SOLVENT FREE MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF HETEROCYCLIC SCAFFOLDS

Ph. D. THESIS

by

ABDULKADIR SHUBE HUSSEN

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY ROORKEE
ROORKEE-247667 (INDIA)
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ROORKEE

CANDIDATE'S DECLARATION

I hereby certify that the work which is being presented in the thesis entitled, "**SOLVENT FREE MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF HETEROCYCLIC SCAFFOLDS** " in the partial fulfilment of the requirement for the award of the Degree of Doctor of philosophy and submitted in the Department of Chemistry of the Indian Institute of Technology Roorkee is an authentic record of my own work carried out during a period from July 2015 to May 2019 under the supervision of Dr. Anuj Sharma, Associate Professor, Department of Chemistry, Indian Institute of Technology Roorkee, Roorkee.

The matter presented in this thesis has not been submitted by me for award of any other degree of this or any other Institution.

(ABDULKADIR SHUBE HUSSEN)

This is to certify that the above statement made by the candidate is correct to the best of my knowledge.

(Anuj Sharma)
Supervisor

The Ph.D. Viva-Voce Examination of Mr. Abdulkadir Shube Hussen, Research Scholar has been held on ……..

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This isto certify that the student has made all corrections in the thesis.

Signature of Supervisor **Head of the Department**
Dated …….

Dedicated to My Parents & Family

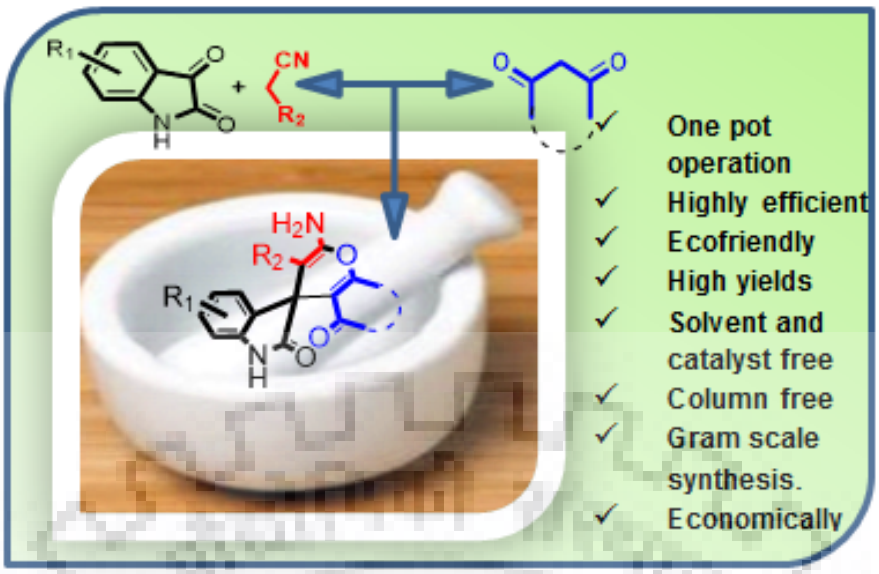
ABSTRACT OF THE THESIS

Thesis Title: SOLVENT FREE MULTICOMPONENT REACTIONS FOR THE SYNTHESIS OF HETEROCYCLIC SCAFFOLDS

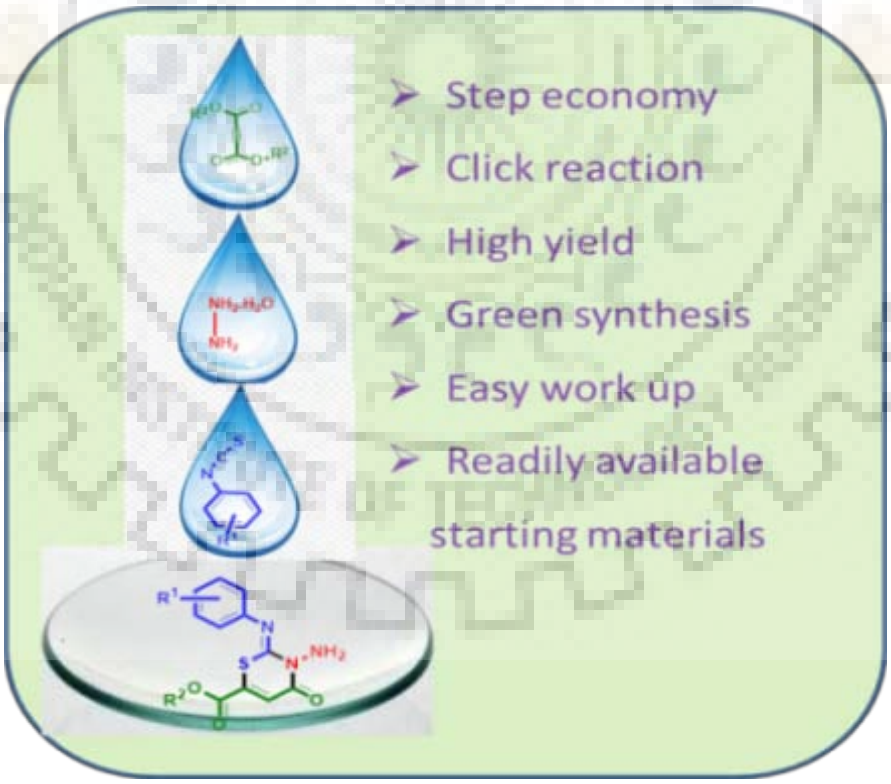
The central theme of this thesis is designing**,** synthesis and spectral characterization of synthesized heterocyclic organic compounds containing N, O and/or S atoms in their ring. The thesis highlights novel strategies focusing on sustainable synthesis which were accomplished in the absence of solvent under mechanochemical or microwave irradiation approaches which have been attracting considerable interest in the past few decades and becoming the mainstream route of synthesis in modern organic synthesis. The thesis further illustrates the advantages that an organic chemist render as a result of endowing themselves with the necessary skills emanating from the idea of working principles suggested in green synthesis.

The whole thesis is divided into five principal chapters. **Chapter-1** is an introduction dealing with the background of the research work and addresses current challenges and objectives of the study. This chapter gives bird's-eye view of the progress and advancement in mechanochemical and solvent free microwave irradiation based chemical transformations synchronized with the idea of multicomponent reaction (MCRs) approach.

Chapter-2 Describes an efficient mechanochemical (- hand grinding) synthesis of pyran fused spirooxindoles under solvent and catalyst free condition. This synthetic strategy showed promising green metrics score at multigram scale synthesis confirming its competency at large scale production.



Chapter-3 Describes regioselective synthesis of functionalized [1, 3]-thiazine-4-ones *via* multicomponent click reaction approach under exceptionally green profile. It renders the benefit for fast organic reactions involved in the process of drug discovery over its time taking other combinatorial ways.



Chapter-4 Illustrates synergistic collaborative action of solvent free microwave irradiation and mechanochemical approaches for the synthesis of oxindoles-β-enaminones hybrids

through one pot two-steps mechanochemical four component reaction under solvent and catalyst free condition.

Chapter-5 Describes ammonium chloride assisted microwave mediated domino multicomponent reaction: An efficient and sustainable access for the synthesis of quinazolin-4(3H)-imines under solvent free condition. It illustrates the benefit this novel strategy provides with respect to the previously reported work in this area.

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ABBREVIATIONS

&	And
^{13}C	Carbon-13
^{1}H	Hydrogen
3CR	3 Component reaction
AcOH	Acetic acid
AE	Atom efficiency
ACN	Acetonitrile
CE	Carbon efficiency
COX	Cyclooxgenase
CuAAC	Copper azide acetylene cycloaddition
DCM	Dichloromethane
DEAD	Diethyl acetylene dicarbxlate
DMAD	Dimethyl acetylene dicarboxylate
DMAP	4-Dimethylaminopyridine
DMF	*N*, *N*-dimethylformamide
DMSO	Dimethyl sulfoxide
E-factor	Sheldon environmental impact factor
EtOH	Ethanol
FTIR	Fourier transform infrared spectroscopy
G-10	Glass vial 10
G-30	Glass vial 30
H	Hydrogen
h	hour
HPA	Hetero poly acid
HRMS	High-resolution mass spectroscopy
HSBM	High speed ball milling
HSVM	High speed vibrational motion
I_2	Iodine molecule
IG	Isinglass
IL	Ionic liquids
LAG	Liquid assisted grinding
MAOS	Microwave assisted organic synthesis
MCR	Multicomponent reaction
MeOH	Methanol

MHz	Mega hertz
mL	Milli liter
N	Nitrogen
Na	Sodium
Nd	Not determined
NMR	Nuclear magnetic resonance
NPs	Nano particles
PEG	Poly ethylene glycol
PMI	Process mass intensity
Ppm	Parts per million
***P*-TSA**	*Para*- Toluene sulfonic acid
RME	Reaction mass efficiency
RMI	Reaction mass Intensity
Rpm	Rotations per minute
Rt	Room temperature
S	Sulfur
SFR	Solvent free reaction
THQ	Tetrahydroquinoline
TLC	Thin layer chromatogyaphy
TMSCl	Trimethylslyl chloride
α	alpha
β	Beta
δ	delta
THP	Tetrahydrpyridine

Table of Content

List of Figures

List of Tables

List of Schemes

Chapter 1 General Introduction

1.1 Background

The art of organic synthesis is the basis of chemical research which is targeting synthesis of specific desired product or leading to unexpected serendipitous discovery. Chemistry is a science of matter and involving energy in different form for its transformations which makes it broader in scope and covers basic aspect of life. The clothes we wear, the medicine we use to safeguard ourselves from killing diseases, the food we eat, the agrochemicals and functional materials [1,2] we use in our everyday life, all seek skillful synthetic techniques to undergo chemical transformations which lead to their access in environmentally compatible and benign ways. These reactions can happen in countless ways which can be broadly categorized into sequential and multicomponent reactions. It is confirmed that multicomponent reactions impart desirable characteristics which are advocated by modern organic synthesis over sequential ones.

1.2 What is a multicomponent reaction?

Multicomponent reaction (MCRs) is a convergent reaction, in which three or more starting materials react to form a product where basically all or most of the atoms contribute to the newly formed product [3,4]. In diversity and complexity oriented modern organic synthesis, multicomponent reactions especially the ones synchronized with mechanochemistry, owing to their combined capacity to high efficiency, operational simplicity and selectivity is advantageous over sequential multistep reaction counterparts in chemical biology and drug discovery.

1.3 Historical background of multicomponent reaction

MCRs have a long history where the discovery of most of them dates back to the beginning of 19th century when most classical multicomponent reactions were flourished. If not the first, one of the earliest multicomponent reaction strategy is Strecker reaction, which is a 3-component reaction formulated by Strecker in 1850 involving carbonyl compounds (**1**), primary or secondary amines and cyanide function to synthesize α-amino acids (**3**) *via* hydrolysis of α-amino cyanides (**2**) (**Fig. 1.1**) [5].

Figure 1.1 Strecker reaction to synthesize amino acids.

The other profound MCR strategy referred to as Hantzsch reaction which is useful for the synthesis of biologically relevant dihydropyridine scaffolds (**7**) is a 3-CR involving aryl aldehydes (**1**), 1,3-dicarbonyl compounds (**5**) and ammonium acetate (**6**) under acidic conditions (**Fig. 1.2**).

Figure 1.2 Classical Hantzsch reaction for the synthesis of dihydropyridines.

Many of the historically significant MCRs were developed around the carbonyl and amine functionalities. Many of these MCRs have witnessed a huge resurgence in the last few decades and have been summarized in **Table 1.1**.These multicomponent reactions as summarized in **Table 1.1** have been extensively used in the synthesis of myriads of biologically significant five or six membered heterocyclic compounds containing N, O and S atoms in simple or fused ring systems.

Table 1.1 Some classical multicomponent reactions

Entry	Name of chemical reaction	Year of discovery	Reaction
1	Biginelli Reaction[6]	1891	
2	Bucherer-Burgs hydantion synthesis[7]	1934	
3	Mannich Reaction[8]	1912	
4	Passerini reaction[9]	1921	
5	Ugi reaction[10]	1959	

6	Gewald reaction[11]	1961	
7	GBB Reaction[12]	1998	
8	van Leusen reaction[13]	1977	
9	Povarov Reaction[14]	1963	
10	Doebner Reaction[15]	1881	

1.4 Advantages of Multicomponent Reactions

Generally, MCRs offer features of green synthesis such as operational simplicity and efficiency over divergent sequential and multi-step conventional reactions. Most MCRs are known to deliver better selectivity and atom economy [16]. MCR is the best approach towards diversity oriented synthesis which is difficult to access under linear conventional routes. MCRs with a few components through enough diversity points can lead to a product library of hundreds of compounds. For example, a 4-CR can give 10,000 compounds when 10 variants of each component are employed. This demonstrates that MCRs are economical with resource allocation and can have profound bearing in areas like drug discovery and development as high throughput synthesis becomes a real possibility with these reactions.

1.5 Multicomponent reactions and green synthesis

It's obvious that multicomponent reactions owing to their operational simplicity, high efficiency and in some cases high selectivity make them green in approach towards organic synthesis. In green synthesis, efficient way of energy transfer should be addressed in addition to efficient material transformation. In this regard, utilization of efficient source of energy such as microwave irradiation, specifically, under solvent free condition and/or mechanochemical route of synthesis are promising targets in modern organic synthesis. The idea of green chemistry / green synthesis/ was coined by Paul Anastas and John Warner which comprised 12 working principles referred to as the 12 principles of green chemistry [17,18]. According to them, it refers to a pathway that allows humanity to meet the current environmental and human health, economic and social needs without compromising the success of the future generations [19]. It was suggested that organic synthetic chemist must strictly follow these principles as a check list or manual to materialize green chemical transformations in industries and academia. One of the critical issues to be addressed in green synthesis is solvent management. It's known that right from its inception, solution based organic reactions dominated chemical research. One of the reasons that impacted researchers to view chemical transformation from such a specific angle began with the idea of famous Greek Philosopher Aristotle who believed chemical reactions/ changes/ were confined to the presence of fluid saying "No Coopora nisi Fluida", which meant that no reaction occurs in the absence of solvents [20]. In solutions based organic synthesis, volatile organic solvents were

extensively used regardless of their volatile nature which could be responsible for easy emission to ecosystem and thereby affecting living and non-living things and their interactions.

One of the most sought after green approaches to circumvent the threat related to solvent management in organic synthesis is MECHANOCHEMICAL [21–31] approach or SOLVENT FREE MICROWAVE ASSISTED ORGANIC SYNTHESIS which has been proven to be more efficient and selective over solution based synthesis.

1.6 Solvent-free microwave assisted organic synthesis

Among radiant energy sources, microwave irradiation plays prominent role in enhancing efficiency of reaction by minimizing the time of reaction. In some cases it also can replace volatile organic solvents with water and facilitates green synthesis. Myriads of chemical transformations irradiated by microwave irradiation have been effected under solvent free condition [32–35]. For example, synthesis of scaffolds which are valuable in material and supra molecular chemistry attracted tremendous attention among scientific community in the past few decades. Migallon and Hoz (2015) reported a green protocol aiming at waste minimization by synthesizing 1,3,5-triazine derivatives (**30**) under solvent free microwave irradiated condition through reaction of aromatic and aliphatic amines (**13**) with triazines such as 2-Cl-dicyclohexyl-1,3,5-triazine (**29**) (**Fig. 1.3**) [33].

Figure 1.3 Synthesis of 1,3,5-triazines under solvent free microwave irradiated condition.

Flavones are important natural products owing to their broad biological activities [36–42] such as Leishimanicidal, anti HIV, vasodilator, antiviral, antioxidant, DNA cleavage, anticancer, etc. Synthesis routes of these compounds were commonly accessed by the approach developed by Robinson and Venkataraman which involved many steps. Recently, due to the emphasis given to clean synthesis, Seijas and Tato *et al.* (2005) reported a solvent-free synthesis of functionalized flavones (**32**) under microwave irradiated condition through reaction of β-ketoesters (**5**) with phloroglucinol (**31**) (**Fig. 1.4**) [43].

Figure 1.4 Synthesis of functionalized flavones under solvent free microwave irradiated condition.

1.7 Mechanochemical induced synthesis

Mechanochemistry is defined as “a chemical reaction that is induced by direct absorption of “mechanical energy/force” [44]. Mechanochemistry covers wide synthetic processes ranging from grinding to ball milling, sonication, etc., where hand grinding is usually performed with the help of a mortar and pestle, while mechanical milling is generally conducted in a mixer/shaker mill or a planetary mill at a frequency of 5-60 Hz [27]. Mechanochemical strategy can be performed under different sets of conditions.

1.7.1 Historical Background of Mechanochemistry

Mechanochemistry has an old history in the fields of mining, polymers science and inorganic transformations. The application of mechanochemistry in organic synthesis seemed to come into existence later. The first documented application of mechanochemical method in organic synthesis is probably the work of Ling and Baker in 1893 when they prepared halogen derivatives of quinhydrone [45]. This profound discipline has been dormant for very long period of time and curtailed in obscurity for centuries, probably, because of limited mechanistic understanding of the subject. In recent last few decades, it was undergoing an exciting period of rediscovery and renaissance to evolve to present attractive status in modern organic synthesis [46,47].

1.7.2 Mechanochemical synthetic approaches

Mechanochemical reactions can be assisted by adding solid or liquid auxiliaries depending upon type of reactants. Generally, if the starting materials are found in liquid state, solids like SiO_2, Al_2O_3, NaCl and KBr are commonly used to enhance friction thereby accelerating transfer of mechanical energy, which is responsible for the formation or breaking of bonds during the reaction.

1.7.2.1 Solvent free mechanochemical synthesis

Generally, copper catalyzed azide-alkyne reaction (click reaction), which was coined by Sharpless was supposed to be carried out in aqueous medium, but due to solubility problem in some derivatives, the reaction needed complementary solvents like DMF (not green solvent). To circumvent this drawback, Mack *et al*. (2013) reported the first copper vial catalyzed CuAAC reaction under solvent-free mechanochemical condition. This strategy enabled the reaction to be conducted not only in the absence of solvent, but also replaced the copper catalyst by the copper vial. The reaction involved milling of alkynes (**33**) and benzyl bromides (**34**) in the presence of sodium azide in copper vial for 15 minutes to synthesize desired products triazole (**35**) (**Fig. 1.5**) [48].

Figure 1.5 Mechanochemical induced synthesis of triazoles under solvent free condition.

1.7.2.2 Liquid assisted grinding (LAG)

Liquid assisted grinding (LAG) also known as solvent drop grinding [49,50] which is an extension of traditional solvent-free mechanochemical method in which a small amount of liquid is added to accelerate rate of the reaction. An important parameter of LAG experiments is that the ratio of liquid to be added to the amount of total reagents used in the reaction (μL/mg), denoted by η. A value of η =0 represents neat, or dry grinding, whereas η $\geq$ 10 represents atypical reaction in solution. For the reaction to be considered an example of LAG, η is usually between 0 and 1[51].

In 2017, Browne *et al*. found out that mechanochemical reaction, i.e., milling of di-benzoyl methane (**36**) with selectfluor (**37**) in the absence of solvent achieved a 3:1ratio of monofluorinated: difluorinated (**38:39**) product. Addition of acetonitrile (~10% of total volume to materials present) improved selectivity to 50:1 (**Fig. 1.6**) [52].

Figure 1.6 Acetonitrile assisted fluorination of 1,3-dicarbonyl compounds.

Furthermore, Banerjee and Chatterjee *et al*. (2014) reported efficient and environmentally benign protocol based on liquid assisted grinding (LAG) which was instrumental in combinatorial assembly of broad library of compounds under operationally simple synthetic procedure from readily available starting materials 2-amino phenol or *o*-phenylenediamine or 2-aminothiophenol **(40)** and aromatic aldehydes (**1**) to synthesize scaffolds (**41)** (**Fig.1.7**) [53]

Figure 1.7 (LAG) route to 2 substituted benzothiazoles /oxazoles/ imidazoles.

1.7.2.3 Solid promoted mechanochemical approach

Recently, polymer assisted grinding is commonly appearing in mechanochemical transformations. Polymers, owing to their unique mechanical properties such as strength, toughness, and elasticity are well suited to transiently accumulate mechanical energy along the backbone. This behavior and the quest for stimuli-responsive materials have resulted in mechanoresponsive polymers that use mechanical energy to drive chemical transformations [44]. Xu *et al*. reported iodine promoted and

silica gel supported synthesis of 1,2'-pyrrolinyl-spirooxindoles (**44)** through reaction of isatin based intermediate (**42**) and β-enaminone (**43**) under solvent free conditions (**Fig. 1.8**) [54].

Figure 1.8 Silica gel supported mechanochemical synthesis of 2'- pyrrolinyl-spirooxindoles.

1.8 Mechanochemical induced synthesis of heterocycles

Heterocycles refer to cyclic compounds with at least one hetero atom in the ring [55]. Heterocyclic compounds are found in myriads of naturally occurring compounds such as alkaloids and have been proven to depict broad biological activities. Heterocyclic compounds prevail among agrochemicals, dyes etc. [56], and organic synthesis aiming at construction of these moieties under ambient condition with high efficiency, selectivity, resource effective ways such as mechanochemistry and /or solvent free microwave irradiated approaches have attracted tremendous attention among synthetic community. The most frequently encountered heterocyclic compounds are five membered and six membered N, O and S containing rings.

1.8.1 N- Containing five membered heterocyclic compounds

1.8.1.1 Mechanochemical synthesis of pyrroles

Pyrrole is a key constituent of myriads of profound heterocyclic moieties ubiquitously prevailed in porphyrins and vitamins and known to do life sustaining duty [57]. It is constituent of many alkaloids such as sceletium alkaloid [58]. It is also widely used as building units of optical materials [59, 60]. The classical methods used for construction of these scaffolds include Hantzsch, Paal-Knorr [61,62] and Barton-Zard [58, 63, 64] amongst many others. However, green methods

of synthesis such as mechanochemical approach are always sought. To this end, Perumal and coworkers reported mechanochemical assisted assembly of fused pyrrole derivatives dihydroindeno [1,2-*b*] (**47**) by manual grinding equimolecular amounts of (*E*)-3- (dimethylamino)-1-arylprop-2-en-ones (**45**) with aniline derivatives (**13)** and ninhydrine (**46**) in the presence of drops of acetic acid and the products were isolated in pure state without the need for chromatographic purification (**Fig.1.9**) [65].

