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SYNERGISTIC EFFECT OF ETHYL LACTATE/GVL: A NEW ROUTE FOR THE SYNTHESIS OF SPIROOXINDOLE-INDAZOLONES AND ITS DERIVATIVES

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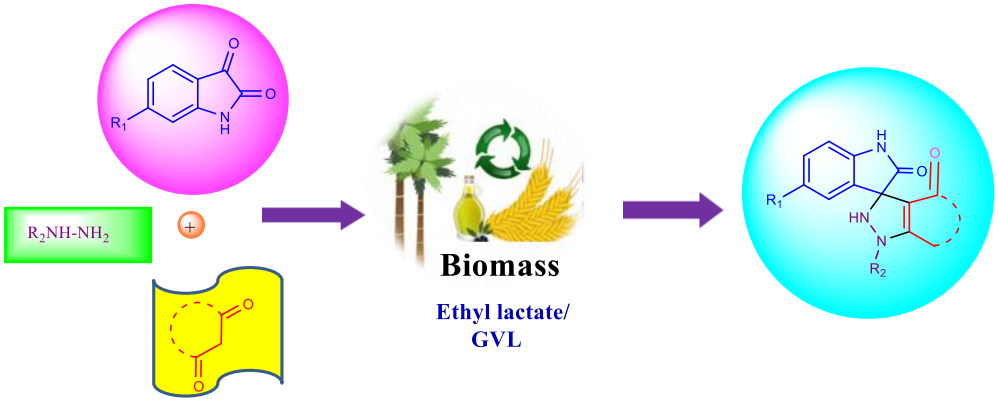
Abstract: A clean and efficient, versatile, one pot, catalyst free, multicomponent strategy for the synthesis of spirooxindole-indazolones and its derivatives is reported. Synergistic effect of a green solvent system i.e. Ethyl lactate and γ- valero lactone (GVL), enhance the product yield and make this protocol superior than previously reported method by our group. This method includes several benefits like green solvent system, synergistic effect, high atom economy, good to excellent yield etc. making it valuable green alternative to the existing methods.

Keywords: Ethyl lactate, GVL, Green solvents, Indazolones, Synergistic effect, Spirooxindole.

Introduction

Spirooxindole is an essential heterocyclic moiety found in a range of alkaloids and biologically



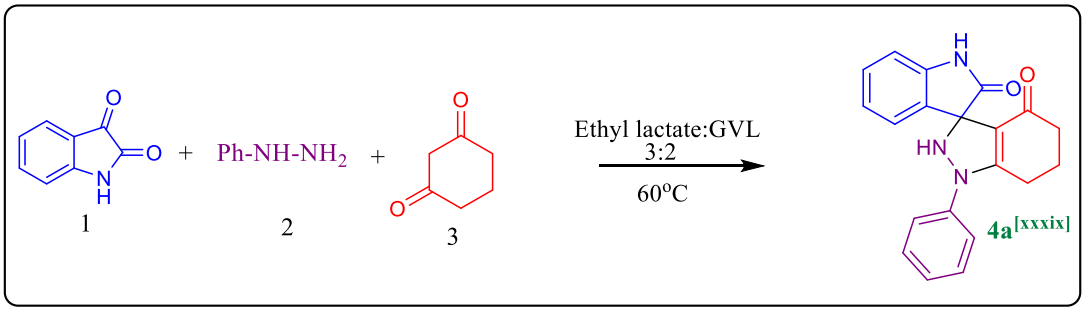
active compounds as a key structural motif.[i-iii] Spirooxindole compounds display a variety of important biological activities, such as anti-HIV[iv], anti-cancer[v], anti-tuberculosis[vi], anti-oxidation[vii], antifungus[viii], anti-malarial[ix] and other pharmacological activities.[x]Despite the fact that a vast number of synthetic methods of spirooxindoles have been reported to date, organic chemists still face a major problem in developing more efficient approaches for accessing existing and novel spirooxindole derivatives.[xi-xiii] Indazolones are a biologically significant class of molecules from a medical perspective, constructing hybrid compounds with

both the spirooxindole and indazolone motifs linked onto one platform is extremely desirable.[xiv-xv]

Due to a growing awareness of the need to avoid environmental harm as well as economic costs, the use of environmentally friendly green approaches in organic synthesis has experienced a significant growth in the last few decades.[xvi]

In this context, a significant emphasis area has been to replace hazardous petroleum-based organic solvents with safe, inexpensive, and ecologically friendly solvents derived from bio-renewable feed-stocks.[xvii-xviii] As a result, biomass-derived reaction media like lactic acid[xix], 2-methyl-THF[xx], ethyl lactate[xxi], glycerol[xxii], and γ- valerolactone[xxiii], among others, are growing rapidly as suitable alternatives to conventional solvents. Among these, ethyl lactate and GVL have emerged as an efficient and practical solvent in synthetic chemistry, as it fits a number of characteristics, including non-flammability, nontoxicity, non-volatility, and ease of availability[xxiv-xxv], thereby meeting the majority of green chemistry criteria.

