N for synthesized compounds was carried out by a Heraeus CHN–O-Rapid analyzer. Energy-dispersive X-ray Spectroscopy (EDX) was performed by Mira 3-XMU FESEM (Tescan Co, Brno, Czech Republic).

Preparation of TiO_2/Fe_3O_4MNPs:

Tetraethylorthotitanat (1.5 g) and $FeCl_2.4H_2O$ (1.5 g) was solved in *Petasites hybridus* rhizome water extract (30 mL) at 100 °C in round bottom flask for 5 h. Then it was cooled to room temperature, sonicated for 30 min and were centrifuged at 7000 rpm for about 10 min for removing the unwanted organic matters and then were filtered. The precipitate was filtered and cleaned with distilled water and ethanol (96%) for several times. The samples were then heated at 300 °C for 1 h. Produced bio-TiO_2/Fe_3O_4 MNPs was dried in the air at room temperature during 24 h.

Synthesis of Ag/TiO_2/Fe_3O_4MNCs

In a typical method, 0.1 g of prepared TiO_2/Fe_3O_4 MNPs and $AgNO_3$ (1.5 g) and was dispersed in 100 mL *Petasites hybridus* rhizome water extract and the mixture was sonicated at 100 ºC for 45 min. After cooling at r.t., the product was washed several times with water and ethanol respectively and separated with external magnetic field to afford the Ag/TiO_2/Fe_3O_4 MNCs.

Synthesis of Ag/TiO_2/Fe_3O_4@MWCNTs MNCs

In a typical method, 0.1 g of prepared TiO_2/Fe_3O_4 MNPs, $AgNO_3$ (1.5 g) and multi walled carbon nanotubes (MWCNTs) (0.1 g) was dispersed in 100 mL *Petasites hybridus* rhizome water extract and the mixture was sonicated at 100 ºC for 45 min. After cooling at r.t., the product was washed several times with water and ethanol respectively and separated with external magnetic field to afford the Ag/TiO_2/Fe_3O_4@MWCNT MNCs.

General procedures for the preparation of (5a-5j)

The mixture of enamin **1 (**1 mmol), isatin **2** (1 mmol) and malononitrile **5** (1 mmol) was stirred for 45 min in the presence of Ag/TiO_2/Fe_3O_4@MWCNTs MNCs as catalyst and Et_3N (10 mol%) in water at room temperature. After this time, activated acetylenic compounds **3** (1 mmol) was added to last mixture of reaction and new mixture was stirred for 1 h. After completion of reaction that was monitored by (TLC control (hexane–AcOEt, 5:1), the solid was separated by filtration and washed with EtOAC (Ethylacetate) for separating of catalyst. Then the column chromatography [silica gel (230–240 mesh; Merck), hexane/EtOAc 6:1] employed for purification of the residue to afforded pure title compounds.

Dimethyl 6,6-dicyano-4-(4-methoxyphenyl)-2',7-dioxo-6,7-dihydrospiro[cyclopenta [b]pyridine-5,3'-indoline]-2,3-dicarboxylate (5a):

Pale **y**ellow powder, m.p. 132-134 °C, Yield: 0.99 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 3345, 2198, 1735, 1725, 1589, 1478, 1386 and 1295 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm: 3.78 (3 H, s, MeO), 3.83 (3 H, s, MeO), 3.87 (3 H, s, MeO), 6.98 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.38 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.42 (1 H, t, ^3J = 7.6 Hz, CH), 7.56 (1 H, t, ^3J = 7.6 Hz, CH), 7.67 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.22 (1 H, d, ^3J = 7.6 Hz, CH), 10.32 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 51.2 (MeO), 52.4 (MeO), 55.7 (MeO), 58.2 (C), 59.6 (C), 110.6 (CH), 111.5 (CN), 112.3 (CN), 113.6 (2 CH), 119.5 (2 CH), 120.3 (C), 121.2 (CH), 123.4 (CH), 131.2 (CH), 135.2 (C), 136.4 (CH), 140.2 (C), 146.3 (C), 147.2 (C), 150.6 (C), 152.3 (C), 156.3 (C), 164.2 (C=O), 165.2 (C=O), 167.3 (C=O), 187.2 (C=O). EIMS (70 eV): m/z (%) = 522 (15) M+**.**, 491 (68) [M-31]+**.**, 31 (100) [M-491] +**.**. Anal. Calcd for $C_{28}H_{18}N_4O_7$ (522.47): C, 64.37; H, 3.47; N, 10.72. Found: C, 64.52; H, 3.63; N, 10.93 %.

