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An efficient one-pot synthesis of novel isatin-based 2-amino thiazol-4-one conjugates using MgO nanoparticles in aqueous media

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ABSTRACT

An efficient and green approach for the preparation of novel isatin-based conjugates with 2-amino thiazol-4-ones is described by the one-pot reaction of isatin derivatives, rhodanine, and secondary amines in the presence of magnesium oxide nanoparticles as a heterogeneous catalyst in water as a green solvent at room temperature. This new protocol provides products in good yields and short reaction times using a simple work-up procedure. The structure of one representative compound has been confirmed by X-ray single-crystal analysis.

1. Introduction

Thiazolidinone derivatives have been shown to exhibit a wide range of interesting biological activities [1–3]. They are reported to have anti-tumor [4,5], anticonvulsant [6,7], antibacterial [8], antiviral [9], cardiotonic [10,11], and anti-diabetic [12,13] properties. In particular, the 2-amino-5-alkylidene-thiazol-4-one core is found in more than 15,000 molecules synthesized so far [14]. On the other hand, isatin (1*H*-indole-2,3-dione) derivatives are the privileged scaffold in the modern medicinal chemistry that has a broad spectrum of biological activities, such as anticancer [15], anti-tumor [16], anti-inflammatory, hypoglycemic, analgesic, and anti-pyretic properties [17]. Based on these observations, it could be anticipated that the combination of the two above-mentioned scaffolds in one molecule could produce an interesting series of compounds with enhanced biological activity. Some known examples of such hybrid molecules with anticancer activity are shown in Fig. 1 [18,19].

Metal oxide nanoparticles have found excellent applications as active adsorbents for gases, for the destruction of hazardous chemicals [20,21], and as catalysts for various organic transformations [22–24]. Their high reactivity is due to their limited size and a high density of corner or edge surface sites [25,26]. Among them, magnesium oxide nanoparticles (MgO–NPs) are most widely used as heterogeneous catalysts and exhibit high activities in numerous base-catalyzed organic reactions [27].

In continuation of our previous works for the synthesis of novel biologically active heterocyclic compounds and the use of green chemical techniques in organic synthesis [28–31], we report herein an efficient and convenient one-pot synthesis of a variety of novel isatin-based conjugates with 2-amino thiazol-4-ones using MgO–NPs as a heterogeneous catalyst in aqueous medium at room temperature (Scheme 1). It involves the displacement of rhodanine thiocarbonyl sulfur with the amine, the resulting aminothiazolone being condensed with the carbonyl group in position 3 of isatin via

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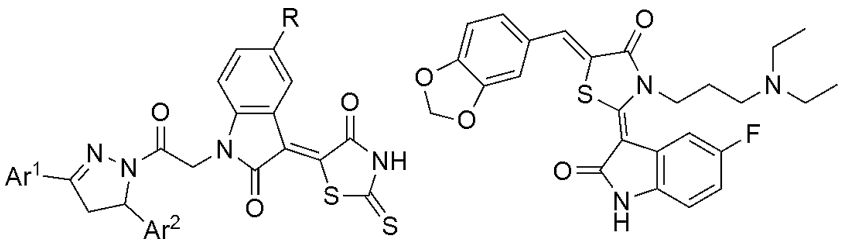
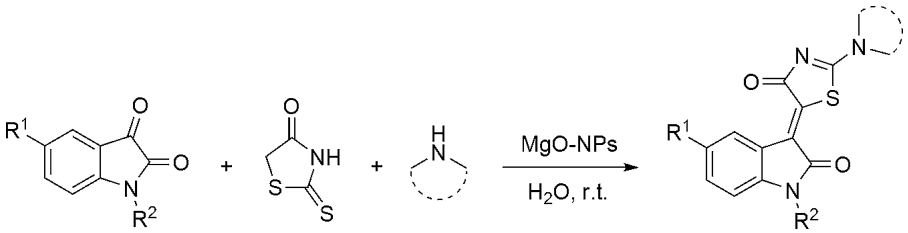


Fig. 1. Structure of some isatin-thiazolidinone hybrid molecules with anticancer activity.



Scheme 1. Preparation of isatin-based 2-amino thiazol-4-one conjugates.

Knoevenagel condensation [32–34]. Alternatively, rhodanine is first condensed with the carbonyl, and the resulting alkylidene rhodanine is reacted with an amine [35–38]. It should be noted that the reaction of secondary amines with isatin derivatives leads to the formation of 3-dialkylamino-3-hydroxy-2,3-dihydro-1*H*-indol-2-ones and further indole cycle opening [39], so that these isatin-based conjugate compounds were synthesized by multi-step reactions under harsh reaction conditions [40]. Therefore, this is the first report of the use of a one-pot method for the synthesis of these compounds.

