DESIGN AND SYNTHESIS OF BENZENE-FUSED HETEROCYCLES:
AMINOPYRIDAZINONES, CHROMENOPYRIDINONES AND
BENZOPYRAZOLOXAZEPINES

A THESIS SUBMITTED TO
THE GRADUATE SCHOOL OF NATURAL AND APPLIED SCIENCES OF
MIDDLE EAST TECHNICAL UNIVERSITY

BY

SELBİ KESKİN

IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY
IN
CHEMISTRY

AUGUST 2015
Approval of the thesis:

**DESIGN AND SYNTHESIS OF BENZENE-FUSED HETEROCYCLES: AMINOPYRIDAZINONES, CHROMENOPYRIDINONES AND BENZOPYRAZOLOXAZEPINES**

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ABSTRACT

DESIGN AND SYNTHESIS OF BENZENE-FUSED HETEROCYCLES: AMINOPYRIDAZINONES, CHROMENOPYRIDINONES AND BENZOPYRAZOLOXAZEPINES

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August 2015, 299 pages

The interest in the synthesis of heterocyclic compounds has increased day by day due to their biological activities. This study focuses on the synthesis of different benzene-fused heterocycles. In the first part, we synthesized novel class of compounds, 4-aminophthalazin-1(2H)-ones starting from methyl 2-(2-methoxy-2-oxoethyl)-benzoate. Methylene group in this starting material was oxidized to the corresponding ketoester. Reaction of ketoesters with hydrazine derivatives provided the hydrazone derivatives. An intramolecular cyclization in the presence of thionyl chloride formed fused pyridazinone skeleton. Hydrolysis of the remaining ester groups and transformation of the acid functionalities to the acyl azides followed by Curtius rearrangement gave the isocyanates. Reaction of the isocyanates with methanol and water produced urethane and aminopyridazinone derivatives, respectively.

In the second part of this thesis, a concise and regioselective approach to the synthesis of chromenopyridine and chromenopyridinone derivatives was developed. The synthetic strategy relies on the O-propargylation of aromatic hydroxyaldehydes followed by the reaction with propargylamine. The intramolecular cycloaddition reaction between the alkyne and azadiene, which was formed as an intermediate, furnished the desired skeleton. Benzopyrazoloxazepine and benzopyrazoloxazocine skeletons were also formed via alkyne cyclization in the presence of gold catalyst.

Keywords: pyridazinone, phthalazinone, chromenopyridine, benzopyrazoloxazepine, benzopyrazoloxazocine.
ÖZ

BENZEN HALKASINA KONDENSE OLMUŞ HETEROHALKALI BİLEŞİKLERİN SENTEZLERİ İÇİN YENİ YÖNTEMLERİN GELİŞTİRİLMESİ: AMİNOFTALAZİNONLAR, KROMENOPİRİDİNONLAR VE BENZOPİRAZOLOKZAZEPİNLER

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Çalışmanın ikinci kısmında, kromenopiridinon türevlerinin sentezleri için yeni bir yöntem geliştirildi. Bu sentetik yol, ilk olarak aromatik hidroksialdehitlerin O-propargillenmesi ve bu bileşiklerin propargil amin ile reaksiyonunu içermektedir. Alkin ve azadien arasındaki molekülü siklokatılm reaksiyonu sonucunda ilgili hetero halkalı iskelet elde edildi. Ayrıca, benzopirazolokzazepin ve benzopirazolokzazosin iskeletleri de altı tuzları katalizörlüğünde molekülüси alkin halkalaşmasıyla elde edildi.

Anahtar Kelimeler: piridazinon, ftalazinon, kromenopiridinon, benzopirazolokzazepin, benzopirazolokzazosin.
ACKNOWLEDGEMENT

I would like to express my deep thanks to my supervisor Prof. Dr. Metin Balcı for his guidance, endless support, valuable advices, and encouragements. It was a great chance for me to be a student of Prof. Balcı.

I wish to thank Dr. Gani KOZA for his sincere assistance and advices through this research.

I am particularly grateful for working with SYNTHOR group, Serdal Kaya, Yasemin Altun, Merve Gökçen Bekarlar, Melek Sermin Özer, Dilem Doğan, Zeynep Ekmekçi, Benan Kılbaş, Nalan Çokol, Özlem Sari, Işıl Yenice, Sultan Aslan, Merve Sinem Özer, Çağatay Dengiz, Yasemin Dinçoflaz, Furgan Aslanoğlu, Emrah Karahan, Başak Öztürk, Selin Ceyhan, Fatih Şeybek, Dilgeş Baskın, Emre Hoplamaz, Kübra Kılıç, Meltem Tan, Nurettin Mengeş, Sinan Baçekteken, Yasin Çetinkaya, Raşit Çalışkan, Kıvılcım Şendil. Without their warm friendship, great support and assistance, this research process would have been difficult.

I would like to thank all of the members of Chemistry Department.

I would like to thank TÜBİTAK (Scientific and Technological Research Council of Turkey, Project no: TBAG 112T360 and TBAG 110R001) and ÖYP for their financial support.

Finally, my special appreciation and great gratitude is devoted to my family for their endless love, and encouragement in every moment of my life. Specially, to my sister Semra Keskin and my cousins Duygu Özdemir, Gökçe Batur for their patience, moral support.
To my beloved sister, Semra...
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LIST OF ABBREVIATIONS

**DIAD**: Diisopropyl azodicarboxylate

**DBU**: 1,8-Diazabicyclo[5.4.0]undec-7-ene

**DIPA**: Diisopropylamine

**NBS**: N-Bromosuccinimide

**AIBN**: Azobisisobutyronitrile

**APOs**: Aminophthalazinones

**DCC**: N,N’-Dicyclohexylcarbodiimide

**AHAS**: Acetohydroxyacid synthase

**RCM**: Ring Closure Metathesis

**EOMO**: Ethoxy methyl ether

**TBAF**: Tetra-\(n\)-butylammonium fluoride

**DCE**: 1,2-dichloroethane
CHAPTER 1

THE SYNTHESES OF AMINOPYRIDAZINONE DERIVATIVES

1.1 INTRODUCTION

1.1.1 Pyridazines and Pyridazinones

Pyridazine 1 and pyridazinone 2 are six-membered heterocycles which have two adjacent nitrogen atoms. The compounds having these skeleton are found in a lot of natural compounds and have a wide range of pharmaceutical activity.

It is known that pyridazines have antimicrobial,\(^1\) anti-hypertensive\(^2\) and anticancer activities.\(^3\) Pyridazinone derivatives are also well known for the treatment of cardiovascular and heart diseases.\(^4,5\) In addition, pyridazinones are used for the treatment of some diseases, such as platelet aggregation inhibitors,\(^6\) inhibitor of cyclooxygenase-2 (COX-2),\(^7\) inhibitors of adenosine 3',5'-cyclic phosphate phosphodiesterase III (CAMP PDE III),\(^8\) p38 MAP kinase inhibitors,\(^9\) and in compounds with antihypertensive, antithrombotic, antiinflammatory and antiulcer activities.\(^10,11\)

Some commercially available drugs have pyridazine 1 skeleton in their structures. For example, Brantur 3 is a drug which is used for the treatment of depression.\(^12\) Azaphen (pipofezine) 4 is the other drug that has anti-depressant activity.\(^13\)
Pyridazinones have also importance in terms of agriculture. They are widely used as herbicides to kill pests and unwanted plants. Credazine 5 containing the ether linkage between pyridazine and substituted benzene, pyrdate 6 having thiocarbonate composition and pyridafol 7 consisting alcohol unit are the examples of herbicides. 14
Brompyrazon $^{8}$ and metflurazon $^{9}$ contain amine functional group in their skeleton and also they have halides such as bromine and florine. Several pyridazinone herbicides contain carboxylic acid as well as halogen group, such as oxapyrazon $^{10}$ and flufenpyr $^{11}$.

1.1.1.1 The Synthesis of Pyridazines and Pyridazinones

Song et al.$^{18}$ used a mild and effective method for the preparation of pyridazinone derivatives (Scheme 1). They used benzene $^{12}$ and mucochloric acid $^{13}$ as the starting materials to synthesize compounds $^{16}$ via $^{14}$ and $^{15}$. The synthesized compounds were subjected to fungicidal activities in vitro against G. zeae, F. Oxysporum and C. Mandshurica. They found that compounds $^{16a}$ displayed good antifungal activities.

![Scheme 1](image)

A series of novel benzoylpyridazyl ureas were designed and synthesized starting from maleic anhydride $^{17}$ and hydrazine monohydrate by Wang and coworkers (Scheme 2).$^{19}$ They observed that these compounds exhibited larvicidal activities against oriental armyworm and in particular, compound $^{22}$ displayed comparable activity to the commercial insecticide Hexaflumuron.
Ring closing metathesis (RCM) can be used to construct aromatic heterocycles. In 2009, Donohoe et al. synthesized pyridazinone derivatives by using RCM for the first time (Scheme 3). According to this synthetic pathway, firstly, commercially available H$_2$NNHTs was allylated at the more acidic nitrogen by either selective deprotonation and reaction with an allylic halide or by a Mitsunobu reaction. Then, the resulting hydrazines was acylated on the free NH$_2$ group by reaction with acryloyl chloride to give corresponding product. Finally, these compounds were subjected to RCM using standard conditions. The RCM reaction and subsequent DBU elimination was performed in one-pot reaction and in high yields. Activation of the heterocycles with Tf$_2$O resulted in the formation of pyridazine derivative (Scheme 3).
1.1.2 Benzopyridazines and Benzopyridazinones

Benzopyridazines 28 and benzopyridazinones 29, also known as phthalazines and phthalazinones, are heterocyclic compounds that contain benzene fused pyridazine and pyridazinone skeletons.

Phthalazinone derivatives are found in skeleton of some commercially available drugs like pyridazinones. For instance, hydralazine 30 contains phthalazinone skeleton. It is used to treat hypertension for pregnant. Azelastine 31 having benzopyridazinone skeleton is a potent, second-generation histamine antagonist. Vatalanib 32 belongs to a class of drugs which block the formation of new blood vessels. Joensuu et al. determined that vatalanib is active in patients who have imatinib-resistant GIST or imatinib and sunitinib-resistant GIST.
Phthalazinone derivatives are also found as an inhibitor. For example, methylphthalazin-1-one 33 is the inhibitor of acetohydroxyacid synthase (AHAS). This enzyme accelerates the biosynthesis of branched-chain amino acids including leucine and valine.24

4-Aminophthalazin-1(2H)-ones (APOs) 34 have shown potential as anticancer agents25 and in the treatment of autoimmune and inflammatory diseases.26 Recently, 2-phenyl APOs have been reported as a decorable core skeleton for the design of potent and selective human A3 adenosine receptor antagonists.27
1.1.2.1 The Synthesis of Benzopyridazines and Benzopyridazinones

Phthalazine 41 was synthesized according to Scheme 4. Lactone 35 was nitrated and then reduced to give the aniline derivative 36. Diazotization of compound 36 in the presence of KI resulted in the formation of the iodobenzofuran 37. Trifluoromethylation of 37 gave compound 38 by using copper as a catalyst. Compound 38 was brominated and heated in the presence of hydrazine to give the phthalazine 40, which was converted to chloride 41 (Scheme 4).

Herberich \textit{et al.}\textsuperscript{29} described a concise and efficient synthesis of p38 MAP kinase inhibitor 49 having phthalazine scaffold. For this purpose, 4-bromo-2-methylbenzonitrile (42) was chosen as a starting material. In the first step, radicalic bromination of compound 42 was carried out. Then, the hydrative cyclization of 2-(di-bromomethyl)benzonitrile (43) to hydroxyisoindolinone 44 was achieved. To
construct phthalazine skeleton, hydroxyisoindolinone 44 was reacted with hydrazine hydrate in the next step. To obtain 6-bromo-1-(4-morpholinyl)phthalazine (47), firstly chlorination reaction with POCl₃ was carried out and then nucleophilic displacement of the chloride with an appropriate amine followed by Suzuki coupling with boronic ester 48 provided corresponding aminophthalazine 49 (Scheme 5).

Scheme 5

1.1.3 Cyclization with Hydrazine

Hydrazine is an inorganic compound and it is highly toxic and dangerous if it is not stored in solvent. Therefore it is mainly used as hydrazine monohydrate. It has basic property (pKa = 8.1). Hydrazines are very useful compounds for organic synthesis. For example, it is used for reduction, hydrazone formation, and deprotection of
phthalimides. In addition to these, hydrazine derivatives are usually used for the
construction of some heterocyclic compounds, such as pyrazole, indazole, and
triazoles. For instance, Hulma et al.\textsuperscript{30} synthesized a series of 3-hydroxyppyrazoles via
a tandem Ugi/debenzylation/hydrazine-mediated cyclization sequence. Ugi product \textsuperscript{54}
was initially prepared in a one-pot reaction starting from 2,4-dimethoxybenzenylamine
(\textsuperscript{50}), 4-bromobenzoic acid (\textsuperscript{51}), phenylglyoxal (\textsuperscript{52}), and 4-tert-butyl-cyclohexen-1-yl
isocyanide (\textsuperscript{53}). Subsequent treatment of \textsuperscript{54} with hydrazine mono-hydrochloride in
ethanol, accelerated by using microwave irradiation, resulted in the formation of 3-
hydroxyppyrazole \textsuperscript{55} in 45\% isolated yield. To remove 2,4-dimethoxybenzyl group
from \textsuperscript{55}, it was treated with 10\% TFA/DCE solution at 80 °C for 10 min. under
microwave irradiation and corresponding 3-hydroxyppyrazole \textsuperscript{56} was formed (Scheme 6).

\textbf{Scheme 6}

Flores-Alamo et al.\textsuperscript{31} obtained tris[2-(2H-indazol-2-yl)ethyl]amine (\textsuperscript{61}) in three steps.
In the first step, tris[N-2-(nitrobenzylideneamino)ethyl]amine (\textsuperscript{59}) was formed by
condensation between 2-nitrobenzaldehyde (\textsuperscript{57}) and tris(2-aminoethyl)amine (\textsuperscript{58})
according to literature procedure.\textsuperscript{32} Then, selective reduction of imine bonds with NaBH\textsubscript{4} in methanol gave the corresponding amine 60. To the amine solution in ethanol, Pd/C was added and the resulting mixture was refluxed for 4 h. After addition of hydrazine monohydrate, corresponding product 61 was formed (Scheme 7).

\begin{center}
\textbf{Scheme 7}
\end{center}

Zhou \textit{et al.}\textsuperscript{33} used hydrazine derivatives for cyclization reactions. Through the radical cyclization of 2-isocyanobiphenyls with hydrazine derivatives under environmentally friendly conditions, they constructed phenanthridine framework, such as 63, a common structural unit present in a wide variety of naturally occurring alkaloids (Scheme 8).
Mohana et al.\textsuperscript{34} firstly synthesized 5-(2,6-difluorophenyl)-N\textsuperscript{3}-(4-fluorophenyl)-4H-1,2,4-triazole-3,4-diamine (66) starting from 2,6-difluorobenzohydrazide (64) and 4-fluorophenylisothiocyanate and then compound 66 was reacted with fluoro substituted benzaldehydes to yield Schiff bases 67 and its different derivatives. Antiproliferative activity was evaluated for the new synthesized compounds (Scheme 9).
1.1.4 Aim of the Study

The aim of this thesis was the development of new synthetic methodologies for the synthesis of phthalazinone 71 and aminophthalazinone 74 derivatives starting from the ketomonoester 70. Firstly, the half ester 69 should be synthesized starting from the homophthalic acid 68. Ketomonoester, key compound of this study, will be obtained by the oxidation reaction (Scheme 10).

![Scheme 10](image)

After getting key compound 70, we planned to apply ring closure reaction by using hydrazine derivatives to form corresponding phthalazinone skeleton 71. After that we focused on the synthesis of aminophthalazinone 74 since the compounds having –NH or –NH₂ groups generally increases the biological activity of compounds. For this purpose, ester functionality in 71 should be firstly converted to acyl azide 72 (Scheme 11).

![Scheme 11](image)

Later, acyl azide 72 can be converted to urethane and also amine functionalities and corresponding products, 73 and 74, may be obtained (Scheme 12).
Scheme 12
1.2 RESULTS AND DISCUSSION

1.2.1 Synthesis of Phthalazinone Derivatives

1.2.1.1 Synthesis of Ketoester

To synthesize phthalazinone derivatives, commercially available homophthalic acid 68 was first reacted with thionyl chloride to give an anhydride 75 which was then treated with methanol to produce half ester 69 according to literature procedure\textsuperscript{35} (Scheme 13).

![](image1.png)

Scheme 13

A methylene group next to a carbonyl group can be oxidized to an α-diketone by using SeO\textsubscript{2} that is known as Riley oxidation (Scheme 14).\textsuperscript{36}

![](image2.png)

Scheme 14
For this conversion, the methylene group between the benzene ring and the carbonyl group in 69 was successfully oxidized to corresponding ketoester 70. Firstly, the reaction was tried in dioxane as a solvent. Unfortunately, the oxidation reaction failed. Therefore, we decided to increase reaction temperature by using different solvents. When the reaction was carried out in xylene at reflux temperature, xylene was also oxidized and the desired oxidation compound 70 could not be purified successfully. So we decided to use anisole that has higher boiling point (154 °C). Finally, treatment of half ester 69 with SeO₂ in anisole afforded the ketoester 70 in 51% yield (Scheme 15).

![Scheme 15](image_url)

### 1.2.1.2 Cyclization with Hydrazine Derivatives

Intramolecular cyclization reactions were achieved by reacting starting compound 70 with hydrazine derivatives. In this step, THF or methanol was used as a solvent depending on the hydrazine used. We used seven different hydrazine derivatives. While THF was used for the reaction with methyl hydrazine as a solvent, methanol was used for the other derivatives due to solubility problem. The formed hydrazones 78a-g were not isolated and used for further reactions. The solvent was evaporated and the acid functionalities in 78a-g were converted to acyl chlorides 79a-g by using thionyl chloride. The in situ generated acyl chlorides, 79a-g underwent intramolecular cyclization reaction by attacking of amine nitrogen atom to the carbonyl group to form the desired cyclization products 71a-g (Scheme 16).

Formation of the these bicyclic compounds 71a-g was verified by ¹H and ¹³C NMR analysis. Compound 71f has one flourine atom attached to the benzene ring. In the ¹H NMR spectrum, the singlet at 4.55 ppm belongs to the ester functionality. Also, there is an AA’BB’X system in the NMR spectrum. A part of AA’BB’X system resonates as multiplet at 7.71-7.66 ppm while B part of AA’BB’X system resonates also as
multiplet at 7.25-7.19 ppm (Figure 1). The symmetrical distribution of signals are lost due to the coupling with fluorine atom.

Scheme 16

Figure 1: $^1$H NMR Spectrum of Compound 71f
In the case of $^{13}$C-NMR spectrum of 71f, $^{19}$F coupled with $^{13}$C atoms on the benzene ring and split the $^{13}$C signals into doublet according to equation $m=2I+1$ since the spin quantum number ($I$) of $^{19}$F is $\frac{1}{2}$. The coupling constant of $^{13}$C-$^{19}$F over one bond ($^1J_{C-F}$) is largest one which is 248.1 Hz. As the distance between $^{13}$C and $^{19}$F increases, the coupling constant decreases. The coupling constant of $^{13}$C-$^{19}$F over two bonds ($^2J_{C-F}$) is 22.8 Hz. The other coupling constants, ($^3J_{C-F}$) and ($^4J_{C-F}$), are 7.3 Hz and 3.1 Hz, respectively (Figure 2).

![Figure 2: $^{13}$C NMR Spectrum of Compound 71f](image)

On the other hand, the compound 71g has two fluorine atoms attached to the phenyl ring and therefore, all the carbons of phenyl group split into doublet of doublets (Figure 3). The carbons directly attached to fluorine atoms have the largest coupling constants ($^1J$) about 251.6 and 255.7 Hz and also they show further couplings of 11.1 and 12.6 Hz, respectively due to fluorine atom in the meta-position ($^3J$). Furthermore, coupling constant of the quaternary carbon attached to the nitrogen is 22.7 Hz due to fluorine atom in ortho-position. Same carbon also has para coupling which is 3.7 Hz. The carbon that resonates at 105.1 ppm has two ortho-coupling, ($^2J = 26.4$ and 23.5 Hz).
1.2.1.3 Hydrolysis of Ester Functional Groups in 71a-g

Phthalazinone skeletons having ester functional groups 71a-g were hydrolyzed under basic conditions in THF-methanol mixture. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water. The water phase was acidified with aq. HCl, the acids 80a-g were extracted with ethyl acetate (Scheme 17). The acids 80a-g formed were analyzed by $^1$H and $^{13}$C NMR spectra. Dissapearance of peaks belonging to ester protons around 4 ppm in $^1$H NMR and 53 ppm in $^{13}$C NMR spectra was the proof of hydrolysis.
1.2.1.4 Synthesis of Acyl Azides 72a-g

Acyl azides 72a-g were synthesized starting from corresponding acid 80a-g. Firstly, these acid functionalities were converted to the corresponding acyl chlorides 81a-g to activate acid functionality by using oxalyl chloride and catalytic amount of DMF. Later, solvent was evaporated to give the acyl chlorides 81a-g.

The acyl chlorides were not isolated and reacted with NaN₃ in acetone/water to form corresponding acyl azides 72a-g (Scheme 18). The formation of acyl azides was established by IR analysis. The peak around 2100 cm⁻¹ is typical for azides and support the formation of desired conversion. In figure 4, IR Spectrum of compound 72c is shown and the peak at 2120 cm⁻¹ is the indicator of the formation of the corresponding acyl azide.
1.2.1.5 Synthesis of Isocyanates 86a-g via Curtius Rearrangement

An acyl azide 82 forms corresponding isocyanate 85 by heating. During this process, nitrogen gas is released to form acyl nitrene 84 that is an electron deficient intermediate and it rearranges to isocyanate 85 (Scheme 19). This reaction is called Curtius rearrangement.37

To apply Curtius rearrangement, the acyl azide derivatives 72a-g were dissolved in benzene, an aprotic solvent, and heated. Formed isocyanates 86a-g were not isolated. They were directly used for the next step (Scheme 20).
1.2.1.6 Synthesis of Urethanes 73a-g

Isocyanates are quite reactive. The carbon atom of isocyanate is so electrophilic that they can be trapped by various nucleophiles. The reaction of 86a-g with methanol resulted in the formation of corresponding urethane derivatives 73a-g (Scheme 21).

![Scheme 20]

Scheme 20

1.2.1.7 Synthesis of Aminophthalazinone Derivatives 74a-g

Hydrolysis of isocyanate in acidic medium resulted in the formation of corresponding amine functionality. Aminophthalazinone derivatives 86a-g were formed by addition of 8 M HCl solution to the isocyanate in benzene (Scheme 22).
To prevent the intermolecular reaction between the formed amines and unreacted isocyanates, we run this reaction under acidic condition.
CHAPTER 2

THE SYNTHESIS OF CHROMENOPYRIDINONES AND BENZOPYRAZOLOXAZEPINES

2.1 INTRODUCTION

2.1.1 Isocoumarins

Isocoumarins 87 are the heterocyclic compounds having a lactone ring fused to benzene ring. They are found in many natural products which show wide range of biological activities, such as antiallergic and antimicrobial, immunomodulatory, cytotoxic, antiinflamatory, antiangiogenic, and antimalaria. They can be isolated from plants, molds, bacteria, and lichens.

Three different isocoumarin derivatives 88-90 were isolated from Nicotiana tabacum which is a herbaceous plant in the Solanaceae that originated in the tropical Americas and cultivated worldwide as the primary commercial source of tobacco. Yang et al. prepared 70% aq. acetone extract from the roots and stems of Nicotiana tabacum and this extract was partitioned between EtOAc and H2O. The EtOAc layer was subjected to column chromatography on silica gel, RP-18 and preparative HPLC to afford compounds 88-90, three new isocoumarin derivatives which named tabaisocoumarins A–C.
Bergenin 91 is a colourless crystalline polyphenol which was isolated from medicinal plants like *Bergenia crassifolia*, *Sacoglottis gabonensis*, *Corylopsis spicata*, *Caesalpinia digyna* etc. Bergenin exhibits antihepatotoxic,\(^4^7\) anti-HIV,\(^4^8\) antiarhythmic,\(^4^9\) antioxidant,\(^5^0\) anti-inflammatory,\(^5^1\) and immunomodulatory\(^5^2\) properties.

Cytogenin 92 is a natural isocoumarin. It also has different biological activities. For example, cytogenin shows antitumor activity against a syngeneic murine transplantable tumor.\(^5^3\) In addition to this activity, there are different properties of cytogenin like antiogenic,\(^5^4\) antidiabetic\(^5^5\) activities.

Kittakopp and coworkers isolated halorosellins A 93 and B 94 which are structurally unique isocoumarin glucosides from the EtOAc extract of a broth of the marine fungus *Halorosellinia oceanica* in 2002.\(^5^6\)
2.1.1.1 The Synthesis of Coumarins

A novel fused isocoumarin skeleton has been synthesized through selective domino multicyclizations by starting from homophthalic acid 68 and 2,3-diphenylacryloyl chloride (95) at 200 °C with a catalyst under the solvent free reaction conditions. Hexacyclic fused isocoumarin framework with two stereogenic centers were assembled in a convenient one-pot synthesis in good yield (Scheme 23).

![Scheme 23](image)

A synthetic pathway has been developed for the formation of the isocoumarin cytogenin 92 and NM-3 105 by the Taylor et al. Regioselective methylation was done to give the 4-methoxy derivative followed by protection of the phenolic hydroxyl group. The reaction between the compound 100 and LDA resulted in the benzylic anion quenched with CO₂ to obtain homophthalic acids 101. In the presence of DCC, coupling with Meldrum's acid and then heating with tert-butyl alcohol in benzene at reflux temperature gave 102 including the ketoester. Lactonization was achieved by usage of LDA, through an intermediate dianion, which provided the isocoumarin 103. The compound 104 was formed by the ester enolate alkylation with methyl iodide in the presence of LDA. The product was subjected to sequential tert-butyl ester cleavage.
with HCl/isopropyl alcohol and ethoxymethyl ether removal by the treatment of TFA and finally, NM-3 105 was obtained (Scheme 24).

Scheme 24

In 2015, Li and coworkers demonstrated the sequential combination of the Passerini three-component reaction with aldol condensation starting from low-cost and readily accessible 2-formylbenzoic acid 106 and isocyanide 107 with arylglyoxals 108 (Scheme 25).58

Scheme 25
Thunberginol A 125 and B 126 are important antimicrobial, antiallergic and anticancer isocoumarines isolated from Hydrangea Dulcis Folium. Rossi et al. designed a
synthetic pathway for the synthesis of these two natural isocoumarines by iodosylation of methyl-2-(arylethynyl)benzoic acids, 110 and 111. They firstly converted the hydroxyl groups to methoxy groups to obtain 112 and 113. After that, o-hydroxy esters 114 and 115 were obtained by the usage of 1.1 equivalent of BCl3. Formed esters 114 and 115 were reacted with NaH in DMF followed by treatment with perfluoro-1-butanesulfonyl fluoride to provide 116 and 117 in high yield. Then, these nonaflates 116 and 117 were reacted with excess of 3,4-dimethylethynyl zinc chloride 118 in the presence of Pd2(dibenzylideneacetone)3 and 1,1′-bis(diphenylphosphino)ferrocene to obtain the compounds 119 and 120. Reaction between these esters and iodine in acetonitrile followed by the treatment with aqueous sodiumbisulfite resulted in the formation of 4-aryl-3-iodoisocoumarin 121 and 122. In the following step, iodine was replaced with hydrogen and then O-demethylation was achieved with BBr3 giving the isocoumarines thunberginol A 125 and B 126. Both of these compounds were found to be significantly active in the NCI 3-cell line (Scheme 26).

2.1.2 Chromenopyridine and Chromenopyridinone

Chromenopyridine 127 and chromenopyridinone 128 are heterocyclic compounds with a 2H-chromene ring and a 2H-chromen-2-one ring fused to a pyridine ring are well-known for their pharmacological properties, such as antimicrobial,61,62 antiinflammatory,61 antibacterial,63,64 antifungal,64 and anticancer65 activities.

![127](image)
![128](image)

In addition to these activities, Vu and coworkers identified the 6H-chromeno[4,3-b]quinolines 129 as a new series of estrogen receptor β-selective ligand,66 which was developed by rigidifying the 2-phenylquinoline framework.
Cheng et al. reported a novel series of small chromene-based TNF-α inhibitors. Tumor Necrosis Factor α, TNF-α, is a pro-inflammatory cytokine secreted by a variety of cells, including monocytes and macrophages, in response to many inflammatory stimuli or external cellular stress. Macromolecular TNF-α inhibitors have been shown to be useful for the treatment of autoimmune and inflammatory diseases. They were approved for reducing the sign and symptom of moderate to severe rheumatoid arthritis, psoriatic arthritis, and Crohn’s disease.