Figure 1.9 Manual grinding induced synthesis of pyrrole.

1.8.1.2 Synthesis of imidazole and its analogues

Classical Bucherer-Bergs reaction was first reported in 1934. It is one of the strategies of synthesizing imidazole analogues (imidazolidine-2,4-dione). Researchers have been targeting synthesis of these moieties because of its wide spectrum of biological activities such as antiepileptic, anticonvulsant, anti-androgenic antidiabetic and anti-fungal activities etc.[66,67] Recently, Maddah *et al*. demonstrated that this reaction can be applied to mechanochemical way of synthesis when they synthesized hydantions (**48**) through reaction of ketones (**10**) in the presence of potassium cyanide and ammonium carbonate assisted by mechanochemical methodology (**Fig.1.10**) [68].

Figure 1.10 Mechanochemical induced and ZnO-NPs catalyzed synthesis of hydantions.

1.8.1.3. Imidazole synthesis

Imidazole moieties, specifically, tetra substituted ones are indispensable constituent of myriads of biologically active molecules and green synthetic routes leading to the construction of this scaffold such as solvent free microwave irradiation is appealing from sustainable synthesis point of view. Das *et al*. (2013) synthesized tetra substituted imidazole (**50**) *via* combinatorial transformation of benzyl (**49**), aldehydes (**1)** and amine (**13)** derivatives in the presence of ammonium acetate under solvent free microwave irradiation (**Fig.1.11**) [69].

Figure 1.11 IL Catalyzed and MW assisted synthesis of imidazoles under solvent free condition.

1.8.2 O-Containing five membered heterocyclic compounds

Synthesis of furans or dihydrofurans

Cheng and co-workers back in 1993 synthesized a number of benzo[*b*]naphtha [2,3-*d*]furan-6,11-diones (**51**) and found out in vitro inhibitory action against the growth of human promyelocytic leukemia cells (HL-6) [70]. Likewise, compounds Cordarone (**52**) and (-)(-BPAP) (**53**) (**Fig.1.12**) [71] bearing furan core structure are medicinally established scaffolds which are used to treat irregular heart beat and antidepressant respectively. In this context, searching for efficient and environmentally compatible protocol for their synthesis is highly demanding.

Figure 1.12 Biologically potent furan nucleus bearing scaffolds.

To this end, Chuang *et al*. reported grinding induced diastreoselective synthesis of *trans*-2,3-disubstituted dihydrofurans (**55**) from aldehydes (**1**), 1,3-dicarbonyl compounds (**5)** and *N*-phenacyl pyridinium bromides (**54**) under weakly basic condition (**Fig. 1.13**) [72].

Figure 1.13 Mechanochemical induced synthesis of dihydrofurans.

1.8.3 S-Containing five membered heterocyclic compounds

Thiophene synthesis

Thiophenes, specifically, 2-aminothiophenes are promising and versatile building blocks for the synthesis of profound scaffolds with huge applications in various industries such as dyeing and pharmaceutical industries [73,74]. These moieties have been proven to be biologically active and have depicted broad spectrum of biological activities. The synthesis of these moieties based on conventional route of synthesis were inefficient in some cases and search for general and promising alternative strategy based on Gewald reaction has been continued. In this regard, Mack and coworkers found out that Gewald reaction can be performed well under mechanochemistry to synthesize thiophene scaffolds (**56**), through reaction of ethylcyanoacetate (**26b**), ketones (**10**) and elemental sulfur (**Fig.1.14**) [75].

Figure 1.14 Mechanochemical induced thiophene synthesis.

In 2013, Singh *et al*. reported DMAP mediated one-pot domino thienannullation for the synthesis of naphtha [2,3-*b*] thiophenes (**59**) under green mechanochemical method *via* coupling of (**57**) with naphthalene-1,4-dione (**58**) in the presence of DMAP (**Fig.1.15**) [76].

Figure 1.15 DMAP catalyzed mechanochemical induced synthesis of thiophenes.

1.8.4 Synthesis of N and O-containing five membered heterocycles

Synthesis of oxazolones (azalactones)

These profound moieties are important from application and synthetic perspectives as they are ubiquitously employed in the synthesis of several small molecules such as amino acids [73]. Devising synthetic routes which are highly efficient and selective in nature under ambient and green approaches seems indispensible. In this regard, Fahmy *et al*. developed mechanochemical multicomponent reaction strategy which involved the reaction of benzoyl chloride (**61**) with glycine (**60**) to form azalactone which reacted with aryl aldehydes **(1)** derivatives through Knoevenagel condensation to form oxazolones (**62**) (**Fig**.**1**.**16**) [77].

Figure 1.16 Grinding assisted three component reaction for the synthesis of oxazolones.

1.8.5 Synthesis of N Containing six membered heterocycles

1.8.5.1 Synthesis of dihydropyridines (DHPs)

Hantzsch reported the first synthesis of DHP in 1882 in the course of developing his useful synthetic method for pyridine [78]. 1,4-dihydropyridine derivatives such as Felodipine (**75**), Melodipine (**63**), Nifedipine (**64**) are commercial drugs tacrine (**65**) analogs are very important calcium channel modulators, and have been developed as cardiovascular and antihypertensive drugs (**Fig.1.17**) [79]. Recently, these scaffolds were found to be potent acetyl cholinesterase inhibitors and synthesis of these scaffolds in sustainable way caught considerable attention of researchers.

Figure 1.17 Examples of medicinally established THPs and tacrine.

In this respect, Kumar *et al.* (2017), reported grinding induced catalyst and solvent free domino multicomponent reaction strategy for the synthesis of 1,4-dihydropyridines (**68**) through reaction of diethyl acetylene dicarboxylate (**66a)**, aromatic aldehydes (**1**), aryl amines (**13**) and Malononitrile derivatives **26** (**Fig.1.18**) [80].

Figure 1.18 Solvent and catalyst free mechanochemical induced synthesis of THPs.

In this chemical transformation, aryl benzaldehyde (**1**) and malononitrile derivatives (**26**) undergo Knoevenagel condensation to form adduct (**67**) and at the same time alkyl acetylene dicarboxylates (**67a**) react with aniline derivatives (**13a**) to form enaminones (**68**), which upon

Michael addition with the Knoevenagel adduct (**67**) provides the intermediate that undergoes intramolecular cyclization to give the desired product dihydropyridines (**69**). The mechanism of the reaction is presented in **Fig.1.19**.

Figure 1.19 The mechanism of reaction for mechanochemical mediated synthesis of THPs.

1.8.5.2 Tetrahydroquinoline (THQs) synthesis

THQs are medicinally important scaffolds to become center of focus in chemical research aiming at drug discovery. One of the most famous and more effective strategies toward combinatorial assembly of these moieties is the [4+2] Povarov reaction which is based on Diels-Alder cycloaddition reaction. In this regard, the green method based on mechanochemistry was developed by Zang *et al*. (2014) for the synthesis THQs (**72**) through the reaction of aryl aniline (**13**), aryl aldehydes (**1**) and styrene (**71**) in the presence of the catalyst $FeCl_3$ (**Fig.1.20**) [81].

Figure 1.20 Mechanochemical induced synthesis of THQs.

1.8.5.3 Pyrimidine synthesis

Pyrimidine derivatives are parts and parcel of myriads of life tuning molecules such adenine, cytosine, xanthine alkaloids and many other medicinally prominent scaffolds in nature and synthetic ones [82]. They exhibit broad spectrum of biological activities [83-90] such as antifungal, anticancer, antidiabetic, antivirus, anticonvulsant, antimicrobial, antioxidant, antihypertensive, antipyretic, anti-allergic, anti-Leishmanial, central nervous system anti-depressant properties, and calcium channel blockers. It is worth mentioning to note that some pyrimidine containing molecules such as epirizole (**72**) and afloqualone (**73**) [91] depict anti-inflammatory, anti-HIV and antihypertensive activities (**Fig.1.21**).

Figure 1.21 Examples of biologically potent pyrimidine molecules.

The synthetic history of pyrimidines dates back to the discovery of classical Biginelli reaction in the 19th century which contributed to the synthesis of these scaffolds under different conditions. Nevertheless, the search for promising greener route of synthesis was never seized. For example, Kaur *et al*. (2016) developed efficient and environmentally benign mechanochemical induced solvent-less green method utilizing ZnO NPs as a catalyst through reaction comprising aromatic aldehyde (**1)** alkylacetoacetates (**5)** and urea/thiourea (**8**) or 2-amino benzothiazole or 2-aminobenzoimidazole to synthesize pyrimidine (**75**) fused three cyclic system or single heterocycle bearing pyrimidine nucleus (**Fig. 1.22**) [92].

Figure 1.22 ZnO NPs catalyzed synthesis of pyrimidine containing scaffolds.

1.8.6 Synthesis of fused heterocyclic frame works

1.8.6.1 Imidazo [1,2-a]pyridine

Imidazo-pyridines are well known scaffolds displaying broad spectrum of biological activities such as antiulcer, antibacterial, anticancer, analgesic, antituberculosis, ant-inflammatory and antifungal activities [93–100] and were given a tag known as "drug prejudice". The synthesis of these profound moieties is interesting from application point of view and development of green synthesis routes is desirable. Hence, Zang *et al*. (2016) reported sustainable protocol induced by high speed ball milling mechanochemistry for the synthesis of IPs (**79**) employing 2-amino pyridines (**77**) and acetophenones (**10a**) derivatives under I_2 and DMAP catalyzed condition (**Fig. 1.23**) [101].

Figure 1.23 I_2 and DMAP catalyzed ball milling assisted synthesis of IPs.

In this reaction, acetophenone (**10a**) reacts with molecular iodine to form α-carbon iodinated intermediate (**77**) which further undergoes nucleophilic substitution with 2-aminopyridine (**76**) to form an intermediate with two active sites: carbonyl and amino functionalities. This adduct finally cyclizes through intramolecular fashion condensation reaction to form tertiary alcohol bearing moiety which up on dehydration provides the final desired product 2-phenyl imidazo pyridine (**78**). The mechanism of reaction is presented in **Fig. 1.24**.

Figure 1.24 Mechanism of reaction for the synthesis of imidazo-pyridines.

1.8.6.2 Pyrrole based polycyclic compounds

Synthesis of polycyclic heterocyclic scaffolds based on privileged simple core structures such as pyrrole is crucial in modern organic synthesis dealing with drug discovery owing to their impressive synergistic broad spectrum of biological activities. For example, for the synthesis of

poly heterocyclic scaffolds presented in **Fig.1.25**, a green mechanochemical route has been developed by Mendez *et al*.(2017), which is a mild and general synthesis strategy for the synthesis of fused heterocycles through three component reaction using *in situ* produced intermediates enaminones (**82**) , which was obtained from reaction of acyclic 1,3-dicarbonyl compounds(**5**) with 2,2-dimethoxyethylamine (**81**) and iodinated tetralone based intermediate, which was produced from reaction of tetralone derivatives (**79**) with the help of NIS. Finally, pyrrole containing scaffolds **(83)** under mechanochemical operation using catalytic amount of TMSOTf in DCM as a solvent provided the final desired polycyclic molecules (**84**) (**Fig. 1.25**) [102].

Figure 1.25 Mechanochemical induced stepwise synthesis of polycyclic fused heterocycles.

1.8.6.3 Pyrano [2, 3-*d*] pyrimidine-2, 4(1*H*, 3*H*)-diones

Pyrimidine derivatives, specifically, pyran fused ones such as pyrano [2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-diones are known for their broad biological activity such as antitumor, analgesic, antibacterial and antifungal [103]. It is desirable to design highly efficient and sustainable methodology of synthesis which improves the drawbacks of previously existing protocols. Accordingly, Jamal *et al*.(2009) reported one of the earliest reports involving ball milling strategy encompassing 3 component reaction under solvent and catalyst free condition for the synthesis of pyrano [2,3-*d*]pyrimidine-2,4(1*H*, 3*H*)-diones (**86**) from aromatic aldehydes (**1**), malononitrile (**26a**) and barbituric acid (**85**) (**Fig. 1.26**) [104].

Figure 1.26 Mechanochemical induced synthesis of pyrano fused pyrimidines under solvent and catalyst free conditions.

In this route of synthesis, arylaldehyde (**1**) reacts with malononitrile (**26a**) to form Knoevenagel adduct (**80**) which undergoes Michael addition type reaction with barbituric acid (**86**) to provide the intermediate that finally cyclizing intramolecular fashion to form the final desired product (**87**). The mechanism of the reaction is presented in (**Fig. 1.26**).

Figure 1.27 Mechanism of reaction for the synthesis of pyrano pyrimidines.

1.9 Objectives of the thesis

Solution based chemistry dominated chemical research going on in academia and industries for very long period of time. As the time went on, the environmental impact of these transformations began to manifest itself on living and non-living things in the world. The society began putting the scientific community under pressure and the researchers trying to address this critical issue by adjusting the mechanism of synthesis. The major problems in organic synthesis were found to be emanating from solvent management and the researchers for the past few decades have been focusing on green synthesis, which gives big emphasis on solvent management in organic synthesis, i.e., either using green solvent or no solvent. The **objective of my work** was designing, synthesis and characterization of biologically relevant scaffolds based on green routes of synthesis, i.e., without using solvent. In this regard, the work presented in chapters 2-5 has all been performed under solvent free condition and reported along with general introduction (chapter-1)

Chapter-2 is Mechanochemical-(Hand-Grinding) Assisted Domino Synthesis of Fused Pyran-Spirooxindoles under Solvent-and Catalyst-Free Condition

Chapter -3 Regioselective Synthesis of Functionalized 1, 3-Thiazine-4-ones *via* Multicomponent Click Reaction Approach

Chapter-4 Synthesis of Oxindoles-β-Enaminones Hybrids through One Pot Two-Steps Mechanochemical Four Component Reaction under Solvent and Catalyst Free Condition and

Chapter-5 Ammonium Chloride Assisted Microwave Mediated Domino Multicomponent Reaction: An Efficient and Sustainable Access for the Synthesis of Quinazolin-4(3*H*)-imines under Solvent Free Condition. The overall skeleton of the thesis is summarized in **Fig.1.28**.

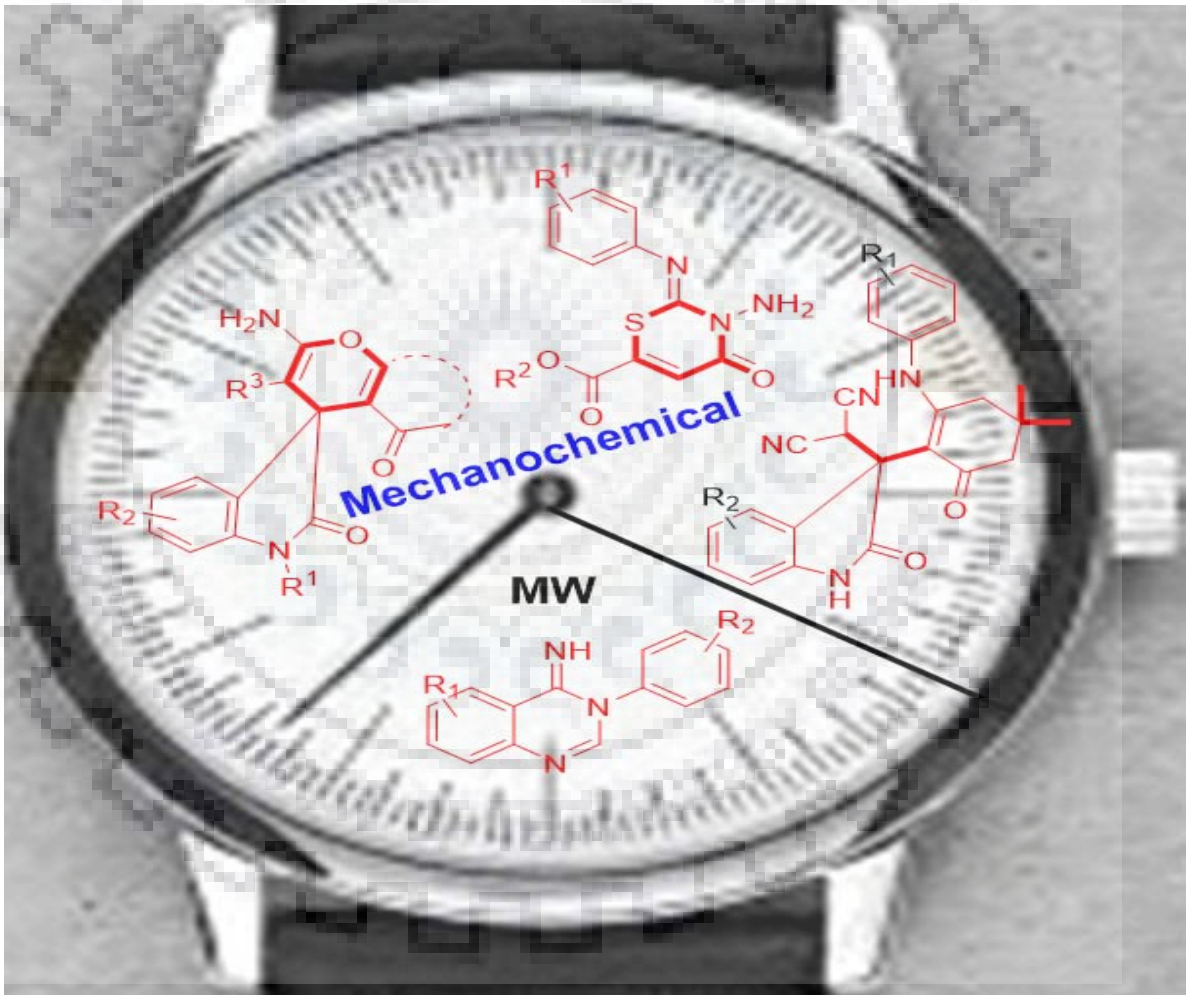

Figure 1.28 Graphical abstract of the thesis.

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Chapter 2

Mechanochemical-(Hand-Grinding-) Assisted Domino Synthesis of Fused Pyran-Spirooxindoles under Solvent- and Catalyst-Free Condition

2.1 Graphical Abstract of the Chapter

2.2 Introduction

Over the past few decades mechanochemistry has been undergoing extraordinary advancement and able to make giant forays into the domain of green synthesis, owing to its clean, safe, mild, efficient, atom economical (with less auxiliaries) and ideally green attributes [1–4]. This approach avoids the limitations associated with solution based chemistry such as solubility and solvolysis which is also believed to enhance reactivity of a system. Mechanochemical strategies require either no solvent at all [5–10] or needs it in minimum amount (LAG) [11–17]. Mechanochemistry includes ball milling, manual mortar and pestle assisted hand grinding and ultra-sonication. Ball milling as one aspect of mechanochemical method, which is dominant over other ways of executing chemical transformations as it can be regulated in terms of energy and time [18–20] and has been hailed as more accurate and reproducible grinding method. However, inaccessibility of this instrument in every bench top, owing to its space and soared pricing makes hand grinding a simple and effective alternative for ball milling transformations.

Mechanochemistry is effective in almost every class of chemical reactions, but the most commonly encountered ones have been Diels-Alder, Knoevenagel condensation, Aldol reaction, Michael addition, nitrone, oxime, enamine and imine formation reactions [21,22]. Mechanochemistry as a green element, specifically, when encompassing one pot multicomponent cascade reaction is a point of focus in green synthesis as it enables generating desired product with high efficiency and atom economy [23].

Pyran fused spiro-oxindoles as hybrid heterocycles of nitrogen and oxygen have created immense interest due to their fascinating architectures [24] and a wide spectrum of pharmacological applications such as anti-cancer, anti-bacterial, anti-fungal, anti-inflammatory, anti-tubercular, anti-Leishmanial, anti-Alzheimers and anti-HIV activities [25–29]. Many of these moieties have been at the forefront of promising biological applications. **Figure 2.1** depicts for example, compound **I**, which exhibits cytotoxicity having IC_{50} = 11 µM against MDA-MB-231 cancer cell lines and compound **II**, which shows IC_{50}= 6.9 µM against MDA cell lines [30,31] and compound **III** also acts as P38 α inhibitor [32].

Figure 2.1 Examples of highly potent heterocycles, containing fused pyran-oxindole core.

At the same time, ensuing applications of oxindole-pyran conjugates in agriculture and material science owe huge interest in synthetic routes leading to their formation [33].

2.3 Survey of the existing literature

When the existing literature to date has been assessed, it has been realized that 2-amino-2-oxo-spiro [indoline-3,4'-pyran]-3'-carbonitriles have been dominantly synthesized employing conventional methods. Generally speaking, these methodologies are relatively less effective in terms of efficiency (atom, energy, resource allocation, money management) and selectivity which results in undesired products hazardous in nature. Moreover, use of volatile organic solvents is also not benign environmentally. Amongst myriads of synthetic strategies based on conventional route of synthesis of these scaffolds, a few recent ones are highlighted. Wu *et al*. (2018) reported synthesis of (**4a**) using substrates dimedone (**3a**) and isatylidene (**1a+2a**) as intermediate reactant and squaramide chiral organo-catalyst (C_{15}) and CH_2Cl_2 as a solvent (**Fig. 2.2**) [34].

Figure 2.2 Synthesis of spirooxindoles by using bifunctional catalyst C_{15}.