2. Results and discussion

First of all, the model reaction of isatin (0.5 mmol), rhodanine (0.5 mmol), and morpholine (0.5 mmol) was optimized under a variety of conditions, and the results are summarized in Table 1. The reaction was first tried with an excess amount (2 equiv.) of morpholine at room temperature in water for 210 min. The yield (isolated) of the desired product was only 10%. However, 5% yield was obtained at 115 min under refluxing conditions. This is because of the nucleophilic attack of the amine to the carbonyl of isatin and the formation of the two-component by-products at high temperature and in the presence of an excess amount of amine [39]. Therefore, using an equivalent amount of amine at low temperature is an essential criterion for good yield and clean reaction. However, when we used 1 equiv. of each compound (rhodanine, isatin, and morpholine) under reflux and catalyst-free conditions, we isolated only 13% of the desired product. Therefore, the presence of a base catalyst is necessary for the Knoevenagel condensation between rhodanine and ketones, particularly, when equivalent quantities of amine are used.

Then, the reaction was examined in the presence of different base catalysts (Table 1). As it is indicated, the yield is decreased with increasing base strength. This is probably due to the minimization of two-component by-products with weaker base catalyst, though with a higher reaction time. However, MgO–NPs (20 nm diameter, SSA: $> 60\ M^2/g$) as a heterogeneous base catalyst gave a maximum 82% yield, whereas when we used bulk MgO, a lower yield of 63% was isolated in the presence of a larger equivalent amount of catalyst. Using 30 mol% of MgO–NPs in water at room temperature is sufficient to push this reaction forward and the yield did not increase largely with a higher amount of catalyst (Table 1, entry 12). The study of the effect of temperature on this reaction indicated that high temperatures could not improve the reaction rate (Table 1, entry 16). The effect of the solvent was also studied. It was observed that using water as the reaction solvent, the reaction time becomes shorter and the yield higher.

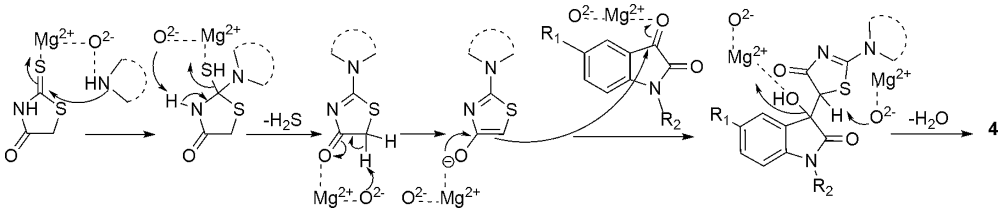
After optimization of the model reaction, a variety of isatin-based 2-amino thiazol-4-one conjugates were synthesized with the three-component reaction of rhodanine (1 equiv., 0.5 mmol), secondary amines (1 equiv., 0.5 mmol), and a variety of isatin derivatives (1 equiv., 0.5 mmol) according to Scheme 1. The products were obtained in excellent yields with high purity (Table 2). The structure of the products was confirmed by IR, ^{1}H and ^{13}C NMR spectroscopy, mass spectrometry, and by single-crystal X-ray diffraction analysis (see Fig. 2 and Supplementary data).

The mass spectrum of **4b** displayed the molecular ion ($M^{+\cdot}$) peak at *m/z* 299, which was consistent with the product's structure. The ^{1}H NMR spectrum of **4b** in DMSO exhibited one multiplet and two triplet signals due to the four methylene groups of pyrrolidine (δ = 1.97–2.07, 3.68 and 3.74). The aromatic protons appeared as two doublets at 6.93 and 9.00, and two triplets at 7.06 and 7.35 ($^3J_{HH}$ = 7.6 Hz). The proton-decoupled ^{13}C NMR spectrum of **4b** showed 15 distinct resonances, in agreement with the proposed structure. The ^{1}H NMR spectrum of all the compounds indicated that one aromatic proton is more

Table 1
Optimization of the reaction conditions[a].

Entry	Morpholine (equiv.)	Catalyst (equiv.)	Solvent	Temperature (°C)	Time (min)	Isolated yields (%)
1	2	–	H_2O	RT	210	10
2	2	–	H_2O	Reflux	115	5
3	1	–	H_2O	RT	240	13
4	1	NaOH (0.1)	H_2O	RT	50	15
5	1	K_2CO_3 (0.1)	H_2O	RT	60	22
6	1	DBU (0.1)	H_2O	RT	75	27
7	1	Et_3N (0.1)	H_2O	RT	95	35
8	1	TiO_2 (0.5)	H_2O	RT	140	32
9	1	Bulk MgO (0.5)	H_2O	RT	150	63
10	1	MgO–NPs (0.1)	H_2O	RT	120	58
11	1	MgO–NPs (0.3)	H_2O	RT	120	82
12	1	MgO–NPs (0.5)	H_2O	RT	110	82
13	1	MgO–NPs (0.3)	DCM	RT	160	60
14	1	MgO–NPs (0.3)	Dry EtOH	RT	165	64
15	1	MgO–NPs (0.3)	THF	RT	210	58
16	1	MgO–NPs (0.3)	H_2O	Reflux	110	82

[a] Reaction conditions: rhodanine (1 equiv., 0.5 mmol), isatin (1 equiv., 0.5 mmol), different amounts of morpholine, different catalysts, different temperatures, stirring.



