DEVELOPMENT OF A SYNTHETIC METHODOLOGY FOR THIENOPYRIDINONE AND THIENODIAZEPINONE DERIVATIVES AND BENZIMIDAZO-OXAZEPINES

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ABSTRACT

DEVELOPMENT OF A SYNTHETIC METHODOLOGY FOR THIENOPYRIDINONE AND THIENODIAZEPINONE DERIVATIVES AND BENZIMIDAZO-OXAZEPINES

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Thienopyridinone and thienodiazepinone derivatives are known for their diverse pharmacological activities. Pyridinones and diazepinones play an important role in inhibition of some enzymes such as glycogen synthase kinase-3β and regulation of various cell functions. They also demonstrate an interesting property in the repair of damaged DNA. In the first part of this thesis, we synthesized thienopyridinone and thienodiazepinone derivatives. Aminothiophene derivatives were successfully synthesized via Gewald type reaction which was followed by the conversion to iodo- and bromo-thiophene derivatives via modified Sandmayer reaction. Sonogashira cross-coupling reaction was used to generate carbon-carbon single bond between the thiophene ring and alkyne derivatives. Cyclization of those compounds with hydrazine hydrate gave target molecules.

Imidazole derivatives exhibit a wide range of bioactivities, therefore they are of intensive synthetic interest. They are also used as precursors for the synthesis of heterocycles having pharmaceutical properties. In the second part of this thesis, a concise and efficient approach to the synthesis of benzimidazo-oxazepine derivatives was developed. The synthetic strategy relies on the O-propargylation of salicyl aldehyde derivatives followed by Sonogashira cross-coupling reaction for further derivatization. Resulting alkyne derivatives were converted into the corresponding
imidazole rings under acidic condition. NaH-mediated cyclization gave desired compounds, benzimidazo-oxazepines.

**Keywords:** thienopyridinone, thienodiazepinone, imidazole, benzimidazole, oxazepine, benzimidazo-oxazepine.
ÖZ

ТИЙЕНОПИРИДИНОН,ТИЙЕНОДИАЗЕПИНОН

ВЕ

БЕНЗИМІДАЗО-ОКЗАЗЕПІН ТЮРЕВЛЕРİNİN СЕНТЕЗİ İÇİN

YÖNTEM GELİŞTİRME

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İmidazol türevleri, biyolojik aktivite gösteren özellikleri ile bilim dünyasında dikkat çeken moleküler sınıflına girmişlerdir. Aynı zamanda ilaç kimyasında kullanılan bazı heterosiklik bileşiklerin sentezi için kullanılan önemli çıkış bileşikleridir. Çalışmanın ikinci kısmında, benzimidazo-okzazepin türevi sentezi için yeni bir metotun geliştirilmesi planlandı. İlk olarak, salisilaldehit ve türevlerinin hidroksil grubuna bazık ortamda farklı propargil grupları takıldı. Alkin grubundan türevlendirme çalışmalarını için Sonogashira kenetlenmesi başarıyla uygulandı. Daha
sonra bu bileşiklerin O-diaminobenzen ile kondenzasyonu sağlanarak halkaşma için gerekli fonksiyonel gruplar moleküle takıldı. İlgili imidazol türevleri sentezlendiğten sonra bu bileşiklerin NaH ile reaksiyonu sonucunda hedeflenen kapanma ürünleri yüksek verimle elde edildi.

**Anahtar Kelimeler:** tiyenopiridinon, tiyenodiazepinon, imidazol, benzimidazol, okzazepin, benzimidazo-okzazepin.
To my husband Onur and daughter Nur…
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TABLE OF CONTENTS

ABSTRACT ................................................................................................................................. v
ÖZ ........................................................................................................................................... vii
ACKNOWLEDGEMENT .......................................................................................................... x
TABLE OF CONTENTS .......................................................................................................... xi
LIST OF FIGURES .................................................................................................................. xvii
LIST OF SCHEMES ............................................................................................................. xxiv
LIST OF ABBREVIATIONS ................................................................................................... xxvii

CHAPTERS

1. DEVELOPMENT OF A SYNTHETIC METHODOLOGY FOR THIENOPYRIDINONE AND THIENODIAZEPINONE DERIVATIVES ......... 1
   1.1 INTRODUCTION ........................................................................................................... 1
       1.1.1 Pyridinone ............................................................................................................. 2
       1.1.2 Thienopyridinone ................................................................................................. 2
       1.1.3 Synthesis of thienopyridinone ............................................................................ 3
       1.1.4 Thienopyrimidinone ........................................................................................... 5
       1.1.5 Pyridazinone ........................................................................................................ 6
       1.1.6 Benzo- and thienopyridazinone ......................................................................... 6
           1.1.6.1 Synthesis of thienopyridazinone derivatives ................................................. 7
       1.1.7 Diazepinone .......................................................................................................... 8
       1.1.8 Synthesis of diazepinones .................................................................................. 9
           1.1.8.1 Synthesis of fused diazepinones ................................................................ 10
       1.1.9 Aim of the study .................................................................................................. 12
   1.2 RESULTS AND DISCUSSION ..................................................................................... 14
       1.2.1 Synthesis of aminothiophene derivatives ......................................................... 14
           1.2.1.1 Synthesis of ethyl 2-aminothiophene-3-carboxylate (37) ......................... 14
           1.2.1.2 Synthesis of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (40) ......................................................................................................................... 15
           1.2.1.3 Synthesis of ethyl 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate (59) ......................................................................................................................... 17
1.2.2 Synthesis of ethyl 2-iodothiophene-3-carboxylate (38) .................. 17
1.2.3 Synthesis of ethyl 2,5-dibromothiophene-3-carboxylate (63) ........ 20
1.2.4 Synthesis of ethyl 2-bromo-4,5,6,7-tetrahydrobenzo[\textit{b}]thiophene-3-carboxylate (41) ....................................................... 23
1.2.5 Sonogashira cross-coupling reaction ......................................... 24
   1.2.5.1 Sonogashira cross-coupling reactions applied to iodothiophene 38... 26
      1.2.5.1.1 Synthesis of ethyl 2-(phenylethynyl)thiophene-3-carboxylate (42a) .......................................................... 26
      1.2.5.1.2 Synthesis of ethyl 2-(hept-1-yn-1-yl)thiophene-3-carboxylate (42b) and ethyl 2-(hex-1-yn-1-yl)thiophene-3-carboxylate (42c) .... 28
   1.2.5.2 Sonogashira cross-coupling reaction applied to bromothiophene 41 ........................................................................................................ 29
      1.2.5.2.1 Synthesis of ethyl 2-(phenylethynyl)-4,5,6,7-tetrahydrobenzo[\textit{b}]thiophene-3-carboxylate (45a) ........................................ 29
      1.2.5.2.2 Synthesis of ethyl 2-(hept-1-yn-1-yl)-4,5,6,7-tetrahydrobenzo[\textit{b}]thiophene-3-carboxylate (45b) and ethyl 2-(hex-1-yn-1-yl)-4,5,6,7-tetrahydrobenzo[\textit{b}]thiophene-3-carboxylate (45c) .......................... 30
   1.2.5.3 Synthesis of ethyl 2,5-bis(phenylethynyl)thiophene-3-carboxylate (74) ......................................................................................... 32
1.2.6 Cyclization with hydrazine monohydrate .................................... 33
   1.2.6.1 Cyclization of phenylethynylthiophene 42a with hydrazine mono
   hydrate .......................................................................................... 33
   1.2.6.2 Cyclization of ethyl 2-(hept-1-yn-1-yl)thiophene-3-carboxylate (42b) and ethyl 2-(hex-1-yn-1-yl)thiophene-3-carboxylate (42c) with hydrazine monohydrate ......................................................... 35
   1.2.6.3 Cyclization of ethyl 2-(phenylethynyl)-4,5,6,7-tetrahydrobenzo
   [\textit{b}]thiophene-3-carboxylate (45a) with hydrazine monohydrate ............. 37
   1.2.6.4 Cyclization of ethyl 2-(hept-1-yn-1-yl)-4,5,6,7-tetrahydrobenzo
   [\textit{b}]thiophene-3-carboxylate (45b) and ethyl 2-(hex-1-yn-1-yl)-4,5,6,7-
tetrahydrobenzo[\textit{b}]thiophene-3-carboxylate (45c) with hydrazine mono
   hydrate .................................................................................................. 41

2. DEVELOPMENT OF A SYNTHETIC METHODOLOGY FOR THE
SYNTHESIS OF BENZIMIDAZO-OXAZEPINES .................................. 43
2.1 INTRODUCTION ................................................................................................................. 43
2.1.1 Imidazole ......................................................................................................................... 44
2.1.2 Benzimidazole .................................................................................................................. 45
2.1.3 Synthesis of benzimidazole derivatives ............................................................................. 46
2.1.4 Oxazepine .......................................................................................................................... 48
2.1.5 Synthesis of oxazepine derivatives ..................................................................................... 49
2.1.6 Benzoazepine and benzimidazo-oxazepine ...................................................................... 50
2.1.7 Synthesis of benzoazepine and benzimidazo-oxazepine .................................................... 51
2.1.8 Aim of the study ................................................................................................................. 54

2.2 RESULTS AND DISCUSSION .............................................................................................. 56
2.2.1 Synthesis of methyl 2-methylfuran-3-carboxylate (116) .................................................... 56
2.2.2 Synthesis of methyl 2-formylfuran-3-carboxylate (129) ...................................................... 57
2.2.3 Synthesis of methyl 2-(1H-benzo[d]imidazol-2-yl)furan-3-carboxylate (117) ..................... 58
2.2.4 Attempted incorporation of an alkyne functionality to benzimidazole 117 and synthesis of 118 .......................................................................................................................................... 59
2.2.5 Synthesis of O-propargylated salicyl aldehydes ................................................................. 61
2.2.6 Derivatization of 120a with Sonogashira cross-coupling reaction ...................................... 62
2.2.7 Synthesis of O-substituted salicyl aldehydes 120f and 120g .............................................. 63
2.2.8 Condensation reaction of salicyl aldehyde derivatives ....................................................... 65
2.2.9 Cyclization reactions of salicyl aldehyde derivatives 120e, 120g and 120d .......................... 67
2.2.10 NaH Mediated cyclization reactions of phenyl-substituted benzimidazoles .................... 71
2.2.11 Synthesis of 1-(2-oxopropyl)-1H-pyrrole-2-carbaldehyde (143) and 1-(prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde (144) .................................................................................. 80
2.2.12 Reaction of 144 and 143 with o-diaminobenzene followed by NaH-mediated cyclization reaction .................................................................................................................. 81

3. CONCLUSION ......................................................................................................................... 83

4. EXPERIMENTAL .................................................................................................................... 89
4.1 General .................................................................................................................................. 89
4.1.1 Synthesis of ethyl 2-aminothiophene-3-carboxylate (37) .................................................. 90
4.2 General procedure for the synthesis of substituted 2-amino-3-carboxylate .......................... 90
4.4.1 Synthesis of ethyl 2,5-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate (59) ........................................... 90
4.4.2 Synthesis of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (40) ................................................... 91
4.5 Synthesis of ethyl 2-iodothiophene-3-carboxylate (38) ...................... 91
4.6 General procedure of Sonogashira cross-coupling reaction to bromothiophene ............................... 92
  4.6.1 Synthesis of ethyl 2,5-dibromothiophene-3-carboxylate (63) .......... 92
  4.6.2 Synthesis of ethyl 2-bromo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (41) and ethyl 4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (70) ............ 93
4.7 General procedure of Sonogashira cross-coupling reaction to iodothiophene ........................................ 93
  4.7.1 Synthesis of ethyl 2-(phenylethynyl)thiophene-3-carboxylate (42a) .... 94
  4.7.2 Synthesis of ethyl 2-(hept-1-yn-1-yl)thiophene-3-carboxylate (42b) ......... 94
  4.7.3 Synthesis of ethyl 2-(hex-1-yn-1-yl)thiophene-3-carboxylate (42c) ....... 95
4.8 General procedure of cyclization reaction ......................................... 98
  4.8.1 Synthesis of 5-amino-6-phenylthieno[3,2-c]pyridin-4(5H)-one (43a) .... 98
  4.8.2 Synthesis of 5-amino-6-pentylothieno[3,2-c]pyridin-4(5H)-one (43b) ..... 99
  4.8.3 Synthesis of 5-amino-6-butylothieno[3,2-c]pyridin-4(5H)-one (43c) .... 99
4.9 Synthesis of 2-amino-3-phenyl-6,7,8,9-tetrahydrobenzo[4,5]thieno[3,2-c]pyridin-1(2H)-one (46a) and 4-phenyl-2,5,7,8,9,10-hexahydro-1H-benzo[4,5]thieno[3,2-d][1,2]diazepin-1-one (47) .................................. 100
  4.9.1 Synthesis of 2-amino-3-pentyl-6,7,8,9-tetrahydrobenzo[4,5]thieno[3,2-c]pyridin-1(2H)-one (46b) .................................. 100
  4.9.2 Synthesis of 2-amino-3-buty1-6,7,8,9-tetrahydrobenzo[4,5]thieno[3,2-c]pyridin-1(2H)-one (46c) .................................. 101
4.10 Synthesis of methyl 2-methylfuran-3-carboxylate (116) .................... 101
4.9 Synthesis of methyl 2-formylfuran-3-carboxylate (129) ........................................ 102
4.10 General procedure for the synthesis of substituted imidazoles ............................. 102
  4.10.1 Synthesis of methyl 2-(1H-benzo[d]imidazol-2-yl)furan-3-carboxylate (117) ................................................................. 103
4.11 Synthesis of 4H-benzo[d]furo[2′,3′:3,4]pyrrolo[1,2-α]imidazol-4-one (118) ........ 103
4.12 General procedure of O-propargylation ...................................................... 104
  4.12.1 Synthesis of 2-(prop-2-yn-1-yloxy)benzaldehyde (120a) ..................... 104
  4.12.2 Synthesis of 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (120b) ...... 104
  4.12.3 Synthesis of 3-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde (120c). 105
  4.12.4 Synthesis of 2-(but-2-yn-1-yloxy)benzaldehyde (120f) ...................... 105
  4.12.5 Synthesis of 2-(2-formyolphenoxy)acetonitrile (120g) ......................... 106
  4.12.6 Synthesis of 2-((3-phenylprop-2-yn-1-yloxy)benzaldehyde (120d) ... 106
  4.12.7 Synthesis of 2-((3-(4-nitrophenyl)prop-2-yn-1-yloxy)benzaldehyde (120e) ............................................................................ 107
4.13 Synthesis of 2-(2-(prop-2-yn-1-yloxy)phenyl)-1H-benzo[d]imidazole (121a) ......................................................................................................................... 107
4.14 Synthesis of 2-(5-bromo-2-(prop-2-yn-1-yloxy)phenyl)-1H-benzo[d]imidazole (121b) ......................................................................................................................... 108
4.15 Synthesis of 2-(3-methoxy-2-(prop-2-yn-1-yloxy)phenyl)-1H-benzo[d]imidazole (121c) ......................................................................................................................... 108
4.16 Synthesis of 2-(2-(but-2-yn-1-yloxy)phenyl)-1H-benzo[d]imidazole (121f) 109
4.17 Synthesis of 2-((2-((3-phenylprop-2-yn-1-yloxy)phenyl)-1H-benzo[d]imidazole (121d) ......................................................................................................................... 109
4.18 Synthesis of 1-(2-oxopropyl)-1H-pyrrole-2-carbaldehyde (143) .................... 110
4.19 Synthesis of 1-(prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde (144) ............. 110
4.20 Synthesis of 2-((prop-2-yn-1-yl)-1H-pyrrol-2-yl)-1H-benzo[d]imidazole (145) ......................................................................................................................... 111
4.21 Synthesis of 7-(4-nitrobenzylidene)-6,7-dihydrobenzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepine (122e) ......... 111
4.22 Synthesis of benzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepin-7(6H)-imine (122g) ................................................................................................................................. 112
4.23 General procedure of cyclization with NaH ................................................. 113
  4.23.1 Cyclization of 121a with NaH .................................................................. 113
  4.23.2 Synthesis of 7-methylene-6,7-dihydrobenzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepine (122a) ........................................................................................................... 113
  4.23.3 Synthesis of 6-methylbenzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepine (140b) ................................................................................................................................. 114
4.23.4 Cyclization of 121b with NaH ................................................................. 114
4.23.5 Synthesis of 2-bromo-7-methylene-6,7-dihydrobenzo[f]benzo[4,5]
imidazo[1,2-][1,4] oxazepine (122b) ................................................................. 114
4.23.6 Synthesis of 2-bromo-6-methylbenzo[f]benzo[4,5]imidazo[1,2-][1,4]
oxazepine (141b) ............................................................................................. 115
4.23.7 Cyclization of 121c with NaH ................................................................. 115
4.23.8 Synthesis of 4-methoxy-7-methylene-6,7-dihydrobenzo[f]benzo[4,5]
imidazo[1,2-][1,4] oxazepine (122c) and 4-methoxy-6-methylene-6,7-dihydro
benzo[f]benzo [4,5] imidazo[1,2-][1,4]oxazepine (135a) ................................. 115
4.23.9 Synthesis of 4-methoxy-6-methylbenzo[f]benzo[4,5]imidazo[1,2-][1,4]
oxazepine and 4-methoxy-7-methylbenzo[f]benzo[4,5]imidazo[1,2-][1,4]
oxazepine (135b and 123c) ............................................................................... 116
4.23.10 Cyclization of 121d with NaH ............................................................... 117
(146) ............................................................................................................. 117

REFERENCES .................................................................................................... 119
APPENDICES .................................................................................................... 127
A. SPECTRAL DATA ......................................................................................... 127
CURRICULUM VITAE ...................................................................................... 205
LIST OF FIGURES

