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Ru(II)/PEG-400: A green synthesis of indolyl-oxindoles and indolyl-cyclohexane-dione hybrids as potential antimicrobial agents

Shaila S Wagh[a], Arvind M Patil[b] & Hanmant M Kasralikar[c,*]

[a]Department of Chemistry, Adarsh College, Hingoli, Maharastra 431 513, India

[b]SPHJ Science College, Chandwad, Maharastra 433 109, India

[c]Department of chemistry, L. B. S. Mahavidyalaya, Dharmabad, Maharastra 431 809, India

*E-mail: kasralikerhm1979@gmail.com

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A green and sustainable methodology has been successfully employed for the synthesis of 3-Indolyl-3-hydroxy oxindoles and 3-indolyl-3-hydroxy-5,5-dimethylcyclohexane-1,3-dione derivatives using Ru(II)/PEG-400 as a homogeneous recyclable catalytic system from substituted isatin with indole and dimedone. Short reaction time, simple extraction procedure, substrate scope with high yield of the product, biodegradable solvent and recyclability of the catalyst without loss of its activity enhances the efficiency of the proposed protocol. The synthesized compounds are studied for their antimicrobial activity.

Keywords: Green and sustainable methodology, Ru(II)/PEG-400, Homogeneous catalyst

The indole and isatin ring system has found in many biologically active molecules as well as in natural products.[1,2] Some derivatives of isatin are key intermediates in the synthesis of natural products.[2] Isatins are recognizable for their diverse biological activity such as inhibition of the proteasome, antagonizing GHSR, and inhibiting the growth of human cancer cells [3-5] and indole fragment is featured widely in a variety of biologically active compounds. The spiro-fused compounds of isatin and indole possess a wide spectrum of biological activity such as anti-inflammatory activities,[6] used as hormone secretagogue[7] for cancer chemotherapy,[8] also useful for the synthesis of chiral ligands.[9] Indole containing hetrocycles were synthesized using various catalytic methods.[10-15] Due to different biological activities associated with various oxindole derivatives,[16] the synthesis of monosubstituted 3-indolyl-3-hydroxy oxindoles by Friedel-Crafts reaction is one of the synthetically useful transformations of indoles with electron-deficient carbonyl compounds such as isatins.[17]

The most attractive application of isatins in organic synthesis is certainly due to the highly reactive C-3 carbonyl group, which is a prochiral center. The reactions of the C-3 carbonyl group of isatins, by nucleophilic additions or spiroannulation, transform it into 2-oxindole derivatives. 2-oxindoles, when spiro-fused to other cyclic frameworks, have drawn tremendous interest of researchers in the area of synthetic organic and medicinal chemistry, because they occur in many natural products such as spirotryprostatins, horsfiline, gelsemine, gelseverine, rhynchophylline, elacomine (Fig. 1) and have been reported to have various types of bioactivity,[18] such as progesterone receptor modulators,[19] anti-HIV,[20] anticancer,[21] antitubercular,[22] antimalarial [23,24] and MDM2 inhibitor.[25]

The aldol reaction is a well-known carbon–carbon bond forming reaction.[26, 27] In its usual form, it involves the nucleophilic addition of aldehyde or ketone enolate to carbonyl group to form hydroxycarbonyl compound, which is called aldol, a structural unit occurring in many natural molecules and pharmaceuticals.[28] Therefore, we also decided to synthesize hybrid compounds of isatin and dimedone.