Likewise, L. Moradi and Z. Ataei, (2017) disclosed construction of 2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitriles (**4**) employing isatin (**1**), compounds with active methylene group such as malononitrile (**2a**) and 1,3-dicarbonyl compounds like dimedone (**3a-3d**) and 7'-amino-2,2',4'-trioxo-1',2',3',4'-tetrahydrospiro[indoline-3,5'-pyrano[2,3-d]pyrimidine]-6-carbonitrile (**5**), using isatin derivatives (**1**), active methylene bearing compounds like malononitrile (**2**) and barbituric acid (**3e-3f**) using CuO nanoparticles (NPs) in EtOH at room temperature. Use of expensive metal based nano catalyst used is the drawback in this method (**Fig. 2.3**) [35].

Figure 2.3 Synthesis of spirooxindoles using CuO NPs in ethanol.

Nongkhlaw *et al*. (2016) reported synthesis of pyran fused oxindoles **4-6** from the reaction of isatin (**1a**), malononitrile (**2a)** and dimedone (**3a**,**3c**), 4-hydroxycoumarin(**3d**) and barbituric acid (**3e**,**3f**) respectively and the second set of pyran fused oxindoles **8-10** from the reaction of isatin (**1a)**, 3-methyl-1H-pyrazol-5-amine **(7a)** and dimedone, (**3a**,**3c**) 4-hydroxycoumarin (**3d**).and barbituric acid (**3e**, **3f**) respectively. by using iron based nanoparticles encapsulated with SiO_2 and vitamin B_1 as catalyst under ultrasonic condition (**Fig. 2.4**) [36]. In this case, green protocol is developed, but operational procedure is not straight forward, i.e., preparation of catalyst system is complex and economically not affordable.

Figure 2.4 Fe_2O_3 nanoparticles encapsulated with SiO_2 and vitamin B1 catalyzed synthesis of spirooxindoles.

Nasseri *et al*. (2015) synthesized pyran fused spirooxindoles (**4**) and (**5**) using isatin derivatives (**1**), malononitrile **2a** and 1,3-dicarbonyl compounds (**3**) using NiO NPs as a catalyst and water as a

solvent at room temperature. This work suffers from narrow diversity where one of the three components, i.e., malononitrile **2a** is not varied (**Fig. 2.5**) [37].

Figure 2.5 NiO NPs catalyzed synthesis of spirooxindoles.

Kidwai *et al*. (2012) disclosed synthesis of pyran fused spirooxindoles (**4**) and (**5**) from reaction of isatin **1a**, malononitrile **2a** and dimedone derivatives (**3a-3c**) and 4-hydroxycoumarin respectively in one hand and the second set of pyran fused spirooxindoles (**11**) and (**12**) from reaction of acenaphthylequinone (**1b**), malononitrile **2a** and dimedone derivatives (**3a-3c**) and 4-hydroxycoumarin respectively using gold (III) chloride ($HAuCl_4.3H_2O$) in PEG as solvent (**Fig.2.6)** [38]. One obvious drawback of this method is the use of expensive gold as a catalyst.

Figure 2.6 Gold (III) chloride catalyzed synthesis of spirooxindoles.

Meanwhile, in 2012, Safaei and Shekouhy *et al.* reported a synthetic strategy leading to the synthesis of 2-amino-2-oxospiro [indoline-3,4'-pyran]-3'-carbonitriles (**4-6)** through reaction of isatin (**1**), malononitrile (**2**) and 1,3-dicarbonyl compounds dimedone,(**3a**, **3c**). 4-hydroxycoumarin (**3d**) and barbituric acid (**3e**) respectively along with their other related desired products and (**13-15**) from reaction of isatin (**1**), malononitrile (**2**) and C-H acid compounds 5-methyl-2-phenyl-2,4-dihydro-3*H*-pyrazol-3-one (**3g**), 2-naphthanol (**3h**) and 1-naphthanol (**3i**) respectively. using glycerol both as a solvent and a promoter (**Fig. 2.7**) [39]. In this approach, the process of recovery of glycerol might pose problems due to its high boiling point.

Figure 2.7 Glycerol promoted synthesis of spirooxindoles.

In 2016, Farhadina *et al.* reported a synthetic protocol utilizing biocatalyst derived from swim bladders of Caspian sea fish for the synthesis of 2-amino-2-oxospiro [indoline-3,4'-pyran]-3'-carbonitriles (**4-6)** through reaction of isatin (**1**), malononitrile (**2)** and 1,3-dicarbonyl compounds, dimedones (**3a**, **3c**) and 4-hydroxycoumarine, (**3d**) and barbituric acids (**3e**, **3f**) respectively and **16** from reaction of isatin (**1**), malononitrile (**2)** and 1,3-dicarbonyl compound, 1,3-pantane-dione (**3j**) in the presence of Caspian Isinglass (IG) (**Fig.2.8**) [40]**.** Although the method is good, however, accessing the catalyst system is not straight forward**.**

Figure 2.8 IG catalyzed synthesis of spirooxindoles.

A similar enzymatic catalyzing process was employed back in 2011, when Zhang *et al*. reported synthesis of pyran fused spirooxindoles (**4**) through reaction of isatin (**1**), malononitrile (**2)** and cyclic 1,3-dicarbonyl compounds (**3a**, **3c**) derivatives and **17** from reaction of isatin (**1**), malononitrile (**2**) and acyclic 1,3-dicarbonyl compound, ethyl acetoacetate (**3k**) using lipase from porcine pancreas (PPL) as a catalyst in the presence of water and ethanol as a solvent (**Fig.2.9**) [41]. The long reaction time and obscure nature of catalyst are two drawbacks with this method.

Figure 2.9 PPL catalyzed synthesis of spirooxindoles synthesis.

In addition to the methods described above, there are several other examples for the synthesis of pyran fused oxindoles using ionic liquids, NPs, biocatalysts, combination of nano and biocatalysts

etc. It's beyond the scope of this chapter to highlight each and every work. However, a few of the remaining ones have been summarized in **Table 2.1**.

Table 2.1 Summary of conventional routes of synthesis of pyran fused spirooxindoles

s/no	Authors	Publication year	Reaction system	Reference
1	Hasaninejad *et al*.	2015	PEG400/K_2CO_3	[42]
2	Singh *et al*.	2018	Glucose-water synergy	[43]
3	Moslemin and Yan *et al*.	2015	Alum.SiO_2 based NPsin piperidine	[44]
4	Kashinath *et al*.	2017	L-Proline-Melamine	[45]
5	Shirini *et al*.	2016	C_4(DABCO-$SO_3H)_2$.4Cl	[46]
6	He and Guan *et al*.	2015	A-amylase from hog pancreas	[47]
7	Xu and Yu *et al*.	2017	DABCO based ionic liquid	[48]
8	Moghadam and Miri	2011	[Bmim]BF_4	[49]
9	Shi *et al*.	2012	Ultrasound- assisted	[50]
10	Yuan *et al*.	2010	Catalyzed by Cupreine	[51]

Interestingly, there is only one example where spirooxindoles have been synthesized using mechanochemistry. Singh *et al*. (2014) reported synthesis of 2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3'-indoline]-3-carbonitrile (**5**) by grinding a mixture of isatin (**1**), malononitrile **2** and dimedone (**3)** derivatives employing Bim(OH) and chitosan as a catalyst and C_2H_5OH as a solvent (**Fig. 2.10**) [52]. The greenness of this protocol is obvious, but the main drawback of this protocol is narrow scope as only 10 molecules were synthesized by this strategy.

Figure 2.10 Chitosan and Bim(OH) assisted and mechanochemical induced synthesis of spirooxindole 4.

Taking into account the comprehensive benefits that mechanochemical methods provide which were described in detail in chapter 1, mechanochemical domino synthesis of fused pyran-spirooxindoles under solvent-and catalyst-free condition, would be an ideal alternative to previous protocols suffering from one drawback or other.

Therefore, in line with developing green chemical routes [53–57] for preparing useful heterocycles and their hybrids in my laboratory, new method is herein reported involving a novel mechanochemical domino synthesis of 2-amino-2-oxo-spiro[indoline-3,4'-pyran]-3'-carbonitrile at room temperature under solvent and catalyst free conditions.

2.4 Results and Discussion

Keeping intent on developing an environmentally benign synthetic method, initially grinding isatin **1a** (0.5 mmol), malononitrile **2a** (0.5 mmol) and dimedone **3a** (0.5 mmol) as model substrates without any catalyst and solvent (**Table2.1**) was examined. Unfortunately, the reaction did not work and multiple unidentifiable products were being formed. This indicated that addition of all three substrates at once might not be a good strategy and next, alternative synthesis approach targeting step wise reaction strategy by adding only two reactants at a time implemented, i.e., isatin **1a** and malononitrile **2a** were ground. After 10 minutes of gentle grinding, the completion of

reaction was indicated by TLC. Next, the third component, malononitrile **3a** was added and grinding continued for further 15 minutes in the same manner**.**

Table 2.2 Table of optimization of reaction condition

Entry	Promoter	Time (min.)	Yield[b] (%)
1	-	25	94
2	H_2O	23	94
3	Glycerol	26	93
4	PEG-400	27	92

[a]General reaction conditions: Isatin **1a** (0.5 mmol) and malononitrile **2a** (0.5 mmol), has been ground for about 10 minutes followed by mixing of dimedone **3a** (0.5 mmol) and the further grinding of the reaction mixture for another 15 minutes. [b]Isolated yield from mechanochemical reaction at room temperature for 25 minutes.

Gratifyingly, the formation of the desired product occurred with 94% yield (**Table 2.2, entry 1**). In order to study the effect liquid assisted grinding (LAG), the same reaction was performed under different solvents such as water, glycerol and PEG-400 each about two drops. Nevertheless, any significant improvement was not observed in both time and yield in either of the cases. Results are delineated in (**Table 2.2, entries 2-4**). Finally, based on optimum work condition, it was concluded that grinding of isatin **1a** (0.5 mmol) and malononitrile **2a** (0.5 mmol) for 10 minutes followed by addition of dimedone **3a** (0.5 mmol) and subsequent grinding for 15 minutes to be the optimized protocol for the reaction.

Scheme 2.1 Scope of reaction.

Table 2.3 Library of synthesized compounds

Next, exploring substrate scope for the developed reaction strategy performed. Varieties of cyclic 1,3-dicarbonyl compounds such as dimedone and its derivatives, 4-hydroxycoumarin and 4-hydroxy-6-methyl-2-pyrone, isatin derivatives (with electron donating and electron withdrawing

groups), acenaphthoquinone, malononitrile, ethyl cyanoacetate were employed in the study and were found tolerant to this method giving excellent yield of the respective products in the range of 87-95 % (**Scheme 2.1** and **Table 2.3** products (**4a-4q**). Unfortunately, reagents like 1-methyl isatin, 2-cyanoacetamide and acyclic 1,3-dicarbonyl compounds such as ethylacetoacetate gave trace amount of products probably because of electronic effects (**Table 2.3**, molecules **4r** and **4s**). It is worthy to note that in all cases, the spectroscopically pure products were obtained by mere filtration of the crude product from water and no tedious workups or column chromatography was required.

Scheme 2.2 Multigram scale synthesis of 2-Amino-7,7-dimethyl-2', 5-dioxo-5, 6,7, 8-tetrahydospiro [chromene-4, 3'-indoline]-3-carbonitrile (**4a**).

Figure 2.14 Portions of time dependent IR taken at 10^{th}, 12^{th} and 15^{th} minutes of grinding (spectra A, B and C) respectively.

Finally, we conducted synthesis of **4a** on multigram scale, i.e., (5 mmol) of **1a**, **2a** and **3a** and the product was obtained in excellent 92% yield (**Scheme 2.2**). In order to assess the "greenness" of our methodology, we calculated a set of green metrics such as Sheldon environmental impact

Scheme 2.3 Plausible mechanism of the reaction.

factor (E-factor), atom economy (AE), process mass intensity (PMI), carbon efficiency (CE) and reaction mass efficiency to evaluate the rate of transformation of reactants into products [58-63]. The resulting numbers such as E-factor (0.054) and high values of 95%, 95% and 94.91% for AE, RME, and CE respectively clearly indicate that our present methodology is green and would be feasible for automation.

In order to ascertain the postulated mechanism, the intermediate Knoevenagel product **A** after grinding **1a** with malononitrile was isolated and its spectral information confirmed the structure Moreover, time dependent IR studies were performed in which IR spectra were taken at 10th minute, 12th minute and 15th minute as shown in **Figure 2.14** (A, B and C respectively), which shows emphasized portions of IR spectra (supporting information). At the 10th minute upon grinding of **1a** and **2a**, the IR shows a nitrile peak at 2231 cm^{-1}and an amide carbonyl at 1734 cm^{-1}. This confirms the Knoevenagel product as TLC at this juncture had no starting material left. At the 12th minute, lowering of the value of nitrile peak at 2195 cm^{-1} indicate a Michael adduct **B** formed by the reaction of **A** and dimedone. This is further indicated by carbonyl peaks at the region of 1740 cm^{-1} which correspond to dimedone carbonyl. Lastly, at the 15th minute the IR confirms formation of the product **4a** as peaks at 3376 cm^{-1} and 3314 cm^{-1} for the NH_2 group appear for the first time and carbonyl peak comes down to 1725 cm^{-1} in a conjugated environment.

Based on some of the previous reports, [64-65] herein the plausible mechanism for this reaction has been proposed (**Scheme 2.3**). In our synthetic strategy, Isatin **1a** and malononitrile **2a** upon grinding led to the formation of Knoevenagel condensation product, intermediate **A.** Michael addition of dimedone **3a** with **A** resulted in the formation of another intermediate **B**, which tautomerised to **C** in a reversible manner. Finally, enolic alcohol cyclizes at CN group giving rise to intermediate **D** which tautomerises to the final desired product **4a**.

2.5 Conclusions

Highly efficient and green protocol based on mechanochemical approach, i.e., hand-grinding under solvent and catalyst free condition encompassing domino multicomponent reaction has been developed. In this methodology readily available starting chemicals like isatin and its derivatives, malononitrile or ethyl cyanoacetate and cyclic 1, 3-dicarbnyl compounds have been utilized to synthesize 2-amino-2-oxospiro [indoline-3,4'-pyran]-3'-carbonitriles. The method involves easy work up merely filtration to give excellent yields under exceptionally green condition.

2.6 Experimental Section

2.5.1 General Experimental Detail

The reactions were performed by hand grinding tools mortar and pestle made of ceramics for hand grinding in our laboratory. ^{1}HNMR spectra were recorded on a Jeol Resonance ECX-400II (400 MHz); Chemical shifts (δ in ppm) and coupling constant (*J* in Hz) are calibrated relative to internal solvent tetramethylsilane TMS (δ_H = 0.00 ppm). In the ^{1}H NMR data, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, dd = double doublets, and brs = broad singlet. ^{13}C NMR spectra were recorded on a Jeol Resonance ECX-400II (100 MHz) at R.T in DMSO-d_6.

Analysis of the reactions was done by thin layer chromatography (TLC). For this, Merck precoated silica gel TLC plates (Merck® $60F_{254}$) were used. All the reagents were purchased from Sigma Aldrich and Alfa Aesar. Solvents for optimization purpose were purchased from locally available commercial sources and used as received.

2.5.2 General procedure for the synthesis of fused pyrano-spirooxindoles

Using mortar and pestle for hand-grinding, after gentle grinding of isatins **1a-d** (0.5 mmol) or acenaphthoquinone **1e** (0.5 mmol), malononitrile **2a** or ethyl cyanoacetate **2b** (0.5 mmol) for about 10 minutes the completion of reactions indicated by TLC, the third components enolizable cyclic 1,3-dicarbonyl compounds **3a-e** were mixed and grinding continued for another 10 minutes. The solid products obtained were filtered and washed with water (5 mL x 2). To study liquid assisted grinding (LAG), the same reaction has been performed using two about drops of H_2O, glycerol and EPG-400 (**Table 1. entries 2-4**). The products isolated were pure enough to be characterized by FTIR, ^{1}H-NMR, ^{13}C NMR and CHNS analysis.

Spectral Data for All Compounds (4a-q)

1. **2-Amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydospiro[chromene-4,3'-indoline]-3-carbonitrile (4a)**.

White powder (yield 94%); melting point 289-292 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:** δ (ppm) 10.37 (s, 1H), 7.18 (s, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 6.8 Hz, 1H), 6.85(t, *J* = 7.2 Hz, 1H), 6.75(d, *J* = 7.6 Hz, 1H), 2.51(s, 2H), 2.09 (dd, *J* = 30.4 Hz, 2H), 0.99 (s, 3H), 0.96(s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)**:** δ (ppm) 195.5, 178.6, 164.7, 159.3, 142.5, 134.9, 128.7, 123.5, 122.3, 117.9, 111.3, 109.8, 58.0, 50.5, 47.3, 32.5, 28.1, 27.5; IR spectra (4000-600 cm^{-1}): υ_{max} 3450, 2111, 1634; Elem. Anal**.** For $C_{14}H_{11}N_3O_3$ Calcd**:** C, 68.05, H, 5.11, N, 12.53%; found: C, 67.88, H, 5.04; N, 12.68%

2. **2-Amino-7-methyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4b)**.

White powder (yield 91%); melting point 288-291 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:** δ (ppm) 10.38 (s, 1H), 7.17 (s, 2H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.94 (t, *J* = 7.2 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 7.6 Hz, 1H), 2.64-2.57 (m, 1H), 2.46-2.42(m, 1H), 2.24-2.16(m, 2H), 2.04-1.97(m, 1H), 1.00(s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 195.6, 178.7, 165.5, 159.2, 142.5, 135.0, 128.7, 123.6, 122.3, 117.9, 111.8, 109.7, 58.0, 47.4, 44.8, 34.6, 27.9, 20.5; IR (4000-600 cm^{-1}): υ_{max} 3303, 3237, 3157, 2194, 1724, 1678; Elem. Anal. for $C_{18}H_{15}N_3O_3$ Calcd: C, 67.28; H, 4.71; N, 13.08 %; found: C, 67.32; H, 4.68; N, 13.02 %.

3. **2-Amino-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4, 3'-indoline]-3-carbonitrile(4c).**

White powder (yield 89%); melting point, 290-292 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:** δ (ppm) 10.38 (s, 1H), 7.16 (s, 2H), 7.10 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 7.2 Hz, 1H), 6.85 (t, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 2.59 (t, *J* = 6.0 Hz, 2H), 2.19-2.15 (m, 2H), 1.89-1.83 (m, 2H).^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 195.8, 178.8, 166.7, 159.2, 142.4, 135.0, 128.7, 123.7, 122.3, 117.9,

112.3, 109.8, 58.0, 47,4, 36.8, 27.2, 20.3; IR (6000-600 cm^{-1}): υ_{max} 3368, 3295, 3132, 2191, 1707, 1682; Elem. Anal. for $C_{17}H_{13}N_3O_3$ Calcd: C, 66.44; H, 4.26; N, 13.67 %; found: C, 66.37; H, 4.13; N, 13. 61 %.

4. 2-Amino7,7-dimethyl-5'-nitro-2,5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile(4d).

Yellow solid (yield 95%); melting point 291-294 ^oC; ^1H NMR (400 MHz**,** DMSO-d_6)**:** δ (ppm) 11.16 (s, 1H), 8.11(d, *J* = 8.8 Hz 1H,), 7.92 (s, 1H), 7.42 (s, 2H), 6.99 (d, *J* = 8.4 Hz, 1H), 2.61 (d, *J* = 17.6 Hz, 1H), 2.46 (s, 1H), 2.12(q, *J* = 26.8 Hz, 2H), 0.98(s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6)**:** δ (ppm) 195.9, 179.1, 165.7, 159.6, 149.1, 142.9, 135.8, 119.3, 117.5, 115.0, 110.2, 109.9, 56.4, 50.3, 47.4, 32.5, 28.1, 27.5; IR (4000-600 cm^{-1})**:** υ_{max} 3385, 3185, 2191, 1741, 1680, 1338; Elem. Anal. for $C_{19}H_{16}N_4O_5$ Calcd: C, 60.00; H, 4.24; N, 14.73 %; found: C, 59.54; H, 4.41; N, 14.69 %.

5. 2-Amino-7'-methyl-5-nitro-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3'-carbonitrile (4e)

Yellow solid (yield 94 %); melting point 289-291 ^oC; ^1H NMR (400 MHz, d^6-DMSO)**:** δ (ppm) 11.14-11.12 (br s, 1H), 8.11 (d, *J* = 8.4 H z, 1H), 7.96 (d, *J* =20.4Hz, 1H), 7.40 (s, 2H), 6.97 (d, *J* = 8.8 Hz, 1H), 2.62-2.51 (m, 2H), 2.23-2.20 (m, 2H), 2.07-2.00(m, 1H), 0.98-0.96 (m, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)**:** δ (ppm) 196.0, 179.1, 167.1, 166.7, 159.5, 149.1, 142.9, 136.0, 126.3,117.6, 110.9, 109.9, 56.5, 47.6, 44.6, 34.7, 28.1, 20.8; IR (6000-400 cm^{-1}): υ_{max} 3481**,** 3428, 3167, 2192, 1749, 1661, 1135; Elem. Anal. for $C_{18}H_{14}N_4O_5$ Calcd: C, 59.02; H, 3.85; N, 15.29 %; found: C, 58.57; H, 3.91; N, 15.21%.

