Sustainable Chemistry and Pharmacy 35 (2023) 101228

Contents lists available at ScienceDirect

Sustainable Chemistry and Pharmacy

journal homepage: www.elsevier.com/locate/scp

Zingiber zerumbet: A green and ecofriendly natural surfactant for the synthesis of Bis(indolyl)methane, tris-indoline and spirooxindole derivatives

Aboli Sapkal [a], Suraj Attar [a], Jaykumar Chavan [b], Arjun Kumbhar [c], Santosh Kamble [a, *]

[a] *Department of Chemistry, Yashavantrao Chavan Institute of Science, Lead College of Karmaveer Bhaurao Patil University, Satara, 415001, Maharashtra, India*

[b] *Department of Botany, Yashavantrao Chavan Institute of Science, Lead College of Karmaveer Bhaurao Patil University, Satara, 415001, Maharashtra, India*

[c] *Department of Chemistry, Vivekanand College, Kolhapur (Autonomous), 416003, Maharashtra, India*

ARTICLE INFO

Handling Editor: Fabio Aricò

Keywords:
Ultrasonication
Natural surfactant
Zingiber zerumbet
Bis(indolyl)methanes
Tris-indolines
Spirooxindoles

ABSTRACT

The present study aimed to the greener and eco-friendly synthesis of bis(indolyl)methane, tris-indoline, and spirooxindole derivatives in the natural surfactant of *Zingiber zerumbet* under ultrasonic irradiation. This synthetic protocol has a green aspect that avoids the use of toxic catalysts, solvents, and harsh reaction conditions. In addition, ultrasonication improves the yield of reactions and also shortens the reaction time. The reaction proceeds smoothly with a natural extract of *Z. zerumbet* at room temperature. Eventually, the present method is a green, environmentally sound alternative to the existing protocols in terms of sustainability and economics. Moreover, the extract of *Z. zerumbet* can be reused many times with a slight decrease in product yields.

1. Introduction

Indole and its derivatives are very important scaffolds present in mammals in the form of amino acids such as tryptamine, tryptophan, serotonin, and melatonin (Wu and Gribble, 2010). In addition, indole scaffolds are a vital part of various pharmaceutical and agrochemical products such as the antidepressant drug indopan, the nonsteroidal anti-inflammatory drug indomethacin, the hypertensive drug dimebon, the antiviral agent arbidol, and indoyl acetic acid, which enhances plant growth (Bugaenko et al., 2019) [Fig. 1].

Owing to the diverse useful properties of these molecules such as bis(indolyl)methane, tris -indolines, chemists are constantly developing new methodologies for the synthesis of such scaffolds. Most of these methodologies involve the use of 12-tungstophosphoric acid (Rahimi et al., 2015), amberlyst-15 (Sarrafi et al., 2012), CAN (Wang and Ji, 2006), $Bi(OTf)_3$ (Yadav et al., 2006), succinimide-*N*-sulfonic acid (Shirini and Khaligh, 2013), silica-supported $In(acac)_3$ (Sharma and Sharma, 2010), bromine/para toluene sulphonic acid (Huang et al., 2015), thiamine hydrochloride (Mathavan et al., 2019), $VOSO_4$ (Swain et al., 2022), lambert salt ($[Ph_3C][B(C_6F_5)_4]$) (Khan et al., 2021), heterogeneous TiO_2 nanoparticles (Dwivedi et al., 2018) or to develop greener routes other methods such as $ZnCl_2$-Urea as deep eutectic solvents ultrasound irradiation (Seyedi et al., 2015), $H_3PW_{12}O_{40}$ (Amrollahi and Kheilkordi, 2016), *n*-hexene sulphonic acid sodium salt (Joshi et al., 2010), aqueous ethyl lactate (Gao et al., 2017), itaconic acid (Kasar and Thopate, 2018), Lewis acid-surfactant-SiO_2-combined nanocatalyst (Wu et al., 2019) were reported for the synthesis of bis

* Corresponding author.
E-mail address: santosh.san143@gmail.com (S. Kamble).

https://doi.org/10.1016/j.scp.2023.101228
Received 2 June 2023; Received in revised form 3 August 2023; Accepted 10 August 2023

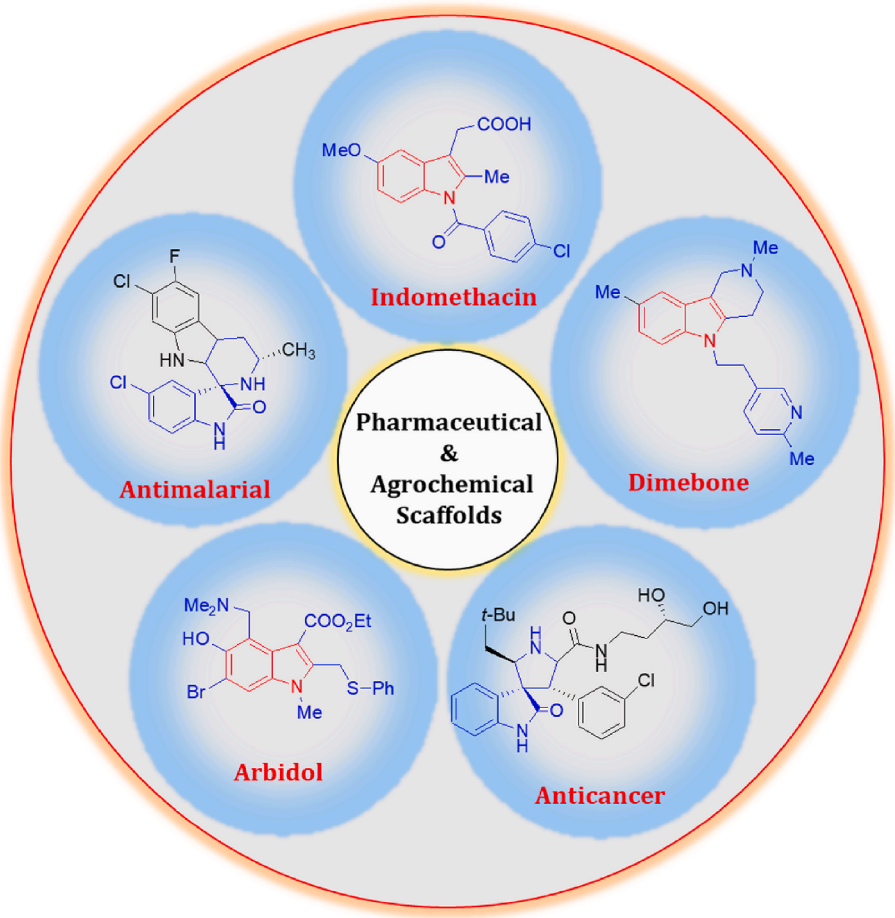


Fig. 1. Pharmaceutical and agrochemical active Indole and Spirooxindole scaffolds.

(indolyl)methane and tris-indoline. Furthermore, sulfonic acid-functionalized mesoporous silica nanoparticles (SAMSNs) were listed as an efficient catalyst for these synthesis (Mehrasbi et al., 2015).

Spirocyclic scaffolds are one of the important classes of asymmetric synthesis (Yu et al., 2015). A spirocyclic framework contains two rings joined at one atom and is important from stereochemical point of view (Mei and Shi, 2018). It was evidenced that the presence of two or more different heterocyclic moieties in single molecule increases biomedical properties remarkably (Shanthi et al., 2007). These alkaloids were naturally isolated from Rubiaceae and Apocynaceae plants (Zhou et al., 2020) and also found in the tissues and fluids of mammals (Kaur et al., 2016). In this connection, spirooxindole, plays a vital role due to their biological and pharmacological activities (Ding et al., 2006), such as anti-tumor (Yong et al., 2007), anti-oxidant (Yasuda et al., 2013), anti-alzheimer's (Watanabe et al., 2012), anti-malarial (Yeung et al., 2010), neuroprotective (Ingrand et al., 2007), spermicidal (Paira et al., 2009), analgesic activity (Chowdhury et al., 2011), anti-bacterial (Singh et al., 2014), and anti-fungal activities (Hussein and Abdel-Monem, 2011). Spirooxindoles are also found in many naturally occurring compounds. There are many important drugs, such as anticancer and antimalarial drugs, that contain the core structure of spirooxindole (Fig. 1). With such a wide spectrum of biological activities, chemists constantly engage in developing various methodologies for their synthesis such as Ni NPs (Khurana and Yadav, 2012), $ZnFe_2O_4$ (Hasani and Irizeh, 2018), sodium stearate (Wang et al., 2010), Borax (Molla et al., 2018), GN/SO_3H (Allahresani et al., 2018a), $CoFe_2O_4@SiO_2$ (Hemmat et al., 2019), TEBA (Zhu et al., 2007), NEt_3 (Mortikov et al., 2008), SBA-PR-NH_2 (Ziarani et al., 2012), Alum (Karimi and Sedaghatpour, 2010), $SiO_2@g\text{-}C_3N_4$ (Allahresani et al., 2018b) and $NiO@g\text{-}C_3N_4$ (Amini Moqadam et al., 2020) nanocomposites, hydrotrope-NaPTS (Kamat et al.) and $CaFe_2O_4@MgAl\text{-}LDH$ (Salimi et al., 2021).

Nonetheless, most of these methodologies have some bad impact on the environment. In order to address these issues, we developed a more environmentally benign methodology for the synthesis of bis(indolyl)methane, tris-indoline, and spirooxindole derivatives by the use of biosurfactants. Bio-surfactant is a greener agent that keeps the environment clean by contributing less hazardous chemicals (Chavan et al., 2016). The medium for this reaction is a natural extract; therefore, the reaction takes place in a greener environment. Thus, it contributes to sustain the green principle while saving economy as well as environment by using a naturally available *Zingiber zerumbet*.

Zingiber zerumbet (L.) Roscoe ex Sm., is widely known as 'Shampoo Ginger'. It is an aromatic and rhizomatous herb that crops up naturally in the Himalaya and the Western Ghats of India (Chavan et al., 2018). The mucilaginous essence found in the *Z. zerumbet*

inflorescence was used as shampoo and natural hair conditioner (Sabu, 2003). It has been traditionally used as a home remedy for fever, cough, toothache, and Indian cuisine. It is a traditional herbal medicine, an appetizer, and a food flavouring agent. This natural extract of *Zingiber zerumbet* has pH 5.2, which is weakly acidic in nature. Phytochemical analysis reveals the presence of terpenes, polyphenols, sesquiterpenes, and flavonoids that are rich in α-pinene, β-pinene, camphor, β-caryophyllene, linalool, borneol, and α-terpineol (Koga et al., 2016), (Nigam and Levi, 1963). Along with these, it also shows diverse pharmacological activities, namely anti-inflammatory (Zakaria et al., 2011), anti-microbial (Phongpaichit et al., 2006), anti-malarial (Sriphanaa et al., 2013), and anti-tumour (Huang et al., 2005).

Ultrasonic irradiation is a well-established, greener methodology that is significantly employed in organic synthesis. It reduces the reaction time in the refraction cycle of cavitation process, in which the molecules of the liquid are separated, generating bubbles that subsequently collapse in the compression cycle. These rapid and violent implosions generate short-lived regions with high temperatures, pressures, and heating, with cooling rates above 10-billion-degree centigrade per second. These localized hot spots can act as microreactors in which the energy of sound is transformed into a useful chemical form (SrivastavaRAWN Filho et al., 2009; Duarte et al., 2010; Stefani et al., 2005). Overall, this methodology is easy to handle and uses clean reaction media that selectively increase reactivity and produce a good yield (Deshmukh et al., 2001).

We recently synthesized many heterocyclic compounds (Kumbhar et al., 2016), using hydrotrope (Kumbhar et al., 2012) (Jadhav et al., 2016; Sapkal and Kamble, 2020; Sapkal et al., 2022) as well as biosurfactants (Patil et al., 2020). Both these served as excellent reaction media to carry out the reaction in water. In continuation with this, the present study aimed to the greener and eco-friendly synthesis of bis(indolyl)methane, tris-indoline, and spirooxindole derivatives in aqueous natural surfactant of *Zingiber zerumbet* under ultrasonic irradiation (Fig. 2).

