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A microwave assisted greener protocol for the regio- and stereoselective synthesis of trispiropyrrolidine derivatives: An Ionic liquid mediated three component reaction

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Abstract: A highly efficient regio- and stereoselective microwave assisted ionic liquid mediated multi-component reaction of 7,9-bis[(E)arylidene]-1,4-dioxa-spiro[4,5]decane-8-ones, sarcosine and substituted isatin are illustrated to achieve trispiropyrrolidine derivatives synthesis. The main features of this procedure are the use of butylmethylimidazolium tetrafluoroborate ([Bmim]BF_4) ionic liquid as a solvent also acts as a catalyst, mild reaction conditions, high to excellent product yield, convenient operation and easy workup procedures. Most important things are that the use of ionic liquid makes this protocol environmental friendly, gives higher atom economy, and shortened the reaction time.

Keywords: Trispiro[indoline-3,2′-pyrrolidines] derivatives, stereoselectivity

Introduction:

In the context of a global energy requirement there are growing an awareness of pressing need for greener, more sustainable technologies. The development of efficient, practical and environmentally friendly methods for the construction of complex compounds are one of the main priorities of modern organic chemistry.[1] Sightseeing the efficient approaches for the construction of biologically potent heterocyclic compounds with high structural diversity and complexity is an unending task in synthetic organic chemistry.[2] The evolution of novel methodologies help in the optimal design and operation of industrial and pharmaceutical production of fine chemicals and pharmaceutics taking into account multiple objectives such as the minimization of the environmental impact, the investment and the cost of the product.[3] Alternative energy sources, alternative solvents and multicomponent strategy are effective tools in current drug discovery process in terms of lead finding and lead optimization.[4] In the midst of them microwave assisted technique blossomed into an efficient energy source for variety of application in organic synthesis and create new dimension to greener chemistry because of

their unique advantages that are significant rate enhancements, ease of manipulation and work-up, high yield, clean reaction, as well as less environmental polluting process.[5-6] Although the MW-assisted reactions in organic solvent have developed rapidly, the focus is now shifted to environmentally friendlier methods, which explore the using of MW irradiation in conjugation and solvent free conditions or benign reaction media.[7]

The use of alternative reaction media is also another aspect that circumvents the problems associated with many of the traditional volatile organic solvent also provides opportunities for facilitating the recovery and recycling of the catalyst. Over the past decades, ionic liquids (ILs) have attract much interest as efficient and ecofriendly reaction media which are different from classical conventional ones owing to their marvelous properties such as very high heat capacity, negligible vapor pressure, low toxicity, high polarity, low inflammability, high thermal and chemical stability, solvent power, reusability, and structural versatility. [8] Such properties lead to better catalysts and solvents for a variety of reactions. The involvement of reactant molecules in solvent cavities due to the inner pressure created by ionic environment of the ionic liquid is probably responsible for the rate enhancement. [8] Amongst the [Bmim]BF_4 ionic liquid have also been employed as acid catalysts and solvent to perform multicomponent reaction. [9]

The use of microwave irradiation as a heating source in combination with ILs as catalyst and solvent for the organic synthetic transformation opened a new area for investigation during the past several years. Through this combination, ionic liquids can absorb the irradiation very efficiently and transfer energy quickly in a way that has potential to efficient catalyzes some reactions. [10-11]

The spirooxindole skeletons in particular have captured tremendous attention among synthetic and medicinal chemists, due to their prevalence in a broad spectrum of natural product phytochemicals either in alkaloids, lactones or terpenoids [12] as well as medicinal agent. In fact, these derivatives have been described with diverse biological activities, ranging from anti-tumor, antimicrobial, anti-HIV, antipyretics agents to sodium channel blockers and antimalarials. Representative member of this group are alkaloids spirotryprostanins, mitraphylline, Horsifiline, coerulescine, elacomine, pteropodine, formosanine, rychnophyilline, isorhyncophylline, strychnofoline, and alstonisine etc. (**Fig. 1**) which display a broad range of biological activity. [13]

