

Exploration of Biodegradable Deep Eutectic Solvent in the Henry Reaction to afford 3-Hydroxy Oxindole Scaffolds

^{1*}Pramod B. Thakur, ²Rupashri K. Kadu, ³Ganesh A. Thakur,

^{1,2,3}Department of Chemistry, Rayat Shikshan Sanstha's, Mahatma Phule Arts, Science & Commerce College, Panvel (Affiliated to University of Mumbai, Mumbai), District-Raigad, Navi Mumbai, Maharashtra – 410206, India.

Abstract : In the current manuscript demonstrates biodegradable deep eutectic solvent ([Ch][Cl]-Urea) mediated Henry reaction of a variety of isatins with nitroalkanes at room temperature to afford, 3-hydroxy-3-(nitroalkyl)-oxindoles in very good yields. The developed reaction is found general which tolerated variety of functional groups like alkyl, phenyl and halides. Furthermore the developed method is column chromatography free protocol which has afforded sufficiently pure compounds just by filtration process without employing aqueous work-up extraction step. Moreover the high diastereoselectivity can also be achieved without using catalyst or chiral mediator. Wide scope of substrates with high yields and mild reaction condition are the notable features of our protocol. The developed method may be useful in the synthesis of new natural products and biologically important 3-hydroxy oxindole analogues under mild reaction conditions.

Keywords - DES; Henry Reaction; Isatin; Nitroalkane; Oxindole; Green Chemistry.

I. INTRODUCTION

The Henry reaction which is also known as nitroaldol reaction is a Carbon-Carbon bond formation reaction of nitroalkanes and carbonyls under basic condition¹. Reactions of nitroalkanes with isatins under Henry/nitroaldol reaction are explored to afford 3-Nitroalkyl substituted 3-hydroxy-oxindole framework. These frameworks not only have an interesting molecular architecture, but also have a densely functionalized core and exhibit significant bioactivities². Furthermore this framework also has been explored as an key precursor in the preparation of natural products and biologically active molecules. Representative examples include horsfiline, coerulecine, spirobrassinin, phytoalexins and 3-β amino-2-oxindoles (Figure 1).

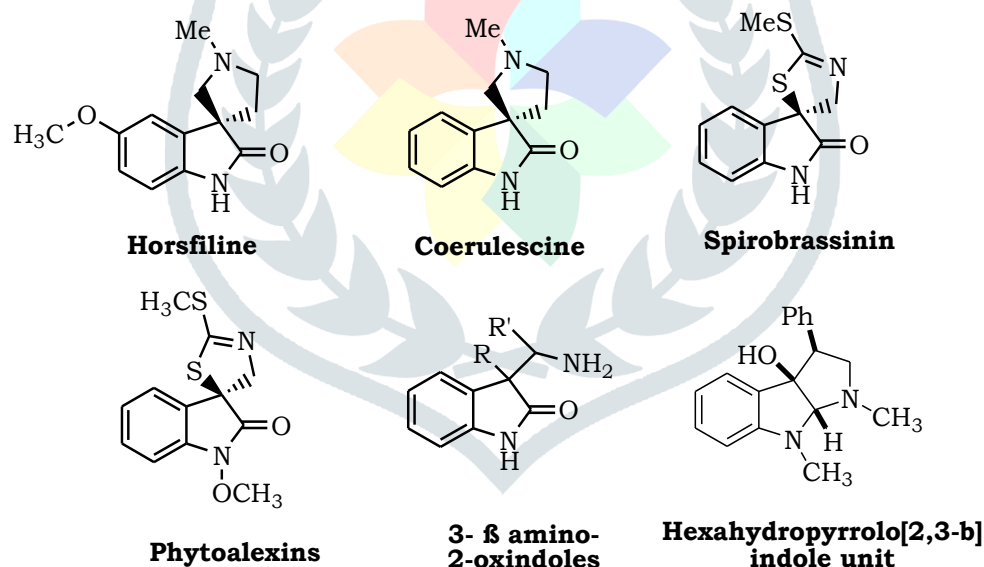


Figure 1: Representatives examples of compounds obtained from 3-nitroalkyl substituted 3-hydroxy-oxindole precursor