2. Experimental section

2.1. General

Inflorescence of *Zingiber zerumbet* is collected from botanical garden of Y. C. Institute of Science, Satara, India. All other chemicals were purchased from Loba and Sigma-Aldrich chemical companie and used without further purification. Melting points of products

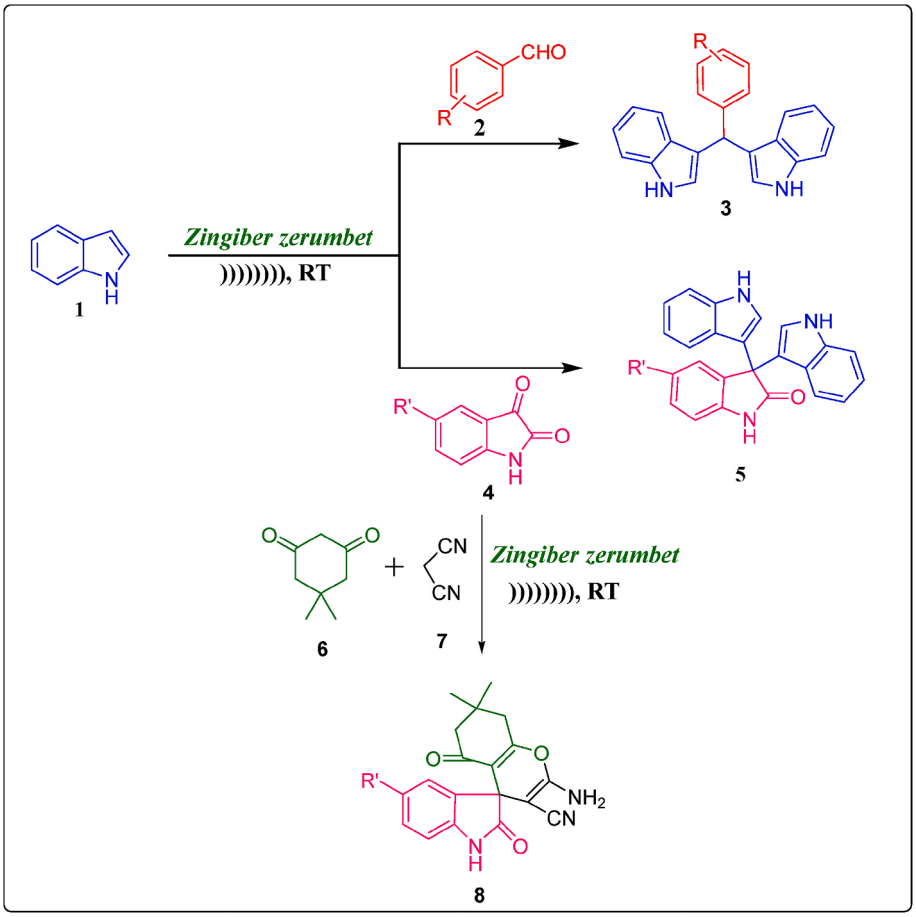


Fig. 2. Synthesis of bis(indolyl)methane, tris-indoline and spirooxindole derivatives using *Zingiber zerumbet*.

were determined on electrical melting point apparatus EQ 730A-EQUIPTRONICS and are uncorrected. Infrared spectra were recorded on a lamda FTIR 750 spectrometer. The samples were examined as KBr discs ~5% w/w. ^{1}H NMR,^{13}C NMR spectra were recorded on a Bruker Ascend 400 MHz spectrometer using DMSO as solvent and TMS as internal reference. Sonication was performed in a SPECTRALAB-UCB-30 ultrasonic bath with a frequency of 40 kHz. Microscopic imgages taken on Olympus B × 53 phase contrast microscope. Density study performed on Density Meter DMA 4100 M, Anton-Paar, Austria. Viscosity measured on Viscometer available in the laboratory.

2.2. Collection of 'Zingiber zerumbet' inflorescence juice

Inflorescence of *Zingiber zerumbet* is collected from botanical garden of Y. C. Institute of Science, Satara, India. Juice was removed by hand pressing of the inflorescence (Fig. 3), which is a viscous liquid commonly used as natural conditioner and natural surfactants. It was collected and stored at 4 °C until further use.

Synthesis of bis(indolyl)methane: In a round bottom flask containing 5 ml of *Z. zerumbet* extract, aldehyde (1 mmol), and indole (2 mmol) kept in a sonicator bath, the resultant reaction mixture was irradiated under ultrasonic irradiation at room temperature for an appropriate time (Table 1) until the reaction was completed. The progress of the reaction was monitored by TLC (*n*-Hexane: EA 8:2). The colored solid product formed after the completion of the reaction was filtered and recrystallized in ethyl acetate to get a pure product.

Synthesis of Tris-indoline: In a round bottom flask containing 5 ml of *Z. zerumbet* extract, isatin (1 mmol), and indole (2 mmol) kept in a sonicator bath, the resultant reaction mixture was irradiated under ultrasonic irradiation at room temperature for an appropriate time (Table 1) until the reaction was completed. The progress of the reaction was monitored by TLC (*n*-Hexane: EA 8:2). The colored solid product formed after the completion of the reaction was filtered and recrystallized in ethyl acetate to get a pure product.

2.3. Synthesis of spirooxindole

Isatin (1 mmol), malononitrile (1 mmol), and the active methylene compound (1 mmol) were added to a 5 ml extract of *Z. zerumbet* in the round bottom flask. Then the reaction mixture was placed in a bath sonicator and irradiated under ultrasonic irradiation at

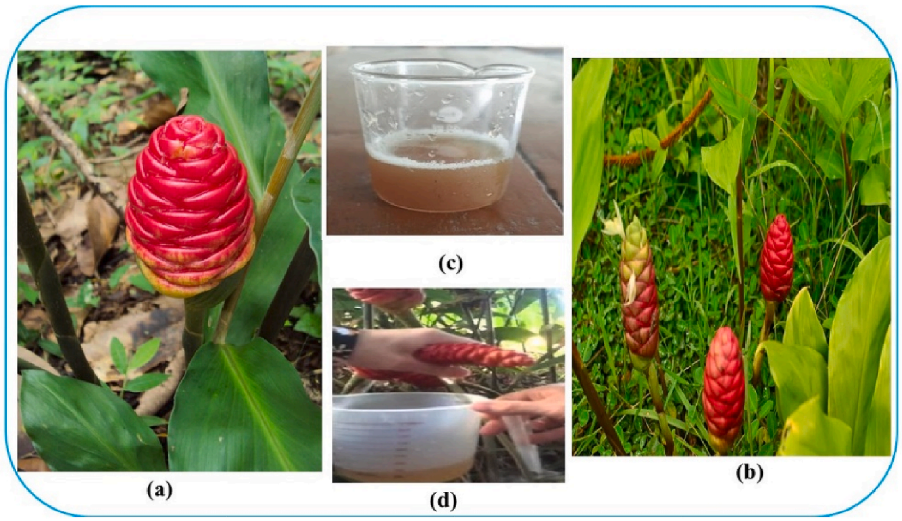


Fig. 3. (a) Inflorescence of *Zingiber zerumbet*, (b) inflorescence with flowers of *Z. zerumbet*, (c) extract/juice of *Z. zerumbet*, (d) collection of extract/juice.

Table 1
Optimization of reaction conditions for synthesis of bis(indolyl)methane[a].

Entry	Reaction condition	T (°C)	Time (h/days)	Yield (%)
1	Water	RT	24 h	trace
2	US	RT	30 min	20
3	Water, US	RT	50 min	25
4	*Zingiber zerumbet*	RT	2 days	trace
5	*Zingiber zerumbet*	50	24 h	50
6	*Zingiber zerumbet*	65	6 h	60
7	*Zingiber zerumbet*, US	RT	5 min	92
8	*Zingiber zerumbet*, US	45	10 min	90

US-Ultra sound irradiation.
[b]Isolated yields.
[a] Reaction conditions: 4-nitrobenzaldehyde (1 mmol), indole (2 mmol), Bio extract of *Zingiber zerumbet* (5 mL).

room temperature for the appropriate time until the completion of the reaction was monitored by TLC (nHexane: EA 6:4). The solid product was separated by simple filtration. The isolated crude product was recrystallized with ethanol.

