SYNTHESIS OF INDOLE FUSED HETEROCYCLIC COMPOUNDS

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SYNTHESIS OF INDOLE FUSED HETEROCYCLIC COMPOUNDS

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Nitrogen containing heterocyclic compounds show wide range of biological activities so their syntheses have always been attractive area in organic chemistry. Indole derivatives, which are one of the important example of these biological active compound, are precursors to many pharmaceuticals. The aim of this research is to develop new synthetic methodologies leading to the synthesis of new derivatives of pyrimidoindole and quinoline, which have been found to show important biological activities. In this study, an indole derivative was used as a starting compound which was obtained using reaction of Fischer indole cyclization reaction. Reactive molecules such as acyl azide and isocyanate were used as key step reactants and also Curtius rearrangement reaction was used to converte acyl azide to isocyanate. Isocyanates were converted into the corresponding urethane or urea derivatives by treatment with different alcohols and amines, respectively. To reach target pyrimidoindole skeleton, these urea derivatives were used for the intramolecular cyclization. In the second part of this study, ozonolysis reaction were studied on the starting indole compound for obtaining quinoline skeleton.

**Keywords:** Indole, pyrimidoindole, quinoline, acyl azide, isocyanate, Fischer indole synthesis
ÖZ

İNDÖLE KAYNAŞMİŞ HETEROSİKLİK BİLEŞİKLERİN SENTEZİ

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABSTRACT</td>
<td>v</td>
</tr>
<tr>
<td>ÖZ</td>
<td>vi</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>vii</td>
</tr>
<tr>
<td>TABLE OF CONTENTS</td>
<td>ix</td>
</tr>
<tr>
<td>FIGURES</td>
<td>xi</td>
</tr>
<tr>
<td>SCHEMES</td>
<td>xiii</td>
</tr>
<tr>
<td>CHAPTER 1: INTRODUCTION</td>
<td>1</td>
</tr>
<tr>
<td>1.1 Indoles</td>
<td>1</td>
</tr>
<tr>
<td>1.1.1 The Synthesis of indole</td>
<td>4</td>
</tr>
<tr>
<td>1.2 [2,3]-Fused Indole Derivatives</td>
<td>11</td>
</tr>
<tr>
<td>1.3 Quinoline</td>
<td>17</td>
</tr>
<tr>
<td>1.4 The aim of the thesis</td>
<td>19</td>
</tr>
<tr>
<td>CHAPTER 2: RESULTS AND DISCUSSION</td>
<td>21</td>
</tr>
<tr>
<td>2.1 Synthesis of the pyrimidoindole derivatives</td>
<td>21</td>
</tr>
<tr>
<td>2.1.1 Synthesis of the starting compound: Ethyl 3-(2-ethoxy-2-oxoethyl)-1H-indole-2-carboxylate</td>
<td>21</td>
</tr>
<tr>
<td>2.1.2 Synthesis of bis(acyl azide) 140</td>
<td>22</td>
</tr>
<tr>
<td>2.1.3 Synthesis of diurethane derivative 141 from bis(acyl azide) 140</td>
<td>23</td>
</tr>
<tr>
<td>2.1.4 Reaction of urethane 141 with bases</td>
<td>24</td>
</tr>
<tr>
<td>2.1.5 Synthesis of mono isocyanate from bis(acyl azide) 140</td>
<td>25</td>
</tr>
<tr>
<td>2.1.6 Reaction of isocyanate with different nucleophiles</td>
<td>26</td>
</tr>
<tr>
<td>2.1.6 Synthesis of pyrimidoindole derivatives via acyl azide derivatives</td>
<td>28</td>
</tr>
<tr>
<td>2.1.7 Synthesis of N-isopropyl-3-(((isopropylamino)carbonyl)amino)methyl)-1H-indole-2-carboxamide and N-isopropyl-3-[2-(isopropylamino)-2-oxoethyl]-1H-indole-2-carboxamide</td>
<td>29</td>
</tr>
<tr>
<td>2.2Synthesis of quinoline</td>
<td>30</td>
</tr>
<tr>
<td>2.2.1 Synthesis of Ethyl 3-(2-[[ethoxy(oxo)acetyl]amino]phenyl)-3-oxopropanoate via ozonolysis</td>
<td>30</td>
</tr>
<tr>
<td>2.2.2 Synthesis of Diethyl 4-(acetyloxy)quinoline-2,3-dicarboxylate</td>
<td>31</td>
</tr>
<tr>
<td>CHAPTER 3: EXPERIMENT</td>
<td>34</td>
</tr>
<tr>
<td>3.1 General</td>
<td>34</td>
</tr>
<tr>
<td>3.2 Synthesis of (2E)-2-(phenylhydrazono)pentanedioic acid$^{108}$</td>
<td>35</td>
</tr>
<tr>
<td>3.3 Synthesis of ethyl 3-(2-ethoxy-2-oxoethyl)-1H-indole-2-carboxylate$^{108}$</td>
<td>35</td>
</tr>
<tr>
<td>3.4 Synthesis of 3-(carboxymethyl)-1H-indole-2-carboxylic acid</td>
<td>36</td>
</tr>
<tr>
<td>3.5 Synthesis of 3-(2-chloro-2-oxoethyl)-1H-indole-2-carbonyl chloride</td>
<td>36</td>
</tr>
</tbody>
</table>
3.6 Synthesis of 3-(2-azido-2-oxoethyl)-1H-indole-2-carbonyl azide..............................36
3.7 Synthesis of Methyl [2-[(methoxycarbonyl)amino]-1H-indol-3-yl]methyl carbamate37
3.8 Synthesis of 3-(2-isocyanato-2-oxoethyl)-1H-indole-2-carbonyl azide........................37
3.9 Synthesis of 3-[(anilinocarbonyl)amino]methyl]-1H-indole-2-carbonyl azide.............38
3.10 Synthesis of 1-[(3-[(methoxycarbonyl)amino]methyl]-1H-indol-2-yl]carbonyl]triaza-1,2-dien-2-ium .................................................................38
3.11 Synthesis of 2-oxo-N-phenyl-1,2,4,9-tetrahydro-3H-pyrimido[4,5-b]indole-3-carboxamide ..........................................................................................38
3.12 Synthesis of 3-[(isopropylamino)carbonyl]amino]methyl]-1H-indole-2-carbonyl azide.................................................................39
3.13 Synthesis of N-isopropyl-2-oxo-1,2,4,9-tetrahydro-3H-pyrimido[4,5-b]indole-3-carboxamide ..................................................................................39
3.15 Synthesis of N-(tert-butyl)-2-oxo-1,2,4,9-tetrahydro-3H-pyrimido[4,5-b]indole-3-carboxamide ..................................................................................40
3.16 Synthesis of N-isopropyl-3-[(isopropylamino)carbonyl]amino]methyl]-1H-indole-2-carboxamide ..................................................................................41
3.17 Synthesis of N-isopropyl-3-[2-(isopropylamino)-2-oxoethyl]-1H-indole-2-carboxamide ................................................................................41
3.18 Synthesis of Ethyl 3-(2-[(ethoxy]oxo)acetyl]amino]phenyl]-3-oxopropanoate ......42
3.19 Synthesis of Diethyl 4-hydroxyquinoline-2,3-dicarboxylate.................................42
3.20 Synthesis of Diethyl 4-(acetyloxy)quinoline-2,3-dicarboxylate..............................43
CHAPTER 4..........................................................................................44
CONCLUSION ......................................................................................44
REFERENCES ......................................................................................46
APPENDIX ..........................................................................................51
A. SPECTRAL DATA ...........................................................................51
FIGURES

Figure 1 IR spectrum of compound 158 .................................................. 26
Figure 2 A part of HMBC experiment of compound 165 .......................... 30
Figure 3 $^1$H NMR spectrum of compound 146 .................................... 51
Figure 4 $^{13}$C NMR spectrum of compound 146 .................................... 52
Figure 5 IR spectrum of compound 146 .................................................. 52
Figure 6 $^1$H NMR spectrum of compound 138 ....................................... 53
Figure 7 $^{13}$C NMR spectrum of compound 138 ..................................... 53
Figure 8 IR spectrum of compound 138 .................................................. 54
Figure 9 $^1$H NMR spectrum of compound 151 ....................................... 54
Figure 10 $^{13}$C NMR spectrum of compound 151 .................................... 55
Figure 11 IR spectrum of compound 151 ................................................ 55
Figure 12 $^1$H NMR spectrum of compound 152 ....................................... 56
Figure 13 $^{13}$C NMR spectrum of compound 152 .................................... 56
Figure 14 IR spectrum of compound 152 ................................................ 57
Figure 15 $^1$H NMR spectrum of compound 140 ....................................... 57
Figure 16 $^{13}$C NMR spectrum of compound 140 .................................... 58
Figure 17 IR spectrum of compound 140 ................................................ 58
Figure 18 $^1$H NMR spectrum of compound 141 ....................................... 59
Figure 19 $^{13}$C NMR spectrum of compound 141 .................................... 59
Figure 20 IR spectrum of compound 141 ................................................ 60
Figure 21 $^1$H NMR spectrum of compound 158 ....................................... 60
Figure 22 $^{13}$C NMR spectrum of compound 158 .................................... 61
Figure 23 IR spectrum of compound 158 ................................................ 61
Figure 24 $^1$H NMR spectrum of compound 160 ....................................... 62
Figure 25 $^{13}$C NMR spectrum of compound 160 .................................... 62
Figure 26 IR spectrum of compound 160 ................................................ 63
Figure 27 $^1$H NMR spectrum of compound 159 ....................................... 63
Figure 28 $^{13}$C NMR spectrum of compound 159 .................................... 64
Figure 29 IR spectrum of compound 159 ................................................ 64
Figure 30 $^1$H NMR spectrum of compound 157a ..................................... 65
Figure 31 $^{13}$C NMR spectrum of compound 157a .................................... 65
Figure 32 IR spectrum of compound 157a .............................................. 66
Figure 33 $^1$H NMR spectrum of compound 161 ....................................... 66
Figure 34 $^{13}$C NMR spectrum of compound 161 .................................... 67
Figure 35 IR spectrum of compound 161 ................................................ 67
Figure 36 $^1$H NMR spectrum of compound 157b ..................................... 68
Figure 37 $^{13}$C NMR spectrum of compound 157b .................................... 68
Figure 38 IR spectrum of compound 157b .............................................. 69
Figure 39 $^1$H NMR spectrum of compound 162 ....................................... 69
Figure 40 $^{13}$C NMR spectrum of compound 162 .................................... 70
Figure 41 IR spectrum of compound 162 ................................................ 70
Figure 42 $^1$H NMR spectrum of compound 157c ..................................... 71
Figure 43 $^{13}$C NMR spectrum of compound 157c .................................... 71
Figure 44 IR spectrum of compound 157c ................................................................. 72
Figure 45 $^1$H NMR spectrum of compound 165 ......................................................... 72
Figure 46 $^{13}$C NMR spectrum of compound 165 ......................................................... 73
Figure 47 IR spectrum of compound 165 ................................................................. 73
Figure 48 HMBC spectrum of compound 165 .......................................................... 74
Figure 49 COSY spectrum of compound 165 .......................................................... 74
Figure 50 HSQC spectrum of compound 165 .......................................................... 75
Figure 51 $^1$H NMR spectrum of compound 166 ......................................................... 75
Figure 52 $^{13}$C NMR spectrum of compound 166 ......................................................... 76
Figure 53 IR spectrum of compound 166 ................................................................. 76
Figure 54 HMBC spectrum of compound 166 .......................................................... 77
Figure 55 HSQC spectrum of compound 166 .......................................................... 77
Figure 56 COSY spectrum of compound 166 .......................................................... 78
Figure 57 $^1$H NMR spectrum of compound 167 ......................................................... 78
Figure 58 $^{13}$C NMR spectrum of compound 167 ......................................................... 79
Figure 59 IR spectrum of compound 167 ................................................................. 79
Figure 60 $^1$H NMR spectrum of compound 174 ......................................................... 80
Figure 61 $^{13}$C NMR spectrum of compound 174 ......................................................... 80
Figure 62 IR spectrum of compound 167 ................................................................. 81
Figure 63 $^1$H NMR spectrum of compound 178 ......................................................... 81
Figure 64 $^{13}$C NMR spectrum of compound 178 ......................................................... 82
Figure 65 IR spectrum of compound 167 ................................................................. 82
SCHEMES