Scheme 2. Proposed mechanism for the synthesis of compounds **4a**–**p**.

deshielded than the other aromatic ones (~9 ppm). As indicated in the ORTEP diagram of **4b**, this is probably because all the compounds have Z diastereochemistry, so, the anisotropic effects of the carbonyl group in the thiazolone ring deshielded the adjacent aromatic proton. The selected bond distances and angles for **4b** are listed in Table 3.

A plausible mechanism for the formation of product **4** is given in Scheme 2. Here, the condensation of rhodanine with the amine preceded the Knoevenagel condensation, as confirmed by the ^{1}H NMR spectra of the isolated product obtained by quenching the reaction of rhodanine, morpholine and isatin after few minutes. The quenching was done by simply removing the catalyst from the reaction mixture through filtration. This three-component reaction proceeds via the dual activation of substrates by MgO–NPs, which have a number of anionic oxidic Lewis basic (O^{2-}/O^-) and hydroxylic Brønsted basic (OH) sites along with

Table 2
Preparation of 3-(2-amino-4-oxo-1-yl-4*H*-thiazol-5-ylidene)-1,3-dihydro-indol-2-ones[a].

Entry	Product	R^1	R^2	Amine	Time (min)	Melting point (°C)	Yield (%)
1	**4a**	H	H	Piperidine	95	345–347	85
2	**4b**	H	H	Pyrrolidine	45	250–252	80
3	**4c**	H	H	Piperazine	105	296–298	83
4	**4d**	H	H	Morpholine	120	368–370	82
5	**4e**	Br	H	Piperidine	100	346–348	78
6	**4f**	Br	H	Pyrrolidine	50	359–361	76
7	**4g**	Cl	H	Piperidine	90	346–348	80
8	**4h**	Cl	H	Pyrrolidine	60	347–349	79
9	**4i**	Cl	H	Diethyl amine	35	289–291	84
10	**4j**	Cl	H	Morpholine	110	350–352	86
11	**4k**	H	Benzyl	Piperidine	85	224–226	76
12	**4l**	H	Benzyl	Pyrrolidine	125	196–198	83
13	**4m**	H	Benzyl	Morpholine	120	260–262	88
14	**4n**	H	CH_2CO_2Et	Piperidine	105	214–216	87
15	**4o**	H	CH_2CO_2Et	Morpholine	130	289–291	84
16	**4p**	Cl	CH_2CO_2Et	Piperidine	95	225–227	81

[a] Reaction and conditions: isatin derivatives (1 equiv., 0. 5 mmol), rhodanine (1 equiv., 0. 5 mmol), amines (1 equiv., 0.5 mmol), MgO-NPs (0.3 equiv., 0.15 mmol), 3 mL H_2O, room temperature, stirring.

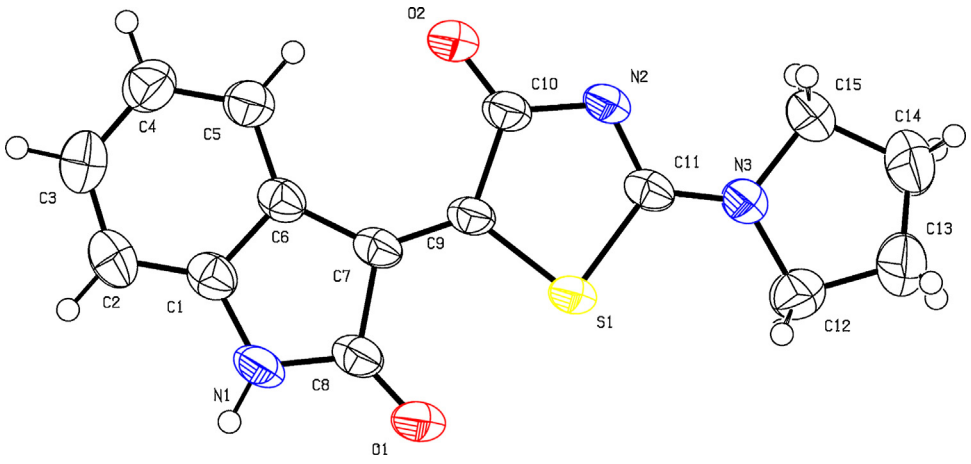


Fig. 2. ORTEP diagram of compound **4b**.

Table 3
Selected bond lengths (Å) and angles (°) for **4b**.

C(7)–C(9)	1.349(4)	O(2)–C(10)–C(9)	123.7(3)
C(11)–N(2)	1.319(4)	C(7)–C(9)–C(10)	127.7(3)
C(11)–N(3)	1.314(4)	C(9)–C(7)–C(6)	134.8(3)
C(11)–S(1)	1.776(3)	C(11)–N(3)–C(15)	121.3(3)
C(10)–O(2)	1.209(4)	N(3)–C(11)–S(1)	119.8(3)
C(5)–H(5)	0.9300	O(1)–C(8)–C(7)	126.5(3)
C(6)–C(7)	1.467(5)	O(2)–C(10)–C(9)	123.7(3)

Mg^{2+} as a Lewis acid site [27]. The Lewis base moiety of the catalyst activates the methylene group of rhodanine. The carbonyl oxygen of isatin coordinates with the Lewis acid moiety, increasing the electrophilicity of the carbonyl carbon and thereby, making it possible to carry out the reaction at room temperature and in a short time.