γ - valerolactone (GVL), a naturally occurring molecule in fruits that can also be generated from carbohydrate-based biomass, is gaining popularity.[xxvi-xxvii] GVL has been identified as a sustainable dipolar aprotic solvent for many processes, such as biomass conversion, Sonogashira reaction, and Heck coupling reactions, due to its good qualities of low toxicity, biodegradation, and low vapour pressure.[xxviii-xxx] GVL has a high boiling point of 207°C and a low melting point of 31°C. It is a colourless liquid with a low viscosity at ambient temperature. In a multistep procedure, it can be easily produced from cellulose or hemicellulose, and hence from non-food biomass.[xxxi-xxxii] Ethyl lactate is a novel green solvent that is an ester of lactic acid. It is a plant-based agrochemical solvent. The solvent is safe for the environment because it degrades gradually into carbon dioxide and water.[xxxiii] Ethyl lactate shows a remarkable properties such as high boiling point, low surface tension, low vapour pressure and it has high flash point and low volatility.[xxxiv-xxxv] As a proton donor or acceptor, it can establish intramolecular and intermolecular hydrogen bonds.[xxxiii] In oils, it can also cause vander waals interactions.[xxxvi] As a result, ethyl lactate may dissolve in both polar and non-polar media, allowing it to recover compounds with a broad spectrum of polarity without the use of a co-solvent.[xxxvii] Ethyl lactate is widely utilised in the food, pharmaceutical, and cosmetic sectors because to its hygroscopic and emulsifying properties.[xxxviii] To the best of our knowledge, synthesis of spirooxindole-indazolones and its derivatives is reported only by our research group previously by using glycerol as a green solvent[xxxix] and, in continuation with our research interest in synthesising heterocyclic molecules using green methodology[xl],we synthesised this compound by using GVL and ethyl lactate as a green solvent. We found that due to synergistic effect of ethyl lactate-GVL, product yield was increased as per our expectations, where ethyl lactate act as promoter to enhance the product yield (Scheme 1).



Scheme 1 Synthesis of 1-phenyl-1,2,6,7-tetrahydrospiro[indazole-3,3'-indoline]-2',4(5H)-dione**4a**.

Results and Discussion; We began with a model reaction in which isatin 1 (1mmol) and phenyl hydrazine 2 (1mmol) were reacted in water at a specific temperature. There was no hydrazone formation after 14 hours of stirring. We repeat the same reaction were carried out in reflux condition, the formation of hydrazone was seen after 12 hours of stirring. However, just a trace amount of a new product was found after the addition of dimedone 3 (1mmol). The experiment was now conducted at room temperature in the presence of glycerol, but the results were not satisfactory. To improve the yield of the product, we used ethyl lactate instead of glycerol, and the result was remarkably similar. However, promising results were obtained when the reaction was performed at 60^{o}C in a combination of ethyl lactate -water (4:1). The addition of isatin (1) and phenyl hydrazine (2), a new spot formed on the TLC, which we assumed was the predicted hydrazone. After 30 minutes, the istain was completely disappear. At this time, we added dimedone and kept stirring at reflux until the hydrazone spot was entirely gone (TLC).When spirooxindole-indazolone 4a was isolated and identified as the product, it resulted in an 84% increase in yield and a (4h) reduction in reaction time. Now improving the yield we used GVL in place of ethyl lactate but result is remarkably similar as previous. Now we used the mixture of GVL: water (4:1) only trace amount of product obtain. Further, to enhance the yield of the product, we used a 4:2 mixture of ethyl lactate and glycerol, which has a synergistic effect at 80^{o}C, resulting in 88% of yield and a reduction in reaction time (3.5 h). For better yield we used 3:2 mixture of ethyl lactate and GVL, which also shows synergistic effect at 90^{o}C, resulting in a dramatic increase in yield (93%) and a reduction in reaction time (2.5 h). There was no difference in yield or reaction time when the reaction was carried out at a lower temperature (75^{o}C). However, no difference in yield or reaction time was detected when the reaction temperature was reduced further (to 60^{o}C). However, as the reaction temperature was lowered further (50^{o}C), the yield was significantly reduced and the reaction time increased. Performing the same experiment at room temperature resulted in a further decrease in yield and an increase in reaction time. Increasing the proportion of GVL in the ethyl lactate-GVL solvent system (1:1) resulted in a considerable decrease in yield. The best conditions for performing the above reaction were at 60°C with an ethyl lactate-GVL mixture (3:2) as a reaction medium under catalyst free parameters, yielding the required spirooxindole-indazolone 4a in 93% yield in 2.5 h (Table 1, entry 14).

Table 1 Optimization conditions for the formation of 4a[a].

