The thesis is divided into the following five chapters, Chapter 2 is further divided into two sections, *i.e.* Section-A and Section-B.

**Chapter 1:** Introduction to Diversity Oriented Synthesis (DOS) Using Metal Catalysis and Multicomponent Reactions

**Chapter 2:** Development of Synthetic Protocols to Generate Diversely Substituted Fused Indole Derivatives

- **Section A:** Diversity Oriented Approach to Spiroindolines: Post-Ugi Gold-Catalyzed Diastereoselective Domino Cyclization
- **Section B:** Switching the Regioselectivity *via* Indium(III) and Gold(I) Catalysis: A Post-Ugi Intramolecular Hydroarylation to Azepino- and Azocino-[*c,d]*indolones

**Chapter 3:** Post-Ugi Gold(I) and Platinum(II) Catalyzed Intramolecular Hydroarylation to Synthesize Fused Pyrrole Derivatives

**Chapter 4:** An Expedient Route to Imidazo[1,4]diazepin-7-ones *via* a Post-Ugi Gold- Catalyzed Heteroannulation

**Chapter 5:** Design and Synthesis of Novel *N*-Alkyl 5-benzoyl 2-pyridone Derivatives and their Biological Evaluation

A brief account of each chapter is given below:

**Chapter 1: Introduction to Diversity Oriented Synthesis (DOS) Using Metal Catalysis and Multicomponent Reactions**

Heterocyclic frameworks are ubiquitous in natural products, pharmaceuticals, organic materials, and numerous functional molecules. The importance of these organic moieties in contemporary chemical biology and medicinal research is undisputed. Synthetic organic chemists provide access to structurally complex and functionally diverse sets of compounds and thus supply the feedstock for advanced research in chemical biology. The goal is to identify potent and selective molecular modulators of all cellular processes, including the growing number of non-classical biological targets considered “undruggable”—that is, cannot be addressed with medication. As a consequence, the ongoing interest in developing new versatile and efficient synthesis of heterocycles has always been a thread in the synthetic chemistry community. In the
past decade the productive concepts of multi-component processes, domino reactions and sequential transformations, where complex and highly diverse structures are created in a one-pot fashion, have considerably stimulated both academia and industry. In the year 2000, Schreiber introduced the concept of diversity oriented synthesis (DOS). As diversity oriented synthesis, particularly multi-component reactions (MCR) are masterpieces of synthetic efficiency and reaction design. Several descriptive tags are regularly attached to MCRs, e.g.

i. They are atom economic

ii. They are efficient.

iii. They are convergent

iv. They exhibit a very high bond-forming-index (BFI).

Therefore MCRs are often a useful alternative to sequential multistep synthesis. Advances in technology have brought an explosion in the number of possible drug targets with the use of transition and post-transition metal catalyzed reactions imparting high regioselectivity. Among various metals employed, Au(I)-, Pt(II)- and In(III)-catalyzed tandem carbocyclization and heteroannulation reactions have acquired considerable attention because these metals can activate various π-systems (i.e. alkynes, alkenes, and allenes) towards the nucleophilic attack, at low catalyst loading and under exceedingly mild reaction conditions. The investigations of mechanistic pathways for these metal catalyzed reactions with alkynes and the development of novel gold-, platinum- and indium-catalyzed reactions are currently the hot topic of research in the field of synthetic organic chemistry. The work presented in Chapter 1 describe the introduction about the utility of diversity oriented synthesis (DOS) approach in heterocyclic chemistry employing metal-catalysis and multicomponent reaction.

Chapter 2: Development of Synthetic Protocols to Generate Diversely Substituted Fused Indole Derivatives

The indole ring system represents one of the most abundant and important heterocycles in nature. Found in a hugely diverse array of biologically significant natural compounds, from simple derivatives such as the neurotransmitter serotonin to complex alkaloids such as the clinically used anticancer agent mitomycin C and vinblastine, and the antihypertensive alkaloid reserpine, the importance of indoles to biological chemistry cannot be overstated.

This chapter is divided into two sections, i.e. Section-A and Section-B:
Section-A: Diversity Oriented Approach to Spiroindolines: Post-Ugi Gold-Catalyzed Diastereoselective Domino Cyclization: Spiroindolines are prominent molecular motifs frequently encountered in the large family of alkaloids, that includes communesines, perophoramidines, etc., which display distinct pharmacological properties. These fused polycyclic systems featuring quaternary stereocenters, challenge organic chemists to develop nontrivial synthetic approaches.

In the present work, we have achieved a post-Ugi gold-catalyzed intramolecular domino cyclization sequence producing spiroindolines. The first step in the sequence is an Ugi-four component reaction (Ugi-4CR) with the use of 2-alkynoic acids as alkyne source (Scheme 1) and in another sequence, propargyl amines act as alkyne source (Scheme 2). The second step is a cationic gold-catalyzed intramolecular hydroarylation tandem cyclization to produce spiroindolines with complete diastereoselectivity. This synthetic sequence is atom-economical and mild conditions are applied to generate a very complex molecular structure from readily available starting materials.