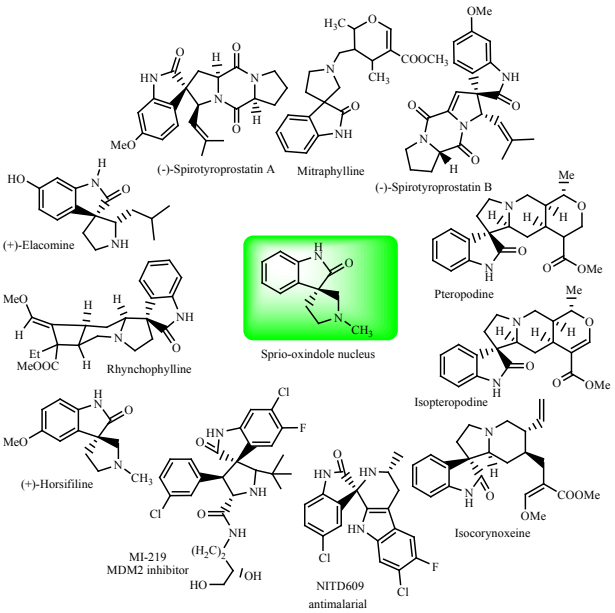


Fig. 1: Spiro-oxindole nucleus containing natural product and drugs

For example, spirotryprostatins **A** and **B** isolated from the fermentation broth of *Aspergillus fumigatus*, have been shown to completely inhibit the G2/M progression of cell division in mammalian tsFT210 cells.[13a, 14] Furthermore, the natural product isopteropodine has been shown to modulate the function of muscarinic and serotonin receptors.[15] In addition,

alstonisine, a natural alkaloid, was firstly isolated from *Alstonia muelleriana* and several biomimetic analogs of alstonisine have been investigated.[16] From the last two decades; we have perceived great deal of attention towards the development of creative methodologies for the generation of diverse spirooxindole moieties. Specifically, numerous multifunctional polycyclic spirooxindole compounds, highlighting organizational complication with distinct 3-D structure, have been established[17-21] to correlate with a wide range of biological properties and pharmacological activities (**Fig. 2**) such as antimicrobial[22], inhibitors of human NK-I receptor and potential antileukemic and anticonvulsant agents [23], and anticancer [24, 23] antimicrobial[25], antitubercular and inhibitory activity against acetyl cholinesterase (AChE) [26], antidiabetic activity [27], anti-inflammatory. [28]

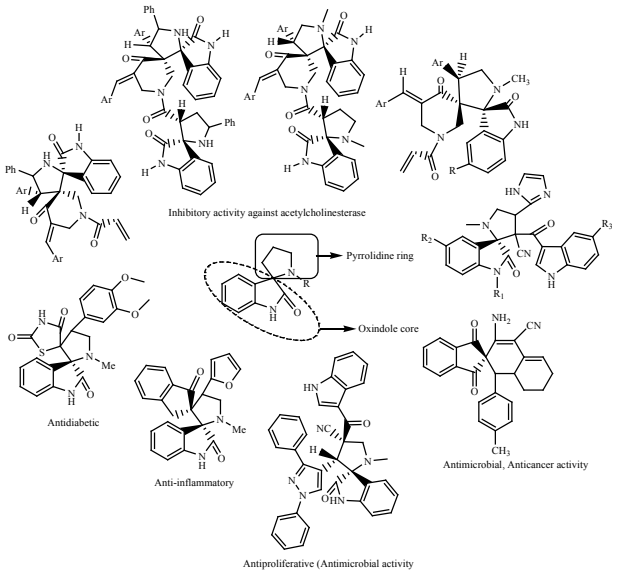
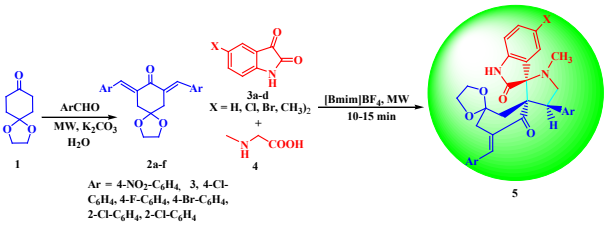


Fig 2. Some biologically important compounds containing spiro[pyrrolidine-2,3'-oxindole] core

As a consequence there is a huge interest in industry and academia to develop novel spiro-oxindole with interesting biological activities. Various synthetic methods to produce spiroheterocyclic compound have been reported. [29] In addition, 1,3-dioxolane derivatives having important chemical utilities, with interesting biophysical properties. *Itraconazole* containing 1,3-dioxolane pharmacophore possesses potent antiangiogenic activity both '*in vitro*' and '*in vivo*' [30]. In this context, as our continuous interest in developing new synthetic methods for the synthesis of pharmaceutically compounds[4(a& b), 9, 31], we envisioned that a 1,3-dipolar cycloaddition reaction between 7,9-bis[(E)arylidene]-1,4-dioxa-spiro[4,5] decane-8-ones, sarcosine and substituted isatins is described to achieve trispiropyrrolidine derivatives in ionic liquid (**Scheme 1**). Although each of the recent methods of the cycloaddition reactions had their own merits, but some methods are weakened by at least one limitation, such as low yield, complicated workup procedure, technical intricacy and no recovery of catalyst and solvent. Therefore, the development of a simple and efficient method for synthesis of trispirooxindole derivatives *via* 1,3-dipolar cycloaddition reactions addressing the management of the above mentioned drawbacks would be an interesting challenge.