Entry	**Solvent**	**Temperature**	**Time**	**Yield 4%[b]**
1.	Water	RT	14 h	No reaction
2.	Water	Reflux	12 h	Trace amount
3.	Glycerol	75 °C	6h	78
4.	Ethyl lactate	60^{o}C	4h	87
5.	Ethyl lactate: Water / 4:1	60^{o}C	4h	84
6.	Ethyl lactate: Water / 1:1	60^{o}C	4h	76
7.	GVL	60^{o}C	5h	77
8.	GVL: Water / 4:1	75^{o}C	5h	Trace amount
9.	GVL: Water / 3:2	75^{o}C	6h	Trace amount
10.	Ethyl lactate: Glycerol / 4:2	80 °C	3.5h	88
11.	Ethyl lactate: Glycerol / 4:2	RT	4h	80
12.	Ethyl lactate: GVL / 3:2	90^{o}C	2.5h	93
13.	Ethyl lactate: GVL / 3:2	75^{o}C	2.5h	93
14.	**Ethyl lactate: GVL / 3:2**	**60^{o}C**	**2.5h**	**93**
15.	Ethyl lactate: GVL / 3:2	RT	6h	82
16.	Ethyl lactate: GVL / 1:1	80^{o}C	5h	78

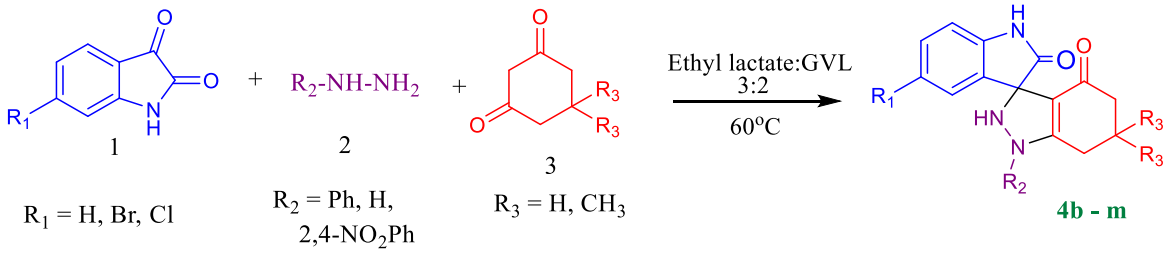
17.	Ethyl lactate: GVL / 1:1	60°C	5h	78

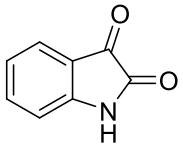
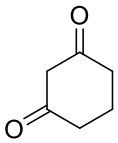
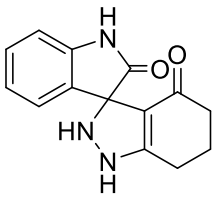
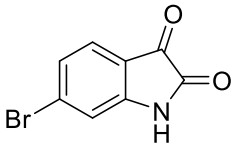
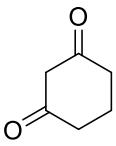
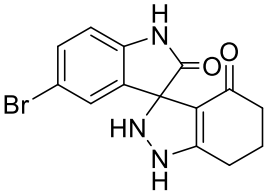
[a] All reactions were carried out with 1 (1 mmol), 2 (1mmol), 3 (1mmol) in 5 mL solvent under air.
[b]Isolated yields.

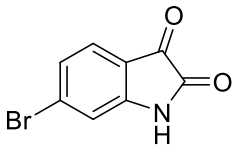
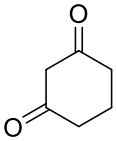
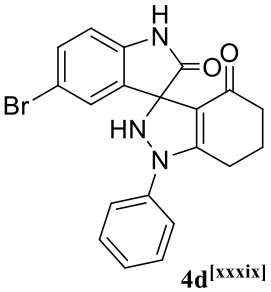
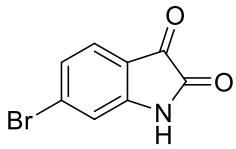
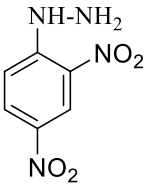
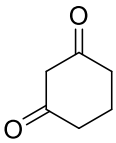
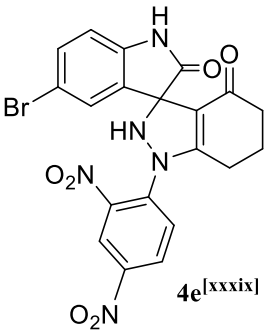
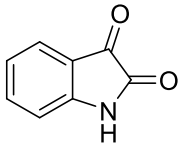
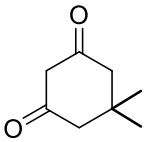
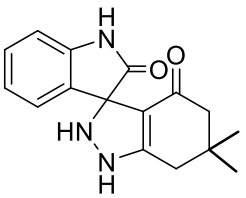
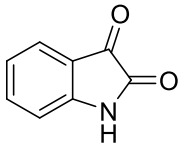
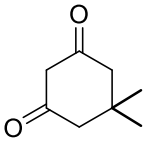
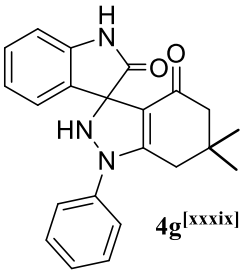
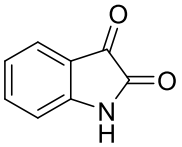
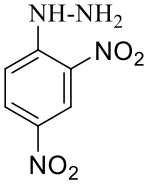
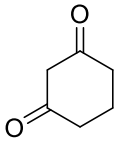
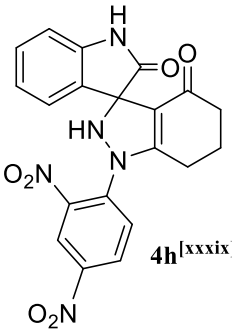
Once ideal conditions for conducting this reaction have been identified, the scope and efficiency of the developed synthetic protocol was explored under the optimized reaction conditions with isatins, hydrazines and dimedones having different substituents, to furnish the corresponding spirooxindole-indazolones. In all the cases the desired product were obtained in high yields and short reaction times (Table 2).