Isatins have been utilized in different organic reactions for the construction of miscellaneous Heterocycles.[29-31] Plentiful methodologies have been developed to synthesize these bioactive motifs by reaction of isatin with ketone, that includes catalysts like a base,[32,33] organic molecules, or a metal complex,[34-40] in the presence of dimethyl amine,[41] β-cyclodextrin (β-CD),[42] Triton-B[43] and by electrolysis process.[44] However, longer reaction time and difficulties in the separation of the product are some of

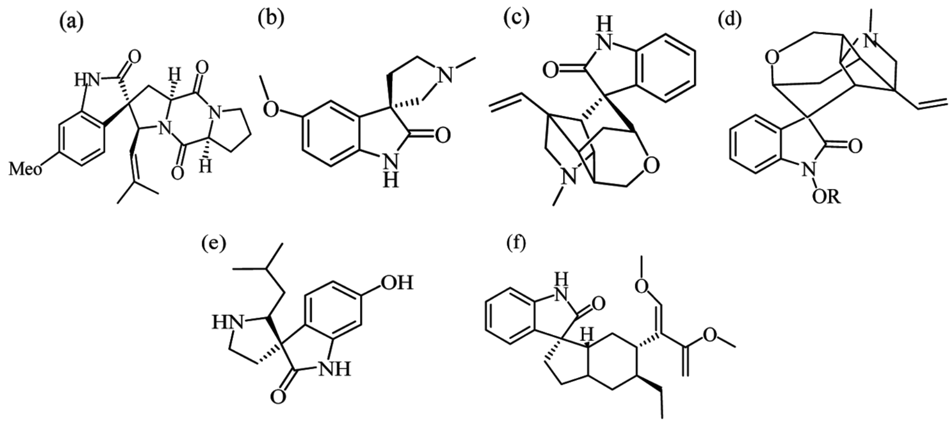


Fig. 1 — Frameworks of natural products: (a) Spirotryprostatins, (b) Horsfiline, (c) Gelsemine, (d) Gelseverine, (e) Rhynchophylline and (f) Elacomine

the drawbacks of these reactions. In recent years, owing to a growing need for more environmentally acceptable processes, the direction of chemical research has shifted more towards the use of eco-friendly solvents and reusable catalysts.[45,46] Water has been used as the green medium for synthesis of 3-hydroxy-2-oxindoles,[47-49] but has limitations of the low solubility of the substrates, compatibility with reagents, and mostly associated with long reaction time. Further, the nature of catalyst and solvent also affects the adduct of the aldol condensation reaction and obtained conjugated enone instead of β-hydroxyl ketone.[50-52]

Thus, there is need to develop a generally applicable, mild and environmentally benign practical methodology for the synthesis of hybrid compounds of isatin with indole and dimedone. To overcome all these constraints, considerable attention has been dedicated towards the development of a potent and recyclable catalytic method. Considering the advantage of PEGs as a green and sustainable solvent system and ruthenium complexes have gained promising and economic recyclable catalysts, herein, we aimed first time the synthesis of hybrid moieties of isatin with indole and dimedone using Ru(II)/PEG-400 as homogeneous recyclable catalytic system and studied their antimicrobial activities.

Experimental Details

General details

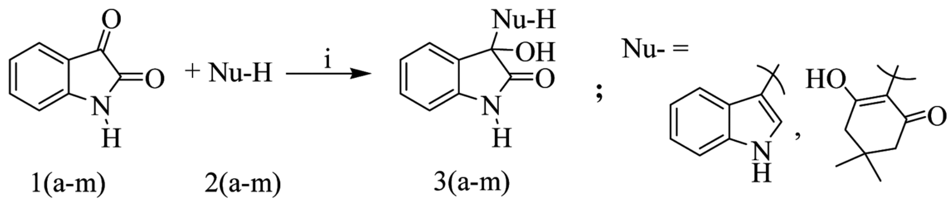
All solvents were used as commercial anhydrous grade without further purification. Aluminium sheets 20 x 20 cm, Silica gel 60 F_{254}, Merck grade, was used for thin layer chromatography to determine progress of reaction. Melting points were determined in open capillary tube and are uncorrected. IR, ^{1}H and ^{13}C-NMR spectra were recorded on a Brucker AV-300 MHz and 75 MHZ spectrometer in $CDCl_3$, solvent. Mass spectra were taken on Polaris-Q Thermo Scientific MS.