3. Experimental

3.1. Materials and techniques

All the chemicals and reagents were purchased from Fluka and Merck and used without further purification. Magnesium oxide nanoparticles were obtained from US Research Nanomaterials, Inc. (USA). Melting points were measured on an Electrothermal 9100 apparatus. NMR spectra were recorded with a Bruker DRX-400 AVANCE instrument (400.1 MHz for ^{1}H, 100.6 MHz for ^{13}C) with DMSO as the solvent. Chemical shifts (δ) are given in parts per million (ppm) relative to TMS, and coupling constants (J) are reported in hertz (Hz). IR spectra were recorded on an FT–IR Bruker vector 22 spectrometer. Mass spectra were recorded on a Finnigan-Matt 8430 mass spectrometer, operating at an ionization potential of 70 eV. Elemental analyses were carried with a PerkinElmer 2400II CHNS/O Elemental Analyzer.

3.2. General procedure for the synthesis of compounds 4a–p

A mixture of rhodanine (0.5 mmol), amine (0.5 mmol), and isatin derivatives (0.5 mmol) in water (3 mL) in the presence of 6 mg (30 mol%) of MgO as a catalyst was stirred at room temperature for the specified time period. The completion of the reaction was indicated by the disappearance of the starting material, evidenced by thin layer chromatography (EtOAc/*n*-hexane, 14:6). After completion of the reaction, the precipitate was filtered out, washed with water, taken in hot methanol and filtered to separate the products from the catalyst. Finally, the solvent was evaporated from product in a rotary evaporator.

3.3. Physical and spectra data for compounds 4a–p

3.3.1. 3-(4-Oxo-2-piperidin-1-yl-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (4a)

Orange powder, mp: 345–347 °C; yield (0.13 g, 85%); IR (KBr) ν_{max}: 3353 (NH), 1694 (C=O), 1612 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.65 (brs, 2H, CH_2), 1.70 (brs, 4H, $2CH_2$), 3.67 (brs, 2H, CH_2), 3.93 (m, 2H, CH_2), 6.93 (d, $^3J_{HH}$ = 7.2, 1H, CH_{Ar}), 7.05 (td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2, 1H, CH_{Ar}), 7.35 (td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2, 1H, CH_{Ar}), 8.99 (d, $^3J_{HH}$ = 7.60, 1H, CH_{Ar}), 11.14 (s,1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.8, 25.7, 26.3, 49.5, 49.9, 110.5, 120.9, 122.3, 125.4, 128.6, 132.0, 138.2, 143.4, 169.4, 176.1, 179.6; MS, *m/z*: 313.1 ($M^{+\cdot}$). Anal. calcd for $C_{16}H_{15}N_3O_2S$ (313.09): C, 61.32; H, 4.82; N, 13.41; S, 10.23. Found: C, 61.07; H, 4.79; N, 13.60; S, 10.28.

3.3.2. 3-(4-Oxo-2-pyrrolidin-1-yl-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (4b)

Orange powder, mp: 250–252 °C; yield (0.12 g, 80%); IR (KBr) ν_{max}: 3200 (NH), 1696 (C=O), 1616 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.97–2.07 (m, 4H, $2CH_2$), 3.68 (t, $^3J_{HH}$ = 6.8, 2H, CH_2), 3.74 (t, $^3J_{HH}$ = 6.8, 2H, CH_2), 6.93 (d, $^3J_{HH}$ = 7.6, 1H, CH_{Ar}), 7.06 (td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2, 1H, CH_{Ar}), 7.35 (td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2, 1H, CH_{Ar}), 9.00 (d, $^3J_{HH}$ = 7.6, 1H, CH_{Ar}), 11.14 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.8, 25.4, 48.9, 51.2, 110.6, 120.9, 122.3, 125.5, 128.6, 132.0, 138.4, 143.4, 169.4, 174.2, 179.0; MS, *m/z*: 299.0 ($M^{+\cdot}$). Anal. calcd for $C_{15}H_{13}N_3O_2S$ (299.07): C, 60.18; H, 4.38; N, 14.04; S, 10.71. Found: C, 60.37; H, 4.29; N, 14.11; S, 10.80. Crystal data for 4b $C_{15}H_{13}N_3O_2S$ (CCDC 928872): M_w: 299.35, Monoclinic, space group $P21/c$, unit

cell dimensions $a = 10.2332(10)$ Å, $b = 8.3723(14)$ Å, $c = 16.2241(17)$ Å, $\alpha = \beta = \gamma = 90°$, volume = 1385.5(3) Å^3, $Z = 4$, $D_{Calc.} = 1.435$ mg/m^3, $F(000) = 624$, crystal dimension $0.23 \times 0.20 \times 0.15$ mm, radiation, Mo Kα ($\lambda = 0.71073$ Å), θ range: 2.00–29.28, Index ranges:$-14 \le h \le 13$,$-11 \le k \le 9$,$-22 \le l \le 22$, absorption correction: numerical, data/restraints/parameters: 3728/0/190, goodness-of-fit on F^2: 1.050, final R indices [$I > 2\ \sigma(I)$]: $R_1 = 0.0805$, $wR_2 = 0.1285$, largest diffraction peak and hole: 0.250 and –0.257 e Å^{-3}.