In as much as the synthesis of spiroheterocyclic compounds by the 1,3-dipolar cycloaddition of azomethineylides and arylidene derivatives are known[32], but to the best of our knowledge, there is no report for the microwave assisted ionic liquid mediated design and synthesis of trispiropyrrolidine derivatives using isatin, sarcosine and bisarylidene substituted spiro[4,5] decan-8-one in so far.



Scheme 1. Synthesis of trispiro-oxindole derivatives

We have explored the improved methodology

[33] for the synthesis of trispiro[indoline-3,2′-pyrrolidine] derivatives using ionic liquid under microwave irradiation. Utilization of our improved method reduced the reaction time with a concomitant increase in the yield and recovery of the solvent etc.

Materials and Methods

Analytical grade solvents and commercially available reagents were used without further purification. The melting points of all compounds were determined on a Toshniwal apparatus in capillary and uncorrected. The purity of compounds was checked on thin layers of silica Gel-G coated glass plates and hexane:ethyl acetate (7:3) as eluent. IR spectra were recorded on a Shimadzu FT IR-8400S spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in dimethyl sulfoxide (DMSO-d_6) as a solvent on a Bruker Avance spectropho-tometer at 400 and 100 MHz, respectively. Chemical shifts are expressed in parts per million (ppm) using tetramethylsilane (TMS) as an internal standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = trip-let, q = quartet, m = multiplet. The Mass spectra of representative compounds were obtained using Agilent 1100 series MSD. The microwave-assisted reactions were carried out in a MAS-II microwave oven (2450 MHz, Sineo Microwave Chemistry Technology Company, Shanghai, China) with a maximum power output of 1000 W. This system is equipped with a power and temperature feedback control switch.

General procedure for the synthesis of trispiro-pyrrolidine 5

An equimolar mixture of appropriate 7,9-bis[(E) arylidene]-1,4-dioxa-spiro[4,5]decane-8-ones **2a-f** (1 mmol), isatin **3a-d** (1 mmol), and sarcosine **4** (1 mmol) and [Bmim]BF_4 ionic liquid (2–3 mL) under microwaves. All these reactions were carried out by microwave irradiation for 10-15 min. at the power level 250 W and at the temperature of 150° C which was recorded by the temperature probe of the microwave. After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3x10 mL). The combined ether extracts were concentrated in vacuum at 80 °C overnight. For further purification, the solid products were recrystallized from ethanol and the similar procedure was followed for the synthesis of all the products without any need for column chromatography. All the synthesized compounds were well characterized by ^{1}H NMR, ^{13}C NMR, and Mass analysis.

Spectral analysis:

Compound 5a: IR (KBr, ν_{max}): 2875, 1720, 1690 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.64 (d, 1H, J = 14.8 Hz), 1.94 (s, 3H, N-CH_3), 2.44-2.51 (m, 2H), 2.58-2.62 (m, 2H), 3.02-3.08 (m, 1H), 3.33-3.37 (m, 1H), 3.42-3.64 (m, 4H, $(OCH_2)_2$), 4.70 (t, 1H, J = 9.2 Hz), 6.71-7.67 (m, 11H, Ar-H and = CH-Ar), 10.67 (s, 1H, NH); ^{13}C NMR (100 MHz): δ 34.50, 35.68, 37.57, 47.93, 56.86, 61.37, 63.41, 64.35 (spiro C), 77.08 (spiro C), 105.22 (spiro C), 109.25, 121.23, 124.65, 127.23, 129.21, 129.49, 129.96, 130.56, 130.77, 131.19, 131.84, 132.44, 134.93, 135.26, 135.45, 135.56, 140.72, 142.88, 176.21 (C=O), 198.51 (C=O). MS (m/z): 643.06 $[M+H]^+$.

Compound 5b: IR (KBr, ν_{max}): 2860, 1700, 1695 cm^{-1}; ^{1}H NMR (400 MHz): δ 1.66 (d, 1H, J = 14.8 Hz), 1.96 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 2.13 (s, 3H, N-CH_3), 2.47-2.63 (m, 4H), 2.97-3.00 (m, 1H), 3.34-3.8 (m, 1H), 3.49-3.61 (m, 4H, $(OCH_2)_2$), 4.70 (t, 1H, J = 8.8 Hz), 6.65-7.73 (m, 9H, Ar-H and = CH-Ar), 10.62 (s, 1H, NH); ^{13}C NMR (100 MHz): δ 16.09, 20.60, 34.73, 35.60, 37.67, 47.80, 56.97, 61.65, 63.48, 64.39 (spiro C), 77.71 (spiro C), 105.27 (spiro C), 118.18, 124.27, 125.23, 129.50, 129.77, 129.98, 130.53, 130.65, 130.85, 130.91, 131.24, 133.77, 135.34, 135.83, 138.93, 140.88, 176.87 (C=O), 198.39 (C=O). MS (m/z): 671 $[M+H]^+$.