Based on this work and our continued interest in the transition metal-catalysis, multicomponent reactions and the chemistry of the indole core, we herein discussed a post-Ugi gold-catalyzed intramolecular domino cyclization sequence for the synthesis
of spiroindolines. This observation was remarkable as the attack on the α-position of an alkyne conjugated with amide is rare and trapping of the spiro-intermediate by a sterically hindered tert-butyl amide is rather unexpected, not to mention the observed diastereoselectivity. The mechanistic cycle during the course of the intramolecular domino cyclization reaction was further confirmed by X-ray crystallography of spiroindoline 6a.

Section B: Switching the Regioselectivity via Indium(III) and Gold(I) Catalysis: A Post-Ugi Intramolecular Hydroarylation to Azepino- and Azocino-[cd]indolones. Indium- and gold-mediated carbocyclization and heteroannulation reactions have recently been reported as mild and efficient procedures imparting high regioselectivity. Many elegant approaches involving gold-catalyzed carbocyclizations are also reported for the generation of structurally cumbersome heterocycles. Indole-based natural products that contain a tricyclic azepino- or azocino-[cd]indolone core have emerged as interesting targets for their intriguing biological activities and molecular architectures. In spite of recent advances, the synthesis of such natural products is often complicated by the lack of adequate synthetic methods for producing the tricyclic azepino- or azocino-[cd]indolone core. Considering the importance of such fused heterocycles, and our interest in indole core derivatives, we have demonstrated that indium(III) and gold(I) act as selective catalysts towards exo- and endo-dig intramolecular cyllization. In the present work and our interest in exploring the combination of metal-catalysis and multicomponent reactions, we envisaged that a post-Ugi regioselective intramolecular hydroarylation reaction could provide an expedient access to azepino- and azocino-[cd]indolone systems (Scheme 3). Employing indium(III)- or gold(I)-catalysis, the ring closure can be directed towards an exo-dig or endo-dig cyclization respectively, resulting in the formation of 7- and 8-membered ring compounds. A wide range of functional groups, introduced during Ugi reaction, is tolerated.

To further demonstrate the synthetic utility of the developed methodology, propargyl amine as the alkyne source and phenyl acetic acid were used for the synthesis of Ugi-adduct (5k). When this Ugi-adduct (5k) was subjected to the intramolecular hydroarylation employing indium(III) or gold(I) as catalysts, exclusive formation of the exo-dig cycloisomerized product (6k) was observed in 62 % and 70 % yields, respectively (Scheme 4). In both the catalytic systems the intramolecular cyclization was taking place in exo-dig manner followed by cycloisomerization.

Scheme 4. Amine as an alkyne source.

Chapter 3: Post-Ugi Gold(I) and Platinum(II) Catalyzed Intramolecular Hydroarylation to Synthesize Fused Pyrrole Derivatives.

Azepines and pyridines fused with an aryl or heteroaryl subunit represent a widely studied class of biologically interesting medium-sized ring systems. Pyrrole and indole fused heterocycles are the basic structural units of a variety of biologically interesting natural and synthetic compounds. In particular six- and seven-membered nitrogen containing heterocycles are prominently present in nature. A plethora of literature is available for the construction of these heterocyclic systems employing various multistep synthetic sequences. Although these approaches are useful for the construction of specific molecules, a general highly chemo-, regio- and stereo-selective methodology is desirable.
Recent developments in transition metal-catalyzed alkyne activation have opened the way for the synthesis of various carbocycles and heterocycles. Compared to other transition metals, the selectivity of gold- and platinum-catalysts towards alkyne activation is remarkable. Although successful, most strategies lack the aspect of diversity. One of the best ways to address this is the application of multicomponent reactions allowing the introduction of various functional groups in one step.

In the present work, which is dedicated to the development of new diversity-oriented methodologies based on transition metal-catalysis and multicomponent reactions, we developed a switch in regioselectivity using gold(I) and platinum(II) catalysts, for the formation of biologically interesting heterocycles i.e. pyridinones or azepinones. We further performed a detailed study of the scope of these protocols employing different heterocycles such as pyrrole, thiophene, benzothiophene and indole (Schemes 5 and 6).

**Scheme 5.** Synthesis of pyridinones/azepinones derivatives via intramolecular hydroarylation.

**Scheme 6.** Intramolecular hydroarylation employing different heterocycles such as benzothiophene and indole.
Recently Padwa and co-workers have reported an elegant approach comprising a
gold-catalyzed cycloisomerization of \( N \)-propargylindole-2-carboxamides and have
shown its applications for the synthesis of Lavendamycin analogues. Considering the
importance of these heterocycles, we continued with our recent work and documented
a diversity-oriented approach comprising an Ugi-4CR and a gold(I)-catalyzed
hydroarylation followed by cycloisomerization under very mild reaction conditions.
This gives direct access to the synthesis of biologically important heterocycles such as
pyrrolopyridines, pyridoindoles and azepinoindoles in very good yields (Scheme 7).