6. 2-Amino-5'-nitro-2',5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3'-indoline]-3-carbonitrile (4f)

Yellow solid (yield 92 %); melting point 290-292 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 11.15 (s, 1H), 8.11 (dd, *J* = 8.8 Hz, 1H), 7.99 (d, *J* =2.4 Hz, 1H,), 7.41 (s, 2H), 6.97 (d, *J* = 8.4 Hz, 1H), 2.64 (t, J= 6.4Hz, 2H,), 2.21 (t, *J* =6.4 Hz, 2H), 1.95-1.86 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 196.0, 179.3, 167.7, 159.4, 149.1, 142.9, 136.0, 126.3, 119.7, 117.6, 111.3, 109.9, 56.4, 47,5, 36.6, 27.3, 20.2; IR (4000-600 cm^{-1}): υ_{max} 3350, 3140, 2195, 1744, 1722, 1683; Elem. Anal. for $C_{17}H_{12}N_4O_5$ Calcd: C, 59.02; H, 3.85; N, 15.29 %; found: found: C, 58.04; H, 3.98; N, 15.22%

7. 2-Amino-5'-methoxy-7,7'-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro [chromene-4,3'-indoline]-3-carbonitrile (4g)

Grey powder, m.p. 288-291 ^{o}C (yield 90%); ^{1}H NMR (400MHz, DMSO-d_6): δ (ppm) 10.19 (s, 1H), 7.18 (s, 2H), 6.67 (s, 2H,), 6.56 (s, 1H), 3.61 (s, 3H), 2.46 (s, 2H,), 2.09 (dd, *J* =21.6Hz, 2H), 0.98 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 195.5, 178.5, 164.7, 159.3, 155.5, 136.2, 135.9, 117.9, 113.1, 111.2, 110.6, 110.1, 58.0, 55.9, 50.5, 47.8, 32.5, 28.1, 27.6; IR spectra (6000-400 cm^{-1}): υ_{max} 3374, 3321, 3157, 2191, 1713, 1668; Elem. Anal. for $C_{20}H_{19}N_3O_4$ Calcd: C, 65.74, H, 5.24, N, 11.50 %; found: C, 57.96, H, 3.43, N, 15.90 %; found: C, 64.98; H, 5.30, N, 11.41 %

8. 2-Amino-5'-methoxy-7-methyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4h).

Grey powder (yield 89%); m.p. 288-291 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) 10.18-10.16 (m, 1H), 7.17 (s, 2H), 6.68-6.63 (m, 2H,), 6.58 (d, *J* = 12.8 Hz, 1H), 3.62 (s, 3H), 2.64-2.55 (m, 2H,), 2.24-2.17 (m, 2H), 2.04-1.97 (m, 1H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 195.5, 178.5, 166.0, 165.4, 159.2, 155.5, 136.3, 117.9, 113.1, 111.8, 110.7, 110.0, 58.0, 55.9, 47.9, 44.9, 34.7, 27.9, 20.6; IR (6000-400 cm^{-1}): υ_{max} 3371, 3288, 3147, 2192,

1716, 1670; Elem. Anal. for $C_{19}H_{17}N_3O_4$ Calcd: C, 64.95, H, 4.88, N, 11.96 %; found: C, 64.43; H,4.92 N, 11.73%

9. 2-Amino-5'-methoxy-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile (4i)

Grey powder (yield 87%); m.p. 290-291 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:** δ (ppm) 10.22 (s, 1H), 7.22 (s, 2H), 6.73-6.68 (m, 2H,), 6.65 (d, *J* =2 H z, 1H), 3.67(s, 3H), 2.65 (t, *J* = 5.2 Hz, 2H), 2.25-2.22 (m, 2H,), 1.96-1.90 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) 195.5, 178.5, 166.5, 159.1, 155.4, 136.3, 135.8, 117.8, 113.0, 112.3, 110.8, 109.9, 58.1, 55.8, 47.8, 36.9, 27.2, 20.2; IR (6000-400 cm^{-1}): υ_{max} 3359, 3288, 3176, 2189, 1703, 1661, 1128; Elem. Anal. for $C_{18}H_{15}N_3O_4$, Calcd: C, 64.95, H, 4.88, N, 11.96 %; found: C, 64.54; H, 5.04; N, 11.75%**.**

10. 2-Amino-5',7,7-trimethyl-2',5-dioxo-5,6,7,8-tetrahydospiro[chromene-4,3'-indoline]-3-carbonitrile(4j).

White powder (yield 89%); m.p. = 289-291 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:** δ (ppm) 10.27 (s, 1H), 7.18 (s, 2H), 6.90 (d, *J* =8.0 Hz, 1H), 6.74 (s, 1H), 6.64 (d, *J* = 8.0Hz, 1H), 2.46 (s, 2H), 2.15 (s, 3H), 2.09 (s, 2H), 0.98 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 195.5, 178.6, 164.6, 159.2, 140.1, 135.0, 131.0, 129.0, 124.1, 117.9, 111.3, 109.5, 58.1, 50.5, 47.3, 32.5, 28.0, 27.7, 21.2; IR (6000-400 cm^{-1})**:** υ_{max} 3353, 3308, 3241, 2193, 1718, 1679; Elem. Anal. for $C_{20}H_{19}N_3O_3$ Calcd: C, 68.75, H, 5.48, N, 12.03 %; found: C,68.09; H,5 85; N, 11.86%

11. 2-Amino-5',7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydospiro[chromene-4,3'-indoline]-3-carbonitrile(4k).

^{1}H NMR (400MHz, DMSO-d_6)**:** δ (ppm) 10.30-10.28 (m, 1H), 7.20(s, 2H), 6.94(d, J=6.4Hz, 1H), 6.80(d, *J* =10.0 Hz, 1H), 6.67(d, *J* = 6.4 Hz, 1H), 2.68-2.63(m, 2H), 2.29-2.25(m, 2H), 2.21(s, 3H), 2.09-2.03(m, 1H), 1.02(d, *J* =4.8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)**:** δ (ppm) 195.4, 178.5, 165.8, 165.3, 159.1, 140.1, 130.9, 128.9, 117.8, 115.0, 111.9,109.4, 58.2, 47.4, 44.8, 34.7, 27.9, 21.1, 20.6; IR (6000-400 cm^{-1})**:** υ_{max} 3370, 3311, 3161, 2192, 1728, 1684, 1656; Elem. Anal. for $C_{19}H_{17}N_3O_3$ Calcd: C, 68.05, H, 5.11, N, 12.53 %; found: C, 67.67; H,5,22; N, 12.35 % .

12. 2-Amino-5'-methyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carbonitrile(4l).

Yellow solid (yield 90%); m.p. ^{1}H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 10.23(s, 1H), 7.14(s, 2H), 6.89 (d, J=8.0Hz, 1H), 6.77 (s, 1H), 6.62 (d, *J* =7.6 Hz, 1H), 2.61 (t, *J* = 6.4 Hz, 2H), 2.46 (t, *J* = 2.0Hz, 2H), 2.16 (s, 3H), 1.91-1.85 (m, 2H); ^{13}C NMR (100 MHz, DMSO-d_6)**:**δ (ppm) 195.5, 178.6, 166.5, 159.1, 140.1, 135.2, 130.9, 128.9, 124.3, 117.9, 112.5, 109.4, 58.3, 47.4, 36.9, 27.2, 21.3, 20.3; IR (6000-400 cm^{-1}): υ_{max} 3367**,** 3290, 3150, 2195, 1711, 1684, 1194; Elem. Anal. for $C_{18}H_{15}N_3O_3$ Calcd: C, 67.28, H, 4.71, N, 13.08 %; found: C,67.05; H,4.88;N, 12.78 %

13. 2'-Amino-5-nitro-2,5'-dioxo-5'-H-spiro[indoline-3,4'-pyrano[3,2-c]chromene]-3'-carbonitrile (5m).

Yellow solid (Yield 90%); m.p.=152 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:** δ (ppm) 11.40 (s, 1H), 8.31 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.81 (s, 2H), 7.74 (t, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* =8.0 Hz, 1H), 7.06 (d, J=8.8Hz, 1H); ^{13}C NMR (100 MHz**,** DMSO-d_6)**:** δ (ppm) 178.3, 159.3, 159.2, 156.3, 149.1, 143.3, 136.9, 134.5, 134.3, 126.8, 125.5, 123.3, 122.8, 121.0, 117.2, 113.2, 110.2, 100.7, 56.2, 48.3; IR

spectra (6000-400 cm^{-1})**:** V_{max} 3303, 3208,2203, 1743, 1705, 1673; Elem. Anal. for $C_{18}H_{15}N_3O_3$ Calcd: C, 59.71, H, 2.51, N, 13.93 %; found: C, 57.08; H, 2.60; N, 13.23%

14. 2'-Amino-7'-methyl-5-nitro-2,5'-dioxo-5'H-spiro[indoline-3,4'-pyrano[4,3-b]pyran]-3'-carbonitrile (5n).

White solid (Yield 91%); m.p. =154 ^oC; ^1H NMR (400 MHz, DMSO-d_6)**:** δ (ppm) 11.31 (s, 1H), 8.17-8.15 (m, 2H), 7.61 (s, 2H), 7.01 (d, *J* = 8.4 Hz, 1H), 6.36 (s, 1H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)**:** δ (ppm) 178.5, 164.7, 160.8, 159.5, 149.2, 143.2, 134.6, 126.8, 117.5, 110.2, 98.7, 97.8, 56.0, 47.7, 19.8; IR (6000-400 cm^{-1}): υ_{max} 3449, 3352, 3205, 2201, 1734, 1702; Elem. Anal. for $C_{17}H_{10}N_4O_6$ Calcd: C, 55.74, H, 2.75, N, 15.30 %; found: C, 54.43 H,2.79; N, 14.93%

15. 2-Amino-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydrospiro[acenaphthylene-1,4'-chromene]-3'-carbonitrile (5o).

White powder (Yield 92%); m. p. 290 ^{o} C (^1H NMR (400 MHz, DMSO-d_6)**:** δ (ppm) 8.22 (d, J=8Hz, 1H), 7.89 (d, J=7.2Hz, 2H), 7.79 (t, *J* =7.2Hz, 1H), 7.62 (t, *J* =7.2 Hz, 1H), 7.35 (d, *J* =6.4 Hz, 1H), 7.28 (s, 2H), 2.58 (s, 2H), 2.09-2.00 (m, 2H), 0.98 (d, *J* =6.4 Hz, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6)**:** δ (ppm) 204.1, 195.8, 165.1, 159.3, 143.7, 141.0, 132.7, 131.9, 130.3, 129.4, 128.9, 125.0, 121.9, 120.3, 118.0, 112.5, 58.5, 51.4, 50.2, 32.5, 27.9, 27.7; IR (6000-400 cm^{-1}): υ_{max} 3150, 2953, 2194, 1733, 1602, 1400, 1113; Elem. Anal. for $C_{23}H_8N_2O_3$ Calcd: C, 74.58.71; H, 4.90; N, 7.56 %; found: C, 73.57; H,4.95; N, 6. 97%

16. Ethyl-2-amino-7,7-dimethyl-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'indoline]-3'-carboxylate (4p)

White powder (Yield 90%); m.p. 294 ^{o}C (^{1}H NMR (400 MHz, DMSO-d_6)**:** δ (ppm) 10.09 (s, 1H), 7.80 (s, 2H), 7.00 (t, *J* =7.6 Hz, 1H), 6.79 (d, J=6.8Hz, 1H), 6.72 (t, *J* = 7.6 Hz, 1H), 6.63 (d, *J* = 7.6 Hz, 1H), 3.66 (q, 2H), 2.49 (dd, *J* = 38.8Hz, 2H), 2.04 (dd, 54.8Hz, 2H), 0.98 (s, 3H), 0.90 (s, 3H), 0.76 (t, 3H); ^{13}C NMR (100 MHz, d^6-DMSO)**:** δ (ppm) 195.2, 180.3, 168.2, 162.9, 159.7, 144.6, 136.5, 127.7, 122.8, 121.1, 113.6, 108.7, 76.9, 59.4, 51.2, 47.2, 32.1, 28.3, 27.2, 13.6; IR (6000-400 cm^{-1}): υ_{max} 3370, 3243, 3117, 1717, 1687, 1667, 1056. Elem. Anal. for $C_{21}H_{22}N_2O_5$ Calcd : C, 65.96, H, 5.80, N, 7.33%; Found: C, 66,99; H, 5.91; N, 7.89%

17. Ethyl-2amino-7,7-dimethyl-5'-nitro-2',5-dioxo-5,6,7,8-tetrahydrospiro[chromene-4,3'-indoline]-3-carboxylate 4q)

White powder (Yield 92%); m.p. 294 ^{o}C ^{1}H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 10.93 (s, 1H), 8.05 (d, *J* =8.8 Hz, 1H), 7.97 (s, 2H), 7,72 (bs, 1H), 6.85 (d, J=8.4Hz, 1H), 3.69 (q, *J* =6.8 Hz, 2H), 2.60-2.52 (m, 2H), 2.07 (dd, *J* = 20.8 Hz, 1H), 0.96(s, 3H), 0.92 (s, 3H), 0.77(t, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)**:** δ (ppm) 195.7, 181.0, 167.7, 164.1, 159.9, 151.5, 142.1, 137.7, 118.6, 112.7, 108.3, 106.2, 75.6, 59.7, 59.0, 32.1, 27.8, 13.7, 13.6; IR (6000-400 cm^{-1}): υ_{max} 3337, 3293, 3194, 1734, 1687, 1652, 1059; Elem. Anal. for $C_{21}H_{21}N_3O_7$ Calcd : C, 59.01; H, 4.95; N, 9.83%; Found: C, 58,13; H, 5.91; N, 9.11%

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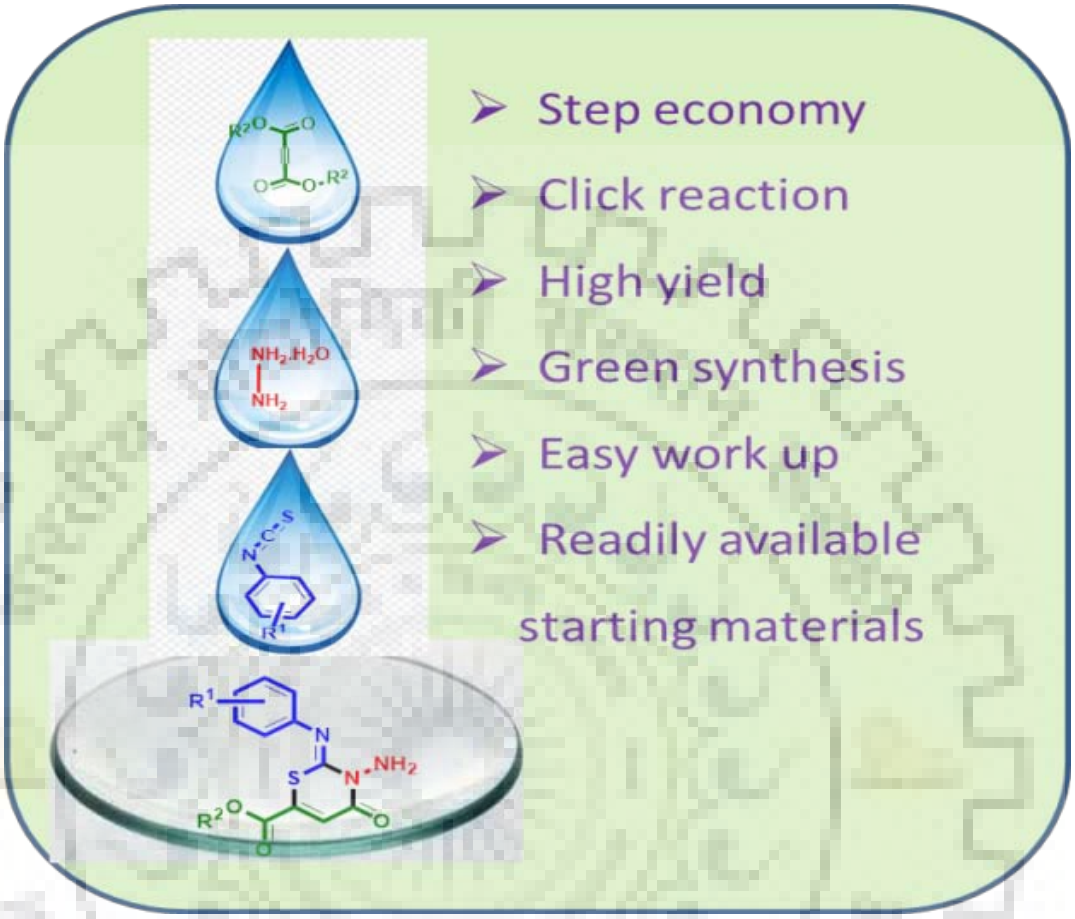
Chapter 3

Regioselective Synthesis of Functionalized 1, 3-Thiazine-4-ones via Multicomponent Click Reaction Approach

3.1 Graphical Abstract of the Chapter



3.2 Introduction

Over the last few decades, rapid synthetic strategies such as click reactions have attracted a lot of attention due to their instant efficacy to assemble myriads of scaffolds having prominent applications in the fields of material science (fluorescence, polymers, and dyes), agriculture and medicinal chemistry. Even though, the most famous and ubiquitously encountered click reaction remains 1,3-dipolar cycloaddition or Huisgen cycloaddition reaction, other types of click reactions have been discovered. By definition, a reaction may be construed a "click reaction" if it involves readily available starting materials, use of benign solvent, easy product isolation, generating inoffensive byproducts, high atom economy, stereospecificity and physiologically stable product [1–15].

Thiazinones are bio-active heterocyclic moieties which exhibit an array of pharmaceutical activities such as anticonvulsant, antifungal, anticancer, antituberculosis, antidiabetic, antiarrhythmic, anti-malarial and anti-HIV activities [16–20]. Several functionalized thiazinones are supposed to be constituent entities of natural products. **Figure 3.1** depicts the presence of "thiazinones" in some biologically active scaffolds. Compound **1**, for example, was studied to inhibit proliferation and viability of lung cancer A549, colon cancer HT-29 and gliona C_6 cells [21]. Likewise, compound **2** were evaluated for their cytotoxicity on human liver cancer cells line Hep G2 showed promising result [8]. Meanwhile, compound **3** was identified as adenosine antagonist [22]. Likewise, functionalized Quinoline incorporated 1,3-thiazinan-4-one, compound **4** was studied to show *in vitro* antitubercular activity (**Fig. 3.1)** [23]. Similarly, imidazole fused 1,3-thiazine-4-one compound **5** has been identified as antibacterial activity [23].

3.3 Survey of existing routes of synthesis

According to the existing literature to date, many methodologies for the preparation of thiazinones have been developed so far. This chapter highlights the latest work performed in this area. For example, in 2007, Nelson and his co-workers developed cinchona alkaloid catalyzed cyclocondensation between acid chlorides (**7**) and α-amidosulphones (**8)** to yield *cis*-4,5-disubstituted thiazine (**9**) using catalytic amount of $LiClO_4$ and $^{i}Pr_2NEt$ (**Fig. 3.2**) [24].

Figure 3.1 Biologically active molecules containing THIAZINONE scaffold.

Figure 3.2 Cinchona alkaloid catalyzed synthesis of thiazin-6-one.

The weak side of this protocol is preparation of prefunctionalized reactants, using highly volatile organic solvent (DCM) and attaining very low temperature (-78 ^{o}C). Moreover, in 2014, Majumdar *et al.* synthesized 1,4-thiazine-3-one (**12**) derivatives from 2-chloro-*N*-methylacetamide (**10**) and $Na_2S.xH_2O$ (**11**) using ferric chloride as catalyst and DMF as a solvent (**Fig. 3.3**) [25].

Figure 3.3 $FeCl_3$ catalyzed synthesis of thiazinones.

The drawback of this methodology is prefunctionalization of the starting material. At the same time, the organic solvent employed is environmentally not benign.

Afterwards, in 2016, Chen and his-coworkers designed copper-mediated annulation of *N*-arylbenzamide substrates (**13**) with 2-mercaptoimidazole (**14**) to produce polycyclic fused imidazo [2,1-*b*][1,3] thiazinones (**15**) in the presence of DMSO under inert atmosphere (**Fig. 3.4**) [26].

Figure 3.4 Cu $(OAc)_2$ catalyzed synthesis of thiazine-nucleus.

The need to use inert atmosphere and long reaction time required in this strategy are the likely drawbacks of this work.

Recently, in 2016, our group prepared substituted thiazinones (**20**) utilizing thiourea (**16**), alkylpropiolates (**17**), aldehydes (**18**) and isocyanides (**19**) in a two-step approach using ethanol as a solvent (**Fig. 3.5** (d) [27].

Figure 3.5 Microwave irradiated synthesis of thiazin-4-ones.

The reaction involves two steps. The first step is the formation of the intermediate 2-amino [1,3]-thiazin-4-one (**21**), which reacts with aryladehydes (**18**) to form reactive imine functionality, which undergo [4+1] cycloaddition with isocyanide derivatives (**19**) to provide imidazole fused with [1,3]-thiazin-4-one (**20**). The plausible mechanism of this reaction is given in **Fig. 3.6.**

Figure 3.6 Mechanism of the reaction for the synthesis imidazole fused thiazinone.

Long reaction time and maintaining low temperature for first step are the shortcomings of this protocol.

Likewise, Kaliban and his co-workers (2015) reported stepwise synthesis of thiazin-4-one (**24**) starting with presynthesized cyclic aminones (**22**) and making it react with hydrazine carbothiamide (**23**) under reflux in methanol [28] (**Fig. 3.7**). The reaction seems straight forward, but it is not one step synthesis as they were synthesizing cyclic aminones. The other drawback of this strategy is that only 8 scaffolds were synthesized.

Figure 3.7 Synthesis of thazin-4-ones under reflux in methanol.

Figure 3.8 NaOH catalyzed synthesis of spiro-substituted thiazine nucleus

Likewise, Zhuang *et al*. (2011) reported a microwave irradiated three component reaction involving two steps for the synthesis of spiro-substituted 1,3-thazine (**28**) using cyclic or acyclic

ketones (**25**), thiocyanates (**26**) and cyanoacetamide (**27**) in strongly basic condition in DMF followed by neutralization (**Fig. 3.8**) [29].

The mechanism of reaction involves Knoevenagel type condensation of thiocyanates with cyanoacetamide, which subsequently reacts with carbonyl group of butanone in two different path ways as it has been illustrated in **Fig. 3.9** to provide the desired corresponding final products (**28**).

Figure 3.9 Mechanism of the reaction for the synthesis of spiro cyclic thiazinones.