The Michael addition reaction of oxindole and nitro olefins also affords 3-nitroalkyl substituted 3-hydroxy-oxindole framework. These frameworks are also successfully utilized for the preparation of naturally important hexahydropyrrolo[2,3-b]indole unit. Due to such importance of 3-nitroalkyl substituted 3-hydroxy-oxindole framework in the synthesis of natural products and biologically active compounds, it is attractive to develop a mild and efficient method to synthesize such a molecular framework. Till now different approaches have been reported to synthesize 3-nitroalkyl substituted 3-hydroxy-oxindole framework. The direct addition of nitroalkanes to isatins using Henry reaction is very straightforward and classical approach used to synthesize this framework. These different methods used to synthesize 3-nitroalkyl substituted 3-hydroxy-oxindole frameworks are summarized here. Lindwall *et al*³ reported the first synthesis of 3-nitroalkane substituted 3-hydroxy oxindole by using Henry reaction of nitromethane with N-alkyl isatin in the presence of diethylamine in ethanol at 0°. After this report, Chen *et al*⁴, Palmisano *et al*⁵, Meshram *et al*^{6,7} also reported the Henry reaction of nitromethane with isatin to afford 3-nitroalkane substituted 3-hydroxy oxindole. Michail *et al*⁸ carried out Henry reaction using sodium iodide in methanol under electrochemical reaction set-up. Liu *et al*⁹ reported asymmetric version of Henry reaction of nitroalkane with isatin to synthesize enantioselective 3-nitroalkane substituted 3-hydroxy oxindole was reported by using cupreine catalyst in 2011. Later in the same year Li *et al*¹⁰ and Likhari *et al*¹¹ also reported the enantioselective Henry reaction to afford chiral 3-nitroalkane substituted 3-hydroxy oxindole under different reaction conditions.

The physical and solvent properties of Deep eutectic solvents have are matching with ionic liquids having discrete ions. Abbott et al¹² have done pioneering work on Deep eutectic solvents obtained from choline chloride. Choline or its deep eutectic mixture is found to be environmental friendly biodegradable compound¹³. Furthermore, Urea is important precursor of all animals. In the context of the inexpensiveness of these two components, the processes that such ([Ch][Cl]-Urea) based deep eutectic solvent will be defiantly treated as economically viable method. Ionic liquids no more treated as green solvents as they are equally toxic like organic solvents^{14,15}. The best solution to overcome toxic effect is to use deep eutectic solvent. Yet, the many organic reactions have not tested in deep eutectic solvent. In this context, we have explored the choline chloride ([Ch][Cl])-Urea based DES for the Henry reaction between isatin and nitroalkane to afford 3-nitroalkyl substituted 3-hydroxy-oxindole framework.

II. GENERAL METHOD:

Preparation of ([Ch][Cl])-Urea based Deep Eutectic Solvent:

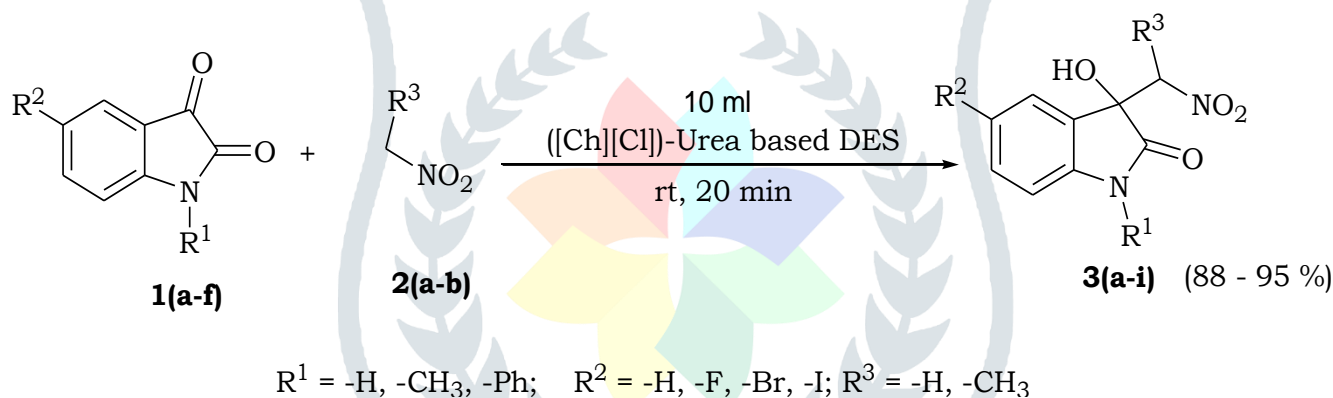
The choline chloride -Urea based DES was prepared by mixing 1: 2 mol ratio of choline chloride and urea respectively. The mixture was heated at 74 °C to get a clear solution of DES.