FIGURES

Figure 1. Structure of MCHR1 ligand ....................................................... 2
Figure 2. The H3 receptor antagonist ....................................................... 2
Figure 3. Biologically active thienopyridinone derivative............................ 3
Figure 4. Thienopyrimidinone SIRT2 inhibitor .......................................... 6
Figure 5. Biaryl-substituted pyridazinone 13 ............................................ 6
Figure 6. Melanin concentrating hormone receptor ligand antagonists .......... 7
Figure 7. Pyrolo diazepinone 23 and pyrolobenzodiazepinone 24 ............... 9
Figure 8. Structures of biologically important thiophene-fused 25 and 26 ....... 9
Figure 9. 1H-NMR spectrum of compound 38 ........................................... 19
Figure 10. 1H-NMR spectrum of a mixture 61 and 62 ................................. 20
Figure 11. 1H-NMR spectrum of compound 42a ....................................... 27
Figure 12. 13C-NMR spectrum of compound 42a ....................................... 27
Figure 13. Crude 1H-NMR spectrum of compound 42b ............................. 29
Figure 14. 1H-NMR spectrum of compound 45b ....................................... 31
Figure 15. 13C-NMR spectrum of compound 45b ..................................... 32
Figure 16. 1H-NMR spectrum of compound 43a ....................................... 35
Figure 17. 1H-NMR spectrum of compound 43c ....................................... 36
Figure 18. 13C-NMR spectrum of compound 43c ..................................... 37
Figure 19. Plausible seven- and six-membered ring products 47 and 77 ......... 38
Figure 20. 1H-NMR spectrum of compound 47 ........................................ 39
Figure 21. HSQC spectrum of compound 47 ............................................ 39
Figure 22. HMBC spectrum of compound 47 ........................................... 40
Figure 23. Expanded HMBC spectrum of compound 47 ............................ 41
Figure 24. Expanded 1H-NMR spectrum of compound 46c ...................... 42
Figure 25. Antifungal agents .................................................................... 44
Figure 26. Structure of SB203580 ............................................................ 44
Figure 27. The structures against HIV replication ...................................... 45
Figure 58. $^{13}$C-NMR spectrum of compound 40................................. 131
Figure 59. IR spectrum of compound 40 ............................................. 131
Figure 60. $^1$H-NMR spectrum of compound 38................................. 132
Figure 61. $^{13}$C-NMR spectrum of compound 38................................. 132
Figure 62. IR spectrum of compound 38 ............................................. 133
Figure 63. $^1$H-NMR spectrum of compound 63................................. 133
Figure 64. $^{13}$C-NMR spectrum of compound 63................................. 134
Figure 65. IR spectrum of compound 63 ............................................. 134
Figure 66. $^1$H-NMR spectrum of compound 41................................. 135
Figure 67. $^{13}$C-NMR spectrum of compound 41................................. 135
Figure 68. IR spectrum of compound 41 ............................................. 136
Figure 69. $^1$H-NMR spectrum of compound 70................................. 136
Figure 70. $^{13}$C-NMR spectrum of compound 70................................. 137
Figure 71. IR spectrum of compound 70 ............................................. 137
Figure 72. $^1$H-NMR spectrum of compound 42a............................... 138
Figure 73. $^{13}$C-NMR spectrum of compound 42a............................... 138
Figure 74. IR spectrum of compound 42a ........................................... 139
Figure 75. $^1$H-NMR spectrum of compound 42b............................... 139
Figure 76. $^{13}$C-NMR spectrum of compound 42b............................... 140
Figure 77. IR spectrum of compound 42b ........................................... 140
Figure 78. $^1$H-NMR spectrum of compound 42c............................... 141
Figure 79. $^{13}$C-NMR spectrum of compound 42c............................... 141
Figure 80. IR spectrum of compound 42c ........................................... 142
Figure 81. $^1$H-NMR spectrum of compound 45a............................... 142
Figure 82. $^{13}$C-NMR spectrum of compound 45a............................... 143
Figure 83. IR spectrum of compound 45a ........................................... 143
Figure 84. $^1$H-NMR spectrum of compound 45b............................... 144
Figure 85. $^{13}$C-NMR spectrum of compound 45b............................... 144
Figure 86. IR spectrum of compound 45b ........................................... 145
Figure 87. $^1$H-NMR spectrum of compound 45c............................... 145
Figure 88. $^{13}$C-NMR spectrum of compound 45c............................... 146
Figure 89 IR spectrum of compound 45c ........................................... 146
Figure 90. $^1$H-NMR spectrum of compound 74............................... 147
Figure 91. $^{13}$C-NMR spectrum of compound 74.......................................................... 147
Figure 92. IR spectrum of compound 74...................................................................... 148
Figure 93. $^1$H-NMR spectrum of compound 43a...................................................... 148
Figure 94. $^{13}$C-NMR spectrum of compound 43a...................................................... 149
Figure 95. IR spectrum of compound 43a...................................................................... 149
Figure 96. $^1$H-NMR spectrum of compound 44.......................................................... 150
Figure 97. IR spectrum of compound 44...................................................................... 150
Figure 98. $^1$H-NMR spectrum of compound 43b...................................................... 151
Figure 99. $^{13}$C-NMR spectrum of compound 43b...................................................... 151
Figure 100. IR spectrum of compound 43b................................................................. 152
Figure 101. $^1$H-NMR spectrum of compound 43c...................................................... 152
Figure 102. $^{13}$C-NMR spectrum of compound 43c...................................................... 153
Figure 103. IR spectrum of compound 43c...................................................................... 153
Figure 104. $^1$H-NMR spectrum of compound 46a...................................................... 154
Figure 105. $^{13}$C-NMR spectrum of compound 46a...................................................... 154
Figure 106. IR spectrum of compound 46a...................................................................... 155
Figure 107. $^1$H-NMR spectrum of compound 47.......................................................... 155
Figure 108. $^{13}$C-NMR spectrum of compound 47...................................................... 156
Figure 109. HMBC spectrum of compound 47.............................................................. 156
Figure 110. HSQC spectrum of compound 47.............................................................. 157
Figure 111. IR spectrum of compound 47...................................................................... 157
Figure 112. $^1$H-NMR spectrum of compound 46b...................................................... 158
Figure 113. $^{13}$C-NMR spectrum of compound 46b...................................................... 158
Figure 114. IR spectrum of compound 46b...................................................................... 159
Figure 115. $^1$H-NMR spectrum of compound 46c...................................................... 159
Figure 116. $^{13}$C-NMR spectrum of compound 46c...................................................... 160
Figure 117. IR spectrum of compound 46c...................................................................... 160
Figure 118. $^1$H-NMR spectrum of compound 116...................................................... 161
Figure 119. $^{13}$C-NMR spectrum of compound 116...................................................... 161
Figure 120. IR spectrum of compound 116...................................................................... 162
Figure 121. $^1$H-NMR spectrum of compound 129...................................................... 162
Figure 122. $^{13}$C-NMR spectrum of compound 129...................................................... 163
Figure 123. IR spectrum of compound 129...................................................................... 163
Figure 124. $^1$H-NMR spectrum of compound 117 ........................................ 164
Figure 125. $^{13}$C-NMR spectrum of compound 117 .................................... 164
Figure 126. IR spectrum of compound 117 .................................................... 165
Figure 127. $^1$H-NMR spectrum of compound 118 .................................... 165
Figure 128. $^{13}$C-NMR spectrum of compound 118 .................................... 166
Figure 129. IR spectrum of compound 118 .................................................... 166
Figure 130. $^1$H-NMR spectrum of compound 120a .................................. 167
Figure 131. $^{13}$C-NMR spectrum of compound 120a .................................. 167
Figure 132. IR spectrum of compound 120a .................................................. 168
Figure 133. $^1$H-NMR spectrum of compound 120b .................................. 168
Figure 134. $^{13}$C-NMR spectrum of compound 120b .................................. 169
Figure 135. IR spectrum of compound 120b .................................................. 169
Figure 136. $^1$H-NMR spectrum of compound 120c .................................. 170
Figure 137. $^{13}$C-NMR spectrum of compound 120c .................................. 170
Figure 138. IR spectrum of compound 120c .................................................. 171
Figure 139. $^1$H-NMR spectrum of compound 120f .................................. 171
Figure 140. $^{13}$C-NMR spectrum of compound 120f .................................. 172
Figure 141. $^1$H-NMR spectrum of compound 120g .................................. 172
Figure 142. $^{13}$C-NMR spectrum of compound 120g .................................. 173
Figure 143. IR spectrum of compound 120g .................................................. 173
Figure 144. $^1$H-NMR spectrum of compound 120d .................................. 174
Figure 145. $^{13}$C-NMR spectrum of compound 120d .................................. 174
Figure 146. IR spectrum of compound 120d .................................................. 175
Figure 147. $^1$H-NMR spectrum of compound 120e .................................. 175
Figure 148. $^{13}$C-NMR spectrum of compound 120e .................................. 176
Figure 149. IR spectrum of compound 120e .................................................. 176
Figure 150. $^1$H-NMR spectrum of compound 121a .................................. 177
Figure 151. $^{13}$C-NMR spectrum of compound 121a .................................. 177
Figure 152. IR spectrum of compound 121a .................................................. 178
Figure 153. $^1$H-NMR spectrum of compound 121b .................................. 178
Figure 154. $^{13}$C-NMR spectrum of compound 121b .................................. 179
Figure 155. IR spectrum of compound 121b .................................................. 179
Figure 156. $^1$H-NMR spectrum of compound 121c .................................. 180
Figure 157. $^{13}$C-NMR spectrum of compound 121c ........................................... 180
Figure 158. IR spectrum of compound 121c .......................................................... 181
Figure 159. $^1$H-NMR spectrum of compound 121f ............................................. 181
Figure 160. $^{13}$C-NMR spectrum of compound 121f ............................................ 182
Figure 161. IR spectrum of compound 121f .......................................................... 182
Figure 162. $^1$H-NMR spectrum of compound 121d ............................................. 183
Figure 163. $^{13}$C-NMR spectrum of compound 121d ............................................ 183
Figure 164. IR spectrum of compound 121d .......................................................... 184
Figure 165. $^1$H-NMR spectrum of compound 143 ............................................. 184
Figure 166. $^{13}$C-NMR spectrum of compound 143 ............................................. 185
Figure 167. $^1$H-NMR spectrum of compound 144 ............................................. 185
Figure 168. $^{13}$C-NMR spectrum of compound 144 ............................................. 186
Figure 169. IR spectrum of compound 144 .......................................................... 186
Figure 170. $^1$H-NMR spectrum of compound 145 ............................................. 187
Figure 171. $^{13}$C-NMR spectrum of compound 145 ............................................. 187
Figure 172. IR spectrum of compound 145 .......................................................... 188
Figure 173. $^1$H-NMR spectrum of compound 122e ........................................... 188
Figure 174. $^{13}$C-NMR spectrum of compound 122e ........................................... 189
Figure 175. IR spectrum of compound 122e .......................................................... 189
Figure 176. $^1$H-NMR spectrum of compound 122g ........................................... 190
Figure 177. $^{13}$C-NMR spectrum of compound 122g ........................................... 190
Figure 178. IR spectrum of compound 122g .......................................................... 191
Figure 179. $^1$H-NMR spectrum of compound 122a ........................................... 191
Figure 180. $^{13}$C-NMR spectrum of compound 122a ........................................... 192
Figure 181. IR spectrum of compound 122a .......................................................... 192
Figure 182. $^1$H-NMR spectrum of compound 140b ........................................... 193
Figure 183. $^{13}$C-NMR spectrum of compound 140b ........................................... 193
Figure 184. IR spectrum of compound 140b .......................................................... 194
Figure 185. $^1$H-NMR spectrum of compound 122b ........................................... 194
Figure 186. $^{13}$C-NMR spectrum of compound 122b ........................................... 195
Figure 187. IR spectrum of compound 122b .......................................................... 195
Figure 188. $^1$H-NMR spectrum of compound 141b ........................................... 196
Figure 189. $^{13}$C-NMR spectrum of compound 141b ........................................... 196
LIST OF SCHEMES

SCHEMES

Scheme 1. Synthesis of N-aminothieno[3,2-c] pyridine-4-one (7) ........................................ 4
Scheme 2. Synthesis of thienopyridinone derivative 11 ......................................................... 5
Scheme 3. Synthesis of fused pyrazinone 19 .......................................................................... 8
Scheme 4. Synthesis of MCH1R ligand 22 ............................................................................. 8
Scheme 5. Synthesis of diazepinones 30a-d........................................................................ 10
Scheme 6. Synthesis of diazepinones 35a-f........................................................................ 11
Scheme 7. Synthesis of aminothiophenes 37 and 40 and halothiophenes 38 and 41...................... 12
Scheme 8. Synthetic pathway for the formation of thienopyridinones and thienodiazepinones .................................................................................................................. 13
Scheme 9. Synthesis of aminothiophene 37 .......................................................................... 14
Scheme 10. Schematic pathway for the formation of compound 37 ........................................ 15
Scheme 11. Synthesis of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (40) ........................................................................................................................................ 15
Scheme 12. Mechanism for the formation of 40 ...................................................................... 16
Scheme 13. Synthesis of ethyl 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate (59) .................................................................................................................................. 17
Scheme 14. Competitive side reactions .................................................................................... 18
Scheme 15. Synthesis of iodothiophene 38 with side products 60-62 ........................................ 18
Scheme 16. Synthesis of dibromothiophene 63 ........................................................................ 20
Scheme 17. Proposed mechanism for the Cu-mediated carbon–hydrogen bromination of thiophene derivative 63 ........................................................................................... 22
Scheme 18. Bromination of aminothiophene 40 with CuBr2 ................................................. 23
Scheme 19. Sonogashira cross-coupling reaction .................................................................... 24
Scheme 20. Catalytic cycle of Sonogashira cross-coupling reaction ........................................ 25
Scheme 21. Cross-coupling reaction to 38 .............................................................................. 26
Scheme 22. Synthesis of heptyne- and hexyne-substituted thiophenes 42b and 42c............ 28
Scheme 23. Phenylacetylene coupling to compound 41 .................................................. 30
Scheme 24. Synthesis of hexynyl and heptynyl substituted thiophenes 45b and 45c ................................................................. 30
Scheme 25. Synthesis of ethyl 2,5-bis(phenylethynyl)thiophene-3-carboxylate (74) .............................................................. 32
Scheme 26. Hydrazinolysis reaction of 42a ................................................................. 34
Scheme 27. Synthesis of thienopyridinone 43b and 43c ............................................. 35
Scheme 28. Synthesis of thienopyridinone 46a and thienodiazepinone 47 .......... 38
Scheme 29. 6-endo-dig ring closing product 46b and 46c formation ...................... 42
Scheme 30. Synthesis of compound 90 .................................................................... 47
Scheme 31. Synthesis of 93a-e .............................................................................. 48
Scheme 32. Synthesis of 99a-d .............................................................................. 50
Scheme 33. Synthesis of antiproliferatively active compound 104 ...................... 52
Scheme 34. Synthesis of benzoazepine 110 ............................................................ 52
Scheme 35. Proposed mechanism for formation of compound 110 ................. 53
Scheme 36. Schematic pathway for the formation of benzimidazole-fused cyclization product 118 ................................................................. 54
Scheme 37. Synthetic plan for the formation of 122 and 123 .............................. 55
Scheme 38. Synthesis of substituted furane 116 ..................................................... 56
Scheme 39. The reaction mechanism for the formation of 116 ......................... 56
Scheme 40. Oxidation to aldehyde 129 .................................................................. 57
Scheme 41. Synthesis of furane-substituted benzimidazole 117 ....................... 58
Scheme 42. Proposed mechanism for the formation of benzimidazole skeleton .... 59
Scheme 43. Cyclization product 118 formation ..................................................... 60
Scheme 44. Synthesis of O-propargylated salicyl aldehyde 120a .................... 61
Scheme 45. O-propargylation of substituted salicyl aldehydes 119b and 119c .... 61
Scheme 46. Sonogashira cross-coupling reactions of compound 120a ............ 63
Scheme 47. Synthesis of O-substituted salicyl aldehydes .................................. 63
Scheme 48. Synthesis of substituted benzimidazoles 121 .................................... 65
Scheme 49. Cyclization reaction of 121d with NaH ................................................. 67
Scheme 50. Cyclization reaction of 120e ................................................................ 68
Scheme 51. Cyclization reaction of 120g ................................................................ 69
Scheme 52. Resonance form of intermediate 133 .................................................. 70
Scheme 53. Cyclization reactions of 121c and formation of 122c, 135a, and 135b...

Scheme 54. Tentative reaction mechanism for the formation of 122c...

Scheme 55. Formation mechanism of the products 135a and 135b...

Scheme 56. NaH-supported cyclization reaction of 121c at 85 °C...

Scheme 57. Tentative mechanism for the formation of 123c...

Scheme 58. Cyclization reactions of 121a and formation of 122a, 140a and 140b...

Scheme 59. Conversion of 122a to 123a via NaH...

Scheme 60. Cyclization reactions of 121b and formation of 122b, 141a, and 141b...

Scheme 61. N-propargylation of pyrrolealdehyde...

Scheme 62. Reaction pathway for formation of 146...

Scheme 63. One-pot synthesis of benzimidazo-pyrrolo-pyrazine 146...

Scheme 64. Synthesis of 37...

Scheme 65. Synthesis of 40 and 59...

Scheme 66. Halothiophene formation...

Scheme 67. Alkyne-substituted thiophene synthesis...

Scheme 68. Cyclization reaction with hydrazine hydrate...

Scheme 69. Synthesis of 118...

Scheme 70. Synthesis of O-propargylated salicylaldehyde derivatives...

Scheme 71. Benzimidazole formation...

Scheme 72. NaH-mediated cyclization reaction of 121...

Scheme 73. Benzimidazo-pyrrolo-pyrazine formation...
### LIST OF ABBREVIATIONS

**ABBREVIATIONS**

- **Chk1**: Check point kinase 1
- **DHP**: Dihydropyran
- **DIPA**: Diisopropylamine
- **Fmoc**: Fluorenylmethyloxycarbonyl
- **HMBC**: Heteronuclear Multiple Bond Correlation
- **HOBt**: Hydroxybenzotriazole
- **HSQC**: Heteronuclear single quantum correlation
- **MCH**: Melanin-concentrating hormone
- **MCHR**: Melanin-concentrating hormone receptor
- **TBAI**: Tetrabutylammonium iodide
- **TBTU**: 2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethylammonium tetrafluoroborate
- **TEA**: Triethanolamine
- **TFA**: Trifluoroacetic acid
- **Tf₂O**: Trifluoromethanesulfonic anhydride
- **THP**: Tetrahydropyranyl acetal
- **TLC**: Thin layer chromatography
- **p-TsOH**: p-Toluenesulfonic acid
CHAPTER 1

DEVELOPMENT OF A SYNTHETIC METHODOLOGY
FOR
THIENOPYRIDINONE AND THIENODIAZEPINONE DERIVATIVES

1.1 INTRODUCTION

Cancer has become one of the most vital and incurable diseases in the world since there are many people died in recent years. According to a research in 2000, more than 10 million people developed a tumor inside their body and more than half of those people died.\textsuperscript{1} Thiophene-based structures have attracted a great deal of attention due to their binding properties to tumor in a cell. Many modelings such as pharmacophore and atom based 3D-QSAR were applied to the structures with thiophene moiety, it was proven that it had binding affinity for antitumor activity.\textsuperscript{2} The number of obese people have gradually increased in recent years.\textsuperscript{3} Melanin-concentrating hormone (MCH) is involved in the feed control in human body and this hormone leads to increase in feeding and weight when it chronically treats with the rat.\textsuperscript{4,5} The melanin-concentrating hormone receptor 1 (MCH1R) has recently attracted considerable interest as target molecule (Figure 1). There are already some ligands which have high affinity to MCH1R.\textsuperscript{6} Scientists have drawn attention to design novel ligands having high affinity to MCH with thiophene moiety which has anorectic effect on those people.\textsuperscript{7}
Alzheimer’s disease has become one of the most important diseases in the world because there have been 24 million people being effected worldwide. Pyridinone derivatives are well-known drugs for Alzheimer’s disease therapy. While H₃ receptor causes degradation in release of some neurotransmitters such as acetylcholine, serotonin, noradrenaline, and dopamine, H₃ receptor antagonists regulate the level of those neurotransmitters in the brain which provide mental health for patients with Alzheimer’s disease. Pyridinone derivative 2 (Figure 2) has been employed as H₃ receptor antagonist and it demonstrated positive result as therapeutic agents.

There have been various derivatives of thienopyridinone used in regulation of cell functions. To exemplify, compound 3 showed high cell activity as inhibition of
enzymes such as glycogen kinase synthase-β (Figure 3). Furthermore, this skeleton is well-known drug candidate structure.

![Figure 3. Biologically active thienopyridinone derivative](image)

It has also effect on repair of DNA damage and is used as theurepatic agent for cancer cells. Its derivatives are known as to show great affinity to some receptors which are involved in regulation of some neurotransmitters. For instance, N-substituted thienopyridinone derivatives play an important role against Gram negative bacteria.9

### 1.1.3 Synthesis of thienopyridinone

Check point kinase 1 (Chk1), serine/threonine-specific protein kinase, plays an important role in cell regulation once DNA is damaged, that’s why synthesis of its inhibitor has drawn attention by organic chemists. In literature, there are already published Chk1 inhibitors classified as first generation, however, there is no enough molecules having promosing affinity to Chk1. Thiophene-fused pyridine derivatives are well known compounds working as a Chk1 activator for DNA damage repair. Sahu et al.9 (Scheme 1) investigated an efficient and economical way to synthesize N-aminothieno[3,2-c]pyridine-4-one from thieno[3,2-c]pyran-4-one (7) which was prepared from 4-(methylthio)-2-oxo-6-(p-tolyl)-2H-pyran-3-carbonitrile (4). Carbonitrile derivative 4 was reacted with methyl thioglycolate (5) to generate compound 6 in situ followed by addition of hydrazine hydrate to provide N-aminothieno[3,2-c] pyridine-4-one (7).
In 2009, Brouillette et al.\textsuperscript{10} developed a new methodology for synthesis of thienopyridinone derivatives \textbf{11} by using corresponding thienodiazepinones \textbf{8} as the starting materials (Scheme 2). After generation of Boc-protected thienodiazepinones \textbf{8}, they were treated with Grignard reagent to afford compound \textbf{9}. Abstraction of $\alpha$-proton of ketone \textbf{9} in the presence of KOtBu in THF was followed by attacking of the
resulting carbanion to the carbonyl group conjugated with the benzene ring to give 10. Dehydration was carried out under acidic condition that afforded compound 11.

**Scheme 2. Synthesis of thienopyridinone derivatives 11**

1.1.4 Thienopyrimidinone

Enzymes are proteins which are responsible for biochemical reactions in living cells. Some enzymes such as sirtuins (SIRTs) plays a significant role in many biological processes as deacylation of NAD$^+$, aging, inflammation and repair of DNA.