Figure 3.10 Two-step synthesis of imidazole fused [1, 3] thiazin-4-ones.

The last, but not the least example is the research work of Shea and his co-workers (2005) when they reported two step reaction involving reaction of aryl aldehydes (**18**) with thiamide **(32**) reacting with brominated carboxylic acid (**33**) to produce the intermediate bearing imidazole and thia ether moieties (**34**) which upon annulation with **35** gave rise to imidazole fused [1,3]-thiazin-4-ones (**Fig 3.10**) [30].

Overall, factors like pre-functionalization of starting materials, expensive reagents, poor atom economy, tedious work up, complex purification protocols, non-benign solvents, requirement of inert atmosphere and non-ambient temperature warrant a mild, sustainable yet prominent alternative for previously reported methods.

Therefore, in continuation to the on-going interest of our group in synthesizing novel heterocyclic scaffolds in green and sustainable ways [31–35], a click synthesis of functionalized thiazine core bearing reactive amine using phenylisothiocyanate, hydrazine and DEAD by merely mixing the substrates to obtain desired products in excellent yield and purity is presented in this chapter.

3.4 Results and discussion

Targeting environmentally benign set of conditions, initially commercially available starting materials phenylisothiocyanate (**26a)** (0.5 mmol), hydrazine monohydrate (**38a)** (0.5 mmol) and

Scheme 3.1 Three component reaction of phenyl isothiocyanate (**26a**), hydrazine monohydrate (**38a**) and diethylacetylenedicarboxylate (**39a**) to form (**40a**).

diethylacetylenedicarboxylate (DEAD) (**39a)** (0.5 mmol) mixed as model substrates have been mixed without solvent and catalyst at room temperature (**Scheme 3.1**). Unfortunately, the reaction did not work well as multiple spots were seen on TLC even after hours of stirring the reaction mixture. However, the fact that there was no starting material left unreacted led us to believe that we could continue to make them react at room temperature.

According to the results obtained, a stepwise single pot reaction strategy was developed. To begin with, phenylisothiocyanate (**26a)** (0.5 mmol) and hydrazine monohydrate (**38) (**0.5 mmol) (both in liquid states) were mixed. As soon as **39a** and **38** were mixed on watch glass with the help of syringe and spatula, a white solid was immediately formed (the completion of the reaction was indicated by TLC). Next, to this white solid, we added the third component, diethylacetylenedicarboxylate (**39a)** (0.5 mmol). Gratifyingly, as soon as the third component was added, the white powder turned into a yellow solid and provided 92% yield of the desired thiazinone (**38a)** upon merely washing with ethanol (**Figure 3. 2**). The progress of the reaction is depicted in **Figure 3.2**. Even though there are three possible products (**40a**, **40a**'and **40a**") from our reaction, the NMR data shows 100% formation of isomer **40a** over **40a'** and **40a''** indicating regioselectivity of our protocol (**Scheme 3.1).**

Scheme 3.2 Formation of ethyl -3-amino-4-oxo-2-(phenylimino)-3, 4-dihydro-2H-1, 3-thiazine-6-carboxylate (**40a**) by domino 3 component click reactions.

Since the reaction was spontaneously "click" and yielded the product in excellent amount, reaction conditions such as temperature, mode of mixing or solvents were not optimized. However, in order to reach the optimum ratio of substrates, four sets of experiments were performed with different ratio of substrates and the results are shown in **Figure 3 11**. It was found that 1.2 equivalent of DEAD provided maximum yield of 94 % of (**40a).**

Figure 3.1 Percentage yield of products vs. varied mole ratio of reactants for the formation of ethyl-3-(2-cyanoacetamido)-4-oxo-2(phenyl imino)-3,4-dihydro-2H-1, 3-thazine-6-carboxylate (**40a**)(Dotted bars show the components in excess in each last 3 cases where first (**26a)** then (**38)** and (**26a)** used in excess respectively).

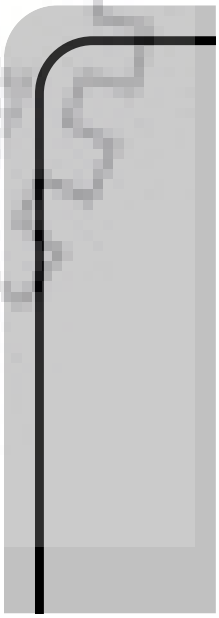
Based on the observations of the results delineated in **Fig. 3**, we came to conclude that the optimum condition for our protocol is mixing phenylisothiocyante **25a** (0.5 mmol), hydrazine monohydrate (**38)** (0.5 mmol) with syringe and spatula, and adding the third component, diethylacetylenedicarboxylate (**39a)** (0.6 mmol) and mixing thoroughly for about one minute to get the yellow colored desired product (**40a)**. To check the hypothesized domino effect, the reaction has been carried out by changing order of mixing of the model substrate reagents. First, hydrazine monohydrate (**38)** and diethylacetylenedicarboxylate (**39a)** were mixed which resulted in the formation of the addition product **I** in an exothermic manner. Unfortunately, the intermediate

formed (golden yellow liquid solution), did not react further with phenylisothiocyanates (**26a)** to provide **II** even after hours of stirring at room temperature (**Scheme 3.3**).

Scheme 3.3.Control experiment.

This observation clearly indicated that our protocol proceeds *via* only one route, as shown in **Scheme 3.2**. After optimum condition is established, it has been progressed to evaluate the scope and limitations of the present protocol by assembling library of functionalized thiazinones using aryl isothiocynates (26a-g) with electron withdrawing and donating groups, hydrazine monohydrate and DEAD/DMAD (Table 3.1). The results are outlined in **Table 3.1**. Gratifyingly, in most of the cases, phenylisothiocyanate derivatives irrespective of their electronic nature (electron withdrawing, **40b-c**, **40f** and **40j** and electron donating groups, **40e**, **40g**, **40h, 40i, 40k** and **40l**), were tolerant towards the formation of the desired products in good to excellent yields, 80-94 %. Substituted isothicyanate provided better yields of the corresponding product **40b** in comparison to 2-Cl substituted isothicyanate, probabily because of steric effect in the case of **40f** where Cl substituent is at *ortho* position.

Table 3.1 Library of synthesized compounds[a]



General reaction condition: [a]Phenylisothiocyante **26** (0.5 mmol) and hydrazine monohydrate, **38** (0.5 mmol) were mixed on the watch glass to yield the white solid. To this solid, dialkylacetylenedicarboxylate **39** (0.6 mmol) was added and the white product turned yellow in click reaction**.** nd= not determined

Scheme 3.4 Multigram level synthesis of ethyl (Z)-3-amino-4-oxo-2-(phenyl imino)-3, 4-dihydro-2H-1, 3-thiazine-6-carboxylate (**40a**)

Moreover, employing DMAD or DEAD hardly brought any change in reaction efficiency. Generally, fluorine containing compounds are known to exhibit better bioactivity profile than non-fluorinated counterpart scaffolds[36–39]. Gratifingly, herein, this method successfully incorporated fluoro thiazinones, **40c** and **40j** respectively in 91 and 92 % yields. Similarly, -Cl substituent on phenylisothiocyanate provided thiazinones **40b** and **40f** which can be used for further functionalization. It is also worthy to note that ethyl group at 2^{nd} position in phenylisothiocyanate was well tolerated to yield the respective thiazinones **40e** and **40i** in 91 and 90 % yields respectively. In few cases, sterically hindered phenylisothiocyanates failed to produce their corresponding products **40m** and **40n**. In addition to it, this method worked only with arylisothiocyanates as alkylisothiocyanate derivatives *viz*; cyclohexyl isothiocyanates did not provide products, **40o** and **40p** significantly.

Lastly, synthesis of **40a** was performed on multigram scale, using 5 mmol of each of **26a**, **38** and **39a,** which provided **40a** in 90 % yield (**Scheme 3.4**). In order to evaluate the "greenness" of our robust protocol, a series of green metrics such as Sheldon environmental impact factor (E-factor), atom economy (AE), carbon efficiency (CE) and reaction mass efficiency have been calculated [40–45]. The resulting scores such as low E-factor (0.075) and high values of 82 %, 93 % and 87 % for AE, RME and CE respectively clearly indicate that our present methodology is green and would be feasible for scale up synthetic applications.

Based on previous report and control experiment, plausible mechanism of the reaction in **Scheme 3.5** has been proposed. Accordingly, phenylisothiocyanate **26a** reacts with hydrazine monohydrate **38** in a click fashion to give the intermediate **A**, which upon thia-Michael addition with

diethylacetylenedicarboxylate **39a** leads to formation of adduct **B**. Finally, **B** undergoes intramolecular cyclization to construct desired product **40a**.

Scheme 3.5.Plausible mechanism of the reaction.

3.5 Conclusions

A versatile, catalyst-free, green protocol for the synthesis of functionalized thiazine nuclei with 100% regioselectivity has been developed. The method involves simple procedure, easy work up, atom and step efficient domino multicomponent reaction from readily available starting materials

phenylisothiocyanates, hydrazine monohydrate, and dialkylacetylenedicarboxylates (DEAD and DMAD) by click reaction at room temperature.

3.6 Experimental Section

3.6.1 General Experimental Detail

The reactions were performed by merely mixing the starting materials using spatula on watch glass in a click fashion leading to the formation of library of functionalized thiazinones (monitored by TLC). ^{1}H NMR spectra were recorded on a Jeol Resonance ECX-400II (400 MHz); Chemical shifts (δ in ppm) and coupling constant (*J* in Hz) are calibrated relative to internal solvent tetramethylsilane TMS (δ_H = 0.00 ppm). In the ^{1}H NMR data, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, dd = double doublets and brs = broad singlet. ^{13}C NMR spectra were recorded on a Jeol Resonance ECX-400II (100 MHz) at R.T. in $CDCl_3$.

Analysis of the reactions was done by thin layer chromatography (TLC). For this, Merck precoated silica gel TLC plates (Merck® $60F_{254}$) were used. All the reagents were purchased from Sigma Aldrich and Alfa Aesar. Solvents for optimization purpose were purchased from locally available commercial sources and used as received.

3.6.2 General procedure for the synthesis of 40

Phenylisothiocyante **26** (0.5 mmol), hydrazine monohydrate, **38** (0.5 mmol) were mixed on the watch glass to yield the white solid. To this solid, diethylacetylenedicarboxylate **39** (0.6 mmol) was further mixed and the yellow solid product thus obtained was collected and washed with cold ethanol.

3.6.3 Characterization Data of Synthesized Compounds

1. Ethyl-3-amino-4-oxo-2-(phenylimino)-3,4-dihydro-2H-1,3-thiazine-6-carboxylate (40a):

Yellow solid (94%); m.p. 152-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.36 (t, 2H, J = 8.0 Hz), 7.19 (t, 1H, *J* = 7.6 Hz), 7.01 (d, 2H, *J* = 8.0 Hz), 6.96 (s, 1H), 4.85 (s, 2H), 4.25 (q, 2H, *J* = 8.0 Hz), 1.3 (t, 3H,

J = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 165.9, 161.6, 149.4, 146.6, 139.2, 129.6, 125.7, 121.2, 117.5, 61.9, 14.2; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) = 3449, 3299, 3149, 3031, 2357, 1724, 1686; Elemental analysis calcd (%) for $C_{13}H_{13}N_3O_3S$: C 53.60, H 4.50, N 14.42, S 11.00; found: C 52.87, H 4.08, N 14.10, S 10.46.

2.Ethyl-3-amino-2-((3-chlorophenyl)imino)-4-oxo-3,4-dihydro-2H-1,3-thiazine-6-carboxylate (40b):

Yellow solid (90%); m.p. 166-167 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.28 (t, 1H, *J* = 8.0 Hz), 7.16 (d, 1H, *J* = 10.8 Hz), 7.01-6.99 (m, 1H), 6.97 (s, 1H), 6.89 (d, 1H, *J* = 11.2 Hz), 4.83 (s, 2H), 4.26 (q, 2H, *J* = 7.2 Hz), 1.30 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 165.8, 161.5, 150.5, 147.8, 138.7, 135.1, 130.6, 125.7, 121.6, 119.4, 118.0, 62.1, 14.2; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) = 3302, 3143, 3040, 2360, 1736, 1692, 1656; Elemental analysis calcd (%) for $C_{12}H_{11}N_3O_3S$: C 46.23, H 3.23, Cl 11.37, N 13.48, S 10.28; found: C 45.75, H 2.87,Cl 10.94, N 13.02, S 9.72.

3. **Ethyl-3-amino-2-((4-fluorophenyl)imino)-4-oxo-3,4-dihydro-2H-1,3-thiazine-6-carboxylate (40c)**:

Yellow solid (91%); m.p. 156-157 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.06 (t, 2H, *J* = 8.4 Hz), 7.00-6.98 (m, 3H), 4.83 (s, 2H), 4.26 (q, 2H, *J* = 7.2 Hz), 1.3 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.8, 161.7(d, 2C, *J* = 1 Hz), 159.4, 149.9 142.6, 138.8, 122.7, 117.7, 116.3, 62.0, 14.2; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) = 3293, 3149, 3034, 2334, 2913, 1730, 1642; Elemental analysis calcd (%) for $C_{13}H_{12}FN_3O_3S$: C 50.48, H 3.91, F 6.14, N 13.59, S 10.36; found: C 50.47, H 3.77, N 13.10, S 9.95

4. Methyl-3-amino-4-oxo-2-(phenylimino)-3,4-dihydro-2H-1,3-thiazine-6-carboxylate (40d):

Yellow solid (94%); m.p. 150-153 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.35 (t, 2H, *J* = 8.0 Hz), 7.18 (t, 1H, *J* = 8.0 Hz), 6.99 (d, 2H, *J* = 8.0 Hz), 6.95 (s, 1H), 4.88 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 165.8, 161.9, 150.5, 147.8, 140.1, 130.0, 125.6, 121.4, 116.1, 62.0; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) = 3302, 2949, 2363, 1730, 1692, 1645; Elemental analysis calcd (%) for $C_{12}H_{11}N_3O_3S$: C 51.98, H 4.00, N 15.15, S 11.96; found: C 51.45, H 3.67, N 14.83, S 11.01.

5. **Ethyl-3-amino-2-((2-ethylphenyl)imino)-4-oxo-3,4-dihydro-2H-1,3-thiazine-6-carboxylate (40e):**

Yellow solid (91%); m.p. 150-152 ^{o}C; ^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) = 7.23 (d, 1H, *J* = 7.2 Hz), 7.18-7.10 (m, 2H), 6.94 (s, 1H), 6.84 (d, 1H, *J* =7.6 Hz), 4.91 (s, 2H), 4.23 (q, 2H, *J* = 7.2 Hz), 2.54 (q, 2H, *J* = 7.6 Hz) 1.28 (t, 3H, *J* = 6.8 Hz), 1.13 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 165.9, 161.6, 149.0, 144.8, 139.4, 136.3, 129.2, 126.8, 126.0, 119.9, 117.4, 61.9, 24.7, 14.7, 14.2; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) = 3295, 3158, 3066, 2928, 1736, 1697, 1657; Elemental analysis calcd (%) for $C_{15}H_{17}N_3O_4S$: C 56.41, H 5.37, N 13.16, S 10.04; found: C 56.07, H 5.64, N 12. 83, S 9.45.

6. Ethyl-3-amino-2-((2-chlorophenyl)imino)-4-oxo-3,4-dihydro-2H-1,3-thiazine-6-carboxylate (40f):

Yellow solid (80%); m.p. 162-163 ° C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.42 (d, 1H, *J* = 8.0 Hz), 7.26-7.22 (m, 1H), 7.12 (t, 1H, *J* = 7.2 Hz), 6.98-6.97 (m, 2H), 4.89 (s, 2H), 4. 24 (q, 2H, *J* = 4.0 Hz), 1.29 (t, 3H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 165.8, 161.7, 151.5, 143.9, 138.8, 130.4, 127.8, 126.6, 121.8, 118.0, 117.9, 62.0, 14.2; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) = 3291, 3241, 2961, 2873, 2322, 1736, 1695, 1651; Elemental analysis calcd (%) for $C_{14}H_{15}N_3O_4S$: C 47.93, H 3.71, Cl 10.88, N 12.90, S 9.84; found: C47.22, H 3.23, N 12.34, S 9.32.

7. **Ethyl-3-amino-2-((4-methoxyphenyl)imino)-4-oxo-3,4-dihydro-2H-1,3-thiazine-6-carboxylate (40g):**

Yellow solid (89%); m.p. 131-132 ^{o} C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.98 (d, 2H, *J* = 8.8 Hz), 6.94 (s, 1H), 6.89 (d, 2H, *J* = 8.8 Hz), 4.86 (s, 2H), 4.25 (q, 2H, *J* = 8.0 Hz), 3.80 (s, 3H), 1.3 (t, 3H, *J* = 4.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 165.9, 161.5, 157.6, 148.6, 139.6, 139.3, 122.5, 117.3, 114.8, 61.9, 55.6, 14.2; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) = 3423, 3170, 2913, 2351, 1730, 1636; Elemental analysis calcd (%) for $C_{14}H_{15}N_3O_4S$: C 52.33, H 4.71, F 6.14, N 13.08, S 9.98; found: C 51.87, H 3.64, N 1283, S 9.45.

8. **Methyl-3-amino-2-((4-methoxyphenyl)imino)-4-oxo-3,4-dihydro-2H-1,3-thiazine-6-carboxylate (40h):**

Yellow solid (90%); m.p. 123-124 ° C; 1H NMR (400 MHz, $CDCl_3$): δ (ppm) = 6.99 (s, 1H), 6.96 (d, 2H, *J* = 8 Hz), 6.90 (d, 2H, *J* = 12.0 Hz), 4.87 (s, 2H), 3.81 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.3, 161.4, 157.6, 148.4, 139.6, 139.5, 122.5, 116.8, 114.8, 55.6, 31.0; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) = 3324, 3186, 3072, 1708, 1673, 1608; Elemental analysis calcd (%) for $C_{13}H_{13}N_3O_4S$: C 50.81, H 4.26, N 13.67, S 10.43; found: C 50.33, H 3.91, N 13.13, S 10.00.

9. **Methyl-3-amino-2-((2-ethylphenyl)imino)-4oxo-3,4-dihydro-2H-1,3-thiazine-6-carboxylate (40i)**

Yellow solid (90%); m.p. 122-124 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.21 (d, 1H, *J* = 7.6 Hz), 7.16-7.08 (m, 2H), 6.91 (s, 1H), 6.81 (d, 1H, *J* = 7.2 Hz), 4.98 (s, 2H), 3.75 (s, 3H), 2.52 (q, 2H, *J* = 7.6 Hz), 1.10 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.2, 161.6, 148.9, 144.8, 139.7, 136.3, 129.3, 126.8, 125.9, 119.9, 116.9, 52.7, 24.7, 14.7; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) = 3293, 3243, 3181, 2928, 2956, 1742, 1702, 1660; Elemental analysis calcd (%) for $C_{14}H_{15}N_3O_4S$: C 55.07,

H 4.95, N 13.76, S 10.50; found: C 54.68, H 4.63, N 13.43, S 10.27.

10. Methyl-3-amino-2-((4-fluorophenyl)imino)-4-oxo-3,4-dihydro-2H-1,3-thiazine-6-carboxylate (40j):

Yellow solid (91%); m.p. 162 °C; ^{1}H NMR (400MHz, $CDCl_3$): δ (ppm) = 7.08-7.05 (m, 2H), 7.00-6.99 (m, 1H), 6.97 (s, 1H), 4.83 (s, 2H), 3.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) 166.3, 161.9, 161.6, 142.6 (d, 2C *J*=3 Hz) 139.1, 122.8(d, *J* = 4 Hz), 117.3, 116.5, 116.3, 52.8; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) : 3293, 3149, 3034, 2334, 2913, 1730, 1642; Elemental analysis calcd (%) for $C_{13}H_{12}FN_3O_3S$: C 50.48, H 3.91, F 6.14, N 13.59, S 10.36; found: C 50.47, H 3.77, N 13.10, S 9.95

11. Ethyl-3-amino-2-((p-tolyl) imino)-4-oxo-3,4-dihydro-2H-1,3-thiazine-6-Carboxylate (40k):

Yellow solid (90%); m. p. 168 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.15 (d, 2H, *J* = 8.0 Hz), 6.94 (s, 1H), 6.90 (d, 2H, *J*=8 Hz), 4.86 (s, 2H), 4.24 (q, 2H, *J* = 7.2 Hz), 1.29 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 165.9, 161.6, 149.1, 144.0, 139.3, 135.4, 130.1, 121.1, 117.3, 61.9, 21.0, 14.2; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) = 3302, 3143, 3040, 2360, 1736, 1692, 1656. Elemental analysis calcd (%) for $C_{14}H_{15}N_3O_3S$: C 55.07, H 4.95, N 13.76, S 10.50; found: C 54.00, H 5.27, N 13.21, S 9.37.

12. Methyl-3-amino-2-((p-tolyl)imino)-4-oxo-3,4-dihydro-2H-1,3-thiazine-6-Carboxylate (40l):

Yellow solid (90%); m. p. 166 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.15 (d, 2H, *J* = 8.0 Hz), 6.93 (s, 1H), 6.89 (d, 2H, *J*=8.4 Hz), 4.90 (s, 2H), 3.78 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ (ppm) = 165.9, 161.6, 149.1, 144.0, 139.3, 135.4, 130.1, 121.1, 117.3, 61.9, 21.0, 14.2; IR (4000-600 cm^{-1}): v_{max} (cm^{-1}) = 3302, 3143, 3040, 2360, 1736, 1692, 1656. Elemental analysis calcd (%) for $C_{13}H_{13}N_3O_3S$: C 53.60, H 4.50, N 14.42, S 11.00; found: C 52.98, H 5.36, N 14.27, S 10.67.