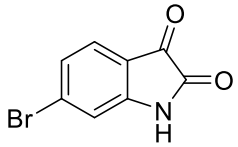
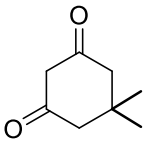
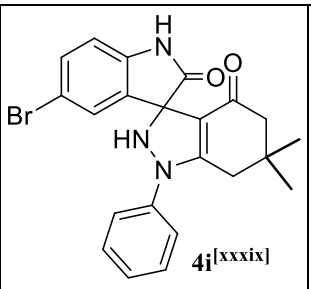
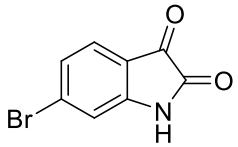
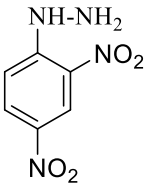
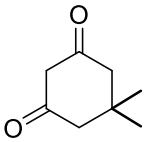
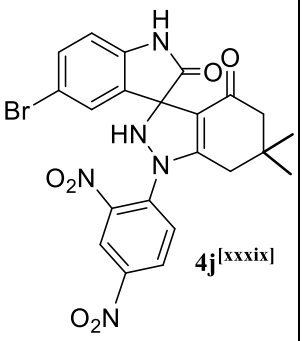
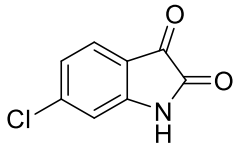
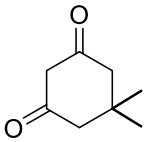
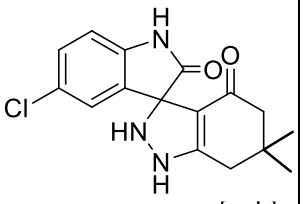
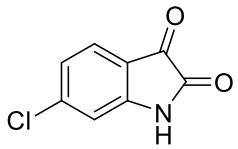
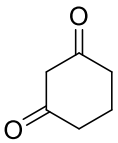
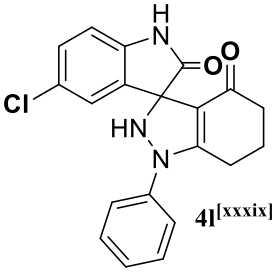
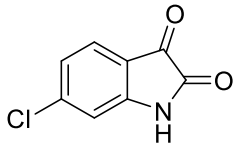
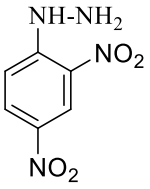
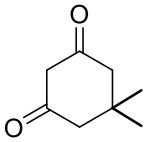
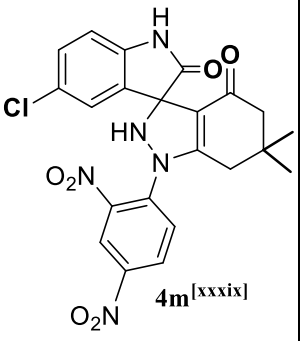
It was found that simple hydrazine produced the best results. There was a slight decrease in yield and a slight increase in reaction time in the case of phenyl hydrazine. Due to the presence of the strongly electron-withdrawing nitro group on the phenyl ring, when 2, 4- dinitrophenyl hydrazine was employed, there was a marked reduction in yield and an increase in reaction time. The substitutions on dimedone and isatin had no influence on the yield or reaction time.