Furthermore, chromeno[4,3-b]quinoline and chromene derivatives were found to have other activities, such as fluorescent pH sensors. Lin et al. successfully synthesized two chromenoquinoline derivatives 130, 131 and studied their photophysical properties. They observed that compounds 130 and 131 with electron donating group have pKa values of 4.38 and 6.27, respectively. The favorable features of the sensor 131 include large emission ratios, high selectivity, and good reversibility. Significantly, the sensor 131 can be employed as a ratiometric fluorescent pH sensor for monitoring pH variations from neutral to acidic conditions in living cells.

Amlexanox 132 is an example of an approved drug containing a chromeno[2,3-b]pyridine framework, which is a commonly prescribed anti-allergic, and antiinflammatory properties. It has been used for treatment of asthma and aphthous
Together with its activity on nonsense mutation containing genes, the relative safety of amlexanox and its current use as an oral treatment of asthma.

![Amlexanox](image)

2.1.2.1 The Synthesis of Chromenopyridine and Chromenopyridinone

An efficient and straightforward method for the synthesis of chromeno[2,3-b]pyridines 136 via the catalyst-free, three-component condensation of 3-formylchromones 133, dialkyl acetylenedicarboxylate (134), and amines 135 was reported by Bazgir and co-workers. They obtained different derivatives in good yields (70-86%) (Scheme 27).

![Scheme 27](image)

Lee and co-workers synthesized a lot of chromenopyridine derivatives 139 and evaluated for topo I and II inhibitory activities along with cytotoxicity against several human cancer cell lines. Some of these derivatives displayed significant topo I inhibitory activity, and some of them exhibited moderate topo II inhibitory activity. Compounds having furanyl, phenyl and pyridinyl substituents 140a, 140c, 140e exhibited strong cytotoxicity (Scheme 28).

32
In 2013, Patel and coworkers developed a highly efficient and practical route for the synthesis of 2-(2-oxo-2H-chromen-3-yl)-5H-chromeno[4,3-b]pyridin-5-ones (143). They studied their antimicrobial activities and found that compounds 143a-e were the most efficient members of the series (Scheme 29).

Plas and coworkers have constructed chromenopyridinone skeleton 147 by using [4 + 2] cycloaddition reaction. The intramolecular [4 + 2] Diels–Alder cycloaddition
reactions play a very important role in the design of heterocyclic scaffolds. It requires
efficient linking of the two reacting moieties. According to their methodology, the
compound 145, synthesized from o-hydroxybenzamidine 144 in a few steps, undergo
an intramolecular Diels–Alder reaction and a subsequent retro-Diels–Alder reaction
to yield the chromenopyridines 147 (Scheme 30).

![Scheme 30](image)

Palacios et al.\textsuperscript{78} reported the synthesis of a variety of tricyclic and tetracyclic
condensed chromenopyridines using an aza-Wittig reaction of N-vinylphosphazenes
with functionalized aldehydes. In their methodology, they firstly investigated the
readily available 2-allyloxybenzaldehyde (149a) and 2-propargyloxybenzaldehyde
(149b) for aza-Wittig reaction as a model system. These aldehydes were reacted with
N-vinyl phosphazenes 148a-f in refluxing chloroform to form electronically neutral
azadienes 150a and 150b (Scheme 31).

![Scheme 31](image)

<table>
<thead>
<tr>
<th>148a</th>
<th>R = 2-furyl, R\textsuperscript{1} = Ph (E)</th>
</tr>
</thead>
<tbody>
<tr>
<td>148b</td>
<td>R = 2-thienyl, R\textsuperscript{1} = Ph (E)</td>
</tr>
<tr>
<td>148c</td>
<td>R = Ph, R\textsuperscript{1} = Ph (E)</td>
</tr>
<tr>
<td>148d</td>
<td>R = 3-pyridinyl, R\textsuperscript{1} = Ph (E)</td>
</tr>
<tr>
<td>148e</td>
<td>R = H, R\textsuperscript{1} = Ph (E, Z)</td>
</tr>
<tr>
<td>148f</td>
<td>R = H, R\textsuperscript{1} = CH\textsubscript{3} (E, Z)</td>
</tr>
</tbody>
</table>

150a R\textsuperscript{2} = allyl
150b R\textsuperscript{2} = propargyl
After formation of diene and dienophile system, heating compounds 150a and 150b at reflux temperature of xylene afforded polyheterocyclic compounds 151 through simultaneous formation of two rings (Scheme 32).

![Scheme 32](image)

More recently, a new [3 + 2 + 1] cycloaddition strategy was demonstrated using an aldehyde 149b, an aldimine of a glycine ester 152, and a terminal triple bond with AuCl$_3$ catalyst to generate novel fused-tricyclic heterocycles such as 5H-chromeno[4,3-c]pyridine 153 (Scheme 33).

![Scheme 33](image)

Recently, Singh et al. attempted to prepare 5H-chromeno[3,4-c]pyridine derivatives 157 by adopting an established strategy related to the domino Knoevenagel/Diels–Alder reaction, involving O-propargyl salicylaldehyde 149b and malononitrile or ethyl cyanoacetate or cyanoacetamide (154) (Scheme 34). Unfortunately, instead of formation of the expected product 157, the product 155 was formed.
2.1.3.1 The Synthesis of Chromenopyridine and Chromenopyridinone

The work for systematic synthesis of pyridine-fused coumarins is quite rare although the skeleton is so important for organic and medicinal chemistry. For example, Yang et al. synthesized pyridine-fused coumarins, including benzochromenopyridines 162, via a cascade reaction from chromone derivatives 160 in an environmentally friendly aqueous medium. This cascade reaction involves a chemoselective Michael addition–heterocyclization-intramolecular cyclization sequence (Scheme 35).
In 2006, Sallam and coworkers synthesized a number of new benzo[h]- and benzo[f]chromeno[2,3-b] pyridine-5-ones derivatives 164-166 starting from benzo[h]- and benzo[f]-chromone-carbonitriles 163a and 163b (Scheme 36).84

Scheme 36

Benzochromenoquinolines include benzochromenopyridine skeletons and only a few reports are available in the literature for the synthesis of 6H-chromeno[4,3-b]quinolines. Nagarajan et al.85 reported the synthesis of 6H-chromeno[4,3-b]quinolines. In their synthetic methodology, the mixture of copper(I) iodide and lanthanum triflate were used as an efficient catalyst. Especially, 8H-benzo[5,6]chromeno[4,3-b]quinoline (169) was synthesized starting from aniline (167) and O-propargylated naphthaldehyde 168 (Scheme 37).
2.1.4 Benzoazepines

Oxazepine 170 is seven-membered unsaturated heterocycle containing five carbon atoms, one nitrogen and one oxygen atom (these atom can be adjacent or not), and three double bonds. Benzoazepine 171 is a bicyclic heterocyclic compound that composed of a benzene ring fused to an oxazepine ring.

The compounds having oxazepine skeleton shows some pharmacological properties, such as antipsychotic drugs,\textsuperscript{86} anticancer,\textsuperscript{87} and anti-tumor activities\textsuperscript{88}.

Loxazepine 172 is a typical neuroleptic that shows great structural and functional homology to a typical antipsychotic clozapine 173 which belongs to class of dibenzodiazepines.\textsuperscript{89} It is used primarily in the treatment of schizophrenia. Loxazepine may be metabolized by N-methylation to amoxapine 174 which tetracyclic antidepressant of the dibenzoxapine family.
Piclozotan (SUN-N4057)\textsuperscript{90} 175 is a selective 5-HT\textsubscript{1A} receptor agonist which possess 1,4-benzoazepine scaffold and neuroprotective effects in animal studies.

\[
\text{piclozotan ~ 175}
\]

Rocastine (AHR-11325) 176 which also contains benzoxazepine skeleton, has a rapid-acting, potent, non-sedating antihistamine activity.\textsuperscript{91}

\[
\text{Rocastine ~ 176}
\]

In addition to these, SC-19220\textsuperscript{92} 177 is used as prostaglandin receptors antagonists and also the utility of dibenzo[\textit{b,f}][1,4]oxazepines has recently extended to the design of
potent progesterone receptor antagonists $^{178,93}$ TRPA1 ion channel modulators $^{179,94}$ and histone deacetylase inhibitors $^{180,95}$ p38 MAP kinase inhibitors $^{181,96}$

2.1.4.1 The Synthesis of Benzoxazepines

Buchwald and coworkers$^{97}$ designed a practical and general method for the Pd-catalyzed synthesis of dibenzodiazepines and dibenzoxazepines that are important class of heteroaromatic compounds. Their synthetic strategy includes firstly the formation of the precursor $^{184}$ starting from phenol $^{182}$ with aryl chloride $^{183}$ in the presence of picolinic acid, CuI, and K$_3$PO$_4$ in DMSO. After that, in the presence of catalytic amount of palladium, the precursor $^{184}$ generated intermediate $^{185}$ via cross-coupling with ammonia and then the corresponding dibenzoxazepine $^{186}$ was obtained (Scheme 38).

![Scheme 38](image-url)
In 2006, (E)-7-chloro-11-(4-methylpiperazin-1-yl)dibenzo[b,f][1,4]oxazepine (191) was synthesized by Leurs and coworkers. They obtained also benzodiazepine derivatives. They evaluated biological activities of the formed products. According to their results, dibenzoazepine derivative 191 is a potent H4R agonist. In their methodology, firstly, substituted fluoro acid 188 was converted to the corresponding acyl chloride by using SOCl2, which was then added to a solution of chlorinated o-aminophenol 187 and triethylamine in THF to form the respective amide intermediate 189. Ring closure of the amide was done by using NaOH in DMF. POCl3 was used to convert the benzoxazepines 191 to iminochlorides which could then reacted with N-methyl piperazine (Scheme 39).

Scheme 39

Dibenzo[b,f][1,4]oxazepine derivatives possess diverse pharmacological activities. Zaware et al. reported a new method for synthesis of dibenzo[b,f][1,4]oxazepine derivatives 195 in 2014. Seven of them were designed as analogs of the antipsychotic drug loxapine 172 and antidepressant amoxapine 174.
The key transformations include generation of a carbamate intermediate 193 using phenyl chloroformate. A microwave-induced transformation of this intermediate to various urea derivatives 194 was performed, and as a result of the subsequent phosphorous oxychloride induced cyclocondensation, final products 195 was obtained (Scheme 40).

2.1.5 Benzoxazocines

Oxazocine 196 is eight-membered heterocycle containing six carbon atoms, one nitrogen and one oxygen atom. Benzoxazocine 197 is also a bicyclic heterocyclic compound that composed of a benzene ring fused to an oxazocine ring.

Dibenzoazocine framework constitutes an important structural motif present in biologically active molecules. For example, their inhibitory activity against hepatitis
C,\textsuperscript{100} as well as CNS and antithrombotic activity,\textsuperscript{101} atropisomeric property and the NK1 antagonist activity\textsuperscript{102} are recognized.

Nefopam hydrochloride is a potent analgesic compound commercialized in most of Western Europe for over 20 years. Nefopam \textbf{198} possesses a profile distinct from that of opioids or anti-inflammatory drugs. Fernandez-Sanchez and coworkers\textsuperscript{103} reported that the analgesic nefopam hydrochloride can reduce calcium influx and effectively prevent intracellular formation of cyclic guanosine monophosphate (cGMP) and neuronal death following the activation of voltage-sensitive calcium channels in cultured cerebellar neurons. Their results are consistent with a presynaptic action of nefopam that may be of interest in reducing the excessive release of endogenous glutamate involved in neurological and neuropsychiatric disorders.\textsuperscript{103}

![Nefopam](image)

\textbf{2.1.5.1 The Synthesis of Benzoxazocine}

The benzoxazocine derivatives have received considerable attention due to their pharmacological properties. In 2011, Wahab \textit{et al.}\textsuperscript{104} synthesized diiodocoumarin and benzoxazocine derivatives and evaluated their biological activities. According to their methodology, reaction of \textbf{199} with acetone in the presence of NH\textsubscript{4}OAc or methylamine at room temperature for 7 days gave 1,3-oxazocine-5-carboxylate derivatives \textbf{202a} and \textbf{202b}. The formation of \textbf{202} indicates that the activated methylene compounds attack at the olefinic bond in \textbf{199} under Michael reaction conditions to yield a cyclic product, which followed hydrolysis by NH\textsubscript{3} or MeNH\textsubscript{2} and cyclization through the elimination of H\textsubscript{2}O (Scheme 41).\textsuperscript{104}
They found that these oxazocines 202 have an antimicrobial activity greater than that of the standard antibiotic ampicillin or the standard antifungal claforan.

The diversity-oriented synthesis of oxygen and nitrogen containing heterocycles represents an important task because of the widespread occurrence of such structural motifs and their use in drug delivery. For example, substituted benzoxazocines and pharmaceutically acceptable salts may be useful as analgesic agents and for the treatment of emesis, depression, posttraumatic stress disorders, attention deficit disorders, obsessive compulsive disorders, sexual dysfunction and centrally acting skeletal muscle relaxants. In 2009, Ramachary et al. reported for the first time the organocatalytic approach to the high yielding synthesis of functionalized benzoxazocines 207 from a three-step sequence using amine/potassium carbonate/sodium hydride/ruthenium catalysis through cascade enamine amination/iso-aromatization/O-allylation, N-allylation, and diene or enyne metathesis as key steps starting from commercially available Hagemann’s esters 203, nitrosobenzenes, allyl bromide, secondary amine and Grubbs 1st generated ruthenium catalyst (Scheme 42).
A short and high yield route to synthesize dibenz[b,f][1, 5]oxazocines 212 has been developed using Pd catalyzed intramolecular cycloamination reaction by Chattopadhyay et al. Receptor binding assay using [125I]-dynorphin demonstrated that one of the derivative showed selective κ-opioidergic property. In terms of their optimized synthetic route, the starting material 210 was prepared by benzylation of commercially available salicylaldehyde 208 with substituted 2-bromobenzyl bromide 209 in the presence of anhydrous potassium carbonate. Imine formation with aniline and subsequent NaBH₄ reduction in ethanol afforded the desired amines  in good yield. Among the various catalysts used in the synthesis of dibenzoazocines, Pd₂(di-benzylideneacetone) gave the best result for the cyclization step. Use of a proper base was also important to obtain good yield. They determined that the combined effect of KO-tBu and K₂CO₃ produced significant increase in the yield. For the investigation of solvent effect, they used different solvents (THF, EtOH, toluene, 1,4-dioxane) and suggested that toluene was the best solvent of choice. Application of the reagents Pd₂(dba), ±BINAP, and KO-t-Bu + K₂CO₃ in toluene  gave the desired product in 77% yield (Scheme 43).
2.1.6 Pyrazoles

Pyrazoles are the heterocyclic organic compounds that contain a 5-membered ring having three carbon atoms and two adjacent nitrogen atoms. There are lots of examples which include pyrazole units as core structures in the pharmaceutical industry. Some molecules containing pyrazole skeleton show antiproliferative,\textsuperscript{109} antitumor\textsuperscript{110} and antibacterial\textsuperscript{111} properties. The pyrazole ring is present as the core in a variety of leading drugs such as Celecoxib \textbf{213}, Lonazolac \textbf{214}, Rimonabant \textbf{215}.

\begin{center}
\textbf{Scheme 43}
\end{center}
2.1.6.1 The Synthesis of Pyrazoles

Importance of the pyrazole based molecules because of their biological activities attracted high attention of scientists. The wide range of methods were developed for construction of substituted pyrazoles. Generally, pyrazoles are synthesized by

- the reaction of 1,3-diketones with hydrazines,
- 1,3-dipolar cycloaddition of diazo compounds to alkynes and
- the reaction of α,β-unsaturated aldehydes and ketones with hydrazines.

Example of the reaction of 1,3-diketones 218 with hydrazines was published by Heller and coworkers in 2006. They firstly synthesized 1,3-diketones 218 as intermediates from ketones 216 and benzoyl chlorides 217 in the presence of LiHMDS. These diketones 218 were treated in situ with hydrazines to form pyrazoles 219 in good yields. Their methodology was extremely fast, general, and chemoselective (Scheme 44).

![Scheme 44](image)

One-pot synthesis of 3,5-diaryl-4-bromopyrazoles via 1,3-dipolar cycloaddition of diazo compounds and alkynyl bromides has been developed by Wei et al. The diazo compounds and alkynyl bromides were generated in situ from tosylhydrazones and gem-dibromoalkenes, respectively. When they used ketone-derived hydrazones, 3,5-diaryl-4-bromo-3H-pyrazoles 222 were obtained and the isomerization products
3,5-diaryl-4-bromo-1H-pyrazoles 223 were formed when they used aldehyde-derived hydrazones. The reaction exhibited high regioselectivity and good functional group tolerance (Scheme 45).

Scheme 45

Multisubstituted pyrazoles 226 were efficiently obtained by cyclocondensation of β-thioalkyl-α,β-unsaturated ketones (224) with hydrazines 225 in the presence of t-BuOK or HOAc in refluxing t-BuOH by Jin et al. An one-pot synthetic protocol through tandem Liebeskind–Srogl cross-coupling/cyclocondensation using α-oxoketene dithioacetals as the starting materials was also realized for the same purpose. This methodology has exhibited exclusive regioselectivity for the target products 226, generating no pyrazole tautomers (Scheme 46).

Scheme 46

2.1.7 Gold Catalyzed Alkyne Cyclization

Gold is a heavy metal in a group known as the transition metals. Among the relatively few gold compounds of practical importance are gold chloride, AuCl; gold trichloride, AuCl₃; and chlorauric acid, HAuCl₄. AuCl is in the +1 oxidation state and in the latter two, the +3 state. In recent years, there has been a revolution in the chemistry of gold.
Nowadays, there is an amazingly generous chemistry of catalysis based on gold nanoparticles and complexes. Since the prediction was made that gold would be the best catalyst for the hydrochlorination of acetylene, there has been a spectacular growth in gold-based reactions of acetylenes.\textsuperscript{116}

A number of synthetic methods for nitrogen containing heterocycles have been developed. Especially, transition metal catalyzed synthesis of heterocyclic compounds has been studied in last decade. For example, Reddy and coworkers reported that $\text{AuCl}_3$ catalyzed intramolecular cyclization reaction of $O$-alkynyloximes \textbf{227} in 1,4-dioxane at 80 °C to produce isoquinoline \textbf{230} derivative with excellent yield (Scheme 47).\textsuperscript{117}

![Scheme 47](image)

Karunakar \textit{et al.}\textsuperscript{118} have developed a straightforward one pot synthesis of 3-methylene-1-pyrrolines \textbf{233} with quaternary stereocenter and exocyclic double bonds from the reaction between N-propargylic β-enaminones \textbf{231} and arynes \textbf{232} under different reaction conditions where they also used various catalysts. Highest yield for \textbf{233} was obtained while utilizing the combination of $\text{AuClPEt}_3$ (10 mol\%) and $\text{AgSbF}_6$ (15 mol\%) in CH$_3$CN at 80 °C (Scheme 48).

![Scheme 48](image)
In 2009, Aponick and coworkers have developed an extremely mild and efficient method for the preparation of furans, pyrroles, and thiophenes by gold-catalyzed dehydrative cyclizations. The reactions were carried out by starting from very simple and readily available heteroatom-substituted propargylic alcohols. The reactions are fast, high-yielding, and easy to apply, giving essentially pure aromatic heterocycles in minutes under open-flask conditions with catalyst loadings as low as 0.05 mol % (Scheme 49).

![Scheme 49](image)

2.1.8 Aim of the Study

The aim of this part was the development of new synthetic methodologies for the synthesis of (benzo)chromenopyridinone, benzopyrazoloxazepine, and benzopyrazoloxazocine derivatives. We were interested in construction of these type of skeletons because their important pharmacological properties as well as for their fused structures. The construction of fused heterocycles are also important for the organic and pharmaceutical chemistry. Firstly, we focused on synthesis of chromenopyridinone derivatives. For this purpose, we planned to start from substituted salicylaldehydes. Firstly, O-propargylated salicylaldehydes should be synthesized starting from the substituted salicylaldehydes as the key compounds. Additionally, Sonogashira cross-coupling reaction can be used to get conjugated system with alkyne functionality (Scheme 50).
After getting the key compounds, we planned to incorporate second propargyl group into the molecule using propargylamine and then apply intramolecular cyclization reaction. At the end of these reactions, we expect to synthesize tricyclic chromenopyridine derivatives 238 via [4+2] intramolecular heterocyclization. Furthermore, we were interested in the synthesis of chromenopyridinones 239. To obtain these compounds, chromenopyridine 238 may be submitted to oxidation reaction (Scheme 51).

To explore the scope of the reaction, isomeric hydroxynaphthaldehydes can also be evaluated. Same methodology will be applied to these system to form tetracyclic benzochromenopyridinone derivatives 240-242 (Scheme 53).
In the second part of this thesis, we were interested in design of benzopyrazoloazepines which contain fused benzene, oxazepine and pyrazole ring. In the literature, there are a lot of examples showing important activities of benzoxazepine and pyrazole ring. Therefore, we planned to combine these two skeletons. We thought that this combination might increase the biological activities of compounds. For this purpose, we firstly planned to construct pyrazole skeleton that connected to benzene ring starting from salicylic acid 243 (Scheme 53).

After that, the compounds having pyrazole unit should be reacted with propargyl bromide in the presence of a base to give $O$-propargylated compounds 246. The compounds having propargyl and NH group as a nucleophilic center will be treated with gold salts or base to achieve an intramolecular cyclization reaction. At the end of this reaction we expect the formation of tricycles 247 and 248 with interesting structures (Scheme 54).
Scheme 54
2.2 RESULTS AND DISCUSSION

2.2.1 Synthesis of Chromenopyridinone Derivatives

2.2.1.1 The Synthesis of O-propargylated Aldehydes

For the construction of the chromenopyridine skeleton, firstly we synthesized 2-(prop-2-yn-1-yloxy)benzaldehyde (149b) starting from salicylaldehyde 208. Treatment of salicylaldehyde 208 with propargyl bromide in the presence of potassium carbonate afforded the compound 149b in 84% yield (Scheme 55).

For the derivatization, we used substituted salicylaldehydes. Same methodology was applied to the aldehydes, 249 and 250, having substituent at meta-position referred to aldehyde functionality. Corresponding O-propargylated products 251 and 252 were obtained in yields of 97% and 92%, respectively (Scheme 56).

![Scheme 55](image_url)

![Scheme 56](image_url)
Figure 5: $^1$H and $^{13}$C NMR Spectra of Compound 149b

Formation of these propargylated compounds was verified by $^1$H and $^{13}$C NMR spectral analysis. In the $^1$H NMR spectrum of compound 149b, there is long range
coupling ($^4J$) between methylene and alkyne protons. Therefore, the CH$_2$ protons of propargyl group resonates as doublets at 4.84 ppm while acetylenic proton resonates as triplets at 2.57 ppm. The chemical shift of acetylenic protons is found at high field because acetylene protons are located along the molecular axis, they are strongly shielded. The corresponding coupling constant ($^4J$) is 2.4 Hz. Acetylenic carbons resonate at 76.6 and 77.8 ppm in the $^{13}$C NMR spectrum. The NMR spectra of the other derivatives were also in agreement with the proposed structures. The $^1$H and $^{13}$C NMR spectra of compound 149b are shown in Figure 5.

After successful synthesis of these derivatives we decided to introduce some substituents at the terminal alkyne carbon atom to test the reactivity of disubstituted alkynes since they are usually less reactive than terminal alkynes. For the synthesis of desired aldehydes, 1-bromobut-2-ynyl (253) was used as a reagent instead of propargyl bromide. The reaction between salicylaldehyde derivatives 208, 249, and 250, and 1-bromo-2-butynyl (253) in the presence of potassium carbonate resulted in the formation of substituted alkynes 254-256 in high yields (Scheme 57).

![Scheme 57](image_url)

The characterization of these compounds was done by using $^1$H and $^{13}$C NMR spectra. In the $^1$H NMR spectrum of 254, methyl group resonates as triplet at 1.87 ppm while CH$_2$ protons resonates as quartet at 4.79 ppm. The long-range coupling constant ($^5J$) between the relevant protons was measured as 2.3 Hz. The methyl carbon atom resonates at 3.49 ppm, which is a quite high field for a terminal methyl carbon atom. This high-field resonance can be explained by the presence of methyl carbon atom in shielding zone of acetylene group. The $^1$H and $^{13}$C NMR spectra of compound 254 are given in Figure 6.
2.2.1.2 Synthesis of Conjugated Alkyne Functionalities

To test the effect of substituents conjugated with alkyne functionality, we synthesized the compounds 261 and 262. The Sonogashira cross-coupling reaction\textsuperscript{120-122} was used for the synthesis of the desired starting materials. For the Sonogashira coupling reaction, we used a palladium catalyst and a copper(I) cocatalyst in the presence of a base, in which terminal alkynes and aryl halides undergo coupling reaction. The proposed mechanism for the coupling reaction is shown in the Scheme 58.
dichloride is reduced by phosphine, amines and ethers to PdL$_2$. Oxidative addition of R$_1$-X (aryl, hetaryl, vinyl) took place to generate the activated palladium species a. On the other hand, Cu catalytic cycle provided copper acetylide b, which then participates in the transmetalation step to form c. Finally reductive elimination provided coupling product d and regeneration of palladium catalyst (Scheme 58).

\[ \text{Scheme 58} \]

We applied Sonogashira coupling to 2-(prop-2-yn-1-ylxy)benzaldehyde (149b) to generate the coupling products 257 and 258 (Scheme 59).

\[ \text{Scheme 59} \]
2.2.1.3 Construction of Chromenopyridine Skeleton via Alkyne Cyclization

After successful synthesis of the starting compound, \(O\)-propargylated salicylaldehyde 149b, we planned to incorporate the second propargyl group into the molecule and then apply intramolecular cyclization reaction between two propargyl groups to obtain chromenopyridine scaffold. For introduction of the second propargyl group, the compound 149b was reacted with the propargylamine in the presence of DBU. This reaction resulted in the formation of tricyclic product 259 instead of the formation of the expected imine 260 (Scheme 60).

![Scheme 60](image)

The structure of 259 was determined by 1D and 2D (DEPT, COSY, HSQC, and HMBC) NMR spectral data. In the \(^1\)H NMR spectrum, the methylene protons of the chromene ring resonate at 5.19 ppm as singlet and the methyl protons connected to pyridine ring also resonate at 2.36 ppm as singlet. Beside the benzene protons, there are additional two peaks in the aromatic region belonging to pyridine protons. Moreover, HMBC spectrum has important correlations for characterization of the structure. In the HMBC spectrum, we focused on the correlations of the carbon atom C-4. As expected, there are correlations between the carbon atom C-4 and the protons H-6, H-11, H-8, and CH\(_2\). These correlations support the suggested structure (Figure 7).
A tentative mechanism for the formation of 259 is outlined in Scheme 61. It is proposed that the first step is formation of the condensation product, imine 260. With this step, two alkyne functionalities were now incorporated into the starting molecule. The terminal alkyne connected to the imine group can undergo base-catalyzed isomerization to form an allene structure 261, which is conjugated with the imine double bond. Recently, we demonstrated that alkynes having similar structures can easily undergo isomerization into the corresponding allenes upon treatment with bases. Then, the intramolecular [4+2] heterocycloaddition reaction between the alkyne and the diene system (formed with the imine and allene double bond) afforded, after a 1,5-H shift, the tricyclic product 259.
2.2.1.4 Synthesis of Chromenopyridine Derivatives

Formed O-propargylated salicylaldehydes, 251 and 252, with substituents at the meta-position (referred to the aldehyde functionality), were also reacted with propargylamine in the presence of base to give the corresponding heterocyclization products, 263 and 264, in good yields (Scheme 62). We were able to show that these compounds 251 and 252 were also suitable substrates for the synthesis of chromenopyridine derivatives.

Scheme 62

Same methodology was applied to the compounds, 254-256, having methyl substituted alkyne functionality and the compounds 257 and 258 that containing conjugated systems with triple bonds. All of these compounds were treated with propargylamine in the presence of DBU at reflux temperature of ethanol and the
reactions resulted in the formation of corresponding chromenopyridine derivatives, 265-269 in good yields. Reaction times and yields are shown below (Scheme 63).