General Procedure for the synthesis of 3-indolyl-3-hydroxy oxindoles and 3-Indolyl-3-Hydroxy-5,5-dimethylcyclohexane-1,3-dione

Substituted Isatin (1 mmol) and substituted indol/dimedone (1 mmol) was added into PEG-400 (5 mL) solvent containing $[Ru(p\text{-}Cymene)Cl_2]_2$ (5 mol%) catalyst. The mixture was stirred at 80°C for half an hour. After completion of the reaction, the reaction mixture was allowed to cool down to room temperature and then extracted with 5-7 mL of diethyl ether for three to four times. Extracted diethyl ether was concentrated under reduced pressure to get the crude residue, which was then purified by recrystalisation with ethanol to get the desired pure product. The reaction scheme is shown in Scheme 1.

3-hydroxy-3-(1H-indol-3-yl)indolin-2-one (3a): White solid; M.P. 292-294°C; IR (KBr): 3401, 3304, 2924, 1723,1615, 1470, 442,661,603,491 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δppm 3.25 (s, 1H), 7.18 (d, 2H), 7.21-7.30 (dd, 4H), 7.35-7.42 (m, 3H), 7.59-7.61 (d, 1H), 8.05(s,1H), 9.77(s,1H); ^{13}C NMR (75 MHz, $CDCl_3$):δppm 95.3, 111.6, 112.7, 117.1, 118.8, 119.6, 119.9, 122.2, 123.6, 125.4, 128.4, 132.3, 134.7,136.2,139.9,167.8; m/z: 264(M^+); Anal. calcd. for: $C_{16}H_{12}N_2O_2$ (%): C, 72.72; H, 4.58; N,10.60. Found (%): C, 72.40; H, 4.66; N, 10.50.

3-hydroxy-3-(2-methyl-1H-indol-3-yl)indolin-2-one (3b): White solid; M.P.180-182°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δppm 3.75 (s, 1H), 7.14-7.16 (d, 2H), 7.25-7.30 (m, 3H), 7.40-7.42(d, 4H), 7.61-7.66



Reagent and Conditions: i) $[Ru(P\text{-}Cymene)Cl_2]_2$ / PEG:400, stir, 30 min at 80°C, 95-98%

Scheme 1 — General reaction scheme for the synthesis of compound 3

(t,1H), 9.10 (s, 1H), 10.33 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$):δppm 12.4, 90.4, 111.8, 116.5, 117.9, 123.8, 124.2, 124.6, 125.0, 125.5, 130.4, 132.5, 133.3, 135.0, 141.8, 166.0; m/z : 278 (M^+); Anal. calcd. for: $C_{17}H_{14}N_2O_2$ (%): C, 73.37; H, 5.07; N, 10.07. Found (%): C, 73.60; H, 4.93; N, 10.18.

3-(5-bromo-1H-indol-3-yl)-3-hydroxyindolin-2-one (3c*):* White solid; M.P. 312-314°C; IR(KBr): 3411, 3310, 2924, 1723, 1674, 1455, 797,749,496, cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δppm 3.77 (s, 1H), 5.94-5.96 (d, 1H), 6.04 (s, 1H), 6.20 (s, 1H), 6.39-6.61 (m, 3H), 6.73-6.76 (d, 2H), 9.7(s,1H), 10.21(s,1H); ^{13}C NMR (75 MHz, $CDCl_3$):δppm 95.5, 111.1, 112.3, 113.3, 116.5, 116.9, 117.2, 124.0, 124.4, 126.0, 130.4, 132.1, 134.5, 141.7, 169.2; m/z : 342 (M^+); Anal. calcd. for: $C_{16}H_{11}BrN_2O_2$ (%): C, 56.00; H, 3.23; N, 8.16. Found (%): C, 56.23; H, 3.35; N, 8.10.

