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Chapter

Low Melting Mixture of L-(+)-Tartaric Acid and *N,N′*-Dimethyl Urea: A New Arrival in the Green Organic Synthesis

Rashid Ali

Abstract

After the first report of deep eutectic mixtures by the team of Abbott in 2003, the advent of green synthesis has been progressively changing the way synthetic chemistry is thought and also taught. Since then, a plethora of efforts worldwide have been taken to stretch the ideas of sustainable as well as environmentally benign approaches to do the crucial synthetic organic transformations under operationally simple yet effective conditions. Although, till date, several green synthetic strategies for examples ultrasound, microwaves, flow as well as grindstone chemistry etc., and green reaction media (e.g. ionic liquid, water, $scCO_2$, and so forth) have successfully been invented. But a low melting mixture of L-(+)-tartaric acid (TA) and *N,N′*-dimethylurea (DMU), usually plays a double and/or triple role (solvent, catalyst, and/or reagent), though still infancy but enjoys several eye-catching properties like biodegradability, recyclability, non-toxicity, good thermal stability, tunable physiochemical properties, low vapor pressure as well as reasonable prices in addition to the easy preparation with wide functional groups tolerance. To this context, keeping the importance of this novel low melting mixture in mind, we intended to reveal the advancements taken place in this wonderful area of research since its first report by the Köenig's group in 2011 to till date. In this particular chapter, firstly we would disclose the importance of the green synthesis followed by a brief description of deep-eutectic solvents (DESs) particularly emphasizing on the role of L-(+)-TA and DMU from modern synthetic chemistry perspective.

Keywords: low melting mixture, 1,3-dimethyl urea, tartaric acid, sustainable chemistry, synthesis

1. Introduction

As can be inspected from the literature, there were rising concerns in the mid-1980s, regarding the plentiful of the waste being produced by the chemical industry [1, 2]. A paradigm change was undoubtedly desirable, from the old-fashioned perceptions of reaction selectivity, and efficiency which emphasis fundamentally on the chemical yields, to one that allocates the value to the enlargement of the bulk raw materials exploitation, avoidance of the utilization of the hazardous chemicals/reagents/solvents and also preventation of the waste being formed within the

boundaries of environmental awareness. To this context, in 1987, the term sustainable development was coined by Brundtland, in his report; he mainly focused on the emergence of the societal and industrial development to afford an escalating global population with a suitable value of life in such a way that it should be sustainable over a long period of time [3]. Therefore, complete balance necessities to be found among the three Ps-planet, people, profit i.e. environmental impact, societal equity and economic development. More specifically, in sharp contrast to the green chemistry, sustainable development also comprises an economic factor and if a technology is not economically viable, it could not be sustainable for a long time. Remarkably, a tremendous curiosity in sustainable and green progress, united with a cultivating concern for the climate change, has engrossed attention on resource competence and also driving the shift from a conventional linear flow of bulk materials in a "take–make–use–dispose"economy, towards the greener and even more sustainable globular economy. Interestingly, since the 12 principles of green chemistry (*Prevention of waste; Atom economy; Less hazardous chemical syntheses; Designing safer chemicals with fewer hazards; Safer solvents and auxiliaries; Design for energy efficiency; Use of renewable feedstocks; Reduce derivatives during synthesis; Catalysis; Design for degradation; Real-time analysis for pollution prevention; Inherently safer chemistry for accident prevention*), postulated by Anastas & Warner in 1998 [4], scientists around the world are trying to reduce the volatile organic solvents (VOCs) which generally are the major portion (approx. 80% of the total content) of the reaction vessel as compare to the reactants/reagents, and also has the tendency to escape into the environment, which in turns contribute to ozone depletion as well as smog in urban areas, and hence extremely dangerous for mankind [5]. Therefore, great efforts are being put forward to reduce these hazardous VOCs, and the corrosive acid catalysts, participating in the reaction to make the chemical processes even more sustainable and environmentally friendlier [6]. To this context, over the past few decades, several surrogates for instance water, ionic liquids, supercritical fluids, and switchable solvents in addition to many green strategies such as ultrasound, flow chemistry, biocatalysis, microwaves, and multi-component etc., have successfully been developed [7–9]. Generally, water is thought to be an archetype solvent as it enjoy many classical properties, nonetheless it not only suffer from insolubility issues with the majority of organic compounds but also has a difficulty of removing it after the completion of the reaction because of its high boiling point, and even in many cases compounds gets decompose into the water in addition, some reactions for example amidations and transesterifications, can not be performed in water because of competing product hydrolysis [10]. On the other hand, supercritical fluids which possess low vapor pressure along with the advantages of easy disposal/removal, and recycling, are thought to be the best eco-friendly substitutes of VOCs, but, they requires more sophisticated equipment to perform the reaction. To this context, researchers turn their attention towards the ionic liquids due to their remarkable physiochemical properties but owing to their high cost as well as involvement of the non-renewable resources besides purification before their usage make them of bit doubt from green perception [11]. Consequently, bearing in mind, the urgency of the suitable alternative green solvents in place of conventional solvents to carry out the crucial synthetic transformations for sustainable development in R and D and also for the chemical industry, Abbott's 2003 discovery of the deep eutectic solvents (DESs), also known as low transition temperature mixtures (LTTMs), or low-melting mixtures (LMMs) or deep eutectic ionic liquids (DEILs), has become one of the strongest pillars to the modern synthetic community. Generally, in DES, two/three components are mixed in an appropriate amount to generate a eutectic mixture with lower melting point as compare to the individual components being used [12–15]. As a consequence, an infinite number of melts involving different compositions/components with

distinctive properties like price of the raw materials, melting point, polarity, dissolving ability etc., can be accomplished effortlessly. Interestingly, because of the involvement of non-covalent interactions including hydrogen bonds, it has been noticed that the melting points of the DESs are generally below 100°C, even some of them are liquid at room temperature, and they have been the role model among the greener solvents over the past two decades to both academic as well as industrial community because of their remarkable properties and benefits such as biodegradability, low cost and low vapor pressure in addition to non-toxicity and good thermal stability. Among the DESs, a low melting mixture of DMU/TA can be regarded as the solvent of the 21st century, as it hold the following features: (i) Generally, it does not require tedious work-up after the reaction is being completed, rather, just filtration after addition of the water to the reaction mixture while hot, furnishes the analytically pure compounds and most of the time no need of chromatographic purification but simple recrystallization provides the pure form of the required products; (ii) the melting mixture can willingly be recovered and recycled several times without any substantial loss in the activity; (iii) the reaction cleanly underwent towards the product formation at faster rate as compare to the known procedure, and mostly better yields are obtained under operationally simple reaction conditions; (iv) No additional catalyst and solvents are needed in this method, as in conventional procedure, generally both, the corrosive catalysts as well as hazardous, flammable, and volatile organic solvents are being employed; (v) No inert atmosphere is required for a reaction to be successfully completed in parallel yields; (vi) This method also provide good selectivity and also exhibit excellent functional group tolerance; (vii) Easy preparation of the melt from the bulk renewable resources and no further purification before its utilization is needed; (viii) improved safety and very simple handling as comparison to the conventional practices.