2.4. Spectral data of synthesized compounds

1) **3,3′(phenylmethylene)bis(1H-indole)(3a):** Pink solid, M. P. 126–128°C. ^{1}H NMR (400 MHz, DMSO): δ 8.05 (s, 2H), 7.40 (d, 2H, *J* = 8.2 Hz), 7.35 (d, 4H, *J* = 8.2 Hz), 7.28–7.27 (m,2H), 7.22 (d, 1H, *J* = 7.5 Hz), 7.17 (t, 1H, *J* = 7.0 Hz), 7.01 (t, 2H, *J* = 7.5 Hz), 6.64 (s, 2H), 5.89 (s, 1H); ^{13}C NMR: 144.09, 136.68, 128.75, 128.26, 127.07, 126.16, 123.73, 121.88, 119.92, 119.57, 119.18, 111.14, 40.20 ppm.
2) **3,3-Bis(indolyl)-4-nitrophenylmethane (3b):** Yellow Solid, M.P. 221–223°C. IR (KBr): ῡ = 3426, 2925, 1741, 1637, 1550, 1457, 1342, 1016, 744 cm $^{-1}$. ^{1}H NMR (400 MHz, DMSO): δ 10.38 (s, 2H), 8.01 (d, 2H, *J* = 8.0 Hz), 7.45 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 8.0 Hz), 7.20 (d, 2H, *J* = 7.5 Hz), 7.0 (t, 2H, *J* = 7.5 Hz), 6.82 (t, 2H, *J* = 7.0 Hz), 6.65 (s, 2H), 5.87 (s, 1H); ^{13}C NMR: 153.0, 146.17, 136.99, 129.58, 126.62, 124.18, 123.43, 121.43, 119.12, 118.74, 116.98, 111.79 ppm.
3) **4-Chlorophenyl-3,3-bis(indolyl)methane (3c):** Pink Solid, M.P. 76–78°C. IR (KBr): ῡ = 3409, 2927, 1623, 1521, 1488, 1455, 1276, 1207, 1069, 1010, 742 cm $^{-1}$. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (s, 2H), 7.39 (m, 4H), 7.37 (m, 4H), 7.19 (t, 2H, *J* = 7.5 Hz), 7.03 (t, 2H, *J* = 7.5 Hz), 6.61 (s, 2H), 5.87 (s, 1H); ^{13}C NMR: 142.6, 136.7, 131.7, 130.1, 128.4, 126.9, 123.6, 122.1, 119.8, 119.3, 119.1, 111.2, 44.9 ppm.
4) **3,3'-(*p*-tolylmethylene)bis(1H-indole) (3e):** Red solid, M.P. 98–100°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.70 (br s, 2H), 7.37 (d, 2H, *J* = 8.0 Hz), 7.27 (d, 2H, *J* = 8.5 Hz), 7.20 (d, 2H, *J* = 8.0 Hz), 7.14 (t, 2H, *J* = 7.5 Hz), 7.06 (d, 2H, *J* = 8.0 Hz), 6.98 (t, 2H, *J* = 7.5 Hz), 6.55 (d, 2H, *J* = 2.0 Hz), 5.82 (s, 1H), 2.30 (s, 3H, CH_3); ^{13}C NMR: 141.0, 136.7, 135.4, 128.9, 128.5, 127.1, 123.5, 121.8, 119.9, 119.1, 110.9, 21.05 ppm.
5) **3,3'-((4-methoxyphenyl)methylene)bis(1H-indole) (3f):** Red Solid, M.P. 190–192°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (brs, 2H), 7.14–7.19 (m, 6H), 7.03 (t, 2H, *J* = 8.2 Hz), 6.98 (t, 2H, *J* = 8.0 Hz), 6.83 (d, 2H, *J* = 6.9 Hz), 6.65 (d, 2H, *J* = 1.2 Hz), 5.84 (s, 1H), 3.78 (s, 3H); ^{13}C NMR: 160.12, 135.68, 133.40, 130.09, 129.74, 128.23, 127.47, 125.14, 122.66, 121.89, 119.33, 119.20, 111.07, 52.60, 40.19 ppm.
6) **4-(di91H-indol-3-yl)methyl)-*N*,*N*-dimethylaniline(3g):** Pink solid, M.P. 169–172°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (br s, 2H), 7.25–7.35 (m, 8H), 7.15 (t, 2H, *J* = 7.5 Hz), 7.00 (t, 2H, *J* = 7.0 Hz), 6.67 (br s, 2H), 5.82 (s, 1H); ^{13}C NMR: 155.10, 136.13, 131.23, 127.00, 126.09, 123.67, 121.12, 119.43, 118.29, 112.23, 111.27, 110.11, 54.82, 41.06 ppm
7) **3,3'-((4-flurophenyl)methylene)bis(1H-indole) (3j):** Pink solid, M.P. 72–74°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (s, 2H), 7.40 (d, 2H, *J* = 8.0 Hz), 7.36–7.34 (m, 2H), 7.30–7.28 (m, 2H), 7.23 (d, 1H, *J* = 7.5 Hz), 7.19–7.15 (m, 3H), 7.01 (t, 2H, *J* = 8.0 Hz) 6.63 (s, 2H), 5.89 (s, 1H); ^{13}C NMR: 170.12, 136.68, 133.40, 130.09, 128.74, 128.23, 127.07, 126.14, 123.66, 121.89, 119.33, 119.20, 111.07, 40.19 ppm.
8) **3,3'-(phenylmethylene)bis(1-methyl-1H-indole) (3l):** Pink Solid, M.P. 202–204°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ7.37–7.36 (m, 2H), 7.32–7.30 (m,2H), 7.27–7.25 (m, 5H), 7.24–7.23 (m,1H), 7.22–7.21 (m, 1H), 7.02 (t, 2H), 6.52 (s, 2H), 5.86 (s, 1H), 3.70 (s, 6H); 142.99, 137.44, 131.64, 130.43, 128.24, 128.26, 127.24, 121.55, 119.91, 118.75, 117.70, 109.14, 39.44, 32.74 ppm.
9) **3,3'-((4-chlorophenyl)methylene)bis(1-methyl-1H-indole) (3m):** Pink Solid, M.P. 210–212°C. IR (KBr): ῡ = 2921, 1589, 1511, 1338, 1004, 736 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, 2H, *J* = 8.0 Hz), 7.30 (d, 2H, *J* = 8.0 Hz), 7.27 (m, 4H), 7.25 (d, 2H, *J* = 7.5 Hz), 7.02 (d, 2H, *J* = 7.0 Hz), 6.52 (s, 2H), 5.86 (s, 1H), 3.70 (s, 6H); ^{13}C NMR: 143.0, 137.40, 131.64, 130.03, 128.33, 127.44, 126.22, 121.55, 119.91, 118.75, 117.70, 109.0, 39.48, 32.71 ppm
10) **3,3'-((4-nitrophenyl)methylene)bis(1-methyl-1H-indole) (3n):** Yellow Solid, M.P. 215–217°C. IR (KBr): ῡ = 3050, 2927, 1484, 1224, 1172, 1148, 1093, 996, 813, 732, 673 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3): δ 8.14 (d, 2H, *J* = 8.0 Hz), 7.52 (d, 2H, *J* = 4.0 Hz), 7.32 (m, 4H), 7.26 (d, 2H, *J* = 8.0 Hz), 7.02 (d, 2H, *J* = 8.0 Hz), 6.55 (s, 2H), 5.98 (s, 1H), 3.72 (s, 6H); ^{13}C NMR: 152.31, 146.47, 137.42, 129.47, 128.29, 127.03, 123.62, 121.82, 119.64, 119.03, 116.60, 109.33, 40.07, 32.78 ppm.
11) **3,3'-(*p*-tolylmethylene)bis(1-methyl-1H-indole) (3o):** Yield: 90%; M.P. 147–149°C. ^{1}H NMR (400 MHz, CDCl3): δ 7.36 (d, 2H, *J* = 8.6 Hz), 7.32 (d, 2H, *J* = 8.0 Hz), 7.28–7.27 (m, 3H), 7.25 (s, 1H), 7.24–7.23 (m, 1H), 7.22–7.21 (m,1H), 7.01 (t, 2H, *J* = 7.0 Hz), 6.52 (s, 2H), 5.86 (s, 1H), 3.70 (s, 6H), 2.50 (s, 3H); ^{13}C NMR: 142.39, 137.40, 131.64, 130.03, 128.53, 128.26, 126.22, 121.55, 119.95, 118.75, 117.70, 109.34, 39.43, 32.31, 21.29 ppm.
12) **[3,3':3′,3″-terindolin]-2′-one (5a):** Yield: 92%; white solid; m.p. 314–318°C. IR (KBr, cm^{-1}): 3428, 3324, 1707, 1613, 1468, 1106, 932, 736; ^{1}H NMR (400 MHz, DMSO- *d6*) δ 10.28 (s, 2H), 10.13 (s, 1H), 7.26–7.24 (m, 4H), 7.20 (t, 1H, *J* = 7.5 Hz), 7.11 (t, 1H, *J* = 7.0 Hz), 6.96–6.93 (m, 3H), 6.91–6.83 (m, 3H), 6.72 (s, 2H); ^{13}C NMR (400 MHz, DMSO- *d6*): δ 179.8, 141.3, 137.6, 134.9, 127.8, 126.0, 125.2, 124.7, 121.8, 121.2, 121.1, 118.6, 114.6, 111.6, 109.9, 53.2 ppm.
13) **5′-nitro-[3,3':3′,3″-terindolin]-2′-one (5b):** Yield: 90%; yellow solid, m.p. 298–299°C. IR (KBr, cm^{-1}): 3384, 2917, 1707, 1519, 1454, 1175, 1018, 744; ^{1}H NMR (400 MHz, DMSO- *d6*) δ 10.84 (s, 1H), 10.29 (s, 2H), 8.09 (dd, 1H, *J* = 8.5, 2.1 Hz), 7.99 (d, 1H), 7.61 (d, 2H, *J* = 2.5 Hz), 7.04–7.00 (m, 3H), 6.99–6.97 (m, 3H), 6.83 (s, 2H), 6.77 (m, 2H); ^{13}C NMR (400 MHz, DMSO- *d6*) δ 179.6, 148.1, 142.5, 137.5, 135.6, 125.8, 125.6, 124.8, 121.5, 120.7, 120.2, 118.8, 112.0, 111.6, 110.1, 53.0 ppm.
14) **5′-chloro= [3,3':3′,3″-terindolin]-2′-one (5c):** Yield: 90%; white solid, m.p. 297–299°C. IR (KBr, cm^{-1}): 3363, 2925, 1700, 1475, 1170, 738; ^{1}H NMR (400 MHz, DMSO- *d6*) δ 10.84 (s, 1H), 10.15 (s, 2H), 7.49–7.44 (m, 2H), 7.23–7.19 (m, 3H), 7.07–7.04 (m, 2H), 6.94–6.92 (m, 2H), 6.84 (d, 2H, *J* = 8.1 Hz), 6.74–6.72 (m, 2H); ^{13}C NMR (400 MHz, DMSO- *d6*) δ

179.09, 140.42, 137.33, 136.82, 128.54, 127.80, 125.87, 125.09, 124.68, 121.34, 120.98, 118.69, 113.94, 111.87, 111.23, 53.31 ppm.

15) **5′-methoxy-[3,3':3′,3″-terindolin]-2′-one (5d):** Yield: 88%; white solid, m. p. 290–292°C. IR (KBr, cm $^{-1}$): 3384, 2928, 1686, 1484, 1191, 734, 572; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.91 (s, 2H), 9.66 (s, 1H), 7.64 (d, 2H, J = 8.0 Hz), 7.40 (m, 3H), 7.24 (d, 2H, J = 8.5 Hz), 7.07 (d, 2H, J = 7.5 Hz), 6.93 (m, 2H), 6.74 (s, 2H), 3.58 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 179.4, 155.0, 137.3, 136.2, 134.9, 128.6, 126.0, 125.9, 124.6, 121.7, 118.5, 114.6, 112.0, 11.1, 110.2, 55.6, 53.2 ppm.

16) **5′-bromo-[3,3':3′,3″-terindolin]-2′-one (5e):** Yield: 90%; white solid, m.p. 300°C. ^{1}H NMR (400 MHz, DMSO- *d6*) δ 10.33 (s, 1H), 10.15 (s, 2H), 7.49–7.46 (m, 2H), 7.28–7.21 (m, 2H), 7.11–7.01 (m, 2H), 6.96–6.90 (m, 2H), 6.81 (d, 2H, J = 8.4 Hz), 6.74 (m, 2H); ^{13}C NMR (400 MHz, DMSO- *d6*) δ 179.31, 140.42, 137.83, 136.82, 128.54, 127.80, 125.87, 125.09, 124.68, 121.34, 120.98, 118.69, 113.44, 111.37, 111.31, 53.33 ppm.

17) **1,1″-dimethyl-[3,3':3′,3″-terindolin]-2′-one (5f):** Yield: 92%; white solid, m.p. >300°C. IR (KBr, cm^{-1}): 3056, 1696,1470, 1328, 1240, 734; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.04 (s, 1H), 7.68 (d, 1H), 7.39 (d, 1H, J = 8.2 Hz), 7.33 (d, 1H, J = 8.0 Hz), 7.27–7.26 (m, 2H), 7.19–7.15 (m, 2H), 7.09 (d, 1H, J = 7.4 Hz), 7.01 (d, 2H, J = 7.2 Hz), 6.93–6.92 (m, 2H), 6.87 (s, 2H), 3.68 (s, 6H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 178.47, 139.55, 137.11, 129.17, 128.94, 128.15, 126.20, 125.51, 123.22, 121.66, 121.34, 120.85, 119.11, 112.74, 109.38, 53.48, 32.83 ppm.

18) **1,1″-dimethyl-5′-nitro-[3, 3':3′,3″-terindolin]-2′-one (5g):** Yield: 88%; m.p. >300°C. IR (KBr): ῡ = 3364, 2933, 1739, 1615, 1508, 1478,1331, 1075, 736, 558 cm- ^{1}; ^{1}H NMR (400 MHz, DMSO- *d6*) δ 11.34 (s, 1H), 8.25 (m, 1H), 7.98 (d, 2H, J = 8.6 Hz), 7.41 (d, 2H, J = 8.0 Hz), 7.25 (d, 2H, J = 8.2 Hz), 7.21 (d, 1H, J = 8.4 Hz), 7.11 (t, 2H, J = 7.5 Hz), 7.01 (s, 2H), 6.88 (t, 2H, J = 7.5 Hz), 3.72 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 179.11, 148.16, 142.71, 137.88, 129.17, 126.17, 125.92, 121.76, 120.95, 120.58, 119.19, 112.31, 110.46,110.39, 109.99, 58.23, 32.84 ppm.

19) **5′-chloro-1,1″-dimethyl-[3,3':3′,3″-terindolin]-2′-one (5h):** Yield: 90%; m.p. 295–297°C. IR (KBr): ῡ = 3242, 1715, 1613, 1471, 1369, 820, 750, 558 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO- *d6*) δ 10.76 (s, 1H), 7.49–7.47 (m, 1H), 7.39 (d, 2H, J = 8.4 Hz), 7.30–7.28 (m, 1H), 7.22–7.19 (m, 2H), 7.11–7.08 (m, 2H), 7.00 (d, 1H, J = 8.4 Hz), 6.93 (s, 1H), 6.86 (t, 2H, J = 7.5 Hz), 3.72 (s, 6H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 178.59, 140.86, 137.81, 136.91, 128.98, 128.34, 126.29, 125.95, 125.11, 121.62, 121.13, 119.02, 113.12, 111.59, 110.32, 58.48, 32.82 ppm.

20) **5′-bromo-1,1″-dimethyl-[3,3':3′,3″-terindolin]-2′-one (5i):** Yield: 88%; m.p. .300°C. ^{1}H NMR (400 MHz, DMSO- *d6*) δ 10.76 (s, 1H), 7.49 (d, 1H, J = 8.0 Hz), 7.40 (d, 2H, J = 8.6 Hz), 7.30–7.29 (m, 1H), 7.22–7.20 (m, 2H), 7.10–7.07 (m, 2H), 7.01 (d, 1H J = 8.0 Hz), 6.93 (s, 2H), 6.87–6.84 (m, 2H), 3.72 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 178.28, 141.66, 137.81, 136.91, 129.98, 128.34, 126.29, 125.95, 125.11, 121.62, 121.13, 119.02, 113.12, 111.59, 110.39, 57.23, 32.89 ppm.

21) **5′-methoxy-1,1″-dimethyl-[3,3':3′,3″-terindolin]-2′-one (5j):** Yield: 90%; m.p. >300°C. IR (KBr): ῡ = 3100, 2933, 1706, 1488, 1330, 1201, 1036, 741; ^{1}H NMR (400 MHz, DMSO- *d6*) δ 10.45 (s, 1H), 7.37 (d, 2H, J = 8.0 Hz), 7.10–7.07 (m, 3H), 6.91 (s, 2H), 6.84 (d, 2H, J = 7.5 Hz), 6.83–6.80 (m, 2H), 3.71 (s, 6H), 3.61 (s, 3H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 179.84, 147.16, 141.71, 137.18, 128.17, 126.17, 125.95, 121.66, 120.95, 120.58, 119.19, 112.35, 110.46, 110.39, 109.96, 68.16, 58.16, 32.16 ppm.