General procedure for ([Ch][Cl])-Urea based DES mediated synthesis of 3-(nitroalkane) substituted, 3-hydroxy oxindole:

In the 10 ml choline chloride -Urea based DES, isatins (**1a-f**) (1.0 mmol) were added. To the above reaction mixture, nitroalkane (**2a-b**) (2mmol) were added under nitrogen atmosphere. This reaction mixture was further stirred at desired time at RT. After the reactin, the reaction mixture was filtered to obtain the crude solid products. The residue was dried, purified by column chromatography and subjected for structure elucidation. The filtrate obtained was ([Ch][Cl])-Urea based DES which was dried by applying vacuum and reused in next reaction. The crude products were having good purity which were further purified by column chromatography using ethyl acetate:hexane (1:3 to 1:1) as eluent.

III. RESULTS AND DISCUSSION

As our interest and expertise in this area¹⁶, we visualize that the Henry reaction of isatin with nitroalkane might be readily proceed without use of additional catalyst under basic ([Ch][Cl])-Urea based DES. This is because carbon atom of β -carbonyl group of isatin is electron deficient and become soft target for nucleophiles. In literature, no method is described for the Henry reaction of isatin with nitroalkane using ([Ch][Cl])-Urea based DES. Hence, herein, we disclose results of the initial study of ([Ch][Cl])-Urea based DES mediated Henry reaction of isatin and nitroalkane. (**Scheme 1**).

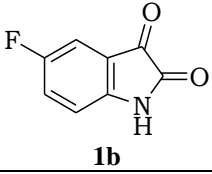
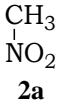
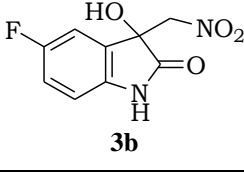
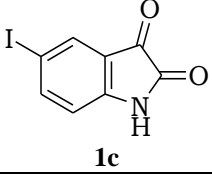
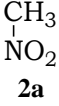
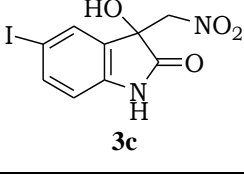
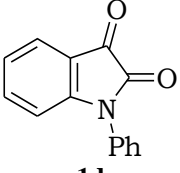
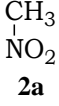
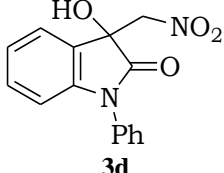
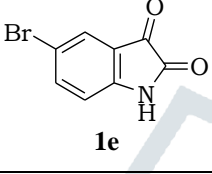
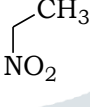
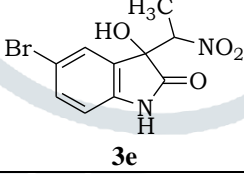
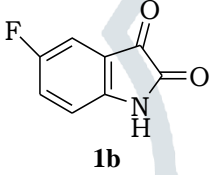
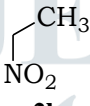
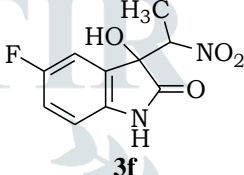
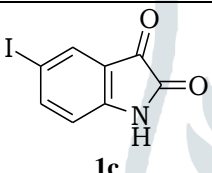
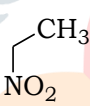
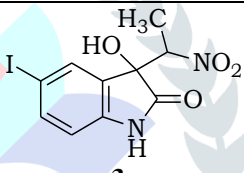
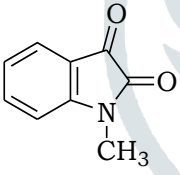
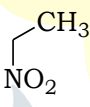
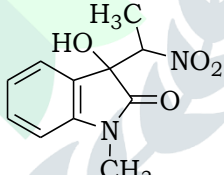
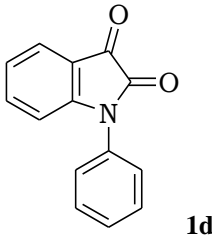
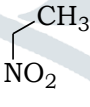
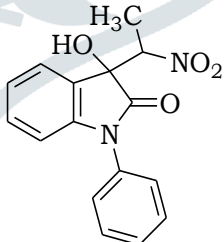