Scheme 1 Resonance structures of indole ................................................................. 1
Scheme 2 Fischer indole synthesis .............................................................................. 5
Scheme 3 Accepted mechanism for the Fischer indole synthesis ............................... 5
Scheme 4 The Japp-Klingemann reaction ................................................................... 6
Scheme 5 The Japp-Klingemann reaction ................................................................... 6
Scheme 6 Buchwald-Hartwig amination ..................................................................... 7
Scheme 7 Gassman indole synthesis .......................................................................... 7
Scheme 8 Bartoli indole synthesis .............................................................................. 8
Scheme 9 Reissert indole synthesis ........................................................................... 8
Scheme 10 Leimgruber-Batcho Synthesis .................................................................. 9
Scheme 11 Larock indole synthesis .......................................................................... 9
Scheme 12 Nenitzescu indole synthesis ................................................................. 9
Scheme 13 Castro indole synthesis ........................................................................... 9
Scheme 14 Castro indole synthesis .......................................................................... 10
Scheme 15 Synthesis of N-substituted-2-hydroxyindole from homophthalic acids .... 10
Scheme 16 Annulation of pyridine ring to form α-carboline derivative 86 .............. 12
Scheme 17 Intramolecular Diels–Alder reaction of pyrazinone derivative 87 ........ 13
Scheme 18 Synthesis of 5H-pyridazino[4,5-b]indole (100) ..................................... 14
Scheme 19 Synthesis of pyridazinone derivatives 103 ................................. 14
Scheme 20 Synthesis of pyrimido[4,5-b] and [5,4-b]indoles ............................... 16
Scheme 21 Synthesise pyrimido[4,5-b]indole via Nenitzescu synthesis .............. 16
Scheme 22 The Conrad-Limpach quinoline synthesis ............................................ 18
Scheme 23 The Friedländer quinoline synthesis ...................................................... 18
Scheme 24 Target molecules of the study ................................................................ 19
Scheme 25 Synthesis route of pyrimidoindole derivatives .................................... 19
Scheme 26 Synthesis of diester 138 ........................................................................ 21
Scheme 27 Mechanism for the synthesis of 138 ..................................................... 22
Scheme 28 Synthesis of 153 .................................................................................. 23
Scheme 29 Synthesis of diurethane 141 ................................................................. 24
Scheme 30 Ring closure reaction of compound 141 ............................................. 24
Scheme 31 Synthesis of mono isocyanate 158 ....................................................... 25
Scheme 32 Reaction of isocyanate with different nucleophiles ............................ 27
Scheme 33 Synthesis of pyrimidoindole derivative 163 ..................................... 28
Scheme 34 Synthesis of pyrimidoindole derivatives 137a-c .............................. 28
Scheme 35 Synthesis of compounds 165 and 166 .............................................. 29
Scheme 36 Ozonolysis of diester 138 ................................................................. 31
Scheme 37 The mechanism of the ozonolysis reaction of 138 ......................... 31
Scheme 38 Synthesis of quinoline 170 .................................................................. 32
Scheme 39 The synthesis mechanism of 174 ....................................................... 32
Scheme 40 The synthesis of 178 ........................................................................... 33
Scheme 41 First synthesis route of pyrimidoindole derivatives .......................... 44
Scheme 42 Second synthesis route of pyrimidoindole derivatives ...................... 45
Scheme 43 Synthesis route of quinoline derivative ............................................. 45

xiii
LIST OF ABBREVIATIONS

COSY : Correlation spectroscopy
DEPT : Distortionless enhancement by polarization transfer
DMF : Dimethylformamide
DMSO : Dimethylsulfoxide
HETCOR : Heteronuclear Correlation Spectroscopy
HMBC : Heteronuclear multi-bond coherence
HMQC : Heteronuclear multiple quantum coherence
HRMS : High Resolution Mass Spectrum
AIBN: Azobisisobutyronitrile
PPA: Polyphosphoric acid
LiHDMS: Lithium bis(trimethylsilyl)amide
BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
CHAPTER 1

INTRODUCTION

1.1 Indoles

Indole (1) is a bicyclic aromatic heterocyclic compound which is benzene (2) fused through 2 and 3 position of pyrrole ring (3).

Indole has 10 π electrons arising from double bonds and lone pair on nitrogen which are delocalized around the indole ring. In all resonance structures (Scheme 1), some negativity and increased electron density on carbon atoms lead to their description as π-excessive. Because of the delocalization of 10 electrons on 9 atoms (eight carbons and one nitrogen), indole is called as a π-excessive heterocycle. Because of the π-excessive property, indole shows enhanced reactivity in electrophilic aromatic substitution, compared to benzene.

As lone pair of nitrogen is involved in aromatic ring current, indole behaves as a weak base, like pyrrole. So, indole and its derivatives are quite reactive towards strong acids. As a result of various molecular orbital calculations, the C-3 site of indole has the highest electron density and it is the most reactive position towards electrophilic substitution reactions. The C-2 position is the second most reactive site of indole toward electrophiles. The N-H bond in the indole skeleton is weakly acidic. Strong bases can be used to deprotonate the N-H proton. So, under basic conditions, N-substitution reactions, such as alkylations, acylations and transition metal catalyzed arylations take place.
Indole skeleton is present in the structure of many natural products with high structural complexities and biologically active molecules. For this reason, indole and indole derivatives have been used, continuously, in different research areas such as pharmaceuticals, fragrances, agrochemicals, pigments, and material science.

One of the most important indole derivatives is an essential amino acid, tryptophan (4). It is one of the 22 naturally occurring amino acids. This amino acid can not be synthesized by the organisms but must be in their daily diet. Tryptophan plays an important role as a building block in protein biosynthesis. Tryptophan containing proteins have reducing effect on depression and insomnia related with hormonal fluctuations.

Tryptophan is a biochemical precursor to the family of tryptamines, such as serotonin (5-hydroxytryptamine) (5), a key neuro-transmitter in the central nervous system, and melatonin (6), a hormone that regulates function of smooth muscle in the cardiovascular and gastrointestinal systems.

Beside tryptamines, the auxins (phytohormone) are synthesized from tryptophan in human body. Auxins are essential for plant body development. They are found in nature as indole-3-acetic acid (7) and may also be synthesized as indole-3-butyric acid (8).
The indole structure is also present in the indole-3-carbinol (9) which is an important antitumor agent. Controlled researches on the indole-3-carbinol which have been conducted on using laboratory animals and cultured cells, show that it prevents the binding of aflatoxin to DNA. As a result of this blocking, the carcinogenic effects of aflatoxins decrease.\textsuperscript{9-11} A different research also indicates that indole-3-carbinol is effective in the prevention of breast cancer via eliminating the estrogen receptor sites on the membranes of breast.\textsuperscript{12} In addition to these effects, some studies were also carried out on indole-3-carbinol synthesis which showed that it has positive effect on the treatment of skin cancer.\textsuperscript{13}

There are many drugs in circulation whose structures contain the indole nucleus, including sumatriptan (10), a tryptamine\textsuperscript{14} derivative used in treatment of migraine headaches, indomethacin (11) and ethodolac (12),\textsuperscript{15} which are used as non-steroidal anti-inflammatory drugs, and pindolol (13), a β-adrenoceptor antagonist.\textsuperscript{16}
Most of the indole derivatives, which are obtained naturally, are biologically active. For example, reserpine (14) is an antipsychotic and antihypertensive drug which is isolated from the dried root of rauwolfia serpentina (Indian snakeroot), however, today it is rarely used because of its various side effects.\textsuperscript{17} Another example is ellipticine (15) which is an anti-tumor active compound.\textsuperscript{18} Vincristine (16) is a mitotic inhibitor which means that inhibition of mitosis or cell division and used in cancer chemotherapy.\textsuperscript{19,20} Moreover, cytotoxic eudistalbin (17) and dihydroflustramine (18), which has anti-microbial and anti-parasitic activities, are that isolated from marine organisms.\textsuperscript{21}

1.1.1 The Synthesis of indole

The Fischer indole synthesis which was first discovered by a German chemist, Hermann Emil Fischer, in 1883\textsuperscript{22} is the most widely used method among all other indole synthesis.\textsuperscript{23} Basic principle of the fischer indole cyclization reaction is that under acidic conditions, aryl hydrazones (21), which are easily synthesized by condensation of a ketone (20) or an aldehyde with an phenyl hydrazine 19, are converted into substituted indoles (22) with the loss of ammonia (Scheme 2).
The mechanism includes a [3,3]-sigmatropic rearrangement of the ene-hydrazine 23 isomers form of the aryl hydrazone, with cleavage of the N-N bond and formation of a C-C bond. After aromatization, imine 24 form converts into the intermediate 25, then completion of the cyclization produces a cyclic aminoacetal 26. Aromatization by loss of ammonia because of acidic medium provides the substituted indoles 22 (Scheme 3).

Protic and Lewis acids (LA) can be used in the Fischer indole cyclization reactions as catalysts. Acid catalysts accelerate the sigmatropic rearrangement as well as the protonation of aryl hydrazone and ene-hydrazone formation.  

The Fischer indole synthesis allows the attachment amount of different substituents at the 2- and 3- positions and on the aromatic ring with by using different substituted ketones, benzene and hydrazine derivatives.

The Japp-Klingemann coupling of aryl diazonium salts 28 with β-ketoester 29 or β-ketoacid 30 provides an alternative synthesis of aryl hydrazone derivatives (31, 32) which are used in Fischer indole synthesis as intermediates. If β-ketoesters are directly treated with aryl diazonium salt, deacylation follows coupling and then indolization occurs to form indole-2-carboxylate ester (33) by Fischer indole mechanism. When β-ketoacid is used, decarboxylation occurs and the final product is 2-acylindole (34) (Scheme 4).
Recently, some studies on Fischer indole synthesis introduced novel approaches to the traditional synthesis with respect to hydroamination process. For instance, using hydroamination of alkyne syntheses to intermediate aryl hydrazone. Intermolecular titanium amine-catalyst hydroamination reaction of alkynes with 1,1-disubstituted hydrazines forms aryl hydrazone derivatives which are then converted into corresponding indole by using ZnCl₂ as catalyst (Scheme 5). There are different examples of hydroamination process for the formation of aryl hydrazone by using different catalyst.