22) **2-amino-7,7-dimethyl-2′,5-dioxo-1′,2′,5,6,7,8-hexahydrospiro[[1]benzopyran-4,3′-indole]-3-carbonitrile (8a):** White solid; m.p. 286–288°C. IR (KBr): ῡ = 3384, 3318, 3153, 2959, 2194, 1720, 1681, 1658, 1473, 1343, 1224, 1055, 903 cm $^{-1}$; ^{1}H NMR (DMSO-d_6, 400 MHz) ∂: 10.40 (s, 1H, NH), 7.23 (s, 2H, NH $_2$), 7.14 (t, 1H, ArH), 6.98 (d, 1H, J = 7.0 Hz ArH), 6.89 (t, 1H, J = 7.5 Hz ArH), 6.80 (d, 1H, J = 7.7 Hz ArH), 2.56 (m, 2H, CH_2), 1.59 (m, 2H, CH $_2$), 1.03 (s, 3H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂: 195.31,178.46, 164.58, 159.20, 142.48, 134.85, 128.60, 123.44, 122.12, 117.78, 111.22, 109.57, 57.93, 5 0.94, 47.26, 32.39, 28.04, 27.46.

23) **7′-amino-2,2′2,4′-trioxo-1′,2′,3′,4′,-tetrahydrospiro[indoline-3,5′-pyrano[2,3 d]pyrimidine]-6′-carbonitrile (8b):** White solid; m.p. >300°C IR (KBr): ῡ = 3355, 3293, 3143, 2827, 2202, 1690, 1671, 1392, 1336, 1112 cm $^{-1}$; ^{1}H NMR (DMSO-d_6, 400 MHz) ∂: 10.87 (s, 1H), 10.32 (s, 2H), 7.70 (s, 2H), 7.56 (d,1H, J = 7.5 Hz), 6.99 (m, 2H); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂: 178.40, 161.81, 158.84, 153.69, 149.70, 142.15, 133.40, 128.50, 125.91, 123.71, 117.19, 110.03, 87.23, 58.08, 47.02.

24) **7′-amino-2′-2′-dimethyl-2,4′-dioxo-4′h-spiro[indoline-3,5′-pyrano[2,3-d][1,3]dioxine]-6′-carbonitrile (8c):** White solid; m.p. 187–190°C. IR (KBr): ῡ = 3384, 3300, 3147, 2929, 2190, 1720, 1654, 1348, 1220 cm $^{-1}$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.22 (s, 1H), 7.89 (d, 1H), 7.57 (d, 1H), 7,14–7.12 (m, 2H), 6.95 (s, 2H), 1.40 (s, 6H); ^{13}C NMR (400 MHz, DMSO-*d6*) δ 178.47, 164.58, 159.20, 142.49, 134.85, 128.60, 123.45, 122.12, 117.78, 111.22, 109.67, 87.23, 57.93, 50.44, 28.04 ppm.

25) **2-amino-7,7-dimethyl-5′-nitro-2′,5-dioxo-5,6,7,8 tetrahydrospiro[chromene-4,3′ indoline]-3-carbonitrile (8d):** Yellow solid; m.p. >300°C.^{1}H NMR (DMSO-d_6, 400 MHz) ∂: 11.00 (s, 1H, NH), 8.03 (s, 1H, ArH), 7.76 (d, 2H, J = 8.4 Hz, ArH), 6.94 (s, 2H, NH $_2$), 2.49 (q, 2H, J = 16 Hz, CH_2), 2.10 (s, 2H, CH_2), 1.02 (s, 6H, CH_3); ^{13}C NMR (DMSO-d_6 $_6$, 400 MHz) ∂: 195.29, 178.97, 165.12, 159.45, 148.81, 142.88, 135.24, 125.76, 118.99, 117.19, 110.49, 109.71, 56.76, 50.39, 47.31, 32.35, 28.10, 27.88 ppm.

26) **2-amino-5′-chloro-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3′-indoline]-3-carbonitrile (8e):** Pink solid; m.p. 286–288°C. IR (KBr): ῡ = 3286, 3154, 2958, 2190, 1725, 1652, 1479, 1349, 1220, 1056, 809 cm $^{-1}$; ^{1}H NMR (DMSO-d_6, 400 MHz) ∂: 10.33 (s, 1H, NH), 7.02 (d, 1H, ArH), 6.83 (s, 1H, ArH), 6.72 (d, 1H, ArH), 6.62 (s, 2H, NH $_2$), 2.45 (s, 2H, CH_2), 2.10, (s, 2H, CH_2), 1.00 (s, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂: 195.07, 178.31, 164.59, 159,27, 141.16, 136.36, 128.28, 126.53, 123.43, 117.42, 110.95, 110.86, 57.48, 50.52, 47.50, 32.29, 27.99, 27.66.

27) **2-amino-5′-methoxy-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3′-indoline] -3-carbonitrile (8f):** Brown gray solid; m.p. 287–289°C IR (KBr): $\bar{\upsilon}$ = 3384, 3309, 3160, 2925, 2188, 1718, 166, 1600, 1484, 1351, 1205, 1029, ^{1}H NMR (DMSO-d_6, 400 MHz) ∂: 9.99 (s, 1H, NH), 7.65 (s, 2H, NH $_2$), 6.68 (d, 1H, J = 7.5 Hz ArH), 6.66 (d, 1H, J = 7.0 Hz ArH), 6.45 (s, 1H, ArH), 3.62 (s, 3H, OCH $_3$), 2.44 (m, 2H, CH_2), 2.09 (m, 2H, CH_2), 1.02 (s, 3H, CH $_3$), 0.98 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂: 194.90, 178.53, 164.19, 159.15, 155.46, 135.77, 135.58, 117.59, 112.85, 111.33, 110.22, 110.07, 58.32, 55.60, 50.60, 47.69, 32.23, 28.33, 27.66.

28) **7′amino-5-bromo-2,2′,4′-trioxo-1′,2′,3′,4′-tetrahydrospiro [indoline-3,5′-pyrano [2,3-*d*] pyrimidine] -6′-carbonitrile (8g):** White solid; m.p. 225–227°C. ^{1}H NMR (DMSO-d_6, 400 MHz) ∂:10.95 (s, 1H, NH), 10.69 (s, 2H, NH), 7.31 (s, 2H, NH $_2$), 7.57 (s, 1H, ArH), 6.78 (d, 1H, ArH), 6.86 (1H, d, ArH); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂: 179.40, 162.82, 158.24, 153.69, 148.30, 142.15, 133.40, 128.23, 126.61, 123.71, 122.30, 117.29, 87.23, 58.23, 47.30 ppm.

29) **2-amino-5′-bromo-7,7-dimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospriro [chromene-4,3′-indoline] -3-carbonitrile (8h):** Pink solid, m.p. >300°C. ^{1}H NMR (DMSO-d_6, 400 MHz) ∂: 10.33 (s, 1H, NH), 7.68 (s, 1H, ArH), 7.02 (d, 1H, J = 7.5 Hz ArH), 6.83 (d, 1H, J = 7.0 Hz, ArH) 6.62 (s, 2H, NH $_2$), 2.49 (d, 2H, J = 10.0 Hz, CH_2), 2.10 (s, 2H, CH_2), 6.19 (s, 6H, CH_3); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂: 195.29, 179.27, 164.59, 159.27, 141.66, 136.36, 128.28, 126.53, 123.43, 117.01, 110.95, 110.86, 57.49, 50.52, 47.52, 32.29, 28.01 ppm.

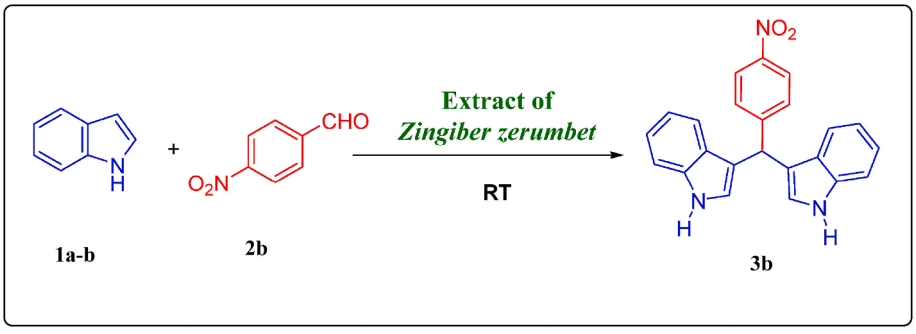
30) **2-amino-5′,7,7-trimethyl-2′,5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3′-indoline] -3-carbonitrile (8j):** Light pink solid, m.p. 281–283°C. ^{1}H NMR (DMSO-d_6, 400 MHz) ∂: 9.99 (s, 1H, NH), 7.65 (s, 2H, NH_2), 6.66 (d, 1H, J = 7.4 Hz ArH), 6.60 (m, 1H, ArH), 6.45 (s, 1H, ArH), 2.49 (s, 3H, CH $_3$), 2.44 (s, 2H, CH_2), 2.09 (d, 2H, J = 9.9 Hz CH_2), 1.02 (s, 3H, CH $_3$), 0.98 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6, 400 MHz) ∂: 194.58, 177.58, 163.18, 159.14, 155.46, 139.77, 135.58, 139.77, 135.58, 117.60, 112.85, 111.33, 110.22, 110.07, 58.32, 50.66, 47.69, 32.23, 28.33, 27.86, 22.07 ppm.

3. Result and discussion

Collection of extract of *Zingiber zerumbet*: The efficiency in dissolving non-polar compounds has made aqueous surfactants better alternatives to harmful volatile organic solvents in various applications (Mote et al., 2010). Surfactant forms the micelles, which are similar to colloidal aggregation. This micelle formation occurs above the critical micelle concentration (CMC). A low concentration of CMC means requiring less surfactant to decrease the surface tension. The viscous juice present in the inflorescence of *Z. zerumbet*, acts as a natural conditioner as well as biosurfactant (Yu et al., 2008). This viscous extract mainly contains different saponins, due to which it acts as a surfactant. Inflorescence of *Zingiber zerumbet* is collected from botanical garden of Y. C. Institute of Science, Satara, India. Bio extract was removed by hand pressing of the inflorescence (Fig. 3), which is a viscous liquid. It was collected and stored at 4°C temperature in refrigerator until further use. The pH of the collected natural bio-extract was measured using digital pH meter before use and it was 5.2. The density study of *Zingiber zerumbet* bio-extract carried with and without filtration. The density with filtration observed 0.9976 g/cm^3 at 25°C with specific gravity1.0005 while the density without filtration observed 0.9985 g/cm^3 at 25°C with specific gravity1.0015. The viscosity study of *Zingiber zerumbet* bio-extract observed at 0.856 cPa on 25°C. This study reveals that the *Zingiber zerumbet* bio-extract used as reaction medium for organic transformation as like aqueous medium.

Applications of extract of *Zingiber zerumbet* for the synthesis of bis(indolyl)methane: Initially, with the aim of optimize the reaction conditions, 4-nitrobenzaldehyde (1 mmol) was reacted with indole (2 mmol) in 5 ml of *Z. zerumbet* at room temperature (Scheme 1).

We found a very trace amount of product (Table 1, **Entry 1–4)**, from which it was confirmed that reaction medium is a very important factor that influences reaction progress. At the time of screening conditions, we observe that in the presence of water and in the absence of surfactant, a trace amount of product is produced (Table 1). In order to maximise the yield of the desired bis(indolyl) methane product and decrease the time of reaction, we performed the model reaction under US irradiation. The significant improvement in yield as well as reaction time occurred under ultrasound irradiation. Ultrasound irradiation not only increases the yield but also minimises the reaction time (Table 1). But we continue the reaction under the same conditions for more time due to ultrasonic waves the temperature of the ultrasonic bath increases, which has no positive effect on reaction yield but makes the product slightly



Scheme 1. *Zingiber zerumbet* extracted surfactant mediated synthesis of bis(indolyl)methane.

sticky. In order to study the effect of extract on reaction, the model reaction was carried out under different reaction conditions (Table 1).

The weak acidic nature and surfactant property produces synergistic effect which activate the reactant molecules, reaction proceed smoothly within in a short period of time. The Extract of *Zingiber zerumbet* is a natural surfactant or natural shampoo due to which, during the reaction progress, it was observed that, the clear initial reaction mixture turned turbid, indicated the formation of micelle-like colloidal aggregation as observed in microscopic images for the reaction of the model scheme of synthesis of bis(indolyl) methane (Fig. 4). The micelle is created above the critical micelle concentration (CMC) due to which reactant molecules comes in self-assembly to from aggregation in solution, which gives conversion of the true solution in to turbid colloidal dispersion. This micellar solution is an actual colloidal dispersion of produced surfactant molecules. In this micellar medium hydrophobic part move apart while hydrophilic part attracted towards the reactant in aggregation. During this aggregation, reactant molecules brought close proximity to each other, and interactions take place between them that form the organic transformation between them (Fig. 5).