5-fluoro-3-hydroxy-3-(1H-indol-3-yl)indolin-2-one (3d): White solid; M.P. 199-201°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δppm 3.25 (s, 1H), 7.142-7.146 (d, 1H), 7.25-7.30 (m, 2H), 7.40 -7.42(d, 4H),7.61-7.66 (m, 2H), 10.30 (s, 1H), 10.53(s,1H); ^{13}C NMR (75 MHz, $CDCl_3$):δppm 91.2, 110.1, 111.3, 115.5, 116.9, 117.2, 122.4, 124.0, 125.4, 126.0,131.4, 132.1, 134.5, 137.7, 169.5; m/z : 282 (M^+); Anal. calcd. for: $C_{16}H_{11}FN_2O_2$ (%): C, 68.08; H, 3.93; N, 9.92. Found (%): C, 67.85; H, 3.84; N, 9.86.

3-hydroxy-5-methyl-3-(2-methyl-1H-indol-3-yl) indolin-2-one (3h): White Solid; M.P. 223-225°C; ^{1}H NMR ($CDCl_3$, 300 MHz):2.35 (s, 1H), 2.74 (s, 1H), 3.42 (s, 1H), 7.14-7.16 (d, 1H), 7.25-7.30 (m, 3H), 7.40-7.42 (d, 4H), 9.30 (s, 1H), 10.33(s,1H); ^{13}C NMR (75 MHz, $CDCl_3$):δppm 17.6, 29.2, 90.9, 111.5, 112.8, 117.2, 118.6, 119.6, 119.9, 122.1, 122.7, 125.4, 128.8, 132.1, 133.7, 136.6, 137.9, 169.8; m/z: 292 (M^+); Analysis calc. for(%): $C_{18}H_{16}N_2O_2$: C, 73.94; H, 5.52; N, 9.58. Found (%): C, 73.68; H, 5.40; N, 9.54.

3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocy clohex-1-enyl)indolin-2-one (3i): White solid; 167-169°C; ^{1}HNMR ($CDCl_3$, 300 MHz): δppm 1.05 (s, 3H), 1.16 (s, 3H), 2.38-2.39 (d, 2H), 2.58-2.71 (q, 2H), 5.0 (s, 1H), 7.27-7.32 (m, 2H), 7.48–7.53 (m, 1H), 8.52 (s, 1H), 10.85 (s, 1H); ^{13}CNMR (75 MHz): δppm 27.2, 29.3, 45.4, 50.0, 81.4, 108.4,114.3, 116.9, 124.4,130.4,136.1,159.2, 169.5, 181.7, 201.4 ; m/z: 287 (M^+). Anal. Calcd. for $C_{16}H_{17}NO_4$ (%): C, 66.89; H, 5.96; N, 4.88. Found (%): C, 66.97; H, 6.10; N, 4.77.

5-fluoro-3-hydroxy-3-(2-hydroxy-4,4-dimethyl-6-oxocyclohex-1-enyl)indolin-2-one(3j): White solid; M.P.172-174°C; IR (KBr): 3194, 2993, 1722, 1606, 1474, 1363, 1302, 1242 cm^{-1}. ^{1}HNMR ($CDCl_3$, 300 MHz): δppm 0.95 (s, 6H), 2.13–2.23 (m, 4H), 3.12 (s, 3H), 6.97 (d, 1H), 6.98 (t, 1H), 7.14 (d, 1H), 7.26 (t, 1H), 9.02–11.30 (br s, 2H, OH); ^{13}C NMR (75 MHz): δppm 26.2, 27.4, 31.6, 46.6 (br), 77.4, 108.5, 110.8, 122.3, 122.7, 129.6, 131.8, 144.2, 175.3, 186.2 (br); m/z :324 [M^+],. Anal. Calcd. for $C_{17}H_{19}NO_4$ (%): C, 67.76; H, 6.36; N, 4.65. Found (%): C, 67.83; H, 6.46; N, 4.49.