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Chapter 4

Synthesis of Oxindoles-β-Enaminones Hybrids through One Pot Two-Steps Mechanochemical Four Component Reaction under Solvent and Catalyst Free Condition

4.1 Graphical Abstract of the Chapter

4.2 Introduction

Organic compounds bearing oxindoles core structure such as isatin (indoline-2,3-dione), are becoming focal point in chemical research and organic syntheses incorporating this profound moieties have been, specifically, cyclic ones have also been investigated for biological activities such as anticonvulsant extensively studied. Oxindoles are constituent of several bioactive natural products such as alkaloids to induce apoptosis in proliferating G0/G1-arrested and bcl-2-expressing acute lymphoblastic leukaemia cells [1]. Oxindoles have been proven to show broad spectrum of biological activities such as antibacterial, antimicrobial and anti-fungal, anti-inflammatory and analgesic, antiviral, and anti-HIV [2–9] properties. Likewise, medicinally prominent organic scaffolds, β-enaminones activity and promising result was found [10–12]**.**

One of the powerful strategies emerging in the area of medicinal chemistry is combining medicinally significant entities under a single molecular platform in order to modulate biological processes with multiple or combined activities [13–16]. To this end, the synthesis of hybrid molecules comprising oxindoles and cyclic β-enaminones in order to have a better pharmacological profile has been hypothesized and designed in a novel strategy of coupling them at C-3 of isatin and its derivatives [17]. In the past, β-enaminones derived from dimedone and tetronic acid forming hybrids with oxindoles at C-3 (compounds (**1**), (**2**), (**3**) and (**4**)) were found imparting cytotoxicity to A549, 786-0, ECA109 and BT 474 cancer cell lines (**Fig. 4.1**) [18]. We specifically believed that β-enaminones derived from dimedone might improve lipophilicity of highly polar oxindoles and thereby would enhance its bioactivity [19–24].

Figure 4.1 Cytotoxicity of hybrids of cyclic β-enaminones and oxindoles against cancer cell lines

4.3 Literature Survey

As per the literature survey to date**,** various methodologies have been developed for the synthesis of cyclic enaminones which will be highlighted in this chapter.

In 2015, Hao, Tu and Jiang *et al*. reported synthesis of cyclic enaminones **(7)** involving isocyanide **(5)** insertion using iodinated acetophenone derivatives **(6)**, $Pd(OAc)_2/P(n\text{-}Bu)_3$ as a catalyst system and 1, 4-dioxane as a solvent (**Fig. 4.2**) [25].

Figure 4.2 Synthesis of cyclic enaminones by isocyanides insertion using $Pd(OAc)_2$.

The use of costly catalyst system and foul smelling isocyanides are imminent drawbacks of this method. Furthermore, Foroumadi *et al*. (2018) disclosed synthesis of cyclic enaminones based on reusable magnetic nano catalyst graphene oxide incorporated strontium nano particles for mild synthesis of β–enamino-ketones **(10)** through coupling of aniline derivatives **(8)** with cyclic and acyclic 1,3-dicarbonyl compounds (**9)**(**Fig. 4.3**) [26].

Figure 4.3 Synthesis of enaminones catalyzed by reusable magnetic nano catalyst graphene oxide incorporated strontium nano particle.

Similarly, Eidi *et al*. (2018), reported synthesis of β-enaminones **(10)** employing recyclable nano-$CoFe_2O_4$ via coupling of aniline derivatives **(8)** with 1,3-di-carbonyl compounds **(9)** (**Fig.4.4**)[27].

Figure 4.4 Nano-$CoFe_2O_4$ catalyzed synthesis β-enaminones

Khospour and Khodaei *et al*. (2004) reported regio and chemoselective synthesis of acyclic β-enaminones (**10**) using $Bi(TFA)_3$ as a reusable catalyst in aqueous media through reaction of primary amines (**8**) and 1,3-dicarbonyl compounds (**9**) (**Fig. 4.5**)[28].

Figure 4.5 Synthesis of acyclic β-enaminones using recyclable catalyst system

Beside highlighted protocols, there are several other methodologies for the construction of β-enaminones involving catalysts such as Cu NPs, [29] silica chloride [30] and $NaAuClO_4$ [31].

Next, the coupling of enaminones with oxindoles has been investigated and found that this reaction has been reported scarcely. There is only one report by Shi *et al*. in 2016 wherein the authors reported construction of cyclic β-enaminones-based 3-substituted 3-amino-2-oxindole scaffolds (**12**) *via* chiral phosphoric acid-catalyzed enantioselective addition reaction of cyclic enaminones to isatin derived imines. (**Fig. 4.6**) [18].

Figure 4.6 Cyclic enaminones based enantioselective synthesis of highly functionalized oxindoles

Based on all the above, and in continuation to our work in developing green chemical routes for heterocyclic synthesis,[32–38] and the current organic interest aimed at constructing molecules through mechanochemistry [39–48] and solvent free microwave synthesis [49–52], a mild synthetic route for combinatorial assembly of β-enaminones and oxindoles hybrids has been targeted. Hypothesis for this conversion was based on a premise that microwave irradiation would be sufficient for *in situ* formation of β- enaminones, from dimedone and aniline derivatives, and thereby subsequent Domino reaction with Knoevenagel adduct of isatin and malononitrile would provide us the required product. In this chapter a unique combination of microwave irradiation for synthesis of β-enaminones (synthesized *in situ*) and mechanochemical approach for its subsequent reaction with Michael adduct of isatin (**11**) and malononitrile (**12a**) has been successfully presented. Overall, the method in the present chapter has been developed encompassing one pot, two step four component reaction for the synthesis of biologically significant spiro-oxindoles hybrid molecules.

Scheme 4.1.Two-step four component reaction for the synthesis of diverse spiro-oxindoles

4.4 Results and Discussion

The investigation for the formation of β-enaminones formation has been started by carrying out expeditious microwave irradiation expecting that radiant energy would be sufficient enough to initiate coupling of dimedone and aniline in the absence of any solvent (**Table 4.1**).Therefore, in one reaction, dimedone (0.5 mmol) and aniline (0.5 mmol) was irradiated under microwave at 170 ^{o}C for 15 min, and pleasingly 60% of the product enaminones was obtained. Later, it was found that the best conversion was achieved when the reactants were irradiated at 180 ^{o}C for 15 min (**Table 4.1, entry 2**) When either the temperature or time was increased, the extent of the product formation decreased indicating that the optimum reaction condition was microwave irradiation of aniline and dimedone derivatives at 180 ^{o}C for 15 min. which gave rise to β-enaminone formation in 95% yield (**Table 4.1, entry 2)**.

Table 4.1 Optimization of reaction condition for the synthesis of β-enaminones [a']

Entry	T(°C)	Time (Min)	Yield (%)[b']
1	170	15	60
2	**180**	**15**	**95**
3	190	15	84
4	180	20	79

[a'] Reaction condition: In a 10 mL vial 0.5 mmol of dimedone **9a** and 0.5 mmol of aniline **8a** were irradiated using microwave under solvent and catalyst free condition at the temperature of 180 °C for 15 minutes. [b'] Isolated product of β-enaminone

Once the *in situ* synthesis of β-enaminones has been completed, the reaction mixture was cooled down and the subsequent feasibility of our hypothesized synthesis of β-enaminones-oxindoles hybrid molecules was probed. To begin with, Knoevenagel adduct of isatin **13a** (0.5 mmol) and malononitrile **14a** (0.5 mmol) was formed by grinding the mixture for 10 min., when TLC confirmed the formation of adduct. To this was added cooled crude mixture of β-enaminones, as shown previously, and grinding continued for 25 min. till the completion of reaction. This resulted in 67% of the product β-enaminones-oxindoles hybrid (**Table 4.2, entry 1**). Increase in time of grinding was not found helpful. At this point, it was decided to resort to LAG by adding a few drops of water to the above reaction. Pleasingly, complete conversion of the reactant under LAG was observed [53–55] and 92% of yield the spirooxindole **16a** was obtained (**Table 4.2, entry 3**). Longer time of grinding did not make any improvement (**Table 4.2, entry 4**) and the condition stated in **Table 4.2, entry 3** was considered as the optimum one. Therefore the optimized protocol was microwave irradiation of aniline **8a** (0.5 mmol) and dimedone **9a** (0.5 mmol) for 15 min at 180 °C and hand grinding of Isatin **13a** (0.5 mmol) and malononitrile **14a** (0.5 mmol), for 10 min separately followed by addition of both the intermediate product mixtures along with a few drops

of water and further grinding for additional 25 min to provide β–enaminones-oxindoles hybrid moieties in excellent yield.

Table 4.2 Optimization of reaction condition [a]

Entry	(promoter)	Time (minutes)	Yield (%)[b]
1	-	25	67
2	-	30	70
3	Drops of water	25	92
4	Drops of water	30	92

[a]Reaction condition: In a 10 mL vial, aniline **8a** (0.5 mmol) and dimedone **9a** (0.5 mmol) were reacted under microwave irradiation for 15 min at 180 °C; Isatin **13a** (0.5 mmol) and malononitrile **14a** (0.5 mmol), have been hand ground for 10 min and the crude enaminone was added along with a few drops of water and the reaction mixture was further ground for additional 25 min to provide β–enaminones-oxindoles hybrid moieties. [b] Isolated products.

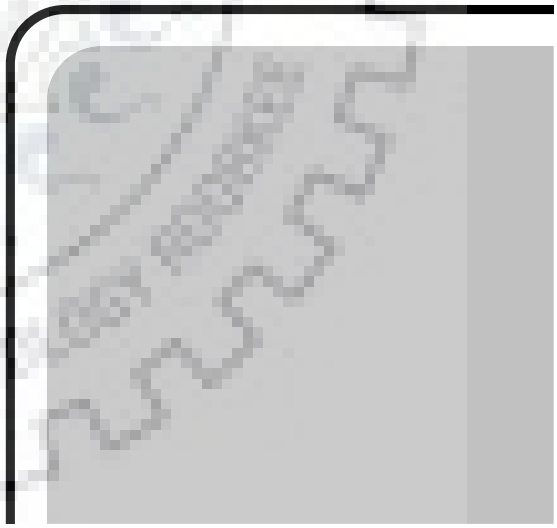
Having established optimum condition, we set out to explore the scope of this reaction. Both the activated and deactivated forms of isatin and aniline have been employed. Surprisingly, most reactants were highly tolerant to this specific route of synthesis and gave rise to respective products in high yields as compiled in **Table 4.3**. For example, deactivated isatin derivatives bearing electron donating groups, **13g** and **13i** (**Table 4.3, entries 7 and 9**) proved just slightly less reactive compared to activated isatins such as **13c**, **13d** and **13e** (**Table 4.3, entries 3, 4 and 5**). On the other hand, it has been noticed that anilines with electron withdrawing groups such as **8f**, **8h** and **8i** achieved 90%, 85% and 88% yields respectively and were comparatively less effective in

comparison to anilines with electron donating groups such as **8b**, **8c**, **8e** and **8k**. Reactions with isatin having electron withdrawing groups and anilines with electron donating groups repeatedly provided maximum yield of the respective product, e.g. **16c**, **16d** and **16e** were formed in 93%, 95% and 96% yield respectively. As per literature survey study, generally, fluorine bearing organic scaffolds are known to exhibit broad spectrum of biological activities than non-fluorinated ones [56–58]. To our delight, herein, our robust protocol successfully incorporated fluoro derivatives, **16j** and **16l** in both 92 % yields (**Table 4. 3, entries 10 and 12**).

Table 4.3 Library of synthesized compounds

Mechanism of the reaction

In line with the previous reports and the results of the present work, a plausible mechanism for the synthesis of β–enaminones-oxindoles hybrids has been presented in **Scheme 4.2.** Isatin undergoes Knoevenagel condensation with malononitrile by mechanically induced energy/force to give 2-(2-oxindolin-3-ylidene) malononitrile **I**. On the other hand, microwave irradiated components, aniline and dimedone react to produce β–enaminone **II** *in situ***,** which reacts with **I** in Michael addition fashion to provide the desired β- enaminone-oxindole hybrid molecule **16a (Scheme 4.2**).



Scheme 4.2 Plausible mechanism of the reaction

At the end, the coupling of β-enaminone derived from aniline (**8a**) and dimedone (**9a**) with the ground mixture of isatin **13a** and malononitrile **14a** has been carried out for the synthesis of β-enaminone -oxindole hybrid **16a** on multigram scale using 5.0 mmol of each of the reactants which

provided the desired product in excellent 90% of yield (**Table4.4**). In order to numerically describe the "greenness" of our methodology [59–61] the green metrics such as atom economy (AE), environmental impact factor (E-factor), carbon efficiency (CE), reaction mass efficiency (RME) and process mass intensity (PMI) have been calculated and the data has been compiled in **Table 4.4**.

Table 4.4 Green metrics calculation summary

Green metrics	AE	E-factor	CE	RME	PMI
Result	83%	0.111	90%	90%	1.111

[a"] Reaction condition: In a 30 mL vial, aniline **8a** (5 mmol) and dimedone **9a** (5 mmol) were reacted under microwave irradiation for 15 min at 180 °C; Isatin **13a** (0.5 mmol) and malononitrile **14a** (0.5 mmol), have been hand ground for 10 min and the crude enaminone was added along with a few drops of water and the reaction mixture was further ground for additional 25 min to provide β–enaminones-oxindoles hybrid moieties.

Now here the calculated results summarized in the table showed that the low E-factor (0.111) and higher values of AE (83%), CE (90%) and RME (90%) are indicative of the applicability of this route of synthesis for large scale production of desired products under environmentally benign condition. More importantly, the low score of E-factor also depicted the protocol worked in accordance with the underlying principles of green synthesis.

4.5 Conclusions

In summary, it has been concluded that an efficient and sustainable novel tool has been devised for coupling biologically significant entities such as oxindoles and β-enaminones to construct β-enaminones-oxindoles hybrids which are more dynamic in terms of biological activities emanating from constituent parts. The designed protocol is highly strategic from synthetic point of view as it can serve as a spring board for diversity oriented synthesis.

4.6 Experimental Section

4.6.1 General Experimental Detail

^{1}HNMR spectra were recorded on a Jeol Resonance ECX-400II (400 MHz); Chemical shifts (δ in ppm) and coupling constant (*J* in Hz) are calibrated either relative to internal solvent tetramethylsilane TMS (δ_H = 0.00 ppm) or DMSO-d_6 (δ_H =2.46 ppm). In the ^{1}H NMR data, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, brs = broad singlet. ^{13}C NMR spectra were recorded on a Jeol Resonance ECX-400II (100 MHz) at room temperature in DMSO-d_6; chemical shifts are calibrated relative to DMSO-d_6 (δc = 77.0 ppm). IR spectra were recorded on Perkin Elmer FT-IR spectrometer -spectrum two. Melting points were performed with *optimelt* automated melting point system.

The reactions were performed in a G-10 Borosilicate glass vial sealed with Teflon septum in Anton Paar Monowave 300 reactor®, operating at a frequency of 2.455 GHz with continuous irradiation power of 0 to 300 W. Analysis of the reactions were done by thin layer chromatography (TLC). For this, Merck precoated silica gel TLC plates (Merck® $60F_{254}$) were used. Reagents were purchased from Sigma Aldrich and Alfa Aesar. All solvents; methanol (MeOH), hexane, ethyl acetate and diethyl ether all were purchased from locally available commercial sources and used as received. A variety of 5-aryl-1, 3, 4-thiadiazol-2-amines and 2-oxo-2*H*-chromene-3-carbaldehyde were prepared according to literature procedure [1-2].

4.6.2 General Procedure for the synthesis of β–enaminones-oxindoles (16a-4n)

Aniline **8a- 8d** and 1,3-dicarbonyl compounds **9a-9b** (0.5 mmol) were taken in G-10 glass vial capped with Teflon septum. After that, the reaction vial was subjected to microwave irradiation with the initial ramp time of 1 minute at 60 °C and then raised the temperature to 180 °C with the holding time of 15 minutes. Next, this microwave irradiated reaction mixture was added to previously manually ground products of Isatin **13a-13e** (0.5 mmol) and malononitrile **14a** (0.5 mmol) which was ground for about 10 minutes. Next, LAG was performed for about 25 minutes and completions of the reactions were confirmed by TLC, the solid products obtained were washed using water. The identities of all products **16a-16n** were confirmed by FTIR, ^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis.

1. **2-(3-(4, 4-dimethyl)-6-oxo-2-(phenylamino)cyclohex-1-en-1-yl)-2-Oxoindolin-3-yl) malononitrile (16a)**

Red solid (92%); m.p**.** = 152-154 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6):δ (ppm) 7.87 (d, *J* = 7.6 Hz, 1H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.12 (t, *J* = 7.6 Hz, 2H), 6.93 (d, *J* = 8.0 Hz, 1H), 5.30 (s, 1H), 2.37 (s, 2H), 2.04 (s, 2H), 1.01(s, 6H); ^{13}C NMR (100 MHz**,** $CDCl_3$)**:**δ (ppm) 196.0, 164.3, 160.6, 151.2, 147.0, 139.7, 138.3, 129.7, 126.4, 124.9, 123.5, 123.4, 119.2, 113.6, 112.2, 112.1, 97.2, 81.1, 50.7, 42.6, 32.8, 28.5; IR (4000-600 cm^{-1}): υ_{max} 3242, 2232, 1721, 1580; Elem. Anal**.** For $C_{25}H_{22}N_4O_2$ Calcd**:** C, 73.15, H, 5.40, N, 13.65 %; found: C, 72.97, H, 5.45; N, 13.42 %

2. 2-(3-(2-((4-methoxyphenyl) amino)4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-2-oxoindolin-3-yl) malononitrile (16b).

Red solid **(**95%); m.p.= 144-145; ^{1}H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 7.85 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* =7.6 Hz, 1H), 7.16-7.03 (m, 3H), 6.95-6.90 (m, 3H), 5.09 (s, 1H), 3.72 (s, 3H), 2.32 (s, 2H), 2.01 (s, 2H), 0.99 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$)**:**δ (ppm) 196.3, 162.4, 157.0, 151.1, 146.7, 138.4, 131.9, 126.4, 125.8, 123.5, 119.0, 114.9, 113.5, 112.1, 112.0, 95.9, 81.2, 55.8, 50.5, 42.3, 32 .8, 28.4. IR (4000-600 cm^{-1}): υ_{max} 3451, 2236, 1739, 1638; Elem. Anal**.** For $C_{26}H_{24}N_4O_3$ Calcd**:** C, 70.89, H, 5.49, N, 12.72 %; found: C, 70.75, H, 5.54, N, 12.65 %.

3. 2-(3-(4,4-dimethyl)-6-oxo-2-(*p*-tolylamino)cyclohex-1-en-1-yl)-5-nitro-2-oxoindolin-3-yl) malononitrile (16c)

Red solid (93%), m.p. = 110-111 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 8.50-7.90 (m, 1H), 7.38 (d, *J* = 7.2 Hz, 1H), 7.13 (d, *J* = 7.6 Hz, 3 H), 7.00 (d, *J* = 7.6 Hz, 2H), 5.20 (s, 1H), 2.31 (s, 2H), 2.22 (s, 3H), 2.00 (s, 2H), 0.96 (s, 6 H); ^{13}C NMR (100 MHz, DMSO-d_6)**:**δ (ppm) 194.9.0, 180.7, 164.5, 153.9, 152.7, 151.7, 149.8, 148.8, 142.9, 133.2, 130.2, 121.2, 119.2, 113.0, 112.4, 111.4, 109.5, 83.5, 50.6, 49.5, 32.8, 28.5, 28.1, 27.8; IR (4000-600 cm^{-1}): υ_{max} 3582, 2237, 1734, 1608; Elem. Anal**.** For $C_{26}H_{24}N_4O_2$ Calcd**:** C, 73.50, H, 5.70, N, 13.20 %; found: C, 73.43, H, 5.74, N, 13.14 %

4. 2-(3-(4,4-dimethyl-6-oxo-2-(phenylamino) cyclohex-1-en-1-yl)-5-nitro-2-oxindolin-3-yl)malononitrile (16d)

Red solid (95%); m.p. = 122-124 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 8,78 (s, 1H), 8.60-8.00 (m, 1H), 7.58 (d, *J* = 6.0 1H), 7.33 (t, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.0 Hz, 2H), 7.09 (t, *J* = 7.2 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 1H), 2.34 (s, 2H), 2.01 (s, 2H), 0.98 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6)**:**δ (ppm) 196.7, 195.2, 180.7,

161.2, 153.8, 152.0, 148.6, 142.9, 139.4, 138.1, 135.9, 129.9, 129.7, 123.5, 119.2, 109.5, 49.4, 32.8, 32.7, 28.4, 28.0, 27.7; IR (4000-600 cm^{-1}): υ_{max} 3357, 2235, 1746, 1598; Elem. Anal**.** For $C_{25}H_{21}N_5O_4$ Calcd**:** C, 73.50, H, 5.70, N, 13.20 %; found: C, 73.43, H, 5.74, N, 13.14 %.

5. **2-(3-(2-((4-methoxyphenyl) amino)-4,4-dimethyl-6oxocyclohex-1-en-1-yl)-5-nitro-2-oxoindolin-3yl)malononitrile (16e)**

Red solid (96%); m.p. =115-117 ^oC; ^1H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 8.75-7.95 (m, 2H), 7.04 (d, *J* = 8.8 Hz, 3H), 6.89 (d, *J* = 8.8 Hz, 2H), 5.01 (s, 1H), 3.69 (s, 3H), 2.19 (s, 2H), 1.98 (s, 2H), 0.96 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6)**:**δ (ppm) 196.2, 195.2, 180.8, 162.3, 160.4, 157.0, 154.3, 152.3, 148.6, 142.9, 138.2, 131.9, 128.1, 125.8, 119.2, 114.9, 109.4, 56.0, 55.7, 32.8, 32.7, 28.4; IR (4000-600 cm^{-1}): υ_{max} 3216, 2234, 1743, 1570; Elem. Anal**.** For $C_{25}H_{21}N_5O_4$ Calcd**:** C, 73.50, H, 5.70, N, 13.20 %; found: C, 73.43, H, 5.74, N, 13.14 %.