There are various isomers of sirtuins in human body all of which have different specifications. Since some of them have capability of linkage to disease cell to decrease its activity, scientists have drawn attention to synthesis of their derivatives. Selective SIRT2 suicide inhibitor has known to take a role in proteolytic degradation of c-Myc. Previously, thienopyrimidinone SIRT2 inhibitor (12) (Figure 4) has been reported with high selectivity to SIRT2.
Figure 4. Thienopyrimidinone SIRT2 inhibitor

1.1.5 Pyridazinone

PDE4 has various types of cell functions such as controlling the level of cyclic nucleotide cAMP which is used for giving responses to biological agents through activation of adenylyl cyclase.\(^\text{17}\) PDE4 is used as anti-inflammatory agent for asthma\(^\text{18}\) as well as it is a member of nucleotide degrading enzyme family. Gr. cia et al.\(^\text{20}\) prepared oral PDE4 program and tested a series of pyridazinone compounds used as inhaled inhibitors of PDE4. It gave a positive result as to show excellent activity like inhaled inhibition enzyme, PDE4\(^\text{19}\) that’s why at this point they aimed to synthesize pyridazinone analogues as 13 (Figure 5) used as inhaled inhibitor of PDE4.\(^\text{20}\)

Figure 5. Biaryl-substituted pyridazinone 13

1.1.6 Benzo- and thienopyridazinone

Some benzo- and thienopyridazinone derivatives have been used as mimics of melanin-concentrating hormone receptor. Thienopyridazinones have also been known
to show high affinity to this receptor and high brain penetration. It sends a signal to brain no food intake thus helps weight lose with dose-dependent. Synthesis of melanin-concentrating hormone receptor ligand antagonists has gained a great deal of importance by scientists because some evidence emerged that these structures have a significant role for such antagonists in the treatment of anxiety and depression as well.21,22,23 Figure 6 shows thienopyridazinone 14 and benzopyridazinone 15 structures used as MCH1R antagonists.7

![Figure 6. Melanin concentrating hormone receptor ligand antagonists](image)

1.1.6.1 Synthesis of thienopyridazinone derivatives

Since thienopyridazinones and its derivatives have important role in regulation of nervous system, synthetic organic chemists draw attention to incorporation of new substituents to this skeleton. Dyck et al.7 described a concise and efficient synthesis of derivatives of compound 14 utilized as MCH1R ligand (Scheme 3).

For this purpose, 4,5-dichloropyridazinone (16) was used as the starting material. NH-group was protected as tetrahydropyranyl acetal derivative and methanolysis was carried out selectively to give compound 17. For introduction of arylacetone group compound 17 was first converted to the corresponding triflate followed by Sonogashira cross-coupling reaction to furnish compound 18. Cyclization with Na2S in DMF at 70 °C gave pyridazinone 19.
For the construction of the compound 22 (Scheme 4), 20 was reacted with 3-(alkylamino)pyrrolidine in the presence of TsOH. Pyrrolidine functionality was successfully introduced to the system at 110 °C and 21 was formed exclusively. Compound 21 was reacted with 19 in the presence of Cul, 1,2-trans-aminocyclohexane, and Cs₂CO₃ in dioxane that resulted in the formation of 22.

**Scheme 4. Synthesis of MCH1R ligand 22**

### 1.1.7 Diazepinone

The synthesis of nitrogen containing heterocycles has attracted considerable interest due to their wide range of biological activities. In particular, seven-membered \( N \)-heterocycles are privileged structures such as 23 and 24 (Figure 7) are present in some
pharmaceuticals. The pyrrolobenzodiazepine 24 forms the natural anthramycin family of antitumor antibiotic skeleton. Synthetic pyrrolobenzodiazepines have recently been used as non-nucleoside reverse transcriptase inhibitors.24

Figure 7. Pyrolodiazepinone 23 and pyrolobenzodiazepinone 24

Benzo[1,4]diazepin-2-ones are privileged structures25,26 due to the fact that they are present in various types of biologically active molecules. Synthesis of the heterocycles which are composed of these skeletons have attracted considerable attention since they are involved in the well-known drugs used in the treatment of coronary artery disease, peripheral vascular disease, and cerebrovascular disease.27 Clotiazepam (25) (Figure 8) is thienodiazepine-based structure drug with anxiolytic, anticonvulsant, sedative, and muscle relaxant properties.28,29 Furthermore, well-known compound 26 (Figure 8) is used in regulation of some cell functions as AMP-activated protein kinase regulators for the treatment of diabetes, metabolic syndrome, and obesity.30,31

Figure 8. Structures of biologically important thiophene-fused 25 and 26

1.1.8 Synthesis of diazepinones

α-Aminoacyl-β-amino esters 28a-d were synthesized by the reaction of β-amino esters 27a-d with the N-Boc-amino acid using respectively 2-(1H-benzotriazole-1-yl)-
1,1,3,3-tetramethylammonium tetrafluoroborate (TBTU) and hydroxybenzotriazole (HOBt) in dichloromethane. Compound 28a-d were isolated and treated with an excess of freshly prepared vinlylmagnesium bromide (600 mol %) in the presence of copper cyanide (30-40 mol %) in THF at -78 °C to room temperature. Diazepinones 30a-d were synthesized from homoallylic ketones 29a-d by a route featuring deprotection of Boc group in the presence of TFA/DCM (1:1), treatment of the trifluoroacetate salt with triethylamine at 0 °C, and reduction of the imine intermediate with sodium triacetoxyborohydride in dilute dichloroethane (Scheme 5).24

**Scheme 5. Synthesis of diazepinones 30a-d**

**1.1.8.1 Synthesis of fused diazepinones**

Diazepinone-fused derivatives play an important role in medicinal chemistry because of their significant properties as therapeutics. This has encouraged the scientists for the synthesis of new classes of heterocyclic systems including diazepinone scaffold. Although heterocyclic systems having diazepinone system, imidazo[2,1-b][1,3,4]thiadiazole32,33 and an imidazo[2,1-b][1,3]thiazole34,35 individually showed
incredible biological activities. Diazepinone system linked to those heterocycles have not been previously reported. Kolavi et al.\textsuperscript{36} proposed a concise and efficient synthesis of diazepinone derivatives fused to those heterocycles (Scheme 6).

![Scheme 6. Synthesis of diazepinones 35a-f](image)

The benzopyran-2-ones 32a-f were used for the synthesis of 35. The required 3-(2-alky/arylimidazo[2,1-b]-[1,3,4]thiadiazol-6-yl)-2H-chromen-2-ones (33) were prepared by the reaction of 2-amino-5-alkyl/aryl-1,3,4-thiadiazoles (31) with 3-(bromoacetyl)coumarins (32). The 5-carbaldehydes 34a-f were obtained by the Vilsmeier–Haack reaction on 33a-f. Treatment of these compounds with hydrazine hydrate in ethanol/KOH under reflux conditions provided the ring-transformed derivatives via lactone ring opening by intramolecular nucleophilic attack of the –NH\textsubscript{2} group of the intermediate hydrazone which could not be isolated. Initial step in the mechanism of this reaction is intramolecular nucleophilic attack at the lactone carbonyl of the coumarin leading to the formation of diazepinones 35a-f.


1.1.9 Aim of the study

The aim of this thesis was to develop a synthetic methodology for thienopyridinone and thienodiazepinone derivatives. For the formation of thiophene skeleton such as 37 and 40, 1,4-dithiane-2,5-diol (36) and cyclohexanone (39) were planned to be used as starting materials (Scheme 7).

![Scheme 7. Synthesis of aminothiophenes 37 and 40 and halothiophenes 38 and 41](image)

After the construction of aminothiophene skeletons as key compounds via Gewald type reaction, iodide and bromide will be attached to the alpha position of thiophene ring with replacement of amino moiety through modified Sandmayer reaction. Application of Sonogashira cross-coupling reaction to halothiophenes 38 and 41 will result in the formation of 42 and 45.

The final step, cyclization of 42 and 45 with hydrazine monohydrate should provide the desired thienopyridinone 43 and 46 and thienodiazepinone derivatives 44 and 47 (Scheme 8).
Scheme 8. Synthetic pathway for the formation of thienopyridinones and thienodiazepinones
1.2 RESULTS AND DISCUSSION

1.2.1 Synthesis of aminothiophene derivatives

1.2.1.1 Synthesis of ethyl 2-aminothiophene-3-carboxylate (37)

Dithiane 36 was used as starting material to form thiophene skeleton having amine functionality at its α–position using the Gewald type reaction (Scheme 9).37

\[
\begin{align*}
\text{HO-S-S-OH} & \quad \underset{\text{NEt}_3}{\xrightarrow{\text{DMF}, \text{r.t., 3 h}, \text{70\%}}} \quad \text{S-\text{NH}_2} \\
36 & \quad 48 & \quad 37 \\
\end{align*}
\]

Scheme 9. Synthesis of aminothiophene 37

The methylene group in ethyl cyanoacetate (48) is activated by two electron-withdrawing groups for deprotonation. In this version of Gewald type reaction, the more stable dimeric form 36 of α-sulfonylaldehyde 49 was used to construct the thiophene skeleton. Compound 36 was dissolved in DMF at room temperature. After addition of ethyl cyanoacetate (48), followed by addition of NEt3 compound 37 was formed.

We assume that the first step is the abstraction of a proton in 48, in the presence of NEt3. The resulting carbanion undergoes a nucleophilic attack to the aldehyde group in 49 to form the intermediate 50 accompanied by Knoevenagel-Cope condensation reaction. Intramolecular nucleophilic attack of the sulfur anion to the carbon atom of the cyano group affords 37 which in principle exists in equilibrium with the tautomeric forms cyclic imine 51 (Scheme 10). However, it was proven that amino-form 37 is the most stable structure and equilibrium is shifted to the side of amine.38,39,40,41,42

The \(^1\)H- and \(^{13}\)C-NMR spectral data were in agreement with the structure of 37. Two thiophene protons resonate at 6.98 and 6.18 ppm with a coupling constant of \(J = 5.7\) Hz. The NH\(_2\) protons resonate as a broad singlet at 5.93 ppm.
1.2.1.1 Synthesis of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[\textit{b}]thiophene-3-carboxylate (40)

After successful synthesis of the aminothiophene derivative 37, we focused on the synthesis of further substituted aminothiophenes. Base-promoted Gewald type reaction was used to generate 40. In the second version of the Gewald type reaction, any ketone having an \(\alpha\)-proton can be used as starting material to form thiophene scaffold. Incorporation of cyclohexanone (39) into the system afforded corresponding amine 40 (Scheme 11).

**Scheme 10.** Schematic pathway for the formation of compound 37

**Scheme 11.** Synthesis of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[\textit{b}]thiophene-3-carboxylate (40)
This particular version of Gewald type reaction involves a base-promoted sulfur addition. After deprotonation of 48, the formed carbanion undergoes a nucleophilic addition to the carbonyl group in 39 to form intermediate 55. Morpholine reacts with elemental sulfur 53 to form sulfur ylide 54. Intermediate 55 reacts with 54 to generate sulfur adduct 56. Intramolecular cyclization reaction of 56 involving sulfur attack to the carbon atom of cyano group affords 57 which is in equilibrium with its cyclic amine form 40 as shown in Scheme 12.

Scheme 12. Mechanism for the formation of 40

The $^1$H-NMR spectrum is in agreement with the structure 40. The NH$_2$ protons resonate at 5.95 ppm as a broad singlet. The methylene protons attached to the thiophene ring resonate as multiplets at 2.70 and 2.49 whereas the remaining methylene protons appear at 1.75 ppm as multiplet as expected.
1.2.1.3 Synthesis of ethyl 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate (59)

Similar reaction was carried out with cyclopentanone. By application of the same methodology as described above, the expected product, cyclopentene-fused aminothiophene derivative 59 was obtained in a yield of 30% (Scheme 13).

Completion of the reaction was followed by GC-MS which displayed a signal with the mass of 211.1 g/mol. The NMR spectral data were in agreement with the structure of 59. In the $^1$H-NMR spectrum, the NH$_2$ protons resonate at 5.84 ppm as a broad singlet. The CH$_2$ protons give rise to multiplets due to the coupling with neighboring methylene protons at 2.81, 2.72, and 2.31 ppm.

### Scheme 13. Synthesis of ethyl 2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate (59)

1.2.2 Synthesis of ethyl 2-iodothiophene-3-carboxylate (38)

Sandmayer reaction was applied to 37 for the formation of 38. Conventional Sandmayer reaction involving initial diazotization of the arylamine followed by addition of the diazonium salt to the cuprous halide in an aqueous solution with the corresponding halogen acid is reported. Nevertheless, there are numerous competitive side reactions (Scheme 14) decreasing the yield of targeting Sandmayer products.\textsuperscript{43}
The overall reaction was reported in the literature as shown below.

$$2\text{ArNH}_2 + 2\text{RONO} + \text{CuX}_2 \rightarrow 2\text{ArX} + 2\text{ROH} + \text{CuO} + 2\text{N}_2 + \text{H}_2\text{O}$$

We applied the Sandmayer reaction to \(\text{37}\) in the presence of \(t\)-butyl nitrite and CuI in CH\(_3\)CN as shown in Scheme 15. Three side products \(\text{60, 61, and 62}\) were formed when the reaction was carried out in a non-dry solvent. The isolated yield of the desired product \(\text{38}\) was very low due to the fact that separation of \(\text{38}\) from \(\text{60}\) was very difficult. The yields of all compounds were determined by analysis of the \(^1\text{H}-\text{NMR}\) spectrum of the mixture.

The NMR spectral data were in agreement with the structure of \(\text{38}\) (Figure 9). Two thiophene protons resonates at 7.41 and 7.33 ppm with a coupling constants of \(J = 5.6\) Hz which is in the expected range.
Since the chemical shift difference between adjacent protons is not much larger than the coupling constant, it gives an AB-system by which roof effect is obviously detected with the ratio $\Delta\delta/J = 5.72$.

The characterization of 61 and 62 was done by GC-MS and NMR analyses. It is known that the coupling constant $^3J$ between two adjacent protons of thiophene and that the $^4J$ coupling are in specific range, 5-6 Hz and 0-3 Hz, respectively. Careful inspection of the $^1H$-NMR spectrum of 62, shows the presence of two adjacent protons resonating at 7.49 and 7.24 ppm with a coupling constant of $J = 5.4$ Hz (Figure 10.). On the other hand, an additional thiophene proton attached to the other thiophene ring gives rise to a singlet at 7.58 ppm that means there is only one proton attached to thiophene ring. Compound 61 gives four different signals shown with black arrow (Figure 10) and two of which resonate at 7.50 and 7.23 ppm with a coupling constant of $J = 5.6$ Hz and the other thiophene protons appear as two distinct signals at 8.15 and 7.75 ppm with a coupling constant of $J = 1.4$ Hz clearly indicating 1,3 position of the protons.

When we evaluate the polarities of the products, one can easily notice that these compounds 61 and 62 have similar polarities which prevented the separation and isolation of individual products.
1.2.3 Synthesis of ethyl 2,5-dibromothiophene-3-carboxylate (63)

During iodination of 37 several side products were formed. Therefore, we aimed to synthesize the corresponding bromo compounds according to literature procedure with the expectation that the ratio of the side products would be reduced. For this reason 37 was treated with CuBr₂ in presence of t-butyl nitrite, surprisingly, 2,5-dibromo adduct 63 was formed as the sole product (Scheme 16). Unfortunately, mono-brominated compound was not formed even in traces.

Scheme 16. Synthesis of dibromothiophene 63

The fact that the only dibromo compound 63 was produced, can be explained on the basis of two steps reaction. We assume that the initially formed monobromide,
structure 64 formed after the Sandmayer reaction, undergoes subsequent bromination. It is likely that the compound 64 is much more reactive than the starting material so that the reaction cannot be controlled at the stage of monobromide 64. At this stage, CuBr₂ has gained a great deal of importance while discussing reaction mechanism. Copper is an important catalyst involved in organometallic reactions with its complexes with oxidation states ranging from 0 to +4 although the +2 (cupric) and the +1 (cuprous) oxidation states are by far the most common. Hence, its reaction mechanism may change depending upon the condition and reactant structure. In recent years, researchers proposed Cu-mediated/catalyzed carbon–hydrogen activation reaction mechanisms for the formation of carbon–heteroatom bonds. In one of these mechanisms (Scheme 17), species of Cu(III) are suggested as key intermediates that can promote the transformation of carbon–hydrogen bonds. Cu(I) and Cu(II) are the most common oxidation states, while Cu(III) is scarce in inorganic and coordination chemistry. On the basis of the related literature we proposed a 2Cu(II) → Cu(III) + Cu(I) mechanism for the bromination reaction as shown in Scheme 17. The coordination of Cu(II) with the carbonyl group in 64 forms the Cu(II) intermediate 65. Intermediate 65 is converted to the high valence Cu(III) intermediate 66 under the oxidation conditions of CuBr₂, and the CuBr₂ is converted into CuBr.⁴⁵,⁴⁶,⁴⁷,⁴⁸
Scheme 17. Proposed mechanism for the Cu-mediated carbon–hydrogen bromination of thiophene derivative 63.

Then, nucleophilic attack of the thiophene ring to the Cu(III) in the intermediate 67 generates Cu(III) intermediate 68 via intermediate 67 through a dearomatization and rearomatization processes. Finally, the reductive elimination of intermediate 68 generates intermediate 69 and the nucleophilic attack of a bromine ion to the active intermediate 69 provides dibrominated product 63.
1.2.4 Synthesis of ethyl 2-bromo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (41)

As discussed in the previous section, there were numerous competitive side reactions during iodination of aminothiophene 37. Therefore, our efforts were directed toward the use of substituted thiophenes such as 40 as the key compound to hinder possible coupling reactions between the thiophene rings. Modified Sandmayer reaction was applied to 40 in the presence of t-butyl nitrite with CuBr₂ in CH₃CN to obtain target compound 41. We obtained the desired compound 41 in a yield of 70%. However, the reduced product 70 was also formed in a yield of 15% (Scheme 18).

![Scheme 18. Bromination of aminothiophene 40 with CuBr₂](image)

<table>
<thead>
<tr>
<th></th>
<th>41</th>
<th>70</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) (in non-dry solvent)</td>
<td>70%</td>
<td>15%</td>
</tr>
<tr>
<td>b) (in dry solvent)</td>
<td>90%</td>
<td>-</td>
</tr>
</tbody>
</table>

When the reaction was carried out under the dry condition, product distribution was changed, the yield of the major product 41 was significantly increased and no trace of the side product 70 was detected.

Formation of compounds 41 and 70 was proven by ¹H-NMR. The ¹H-NMR spectrum of 41 shows two distinct signals at 2.75 and 2.63 ppm as quasi triplets arising from the protons d and a. Multiplet at 1.78 ppm belongs to the b and c protons. For the compound 70, the thiophene proton resonates at 7.9 ppm as a singlet as expected from the structure. The other peaks present on cyclohexane ring resonate at 2.75 and 2.89 ppm as quasi triplets and multiplet at 1.81 ppm arising from other methylene protons on the cyclohexene ring.
1.2.5 Sonogashira cross-coupling reaction

The Sonogashira cross-coupling reaction is used for the coupling of aryl halides and terminal acetylenes for the formation of C(sp$^2$)–C(sp) bond.$^{50,51}$ Traditional palladium ligands in combination with CuI have been preferred although there are numerous metal catalysts claimed to be effective.$^{52}$ The most commonly used catalytic systems for this transformation include PdCl$_2$(PPh$_3$)$_2$, PdCl$_2$/PPh$_3$, and Pd(PPh$_3$)$_4$ together with CuI as the cocatalyst and amines are used as the solvents or cosolvents. This method is one of the most convenient methods for the straightforward construction of sp$^2$–sp carbon–carbon bonds in synthetic chemistry.$^{53,54}$ Sonogashira reactions are carried out under inert atmosphere using dry solvents. General reaction representation of Sonogashira cross-coupling reaction is shown in Scheme 19.

\[ R≡H + R'−X \xrightarrow{\text{Pd cat. Cu cat. base, rt}} R\equiv R' \]

$R' = \text{aryl or vinyl}$

$X = \text{I, Br, Cl or OTf}$

Scheme 19. Sonogashira cross-coupling reaction

The Sonogashira cross-coupling reaction was first reported by Sonogashira et al. in 1975. Cassar, Dieck and Heck used relatively harsh reaction conditions, such as high temperature and obtained the same reaction products. While these researchers used only palladium catalyst for coupling, Sonogashira used both, palladium and copper as catalysts simultaneously. These results inspired the development of reaction conditions of Sonogashira cross-coupling reaction such as the ability to carry out the reactions at room temperature and to increase in the reactant reactivity. This development made the Sonogashira cross-coupling reaction very useful for alkynylation of aryl and alkenyl halides.$^{55,56}$ Although the reaction has attracted high attention of organic chemists who reported various coupling products with their proposed mechanism. Recent proposed mechanism represents the catalytic cycle of Sonogashira cross-coupling reaction as shown in Scheme 20.$^{56}$

In this catalytic cycle, the first step is activation of palladium which involves conversion of palladium (II) into active palladium (0) through reduction. The active
palladium catalyst is the 14 electron compound Pd(0)L₂, complex \( \text{A} \), which reacts with the organohalide compound in an oxidative addition to form a Pd(II) intermediate, complex \( \text{B} \). This step is the rate-determining step of the reaction. In the copper catalytic cycle, copper coordinates to triple bond and plays a significant role in increasing the acidity of acetylene proton.