Another example for the synthesis of aryl hydrazone is Buchwald–Hartwig amination which is a palladium catalyst coupling method. The reaction starts with Pd-catalyzed cross-coupling of aryl bromide with benzophenone hydrazone to produce N-aryl benzophenone hydrazones. Hydrolysis of followed by reaction with ketone provides the corresponding indole derivate in a one pot process (Scheme 6). The advantage of this process is that it is not necessary to isolate any intermediate.
Scheme 6 Buchwald-Hartwig amination

Gassman indole synthesis\(^{29}\) produces substituted indoles from aniline (43) in a one pot reaction. First, oxidation of aniline using \(\text{tert-}\)butyl hypochlorite (tBuOCl) forms chloroamine (44) which then reacts with a \(\beta\)-carbonyl sulfide derivative to produce anilinosulfonylum salt (45). In the last part of the reaction, addition of the \(\text{tert-}\)ethyl amine as a base results in formation of ylide 46 which immediately undergoes a [2,3]-sigmatropic rearrangement to give the ketone 47. After condensation, corresponding sulfur substituted indoles 48 are obtained (Scheme 7). It is easy to convert sulfur substituted indole into 3\(H\)-indole using Raney nickel.

Scheme 7 Gassman indole synthesis

In the Bartoli indole synthesis,\(^{30-32}\) 7-substituted indoles 51 are synthesized by reacting of \(o\)-substituted nitrobenzenes 49 with vinyl Grignard reagents 50 (Scheme 8). \(o\)-Substituted
nitrobenzene must be used for this reaction. Otherwise, the reaction is not successful. As a result of a [3,3]-sigmatropic rearrangement in the mechanism due to the steric bulk of the ortho group. The desired indole derivatives cannot be obtained by using m- or p-substituted nitrobenzene derivatives. The bulky groups at o-position are responsible for a [3,3]sigmatropic shift, which is necessary for the formation of o-substituted indole derivatives. Especially, bromine is a good substituent on the benzene ring that can increase the possibility of sigmatropic rearrangement and it can easily be removed from benzene ring at the end of the reaction. Bartoli indole synthesis is the most efficient method to form indoles substituted on both the benzene ring and the pyrrole ring.

![Scheme 8 Bartoli indole synthesis](image)

The Reissert indole synthesis\(^{33}\) is a base catalyst process to form substituted indole from o-nitrotoluene (52) and diethyl oxalate (53). According to the mechanism of formation, o-nitrotoluene reacts with the diethyl oxalate in the presence of base (KOEt) to give the potassium salt of o-nitrophenylpyruvate (54). Under catalytic hydrogenation conditions, reductive cyclization of this potassium salt generates the amino ketone (55) which was converted into indole-2-carboxylates (56) (Scheme 9). The reductive cyclization has been conducted under different catalytic conditions which are Pt/AcOH, Pd-C/EtOH\(^{34}\) and SnCl\(_2\)-TiCl\(_3\)\(^{35}\).

![Scheme 9 Reissert indole synthesis](image)

Leimgruber–Batcho synthesis\(^{36}\) is a benzene substituted indole synthesis method in which condensation of o-nitrotoluene (52) with N,N-dimethylformamide dimethyl acetate (57) in the presence of pyrrolidine (58) provides o-nitro-β-pyrrolidinostyrene (59). Treatment of 59 with Raney nickel gives the indole 60 substituted only at the benzene ring (Scheme 10).
The Larock indole synthesis\textsuperscript{37} is a more effective method for the synthesis of 2,3-substituted indole (63). It is a single step reaction and also its starting materials are commercially available. In this reaction, unsymmetrical alkyne (62) is submitted to regioselective annulation with \textit{o}-idoaniline (61) under Pd-catalytic condition (Scheme 11). After cyclization, C2 position of the indole is occupied with the bulkiest substituent (R\textsubscript{L}).

<chemical diagram>  

**Scheme 11 Larock indole synthesis**

The Nenitzescu indole synthesis\textsuperscript{38} is used for the preparation of 5-hydroxyindole derivative (66) with substitution in both ring from 1,4-benzoquinone (64) and a \textit{β}-enaminoester (65) (Scheme 12).

<chemical diagram>  

**Scheme 12 Nenitzescu indole synthesis**

Castro indole synthesis\textsuperscript{39} involves 5-\textit{endo-dig} cyclization of alkynylaniline which is a condensation product of \textit{o}-idoaniline (67) with cuprous acetylides (68). The result of this cyclization opens up a way to the construction of various indole derivatives 69 (Scheme 13).

<chemical diagram>  

**Scheme 13 Castro indole synthesis**
Radical cyclization process has also been used for the synthesis of indole derivatives. For instance, Fukuyama et al. have developed a new approach to indole cyclization.\textsuperscript{40,41} In the Fukuyama indole synthesis, a wide range of poly substituted indole derivatives (71) can be prepared by using radical cyclization of 2-alkenylthioanilides (70) (Scheme 14). Usually, tri-$n$-butyl tin hydride is utilized as the reducing agent and 2,2'-azobisisobutyronitrile (AIBN) is used as a radical initiator. Many natural product synthesis have been constructed by using this method.\textsuperscript{42–44}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{Scheme_14.png}
\caption{Castro indole synthesis}
\end{figure}
\end{center}

Recently, Balci et al. have synthesized indole derivatives starting from homophthalic acid derivatives 72. First, homophthalic acids were converted to urea derivative 75 by using isocyanate intermediates 74 which were obtained from azide derivatives 73 via Curtius rearrangement. The ring closure reaction of 75 formed the intermolecular condensation product, $N$-substituted 2-hydroxyindole derivatives 76 (Scheme 15).\textsuperscript{45}

\begin{center}
\begin{figure}
\centering
\includegraphics[width=0.8\textwidth]{Scheme_15.png}
\caption{Synthesis of $N$-substituted-2-hydroxyindole from homophthalic acids}
\end{figure}
\end{center}
1.2 [2,3]-Fused Indole Derivatives

Pyrido[2,3-b]indole (α-carboline) (77) is a tricyclic alkaloid which consists of pyridine ring (78) fused to 2, 3 position of indole ring (1).

α-Carbolines are wide range family of compounds with well-known biological activities, such as antitumor,\textsuperscript{46,47} antiviral,\textsuperscript{48} cytotoxic,\textsuperscript{49} antinflammatory,\textsuperscript{49} and anxiety releasing.\textsuperscript{50} In addition, they are useful for the treatment of cancer and immune-related diseases.\textsuperscript{51} Many naturally occurring alkaloids have pyrido[2,3-b]indole skeleton in their structures. For example, grossularines 1 (79) and 2 (80)\textsuperscript{47,52} were the first isolated naturally occurring α-carboline derivatives having antitumor properties. They were first isolated in 1989 from Dendrodoa grossularia, which have important affects towards solid human tumor cell lines. Another example is mescengricin (81)\textsuperscript{53} isolated as a reddish brown powder from Cryptolepis sanguinolenta to protect chick primary mescencephalic neuronal cells from the L-glutamate toxicity which causes neuronal degeneration during cerebral ischemia and subsequent reperfusion injury. The last example of naturally isolated α-carboline is cryptotackieine (82)\textsuperscript{54} isolated from Streptomyces griseoflavus which is a shrub found in West Africa together with its methyl derivatives have biological properties including antimuscarinic, antibacterial, antiviral, antymicotic, antihyperglycemic, and cytotoxic activities in vivo, and significant antitumor properties in vitro.\textsuperscript{55} Moreover, α-carboline were obtained from condensation of cigarette smoke and pyrolysis of protein-containing food products.\textsuperscript{56,57}
In literature, the best known synthetic approaches to α-carboline involve annulation of pyridine ring to 2-amino 3-substituted indole derivatives. As shown in the Scheme 16, condensation of o-aminonitrile derivative of indole 83 with 1,1-dimethoxy-N,N-dimethylethanamine (DMA-DMA) gave the acetamidine derivative 84. Protection of N1 position of 84 with a methyl group by treatment with methyl iodide enables ring formation under hard conditions. For achievement of ring closure in this reaction, N1 protected acetamidine 85 was converted into corresponding pyridoindole derivative 86 by refluxing in toluene with freshly powdered sodium amide as a strong base. 58.

Scheme 16 Annulation of pyridine ring to form α-carboline derivative 86
The different type of α-carboline synthesis approach includes intramolecular Diels–Alder reaction of alkyl substituted 2(1H)-pyrazinone derivatives 87. In one of the examples from the literature, the pyridoindole derivative 89 has been obtained from cyclization reaction of 87 in the presence of intermediate 88 under reflux condition. Because of this intermediate, a trace amount of corresponding β-carboline 90 was characterized (Scheme 17). 59

Scheme 17 Intramolecular Diels–Alder reaction of pyrazinone derivative 87

Pyridazinoindoles' isomers (Scheme 18) can be considered as aza analogs of different carbolines, especially β- and γ-carbolines such as 94 and 95, which present in many compounds of high physiological activities. 60

Pyridazinoindole aromatic structures 91-93 are pyridazine 96 fused indole derivatives in which the positions of two N-atoms in pyridazine ring are varied. Derivatives of this heterocyclic compounds reveal different important biological activities, such as; antitumor, 61 antihypertensive, 62 antibacterial, anticonvulsive, 63 tuberculostatic, monoamine oxidase inhibitory, 64 blood platelet aggregation inhibitory and thromboxane inhibitory. 65

Surprisingly few synthetic applications have been known so far, despite having its biological activities and preparation simplicity. Benson and his co-worker 66 reported first the
preparation of $5H$-pyridazino[4,5-$b$]indole (100) via cycloaddition of 3-methylindole (97) with the 1,2,4,5-tetrazine (98). Scheme 18 shows the intermediate 99 of this cycloaddition reaction which undergoes N$_2$ elimination followed by hydrogen transfer to form the cycloadduct 100.

![Scheme 18 Synthesis of $5H$-pyridazino[4,5-$b$]indole (100)](image)

Another effective method for synthesizing the pyrimidoindole derivative is based on cyclization process of 2,3-dicarboxylated indole derivatives with hydrazine. In the literature, some examples are reported using this method. One of them is the synthesis of pyridazinone derivatives 103 from N-alkyl 2,3-substituted indole derivatives 102 which was obtained from N-alkyl 2-carboxylic acid ester indole derivative 101 via Vilsmeier–Haack reaction (Scheme 19).

![Scheme 19 Synthesis of pyridazinone derivatives 103](image)

Pyrimido[4,5-$b$]indole (104) and pyrimido[5,4-$b$]indole (105) are the “privileged” indole fused heterocycles which contain pyrimidine ring (106). Their derivatives show biological activity of various types. It is reported that these compounds have anti-asthma, antihypertensive and anti-inflammatory, analgesic and inotropic activities. Studies have shown that they act as $\alpha_1$-adrenergic receptor ligands or A$_1$-adenosine receptor antagonists, potential tyrosine kinases (PTK) inhibitors, CFR-1 and neuro-peptide Y receptor ligands. As a result of their biological activities, it has been reported as some neuro-protective drugs in the treatment of several neurodegenerative disorders such as Amyotrophic Lateral Sclerosis (ALS), Parkinson's disease or Alzheimer's disease.
There are compounds with pharmacologically activities containing pyrimidoindole skeleton, such as; 9H-pyrimido[4,5-b]indol-4-amine\(^7\) (107) which is \(A_1\)-adenosine receptor antagonists, \(\alpha_1\)-adrenergic receptor ligand 108 which is used for cardiovascular diseases\(^,\)\(^7\)\(^5\), antiasthma active PNU-142731A\(^7\)\(^0\) (109), and the last one APEPI (110) which is a potent \(A_1\)-adenosine receptor antagonist\(^7\)\(^6\).