Bearing all the above mentioned applications and peculiar physiochemical properties of the DMU/TA melt in mind, which we still feel is immature, although employed for a variety of successful reactions for instance Diels-Alder reaction,

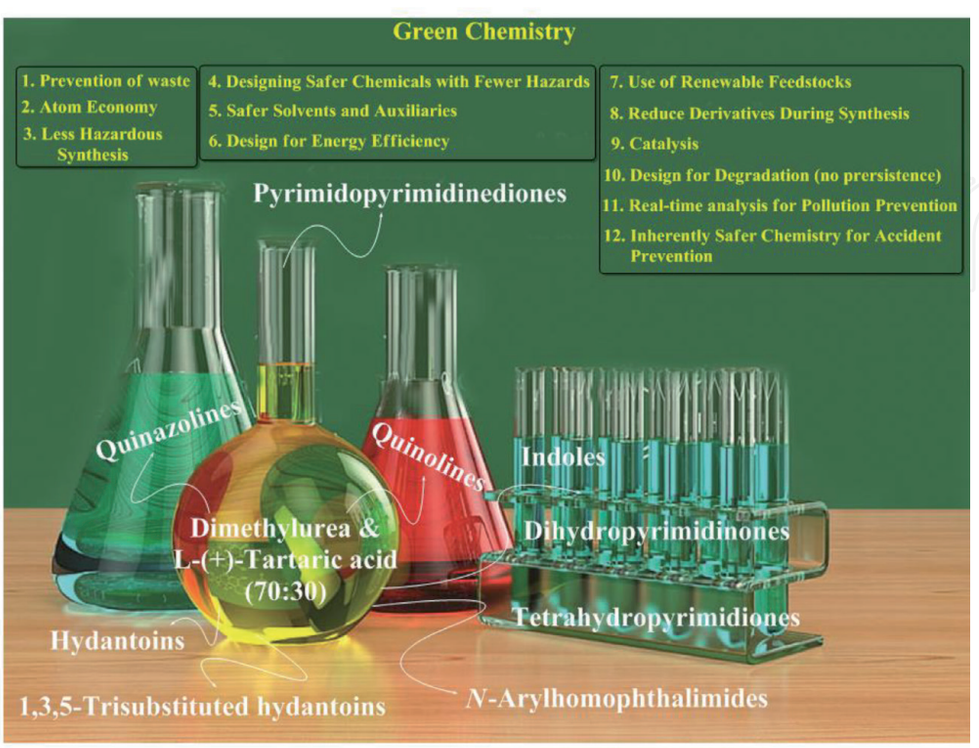


Figure 1.
12 principles of green chemistry and the achievements made in DMU/TA.

Stille, Sonogashira, Suzuki, and Heck coupling reactions, Biginelli reaction, 1,3-dipolar reaction, in addition to its applicability for the synthesis of quinolines, arylhomophthalimides, prymidopyrimidinediones, tetrahydropyrimidinones, hydantoins, dihydropyrimidinones, quinazolines, and a variety of functionalized indole systems with excellent selectivity in decent yields. Interestingly, the beauty of this method is its double and triple role in the reaction vessel to facilitate the accomplishment of the reactions in a clean and smooth fashion without the involvement of any catalyst/additives or solvent. In short, after a brief introduction related to the sustainability and green synthetic approaches, herewith, we have tried to display a deep survey of what has already been done in this field, and open the opportunities to the young researches to find out the new advances by employing this DES and also medium engineering might be utilized to optimize the synthetic utility of various other combinations of the DESs. Green chemistry 12 principles as well as the achievements made by employing a low melting mixture of DMU/TA in the domain of synthetic organic chemistry are displayed in the **Figure 1**.

2. Construction of indole systems under a low melting mixture of DMU/TA

The name indole was originated from portmanteau, a combination of both the words, indigo and oleum which was first isolated from the indigo dye, while treating it with oleum [16, 17]. As can be inspected from the literature, indole scaffold, a notable privileged lead bicyclic aromatic system (10π-electrons), formally known as benzopyrrole, have immeasurable potential applications ranging from the broad-spectrum biological (e.g. *anti*-HIV, antiviral, antimicrobial, antidiabetic, antimalarial, *anti*-cholinesterase, anticancer, *anti*-inflammatory, antioxidant, *anti*-tubercular, *anti*-hypertensive, *anti*-convulsant, *anti*-analgesic, and *anti*-depressant activities etc.), agrochemical and clinical applications to the novel therapeutic agents in addition to their usage as dyes, and smart functional materials as well [18–20]. Interestingly, this venerable heterocyclic moiety is not only a part of several important drug molecules and remarkable receptors in host-guest chemistry but also reside in a variety of medicinally active natural products for instance strychnine, reserpine, alstonine etc.; widespread in diverse species of animals, plants, marine organisms, and the part of lysergic acid diethylamide (LSD) as well [21]. More interestingly, they have inimitable property of mimicking the structure of peptides and nicely bind to the enzymes, in addition to exhibit the momentous pharmacological, physiological, synthetic and industrial applications [22]. A list of some important biologically active molecules (**1–12**) containing the indole moiety is depicted in the **Figure 2** [23, 24].

The typical Fischer indolization (FI) reaction involving arylhydrazine (**13)** and aldehyde/ketone (**14**) in the presence of appropriate acid or acid catalyst along with its systematic mechanistic pathway is displayed in the **Figure 3**. Although, a number of pathways were anticipated for the FI, but the one proposed in 1924 by G.M. Robinson and R. Robinson was the most accepted by the scientific community as it was established by both kinetic as well as the spectroscopic means (**Figure 3**) [25]. The mechanism for this particular reaction commence with the activation of the carbonyl carbon of **14** through the protonation with acid/acid catalyst, employed in the operation, which on further reaction with **13** provide the *N*-arylhydrazone intermediate (**17**). Next, the intermediate (**17**) afforded the ene-hydrazine intermediate (**18**) by means of tautomerization, which upon subsequent [3,3]-sigmatropic rearrangement, distracting the aromaticity of aryl ring