Compound 5c: IR (KBr, ν_{max}): 2870, 1720, 1680 cm^{-1}; ^1H NMR (400 MHz): δ 1.69 (d, 1H, J = 14.8 Hz), 1.99 (s, 3H, N-CH_3), 2.23-2.32 (m, 4H), 3.00-3.12 (m, 1H), 3.32-3.37 (m, 1H), 3.47-3.64 (m, 4H, $(OCH_2)_2$), 4.73 (t,1H, J = 8.8 Hz), 6.63-7.78 (m, 10H, Ar-H and = CH-Ar), 10.65 (s, 1H, NH); ^{13}C NMR (100 MHz): δ 34.64, 35.63, 37.59, 46.85, 56.86, 61.67, 63.42, 64.47 (spiro C), 77.77 (spiro C), 105.35 (spiro C), 110.32, 118.15, 121.25, 123.33, 128.25, 128.87, 128.76, 129.53, 129.65, 130.56, 130.77, 131.37, 133.64, 134.34, 136.83, 139.93, 141.86, 176.27 (C=O), 198.33 (C=O). MS (m/z): 677 $[M+H]^+$.

Compound 5d: IR (KBr, ν_{max}): 2900, 1720, 1680 cm^{-1}; ^1H NMR (400 MHz): δ 1.69 (d, 1H, J = 14.8 Hz), 1.99 (s, 3H, N-CH_3), 2.45-2.57 (m, 4H), 2.83-2.99 (m, 1H), 3.32-3.40 (m, 1H), 3.45-3.56 (m, 4H, $(OCH_2)_2$), 4.84 (t, 1H, J = 9.2 Hz), 6.65-8.30 (m, 13H, Ar-H and = CH-Ar), 10.63 (s, 1H, NH); ^{13}C NMR (100 MHz): δ 34.24, 35.74, 37.87, 48.80, 56.84, 61.68, 63.45, 64.26 (spiro C), 77.89 (spiro C), 105.17 (spiro C), 118.47, 124.77, 125.26, 129.34, 129.89, 130.33, 130.55, 131.26, 133.46, 135.43, 135.75, 138.95, 141.52, 142.36, 145.39, 147.65, 176.35 (C=O), 198.74 (C=O). MS (m/z): 597 $[M+H]^+$.

Compound 5e: IR (KBr, ν_{max}): 2875, 1717, 1682 cm^{-1}; ^1H NMR (400 MHz): δ 1.683 (d, 1H, J = 14.8 Hz), 1.99 (s, 3H, CH_3), 2.043 (s, 3H, CH_3), 2.143 (s, 3H, N-CH_3), 2.52-2.65 (m, 4H), 2.87-2.92 (m, 1H), 3.39-3.49 (m, 1H), 3.54-3.59 (m, 2H, OCH_2), 3.69-3.74 (m, 2H, OCH_2), 4.87 (t, 1H, J = 9.2 Hz), 6.681-8.245 (m, 11H, Ar-H and = CH-Ar), 10.65 (s, 1H, NH); ^{13}C NMR (100 MHz): δ 16.08, 20.57, 34.66, 35.77, 37.90, 48.54, 56.99, 61.89, 63.51, 64.38 (spiro C), 77.66 (spiro C), 105.07 (spiro C), 118.23, 122.94, 123.54, 124.13, 125.21, 129.84, 130.63, 130.97, 131.88, 134.16, 137.15, 138.97, 141.18, 142.90, 146.20, 146.74, 147.87, 176.76 (C=O), 198.37 (C=O). MS (m/z): 625 $[M+H]^+$.

Compound 5f: IR (KBr, ν_{max}): 2850, 1730, 1690 cm^{-1}; ^1H NMR (400 MHz): δ 1.64 (d, 1H, J = 14.8 Hz), 1.92 (s, 3H, N-CH_3), 2.46-58 (m, 4H), 2.85-2.90 (m, 1H), 3.31-3.38 (m, 1H), 3.42-3.55 (m, 4H, $(OCH_2)_2$), 4.88 (t, 1H, J = 9.2 Hz), 6.56-8.25 (m, 12H, Ar-H and = CH-Ar), 10.66 (s, 1H, NH); ^{13}C NMR (100 MHz): δ 34.87, 35.69, 37.77, 47.80, 56.72, 62.67, 63.33, 64.38 (spiro C), 77.61 (spiro C), 105.29 (spiro C), 118.46, 124.68, 125.65, 129.25, 129.67, 130.47, 131.50, 132.62, 132.46, 134.45, 135.55, 139.95, 141.48, 141.54, 144.99, 146.54, 147.85, 176.35 (C=O), 198.74 (C=O). MS (m/z): 631 $[M+H]^+$.