The general routes to synthesize pyrimido[4,5-b]indole or pyrimido[5,4-b]indole derivatives involve amidation of 2-halo 3-carbonylindoles 111 and 2-formyl 3-haloindoles 114 respectively. A recent example of this method was published by Nagarajan et al. As shown in Scheme 20, pyrido[4,5-b]indole derivatives 113 were obtained from cyclization of 112 which were easily synthesized from Pd-catalyzed amidation of 2-halo 3-carbonylindole. Moreover, pyrimido[5,4-b]indole derivatives 116 was synthesized starting from a different substituted indole 114 by using same procedure (Scheme 20)\(^7\).
Troschütz et al. published another efficient method to synthesize pyrimido[4,5-b]indole via Nenitzescu synthesis. It was reported that the mechanism for this reaction was probably the same as the Nenitzescu synthesis mechanism. As shown in Scheme 21, addition of pyrimidine-2,4,6-triamine (118) to 1,4-benzoquinone (117) formed a Michael addition product 119. After oxidation of 119 by 117, which then converted into hydroquinone (120), quinone intermediate 121 was obtained. Intramolecular cyclization and then dehydration by 120 formed final product, 2,4-disubstituted pyrimido[4,5-b]indol-5-ol (122).
1.3 Quinoline

Quinoline (123) is a benzo-fused pyridine and aromatic heterocyclic compound which was first isolated from coal tar in 1834 by F. Runge.\(^8^9\) It is used as an intermediate in production of dye, polymer and agrochemical and in metallurgical chemistry.

\[
\begin{align*}
\text{quinoline} \\
\text{123}
\end{align*}
\]

There are many naturally occurring quinoline derivatives with diverse pharmacological properties.\(^8^1-8^5\) The alkaloid quinine (124) was isolated from cinchona tree bark, which had been already known its antimalarial property.\(^8^6\)

\[
\begin{align*}
\text{quinine} \\
\text{124}
\end{align*}
\]

Antimalarial quinoline derivatives have been synthetically obtained for drug industry since the first isolation of cinchona.\(^8^7,8^8\) Another class of drugs containing quinoline ring is the antibiotics.\(^8^9\) Wide range of biological activities have been found in the quinoline derivatives with the further development in the medicinal chemistry; such as, anti-inflammatory,\(^9^0,9^1\) anti-asthmatic,\(^9^2\) antibacterial,\(^9^3,9^4\) antihypertensive,\(^9^5\) anticancer\(^9^6,9^7\) and tyrosine kinase inhibitory agents.\(^9^8\)

Besides their biological activities, quinolines are currently used in the synthesis of polymer which are thermally stable transparent materials in the fields of electronics, optoelectronics and non-linear optics.\(^9^9-1^0^1\)

Various synthetic methods to obtain quinoline ring have been developed because of the prominence of the ring system in natural products and pharmaceuticals. Although a lot of quinoline synthesis procedures were developed, named after their inventors, some of them will be shortly mentioned here.

In the Conrad-Limpach synthesis, 4-quinolone derivatives 128 were synthesized by using thermal reaction between substituted anilines 125 and \(\beta\)-ketoesters 126. First condensation products 127 are formed. For the cyclization of condensation products 127, solvents with high boiling points such as mineral oil (b.p. > 275 °C), diphenyl ether (b.p. = 259 °C) must
be used. High temperature cyclization is followed by elimination of alcohol to give the corresponding 2,3-substituted quinolones 128 (Scheme 22).  

\[ \text{Scheme 22 The Conrad-Limpach quinoline synthesis} \]

The Conrad-Limpack synthesis is still in use today, with some modifications to obtain many 4-aminoquinolines (129) which are derivatives of antimalarial drugs chloroquine (130).  

Another mostly used quinoline synthesis method is the Friedländer synthesis. In this method, \( o \)-amino aryl aldehydes (or ketones) 131 undergo condensation with an enolizable carbonyl compound 132 via aldol condensation to give the intermediate 133. Base or acid catalyzed cyclization process of 133 followed by elimination of water results in the formation of substituted quinolines 134 (Scheme 23).  

\[ \text{Scheme 23 The Friedländer quinoline synthesis} \]

Niemntowski variation is an extension of the Friedländer synthesis, in which biological active 4-quinolinols 135 are synthesized using this method. Another extension of the Friedländer synthesis is the Pfitzinger method, in which the starting material is much more stable than the Friedländer's and antibacterial active quinoline-4-carboxylic acid derivatives 136 are synthesized using this method.
1.4 The aim of the thesis

The main aim of this thesis was to develop new synthetic methodologies for the construction of pyrimidoindole 137 and quinoline derivatives 139 starting from the 2,3-diester substituted indole derivative 138.

Scheme 24 Target molecules of the study

First, diester 138 will be converted into the corresponding acyl azide 140, which then will be used as a key compound for the synthesis of pyrimidoindole derivatives 137. Intramolecular cyclization of the 2,3-diurethane substituted indole derivative 141, obtained by thermolysis of bis(acyl azide) 140 in methanol, under basic condition, should give 137 (Scheme 25).

Scheme 25 Synthesis route of pyrimidoindole derivatives

Alternatively, corresponding bis(acyl azide) 140 will be converted into the monoisocyanate 142 via controlled Curtius rearrangement to obtain the mono urethane derivatives 143 which
will be trapped with various nucleophiles. Then, the generated urea derivatives will be used in intramolecular cyclization reaction to synthesize the various pyrimidoindole derivatives 137 (Scheme 25).

In the second part of this work, conversion of the 2,3-diester substituted indole derivative 138 to the quinoline derivative 139 via ozonolysis reaction will be studied.
CHAPTER 2

RESULTS AND DISCUSSION

2.1 Synthesis of the pyrimidoindole derivatives

2.1.1 Synthesis of the starting compound: Ethyl 3-(2-ethoxy-2-oxoethyl)-1H-indole-2-carboxylate

Ethyl 3-(2-ethoxy-2-oxoethyl)-1H-indole-2-carboxylate 138 was chosen as the starting compound which was already synthesized by Robinson and Good in 1957 by using Fischer indole synthesis. The diester derivative 138 was prepared from (2E)-2-(phenylhydrazono)pentanedioic acid 146 under strong acidic condition in ethanol at reflux. Phenylhydrazine hydrochloride was treated with ketoglutaric acid in water at room temperature to give condensation product, dicarboxylic acid 146 (Scheme 26).

![Scheme 26 Synthesis of diester 138](image)

According to the formation of mechanism of 138, firstly condensation reaction between phenylhydrazine hydrochloride (144) and ketoglutaric acid (145) forms phenylhydrazone
146, which isomerizes to the respective enamine 147. H⁺-Catalyzed isomerization of the double bond in 147 followed by new C-C bond formation via [3,3]-sigmatropic rearrangement produces imine 148. Aromaticity is regained by tautomerization of proton in 148 to form 149. Cyclization of 149 provide 150. Resulting aminoacetal 150 eliminates NH₃ to give indole 151 which undergoes esterification reaction with ethanol (Scheme 27).

Scheme 27 Mechanism for the synthesis of 138

2.1.2 Synthesis of bis(acyl azide) 140

For the synthesis of the bis(acyl azide) 140, firstly base promoted hydrolysis reaction was done on the diester 138 in the solution of methanol/water (1:1) under reflux temperature to obtain diacid 151. For the formation of bis(acyl azides) 140, it was necessary to convert diacid functionalizes first into the corresponding bis(acylchloride) since chlorine is a better leaving group than the hydroxy groups. In this conversion, oxalyl chloride was used as chlorination agent in the presence of dimethyl formamide as a catalyst in dichloromethane at room temperature. The completion of the reaction was determined by observation of a clear solution because diacid 151 was not soluble in dichloromethane whereas the formed acylchloride 152 was soluble. The loss of signal of the broad hydroxy protons at around 12.6 ppm in NMR spectrum confirmed that chlorination was completed successfully. Then, a solution of chlorinated compound 152 in acetone was treated with aqueous sodium azide solution to form bis(acyl azide) 140 (Scheme 28). Appearance of the characteristic peak of the azides at around 2100 cm⁻¹ in IR spectrum confirmed the formation of bis(acyl azide) 140.
2.1.3 Synthesis of diurethane derivative 141 from bis(acyl azide) 140

The diurethane derivative 141 was synthesized by heating of bis(acyl azide) 140 in methanol. This conversion involves an diisocyanate intermediate 154 which is the Curtius rearrangement product of 140. This intermediate is very reactive therefore undergoes a nucleophilic attack of methanol to produce diurethane derivative 141 in 80% of yield (Scheme 29).
The formed compound was purified by column chromatography and its structure was established by NMR spectroscopy. The synthesized urethane derivative 141 was the key compound for the synthesis of target heterocycles, pyrimidoindole derivatives.

2.1.4 Reaction of urethane 141 with bases

It was expected that there were two possible ring formation reaction pathways on the diurethane 141 because of two different nitrogen units in the molecule (Scheme 30). Our prediction was that base would remove one of the acidic protons on the nitrogen atoms and the formed anion which would attack the carbonyl group of the other urethane group to form a new ring.

We have tried various bases such as potassium carbonate (K$_2$CO$_3$),$^{35}$ lithium bis(trimethylsilyl)amide (LiHDMS)$^{109}$ and sodium hydride (NaH).$^{110,111}$ Unfortunately, expected ring closure products 155 and/or 156 were not formed in the all efforts to the ring
closure reaction of urethane derivative \textit{141}. At different temperatures, in some cases the unreacted starting material was isolated, in some cases the compound was decomposed.

After the failure of the ring closure reaction under basic condition, we decided to change our synthetic strategy and to prepare mono acyl azide \textit{143} which would eventually give cyclization reaction without using any base.\textsuperscript{112}

\textbf{2.1.5 Synthesis of mono isocyanate from bis(acyl azide) \textit{140}}

For the synthesis of a mono isocyanate derivative \textit{158}, a suitable intermediate for cyclization reaction, bis(acyl azide) \textit{140} was heated at 35-40 °C for 2 days. Acyl nitrene intermediate \textit{157} was formed via nitrogen gas evaluation (Scheme 31). The acyl azide functionality connected to a methylene group in \textit{140} is much more reactive than the other one. The other acyl azide group conjugated with indole ring is much more stable and therefore was not converted to isocyanate at given temperature range.

\begin{center}
\textbf{Scheme 31 Synthesis of mono isocyanate \textit{158}}
\end{center}

The chemical shifts of -CH$_2$- protons in $^1$H NMR spectrum and that of carbonyl carbon of isocyanate in $^{13}$C NMR spectrum were different from that of acyl azide \textit{140}. This difference have proven the conversion. Because isocyanate groups shifted the protons to lower field more than acylazide groups, -CH$_2$- protons of \textit{140} appeared at 4.28 ppm whereas that of \textit{158} appeared at 5.01 ppm. Also, carbonyl carbon of acylazide group resonated at much lower field than that of isocyanate group in $^{13}$C NMR spectrum.