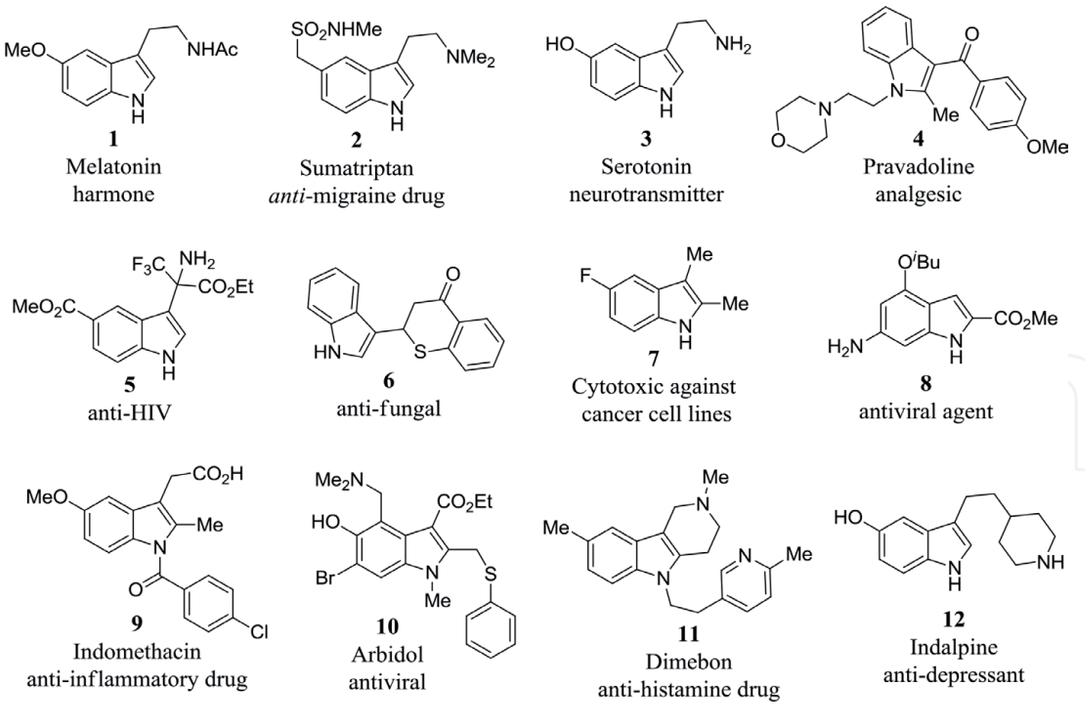


Figure 2.
Structures of some important biologically active indole derivatives.

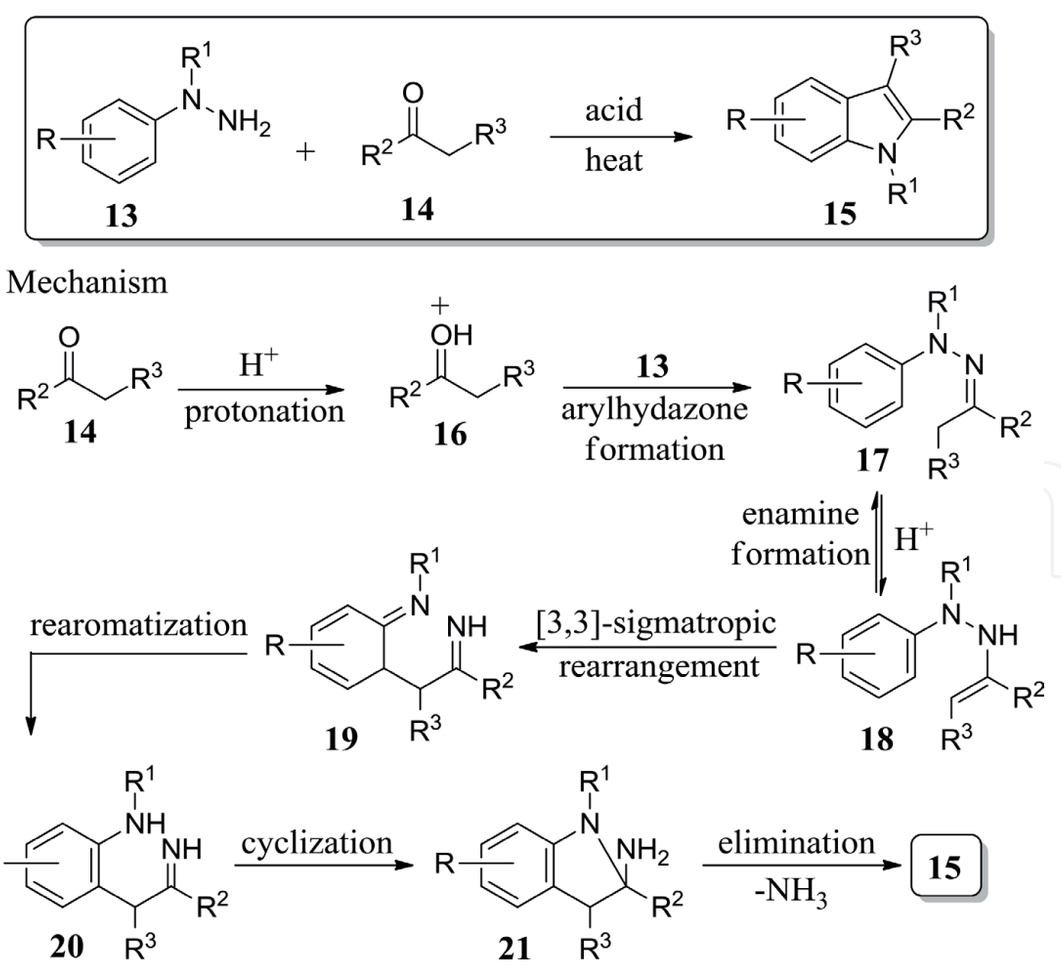


Figure 3.
Representation of indole formation along with the plausible mechanism.

system, followed by rearomatization deliver another intermediate (**20**) through the *bis*-iminobenzyl ketone (**19**). Latter furnishes the required indole derivatives (**15**) by virtue of cyclization followed by the loss of ammonia molecule *via* **21** (**Figure 3**). Interestingly, it has been observed that the reaction conditions as well as the nature of the substrate decide the rate determining step (rds). Generally, ene-hydrazine intermediate (**18**) formation or the [3,3]-sigmatropic rearrangement step has been noticed as the rate-limiting step depending on the situation, as discussed further below. The [3,3]-sigmatropic rearrangement has been observed as rate determining step, in a specific case of *α-N*-acyl hydrazones in addition to weak acidic solutions as well as when ammonia elimination is prevented due to steric effects [25]. Whileas, in most of the cases including the strong acidic condition favors the ene-hydrazine (**18**) formation as the rds-step of the reaction. More specifically, unsymmetrical 1,l-diarylhydrazines under strong acidic condition provide the indolization at most activated ring (i.e. most susceptible to the protonation), whileas under neutral reaction conditions almost equal amount of isomers are generally being formed.