Dimethyl 6,6-dicyano-4-(4-methylphenyl)-2',7-dioxo-6,7-dihydrospiro[cyclopenta [b] pyridine-5,3'-indoline]-2,3-dicarboxylate (5b):

Pale **y**ellow powder, m.p. 128-130 °C, Yield: 0.96 g (95%). IR (KBr) (ν_{max}/cm^{-1}): 3352, 2234, 1738, 1726, 1587, 1486, 1354 and 1283 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm: 2.27 (3 H, s, Me), 3.78 (3 H, s, MeO), 3.83 (3 H, s, MeO), 7.28 (1 H, d, ^3J = 7.7 Hz, CH), 7.36 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.45 (1 H, t, ^3J = 7.6 Hz, CH), 7.58 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.96 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.24 (1 H, d, ^3J = 7.6 Hz, CH), 10.43 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 21.6 (Me), 51.8 (MeO), 52.6 (MeO), 58.3 (C), 59.7 (C), 110.7 (CH), 111.8 (CN), 112.6 (CN), 119.2 (C), 121.3 (CH), 123.5 (CH), 126.4 (2 CH), 131.2 (2 CH), 132.3 (CH), 133.2 (C), 134.5 (C), 136.2 (C), 140.7 (C), 143.2 (C), 146.5 (C), 147.2 (C), 150.3 (C), 163.2 (C=O), 164.7 (C=O), 165.6 (C=O), 186.2 (C=O). EIMS (70 eV): m/z (%) = 506 (10) M+**.**, 475 (78) [M-31] +**.**, 31 (100) [M-475] +**.**. Anal. Calcd for $C_{28}H_{18}N_4O_6$ (506.47): C, 66.40; H, 3.58; N, 11.06. Found: C, 66.52; H, 3.72; N, 11.18 %.

Dimethyl 6,6-dicyano-4-(4-ethylphenyl)-2',7-dioxo-6,7-dihydrospiro[cyclopenta [b] pyridine-5,3'-indoline]-2,3-dicarboxylate (5c):

Pale **y**ellow powder, m.p. 135-137 °C, Yield: 0.96 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 3358, 2237, 1742, 1728, 1593, 1487, 1357 and 1292 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm: 1.32 (3 H, t, $^3J_{HH}$ = 7.4 Hz, Me), 2.86 (2 H, q, $^3J_{HH}$ = 7.4 Hz, CH_2), 3.75 (3 H, s, MeO), 3.86 (3 H, s, MeO), 7.23 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.32 (1 H, d, $^3J_{HH}$ = 7.6 Hz, CH), 7.43 (1 H, t, ^3J = 7.6 Hz, CH), 7.52 (1 H, t, ^3J = 7.6 Hz, CH), 7.89 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.26 (1 H, d, ^3J = 7.6 Hz, CH), 11.23 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 15.6 (Me), 28.6 (CH_2), 51.6 (MeO), 52.4 (MeO), 58.4 (C), 59.8 (C), 110.5 (CH), 111.3 (CN), 112.5 (CN), 119.3 (C), 121.5 (CH), 123.6 (CH), 126.5 (2 CH), 131.3 (CH), 133.2 (C), 136.2 (2 CH), 137.3 (C), 140.2 (C), 143.2 (C), 144.5 (C), 147.2 (C), 148.3 (C), 150.5 (C), 163.5 (C=O), 164.8 (C=O), 165.8 (C=O), 188.3 (C=O). EIMS (70 eV): m/z (%) = 520 (10) M+**.**, 489 (68) [M-31] +**.**, 31 (100) [M-489] +**.**. Anal. Calcd for $C_{29}H_{20}N_4O_6$ (520.49): C, 66.92; H, 3.87; N, 10.76. Found: C, 67.12; H, 3.96; N, 10.93 %.

Diethyl 6,6-dicyano-4-(4-methylphenyl)-2',7-dioxo-6,7-dihydrospiro[cyclopenta [b] pyridine-5,3'-indoline]-2,3-dicarboxylate (5d):