Table 2. Substrate scope[a]



Entry	Isatin	Hydrazine	Dimedone	Product	Time (h)	Yield %[b]
1.		NH_2-NH_2		 **4b**[xxxix]	1.5	94
2.		NH_2-NH_2		 **4c**[xxxix]	1.5	94

3.		Ph-NH-NH_2		 **4d**[xxxix]	2	93
4.				 **4e**[xxxix]	3	81
5.		NH_2-NH_2		 **4f**[xxxix]	1.5	95
6.		Ph-NH-NH_2		 **4g**[xxxix]	2	93
7.				 **4h**[xxxix]	3	82

8.		Ph-NH-NH_2		 **4i**[xxxix]	2	93
9.				 **4j**[xxxix]	3	82
10.		NH_2-NH_2		 **4k**[xxxix]	2	93
11.		Ph-NH-NH_2		 **4l**[xxxix]	3	91
12.				 **4m**[xxxix]	3	82

[a]All reactions were carried out with 1 (1 mmol), 2 (1mmol) and 3 (1mmol) in 5 mL solvent under air. [b]Isolated yields.

Figure 1 illustrates a proposed mechanism for the production of spirooxindole-indazolones. The reaction starts with the formation of the anion I with the help of ethyl lactate - GVL, which then attacks the hydrazone C=N bond, followed by the attack of the hydrazone inner nitrogen lone pair on the dimedone carbonyl, results in cyclization followed by dehydration to afford the corresponding product.

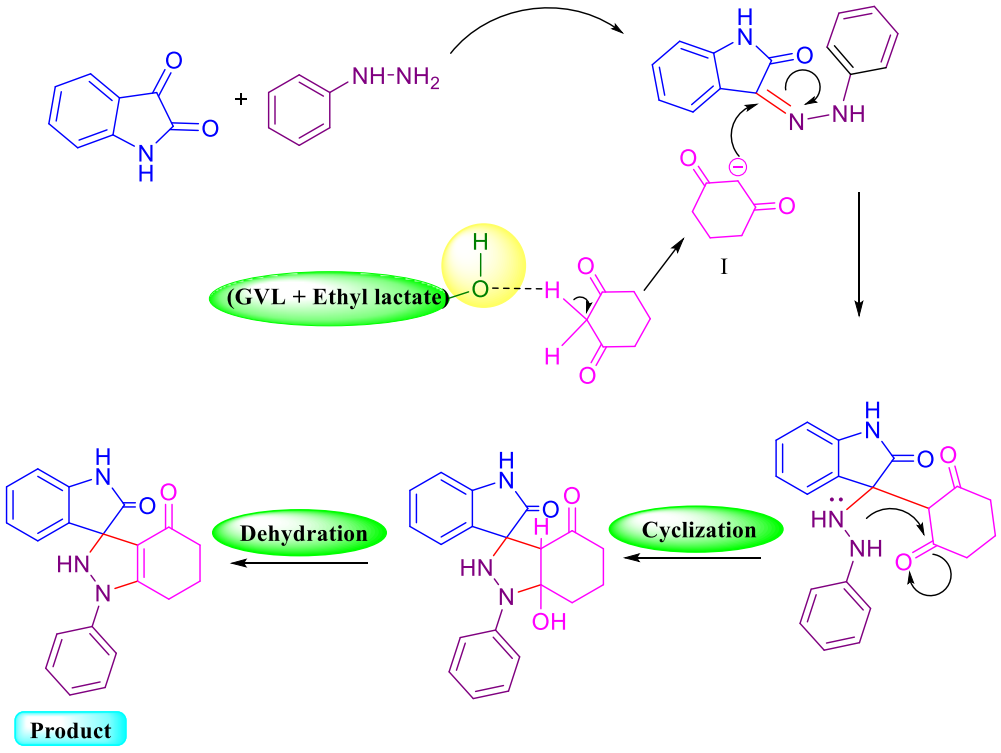


Figure 1: Plausible mechanism for formation of spirooxindoles- indazolones.

Conclusion

In conclusion, we have designed a simple and efficient multi-component one-pot green approach for producing spirooxindole-indazolones. To the best of our knowledge this is the second green, catalyst free synthesis of spirooxindole-indazolones. This method's include several advantages such as, utilisation of a green solvent system which shows synergistic effect, catalyst-free moderate reaction conditions, high yields, quick reaction times, excellent atom economy, and an easy workup procedure. The tricyclic spirooxindole-indazolones frameworks created in this study could be useful as drug discovery scaffolds.

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Reference

i Zhou L. M.; Qu R.Y; Yang G. F.; An overview of spirooxindole as a promising scaffold for novel drug discovery; Expert Opinion on Drug Discovery; 2020, **15**(5), 603-625.; (b) Boddy A. J; Bull J. A.; Stereoselective synthesis and applications of spirocyclic oxindoles; Organic Chemistry Frontiers, 2021, **8**(5), 1026-1084.

ii (a) Xiong C; Cheng K; Wang J; Yang F; Lu J; Zhou Q.; Iodine-Catalyzed Aerobic Oxidation of Spirovinylcyclopropyl Oxindoles to Form Spiro-1, 2-dioxolanes Diastereoselectively; Journal of Organic Chemistry; 2020, **85**(14), 9386-9395.; (b) Mei