Compound 5g: IR (KBr, ν_{max}): 3245, 1710, 1680 cm^{-1}; ^1H NMR (300 MHz,): δ 1.28 (d, 1H, J = 15 Hz), 1.91 (s, 3H, N–CH_3), 2.03–2.14 (m, 2H), 3.03 (m, 1H), 3.28 (m, 1H), 3.42–3.56 (m, 4H, $(OCH_2)_2$), 3.70 (t, 1H, J = 9.3 Hz), 5.01(t, 1H, J = 9.3 Hz), 6.73–7.97 (m, 13H, Ar–H and =CH–Ar), 10.63 (s, 1H, N–H); ^{13}C NMR (75 MHz): δ 34.14, 36.85, 37.43, 45.36, 56.30, 59.40, 63.34, 64.32 (spiro C), 76.21 (spiro C), 105.44 (spiro C), 109.00, 121.51, 125.35, 126.51, 126.98, 128.49, 129.13, 129.55, 130.42, 130.63, 131.53, 132.86, 134.08, 134.58, 135.28, 137.26, 175.46 (C=O), 198.43 (C=O); MS (m/z): 543 $[M+H]^+$.

Compound 5h: IR (KBr, ν_{max}): 3280, 1707, 1684 cm^{-1}; ^1H NMR (300 MHz): d 1.59 (d, 1H, J = 15 Hz), 1.93 (s, 3H, N–CH_3), 2.42–2.61(m, 2H), 2.97 (m, 1H), 3.30 (m, 1H), 3.46–3.61 (m, 5H, $(OCH_2)_2$ and 1H), 4.75 (t, 1H, J = 9.4 Hz), 6.68–7.46 (m, 13H, Ar–H and =CH–Ar), 10.60 (s, 1H, N– H); 13C NMR (75 MHz): δ 34.58, 35.70, 37.63, 47.93, 57.06, 61.39, 63.32, 64.28 (spiro C), 77.07 (spiro C), 105.51 (spiro C), 109.18, 114.61, 114.89, 115.38, 115.67, 121.19, 125.17, 127.23, 129.14, 131.24, 131.90, 132.02, 132.32, 133.67, 135.73, 142.99, 176.33 (C=O), 198.80 (C=O). MS (m/z): 576 $[M+H]^+$.

Compound 5i: IR (KBr, ν_{max}): 3285, 1709, 1688 cm^{-1}; ^1H NMR (300 MHz) δ 1.77 (d, 1H, J = 14.7 Hz), 2.08 (s, 3H, N–CH_3), 2.42–2.57 (m, 2H), 3.03 (m, 1H), 3.45 (t, 1H, J = 8.6 Hz),

3.55–3.63 (m, 4H, $OCH_2)_2$, 3.76 (t, 1H, J = 8.7 Hz), 4.78 (t, 1H, J = 8.7 Hz), 6.74–7.53 (m, 13H, Ar–H and =CH–Ar), 10.49 (s, 1H, NH); ^{13}C NMR (75 MHz): δ 35.95, 46.26, 52.34, 55.17, 57.87, 60.66, 61.45, 65.73 (spiro C), 79.21 (spiro C), 105.29 (spiro C), 110.25, 115.67, 122.01, 122.75, 127.54, 128.18, 128.49, 128.63, 129.28, 130.58, 131.53, 132.97, 135.07, 135.16, 136.2, 140.1, 177.86 (C=O), 198.67 (C=O); MS (m/z): 665 $[M+H]^+$.

Compound 5j: IR (KBr, ν_{max}): 3270, 1717, 1682 cm-1; ^{1}H NMR (300 MHz): δ 1.29 (d, 1H, J = 15 Hz), 1.93 (s, 3H, N–CH3), 2.09–2.22 (m, 2H), 3.03 (m, 1H), 3.28 (m, 1H), 3.40–3.56 (m, 4H, $OCH_2)_2$, 3.71 (t, 1H, J = 9.0 Hz), 4.96 (t, 1H, J = 9.0 Hz), 6.76–7.90 (m, 12H, Ar–H and =CH–Ar), 10.79 (s, 1H, NH); ^{13}C NMR (75 MHz): δ 34.44, 35.81, 37.55, 48.36, 57.62, 61.00, 63.26, 64.05 (spiro C), 77.18 (spiro C), 105.41 (spiro C), 109.01, 114.13, 114.39, 114.88, 115.16, 120.88, 126.89, 128.76, 130.92, 131.41, 132.06, 132.16, 133.34, 136.03, 142.90, 176.27 (C=O), 198.98 (C=O). MS (m/z): 610 $[M+H]^+$.