Scheme 63

2.2.2 Synthesis of Chromenopyridinone Derivatives

The second objective of this part was the synthesis of chromenopyridinone derivatives 270a-h. For this purpose, chromenopyridine derivatives 259 and 263-269 were submitted to oxidation reaction using different oxidizing agents. Firstly, selenium dioxide was used as oxidant, however, we were not able to get any oxidation product. Manganase dioxide worked, the conversion was too low although the reaction time was prolonged. Finally, we tried chromium trioxide and observed that it oxidized methylene group in chromenopyridinone skeleton most effectively. After optimization of the reaction condition, we applied this condition to all chromenopyridine derivatives and obtained chromenopyridinone derivatives 270a-h in high yields (Scheme 64).
1.2.3 Synthesis of Benzochromenopyridinone Derivatives

To explore the scope of this reaction, three isomeric hydroxynapthaldehydes 271-273 were also evaluated. These aldehydes were prepared according to literature procedures. To synthesize two of them, hydroxy-naphthalanes, 271 and 272, were chosen as starting materials. Last one was obtained by the reduction of acid functionality of the hydroxynaphtanoic acid 273 to aldehyde functionality (Scheme 65).

```
<table>
<thead>
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<th>R¹</th>
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<th>R³</th>
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</tr>
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<tr>
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<td>H</td>
<td>pyridyl</td>
<td>98</td>
</tr>
</tbody>
</table>
```

**Scheme 64**

**Scheme 65**

64
Later, the O-propargylated naphthaldehydes 277-279 were prepared from the corresponding hydroxynaphthaldehydes 274-276 by using propargyl bromide and potassium carbonate with good to excellent yields as described below (Scheme 66). Using the optimized conditions, naphthaldehydes 168 and 277-278 were treated with propargylamine and DBU under the reflux temperature of ethanol. The isomeric benzochromenopyridine derivatives 279-281 were formed in high yields (Scheme 66).

Oxidation of those compounds 279-281 with CrO3 in methylene dichloride resulted in the formation of the corresponding benzochromenopyridinone derivatives 240-242 (Scheme 67). The characterization of all compounds was done by using 1H and 13C NMR spectra.
2.2.4 Synthesis Benzopyrazoloxazepine and Benzopyrazoloxazocine Derivatives

2.2.4.1 Synthesis of Phenyl Substituted Pyrazolyl Phenol 286

To obtain fused tricyclic compound, benzopyrazoloxazepine and benzopyrazoloxazocine, we firstly planned to construct pyrazole skeleton that connected to benzene ring starting from salicylic acid 243. For this purpose, salicylic acid was converted to the acetyl salicylic acid 282. Then the formed product was treated with oxalyl chloride in the presence of catalytic amount of DMF to form acyl chloride 283 that was directly used for the next step, Sonogashira coupling reaction. First we reacted salicylic acid 243 with oxalyl chloride to obtain corresponding acyl chloride. But the reaction did not take place. We thought that the intramolecular hydrogen bonding (possible hydrogen bondings are shown below) prevents the occurrence of this reaction (Scheme 68).
Due to this reason, we decided to protect phenolic OH group by acetylation reaction and then to convert acid functionality into acyl chloride. This methodology worked and we optimized the reaction condition (Scheme 69).

Scheme 69

Acyl chloride was not isolated, it was used directly for Sonogashira coupling reaction. The reaction between acyl chloride 283 and phenylacetylene 284 in the presence of PPh₃, CuI, PdCl₂ and triethylamine resulted in the formation of corresponding ynone 285 (Scheme 70).

Scheme 70

The formation of the product 285 was verified by ¹H and ¹³C NMR analysis. In the ¹³C NMR spectrum, the peaks at 88.8 and 92.8 ppm belonging to acetylene group shows the incorporation of acetylene unit into the molecule.

To construct pyrazole skeleton 286, the compound 285 was treated with hydrazine monohydrate in methanol at reflux temperature. While forming pyrazole core, removal
of acetate group was occurred at the same time because of excess amount of hydrazine (Scheme 71).

\[
\begin{align*}
\text{285} & \xrightarrow{\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}} \text{MeOH, reflux, overnight} \quad 94\% \\
\text{286}
\end{align*}
\]

**Scheme 71**

The \(^1\)H NMR spectrum of compound 286 was completely in agreement with the proposed structure. The singlet at 6.92 ppm belongs to the proton of the pyrazole ring. Also, dissaparence of singlet belonging to acetyl protons at 2.36 ppm showed the removal of acetate group.

Proposed mechanism for the formation of pyrazolyl phenol 286 is shown above (Scheme 72). Corresponding hydrazone 287 is firstly formed. Then, the nonbonding electrons of \(\text{-NH}_2\) group attacks \(\beta\)-carbon atom of triple bond to form the intermediate 264. On the other hand, due to usage of the excess amount of hydrazine, it attacks also the carbonyl carbon of acetate group and causes the removal of acetate group to form
the corresponding product 286. The formed pyrazole ring has two tautomers as shown above.

### 2.2.4.2 Synthesis and Characterization of Precursors of Gold Catalyzed Cyclization Reaction

After construction of pyrazole ring, we planned to connect propargyl group to oxygen atom. For this purpose, propargyl bromide was used in the presence of potassium carbonate in DMF. This reaction was monitored on TLC. After completion of the reaction, two products, 290 and 291, were isolated (Scheme 73) in 76% and 24% yields, respectively.

![Scheme 73](image)

For the characterization studies of these products, we benefitted from 1D and 2D NMR spectra. The major product 290 of this reaction was easily characterized by using the $^{13}$C NMR spectrum. The signal of CH$_2$ carbon connected to the oxygen atom resonates at 56.7 ppm, while the CH$_2$ carbon connected to the nitrogen atom of the minor product 291 resonates at 39.9 ppm. As expected the inductive effects of oxygen and nitrogen atoms are responsible for this large chemical shift difference of about 17 ppm. On the other hand, two isomeric structures can be proposed for the minor product due to the resonance forms of pyrazole ring. Their structures are shown below (Scheme 74).

![Scheme 74](image)
With the help of 1D and 2D NMR spectra we were not able to distinguish between these possible structures. Firstly, we recorded the HMBC spectrum of the minor product. The methylene protons correlates with one of the quaternary carbons. This quaternary carbon atom may be the carbon atom A or B. However, this information was not enough to distinguish between those isomers.

![HMBC Spectrum of Minor Product](image)

**Figure 8: HMBC Spectrum of Minor Product**

To make a clear-cut differentiation between these isomers we decided to synthesize an unsubstituted pyrazole skeleton. In the case of a structure 293 the methylene protons should correlate with -CH=CH carbon atoms. In the case of a structure such as 294 CH\textsubscript{2} protons should correlate with the quaternary carbon of pyrazole ring (Scheme 75).

![Scheme 75](image)
2.2.4.2.1 Construction of Unsubstituted Pyrazole Skeleton and Incorporation of Propargyl Group

For the construction of unsubstituted pyrazole skeleton, we again started from the salicylic acid 243. Firstly, it was converted to acetylsalicylic acid 282. Acetyl salicylic acid 282 was treated with oxalyl chloride in the presence of DMF and corresponding acyl chloride 283 was reacted with trimethylsilylacetylene in the Sonogashira coupling condition. After the completion of the reaction, crude product was subjected to silica gel to purify the product. Two products were isolated after the column chromatography. During column chromatography, trimethylsilyl group was hydrolyzed because of the acidity of silica gel. Actually, the hydrolysis product 296 was the desired product. The unhydrolized reaction product 295 was treated with tetrabutylammonium flouride (TBAF) and was converted into 296. (Scheme 76).

![Scheme 76](image_url)

The characterization studies of compound 295 and 296 were done with the help of 1D NMR spectra. In the $^1$H NMR spectrum of compound 295, there was specific signal belonging to CH$_3$ groups of trimethylsilyl group at 0.25 ppm appearing as singlet. These methyl carbon atoms resonate at -0.6 ppm in the $^{13}$C NMR spectrum. After
hydrolysis of compound 295, the singlet in the $^1$H NMR spectrum disappeared and new signal belonging to acetylene proton appeared at 3.42 ppm in the $^1$H NMR spectrum of the hydrolysis product 296.

The reaction between compound 296 and hydrazine monohydrate resulted in the formation of our desired product 297 (Scheme 77).

![Scheme 77](image)

After construction of unsubstituted pyrazole skeleton 297, the compound was reacted with propargyl bromide in the presence of K$_2$CO$_3$ and two products, 298 and 293 were isolated (Scheme 78).

![Scheme 78](image)

These products, 298 and 293, were analyzed by using 1D and 2D NMR spectra. Firstly, we determined the skeleton of propargylated compound 293 and then the exact position of propargyl group. For this reason, the HMBC spectrum of the product was recorded (Figure 9).
Figure 9: HMBC Spectrum of Compound 293
The $^1$H NMR spectrum of 293 shows a doublet at 4.98 ppm arising from CH$_2$ protons. These protons correlate with acetylene carbons (C7 and C8) and one of the sp$^2$ hybridized carbon atom. From the HSQC spectrum (Figure 10) we were able to reveal that this sp$^2$ hybridized carbon atom belongs to the pyrazole ring. With these results in hand, we assigned the structure 293 to the minor product. In the case of a structure such as 294 a correlation between the CH$_2$ protons and a quaternary carbon atom of pyrazole ring should be observed.

Figure 10: HSQC Spectrum of Compound 293

Next, we should address the question why the propargyl group was regiospecifically bonded to one of the nitrogen atoms? We assume that the hydrogen bonding is responsible for this case. In the form A of compound 297 (Scheme 80), there is hydrogen bonding between NH proton and electronegative oxygen. On the other hand, in the form B of compound 297, there is also hydrogen bonding between OH proton and electronegative nitrogen atom. However, since the OH proton more acidic than the NH proton, the tendency of OH proton to make hydrogen bonding will be greater than the NH proton. Therefore, we assume that the structure B is dominating structure where NH proton is susceptible to proton abstraction to bond the propargyl group (Scheme 79).
2.2.4.3 Intramolecular Cyclization Reactions of O-propargylated Compounds via Gold Catalysis

After obtaining O-propargylated compound 290, we applied an intramolecular cyclization reaction by using gold catalysis. Firstly, we chose gold (III) chloride as a catalyst. This reaction was carried out in acetonitrile at room temperature and monitored on TLC. After the completion of the reaction, we isolated two products, 299 and 300. One of the product 299 had oxazocine ring while the other one 300 had oxazepine unit (Scheme 80).

Furthermore, we checked the effect of the temperature on the distribution of the products. For this purpose, the reaction temperature was raised up to 45 °C. Three products; 299, 300, and 301 were formed at this temperature. These products were separated by silica gel column chromatography and preparative TLC (Scheme 81).
The structures of these products, 299, 300, and 301 were determined by using 1D and 2D NMR spectra. There are three specific signals in the $^1$H NMR spectrum of compound 299. The CH$_2$ protons resonate at 4.87 ppm as doublet of doublets with coupling constants of $J = 3.6$ and 1.9 Hz. The larger coupling is due to the vicinal coupling, whereas the smaller coupling is arising from the allylic coupling $^4J$ with the olefinic proton. H$_b$ proton resonance at 5.42 ppm appears as doublet of triplets ($J = 9.9$ and 3.6 Hz) while H$_a$ proton resonates at 7.06 ppm as doublet of triplets ($J = 9.9$ and 1.9 Hz) as expected (Figure 11).

![Figure 11: $^1$H NMR Spectrum of Compound 299](image_url)
For the characterization of the minor product 301, 1D NMR spectra were used. The presence of a methyl signal at 2.24 ppm with a coupling constant of $J = 1.4$ Hz as well as a broad quartet resonance ($H_a$) at 6.30 ppm coupled with the methyl protons ($J = 1.4$ Hz) supported the formation of the proposed structure 301 (Figure 12). The pyrazol proton appears at 6.86 ppm as singlet.

Figure 12: $^1$H NMR Spectrum of Compound 301
Figure 13: HSQC Spectrum of Compound 300

Figure 14: $^1$H NMR Spectrum of Compound 300
The structure of the compound with the exocyclic methylene group 300 was verified by $^1$H and $^{13}$C NMR analysis. The methylene protons resonates separately at 4.95 ppm (H$_a$) and 6.06 ppm (H$_b$). Analyzing of HSQC spectrum (Figure 13) of compound 300 confirmed that the signals belonging to H$_a$ and H$_b$ correlates with the same carbon signal. The chemical shift difference is due to the presence of the H$_b$ proton in the deshielding zone of the pyrazole ring. Also, CH$_2$ protons in the ring resonates as singlet at 6.81 ppm while the pyrazole proton appears at 7.03 ppm as singlet (Figure 14).

After correct assignments of the structures, the reaction conditions were changed in order to see whether the formation of one or two products can be controlled or not. We showed that increasing of the reaction temperature from 25 ºC to 40-50 ºC resulted in the formation of 301 at the cost of 300, whereas the amount of the major product 299 did not change remarkably (Scheme 81 and Scheme 82). It is likely that the compound 301 is formed by the isomerization of 300. Therefore, the reaction temperature was increased. The exocyclic compound 300 was not observed. Two products 299 and 301 were formed in 50% yields (Scheme 82).

To show that the compound 301 is a secondary product and formed by isomerization, 300 was separately submitted to gold-catalyzed reaction under the same reaction conditions. It was shown that the reactant 300 was converted to the compound 301, quantitatively (Scheme 83).
Mechanistically, this cyclization reaction was started with coordination of gold (III) chloride with triple bond. After the coordination of gold, there were two possible centers for the attacking of nucleophilic nitrogen of pyrazole skeleton as shown below (Scheme 84). When the nitrogen atom attacks the internal carbon atom of acetylene (pathway a), compound 300 can be formed. If the reaction progresses through the pathway b, compound 299 can be formed. At high temperatures, isomerization took place and the compound 300 was converted to the compound 301.

Furthermore we were interested in the AuCl-catalyzed reaction of 290 to determine the effect of gold (I) on the distribution of the products as well as on ratio. For this reason, 290 was reacted with AuCl in acetonitrile at reflux temperature. Similarly, two products, 299 and 301, were isolated from this reaction (Scheme 85).
The compound 297 having unsubstituted pyrazole skeleton was also treated with AuCl₃. This reaction was carried out in acetonitrile at reflux temperature and monitored on TLC. After consuming of the starting material (18 h), we terminated the reaction. Three products, 302, 303, and 304, were isolated from the reaction (Scheme 86).

2.2.4.4 Synthesis and Cyclization Reactions of Conjugated Alkynes

For derivatization of these important tri- and tetracyclic compounds, the starting material 290 was submitted to Sonogashira coupling reaction. The compound 290 was reacted with iodobenzene or bromopyridine in the presence of PPh₃, CuI, PdCl₂ and DIPA in dry tetrahydrofuran under nitrogen atmosphere. These reaction were monitored on TLC. After the completion of the reactions, the corresponding coupling products 305 and 306 were isolated after column chromatography (Scheme 87).
To test the effect of substituents conjugated with alkyne functionality, the compound \(305\) was firstly treated with \(\text{AuCl}_3\) in acetonitrile at reflux temperature. Two products were formed. Careful analysis of the structures indicated the formation of products, benzopyrazolooxazepines. Unfortunately, the expected product with 8-membered ring system was not formed (Scheme 88).

Same methodology was applied to the compound \(306\). Similarly, this reaction also resulted in the formation of 7-membered ring systems \(309\) and \(310\) (Scheme 89).
We assume that Au(III) first activates the triple bond. Actually, the positive charge should be closer to the benzene ring attached to the alkyne functionality, which would support the formation of a oxazocine unit. Since oxazocine derivative is not formed, we assume that alkyne first undergoes an isomerization reaction to form the corresponding allene 311, which may be responsible for cyclization reaction. To support this proposal we decided to synthesize the allene on an independent way and to study the cyclization reaction.

**Scheme 89**

2.2.5 Intamolecular Cyclization Reaction of O-propargylated Compound Under Basic Condition

After examining the intramolecular cyclization reactions via gold salts, we decided to use a base for the cyclization. We chose NaH as a base. The reaction of compound 290 was carried out in dry DMF at rt for 18 h. Two products; 300 and 301 were formed, which were identical with those compounds formed by gold-catalyzed cyclization reaction of 290 (Scheme 90).
We realized that the eight-membered ring system was not formed under basic condition. In the light of these results, we can propose that this reaction progresses via allene intermediate. The central carbon atom of allene unit has a positive character, which can be nicely seen from the 13C NMR shift data of an allene system. The central carbon atom of allene resonates at about 200 ppm while the terminal carbons resonate at about 90 ppm (Scheme 91). It means that the middle carbon is the most electropositive carbon of an allene unit and can easily be attacked by nucleophiles.

13C Chemical Shifts in ppm

We propose that the starting material 290 of the reaction first underwent an isomerization reaction under the basic condition to form the corresponding allene 311 as the intermediate. After the formation of allene, nitrogen anion formed after proton abstraction, exclusively attacks the central carbon atom of allene due to the electropositive character. Two different carbanions may be formed depending which double bond is opened. The formed product can arise from two different intermediates. It is also possible that first 300 is formed exclusively. The product 301 may be a secondary product formed by the isomerization of 300 under the basic conditions. (Scheme 92).
Previously, we discussed the formation of \( N \)-propargylated compound \( 291 \) (Scheme 79). To test whether this compound can undergo a cyclization reaction or not, \( 291 \) was submitted to a gold-catalyzed as well as to base-catalyzed cyclization reactions under the similar conditions as discussed before. After three days, there was no change in the case of gold-catalyzed reaction. (Scheme 93).

The base-catalyzed reaction gave the corresponding allene \( 312 \) as expected. However, there was no cyclization product derived from \( 312 \) (Scheme 94).
The formation of allene was established by NMR spectral data. The $^{13}$C NMR spectrum showed resonance signal at 203.7 ppm indicating the formation of the allenic structure (Figure 15).

![NMR spectrum of Compound 312](image)

**Figure 15: $^{13}$C NMR Spectrum of Compound 312**

The cyclization reaction of compound 291 was tried at higher temperatures in DMF. Unfortunately, no cyclization product was observed.
CONCLUSION

Heterocyclic compounds are important compounds as pharmacologically and biologically. In our project, we have firstly developed a new synthetic methodology for the synthesis of phthalazinone and aminophthalazinone derivatives which might have important biological activities.

Scheme 95

87
We synthesized aminophthalazinone derivatives $74a-g$ (Scheme 95). For this synthesis, we started from the homophthalic acid $68$. Firstly, esterification was carried out to obtain compound $69$ regioselectively. After that, methylene group in $69$ was oxidized to ketone $70$ with SeO$_2$. Intramolecular cyclization was achieved by using seven different hydrazine derivatives. Hydrolysis of ester functionalities in $71a-g$ resulted in the formation of corresponding acids $80a-g$. Formed acid derivatives were converted to acyl azides $72a-g$. The acyl azides $72a-g$ were heated at reflux temperature of methanol to give the corresponding urethanes $73a-g$. On the other hand, aminophthalazinone derivatives $74a-g$ were synthesized by treatment of isocyanates with 8 M HCl. This part of the work was published in 2013.$^{129}$

In the second part of thesis, we described a concise synthetic methodology for (benzo)chromenopyridine and (benzo)chromenopyridinone derivatives which might have important biological activities. This methodology has a two step process starting from the commercial starting material, salicylaldehyde 208 (Scheme 96).

![Scheme 96](Image of Scheme 96)

This methodology was successfully extended to the synthesis of polycyclic systems. The key features of this method includes (i) the synthesis of O-propargylated benz- and naphthaldehydes; (ii) the introduction of substituents into the alkyne functionality by Sonogashira cross-coupling to obtain precursors of the cyclization reactions (Scheme 97).
(iii) Alkyne cyclization via heterocycloaddition to form the chromenopyridine scaffold; and (iv) CrO$_3$ oxidation reaction.

This synthetic strategy also represents a reasonable methodology, that will allow us to introduce various substituents into all positions of the target compounds (Scheme 98).
The structures of synthesized benzochromenopyridine and benzochromenopyridinone derivatives are shown below (Scheme 99). This part of the work was published in 2015.\textsuperscript{130}

Scheme 99

In the last part of study, we constructed benzene fused oxazepine and oxazocine units which are important heterocycles for the synthetic organic chemist. Also, the obtained compounds contain pyrazole unit. The newly synthesized compounds contain oxazepine, oxacine units as well as pyrazole units. Therefore, these compounds might have important activities. Firstly we constructed pyrazole skeleton that connected to benzene ring starting from the salicylic acid. The obtained compound 245 also have \textit{o}-hydroxy group. Propargyl group was attached to the oxygen atom in the presence of a base. Later, we succeeded in intramolecular cyclization by using gold catalys or a base via alkyne cyclization (Scheme 100).
Scheme 100
Nuclear magnetic resonance (\(^1\text{H} \text{NMR}\) and \(^{13}\text{C} \text{NMR}\)) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in DMSO-\(d_6\) and CDCl\(_3\) with TMS as internal reference. Chemical shifts (\(\delta\)) were expressed in units parts per million (ppm). Spin multiplicities were specified as singlet (s), doublet (d), doublet of doublets (dd), doublet of triplets (dt), triplet (t) and multiplet (m) and coupling constants (\(J\)) were reported in Hertz (Hz). Infrared spectra were recorded on a Bruker Platinum ATR FT-IR spectrometer and Thermo Scientific Nicolet IS10 ATR FT-IR spectrometer. Band positions were reported in reciprocal centimeter (cm\(^{-1}\)). Mass spectra were recorded by Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) LC/MS on Agilent 1200/6530. Column chromatographic separations were performed by using Merck Silica Gel 60 plates with a particle size of 0.063–0.200 mm. Thin layer chromatography (TLC) was performed by using 0.25 mm silica gel plates purchased from Merck. Compounds were named by using ChemDraw Ultra 12.0. Solvents were purified as reported in the literature.\(^{131}\)

4.2 2-[Methoxy(oxo)acetyl]benzoic acid (70)

The monoester 69 (4.0 g, 20.61 mmol) was dissolved in anisole (40 mL) and SeO\(_2\) (3.43 g, 30.93 mmol) was added. The mixture was heated at reflux temperature for 6 h. The reaction mixture was cooled, filtered, and washed with ethyl acetate (100 mL). The filtrate was evaporated. The crude product was purified by column chromatography.
(silica gel) eluting with hexane/EtOAc (5:1, 2:1) to give oxidized monoester 70 as a white solid (2.2 g, 51%), mp 72-73 °C (lit. mp 74-85 °C).\footnote{\textbf{1H NMR} (400 MHz, CDCl$_3$) $\delta$ 7.95 (dt, $J = 7.6, J = 0.8$ Hz, H$_3$), 7.77 (dt, $J = 7.5, J = 1.1$ Hz, H$_4$), 7.68 (dt, $J = 7.5, J = 1.0$ Hz, H$_6$), 7.58 (dt, $J = 7.6, J = 0.8$ Hz, H$_5$), 3.82 (s, 3H, -OCH$_3$).
\textbf{13C NMR} (100 MHz, CDCl$_3$) $\delta$ 168.3, 167.9, 167.8, 144.8, 134.9, 131.5, 127.0, 125.8, 122.9, 54.3.
\textbf{IR} (KBr, cm$^{-1}$) 3507, 3431, 3046, 2853, 1770, 1735, 1465, 1289, 1230, 1149, 1112.
\textbf{Elemental Analysis} [found: C, 57.83; H, 3.99. C$_{10}$H$_8$O$_5$ requires C, 57.70; H, 3.87%].

### 4.3 Methyl 3-methyl-4-oxo-3,4-dihydropthalazine-1-carboxylate (71a)

Methyl hydrazine (0.35 mL, 6.7 mmol) was added to a stirred solution of the monoester 70 (1.4 g, 6.7 mmol) in dry THF (25 mL) and stirred at 50 °C for 3 h. The mixture was cooled to rt, thionyl chloride (1 mL, 13.5 mmol) was added dropwise and then stirred at 50 °C for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with dichloromethane/ethyl acetate/hexane (1:1:1) to give a white solid 71a (1.0 g, 68%), mp 125-126 °C. \textbf{1H NMR} (400 MHz, CDCl$_3$) $\delta$ 8.57 (ddd, $J = 8.2, 1.2$, 0.6 Hz, H$_5$), 8.40 (ddd, $J = 8.0, 1.4$, 0.4 Hz, H$_6$), 7.79 (ddd, $J = 8.4, 7.3$, 1.5 Hz, H$_8$), 7.73 (ddd, $J = 8.0, 7.7$, 1.3, H$_7$), 3.96 (s, 3H, -OCH$_3$), 3.87 (s, 3H, -NCH$_3$). \textbf{13C NMR} (100 MHz, CDCl$_3$) $\delta$ 163.7, 159.7, 135.1, 133.6, 131.8, 128.1, 127.5, 126.9, 126.3, 53.0, 40.1. \textbf{IR} (KBr, cm$^{-1}$) 3046, 2952, 1720, 1675, 1443, 1213, 1159. \textbf{Elemental Analysis}: [found: C, 60.19; H, 4.78; N, 12.31. C$_{11}$H$_{10}$N$_2$O$_3$ requires C, 60.55; H, 4.62; N, 12.31%].

### 4.4 Methyl 4-oxo-3-phenyl-3,4-dihydropthalazine-1-carboxylate (71b)

Phenyl hydrazinium chloride (1.1 equiv) was added to a stirred solution of the monoester 70 (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 70 °C for 4 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL). Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl
acetate/hexane (1:4) to give a white solid 71b (1.1 g, 74%), mp 111-112 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.67 (dd, \(J = 8.2, 1.1, 0.4 \text{ Hz}, H_5\)), 8.56 (dd, \(J = 8.0, 1.1, 0.4 \text{ Hz}, H_8\)), 7.93 (ddd, \(J = 8.2, 7.4, 0.5 \text{ Hz}, H_6\)), 7.86 (ddd, \(J = 8.5, 7.3, 1.2 \text{ Hz}, H_7\)), 7.72-7.68 (m, \(H_2^\prime\) and \(H_6^\prime\)), 7.56-7.51 (m, \(H_3^\prime\) and \(H_5^\prime\)), 7.44 (tt, \(J = 7.4, 1.2 \text{ Hz}, H_4\)), 4.04 (s, 3H, -OCH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 163.8, 159.1, 141.4, 136.1, 134.0, 132.1, 128.9, 128.4, 128.3, 127.7, 127.6, 126.4, 125.8, 53.0. IR (KBr, cm\(^{-1}\)) 3040, 2954, 1719, 1666, 1595, 1427, 1321, 1234, 1175, 1143, 1027. **Elemental Analysis** [found: C, 68.45; H, 4.40; N, 9.95. C\(_{16}\)H\(_{12}\)N\(_2\)O\(_3\) requires C, 68.56; H, 4.32; N, 9.99%].

4.5 Methyl 3-(4-methylphenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylate (71c)

\(p\)-Tolylhydrazinium chloride (1.1 equiv) was added to a stirred solution of the monoester 70 (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 50 °C for 4 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL). Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:4) to give a white solid 71c (2.1 g, 74%), mp 152-153 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.59 (br dd, \(J = 7.9, 0.8 \text{ Hz}, H_5\)), 8.47 (dd, \(J = 7.9, 1.0 \text{ Hz}, H_8\)), 7.83 (ddd, \(J = 8.3, 7.3, 1.5 \text{ Hz}, H_6\)), 7.76 (ddd, \(J = 8.4, 7.4, 1.2 \text{ Hz}, H_7\)), 7.48-7.45 (m, \(H_2^\prime\) and \(H_6^\prime\)), 7.25-7.22 (m, \(H_3^\prime\) and \(H_5^\prime\)), 3.94 (s, 3H, -OCH\(_3\)), 2.35 (s, 3H, -CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 163.8, 159.1, 138.9, 138.3, 135.9, 133.9, 132.0, 129.5, 128.4, 127.7, 127.5, 126.3, 125.6, 53.0, 21.1. IR (KBr, cm\(^{-1}\)) 3050, 2950, 1679, 1647, 1515, 1329, 1238, 1142. **Elemental Analysis** [found: C, 69.04; H, 4.71; N, 9.40. C\(_{17}\)H\(_{14}\)N\(_2\)O\(_3\) requires C, 69.38; H, 4.79; N, 9.52%].
p-Methoxyphenylhydrazinium chloride (1.1 equiv) were added to a stirred solution of the monoester 70 (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 50 °C for 2.5 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL).

Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:9) to give a white solid 71d (0.83 g, 56%), mp 181-182 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.59 (br d, $J = 8.7$ Hz, H$_5$), 8.47 (dd, $J = 8.0$, 1.2 Hz, H$_8$), 7.83 (ddd, $J = 8.7$, 7.3, 1.4 Hz, H$_6$), 7.77 (ddd, $J = 8.3$, 7.7, 1.2 Hz, H$_7$), 7.53-7.48 (m, A-part of AA’BB’ system, H$_2$’ and H$_6$’), 6.97-6.93 (m, B-part of AA’BB’ system, H$_3$’ and H$_5$’), 3.94 (s, 3H, -OCH$_3$), 3.80 (s, 3H, -OCH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 163.8, 159.3, 159.2, 135.8, 134.4, 133.9, 132.0, 128.3, 127.7, 127.5, 127.1, 126.3, 114.1, 55.6, 53.0. IR (KBr, cm$^{-1}$) 3000, 2953, 1722, 1671, 1513, 1435, 1253, 1144, 1046. Elemental Analysis [found: C, 65.45; H, 4.84; N, 8.95. C$_{17}$H$_{14}$N$_2$O$_4$ requires C, 65.80; H, 4.55; N, 9.03%].