3.3.3. 3-(4-Oxo-2-piperazin-1-yl-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (4c)

Orange powder, mp: 296–298 °C; yield (0.13 g, 83%); IR (KBr) ν_{max}: 3362 (NH), 1697 (C=O), 1617 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 2.83–2.88 (m, 4H, 2CH$_2$), 3.61 (m, 2H, CH$_2$), 3.88, (m, 2H, CH$_2$), 6.93 (d, $^3J_{HH}$ = 7.6, 1H, CH$_{Ar}$), 7.05 (t, $^3J_{HH}$ = 7.6, 1H, CH$_{Ar}$), 7.35 (t, $^3J_{HH}$ = 7.6, 1H, CH$_{Ar}$), 8.98 (d, $^3J_{HH}$ = 7.6, 1H, CH$_{Ar}$), 11.13 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 45.5, 46, 49.9, 50.0, 110.6, 120.9, 122.3, 125.5, 128.6, 132.0, 137.8, 143.4, 169.4, 176.5, 179.4; MS, *m/z*: 314.1 (M$^{+\cdot}$). Anal. calcd for $C_{15}H_{14}N_4O_2S$ (314.08): C, 57.31; H, 4.49; N, 17.82; S, 10.20. Found: C, 57.70; H, 4.42; N, 17.68; S, 10.12.

3.3.4. 3-(2-Morpholin-4-yl-4-oxo-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (4d)

Orange powder, mp: 368–370 °C; yield (0.13 g, 82%); IR (KBr) ν_{max}: 3404 (NH), 1700 (C=O), 1615 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.73–3.77 (m, 6H, 3CH$_2$), 3.96 (m, 2H, CH$_2$), 6.93 (d, $^3J_{HH}$ = 7.6, 1H, CH$_{Ar}$), 7.06 (t, $^3J_{HH}$ = 7.6, 1H, CH$_{Ar}$), 7.35 (t, $^3J_{HH}$ = 7.6, 1H, CH$_{Ar}$), 9.00 (d, $^3J_{HH}$ = 7.6, 1H, CH$_{Ar}$), 11.15 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 48.6, 48.7, 66.0, 66.2, 110.6, 121.0, 122.3, 125.8, 128.6, 132.2, 137.5, 143.5, 169.4, 177.2, 179.4; MS, *m/z*: 315.0 (M$^{+\cdot}$). Anal. calcd for $C_{15}H_{13}N_3O_3S$ (315.07): C, 57.13; H, 4.16; N, 13.33; S, 10.17. Found: C, 56.86; H, 4.07; N, 13.52; S, 9.94.

3.3.5. 5-Bromo-3-(4-oxo-2-piperidin-1-yl-4H-thiaz ol-5-ylidene)-1,3-dihydro-indol-2-one (4e)

Orange powder, mp: 346–348 °C; yield (0.15 g, 78%); IR (KBr) ν_{max}: 3399 (NH), 1702 (C=O), 1615 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.62–1.75 (m, 6H, 3CH$_2$), 3.68 (brs, 2H, CH$_2$), 3.95 (m, 2H, CH$_2$), 6.90 (d, $^3J_{HH}$ = 8.4, 1H, CH$_{Ar}$), 7.53 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2, 1H, CH$_{Ar}$), 9.19 (d, $^4J_{HH}$ = 2, 1H, CH$_{Ar}$), 11.10 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.8, 25.8, 26.4, 49.7, 50.0, 112.4, 113.9, 122.7, 124.1, 130.6, 134.1, 140.1, 142.5, 168.8, 175.9, 179.3; MS, *m/z*: 393.1 (M$^{+\cdot}$+2) 391.1 (M$^{+\cdot}$). Anal. calcd for $C_{16}H_{14}BrN_3O_2S$ (391.00): C, 48.99; H, 3.60; N, 10.71; S, 8.17. Found: C, 48.76; H, 3.60; N, 10.60; S, 8.31.

3.3.6. 5-Bromo-3-(4-oxo-2-pyrrolidin-1-yl-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (4f)

Brown powder, mp: 359–361 °C; yield (0.14 g, 76%); IR (KBr) ν_{max}: 3325 (NH), 1698 (C=O), 1591 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.94–2.09 (m, 4H, 2CH$_2$), 3.68 (t, $^3J_{HH}$ = 6.8, 2H, CH$_2$), 3.74 (t, $^3J_{HH}$ = 6.8, CH$_2$), 6.90 (d, $^3J_{HH}$ = 8.4, 1H, CH$_{Ar}$), 7.52 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2, 1H, CH$_{Ar}$), 9.18 (d, $^4J_{HH}$ = 2, 1H, CH$_{Ar}$), 10.97 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.8, 25.3, 49.1, 51.3, 112.5, 113.9, 122.5, 124.3, 130.6, 134.1, 135.8, 142.5, 168.8, 173.9, 179.3; MS, *m/z*: 378.9 (M$^{+\cdot}$+2), 376.9 (M$^{+\cdot}$). Anal. calcd for $C_{15}H_{12}BrN_3O_2S$ (376.98): C, 47.63; H, 3.20; N, 11.11; S, 8.48. Found: C, 47.80; H, 3.35; N, 11.18; S, 8.03.