Result and Discussion

We initiated our investigation by choosing the reaction of isatin with the indole for the synthesis of 3-hydroxy-3-(1H-indol-3-yl) indolin-2-one **3a** as a model reaction (Table 1). Initially, commercially available iodine, $PdCl_2$, $Zn(OTf)_2$ and ruthenium catalysts (each, 5 mol%) were tested for model reaction at room temperature in different solvent systems. At first, to get the desired product we applied iodine catalyst in water but it gives only 65% of product yield with approximately one-hour reaction time. Latter on for the screening of reaction conditions, $PdCl_2$ and $Zn(OTf)_2$ were also tested in water and ethanol but desired product obtained with poor yield and requires longer reaction time. Unexpectedly, ruthenium catalyst $[Ru(p\text{-cymene})Cl_2]_2$ exhibited the good catalytic activity in 1,2-DCE, ethanol and chloroform providing 80-85% yield of the desired product **3a** with short reaction time (Table 1; entry 6, 7 and 8, respectively). In order to make proposed protocol more greener and catalytic media

Table 1 — Screening of the reaction conditions for the synthesis of 3-indolyl-3-hydroxy-oxindoles

Entry	Catalyst	Solvent	Catalytic loading (mol %)	Reaction time (min)	Yield (%)
1	Iodine	Water	5	65	65
2	$PdCl_2$	Ethanol	5	70	56
3	$PdCl_2$	Water	5	130	40
4	$Zn(OTf)_2$	Water	5	90	70
5	$Zn(OTf)_2$	Ethanol	5	100	75
6	[Ru(*p*-cymene)Cl_2]$_2$	1,2-DCE	5	60	80
7	[Ru(*p*-cymene)Cl_2]$_2$	Ethanol	5	62	82
8	[Ru(*p*-cymene)Cl_2]$_2$	Chloroform	5	65	85
9	[Ru(*p*-cymene)Cl_2]$_2$	PEG-400	5	40	90*

* Reaction proceeds under same condition

Table 2 — Effect of catalytic concentration and temperature in PEG-400

Entry	Catalyst	Solvent	Catalytic loading (mol %)	Temperature (^{o}C)	Time (min)	Yield (%)
1	[Ru(*p*-cymene)Cl_2]$_2$	PEG-400	5	25	40	90*
2	[Ru(*p*-cymene)Cl_2]$_2$	PEG-400	3	25	75	85
3	[Ru(*p*-cymene)Cl_2]$_2$	PEG-400	10	25	60	76
4	[Ru(*p*-cymene)Cl_2]$_2$	PEG-400	5	60	50	91
5	[Ru(*p*-cymene)Cl_2]$_2$	PEG-400	5	80	30	95
6	[Ru(*p*-cymene)Cl_2]$_2$	PEG-400	5	90	28	80

reusable, the reaction was attempted in PEG-400 as a biodegradable solvent. Gratifyingly, highest desired product was obtained giving 90% yield with short reaction time than earlier (Table 1, entry 9).