![Scheme 20](image)

**Scheme 20.** Catalytic cycle of Sonogashira cross-coupling reaction

Amine base abstracts this proton and form its salt. Transmetallation involves the transfer of organic part of copper complex to palladium that provides complex \( \text{C} \). Subsequent cis-trans isomerization gives complex \( \text{D} \) followed by reductive elimination which affords the coupling product \( \text{E} \) and palladium complex with palladium (0).

In the light of this information, we applied the Sonogashira cross-coupling reaction to our halothiophenes under the conditions which we developed. We used THF as a solvent and NEt₃/DIPA as a base. PdCl₂/CuI catalyst couple was used in presence of PPh₃ to afford our target alkyne substituted thiophenes.
1.2.5.1 Sonogashira cross-coupling reactions applied to iodothiophene 38

1.2.5.1.1 Synthesis of ethyl 2-(phenylethynyl)thiophene-3-carboxylate (42a)

The palladium-catalyzed Sonogashira coupling reaction of 38 with phenylacetylene using NEt₃ as a base was first examined. The reaction was carried out under nitrogen atmosphere at reflux temperature. At first, PdCl₂, PPh₃, and CuI in THF were added into reaction vessel and stirred under nitrogen atmosphere for 15 min. After subsequent addition of alkyne and NEt₃ the resulting mixture was stirred for 6 h at reflux temperature affording compound 42a in 45% yield with the formation of homocoupling product 71 (Scheme 21).

![Scheme 21. Cross-coupling reaction to 38](attachment:image.png)

The formation of 42a was confirmed by ¹H and ¹³C-NMR spectra as shown in Figure 11 and Figure 12. As we described in the previous section, one could easily show the existence of thiophene skeleton by evaluating the coupling constant between the thiophene protons. There are two protons in aromatic region giving two distinct signals at 7.47 and 7.20 ppm with a coupling constant of $J = 5.3$ Hz. The resonance signals of the benzene ring appear as two separate multiplets at 7.57 and 7.36 ppm. Methyl and methylene protons of ester functionality resonate at 4.39 and 1.42 ppm, respectively.
The $^{13}$C-NMR spectrum also supported the formation of compound 42a. If we analyze the $^{13}$C-NMR spectrum, one can realize the existence of two signals resonating at 98.9 and 81.8 ppm arising from the acetylene unit. In the $sp^2$-region, there are two intense peaks at 131.6 and 128.4 ppm arising from the $o$- and $m$-carbons of the phenyl group.
1.2.5.1.2 Synthesis of ethyl 2-(hept-1-yn-1-yl)thiophene-3-carboxylate (42b) and ethyl 2-(hex-1-yn-1-yl)thiophene-3-carboxylate (42c)

After successful synthesis of 42a, we applied the coupling reaction to compound 38 with different alkynes such as hexyne and heptyne (Scheme 22).

![Scheme 22](image)

**Scheme 22.** Synthesis of heptyne- and hexyne-substituted thiophenes 42b and 42c

At first, we examined the reaction of compound 38 with heptyne. The reaction was monitored by TLC and we concluded that the reaction time was not affected significantly when compared to that of phenylacetylene coupling. However, in this case, only trace amount homocoupling product was formed as one can see from the crude NMR spectrum in Figure 13. The $^1$H- and $^{13}$C-NMR spectra are consistent with the proposed structure 42b. In the $^1$H-NMR spectrum of 42b, there are two doublets in the aromatic region with a coupling constant of $J = 5.4$ Hz that belong to adjacent thiophene protons. The triplet signals at 2.5 ppm is arising from methylene protons a directly connected to acetylene unit.

Other aliphatic protons b, c, d, and methyls of alkyl chain and ethyl ester resonate in the range of 1.8-0.9 ppm.
We obtained similar results when hexyne was used as an alkyne source. The NMR spectrum of compound 42c was straightforward. The fact that one methylene group was missing compared to the NMR spectrum of 42b clearly indicated the formation of the desired coupling product.

1.2.5.2 Sonogashira cross-coupling reaction applied to bromothiophene 41

1.2.5.2.1 Synthesis of ethyl 2-(phenylethynyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (45a)

As demonstrated in Scheme 23, coupling of 41 with phenylacetylene was also performed smoothly which gave the corresponding product 45a in 60% yield. We used the same coupling reagents which were used for the coupling reactions of 38 (Scheme 23). Additionally, diisopropylamine was used as a base as to increase the yield of the reaction.
The $^1$H- and $^{13}$C-NMR spectra are compatible with the proposed structure 45a. Phenyl protons resonate as two separate multiplets at 7.52 and 7.34 ppm. In aliphatic region, there are two quasi triplets at 2.83 and 2.73 arising from the a and b protons attached to thiophene skeleton. The reason for low field resonance of a protons is that it is close to the sulfur atom which inductively pulls its electrons (-I) through sigma bond.

The methylene proton resonances c and d are overlapped and appear as a multiplets at 1.8 ppm. The $^{13}$C-NMR spectrum is also fully consistent with the proposed structure. The resonances at 97.6 and 82.9 ppm clearly demonstrate the incorporation of the alkyne unit into the molecule.

1.2.5.2.2 Synthesis of ethyl 2-(hept-1-yn-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (45b) and ethyl 2-(hex-1-yn-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (45c)

Treatment of compound 41 with Sonogashira coupling reagents in the presence of hexyne and heptyne at the reflux temperature provided thiophene substituted alkyne derivatives 45b and 45c (Scheme 24).
The formation of compounds 45b and 45c was determined by $^1$H- and $^{13}$C-NMR spectra. Comparison of the $^1$H-NMR spectrum of 45b with those of 45a shows the similarity of the resonances arising from the cyclohexene ring showing the presence of two quasi triplets and two multiplets overlapped at 1.8 ppm as in the $^1$H-NMR spectrum of 45a. The heptynyl resonances of 45b has also similar chemical shifts and coupling constants as described in the $^1$H-NMR spectrum of 42b. Eleven carbon resonances observed in the sp$^3$-region also support the proposed structure. Again the presence of two distinct resonances at 99.8 and 73.7 ppm in $^{13}$C-NMR shows the presence of alkyne unit in the structure. The other five carbon peaks in sp$^2$-region belong to thiophene quaternary carbons and carbonyl carbon.

We applied the coupling reaction to compound 41 in presence of heptyne. The formation of 45c was also proven by $^1$H- and $^{13}$C-NMR spectra. The $^1$H-NMR spectrum is similar to that of compound 45b.

Figure 14. $^1$H-NMR spectrum of compound 45b
1.2.5.3 Synthesis of ethyl 2,5-bis(phenylethynyl)thiophene-3-carboxylate (74)

The versatility of Sonogashira coupling reaction was further demonstrated by the synthesis of coupling product 74 from dibromothiophene 63 in the presence of phenylacetylene (Scheme 25).

![Scheme 25. Synthesis of ethyl 2,5-bis(phenylethynyl)thiophene-3-carboxylate (74)](image)

Its formation was verified by $^1$H- and $^{13}$C-NMR spectra. In the $^1$H-NMR spectrum, there are ten aromatic protons resonating as three distinct multiplets at 7.58, 7.52 and 7.38 ppm and the integral values of which are consistent with the number of phenyl protons. The other singlet resonating at 7.60 ppm belongs to the thiophene proton. The
\(^{13}\)C-NMR spectrum clearly shows us the incorporation of two alkynes into the system including four acetylene carbons. The resonances of those carbons are observed at 99.6, 94.5, 81.6, and 81.3 ppm.

### 1.2.6 Cyclization with hydrazine monohydrate

Hydrazine is a kind of a base and it can be used as nucleophile in organic reactions. Its basic character and nucleophilicity makes it very useful compound for organic synthesis. It has two lone pairs which provides attack to any electron deficient center. It is a kind of a base because when it is dissolved in water, its acidic form is readily formed. Moreover, it has two adjacent nitrogen atoms by which its addition reaction followed by cyclization reaction can afford biologically important heterocyclic compounds. In the light of this information, we used hydrazine monohydrate for cyclization to afford thienopyridinone and thienodiazepinone derivatives.

#### 1.2.6.1 Cyclization of phenylethynylthiophene 42a with hydrazine monohydrate

We treated 42a with excess hydrazine monohydrate in methanol and the resulting reaction mixture was heated at reflux temperature and stirred well. The reaction was controlled by TLC.
We observed that hydrazinolysis of compound 42a led to the cyclization products thienopyridinone 43a and thienodiazepinone 44 with the formation of corresponding hydrazide 75a as an intermediate as shown in Scheme 26.

The $^1$H- and $^{13}$C-NMR spectra are consistent with the proposed structure 43a. The NH$_2$ protons resonate as a broad singlet at 5.03 ppm and the olefinic proton resonates at 6.64 ppm as singlet as shown in Figure 16. These two characteristic peaks and disappearance of ester group clearly show us the formation of compound 43a.
1.2.6.2 Cyclization of ethyl 2-(hept-1-yn-1-yl)thiophene-3-carboxylate (42b) and ethyl 2-(hex-1-yn-1-yl)thiophene-3-carboxylate (42c) with hydrazine monohydrate

To validate this methodology, we applied the cyclization reaction to compound 42b and 42c. The reaction proceeded under the same condition with that of compound 42a. The reaction was monitored by TLC.

![Figure 16. $^1$H-NMR spectrum of compound 43a](image)

**Scheme 27. Synthesis of thienopyridinone 43b and 43c**

We treated compound 42b and 42c with hydrazine monohydrate to form hydrazides as intermediates. Subsequent intramolecular cyclization reaction involving nitrogen
attack to triple bond carbon afforded only compound 43b and 43c in high yields (Scheme 27). In this particular reaction, there was no diazepinone formation.

The formation of 43b and 43c was established by ¹H- and ¹³C-NMR spectra. In the ¹H-NMR spectrum of the compound 43c (Figure 17), there are two thiophene protons resonating at 7.59 and 7.20 ppm with a coupling constant of $J = 5.4$ Hz. The olefinic proton and NH₂ protons resonate as singlets at 6.56 and 4.96 ppm, respectively. The methylene protons attached directly to the double bond resonate as a broad triplet at 2.85 ppm.

The carbon chemical shifts of 43c is shown in Figure 18. The ¹³C-NMR spectrum clearly demonstrates the formation of cyclization products. Furthermore, disappearance of alkyne carbon signals and appearance of a singlet at 100.1 ppm supports the formation of a cyclization product. The remaining carbon atoms from the hydrocarbon tail resonate below 30.5 ppm which is an agreement with the proposed structure.

![Figure 17. ¹H-NMR spectrum of compound 43c](image)

As we discussed in the previous section that the NMR spectra of the coupling products with hexyne and heptyne are not significantly affected by the presence of an additional
methylene group. The $^1$H-NMR spectrum of $43c$ differs from that of $43b$ just by the presence of an additional methylene group.

![Image of 13C-NMR spectrum of compound 43c]

**Figure 18.** $^{13}$C-NMR spectrum of compound $43c$

1.2.6.3 Cyclization of ethyl 2-(phenylethynyl)-4,5,6,7-tetrahydrobenzo
[b]thiophene-3-carboxylate (45a) with hydrazine monohydrate

Access to these valuable scaffolds (thienopyridinone and thienodiazepinone) encouraged us to apply cyclization reaction to different alkyne substituted thiophenes. Treatment of compound 45a with hydrazine monohydrate in methanol under reflux condition afforded thienopyridinone 46a and thienodiazepinone 47 via 6-endo-dig and 7-endo-dig cyclization reactions (Scheme 28).

The $^1$H- and $^{13}$C-NMR spectra are consistent with the structures 46a and 47. Moreover, we determined the exact structures of those compounds by using 2D-NMR spectra.
In the $^1$H-NMR spectrum of the seven-membered ring 47, there are two significant resonances appearing at 4.10 and 8.6 ppm which were assigned to methylene protons and NH proton, respectively. These signals are the fingerprint of the formation of compound 47. Eight protons in the aliphatic region and five protons in the aromatic region are arising from cyclohexene ring and phenyl group, respectively.

However, from the 1D NMR spectra we could not distinguish between the structures 47 and 77 (Figure 19). The 1D NMR spectra can also be in agreement with the structure 77 (Figure 20). In order to make a clear-cut differentiation between these two structures, we recorded 2D NMR spectra of the compound.

**Scheme 28.** Synthesis of thienopyridinone 46a and thienodiazepinone 47

![Scheme 28](image_url)
We utilized HSQC and HMBC spectra for exact structure determination. First, we used the HSQC spectrum (Figure 21) to determine the methylene carbon atom. If we draw a perpendicular line from the methylene protons at 4.07 ppm to other axis, the line intersects cross peak indicating that these protons bear the carbon resonating at 30.2 ppm.

Figure 20. $^1$H-NMR spectrum of compound 47

Figure 21. HSQC spectrum of compound 47
Long-range heteronuclear correlation is observed in HMBC spectra which provides us very useful information about the structure. Since, it gives a correlation between proton and carbon peaks separated by multiple bonds (usually two or three), this spectrum suggests indirect way of information for the carbon and hydrogen connectivities. In the case of structure 77 we should observe a strong correlation between the methylene carbon atom and the aromatic protons. However, careful inspection of the HMBC spectrum doesn’t show any correlation between the relevant atoms. Therefore, we can exclude the structure 77 because of the absence of a correlation between CH carbons of phenyl group and the CH$_2$ protons (Figure 22 and Figure 23).

![HMBC spectrum of compound 47](image)

**Figure 22.** HMBC spectrum of compound 47

On the other hand, the strong correlation between the methylene protons and thiophene carbon atoms strongly supports the presence of a seven-membered ring.
1.2.6.4 Cyclization of ethyl 2-(hept-1-yn-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (45b) and ethyl 2-(hex-1-yn-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (45c) with hydrazine monohydrate

Reaction of 45b and 45c with hydrazine monohydrate in methanol under reflux condition, contrary to the result obtained with 45a, resulted in the formation of cyclization products with six-membered ring (Scheme 29). The reaction proceeded with excellent regioselectivity between 5-exo-dig and 6-endo-dig ring closure. The 6-endo-dig cyclization products 46b and 46c were exclusively formed.
It was seen in the expanded $^1$H-NMR spectrum of 46c (Figure 24) that there were no methylene proton resonances which was a strong evidence for the formation of six-membered ring product, thienopyridinones 46b and 46c.
CHAPTER 2

DEVELOPMENT OF A SYNTHETIC METHODOLOGY
FOR THE SYNTHESIS OF BENZIMIDAZO-OXAZEPINES

2.1 INTRODUCTION

Heterocyclic compounds are the cyclic organic compounds which contain at least one heteroatom in their structures. They play significant roles in the metabolism of all living cells; a great number of them are five- and six-membered rings. Those structures have received considerable attention due to the fact that they have an important role as pharmaceuticals in medical chemistry and also they are frequently found in a wide variety of biomolecules such as enzyme, vitamins, and natural products. Moreover, they can be used as antifungal, antiinflammatory, antibacterial, antioxidant, anticonvulsant, antiallergic, anti-HIV, antidiabetic, anticancer, insecticidal agents, and enzyme inhibitors. In addition, biological molecules such as DNA, RNA, hemoglobin, vitamins and many more contain a heterocyclic ring in their major skeletons. There is a great number of pharmacologically active heterocyclic compounds, many of which can be used in clinical applications.

Wahbi et al. synthesized heterocyclic compounds having pyrrole, furan, and thiophene skeletons. They used some theoretical calculations in order to show their activities as antifungal agents. The structures of these compounds showing most promising results are given in Figure 25.
2.1.1 Imidazole

Imidazole is a five-membered heterocycle that contains two nitrogen atoms on the ring. Imidazole is generally regarded as being aromatic. The electrons on sp$^3$ hybridized nitrogen atom are delocalized through $\pi$-orbitals so the lone pairs are contributed to resonance stabilization. As a consequence, it is a cyclic, conjugated system with six $\pi$-electrons being an aromatic compound. Dewar et al.$^60$ calculated the resonance energy of imidazole as 15.4 kcal/mol. In order to compare this value with those of well-known aromatic compounds like benzene, pyridine, and pyrrole, they also calculated the resonance energies for those compounds and found the values of 20.0, 20.9, and 8.5 kcal/mol, respectively, which are close to that of imidazole. Similarly, the resonance energies of benzimidazole and naphthalene were also calculated as 30.9 kcal/mol and 30.5 kcal/mol, respectively.

Imidazole derivatives have attracted considerable attention due to their biological properties as therapeutics. In addition to this, they are involved in the inhibition of some enzymes. Young et al.$^61$ found how SB203580 (81) (Figure 26) binds to the ATP binding site and subsequently inhibits p38 kinase catalytic activity. They synthesized pyridinyl imidazoles and evaluated their inhibition properties on p38 mitogenactivated protein kinase.

![Figure 25. Antifungal agents](image)

![Figure 26. Structure of SB203580](image)
2.1.2 Benzimidazole

Benzimidazole is a heterocyclic compound consisting of a fused benzene and imidazole ring and its derivatives have drawn considerable attention due to their diverse biological activities. They are well known compounds with their enzyme inhibition properties. Benzimidazole is a class of a heterocyclic compound that exhibit a wide range of biological activities such as antimicrobial, antiviral, antidiabetic, anticancer activity, numerous antioxidant, antiparasitic, antihelmintics, antiproliferative, anti-HIV, anticonvulsant, antiinflammatory, antihypertensive, antineoplastic, proton pump inhibitor, and antitrichinellosis.\(^62\)

Hepatitis B virus (HBV) has become one of the most important diseases in the world because there have been two billion people being effected worldwide\(^63\) and 0.5-1.2 million people died annually from the resulting cirrhosis, liver failure, and hepatocellular carcinoma.\(^64\) The remarkable biological activity of imidazole skeleton has inspired the development of new imidazole derivatives. Benzimidazoles are regarded as being used in inhibition of HIV DNA synthesis. Li et al.\(^65\) proposed an efficient and concise synthetic way to a series of new class of benzimidazole derivatives and evaluated them for their antihepatitis B virus (HBV) activity and cytotoxicity. Compounds 82 and 83 (Figure 27) demonstrated high activity against HIV replication with high antiviral potency (IC\(_{50}\)=0.9 and 0.7 µM, respectively).

\[\text{Figure 27. The structures against HIV replication}\]

In recent years, bacteria gained high resistance to antibiotics that brought organic chemists to synthesize a new generation of antibacterial agents. Benzimidazole derivatives are well known compounds as being employed in drug discovery.
particularly as used for antibacterial, antiviral, and antifungal activities\textsuperscript{62} that’s why they focused on the synthesis of novel benzimidazole derivatives structurally different from existing antibacterial agents. Kumar \textit{et al.}\textsuperscript{66} proposed a synthetic pathway for novel 2-(6-fluorochroman-2-yl)-1\textit{H}-benzimidazole (84) (Figure 28) which show promising antibacterial activity against Salmonella typhimurium.

![Figure 28. The structure against Salmonella thphimurium](image)

Malaria has been a vital disease caused 350-500 million clinical events in a year and led to over one million deaths. Children under 5 years old in sub Saharan Africa were affected from this disease. Malaria is as serious disease as HIV/AIDS and tuberculosis.\textsuperscript{62} Camacho \textit{et al.}\textsuperscript{67} reported a series of \textit{N}-substituted-2-(5-nitrofuran or 5-nitrothiophen-2-yl)-3\textit{H}-benzo[\textit{d}]imidazole-5-carboxyhydrazide derivatives 85 as shown in Figure 29 and screened for their antimalarial activity in rodent Plasmodium berghei.