The visual exploitation of the reaction progress also observed by change in color during the synthetic transformation such as at the beginning, the brownish colored reaction mixture turned to a yellow-colored turbid emulsion (Fig. 6) which indicate that there is creation of micelle or micelle like colloidal suspension in which aggregation takes place. Overall, product formation occurs very easily at the core of the micelle. Therefore, the present strategy discloses the green and efficient methodologies for the synthesis of bis(indolyl) methane.

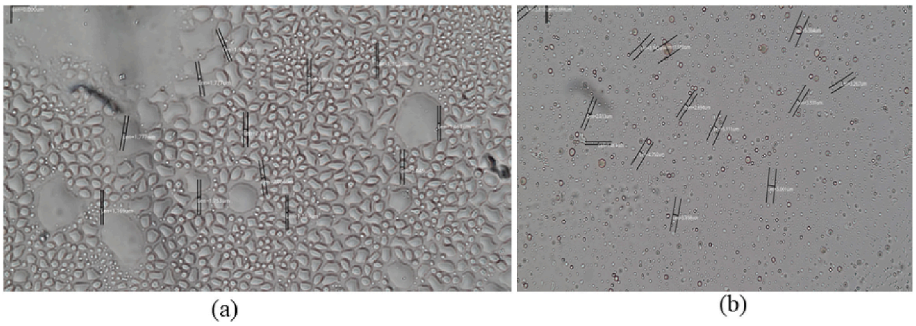


Fig. 4. Microscopic images of (a) extract/juice of *Zingiber zerumbet* and (b) reaction mixture in *Zingiber zerumbet*.

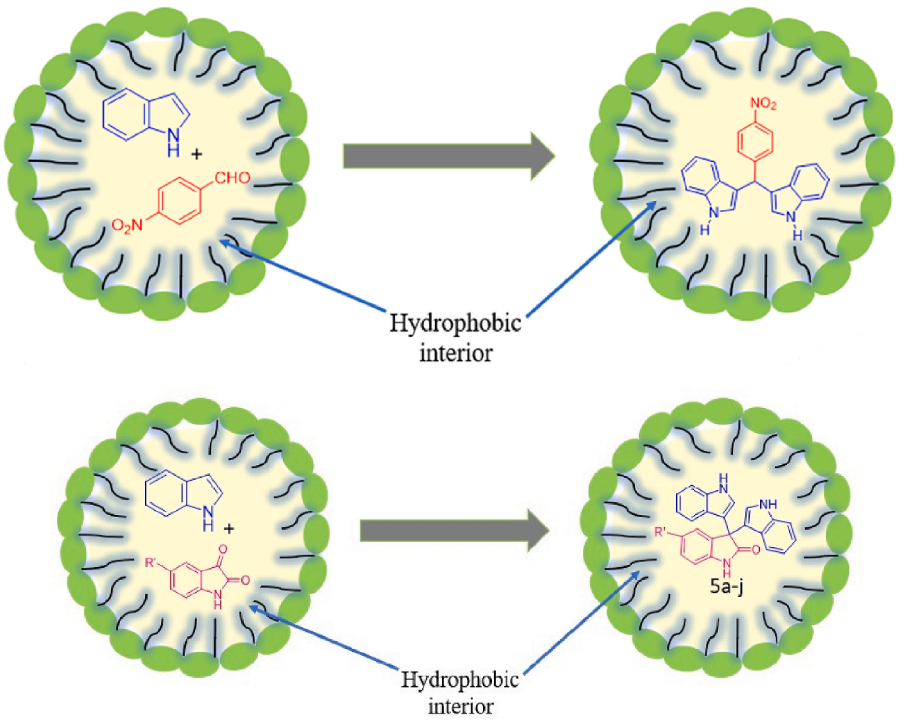


Fig. 5. Mechanistic role of micellar surfactant "*Zingiber zerumbet*" for bis(indolyl)methane and tris-indoline formation.

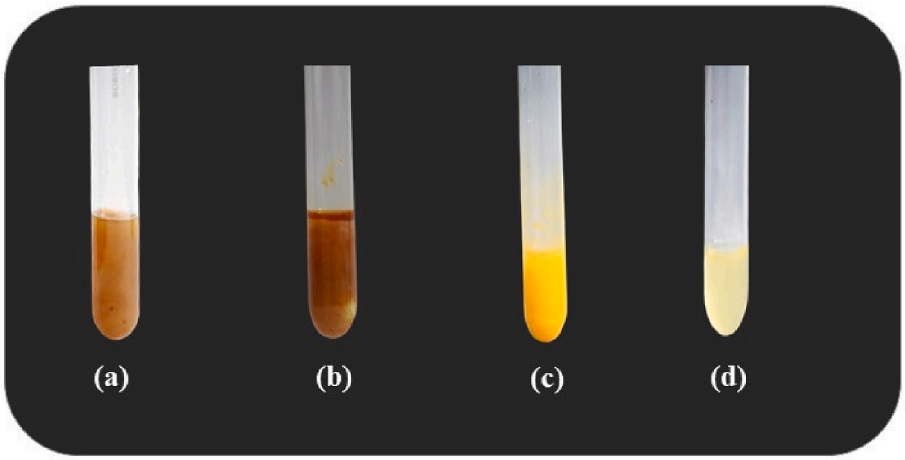
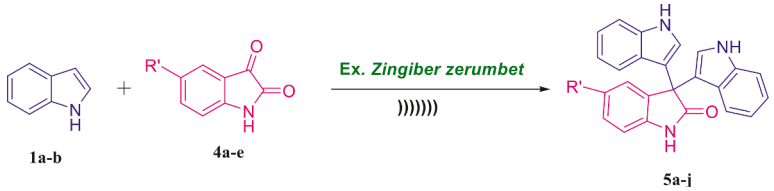


Fig. 6. Photographs of (a) extract/juice of *Zingiber zerumbet,* (b) reactants in *Zingiber zerumbet extract,* (c) formation of product and (d) *Zingiber zerumbet extract* after reaction.

After optimizing reaction conditions, we apply the same strategy to different aldehydes and indoles in 5 ml of *Z. zerumbet* under ultrasound irradiation (Table 2). Benzaldehyde with an electron-withdrawing group gives a better yield than electron-donating group.

Applications of extract of *Zingiber zerumbet* for the synthesis of tris-indoline*:* The scope of the protocol was further extended to the synthesis of tris-indoline by reacting isatin (1 mmol) with indole (2 mmol) under optimized reaction conditions in 5 ml of bio extract of *Zingiber zerumbet* under ultrasound irradiation (Table 1).

In order to study the effectiveness of the present protocol, we prepared different derivatives of tris-indolines by reacting different substituted isatins and 1-methyl indole (Table 3). The presence of electron-donating and -withdrawing groups on the benzene ring of isatins shows slight influence on the yield of the reaction.



Applications of extract of *Zingiber zerumbet* for the synthesis of spirooxindoles*:* We extended this protocol for the synthesis of spirooxindole derivatives in which equimolar quantities of isatin, malononitrile, and dimedone was reacted under different reaction conditions. For the selection of a suitable solvent the model reaction was carried out in water, ethanol, methanol, and a combination of water and ethanol (1:1) (Table 4). We performed the model reaction in a natural extract of *Zingiber zerumbet* and also without surfactant under ultrasound irradiation. A trace amount of product was observed when the reaction was carried out without surfactant. Therefore, selected surfactant gives better results within in a short period of time. Under the optimized reaction conditions, a series of spirooxindoles were synthesized by using different active methylene groups and substituting isatin (Table 5).

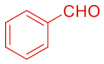
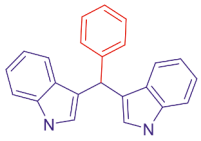
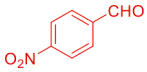
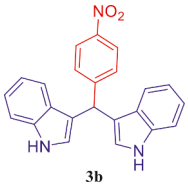
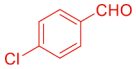
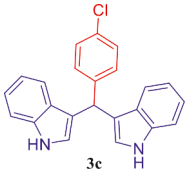
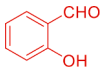
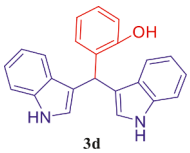
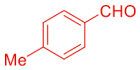
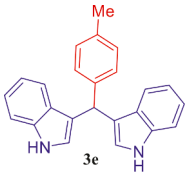
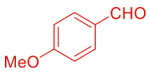
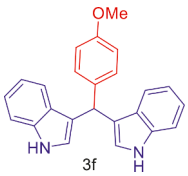
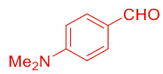
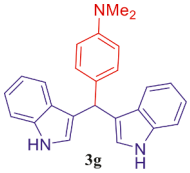
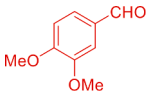
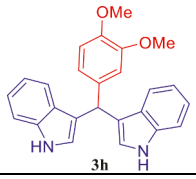
The catalytic role of *Zingiber zerumbet in the synthesis of spirooxindole is such that* it creates a micellar medium in which isatin, malononitrile, and 1,3-dicarbonyl compounds react with each other to produce spirooxindole molecules. In the micellar medium, hydrophobic moieties move apart from each other, forming a micellar core in which reactant molecules come in close and react with each other to produce organic transformation (Fig. 7). However colloidal particles inside the hydrophobic core in micellar medium of natural surfactant where the reaction takes place more easily.

Recyclability of Natural Surfactant *Zingiber zerumbet* in the synthesis of bis(indolyl)methane: The feasibility of recycling the catalyst was also examined for the model reaction. After the reaction was complete, the product was separated by filtration. The bio-extract was then reused for the next reaction cycle. The recycling results show that *Zingiber zerumbet* can be recycled at least four times with a slight decrease in product yield (Fig. 8). Change in pH was examined by measuring the pH of the bio extract after each cycle and we observed a slight increase in pH value from 5.2 to 5.5 after the fourth run. Very less change in yield in the product was observed after the fourth run which may be due to no significant change in the pH value of the bio extract.

4. Conclusion

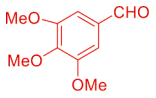
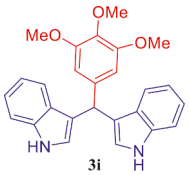
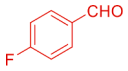
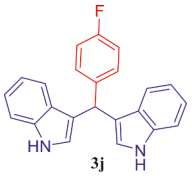
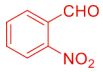
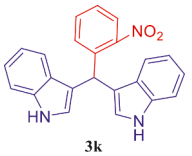
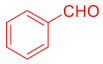
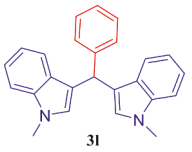
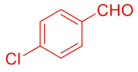
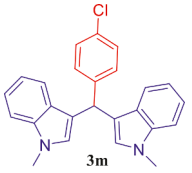
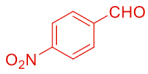
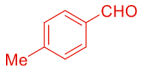
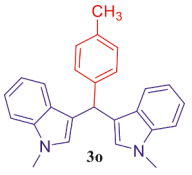
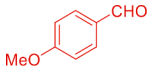
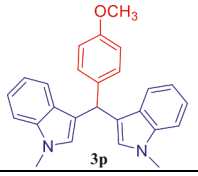
In conclusion, we reported a simple and new approach for the clean and ecofriendly synthesis of bis indoles, trisindolines, and spirooxindoles by the combination of the natural surfactant (*Zingiber zerumbet)* and ultrasound irradiation. This perspective shows the

Table 2
Synthesis of bis(indolyl)methanes using natural surfactant of *Z. zerumbet* under ultrasound irradiation[a].