4.7 Methyl 3-(4-chlorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylate (71e)

$p$-Chlorophenylhydrazinium chloride (1.1 equiv) was added to a stirred solution of the monoester 70 (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 65 °C for 4 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL). Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:4) to give a white solid 71e (0.65 g, 80%), mp

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179-181 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.67 (br d, $J$ = 8.1 Hz, H$_5$), 8.55 (dd, $J$ = 7.9, 0.8 Hz, H$_8$), 7.94 (ddd, $J$ = 8.2, 7.7, 1.4 Hz, H$_6$), 7.87 (ddd, $J$ = 8.5, 7.6, 1.2 Hz, H$_7$), 7.69-7.66 (m, A-part of AA’BB’ system, H$_2'$ and H$_5'$), 7.52-7.48 (m, B-part of AA’BB’ system, H$_3'$ and H$_6'$), 4.04 (s, 3H, -OCH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.6, 159.0, 139.8, 136.4, 134.0, 132.3, 129.0, 128.2, 127.6, 127.5, 126.5, 53.1. IR (KBr, cm$^{-1}$) 3089, 2953, 1723, 1683, 1505, 1483, 1435, 1323, 1233, 1171, 1143, 1056, 1046. Elemental Analysis [found: C, 64.04; H, 3.70; N, 9.22. C$_{16}$H$_{11}$FN$_2$O$_3$ requires C, 64.43; H, 3.72; N, 9.39%].

4.8 Methyl 3-(4-fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylate (71f)

$p$-Florophenylhydrazinium chloride (1.1 equiv) were added to a stirred solution of the monoester 70 (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 65 °C for 4 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL). Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:3) to give a white solid 71f (1.05 g, 73%), mp 125-127 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.69 (br d, $J$ = 8.0 Hz, H$_5$), 8.56 (dd, $J$ = 7.9, 0.9 Hz, H$_8$), 7.93 (ddd, $J$ = 8.6, 7.4, 1.4 Hz, H$_6$), 7.88 (ddd, $J$ = 8.3, 7.4, 1.2 Hz, H$_7$), 7.71-7.66 (m, A-part of AA’BB’X system, H$_2'$ and H$_5'$), 7.25-7.19 (m, B-part of AA’BB’X system, H$_3'$ and H$_6'$), 4.05 (s, 3H, -OCH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.6, 162.1 (d, $J$ = 248.1 Hz), 159.1, 137.3 (d, $J$ = 3.0 Hz), 136.2, 134.1, 132.2, 128.3, 127.8, 127.7, 127.6 (d, $J$ = 7.3 Hz), 126.5, 115.8 (d, $J$ = 22.8), 53.1. IR (KBr, cm$^{-1}$) 3089, 2953, 1723, 1683, 1505, 1483, 1435, 1323, 1171, 1143, 1091, 1064, 1046. Elemental Analysis [found: C, 66.40; H, 3.70; N, 9.22. C$_{16}$H$_{11}$FN$_2$O$_3$ requires C, 64.43; H, 3.72; N, 9.39%].

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4.9 Methyl 3-(2,4-difluorophenyl)-4-oxo-3,4-dihydro-phthalazine-1-carboxylate (71g)

2,4-Diflorophenylhydrazinium chloride (1.1 equiv) was added to a stirred solution of the monoester 70 (1.0 g, 4.8 mmol) in dry methanol (50 mL). This mixture was stirred at 65 °C for 4 h. The solvent was evaporated and the residue was dissolved in dry benzene (70 mL). Thionyl chloride (4 equiv) was added dropwise and then the mixture was stirred for 18 h. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with ethyl acetate/hexane (1:3) to give a white solid 71f (0.5 g, 61%), mp 120-121 °C. 1H NMR (400 MHz, CDCl3) δ 8.67 (br d, J = 8.1 Hz, H6), 8.54 (dd, J = 7.7, 1.2 Hz, H5), 7.95 (dt, J = 8.3, 1.4 Hz, H8), 7.88 (br dt, J = 7.8, 0.8 Hz, H6), 7.56-7.50 (m, H7), 7.09-7.01 (m, H3 and H5), 4.04 (s, 3H, -OCH3).

13C NMR (100 MHz, CDCl3) δ 163.4, 163.0 (dd, J = 251.6, 1.1 Hz), 158.7, 157.7 (dd, J = 255.7, 12.6 Hz), 137.0, 134.3, 132.4, 129.9 (dd, J = 10.3, 1.8 Hz), 127.8, 127.8, 127.5, 126.6, 125.5 (dd, J = 13.0, 4.1 Hz), 111.9 (dd, J = 22.7, 3.7 Hz), 105.1 (dd, J = 26.4, 23.5 Hz), 53.1. IR (KBr, cm−1) 3021, 2970, 1742, 1679, 1605, 1533, 1434, 1352, 1330, 1274, 1230, 1170, 1143, 1073.

Elemental Analysis [found: C, 60.59; H, 3.32; N, 8.76. C16H10F2N2O3 requires C, 60.76; H, 3.19; N, 8.86%].

4.10 3-Methyl-4-oxo-3,4-dihydropthalazine-1-carboxylic acid (80a)

The ester 71a (1.0 g, 4.59 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 40 °C for 1.5 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried over MgSO4 and the solvent was evaporated. The acid derivative 80a was obtained as a white solid. (0.8 g, 85%), mp 246-247 °C. 1H NMR (400 MHz, DMSO-d6) δ 8.53 (br d, J = 8.1 Hz, H5), 8.27 (br d, J = 7.8 Hz, H8), 7.94 (br t, J = 7.7 Hz, H6),
7.86 (br t, J = 7.5 Hz, H7), 3.77 (s, 3H, -CH3). $^{13}$C NMR (100 MHz, DMSO-d$_6$) δ 164.4, 158.6, 135.4, 133.6, 131.9, 127.4, 126.8, 126.2, 126.0, 40.1. IR (KBr, cm$^{-1}$) 3017, 2875, 1716, 1624, 1575, 1489, 1415, 1346, 1311, 1209, 1186, 1063. **Elemental Analysis** [found: C, 58.49; H, 4.07; N, 13.43. C$_{10}$H$_8$N$_2$O$_3$ requires C, 58.82; H, 3.95; N, 13.72%].

**4.11 4-Oxo-3-phenyl-3,4-dihydrophthalazine-1-carboxylic acid (80b)**

The ester 71b (1.0 g, 3.57 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 40 °C for 1.5 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried over MgSO$_4$ and the solvent was evaporated. The acid derivative 80b was obtained as a white solid. (0.80 g, 85%), mp 217-218 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.13 (br d, J = 8.2 Hz, H$_5$), 8.48 (dd, J = 7.8, 0.8 Hz, H$_8$), 7.90 (dt, J = 7.6, 1.4 Hz, H$_6$), 7.83 (dt, J = 8.1, 1.1 Hz, H$_7$), 7.56-7.54 (m, H$_2$ and H$_6$), 7.51-7.47 (m, H$_3$ and H$_5$), 7.42 (tt, J = 7.2, 1.1 Hz, H$_4$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 161.6, 159.2, 140.1, 134.6, 133.1, 132.9, 129.2, 128.9, 128.4, 127.7, 127.6, 127.3, 125.7. IR (KBr, cm$^{-1}$) 2859, 1735, 1708, 1686, 1596, 1576, 1432, 1317, 1281, 1157, 1125; HRMS-ESI [M + Na]$^+$ calcd for C$_{15}$H$_{10}$N$_2$NaO$_3$ 267.0764, found: 267.0731.

**4.12 3-(4-Methylphenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (80c)**

The ester 71c (1.0 g, 3.4 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 40 °C for 1.5 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and
extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried over MgSO₄ and the solvent was evaporated. The acid derivative **80c** was obtained as a white solid. (1.05 g, 90%), mp 204-205 °C. **¹H NMR** (400 MHz, CDCl₃) δ 9.11 (dd, J = 8.3, 0.6 Hz, H₅), 8.47 (dd, J = 7.9, 0.9 Hz, H₈), 7.89 (ddd, J = 8.4, 7.2, 1.2 Hz, H₆), 7.82 (ddd, J = 8.3, 7.2, 1.4 Hz, H₇), 7.43-7.40 (m, A-part of AA´BB´ system, H₂ and H₆), 7.28-7.26 (m, B-part of AA´BB´ system, H₃ and H₅), 2.38 (s, 3H, -CH₃). **¹³C NMR** (100 MHz, CDCl₃) δ 162.0, 159.3, 139.0, 138.1, 134.6, 133.1, 132.8, 129.7, 128.3, 127.7, 127.4, 127.3, 125.5, 21.2. **IR** (KBr, cm⁻¹) 3003, 2970, 1738, 1705, 1682, 1510, 1433, 1320, 1250, 1183, 1171; **HRMS-MALDI** [M - H]⁺ calcd for C₁₆H₁₁N₂O₃ 279.0769; found: 279.0779.

**4.13 3-(4-Methoxyphenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (80d)**

The ester **71d** (1.0 g, 3.22 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 45 °C for 16 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried (MgSO₄) and the solvent was evaporated. The acid derivative **80d** was obtained as a white solid. (1.01 g, 87%), mp 219-220 °C. **¹H NMR** (400 MHz, DMSO-d₆) δ 8.57 (br d, J = 8.0 Hz, H₅), 8.37 (br dd, J = 7.8, 0.7 Hz, H₈), 8.02 (ddd, J = 8.4, 7.4, 1.3 Hz, H₆), 7.94 (dt, J = 8.0, 1.0 Hz, H₇), 7.56-7.52 (m, A-part of AA´BB´ system, H₂ and H₆), 7.10-7.06 (m, B-part of AA´BB´ system, H₃ and H₅), 3.83 (s, 3H, -OCH₃). **¹³C NMR** (100 MHz, DMSO-d₆) δ 164.5, 158.7, 158.4, 158.4, 158.4, 158.4, 134.3, 134.0, 132.2, 127.8, 127.5, 127.2, 126.7, 126.4, 113.8, 55.4. **IR** (KBr, cm⁻¹) 2989, 2839, 2560, 1701, 1609, 1511, 1436, 1313, 1248, 1160. **Elemental Analysis** [found: C, 64.52; H, 4.00; N, 9.28. C₁₀H₁₂N₂O₄ requires C, 64.86; H, 4.08; N, 9.46%].
4.14 3-(4-Chlorophenyl)-4-oxo-3,4-dihydropthalazine-1-carboxylic acid (80e)

The ester 71e (1.0 g, 3.17 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 60 °C for 4 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried over MgSO₄ and the solvent was evaporated. The acid derivative 80e was obtained as a white solid. (1.0 g, 74%), mp 208-209 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.58 (br d, J = 7.7 Hz, H₅), 8.39 (dd, J = 8.8, 0.9 Hz, H₈), 8.04 (dt, J = 7.3, 1.5 Hz, H₆), 7.96 (dt, J = 8.0, 1.2 Hz, H₇), 7.72-7.69 (m, A-part of AA’BB’ system, H₂ and H₆), 7.41-7.37 (m, B-part of AA’BB’ system, H₃ and H₅). ¹³C NMR (100 MHz, DMSO-d₆) δ 164.3, 158.3, 140.1, 137.1, 134.2, 132.4, 132.3, 128.6, 127.9, 127.7, 127.2, 126.7, 126.5. IR (KBr, cm⁻¹) 3003, 2970, 1738, 1683, 1484, 1431, 1372, 1319, 1230, 1154. HRMS-MALDI [M + H]^+ calcd for C₁₅H₁₀ClN₂O₃ 301.0380, found: 301.0371.

4.15 3-(4-Fluorophenyl)-4-oxo-3,4-dihydropthalazine-1-carboxylic acid (80f)

The ester 71f (1.0 g, 3.35 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 60 °C for 2 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 × 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 × 75 mL). The combined organic phases were dried over MgSO₄ and the solvent was evaporated. The acid derivative 80f was obtained as a white solid. (0.96 g, 77%), mp 215-217 °C. ¹H NMR (400 MHz, DMSO-d₆) δ 8.58 (br d, J = 8.2 Hz, H₅), 8.38 (dd, J = 7.9, 0.8 Hz, H₈), 8.04 (dt, J = 7.4, 1.4 Hz, H₆), 7.96 (dt, J = 8.2, 1.1 Hz, H₇), 7.71-7.68 (m, A-part of AA’BB’X system, H₂ and H₆), 7.41-7.37 (m, B-part of AA’BB’X system, H₃ and H₅). ¹³C NMR (100 MHz, DMSO-d₆) δ 173.1, 168.6, 167.1 (d, J = 245.6 Hz), 143.1 (d, J = 3.0 Hz), 140.5, 139.2, 138.0, 128.4 (d, J = 8.8 Hz),
127.8, 127.2, 126.7, 126.4, 115.5 (d, J = 22.8 Hz). IR (KBr, cm\(^{-1}\)) 2980, 2643, 1736, 1672, 1629, 1507, 1481, 1404, 1346, 1294, 1234, 1216, 1174, 1151, 1130, 1015.

HRMS-MALDI [M + H]\(^+\) calcd for C\(15\)H\(10\)FN\(2\)O\(3\) 285.0675, found: 285.0666.

4.16 3-(2,4-Difluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carboxylic acid (80g)

The ester 71g (1.0 g, 3.16 mmol) was dissolved in THF (50 mL), methanol (25 mL), and water (1 mL). To the resulting solution, a solution of 2 M KOH in MeOH (3 equiv) was added and stirred at 60 °C for 2 h. After the completion of the reaction, the solvent was evaporated and the residue was dissolved in water (15 mL) and extracted with ethyl acetate (3 \times 50 mL). The water phase was acidified to pH = 2 by addition of 1 M HCl and extracted with ethyl acetate (3 \times 75 mL). The combined organic phases were dried over MgSO\(_4\) and the solvent was evaporated. The acid derivative 80g were obtained as a white solid. (0.93 g, 98%), mp 225-226 °C. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) 8.57 (dd, \(J = 8.2, 0.4\) Hz, H\(_5\)), 8.37 (dd, \(J = 7.9, 0.8\) Hz, H\(_8\)), 8.07 (dt, \(J = 7.9, 1.4\) Hz, H\(_6\)), 7.98 (dt, \(J = 8.0, 1.2\) Hz, H\(_6'\)), 7.76 (dt, \(J = 8.8, 6.1\) Hz, H\(_5'\)), 7.57 (ddd, \(J = 10.4, 9.2, 2.8\) Hz, H\(_7\)), 7.35-7.30 (m, H\(_3'\)).

\(^{13}\)C NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 163.3, 161.3 (dd, \(J = 248.7, 11.5\) Hz), 157.2, 156.2 (dd, \(J = 252.7, 13.2\) Hz), 137.0, 133.7, 131.9, 130.1 (d, \(J = 10.2\) Hz), 126.5, 126.4, 125.9, 125.8, 124.8 (dd, \(J = 13.0, 4.1\) Hz), 111.4 (dd, \(J = 22.6, 3.4\) Hz), 104.0 (dd, \(J = 27.1, 24\) Hz). IR (KBr, cm\(^{-1}\)) 3079, 1730, 1658, 1615, 1604, 1511, 1352, 1274, 1229, 1177, 1159, 1148. Elemental Analysis: [found: C, 59.28; H, 2.74; N, 8.92. C\(15\)H\(8\)FN\(2\)O\(3\) requires C, 59.61; H, 2.67; N, 9.27%].

4.17 General Procedure for the Synthesis of Acyl Azide Derivatives (72a-g)

Oxalyl chloride (2 equiv) was added to a stirred suspension of acids 80a-g (1.0 g) in dichloromethane at rt and then DMF (3 drops) were added. After 10 min, all acid dissolved and the solution was stirred at rt for 90 min. The solvent and excess oxalyl chloride were evaporated. The residue was dissolved in acetone (15 mL) and cooled in an ice bath. A solution of NaN\(_3\) (2 equiv) in water (1 mL) was added dropwise and stirred in an ice-cooled bath for 90 min. The mixture was extracted with ethyl acetate (200 mL) and water (100 mL). The combined water layers were extracted with EtOAc.
(3 × 75 mL), dried over MgSO$_4$ and the solvent was evaporated. The crude product was purified by column chromatography eluting with ethyl acetate/dichloromethane/hexane (2:2:1) to give acyl azide derivatives 72a-g as white solids.

4.17.1 3-Methyl-4-oxo-3,4-dihydrophthalazine-1-carbonyl azide (72a).

(0.90 g, 81%), mp 110-111 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.75 (br d, J = 7.9 Hz, H$_5$), 8.39 (dd, J = 7.9, 1.1 Hz, H$_8$), 7.82 (ddd, J = 8.6, 7.3, 1.5 Hz, H$_7$), 7.75 (ddd, J = 8.2, 8.1, 1.2 Hz, H$_6$), 3.88 (s, 3H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.3, 159.0, 133.3, 131.8, 131.3, 127.1, 126.5, 126.2, 125.4, 39.5. IR (KBr, cm$^{-1}$) 3123, 2162, 1673, 1603, 1447, 1346, 1322, 1289, 1201, 1044.

4.17.2 4-Oxo-3-phenyl-3,4-dihydrophthalazine-1-carbonyl azide (72b)

(0.82 g, 75%), mp 87-88 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.78 (br d, J = 8.2 Hz, H$_5$), 8.47 (dd, J = 7.9, 0.9 Hz, H$_8$), 7.87 (dt, J = 7.3, 1.4 Hz, H$_6$), 7.79 (dt, J = 8.0, 1.2 Hz, H$_7$), 7.62-7.58 (m, H$_2$ and H$_6$), 7.48-7.43 (m, H$_3$ and H$_5$), 7.37 (tt, J = 7.6, 1.2 Hz, H$_4$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 169.3, 159.0, 133.3, 131.8, 131.3, 127.1, 126.5, 126.2, 125.4, 39.6. IR (KBr, cm$^{-1}$) 3038, 2924, 2140, 1681, 1595, 1488, 1344, 1318, 1227, 1185, 1126, 1075.

4.17.3 3-(4-Methylphenyl)-4-oxo-3,4-dihydrophthalazine-1-carbonyl azide (72c)

(1.05 g, 97%), mp 111-112°C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.77 (br d, J = 8.3 Hz, H$_5$), 8.45 (br d, J = 7.9 Hz, H$_8$), 7.87-7.83 (m, H$_6$), 7.80-7.75 (m, H$_7$), 7.47-7.44 (m, A-part of AA′BB′ system, H$_2$ and H$_6$), 7.26-7.24 (m, B-part of AA′BB′ system, H$_3$ and H$_5$), 2.35 (s, 3H, -CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.3,159.2,138.7, 138.6, 134.6, 134.3, 132.2, 129.6, 128.1, 127.7, 127.5, 126.2, 125.4, 21.2. IR (KBr, cm$^{-1}$) 3110, 2917, 2121, 1793, 1752, 1681, 1604, 1510, 1346, 1181, 1127.
4.17.4 3-(4-Methoxyphenyl)-4-oxo-3,4-dihydrophthalazine-1-carbonyl azide (72d) (1.01 g, 94%), mp 110-111 °C. \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.78 (dd, \( J = 8.3, 0.5 \) Hz, H\(_5\)), 8.46 (dd, \( J = 7.9, 0.9 \) Hz, H\(_8\)), 7.86 (dt, \( J = 7.3, 1.4 \) Hz, H\(_6\)), 7.78 (dt, \( J = 8.0, 1.2 \) Hz, H\(_7\)), 7.52-7.48 (m, A-part of AA`BB` system, H\(_2\)' and H\(_6\)'), 6.98-6.94 (m, B-part of AA`BB` system, H\(_3\)' and H\(_5\)'), 3.80 (s, 3H, -OCH\(_3\)). IR (KBr, cm\(^{-1}\)) 3078, 2954, 2146, 1724, 1694, 1676, 1509, 1323, 1252, 1173, 1031.

4.17.5 3-(4-Chlorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carbonyl azide (72e) (1.0 g, 92%), mp 123-124 °C. \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.77 (dd, \( J = 8.3, 0.53 \) Hz, H\(_5\)), 8.46 (dd, \( J = 7.9, 0.9 \) Hz, H\(_8\)), 7.87 (dt, \( J = 7.3, 1.4 \) Hz, H\(_6\)), 7.79 (dt, \( J = 8.0, 1.2 \) Hz, H\(_7\)), 7.60-7.56 (m, A-part of AA`BB` system, H\(_2\)' and H\(_6\)'), 7.44-7.40 (m, B part of AA`BB` system, H\(_3\)' and H\(_5\)'). IR (KBr, cm\(^{-1}\)) 3093, 2969, 2146, 1735, 1691, 1608, 1449, 1439, 1347, 1319, 1276, 1201, 1129, 1069.

4.17.6 3-(4-Fluorophenyl)-4-oxo-3,4-dihydrophthalazine-1-carbonyl azide (72f) (0.96 g, 89%), mp 117-118 °C. \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 8.78 (dd, \( J = 8.2, 0.4 \) Hz, H\(_5\)), 8.46 (ddd, \( J = 8.0, 0.7, 0.6 \) Hz, H\(_8\)), 7.90-7.85 (m, H\(_6\)), 7.82-7.78 (m, H\(_7\)), 7.62-7.56 (m, A-part of AA`BB`X system, H\(_2\)' and H\(_6\)'), 7.17-7.11 (m, B-part of AA`BB`X system, H\(_3\)' and H\(_5\)'). \( ^{13}C \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 170.2, 162.2 (d, \( J = 248.7 \) Hz), 159.1, 137.1 (d, \( J = 3.0 \) Hz), 135.0, 134.5, 132.4, 128.3, 128.0, 127.6 (d, \( J = 15.3 \) Hz), 127.4, 126.3, 115.9 (d, \( J = 22.9 \) Hz). IR (KBr, cm\(^{-1}\)) 3131, 2940, 2148, 1698, 1683, 1603, 1507, 1350, 1325, 1237, 1182, 1128, 1076.
4.17.7 3-(2,4-Difluorophenyl)-4-oxo-3,4-dihydropthalazine-1-carbonyl azide (72g)

(0.93 g, 86%), mp 104-105 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.75 (br d, $J$ = 8.4 Hz, H$_5$), 8.44 (dd, $J$ = 7.9, 0.9 Hz, H$_6$), 7.87 (dt, $J$ = 7.8, 1.4 Hz, H$_6$), 7.80 (dt, $J$ = 8.1, 1.1 Hz, H$_7$), 7.45-7.40 (m, H$_6$), 7.00-6.92 (m, H$_3$ and H$_5$). IR (KBr, cm$^{-1}$) 3092, 2969, 2146, 1692, 1607, 1507, 1481, 1346, 1319, 1276, 1201, 1179, 1129, 1109, 1069.

4.18 General Procedure for the Synthesis of Urethane Derivatives 73a-g

The acyl azide derivatives 72a-g (0.25 g) were dissolved in dry benzene (40 mL) and heated at reflux for 90 min. To this solution, dry MeOH (2 mL) was added and stirred at same temperature for 2-16 h. The reaction was monitored on TLC. The solvent and excess methanol were evaporated. The crude product was purified by column chromatography (silica gel) with suitable eluent to give urethane derivatives 73a-g as white solids.

4.18.1 Methyl (3-methyl-4-oxo-3,4-dihydropthalazin-1-yl)carbamate (73a)

(0.24 g, 96%), mp 173-174 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.38-8.35 (m, H$_8$), 7.73-7.71 (m, H$_5$, H$_6$ and H$_7$), 6.81 (b s, 1H, -NH), 3.73 (s, 3H, -OCH$_3$), 3.73 (s, 3H, -NCH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 159.4, 155.4, 137.2, 132.9, 132.0, 128.6, 127.6, 127.1, 124.7, 53.1, 39.3. IR (KBr, cm$^{-1}$) 3218, 2950, 1734, 1626, 1578, 1556, 1489, 1452, 1353, 1230, 1060. [found: C, 56.45; H, 4.83; N, 17.94. C$_{11}$H$_{11}$N$_3$O$_3$ requires C, 56.65; H, 4.75; N, 18.02%].

4.18.2 Methyl (4-oxo-3-phenyl-3,4-dihydropthalazin-1-yl)carbamate (73b)

(0.21 g, 85%), mp 175-176 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.57-8.54 (m, H$_5$), 7.90-7.86 (m, H$_6$, H$_7$ and H$_8$), 7.70-7.67 (m, H$_2$ and H$_6$), 7.54-7.50 (m, H$_3$ and H$_5$), 7.41 (tt, $J$ = 7.4, 7.4 Hz, H$_4$), 6.77 (br s, 1H, -NH), 3.85 (s, 3H, -OCH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 158.9, 155.5, 147.1, 141.4, 143.8, 133.3, 132.2, 129.3, 128.8, 127.8, 127.3, 125.6, 125.0, 53.1. IR (KBr, cm$^{-1}$) 3276, 3010, 2969, 2955, 1737,
1706, 1668, 1595, 1556, 1484, 1455, 1313, 1254, 1055. **Elemental Analysis** [found: C, 65.00; H, 4.27; N, 13.87. C₁₆H₁₃N₃O₃ requires C, 65.08; H, 4.44; N, 14.23%].

### 4.18.3 Methyl [3-(4-methylphenyl)-4-oxo-3,4-dihydropthalazin-1-yl]carbamate (73c)

(0.21 g, 80%), mp 195-196 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.43 (m, H₅), 7.77-7.70 (m, H₆, H₇ and H₈), 7.44-7.40 (m, A-part of AA’BB’ system, H₂ and H₈), 7.17 (m, B-part of AA’BB’ system, H₃ and H₅), 7.00 (br s, 1H, -NH), 3.72 (s, 3H, -OCH₃), 2.30 (s, 3H, -CH₃). **¹³C NMR** (100 MHz, CDCl₃) δ 158.9, 155.6, 138.9, 138.1, 137.8, 133.2, 132.1, 129.4, 129.3, 127.7, 127.3, 125.4, 125.0, 53.1, 21.1. **IR** (KBr, cm⁻¹) 3206, 3112, 2915, 1709, 1668, 1591, 1512, 1469, 1447, 1354, 1332, 1313, 1180, 1064. **Elemental Analysis** [found: C, 65.98; H, 4.83; N, 13.23. C₁₇H₁₅N₃O₃ requires C, 66.01; H, 4.89; N, 13.58%].

### 4.18.4 Methyl (3-(4-methoxyphenyl)-4-oxo-3,4-dihydropthalazin-1-yl)carbamate (73d)

(0.21 g, 83%), mp 153-154 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.46-8.44 (m, H₅), 7.80-7.74 (m, H₆, H₇ and H₈), 7.50-7.46 (m, A-part of AA’BB’ system, H₂ and H₈), 6.95-6.91 (m, B-part of AA’BB’ system, H₃ and H₅), 6.67 (br s, 1H, -NH), 3.79 (s, 3H, -OCH₃), 3.75 (s, 3H, -OCH₃). **¹³C NMR** (100 MHz, CDCl₃) δ 158.8, 158.7, 155.3, 137.8, 134.2, 133.0, 131.9, 129.0, 127.5, 127.1, 126.6, 124.7, 113.7, 55.3, 52.9. **IR** (KBr, cm⁻¹) 3264, 3070, 2951, 1731, 1587, 1599, 1505, 1466, 1452, 1305, 1239, 1178, 1131, 1009. **Elemental Analysis** [found: C, 62.97; H, 4.70; N, 12.88. C₁₇H₁₅N₃O₄ requires C, 62.76; H, 4.65; N, 12.92%].

### 4.18.5 Methyl (3-(4-chlorophenyl)-4-oxo-3,4-dihydropthalazin-1-yl)carbamate (73e)

(0.23 g, 92%), mp 178-179 °C. **¹H NMR** (400 MHz, CDCl₃) δ 8.45-8.43 (m, H₅), 7.82-7.74 (m, H₆, H₇ and H₈), 7.60-7.56 (m, A-part of AA’BB’ system, H₂ and H₈), 7.38-7.35 (m, B-part of AA’BB’ system, H₃ and H₅), 6.83 (s,
1H, -NH), 3.75 (s, 3H, -OCH₃). ¹³C NMR (100 MHz, CDCl₃) δ 158.8, 155.4, 139.9, 138.4, 133.5, 133.3, 132.4, 129.2, 128.8, 127.9, 127.2, 126.7, 124.9, 53.2. IR (KBr, cm⁻¹) 3221, 3053, 2969, 1705, 1668, 1597, 1524, 1485, 1327, 1249, 1173, 1132, 1069, 1041, 1021, 1009. HRMS-MALDI [M + H]⁺ calcd for C₁₆H₁₃ClN₃O₃ 330.0645, found : 330.0688.