3.3.7. 5-Chloro-3-(4-oxo-2-piperidin-1-yl-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (4g)

Orange powder, mp: 346–348 °C; yield (0.14 g, 80%); IR (KBr) ν_{max}: 3402 (NH), 1701 (C=O), 1618 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.60–1.73 (m, 6H, 3CH$_2$), 3.67 (brs, 2H,–CH$_2$), 3.94 (m, 2H, CH$_2$), 6.94 (d, $^3J_{HH}$ = 8.4, 1H, CH$_{Ar}$), 7.40 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2, 1H, CH$_{Ar}$), 9.05 (d, $^4J_{HH}$ = 2, 1H, CH$_{Ar}$), 11.27 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 23.8, 25.8, 26.4, 49.7, 50.0, 111.9, 111.9, 122.2, 126.1, 127.9, 131.3, 142.0, 142.1, 169.2, 175.9, 179.6; MS, *m/z*: 349.1 (M$^{+\cdot}$+2), 347.1 (M$^{+\cdot}$). Anal. calcd for $C_{16}H_{14}ClN_3O_2S$ (347.05): C, 55.25; H, 4.06; N, 12.08; S, 9.22. Found: C, 55.49; H, 3.93; N, 12.37; S, 9.40.

3.3.8. 5-Chloro-3-(4-oxo-2-pyrrolidin-1-yl-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (4h)

Orange powder, mp: 347–349 °C; yield (0.13 g, 79%); IR (KBr) ν_{max}: 3210 (NH), 1705 (C=O), 1617 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.96–2.08 (m, 4H, 2CH$_2$), 3.69 (t, $^3J_{HH}$ = 6.8, 2H, CH$_2$), 3.75 (t, $^3J_{HH}$ = 6.8, 2H, CH$_2$), 6.94 (d, $^3J_{HH}$ = 8.4, 1H, CH$_{Ar}$), 7.40 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.4, 1H, CH$_{Ar}$), 9.06 (d, $^4J_{HH}$ = 2.4, 1H, CH$_{Ar}$), 11.27 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.8, 25.4, 49.1, 51.3, 111.9, 122.2, 124.4, 126.1, 127.9, 131.3, 131.3, 142.2, 169.1, 174.0, 178.9; MS, *m/z*: 335.0 (M$^{+\cdot}$+2), 333.0 (M$^{+\cdot}$). Anal. calcd for $C_{15}H_{12}ClN_3O_2S$ (333.03): C, 53.97; H, 3.62; N, 12.59; S, 9.61. Found: C, 54.26; H, 3.58; N, 12.75; S, 9.49.

3.3.9. 5-Chloro-3-(2-diethylamino-4-oxo-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (4i)

Orange-red powder, mp: 289–291 °C; yield (0.14 g, 84%); IR (KBr) ν_{max}: 3483 (NH), 1689 (C=O), 1651 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.151 (t, $^3J_{HH}$ = 7.2, 3H, CH$_3$), 2.92 (q, $^3J_{HH}$ = 7.2, 2H, CH$_2$), 6.88 (d, $^3J_{HH}$ = 8.4, 1H, CH$_{Ar}$), 7.31 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2.4, 1H, CH$_{Ar}$), 9.12 (d, $^4J_{HH}$ = 2.4, 1H, CH$_{Ar}$), 10.95 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 11.7, 41.9, 111.3, 117.4, 123.0, 125.6, 127.0, 129.7, 141.8, 148.8, 169.1, 176.0, 184.1; MS, *m/z*: 337.1 (M$^{+\cdot}$+2), 335.1 (M$^{+\cdot}$). Anal. calcd for $C_{15}H_{14}ClN_3O_2S$ (335.05): C, 53.65; H, 4.20; N, 12.51; S, 9.55. Found: C, 53.92; H, 4.39; N, 12.07; S, 9.83.

3.3.10. 5-Chloro-3-(2-morpholin-4-yl-4-oxo-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (4j)

Brick-red powder, mp: 350–352 °C; yield (0.15 g, 86%); IR (KBr) ν_{max}: 3409 (NH), 1705 (C=O), 1617 (C=N) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.67–3.79 (m, 6H, 3CH$_2$), 3.96 (m, 2H, CH$_2$), 6.95 (d, $^3J_{HH}$ = 8, 1H, CH$_{Ar}$), 7.41 (dd, $^3J_{HH}$ = 8.4, $^4J_{HH}$ = 2, 1H, CH$_{Ar}$), 9.03 (d, $^4J_{HH}$ = 2, 1H, CH$_{Ar}$), 11.29 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 48.8, 48.9, 66.0, 66.2, 112.0, 122.1, 124.6, 126.1, 127.8, 131.4, 139.4, 142.2, 169.1, 177.0, 179.4; MS, *m/z*: 351.0 (M$^{+\cdot}$+2), 349.0 (M$^{+\cdot}$). Anal. calcd for $C_{15}H_{12}ClN_3O_3S$ (349.03): C, 51.51; H, 3.46; N, 12.01; S, 9.17. Found: C, 51.36; H, 3.41; N, 12.29; S, 9.12.