Scheme 1 Synthesis of 3-hydroxy-3-(nitroalkyl)-oxindole derivative

We starts this study by reacting isatin with nitromethane using 10 ml ([Ch][Cl])-Urea based DES. At the beginning, the reaction mixture was red in colour. After 20 minutes, we observed the formation of buff white precipitate in the round bottom flask. We have isolated the obtained buff white precipitate by filtration. The obtained solid was dried, purified and submitted for structure elucidation. The filtrate obtained was ([Ch][Cl])-Urea based DES which was dried by applying vacuum and reused in next reaction. After obtained characterization data and comparison of it with reported data, the formation of 3-hydroxy-3-(nitromethyl) indolin-2-one was confirmed. This results shows that, choline chloride ([Ch][Cl])-Urea based DES is sufficient for Henry reaction between isatin and nitroalkane to afford 3-nitroalkyl substituted 3-hydroxy-oxindole framework under catalyst-free condition. With these promising results in hand, we tested the substrate scope of different isatin and nitroalkanes Range of isatin derivatives bearing halogen atom underwent smooth reaction with nitromethane and resulted into corresponding products in very good yields. Encouraged by the above results we next reacted *N*-methyl/phenyl protected isatins with nitro methane and nitro ethane which showed expected results (**Table 1**).

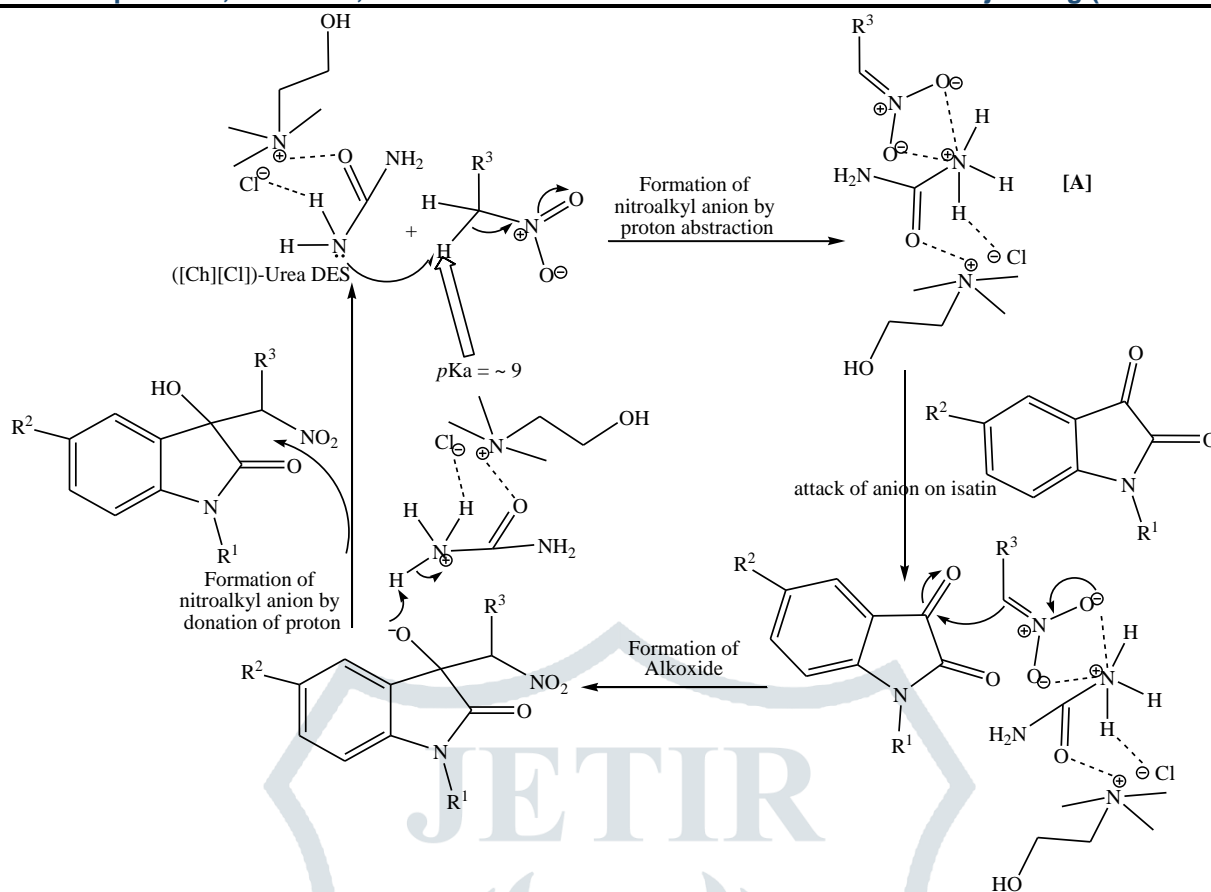
Table 1 Synthesis of 3-hydroxy-3-(nitroalkyl)-oxindole derivatives

Entry	Isatin (1a-f)	Nitroalkane (2a-b)	Product (3a-i)	Time (min)	Yield ^b (%)
1		$\begin{matrix} CH_3 \\ \\ NO_2 \end{matrix}$ 2a		20	95

2	 1b	 2a	 3b	20	96
3	 1c	 2a	 3c	20	95
4	 1d	 2a	 3d	20	96
5	 1e	 2b	 3e	20	96 (77:29)*
6	 1b	 2b	 3f	20	94 (67:33)*
7	 1c	 2b	 3g	20	92 (91:09)*
8	 1f	 2b	 3h	20	94 (67:37)*
9	 1d	 2b	 3i	20	91 (72:28)*

^a Reactions condition : All reactions were performed with isatins **1(a-f)** (1mmol), nitroalkane **2(a-b)** (2 mmmol) in 10 ml ([Ch][Cl])-Urea based DES at room temperature. ^b Isolated yields of purified products. * Inseparable mixture of diastomers, *threo:erythro* ratio written in parentheses.

The tentative mechanistic pathway proposed for the ([Ch][Cl])-Urea based DES mediated Henry reaction of isatins is shown in **Scheme 2**. We reasoned that, ([Ch][Cl])-Urea based DES works dually as a solvent and mild base to form nitroalkyl anion [A]. This nitroalkyl anion (azinate) attack on carbon atom of β -carbonyl group of isatin to provide desired product. We assume that, due to the distinctive basicity and polarity associated with ([Ch][Cl])-Urea based DES, it efficiently forms and stabilise nitroalkyl anion and hence resulted in to the high yields of products.



Scheme 4: Proposed mechanistic pathway of DES mediated Henry reaction of Isatin.