4.18.6 Methyl (3-(4-fluorophenyl)-4-oxo-3,4-dihydrophthalazin-1-yl)carbamate (73f) (0.25 g, 99%), mp 190-192 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.44-8.42 (m, H₅), 7.79-7.74 (m, H₆, H₇ and H₈), 7.58-7.54 (m, A-part of AA’BB’X system, H₂ and H₆), 7.10-7.05 (m, B-part of AA’BB’X system, H₃ and H₅), 6.90 (s, 1H, -NH), 3.74 (s, 3H, -OCH₃). ¹³C NMR (100 MHz, CDCl₃) δ 161.7 (d, J = 246.1 Hz), 158.9, 155.4, 138.2, 137.4 (d, J = 3.0 Hz), 133.4, 132.4, 129.2, 127.8, 127.4 (d, J = 8.7 Hz), 127.3, 125.0, 115.6 (d, J = 22.7 Hz), 53.2. IR (KBr, cm⁻¹) 3221, 3072, 2923, 1705, 1665, 1587, 1556, 1504, 1454, 1324, 1256, 1213, 1140, 1058. Elemental Analysis: [found: C, 61.08; H, 4.11; N, 13.09. C₁₆H₁₁FN₃O₃ requires C, 61.34; H, 3.86; N, 13.41%].

4.18.7 Methyl (3-(2,4-difluorophenyl)-4-oxo-3,4-dihydro-phthalazin-1-yl)carbamate (73g) (0.24 g, 97%), mp 202-203 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.45-8.42 (m, H₅), 7.85-7.76 (m, H₆, H₇ and H₈), 7.45-7.40 (m, H₆), 6.97-6.90 (m, H₃ and H₅), 6.65 (s, 1H, -NH), 3.75 (s, 3H, -OCH₃). ¹³C NMR (100 MHz, CDCl₃) δ 162.7 (dd, J = 249.7, 11.0 Hz), 158.7, 156.6 (dd, J = 254.1, 12.6 Hz), 155.3, 138.8, 133.6, 132.5, 129.8 (dd, J = 10.1, 1.5 Hz), 128.7, 127.8, 127.5, 125.5 (dd, J = 12.8, 4.1 Hz), 125.3, 111.8 (dd, J = 22.5, 3.6 Hz), 105.0 (dd, J = 26.3, 23.6 Hz), 53.2. IR (KBr, cm⁻¹) 3198, 3062, 2970, 2948, 1730, 1650, 1606, 1589, 1509, 1486, 1238, 1216, 1148, 1056. Elemental Analysis: [found: C, 58.30; H, 3.44; N, 12.27. C₁₆H₁₁F₂N₃O₃ requires C, 58.01; H, 3.35; N, 12.68%].
4.19 General Procedure for the Synthesis of Aminophthalazinone Derivatives

(74a-g)

The acyl azide derivatives 72a-g (0.3 g, 0.92-1.3 mmol) were dissolved in dry benzene (30 mL) and heated at reflux for 90 min. The solution was cooled to 40 °C and HCl (10 mL, 8 M) was added. The mixture was stirred at rt for 15 min.- 4 h and then the pH value was adjusted to pH 10 by the addition of 10% NaOH solution. The mixture was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were dried over MgSO₄ and the solvent was evaporated. The crude product was purified by column chromatography eluting with ethyl acetate/dichloromethane (1:2) to give amine derivatives 74a-g as white solids.

4.19.1. 4-Amino-2-methylphthalazin-1(2H)-one (74a)

(0.18 g, 79%), mp 151-153°C. ¹H NMR (400 MHz, CDCl₃) δ 8.44-8.39 (m, H₅), 7.75-7.71 (m, H₇ and H₈), 7.62-7.58 (m, H₆), 3.65 (s, 3H, -OCH₃). ¹³C NMR (100 MHz, CDCl₃) δ 158.3, 144.6, 132.5, 131.7, 128.8, 127.7, 124.4, 122.3, 38.5. IR (KBr, cm⁻¹) 3392, 3329, 3203, 1624, 1560, 1497, 1436, 1365, 1133, 1104. HRMS-ESI [M + Na]⁺ calcd for C₉H₉N₃NaO 198.0638, found: 198.0624.

4.19.2. 4-Amino-2-phenylphthalazin-1(2H)-one (74b)

(0.19 g, 80%), mp 176-178 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.50-8.48 (m, H₅), 7.80-7.73 (m, H₇ and H₈), 7.67-7.63 (m, 6, 7.62-7.59 (m, H₂ and H₆), 7.43-7.38 (m, H₃ and H₅), 7.27 (tt, J = 7.4, 1.1 Hz, H₄), 4.13 (br s, 2H, -NH₂). ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 144.8, 141.7, 132.7, 131.6, 129.1, 128.4, 127.9, 127.1, 125.5, 124.2, 122.2. IR (KBr, cm⁻¹) 3421, 3319, 3212, 3064, 1609, 1592, 1578, 1552, 1494, 1455, 1342, 1311. HRMS-MALDI [M + H]⁺ calcd for C₁₄H₁₂N₃O 238.0980, found: 238.0996.
4.19.3. 4-Amino-2-(4-methylphenyl)phthalazin-1(2H)-one (74c)

(0.22 g, 95%), mp 208-209 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.50-8.48 (m, H\textsubscript{5}), 7.80-7.72 (m, H\textsubscript{7} and H\textsubscript{8}), 7.64-7.62 (m, H\textsubscript{6}), 7.48-7.45 (m, A-part of AA`BB` system, H\textsubscript{2`} and H\textsubscript{6`}), 7.23-7.20 (m, B-part of AA`BB` system, H\textsubscript{3`} and H\textsubscript{5`}), 4.33 (br s, 2H, -NH\textsubscript{2}), 2.32 (s, 3H, -CH\textsubscript{3}). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 158.1, 144.9, 139.6, 137.2, 132.9, 131.7, 129.4, 129.3, 128.2, 125.5, 124.5, 122.5, 21.1. IR (KBr, cm\textsuperscript{-1}) 3295, 3195, 3016, 2970, 1738, 1623, 1574, 1553, 1514, 1354, 1229, 1216, 1205. Elemental Analysis [found: C, 71.53; H, 5.09; N, 16.54. C\textsubscript{15}H\textsubscript{13}N\textsubscript{3}O requires C, 71.70; H, 5.21; N, 16.72%].

4.19.4. 4-Amino-2-(4-methoxyphenyl)phthalazin-1(2H)-one (74d)

(0.23 g, 94%), mp 274-275 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.50 (dd, \(J = 8.0, 0.8\) Hz, H\textsubscript{5}), 7.79-7.73 (m, H\textsubscript{7} and H\textsubscript{8}), 7.57-7.54 (m, H\textsubscript{6}), 7.55-7.51 (m, A-part of AA`BB` system, H\textsubscript{2`} and H\textsubscript{6`}), 6.90-6.86 (m, B part of AA`BB` system, H\textsubscript{3`} and H\textsubscript{5`}), 3.76 (s, 3H, -OCH\textsubscript{3}). \textsuperscript{13}C NMR (100 MHz, DMSO-d\textsubscript{6}) \(\delta\) 159.0, 158.1, 153.8, 138.9, 134.6, 133.3, 132.4, 129.4, 128.1, 126.8, 123.5, 114.1, 55.5. IR (KBr, cm\textsuperscript{-1}) 3247, 3144, 2839, 1683, 1666, 1650, 1630, 1561, 1508, 1469, 1447, 1323, 1308, 1249, 1170, 1028. HRMS-MALDI [M + H]\textsuperscript{+} calcd for C\textsubscript{15}H\textsubscript{14}N\textsubscript{3}O\textsubscript{2} 268.1086, found: 268.1112.

4.19.5. 4-Amino-2-(4-chlorophenyl)phthalazin-1(2H)-one (74e)

(0.24 g, 98%), mp 214-215 °C. \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 8.48-8.46 (m, H\textsubscript{5}), 7.80-7.72 (m, H\textsubscript{7} and H\textsubscript{8}), 7.64-7.61 (m, H\textsubscript{6}), 7.62-7.58 (m, A-part of AA`BB` system, H\textsubscript{2`} and H\textsubscript{6`}), 7.36-7.32 (m, B-part of AA`BB` system, H\textsubscript{3`} and H\textsubscript{5`}), 4.40 (br s, 2H, -NH\textsubscript{2}). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 158.1, 145.1, 140.5, 133.2, 132.6, 132.0, 129.3, 128.7, 128.3, 126.8, 124.5, 22.4. IR (KBr, cm\textsuperscript{-1}) 3453, 3344, 3220, 3035, 1738, 1617, 1589, 1577, 1551, 1490, 1430, 1347, 1088, 683. HRMS-MALDI [M + H]\textsuperscript{+} calcd for C\textsubscript{14}H\textsubscript{11}ClN\textsubscript{3}O 272.0591, found: 272.0586.
4.19.6. 4-Amino-2-(4-fluorophenyl)phthalazin-1(2H)-one (74f)

(0.22 g, 92%), mp 224-225 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.49-8.47 (m, H₅), 7.81-7.74 (m, H₇ and H₈), 7.65-7.62 (m, H₆), 7.61-7.58 (m, A-part of AA’BB’X system, H₂ and H₆), 7.10-7.06 (m, B-part of AA’BB’X system, H₃ and H₅), 4.36 (br s, 2H, -NH₂). ¹³C NMR (100 MHz, CDCl₃) δ 161.4 (d, J = 246.8 Hz), 158.1, 145.0, 138.0 (d, J = 3.1 Hz), 133.1, 131.9, 129.3, 128.3, 127.4 (d, J = 8.6 Hz), 124.5, 122.4, 115.4 (d, J = 22.8 Hz). IR (KBr, cm⁻¹) 3479, 3358, 3227, 3071, 1617, 1578, 1552, 1431, 1352, 1211, 1153; HRMS-MALDI [M + H]⁺ calcd for C₁₄H₁₁FN₃O 256.0886, found : 256.0888.

4.19.7. 4-Amino-2-(2,4-difluorophenyl)phthalazin-1(2H)-one (74g)

(0.23 g, 94%), mp 187-188 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.48-8.46 (m, H₅), 7.83-7.75 (m, H₇ and H₈), 7.65-7.63 (m, H₆), 7.44 - 7.39 (m, H₆), 6.97-6.87 (m, H₃ and H₅), 4.34 (br s, 2H, -NH₂). ¹³C NMR (100 MHz, CDCl₃) δ 161.4 (dd, J = 245.7, 11.1 Hz), 157.1, 156.7 (dd, J = 253.8, 12.6 Hz), 144.4, 132.3, 131.0, 128.9 (dd, J = 10.2, 2.1 Hz), 127.7, 127.2, 125.2 (dd, J = 12.9, 4.2 Hz), 123.8, 121.7, 110.7 (dd, J = 22.5, 3.7 Hz), 103.9 (dd, J = 26.3, 23.7 Hz). IR (KBr, cm⁻¹) 3469, 3343, 3220, 3071, 1738, 1621, 1579, 1553, 1507, 1453, 1429, 1357, 1269, 1253, 1141, 1099, 964. HRMS-MALDI [M + H]⁺ calcd for C₁₄H₁₀F₂N₃O 274.0792, found: 274.0790.

4.20 General Procedure for the Synthesis of Substituted 2-(Prop-2-yn-1-yloxy)benzaldehyde: Aromatic hydroxyaldehyde (10 mmol) was dissolved in 5 mL of DMF and anhydrous K₂CO₃ (12.0 mmol) was added to this solution at rt. After stirring for 20 min., propargyl bromide (11.0 mmol) was added and the resulting mixture was stirred overnight at rt. After the completion of the reaction, ethyl acetate (30 mL) was added, the organic phase was washed with water (3 × 50 mL) and then dried over MgSO₄. Removal of solvent gave the product.
4.20.1 2-(Prop-2-yn-1-yloxy)benzaldehyde (149b)

Salicylaldehyde (208) (1.0 g, 8.19 mmol) was reacted with anhydrous K₂CO₃ (1.7 g, 12.3 mmol) and propargyl bromide (1.05 mL, 9.82 mmol) as described above to give the product 149b as colorless cubic crystals from chloroform (1.1 g, 84%), mp 68-69 °C (Lit. mp, 69-70 °C¹). ¹H NMR (400 MHz, CDCl₃) δ 10.49 (s, -COH), 7.87 (dd, J = 7.7, 1.8 Hz, H₆), 7.57 (ddd, J = 8.6, 7.3, 1.8 Hz, H₄), 7.15 – 7.05 (m, H₃ and H₅), 4.84 (d, J = 2.4 Hz, H₁′), 2.57 (t, J = 2.4 Hz, C=CH). ¹³C NMR (100 MHz, CDCl₃) δ 189.6, 159.9, 135.8, 128.6, 125.6, 121.8, 113.3, 77.8, 76.6, 56.5. IR (KBr, cm⁻¹) 3270, 2887, 2117, 1678, 1594, 1456, 1286, 1221, 1191, 1006, 757, 676, 654, 609. HRMS-TOF [M - H] Calcd for C₁₀H₇O₂ 159.04515, found : 159.04432.

5-Bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (251)

5-Bromo-salicylaldehyde (249) (2.0 g, 9.95 mmol), K₂CO₃ (2.1 g, 14.9 mmol) and propargyl bromide (1.3 mL g, 11.9 mmol) were reacted as described above to give the product 251 as white needles crystals from chloroform/hexane (2.3 g, 97%), mp 94-95 °C (Lit. mp, 94-96 °C¹). ¹H NMR (400 MHz, CDCl₃) δ 10.40 (s, -COH), 7.96 (d, J = 2.6 Hz, H₆), 7.65 (dd, J = 8.9, 2.9 Hz, H₄), 7.04 (d, J = 8.9 Hz, H₃), 4.83 (d, J = 2.4 Hz, H₁′), 2.58 (t, J = 2.4 Hz, C=CH). ¹³C NMR (100 MHz, CDCl₃) δ 188.2, 158.7, 138.2, 131.3, 126.9, 115.5, 114.7, 77.3, 77.1, 56.8. IR (KBr, cm⁻¹) 3099, 3080, 2870, 2762, 2120, 1680, 1589, 1472, 1454, 1395, 1291, 1275, 1216, 1183, 1124, 1011, 927, 906, 877, 815, 784, 684, 620, 588. HRMS-TOF; [M - H] Calcd for C₁₀H₉BrO₂ 236.95567, found: 236.95485.

3-Methoxy-2-(prop-2-ynloxy)benzaldehyde (252)

3-Methoxy-salicylaldehyde (250) (2.0 g, 13.1 mmol), K₂CO₃ (2.7 g, 19.7 mmol), and propargyl bromide (1.7 mL, 15.8 mmol) were reacted as described above to give the product 252 as colorless cubic crystal from chloroform/hexane (2.3 g, 92%), mp 49-50 °C (Lit. 49-50 °C¹). ¹H NMR (400 MHz, CDCl₃) δ 10.50 (s, -COH), 7.46 (dd, J = 7.2, 2.1 Hz, H₆), 7.22 – 7.13 (m, H₅ and H₄), 4.89 (d, J = 2.4 Hz, H₁′), 3.91 (s, -OCH₃), 2.48 (t, J = 2.4 Hz, C=CH). ¹³C NMR (100 MHz, CDCl₃) δ 190.64, 152.95, 149.58, 131.25, 111
125.00, 118.97, 117.86, 77.29, 77.11, 60.94, 56.14. IR (KBr, cm⁻¹) 3266, 2950, 2890, 2838, 2118, 1476, 1437, 1383, 1317, 1266, 1250, 1202, 1178, 1066, 982, 913, 782, 749, 666, 650, 602. HRMS-TOF [M-H]⁺ Calcd for C₁₁H₉O₃ 189.0572, found: 189.05505.

4.20.4 2-(But-2-ynyloxy)benzaldehyde (254)

Salicylaldehyde (208) (0.5 g, 4.1 mmol), 1-bromobut-2-yne 253 (0.66 mL, 6.14 mmol), and K₂CO₃ (0.68 g, 4.9 mmol) in 5 mL of DMF were reacted as described above to give the product 254 as colorless oil (0.71 g, 99%). ¹H NMR (400 MHz, CDCl₃) δ 10.49 (s, -COH), 7.85 (dd, J = 7.7, 1.8 Hz, H₆), 7.56 (dd, J = 8.5, 7.4, 1.8 Hz, H₄), 7.11 (br d, J = 8.4 Hz, H₃), 7.06 (br t, J = 7.5 Hz, H₅), 4.78 (q, J = 2.3 Hz, H₁′), 1.86 (t, J = 2.3 Hz, -CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 189.5, 160.1, 135.7, 128.2, 125.3, 121.2, 113.3, 84.7, 73.4, 57.0, 3.5. IR (KBr, cm⁻¹) 2917, 2864, 2231, 1686, 1597, 1480, 1458, 1397, 1369, 1286, 1261, 1217, 1190, 1162, 1102, 1042, 995, 831, 755, 645, 595. HRMS-TOF [M+Na]⁺ Calcd for C₁₁H₉NaO₂ 197.05785, found: 197.05761.

4.20.5 5-Bromo-2-(but-2-ynyloxy)benzaldehyde (255)

5-Bromo-salicylaldehyde (249) (2.0 g, 9.95 mmol), 1-bromobut-2-yne 253 (1.05 mL, 11.9 mmol), and K₂CO₃ (2.1 g, 14.9 mmol) in 10 mL of DMF were reacted as described above to give the product 255 as white tiny needle from EtOAc (2.5 g, 99%), mp 79-80 °C. ¹H NMR (400 MHz, CDCl₃) δ 10.39 (s, -COH), 7.94 (d, J = 2.6 Hz, H₆), 7.63 (dd, J = 8.9, 2.6 Hz, H₄), 7.03 (d, J = 8.9 Hz, H₃), 4.77 (q, J = 2.3 Hz, H₁′), 1.86 (t, J = 2.3 Hz, -CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 188.4, 159.1, 138.2, 131.1, 126.9, 115.7, 114.3, 85.5, 73.0, 57.5, 3.8. IR (KBr, cm⁻¹) 2861, 2246, 1680, 1588, 1474, 1382, 1270, 1235, 1184, 1125, 989, 880, 810, 643. HRMS-TOF [M + Na]⁺ Calcd for C₁₃H₉BrNaO₂ 274.96781, found: 274.97018.
4.20.6 3-Methoxy-2-(but-2ynyloxy)benzaldehyde (256)

3-Methoxy-salicylaldehyde (250) (2.0 g, 13.1 mmol), propargyl bromide (1.4 mL, 15.8 mmol), and K$_2$CO$_3$ (2.7 g, 19.7 mmol) in 10 mL of DMF were reacted as described above to give the product 256 as white tiny needle from EtOAc/petroleum ether (2.5 g, 93%), mp 51-52 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.47 (s, -COH), 7.46 (dd, $J = 7.3, 2.1$ Hz, H$_6$), 7.19 (dd, A-part of AB system, $J = 8.1, 0.7$ Hz, H$_4$), 7.15 (dd, B-part of AB system, $J = 8.1, 2.1$ Hz, H$_4$), 4.80 (q, $J = 2.3$ Hz, H$_1'$), 3.90 (s, -OCH$_3$), 1.76 (t, $J = 2.4$ Hz, -CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.8, 153.2, 149.9, 149.3, 131.6, 124.9, 118.8, 117.8, 85.7, 74.1, 62.0, 56.1, 3.56.

IR (KBr, cm$^{-1}$) 2843, 1682, 1583, 1479, 1442, 1248, 1064, 961, 775, 746.

HRMS-TOF [M+Na]$^+$ Calcd for C$_{12}$H$_{12}$NaO$_3$ 227.06787, found: 227.06991.

4.20.7 2-[(3-Phenylprop-2-ynyl)oxy]benzaldehyde (257)

To a solution of 2-(prop-2-ynyloxy)benzaldehyde (149b) (0.8 g, 5 mmol) in dry THF (8 mL), iodosobenzene (0.6 mL, 5.5 mmol), PPh$_3$ (52 mg, 0.2 mmol), Pd(OAc)$_2$ (11 mg, 0.05 mmol), dry triethylamine (1.5 mL, 7.5 mmol) and CuI (28 mg, 0.15 mmol) were added. The resulting mixture was refluxed overnight. After the completion of the reaction, the solvent was evaporated and the reaction mixture was extracted with ethyl acetate (75 mL) and water (3 × 50 mL). The combined organic layer was washed with brine (50 mL) and dried over MgSO$_4$. After removing of solvent under vacuum, the crude product was purified by column chromatography eluting with ethyl acetate/hexane (1:8) to give 257 as white needle-like crystals from chloroform/hexane (crude yield: 0.96 g, 81%, pure isolated yield: 0.65 g, 55%), mp 79-80 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.53 (s, -COH), 7.88 (dd, $J = 7.7, 1.8$ Hz, H$_6$), 7.59 (ddd, $J = 8.5, 7.4, 1.8$ Hz, H$_4$), 7.45 – 7.40 (m, H$_2$ and H$_6$), 7.36 – 7.28 (m, H$_5$, H$_5$ and H$_3$), 7.21 (br d, $J = 8.4$ Hz, H$_3$), 7.09 (br t, $J = 7.5$ Hz, H$_4$), 5.06 (s, -CH$_2$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 189.8, 160.2, 135.8, 131.9 (2 C), 129.1, 128.7, 128.5 (2 C), 125.8, 122.0, 121.7, 113.6, 88.2, 83.1, 57.5. IR (KBr, cm$^{-1}$) 2888, 1679, 1596, 1479, 1459, 1400, 1284, 1222, 1005, 958, 757, 687. HRMS-TOF [M+Na]$^+$ Calcd for C$_{16}$H$_{12}$NaO$_2$ 259.07295, found: 259.07528.
4.20.8 2-[(3-Pyridin-2-ylprop-2-ynyl)oxy]benzaldehyde (258)

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2-(Prop-2-ynyloxy)-benzaldehyde (149b) (0.8 g, 5 mmol), 2-bromopyridine (1.4 mL, 6 mmol), PPh3 (52 mg, 0.2 mmol), Pd(OAc)2 (11 mg, 0.05 mmol), dry triethylamine (1.5 mL, 7.5 mmol) and CuI (28 mg, 0.15 mmol) in THF (7 mL) were reacted as described above. The residue was purified by column chromatography eluting with ethyl acetate/hexane (1:4 to 1:1) to give the product 258 as white needle-like crystals from chloroform/hexane (1.14 g; NMR yield: 96%, 0.81 g; isolated yield: 69%), mp 103-104 °C. 1H NMR (400 MHz, CDCl3) δ 10.53 (s, -COH), 8.58 (ddd, J = 4.9, 1.8, 0.9 Hz, H6′′), 7.87 (dd, J = 7.7, 1.8 Hz, H6), 7.66 (dt, J = 1.8, 7.8 Hz, H3), 7.59 (ddd, J = 8.6, 7.3, 1.8 Hz, H4′′), 7.43 (dt, J = 1.0, 7.4 Hz, H3′′), 7.29 – 7.24 (m, H4), 7.21 (br d, J = 8.4 Hz, H3′′), 7.12-7.07 (br t, J = 7.4, H5), 5.09 (s, -CH2). 13C NMR (100 MHz, CDCl3) δ 189.6, 160.0, 150.2, 142.3, 136.4, 135.9, 128.7, 127.5, 125.6, 123.6, 121.8, 113.4, 87.2, 82.9, 57.0. IR (KBr, cm⁻¹) 2858, 1682, 1600, 1464, 1379, 1239, 995, 985, 844, 761. HRMS-TOF [M-H] Calcd for C15H10NaNO2 260.0682, found: 260.07134.

4.21 General Procedure for Cyclization of Substituted Aldehydes with Propargylamine.

Substituted benzaldehyde (5 mmol) was dissolved in 15 mL of ethanol. To this solution, DBU (0.8 mL, 5 mmol) and propargylamine (0.66 mL, 10.44 mmol) was added at room temperature and the resulting mixture was refluxed for 2 days. The reaction was monitored on TLC. After the completion of the reaction, the solvent was evaporated and the residual product was dissolved in ethyl acetate (50 mL). The organic solution was washed with water (3 × 50 mL) and brine (50 mL). The combined organic extracts were dried over MgSO4. Removal of the solvent gave the crude product which was crystallized from suitable solvents to give the product.

4.21.1 3-Methyl-5H-chromeno[4,3-b]pyridine (259)

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2-(Prop-2-ynyloxy)benzaldehyde (149b) (0.5 g, 3.12 mmol), DBU (0.47 mL, 3.12 mmol), and propargylamine (0.4 mL, 6.27 mmol) were reacted as described above. The crude product was crystallized from CHCl3/petroleum ether to give 259 as white crystals (580 mg, 94%), mp 174-176 °C. 1H NMR (400 MHz, CDCl3) δ 8.41 (br d, J
= 1.2 Hz, H2), 8.19 (dd, J = 7.7, 1.5 Hz, H10), 7.29 (ddd, J = 8.1, 7.5, 1.7 Hz, H8), 7.25 (s, H4), 7.10 (dt, J = 1.1, 7.6 Hz, H9), 6.96 (dd, J = 8.1, 1.0 Hz, H7), 5.19 (s, H5), 2.36 (s, -CH3). 13C NMR (100 MHz, CDCl3) δ 156.2, 149.8, 146.2, 132.8, 132.4, 131.0, 125.9, 124.5, 123.3, 122.5, 117.1, 68.0, 18.5. IR (KBr, cm⁻¹) 2920, 1719, 1605, 1455, 1254, 1174, 1151, 936, 751. HRMS-TOF [M + H]⁺ Calcd for C13H12NO 198.09134, found: 198.09148.

4.21.2 9-Bromo-3-methyl-5H-chromeno[4,3-b]pyridine (263)

![Diagram of 9-Bromo-3-methyl-5H-chromeno[4,3-b]pyridine](image)

5-Bromo-2-(prop-2-ynyloxy)benzaldehyde (251) (0.4 g, 1.67 mmol), DBU (0.25 mL, 1.67 mmol) and propargylamine (0.22 mL, 3.34 mmol) in 10 mL of ethanol were reacted as described above (reflux overnight) to give 263 as white cubic crystals from EtOH/petroleum ether (420 mg, 91%), mp 91-93 °C. 1H NMR (400 MHz, CDCl3) δ 8.40 (br s, H2), 8.30 (d, J = 2.5 Hz, H10), 7.36 (dd, J = 8.6, 2.5 Hz, H8), 7.25 (br s, H4), 6.83 (d, J = 8.6 Hz, H7), 5.18 (s, H5), 2.37 (s, -CH3); 13C NMR (100 MHz, CDCl3) δ 155.1, 150.0, 144.9, 133.4, 133.1, 132.8, 127.1, 125.7, 125.0, 118.8, 115.0, 68.0, 18.5. IR (KBr, cm⁻¹) 2917, 1685, 1586, 1456, 1259, 1216, 1026, 875, 809, 750. HRMS-TOF [M + H]⁺ Calcd for C13H11BrNO 276.00185, found: 275.99979.

4.21.3 7-Methoxy-3-methyl-5H-chromeno[4,3-b]pyridine (264)

![Diagram of 7-Methoxy-3-methyl-5H-chromeno[4,3-b]pyridine](image)

3-Methoxy-2-(prop-2-ynyloxy)-benzaldehyde (252) (0.4 g, 2.1 mmol), DBU (0.31 mL, 2.1 mmol) and propargylamine (0.27 mL, 4.2 mmol) in 10 mL of ethanol were reacted as described above (reflux overnight) to give the product 264 as white needles from EtOH (0.45 g, 94%), mp 105-106 °C. 1H NMR (400 MHz, CDCl3) δ 8.50 (s, H2), 8.10 (dd, J = 8.0, 1.1 Hz, H10), 7.64 (s, H4), 7.10 (t, J = 8.1 Hz, H9), 7.00 (dd, J = 8.2, 1.2 Hz, H8), 5.28 (s, H5), 3.88 (s, -CH3), 2.43 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 148.8, 146.0, 143.7, 143.1, 138.4, 134.6, 128.2, 123.1, 118.5, 117.5, 115.6, 67.3, 56.3, 18.4. IR (KBr, cm⁻¹) 2943, 2842, 1689, 1581, 1482, 1441, 1270, 1255, 1184, 1103, 1075, 952, 867, 797, 761, 738, 658. HRMS-TOF; [M + H]⁺ Calcd for C14H14NO2 228.10191, found: 228.10159.
4.21.4 3,4-Dimethyl-5H-chromeno[4,3-b]pyridine (265)

2-(But-2-ynyloxy)benzaldehyde (254) (0.4 g, 2.3 mmol), DBU (0.35 mL, 2.3 mmol), and propargylamine (0.3 mL, 4.6 mmol) in 10 mL of ethanol were reacted as described above to give the product 265 as white needles from chloroform/petroleum ether (0.39 g, 81%), mp 153-154 °C. 1H NMR (400 MHz, CDCl3) δ 8.32 (s, H2), 8.17 (dd, J = 7.7, 1.7 Hz, H10), 7.29 (dd, J = 7.8, 1.5 Hz, H7), 7.08 (dt, J = 1.0, 7.6 Hz, H8), 6.94 (dd, J = 8.1, 0.9 Hz, H9), 5.29 (s, H5), 2.29 (s, -CH3), 2.19 (s, -CH3). 13C NMR (100 MHz, CDCl3) δ 155.8, 149.5, 146.2, 140.7, 131.5, 130.7, 124.8, 124.7, 123.6, 122.4, 116.7, 65.7, 17.1, 14.1. IR (KBr, cm⁻¹) 2993, 1595, 1497, 1458, 1385, 1218, 1036, 857, 750. HRMS-TOF; [M + H]+ Calcd for C14H14NO 212.10699, found: 212.10710.