![Figure 29. Antimalarial agents 85](image)

\begin{table}[h]
\centering
\begin{tabular}{|c|c|}
\hline
\textbf{R} & \textbf{85} \\
\hline
1 & H \\
2 & Ph \\
3 & 3-C1Ph \\
4 & 4-C1Ph \\
5 & 3-MeOPh \\
6 & 3,4-MeOPh \\
7 & 3,4,5-MeOPh \\
8 & 3-PhOPh \\
9 & 3-OH-2-Naphtyl \\
\hline
\end{tabular}
\end{table}

2.1.3 \textbf{Synthesis of benzimidazole derivatives}

As mentioned, since bacteria have gained high resistance to existing antimicrobial drugs, design and the synthesis of novel antibacterial agents received considerable
attention. Benzimidazole moiety plays a significant role in drug synthesis so the search for efficient approach to synthesize new class of benzimidazoles with different substituents became the most important issue for medicinal chemistry. Padalkar et al. proposed a class of benzimidazole derivatives acting as antibacterial agents.

Scheme 30. Synthesis of compound 90

Starting with 3(diethylamino)phenol (86), they achieved the synthesis of 4-(diethylamino)-2-hydroxybenzaldehyde (87) by using Vilsmeier–Haack reaction with DMF:POCl₃ at 60 °C which was then treated with substituted o-phenylenediamine in ethanol and PCl₃ at 60 °C to obtain the corresponding 5-(diethylamino)-2-(5-nitro-1H-benzo[d]imidazol-2-yl)phenol (89). Reduction of 89 by using 10% Pd/C in ethanol and hydrazine hydrate afforded targeted benzimidazole 90 (Scheme 30).

Mariappaz et al. suggested a concise and efficient way for the synthesis of 2-substituted benzimidazole derivatives for subsequent anti-inflammatory and analgesic activity testing (Scheme 31). The compounds they synthesized had promising results for the use of those purposes. A mixture of o-phenylenediamine (91) and monochloroacetic acid was heated at the reflux temperature in 4 N hydrochloric acid. After treatment of compound 92 with substituted amine and KI in ethanol, resulting mixture was heated to its reflux temperature to provide benzimidazole derivatives 93a-e (Scheme 31).
Oxazepine is an unsaturated seven-membered heterocycle with a nitrogen replacing a carbon at one position and with an oxygen replacing a carbon at one position. The scientists have drawn attention to the synthesis of this moiety with different substituents due to their wide range of biological activities. This skeleton is involved in synthesis of various drugs used as antithrombotic, antiepileptic, anticonvulsant, antiinflammatory, antifungal, progesterone agonist, antipsychotic, antagonist, analgesic, antihistaminic, and anxiolytics agents.

There are several oxazepine derivatives reported in the literature having a significant role in inhibition of some enzymes (e.g. tyrosine kinase inhibitory). Due to their structural importance in biological science, incorporation of new substituents to this skeleton has received considerable interest from medicinal and organic chemists.

Caba et al. reported a set of synthesis of novel benzoxazepine derivatives and suggested their antiproliferative activity results against the MCF-7 adenocarcinoma cell. The most promising result was obtained from the structure 94 (Figure 30) with its inhibitory effect on cancerous breast cancer cell.

Scheme 31. Synthesis of 93a-e

2.1.4 Oxazepine
Oxazepine derivatives with different moieties were proven to show high anticonvulsant activity. Scientists working on improvement of this effect have drawn attention to synthesis of this scaffold with different substituents. For instance, Deng et al.\textsuperscript{72} synthesized a series of triazalo-benzoxazepines and proposed their anticonvulsant test results. The structure 95 (Figure 31) gave the best result among the triazalo-benzoxazepine derivatives.

2.1.5 Synthesis of oxazepine derivatives

Oxazepines, their aryl-annelated (benzoxazepines) and structural analogues diazepines and thiazepines are very important compounds for synthetic organic chemistry as they are responsible for biological activities of several drugs. Drugs having those skeletons can be used as antidepressant,\textsuperscript{73} anticonvulsant,\textsuperscript{74} antiviral,\textsuperscript{75} antimicrobial,\textsuperscript{76} and antifungal\textsuperscript{77} agents.

Present methods for the synthesis of thioxo-oxazepine derivatives employ often expensive starting materials giving to low yield and provide compounds of limited diversity. Badru et al.\textsuperscript{78} proposed an efficient approach to synthesize thioxo-oxazepines in high yield (Scheme 32).
Maleic anhydride (96) was reacted with primary amine 97 derivatives in dry toluene to afford compound 98. Triethylamine-catalyzed condensation of maleamic acids 98 with thiophosgene under anhydrous conditions gave cyclization product 2-thioxo-1,3-oxazepine-4,7-diones (99) accompanied by nucleophilic attack of O and N of maleamic acid to thiophosgene.

2.1.6 Benzoxazepine and benzimidazo-oxazepine

The benzoxazepines are privileged scaffolds that are present in natural compounds, pharmaceuticals, and functionalized materials. In addition to this, benzoxazepine skeleton plays a significant role in regulation of central nervous system, in the synthesis of anti-breast cancer agents, and HIV inhibition. To exemplify, there are several biologically important compounds constructed from benzoxazepine scaffold like Sintamilv, an antidepressant agent, 100 H1 receptor antagonist (antihistaminic agent ) (101), and Sintamil (102) (Figure 32).
5,6-dihydrobenzo[f]imidazo[1,2d][1,4]oxazepine (103) and compound 104 (Figure 33) show biological activity as therapeutics. Benzimidazo-oxazepine scaffold is also present in several drugs used for the cancer treatment.95

Yin et al.96 synthesized various benzimidazo-oxazepine derivatives and evaluated their activities for PI3K inhibition and the best selectivity was obtained from compound 104.

2.1.7 Synthesis of benzoxazepine and benzimidazo-oxazepine

Yin et al.96 synthesized different derivatives of benzimidazo-oxazepine as PI3K inhibitor. They evaluated them against human tumor cell lines and a great number of them exhibited antiproliferative activity. The most promising result was observed for the compound 104 (Scheme 33).
Zhao et al.\textsuperscript{97} developed a new methodology for the synthesis of benzo-1,4-oxazepines (Scheme 34). For this reaction, 2-(2-dimethylamino-vinyl)-1H-inden-1-ol derivatives were used as a ligand.

\textbf{Scheme 33. Synthesis of antiproliferatively active compound 104}

CuI exhibited superior catalytic efficiency for this transformation. Aniline (108) and (1-chloro-vinyl)-benzene (109) were reacted in the presence of cupper catalyst and indenol based ligand. According to the reaction mechanism, the first step is that ligand coordinates to cupper to form cupper(I) complex (Scheme 35).
Scheme 35. Proposed mechanism for formation of compound 110

After oxidative addition of vinylhalide 109, cupper (III) complex 112 is formed. Subsequent reaction of 112 with aniline generates a new complex 113. The key step is the ortho-carbonylation of the the lastly formed complex 114 followed by reductive elimination to afford 110. It was discovered that this ligand was the ideal choice for this transformation when compared to other derivatives with different R groups as -Cl and -CH$_3$. 
2.1.8 Aim of the study

In this part, our goal was to develop a new synthetic methodology for the synthesis of benzofuropyrrroloimidazolone 118. Starting with the methyl acetoacetate (115), our intention was to generate first a furan system 116 having a methyl group at the $\alpha$-position. Subsequent oxidation followed by condensation reaction with $o$-phenylenediamine would give us benzimidazole skeleton 117. Base-mediated cyclization reaction of 117 would afford 118 (Scheme 36).

![Scheme 36. Schematic pathway for the formation of benzimidazole-fused cyclization product 118](image)

In the second part, our aim was to develop a new methodology for the synthesis of benzimidazole derivatives fused to oxazepine scaffold. For this purpose, 119 was planned to be used as a starting material to generate alkyne substituted aldehyde 120 to be used for the synthesis of benzimidazol derivatives 121 (Scheme 37).
Scheme 37. Synthetic plan for the formation of 122 and 123

Base-mediated cyclization reaction of 121 would result in the formation of 122 and 123.
2.2 RESULTS AND DISCUSSION

2.2.1 Synthesis of methyl 2-methylfuran-3-carboxylate (116)

Methyl acetoacetate (115) was used as the starting material to construct a furan system with methyl group at its α-position. For this purpose, Feist-Benary furan synthesis reaction was used as the critical step (Scheme 38).  

Methyl acetoacetate (115) has a ketone and an ester functionality whose activities are quite different toward nucleophilic reagents. Delocalization of π-electrons of ester group decreases the reactivity of ester carbonyl carbon.
The pKa value of methylene protons is quite low than those of other protons which leads to deprotection of methylene group. Resulting anion 125 attacks the electropositive carbon of 124 to afford 126 as an intermediate. Second proton abstraction from middle carbon forms enolate 127 which undergoes nucleophilic substitution reaction to generate 128 via intramolecular cyclization reaction. Water elimination affords 116 (Scheme 39).

The formation of 116 was verified by $^1$H- and $^{13}$C-NMR spectra. In the $^1$H-NMR spectrum of 116, there are two doublets that appear at 7.23 and 6.63 ppm with a coupling constant of $J = 1.9$ Hz which is a characteristic value for adjacent protons at 2,3-position in furan. It is quite less than those of benzene and thiophene adjacent protons.

2.2.2 Synthesis of methyl 2-formylfuran-3-carboxylate (129)

For further benzimidazole formation reactions it was necessary to convert the methyl group attached to the furan ring into an aldehyde. We utilized oxidation ability of selenium dioxide to afford desired compound 129 (Scheme 40).

\[ \text{CH}_3 \text{C}=\text{CH}_2 \rightarrow \text{CH}_3 \text{C}=\text{O} \]

Scheme 40. Oxidation to aldehyde 129

We used anisole as reaction solvent due to its high boiling point. We achieved the synthesis of compound 129 in 34% yield. In the $^1$H-NMR spectrum of 129, the signal at 10.24 ppm was a strong evidence for the formation of an aldehyde functionality. Moreover, the $^{13}$C-NMR spectrum also supported this formation with the signal of aldehyde carbon at 178.7 ppm.
2.2.3 Synthesis of methyl 2-(1H-benzo[d]imidazol-2-yl)furan-3-carboxylate (117)

Aldehyde 129 and o-phenylenediamine (91) were mixed in DMF, then p-TsOH (20% mol) was added. The solution was heated to 80 °C and stirred at this temperature for appropriate time (monitored by TLC) to afford compound 117 (Scheme 41). By using this methodology, a novel substituted benzimidazole derivative 117 was synthesized with simple and one-pot reaction according to literature procedure.\(^9^9\)

![Scheme 41. Synthesis of furane-substituted benzimidazole 117](image)

The \(^1\)H- and \(^13\)C-NMR spectra are consistent with the proposed structure 117. In the \(^1\)H-NMR spectrum, the broad signal at 12.65 ppm belongs to NH proton that is the strong evidence for the formation of imidazole skeleton. In addition to this, two adjacent furan protons resonating at 7.61 and 6.92 as distinct doublets with the coupling constant of \(J = 1.8\) Hz are also in agreement with the proposed structure. In the \(^13\)C-NMR spectrum, disappearance of the signal at 178.8 belonging to aldehyde carbon atom clearly shows occurrence of condensation reaction.

According to the proposed mechanism, one of the amine groups adds to the aldehyde carbonyl group in the presence of a catalytic amount of p-TSOH. Intramolecular cyclization reaction generates benzimidazole ring. The oxidation of the intermediate with air oxygen afforded substituted imidazole skeletons (Scheme 42).
First we intended to introduce an alkyne functionality to the carbonyl group as shown in the structure 132. For the formation of 130, first 117 should be hydrolyzed to the corresponding acid 130 followed by acylchloride formation using oxalyl chloride. Subsequent Sonogashira cross-coupling reaction would give us corresponding alkyne 132. Reaction of 117 with K$_2$CO$_3$ did not form the expected hydrolysis product 130 (Scheme 43). The structure of the formed product was determined by IR and HRMS analysis. After analysis of IR and HRMS spectra, we concluded that during hydrolysis reaction, cyclization occurred to afford compound 118. As expected, $^1$H-NMR spectra of 118 and 130 are so similar so that information obtained from NMR spectra was not enough for exact structure determination.
In the IR spectrum of compound 118 (Figure 34) there is no –OH peak at around 3500 cm\(^{-1}\) supported the formation of cyclization product 118. Furthermore, the HRMS spectrum also supported the formation of the product 118.
2.2.5 Synthesis of O-propargylated salicyl aldehydes

For the construction of different benzimidazole skeletons, we synthesized O-propargylated salicyl aldehyde 120a starting from salicyl aldehyde (119a). Treatment of 119a with propargyl bromide in presence of potassium carbonate afforded desired product 120a according to literature procedure (Scheme 44).100

Scheme 44. Synthesis of O-propargylated salicyl aldehyde 120a

For derivatization, we used substituted salicyl aldehydes 119b and 119c to synthesize further alkynyl compounds such as 120b and 120c by applying the same reaction procedure as described for the synthesis of 120a (Scheme 45).100

Scheme 45. O-propargylation of substituted salicyl aldehydes 119b and 119c

The $^1$H- and $^{13}$C-NMR spectra verified the formation of the compounds 120b and 120c. In the $^1$H-NMR spectrum of compound 120b shown in Figure 35, phenyl protons resonate at 7.91, 7.63 and 7.04 ppm. The signal at 7.91 ppm appears as doublet and split by the $m$-proton with a coupling constant of $J = 2.5$ Hz. The proton located between the bromine atom and aldehyde group resonates at 7.63 ppm as doublet of doublets with the coupling constants of $J = 8.9$ Hz and 2.5 Hz. The other phenyl proton at 7.04 ppm gave distinct doublet with a coupling constant of $J = 8.9$ Hz. The singlet
at 10.4 ppm belongs to the aldehyde proton. The peak at 4.83 ppm is arising from the methylene protons of the propargyl group. During the analysis of resonances of the methylene protons and alkyne protons, we realized that there is a long-range coupling between these protons. Methylene protons’ signal splits into doublet by the terminal proton of triple bond with a coupling constant of $J = 2.4$ Hz. The terminal alkyne proton gave a triplet at 2.58 ppm with the same coupling constant of $J = 2.4$ Hz.

![NMR spectrum](image)

**Figure 35.** $^1$H-NMR spectrum of the compound 120b

### 2.2.6 Derivatization of 120a with Sonogashira cross-coupling reaction

We attached aryl substituents to acetylene group in 120a by Sonogashira cross coupling reaction according to literature procedure (Scheme 46). Treatment of compound 120a with the Sonogashira reagents in presence of iodobenzene and o-nitroiodobenzene gave us targeted molecules 120d$^{100}$ and 120e.
The formation of compound 120d and 120e was confirmed by \(^1\)H- and \(^{13}\)C-NMR spectra. In the \(^1\)H-NMR spectrum of 120d, the aldehyde proton resonates at 10.54 ppm as a singlet. Resonances between 7.88-7.09 ppm are arising from the phenyl protons. The methylene protons appear as a singlet at 4.93 ppm. In the \(^{13}\)C-NMR spectrum of 120d, triple bond carbons give rise to two separate peaks at 88.2 and 82.9 ppm. The \(^1\)H-NMR spectrum of 120d is similar to that of 120e with the exception that there is an additional proton in the aromatic region.

2.2.7 Synthesis of O-substituted salicyl aldehydes 120f and 120g

After incorporation of aryl substituents to compound 120, we introduced 2-butyne and chloroacetonitrile to the system 119a for the formation of 120f\(^{100}\) and 120g\(^{101}\) (Scheme 47).
Characterization of these compounds was done by $^1$H- and $^{13}$C-NMR spectra analyses. It is obviously seen in the $^1$H-NMR spectrum of 120f (Figure 36) that there is a long range coupling between methylene protons and methyl protons. Methyl protons and methylene protons resonate at 1.86 ppm as triplet and 4.79 ppm as quartet, respectively with a coupling constant of $J = 2.2$ Hz. Moreover, the aldehyde proton gives a singlet at 10.49 ppm. In the $^{13}$C-NMR spectrum of 120f (Figure 37), the methyl carbon resonates at 3.6 ppm. The high field shift is due to the presence of the methyl group in the shielding zone of acetylene group. There are two carbon peaks at 84.7 and 73.3 ppm which belongs to the triple bond.

Figure 36. $^1$H-NMR spectrum of compound 120f
2.2.8 Condensation reaction of salicyl aldehyde derivatives

After successful synthesis of salicyl aldehyde derivatives 120, we constructed different benzimidazole skeletons 121 according to literature procedure as shown in Scheme 48.

The structures were confirmed by \(^1\)H- and \(^{13}\)C-NMR spectra. In the \(^1\)H-NMR spectrum of 120c, two phenyl protons resonances at 8.14 and 7.02 ppm arising from \(o\)- and \(p\)-protons of methoxy group with the coupling constants of \(J = 1.5\) and 8.1 Hz. As it can
be seen in the $^1$H-NMR spectrum (Figure 38), there are two aromatic protons which resonate as a broad singlet. Methoxy protons give a sharp singlet at 4.90 ppm. Furthermore, the IR spectrum of 121c confirms the presence of NH-proton.

![Figure 38. $^1$H-NMR spectrum of compound 121c](image)

In the $^{13}$C-NMR spectrum of 121c there are two acetylene carbons resonating at 78.3 and 77.0 ppm. There is only one aliphatic carbon resonance at 57.3 ppm belonging to the methylene carbon. Other carbons resonate in the sp$^2$ region arising from benzimidazole and benzene carbons (Figure 39).
2.2.9 Cyclization reactions of salicyl aldehyde derivatives 120e, 120g and 120d

Treatment of compound 121d with NaH at room temperature furnished both Z- and E-isomers, 122d-Z and 122d-E.

Scheme 49. Cyclization reaction of 121d with NaH
However, in the case of 120e and 120g, during the formation of benzimidazole skeleton, intramolecular cyclization reaction spontaneously occurred to provide 122e and 122g without isolation of corresponding benzimidazoles (Scheme 50 and Scheme 51). The $^{13}$C-NMR spectrum of 122e was consistent with the proposed structure. The dissappearance of triple bond was the strong evidence for the formation of 122e. Moreover, the chemical shift of methylene carbons is shifted to low field compared to that of starting materials where methylene groups are connected to acetylene group. We assume that the methylene protons in 122e are located in the deshielding zone of the benzene ring.

![Scheme 50. Cyclization reaction of 120e](image)
Scheme 51. Cyclization reaction of 120g

In the $^1$H-NMR spectrum of the compound 122e, there is one additional proton at sp$^2$-region which can be easily assigned to the olefinic proton in 122e (Figure 40).

Figure 40. $^1$H-NMR spectrum of compound 122e
The plausible mechanism involves first the formation of benzimidazole as an intermediate. It was considered that \( o \)-nitro group on phenyl definitely has a significant influence on the reaction. Once the resonance structures of this molecule is analyzed, it can be obviously seen that there is a positive charge on one of the alkyne carbon atom which efficiently activated for an attack from a nucleophile (Scheme 52). The non-bonding electrons on nitrogen atom of benzimidazole skeleton can easily attack the alkyne unit to generate 122e.

![Scheme 52. Resonance form of intermediate 133](image)

The similar case was observed during the reaction of 120g. Intramolecular cyclization reaction involving nitrogen attack to electropositive carbon on cyano group resulted in the formation of 122g. The structure was confirmed by \( ^1H, ^13C \)-NMR and IR spectra as well. As known that triple bond stretching at around 2200 cm\(^{-1}\) can be easily detected in the IR spectrum (Figure 41). Disappearance of nitrile peak supported the formation of cyclization product 122g.

![Figure 41. IR spectrum of compound 122g](image)
2.2.10 NaH Mediated cyclization reactions of phenyl-substituted benzimidazoles

NaH-mediated intramolecular cyclization of O-propargylated benzimidazole derivatives were established in this section. Treatment of 121c with excess NaH at room temperature gave a mixture of three products 122c, 135a, and 135b in a ratio of 2:1:2 (Scheme 53). The ratio of the products was determined by the analysis of the $^1$H-NMR spectrum.

![Scheme 53. Cyclization reactions of 121c and formation of 122c, 135a, and 135b](image-url)

Exo-configurated products 122c and 135a were sucessfully separated by coloumn chromatography. The analytically pure exo-configurated product 135a was obtained after recrystallization using slow vapor deposition technique (chloroform/hexane).