The second and the most reliable proof for the formation of \textit{158} was the IR spectral data. IR spectrum showed characteristic absorption frequency for isocyanates at around 2270-2280 cm$^{-1}$ and that for azide at around 2100 cm$^{-1}$. In the IR spectrum of \textit{158}, two characteristic
sharp signals presented at around 2250 and 2140 cm$^{-1}$, indicating clearly the presence of isocyanate as well as azide functional groups in 158 (Figure 1).

![Figure 1 IR spectrum of compound 158](image)

**2.1.6 Reaction of isocyanate with different nucleophiles**

By using its strong electrophilicity, mono isocyanate 158 was easily trapped by different nucleophiles to obtain various urea and urethane derivatives with acyl azide at second position of the indole.
As shown in the Scheme 32, treatment of mono isocyanate 158 with methanol at 40 °C provided urethane derivative 159. If aniline, isopropylamine and tert-butylamine were used as nucleophiles, 158 was converted into urea derivative 160, 161 and 162, respectively. Amount of the methanol and aniline used in the reaction was not so important to protect acyl azide part of the molecule from nucleophilic attack. However, because of higher nucleophilicity of isopropylamine and tert-butylamine, it was critical to protect acyl azide from nucleophilic attack. Therefore, isopropylamine and tert-butylamine were used in equimolar amounts with 158.

For all cases, replacement of singlets arising from -CH₂- to doublet signals in ¹H NMR spectra proved the generation of -NH protons that would be crucial for the intramolecular cyclization reaction in the following steps. Also, specific IR spectral data of azide was observed in these compound but no isocyanate peak was observed.
2.1.6 Synthesis of pyrimidoindole derivatives via acyl azide derivatives

First of all, the urethane 159 containing an acyl azide functionality was submitted to thermal cyclization process without using any base. Unfortunately, the expected intramolecular cyclization product 163 was not observed when 159 was subjected to Curtius rearrangement by heating in dry THF at reflux temperature of 80 °C (scheme 33).

![Scheme 33 Synthesis of pyrimidoindole derivative 163](image)

In order to increase nucleophilicity of NH in 159, we decided to change our precursor for cyclization. Instead of urethane derivative, urea derivatives were used in the intramolecular cyclization. These functional groups would force the system to undergo intramolecular cyclization. As a result of replacement of OR group with NHR group, Curtius rearrangement of the urea derivative 143, carried out in dry THF at reflux temperature for 24 h, produced the pyrimidoindole derivatives 137a-c (Scheme 34). The reason for successful cyclization may be attributed to the increased nucleophilicity of NH group, which attacks carbonyl carbon of isocanate.

![Scheme 34 Synthesis of pyrimidoindole derivatives 137a-c](image)
The formation of the all pyrimidoindole derivatives 137a-c was proved by $^1$H-NMR, $^{13}$C-NMR, HRMS and IR spectra. Firstly, the doublets of methylene protons arising from the coupling with neighboring -NH proton, were replaced by singlets in 137. Of course, triplet signal belonging to -NH proton in the indole form 143 disappeared and the new singlet signal belonging -NH protons appear in the $^1$H NMR spectra. In the IR spectra, any specific isocyanate or azide absorption frequencies were not observed.

### 2.1.7 Synthesis of N-isopropyl-3-([(isopropylamino)carbonyl]amino)methyl)-1H-indole-2-carboxamide and N-isopropyl-3-[2-(isopropylamino)-2-oxoethyl]-1H-indole-2-carboxamide

When monoisocyanate 158 was treated with MeOH at 40 °C, the corresponding urea derivative 159 was isolated as a single product (Scheme 32). However, when monoisocyanate 158 was treated with isopropylamine at 40 °C in benzene, the expected 161 was not formed. Instead, the unexpected product 165 was obtained by direct attack of isopropylamine to acyl azide carbonyl carbon as well as of isocyanate group (Scheme 35).

![Scheme 35 Synthesis of compounds 165 and 166](image)

To prove the direct attack of the isopropyl amine to acyl azide carbonyl group, bis(acyl azide) 140 was reacted under same condition with isopropyl amine. The substitution product 166 was observed as the sole product (Scheme 35). Doublet -NH proton peak disappeared in $^1$H NMR spectrum of 166 which is the first difference between $^1$H NMR spectrum of 165 and 166. And also, doublet -CH$_2$ protons, resonated at around 4.5 ppm, replaced with singlet at around 3.7 ppm. Again COSY, HMQC and HMBC experiments allowed the correct assignment of the proposed structure of 165, 166. In the HMBC spectrum, correlation between the carbonyl carbon which was affected by amide -NH belonging urea part of the compound and high field doublet which correlated with isopropyl group carbons proved that...
another -NH proton signal which was doublet at the lower field belonged lower arm isopropyl amine of compound (Figure 2).

![Figure 2 A part of HMBC experiment of compound 165](image)

2.2 Synthesis of quinoline

2.2.1 Synthesis of Ethyl 3-(2-[[ethoxy(oxo)acetyl]amino]phenyl)-3-oxopropanoate via ozonolysis

Oxidation of diester 138 by using ozone caused the cleavage of double bond and the formation of new two carbonyl group on the place of double bond carbons. Dimethyl sulfite was used for a reductive workup. After reductive workup, o-substituted aniline derivative 167 was obtained (Scheme 36). $^{13}$C NMR spectrum played an important role for the characterization of the product 167 in which two carbonyl carbon peaks were observed instead of peaks which were in the olefinic region. $^1$H NMR signal of proton of NH shifting to low field was evidence for presence of carbonyl near the nitrogen.
In the mechanism of the ozonolysis reaction of diester 138, first syn addition of ozone 168 to double bond of 138 forms primary ozanide 169. In the second step, spontaneous decomposition of 169 gives a carbonyl oxide 170. In another cyclization, ozonide 171 is formed. Ozonide 171 undergoes reduction by dimethyl sulfite 172 by elimination of dimethyl sulfoxide 173 to obtain 167 (Scheme 37).

2.2.2 Synthesis of Diethyl 4-(acetyloxy)quinoline-2,3-dicarboxylate

Reaction of 167 with potassium carbonate in acetonitrile at 60 °C gave the cyclization product 174 of which fourth position attached hydroxyl group (Scheme 38).
According to mechanism of that reaction, firstly base (K₂CO₃) takes acidic CH₂ proton of 167 to form anion 175. Lone pair of that anion attack to amide carbonyl carbon to give cyclization product 176. Because of basic condition, abstraction of acidic proton eliminate -OH to give quinolone derivative 177. In order to obtained full conjugation, hydrogen transfer mechanism forms final quinoline derivative 174 (Scheme 39).

Because of the hydroxyl group in the 174, it cannot dissolve in the organic solvent but it can dissolve in water. In order to prevent this solubility problem, 174 was converted into quinoline 178 via acetylation reaction in the presence of sodium hydride and acetic anhydride (Scheme 40). This also proved the existence of OH group in the structure. Cyclization product 174 was already characterized from disappearance of singlet signal of acidic CH₂ protons and that of NH proton. In the ¹H NMR spectrum of 178, it was obviously showed that acetyl group was attached to oxygen.
In the literature, there is only one way for the conversion of indole into quinoline derivatives via ozonolysis.\textsuperscript{113} In our way, starting compound and base used in cyclization process are different. By this process new compounds can be synthesized by the attachment of different functional groups to the second, third and fourth positions of quinoline.
CHAPTER 3

EXPERIMENTAL

3.1 General

Nuclear magnetic resonance (1H-NMR and 13C-NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in DMSO-d$_6$, CD$_3$OD and CDCl$_3$ with TMS as internal reference. Chemical shifts (δ) were expressed in units parts per million (ppm). Spin multiplicities were specified as singlet (s), doublet (d), doublet of doublets (dd), doublet of doublet of doublets (ddd), triplet (t) and multiplet (m) and coupling constants (J) were reported in Hertz (Hz).

Infrared spectra were recorded on a Matson 1000 FT-IR spectrometer and Vertex 70 series FT-IR spectrometer. Band positions were reported in reciprocal centimeters (cm$^{-1}$).

Column chromatographic separations were performed by using Fluka 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 Fluka.

Compounds were named by using ChemDraw Ultra 12.0 and ACD NMR.

Solvents were purified as reported in the literature.$^{14}$
3.2 Synthesis of \((2E)-2-(\text{phenylhydrazono})\text{pentanedioic acid}\)\(^{108}\)

Phenylhydrazine hydrochloride (5.73 g, 39.6 mmol) was dissolved in 50 mL of water and the solution was treated with ketoglutaric acid (5.79 g, 39.6 mmol) dissolved in 30 mL of water. The colorless mixture was stirred at room temperature before yellow color was appeared. After yellow solution was obtained, the resulting mixture was stirred 5 more minutes. The resulting yellow solution was poured to ice water mixture with the formation of a yellow oil which crystallized when it was left standing overnight. Vacuum filtration was used for removing from the liquid part and after being washed twice with water, \((2E)-2-(\text{phenylhydrazono})\text{pentanedioic acid} (146) (8.61 g, 92\%)\) was obtained as a yellow crystal; lit. mp: 158-159 °C.

\[^1H\text{-NMR} (400 \text{ MHz, DMSO-}\text{d}_6) \delta 12.587 \text{ (br s, 2H, } -\text{OH}), 10.052 \text{ (s, 1H, } -\text{NH}), 7.26 \text{ (t, } J_{23} = J_{65} = 6.9 \text{ Hz, } 2\text{H, } H-6), 7.20 \text{ (d, } J_{44} = J_{52} = J_{54} = J_{56} = 7.5 \text{ Hz, } 2\text{H, } H-3, H-5), 6.9 \text{ (t, } J_{41} = J_{45} = 7.1 \text{ Hz, } 1\text{H, } H-4), 2.69 \text{ (t, } J_{67} = 6.7 \text{ Hz, } 2\text{H, } H-9), 2.52 \text{ (t, } J_{79} = 6.7 \text{ Hz, } 2\text{H, } H-7)\]

\[^13C\text{-NMR} (100 \text{ MHz, DMSO-}\text{d}_6) \delta 174.0, 164.7, 143.6, 129.2, 128.2, 121.1, 113.2, 30.6, 27.8\]

IR (KBr, cm\(^{-1}\)) 2851, 1699, 1661, 1542, 1416, 1235, 1147, 873

Anal. Calc. For C\(_{11}\)H\(_{12}\)N\(_2\)O\(_4\)C 55.93, H 5.12, N 11.86; found: C 56.06, H 5.36, N 11.84

3.3 Synthesis of ethyl 3-(2-ethoxy-2-oxoethyl)-1H-indole-2-carboxylate\(^{108}\)

10 g of polyphosphoric acid was dissolved in 100 mL of the absolute ethanol and solution was saturated with dry hydrogen chloride which was evolved by dropwise addition of sulfuric acid to sodium chloride for 2 h. \((2E)-2-(\text{phenylhydrazono})\text{pentanedioic acid} (146) (5.0 g, 21.2 mmol)\) was added to saturated solution, heated to the boiling point, and treated again with HCl gas. Strongly acid solution was then stirred under reflux overnight. After allowing the solution to cool, 200 mL crushed ice and water mixture was added and the resulting mixture was left in the refrigerator overnight. Ethyl 3-(2-ethoxy-2-oxoethyl)-1H-indole-2-carboxylate (138) (4.1 g, 14.8 mmol) was isolated by removal of the liquid part of mixture with a vacuum filter and washed twice with water. Its crystal was obtained in chloroform as colorless; mp: 88-89 °C.