Entry	Aromatic aldehyde	Product	Yield[b] (%)	M.P. (°C) [lit]
1		 **3a**	92 (0.296)	126-128 [123–125] Shirini and Khaligh (2013)
2		 **3b**	92 (0.340)	223-225 [220–224] Seyedi et al. (2015)
3		 **3c**	90 (0.324)	76-78 (Brahmachari and Banerjee, 2014; Yuan et al., 2020) Li et al. (2011)
4		 **3d**	86 (0.290)	102-104 [103–105] Shirini and Khaligh (2013)
5		 **3e**	88 (0.298)	98-100 [99–100] Shirini and Khaligh (2013)
6		 3f	86 (0.305)	190-192 [188–189] Joshi et al. (2010)
7		 **3g**	85 (0.310)	169-172 [171–172] Hote et al. (2022)
8		 **3h**	86 (0.330)	198-199 [197–199] Shirini and Khaligh (2013)

(*continued on next page*)

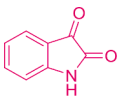
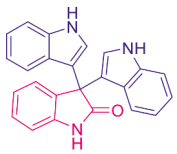
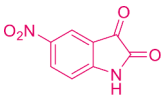
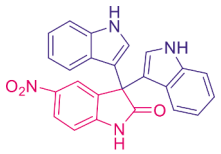
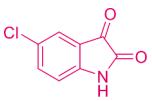
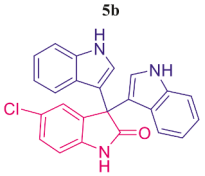
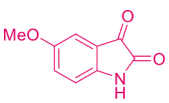
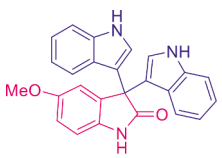
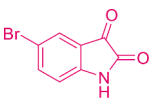
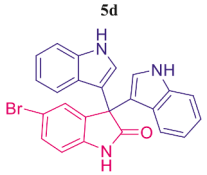
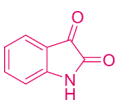
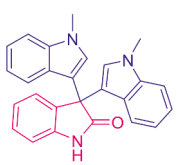
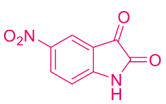
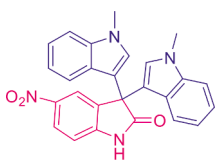
Table 2 (*continued*)

Entry	Aromatic aldehyde	Product	Yield[b] (%)	M.P. (°C) [lit]
9		 **3i**	86 (0.355)	205-206 [202–204] Mathavan et al. (2019)
10		 **3j**	86 (0.295)	72-74 (Zhang et al., 2005; Yu et al., 2014) Gao et al. (2017)
11		 **3k**	84 (0.310)	142-144 [141–143] Zhang et al. (2005)
12		 **3l**	90 (0.315)	202-204 [202–205] Seyedi et al. (2015)
13		 **3m**	92 (0.355)	210-212 [208–209] Li et al. (2011)
14		 **3n**	92 (0.366)	215-217 [216–218] Seyedi et al. (2015)
15		 **3o**	90 (0.325)	147-149 [170–173] Seyedi et al. (2015)
16		 **3p**	92 (0.350)	219-221 [218–219] Li et al. (2011)

[a] Reaction conditions: Aromatic aldehyde (1 mmol), indole (2 mmol), Bio extract of *Zingiber zerumbet* (5 mL) 5 min.
[b] Isolated quantity.

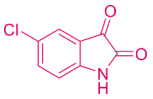
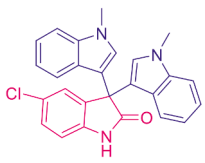
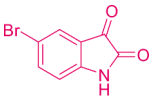
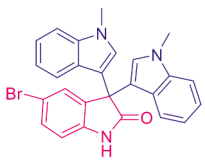
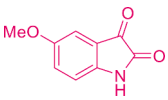
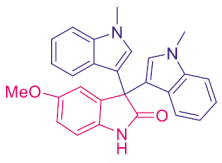
environmentally safe, and cheap organic transformations. Ultrasonic irradiation saves the reaction time and result in a significant improvement in the yields. These methods provide a good alternative to synthetics as well as those that require harsh reaction conditions. Therefore, this protocol highlights and follows various green chemistry principles such as avoiding toxic chemicals, harsh reaction conditions, the use of green solvents, and methodology.

Table 3
Synthesis of tris-indoline using natural surfactant of *Z. zerumbet* under ultrasound irradiation[a].

Entry	Isatin	Product	MP (°C) [Lit.]	Yield[b] (%)
1		 **5a**	314-316 [318–320] (Yu et al., 2014)	92 (0.676)
2		 **5b**	298-299 [281–282] (Yu et al., 2014)	88 (0.360)
3		 **5c**	297-299 [289–291] (Yu et al., 2014)	90 (0.360)
4		 **5d**	290-292 [290] Yu et al. (2014)	90 (0.355)
5		 **5e**	>300 [>300] Brahmachari and Banerjee (2014)	90 (0.394)
6		 **5f**	>300 [>300] Yuan et al. (2020)	92 (0.720)
7		 **5g**	>300 [332–333] (Alimohammadi et al., 2008)	88 (0.380)

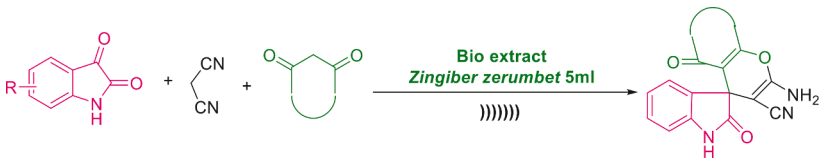
(*continued on next page*)

Table 3 (*continued*)

Entry	Isatin	Product	MP (°C) [Lit.]	Yield[b] (%)
8		 **5h**	295-297 [294–296] (Brahmachari and Banerjee, 2014)	90 (0.380)
9		 **5i**	>300 [>300] Brahmachari and Banerjee (2014)	88 (0.416)
10		 **5j**	>300 (Yuan et al., 2020)	90 (0.380)

[a] Reaction conditions: Isatin (1 mmol), Indole (2 mmol),/Bio extract of *Zingiber zerumbet* (5 mL), US irradiation RT.
[b] Isolated quantity.

Table 4
Optimization of reaction conditions for synthesis of spirooxindoles[a].



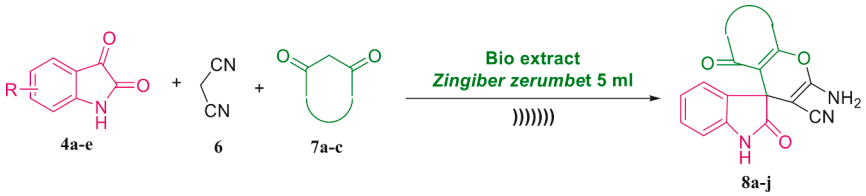
Entry	Solvent	T (°C)	Time (min/h)	Yield (%)
1	–	RT	24 h	trace
3	Water	RT	72 h	20
4	Ethanol	RT	24 h	40
5	Ethanol and Water (1:1)	RT	48 h	40
6	Methanol	RT	48 h	trace
7	Water	60	10 h	30
8	Water: ethanol	60	6 h	50
9	Ethanol	40	4 h	70
10	US	RT	30 min	trace
10	Extract of *Zingiber zerumbet,* US	RT	10 min	92
11	Extract of *Zingiber zerumbet,* US	40	15 min	90
1	Extract of *Zingiber zerumbet* and ethanol (1:1), US	RT	15 min	90

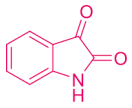
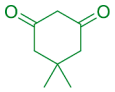
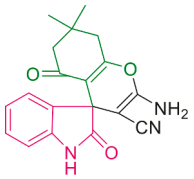
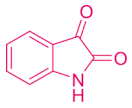
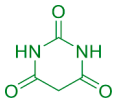
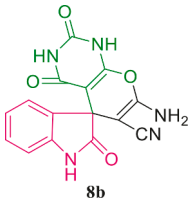
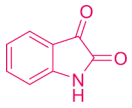
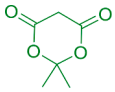
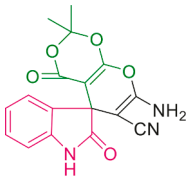
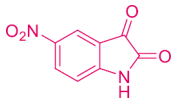
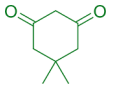
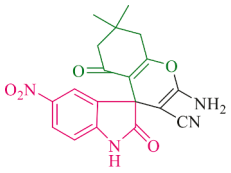
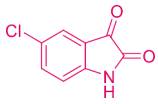
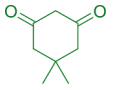
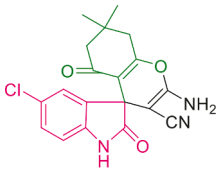
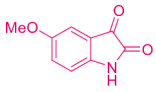
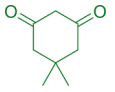
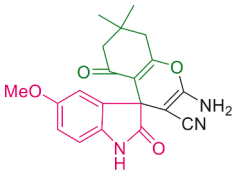
[b]Isolated yields.
[a] Reaction conditions: Isatin (1 mmol), malononitrile (1 mmol), and dimedone (1 mmol) solvent/Bio extract of *Zingiber zerumbet* (5 mL).

Author statement

We certify that we have participated sufficiently in the intellectual content, conception, and design and data collection/experimental work of this research or the analysis and interpretation of the data (when applicable), as well as the writing of the manuscript, to take public responsibility for it.

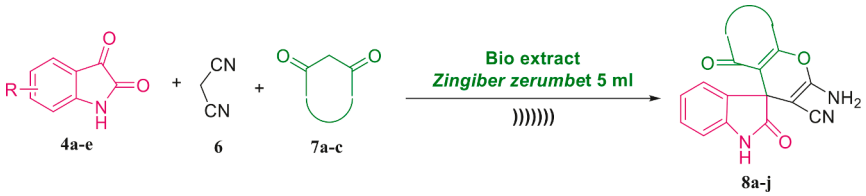
Table 5
Synthesis of spirooxindoles using natural surfactant of *Z. zerumbet* under ultrasound irradiation [a].

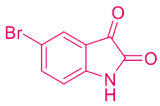
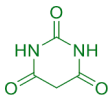
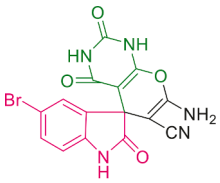
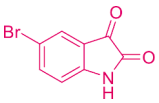
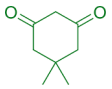
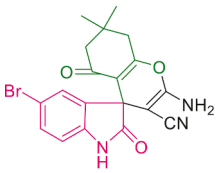
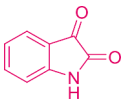
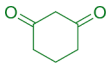
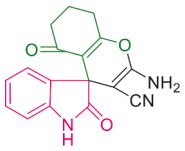
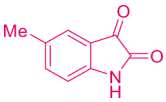
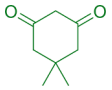
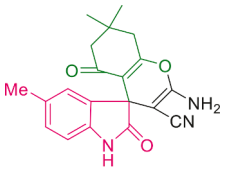


Entry	Isatin	Active methylene	Product	MP (°C) [Lit.]	Yield (%)[b]
1			 **8a**	286-288 [284–285] (Chai et al., 2011)	92 (0.246)
2			 **8b**	>300 [300–302] (Moradi and Ataei, 2017)	86 (0.280)
3			 **8c**	187-190 [182–189] (Azizi et al., 2014)	85 (0.290)
4			 **8d**	>300 [>300] (Chai et al., 2011)	94 (0.360)
5			 **8e**	290-292 [286–288] (Chai et al., 2011)	91 (0.336)
6			 **8f**	285-287 [287–289] (Chai et al., 2011)	91 (0.337)

(*continued on next page*)

Table 5 (*continued*)



Entry	Isatin	Active methylene	Product	MP (°C) [Lit.]	Yield (%)[b]
7			 8g	225-227 [223–225] (Moradi and Ataei, 2017)	90 (0.360)
8			 8h	>300 [307–308] (Zhang et al., 2017)	90 (0.326)
9			 8i	282-283 [277–278] (Chai et al., 2011)	92 (0.285)
10			 8j	281-283 [278–280] (Zhang et al., 2017)	93 (0.326)

[a] Reaction conditions: Isatin (1 mmol), malononitrile (1 mmol), active methylene (1 mmol), solvent/Bio extract of *Zingiber zerumbet* (5 mL), US irradiation RT.
[b] Isolated quantity.

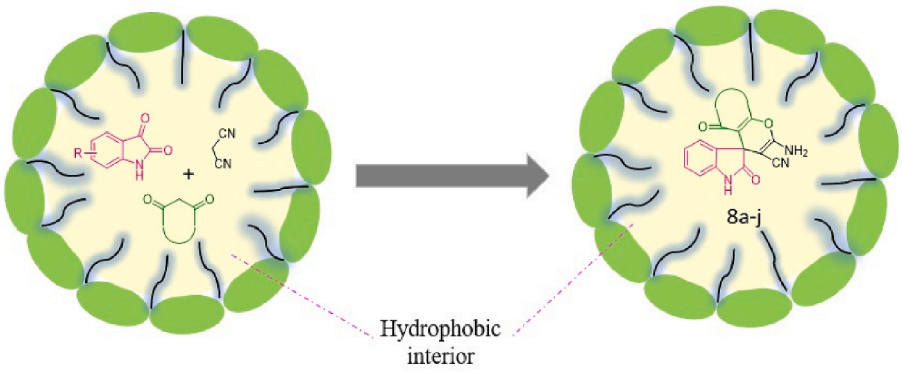


Fig. 7. Mechanistic role of micellar surfactant "*Zingiber zerumbet*" for spirooxindole synthesis.