4.21.5 9-Bromo-3,4-dimethyl-5H-chromeno[4,3-b]pyridine (266)

5-Bromo-2-(but-2-ynyloxy)benzaldehyde (255) (0.5 g, 1.98 mmol), DBU (0.3 mL, 1.98 mmol) and propargylamine (0.5 mL, 7.9 mmol) in 10 mL of ethanol were reacted as described above to give the product 266 as a white powder from chloroform/petroleum ether (0.38 g, 67%), mp 143-144 °C. 1H NMR (400 MHz, CDCl3) δ 8.35 (br s, H10), 8.33 (s, H2), 7.36 (dd, J = 8.6, 2.5 Hz, H8), 6.82 (d, J = 8.6 Hz, H2), 5.29 (s, H5), 2.30 (s, -CH3), 2.20 (s, -CH3). 13C NMR (100 MHz, CDCl3) δ 154.5, 149.4, 144.7, 140.9, 134.1, 132.0, 127.2, 125.1, 124.5, 118.4, 114.8, 65.6, 16.9, 13.9. IR (KBr, cm⁻¹) 2917, 1595, 1455, 1381, 1315, 1219, 1012, 857, 750. HRMS-MALDI [M + H]+ Calcd for C14H13BrNO 290.01750, found: 290.01743.

4.21.6 7-Methoxy-3,4-dimethyl-5H-chromeno[4,3-b]pyridine (267)

3-Methoxy-2-(but-2-ynyloxy)-benzaldehyde (256) (0.5 g, 2.4 mmol), DBU (0.36 mL, 2.4 mmol), and propargylamine (0.3 mL, 4.9 mmol) in 10 mL of ethanol were reacted as described above to give the product 267 as white needle-like crystals from EtOAc (540 mg, 91%), mp 147-148 °C. 1H NMR (400 MHz, CDCl3) δ 8.32 (s, H2), 7.79 (dd, J = 8.0, 1.4 Hz, H10), 7.03 (t, J = 8.0 Hz, H9), 6.91 (dd, J = 8.0, 1.4 Hz, H8), 5.35 (s, H5), 3.91 (s, -OCH3), 2.28 (s, -CH3), 2.18 (s, -CH3). 13C NMR (100 MHz, CDCl3) δ 149.5, 148.5, 146.2, 145.0, 140.7, 131.6, 124.7,
124.4, 121.9, 116.7, 112.9, 66.0, 56.3, 17.1, 14.1. **IR** (KBr, cm\(^{-1}\)) 2916, 1595, 1561, 1441, 1390, 1218, 1176, 1059, 878, 743. **HRMS-TOF** [M + H]\(^+\) Calcd for C\(_{15}\)H\(_{16}\)NO\(_2\) 242.11756, found: 242.11759.

### 4.21.7 3-Methyl-4-phenyl-5H-chromeno[4,3-b]pyridine (268)

![Structure 268]

2-[(3-phenylprop-2-ynyl)oxy]benzaldehyde (257) (170 g, 0.7 mmol), DBU (0.1 mL, 0.7 mmol), and propargylamine (0.14 mL, 2.15 mmol) were reacted as described above (reflux overnight) to give the product 268 as white cubic crystals from chloroform/hexane (186 mg, 95%), mp 140-141 °C. **\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\) 8.50 (s, H\(_2\)), 8.25 (dd, \(J = 7.7, 1.5\) Hz, H\(_{10}\)), 7.52 – 7.40 (m, H\(_{2}'\) and H\(_{6}'\)), 7.33 – 7.26 (m, H\(_{3}'\) and H\(_{5}'\)), 7.18 – 7.14 (m, H\(_{9}\) and H\(_{4}'\)), 7.11 (dt, \(J = 1.1, 7.7\) Hz, H\(_8\)), 6.92 (dd, \(J = 8.1, 0.9\) Hz, H\(_7\)), 4.93 (s, H\(_5\)), 2.11 (s, -CH\(_3\)). **\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)) \(\delta\) 156.0, 150.0, 146.7, 146.2, 136.1, 131.0, 130.6, 129.0 (2C), 128.4, 128.2 (2 C), 124.7, 124.1, 123.6, 122.5, 116.9, 66.3, 17.3. **IR** (KBr, cm\(^{-1}\)) 2922, 1605, 1511, 1456, 1245, 1176, 1030, 832. **HRMS-TOF** [M + H]\(^+\) Calcd for C\(_{19}\)H\(_{16}\)NO 274.12264, found: 274.12436.

### 4.21.8 3-Methyl-4-pyridin-2-yl-5H-chromeno[4,3-b]pyridine (269)

![Structure 269]

2-[(3-pyridin-2-ylprop-2-ynyl)-oxy]benzaldehyde (258) (0.5 g, 2.1 mmol), DBU (0.3 mL, 2.1 mmol) and propargylamine (0.5 mL, 8.4 mmol) in 10 mL of ethanol were reacted as described above to give the product 269 as a light brown powder from EtOH/petroleum ether (540 mg, 93%), mp 115-116 °C.

**\(^1\)H NMR** (400 MHz, CDCl\(_3\)) \(\delta\) 8.78 (ddd, \(J = 4.9, 1.7, 1.0\) Hz, H\(_5\)), 8.52 (br s, H\(_2\)), 8.23 (dd, \(J = 7.8, 1.6\) Hz, H\(_{10}\)), 7.85 (dt, \(J = 1.8, 7.7\) Hz, H\(_5\)), 7.37 (ddd, \(J = 7.7, 4.9, 1.1\) Hz, H\(_5\)), 7.34 – 7.27 (m, H\(_3'\) and H\(_5'\)), 7.11 (dt, \(J = 1.1, 7.6\) Hz, H\(_6\)), 6.92 (dd, \(J = 8.1, 1.0\) Hz, H\(_7\)), 4.97 (s, H\(_5\)), 2.17 (s, -CH\(_3\)). **\(^{13}\)C NMR** (100 MHz, CDCl\(_3\)) \(\delta\) 156.1, 155.2, 150.4, 147.0, 144.4, 136.8, 131.0, 130.0, 124.70, 124.2, 124.1, 123.5, 123.1, 122.4, 116.9, 66.2, 17.1. **IR** (KBr, cm\(^{-1}\)) 2933, 2848, 1732, 1589, 1494, 1434, 1385, 1303, 1275, 1248, 1212, 1039, 1009, 955, 837, 786, 756, 719, 662, 598. **HRMS-TOF** [M + H]\(^+\) Calcd for C\(_{18}\)H\(_{15}\)BrN\(_2\)O 275.11789, found : 275.11910.
4.22 General Procedure for the Oxidation of Chromenopyridine Derivatives

To a suspension of CrO$_3$ (10 mmol) in 15 mL of dichloromethane was added pyridine (15 mmol) at room temperature. The mixture was stirred at room temperature for 20 min and cooled to 0 °C. Then, a solution of chromenopyridine derivative in 4 mL of dichloromethane was added and the mixture was stirred at rt overnight. After the completion of the reaction, the mixture was filtered over silica by using dichloromethane as mobile phase. Solvent was evaporated under the vacuum and the oxidation product was obtained.

4.22.1 3-Methyl-5H-chromeno[4,3-b]pyridin-5-one (270a)

![Diagram of compound 270a]

CrO$_3$ (710 mg, 7.10 mmol), pyridine (0.86 mL, 10.7 mmol), and chromenopyridine derivative 259 (70 mg, 0.355 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product 270a as a white needle-like crystals from EtOAc (74 mg, 99%), mp 182-183 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.86 (br s, H$_2$), 8.56 (br d, $J$ = 7.8 Hz, H$_{10}$), 8.43 (br s, H$_3$), 7.56 (dt, $J$ = 1.3, 7.8 Hz, H$_8$), 7.40 (br t, $J$ = 8.6 Hz, H$_7$ and H$_6$), 2.52 (s, -CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 161.4, 156.7, 152.3, 149.5, 137.7, 134.0, 131.7, 124.9, 124.4, 119.4, 117.2, 116.9, 18.5. IR (KBr, cm$^{-1}$) 2923, 1727, 1603, 1496, 1451, 1252, 1109, 1059, 789, 770. HRMS-TOF; [M + Na]$^+$ Calcd for C$_{13}$H$_9$NaNO$_2$ 234.05255, found: 234.05422.

4.22.2 9-Bromo-3-methyl-5H-chromeno[4,3-b]pyridin-5-one (270b)

![Diagram of compound 270b]

CrO$_3$ (815 mg, 8.15 mmol), pyridine (0.65 mL, 8.15 mmol), and chromenopyridine derivative 263 (75 mg, 0.272 mmol) in 10 mL of dichloromethane were reacted as described above to give the product 270b as white tiny needle from EtOAc (75 mg, 96%), mp 207-208 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.86 (d, $J$ = 2.3 Hz, H$_2$), 8.70 (d, $J$ = 2.3 Hz, H$_3$), 8.42 (dd, $J$ = 2.4, 0.8 Hz, H$_{10}$), 7.64 (dd, $J$ = 8.7, 2.4 Hz, H$_8$), 7.27 (d, $J$ = 8.7 Hz, H$_7$), 2.54 (s, -CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 160.9, 156.9, 151.2, 148.4, 137.9, 134.9, 134.6, 127.3, 121.2, 119.0, 118.1, 117.2, 18.7. IR (KBr, cm$^{-1}$) 2923, 1727, 1603, 1496, 1451, 1252, 1109, 1059, 789, 770. HRMS-TOF [M - H]$^+$ Calcd for C$_{13}$H$_9$BrNO$_2$ 287.96656, found: 287.96444.
4.22.3 7-Methoxy-3-methyl-5H-chromeno[4,3-b]pyridin-5-one (270c)

CrO\(_3\) (100 mg, 0.44 mmol), pyridine (0.7 mL, 8.8 mmol), and chromenopyridine derivative 264 (0.88 g, 8.8 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product 270c as tiny needles from EtOAc (100 mg, 94%), mp 222-223 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.86 (d, \(J = 1.9\) Hz, H\(_2\)), 8.44 (dd, \(J = 2.2, 0.7\) Hz, H\(_4\)), 8.14 (dd, \(J = 8.1, 1.4\) Hz, H\(_{10}\)), 7.33 (t, \(J = 8.1\) Hz, H\(_9\)), 7.12 (dd, \(J = 8.1, 1.3\) Hz, H\(_8\)), 4.00 (s, -OCH\(_3\)), 2.52 (s, -CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 161.0, 156.8, 149.7, 147.7, 142.2, 137.8, 134.2, 124.7, 120.4, 117.1, 115.8, 113.7, 56.4, 18.6. IR (KBr, cm\(^{-1}\)) 2923, 1725, 1564, 1482, 1452, 1186, 1073, 938, 765. HRMS-TOF [M + Na\(^+\)] Calcd for C\(_{14}\)H\(_{11}\)NaNO\(_3\) 264.06311, found: 264.06525.

4.22.4 3,4-Dimethyl-5H-chromeno[4,3-b]pyridin-5-one (270d)

CrO\(_3\) (284 mg, 2.84 mmol), pyridine (0.228 mL, 2.84 mmol), and the chromenopyridine derivative 265 (20 mg, 0.095 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product 270d as a white powder (19.0 mg, 90%), mp 181-182 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.71 (br s, H\(_2\)), 8.56 (dd, \(J = 7.9, 1.5\) Hz, H\(_{10}\)), 7.53 (ddd, \(J = 8.2, 7.4, 1.7\) Hz, H\(_8\)), 7.39 – 7.31 (m, H\(_7\) and H\(_9\)), 2.84 (s, -CH\(_3\)), 2.44 (s, -CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 161.1, 155.5, 152.3, 151.7, 151.4, 133.6, 131.69, 125.1, 124.6, 119.9, 116.7, 116.2, 17.9, 17.8. IR (KBr, cm\(^{-1}\)) 2921, 1726, 1598, 1452, 1257, 1129, 1016, 761. HRMS-TOF; [M - H\(^-\)] Calcd for C\(_{14}\)H\(_{10}\)NO\(_2\) 224.07170, found: 224.06787.

4.22.5 9-Bromo-3,4-dimethyl-5H-chromeno[4,3-b]pyridin-5-one (270e)

CrO\(_3\) (207 mg, 2.07 mmol), pyridine (0.166 mL, 2.07 mmol) and chromenopyridine derivative 266 (20 mg, 0.069 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product 270e as white needles from EtOAc (19 mg, 91%), mp 210-211 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.72 (br s, H\(_2\)), 8.71 (d, \(J = 2.2\) Hz, H\(_{10}\)), 7.61 (dd, \(J = 8.6, 2.2\) Hz, H\(_8\)), 7.22 (d, \(J = 8.7\) Hz, H\(_7\)), 2.84 (s, -CH\(_3\)), 2.45 (s, -CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 160.4, 155.5, 151.8, 151.1, 150.0, 134.4, 134.3, 127.8, 121.6, 118.4, 117.7, 116.2, 17.8, 17.8. IR
(KBr, cm\(^{-1}\)); 2919, 1734, 1553, 1454, 1379, 1251, 1094, 1012, 828, 803. HRMS-TOF M + H\(^{+}\) Calcd for C\(_{14}\)H\(_{11}\)BrNO\(_2\) 303.99677, found: 303.99939.

### 4.22.6 7-Methoxy-3,4-dimethyl-5\(\text{H}\)-chromeno[4,3-\(\text{b}\)]pyridin-5-one (270f)

[Chemical structure image]

CrO\(_3\) (498 mg, 4.98 mmol), pyridine (0.4 mL, 4.98 mmol), and chromenopyridine derivative 267 (60 mg, 0.249 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product 270f as colorless cubic crystals from EtOH (63 mg, 99%), mp 213-214 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.71 (br s, H\(\text{2}\)), 8.13 (d, \(J = 8.0\) Hz, H\(\text{10}\)), 7.30 (t, \(J = 8.0\) Hz, H\(\text{9}\)), 7.09 (d, \(J = 8.0\) Hz, H\(\text{8}\)), 3.99 (s, -OCH\(_3\)), 2.84 (s, -CH\(_3\)), 2.44 (s, -CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 160.3, 155.4, 151.6, 151.3, 147.2, 142.0, 133.6, 124.2, 120.7, 116.2, 116.1, 113.3, 56.4, 17.8, 17.7. IR (KBr, cm\(^{-1}\)) 2918, 1734, 1558, 1485, 1436, 1278, 1129, 1062, 898, 785. HRMS-TOF; [M + Na\(^{+}\)] Calcd for C\(_{14}\)H\(_{11}\)NaNO\(_2\) 278.07876, found: 278.08066.

### 4.22.7 3-Methyl-4-phenyl-5\(\text{H}\)-chromeno[4,3-\(\text{b}\)]pyridin-5-one (270g)

[Chemical structure image]

CrO\(_3\) (384 mg, 3.85 mmol), pyridine (0.31 mL, 3.85 mmol), and chromenopyridine derivative 268 (35 mg, 0.128 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product 270g was as white needles from EtOAc/petroleum ether (33 mg, 90%), mp 134-135 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.89 (br s, H\(\text{2}\)), 8.63 (dd, \(J = 7.9, 1.6\) Hz, H\(\text{10}\)), 7.56–7.35 (m, H\(\text{4}′\), H\(\text{6}′\), H\(\text{2}′\) and H\(\text{8}\)), 7.41–7.35 (m, H\(\text{9}\)), 7.32 (dd, \(J = 8.2, 0.9\) Hz, H\(\text{7}\)), 7.17 – 7.13 (m, H\(\text{3}′\) and H\(\text{5}′\)), 2.14 (s, -CH\(_3\)). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 159.5, 156.2, 153.2, 152.6, 151.0, 138.2, 133.5, 131.8, 128.6 (2 C), 127.8, 126.9 (2 C), 125.0, 124.6, 119.7, 116.8, 115.2, 17.7. IR (KBr, cm\(^{-1}\)) 2922, 1737, 1612, 1450, 1450, 1352, 1155, 1111, 939, 758, 746. HRMS-TOF [M + Na\(^{+}\)] Calcd for C\(_{19}\)H\(_{13}\)NaNO\(_3\) 310.08385, found: 310.08615.

### 4.22.8 3-Methyl-4-pyridin-2-yl-5\(\text{H}\)-chromeno[4,3-\(\text{b}\)]pyridin-5-one (270h)

[Chemical structure image]

CrO\(_3\) (546 mg, 5.46 mmol), pyridine (0.44 mL, 5.46 mmol) and chromenopyridine derivative 269 (50 mg, 0.182 mmol) in 10 mL of dichloromethane were reacted as described above to give the oxidation product 270h as white tiny
needles from EtOAc (49 mg, 98%), mp 199-200 °C. **1H NMR** (400 MHz, CDCl₃) δ 8.94 (br s, H₂), 8.75 (d, J = 3.9 Hz, H₆), 8.62 (dd, J = 8.0, 1.2 Hz, H₁₀), 7.86 (br t, J = 7.4 Hz, H₈), 7.55 (dt, J = 1.2, 7.8 Hz, H₄), 7.40 (br t, J = 7.1 Hz, H₂ and H₅), 7.34 – 7.28 (m, H₇ and H₆'), 2.17 (s, -CH₃). **13C NMR** (100 MHz, CDCl₃) δ 159.6, 156.7, 156.6, 152.3, 150.7, 150.5, 149.6, 136.5, 133.0, 131.7, 124.8, 124.6, 122.7, 122.7, 119.4, 116.7, 114.8, 16.9. **IR** (KBr, cm⁻¹) 2915, 1739, 1611, 1454, 1256, 1119, 941, 761. **HRMS-TOF** [M + Na]⁺ Calcd for C₁₈H₁₂NaN₂O₂ 311.07910, found: 311.08191.

4.23 Synthesis of Naphthaldehydes

4.23.1 1-(Prop-2-ynyloxy)-2-naphthaldehyde (277)

![Diagram of 1-Hydroxy-2-naphthaldehyde](image)

1-Hydroxy-2-naphthaldehyde (274) (160 mg, 0.93 mmol), anhydrous K₂CO₃ (0.19 g, 1.14 mmol), and propargyl bromide (0.12 mL, 1.12 mmol) in 7 mL of DMF were reacted as described above the give the product 277 pale yellow solid (190 mg, 97%), mp 77-78 °C (Lit. mp 78-81 °C). **1H NMR** (400 MHz, CDCl₃) δ 10.65 (d, J = 0.6 Hz, -COH), 8.23 (dd, J = 8.1, 0.6 Hz, H₈), 7.91 (d, J = 8.6 Hz, H₃ and H₄), 7.71 (d, J = 8.6 Hz, H₅), 7.68-7.58 (m, H₆ and H₇), 4.95 (d, J = 2.4 Hz, H₁'), 2.61 (t, J = 2.4 Hz, -C≡CH). **13C NMR** (100 MHz, CDCl₃) δ 190.1, 159.3, 138.1, 129.4, 128.6, 127.7, 127.1, 126.5, 125.5, 123.2, 122.6, 78.4, 77.8, 64.2. **HRMS-TOF** [M + Na]⁺ Calcd for C₁₄H₁₀NaO₂ 233.0573, found: 233.05974.

4.23.2 2-(Prop-2-ynyloxy)-1-naphthaldehyde (168)

![Diagram of 2-Hydroxy-1-naphthaldehyde](image)

2-Hydroxy-1-naphthaldehyde (275) (2.0 g, 11.63 mmol), anhydrous K₂CO₃ (2.4 g, 17.44 mmol) and propargyl bromide (1.5 mL, 13.95 mmol) in 10 mL of DMF were reacted as described above to give the product 168 as colorless crystals (2.2 g, 92%), mp 113-115 °C (Lit. mp 113-115 °C). **1H NMR** (400 MHz, CDCl₃) δ 10.91 (s, -COH), 9.28 (d, J = 8.7 Hz, H₈), 8.08 (d, J = 9.1 Hz, H₄), 7.80 (d, J = 8.2 Hz, H₅), 7.64 (ddd, J = 8.5, 6.9, 1.4 Hz, H₇), 7.45 (ddd, J = 8.0, 6.9, 1.1 Hz, H₆), 7.40 (d, J = 9.1 Hz, H₃), 4.96 (d, J = 2.4 Hz, H₁'), 2.58 (t, J = 2.4 Hz, -C≡CH). **13C NMR** (100 MHz, CDCl₃) δ 192.0, 162.0, 137.4, 131.5, 130.0, 129.2, 128.3, 125.3, 125.2, 118.1, 114.1, 77.8, 76.9, 57.5. **HRMS-TOF** [M + Na]⁺ Calcd for C₁₄H₁₀NaO₂ 233.0573 found: 233.05935.
4.23.3 3-(Prop-2-ynyloxy)-2-naphthaldehyde (278)

3-Hydroxy-2-naphthaldehyde (276) (46 mg, 0.267 mmol), anhydrous K$_2$CO$_3$ (55 mg, 0.4 mmol), and propargyl bromide (35 µL, 0.32 mmol) in 5 mL of DMF were reacted as described above to give the product 278 as white powder (55 mg, 98%), mp 107-109 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.59 (s, -COH), 8.41 (s, H$_1$), 7.91 (d, $J$ = 8.3 Hz, H$_3$), 7.78 (d, $J$ = 8.5 Hz, H$_5$), 7.57 (ddd, $J$ = 8.2, 6.9, 1.2 Hz, H$_7$), 7.42 (ddd, $J$ = 8.2, 6.9, 1.1 Hz, H$_6$), 7.34 (s, H$_4$), 4.94 (d, $J$ = 2.4 Hz, H$_{1'}$), 2.60 (t, $J$ = 2.4 Hz, -C≡CH). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 190.0, 155.6, 137.3, 131.1, 130.1, 129.4, 128.3, 127.0, 126.0, 125.2, 108.3, 77.9, 76.6, 56.5. HRMS-TOF [M + H]$^+$ Calcd for C$_{14}$H$_{11}$O$_2$ 211.07536, found: 211.0757.

4.24 Synthesis of Benzochromenopyridines

4.24.1 2-Methyl-12$H$-benzo[7,8]chromeno[4,3-b]pyridine (279)

1-(Prop-2-ynyloxy)-2-naphtha aldehyde (277) (190 mg, 0.90 mmol), DBU (0.14 mL, 0.90 mmol), and propargylamine (0.18 mL, 2.83 mmol) in 15 mL of ethanol were reacted as described above (reflux overnight) to give the product 279 as yellowish tiny needle crystals from EtOAc (200 mg, 90%), mp 148-149 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.43 (br s, H$_3$), 8.28 (d, $J$ = 8.6 Hz, H$_{10}$), 8.25 – 8.22 (m, H$_5$), 7.84 – 7.79 (m, H$_7$), 7.56 (d, $J$ = 8.6 Hz, H$_6$), 7.53 – 7.45 (m, H$_9$ and H$_8$), 7.27 (br s, H$_{11}$), 5.38 (s, H$_{12}$), 2.36 (s, -CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 152.3, 149.9, 146.9, 135.4, 132.6, 132.0, 127.9, 127.2, 125.8, 125.2, 125.1, 122.4, 121.8, 121.5, 117.8, 68.6, 18.5. IR (KBr, cm$^{-1}$) 2964, 1581, 1453, 1403, 1344, 1256, 1242, 1101, 1002, 954, 818, 778, 749. HRMS-TOF [M + H]$^+$ Calcd for C$_{17}$H$_{14}$NO 248.10699, found: 248.1086.

2-(Prop-2-ynyloxy)-1-naphthaldehyde (168) (150 g, 0.71 mmol), DBU (0.10 mL, 0.71 mmol), and propargylamine (93 µL, 1.42 mmol) in 10 mL of ethanol were reacted as described above (reflux overnight) to give the product 280 as yellowish needles from EtOH (160 mg, 91%), mp 108-109 °C. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.62 (d, \(J = 8.4\) Hz, H\(_{12}\)), 8.55 (d, \(J = 1.5\) Hz, H\(_3\)), 7.83–7.77 (m, H\(_8\) and H\(_9\)), 7.61 (ddd, \(J = 8.5, 6.8, 1.4\) Hz, H\(_{11}\)), 7.43 (ddd, \(J = 8.0, 6.9, 1.1\) Hz, H\(_{10}\)), 7.33 (d, \(J = 1.4\) Hz, H\(_4\)), 7.20 (d, \(J = 8.9\) Hz, H\(_7\)), 5.11 (s, H\(_5\)), 2.39 (s, -CH\(_3\)). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 156.0, 149.1, 148.1, 132.7, 131.8, 131.2, 130.9, 130.6, 128.4, 127.5, 127.0, 126.8, 124.3, 118.1, 116.5, 68.4, 18.3. IR (KBr, cm\(^{-1}\)) 2964, 1597, 1512, 1456, 1383, 1244, 1211, 972, 819, 738. HRMS-TOF [M + H]\(^{+}\) Calcd for C\(_{17}\)H\(_{14}\)NO 248.10699, found: 248.10883.


3-(Prop-2-ynyloxy)-2-naphth-aldehyde (278) (50 mg, 0.238 mmol), DBU (35 µL, 0.238 mmol), and propargylamine (46 µL, 0.71 mmol) in 10 mL of ethanol were reacted as described above (reflux overnight) to give the product 281 as colorless needles from CHCl\(_3\)/hexane (55 mg, 94%), mp 128-129 °C. \(^{1}H\) NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.7 (s, H\(_{12}\)), 8.48 (br s, H\(_2\)), 7.9 (d, \(J = 8.2\) Hz, H\(_{11}\)), 7.71 (d, \(J = 8.2\) Hz, H\(_8\)), 7.43 (ddd, \(J = 8.2, 6.9, 1.2\) Hz, H\(_{10}\)), 7.38-7.34 (m, H\(_9\)), 7.35 (s, H\(_7\)), 7.3 (br s, H\(_4\)), 5.23 (s, H\(_5\)), 2.40 (s, -CH\(_3\)). \(^{13}C\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 153.7, 150.2, 146.1, 135.3, 132.9, 132.7, 130.1, 128.9, 127.2, 127.1, 126.8, 124.5, 124.2, 112.3, 106.4, 68.0, 18.6. IR (KBr, cm\(^{-1}\)) 2920, 1630, 1443, 1241, 1163, 1030, 947, 884, 869, 743. HRMS-TOF [M + H]\(^{+}\) Calcd for C\(_{17}\)H\(_{14}\)NO 248.10699, found: 248.10771.
4.25 Synthesis of Benzochromenopyridinones

4.25.1 2-Methyl-12H-benzo[7,8]chromeno[4,3-b]pyridin-12-one (240)

\[
\begin{align*}
\text{CrO}_3 (0.80 \text{ mg, 8.5 mmol), pyridine (0.68 mL, 8.5 mmol),}
\text{and benzochromenopyridine 279 (70 mg, 0.283 mmol) in 10 mL of dichloromethane were reacted as described}
\text{above to give the oxidation product 240 as white needles}
\text{from EtOAc (74 mg, 81%), mp 260-261 °C.} \\
\text{\textbf{1H NMR} (400 MHz, CDCl}_3) \delta 8.91 (d, J = 2.3 \text{ Hz, H}_3), 8.61 - 8.57 (m, H_{10}), 8.58 (d, J = 8.6 \text{ Hz, H}_5), 8.49 (dd, J = 2.3 \text{ Hz, H}_1), 7.95 - 7.90 (m, H_7), 7.83 (d, J = 8.6 \text{ Hz, H}_6), 7.69 - 7.62 (m, H_9 \text{ and H}_8), 2.55 (s, -CH}_3).
\end{align*}
\]

\[
\text{\textbf{13C NMR} (100 MHz, CDCl}_3) \delta 161.6, 157.0, 150.2, 148.9, 137.8, 135.3, 133.8, 128.4, 128.0, 127.2, 124.8, 123.6, 122.4, 120.4, 117.0, 114.9, 18.6.
\]

\[
\text{\textbf{IR} (KBr, cm}^{-1}) 2918, 1731, 1603, 1492, 1448, 1348, 1295, 1147, 1111, 1061, 943, 776.
\]

\[
\text{\textbf{HRMS-TOF} [M - H]}^+ \text{ Calcd for C}_{17}H_{11}NO_2 260.06716, \text{ found: 260.0717.}
\]

4.25.2 3-Methyl-5H-benzo[5,6]chromeno[4,3-b]pyridin-5-one (241)

\[
\begin{align*}
\text{CrO}_3 (1.62 \text{ g, 16.2 mmol), pyridine (1.3 mL, 16.2 mmol), and}
\text{280 (200 mg, 0.81 mmol) in 15 mL of dichloromethane were reacted as described}
\text{above to give the oxidation product 241 as a white tiny needle-like crystals from chloroform (190 mg,}
\text{90%), mp 244-245 °C.} \\
\text{\textbf{1H NMR} (400 MHz, CDCl}_3) \delta 10.58 (d, J = 8.4 \text{ Hz, H}_{12}), 9.03 (dd, J = 2.4, 0.5 \text{ Hz, H}_2), 8.54 (dd, J = 2.4, 0.8 Hz, H_4), 8.01 (d, J = 8.9 \text{ Hz, H}_8), 7.92 (dd, J = 8.0, 1.2 \text{ Hz, H}_3), 7.75 (ddd, J = 8.6, 6.9, 1.5 \text{ Hz, H}_{11}), 7.59 (ddd, J = 8.0, 6.9, 1.1 \text{ Hz, H}_{10}), 7.52 (d, J = 8.9 \text{ Hz, H}_7), 2.56 (s, -CH}_3).
\end{align*}
\]

\[
\text{\textbf{13C NMR} (100 MHz, CDCl}_3) \delta 161.7, 155.7, 152.6, 152.1, 138.0, 133.4, 132.9, 131.6, 130.7, 128.8, 128.5, 128.0, 125.9, 117.6, 117.5, 112.1, 18.5.} \\
\text{\textbf{IR} (KBr, cm}^{-1}) 2920, 1725, 1554, 1474, 1269, 1218, 1156, 1014, 815, 752.
\]

\[
\text{\textbf{HRMS-TOF} [M + Na]}^+ \text{ Calcd for C}_{17}H_{11}NaNO_2 284.0692, \text{ found: 284.0707.}
\]

4.25.3 3-Methyl-5H-benzo[6,7]chromeno[4,3-b]pyridin-5-one (242)

\[
\begin{align*}
\text{\textbf{CrO}_3 (340 mg, 3.4 mmol), pyridine (0.27 mL, 3.4 mmol), and benzochromenopyridine 281 in 10 mL of}
\text{dichloromethane were reacted as described above to give the oxidation product 242 as colorless cubic crystals}
\end{align*}
\]
from chloroform (43 mg, 98%), mp 287-288 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.10 (br s, H$_{12}$), 8.89 (bd, J = 2.2 Hz, H$_2$), 8.45 (bd, J = 2.2 Hz, H$_4$), 8.04 (bd, J = 8.2 Hz, H$_1$), 7.90 (br d, J = 8.3 Hz, H$_3$), 7.79 (br s, H$_7$) 7.58 (ddd, J = 8.2, 6.9, 1.3 Hz, H$_{10}$), 7.52 (ddd, J = 8.1, 6.9, 1.2 Hz, H$_9$), 2.54 (s, -CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 161.5, 156.8, 149.7, 149.5, 138.1, 135.0, 134.3, 130.7, 129.1, 128.2, 127.6, 126.0, 124.9, 119.3, 117.4, 113.4, 18.6. IR (KBr, cm$^{-1}$) 2920, 1724, 1601, 1486, 1292, 1258, 1179, 1130, 1074, 888, 793, 752. HRMS-TOF; [M + H]$^+$ Calcd for C$_{17}$H$_{12}$NO$_2$ 262.0868, found: 262.08324.