Accordingly, synthetic chemists have long sought approaches for the construction of indole architectures, and a plethora of methods continue to be reported in this trend [26]. Hardly surprising, to date, a myriad of methods involving both intra- and intermolecular transformations for the construction of indole derivatives, particularly the usage of named reactions such as, Gassman, Bartoli, Thyagarajan, Julia, Schmid, Wender, Couture, Kihara, Nenitzescu, Engler, Saegusa, Liebeskind, Sundberg, Hemetsberger, Magnus, Feldman, Reissert, Makosza, Leimgruber–Batcho, Watanabe, Larock, Yamanaka–Sakamoto, Hegedus–Mori–Heck, Fürstner, Castro, Natsume, Nordlander, and so on, have successfully been employed [27]. But, to our best knowledge, despite its numerous complications, rearrangements, and also mechanistic mysteries, Fischer indole protocol, an old yet effective procedure which involve a pericyclic tool namely, [3,3]-sigmatropic rearrangement, remains the epitome for the scientific community around the globe to assemble diverse indole and its congeners [28]. Although, a variety of acid catalysts for example HCl, AcOH, PPA, $TiCl_4$, $ZnCl_2$, $SOCl_2$, PCl_3, TsOH, H_2SO_4, mont-morilloniteclay zeolite etc., have been employed to synthesize the indole framework using FI protocol, but simple, and eco-friendly methods which involve non-hazardous, inexpensive and easily accessible chemicals as well as reagents utilizing the environmentally benign practices are always of particular interest. In this regard, König's group in 2012, first time reported a green approach by employing the FI strategy under a low melting mixture of dimethyl urea (DMU):L-(+)-tartaric acid (TA) in (7:3) ratio to yield a range of indole derivatives in good-to-excellent yields [24]. The beauty of this particular green method relies on the fact that, a clean low melting mixture is generated just by heating the two components in appropriate amount at much lower temperature than its individual components, and can be used without further purification. Herewith, the low melting mixture, acts as mild acidic catalyst (pH 3.7) as well as solvent to furnish the required indoles with great functional group compatibility and selectivity. As can be seen from an inspection of the **Figure 4**, these authors prepared a range of functionalized indole systems (**22–47**) in decent yields using acyclic and cyclicketones in addition to cyclic enol ethers for instance dihydrofuran and dihydropyran. Fascinatingly, optically active ketone deliver the indole with retention of the configuration. Moreover, indolenines (**31**), was also prepared through this powerful technique in respectable yields under mild reaction conditions (**Figure 4**). Besides, hormone melatonin (**25**) and dimebon (**26**) were also obtained by utilizing this wonderful green approach as a crucial step (**Figure 4**). Inspiring form this simple yet powerful procedure and also from the applications of the indole moiety containing molecules, two years later to this report, in 2014, Kotha and his teammates have successfully employed this strategy for the synthesis of C_2-and C_s-symmetric *bis*-indole

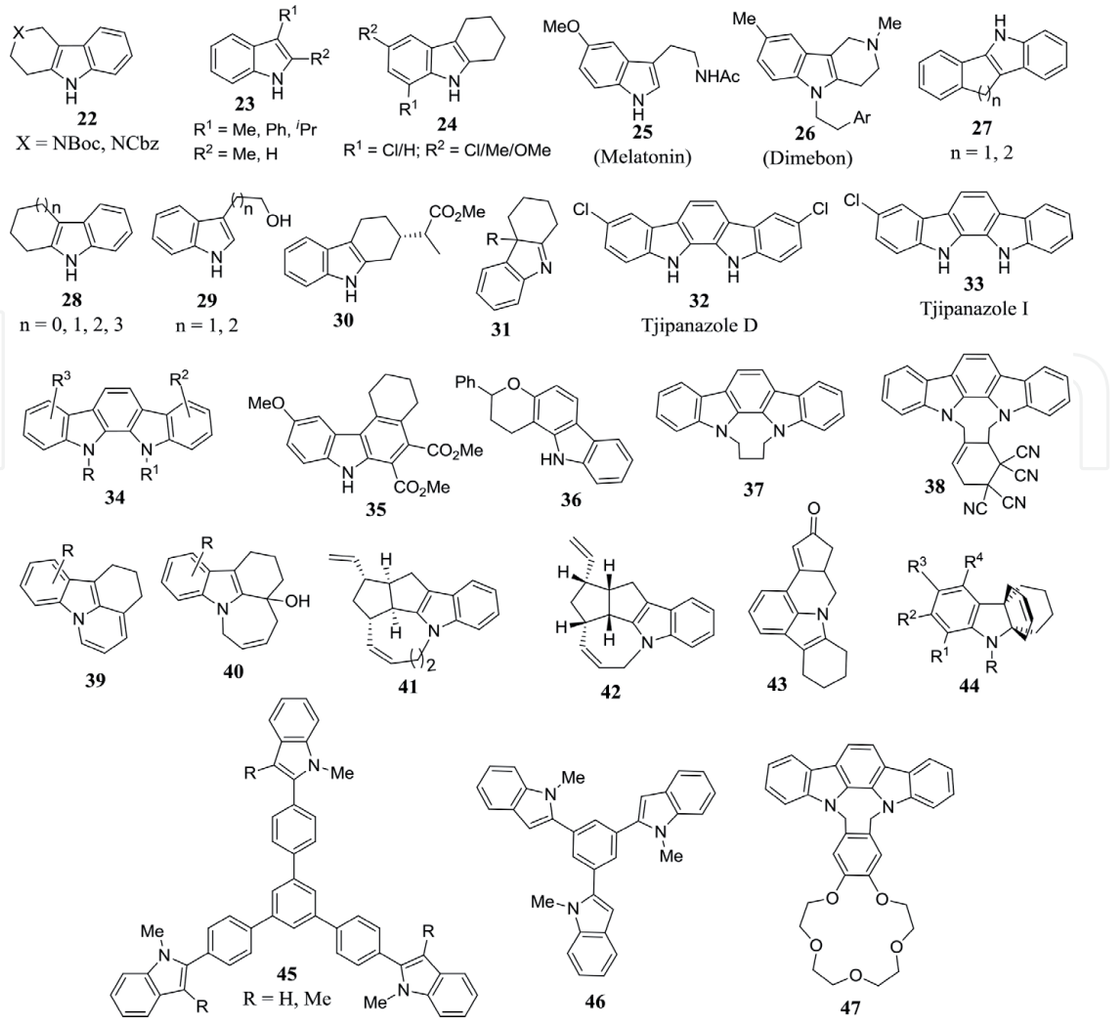


Figure 4.
Indole derivatives constructed using DMU/TA mediated green protocol.