G.J; Shi F.; Catalytic asymmetric synthesis of spirooxindoles: recent developments; Chemical Communications; 2018, **54**(50), 6607-6621.

iii (a) Ramachary D. B.; Venkaiah C; Madhavachary R.; Asymmetric synthesis of druglike six-membered spirooxindoles through an amino enyne catalysis; Organic letters; 2013,**15**(12), 3042-3045; (b) Singh G. S; Desta Z.Y.; Isatins as privileged molecules in design and synthesis of spiro-fused cyclic frameworks; Chemical Reviews; 2012,**112**(11), 6104-6155.

iv Kumari G; Modi M; Gupta S. K; Singh R.K.; Rhodium (II) acetate-catalyzed stereoselective synthesis, SAR and anti-HIV activity of novel oxindoles bearing cyclopropane ring; European Journal of Medicinal Chemistry; 2011, **46**(4), 1181-1188.

v Yu, B.; Yu, D. Q.; Liu, H. M.; Spirooxindoles: Promising scaffolds for anticancer agents; European Journal of Medicinal Chemistry, 2015, **97**, 673-698.

vi Rajesh S. M; Perumal S; Menendez J. C; Yogeeswari P; Sriram D.; Antimycobacterial activity of spirooxindolo-pyrrolidine, pyrrolizine and pyrrolothiazole hybrids obtained by a three-component regio-and stereoselective 1, 3-dipolar cycloaddition; MedChemComm.; 2011, **2**(7), 626-630.

vii Keri, R. S.; Patil, M. R.; Patil, S. A.; Budagumpi, S.; A comprehensive review in current developments of benzothiazole-based molecules in medicinal chemistry; European Journal of Medicinal Chemistry; 2015, **89**, 207-251.

viii Zha, G. F.; Leng, J.; Darshini, N.; Shubhavathi, T.; Vivek, H. K.; Asiri, A. M.; Marwani, H. M.; Rakesh, K. P.; Mallesha, N.; Qin, H. L.; Synthesis, SAR and molecular docking studies of benzo [d] thiazole-hydrazones as potential antibacterial and antifungal agents; Bioorganic & Medicinal Chemistry Letters; 2017, **27**(14), 3148-3155.

ix Yeung, B. K.; Zou, B.; Rottmann, M.; Lakshminarayana, S. B.; Ang, S. H.; Leong, S.Y.; Tan, J.; Wong, J.; Keller-Maerki, S.; Fischli, C. Goh, A.; Spirotetrahydro β-carbolines (spiroindolones): a new class of potent and orally efficacious compounds for the treatment of malaria; Journal of Medicinal Chemistry; 2010, **53**(14), 5155-5164.

x Haddad, S.; Boudriga, S.; Akhaja, T. N.; Raval, J. P.; Porzio, F.; Soldera, A.; Askri, M.; Knorr, M.; Rousselin, Y.; Kubicki, M. M.; Rajani, D.; A strategic approach to the synthesis of functionalized spirooxindole pyrrolidine derivatives: in vitro antibacterial, antifungal, antimalarial and antitubercular studies; New Journal of Chemistry, 2015, **39**(1), 520-528.

xi Zhao, H. W.; Li, B.; Tian, T.; Meng, W.; Yang, Z.; Song, X. Q.; Chen, X. Q.; Pang, H. L.; Highly enantioselective synthesis of chiral pyranonaphthoquinone-fused spirooxindoles through organocatalytic three-component cascade reactions; European Journal of Organic Chemistry; 2015, **15**, 3320-3326.

xii Yang, Z. T.; Zhao, J.; Yang, W. L.; Deng, W. P.; Enantioselective construction of CF3-Containing Spirooxindole γ-Lactones via organocatalytic asymmetric michael/lactonization; Organic letters; 2019, **21**(4), 1015-1020.

xiii Niknam, K.; Abolpour, P.; Synthesis of spirooxindole pyrimidines catalyzed by silica-bonded N-propyltriethylenetetramine as a recyclable solid base catalyst in aqueous medium; Monatshefte fur Chemie-Chemical Monthly; 2015, **146**(4), 683-690.

xiv (a) Raut, S.; Dhotre, B.; Tidke, A.; Pathan, M. A.; An operationally simple and efficient synthesis of 7-benzylidene-substitutedphenyl-3, 3a, 4, 5, 6, 7-hexahydro-2H-indazole by grinding method; Current Organic Synthesis; 2020, **17**(4), 313-321; (b) Nie, H. J.; Guo, A. D.; Lin, H. X.; Chen, X. H.; Rapid and halide compatible synthesis of 2-N-substituted indazolone derivatives via photochemical cyclization in aqueous media; RSC Advances; 2019, **9**(23), 13249-13253.