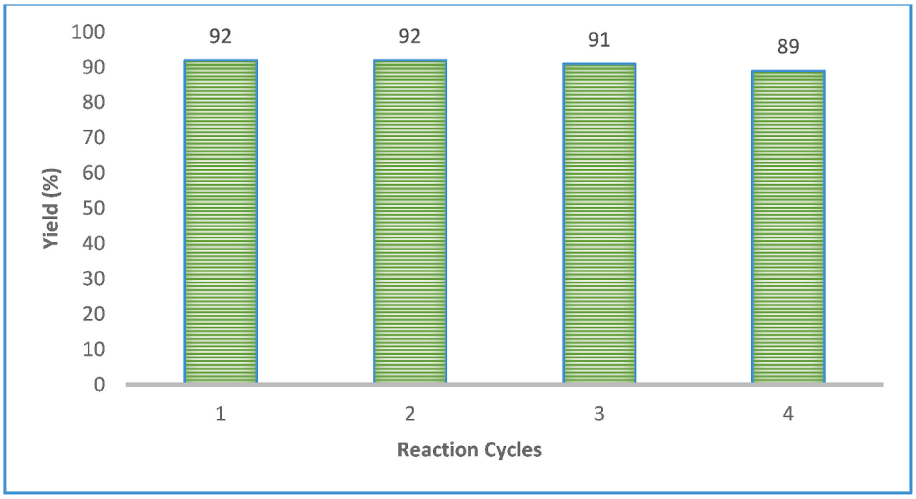


Fig. 8. Recyclability study of *Zingiber zerumbet* in the synthesis of bis(indolyl)methane.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

Acknowledgments

One of the authors, Aboli Sapkal, gratefully acknowledges the financial support from the Sarthi Research Fellowship, Government of Maharashtra. We gratefully acknowledge the financial support from the Department of Science and Technology (DST-SERB) for awarding major research projects under the scheme Empowerment and Equity Opportunities for Excellence in Science, the University Grant Commission (UGC), New Delhi (F. No. 43–104/2014 (SR) dated July 21, 2015) for awarding major research projects, the Rashtriya Uchchatar Shiksha Abhiyan (RUSA), and the Y. C. Institute of Science, Satara, for providing necessary facilities.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scp.2023.101228.

References

Alimohammadi, K., Sarrafi, Y., Tajbakhsh, M., 2008. $H_6P_2W_{18}O_{62}$: a green and reusable catalyst for the synthesis of 3,3-diaryloxindole derivatives in water. Monatshefte Für Chem. - Chem. Mon. 139 (9), 1037–1039. https://doi.org/10.1007/s00706-008-0885-5.

Allahresani, A., Taheri, B., Nasseri, M.A., 2018a. Synthesis of spirooxindole derivatives catalyzed by GN/SO_3H nanocomposite as a heterogeneous solid acid. Res. Chem. Intermed. 44 (11), 6979–6993. https://doi.org/10.1007/s11164-018-3535-5.

Allahresani, A., Taheri, B., Nasseri, M.A., 2018b. A green synthesis of spirooxindole derivatives catalyzed by SiO_2@g-C_3N_4 nanocomposite. Res. Chem. Intermed. 44 (2), 1173–1188.

Amini Moqadam, Z., Allahresani, A., Hassani, H., 2020. An efficiently and quickly synthesized NiO@gC_3N_4 nanocomposite-catalyzed green synthesis of spirooxindole derivatives. Res. Chem. Intermed. 46, 299–311.

Amrollahi, M.A., Kheilkordi, Z., 2016. $H_3PW_{12}O_{40}$-catalyzed one-pot synthesis of bis (indole) derivatives under silent and ultrasonic irradiation conditions in aqueous media. J. Iran. Chem. Soc. 13 (5), 925–929.

Azizi, N., Dezfooli, S., Hashemi, M.M., 2014. Greener synthesis of spirooxindole in deep eutectic solvent. J. Mol. Liq. 194, 62–67.

Brahmachari, G., Banerjee, B., 2014. Facile and one-pot access of 3,3-Bis(indol-3-yl)indolin-2-ones and 2,2-Bis(indol-3-yl)acenaphthylen-1(2H)-one derivatives via an eco-friendly pseudo-multicomponent reaction at room temperature using sulfamic acid as an organo-catalyst. ACS Sustain. Chem. Eng. 2 (12), 2802–2812. https://doi.org/10.1021/sc500575h.

Bugaenko, D.I., Karchava, A.V., Yurovskaya, M.A., 2019. Synthesis of indoles: recent advances. Russ. Chem. Rev. 88 (2), 99.

Chai, S.-J., Lai, Y.-F., Xu, J.-C., Zheng, H., Zhu, Q., Zhang, P.-F., 2011. One-pot synthesis of spirooxindole derivatives catalyzed by lipase in the presence of water. Adv. Synth. Catal. 353 (2–3), 371–375.

Chavan, H.V., Sirsat, D.M., Mule, Y.B., 2016. An environmentally benign synthesis of aryl-hydrazones with aqueous extract of Acacia pods as a natural surfactant type catalyst. Q. J. Iran. Chem. Commun. 4 (4), 359–490. . Serial No. 13, pp. 373–388.

Chavan, J.J., Kshirsagar, P.R., Pai, S.R., Pawar, N.V., 2018. Micropropagation, metabolite profiling, antioxidant activities and chromatographic determination of bioactive molecules across in vitro conditions and subsequent field cultivation stages of 'Shampoo Ginger'(*Zingiber zerumbet* L. Roscoe ex Sm). Biocatal. Agric. Biotechnol. 16, 79–89.

Chowdhury, S., Chafeev, M., Liu, S., Sun, J., Raina, V., Chui, R., Young, W., Kwan, R., Fu, J., Cadieux, J., 2011. "Discovery of XEN907, a spirooxindole blocker of NaV1. 7 for the treatment of pain,". Bioorg. Med. Chem. Lett. 21 (12), 3676–3681.

Deshmukh, R.R., Rajagopal, R., Srinivasan, K.V., 2001. Ultrasound promoted C–C bond formation: heck reaction at ambient conditions in room temperature ionic liquids. Chem. Commun. 17, 1544–1545.

Ding, K., Lu, Y., Nikolovska-Coleska, Z., Wang, G., Qiu, S., 2006. "Structure-based design of spiro-oxindoles as potent, specific small-molecule inhibitors of the MDM2-p53 interaction,". J. Med. Chem. 49 (12), 3432–3435.
Duarte, A., Cunico, W., Pereira, C.M., Flores, A.F., Freitag, R.A., Siqueira, G.M., 2010. Ultrasound promoted synthesis of thioesters from 2-mercaptobenzoxa (thia) zoles. Ultrason. Sonochem. 17 (2), 281–283.
Dwivedi, K.D., Marri, S.R., Nandigama, S.K., Chowhan, L.R., 2018. Exploring TiO_2NPs as efficient catalyst for 1, 6 Michael addition of 3-methyl-5-pyrazolone on 3-methyl-4-nitro-5- alkenyl isoxazoles and rapid synthesis of 3, 3-bis (indolyl) oxindoles in water. Synth. Commun. 48 (20), 2695–2707.
Gao, G., Han, Y., Zhang, Z.-H., 2017. Catalyst free synthesis of bis (indolyl) methanes and 3, 3-bis (indolyl) oxindoles in aqueous ethyl lactate. ChemistrySelect 2 (35), 11561–11564.
Hasani, H., Irizeh, M., 2018. One-pot synthesis of spirooxindole derivatives catalyzed by $ZnFe_2O_4$ as a magnetic nanoparticles. Asian J. Green Chem. 2 (2), 85–95.
Hemmat, K., Nasseri, M.A., Allahresani, A., Ghiami, S., 2019. $CoFe_2O_4$@SiO_2: a magnetically recyclable heterogeneous catalyst for the synthesis of spirooxindole derivatives. J. Organomet. Chem. 903, 120996.
Hote, B.S., Siddiqui, T.A., Pisal, P.M., Mandawad, G.G., 2022. Green approach of solvent-and catalyst free synthesis of bis (indolyl) methanes under visible light irradiation. Polycycl. Aromat. Comp. 42 (4), 1761–1769.
Huang, G.-C., Chien, T.-Y., Chen, L.-G., Wang, C.-C., 2005. Antitumor effects of zerumbone from *Zingiber zerumbet* in P-388D1 cells in vitro and in vivo. Planta Med. 71 (3), 219–224.
Huang, W., Nang, L., Li, X., Yuan, L., Ma, Y., Liang, D., 2015. Bromine/para-Toluenesulfonic acid-catalyzed synthesis of 3, 3-bis (indole-3-yl) indoline-2-(1H)-ones by condensing indoles with isatins. Chin. J. Chem. 33 (10), 1167–1172.
Hussein, E.M., Abdel-Monem, M.I., 2011. Regioselective synthesis and anti-inflammatory activity of novel dispiro [pyrazolidine-4, 3′-pyrrolidine-2′, 3 ″-indoline]-2 ″, 3, 5-triones. ARKIVOC (Gainesville, FL, U. S.) 10, 85–98.
Ingrand, S., Barrier, L., Lafay-Chebassier, C., Fauconneau, B., Page, G., Hugon, J., 2007. The oxindole/imidazole derivative C16 reduces in vivo brain PKR activation. FEBS Lett. 581 (23), 4473–4478.
Jadhav, S.N., Kumbhar, A.S., Rode, C.V., Salunkhe, R.S., 2016. Ligand-free Pd catalyzed cross-coupling reactions in an aqueous hydrotropic medium. Green Chem. 18 (7), 1898–1911.
Joshi, R.S., Mandhane, P.G., Diwakar, S.D., Gill, C.H., 2010. Ultrasound assisted green synthesis of bis (indol-3-yl) methanes catalyzed by 1-hexenesulphonic acid sodium salt. Ultrason. Sonochem. 17 (2), 298–300.
S. Kamat, A. Mane, A. Patil, T. Lohar, and R. Salunkhe, "Hydrotrope assisted synthesis of spirooxindoles and di (indolyl) oxindoles at room temperature," J. Seybold Rep. ISSN NO, vol. 1533, p. 9211..
Karimi, A.R., Sedaghatpour, F., 2010. "Novel mono-and bis (spiro-2-amino-4H-pyrans): alum-catalyzed reaction of 4-hydroxycoumarin and malononitrile with isatins, quinones, or ninhydrin,". Synthesis 2010 (10), 1731–1735.
Kasar, S.B., Thopate, S.R., 2018. Synthesis of bis (indolyl) methanes using naturally occurring, biodegradable itaconic acid as a green and reusable catalyst. Curr. Org. Synth. 15 (1), 110–115.
Kaur, M., Singh, M., Chadha, N., Silakari, O., 2016. Oxindole: a chemical prism carrying plethora of therapeutic benefits. Eur. J. Med. Chem. 123, 858–894.
Khan, J., Tyagi, A., Yadav, N., Mahato, R., Hazra, C.K., 2021. Lambert salt-initiated development of Friedel–crafts reaction on isatin to access distinct derivatives of oxindoles. J. Org. Chem. 86 (24), 17833–17847.
Khurana, J.M., Yadav, S., 2012. Highly monodispersed PEG-stabilized Ni nanoparticles: proficient catalyst for the synthesis of biologically important spiropyrans. Aust. J. Chem. 65 (3), 314–319.
Koga, A.Y., Beltrame, F.L., Pereira, A.V., 2016. Several aspects of *Zingiber zerumbet*: a review. Rev. Bras. Farmacogn. 26, 385–391.
Kumbhar, A., Kamble, S., Barge, M., Rashinkar, G., Salunkhe, R., 2012. Brönsted acid hydrotrope combined catalyst for environmentally benign synthesis of quinoxalines and pyrido[2,3-b]pyrazines in aqueous medium. Tetrahedron Lett. 53 (22), 2756–2760. https://doi.org/10.1016/j.tetlet.2012.03.097.
Kumbhar, A., Jadhav, S., Shejwal, R., Rashinkar, G., Salunkhe, R., 2016. Application of novel multi-cationic ionic liquids in microwave assisted 2-amino-4 H-chromene synthesis. RSC Adv. 6 (23), 19612–19619.
Li, J.-T., Sun, M.-X., He, G.-Y., Xu, X.-Y., 2011. Efficient and green synthesis of bis (indolyl) methanes catalyzed by ABS in aqueous media under ultrasound irradiation. Ultrason. Sonochem. 18 (1), 412–414.
Mathavan, S., Kannan, K., Yamajala, R.B., 2019. Thiamine hydrochloride as a recyclable organocatalyst for the synthesis of bis (indolyl) methanes, tris (indolyl) methanes, 3, 3-di (indol-3-yl) indolin-2-ones and biscoumarins. Org. Biomol. Chem. 17 (44), 9620–9626.
Mehrasbi, E., Sarrafi, Y., Tajbakhsh, M., 2015. Efficient synthesis of 3, 3-di (indolyl) oxindoles catalyzed by sulfonic acid-functionalized mesoporous silica nanoparticles (SAMSNs) in aqueous media. Res. Chem. Intermed. 41 (9), 6777–6787.
Mei, G.-J., Shi, F., 2018. Catalytic asymmetric synthesis of spirooxindoles: recent developments. Chem. Commun. 54 (50), 6607–6621.
Molla, A., Ranjan, S., Rao, M.S., Dar, A.H., Shyam, M., Jayaprakash, V., Hussain, S., 2018. Borax catalyzed domino synthesis of highly functionalised spirooxindole and chromenopyridine derivatives: X-ray structure, hirshfeld surface analysis and molecular docking studies. ChemistrySelect 3 (30), 8669–8677.
Moradi, L., Ataei, Z., 2017. Efficient and green pathway for one-pot synthesis of spirooxindoles in the presence of CuO nanoparticles. Green Chem. Lett. Rev. 10 (4), 380–386.
Mortikov, V.Y., Litvinov, Y.M., Shestopalov, A.A., Rodinovskaya, L.A., Shestopalov, A.M., 2008. Versatile three-component synthesis of 2′-amino-1, 2-dihydrospiro [(3H)-indole-3, 4′-(4′ H)-pyran]-2-ones. Russ. Chem. Bull. 57 (11), 2373–2380.
Mote, K., Pore, S., Rashinkar, G., Kambale, S., Kumbhar, A., Salunkhe, R., 2010. "Acacia concinna pods: as a green catalyst for highly efficient synthesis of acylation of amines,". Arch. Appl. Sci. Res. 2 (3), 74–80.
Nigam, I.C., Levi, L., 1963. Column and gas chromatographic analysis of oil of wild ginger: identification and estimation of some new constituents. Can. J. Chem. 41 (7), 1726–1730.
Paira, P., Hazra, A., Kumar, S., Paira, R., Sahu, K., Naskar, S., Sahu, P., Mondal, S., Maity, A., Banerjee, S., Mondal, N., 2009. Efficient synthesis of 3, 3-diheteroaromatic oxindole analogues and their in vitro evaluation for spermicidal potential. Bioorg. Med. Chem. Lett. 19 (16), 4786–4789.
Patil, S.P., Jadhav, S.N., Rode, C.V., Shejwal, R.V., Kumbhar, A.S., 2020. Bio-surfactant: a green and environmentally benign reaction medium for ligand-free Pd-catalyzed Mizoroki–Heck cross-coupling reaction in water. Transit. Met. Chem. 45 (6), 403–411.
Phongpaichit, S., Vuddhakul, V., Subhadhirasakul, S., Wattanapiromsakul, C., 2006. Evaluation of the antimycobacterial activity of extracts from plants used as self-medication by AIDS patients in Thailand. Pharm. Biol. 44 (1), 71–75.
Rahimi, S., Amrollahi, M.A., Kheilkordi, Z., 2015. An efficient ultrasound-promoted method for the synthesis of bis (indole) derivatives. Compt. Rendus Chem. 18 (5), 558–563.
Sabu, M., 2003. Revision of the genus Zingiber in South India. Folia Malays 4 (1), 25–52.
Salimi, M., Sandaroos, R., Esmaeli-nasrabadi, F., 2021. Efficient synthesis of spirooxindole derivatives by magnetic and recyclable $CaFe_2O_4$@ MgAl-LDH. J. Iran. Chem. Soc. 18 (1), 1–12.
Sapkal, A., Kamble, S., 2020. Sodium toluene-4-sulfonate as a reusable and ecofriendly catalyst for greener synthesis of 5-aminopyrazole-4-carbonitrile in aqueous medium. J. Heterocycl. Chem. 57 (10), 3597–3604.
Sapkal, A., Attar, S., Kadam, A., Gaikwad, P., Kamble, S., 2022. Clean and green approach for synthesis of various derivatives of [1, 3] oxazine in sustainable aqueous hydrotropic medium. Polycycl. Aromat. Comp. 1–13.
Sarrafi, Y., Alimohammadi, K., Sadatshahabi, M., Norozipoor, N., 2012. An improved catalytic method for the synthesis of 3,3-di(indolyl)oxindoles using Amberlyst 15 as a heterogeneous and reusable catalyst in water. Monatshefte Für Chem. - Chem. Mon. 143 (11), 1519–1522. https://doi.org/10.1007/s00706-012-0723-7.
Seyedi, N., Khabazzadeh, H., Saeednia, S., 2015. $ZnCl_2$/Urea as a deep eutectic solvent for the preparation of bis (indolyl) methanes under ultrasonic conditions. Synth. React. Inorg., Met.-Org., Nano-Met. Chem. 45 (10), 1501–1505.
Shanthi, G., Subbulakshmi, G., Perumal, P.T., 2007. A new $InCl_3$-catalyzed, facile and efficient method for the synthesis of spirooxindoles under conventional and solvent-free microwave conditions. Tetrahedron 63 (9), 2057–2063.
Sharma, R.K., Sharma, C., 2010. A highly efficient synthesis of oxindoles using a functionalized silica gel as support for indium (III) acetylacetonate catalyst in an