*3.3.11. 1-Benzyl-3-(4-oxo-2-piperidin-1-yl-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (**4k**)*

Orange powder, mp: 224–226 °C; yield (0.15 g, 76%); IR (KBr) ν_{max}: 1689 (C=O), 1653 (C=N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.50–1.58 (m, 2H, CH_2), 1.58–1.63 (m, 4H, $2CH_2$), 2.98 (m, 4H, $2CH_2$), 5.01 (s, 2H, CH_2), 6.97 (d, $^3J_{HH}$ = 8, 1H, CH_{Ar}), 7.04 (t, $^3J_{HH}$ = 8, 1H, CH_{Ar}), 7.22–7.35 (m, 6H, $6CH_{Ar}$), 9.11 (d, $^3J_{HH}$ = 8, 1H, CH_{Ar}); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 22.4, 23.1, 43.4, 44.5, 109.4, 117.3, 121.1, 122.4, 127.6, 127.9, 129.1, 130.2, 137.0, 138.9, 143.1, 148.3, 168.1, 176.2, 183.9; MS, *m/z*: 403.1 ($M^{+\cdot}$). Anal. calcd for $C_{23}H_{21}N_3O_2S$ (403.14): C, 68.46; H, 5.25; N, 10.41; S, 7.95. Found: C, 68.22; H, 5.37; N, 10.17; S, 7.83.

*3.3.12. 1-Benzyl-3-(4-oxo-2-pyrrolidin-1-yl-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (**4l**)*

Yellow powder, mp: 196–198 °C; yield (0.16 g, 83%); IR (KBr) ν_{max}: 1686 (C=O), 1655 (C=N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.79–1.87 (m, 4H, $2CH_2$), 3.10 (m, 4H, $2CH_2$), 5.01 (s, 2H, CH_2), 6.97 (d, $^3J_{HH}$ = 7.6, 1H, CH_{Ar}), 7.04 (td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 0.8, 1H, CH_{Ar}), 7.23–7.35 (m, 6H, $6CH_{Ar}$), 9.11 (d, $^3J_{HH}$ = 7.6, 1H, CH_{Ar}); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 24.1, 43.4, 45.4, 109.4, 117.3, 121.1, 122.4, 127.6, 127.9, 129.1, 129.1, 130.2, 137.0, 143.1, 148.3, 168.0, 177.8, 183.9; MS, *m/z*: 389.1 ($M^{+\cdot}$). Anal. calcd for $C_{22}H_{19}N_3O_2S$ (389.12): C, 67.84; H, 4.92; N, 10.79; S, 8.23. Found: C, 67.60; H, 5.00; N, 10.84; S, 8.36.

*3.3.13. 1-Benzyl-3-(2-morpholin-4-yl-4-oxo-4H-thiazol-5-ylidene)-1,3-dihydro-indol-2-one (**4m**)*

Yellow powder, mp: 260–262 °C; yield (0.18 g, 88%); IR (KBr) ν_{max}: 1681 (C=O), 1612 (C=N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 3.71–3.80 (m, 6H, $3CH_2$), 3.97 (m, 2H, CH_2), 5.03 (s, 2H, CH_2), 7.06 (d, $^3J_{HH}$ = 8, 1H, CH_{Ar}), 7.11 (t, $^3J_{HH}$ = 8, 1H, CH_{Ar}), 7.24–7.35 (m, 5H, $5CH_{Ar}$), 7.37 (t, $^3J_{HH}$ = 8, 1H, CH_{Ar}), 9.04 (d, $^3J_{HH}$ = 8, 1H, CH_{Ar}); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 43.6, 48.7, 48.8, 66.0, 66.2, 110.0, 120.3, 123.1, 124.6, 127.8, 128.0, 128.1, 129.2, 132.0, 136.5, 138.9, 143.5, 168.1, 176.8, 179.1; MS, *m/z*: 405.1 ($M^{+\cdot}$). Anal. calcd for $C_{22}H_{19}N_3O_3S$ (405.11): C, 65.17; H, 4.72; N, 10.36; S, 7.91. Found: C, 65.01; H, 4.67; N, 10.41; S, 7.80.