xv (a) Zhu, J. S.; Kraemer, N.; Shatskikh, M. E.; Li, C. J.; Son, J. H.; Haddadin, M. J.; Tantillo, D. J.; Kurth, M. J.; N–N Bond Formation between Primary Amines and Nitrosos: Direct Synthesis of 2-Substituted Indazolones with Mechanistic Insights; Organic letters; 2018, **20**(16), 4736-4739; (b) Tsujii, M.; Sonoda, M.; Tanimori, S.; Proline-Mediated Transition Metal-Free Access to 1 H-Indazolones from 2-Halobenzohydrazides; Journal of Organic Chemistry; 2016, **81**(15), 6766-6773.

xvi Gawande, M. B.; Bonifacio, V. D.; Luque, R.; Branco, P. S.; Varma, R. S.; Solvent-free and catalysts-free chemistry: A Benign pathway to sustainability; ChemSusChem; 2014, **7**(1), 24-44.

xvii (a) Rodríguez-Alvarez, M. J.; Garcia-Alvarez, J.; Uzelac, M.; Fairley, M.; O'Hara, C. T.; Hevia, E.; Introducing glycerol as a sustainable solvent to organolithium chemistry: ultrafast chemoselective addition of aryllithium reagents to nitriles under air and at ambient temperature; Chemistry–A European Journal; 2018, **24**(7), 1720-1725; (b) Santoro, S.; Ferlin, F.; Luciani, L.; Ackermann, L.; Vaccaro, L.; Biomass-derived solvents as effective media for cross-coupling reactions and C–H functionalization processes; Green Chemistry; 2017, **19**(7), 1601-1612;

xviii (a) Clarke, C. J.; Tu, W. C.; Levers, O.; Brohl, A.; Hallett, J. P.; Green and sustainable solvents in chemical processes; Chemical Reviews; 2018, **118**(2), 747-800; (b) Sheldon, R. A.; Biocatalysis and green chemistry; Green biocatalysis; 2016, 1-15; (c) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunn, P. J.; CHEM21 selection guide of classical-and less classical-solvents; Green Chemistry; 2016, **18**(1), 288-296.

xix Bodireddy, M. R.; Khaja Mohinuddin, P. M.; Gundala, T. R.; Gangi Reddy, N. C.; Lactic acid-mediated tandem one-pot synthesis of 2-aminothiazole derivatives: A rapid, scalable, and sustainable process; Cogent Chemistry; 2016, **2**(1), 1154237.

xx Jad, Y. E.; Acosta, G. A.; Govender, T.; Kruger, H. G.; El-Faham, A.; de la Torre, B. G.; Albericio, F.; Green solid-phase peptide synthesis 2, 2-Methyltetrahydrofuran and ethyl acetate for solid-phase peptide synthesis under green conditions; ACS Sustainable Chemistry & Engineering; 2016, **4**(12), 6809-6814.

xxi Yang, L.; Wan, J. P.; Ethyl lactate-involved three-component dehydrogenative reactions: biomass feedstock in diversity-oriented quinoline synthesis; Green Chemistry; 2020, **22**(10), 3074-3078.

xxii (a) Diaz-Alvarez, A. E.; Francos, J.; Croche, P.; Cadierno, V.; Recent advances in the use of glycerol as green solvent for synthetic organic chemistry; Current Green Chemistry; 2014, **1**(1), 51-65; (b) Tiwari, J.; Saquib, M.; Singh, S.; Tufail, F.; Singh, J.; Singh, J.; Catalyst-free glycerol-mediated green synthesis of 5′-thioxospiro [indoline-3, 3′-[1, 2, 4] triazolidin]-2-ones/spiro [indoline-3, 3′-[1, 2, 4] triazolidine]-2, 5′-diones; Synthetic Communications; 2017, **47**(21), 1999-2006; (c) Tufail, F.; Singh, S.; Saquib, M.; Tiwari, J.; Singh, J.; Singh, J.; Glycerol-Assisted Facile Approach to Imidazole-Fused Nitrogen-Bridgehead Heterocycles; Chemistry Select; 2017, **2**(21), 6082 – 6089.

xxiii Yan, K.; Yang, Y.; Chai, J.; Lu, Y.; Catalytic reactions of gamma-valerolactone: A platform to fuels and value-added chemicals; Applied Catalysis B: Environmental; 2015, **179**, 292-304.

xxiv Chen, M. N.; Di, J. Q.; Li, J. M.; Mo, L. P.; Zhang, Z. H.; Eosin Y-catalyzed one-pot synthesis of spiro [4H-pyran-oxindole] under visible light irradiation; Tetrahedron; 2020, **76**(14), 131059.

xxv Luo, W.; Sankar, M.; Beale, A. M.; He, Q.; Kiely, C. J.; Bruijnincx, P. C.; Weckhuysen, B. M.; High performing and stable supported nano-alloys for the

catalytic hydrogenation of levulinic acid to γ-valerolactone; Nature Communications; 2015, **6**(1), 1-10.

xxvi Ortiz-Cervantes, C.; Flores-Alamo, M.; Garcia, J. J.;Hydro genation of biomass-derived levulinic acid into γ-valerolactone catalyzed by palladium complexes; Acs Catalysis; 2015, **5**(3), 1424-1431.