\[^1H\text{-NMR} (400 \text{ MHz, CDCl}_3) \delta 8.85 \text{ (s, 1H, } -\text{NH}), 7.58 \text{ (quasi-d, } J_{65} = 8.1 \text{ Hz, } 1\text{H, } H-6), 7.31 \text{ (quasi-d, } J_{54} = 8.3 \text{ Hz, } 1\text{H, } H-3), 7.25 \text{ (ddd, } J_{43} = 8.3 \text{ Hz, } J_{45} = 6.9 \text{ Hz, } J_{46} = 1.0 \text{ Hz, } 1\text{H, } H-4), 7.09 \text{ (ddd, } J_{56} = 8.1 \text{ Hz, } J_{54} = 6.9 \text{ Hz, } J_{53} = 1.0 \text{ Hz, } 1\text{H, } H-5), 4.32 \text{ (q, } J = 7.2 \text{ Hz, } 2\text{H, } -\text{OCH}_2\text{), 4.09} \text{(q, } J = 7.2 \text{ Hz, } 2\text{H, } -\text{OCH}_2\text{), 4.09 (s, } 2\text{H, } -\text{CH}_2\text{), 1.33 (t, } J : 7.2 \text{ Hz, } 3\text{H, } -\text{CH}_3\text{), 1.18 (t, } J = 7.2 \text{ Hz, } 3\text{H, } -\text{CH}_3\text{)\}

\[^13C\text{-NMR} (100 \text{ MHz, CDCl}_3) \delta 171.4, 162.1, 135.8, 127.9, 125.6, 124.5, 12.5, 115.8, 112.0, 61.0, 60.9, 30.8, 14.3, 14.2\]

IR (KBr, cm\(^{-1}\)) 3313, 1716, 1677, 1462, 1239, 1027, 751

Anal. Calc. For C\(_{15}\)H\(_{17}\)NO\(_4\)C 65.44, H 6.22, N 5.09; found: C 65.41, H 6.07, N 5.13
3.4 Synthesis of 3-(carboxymethyl)-1H-indole-2-carboxylic acid

To a stirred solution of ethyl 3-(2-ethoxy-2-o xoethyl)-1H-indole-2-carboxylate (138) (0.5 g, 1.82 mmol) in 50 mL of methanol/H2O (1:1) was added excess potassium carbonate (1.25 g, 9.1 mmol) and the resulting solution was stirred at reflux for 16 h. After the completion of the reaction, the mixture was cooled to room temperature and the solution was acidified by dropwise addition of HCl solution. The mixture was extracted with ethyl acetate (3 x 25 mL), and the combined extracts were dried (MgSO4) and the solvent was removed to give 3-(carboxymethyl)-1H-indole-2-carboxylic acid (151) (0.358 g, 90%) as a brown solid; mp: 208-210 °C

\[ \text{IR (KBr, cm}^{-1}\text{)} \] 3309, 1672, 1551, 1237, 903, 736

\[ \text{HRMS m/z (M-H) calcd for C}_{11}\text{H}_{15}\text{NO}_{4}: 218.04588; \text{found: 218.04761} \]

3.5 Synthesis of 3-(2-chloro-2-oxoethyl)-1H-indole-2-carbonyl chloride

To a suspension of 3-(carboxymethyl)-1H-indole-2-carboxylic acid (151) (0.5 g, 2.28 mmol) in CH2Cl2 (50 mL), oxalyl chloride (0.593 mL, 6.84 mmol) was added quickly at r.t. This was followed by the addition of DMF (2 drops) as catalyst, and the reaction mixture was stirred for 4 h at r.t. The reaction was completed after all the starting material had dissolved in the CH2Cl2. The reaction was concentrated under reduced pressure to get 3-(2-chloro-2-oxoethyl)-1H-indole-2-carbonyl chloride (152) (0.526 g, 90%) as a reddish brown solid.

\[ \text{IR (KBr, cm}^{-1}\text{)} \] 3362, 1797, 1716, 1528, 1388, 1228, 957

\[ \text{HRMS m/z (M-H)} \] calcd for C11H13ClNO: 245.03083; found: 245.03737

3.6 Synthesis of 3-(2-azido-2-oxoethyl)-1H-indole-2-carbonyl azide

To a solution of 3-(2-chloro-2-oxoethyl)-1H-indole-2-carbonyl chloride (152) (0.5 g, 1.95 mmol) in acetonitrile (10 mL) at 0 °C, a solution of NaN3 (0.507 g, 7.8 mmol) in H2O (5 mL) was added. Precipitation was immediately observed. After completion of the addition, the resulting mixture was stirred for 1 h and H2O (25 mL) was added. The mixture was extracted with EtOAc (3 x 75 mL). The organic extracts were dried (MgSO4). After removal of the solvent under reduced pressure, 3-(2-azido-2-oxoethyl)-1H-indole-2-carbonyl azide (140) (0.368 g, 70%) was obtained as a brown solid.
3.7 Synthesis of Methyl {2-[(methoxycarbonyl)amino]-1H-indol-3-yl}methylcarbamate

3-(2-azido-2-oxoethyl)-1H-indole-2-carbonyl azide (140) (0.3 g, 1.11 mmol) was dissolved in MeOH (60 mL) and the mixture was refluxed for 16 h. The reaction was controlled by TLC. After completion of reaction, the solvent was removed under reduced pressure. The residue was chromatographed on silica gel (10 g, EtOAc: n-hexane, 1:1) to give methyl {2-[(methoxycarbonyl)amino]-1H-indol-3-yl}methylcarbamate (141) (0.246 g, 80%) as colorless crystals (methanol); mp: 175-177 °C.

1H-NMR (400 MHz, CDCl3) δ 9.85 (s, 1H, -NH), 9.57 (s, 1H, -NH), 7.44-7.36 (m, 1H, H-6), 7.33-7.27 (m, 1H, H-3), 7.13-7.07 (m, 2H, H-4, H-5), 5.37 (t, J = 5.9 Hz, 1H, -NH), 4.34 (d, J = 5.9 Hz, 2H, -CH2), 3.85 (s, 3H, -OCH3), 3.69 (s, 3H, -OCH3)

13C-NMR (100 MHz, CDCl3) δ 159.3, 154.8, 133.8, 131.8, 126.6, 120.5, 120.1, 115.8, 110.8, 95.6, 52.8, 52.7, 33.6

IR (KBr, cm⁻¹) 3389, 1718, 1671, 1635, 1492, 1473, 1244, 982

HRMS m/z (M+Na) calcd for C13H15N3O4Na: 300.0972; found: 300.09548

3.8 Synthesis of 3-(2-isocyanato-2-oxoethyl)-1H-indole-2-carbonyl azide

3-(2-azido-2-oxoethyl)-1H-indole-2-carbonyl azide (140) (0.3 g, 1.11 mmol) was dissolved in dry benzene (60 mL) and stirred at 40-42 °C for 48 h. The solvent was evaporated to give 3-(2-isocyanato-2-oxoethyl)-1H-indole-2-carbonyl azide (158) (0.204 g, 76%) as a yellow solid.

1H-NMR (400 MHz, DMSO-d6) δ 12.17 (s, 1H, -NH), 7.87 (d, J₆₅ = 8.0 Hz, 1H, H-6), 7.49 (quasi-d, J₃₄ = 8.4 Hz, 1H, H-3), 7.37 (quasi-t, J₅₆ = 7.7 Hz, 1H, H-4), 7.18 (quasi-t, J₃₄ = 7.7 Hz, 1H, H-5), 5.01 (s, 2H, -CH2)

13C-NMR (100 MHz, DMSO-d6) δ 165.2, 136.8, 126.4, 126.3, 124.5, 120.9, 120.5, 119.4, 113.0, 36.4

IR (KBr, cm⁻¹) 3319, 2254, 2140, 1651, 1531, 1438, 1335, 1229, 1190, 1049

37
3.9 Synthesis of 3-[(anilinocarbonylamino)methyl]-1H-indole-2-carbonyl azide

Aniline (0.14 mL, 1.49 mmol) was added to a stirred solution of 3-(2-isocyanato-2-oxoethyl)-1H-indole-2-carbonyl azide (158) (0.3 g, 1.24 mmol) in dry benzene (60 mL) and stirred at room temperature for 30 min. The precipitate was filtered and washed with benzene (50 mL) to give 3-[(anilinocarbonylamino)methyl]-1H-indole-2-carbonyl azide (160) (0.249 g, 60%) as a white solid.

\[1H-NMR\] (400 MHz, DMSO-\(d_6\)) \(\delta\) 12.04 (s, 1H, -NH), 8.56 (s, 1H, -NH), 7.97 (d, \(J_{65} = 8.2\) Hz, 1H, H-6), 7.54 (quasi-d, \(J_{34} = 8.4\) Hz, H-3), 7.45 (dd, \(J_{1819} = J_{2221} = 8.0\) Hz, \(J_{1820} = J_{2220} = 1.0\) Hz, 2H, H-18, H-22), 7.42 (ddd, \(J_{43} = 8.0\) Hz, \(J_{45} = 6.9\) Hz, \(J_{46} = 1.1\) Hz, 1H, H-4), 7.29 (quasi-t, \(J_{1920} = J_{2122} = 7.6\) Hz, 2H, H-19, H-21), 7.22 (ddd, \(J_{56} = 8.0\) Hz, \(J_{54} = 6.9\), \(J_{53} = 0.8\) Hz, 1H, H-5), 6.97 (tt, \(J_{2021} = J_{2019} = 7.3\) Hz, \(J_{2018} = J_{2022} = 1.0\) Hz, 1H, H-20), 6.60 (t, \(J = 5.8\) Hz, 1H, -NH), 4.86 (d, \(J = 5.8\) Hz, 2H, -CH\(_2\)).

3C-NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 165.5, 154.9, 140.4, 137.0, 128.8, 128.6, 128.3, 126.8, 126.3, 124.6, 123.2, 121.5, 121.0, 120.4, 117.5, 112.7, 32.9

IR (KBr, cm\(^{-1}\)) 3327, 2139, 1633, 1595, 1548, 1497, 1455, 1438, 1311, 1231, 1193

3.10 Synthesis of 1-[(3-[(methoxycarbonylamino)methyl]-1H-indol-2-yl)carbonyl]triaza-1,2-dien-2-ium

Excess MeOH (5 mL) was added to a stirred solution of 3-(2-isocyanato-2-oxoethyl)-1H-indole-2-carbonyl azide (158) (0.3 g, 1.24 mmol) in dry benzene (60 mL) and stirred at 40 °C for 2 h. The solvent was evaporated to give the crude product, which was then purified by washing with dichloromethane to give 1-[(3-[(methoxycarbonylamino)methyl]-1H-indol-2-yl)carbonyl]triaza-1,2-dien-2-ium (159) (0.249 g, 60%) as a brown solid.

\[1H-NMR\] (400 MHz, DMSO-\(d_6\)) \(\delta\) 11.89 (s, 1H, -NH), 7.80 (d, \(J_{65} = 8.2\) Hz, 1H, H-6), 7.46 (t, \(J = 5.6\) Hz, 1H, -NH), 7.44 (d, \(J_{44} = 8.3\) Hz, H-3), 7.31 (quasi-t, \(J_{46} = 7.6\) Hz, 1H, H-4), 7.10 (quasi-t, \(J_{45} = 7.5\) Hz, 1H, H-5), 4.72 (d, \(J = 5.6\) Hz, 2H, -CH\(_2\)), 3.52 (s, 3H, -OCH\(_3\)).