Compound 5k: IR (KBr, ν_{max}): 3288, 1706, 1680 cm-1; ^{1}H NMR (300 MHz): δ 1.29 (d, 1H, J = 14.6 Hz), 1.97 (s, 3H, N–CH_3), 2.37–2.44 (m, 2H), 2.89 (m, 1H), 3.39 (m, 1H), 3.49–3.55 (m, 4H, $OCH_2)_2$, 3.79 (t, 1H, J = 7.7 Hz), 5.08 (t, 1H, J = 7.7 Hz), 6.73–7.85 (m, 12H, Ar–H and =CH–Ar), 10.88 (s, 1H, NH); ^{13}C NMR (75 MHz): δ 34.78, 35.71, 37.91, 47.64, 58.15, 61.23, 63.52, 64.56 (spiro C), 79.17 (spiro C), 105.47 (spiro C), 112.37, 115.35, 120.48, 122.56, 127.52, 130.7, 131.89, 132.08, 132.61, 133.6, 134.46, 135.76, 135.47, 137.34, 139.34, 143.94, 178.21 (C=O), 198.65 (C=O); MS (m/z): 655 $[M+H]^+$.

Results and discussion

The trispiropyrrolidine derivatives prepared from dipolarophile 7,9-bis[(E)arylidene]-1,4-dioxa-spiro[4,5]decane-8-ones. This dipolarophile prepared by green approach. In this sequence the reaction spiro[4,5]decan-8-one with various substituted benzaldehydes using water and mild base potassium carbonate (K_2CO_3) under microwave irradiation. This required shorter reaction time and gives excellent yield as compared to conventional method [34]. The geometry of the dipolarophile i.e. olefinic double bond was found to be E as evidenced by ^{1}H NMR spectra wherein the olefinicprotons appeared at δ 7.64–7.67 (s, 2H) and is found to be identical with those of authentic samples prepared by reported method.

Then trispiro derivatives prepared by the three component reaction of initially formed different dipolarophile, substituted isatin and sarcosine in [bmim]BF_4 ionic liquid. To optimization of reaction condition and to establish the practicability of the synthetic strategy multicomponent reaction of Isatin, sarcosine and 7,9-bis[(E)3,4-dichloro-benzylidene]-1,4-dioxa-spiro[4.5]decane-8-ones was chosen as a model (T**able 1**). In order to evaluate the effect of solvent and reaction condition, the reaction was conducted at different solvent at different reaction condition. The collected data presented in entries **1-9** of **Table 1**. This optimization of study revealed that best results were obtained by refluxing the reaction mixture in [Bmim] BF_4 ionic liquid under microwave irradiation for 13 min., providing the trispiro-oxindole pyrrolidine **5a** with an excellent yield (94%) in shorter reaction time (**Table 1**, **Entry 9**).

Table 1

Preparation of 5a in different reaction conditions

Entry	Solvent	Condition	Time	Yield[a] (%)
1	Ethanol	Reflux	5 hrs.	70
2	Methanol	Reflux	5 hrs.	78
3	Methanol	MW	1 hr.	70
4	Acetonitrile	Reflux	5 hrs.	55
5	1,4-dioxane	Reflux	5 hrs.	62

6	THF	Reflux	5 hrs.	50
7	TFE	Reflux	30 min	90
8	[Bmim]BF_4	Reflux	30 min.	80
9	**[Bmim]BF_4**	**Mw**	**13 min.**	**94**

Having established suitable reaction conditions (**Table 1**, **entry 9**), we tried to extend the scope of this reaction using a series of different substituted dipolarophiles **2a-f**. The structure of cycloadducts **5a-k (Fig. 3)** was confirmed through spectroscopic investigation.

Table 2. Synthetic results of 1-N-methyl-spiro[2,3']oxindole-spiro[3,9'']-7''-arylmethylidene-1,4-dioxa-spiro[4",5"]decan-4-aryl-pyrrolidine-8",2'-diones (**5a-k**).