*3.3.14. [2-Oxo-3-(4-oxo-2-piperidin-1-yl-4H-thiazol-5-ylidene)-2,3-dihydro-indol-1-yl]-acetic acid ethyl ester (**4n**)*

Yellow powder, mp: 214–216 °C; yield (0.17 g, 87%); IR (KBr) ν_{max}: 1745, 1674 (C=O) 1611 (C=N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.21 (t, $^3J_{HH}$ = 6.8, 3H, CH_3), 1.61–1.74 (m, 6H, $3CH_2$), 3.67 (brs, 2H, CH_2), 3.94 (brs, 2H, CH_2), 4.16 (q, $^3J_{HH}$ = 6.8), 4.71 (s, 2H, CH_2), 7.15 (m, 2H, $2CH_{Ar}$), 7.43 (t, $^3J_{HH}$ = 7.6, 1H, CH_{Ar}), 9.07 (d, $^3J_{HH}$ = 7.6, 1H, CH_{Ar}); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.5, 23.8, 25.7, 26.3, 41.9, 49.7, 50.0, 61.8, 109.7, 120.2, 123.2, 123.8, 126.7, 128.4, 131.9, 143.4, 168.2, 175.5, 179.2, 179.4; MS, *m/z*: 399.3 ($M^{+\cdot}$). Anal. calcd for $C_{20}H_{21}N_3O_4S$ (399.46): C, 60.13; H, 5.30; N, 10.52; S, 8.03. Found: C, 60.31; H, 5.32; N, 10.37; S, 7.89.

*3.3.15. [3-(2-Morpholin-4-yl-4-oxo-4H-thiazol-5-ylidene)-2-oxo-2,3-dihydro-indol-1-yl]-acetic acid ethyl ester (**4o**)*

Yellow powder, mp: 289–291 °C; yield (0.17 g, 84%); IR (KBr) ν_{max}: 1744, 1679 (C=O) 1611 (C=N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.21 (t, $^3J_{HH}$ = 7, 3H, CH_3), 3.68–3.80 (m, 6H, $3CH_2$), 3.97 (m, 2H, CH_2), 4.16 (q, $^3J_{HH}$ = 7, 2H, CH_2), 4.72 (s, 2H, CH_2), 7.16 (m, 2H, $2CH_{Ar}$), 7.44 (td, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2, 1H, CH_{Ar}), 9.06 (d, $^3J_{HH}$ = 7.6, 1H, CH_{Ar}); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.5, 42.0, 48.7, 48.8, 61.8, 66.0, 66.1, 109.7, 120.2, 123.2, 124.2, 128.4, 132.1, 139.1, 143.5, 168.1, 168.2, 176.7, 179.1; MS, *m/z*: 401.1 ($M^{+\cdot}$). Anal. calcd for $C_{19}H_{19}N_3O_5S$ (401.10): C, 56.85; H, 4.77; N, 10.47; S, 7.99. Found: C, 56.61; H, 4.72; N, 10.27; S, 7.94.

*3.3.16. [5-Chloro-2-oxo-3-(4-oxo-2-piperidin-1-yl-4H-thiazol-5-ylidene)-2,3-dihydro-indol-1-yl]-acetic acid ethyl ester (**4p**)*

Red powder, mp: 225–227 °C; yield (0.18 g, 81%); IR (KBr) ν_{max}: 1742, 1694 (C=O), 1612 (C=N) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ: 1.20 (t, $^3J_{HH}$ = 7.2, 3H, CH_3), 1.52–1.59 (m, 2H, CH_2), 1.60–1.69 (m, 4H, $2CH_2$), 3.01 (m, 4H, $2CH_2$), 4.15 (q, $^3J_{HH}$ = 7.2, 2H, CH_2), 4.68 (s, 2H, CH_2), 7.11 (d, $^3J_{HH}$ = 8.8, 1H, CH_{Ar}), 7.40 (dd, $^3J_{HH}$ = 8.6, $^4J_{HH}$ = 2.4, 1H, CH_{Ar}), 9.05 (d, $^4J_{HH}$ = 2.4, 1H, CH_{Ar}); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 14.5, 22.1, 22,7, 41.9, 44.2, 61.7, 110.6, 122.2, 122.6, 126.6, 126.9, 129.5, 139.2, 141.8, 167.7, 168.3, 172.8, 184.1; MS, *m/z*: 435.3 ($M^{+\cdot}$+2), 433.3 ($M^{+\cdot}$). Anal. calcd for $C_{20}H_{20}ClN_3O_4S$ (433.09): C, 55.36; H, 4.65; N, 9.68; S, 7.39. Found: C, 55.00; H, 4.68; N, 9.47; S, 7.49.

4. Conclusion

In conclusion, we have proposed an efficient, clean, economic and one-pot procedure for the synthesis of novel isatin-based 2-aminothiazol-4-one conjugates by the three-component coupling of isatin, amine, and rhodanine over MgO nanoparticle catalyst in water as a green reaction medium. Mild reaction conditions, short reaction time, excellent yields of the products make this methodology highly significant. It represents a powerfully green technology procedure using an environmentally friendly solvent and avoiding unwanted waste production for the synthesis of new derivatives of isatin. The products were isolated without any further purification process like column chromatography.

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Appendix A. Supplementary data

Supplementary crystallographic data (CCDC 928872 for **4b** contains the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data centre via http://www.ccdc.cam.ac.uk/conts/retrieving.html) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.crci.2013.08.010.

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