systems (**52**, **53**, **58**, **60–62**) from bicyclo-3,7-diones and 1-methyl-1-phenylhydrazine under DMU/TA (7:3) reaction conditions (**Figure 5**) [29]. Later on, Kotha's team nicely expanded this delightful method for the generation of a variety of carbazole derivatives (**32–35**) including pyrano-carbazole (**36**) and *aza*-cyclophane based carbazoles (**37** and **38**) as depicted **Figure 4** [30–32] in **Figure 4**. Interestingly, utilizing this tactic, they have also prepared carbazole-based natural products such as tijapinazole D (**32**) and tijapinazole I (**33**) in addition to the crown-based indolocarbazole (**47**). Moreover, in the laboratory of Kotha's group, diverse heteropolycyclic compounds (**39–43**) in addition to the propellane derivatives (**44**) have been assembled by using ring-closing metathesis (RCM) and Fischer indolization in a low melting mixture of DMU/TA as crucial steps, (**Figure 4**) [33–35]. Keeping the importance of C_3-symmetric molecules in medicinal and bioorganic chemistry besides their vital role in material science and technology, the same group has also prepared star-shaped C_3-symmetric compounds **45** and **46** involving cyclotrimerization and DMU/TA mediated indolization approach (**Figure 4**) [36]. Furthermore, as can be inspected from the **Figure 5**, they design and constructed varied cyclophane derivatives (**48**, **49**, **54**, **55** and **59**) through the involvement of the Grignard reaction, RCM and a low melting mixture mediated indolization sequences in respectable yields because of their applicability in supramolecular chemistry [37–41]. In addition to these, Kotha's group has also prepared diverse polycyclic mono- (**50**, **56**, **63**) and *bis*-indole derivatives (**51**, **57**, **58**, **64**) by means of a deep eutectic mixture of DMU/TA (70:30) under operationally simple reaction conditions [42–45].

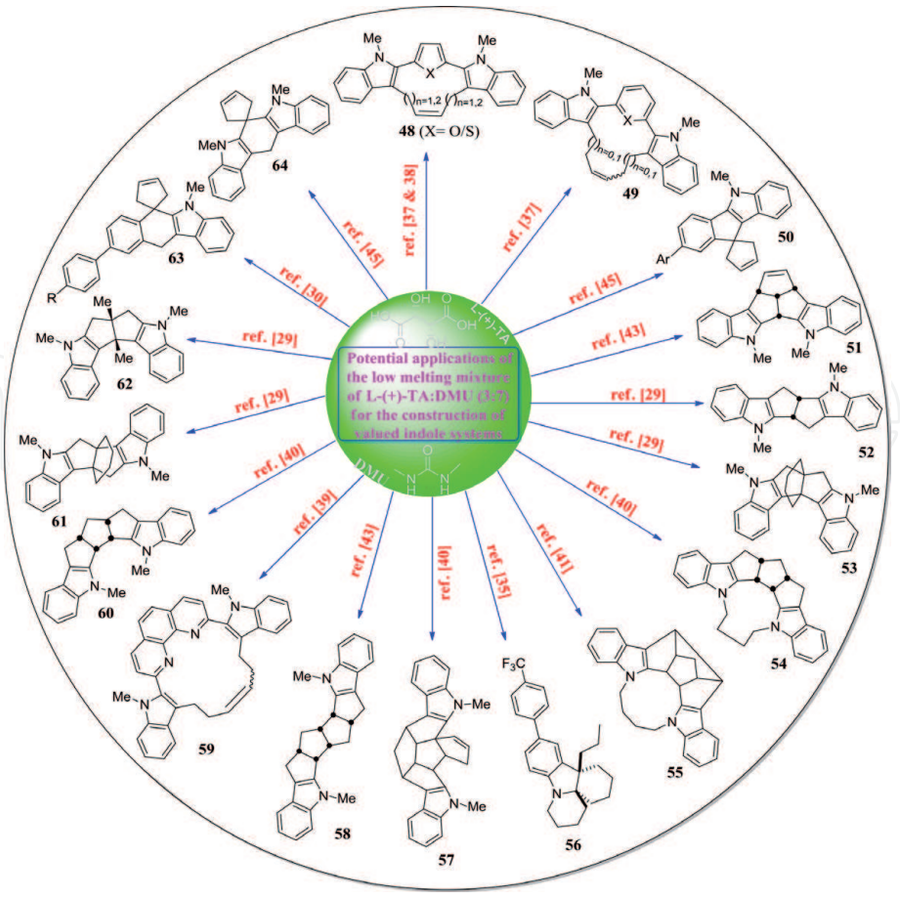


Figure 5.
Diverse indole derivatives assembled via *FI utilizing the DMU/TA mixture.*

3. Synthesis of *bis*-(indolyl)methane, indenylindoles and 2,2-disubstituted indolin-3-ones

In recent past, *bis*-(indolyl)methanes (BIMs) have attracted a tremendous attention of the research community due to their potential applications both in pharmaceuticals and agrochemicals besides their activity in breast tumor cells, bladder cancer and also inhibits proliferation practice as well. Moreover, they display antitumorgenic, antibiotic, antimicrobial activity and *anti*-inflammatory activities etc., and are mostly found in marine natural sources. Fascinatingly, getting inspired from the above applications and also other, if any, the group of Nagarajan constructed the diverse BIMs (**67**) including the natural products arsindoline A and B *via* a green protocol in the presence of DMU:TA (70:30) (**Figure 6**) [46]. Surprisingly, the BIMs were not formed when instead of aldehydes (**66**); cyclicketones (**68**) were treated with indole derivatives in the Kotha's laboratory, rather they received indenylindoles (dienes) **69** under parallel reaction conditions (**Figure 6**) [30]. On the other hand, it has been found that, numerous medicinally active natural and non-natural products possess 2,2-disubstituted indolin-3-one scaffold in addition to their usage as the key building blocks in the total synthesis of diverse indole alkaloids. In this regard, Xie's group involved a deep eutectic mixture of DMU/TA to furnish a range of 2,2-disubstituted indolin-3-one derivatives (**72**) as displayed in the **Figure 6** [47].