S.No.	Ar	X	Time (min.)	Yield (%)
5a.	3,4-diClC_6H_3	H	13	94
5b.	3,4-di$Cl\ C_6H_3$	5,7-diMe	12	90
5c.	3,4-di$Cl\ C_6H_3$	Cl	10	95
5d.	4-$NO_2C_6H_4$	H	12	89
5e.	4-$NO_2C_6H_4$	5,7-diMe	15	87
5f.	4-$NO_2C_6H_4$	Cl	11	91
5g.	4-F-C_6H_4	H	12	92
5h.	2-Cl-C_6H_4	H	14	92
5i.	4-Br-C_6H_4	H	14	90
5j.	2-Cl-C_6H_4	Cl	13	91
5k.	4-Cl-C_6H_4	Br	12	89

The IR spectrum of the cycloadduct **5a** showed three characteristic bands at 2875 cm^{-1}, 1720 cm^{-1} and 1690 cm^{-1} corresponding to the indole

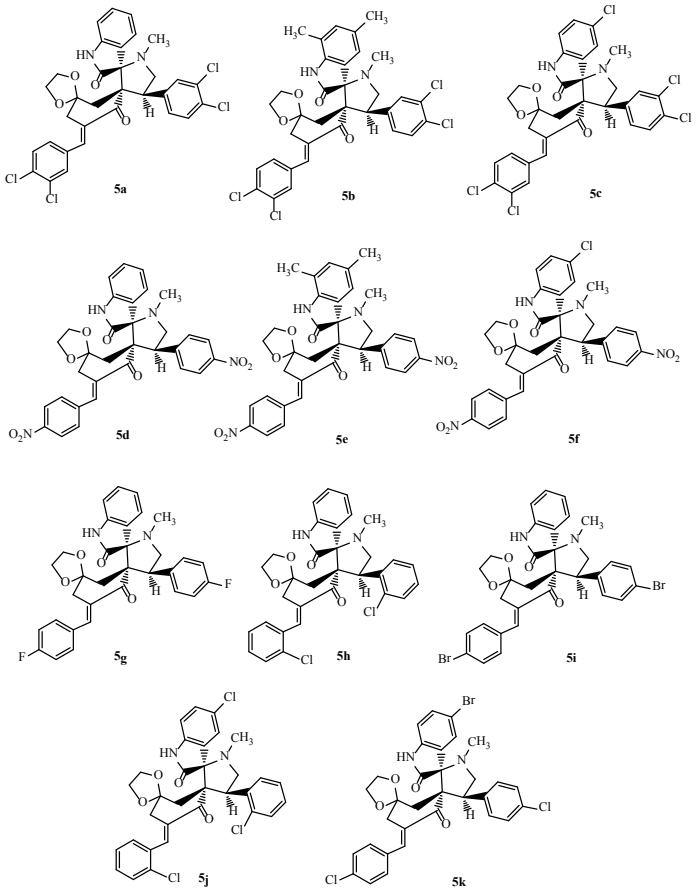
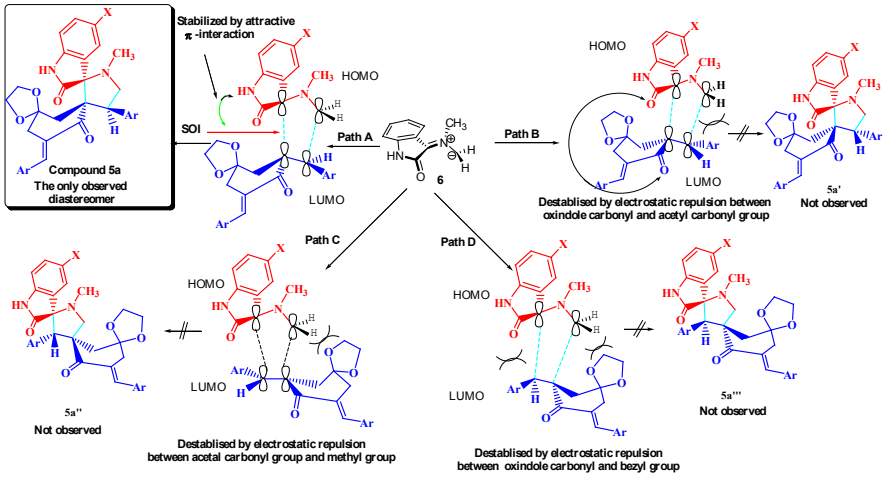