xxvii Alonso, D. M.; Wettstein, S. G.; Mellmer, M. A.; Gurbuz, E. I.; Dumesic, J. A.; ntegrated conversion of hemicellulose and cellulose from lignocellulosic biomass; Energy & Environmental Science; 2013, **6**(1), 76-80.

xxviii Luterbacher, J. S.; Rand, J. M.; Alonso, D. M.; Han, J.; Youngquist, J. T.; Maravelias, C. T.; Dumesic, J. A.; Nonenzymatic sugar production from biomass using biomass-derived γ-valerolactone; Science; 2014, **343**(6168), 277-280.

xxix (a) Ismalaj, E.; Strappaveccia, G.; Ballerini, E.; Elisei, F.; Piermatti, O.; Gelman, D.; Vaccaro, L.; γ-Valerolactone as a renewable dipolar aprotic solvent deriving from biomass degradation for the Hiyama reaction; ACS Sustainable Chemistry & Engineering; 2014, **2**(10), 2461-2464; (b) Strappaveccia, G.; Ismalaj, E.; Petrucci, C.; Lanari, D.; Marrocchi, A.; Drees, M.; Vaccaro, L.; A biomass-derived safe medium to replace toxic dipolar solvents and access cleaner Heck coupling reactions; Green Chemistry; 2015, **17**(1), 365-372.

xxx Duan, Z. Q.; Hu, F.; Highly efficient synthesis of phosphatidylserine in the eco-friendly solvent γ-valerolactone; Green Chemistry; 2012, **14**(6), 1581-1583.

xxxi Alonso, D. M.; Wettstein, S. G.; Dumesic, J. A.; Gamma-valerolactone, a sustainable platform molecule derived from lignocellulosic biomass; Green Chemistry; 2013, **15**(3), 584-595.

xxxii Zhang, Z.; Synthesis of γ-Valerolactone from Carbohydrates and its Applications; ChemSusChem; 2016, **9**(2), 156-171.

xxxiii Kua, Y. L.; Gan, S.; Morris, A.; Ng, H. K.; Ethyl lactate as a potential green solvent to extract hydrophilic (polar) and lipophilic (non-polar) phytonutrients simultaneously from fruit and vegetable by-products; Sustainable Chemistry and Pharmacy; 2016, **4**, 21-31.

xxxiv Garcia, G.; Atilhan, M.; Aparicio, S.; Insights into alkyl lactate+ water mixed fluids; Journal of Molecular Liquids; 2014, **199**, 215-223.

xxxv Yap, C. L.; Gan, S.; Ng, H. K.; Evaluation of solubility of polycyclic aromatic hydrocarbons in ethyl lactate/water versus ethanol/water mixtures for contaminated soil remediation applications; Journal of Environmental Sciences; 2012, **24**(6), 1064-1075.

xxxvi Planer, S.; Jana, A.; Grela, K.; Ethyl lactate: A green solvent for olefin metathesis; ChemSusChem; 2019, **12**(20), 4655-4661.

xxxvii Strati, I. F.; Oreopoulou, V.; Effect of extraction parameters on the carotenoid recovery from tomato waste; International Journal of Food Science & Technology; 2011, **46**(1), 23-29.

xxxviii Wang, Y.; Tashiro, Y.; Sonomoto, K.; Fermentative production of lactic acid from renewable materials: Recent achievements, prospects, and limits; Journal of bioscience and bioengineering; 2015, **119**(1), 10-18.

xxxix Singh, S.; Saquib, M.; Singh, S. B.; Singh, M.; Singh, J.; Catalyst free, multicomponent-tandem synthesis of spirooxindole-indazolones and spirooxindole-pyrazolines: a glycerol mediated green approach; RSC Advances; 2015, **5**(56), 45152-45157.

xl (a) Baranwal, J.; Kushwaha, S.; Singh, S.; Jyoti, A.; Synergistic effect of ethyl lactate/glycerol: A new route for the synthesis of Hexahydro-4H-Indazol-4-one and its derivatives; Heterocyclic Letter; 2022, **12**(3), 621-630; (b) Baranwal, J.; Kushwaha, S.; Singh, S.; Jyoti, A.; A Review on the Synthesis and Pharmacological Activity of

Heterocyclic Compounds; Current Physical Chemistry; 2023, **13**(1), 2-19; (c) Baranwal, J.; Singh, S.; Kushwaha, S.; Jyoti, A.; Acemannan from Aloe Vera Extract: A Catalyst-Free, Approach for the Access of Imidazole-Fused Nitrogen-Bridgehead Heterocycles; Letters in Organic Chemistry; 2023, **20**(5), 446-456; (d) Kushwaha, S.; Baranwal, J.; Singh, S.; Jyoti, A.; A Review on Green Synthesis of Biologically Active Compounds; Current Green Chemistry; 2022, **9**(3), 174-195.

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