![Scheme 7. Synthesis of pyrrolopyridene and azepinoindole derivatives.](image)

**Chapter 4: An Expedient Route to Imidazo[1,4]diazepin-7-ones via a Post-Ugi
Gold-Catalyzed Heteroannulation**

The imidazodiazepinone core is ubiquitous in various natural and synthetic
pharmaceuticals as well as vital intermediates in the synthesis of pentostatin and
cofomycin, both naturally occurring anticancer and antiviral nucleosides. The
commercially available drug bretazenil is used as a partial agonist for GABA\( \_A \)
receptors due to its high affinity to the benzodiazepinone binding site. On the other
hand, flumazenil is a high affinity GABA\( \_A \)-B\( \_Z \) site antagonist that has been used
clinically to treat benzodiazepine intoxication (Figure 5). Most synthetic approaches
towards imidazo[1,4]diazepinones involve multiple step sequences, harsh conditions
and are limited in scope of the substitution pattern of the scaffold. Consequently, it
would be highly desirable to develop a more versatile and milder route for these
compounds. The MCRs may make a major contribution in this endeavors,
Furthermore the combination of MCRs with transition metal-catalysis gives access to
complex molecules in few steps as compared to traditional multistep processes.
In the present work, inspired by the literature reports and our interest in exploring the synthetic utility of both transition metal catalysis and multicomponent reactions, we have elaborated a novel diversity-oriented approach for the synthesis of interesting imidazo[1,4]diazepin-7-ones starting from readily available building blocks (Scheme 8). The first step, the Ugi-4CR, generates diversity, while the second step, an efficient gold(I)-catalyzed heteroannulation, results in the formation of the imidazo[1,4]diazepin-7-one scaffold.

Scheme 8. Synthesis of imidazodiazepinone via intramolecular heteroannulation.

Chapter 5: Design and Synthesis of Novel N-alkyl 5-benzoyl 2-pyridone Derivatives and their Biological Evaluation

2-Pyridone derivatives have attracted considerable attention because this skeleton is present in many compounds that have been isolated from natural substances. It is well-known that 2-pyridone and its derivatives are among the most popular N-heteroaromatic compounds integrated into the structures of many pharmaceutical compounds and the structural units occur in various molecules exhibiting diverse biological activities. Several drugs containing pyridone skeleton are known such as Amrinone and Milrinone or Primacor (used as cardiotonic agents for the treatment of heart failure), Ciclopirox olamine (used for the topical treatment of dermal infections), Irinotecan (used for treatment of ovarian cancer), Perampanel (used for the treatment of Parkinson’s disease), and Pirfenidone (used for the treatment of idiopathic pulmonary fibrosis). Some representatives of 2-pyridones such as ABT-719 and ABT-255 are inhibitors of bacterial DNA gyrase and topoisomerase. Our group’s previous studies on the biological activities of this class of compounds as good anti-proliferative agents have encouraged us to synthesize new analogues for improved efficacy and pharmacokinetic behavior.

The synthesis of target 2-pyridones was achieved by reacting (E)-ethyl 3-(6-chloro-4-oxo-4H-chromen-3-yl)acrylate / (E)-methyl 3-(6-chloro-4-oxo-4H-chromen-3-yl)acrylate with
various primary amines in the presence of triethylamine in ethanol at 80 °C in very good yields (Scheme 9).

![Scheme 9 Synthesis of 2-pyridone analogues.](image_url)

Starting material (E)-ethyl 3-(6-chloro-4-oxo-4H-chromen-3-yl)acrylate / (E)-methyl 3-(6-chloro-4-oxo-4H-chromen-3-yl)acrylate was synthesized starting from acylation of 4-chlorophenol followed by Fries migration giving 1-(5-chloro-2-hydroxyphenyl) ethanone in excellent yield. The 1-(5-chloro-2-hydroxyphenyl)ethanone so obtained was further subjected to Vilsmeir-Haack formylation using dimethylformamide and POCl₃. The resultant chromone carbaldehyde was then subjected to condensation reaction with malonic acid followed by the esterification reaction with conc. H₂SO₄ in excess of ethanol/methanol giving the desired ester (E)-ethyl 3-(6-chloro-4-oxo-4H-chromen-3-yl)acrylate / (E)-methyl 3-(6-chloro-4-oxo-4H-chromen-3-yl)acrylate in very good yield (Scheme 10). The 2-pyridone derivatives were then synthesized via rearrangement of chromonyl esters utilizing various amines giving novel access to N-substituted 2-pyridones.

![Scheme 10. Synthesis of (E)-methyl 3-(6-chloro-4-oxo-4H-chromen-3-yl)acrylate (6) / (E)-ethyl 3-(6-chloro-4-oxo-4H-chromen-3-yl)acrylate (7).](image_url)