6. **2-(3-(4-methyl-6-oxo-2-(*p*-tolylamino)cyclohex-1-en-1-yl)-5-nitro-2-oxoindolin-3-yl)malononitrile(16f)**

Red solid (94% yield); m.p. = 123-125 ^oC; ^1H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 8.60 (bs, 1H), 7.50-7.25 (m, 1H), 7.12 (d, *J* = 8.0 Hz, 4H), 7.00 (d, *J* = 8.0 Hz, 2H), 5.20 (s, 1H), 2.30 (s, 2H), 2.22 (s, 3H), 1.99 (s, 2H), 0.96 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6)**:**δ (ppm) 196.5, 195.2, 180.8, 161.5, 154.0, 152.1, 142.9, 140.4, 138.2, 136.7, 134.5, 133.2, 130.2, 126.0, 123.6, 119.2, 109.4, 50.4, 49.4, 32.8, 32.7, 28.4, 21.0; IR (4000-600 cm^{-1}): υ_{max} 3583, 2238, 1734, 1606; Elem. Anal**.** For $C_{25}H_{21}N_5O_4$ Calcd**:** C, 73.50, H, 5.70, N, 13.20 %; found: C, 73.43, H, 5.74, N, 13.14 %.

7. 2-(3-(4,4-dimethyl-6-oxo-2-(*p*-tolylamino)cyclohex-1-en-1-yl)-5-methoxy-2-oxindolin-3-yl)malononitrile(16g)

Red solid (91%); m.p. = 133-135 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 10.97 (bs, 1H), 8.69 (s, 1H), 7.24 (s, 1H), 7.12 (d, *J* = 8.0 Hz, 2H), 7.02 (d, *J* = 8.0 Hz, 2H), 6.78 (d, *J* = 8.8 Hz, 1H), 5.21 (s, 1H), 3.69(s, 3H), 2,31 (s, 2H), 2.23 (s, 3H), 2.00 (s, 2H), 0.98 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6)**:**δ (ppm) 196.4, 164.1, 161.6, 161.4, 155.4, 151.2, 140.8, 136.7, 134.4, 130.2, 124.6, 123.7, 119.4, 113.4, 113.0, 111.9, 110.7, 81.4, 73.2, 56.2, 50.5,32.8, 28.4, 21.0, 20.9; IR (4000-600 cm^{-1}): υ_{max} 3324, 2232, 1708, 1606; Elem. Anal**.** For $C_{27}H_{26}N_4O_3$ Calcd**:** C, 71.35, H, 5.77, N, 12.33 %; found: C, 71.28, H, 5.80, N, 12.19 %.

8. 2-(3-((4-chlorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-5-nitro-2-oxoindolin-3-yl)malononitrile(16h)

Dark violet solid (Yield 90%); m.p = 142-145 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6):δ (ppm) 8.93 (s, 1H), 8.10 (s,1H), 7.83 (bs, 1H), 7.59 (s,1H), 7.33 (d, *J* = 6.8Hz, 1H), 7.12 (d, *J* = 10 Hz, 2H), 6.98 (d, *J* = 7.2 Hz, 1H), 5.33 (s, 1H), 2.32 (s, 2H), 2.03 (s, 2H),0.96 (s, 3H), 0.84 (s, 3H) ^{13}C NMR (100 MHz, DMSO-d_6):δ (ppm) 197.0, 194.7, 164.1, 160.4, 138.4, 134.0, 131.4, 126.3, 123.4, 122.6, 121.5, 119.0, 113.5, 112.2, 112.0, 98.0, 81.1, 56.5, 32.8, 32.6, 28.3; IR (4000-600 cm^{-1}): υ_{max} 3220, 2191, 1741, 1620; Elem. Anal**.** For $C_{25}H_{20}ClN_5O_4$ Calcd**:** C, 61.23, H, 4.11, N, 14.30 %; found: C, 61.17, H, 4.15, N, 14.19 %.

9. 2-(3-(2-((4-chlorophenayl)amino)-4,4-dimethyl-6oxocyclohex-1-en-1-yl)-5-nitro-2-oxoindolin-3-yl)malononitrile(16i)

Red solid (94%); m.p. = 137-139 ^{o}C; H NMR (400 MHz, DMSO-d_6):δ (ppm) 10.97 (s, 1H), 8.81 (s, 1H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.27 (bs, 1H), 7.15 (d, *J* = 8.4 Hz,3H), 6.79 (d, *J* =7.2 Hz, 1H), 5.29 (s, 1H), 3.70 (s, 3H), 2.33 (s, 2H)2.02 (s, 2H), 0.98 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6):δ (ppm 196.2, 194.4, 164.2, 160.1, 155.4, 151.6, 141.1, 138.8, 129.7, 128.4, 124.8, 119.5, 113.5, 113.0, 111.9, 97.8, 81.3, 56.2, 50.7, 42.6, 32.8, 28.4; IR (4000-600 cm^{-1}): υ_{max} 3259, 2210, 1721, 1579; Elem. Anal**.** For $C_{25}H_{20}ClN_5O_4$ Calcd**:** C, 61.29, H, 4.11, N, 14.30 %; found: C, 61.05, H, 4.15, N, 14.22 %.

10. 2-(7-fluoro-3-(2-((4-methoxyphenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1yl)-2-oxoindolin-3-yl)malononitrile(16j)

Red solid (92%); m.p. = 142-143 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 11.2 (s, 1H), 8.59 (s, 1H), 7.15-7.00 (m, 3H), 7.01-6.70 (m, 3H), 5.06 (s, 1H), 3.70 (s, 3H), 2.30 (s, 2H), 1.99 (s, 2H), 0.98 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6)**:**δ (ppm) 195.5.2, 194.6, 180.2, 161. 8, 160.0, 157.6, 156.9, 153.4, 152.1,, 139.0, 138.2, 132.2 128.5, 125.8, 119.5, 116.0, 115.6, 114.6 (d, *J* = 40Hz), 60.2, 56.0, 55.7,50.7, 49.7, 32.8, 32.7, 28.6, 28.5, 27.4; IR (4000-600 cm^{-1}): υ_{max} 3249, 2238, 1734, 1601; Elem. Anal**.** For $C_{26}H_{23}FN_4O_3$ Calcd**:** C, 68.11, H, 5.06, N, 12.22%; found: C, 67.95, H, 5.15, N, 12.10%.

11 .2-(3-(2-((4-methoxyphenyl)amino)-4-methyl-6oxocyclohex-1-en-1-yl)-5-nitro-2-oxoindolin-3-yl)malononitrile(16k)

Red solid (92%); m.p. = 112-114 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 8.8-7.8(m, 1H), 7.10(bs, 1H), 7.04 (d, *J* = 8.8 Hz, 3H), 6.88(d, *J* = 8.8 Hz, 2H), 5.09(s, 1H), 3.69 (s, 3H), 2.22-2.03 (m, 4H), 1.90-1.80 (m, 1H), 0.96 (d, *J* = 6.0Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)**:**δ (ppm) 197.0, 166.2, 180.8, 164.4,161.5, 158.0, 156.9, 156.4, 149.5,5, 143.9, 132.9, 129.2, 126.7, 120.2, 115.9,112.2, 56.8, 45.9, 37.0, 30.3.3, 22.3; IR (4000-600 cm^{-1}): υ_{max} 3223, 2239, 1734, 1615; Elem. Anal**.** For $C_{25}H_{21}N_5O_5$ Calcd**:** C, 63.69, H, 4.49, N, 14.85 %; found: C, 63.57, H, 4.55, N, 14.69 %

12 2-(5-fluorophenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-2-oxoindolin-3-yl)malononitrile(16l)

Red solid (92%); m.p. = 123-124 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 8.59 (s, 1H), 7.69 (bs, 1H), 7.49 (bs, 1H), 7.13 (s, 1H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.90 (d, *J* = 8.8 Hz, 2H), 5.05 (s, 1H), 3.71 (s, 3H), 2.03 (s, 2H), 1.98 (s, 2H), 0.98 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6)**:**δ (ppm) 195.5, 194.6, 179.9, 164.1, 161.8, 160.4, 156.9, 153.3, 152.1, 140.2 (d, *J* = 10Hz), 132.2, 128.8, 125.8, 122.4, 114.7 (d, *J* = 50 hz),110.3, 56.0, 55.7, 5 0.7, 32.8, 32.6, 28.5, 27.1 ; IR (4000-600 cm^{-1}): υ_{max} 3320, 2219, 1712, 1615; Elem. Anal**.** For $C_{26}H_{23}FN_4O_3$ Calcd**:** C, 68.11, H, 5.06, F, 4.14, N, 12.22 %; found: C, 67.78, H, 5.12, F, 3.79, N, 11.85 %.

13 2-(3-(2-((4-methoxyphenyl)amino)-4-methyl-6-oxocyclohex-1-en-1-yl)-2-oxo-indolin-3-yl)malononitrile(16m)

Red solid (91%); m.p. = 113-115 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6)**:**δ (ppm) 7.83 (d, *J* = 7.60Hz, 1H), 7.52 (t, *J* = 7.2 Hz, 2H), 7.40-7.10 (m, 4H), 6.90 (d, *J* = 8.8 Hz, 3H), 5.05 (s, 1H), 3.69 (s, 3H), 2.30-2.00 (m, 4H) 0.96 (d, *J* = 6.4Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6)**:**δ (ppm) 196.6, 165.1, 164.2, 163.5, 157.1, 151.1, 146.7, 138.4, 131.9, 125.9, 123.4, 119.1, 114.9,113.5, 112.0, 81.2, 55.8, 45.0, 29.3, 21.3 ; IR (4000-600 cm^{-1}): υ_{max} 3250, 2198, 1714, 1615; Elem. Anal**.** For $C_{25}H_{22}N_4O_3$ Calcd**:** C, 70.41, H, 5.20, N, 13.14 %; found: C, 70.35, H, 5.25, N, 13.07 %

14 2-(5-bromo-3-(2-((4-methoxyphenyl)amino)-4,4-dimethyl-6-oxocyclohex-1-en-1-yl)-2-oxoindolin-3-yl)malononitrile(16n)

Red solid(90% yield); m.p. = 121-123 ^{o}C; ^{1}H NMR (400 MHz, DMSO-d_6):δ (ppm) 7.50-7.25 (m, 1H), 7.05 (d, *J* = 8.80 Hz, 3H), 6.90 (d, *J* = 9.2 Hz, 3H), 5.07 (s, 1H), 3.69 (s, 3H), 2.30 (s, 2H), 1.99 (s, 2H), 0.96 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6)**:**δ (ppm) 196.5, 195.2, 180.7, 163.4, 160.4, 157.0, 155.9, 155.4, 148.5, 148.4, 142.9, 131.8, 128.1, 125.7, 119.1, 114.9, 110.2, 55.9, 55.7, 44.9, 36.7, 29.3, 21.2; IR (4000-600 cm^{-1}): υ_{max} 3218, 2232, 1714, 1605; Elem. Anal**.** For $C_{26}H_{23}BrN_4O_3$ Calcd**:** C, 60.12, H, 4.46, N, 10.79 %; found: C, 60.03, H, 4.40, N, 10.68 %

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Chapter 5

Ammonium Chloride Assisted Microwave Mediated Domino Multicomponent Reaction: An Efficient and Sustainable Synthesis of Quinazolin-4(3*H*)-imines under Solvent Free Condition

5.1 Graphical Abstract

5.2 Introduction

Quinazolin-4(3*H*)-imines has been the cornerstone of many biologically important naturally occurring and synthetic N-containing heterocycles. This scaffold acted as a springboard for the assembly of myriads of medicinally profound molecules such as quinazolinones,[1,2] phenylbenzo [4,5] imidazo[1,2-c]quinazoline,[3] benzo[4,5] imidazo[2,1-*b*] qunazolin-12(6*H*)-imine, 2-methyl-H-oxazolo[2,3-*b*]quinazolin-5-imine and 2-methyl-5H-[1,3,4]oxadiazolo[2,3-*b*]quinazolin-5-imine [4] (**Fig.5.1**). Consequently, intensive research work has been going on in this area and medicinally promising molecules such as homobivalent dimers of quinazolinimines such as compounds **I** and **II** which are efficacious at nanomolar level with dirigible selectivity towards butyryl cholinesterase have been synthesized (**Fig.5. 2**) [5,6].

Figure 5.1 Quinazoline and its derivatives

Similarly, these scaffolds have been known to possess broad spectrum of biological activities such as potent EGFR inhibitory, antimalarial, antitumor, anticonvulsive, antimicrobial, anti-viral, anticholinesterase, anti-inflammatory, analgesic and COX-II inhibitory, and α-glucosidase inhibitory activities [7–20].

Figure 5.2 Homo bivalent quinazolin-4(3H)-imines frameworks Cholinesterase inhibitors

5.3 Literature Survey

Assessment of the literature survey shows that in the last few decades, several synthesis strategies for quinazolin-4(3*H*)-imine moieties have been developed. This chapter highlights the development made in designing and synthesizing these scaffolds through a variety of methodologies. To begin with the latest ones, in 2017, Liu and co-workers reported the synthesis of quinazoli-4(3*H*)-imines from aryldiazonium salts (**1**), dry nitriles (**2**) and 2-cyanoanilines (**3**) via metal free tandem approach heating the reaction mixture at 80 ^{o}C for 2 hours (**Fig.5.3**) [21]

Figure 5.3 Aryldiazonium based three component reactions for the synthesis of 2-substituted quinazolin-4(3H)-imines

The drawback of this methodology is the sensitivity to moisture and diazonium chemistry being not trivial. Likewise, Rojas *et al*. (2015) reported synthesis of quinazolin-4(3*H*)-imines (**6**) through reaction of pre synthesized imidoyl chlorides (**5**) with *o*-cyanoaniline (3) using toluene as a solvent and Et_3N as catalyst (**Fig.5.4**) [22].

Figure 5.4 Et_3N catalyzed synthesis of quinazolin-4(3H)-imines

The underlying limitation of this approach is low yield of the products, long duration of the reaction and poor stability of imidoyl chlorides. Furthermore, in 2014, Rayat and co-workers reported a three step synthesis of fused quinazolin-imine (**8**) scaffolds through cyclization of carbodiimide structure (**7**) using water and DCM as a solvent system, Lewis acid as a catalyst and nitromethane at 23 ^{o}C (**Fig.5.5**) [23]. The shortcomings of this strategy are long reaction time, low yields and narrow substrate scope.

Figure 5.5 Cyclization of heteroenyne–allenes in the presence of Lewis acids to give N-fused quinazoliniminium scaffolds

Similarly, Chen *et al*. (2014), reported diverse tandem cyclization of *o*-cyanoanilines (**3**) and diaryliodinium salt with copper catalyst in DCE as a solvent under two different conditions for the assembly of quinazolin-4(3*H*)imine and acridine scaffolds (**Fig.5.6**) [24].

Figure 5.6 $Cu(OTf)_2$ catalyzed synthesis of quinazolin-4(3*H*)-imines

When *o*-cyanoaniline (3) was used in excess, the reaction led to the formation quinazolin-4(3*H*) derivatives, whereas when diaryliodinium salt was employed in excess it gave rise to the formation of aridines (**11**) shown in **Fig. 5.6**. In this reaction *o*-cyanoaniline reacts with diaryliodinim salt in the presence of triflate to provide *N*-(2aminobenzylidyne) benzenium,which can react with either diaryliodinium salt in cyclization reaction involving C-H activation directed by *in situ* generated amine to give rise to the formation of acridine (**11**) or *o*-cyanoaniline to provide the desired quinazolin-4(3*H*)-imine product (**10**).The mechanism of the reaction is presented in **Fig. 5.7**.

Figure 5.7 Mechanism of the reaction under different two conditions giving quinazolin -4(3*H*)-imine and acridine derivatives

Likewise, Koutentis *et al.* (2013) disclosed synthesis of quinazoline-4(3*H*)-imine (**17**) from 2-amino-N'-arylbenzamidines (**12**) and 4,5-dichloro-1,2,3-dithiazolium chloride(**13**) (Apple salt) under base promoted condition (**Fig.5.8**) [25] The limitations of this method are low yields and narrow substrates scope.

Figure 5.8 Amine catalyzed synthesis of quinazolin-4(3*H*)-imines

Mechanistic rationale for the formation of quinzolin-4(3*H*)-imine is as follows. Two routes for the synthesis of these scaffolds are possible. The apple salt (**13**) condenses with 2-amino-*N*'-arylbenzamides at either primary aniline amine or amidino secondary secondary amine to provide adduct **14** or **15** respectively. Finally, these adducts undergo intramolecular cyclization *via* a common spirocyclic intermediate **16**, which undergoes cleavage providing the final desired product **17**. The mechanism of this reaction is presented in in **Fig 5.9.**

Figure 5.9 Mechanism of reaction for apple salt catalyzed synthesis of quinazolin-4(3H)-imines scaffolds.

This methodology involves prefunctionalization of starting materials which means at least two steps were required to obtain the final desired product.

In 2012, Pu and Wu *et al*. disclosed palladium acetate catalyzed three component reaction involving isocyanides (**18**), secondary amines (**19**) and carbodiimide (**20**) for the preparation of quinazolin-3(4*H*)-imines (**21**) (**Fig. 5.10**) [26] The high price of palladium based catalyst hampers the applicability of this method towards large scale production of these moieties.

Figure 5.10 $Pd(OAc)_2$ catalyzed synthesis of quinazolin-4(3H)-imine

Back in 2004, Langer *et al*. disclosed synthesis of two different tricyclic quinazolines (**21**) and (**23**) by reacting 2-(dichlorocyanido)nitrile (**22**) with either phenacylamine (**23)** or glycinate hydrochloride (**24**) (**Fig 5.11**) [4].

Figure 5.11 Sequential Domino synthesis of quinazoline bearing fused heterocyclic scaffolds

The reactions carried out in this protocol led to formation of two sets of heterocycles: quinazolin fused to imidazolinone in one case and oxazol in the other. In this reaction 2-(dichloroisocyanido) benzonitrile (**22**) condenses with acetic hydrazide (**23**) to provide an intermediate **24** which has two reactive sites undergoes intramolecular cyclization *via* nucleophilic substitution to construct 5H-oxadiazolo [2,3-*b*]quinaolin-5-imine (**25**), which under slightly basic condition gives **26.** Under another approach, 2-(dichloroisocyanido) benzonitrile (**22**) reacts with ethylglycinate (**27**) to form another intermediate **28** that cyclizes through reaction of reactive nucleophilic amine and electrophilic nitrile functionalities to provide further another intermediate **29**, which upon intramolecular cyclization for the second time give rise to construed tricyclic fused heterocycle bearing quinazolin-4(3*H*)-imine core 2,3-dihydro-2-oxo-imidazo[1,2-*c*] (**30**) quinazoline.The mechanism of the reaction is presented in **Fig 5.12.**

Or

Figure 5.12 Sequential Domino synthesis of quinazoline bearing scaffolds

Likewise, E. Erba *et al*. (2005), reported synthesis of quinazolin-4(3*H*)- imines (**34**) from reaction of ketones (**31**), primary amines (**32**) and 2-azido-5-nitro benzonitrile (**33**), which was finally transformed to quinazolin-4-amine (**25**)in the presence of basic medium.(**Fig. 5.13**) [27].

Figure 5.13 Azido based synthesis of quinazolin-4(3*H*)-imine and its conversion to quinazolin-4-amine

Early in the year 2000, Suwinski, Syczcpankwiez and coworkers research group reported a two step reaction for the synthesis of quinazolin-4(3*H*)-imine through reaction of *o*-cyanoaniline (**3a**) and formic acid (**38**) and its final conversion to quinazolin-4-ones up on reaction with water under heating described in (**Fig.5.14**) [28].

Figure 5.14 Synthesis of quinazolin-4-one involving quinazolin-4(3*H*)-imine intermediate

The rationale behind the construed of quinazolinone scaffold (**39**) through two component reaction involving *o*-cyanoaniline (**3a**) and formic acid (**38**) is, first **3a** condenses with formic acid (**38**) to provide the intermediate **39** that can undergo condensation with another molecule of **3a** to form another intermediate 40 bearing two reactive sites that undergoes intermolecular cyclization *via* proton shift driven reaction to produce quinazolin-4(3*H*)-imine bearing scaffold (**41**), which upon heating in acidic condition gives the desired quinazolinone final product (**42).** The plausible mechanism of the reaction is presented in **Fig 5.15**.