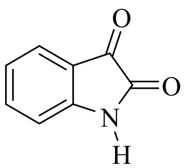
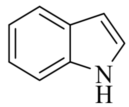
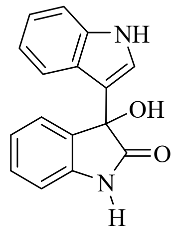
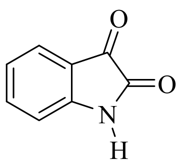
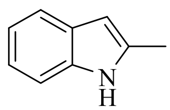
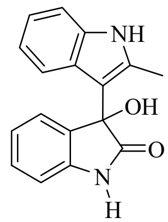
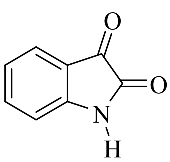
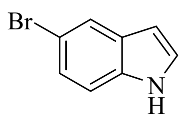
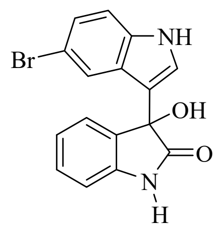
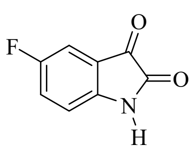
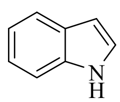
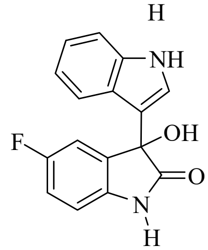
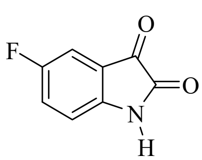
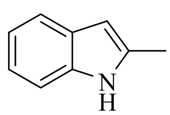
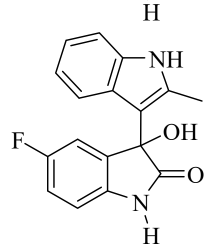
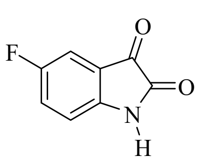
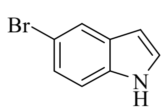
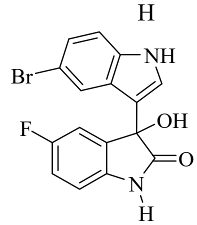
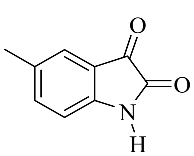
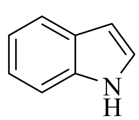
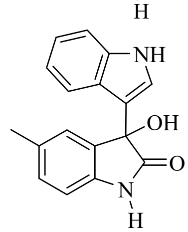
Next, the effect of catalytic loading was determined, by lowering in catalyst concentration to 3 mol% leads to a decrease in yield, whereas with increasing the catalytic loading up to 10 mol% no significant increase in yield of the desired was noted (Table 2, entries 1 and 2). Later, to study the effect of temperature, the reaction was attempted at room temperature as well as at higher temperatures. When the reaction temperature was increased to 60^{o}C and then to 80^{o}C, reaction proceeds faster than the room temperature with increase in yield up to 91 & 95%, respectively (Table 2; entries 3 and 4). While increasing temperature to 90^{o}C the product yield was decreased to 80% (Table 2; entry 5). Thereafter, increasing the temperature above 80°C did not produce any significant change in the product yield.

With satisfying results, obtained using Ru(II)/PEG-400 as a green catalytic system, further we examined this for its reusability. For this, model reaction was conducted using 5 mol% [Ru(*p*-cymene)Cl_2]$_2$ under the standard reaction conditions. After completion of reaction, the reaction mixture was extracted with 5 mL of diethyl ether for two to three times. The extracted diethyl ether contained the product mixture was then subjected for purification. The remaining solvent layer that contained PEG and catalyst could then be reused for the next reaction.

With the identified optimized reaction conditions in hand, the synthetic versatility of the proposed protocol is highlighted by screening the compatibility of a diverse set of isatin and indole/ dimedone bearing both electron donating as well as electron withdrawing substituent. The reaction took place smoothly with a high degree of translation without the formation of any by-product. This methodology was also compatible with various substituted isatins and indoles /dimedones. Several examples illustrating this simple and green methodology are summarized in Table 3. However, this reaction did not proceed when the nitro group was present in the 5-position of the indole ring. From Table 3, we observed that, halogen-substituted isatins react smoothly with indole than methyl-substituted isatin and lead to good yield of the expected product in short time. The counterpart-substituted indoles also react rapidly with isatins and give the product in good yield. Remarkably, it was observed that the methyl substituted indole ring shows an increase in the rate of reactivity and results in good yield of product.