Synthesis of heterocyclic compounds has always been of prime importance to the research community because of their vital role in a numerous areas ranging from material sciences and technology to the pharmaceutical and agrochemical

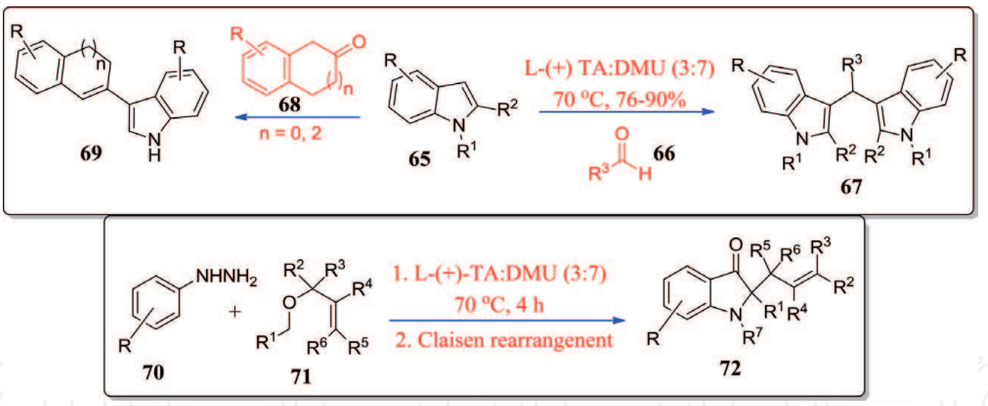


Figure 6.
Synthesis of bis-*(indolyl)methane, indenylindoles and 2,2-disubstituted indolin-3-ones utilizing DMU/TA mediated green approach.*

industries. To the best of our knowledge, to date, a choice of drugs containing heterocyclic scaffolds are available in the world market, and many hundred are under clinical trials around the globe. Therefore, there are always high demands to develop novel strategies for the generation of heterocyclic systems particularly involving milder reaction conditions in an environmentally friendlier manner from easily assessable bulk materials. To this context, although a number of methods having several advantages and disadvantages are available in the literature but in recent years, the deep eutectic solvents have changed the scenario of modern synthetic chemistry by providing a plethora of green approaches towards the construction of these valuable molecules. Among the heterocyclic systems, quinoline scaffold has received a considerable amount of interest because of its availability in a plethora of bioactive molecules. A very simple yet effective green procedure for the synthesis of a variety of quinoline derivatives (**75**) have been developed by Zhang and his co-workers with the involvement of a low melting mixture of DMU:TA (70:30) in moderate-to-excellent yields in a Friedländer fashion (**Figure 7**) [48]. On the other hand, the Biginelli procedure, a multi-component reaction, has been employed for assembling the dihydropyrimidinones (DHPMs) under a green reaction conditions by Köenig's team because of their utility in calcium channel blockers and also as HIV inhibitors and anticancer agent (**Figure 7**) [49]. Captivatingly, this procedure works equally well with masked aldehydes to furnish the required DHPMs in reasonable yields. In another study, the same group has utilized this powerful green methodology for assembling diverse functionalized pyrimidopyrimidinedione derivatives (**85**) with the help of Biginelli reaction in which the low melting mixture play a triple role such as solvent/catalyst/reagent (**Figure 7**) [50]. In this study, although, they have tried several low melting mixtures but DMU/TA in a ratio of 7:3 provided the best results.

In a separate study, Krishnakumar *et al.,* has reported a green chemical procedure for the construction of *N*-arylhomophthalimides (**83**) by employing the Michael addition reaction of the Michael-donor (homophthalimides) **82** with Michael-acceptor (chalcones) **81** in DMU:TA low melting mixture (**Figure 7**) [51]. In this report, the authors have screened various reaction conditions but the mention conditions provided the good results for both electron withdrawing as well as electron donating groups containing contestants.

The hydantoin and its congeners are the key scaffolds from biological point of view as they are the part of various molecules which exhibit a range of activities for instance antidepressants, antiulcer, antidiabetic agents, anticonvulsant, antiarrhythmic, and antiviral etc. Moreover, this moiety also play a significant role in agrochemistry, cosmetic industry, dye-sensitized solar cells, chiral auxiliaries and also used

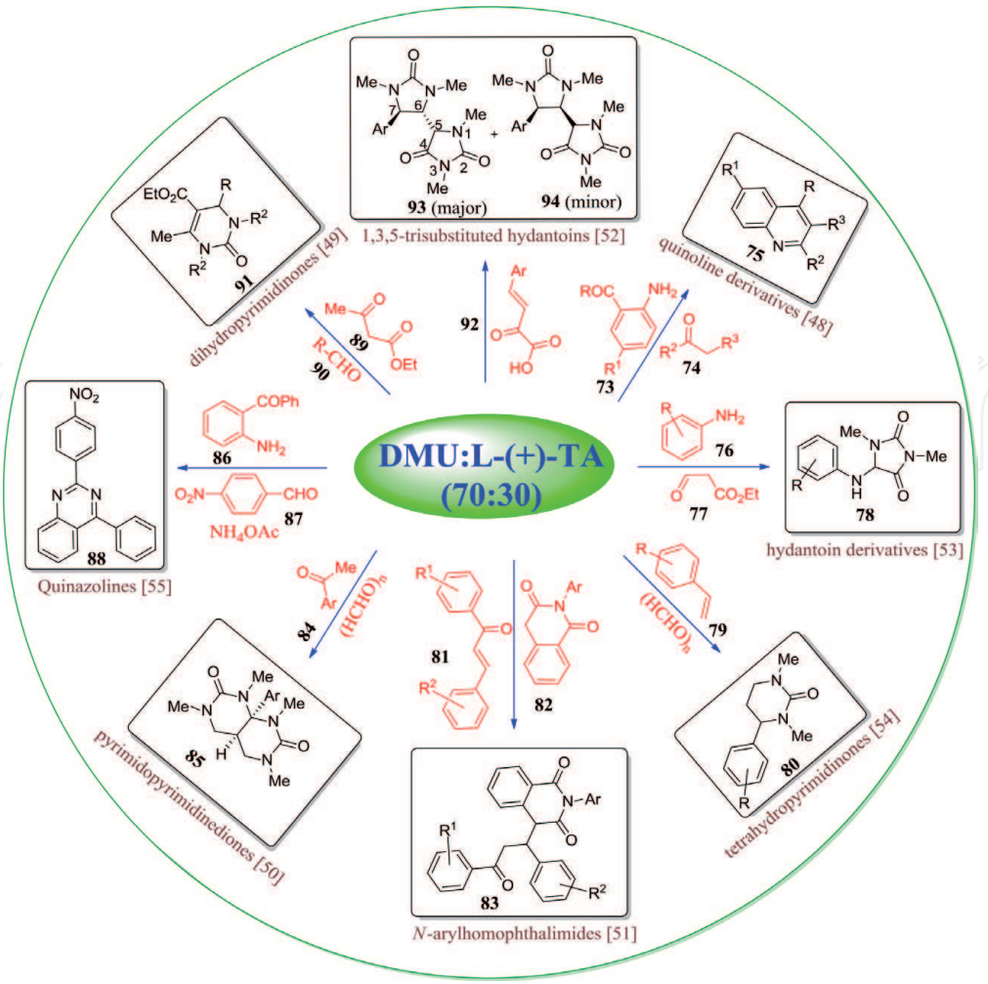


Figure 7.
A variety of heterocycles assembled by employing the DMU/TA melt.