3C-NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) 164.0, 155.1, 135.5, 125.3, 124.5, 123.2, 120.6, 119.9, 118.8, 111.1, 49.8, 33.1

IR (KBr, cm\(^{-1}\)) 2919, 2145, 1696, 1653, 1510, 1237, 1198

3.11 Synthesis of 2-oxo-N-phenyl-1,2,4,9-tetrahydro-3H-pyrimido[4,5-b]indole-3-carboxamide

3-[(anilinocarbonylamino)methyl]-1H-indole-2-carbonyl azide (160) (0.3 g, 0.897 mmol) was dissolved in dry THF (60 mL) and heated at reflux for 24 h. The solvent was evaporated and the crude product was purified by washing with dichloromethane to give 2-oxo-N-
phenyl-1,2,4,9-tetrahydro-3H-pyrimido[4,5-b]indole-3-carboxamide (157a) (0.22 g, 80%) as a yellow solid; mp: 221-223 °C

\[ \text{1H-NMR (400 MHz, DMSO-}d_6\text{)} \delta 11.57 (s, 1H, -NH), 10.84 (s, 1H, -NH), 11.81 (s, 1H, -NH), 7.55 (d, \text{J}_{1819} = \text{J}_{2221} = 7.8 \text{ Hz, 2H, H-18, H-22}), 7.35 (t, \text{J}_{1820} = \text{J}_{2220} = 9.5 \text{ Hz, 2H, H-19, H-21}), 7.32-7.29 (m, 2H, H-19, H-21), 7.09 (t, \text{J}_{2021} = \text{J}_{2019} = 7.3 \text{ Hz, 1H, H-20}), 7.00-6.95 (m, 2H, H-4, H-5), 4.97 (s, 2H, -CH}_2\text{)

\[ \text{13C-NMR (100 MHz, DMSO-}d_6\text{)} \delta 153.8, 152.4, 138.1, 133.8, 131.8, 129.0, 128.9, 124.7, 123.4, 119.6, 119.3, 116.1, 111.3, 85.1, 42.6

\[ \text{IR (KBr, cm}^{-1}\text{)} 3409, 1697, 1593, 1544, 1209, 1129, 736

HRMS m/z (M+H)\text{calcd for C}_{17}H_{15}N_4O_2: 307.11895; found: 307.12089

3.12 Synthesis of 3-({[(isopropylamino)carbonyl]amino}methyl)-1H-indole-2-carbonyl azide

Isopropylamine (0.12 mL, 1.49 mmol) was added to a stirred solution of 3-(2-isocyanato-2-oxoethyl)-1H-indole-2-carbonyl azide (158) (0.3 g, 1.24 mmol) in dry benzene (60 mL) and stirred at room temperature for 30 min. The precipitate was filtered and washed with benzene (50 mL) to give 3-({[(isopropylamino)carbonyl]amino}methyl)-1H-indole-2-carbonyl azide (161) (0.305 g, 82%) as a white solid.

\[ \text{1H-NMR (400 MHz, DMSO-}d_6\text{)} \delta 11.87 (s, 1H, -NH), 7.83 (d, \text{J}_{65} = 8.2 \text{ Hz, H-6}), 7.43 (d, \text{J}_{45} = 8.3 \text{ Hz, 1H, H-3}), 7.31 (t, \text{J}_{54} = 7.6 \text{ Hz, 1H, H-4}), 7.09 (t, \text{J}_{54} = 7.6 \text{ Hz, 1H, H-5}), 6.04 (t, \text{J} = 5.6 \text{ Hz, 1H, -NH}), 5.74 (d, \text{J} = 8.0 \text{ Hz, 1H, -NH}), 4.68 (d, \text{J} = 5.7 \text{ Hz, 2H, -CH}_3\text{), 3.65 (s, J = 6.4 \text{ Hz, 1H, -CH}, 0.99 (d, \text{J} = 6.4 \text{ Hz, 6H, -CH}_3\text{)

\[ \text{13C-NMR (100 MHz, DMSO-}d_6\text{)} \delta 165.5, 157.1, 137.0, 126.9, 126.2, 124.4, 123.9, 121.7, 120.2, 112.6, 40.8, 33.0, 23.2

\[ \text{IR (KBr, cm}^{-1}\text{)} 3333, 2138, 1617, 1558, 1455, 1353, 1233, 1189, 1056

3.13 Synthesis of N-isopropyl-2-oxo-1,2,4,9-tetrahydro-3H-pyrimido[4,5-b]indole-3-carboxamide

3-({[(isopropylamino)carbonyl]amino}methyl)-1H-indole-2-carbonyl azide (161) (0.3 g, 0.999 mmol) was dissolved in dry THF (60 mL) and heated at reflux for 24 h. The solvent was evaporated and the crude product was purified by washing with dichloromethane to give N-isopropyl-2-oxo-1,2,4,9-tetrahydro-3H-pyrimido[4,5-b]indole-3-carboxamide (157b) (0.58 g, 95%) as a yellow solid; mp: 205-207 °C.
3.14 Synthesis of 3-\{\{[(tert-butylamino)carbonyl]amino}methyl\}-1\textit{H}-indole-2-carbonyl azide

Tert-butylamine (0.16 mL, 1.49 mmol) was added to a stirred solution of 3-(2-isocyanato-2-oxoethyl)-1\textit{H}-indole-2-carbonyl azide (158) (0.3 g, 1.24 mmol) in dry benzene (60 mL) and stirred at room temperature for 30 min. The precipitate was filtered and washed with benzene (50 mL) to give 3-\{\{[(tert-butylamino)carbonyl]amino}methyl\}-1\textit{H}-indole-2-carbonyl azide (162) (0.273 g, 70%) as a white solid.

3.15 Synthesis of N-(tert-butyl)-2-oxo-1,2,4,9-tetrahydro-3\textit{H}-pyrimido[4,5-\textit{b}]indole-3-carboxamide

3-\{\{[(tert-butylamino)carbonyl]amino}methyl\}-1\textit{H}-indole-2-carbonyl azide (162) (0.3 g, 0.954 mmol) was dissolved in dry THF (60 mL) and heated at reflux for 24 h. The solvent was evaporated and the crude product was purified by washing with dichloromethane to give N-(tert-butyl)-2-oxo-1,2,4,9-tetrahydro-3\textit{H}-pyrimido[4,5-\textit{b}]indole-3-carboxamide (157c) (0.273 g, 95%) as a white solid; mp: 210-211 °C.
3.16 Synthesis of N-isopropyl-3-([(isopropylamino)carbonyl]amino)methyl)-1H-indole-2-carboxamide

Excess isopropylamine (5 mL) was added to a stirred solution of 3-(2-isocyanato-2-oxoethyl)-1H-indole-2-carbonyl azide (158) (0.1 g, 0.41 mmol) in benzene (50 mL) at 40 °C for 2 h. After completion the reaction, the solvent was removed under reduced pressure and the residue was crystallized (chloroform - n-hexane) to give N-isopropyl-3-([(isopropylamino)carbonyl]amino)methyl)-1H-indole-2-carboxamide (165) (0.129 g, 98%) as a white crystal; mp: 248-249 °C.

3.17 Synthesis of N-isopropyl-3-[2-(isopropylamino)-2-oxoethyl]-1H-indole-2-carboxamide

Excess isopropylamine (5 mL) was added to a stirred solution of 3-(2-azido-2-oxoethyl)-1H-indole-2-carbonyl azide (140) (0.3 g, 1.11 mmol) at 40 °C for 3 h. After completion the reaction, the solvent was removed under reduced pressure and the residue was crystallized (methanol) to give N-isopropyl-3-[2-(isopropylamino)-2-oxoethyl]-1H-indole-2-carboxamide (166) (0.2 g, 75%) as white crystal; 250-252 °C.


\[ ^1\text{H-NMR} \ (400 \ MHz, \ DMSO-d_6) \ \delta \ 11.39 \ (s, \ 1H, \ -NH), \ 9.85 \ (d, \ J = 7.2 \ Hz, \ 1H, \ -NH), \ 8.49 \ (d, \ J = 7.6 \ Hz, \ 1H, \ -NH), \ 7.83 \ (d, \ J_{45} = 8.0 \ Hz, \ 1H, \ H-6), \ 7.37 \ (d, \ J_{34} = 8.2 \ Hz, \ 1H, \ H-3), \ 7.17 \ (dd, \ J_{43} = 8.0 \ Hz, \ J_{45} = 7.1 \ Hz, \ J_{46} = 0.9 \ Hz, \ 1H, \ H-4), \ 7.05 \ (dd, \ J_{56} = 7.9 \ Hz, \ J_{54} = 6.9 \ Hz, \ J_{53} = 0.9 \ Hz, \ 1H, \ H-5), \ 4.10 \ (q, \ J = 6.7 \ Hz, \ 2H, \ -OCH_2), \ 3.82 \ (o, \ J = 6.7 \ Hz, \ 1H, \ -CH), \ 3.72 \ (s, \ 2H, \ -CH_2), \ 1.22 \ (d, \ J = 6.5 \ Hz, \ 6H, \ -CH_3), \ 1.06 \ (d, \ J = 6.6 \ Hz, \ 6H, \ -CH_3) \]

\[ ^{13}\text{C-NMR} \ (100 \ MHz, \ DMSO-d_6) \ \delta \ 171.0, \ 160.7, \ 135.0, \ 130.8, \ 127.4, \ 123.2, \ 119.6, \ 119.2, \ 111.9, \ 109.3, \ 79.1, \ 31.6, \ 30.6, \ 22.5, \ 22.2 \]

IR (KBr, cm\(^{-1}\)) 3406, 3194, 2965, 1583, 1439, 1325, 1251

HRMS m/z (M+Na)\(^+\) calcd for C\(_{17}\)H\(_{23}\)N\(_3\)O\(_2\)Na: 324.1718; found: 324.16825

3.18 Synthesis of Ethyl 3-[(ethoxy(oxo)acetyl)amino]phenyl)-3-oxopropanoate

The solution of ethyl 3-[(ethoxy-2-oxoethyl)-1H-indole-2-carboxylate 138 (0.5 g, 1.82 mmol) in dichloromethane (10 mL) was cooled to -78 °C, and ozone was bubbled through the solution at that temperature until the solution turned light blue (10 min). The O\(_3\) stream was continued for 5 min more. Then, surplus O\(_3\) was removed by passing a stream of O\(_2\) through the solution for 5 min. Excess dimethylsulfide (0.1 mL) was added to cold solution and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under reduced pressure to afford ethyl 3-[(ethoxy(oxo)acetyl)amino]phenyl)-3-oxopropanoate (167) (0.53 g, 95%) as a reddish brown oil.