Fig 3. Library of trispiro[pyrrolidine-2,3'-oxindole] derivatives

-NH, the carbonyl group of ketal and a carbonyl group of amide, respectively. The ^{1}H NMR spectrum of compound **5a** exhibited a sharp singlet at δ 1.94, which corresponds to N-CH_3 protons of pyrrolidine ring. The –NCH_2 proton and benzylic proton of the pyrolidine ring appeared at δ 3.02-3.08 (m, 1H), 3.33-3.37 (m, 1H), 4.70 (t, 1H, J = 9.2 Hz) which explain the regiochemistry of the cycloadduct. In contrast, if the other regioisomer had been formed, the benzylic proton would have appeared as a singlet instead of triplet in the ^{1}H NMR spectrum. The –NH proton of the oxindole framework appeared singlet at δ 10.67 and the aromatic protons appeared as a multiplet in the region δ 6.71-7.67 ppm. In ^{13}C-NMR spectrum of **5a**, the oxindole and cyclohexane carbonyl carbon resonated at δ 176.21 and 198.51 ppm respectively. The three spirocyclic carbon appeared at δ 105.22, 77.08 and 64.35 ppm. Furthermore, the presence of molecular ion peak at m/z 643.06 (M^++1) in the mass spectrum confirmed the formation of the cycloadduct **5a**. A plausible mechanism for the formation of the cycloadducts is proposed in **Scheme 2**. [Bmim]BF_4 play unique role in this cycloaddition due to its Lewis acidity and strong ionizing capacity. The present cycloaddition reaction involves the 1,3-dipolar cycloaddition reaction of dipolarophile and non-stabilized azomethine ylides **6** to afford trispiropyrrolidine derivatives **5a** approach. The hydrogen atom of imidazolium ring being electron-deficient could form hydrogen bonds with carbonyl groups of both isatin **3** and dipolarophile **2**, thereby catalyses reaction. Further, the polar transition state of the reaction could be stabilized well by high ionizing solvent [Bmim] BF_4. Regioselectivity of present cycloaddition reaction is controlled by interaction of HOMO of dipole with LUMO of dipolarophile. In present investigation reaction of azomethine ylide with alkene occurs *via* HOMOazomethineylide-LUMOalkene interaction which results in a lowering of the energy of the LUMO of alkene and thus enhancement of rate as well as regioselectivity of reaction [35, 29a]. The electron rich carbon of the dipole adding to the β-carbon of the α,β-unsaturated moiety of **2** and stereoselective affording only one diastereomer **5a** exclusively, despite the presence of three stereo centers in the product. The formation of one diastereomer can be explained in **Scheme 2.** In this scheme path A is reasonably favored by attractive interaction between aromatic rings and the secondary orbital interaction (SOI) leads to the formation of **5a** rather than **5a′**, **5a″**, **5a‴**.

The recovery and reusability of the ionic liquid (IL) is very important particularly for



Scheme 2. Plausible mechanism for the stereoselective formation of trispiro[pyrrolidine-2,3'-oxindole] derivatives

industrial and commercial purposes and is highly recommended for green processes were also explored in the model reaction. To test the recovery of the ionic liquid [bmim] BF_4, after completion of the reaction, the reaction mixture was washed with diethyl ether (3x10 mL). The combined ether extracts were concentrated in vacuo and viscous ionic liquid was further washed with ether and dried at 80° C under reduced pressure and could be reused at least four times without any appreciable decrease in yield **(Table 3)**. The results showed that the IL could be used at least 4 times without any significant loss in the yield of the reaction.

Table 3. Results for the recycling of ionic liquid [bmim]BF_4 in the synthesis of **5a**

Entry	Cycle	Yield (%)	IL recovered (w/w %)
1	1	94%	97
2	2	90%	92
3	3	84%	90
4	4	80%	85

Conclusion

The combination of ILs with microwave irradiation was effective for eco-friendly synthesis of biologically interesting functionalized trispiropyrrolidinyl derivatives through one pot three component 1,3- dipolar cycloaddition reaction. Catalytic properties of ionic liquids has been proved which avoiding the use of hazardous solvent. The simple experimental and product isolation procedure combined with ease of recovery and reuse of this reaction medium is expected to contribute to the development of green and waste free chemical process intention. The compounds reported herein may be suitable for generation of library of pharmaceutically important drug molecule. The biological evaluations of these complex polycyclic compounds are in progress.

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33. An equimolar mixture of appropriate 7,9-bis[(E)arylidene]-1,4-dioxa-spiro[4,5]decane-8-ones **2a-f** (1 mmol), isatin **3a-d** (1 mmol), and sarcosine **4** (1 mmol) and [Bmim] BF_4 ionic liquid (2–3 mL) under microwaves. All these reactions were carried out by microwave irradiation for 10-15 min. at the power level 250 W and at the temperature of 150^{o} C which was recorded by the temperature probe of the microwave. After completion of the reaction, as indicated by TLC, the reaction mixture was washed with diethyl ether (3x10 mL). The combined ether extracts were concentrated in vacuum at 80 ^{o}C overnight. For further purification, the solid products were recrystallized from ethanol and the similar procedure was followed for the synthesis of all the products without any need for column chromatography. All the synthesized compounds were well characterized by ^{1}H NMR, ^{13}C NMR, and Mass analysis.
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