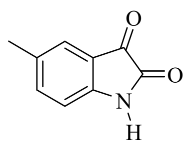
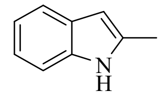
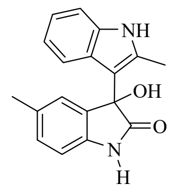
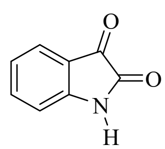
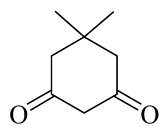
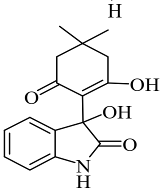
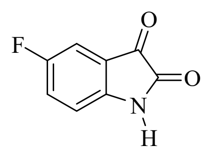
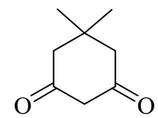
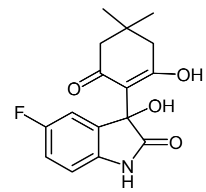
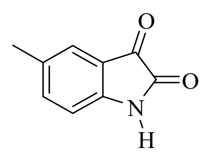
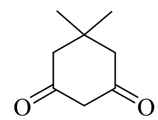
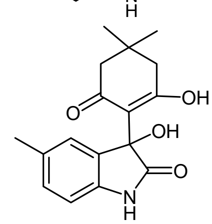
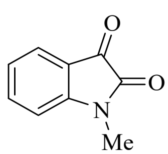
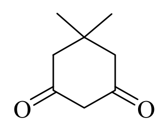
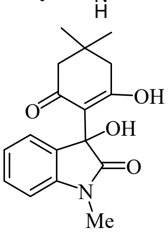
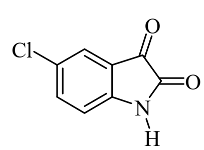
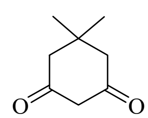
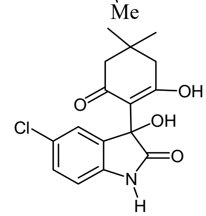
All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR, Mass spectroscopy, and elemental analysis and also by comparison with authentic samples[37,39]. This method affords the products in excellent yields than the earlier methodologies and the ruthenium based homogeneous catalytic system could be reused up to a fourth consecutive cycle without any loss in its activity.

Table 3 — Exploration of substrate scope for the Synthesis of 3-Indolyl-3-hydroxyOxindoles and 3-Indolyl-3-Hydroxy-5,5-dimethylcyclohexane-1,3-dione derivatives[a]

Entry	Substituted Isatin 1(a-m)	Indole/ Dimedone 2(a-m)	Desired Product 3(a-m)	Time (min)	Yield %
a				30	98
b				27	85
c				30	95
d				30	97
e				28	82
f				30	90
g				32	80

(*Contd.*)

Table 3 — Exploration of substrate scope for the Synthesis of 3-Indolyl-3-hydroxyOxindoles and 3-Indolyl-3-Hydroxy-5,5-dimethylcyclohexane-1,3-dione derivatives[a] — (*Contd.*)

Entry	Substituted Isatin 1(a-m)	Indole/ Dimedone 2(a-m)	Desired Product 3(a-m)	Time (min)	Yield (%)
h				35	90
i				30	85
j				28	90
k				30	85
l				35	85
m				30	90

[a] Isatin(1 mmol), indole or dimedone (1 mmol), $[Ru(P\text{-}Cymene)Cl_2]_2$ / PEG:400, stir, 30 min at 80°C, 95-98%

Biological activity

Antibacterial activity

The inhibitory activities of synthesized compounds were studied for their in vitro antibacterial activity against Gram-positive bacteria including *Bacillus subtilis, Klebsiella pneumonia, Enterococcus faecalis (PTCC1778), Streptococcus agalactiae (PTCC 1768)* and Gram-negative bacteria strains including *Pseudomonas aeruginosa (PTCC 1310), Escherichia coli(PTCC 1399), Shigella flexneri (PTCC 1234) and Shigella dysenteriae (PTCC 1188)*] in nutrient agar medium at concentrations of 100 µg/mL, using DMF as solvent by the Agar well diffusion method.[53] The plates were incubated at 37°C for 24 h by adding these solutions to each filter disc. The zones of inhibition were measured in millimeters. The standard drug Gentamicin, (100 µg/mL) was used as a reference drug under similar condition for comparison.