\[ ^1\text{H-NMR} \ (400 \ MHz, \ CDCl_3) \ \delta \ 12.86 \ (s, \ 1H, \ -NH), \ 8.80 \ (d, \ J = 8.4 \ Hz, \ 1H, \ H-6), \ 7.90 \ (dd, \ J_{34} = 8.0 \ Hz, \ J_{45} = 1.1 \ Hz, \ 1H, \ H-3), \ 7.65 \ (quasi-t, \ J = 8.0 \ Hz, \ 1H, \ H-4), \ 7.25 \ (quasi-t, \ J_{54} = 8.0 \ Hz, \ 1H, \ H-5), \ 4.45 \ (q, \ J = 7.1 \ Hz, \ 2H, \ -OCH_2), \ 4.23 \ (q, \ J = 7.1 \ Hz, \ 2H, \ -OCH_2), \ 4.07 \ (s, \ 2H, \ -CH_2), \ 1.45 \ (t, \ J = 7.2 \ Hz, \ 3H, \ -OCH_2CH_3), \ 1.26 \ (t, \ J = 7.1 \ Hz, \ 3H, \ -OCH_2CH_3) \]

\[ ^{13}\text{C-NMR} \ (100 \ MHz, \ CDCl_3) \ \delta \ 196.4, \ 167.0, \ 160.2, \ 155.2, \ 139.4, \ 135.7, \ 131.5, \ 124.1, \ 122.0, \ 121.1, \ 63.6, \ 61.7, \ 47.3, \ 14.0, \ 13.9 \]

IR (KBr, cm\(^{-1}\)) 3207, 2985, 1714, 1654, 1580, 1521, 1276, 1153, 1017

HRMS m/z (M+Na\(^+\)) calcd for C\(_{15}\)H\(_{17}\)NO\(_6\)Na: 330.0969; found: 330.09481

3.19 Synthesis of Diethyl 4-hydroxyquinoline-2,3-dicarboxylate

To a stirred solution of ethyl 3-[(ethoxy(oxo)acetyl)amino]phenyl)-3-oxopropanoate (167) (0.3 g, 0.98 mmol) was dissolved in acetonitrile (20 mL). The solution was heated to 58-60 °C and excess potassium carbonate (0.67 g, 4.88 mmol) was added. The reaction was monitored by TLC. After all starting compound was consumed (2 h), excess potassium carbonate was filtered and the solvent was removed under reduced pressure. The residue was washed with dichloromethane to obtain diethyl 4-hydroxyquinoline-2,3-dicarboxylate (174) (0.2 g, 70%) as brown oil.
1H-NMR (400 MHz, CD3OD) δ 8.33 (d, J56 = 8.2 Hz, 1H, H-5), 7.77 (d, J87 = 8.4 Hz, 1H, H-8), 7.59 (quasi-t, J67 = 7.6 Hz, 1H, H-7), 7.36 (quasi-t, J67 = 7.6 Hz, 1H, H-6), 4.39 (q, J = 7.1 Hz, 2H, -CH2), 4.30 (q, J = 7.0 Hz, 2H, -CH2), 1.41 (t, J = 7.1 Hz, 3H, -CH3), 1.36 (t, J = 7.0 Hz, 3H, -CH3)

13C-NMR (100 MHz, CD3OD) δ 172.9, 168.1, 167.6, 148.3, 129.3, 128.8, 126.9, 124.6, 122.2, 107.5, 60.2, 58.7, 40.4, 14.2, 14.0

IR (KBr, cm⁻¹) 3391, 2981, 1697, 1505, 1304, 1237, 1210, 1138, 1018

HRMS m/z (M+H)⁺ calcd for C₁₅H₁₅NO₅: 290.1034; found: 290.1023

3.20 Synthesis of Diethyl 4-(acytelyoxy)quinoline-2,3-dicarboxylate

To a solution of diethyl 4-hydroxyquinoline-2,3-dicarboxylate (174) (0.3 g, 1.0 mmol) in dry THF (15 mL) at 0°C, sodium hydride (0.025 g, 1.04 mmol) was added and stirred for 30 min. Then acetic anhydride (0.1 g, 1.04 mmol) was added to the solution and stirred at room temperature for 30 min. After completion of the reaction, excess NaH was quenched by the dropwise addition of H₂O (50 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL) and the extracts were dried (MgSO₄). The solvent was removed under reduced pressure and chromatography of the residue on silica gel (10 gr, EtOAc - n-hexane 1:1) gave pure diethyl 4-(acytelyoxy)quinoline-2,3-dicarboxylate (178) (0.23 g, 70%) as a yellow oil.

1H-NMR (400 MHz, CDCl₃) δ 8.28 (quasi-d, J56 = 8.2 Hz, 1H, H-5), 7.94 (quasi-d, J67 = 8.4 Hz, 1H, H-8), 7.86 (quasi-t, J76 = 7.6 Hz, 1H, H-7), 7.70 (quasi-t, J87 = 7.6 Hz, 1H, H-6), 4.51 (q, J = 7.1 Hz, 2H, -CH2), 4.42 (q, J = 7.2 Hz, 2H, -CH2), 2.49 (s, 3H, -COCH3), 1.45 (t, J = 7.1 Hz, 3H, -CH3), 1.39 (t, J = 7.2 Hz, 3H, -CH3)

13C-NMR (100 MHz, CDCl₃) δ 167.7, 165.2, 164.2, 154.2, 149.2, 148.7, 132.0, 130.4, 129.3, 122.8, 122.1, 118.3, 62.6, 62.2, 20.7, 14.2, 14.0

IR (KBr, cm⁻¹) 2983, 1779, 1721, 1368, 1303, 1229, 1175, 1084, 1026

HRMS m/z (M+Na)⁺ calcd for C₁₅H₁₇NO₆: 354.0987; found: 354.09481
We developed new synthetic methodologies for the synthesis of pyrimidoindole (104, 105) and quinoline (123) starting from an indole derivative. Pyrimidoindoles are indole fused heterocycles which contain pyrimidine ring (106) and their derivatives show biological activity of various types. Moreover, Quinoline (123) is a benzo-fused pyridine and aromatic heterocyclic compound. There are many naturally occurring quinoline derivatives with diverse pharmacological properties. Various synthetic methods to obtain quinoline ring have been developed because of the prominence of the ring system in natural products and pharmaceuticals.

In the first part of the study, we focused on the synthesis of pyrimidoindole derivatives. First, starting material indole derivative was synthesized by using Fischer indole cyclization reaction. Then, this indole derivative 138 was converted into the corresponding acyl azide 140, which then was used as a key compound to synthesis of pyrimidoindole derivatives 137. However, intramolecular cyclization of the 2,3-diurethane substituted indole derivative 141, obtained by thermolysis of bis(acyl azide) 140 in methanol, under basic condition, did not give 137 (Scheme 41).

Scheme 41 First synthesis route of pyrimidoindole derivatives

Then, we decided to change our synthetic strategy. First, corresponding bis(acyl azide) 140 was converted into the monoisocyanate 142 via controlled Curtius rearrangement to obtain the mono urethane derivatives 143 which were trapped with various nucleophiles. Then, the generated urea derivatives were used in intramolecular cyclization reaction to synthesize the various pyrimidoindole derivatives 137 (Scheme 42).
In the second part of the work, the synthesis of quinoline derivative was studied. First, oxidation of starting material indole derivative 138 by using ozone caused the cleavage of double bond and after reductive workup, o-substituted aniline derivative 167 was obtained. Under basic condition, 167 was yielded to quinoline derivative 174 with intramolecular cyclization reaction. In order to prevent solubility problem, 174 converted into quinoline 178 via acetylation reaction (scheme 43).
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APPENDIX

A. SPECTRAL DATA

Figure 3 $^1$H NMR spectrum of compound 146
Figure 4 \textsuperscript{13}C NMR spectrum of compound 146

Figure 5 IR spectrum of compound 146
Figure 6 $^1$H NMR spectrum of compound 138

Figure 7 $^{13}$C NMR spectrum of compound 138
Figure 8 IR spectrum of compound 138

Figure 9 $^1$H NMR spectrum of compound 151
Figure 10 $^{13}$C NMR spectrum of compound 151

Figure 11 IR spectrum of compound 151
Figure 12 $^1$H NMR spectrum of compound 152

Figure 13 $^{13}$C NMR spectrum of compound 152
Figure 14 IR spectrum of compound 152

Figure 15 $^1$H NMR spectrum of compound 140
Figure 16 $^{13}$C NMR spectrum of compound 140

Figure 17 IR spectrum of compound 140
Figure 18 $^1$H NMR spectrum of compound 141

Figure 19 $^{13}$C NMR spectrum of compound 141
Figure 20 IR spectrum of compound 141

Figure 21 $^1$H NMR spectrum of compound 158
Figure 22 $^{13}$C NMR spectrum of compound 158

Figure 23 IR spectrum of compound 158
Figure 24 $^1$H NMR spectrum of compound 160

Figure 25 $^{13}$C NMR spectrum of compound 160
Figure 26 IR spectrum of compound 160

Figure 27 $^1$H NMR spectrum of compound 159
Figure 28 $^{13}$C NMR spectrum of compound 159

Figure 29 IR spectrum of compound 159
Figure 30 $^1$H NMR spectrum of compound 157a

Figure 31 $^{13}$C NMR spectrum of compound 157a
Figure 32 IR spectrum of compound 157a

Figure 33 $^1$H NMR spectrum of compound 161
Figure 34 $^{13}$C NMR spectrum of compound 161

Figure 35 IR spectrum of compound 161
Figure 36 $^1$H NMR spectrum of compound 157b

Figure 37 $^{13}$C NMR spectrum of compound 157b
Figure 38 IR spectrum of compound 157b

Figure 39 $^1$H NMR spectrum of compound 162
Figure 40 $^{13}$C NMR spectrum of compound 162

Figure 41 IR spectrum of compound 162
Figure 42 $^1$H NMR spectrum of compound 157c

Figure 43 $^{13}$C NMR spectrum of compound 157c
Figure 44 IR spectrum of compound 157c

Figure 45 $^1$H NMR spectrum of compound 165
**Figure 46** $^{13}$C NMR spectrum of compound 165

**Figure 47** IR spectrum of compound 165
Figure 48 HMBC spectrum of compound 165

Figure 49 COSY spectrum of compound 165
Figure 50 HSQC spectrum of compound 165

Figure 51 $^1$H NMR spectrum of compound 166
Figure 52 $^{13}$C NMR spectrum of compound 166

Figure 53 IR spectrum of compound 166
Figure 54 HMBC spectrum of compound 166

Figure 55 HSQC spectrum of compound 166
Figure 56 COSY spectrum of compound 166

Figure 57 $^1$H NMR spectrum of compound 167
Figure 58 $^{13}$C NMR spectrum of compound 167

Figure 59 IR spectrum of compound 167
**Figure 60** $^1$H NMR spectrum of compound 174

**Figure 61** $^{13}$C NMR spectrum of compound 174
Figure 62 IR spectrum of compound 167

Figure 63 $^1$H NMR spectrum of compound 178
Figure 64 $^{13}$C NMR spectrum of compound 178

Figure 65 IR spectrum of compound 167