as the intermediates for the generation of enantiomerically pure natural and non-natural α-amino acids by means of the dynamic kinetic resolution. Therefore, keeping the consequence of these molecules in mind, König's group in 2013 developed a simple and eco-friendly method for the synthesis of 1,3,5-trisubstituted hydantoin derivatives (**93**/**94**) in excellent yields by means of DMU/TA melt-mediated green approach (**Figure 7**) [52]. Interestingly, during their experimentation, they noted down good diastereoselectivity in which *anti*-isomers were isolated in major amount whileas *syn*-diastereomers were obtained as minor products, confirmed by nuclear overhauser effect (NOE) and X-ray analysis means. On another front, quite recently, Kotha's team has reported mono-hydantoins as well as thiohydantoins by means of three component reaction under low melting mixture of DMU/TA with electron neutral, electron donating, and electron withdrawing groups possessing aniline derivatives (**Figure 7**) [53]. Finally, the tetrahydropyrimidinones (**80**) and quinazoline derivatives (**88**) have been reported, by the groups of Baskaran and Zhang, respectively by employing the same low melting mixture of DMU/TA under similar reaction conditions as can be inspected from the **Figure 7** [54, 55].

4. Conclusions and outlook

In summary, a novel method involving DMU/TA as a low melting mixture has comprehensively been revealed in this chapter, depicting its pivotal role in the heart of modern synthetic organic chemistry particularly for the generation of a variety

of valuable heterocyclic systems. Herein, we have disclosed, a decade advancements made in this field since its inspection (2011). As discussed above in detail, this simple, environmentally benign, cost effective, and productive method has already been shown its impact in the domain of modern preparative chemistry in general, and green chemistry in particular. We assure that this chapter based on greener transformations, will not only help the readers for complete understanding of a low melting mixture of DMU/TA, and its contribution towards the vital synthetic organic transformations, but also would inspire the motivated researchers to exploit the masked opportunities. More importantly, this method might provide a new way to the chiral catalyst mediated reaction since herewith, chiral tartaric acid is part of the melt, and may act as a valuable handle for the generation of chirality in a molecule under the operation.

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Conflicts of interest

The author declare no conflicts of interest.

Author details

Rashid Ali
Organic and Supramolecular Functional Materials Research Laboratory, Department of Chemistry, Jamia Millia Islamia, Jamia Nagar, Okhla, New Delhi, India

*Address all correspondence to: rali1@jmi.ac.in

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References

[1] Sheldon R.A, *Organic synthesis-past, present and future*. *Chem. Ind.* (London) 1992:903.

[2] Sheldon R.A, *Fundamentals of green chemistry: efficiency in reaction design*. *Chem. Soc. Rev.* 2012:41:1437.

[3] *Report of the world commission on environment and development: our common future*; Oxford University Press, Oxford, U.K., 1987.

[4] Anastas P.T, Warner, J.C. *Green chemistry: theory and practice*, Oxford University Press, Oxford, 1998.

[5] Ramón D.J, Guillena G, *Deep eutectic solvents: synthesis, properties, and applications*, Wiley-VCH Verlag GmbH & Co. KGaA, 2019.

[6] Welton T, *Room-temperature ionic liquids. solvents for synthesis and catalysis*. *Chem. Rev*. 1999:99:2071.

[7] Butler R.N, Coyne A.G, Water: nature's reaction enforcer-comparative effects for organic synthesis "in-water" and "on-water" *Chem. Rev*. 2010:110:6302.

[8] Jessop P.G, Ikariya T, Noyori R, Homogeneous catalysis in supercritical fluids *Chem. Rev*. 1999:99:475.

[9] Jutz F, Andanson J.-M, Baiker A, Ionic liquids and dense carbon dioxide: a beneficial biphasic system for catalysis. *Chem. Rev*. 2011:111:322.

[10] Kitanosono T, Masuda K, Xu P, Kobayashi S, Catalytic organic reactions in water toward sustainable society. *Chem. Rev.* 2018:118:679.

[11] Zhang Q, Zhanga S, Deng Y, Recent advances in ionic liquid catalysis. *Green Chem*. 2011:13:2619.

[12] Perna M.P, Vitale P, Capriati V, Deep eutectic solvents and their applications as green solvents. *Curr. Opin. Green Sustain. Chem.* 2020:21:27.

[13] Liu P, Hao J.-W, Mo L.-P, Zhang Z.-H, Recent advances in the application of deep eutectic solvents as sustainable media as well as catalysts in organic reactions. *RSC Adv*. 2015:5:48675.

[14] Smith E.L, Abbott A.P, Ryder K.S, Deep eutectic solvents (DESs) and their applications *Chem. Rev*. 2014:114:11060.

[15] Kotha S, Chakkapalli C, Application of Fischer indolization under green conditions using deep eutectic solvents. *Chem. Rec*. 2017:17:1039.

[16] Fischer E, Jourdan F, Ueber die hydrazine der brenztraubensäure. *Ber. Dtsch. Chem. Ges*. 1883:16:2241.

[17] Robinson B, *The Fischer indole synthesis*, Wiley-Interscience, New York, 1982.

[18] Sundberg R.J, *Indoles*, Academic Press, San Diego, CA, 1996.

[19] Sundberg R.J, '*The chemistry of indoles*', AcademicPress, New York, 1970, Chapter III.

[20] Palmisano G, Penoni A, Sisti M, Tibiletti F, Tollari S, Nicholas K.M, Synthesis of indole derivatives with biological activity by reactions between unsaturated hydrocarbons and aromatic precursors. *Curr. Org. Chem.* 2010:14:2409.

[21] Heravi M.M, Rohani S, Zadsirjan V, Zahedi N, Fischer indole synthesis applied to the total synthesis of natural products. *RSC Adv.* 2017:7:52852.

[22] Kumari A, Singh R.K. Medicinal chemistry of indole derivatives: Current to future therapeutic prospectives. *Bioorg. Chem.* 2019:89:103021.

[23] Colella M, Degennaro, L, Luisi R, Continuous flow synthesis of heterocycles: a recent update on the flow synthesis of indoles. *Molecules*, 2020:25:324.

[24] Gore S, Baskaran S, König B, Fischer indole synthesis in low melting mixtures. *Org. Lett.* 2012:14:4568.

[25] Robinson G.M, Robinson R, The mechanism of E. Fischer's synthesis of indoles. *J. Chem. Soc., Trans.* 1924:**125**:827.

[26] Gribble, G.W, Recent developments in indole ring synthesis-methodology and applications. *Contemp. Org. Synth*. 1994:145.