IV. CONCLUSION

In conclusions, we demonstrated an efficient Henry reaction of a variety of isatins with nitroalkanes in ([Ch][Cl])-Urea based DES at room temperature. Desired products, 3-hydroxy-3-(nitroalkyl)-oxindoles, were obtained in very good yields with high diastereo selectivity in some cases without using catalyst or chiral mediator. The developed reaction is found general which tolerated variety of functional groups like alkyl, phenyl and halides. Furthermore the developed method is column chromatography free protocol which has afforded sufficiently pure compounds just by filtration process without employing aqueous work-up extraction step. Wide scope of substrates with high yields and mild reaction condition are the notable features of our protocol. The developed method may be useful in the synthesis of new natural products and biologically important 3-hydroxy oxindole analogues under mild reaction conditions.

V. Acknowledgments

Authors Rupashri K Kadu and Pramod B Thakur acknowledge Hon. Principal, Dr. Ganesh A. Thakur and Head of the department Mr. G. J. Korane for their support, motivations and encouragement.

REFERENCES

- [1] Tokunaga, T.; Hume, W. E.; Umezome, T.; Okazaki, K.; Ueki, Y.; Kumagai, K.; Hourai, S.; Nagamine, J.; Seki, H.; Taiji, M.; Noguchi H. and Nagata, R. Oxindole Derivatives as Orally Active Potent Growth Hormone Secretagogues. 2001. Journal of Medicinal Chemistry, **44** (26): 4641-4649.
- [2] Anderton, N.; Cockrum, P. A.; Colegate, S. M.; Edgar, J. A.; Flower, K.; Vit, I. and Willing, R. I. 1998. Oxindoles from *Phalaris coerulescens*. Phytochemistry, **48**(3): 437-439.
- [3] Conn, W. R. and Lindwall, H. G. 1936. Oxindole amines from Isatin. Journal of American Chemical Society, **58**(5): 1236-1239.
- [4] Chen, G.; Hao, X.; Sun Q. and Ding, J. 2010. Rapid synthesis and bioactivities of 3-(nitromethylene)indolin-2-one analogues. Chemical Papers, **64**: 673-677.
- [5] Palmisano, G.; Annunziata, R.; Papeo G. and Sisti, M. 1996. Oxindole alkaloids. A novel non-biomimetic entry to (-)-Horsifoline. Tetrahedron Asymmetry, **7**(1): 1-4.
- [6] Meshram, H. M.; Ramesh, P.; Kumar A. S. and Swetha, A. 2011. An efficient and environmentally friendly DABCO catalyzed Henry reaction of isatins. Tetrahedron Letters, **52**(44): 5862-5864.
- [7] Meshram, H. M.; Thakur, P. B.; Bejjam M. B. and Bangade V. M. 2013. DMF mediated Henry reaction of isatins: an efficient synthesis of 3-hydroxy-2-oxindole. Green Chemistry Letters and Reviews, **6**(1): 19-43.
- [8] Michail, N. E.; Alexey, I. I.; Valentina, M. M.; Fructuoso B. and Belen, B. 2008. Electrochemically induced Henry reaction of nitromethane and carbonyl compounds. Tetrahedron **64**(25): 5915-5919.
- [9] Liu, L.; Zhang, S.; Xue, F.; Lou, G.; Zhang, H.; Ma, S.; Duan, W. and Wang, W. 2011. Catalytic Enantioselective Henry Reactions of Isatins: Application in the Concise Synthesis of (S) - (-) - Spirobrassinin. Chemistry: A European Journal, **17**(28): 7791-7795.