The $^1$H-NMR spectra of the exo-configurated products 122c and 135a are consistent with the proposed structures. It is clear from the spectra that there is a significant difference in geminal protons’ resonances of the structures 122c and 135a. As shown in Figure 42, 135a possesses methylene geminal protons resonate at 4.87 and 4.59 ppm with the coupling constant of $J = 1.8$ Hz. Additionally, the singlet peak at 4.81 ppm belongs to methylenic protons of compound 135a. In the $^1$H-NMR spectrum of the compound 122c, ethylene geminal protons resonate at lower field compared to those of compound 135a with distinct broad singlets at 5.69 and 5.52 ppm. The reason behind this observation is the influence of the deshielding effect of the aromatic benzimidazole ring. The singlet resonating at 4.93 ppm is arising from the methylenic protons of 122c (Figure 43).
Figure 42. $^1$H-NMR spectrum of compound 135a

Figure 43. $^1$H-NMR spectrum of compound 122c

These findings were further supported by the single crystal X-ray analysis of 135a (Figure 44).
The formation of 122c starts with the initial base-mediated alkyne-allene isomerization in 121c to form 136 as the intermediate. It is well-established that the central carbon atom in allene 136 is much more electropositive than the terminal carbon atoms. Therefore, the nucleophile exclusively attacks the central carbon atom resulting in the formation of 7-exo-dig cyclization product 122c (Scheme 54).

![Molecular structure of compound 135a](image)

**Figure 44.** The molecular structure of compound 135a determined by single crystal X-ray analysis

However, the formation of the isomeric products 135a and 135b is unusual at first glance. Herein, we propose the following reaction mechanism for their formation (Scheme 55). Abstraction of acidic NH proton generates a carbanion on nitrogen atom of 137 which can undergo a nucleophilic substitution reaction by attacking the methylene group which transfers the propargyl group from the oxygen atom to the
nitrogen atom to form 138. Formation of allene 139 followed by cyclization reaction where the nucleophile exclusively attacks the central carbon atom, results in the formation of 135a and 135b as depicted in Scheme 55. To the best of our knowledge, the reported propargyl transformation is unprecedented in the literature. We assume that the conformational factors are responsible for this interesting transformation. The reaction mechanism will be further investigated with follow-up experiments as well as with theoretical calculations.

Scheme 55. Formation mechanism of the products 135a and 135b

As the next, treatment of 121c with NaH at 85 °C exclusively resulted in the formation of 123c and 135b (Scheme 56).
Scheme 56. NaH-supported cyclization reaction of 121c at 85 °C

Figure 45. 1H-NMR spectrum of a mixture of 123c and 135b.

Unfortunately, the crude reaction could not be purified by column chromatography. The 1H-NMR spectrum of the mixture showed the formation of proposed structures 123c and 135b (Figure 45). The olefinic and methyl protons resonating at 6.56 ppm and 2.22 ppm, respectively, correspond the compound 135b. These signals resonate at higher field compared to those of structure 123c. In compound 135b, oxygen in the oxazepine skeleton pushes electrons mesomerically toward the olefin due to close distance. Thus, the chemical shift of olefinic proton resonates at lower ppm than that of compound 123c. Proposed reaction mechanism for the formation of 123c is shown in Scheme 57.
After the formation of 122c as discussed in Scheme 54, it undergoes isomerization via 1,3-H shift that afforded 123c.

To evaluate the possible substituent effect on the reaction, unsubstituted derivative 121a was submitted to the above mentioned cyclization reaction. Similar to the reaction of 121c, treatment of compound 121a with NaH in DMF at room temperature afforded three isomeric products; exo-configurated 122a and 140a and the endo-configurated 140b in a ratio of 7:1:3 (Scheme 58). The ratio of the products was determined by the analysis of the $^1$H-NMR spectrum. 122a and 140b were separated by column chromatography and characterized as the cyclization products with the exo- and endo-configuration of the double bonds. 140a could not be isolated but characterized as the exo-configurated product by the help of the crude NMR analysis (Figure 46).

**Scheme 57.** Tentative mechanism for the formation of 123c

**Scheme 58.** Cyclization reactions of 121a and formation of 122a, 140a, and 140b
**Figure 46.** The crude $^1$H-NMR of a mixture of cyclization reaction of 121a in DMF

The structures of 122a and 140a were determined by comparison of the $^1$H-NMR spectra with those of compounds 122c and 135a. Ethylene geminal protons of 122a resonate at 5.64 and 5.45 ppm as distinct singlets which are similar to the ones observed in the $^1$H-NMR spectrum of 122c. The singlet observed at 4.73 ppm corresponds to methylenic protons adjacent to the oxygen atom (Figure 47).

**Figure 47.** $^1$H-NMR spectrum of compound 122a.
With the pure 122a in hand, we investigated isomerization of the double bond upon thermal treatment (Scheme 59). The 1H-NMR spectrum of the crude material demonstrated the full conversion of the exo-configurated product 122a into the endo-product 123a via 1,3-H shift.

![Scheme 59. Conversion of 122a to 123a via NaH.](image)

Both 123a and 140b have very similar 1H-NMR spectrum. To obtain conclusive evidence that the structures of the compounds 123a and 140b are not identical, we mixed the pure 123a and 140b. In the 1H-NMR spectrum of 123a and 140b, there were two sets of signals confirming that these two compounds are not identical. Methyl protons of 123a resonate as doublet at 2.30 ppm whereas that of 140b resonates at 2.16 ppm (Figure 48).

![Figure 48. 1H-NMR spectrum of a mixture of 123a and 140b](image)
Finally, the brominated derivative 121b was also submitted to the cyclization reaction (Scheme 60). Treatment of 121b with NaH in DMF at room temperature over night afforded three isomeric products 122b, 141a, and 141b with the exo- and endo-configuration of the double bonds in a ratio of 2:1:7. The ratio of the products was determined by the analysis of the ¹H-NMR spectrum similar to the previous case (Figure 49).

**Scheme 60.** Cyclization reactions of 121b and formation of 122b, 141a, and 141b

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**Figure 49.** The crude ¹H-NMR spectrum of the products formed by cyclization reaction of 121b

122b and 141b were seperated by column chromatography. The characterization of the compounds 122b, 141a and 141b was done by comparison of the ¹H-NMR spectra with those of compounds 122a, 123a, and 140b. The ¹H-NMR spectrum of 141b is shown in Figure 50. The aromatic protons of brom-substituted benzene ring resonate
at 8.36, 7.45 and 7.01 ppm. It is obviously seen that the proton H-1 is split into doublet due to the coupling with \( m \)-proton H-2 with a coupling constant of \( J = 2.5 \) Hz and the proton H-3 couples only with the proton H-2 with a coupling constant of \( J = 8.6 \) Hz. Olefinic proton resonates as quartet at 6.50 ppm and methyl protons resonate at 2.14 ppm as doublet due to the long-range coupling.

![Figure 50. \(^1\)H-NMR spectrum of compound 141b](image)

### 2.2.11 Synthesis of 1-(2-oxopropyl)-\(1H\)-pyrrole-2-carbaldehyde (143) and 1-(prop-2-yn-1-yl)-\(1H\)-pyrrole-2-carbaldehyde (144)

After successful synthesis of \( O \)-propargylated salicylaldehydes and substituted benzimidazoles, our aim was to show general applicability of this reaction. Starting with pyrrole aldehyde, we carried out a similar reaction and synthesized pyrrole substituted benzimidazoles. The first step was to generate \( N \)-substituted pyrrole aldehydes. NaH was added to a solution of \( 1H \)-pyrrole-2-carbaldehyde (142) in DMF. After observation of hydrogen gas evolution, 1-chloropropan-2-one was added to the reaction mixture and stirred at room temperature to afford 143. Treatment of 142 with proargyl bromide in presence of potassium carbonate in DMF afforded 144 (Scheme 61).\(^{102}\)
2.2.12 Reaction of 144 and 143 with o-diaminobenzene followed by NaH-mediated cyclization reaction

Pyrrole substituted benzimidazole 145 was formed by the reaction of o-diaminobenzene and compound 144 as described in the literature. The formed product 145 was treated with NaH at room temperature and afforded cyclization product 146 (Scheme 62).
For the synthesis of 146 we developed another synthetic way. According to this methodology we first reacted 143 with o-diaminobenzene and obtained the corresponding condensation product benzimidazole 147 as the intermediate. The formed benzimidazole 147 underwent cyclization reaction under the same reaction condition to provide 146. (Scheme 63).

**Scheme 63.** One-pot synthesis of benzimidazo-pyrrolo-pyrazine 146
The aim of this thesis was to develop methodologies for the synthesis of organic compounds having potential activities in biological science. In the first part, we developed synthetic methodologies for the formation of thienopyridinone and thienodiazepinone derivatives. Firstly, dithiane 36 was used as the starting material to form thiophene ring 37 having an amine functionality at its α-position using the Gewald type reaction (Scheme 64).

After the synthesis of the unsubstituted aminothiophene 37, 4,5-substituted aminothiophene derivatives 40 and 59 were formed successfully by using the Gewald type reaction (Scheme 65).

Compound 37 was converted into iodo-thiophene 38 in presence of CuI and tert-butyl
nitrite via modified Sandmayer reaction. Treatment of 37 with CuBr₂ in the presence of tert-butyl nitrite afforded compound 63 while 40 formed corresponding bromothiophene 41 (Scheme 66).

Scheme 66. Halothiophene formation

Sonogashira cross-coupling reaction was used to generate carbon-carbon single bond between the thiophene ring and alkyne derivatives to generate 42 and 45 (Scheme 67).
Hydrazines are very useful compounds for organic synthesis used for the construction of important heterocyclic compounds. The obtained compounds were cyclized in the presence of hydrazine hydrate to give corresponding thienopyridinone and thienodiazepinone derivatives (Scheme 68).

**Scheme 67.** Alkyne-substituted thiophene synthesis

**Scheme 68.** Cyclization reaction with hydrazine hydrate
In the second part, we developed a new synthetic methodology for benzimidazo-oxazepine derivatives and benzimidazo-pyrrolo-pyrazine. Feist-Benary furan synthesis reaction was used for the formation of the compound 116 which was oxidized to 129 in the presence of SeO₂. Subsequent imidazole formation was achieved with o-phenylenediamine (91) to afford 117. Hydrolysis of compound 117 under the basic condition gave cyclization product 118 (Scheme 69).

Scheme 69. Synthesis of 118

Starting with 119, O-propargylated salicylaldehyde derivatives 120 were synthesized in the presence of propargyl bromide under the basic condition. Incorporation of substituents into the alkyne functionality by Sonogashira cross-coupling reaction furnished compound 120d and 120e (Scheme 70).
Scheme 70. Synthesis of O-propargylated salicylaldehyde derivatives

Benzimidazole skeleton formation was achieved with the reaction of o-phenylenediamine 91. This particular reaction included condensation and oxidation steps respectively to generate 121 (Scheme 71).

Scheme 71. Benzimidazole formation

Intramolecular NaH-mediated cyclization reaction gave benzimidazo-oxazepine derivatives 122, 123, 135, 140, and 141 (Scheme 72).
Scheme 72. NaH-mediated cyclization reaction of 121

Benzimidazo-pyrrolo-pyrazine 146 was synthesized via NaH-mediated cyclization reaction of compound 145. On the other hand, when 143 was reacted with 91 in presence of catalytic amount of acid, it undergoes the cyclization reaction accompanied by attack of nitrogen to ketone carbon atom followed by water elimination that results in the formation of 146 (Scheme 73).

Scheme 73. Benzimidazo-pyrrolo-pyrazine formation
CHAPTER 4

EXPERIMENTAL

4.1 General

Nuclear Magnetic Resonance ($^1$H-NMR, $^{13}$C-NMR and 2D-NMR) spectra were recorded on a Bruker Instrument Avance Series-Spectrospin DPX-400 Ultrashield instrument in CDCl$_3$, CD$_3$OD, CD$_3$COCD$_3$ and DMSO-$d_6$ with TMS as internal reference. Chemical shifts (δ) were expressed in unit parts per million (ppm). Spin multiplicities were specified as singlet (s), doublet (d), doublet of doublets (dd), 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 centimeters (cm$^{-1}$).

Gallenkamp electronic melting point apparatus was used to obtain melting points.

HRMS data were recorded by Agilent Technologies, 6224 TOF LC/MS-T1200 Series applying the electrospray technique. GC-MS data were recorded by Agilent Technology 7890A using Agilent J&W GC HP-5MS, 30m x 0,250mm x 0,25µm (190915-433:325 °C) column.

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 11.0 and ACD NMR. Solvents were purified as reported in the literature.
4.1.1 Synthesis of ethyl 2-aminothiophene-3-carboxylate (37)

NEt₃ (2.5 g, 25 mmol) was added dropwise to a mixture of 1,4-dithiane-2,5-diol (3.8 g, 25 mmol) and ethyl cyanoacetate (5.65 g, 50 mmol) in DMF (10 mL) at 0 °C and the resulting mixture was stirred at room temperature for 3 h. After completion of the reaction, water (100 mL) was added to the mixture and extracted with (4 x 20 mL) CH₂Cl₂. Collected organic phases were washed with (2 x 20 mL) water and dried over MgSO₄. Evaporation of solvent gave yellow residue which was purified by column chromatography eluting with hexane/EtOAc (5:1) to give 37 (5.9 g, 70%) as a colorless crystal from hexane/ethylacetate, mp 47-49 °C. (lit. mp = 47-48 °C).

1H-NMR (400 MHz, CDCl₃) δ 6.98 (d, J = 5.7 Hz, H₅), 6.18 (d, J = 5.7 Hz, H₄), 5.93 (br s, 2H, NH₂), 4.28 (q, J = 7.1 Hz, 2H, OCH₂), 1.34 (t, J = 7.1 Hz, 3H, CH₃); 13C-NMR (100 MHz, CDCl₃) δ 165.5, 162.8, 125.9, 107.0, 106.9, 59.7, 14.5; IR (cm⁻¹) 3409, 3299, 3172, 2984, 1651, 1266, 1025, 676.

4.2 General procedure for the synthesis of substituted 2-amino-3-carboxylate

A mixture of cyclopentanone/cyclohexanone (11.9 mmol), ethyl cyanoacetate (1.36 mL, 11.9 mmol), morpholine (1.07 mL, 11.9 mmol), and sulphur (0.38 g, 11.9 mmol) in ethanol (15 mL) was heated to reflux temperature and stirred for overnight. After completion of the reaction, solvent was removed under vacuum and the crude solid was washed with cold ethanol and filtered through funnel, dried under vacuum. The crude product was dissolved in dichloromethane (20 mL) and washed with brine (2 x 20 mL). The organic layer was collected, dried over MgSO₄ and concentrated under vacuum to give the desired product.

4.2.1 Synthesis of ethyl-2-amino-5,6-dihydro-4H-cyclopenta[b]thiophene-3-carboxylate (59)

Cyclopentanone (1.05 mL, 11.9 mmol) was reacted with ethyl cyanoacetate (1.36 mL, 11.9 mmol), morpholine (1.07 mL, 11.9 mmol) and sulphur (0.38 g, 11.9 mmol) as
described in general procedure to give the product 59 (0.75 g, 30%) as a brown solid, mp 182-184 °C. (lit. mp = 182.5-183.5 °C).

\[ ^1H-NMR \text{ (400 MHz, CDCl}_3\text{)} \delta 5.84 \text{ (br s, 2H, NH}_2\text{)}, 4.24 \text{ (q, J = 7.1 Hz, 2H, OCH}_2\text{)}, 2.81 \text{ (m, 2H, H6)}, 2.72 \text{ (m, 2H, H4)}, 2.31 \text{ (m, 2H, H5)}, 1.33 \text{ (t, J = 7.1 Hz, 3H, CH}_3\text{);} \]

\[ ^13C-NMR \text{ (100 MHz, CDCl}_3\text{)} \delta 166.3, 165.8, 142.7, 121.3, 102.9, 59.4, 30.7, 28.9, 27.2, 14.4; \text{ IR (cm}^{-1}) \]

3410, 3292, 3170, 2985, 2903, 2855, 1641, 1490, 1257, 1037, 780.

4.2.2 Synthesis of ethyl 2-amino-4,5,6,7-tetrahydrobenzo[\text{b}]thiophene-3-carboxylate (40)

Cyclohexanone (1.26 mL, 11.9 mmol) was reacted with ethyl cyanoacetate (1.96 mL, 11.9 mmol), morpholine (1.07 mL, 11.9 mmol) and sulphur (0.38 g, 11.9 mmol) as described in general procedure to give the desired product 40 (1.68 g, 63%) as a light brown solid, mp 116-117 °C. (lit. mp = 116.2-117.2 °C).

\[ ^1H-NMR \text{ (400 MHz, CDCl}_3\text{)} \delta 5.95 \text{ (br s, 2H, NH}_2\text{)}, 4.25 \text{ (q, J = 7.1 Hz, 2H, OCH}_2\text{)}, 2.70 \text{ (m, 2H, H7)}, 2.49 \text{ (m, 2H, H4)}, 1.75 \text{ (m, 4H, H5 and H6)}, 1.34 \text{ (t, J = 7.1 Hz, 3H, CH}_3\text{);} \]

\[ ^13C-NMR \text{ (100 MHz, CDCl}_3\text{)} \delta 166.0, 161.7, 132.5, 117.6, 105.9, 59.4, 26.9, 24.5, 23.3, 22.8, 14.5; \text{ IR (cm}^{-1}) \]

3399, 3293, 3167, 2987, 2938, 2896, 2840, 1644, 1574, 1488, 1290, 1026, 780.

4.3 Synthesis of ethyl 2-iodothiophene-3-carboxylate (38)

CuI (0.84 g, 4.44 mmol) was dissolved in CH\text{\textsubscript{3}}CN (10 mL) and the resulting mixture was placed into an ice-bath. Tert-butyl nitrite (0.83 mL, 7.1 mmol) was added dropwise into the mixture and the resulting mixture was allowed to stir for 10 minute. Aminothiophene 37 (0.76 g, 4.44 mmol) was dissolved in (5 mL) acetonitrile and added dropwise into the reaction mixture and allowed to stir at room temperature. Reaction was followed by TLC. After completion of the reaction, the mixture was filtered through celite then solvent was removed under vacuum. Water (25 mL) was added to the residue and then extracted with EtOAc (2 x 25 mL). Organic phases were
collected and was washed with brine and then dried over MgSO₄. After removal of solvent, the residue was purified over silicagel eluting with hexane/ethylacetate (50:1) to give the product 38 as a light brown liquid (120 mg, 10%).

\[ \text{H-NMR (400 MHz, CDCl}_3\text{)} \delta 7.41 (d, J = 5.6 \text{ Hz, H5}), 7.33 (d, J = 5.6 \text{ Hz, H4}), 4.35 (q, J = 7.1 \text{ Hz, 2H, OCH}_2), 1.40 (t, J = 7.1 \text{ Hz, 3H, CH}_3); \text{C-NMR (100 MHz, CDCl}_3\text{)} \delta 162.1, 135.5, 131.3, 129.4, 82.3, 61.0, 14.3; \text{IR (cm}^{-1}) 2917, 1710, 1637, 1242, 1148, 1024, 703. \]

4.4 General procedure for the synthesis of bromo thiophene

_Tert_-butyl nitrite (1.55 mL, 13.2 mmol) was added dropwise to a stirred solution of the CuBr₂ (1.94 g, 8.83 mmol) in CH₃CN (15 mL) at 0 °C. A solution of aminothiophene (8.83 mmol) in CH₃CN (10 mL) was added to this mixture and stirred at room temperature. The reaction was followed by TLC. After reaction completion, the mixture was filtered through celite and then solvent was removed under vacuum. 25 mL of 10% HCl solution was added to the mixture and then extracted with EtOAc (2 x 25 mL). Combined organic phases were washed with brine and then dried over MgSO₄. After removal of solvent, the residue was purified over silicagel eluting with hexane/ethylacetate (10:1) to give the desired compound.