[27] Gribble G.W, Recent developments in indole ring synthesis-methodology and applications. *J. Chem. Soc*., *Perkin Trans. 1*. 2000:1045.

[28] Hughes D.L, Progress in the Fischer indole reaction. a review. *Org. Prep. Proced. Int.* 1993:25:607.

[29] Kotha S, Chinnam A.K, Anomalous behaviour of *cis*-bicyclo[3.3.0]octane-3,7-dione and its derivatives during twofold Fischer indole cyclization using low-melting mixtures. *Synthesis,* 2014:301.

[30] Kotha S, Ali R, Saifuddin M, Diversity-oriented approach to natural product inspired pyrano-carbazole derivatives: Strategic utilization of hetero-Diels–Alder reaction, Fischer indolization and the Suzuki–Miyaura cross-coupling reaction. *Tetrahedron,* 2015:71:9003.

[31] Kotha S, Aswar V.R, Chinnam A.K, One-pot synthesis of carbazoles from indoles via a metal free benzannulation. *Tetrahedron Lett*. 2017:58:4360.

[32] Kotha S, Saifuddin M, Aswar V.R. Diversity-oriented approach to indolocarbazoles via Fischer indolization and olefin metathesis: total synthesis of tjipanazole D and I. *Org. Biomol. Chem*. 2016:14:9868.

[33] Kotha S, Ravikumar O, Diversity-oriented approach to carbocycles and heterocycles through ring rearrangement metathesis, Fischer indole cyclization, and Diels–Alder reaction as key steps. *Eur. J. Org. Chem*. 2014:5582.

[34] Kotha S, Aswar V.R, Singhal G, Synthesis of tricyclic units of indole alkaloids: application of Fischer indolization and olefin metathesis. *Tetrahedron,* 2017:73:6436.

[35] Kotha S, Aswar V.R, Ansari S, Selectivity in ring-closing metathesis: synthesis of propellanes and angular aza-tricycles. *Adv. Synth. Catal*. 2019:361:1376.

[36] Kotha S, Todeti S, Das T, Datta A, Synthesis and photophysical properties of C_3-symmetric star-shaped molecules containing heterocycles: a new tactics for multiple Fischer indolization. *ChemistrySelect.* 2018:3:136.

[37] Kotha S, Chinnam, A.K, Shirbhate M.E, Diversity-oriented approach to cyclophanes via Fischer indolization and ring-closing metathesis: substrate-controlled stereochemical outcome in RCM. *J. Org. Chem*. 2015:80:9141.

[38] Kotha S, Chinnam A.K, Shirbhate M.E, Design and synthesis of hybrid cyclophanes containing thiophene and indole units via Grignard reaction, Fischer indolization and ring-closing metathesis as key steps. *Beilstein J. Org. Chem*. 2015:11:1514.

[39] Kotha S, Shirbhate M.E, Chinnam A.K, Sreevani G, Synthesis of phenanthroline and indole based hybrid cyclophane derivatives via ring-closing metathesis. *Heterocycles*, 2016:93:399.

[40] Kotha S, Chinnam A.K, Ali R, Hybrid macrocycle formation and spiro annulation on *cis-syn-cis*-tricyclo[6.3.0.$0^{2,6}$]undeca-3,11-dione and its congeners via ring-closing metathesis. *Beilstein J. Org. Chem*. 2015:11:1123.

[41] Kotha S, Cheekatla S.R, Chinnam A.K, Jain T, Design and synthesis of polycyclic bisindoles via Fischer indolization and ring-closing metathesis as key steps. *Tetrahedron Lett*., 2016:57:5605.

[42] Kotha S, Chinnam A.K, Design of aza-polyquinanes via Fischer indole cyclization under green conditions. *Heterocycles*, 2015:90:690.

[43] Kotha S, Chinnam A, K, Sreenivasachary N, Ali R, Design and synthesis of polycyclic indoles under green conditions via Fischer indolization. *Indian J.Chem*. 2016:55B:1107.

[44] Kotha S, Ali R.A, simple approach to *bis*-spirocycles and spiroindole derivatives via green methods such as Fischer indolization, ring-closing metathesis, and Suzuki–Miyaura cross-coupling. *Turk. J. Chem*. 2015:39:1190.

[45] Kotha S, Ali R, Srinivas V, Krishna N.G, Diversity-oriented approach to spirocycles with indole moiety via Fischer indole cyclization, olefin metathesis and Suzuki–Miyaura cross-coupling reactions. *Tetrahedron*, 2015:71:129.

[46] Jella R.R, Nagarajan R, Synthesis of indole alkaloids arsindoline A, arsindoline B and their analogues in low melting mixture. *Tetrahedron*, 2013:69:10249.

[47] Xia Z, Hu J, Gao Y.-Q, Yao, Q, Xie W, Facile access to 2,2-disubstituted indolin-3-ones via a cascade Fischer indolization/Claisen rearrangement reaction. *Chem. Commun*. 2017:53:7485.

[48] Ma F.-P, Cheng G.-T, He Z.-G, Zhang Z.-H, A new and efficient procedure for Friedländer synthesis of quinolines in low melting tartaric acid-urea mixtures. *Aust. J. Chem*. 2012:65:409.

[49] Gore S, Baskaran S, Köenig B, Efficient synthesis of 3,4-dihydropyrimidin-2-ones in low melting tartaric acid–urea mixtures. *Green Chem*. 2011:13:1009.

[50] Gore S, Baskaran S, Köenig B, Synthesis of pyrimidopyrimidinediones in a deep eutectic reaction mixture. *Adv. Synth. Catal*. 2012:354:2368.

[51] Krishnakumar V, Vindhya N.G, Mandal B.K, Khan F.-R.N, Green chemical approach: low-melting mixture as a green solvent for efficient michael addition of homophthalimides with chalcones. *Ind. Eng. Chem. Res*. 2014:*53*:10814.

[52] Gore S, Chinthapally K, Baskaran S, König B, Synthesis of substituted hydantoins in low melting mixtures. *Chem. Commun*. 2013:49:5052.

[53] Kotha S, Gupta N.K, Aswar V.R, Multicomponent approach to hydantoins and thiohydantoins involving a deep eutectic solvent. *Chem.–Asian J*. 2019:14:3188.

[54] Devi P, Lambu M.R, Baskaran S, A novel one-pot method for the stereoselective synthesis of tetrahydropyrimidinones in a low melting mixture. *Org. Biomol. Chem*. 2020:18:4164.

[55] Zhang Z.-H, Zhang X.-N, Mo L.-P, Li Y.-X, Ma F.-P. Catalyst-free synthesis of quinazoline derivatives using low melting sugar–urea–salt mixture as a solvent, *Green Chem*. 2012:14:1502.