4.26 Synthesis of Benzopyrazolooxazepine and Benzopyrazolooxazocine Derivatives

4.26.1 2-(Acetyloxy)benzoic acid (282)

To salicylic acid 243 (4.0 g, 29 mmol) in an erlenmayer flask, acetic anhydride (10 mL, 100 mmol) and 10 drops 85% phosphoric acid are added. The mixture is stirred well. It was heated in water bath for 10 min. and removed from bath. 4 mL of water was added to the mixture while it was still hot cautiously in one portion. Then, 100 mL of water was added and after a while, crystals began to form. The mixture was cooled in an ice bath to complete the crystallization. The product 282 was collected by filtration, washed with cold water and dried. The product was obtained as white cubic crystal (4.9 g, 95%). Mp = 136-137 °C. (lit. Mp = 136 °C)$^{136}$ $^1$H NMR (400 MHz, CDCl$_3$) δ 8.11 (dd, J = 8.0, 1.6 Hz, H$_6$), 7.62 (dt, J = 1.7, 7.8 Hz, H$_4$), 7.36 (dt, J = 1.0, 7.7 Hz, H$_5$), 7.14 (dd, J = 8.0, 0.9 Hz, H$_3$), 2.35 (s, -CH$_3$). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 170.3, 169.9, 151.4, 135.0, 132.7, 126.3, 124.2, 122.4, 21.1.

4.26.2 General Procedure for Synthesis of Phenyl Acetate Derivatives

Acetylsalicylic acid 282 (1 g, 5.55 mmol) was dissolved in chloroform (15 mL) and to this solution, oxalyl chloride (0.95 mL, 11.1 mmol) was added dropwise. After adding 8-10 drops dry DMF, this mixture was refluxed overnight. Then, it was cooled to rt and the solvent and excess oxalyl chloride was removed under vacumm. To the empty flask, PdCl$_2$ (1% mol), PPh$_3$ (4% mol), CuI (3% mol) and NEt$_3$ (1 mL) were taken. They were stirred at around 50 °C for 5 min under nitrogen atmosphere. Formed acyl chloride 283 was dissolved in 10 mL dry THF and acetylene derivative was added to
this solution in separate flask. The mixture was added to stirred solution at 40 °C. The reaction mixture was refluxed under nitrogen atmosphere. After the completion of the reaction, the solvent was removed under vacuum and the residue was dissolved in EtOAc (100 mL). This solution was washed with water (3 × 75 mL). The organic phase was dried over MgSO₄ and the solvent was removed. The residue was purified by column chromatography.

4.26.2.1 2-(3-phenylprop-2-ynoyl)phenyl acetate (285)

![Chemical structure image]

Acyl chloride 283 formed as described above was reacted with phenyl acetylene (1.22 mL, 11.1 mmol), PdCl₂ (11 mg, 0.062 mmol), PPh₃ (66 mg, 0.25 mmol), CuI (36 mg, 0.189 mmol) and NEt₃ (1 mL) in THF (10 mL) according to general procedure. The reaction mixture was refluxed for 6 h. The residue was purified by column chromatography eluting with ethyl acetate/hexane (1:10 to 1:3) to give the product 285 as yellow viscous liquid (1 g, isolated yield = 68%). ¹H NMR (400 MHz, CDCl₃) δ 8.27 (dd, J = 7.8, 1.6 Hz, H₆), 7.67 – 7.59 (m, H₅, H₂ and H₆'), 7.51 – 7.45 (m, H₄), 7.44 – 7.38 (m, H₃, H₄ and H₅), 7.15 (dd, J = 8.0, 0.9 Hz, H₃), 2.36 (s, -CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 176.1, 169.7, 150.2, 134.8, 133.2, 133.1, 131.0, 129.6, 128.8, 126.3, 124.2, 120.1, 92.8, 87.8, 21.2.

4.26.2.2 2-(3-(trimethylsilyl)propioloyl)phenyl acetate (295)

Acyl chloride 283 formed as described above was reacted with trimethylsilyl acetylene (0.95 mL, 6.66 mmol), PdCl₂ (11 mg, 0.062 mmol), PPh₃ (66 mg, 0.25 mmol), CuI (36 mg, 0.189 mmol) and NEt₃ (1 mL) in THF (10 mL) according to general procedure. The reaction mixture was refluxed for 2 h. The residue was purified by column chromatography by eluting ethyl acetate/hexane (1:50 to 1:8) to give the product 269 as yellow oil (130 mg). The reaction product was hydrolyzed after treatment of silica gel and new product 295 was also collected from the column (410 mg).
1H NMR (400 MHz, CDCl₃) δ 7.50 (dd, J = 7.9, 1.6 Hz, H₆), 7.34 (dt, J = 1.6, 7.7 Hz, H₄), 7.18 (dt, J = 1.0, 7.7 Hz, H₅), 7.07 (dd, J = 7.9, 1.0 Hz, H₃), 2.33 (s, -CH₃), 0.25 (s, -Si(CH₃)₃).

13C NMR (100 MHz, CDCl₃) δ 175.8, 169.6, 150.3, 135.0, 133.8, 129.0, 126.3, 124.2, 101.5, 100.3, 21.2, -0.6.

4.26.2.3 2-Propioloylphenyl Acetate (296)

Unhydrolyzed product 295 of the previous reaction (130 mg, 0.5 mmol) was dissolved in dry THF (5 mL). To this solution, TBAF (1.0 M solution in THF, 0.5 mL, 0.5 mmol) was added and the mixture was stirred for 20 min. in an ice bath. After the completion of the reaction, the reaction mixture was diluted with diethyl ether (40 mL) and was washed with brine (3 × 50 mL). The organic phase was dried over MgSO₄ and the solvent was removed under reduced pressure. The product 296 was obtained as yellow oil (95 mg).

(0.51 g, isolated overall yield from compound 296 = 49%). 1H NMR (400 MHz, CDCl₃) δ 8.25 (dd, J = 7.8, 1.6 Hz, H₆), 7.64 (dt, J = 1.6, 7.8 Hz, H₄), 7.41 (dt, J = 0.6, 7.8 Hz, H₅), 7.13 (br d, J = 8.2 Hz, H₃), 3.42 (s, H₃′), 2.37 (s, -CH₃). 13C NMR (100 MHz, CDCl₃) 175.3, 169.6, 150.4, 135.4, 133.8, 128.7, 126.4, 124.3, 81.0, 80.4, 21.2. IR (KBr, cm⁻¹) 2981, 2094, 1747, 1652, 1602, 1377, 1234, 1184, 1002, 851, 753, 510. HRMS-TOF; [M + Na]⁺ Calcd for C₁₁H₈NO₃ 211.03657, found: 211.0371.

4.26.3 Synthesis of Pyrazoyl Phenols 286 and 297

4.26.3.1 2-(3-phenyl-1H-pyrazol-5-yl)phenol (286)

Phenyl acetate derivative 285 (650 mg, 2.46 mmol) was dissolved in methanol (20 mL). Hydrazine monohydrate (8 eq.) was added to this solution and the reaction mixture was refluxed overnight. After the completion of the reaction, excess methanol was removed under reduced pressure and the residue was dissolved in EtOAc (40 mL). The organic phase was washed with water (3 × 50 mL) and brine (50 mL). The organic phase was dried over
MgSO$_4$ and then the solvent was evaporated. The obtained product 286 was crystallized from CHCl$_3$/petroleum ether as yellow cubic crytals (550 mg, 94%). mp =139-140 °C. (Lit. mp: 144 °C$^{137}$) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.72 (br s, -OH), 7.66 – 7.60 (m, H$_3$, H$_{2''}$ and H$_{6''}$), 7.52 – 7.47 (m, H$_{3''}$ and H$_5''$), 7.46 – 7.41 (m, H$_5$), 7.27 – 7.22 (m, H$_4$), 7.05 (dd, $J = 8.2, 0.9$ Hz, H$_3$), 6.95 (dt, $J = 1.0, 7.6$ Hz, H$_6$), 6.92 (s, H$_4$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.8, 152.8, 144.1, 129.4, 129.2, 128.8, 126.6, 125.7, 119.5, 117.1, 116.6, 99.5.

4.26.3.2 2-(1H-pyrazol-5-yl)phenol (297)

Phenyl acetate derivative 296 (380 mg, 2 mmol) was dissolved in methanol (20 mL). Hydrazine monohydrate (8 eq.) was added to this solution and the reaction mixture was refluxed overnight. After the completion of the reaction, excess methanol was removed under reduced pressure and the residue was dissolved in EtOAc (40 mL). The organic phase was washed with water (3 × 50 mL) and brine (50 mL). The organic phase was dried over MgSO$_4$ and then the solvent was evaporated. The formed product 297 was crystallized from CHCl$_3$/hexane as a white needle crystals (290 mg, 76%). Mp = 92-93 °C (lit. mp = 91-93 °C$^{138}$). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.66 (d, $J = 2.5$ Hz, H$_3$), 7.60 (dd, $J = 7.8, 1.6$ Hz, H$_3$), 7.24 – 7.19 (m, H$_5$), 7.05 (br d, $J = 8.2$ Hz, H$_6$), 6.93 (dt, $J = 1.1, 7.6$ Hz, H$_4$), 6.73 (d, $J = 2.5$ Hz, H$_4$). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 155.8, 151.7, 129.5 (2C), 126.8, 119.6, 117.1, 116.7, 102.1.

4.26.4 Synthesis of Propargylated Compounds

4.26.4.1 Synthesis of 3-phenyl-5-[2-(prop-2-nyloxy)phenyl]-1H-pyrazole (290) and 2-(5-phenyl-1-prop-2-ynyl-1H-pyrazol-3-yl)phenol (291).

The compound 286 (290 mg, 1.23 mmol) was dissolved in dry DMF (10 mL). To this solution, K$_2$CO$_3$ (630 mg, 1.23 mmol) was added directly and the mixture was stirred for 30 min. at room temperature. After that, propargyl bromide (0.45 mL, 1.23 mmol) was added and the reaction mixture was stirred for 18 h at rt. The reaction was monitored on TLC. After the completion of the reaction, the mixture was diluted with EtOAc (50 mL) and the solution was washed with water (4 × 75 mL) and brine (2 × 50 mL). The organic phase was dried over MgSO$_4$ and the solvent was evaporated and
the crude product was purified by column chromatography (silica gel) eluting with hexane/EtOAc (4:1) to give corresponding products 290 (190 mg, 74%) as yellow oil and 291 (60 mg, 26%) as white solid. White tiny needle crystallized from CHCl₃/petroleum ether.

3-phenyl-5-[2-(prop-2ynyloxy)phenyl]-1H-pyrazole (290)

![NMR spectrum of 290](image)

\[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)} \delta \text{7.88 (d, } J = 7.5 \text{ Hz, 2H, arom.), } 7.76 \text{ (br d, } J = 7.7 \text{ Hz, H}_6\text{)}, \text{7.43 (t, } J = 7.6 \text{ Hz, 2H, arom.), } 7.36 - 7.30 \text{ (m, 2H, arom.), } 7.11 \text{ (br t, } J = 7.7 \text{ Hz, 2H, arom.), } 6.97 \text{ (s, H}_4\text{)}, \text{4.85 (d, } J = 2.3 \text{ Hz, -CH}_2\text{)}, \text{2.61 (t, } J = 2.3 \text{ Hz, -C≡CH).} \]

\[ \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{)} \delta \text{154.1, 151.2, 142.0, 133.3, 129.4, 128.8, 128.4, 128.0, 125.8, 122.5, 118.5, 113.3, 100.6, 77.8, 76.8, 56.7.} \]

IR (KBr, cm\(^{-1}\)) 3283, 2923, 1725, 1501, 1480, 1469, 1216, 1050, 1020, 968, 750, 692. \text{HRMS-TOF; [M + H]}^+ \text{Calcd for C}_{18}H_{15}N_2O 275.11789, found: 275.11936.

2-(5-phenyl-1-prop-2-ynyloxy-1H-pyrazol-3-yl)phenol (291)

![NMR spectrum of 291](image)

White tiny needles crystallized from CHCl₃/petroleum ether. mp =122-123 °C. \[ \text{\textsuperscript{1}H NMR (400 MHz, CDCl}_3\text{)} \delta \text{7.66 - 7.41 (m, 6H, arom.), 7.26 - 7.21 (m, 1H, arom.), 7.05 (dd, } J = 8.2, 1.1 \text{ Hz, } H_3\text{)}, 6.92 (dt, } J = 1.1, 7.6 \text{ Hz, } H_4\text{), 6.70 (s, } H_6\text{), 4.90 (d, } J = 2.5 \text{ Hz, -CH}_2\text{)}, 2.45 (t, } J = 2.5 \text{ Hz, -C≡CH).} \]

\[ \text{\textsuperscript{13}C NMR (100 MHz, CDCl}_3\text{)} \delta \text{156.2, 151.6, 144.9, 129.6, 129.5, 129.2, 129.0 (2 C), 126.5, 119.4, 117.3, 116.5, 103.2, 77.7, 74.1, 39.9.} \]

IR (KBr, cm\(^{-1}\)) 2922, 1650, 1578, 1465, 1454, 1367, 1201, 1080, 1004, 956, 890, 744, 756, 690, 680. \text{HRMS-TOF; [M + H]}^+ \text{Calcd for C}_{18}H_{15}N_2O 275.11789, found: 275.11927.

4.26.4.2 Synthesis of 5-[2-(prop-2-ynyloxy)phenyl]-1H-pyrazole (298) and 2-(1-prop-2-ynyloxy-1H-pyrazol-3-yl)phenol (293)

The compound 297 (290 mg, 1.8 mmol) was dissolved in dry DMF (10 mL). To this solution, K\(_2\)CO\(_3\) (630 mg, 1.23 mmol) was added directly and the mixture was stirred for 30 min. at room temperature. After that, propargyl bromide (0.45 mL, 1.23 mmol) was added and the reaction mixture was stirred for 18 h at rt. The reaction was
monitored on TLC. After the completion of the reaction, the mixture was diluted with EtOAc (50 mL) and the solution was washed with water (4 × 75 mL) and brine (2 × 50 mL). The organic phase was dried over MgSO₄ and the solvent was evaporated and the crude product was purified by column chromatography (silica gel) eluting with hexane/EtOAC (8 : 1) to give corresponding products 298 (125 mg, 35%) as yellow oil and 293 (230 mg, 65%) as white solid.

5-[2-(prop-2-ynyloxy)phenyl]-1H-pyrazole (298)

White needle crystal from CHCl₃/petroleum ether. mp = 88-89 °C. ¹H NMR (400 MHz, CDCl₃) δ 10.31 (s, -NH), 7.73 (dd, J = 7.5, 6.3 Hz, H₆), 7.65 (d, J = 5.1 Hz, H₅), 7.40 - 7.20 (m, H₄), 7.20 - 7.00 (m, H₃ and H₅), 6.70 (d, J = 5.1 Hz, H₄), 4.97 - 4.72 (m, CH₂), 2.69 - 2.36 (m, -C≡CH). ¹³C NMR (100 MHz, CDCl₃) δ 154.0, 141.0, 138.6, 129.1, 128.4, 122.4, 119.0, 113.2, 103.5, 77.9, 76.6, 56.6. IR (KBr, cm⁻¹) 2918, 1649, 1578, 1454, 1368, 1219, 1201, 1079, 1012, 1004, 756, 744, 690, 680. HRMS-TOF; [M + H]⁺ Calcd for C₁₂H₁₁N₂O 199.08659, found: 199.0859

2-(1-prop-2-ynyl-1H-pyrazol-3-yl)phenol (293)

¹H NMR (400 MHz, CDCl₃) δ 10.60 (s, -OH), 7.67 (d, J = 2.5 Hz, H₅), 7.56 (dd, J = 7.8, 1.6 Hz, H₃), 7.22 (ddd, J = 8.7, 7.3, 1.6 Hz, H₃), 7.02 (dd, J = 8.2, 1.1 Hz, H₄), 6.91 (dt, J = 1.2, 7.6 Hz, H₄), 6.68 (d, J = 2.5 Hz, H₄), 4.98 (d, J = 2.6 Hz, -CH₂), 2.55 (t, J = 2.6 Hz, -C≡CH). ¹³C NMR (100 MHz, CDCl₃) δ 155.8, 152.0, 130.0, 129.3, 126.4, 119.4, 117.1, 116.5, 102.9, 76.2, 75.2, 41.6. IR (KBr, cm⁻¹) 1622, 1585, 1506, 1417, 1294, 1248, 1208, 1056, 940, 751, 697, 667. HRMS-TOF [M + H]⁺ Calcd for C₁₂H₁₁N₂O 199.08659, found: 199.08661

4.26.5 Formation of cyclization products 299, 300 and 301

3-phenyl-5-[2-(prop-2-ynyloxy)phenyl]-1H-pyrazole (290) (150 mg, 0.75 mmol) was dissolved in acetonitrile and catalytic amount of gold (III) chloride (7 mg, 2.3x10⁻² mmol) was added to this solution. Then, this mixture was stirred at 45 °C for 18 h. The reaction was monitored on TLC. After the consuming of the starting material, acetonitrile was evaporated and the crude product was purified by column
chromatography and preparative TLC eluting with hexane/EtOAC (20 : 1 then 10: 1) to give corresponding products 300 (26 mg, 17%), 299 (82 mg, 55%) and 301 (42 mg, 28%).

4.26.5.1 5-methyl-2-phenylpyrazolo[1,5-d][1,4]benzoxazepine (301)

Yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.89 (d, $J$ = 7.3 Hz, 2H, arom.), 7.57 (dd, $J$ = 7.7, 1.6 Hz, 1H, arom.), 7.44 (t, $J$ = 7.5 Hz, 2H, arom.), 7.38 − 7.32 (m, 2H, arom.), 7.22 (dt, $J$ = 1.1, 7.5 Hz, 1H, arom.), 7.12 (dd, $J$ = 8.0, 1.0 Hz, 1H, arom.), 6.86 (s, H$_1$), 6.30 (q, $J$ = 1.4 Hz, H$_6$), 2.24 (d, $J$ = 1.4 Hz, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.8, 151.6, 143.0, 133.0, 133.0, 130.6, 128.9, 128.7, 128.5, 128.2, 125.9, 125.2, 122.8, 120.9, 102.8, 15.3. IR (KBr, cm$^{-1}$) 3061, 1685, 1468, 1376, 1191, 797, 756. HRMS-TOF; [M + H]$^+$ Calcd for C$_{18}$H$_{15}$N$_2$O 275.11789, found: 275.11993.

4.26.5.2 5-methylene-2-phenyl-5,6-dihydropyrazolo[1,5-d][1,4]benzoxazepine (300)

mp =109-110 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.95 − 7.90 (m, 2H, arom.), 7.84 (dd, $J$ = 8.0, 1.5 Hz, H$_{11}$), 7.47 − 7.41 (m, 2H, arom.), 7.37 (ddd, $J$ = 7.3, 3.7, 1.2 Hz, H$_8$), 7.31 − 7.25 (m, 1H, arom.), 7.18 − 7.13 (m, 1H, arom.), 7.10 (dd, $J$ = 8.1, 1.2 Hz, H$_{10}$), 7.03 (s, H$_1$), 6.06 (s, H$_6$), 4.95 (s, H$_3$), 4.81 (s, -CH$_2$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.5, 152.4, 141.7, 141.6, 132.8, 130.0, 129.0, 128.8, 128.5, 126.1, 123.8, 120.9, 119.7, 104.0, 103.2, 72.7. IR (KBr, cm$^{-1}$) 2987, 1652, 1578, 1452, 1378, 1214, 1017, 884, 770, 699. HRMS-TOF; [M + H]$^+$ Calcd for C$_{18}$H$_{15}$N$_2$O 275.11789, found: 275.11999.
4.26.5.3 2-phenyl-7H-pyrazolo[1,5-e][1,5]benzoxazocine (299)

colorless cubic crystal from CHCl₃-petroleum ether. mp: 118-119 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.88 – 7.83 (m, 2H, arom.), 7.47 – 7.39 (m, 4H, arom.), 7.37 – 7.30 (m, 1H, arom.), 7.25 – 7.17 (m, 2H, arom.), 7.06 (dt, J = 9.9, 1.9 Hz, H₅), 6.66 (s, H₁), 5.42 (dt, J = 9.9, 3.6 Hz, H₆), 4.87 (dd, J = 3.6, 1.9 Hz, -CH₂). ¹³C NMR (100 MHz, CDCl₃) δ 156.3, 153.0, 143.2, 132.9, 131.3, 131.2, 128.9, 128.8, 128.3, 125.9, 124.6, 124.2, 122.1, 118.9, 104.6, 72.4. IR (KBr, cm⁻¹) 2997, 1652, 1579, 1452, 1375, 1212, 1017, 770, 697. HRMS-TOF; [M + H]+ Calcd for C₁₈H₁₅N₂O 275.11789, found: 275.11989.

4.26.6. Formation of Cyclization Products 245b, 246b and 270b

5-[2-(prop-2-ynyloxy)phenyl]-1H-pyrazole (297) (100 mg, 0.5 mmol) was dissolved in acetonitrile (10 mL) and catalytic amount of gold (III) chloride (5 mg, 1.6x10⁻² mmol) was added to this solution. Then, this mixture was refluxed for 18 h. The reaction was monitored on TLC. After the consuming of the starting material, acetonitrile was evaporated and the crude product was purified by column chromatography and preparative TLC eluting with hexane/EtOAC (20 : 1) to give corresponding products 304 (31 mg, 31%), 302 (46 mg, 46%) and 303 (23 mg, 23%).

4.26.6.1 7H-pyrazolo[1,5-e][1,5]benzoxazocine (302)

colorless oil. ¹H NMR (400 MHz, CDCl₃) δ 7.72 (s, H₂), 7.42 (dt, J = 1.7, 7.9 Hz, H₁₂), 7.34 (dd, J = 7.7, 1.6 Hz, H₉), 7.22 – 7.15 (m, H₁₀ and H₁₁), 7.01 (br dt, J = 9.9, 1.8 Hz, H₅), 6.36 (s, H₁), 5.38 (dt, J = 9.9, 3.5 Hz, H₆), 4.84 (dd, J = 3.5, 1.8 Hz, H₇). ¹³C NMR (100 MHz, CDCl₃) δ 156.3, 141.9, 141.2, 131.2, 131.2, 128.7, 124.6, 124.3, 122.1, 118.9, 107.3, 72.4. IR (KBr, cm⁻¹) 2918, 1649, 1578, 1454, 1421, 1219, 1201, 1079, 1012, 756, 744, 733, 690, 680. HRMS-TOF; [M + H]+ Calcd for C₁₂H₁₁N₂O 199.08659, found: 199.08664.
4.26.6.2 5-methylpyrazolo[1,5-d][1,4]benoxazepine (304)

White tiny needles from CHCl₃-petroleum ether. mp: 55-56 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.67 (d, J = 1.9 Hz, H₂), 7.50 (dd, J = 7.7, 1.7 Hz, H₁₁), 7.36 – 7.31 (m, H₉), 7.19 (dt, J = 1.2, 7.5 Hz, H₁₀), 7.10 (dd, J = 8.1, 1.1 Hz, H₈), 6.55 (d, J = 1.9 Hz, H₁), 6.28 (q, J = 1.4 Hz, H₆), 2.19 (d, J = 1.4 Hz, -CH₃). ¹³C NMR (100 MHz, CDCl₃) δ 157.9, 141.7, 140.1, 133.2, 130.7, 129.0, 128.3, 125.3, 122.8, 120.9, 105.6, 15.3. IR (KBr, cm⁻¹) 2967, 1745, 1686, 1470, 1407, 1228, 1201, 1107, 924, 765, 674. HRMS-TOF; [M + H]+ Calcd for C₁₂H₁₁N₂O 199.08659, found: 199.08642

4.26.6.3 5-methylene-5,6-dihydropyrazolo[1,5-d][1,4]benoxazepine (303)

White tiny needles from CHCl₃/petroleum ether. mp = 56-57 °C. ¹H NMR (400 MHz, CDCl₃) δ 7.76 (dd, J = 8.0, 1.5 Hz, H₁₁), 7.67 (d, J = 1.8 Hz, H₂), 7.29 – 7.23 (m, H₉), 7.14 – 7.06 (m, H₈ and H₁₀), 6.71 (d, J = 1.8 Hz, H₁), 6.28 (q, J = 1.4 Hz, H₆), 4.93 (s, H₄), 4.77 (s, H₃). ¹³C NMR (100 MHz, CDCl₃) δ 157.2, 141.5, 140.9, 129.9, 128.8, 123.6, 120.7, 119.6, 119.4, 106.6, 103.2, 72.4. IR (KBr, cm⁻¹) 2923, 1648, 1580, 1532, 1468, 1408, 1382, 1208, 1102, 1002, 923, 878, 786, 764, 522. HRMS-TOF; [M + H]+ Calcd for C₁₂H₁₁N₂O 199.08659, found: 199.08667.

4.26.7 General Procedure of Sonogashira Coupling Reactions for Derivatization

To a solution of 3-phenyl-5-[2-(prop-2-ynloyloxy)phenyl]-1H-pyrazole (290) (0.25 g, 0.9 mmol) in dry THF (10 mL), iodobenzene (0.1 mL, 0.9 mmol) or bromopyridine (0.1 mL, 0.9 mmol), PPh₃ (10 mg, 0.2 mmol), Pd(Cl)₂ (2 mg, 0.05 mmol), dry diisopropylamine (0.2 mL, 1.4 mmol) and CuI (5 mg, 0.15 mmol) were added. The resulting mixture was refluxed for 4 h. After the completion of the reaction, the reaction mixture was cooled to rt and filtered over celite. The residue was washed with ethyl acetate. The organic solvents in filtrate were removed under the vacuum, the crude product was purified by column chromatography eluting with ethyl acetate/hexane (1:20) to give corresponding products 305 and 306.