Antifungal activity

The antifungal activity of synthesized compound was evaluated against *Aspergillus fumigatus* (PTCC

Table 4 — Antibacterial and antifungal activities synthesized compounds

Compd.	Antibacterial activity (zones of inhibition in mm)								Antifungal activity (zones of inhibition in mm)		
	Gram + ve				Gram - ve						
	Bacillus subtilis	*K. pneumonia*	*E. faecalis*	*S. agalactiae*	*P. aeruginosa*	*E. coli*	*S. flexneri*	*S. dysenteriae*	*A. fumigatus*	*C. albicans*	*F. oxysporum*
a	20	12	05	16	18	13	17	-	10	08	04
b	15	16	11	08	10	07	19	10	13	-	10
c	25	21	19	26	17	12	15	04	11	12	08
d	28	15	20	22	19	15	12	15	08	16	07
e	12	18	18	25	15	16	20	18	09	14	05
f	16	20	21	18	21	10	11	17	14	15	03
g	17	10	14	11	07	03	10	11	-	03	-
h	10	-	04	09	12	-	05	08	04	10	-
i	-	05	02	06	08	09	16	07	-	07	01
j	19	19	09	10	13	-	18	13	-	11	-
k	08	-	-	03	05	-	04	05	-	02	-
l	14	24	16	15	20	04	14	16	07	05	-
m	26	22	15	13	16	14	-	06	12	03	-
Gentamicin	31	28	24	32	25	18	22	20	-	-	-
Nystatine	-	-	-	-	-	-	-	-	16	20	12

5009), *Candida albicans* (PTCC5027) and *Fusarium oxysporum* (PTCC 5115) with Sabouraud dextrose agar medium using the agar well diffusion method. At a concentration of 100 µg/mL, the compounds were dissolved in DMF and diluted with distilled water then mixed with the Sabouraud dextrose agar medium. After incubation for 74 h at 37°C, the zones of inhibition were measured in millimeters. Under same condition the standard antifungal drug Nystatin **(**100 µg/ml) was also screened for antifungal activity.

The synthesized 3-indolyl-3-hydroxy-oxindoles and 3-indolyl-3-hydroxy-5,5-dimethylcyclohexane-1,3-dione derivatives were screened for antibacterial and antifungal activity. The observations obtained are presented in Table 4. The antibacterial activity of most of the compounds beside standard drug was found to be statistically good with insignificant difference. All the synthesized derivatives show moderate to good activity against the Gram +ve and –ve bacteria. Compounds **c, d, e, f, l** and **m** shows effective activity against all the Gram +ve and –ve bacteria, comparable with the standard drug Gentamicin. All the compounds show excellent activity against *Candida albicans* and moderate to poor activity against *Aspergillus fumigatus* and *Fusarium oxysporum* fungi comparable to the standard Nystatine. The antimicrobial activity of these compounds has been credited to the presence of the isatine and indole moieties as compared to the dimedone ring in the skeleton of the synthesized compounds. In addition to the structural features, halogen substituents on the isatine and indole moieties are also responsible for the effective activities of the compound.

Conclusion

In summary, this novel work reports efficient and greener homogeneous recyclable Ru(II)/PEG-400 catalytic system for the synthesis of hybrid compounds of isatin with indole and dimedone. This catalytic system could be reused up to fourth cycle with negligible loss in catalytic activity. The advantages of this method include good substrate generality, more economical, use of inexpensive catalyst, mild reaction conditions, experimental operation simplicity, high atom economy, environmental impact and high yields. The antimicrobial activity of these compounds has been enhanced due to the presence of nitrogen containing hetrocyclic ring moieties containing halogen substituents.

Supplementary Information

Supplementary information is available in the website http://nopr.niscpr.res.in/handle/123456789/58776.

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