4.4.1 Synthesis of ethyl 2,5-dibromothiophene-3-carboxylate (63)

_Tert_-butyl nitrite (1.55 mL, 13.2 mmol), CuBr₂ (1.94 g, 8.83 mmol) and aminothiophene 37 (1.5 g, 8.83 mmol) were reacted as described in general procedure. The crude product was purified over silicagel eluting with hexane/ethylacetate (10:1) to give the compound 63 as light orange crystals (1.189 g, 43%) from hexane/ethylacetate, mp 35-37 °C.

\[ \text{H-NMR (400 MHz, CDCl}_3\text{)} \delta 7.36 (s, 1H), 4.33 (q, J = 7.1 \text{ Hz, 2H, OCH}_2), 1.37 (t, J = 7.1 \text{ Hz, 3H, CH}_3); \text{C-NMR (100 MHz, CDCl}_3\text{)} \delta 160.8, 131.9, 131.7, 119.0, 111.3, 61.2, 14.2; \text{IR (cm}^{-1}) 3100, 1716, 1425, 1227, 1148, 1005, 768. \]
4.4.2 Synthesis of ethyl 2-bromo-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (41) and ethyl 4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (70)

Tert-butyl nitrite (1.61 mL, 13.8 mmol), CuBr$_2$ (2.02 g, 9.2 mmol) and aminothiophene 37 (2.1 g, 9.2 mmol) were reacted as described in general procedure. The crude product was purified over silicagel eluting with hexane/ethylacetate (15:1) gave the compound 41 as colorless liquid (1.84 g, 70\%) and compound 70 as a colorless liquid (0.27 g, 15\%).

1H-NMR (400 MHz, CDCl$_3$) $\delta$ 4.33 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 2.75 (m, 2H, H7), 2.63 (m, 2H, H4), 1.78 (m, 4H, H5 and H6), 1.38 (t, $J = 7.1$ Hz, 3H, CH$_3$); 13C-NMR (100 MHz, CDCl$_3$) $\delta$ 162.9, 137.3, 136.1, 130.9, 115.3, 60.7, 26.2, 25.0, 22.8, 22.5, 14.3; IR (cm$^{-1}$) 2980, 2935, 2858, 1708, 1446, 1217, 1145,1031.

4.5 General procedure of Sonogashira cross-coupling reaction to iodothiophene

PdCl$_2$ (0.0026 g, 0.015 mmol), CuI (0.0085 g, 0.045mmol) and PPh$_3$ (0.015 g, 0.06 mmol) in THF (15 mL) were put into two-necked round bottom flask and allowed to stir for 10 minute under nitrogen atmosphere. NEt$_3$ (0.15 mL, 1.11 mmol) and alkyne (0.81 mmol) were added subsequently into reaction vessel. After stirring for 5 minute, iodothiophene (0.2 g, 0.744 mmol) was added and the resulting mixture was heated to reflux temperature and stirred for 4 h. After completion of the reaction, the mixture was cooled to room temperature, filtered through celite bed and the filtrate was concentrated under vacuum. Water (30 mL) was added to crude mass and then extracted with ethyl acetate (3 x 30 mL). The organic layers were collected, combined, washed with brine (2 x 25 mL), and dried over anhydrous MgSO$_4$. The crude product was purified by column chromatography on silica gel to afford the desired product.
4.5.1 Synthesis of ethyl 2-(phenylethynyl)thiophene-3-carboxylate (42a)

PdCl₂ (0.0026 g, 0.015 mmol), CuI (0.0085 g, 0.045 mmol) and PPh₃ (0.015 g, 0.06 mmol), NEt₃ (0.15 mL, 1.11 mmol), phenylacetylene (0.088 mL, 0.81 mmol), iodothiophene (0.2 g, 0.744 mmol) in THF (15 mL) were reacted as described in general procedure. The crude product was purified by column chromatography on silica gel using 10:1 hexane/ethyl acetate to afford the desired product 42a as a light green liquid (0.08 g, 45%).

**1H-NMR** (400 MHz, CDCl₃) δ 7.57 (m, 2H, H6 and H10), 7.47 (d, J = 5.3 Hz, H5), 7.37 (m, 3H, H7, H8, and H9), 7.20 (d, J = 5.3 Hz, H4), 4.39 (q, J = 7.1 Hz, 2H, OCH₂), 1.42 (t, J = 7.1 Hz, 3H, CH₃);

**13C-NMR** δ (100 MHz, CDCl₃) 162.1, 134.4, 131.6, 129.3, 129.0, 128.9, 128.4, 125.7, 122.7, 98.9, 81.8, 61.0, 14.3; **IR** (cm⁻¹) 2980, 2206, 1704, 1238, 1151, 1024, 688.

**HRMS-TOF [M + H]^+** Calcd for C₁₄H₁₉SO₂ 251.11003, found: 251.11125.

4.5.2 Synthesis of ethyl 2-(hept-1-yn-1-yl)thiophene-3-carboxylate (42b)

PdCl₂ (0.0027 g, 0.017 mmol), CuI (0.0096 g, 0.053 mmol), PPh₃ (0.017 g, 0.071 mmol) NEt₃ (0.18 mL, 1.35 mmol), iodothiophene (0.25 g, 0.89 mmol) and 1-heptyne (0.13 mL, 0.97 mmol) in THF (15 mL) were reacted as described in general procedure. The crude product was purified by column chromatography on silica gel using 15:1 hexane/ethyl acetate to afford the desired compound 42b as a light brown liquid (0.13 g, 57%).

**1H-NMR** (400 MHz, CDCl₃) δ 7.38 (d, J = 5.4 Hz, H5), 7.08 (d, J = 5.4 Hz, H4), 4.34 (q, J = 7.1 Hz, 2H, OCH₂), 2.50 (t, J = 7.1 Hz, 2H, H6), 1.65 (m, 2H, H7), 1.45 (m, 2H, H8), 1.37 (m, 5H, H9 and H11), 0.9 (t, J = 7.3 Hz, 3H, H10);

**13C-NMR** (100 MHz, CDCl₃) δ 162.5, 133.6, 130.6, 128.6, 124.4, 101.4, 72.9, 60.6, 31.1, 28.1, 22.2, 20.1, 14.3, 13.9; **IR** (cm⁻¹) 2956, 2930, 2859, 2226, 1704, 1267, 1146, 1025, 708; **HRMS-TOF [M + H]^+** Calcd for C₁₄H₁₈SO₂ 251.11003, found: 251.11125.
4.5.3 Synthesis of ethyl 2-(hex-1-yn-1-yl)thiophene-3-carboxylate (42c)

PdCl$_2$ (0.0018 g, 0.011 mmol), CuI (0.0058 g, 0.033 mmol), PPh$_3$ (0.011 g, 0.044 mmol) NEt$_3$ (0.11 mL, 0.85 mmol), iodothiophene (0.16 g, 0.57 mmol) and 1-hexyne (0.072 mL, 0.63 mmol) in THF (10 mL) were reacted as described in general procedure. The crude compound was purified by column chromatography on silica gel using 10:1 hexane/ethyl acetate to afford the desired compound 42c as a yellow liquid (0.08 g, 60%).

$^1$H-NMR (400 MHz, CDCl$_3$) δ 7.38 (d, $J = 5.4$ Hz, H5), 7.08 (d, $J = 5.4$ Hz, H4), 4.34 (q, $J = 7.1$ Hz, 2H, OCH$_2$), 2.51 (t, $J = 7.1$ Hz, 2H, H6), 1.63 (m, 2H, H7), 1.49 (m, 2H, H8), 1.38 (t, $J = 7.1$ Hz, 3H, H10), 0.9 (t, $J = 7.3$ Hz, 3H, H9); $^{13}$C-NMR (100 MHz, CDCl$_3$) δ 162.5, 133.5, 130.4, 128.6, 124.4, 101.1, 72.4, 60.6, 30.5, 22.1, 19.8, 14.3, 13.6; IR (cm$^{-1}$) 2957, 2932, 2871, 2224, 1704, 1269, 1146, 1025, 70; HRMS-TOF [M + H]$^+$ Calcd for C$_{13}$H$_{18}$SO$_2$ 237.09560, found: 237.09438.

4.6 General procedure of Sonogashira cross-coupling reaction to bromothiophene 41 and 63

PdCl$_2$ (0.0026 g, 0.015 mmol), CuI (0.0085 g, 0.045 mmol) and PPh$_3$ (0.015 g, 0.06 mmol) in THF (15 mL) were put into two-necked round bottom flask and allowed to stir for 10 minute under nitrogen atmosphere. DIPA (0.15 mL, 1.11 mmol) and alkyne (0.81 mmol) were added subsequently into reaction vessel. After stirring for 5 minute, bromothiophene (0.744 mmol) was added and the resulting mixture was heated to reflux temperature. Reaction was controlled by TLC. After completion of the reaction, the mixture was cooled to room temperature, filtered through celite bed and the filtrate was concentrated under vacuum. Water (20 mL) was added to crude mass and then extracted with ethyl acetate (3 x 20 mL). The organic layers were collected, combined, washed with brine (2 x 25 mL), and dried over anhydrous MgSO$_4$. The crude product was purified by column chromatography on silica gel to afford the desired product.
4.6.1 Synthesis of ethyl 2-(phenylethynyl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (45a)

PdCl₂ (0.0026 g, 0.015 mmol), CuI (0.0085 g, 0.045 mmol) and PPh₃ (0.015 g, 0.06 mmol), DIPA (0.15 mL, 1.11 mmol), bromothiophene 41 (0.21 g, 0.744 mmol) and phenylacetylene (0.088 mL, 0.81 mmol) in THF (15 mL) were reacted as described in general procedure. The crude product was purified by column chromatography on silica gel using 15:1 hexane/ethyl acetate to afford the desired compound 45a as an pale yellow crystal from hexane/ethylacetate (0.14 g, 60%), mp 82-84 °C. (lit. mp = 88.5-89.5 °C²).

H-NMR (400 MHz, CDCl₃) δ 7.52 (m, 2H, H8 and H12), 7.34 (m, 3H, H9, H10, and H11), 4.36 (q, J = 7.1 Hz, 2H, OCH₂), 2.83 (qt, 2H, H7), 2.73 (qt, 2H, H4), 1.81, m, 4H, H6 and H5), 1.39 (t, J = 7.1 Hz, 3H, CH₃); C-NMR (100 MHz, CDCl₃) δ 163.2, 138.0, 136.3, 133.1, 131.4, 128.5, 128.4, 125.7, 123.1, 97.6, 82.9, 60.5, 26.2, 25.4, 22.8, 22.4, 14.4; IR (cm⁻¹) 2946, 2905, 2196, 1697, 1224, 1158, 753, 690.¹

4.6.2 Synthesis of ethyl 2-(hepty-1-yn-1-yl)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (45b)

PdCl₂ (0.0026 g, 0.015 mmol), CuI (0.0085 g, 0.045 mmol), PPh₃ (0.015 g, 0.06 mmol), DIPA (0.15 mL, 1.11 mmol), bromothiophene 41 (0.21 g, 0.744 mmol) and 1-heptyne (0.11 mL, 0.81 mmol) in THF (15 mL) were reacted as described in general procedure. The crude product was purified by column chromatography on silica gel using 15:1 hexane/ethyl acetate to afford the desired compound 45b as a yellow solid (0.15 g, 72%), mp 204-206 °C.

H-NMR (400 MHz, CDCl₃) δ 4.32 (q, J = 7.1 Hz, 2H, OCH₂), 2.78 (qt, 2H, H7), 2.68 (qt, 2H, H4), 2.47 (t, J = 7.1 Hz, 2H, H8), 1.79 (m, 4H, H5 and H6), 1.62 (m, 2H, H9), 1.42 (m, 2H, H10), 1.37 (m, 5H, H11 and H13), 0.91 (t, J = 7.1 Hz, 3H, H12); C-NMR (100 MHz, CDCl₃) δ 163.4, 136.4,
135.7, 132.4, 127.0, 99.8, 73.7, 60.3, 31.1, 28.2, 26.1, 25.2, 22.8, 22.5, 22.2, 20.1 14.3, 13.9; IR (cm\(^{-1}\)) 2945, 1608, 1555, 1436, 1272, 1233, 1047, 945, 746; HRMS-TOF [M + H]\(^+\) Calcd for C\(_{18}\)H\(_{24}\)SO\(_2\) 305.16011, found: 305.15698.

4.6.3 Synthesis of ethyl 2-(hex-1-yn-1-yl)-4,5,6,7-tetrahydrobenzo[\(b\)]thiophene-3-carboxylate (45c)

PdCl\(_2\) (0.0035 g, 0.02 mmol), CuI (0.011 g, 0.06 mmol), PPh\(_3\) (0.02 g, 0.08 mmol), DIPA (0.21 mL, 1.57 mmol), bromothiophene 41 (0.30 g, 1.06 mmol) and 1-hexyne (0.13 mL, 1.17 mmol) in THF (15 mL) were reacted as described in general procedure. The crude product was purified by column chromatography on silica gel using 20:1 hexane/ethyl acetate to afford the desired compound 45c as a brown liquid (0.14 g, 45%).

\[ \text{\textsuperscript{1}H-NMR (400 MHz, CDCl}_3\text{)} \delta 4.31 (q, J = 7.2 \text{ Hz}, 2H, OCH\(_2\)), 2.78 (qt, 2H, H7), 2.68 (qt, 2H, H4), 2.47 (t, J = 7.1 \text{ Hz}, 2H, H8), 1.79 (m, 4H, H5 and H6), 1.61 (m, 2H, H9), 1.47 (m, 2H, H10), 1.37 (t, J = 7.1 \text{ Hz}, 3H, H12), 0.91 (t, J = 7.2 \text{ Hz}, 3H, H11); \text{\textsuperscript{13}C-NMR (100 MHz, CDCl}_3\text{)} \delta 163.4, 136.4, 135.7, 132.4, 127.0, 99.8, 73.7, 60.3, 30.6, 26.1, 25.2, 22.8, 22.5, 22.1, 19.8 14.3, 13.6; IR (cm\(^{-1}\)) 2928, 2859, 2196, 1704, 1634, 1271, 1183, 1032, 753, 703; HRMS-TOF [M + H]\(^+\) Calcd for C\(_{17}\)H\(_{22}\)SO\(_2\) 291.14380, found: 291.14133.

4.6.4 Synthesis of ethyl 2,5-bis(phenylethynyl)thiophene-3-carboxylate (74)

PdCl\(_2\) (0.0031 g, 0.018 mmol), CuI (0.010 g, 0.05 mmol), PPh\(_3\) (0.018 g, 0.072 mmol), DIPA (0.18 mL, 1.32 mmol), bromothiophene 63 (0.16 g, 0.45 mmol) and phenylacetylene (0.11 mL, 1.00 mmol) in THF (15 mL) were reacted as described in general procedure. The crude mass was purified by column chromatography on silica gel using 20:1 hexane/ethyl acetate to afford the desired compound 74 as a yellow solid (0.07 g, 45%), mp 72-74 °C.
4.7 General procedure of cyclization reaction

Alkyne-substituted thiophene (0.5 mmol) was dissolved in MeOH (5 mL) and allowed to stir for 5 min under nitrogen atmosphere. Hydrazine monohydrate (0.23 mL, 5 mmol) was added into reaction vessel and the resulting mixture was heated at the reflux temperature. Reaction was controlled by TLC. Removal of the solvent under vacuum gave residue which was then purified by column chromatography on silica gel.

4.7.1 Synthesis of 5-amino-6-phenylthieno[3,2-c]pyridin-4(5H)-one (43a)

A solution of compound 42a (0.13 g, 0.5 mmol) in MeOH (5 mL) was reacted with hydrazine monohydrate (0.23 mL, 5 mmol) as described in general procedure to give the cyclization product 43a as a yellow solid (0.06 g, 55%), mp 126-128 °C and 44 as a pale yellow solid, (0.016 g, 15%), mp 214-216 °C.

**HRMS-TOF** \([M + H]^+\) Calcd for C_{23}H_{16}SO_2 357.09777, found: 357.09438.

**1H-NMR** (400 MHz, CDCl_3) \(\delta\) 7.60 (s, H4), 7.58 (m, 2H, H9), 7.52 (m, 2H, H6), 7.38 (m, 6H, H7, H8, H10, and H11), 4.38 (q, \(J = 7.1\) Hz, 2H, OCH_2), 1.40 (t, \(J = 7.1\) Hz, 3H, CH_3);

**13C-NMR** (100 MHz, CDCl_3) \(\delta\) 161.6, 133.1, 131.7, 131.7, 131.6, 129.2, 129.0, 128.5, 123.1, 122.5, 122.2, 99.6, 94.5, 81.6, 81.6, 61.0, 14.3; **IR** (cm\(^{-1}\)) 3055, 2955, 2915, 2847, 2204, 1708, 1214, 1024, 729, 687.

\[\text{HRMS-TOF} \quad [M + H]^+ \quad \text{Calcd for C}_{23}\text{H}_{16}\text{SO}_2 357.09777, \text{found: 357.09438.}\]
\[ ^1H-NMR \ (400 \text{ MHz, } CDCl_3) \delta 10.05 \ (s, NH), 7.67 \ (m, 2H, \text{ H9 and H13}), 7.55-7.45 \ (m, 5H, H2, H8, H10, H11, \text{ and H12}), 7.31 \ (d, J = 5.3 \text{ Hz, H3}), 6.99 \ (s, NH); \text{ IR (cm}^{-1}) \ 3090, 2981, 1621, 11497, 1272, 1169, 986, 755, 680, 632; \text{ HRMS-TOF}; [M + H]^+ \text{ Calcd for C}_{13}H_{10}N_2SO 243.05985, \text{ found: 243.05866.} \]

4.7.2 Synthesis of 5-amino-6-pentylthieno[3,2-c]pyridin-4(5H)-one (43b)

Compound \textit{42b} (0.12 g, 0.48 mmol) in MeOH (5 mL) was reacted with hydrazine monohydrate (0.23 mL, 5 mmol) as described in general procedure to give the cyclization product \textit{43b} as pale yellow crystals (0.09 g, 80%), mp 30-32 °C.

\[ ^1H-NMR \ (400 \text{ MHz, } CDCl_3) \delta 7.59 \ (d, J = 5.4 \text{ Hz, H2}), 7.20 \ (d, J = 5.4 \text{ Hz, H3}), 6.56 \ (s, H7), 4.96 \ (s, 2H, NH_2), 2.85 \ (t, J = 7.7 \text{ Hz, 2H, H8}), 1.68 \ (m, 2H, H9), 1.40 \ (m, 4H, H10 \text{ and H11}), 0.98 \ (t, J = 7.3 \text{ Hz, 3H, H12}); ^{13}C-NMR \ (100 \text{ MHz, } CDCl_3) \delta 158.1, 146.1, 144.4, 126.4, 123.7, 122.5, 99.0, 31.7, 30.4, 27.0, 21.4, 12.9; \text{ IR (cm}^{-1}) \ 3301, 2927, 2857, 1637, 1558, 724, 703; \text{ HRMS-TOF}; [M + H]^+ \text{ Calcd for C}_{12}H_{16}N_2SO 237.10844, \text{ found: 237.10561.} \]

4.7.3 Synthesis of 5-amino-6-butylthieno[3,2-c]pyridin-4(5H)-one (43c)

Compound \textit{42c} (0.06 g, 0.26 mmol) in MeOH (2.5 mL) was reacted with hydrazine monohydrate (0.12 mL, 2.5 mmol) as described in general procedure to give the cyclization product \textit{43c} as a pale yellow solid (0.05 g, 95%), mp > 300 °C.

\[ ^1H-NMR \ (400 \text{ MHz, } CDCl_3) \delta 7.59 \ (d, J = 5.4 \text{ Hz, H2}), 7.20 \ (d, J = 5.4 \text{ Hz, H3}), 6.56 \ (s, H7), 4.96 \ (s, 2H, NH_2), 2.85 \ (t, J = 7.7 \text{ Hz, 2H, H8}), 1.68 \ (m, 2H, H9), 1.45 \ (m, 2H, H10), 0.98 \ (t, J = 7.3 \text{ Hz, 3H, H11}); ^{13}C-NMR \ (100 \text{ MHz, } CDCl_3) \delta 159.2, 147.1, 145.4, 127.4, 124.5, 123.5, 99.9, 32.4, 30.5, 22.4, 13.9; \text{ IR (cm}^{-1}) \ 3184, 3079, 2949, 2929, 2870, 1644, 1054, 715; \text{ HRMS-TOF}; [M + H]^+ \text{ Calcd for C}_{11}H_{16}N_2SO 223.09207, \text{ found: 223.08996.} \]
4.7.4 Synthesis of 2-amino-3-phenyl-6,7,8,9-tetrahydrobenzo[4,5]thieno[3,2-c]pyridin-1(2H)-one (46a) and 4-phenyl-2,5,7,8,9,10-hexahydro-1H-benzo[4,5]thieno[3,2-d][1,2]diazepin-1-one (47)

Compound 45a (0.2 g, 0.64 mmol) in MeOH (6.5 mL) was reacted with hydrazine monohydrate (0.31 mL, 6.5 mmol) as described in general procedure to give the cyclization products 46a (0.07 g, 40%) as a pale yellow solid, mp 146-148 °C and 47 (0.66 g, 35%) as white tiny needles from hexane/EtOAc, mp 235-237 °C.