Pale **y**ellow powder, m.p. 145-147 °C, Yield: 0.96 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 3363, 2287, 1742, 1727, 1596, 1487, 1356 and 1288 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm: 1.12 (3 H, t, ^3J = 7.4 Hz, Me), 1.28 (3 H, t, ^3J = 7.4 Hz, Me), 2.25 (3 H, s, Me), 4.12 (2 H, q, ^3J = 7.4 Hz, CH_2O), 4.26 (2 H, q, ^3J = 7.4 Hz, CH_2O), 7.26 (1 H, d, ^3J = 7.6 Hz, CH), 7.32 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.43 (1 H, t, ^3J = 7.6 Hz, CH), 7.54 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.03 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.16 (1 H, d, ^3J = 7.6 Hz, CH), 11.34 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.9 (Me), 14.2 (Me), 22.3 (Me), 58.5 (C), 60.2 (C), 61.2 (CH_2O), 62.4 (CH_2O), 110.5 (CH), 110.6 (CN), 111.6 (CN), 119.5 (C), 121.6 (CH), 123.2 (CH), 125.7 (2 CH), 131.5 (2 CH), 132.4 (CH), 133.5 (C), 134.6 (C), 136.4 (C), 140.2 (C), 143.5 (C), 146.6 (C), 147.3 (C), 149.3 (C), 163.8 (C=O), 164.6 (C=O), 165.7 (C=O), 187.9 (C=O). EIMS (70 eV): m/z (%) = 534 (15) M+**.**, 489 (86) [M-45] +**.**, 45 (100) [M-489] +**.**. Anal. Calcd for $C_{30}H_{22}N_4O_6$ (534.52): C, 67.41; H, 4.15; N, 10.48. Found: C, 67.62; H, 4.28; N, 10.63 %.

Methyl 6,6-dicyano-2',7-dioxo-4-(p-tolyl)-6,7-dihydrospiro[cyclopenta[b]pyridine-5,3'-indoline] -3-carboxylate (5e):

Pale **y**ellow powder, m.p. 116-118 °C, Yield: 0.81 g (90%). IR (KBr) (ν_{max}/cm^{-1}): 3373, 2268, 1743, 1725, 1586, 1494, 1367 and 1292 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm: 2.32 (3 H, s, Me), 3.83 (3 H, s, MeO), 7.32 (1 H, d, ^3J = 7.6 Hz, CH), 7.42 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.52 (1 H, t, ^3J = 7.6 Hz, CH), 7.62 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.95 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.12 (1 H, d, ^3J = 7.6 Hz, CH), 8.68 (1 H, S, CH),10.86 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 21.8 (Me), 51.6 (MeO), 59.4 (C), 60.4 (C), 110.2 (CH), 110.8 (CN), 111.7 (CN), 120.3 (CH), 122.5 (C), 123.6 (CH), 126.7 (2 CH), 130.2 (C), 131.5 (CH), 132.7 (CH), 133.8 (2 CH), 134.2 (C), 139.5 (C), 140.2 (C), 141.8 (C), 146.3 (C), 156.8 (C), 166.5 (C=O), 167.3 (C=O), 185.8 (C=O). EIMS (70 eV): m/z (%) = 448 (15) M+**.**, 417 (84) [M – 31] M+**.**, 31 (100) [M-417] +**.**. Anal. Calcd for $C_{26}H_{16}N_4O_4$ (448.43): C, 69.64; H, 3.60; N, 12.49. Found: C, 69.75; H, 3.72; N, 12.63 %.

Methyl 6,6-dicyano-2',7-dioxo-4-(4-methoxyphenyl)-6,7-dihydrospiro [cyclopenta[b] pyridine -5,3'-indoline]-3-carboxylate (5f):

Pale **y**ellow powder, m.p. 124-126 °C, Yield: 0.85 g (92%). IR (KBr) (ν_{max}/cm^{-1}): 3362, 2298, 1742, 1727, 1593, 1486, 1378 and 1286 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ ppm: 3.78 (3 H, s, MeO), 3.85 (3 H, s, MeO), 6.98 (2 H, d, ^3J = 7.8 Hz, 2 CH), 7.36 (1 H, d, ^3J = 7.6 Hz, CH), 7.45 (1 H, t, $^3J_{HH}$ = 7.6 Hz, CH), 7.56 (1 H, t, ^3J = 7.6 Hz, CH), 7.68 (2 H, d, ^3J = 7.8 Hz, 2 CH), 8.19 (1 H, d, ^3J = 7.6 Hz, CH), 8.23 (1 H, S, CH),10.92 (1 H, s, NH). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 52.6 (MeO), 55.7 (MeO), 58.6 (C), 59.6 (C), 110.3 (CH), 111.2 (CN), 112.5 (CN), 116.5 (2 CH), 118.6 (2 CH), 121.2 (CH), 122.5 (C), 123.4 (CH), 130.4 (C), 131.7 (CH), 134.3 (C), 139.5 (C), 140.3 (C), 142.5 (C), 145.8 (C), 156.2 (C), 158.2 (CH), 165.6 (C=O), 168.2 (C=O), 186.5 (C=O). EIMS (70 eV): m/z (%) = 464 (15) M**+.**, 433 (68) [M-31] **+.**, 31 (100) [M-433] **+.**. Anal. Calcd for $C_{26}H_{16}N_4O_5$ (464.43): C, 67.24; H, 3.47; N, 12.06. Found: C, 67.36; H, 3.62; N, 12.18 %.

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