aqueous-acetonitrile medium. J. Mol. Catal. Chem. 332 (1–2), 53–58.
Shirini, F., Khaligh, N.G., 2013. Succinimide-N-sulfonic acid catalyzed synthesis of bis (indolyl) methane and coumarin derivatives under mild conditions. Chin. J. Catal. 34 (10), 1890–1896.
Singh, H., Sindhu, J., Khurana, J.M., Sharma, C., Aneja, K.R., 2014. Ultrasound promoted one pot synthesis of novel fluorescent triazolyl spirocyclic oxindoles using DBU based task specific ionic liquids and their antimicrobial activity. Eur. J. Med. Chem. 77, 145–154.
Sriphanaa, U., Pitchuanchoma, S., Kongsaereeb, P., Yenjaia, C., 2013. Antimalarial activity and cytotoxicity of zerumbone derivatives. Sci. Asia 39, 95–99.
Srivastava, R.M., Rawn Filho, Silva, C.A., Bortoluzzi, A., 2009. Ultrason. Sonochem. 16, 737.
Stefani, H.A., Pereira, C.M., Almeida, R.B., Braga, R.C., Guzen, K.P., Cella, R., 2005. A mild and efficient method for halogenation of 3, 5-dimethyl pyrazoles by ultrasound irradiation using N-halosuccinimides. Tetrahedron Lett. 46 (40), 6833–6837.
Swain, B., Singh, P., Angeli, A., Sahoo, S., Yaddanapudi, V., Supuran, C., Ariffudin, M., 2022. Efficient one-pot synthesis of 3,3-di(indolyl)indolin-2-ones from isatin and indole catalyzed by $VOSO_4$ as non-sulfonamide carbonic anhydrase inhibitors. Anti- Cancer Agents Med. Chem.- Anti-Cancer Agents 22 (13), 2358–2366. https://doi.org/10.2174/1871520622666220202112014.
Wang, S.-Y., Ji, S.-J., 2006. Facile synthesis of 3, 3-di (heteroaryl) indolin-2-one derivatives catalyzed by ceric ammonium nitrate (CAN) under ultrasound irradiation. Tetrahedron 62 (7), 1527–1535.
Wang, L.-M., Jiao, N., Qiu, J., Yu, J.-J., Liu, J.-Q., Guo, F.-L., Liu, Y., 2010. Sodium stearate-catalyzed multicomponent reactions for efficient synthesis of spirooxindoles in aqueous micellar media. Tetrahedron 66 (1), 339–343.
Watanabe, H., Arisawa, M., Narusuye, K., Alam, M., Yamamoto, K., 2012. Synthesis and biological evaluation of novel oxindole derivatives for imaging neurofibrillary tangles in Alzheimer's disease. Bioorg. Med. Chem. Lett. 22 (17), 5700–5703.
Wu, Y.-J., 2010. New indole-containing medicinal compounds. In: Gribble, G.W. (Ed.), Heterocyclic Scaffolds II: Reactions and Applications of Indoles. Springer, Berlin, Heidelberg, pp. 1–29. https://doi.org/10.1007/7081_2010_37Topics in Heterocyclic Chemistry.
Wu, Z., Wang, G., Yuan, S., Wu, D., Liu, W., 2019. Synthesis of bis (indolyl) methanes under dry grinding conditions promoted by a Lewis acid–surfactant–SiO_2-combined nanocatalyst. Green Chem. 21 (13), 3542–3546.
Yadav, J.S., SubbaReddy, B.V., Gayathri, K.U., Meraj, S., Prasad, A.R., 2006. Bismuth (III) triflate catalyzed condensation of isatin with indoles and pyrroles: a facile synthesis of 3, 3- diindolyl-and 3, 3-dipyrrolyl oxindoles. Synthesis 2006 (24), 4121–4123.
Yasuda, D., Takahashi, K., Ohe, T., Nakamura, S., Mashino, T., 2013. Antioxidant activities of 5-hydroxyoxindole and its 3-hydroxy-3-phenacyl derivatives: the suppression of lipid peroxidation and intracellular oxidative stress. Bioorg. Med. Chem. 21 (24), 7709–7714.
Yeung, B., Zou, B., Rottmann, M., Lakhminarayana, S., Ang, S., Leyong, S., Tan, J., Wong, J., Keller-Maerki, S., Fischli, C., Goh, A., Schmitt, E., Krastel, P., Francotee, E., Kuhen, K., Ploufee, D., Henson, K., Wagner, T., Winzeler, E., Petersen, F., Brun, R., Dartois, V., Diagana, T., Keller, T., 2010. Spirotetrahydro β-carbolines (spiroindolones): a new class of potent and orally efficacious compounds for the treatment of malaria. J. Med. Chem. 53 (14), 5155–5164.
Yong, S.R., Ung, A.T., Pyne, S.G., Skelton, B.W., White, A.H., 2007. Synthesis of novel 3′- spirocyclic-oxindole derivatives and assessment of their cytostatic activities. Tetrahedron 63 (25), 5579–5586.
Yu, F., Okamto, S., Nakasone, K., Adachi, K., Matsuda, S., 2008. "Molecular cloning and functional characterization of α-humulene synthase, anpossible key enzyme of zerumbone biosynthesis in shampoo ginger (*Zingiber zerumbet* Smith),". Planta 227 (6), 1291–1299.
Yu, J., Shen, T., Lin, Y., Zhou, Y., Song, Q., 2014. Rapid and efficient synthesis of 3, 3-di (1 H-indol-3-yl) indolin-2-ones and 2, 2-di (1 H-indol-3-yl)-2 H-acenaphthen-1-ones catalyzed by p-TSA. Synth. Commun. 44 (14), 2029–2036.
Yu, B., Yu, D.-Q., Liu, H.-M., 2015. Spirooxindoles: promising scaffolds for anticancer agents. Eur. J. Med. Chem. 97, 673–698.
Yuan, X., Wang, S., Cheng, J., Yu, B., Liu, H.-M., 2020. HFIP-promoted catalyst-free cascade reactions for the synthesis of biologically relevant 3, 3-di (indolyl) indolin-2-ones from indoles and isatins. Chin. Chem. Lett. 31 (9), 2465–2468.
Zakaria, Z.A., Mohamad, A.S., Ahmad, M.S., Mokhtar, A.F., Israf, D.A., Lajis, N.H., Sulaiman, M.R., 2011. Preliminary analysis of the anti-inflammatory activity of essential oils of *Zingiber zerumbet*. Biol. Res. Nurs. 13 (4), 425–432.
Zhang, Z.-H., Yin, L., Wang, Y.-M., 2005. "An efficient and practical process for the synthesis of bis(indolyl)methanes catalyzed by zirconium tetrachloride,". Synthesis 2005 (12), 1949–1954. https://doi.org/10.1055/s-2005-869959.
Zhang, M., Fu, Q.Y., Gao, G., He, H.Y., Zhang, Y., Wu, Y.-S., Zhang, Z.-H., 2017. Catalyst-free, visible-light promoted one-pot synthesis of spirooxindole-pyran derivatives in aqueous ethyl lactate. ACS Sustain. Chem. Eng. 5 (7), 6175–6182.
Zhou, L.-M., Qu, R.-Y., Yang, G.-F., 2020. An overview of spirooxindole as a promising scaffold for novel drug discovery. Expet Opin. Drug Discov. 15 (5), 603–625.
Zhu, S.-L., Ji, S.-J., Zhang, Y., 2007. A simple and clean procedure for three-component synthesis of spirooxindoles in aqueous medium. Tetrahedron 63 (38), 9365–9372.
Ziarani, G.M., Badiei, A., Mousavi, S., Lashgari, N., Shahbazi, A., 2012. Application of amino- functionalized SBA-15 type mesoporous silica in one-pot synthesis of spirooxindoles. Chin. J. Catal. 33 (11–12), 1832–1839.