- [10] Li, M.; Zhang, J.; Huang, X.; Wu, B.; Liu, Z.; Chen, J.; Li, X. and Wang, X. 2011. Asymmetric Nitroaldol Reactions of Nitroalkanes with Isatins Catalyzed by Bifunctional Cinchona Alkaloid Derivatives. *European Journal of Organic Chemistry*, **27**: 5237-5241.
- [11] Sai, P.; Parvathaneni, S.; Keesara, B. K.; Arundhathi, R.; Narsimha, R.; Gajjaia, S. B.; Mohan, R. M. and Likhar, P. R. 2011. Biscinchona alkaloid catalysed Henry reaction of isatins: Enantioselective synthesis of 3-hydroxy-3-(nitromethyl)indolin-2-ones. *Tetrahedron Asymmetry*, **22(24)**: 2099-2103.
- [12] Abbott, A.; Capper, G.; Davies, M. D.; Rasheed, H. R. and Tambyrajah, V. 2001. Preparation of novel, moisture-stable, Lewis-acidic ionic liquids containing quaternary ammonium salts with functional side chains. *Chemical Communications*, **2001(19)**: 2010-2011.
- [13] Ranke, J.; Stolte, S.; Stormann, R.; Arning, J. and Jastorff, B. 2007. Design of sustainable chemical products--the example of ionic liquids. *Chemical Reviews*. **107(6)**: 2183-2206.
- [14] Burrell, A.; Del, S. R.; Baker, S.; McCleskey, T. M. and Baker, G. A. 2007. The large scale synthesis of pure imidazolium and pyrrolidinium ionic liquids. *Green Chemistry*, **9(5)**: 449-454.
- [15] Ranu B. and Jana, J. 2006. Ionic Liquid as Catalyst and Reaction Medium - A Simple, Efficient and Green Procedure for Knoevenagel Condensation of Aliphatic and Aromatic Carbonyl Compounds Using a Task-Specific Basic Ionic Liquid. *European Journal of Organic Chemistry*, **16(6)**: 3767-3770.
- [16] (a) Thakur, P. B.; Sirisha, K.; Sarma, A. V. S.; Nanubolu, J. B. and Meshram, H. M. 2013. Highly regioselective and metal-free γ -addition of β -keto esters to isatins, catalyzed by DABCO: direct access to novel class of diversely functionalized 3-hydroxy-2-oxindole scaffolds *Tetrahedron*, **69(31)**: 6415-6423. (b) Thakur, P. B. and Meshram, H. M. 2014. "On water" highly atom economical and rapid synthesis of a novel class of 3-hydroxy-2-oxindole scaffolds under a catalyst-free and column chromatography-free protocol at room temperature. *RSC Adv.* **4(12)**: 6019-6026. (c) Thakur, P. B.; Nanubolu, J. B. and Meshram, H. M. 2014. DABCO Promoted Regioselective Synthesis of New Diversely Functionalized 3-Hydroxy-2-Oxindole Scaffolds. *Aust. J. Chem.* **67(5)**: 768-776. (d) Thakur, P. B.; Sirisha, K.; Sarma, A. V. S.; Nanubolu, J. B. and Meshram, H. M. 2014. Microwave assisted rapid, catalyst-free, and efficient synthesis of a new class of diversely functionalized 3-hydroxy-2-oxindole scaffolds under aqueous reaction media. *Tetrahedron Lett.* **55(15)**: 2459-2462. (e) Thakur, P. B. and Meshram, H. M. 2015. An Exploration of Organocatalyst 1,4-Diazabicyclo[2.2.2]octane in the Direct Regioselective and Chemoselective γ -Addition of β -Keto Amide on Isatin to Afford Structurally Diverse Molecular Frameworks. *Aust. J. Chem.* **68(3)**: 453-460. (f) Thakur, P. B. and Kadu, R. K. 2016. Rapid, Catalyst-free and Diastereoselective Synthesis of 3-hydroxy-2-oxindole Scaffolds under Microwave Irradiation in Aqueous Reaction Media. *J. Chem. & Cheml. Sci.* **6(11)**: 966-975. (g) Thakur, P. B. and Meshram, H. M. 2014. "On water" catalyst-free, column chromatography-free and atom economical protocol for highly diastereoselective synthesis of novel class of 3-substituted, 3-hydroxy-2-oxindole scaffolds at room temperature. *RSC Adv.* **4(11)**: 5343-5350. (h) Thakur, P. B.; Kadu, R. K. and Thakur, G. A. 2018. Rapid Construction of Bioindole Frameworks Using DABCO Under Aqueous Reaction Media. *JETIR.* **5(11)**: 239-244.