Figure 5.15. Plausible reaction mechanism for the synthesis of quinazolinones involving quinazolin-4(3*H*)-imine intermediate

In spite of the fact that recently the developed strategies made a significant advancement to previous research work, still there are some gaps to be filled such as addressing the issue of multistep reaction, long reaction time, generation of hazardous side products (less selectivity to desired products), employing expensive catalysts and reagents, using volatile organic solvents like DCM and DCE, low yielding protocols, and narrow substrate scope and in a some cases multiple steps were involved .These features are undesirable from environmental impact point of view and it is appealing to design and implement alternative synthesis strategies which operate in sustainable manner[29]. In continuation to our recent research work focusing on sustainable synthesis, [30–37]

herein, efficient (one pot, single step and short reaction time), solvent and metal catalyst free ecofriendly protocol for the synthesis of quinazolin-4(3*H*)-imines has been presented. The remarkable and prominent feature of this strategy is that it involves cheap and readily available starting materials without any prefunctionalization and laboratory grade ammonium chloride as a Bronested acid and the products obtained required no tedious purification procedure (**Table 5.1**)

5.4 Results and Discussion

To probe the feasibility of our proposed protocol, readily available starting materials 2-aminobenzonitrile **3a** (0.5 mmol), aniline **25a** (0.5 mmol) and triethylorthoformate **33a (**0.5 mmol**)** have been irradiated under solvent and catalyst free conditions using microwave as a source of energy. Unfortunately, the reaction did not work out at this instant (**Table 5.1, entry 1**). Next, it was decided to explore the effect of weakly acidic or basic reagents as a catalyst which could probably activate conversion of reactants to desired products. Ammonium acetate was picked as a promoter and the reaction was carried out at 140 ^{o}C for 15 min. This time partial conversion of reactants to products was observed with the yield of 50% (**Table 5.1, entry 2**) Next, ammonium chloride was used under the same condition and pleasingly, the desired product was obtained in excellent yield of 93% (**Table 5.1, entry 3).** Inspired by catalyzing effect of ammonium chloride in entry 3, additional screening of the effects of other reagents such as $ZnCl_2$, $FeCl_3$, oxalic acid mono hydrate, *p*-TSA and $Bi(NO_3)_3.5H_2O$ (**Table 5.1, entry 4-8)** was studied**.** It was observed that, except ammonium chloride, other reagents showed low to moderate catalyzing capacity and it has been concluded that NH_4Cl was found uniquely catalyzing the hypothesized reaction for the synthesis of quinazolin-4(3*H*)-imine (**41a**). Finally, the effect of temperature and time on the catalyzing activity of NH_4Cl was studied (**Table 5.1, entries 10-17**) was studied by tuning combination of temperature and time. The results obtained were summarized in the **table 5.1(entries 10-17**). After observation of all the studies, it was concluded that the optimum reaction conditions for the reaction is microwave irradiation of 2-aminobenzonitrile **3a** (0.5 mmol), aniline **25a** (0.5 mmol), triethylorthoformate **33a (**0.5 mmol**)** and NH_4Cl (0.5 mmol) at 140 ^{o}C for 15 minutes which is in good accordance with previous research findings where ammonium chloride was found activating similar transformations [38].

Table 5.1 Optimization of reaction condition [a]

Entry	Promoter	Temerature (^oC)	Time (min)	Yield (%)
1	-	140	15	nd
2	NH_4Ac	140	15	50
3	NH_4Cl	140	15	93
4	$ZnCl_2$	140	15	48
5	$FeCl_3$	140	15	58
6	Oxalic acid monohydrate acid	140	15	55
7	PTSA	140	15	65
8	$Bi(NO_3)_3.5H_2O$	140	15	70
10	NH_4Cl	130	15	85
11	NH_4Cl	150	15	48
12	NH_4Cl	140	12	57
13	NH_4Cl	140	18	50
14	NH_4Cl	150	12	60
15	NH_4Cl	150	18	70
16	NH_4Cl	130	12	65
17	NH_4Cl	130	18	72

[a] Reaction conditions: 2-amonobenzonitrile **3a** (0.5 mmol), triethylorthoformate **33a(**0.5 mmol) and aniline **25a** (0.5 mmol and 0.5 mmol ammonium chloride under solvent free condition assisted by MWI at 140 ^{o} C for 15 minutes. [b] Isolated yields. nd= not determined..

After establishing the optimum condition of our protocol, it has been intended to investigate the scope and limitation of the developed strategy by synthesizing library of quinazolin-4(3*H*)-imines **41a-41n** for which the data was compiled in **Table 5.2.** The optimized reaction condition extended its efficacy on different starting substrate derivatives 2-aminonbenzonitrile **3a** and **3b,** triethyl orthoformate **33a** and anilines **25a-25j**. Except minor differences noticed in efficacy of aniline substrates such as **25b**, **25c** and **25f** which are activated by electron donating groups providing slightly better yields of 96, 94 and 92 % respectively (**Table 5.2, entries 2, 3 and 6**) over their deactivated counter parts having anilines bearing electron withdrawing groups (**Table 5.2, entries 4, 5, 7-11, 13,14**). As expected¸ amongst deactivated anilines, *m*-positioned electron withdrawing groups on anilines provided better yields as compared to *p*-positioned ones which in turn were

more efficient than *o*-positioned entities [39]. Generally, fluorinated organic compounds are known to be more bio potent than non-fluorinated counter parts [40–42] and to our delight, fluoro derivatives were successfully incorporated into our synthesized compounds and made our protocol more suitable for future biomedical potency. The halo substituents, specifically, the bromo substituents on aryl rings would serve as a spring board for diversity oriented organic synthesis [43–45].

Table 5.2 Library of synthesized compounds

Entry	R^1	R^2	Product	Yields (%)
1	H	Ph	**41a**	93
2	H	4-MeO-Ph	**41b**	96
3	H	4-Me-Ph	**41c**	94
4	H	4-Cl-Ph	**41d**	91
5	H	4-Br-Ph		92

			41e	
6	H	4-MeS-Ph	**41f**	92
7	H	3-Cl-Ph	**41g**	91
8	H	2-Cl-Ph	**41h**	85
9	4-Me	4-Cl-Ph	**41i**	92
10	4-Me	4-Br-Ph	**41j**	93
11	H	4-F-Ph	**41k**	91
12	4-Me	4-OMe-Ph		87

			41l	
13	H	3-NO2-Ph	**41m**	91
14	4-Me	4-F-Ph	**41n**	91

Mechanism of reaction

In accordance with the previous reports and the results of the present work, we propose a plausible mechanism for the synthesis of quinazolin-4(3*H*)-imines in **Scheme 5.1.** Aniline derivatives **3** being more nucleophilic in nature than 2-amino benzonitrile and undergo condensation with orthoformates **2** for the formation of iminic intermediate **I**. 2-aminobenzonitrile through its amine group further reacts with the imine of **I** to achieve intermediate **II** which finally undergoes intramolecular tandem annulation [46] and [1,5] proton shift to give the desired products quinazolin-4(3H)-imines.

Scheme 5.1 Plausible reaction mechanism

Furthermore, we studied the scalability and greenness of our strategy by carrying out the reaction at 5.0 mmol level based on model reaction (**Table 5.3**) which provided **34a** in 90 % yield [29,45–48] and the results obtained were summarized in **Table 5. 3**. Atom economy and carbon efficiency scores were found to be moderate which might be probably because of removal of 3 moles of ethanol (per mole of orthoformate) as byproduct. It is worth mentioning that ethanol as a byproduct is not hazardous and hence does not affect the greenness of our protocol. On contrary to this, E-

factor was observed to be very low, indicating the applicability of our protocol on industrial perspectives in sustainable way.

Table 5.3 Green metrics calculation results for large scale production of 3-phenylquinazolin-4(3H)-imine (**34a**)

Green metrics	AE (%)	CE (%)	RME (%)	PMI	E-factor
Results obtained	62	70	90	1.11	0.11

5.5 Conclusions

In summary, we have developed efficient and sustainable novel strategy for the synthesis of quinazolin-4(3*H*)-imines scaffolds from readily available starting materials 2-amino benzonitrile, triethyl orthoformate and aniline derivatives under solvent free condition assisted by microwave irradiation. The advantages of the present protocol over the previous ones are: simple reaction procedure, easy purification method, single step operation and high yields (85-96%).

5.6 Experimental Section

5.6.1 General Experimental Detail

^{1}HNMR spectra were recorded on a Jeol Resonance ECX-400II (400 MHz); Chemical shifts (δin ppm) and coupling constant (*J* in Hz) are calibrated either relative to internal solvent tetramethylsilane TMS (δ_H = 0.00 ppm) or $CDCl_3$ (δ_H = 7.26 ppm). In the ^{1}H NMR data, the following abbreviations were used throughout: s = singlet, d = doublet, t = triplet, brs = broad singlet. ^{13}C NMR spectra were recorded on a Jeol Resonance ECX-400II (100 MHz) at R.T in $CDCl_3$; chemical shifts are calibrated relative to $CDCl_3$(δc = 77.0 ppm).. IR spectra were recorded

on Perkin Elmer FT-IR spectrometer -spectrum two. Melting points were performed with *optimelt* automated melting point system.

The reactions were performed in a G-10 Borosilicate glass vial sealed with Teflon septum in Anton Paar Monowave 300 reactor®, operating at a frequency of 2.455 GHz with continuous irradiation power of 0 to 300 W. Analysis of the reactions were done by thin layer chromatography (TLC). For this, Merck precoated silica gel TLC plates (Merck® $60F_{254}$) were used. Reagents were purchased from Sigma Aldrich and Alfa Aesar. All solvents; methanol (MeOH), hexane, ethyl acetate and diethyl ether all were purchased from locally available commercial sources and used as received. A variety of 5-aryl-1, 3, 4-thiadiazol-2-amines and 2-oxo-2*H*-chromene-3-carbaldehyde were prepared according to literature procedure [1-2].

5.6.2 General Procedure for the synthesis of quinazolin-3(4*H*)-imines (34a-4n)

2-aminobenzonitrile derivatives **3a** and **3b** (0.5 mmol), triethyl orthoformate **33a** (0.5 mmol), aniline derivatives **25a-25j** and NH_4Cl (1.0 equiv.) were taken in G-10 glass vial capped with Teflon septum. After that, the reaction vial was subjected to microwave irradiation with the initial ramp time of 1 minute at 60 °C and then raised the temperature to 140 °C with the holding time of 15 minutes. After completion of reaction, the solid product obtained was washed using either water or diethyl ether depending on polarity and in some cases recrystallization was done in a mixture of water and ethanol(4:1) The identities of all products **41a-41n** were confirmed by FTIR,^{1}H NMR and ^{13}C NMR spectroscopy and elemental analysis.

Spectral Data of all Compounds (41a-41n)

1) 3-Phenylquinazolin-4(3*H*)-imine (41a)

Yellow solid (93%), m.p 284.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H (ppm) 8.77 (s, 1H), 7.91 (d, *J* = 8.8 Hz, 2H), 7.79 (t, *J* = 8.0 Hz, 1H,), 7.73 (d, *J* = 8.0 Hz, 2H,), 7.64 (bs, 1H), 7.54(t, *J* =7.6 Hz, 1H,), 7.41(t, *J* = 7.6 Hz, 2H,), 7.17(t, *J*= 7.2 Hz, 1H,); ^{13}C NMR ($CDCl_3$, 100 MHz): δc (ppm) 157.7, 155.1, 150.1, 138.2, 133.1, 129.2, 126.8, 124.8, 122.1, 120.5, 115.2; IR (4000-600

cm^{-1}): υ_{max} 3450, 2111, 1634, 1415; Elem. Anal**.** For $C_{14}H_{11}N_3$ Calcd**:** C, 76.00, H, 5.01, N, 18.99 %; found: C, 75.52.88, H, 5.10; N, 19.06 %

2) 4-(4-methoxyphenyl) quinazolin-4(3*H*)-imine (41b)

Grey solid (96%), m.p. 168 °C; ^{1}H NMR ($CDCl_3$, 400 MHz,**):** δ_H (ppm) 8.70 (s, 1H), 7.92-7.84 (m, 2H), 7.75 (t, *J* = 7.2Hz, 1H), 7.69 (bs, 1H), 7.56-7.46(m, 3H), 6.92(d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz,)**:**δc (ppm) 158.2, 157.1, 155.3, 150.0, 133.0, 130.9, 128.8, 126.6, 124.7, 120.7, 115.1, 114.5, 55.6; IR (4000-600 cm^{-1}): υ_{max} 3433, 2069, 1636, 1412 ; Elem. Anal**.** For $C_{15}H_{13}N_3O$ Calcd**:** C, 71.70, H, 5.21, N, 16.72 %; found: C, 69.88, H, 5.28, N, 16.12 %

3) 3-(*p*-tolyl) quinazolin-4(3H)-imine (41c)

Yellow solid (94%); m. p. = 191 ^{o}C; ^{1}H NMR ($CDCl_3$, 400MHz,): δ_H (ppm) 8.73 (s, 1H), 7.95-7.84 (m, 2H), 7.78-7.45 (m, 3H), 7.18(d, *J* = 8.0 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR **(**$CDCl_3$, 100 MHz,)**:** δ_C (ppm) 158.0, 155.2, 150.0, 135.5, 134.7, 133.0, 129.7, 128.8, 126.6, 122.6, 120.8, 115.3, 21.0; IR (4000-600 cm^{-1}): υ_{max} 3470, 2086, 1634, 1415; Elem. Anal**.** For $C_{15}H_{13}N_3$ Calcd**:** C, 76.57, H, 5.57, N, 17.86 %; found: C, 76.34, H, 5.43, N, 17.5 %

4) 3-(4-chlorophenyl) quinazolin-4(3*H*)-imine (41d)

Pale yellow solid (91%); m.p. = 187 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.75 (s, 1H), 7.92 (t, *J* = 8.0 Hz, 2H), 7.80 (t, *J* =8.0 Hz, 1H), 7.70(d, *J* = 8.4 Hz, 2H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.36 (d, *J* = 11.6 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz,)**:** δ_C (ppm) 157.5, 154.8, 149.9, 136.9, 133.2, 129.7, 129.2, 128.9, 126.9, 123.3, 120.7, 116.3, 115.1 IR (4000-600 cm^{-1}): υ_{max} 3444, 2103, 1635, 1414; Elem. Anal**.** For $C_{14}H_{10}ClN_3$ Calcd**:** C, 65.76, H, 3.94, Cl, 13.86, N, 16.43 %; found: C, 64.89, H, 4.03, Cl, 13.57, N, 16.14 %

5) 3-(4-bromophenyl) quinazolin-4(3*H*)-imine (41e)

Pale yellow solid (92%); m.p. = 177 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.77 (s, 1H), 7.91 (t, *J* = 8.0 Hz, 2H), 7.80 (t, *J* =7.2 Hz, 1H), 7.66(d, *J* = 8.8Hz, 2H), 7.60-7.43 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 157.4, 154.9, 150.1, 137.3, 133.2, 132.2, 129.1, 127.0, 123.5, 120.4, 117.4, 115.1; IR (4000-600 cm^{-1}): υ_{max} 3440, 2048, 1637, 1415; Elem. Anal. For $C_{14}H_{10}BrN_3$ Calcd**:** C, 56.02, H, 3.36, N, 14.00 %; found: C, 55.58, H, 3.50, N, 13.63 %

6) 3-(4-methylthio)phenyl) quinazolin-4(3*H*)-imine (41f)

Sandy color solid (92%); m.p. = 171 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz,): δ_H (ppm) 8.74 (s, 1H), 7.90 (d, *J* = 8.8 Hz, 2H), 7.78 (t, *J* =7.6 Hz, 1H), 7.67-7.60 (m, 3H), 7.53 (t, *J* = 7.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 2.48(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$):δ (ppm) 157.7, 155.0, 150.0, 135.7, 134.3, 133.1, 129.0, 128.0, 126.8, 122.8, 120.5, 115.2, 16.7; IR (4000-600 cm^{-1}): υ_{max} 3451, 2084, 1632, 1416; Elem. Anal**.** For $C_{15}H_{13}N_3S$ Calcd**:** C, 67.39, H, 4.90, N, 15.72, S, 11.99 %; found: C, 66.52, H, 4.78, N, 15.58, S, 11.37.

7) 3-(3-chlorophenyl) quinazolin-4(3*H*)-imine (41g)

Pale yellow solid (91%); m.p. = 179 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz,): δ (ppm) 8.79 (s, 1H), 7.94-7.90 (m, 3H), 7.80 (t, *J* = 8.0, 1H), 7.66 (bs, 1H), 7.58-7.52 (m, 2H), 7.31 (t, *J* =8.0 Hz, 1H), 7.13(d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz,)**:**δ (ppm) 157.3, 154.8, 150.1, 139.5, 134.8, 133.2, 130.1, 129.2, 127.0, 124.5, 121.7, 120.3, 119.6, 115.1; IR (4000-600 cm^{-1}): υ_{max} 3429, 2053, 1636, 1402; Elem. Anal**.** For $C_{14}H_{10}ClN_3$ Calcd**:** C, 65.76, H, 3.94, Cl, 13.86, N, 16.43 %; found: C, 65.43, H, 3.63, N, 16.21 %

8) 3-(2-chlorophenyl) quinazolin-4(3*H*)-imine (41h)

Pale yellow solid (85%); m.p. = 303 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.80 (s, 1H), 7.96-7.86 (m, 3H), 7.82 (t, *J* = 8.4 Hz, 1H), 7.62-7.52 (m, 3H), 7.32 (t, *J* =8.0 Hz, 1H), 7.14 (d, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)**:**δ (ppm) 157.3, 154.8, 150.1, 139.5, 134.8, 133.2, 130.1, 129.2, 127.0, 124.5, 121.7, 120.2, 119.6, 115.1; IR (4000-600 cm^{-1}): υ_{max} 3446, 2071, 1637, 1403; Elem. Anal**.** For $C_{14}H_{10}ClN_3$ Calcd**:** C, 65.76, H, 3.94, Cl, 13.86, N, 16.43 %; found: C, 65.45, H, 3.59, N, 16.18 %.

9) 3-(4-chlorophenyl)-7-methylquinazolin-4(3*H*)-imine (41i)

Pale yellow solid (92%); m.p = 146 ^{o}C; ^{1}H NMR ($CDCl_3$, 400 MHz,): δ_H (ppm) 8.68 (s, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.74-7.65 (m, 3H), 7.39- 7.31 (m, 3H), 2.51(s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)**:**δ_C (ppm) 157.5, 154.6, 149.6, 144.3, 136.9, 129.7, 129.1, 128.9, 127.7, 123.3, 120.5, 112.9, 22.0; IR (4000-600 cm^{-1}): υ_{max} 3455, 2071, 1637, 1405; Elem. Anal**.** For $C_{15}H_{12}ClN_3$ Calcd**:** C, 66.79, H, 4.48, Cl, 13.14, N, 15.58 %; found: C, 66.37, H, 4.54, N, 15.33 %

10) 3-(4-bromophenyl)-7-methylquinazolin-4(3*H*)-imine (41j)

Pale yellow solid (93%); m.p.= 192 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.70 (s, 1H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.74-7.66 (m, 3H), 7.39-7.31 (m, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)**:**δ (ppm) 157.4, 154.7, 149.8, 144.2, 136.9, 129.6, 129.2, 128.9, 127.9, 123.2, 120.4, 112.9, 22.0; IR (4000-600 cm^{-1}): υ_{max} 3435, 2059, 1633, 1405; Elem. Anal**.** For $C_{15}H_{12}BrN_3$ Calcd**:** C, 57.34, H, 3.85, Br, 25.43, N, 13.37 %; found: C, 57.09, H, 3.67; N, 13.08 %

11) 3-(4-fluorophenyl quinazolin-4(3*H*)-imine (41k)

Pale yellow solid (91%); m.p. = 194 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.73 (s, 1H), 7.91 (d, *J* = 8.4 Hz, 2H), 7.80 (t, *J* = 7.2Hz, 1H), 7.69-7.64 (m, 2H), 7.57-7.49 (m, 2H), 7.11 (t, J= 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)**:**δ (ppm) 161.1, 158.1, 155.0, 135.1, 133.2, 129.1, 126.8, 124.3, 124.2, 120.4, 116.1, 115.9; IR (4000-600 cm^{-1}): υ_{max} 3432, 2050, 1630, 1405; Elem. Anal**.** For $C_{14}H_{10}FN_3$ Calcd**:** C, 70.28, H, 4.21, F, 7.94, N, 17.56 %; found: C, 69.88, H, 4.12; N, 17.39 %.

12) 3-(4-methoxyphenyl)-7-methylquinazolin-4(3*H*)-imine (41l)

Pale yellow solid (87%); m. p.= 191 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.65 (s, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.65 (s, 1H), 7.54 (d, *J* = 8.8 Hz, 1H), 7.34 (d, *J* = 10.0 Hz, 1H), 6.93 (d, *J* = 8.8 Hz, 1H), 3.78 (s, 3H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$)**:**δ (ppm) 158.0, 157.0, 150.1, 143.8, 131.0, 128.5, 128.1, 124.6, 120.4, 114..9, 114.5, 113.0, 55.6, 21.9; IR (4000-600 cm^{-1}): υ_{max} 3429, 2153, 1642, 1416; Elem. Anal**.** For $C_{15}H_{15}N_3O$ Calcd**:** C, 72.43, H, 5.70, N, 15.84 %; found: C, 71.79, H, 5.85; N, 15.49 %.

13) 3-(3-nitrophenyl)quinazolin-4(3*H*)-imine (41m)

Yellow solid (91%); m.p.= 194 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.86 (s, 1H), 8.63(s, 1H), 8.49 (d, *J* = 8.8 Hz, 1H), 8.31 (d, *J* = 8.8 Hz, 1H),7.86 (d, *J* = 12 Hz, 1H), 7.78 (d, *J* = 8.8 Hz, 1H), 7.61 (dd, *J* = 8.8 Hz, 1H), 7.32 (s, 1H), 7.33-7.20 (m, 1H), 6.91 (d, 9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)**:**δ (ppm) 158.0, 154.6, 150.4, 149.2, 148.3, 134.0, 130.3, 128.3, 127.3, 123.8, 120.5, 118.3, 116.3, 110.5, 107.5; IR (4000-600 cm^{-1}): υ_{max} 3427, 2032, 1652, 1412; Elem. Anal**.** For $C_{14}H_{10}N_4O_2$ Calcd**:** C, 63.15, H, 3.79, N, 21.04 %; found: C, 62.88, H, 3.90; N, 20.89%.

14) 3-(4-fluorophenyl)-7-methylquinazolin-4(3*H*)-imine (41n)

Pale yellow solid (91%); m. p. = 192 ^{o}C; ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.68 (s, 1H), 7.80(d, *J* = 8.4 Hz, 1H), 7.69-7.63 (m, 3H), 7.51 (bs, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.10 (t, *J* = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$)**:**δ (ppm) 161.0, 158.6, 157.6, 154.9, 144.1, 128.8, 128.0, 124.2 (d, J = 10 Hz), 120.3, 116.0, 115.8, 112.8, 22.0; IR (4000-600cm^{-1}): υ_{max} 3430, 2048, 1640, 1400; Elem. Anal**.** For $C_{15}H_{12}FN_3$ Calcd**:** C, 71.13, H, 4.78, N, 16.59 %; found: C, 70.88, H, 4.80; N, 16.30 %.

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