2-{3-[2-(3-phenyl-1H-pyrazol-5-yl)phenoxy]prop-1-ynyl}pyridine (305)
yellow oil.  $^1$H NMR (400 MHz, CDCl$_3$) 8.51 (d, $J = 4.8$ Hz, 1H), 7.83 – 7.77 (m, 2H, arom.), 7.69 (dd, $J = 7.7$, 1.5 Hz, 1H, arom.), 7.60 – 7.52 (m, 1H, arom.), 7.39 – 7.31 (m, 3H, arom.), 7.30 – 7.21 (m, 2H, arom.), 7.20 – 7.16 (m, 1H, arom.), 7.12 (d, $J = 8.4$ Hz, 1H), 7.07 – 7.00 (m, 1H), 6.90 (s, 1H), 5.03 (d, $J = 1.4$ Hz, 2H, H$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 158.0, 154.9, 152.24, 149.3, 142.5, 139.5, 136.6, 132.8, 130.2, 128.9, 128.8, 128.6, 126.2, 126.0, 123.7, 121.7, 120.9, 120.1, 117.5, 104.5, 68.7.

IR (KBr, cm$^{-1}$) 2955, 1640, 1578, 1454, 1363, 1220, 1201, 1079, 955, 755, 744, 690.

HRMS-TOF; [M + H]$^+$ Calcd for C$_{24}$H$_{18}$N$_2$O$_3$ 351.14919, found: 351.14949

3-phenyl-5-[2-[(3-phenylprop-2-ynyl)oxy]phenyl]-1H-pyrazole (306)

isolated yield: (0.21 g, 60%), white needle crystal from CHCl$_3$, mp 137-138 °C.  $^1$H NMR (400 MHz, CDCl$_3$) δ 7.89 – 7.84 (m, 2H, arom.), 7.77 (dd, $J = 7.7$, 1.5 Hz, H$_6$), 7.48 – 7.39 (m, 4H, arom.), 7.38 – 7.30 (m, 5H, arom.), 7.23 (d, $J = 8.2$ Hz, 1H), 7.13 (dt, $J = 0.9$, 7.5 Hz, H$_5$), 6.97 (s, H$_4$), 5.12 (s, -CH$_2$).  $^{13}$C NMR (100 MHz, CDCl$_3$) δ 154.3, 150.8, 142.0, 133.1, 131.9 (2 C), 129.4, 128.9 (2 C), 128.8, 128.4 (2 C), 128.3, 128, 125.8 (2 C), 122.2, 122.0, 118.5, 113.5, 100.6, 88.2, 83.2, 57.4.  IR (KBr, cm$^{-1}$) 3224, 1567, 1491, 1216, 1020, 968, 810, 748,689. HRMS-TOF; [M + H]$^+$ Calcd for C$_{24}$H$_{18}$N$_2$O 351.14919, found: 351.14949

4.26.8 Synthesis of Pyridine Substituted Benzopyrazoloazepine Derivatives

The starting compound (305) (100 mg, 0.28 mmol) was dissolved in acetonitrile (10 mL) and catalytic amount of gold (III) chloride (3 mg, 0.9×10$^{-2}$ mmol) was added to this solution. Then, this mixture was refluxed for 18 h. The reaction was monitored on TLC. After the consuming of the starting material, acetonitrile was evaporated and the crude product was purified by column chromatography and preparative TLC eluting with hexane/EtOAC (20 : 1) to give corresponding products 307 (50 mg, crude yield: 50%), 308 (50 mg, crude yield: 50%)
**1H NMR** (400 MHz, CDCl₃) δ 8.49 (br s, 1H), 7.91 – 7.77 (m, 2H, arom.), 7.56 – 7.49 (m, 2H), 7.42 (br t, J = 7.4 Hz, 2H, arom.), 7.36 – 7.30 (m, 2H, arom.), 7.27 (br d, J = 2.3 Hz, 1H, arom.), 7.19 (dt, J = 0.9, 7.5 Hz, 1H, arom.), 7.10 (dd, J = 7.9, 0.7 Hz, 2H, arom.), 6.81 (s, 1H), 6.45 (s, 1H), 4.24 (s, -CH₂).

**13C NMR** (100 MHz, CDCl₃) δ 157.7, 157.5, 151.5, 148.4, 143.2, 137.5, 135.5, 132.7, 130.8, 129.8, 128.9, 128.8, 128.3, 125.8, 125.3, 124.0, 122.3, 122.1, 121.2, 103.0, 37.3

**HRMS-TOF:** [M + H]⁺ Calcd for C₂₃H₁₈N₃O 352.14444, found: 352.14505.

(5E)-2-phenyl-5-(pyridin-2-ylmethylene)-5,6-dihydropyrazolo[1,5-d][1,4]benzoxazepine (308)

White needles crystal from CHCl₃-petroleum ether. mp: 129-130 °C.

**1H NMR** (400 MHz, CDCl₃) δ 8.66 (d, J = 3.7 Hz, 1H, arom.), 7.97 (d, J = 7.2 Hz, 2H, arom.), 7.83 (d, J = 7.8 Hz, 1H, arom.), 7.69 (dt, J = 7.7, 1.7 Hz, 1H, arom.), 7.66 (s, 1H), 7.47 (t, J = 7.5 Hz, 2H, arom.), 7.43 – 7.37 (m, 2H, arom.), 7.30 (dd, J = 7.9, 1.0 Hz, 1H, arom.), 7.16 (dd, J = 9.3, 5.7 Hz, 3H), 7.07 (s, H₁), 5.77 (s, -CH₂). **13C NMR** (100 MHz, CDCl₃) δ 158.0, 154.9, 152.2, 149.3, 142.5, 139.5, 136.6, 132.8, 130.2, 128.9, 128.8 (2 C), 128.6, 126.2 (2 C), 126.03 123.7, 121.7, 120.9, 120.08, 117.6, 104.5, 68.7. **IR** (KBr, cm⁻¹) 2920, 1650, 1465, 1454, 1367, 1201, 1080, 1004, 890, 756, 743, 680. **HRMS-TOF:** [M + H]⁺ Calcd for C₂₃H₁₈N₃O 352.14444, found: 352.14492.

### 4.26.9 The Synthesis of Benzene Substituted Benzopyrazoloaxazepine Derivatives

The starting compound (308) (180 mg, 0.51 mmol) was dissolved in acetonitrile (15 mL) and catalytic amount of gold (III) chloride (5 mg, 1.5x10⁻² mmol) was added to this solution. Then, this mixture was refluxed for 48 h. The reaction was monitored on TLC. After the consuming of the starting material, acetonitrile was evaporated and the crude product was purified by column chromatography and preparative TLC eluting with hexane/EtOAC (10 : 1) to give corresponding products 309 (135 mg, crude yield: 75%), 310 (45 mg, crude yield: 25%)
5-benzyl-2-phenylpyrazolo[1,5-d][1,4]benzoxazepine (309)

\[ \text{\textbf{H NMR}} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 7.93 - 7.79 \ (m, 2H, \text{arom.}), \]
\[ 7.46 - 7.22 \ (m, 10H, \text{arom.}), \ 6.99 \ (d, \ J = 7.6 \text{ Hz, 2H, arom.}), \]
\[ 6.72 \ (s, 1H, \text{arom.}), \ 6.32 \ (\text{quasi t}, 1H, \text{arom.}), \ 4.87 - 4.78 \ (m, \]
\[ 1H, \text{ A part of AB system}), \ 4.70 - 4.61 \ (1H, \text{ B part of AB system}). \]
\[ \text{\textbf{C NMR}} \ (100 \text{ MHz, CDCl}_3) \ \delta \ 154.5, 154.2, 146.6, \]
\[ 146.3, 134.9, 133.7, 132.8, 130.9, 129.7, 128.6, 128.5, 128.2, 127.1, 125.9, 121.3, \]
\[ 120.4, 117.4, 117.2, 105.0, 77.4, 77.0, 76.7, 65.0. \]
\[ \text{IR} \ (\text{KBr, cm}^{-1}) \ 1654, 1584, 1465, 1448, 1363, 1201, 1079, 1040, 765, 750, 690, 640. \]

\textbf{(5E)-5-benzylidene-2-phenyl-5,6-dihydropyrazolo[1,5-d][1,4]benzoxazepine (310)}

\[ \text{\textbf{H NMR}} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 7.86 - 7.77 \ (m, 1H), \ 7.69 - \]
\[ 7.61 \ (m, 1H), \ 7.41 - 7.25 \ (m, 10H), \ 7.12 \ (t, \ J = 7.4 \text{ Hz, 2H}), \]
\[ 7.06 \ (s, 1H), \ 6.56 \ (s, 1H), \ 4.90 \ (s, 2H). \]
\[ \text{IR} \ (\text{KBr, cm}^{-1}) \ 1464, \ 1442, 1208, 1010, 908, 752, 731, 691, 516. \]
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(114) Sha, Q.; Wei, Y. Synthesis (Stuttg). 2013, 45, 413–420.


APPENDIX A

SPECTRAL DATA

Figure 16: $^1$H NMR Spectrum of Compound 70
Figure 17: $^{13}$C NMR Spectrum of Compound 70

Figure 18: IR Spectrum of Compound 70
Figure 19: $^1$H NMR Spectrum of Compound 71a

Figure 20: $^{13}$C NMR Spectrum of Compound 71a
Figure 21: IR Spectrum of Compound 71a

Figure 22: $^1$H NMR Spectrum of Compound 71b
Figure 23: $^{13}$C NMR Spectrum of Compound 71b

Figure 24: $^1$H NMR Spectrum of Compound 71c
Figure 25: $^{13}$C NMR Spectrum of Compound 71c

Figure 26: IR Spectrum of Compound 71c
Figure 27: $^1$H NMR Spectrum of Compound 71d

Figure 28: $^{13}$C NMR Spectrum of Compound 71d
Figure 29: $^1$H NMR Spectrum of Compound 71e

Figure 30: $^{13}$C NMR Spectrum of Compound 71e
Figure 31: IR Spectrum of Compound 71e

Figure 32: $^1$H NMR Spectrum of Compound 71f
Figure 33: $^{13}$C NMR Spectrum of Compound 71f

Figure 34: $^1$H NMR Spectrum of Compound 71g
Figure 35: $^{13}$C NMR Spectrum of Compound 71g

Figure 36: $^1$H NMR Spectrum of Compound 80a
Figure 37: $^{13}$C NMR Spectrum of Compound 80a

Figure 38: IR Spectrum of Compound 80a
Figure 39: $^1$H NMR Spectrum of Compound 80b

Figure 40: $^{13}$C NMR Spectrum of Compound 80b
Figure 41: IR Spectrum of Compound 80b

Figure 42: $^1$H NMR Spectrum of Compound 80c
Figure 43: IR Spectrum of Compound 80c

Figure 44: $^{13}$C NMR Spectrum of Compound 80c
Figure 45: $^1$H NMR Spectrum of Compound 80d

Figure 46: $^{13}$C NMR Spectrum of Compound 80d
Figure 47: $^1$H NMR Spectrum of Compound 80e

Figure 48: IR Spectrum of Compound 80e
Figure 49: $^{13}$C NMR Spectrum of Compound 80e

Figure 50: IR Spectrum of Compound 80e
Figure 51: $^1$H NMR Spectrum of Compound 80f

Figure 52: $^{13}$C NMR Spectrum of Compound 80f
Figure 53: IR Spectrum of Compound 80f

Figure 54: $^1$H NMR Spectrum of Compound 80g
Figure 55: IR Spectrum of Compound 80g

Figure 56: $^{13}$C NMR Spectrum of Compound 80g
Figure 57: $^1$H NMR Spectrum of Compound 72a

Figure 58: $^{13}$C NMR Spectrum of Compound 72a
Figure 59: IR Spectrum of Compound 72a

Figure 60: IR Spectrum of Compound 72b
Figure 61: $^1$H NMR Spectrum of Compound 72b

Figure 62: $^1$H NMR Spectrum of Compound 72c
Figure 63: IR Spectrum of Compound 72c

Figure 64: $^{13}$C NMR Spectrum of Compound 72c
Figure 65: IR Spectrum of Compound 72d

Figure 66: $^1$H NMR Spectrum of Compound 72d
Figure 67: $^1$H NMR Spectrum of Compound 72e

Figure 68: IR Spectrum of Compound 72e
Figure 69: $^1$H NMR Spectrum of Compound 72f

Figure 70: $^{13}$C NMR Spectrum of Compound 72f
Figure 71: IR Spectrum of Compound 72f

Figure 72: $^1$H NMR Spectrum of Compound 72g
Figure 73: IR Spectrum of Compound 72g

Figure 74: $^1$H NMR Spectrum of Compound 73a
Figure 75: $^{13}$C NMR Spectrum of Compound 73a

Figure 76: IR Spectrum of Compound 73b

179
Figure 77: $^1$H NMR Spectrum of Compound 73b

Figure 78: $^{13}$C NMR Spectrum of Compound 73b
Figure 79: IR Spectrum of Compound 73b

Figure 80: $^1$H NMR Spectrum of Compound 73c
Figure 81: $^{13}$C NMR Spectrum of Compound 73c

Figure 82: IR Spectrum of Compound 73c
Figure 83: $^1$H NMR Spectrum of Compound 73d

Figure 84: $^{13}$C NMR Spectrum of Compound 73d
Figure 85: IR Spectrum of Compound 73d

Figure 86: IR Spectrum of Compound 73e
Figure 87: $^1$H NMR Spectrum of Compound 73e

Figure 88: $^{13}$C NMR Spectrum of Compound 73e
Figure 89: $^1$H NMR Spectrum of Compound 73f

Figure 90: $^{13}$C NMR Spectrum of Compound 73f
Figure 91: IR Spectrum of Compound 73f

Figure 92: $^1$H NMR Spectrum of Compound 73g
Figure 93: IR Spectrum of Compound 73g

Figure 94: $^{13}$C NMR Spectrum of Compound 73g
Figure 95: $^1$H NMR Spectrum of Compound 74a

Figure 96: $^{13}$C NMR Spectrum of Compound 74a
Figure 97: IR Spectrum of Compound 74a

Figure 98: IR Spectrum of Compound 74b
Figure 99: $^1$H NMR Spectrum of Compound 74b

Figure 100: $^{13}$C NMR Spectrum of Compound 74b
Figure 101: $^1$H NMR Spectrum of Compound 74c

Figure 102: $^{13}$C NMR Spectrum of Compound 74c
Figure 103: IR Spectrum of Compound 74c

Figure 104: $^1$H NMR Spectrum of Compound 74d
Figure 105: $^{13}$C NMR Spectrum of Compound 74d

Figure 106: IR Spectrum of Compound 74d
Figure 107: $^1$H NMR Spectrum of Compound 74e

Figure 108: $^{13}$C NMR Spectrum of Compound 74e
Figure 109: IR Spectrum of Compound 74e

Figure 110: $^1$H NMR Spectrum of Compound 74f
Figure 111: IR Spectrum of Compound 74f

Figure 112: $^{13}$C NMR Spectrum of Compound 74f
Figure 113: $^1$H NMR Spectrum of Compound 74g

Figure 114: $^{13}$C NMR Spectrum of Compound 74g
Figure 115: IR Spectrum of Compound 74g

Figure 116: $^1$H NMR Spectrum of Compound 149b
Figure 117: $^{13}$C NMR Spectrum of Compound 149b

Figure 118: IR Spectrum of Compound 149b
Figure 119: $^1$H NMR Spectrum of Compound 251

Figure 120: $^{13}$C NMR Spectrum of Compound 251
Figure 121: IR Spectrum of Compound 251

Figure 122: $^1$H NMR Spectrum of Compound 252
Figure 123: $^{13}$C NMR Spectrum of Compound 252

Figure 124: IR Spectrum of Compound 252
Figure 125: $^1$H NMR Spectrum of Compound 254

Figure 126: $^{13}$C NMR Spectrum of Compound 254
Figure 127: IR Spectrum of Compound 254

Figure 128: $^1$H NMR Spectrum of Compound 255
Figure 129: $^{13}$C NMR Spectrum of Compound 255

Figure 130: IR Spectrum of Compound 255
Figure 131: $^1$H NMR Spectrum of Compound 256

Figure 132: $^{13}$C NMR Spectrum of Compound 256
Figure 133: IR Spectrum of Compound 256

Figure 134: $^1$H NMR Spectrum of Compound 257
Figure 135: $^{13}$C NMR Spectrum of Compound 257

Figure 136: IR Spectrum of Compound 257
Figure 137: $^1$H NMR Spectrum of Compound 258

Figure 138: $^{13}$C NMR Spectrum of Compound 258
Figure 139: IR Spectrum of Compound 258

Figure 140: $^1$H NMR Spectrum of Compound 259
Figure 141: IR Spectrum of Compound 259

Figure 142: $^{13}$C NMR Spectrum of Compound 259
Figure 143: COSY Spectrum of Compound 259

Figure 144: DEPT 90 Spectrum of Compound 259
Figure 145: DEPT 135 Spectrum of Compound 259

Figure 146: HMBC Spectrum of Compound 259
Figure 147: HSQC Spectrum of Compound 259

Figure 148: $^1$H NMR Spectrum of Compound 263
Figure 149: IR Spectrum of Compound 263

Figure 150: $^{13}$C NMR Spectrum of Compound 263
Figure 151: $^1$H NMR Spectrum of Compound 264

Figure 152: $^{13}$C NMR Spectrum of Compound 264
Figure 153: IR Spectrum of Compound 264

Figure 154: $^1$H NMR Spectrum of Compound 265
Figure 155: $^{13}$C NMR Spectrum of Compound 265

Figure 156: IR Spectrum of Compound 265
Figure 157: $^1$H NMR Spectrum of Compound 266

Figure 158: $^{13}$C NMR Spectrum of Compound 266
Figure 159: IR Spectrum of Compound 266

Figure 160: $^1$H NMR Spectrum of Compound 267
Figure 161: IR Spectrum of Compound 267

Figure 162: $^{13}$C NMR Spectrum of Compound 267
Figure 163: $^1$H NMR Spectrum of Compound 268

Figure 164: $^{13}$C NMR Spectrum of Compound 268
Figure 165: $^1$H NMR Spectrum of Compound 269

Figure 166: $^{13}$C NMR Spectrum of Compound 269
Figure 167: $^1$H NMR Spectrum of Compound 270a

Figure 168: $^{13}$C NMR Spectrum of Compound 270a
Figure 169: IR Spectrum of Compound 270a
Figure 170: $^1$H NMR Spectrum of Compound 270b

Figure 171: IR Spectrum of Compound 270b
Figure 172: $^{13}$C NMR Spectrum of Compound 270b

Figure 173: $^1$H NMR Spectrum of Compound 270c
Figure 174: $^{13}$C NMR Spectrum of Compound 270c

Figure 175: IR Spectrum of Compound 270c
Figure 176: $^1$H NMR Spectrum of Compound 270d
Figure 177: IR Spectrum of Compound 270d

Figure 178: $^{13}$C NMR Spectrum of Compound 270d
Figure 179: $^1$H NMR Spectrum of Compound 270e

Figure 180: $^{13}$C NMR Spectrum of Compound 270e
Figure 181: IR Spectrum of Compound 270e

Figure 182: $^1$H NMR Spectrum of Compound 270f
Figure 183: $^{13}$C NMR Spectrum of Compound 270f

Figure 184: IR Spectrum of Compound 270f
Figure 185: $^1$H NMR Spectrum of Compound 270g

Figure 186: $^{13}$C NMR Spectrum of Compound 270g
Figure 187: IR Spectrum of Compound 270h

Figure 188: 1H NMR Spectrum of Compound 270h
Figure 189: $^{13}$C NMR Spectrum of Compound 270h

Figure 190: IR Spectrum of Compound 270h
Figure 191: $^1$H NMR Spectrum of Compound 277

Figure 192: $^{13}$C NMR Spectrum of Compound 277
Figure 193: $^1$H NMR Spectrum of Compound 168

Figure 194: $^{13}$C NMR Spectrum of Compound 168
Figure 195: $^1$H NMR Spectrum of Compound 278

Figure 196: $^{13}$C NMR Spectrum of Compound 278
Figure 197: $^1$H NMR Spectrum of Compound 279

Figure 198: $^{13}$C NMR Spectrum of Compound 279
Figure 199: IR Spectrum of Compound 279

Figure 200: $^1$H NMR Spectrum of Compound 280
Figure 201: $^{13}$C NMR Spectrum of Compound 280

Figure 202: IR Spectrum of Compound 280
Figure 203: $^1$H NMR Spectrum of Compound 281

Figure 204: $^{13}$C NMR Spectrum of Compound 281
Figure 205: IR Spectrum of Compound 281

Figure 206: $^1$H NMR Spectrum of Compound 240
Figure 207: IR Spectrum of Compound 240

Figure 208: $^{13}$C NMR Spectrum of Compound 240
Figure 209: $^1$H NMR Spectrum of Compound 241

Figure 210: IR Spectrum of Compound 241
Figure 211: $^{13}$C NMR Spectrum of Compound 241

Figure 212: $^1$H NMR Spectrum of Compound 242
Figure 213: $^{13}$C NMR Spectrum of Compound 242

Figure 214: IR Spectrum of Compound 242
Figure 215: $^1$H NMR Spectrum of Compound 282

Figure 216: $^{13}$C NMR Spectrum of Compound 282
Figure 217: $^1$H NMR Spectrum of Compound 285

Figure 218: $^{13}$C NMR Spectrum of Compound 285
Figure 219: $^1$H NMR Spectrum of Compound 295

Figure 220: $^{13}$C NMR Spectrum of Compound 295
Figure 221: $^1$H NMR Spectrum of Compound 296

Figure 222: $^{13}$C NMR Spectrum of Compound 296
Figure 223: $^1$H NMR Spectrum of Compound 286

Figure 224: $^{13}$C NMR Spectrum of Compound 286
Figure 225: $^1$H NMR Spectrum of Compound 297

Figure 226: $^{13}$C NMR Spectrum of Compound 297
Figure 227: $^1$H NMR Spectrum of Compound 290
Figure 228: $^{13}$C NMR Spectrum of Compound 290

Figure 229: IR Spectrum of Compound 290
Figure 230: $^1$H NMR Spectrum of Compound 291

Figure 231: $^{13}$C NMR Spectrum of Compound 291
Figure 232: IR Spectrum of Compound 291

Figure 233: $^1$H NMR Spectrum of Compound 293
Figure 234: $^{13}$C NMR Spectrum of Compound 293

Figure 235: DEPT 90 Spectrum of Compound 293
Figure 236: DEPT 135 Spectrum of Compound 293

Figure 237: COSY Spectrum of Compound 293
Figure 238: HMBC Spectrum of Compound 293

Figure 239: HSQC Spectrum of Compound 293
Figure 240: IR Spectrum of Compound 293

Figure 241: $^1$H NMR Spectrum of Compound 298
Figure 242: $^{13}$C NMR Spectrum of Compound 298

Figure 243: DEPT 90 Spectrum of Compound 298
Figure 244: DEPT 135 Spectrum of Compound 298

Figure 245: COSY Spectrum of Compound 298
Figure 246: HMBC Spectrum of Compound 298

Figure 247: HSQC Spectrum of Compound 298
Figure 248: IR Spectrum of Compound 298

Figure 249: $^1$H NMR Spectrum of Compound 301
Figure 250: $^{13}$C NMR Spectrum of Compound 301

Figure 251: DEPT 90 Spectrum of Compound 301
Figure 252: DEPT 135 Spectrum of Compound 301

Figure 253: COSY Spectrum of Compound 301
Figure 254: HMBC Spectrum of Compound 301

Figure 255: IR Spectrum of Compound 301
Figure 256: $^1$H NMR Spectrum of Compound 300

Figure 257: $^{13}$C NMR Spectrum of Compound 300
Figure 258: COSY Spectrum of Compound 300

Figure 259: DEPT 90 Spectrum of Compound 300
Figure 260: DEPT 135 Spectrum of Compound 300

Figure 261: HMBC Spectrum of Compound 300
Figure 262: HSQC Spectrum of Compound 300

Figure 263: IR Spectrum of Compound 300
Figure 264: $^1$H NMR Spectrum of Compound 299

Figure 265: $^{13}$C NMR Spectrum of Compound 299
Figure 266: COSY Spectrum of Compound 299

Figure 267: DEPT 90 Spectrum of Compound 299
Figure 268: DEPT 135 Spectrum of Compound 299

Figure 269: HMBC Spectrum of Compound 299
Figure 270: HSQC Spectrum of Compound 299

Figure 271: IR Spectrum of Compound 299
Figure 272: $^1$H NMR Spectrum of Compound 302

Figure 273: $^{13}$C NMR Spectrum of Compound 302
Figure 274: COSY Spectrum of Compound 302

Figure 275: DEPT 90 Spectrum of Compound 302
Figure 276: DEPT 135 Spectrum of Compound 302

Figure 277: HMBC Spectrum of Compound 302
Figure 278: HSQC Spectrum of Compound 302

Figure 279: IR Spectrum of Compound 302
Figure 280: $^1$H NMR Spectrum of Compound 304

Figure 281: $^{13}$C NMR Spectrum of Compound 304
Figure 282: COSY Spectrum of Compound 304

Figure 283: DEPT 90 Spectrum of Compound 304
Figure 284: DEPT 135 Spectrum of Compound 304

Figure 285: HMBC Spectrum of Compound 304
Figure 286: HSQC Spectrum of Compound 304

Figure 287: IR Spectrum of Compound 304
Figure 288: $^1$H NMR Spectrum of Compound 304

Figure 289: $^{13}$C NMR Spectrum of Compound 303
Figure 290: IR Spectrum of Compound 303

Figure 291: $^1$H NMR Spectrum of Compound 306
Figure 292: $^{13}$C NMR Spectrum of Compound 306

Figure 293: IR Spectrum of Compound 306
Figure 294: $^1$H NMR Spectrum of Compound 305
Figure 295: $^{13}$C NMR Spectrum of Compound 305

Figure 296: IR Spectrum of Compound 305
Figure 297: $^1$H NMR Spectrum of Compound 308

Figure 298: $^{13}$C NMR Spectrum of Compound 308
Figure 299: IR Spectrum of Compound 308

Figure 300: $^1$H NMR Spectrum of Compound 307
Figure 301: $^{13}$C NMR Spectrum of Compound 307

Figure 302: $^1$H NMR Spectrum of Compound 309
Figure 303: $^{13}$C NMR Spectrum of Compound 309

Figure 304: IR Spectrum of Compound 309
Figure 305: IR Spectrum of Compound 310

Figure 306: $^1$H NMR Spectrum of Compound 310
VITA

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WORK EXPERIENCES

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**PUBLICATION LIST:**

**International Refereed Journal Papers**


**PROFESSIONAL MEETINGS AND ACTIVITIES:**

**Conferences**

1. Poster Presentation at “Hesaplamalı Kimya Kongresi”, 02-05 June 2015, Kars-Turkey
   **Keskin, S.**; Basceken, S.; Balci, M., Benzopirazolokzazepin ve benzopirazolokzazosin türeverinin sentezi ve reaksiyon mekanizması üzerine teorik çalışmalar.

   **Keskin, S.**; Balci, M., Synthesis of chromenopyridinone and benzopyrazolooxazepine derivatives via alkyne cyclization.

   **Keskin, S.**; Balci, M., Design and Synthesis of Benzene-Fused Heterocycles: Chromenopyridinones and Benzopyrazolooxazepines.

Keskin, S.; Balci, M., Yeni bir yöntemle kromenopiridin, benzokromenopiridin ve kromenopiridinon türevlerinin sentezleri

5. Poster Presentation at “2. Ulusal Organik Kimya Kongresi”, 24-26 September 2014, Ankara-Turkey
Hoplamaz, E.; Keskin, S.; Balci, M., Benzonaftiridin türevlerinin sentezi için yeni yöntemlerin geliştirilmesi

Keskin, S.; Balci, M., Kromenopiridin, benzokromenopiridin ve kromenopiridinon türevlerinin sentezleri için yeni yöntemlerin geliştirilmesi

7. Poster Presentation at “2. İlaç Kongresi”, 21-23 March 2014, Antalya-Turkey
Hoplamaz, E.; Keskin, S.; Balci, M., Benzonaftiridin türevlerinin sentezi için yeni yöntemleri geliştirilmesi

8. Oral Presentation at “1. İlaç Kongresi”, 29-31 March 2013, Antalya-Turkey
Keskin, S.; Koza, G.; Balci, M., Fталазинон ve aminoftalazinon türevlerinin sentezi için yeni metotların geliştirilmesi

Keskin, S.; Koza, G.; Balci, M., Fталазинон, aminoftalazinon ve benzodiazepinon türevlerinin sentezi

Keskin, S.; Koza, G.; Balci, M., Ftalazinon ve aminoftalazinon türevlerinin sentezi için yeni bir yöntemle sentezleri

Keskin, S.; Koza, G.; Balci, M., Yeni bir yöntemle ftalazinon ve aminoftalazinon türevlerinin sentezi