1H-NMR (400 MHz, CDCl3) δ 7.51 (m, 2H, H10), 7.45 (m, 3H, H11 and H12), 6.61 (s, H4), 5.11 (bs, 2H, NH2), 3.16 (bs, 2H, H9), 2.80 (bs, 2H, H6), 1.88 (m, 4H, H8 and H7); 13C-NMR (100 MHz, CDCl3) δ 158.2, 145.0, 142.4, 135.3, 134.0, 129.2, 128.9, 128.6, 128.1, 126.5, 26.0, 25.5, 23.0; IR (cm⁻¹) 3301, 3059, 2928, 2830, 1635, 1557, 769, 703; HRMS-TOF; [M + H]+ Calcd for C17H16N2SO 297.10850, found: 297.10561.

1H-NMR (400 MHz, CDCl3) δ 8.61 (s, NH), 7.77 (m, 2H, H11), 7.42 (m, 3H, H12 and H13), 4.07 (s, 2H, H5), 2.86 (t, J = 6.1 Hz, 2H, H7), 2.69 (t, J = 5.9 Hz, 2H, H10), 1.79 (m, 4H, H8 and H9); 13C-NMR (100 MHz, CDCl3) δ 164.0, 158.0, 140.1, 137.2, 135.3, 134.5, 130.6, 130.4, 128.8, 127.0, 30.2, 25.7, 25.0, 23.1, 22.3; IR (cm⁻¹) 3162, 3050, 2919, 2850, 1636, 1432, 758, 687; HRMS-TOF; [M + H]+ Calcd for C17H16N2SO 297.10697, found: 297.10561.

4.7.5 Synthesis of 2-amino-3-pentyl-6,7,8,9-tetrahydrobenzo[4,5]thieno[3,2-c]pyridin-1(2H)-one (46b)

Compound 45b (0.1 g, 0.35 mmol) in MeOH (4 mL) was reacted with hydrazine monohydrate (0.17 mL, 4 mmol) as described in general procedure to give the cyclization product 46b (0.09 g, 90%) as a pale yellow solid, mp 69-71 °C.
\textbf{4.7.6 Synthesis of 2-amino-3-butyl-6,7,8,9-tetrahydrobenzo[4,5]thieno[3,2-c]pyridin-1(2\textit{H})-one (46c)}

Compound 45c (0.07 g, 0.26 mmol) in MeOH (3 mL) was reacted with excess hydrazine monohydrate (0.14 mL, 3 mmol) as described in general procedure to give the cyclization product 46c (0.06 g, 80\%) as white tiny needles from hexane/EtOAc, mp 64-66°C.

\textbf{4.8 Synthesis of methyl 2-methylfuran-3-carboxylate (116)}

Methyl acetoacetate 115 (10.0 g, 86.1 mmol) was dissolved in pyridine (50 mL). To the resulting mixture, a solution of chloroacetaldehyde 124 (45\%, 15.5 mL, 107.6 mmol) was added dropwise at room temperature and then stirred at 50 °C for 16 h. The reaction was controlled by TLC. After the completion of the reaction, the mixture was extracted with water (100 mL) and ethyl acetate (3 x 100 mL). The combined organic extracts were washed with 2M of HCl (100 mL), 5\% NaHCO₃ (100 mL), 10\% NaOH
(100 mL) and brine (100 mL) one by one, dried over MgSO\(_4\). Removal of the solvent
gave the crude product, which was then purified by column chromatography eluting
with hexane/EtOAc (5:1). Eluted solvent was evaporated to yield ester 116 as an oily

**1H-NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.22 (d, \(J = 2.0\) Hz, H5), 6.63 (d, \(J = 2.0\)
Hz, H4), 3.82 (s, 3H, OCH\(_3\)); **13C-NMR (100 MHz, CDCl\(_3\)) \(\delta\) 164.5, 159.3, 140.3, 113.2, 110.6, 51.2, 13.6; **IR (cm\(^{-1}\)) 2954, 1819, 1720, 1668, 1438, 1383, 1302, 1120, 1044, 967, 835, 757.

**4.9 Synthesis of methyl 2-formylfuran-3-carboxylate (129)**

The ester 116 (1.0 g, 7.14 mmol) was dissolved in anisole (15 mL). To this solution,
SeO\(_2\) (1.58 g, 14.28 mmol) was added and the mixture was stirred overnight at 160 °C.
The reaction was controlled by TLC. After the completion of the reaction, the reaction
mixture filtered and extracted with water (50 mL) and ethyl acetate (3 x 70 mL). Then
the combined organic extracts were dried over Mg\(_2\)SO\(_4\). Removal of the solvent gave
the crude product, which was then purified by column chromatography eluting with
hexane/EtOAc (5:1). Eluted solvent was evaporated to yield aldehyde 129 as yellow
crystals from hexane/EtOAc (0.38 g, 34%), mp 77-79 °C. (lit.mp = 77-78 °C\(^{98}\)).

**1H-NMR (400 MHz, CDCl\(_3\)) \(\delta\): 10.24 (s, H6), 7.64 (d, \(J = 1.8\) Hz, H5),
6.89 (d, \(J = 1.8\) Hz, H4), 3.95 (s, 3H, OCH\(_3\)); **13C-NMR (100 MHz, CDCl\(_3\)) \(\delta\)
178.8, 162.0, 152.4, 146.7, 126.2, 112.9, 52.5; **IR (cm\(^{-1}\)) 3155, 3131, 1714, 1672, 1577, 1481, 1435, 1403, 1365, 1305, 1266, 1213, 1072, 1044, 891, 807, 756.

**4.10 General procedure for the synthesis of substituted imidazoles**

Aldehyde (2.66 mmol) was dissolved in DMF (8 mL). To this solution, \(o\)-phenylenediamine (91) (2.66 mmol) and \(p\)-TsOH (0.53 mmol) were added at room
temperature and the resulting mixture was heated at 80 °C for 2-3 hours. The reaction
was controlled by TLC. After the completion of the reaction, Na\(_2\)CO\(_3\) (0.53 mmol) was
dissolved in water (100 mL) and was added to this solution dropwise. EtOAc (20 mL)
was added and then extracted with water (2 x 20 mL). The combined organic extracts were dried over MgSO₄. Removal of the solvent gave the crude product which was then purified by column chromatography eluting with hexane/EtOAc (3:1) to give the product.⁹⁹

4.10.1 Synthesis of methyl 2-(1H-benzo[d]imidazol-2-yl)furan-3-carboxylate (117)

Compound 129 (2.66 mmol, 0.41 g), o-phenylenediamine (91) (2.66 mmol, 0.28 g) and p-TsOH (0.53 mmol, 0.09 g) in DMF (8 mL) were reacted as described in general procedure. The resulting residue was purified by column chromatography eluting with hexane/EtOAc (5:1). Eluted solvent was evaporated to yield furane-substituted imidazole 117 as a brown solid (0.48 g, 75%), mp 164-168 °C.

\[
\begin{align*}
\text{1H-NMR} &\text{ (400 MHz, CDCl3)} \delta 12.65 (s, NH), 7.88 (m, H6), \\
& 7.61 (d, J = 1.8 Hz, H5), 7.58 (m, H9), 7.34, (m, 2H, H7 and H8), 6.92 (d, J =1.8 Hz, H4), 4.01 (s, 3H, CH₃); \\
\text{13C-NMR} &\text{ (100 MHz, CDCl3)} \delta 165.4, 148.8, 143.4, 142.1, 123.7, 123.7, 116.1, 112.4, 52.7; \\
\text{IR} &\text{ (cm}^{-1}\text{)} 2954, 2669, 1727, 1615, 1418, 1296, 1282, 1067, 1039, 743; \\
\text{HRMS-TOF}; [M + H]^{+} &\text{ Calcd for C}_{13}\text{H}_{10}\text{N}_{2}\text{O}_{3} 243.07677, \text{ found: 243.07642.}
\end{align*}
\]


Compound 117 (0.15 g, 0.62 mmol) was dissolved in methanol (10 mL) and to this solution, K₂CO₃ (0.1 g, 0.68 mmol) was added and this solution was heated to reflux temperature and stirred for overnight. After the completion of the reaction, it was cooled to room temperature and the solvent was evaporated under vacuum. The residue was dissolved in CH₂Cl₂ (20 mL) and washed with 1N HCl (20 mL) solution. The organic phase was washed with water (20 mL) and brine (20 mL). Collected organic phases were dried over MgSO₄ and removal of the solvent gave the product 118 as a brown solid (0.1 g, 75%), mp>300 °C.
\[ ^1\text{H-NMR} \ (400 \text{ MHz, DMSO-}d_6) \ \delta \ 7.97 \ (d, \ J = 1.8 \text{ Hz, H7}), \]
\[ 7.78 \ (dd, \ J = 3.1 \text{ and } 6.2 \text{ Hz, 2H, H2 and H5}), \]
\[ 7.51 \ (m, \ 2H, \text{ H3 and H4}), \]
\[ 7.13 \ (d, \ J = 1.8 \text{ Hz, H6}); \]
\[ ^1\text{C-NMR} \ (100 \text{ MHz, DMSO-}d_6) \ \delta \ 166.0, 147.2, \]
\[ 135.6, 126.8, 116.0, 115.5, 111.7; \]
\[ \text{IR (cm}^{-1} \text{)} \]
\[ 3126, 1659, 1580, 1485, 1435, 1331, 1260, 1050, 744; \]
\[ \text{HRMS-TOF; } [\text{M + H}]^+ \]
\[ \text{Calcd for C}_{12}\text{H}_6\text{N}_2\text{O}_2 \ 211.04944, \text{ found: 211.0502}. \]

4.12 General procedure of O-propargylation

Aromatic hydroxylaldehyde (10 mmol) was dissolved in DMF (10 mL) and anhydrous K$_2$CO$_3$ (15.0 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 room temperature. After the completion of the reaction, ethyl acetate (30 mL) was added and the organic phase was washed with water (3 × 50 mL) and then dried over MgSO$_4$. Removal of solvent gave the product.

4.12.1 Synthesis of 2-(prop-2-yn-1-yloxy)benzaldehyde (120a)

Salicylaldehyde (119a) (1.0 g, 8.19 mmol) was reacted with anhydrous K$_2$CO$_3$ (1.7 g, 12.3 mmol) and propargyl bromide (1.05 mL, 9.82 mmol) as described in general procedure to give the product 120a as colorless cubic crystals from chloroform (1.1 g, 84%), mp 68-70 ºC. (lit. mp = 68-69 ºC$^{100}$).

\[ ^1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 10.49 \ (s, \ H9), \]
\[ 7.87 \ (dd, \ J = 7.5 \text{ and } 1.8 \text{ Hz, H6}), \]
\[ 7.57 \ (ddd, \ J = 8.6, 7.5 \text{ and } 1.8 \text{ Hz, H4}), \]
\[ 7.12 \ (d, \ J = 8.6 \text{ Hz, H3}), \]
\[ 7.09 \ (t, \ J = 7.5, \text{ H5}), \]
\[ 4.83 \ (d, \ J = 2.3 \text{ Hz, 2H, H7}), \]
\[ 2.57 \ (t, \ J = 2.3 \text{ Hz, H8}); \]
\[ ^1\text{C-NMR} \ (100 \text{ MHz, CDCl}_3) \]
\[ \delta : \ 189.6, 159.7, 135.8, 128.6, 125.6, 121.8, 113.3, 77.8, 76.6, 56.4; \]
\[ \text{IR (cm}^{-1} \text{)} \ 3268, \]
\[ 2117, 1729, 1681, 1597, 1449, 1284, 1207, 1166, 1066, 924, 832, 742, 610. \]

4.12.2 Synthesis of 5-bromo-2-(prop-2-yn-1-yloxy)benzaldehyde (120b)

5-bromo-salicylaldehyde (119b) (2.0 g, 9.95 mmol), K$_2$CO$_3$ (2.1 g, 14.9 mmol) and propargyl bromide (1.3 mL g, 11.9 mmol) were reacted as described in general
procedure to give the product 120b as white needles from chloroform/hexane (2.13 g, 90%), mp 94-96 ºC. (lit. mp = 94-96 ºC\textsuperscript{100}).

\[1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 10.40 \ (s, H_9), \ 7.91 \ (d, J = 2.5 \text{ Hz, H}6), \ 7.63 \ (dd, J = 8.9 \text{ and } 2.5 \text{ Hz, H}4), \ 7.04 \ (d, J = 8.9 \text{ Hz, H}3), \ 4.83 \ (d, J = 2.4 \text{ Hz, H}7), \ 2.58 \ (t, J = 2.4 \text{ Hz, H}8); \ \text{IR} \ \text{cm}^{-1} \ 3233, \ 2981, \ 2882, \ 2117, \ 1681, \ 1589, \ 1478, \ 1454, \ 1395, \ 1291, \ 1275, \ 1218, \ 1183, \ 1124, \ 1001, \ 879, \ 810, \ 732, \ 654, \ 630, \ 581.\]

4.12.3 Synthesis of 3-methoxy-2-(prop-2-yn-1-yloxy)benzaldehyde (120c)

3-Methoxy-salicylaldehyde (119c) (2.0 g, 13.1 mmol), K\textsubscript{2}CO\textsubscript{3} (2.7 g, 19.7 mmol), and propargyl bromide (1.7 mL, 15.8 mmol) were reacted as described in general procedure to yield the product 120c as colorless cubic crystals from EtOAc/hexane (2.3 g, 92%), mp 49-51 ºC. (lit. mp = 49-51 ºC\textsuperscript{100}).

\[1\text{H-NMR} \ (400 \text{ MHz, CDCl}_3) \ \delta \ 10.50 \ (s, H_9), \ 7.44 \ (dd, J = 6.0 \text{ and } 3.4 \text{ Hz, H}6), \ 7.22 – 7.13 \ (m, 2H, H4 and H5), \ 4.88 \ (d, J = 2.4 \text{ Hz, H}7), \ 3.89 \ (s, 3H, OCH}_3), \ 2.52 \ (t, J = 2.4 \text{ Hz, H}8); \ \text{IR} \ \text{cm}^{-1} \ 3265, \ 2889, \ 2837, \ 2118, \ 1681, \ 1589, \ 1477, \ 1449, \ 1249, \ 1179, \ 983, \ 911, \ 749, \ 651.\]

4.12.4 Synthesis of 2-(but-2-yn-1-yloxy)benzaldehyde (120f)

Salicylaldehyde (119a) (0.5 g, 4.1 mmol), 1-bromobut-2-yne (0.66 mL, 6.14 mmol), and K\textsubscript{2}CO\textsubscript{3} (0.68 g, 4.9 mmol) in DMF (5 mL) were reacted as described in general procedure to give the product 120f as a colorless oil (0.68 g, 95%).
1H-NMR (400 MHz, CDCl₃) δ 10.49 (s, H9), 7.85 (dd, J = 7.7 and 1.7 Hz, H6), 7.56 (ddd, J = 8.4, 7.7 and 1.7 Hz, H4), 7.11-7.06 (m, 2H, H3 and H5), 4.79 (q, J = 2.1 Hz, 2H, H7), 1.86 (t, J = 2.1 Hz, 3H, H8); 13C-NMR (100 MHz, CDCl₃) δ 189.7, 160.1, 135.7, 128.2, 125.3, 121.2, 113.3, 84.7, 73.4, 57.0, 3.6; IR (cm⁻¹) 2917, 2864, 2231, 1686, 1597, 1458, 1369, 1286, 1261, 1190, 1162, 1102, 1042, 995, 831, 755, 645, 595.

4.12.5 Synthesis of 2-(2-formylphenoxy)acetonitrile (120g)

Salicylaldehyde (119a) (0.5 g, 4.1 mmol), chloroacetonitrile (0.46 g, 6.14 mmol), and K₂CO₃ (0.68 g, 4.9 mmol) in DMF (5 mL) were reacted as described in general procedure to give the product 120g as an orange crystal (0.63 g, 95%) mp 63-65 °C. (lit. mp =78-80 °C)¹⁰¹

1H-NMR (400 MHz, CDCl₃) δ 10.42 (s, H8), 7.88 (dd, J = 7.6 and 1.6 Hz, H6), 7.63 (m, H4), 7.19 (qt, H3), 7.08 (d, J = 8.4 Hz, H5), 4.93 (s, 2H, H7); 13C-NMR (100 MHz, CDCl₃) δ 188.8, 158.3, 136.1, 129.5, 125.6, 123.3, 114.6, 112.7 53.8; IR (cm⁻¹) 3100, 2117, 1676, 1597, 1483, 1455, 1283, 1231, 1033, 842, 757, 652.

4.12.6 Synthesis of 2-((3-phenylprop-2-yn-1-yl)oxy)benzaldehyde (120d)

PdCl₂ (0.009 g, 0.052 mmol), CuI (0.028 g, 0.15 mmol) and PPh₃ (0.05 g, 0.21 mmol), NEt₃ (0.52 mL, 3.9 mmol), iodophenyl (0.26 mL, 2.36 mmol) and compound 120a (0.42 g, 2.6 mmol) in THF (10 mL) were reacted as described in section 4.6. The residue was purified by column chromatography on silica gel using 15:1 hexane/ethyl acetate to afford the desired compound 120d as a pale yellow solid (0.61 g, 90%), mp 83-84 °C. (lit. mp = 79-80 °C)¹⁰⁰
1H-NMR (400 MHz, CDCl₃) δ 10.54 (s, H10), 7.88 (dd, J = 7.5 and 1.8 Hz, H6), 7.58 (ddd, J = 8.4, 7.5 and 1.8 Hz, H4), 7.43 (m, 2H, H8 and H12), 7.32 (m, 3H, H9, H10 and H11), 7.21 (d, J = 8.4 Hz, H3), 7.09 (t, J = 7.5 Hz, H5), 5.05 (s, 2H, H7);

13C-NMR (100 MHz, CDCl₃) δ 189.7, 160.2, 135.5, 131.8, 128.9, 128.5, 128.4, 128.4, 128.4, 128.4, 121.9, 121.5, 113.5, 88.2, 82.9, 57.2;

IR (cm⁻¹) 3257, 3106, 2861, 2239, 1681, 1598, 1509, 1372, 1205, 1044, 748.

4.12.7 Synthesis of 2-((3-(4-nitrophenyl)prop-2-yn-1-yl)oxy)benzaldehyde (120e)

PdCl₂ (0.155 mmol, 0.026 g), CuI (0.466 mmol, 0.081 g) and PPh₃ (0.62 mmol, 0.16 g), NEt₃ (1.05 mL, 7.78 mmol), p-nitroiodophenyl (2.33 g, 7.78 mmol) and compound 120a (1.34 g, 8.4 mmol) in THF (15 mL) were reacted as described in section 4.6. The crude product was purified by column chromatography on silica gel using 5:1 hexane/ethyl acetate to afford the desired compound 120e as orange crystals (1.9 g, 90%), mp 110-111 °C.

1H-NMR (400 MHz, CDCl₃) δ 10.53 (s, H12), 8.19 (m, 2H, H8 and H11), 7.89 (dd, J = 7.6 and 1.8 Hz, H6), 7.62-7.55 (m, 3H, H4, H9, and H10), 7.17 (d, J = 8.3 Hz, H3), 7.13 (bt, J = 7.6 Hz, H5), 5.10 (s, 2H, H7);

13C-NMR (100 MHz, CDCl₃) δ 189.4, 159.8, 147.5, 135.7, 132.6, 128.8, 128.6, 125.7, 123.6, 121.9, 113.3, 88.1, 86.0, 57.1; IR (cm⁻¹) 3257, 3106, 2860, 2239, 1682, 1589, 1509, 1370, 1339, 1295, 1222, 1204, 759, 747.

4.13 Synthesis of 2-(2-(prop-2-yn-1-yloxy)phenyl)-1H-benzo[d]imidazole (121a)

Compound 120a (1.56 g, 9.72 mmol), o-phenylenediamine (91) (1.048 g, 9.72 mmol) and p-TsOH (1.94 mmol) in DMF (15 mL) were reacted as described in section 4.10. The resulting residue was purified by column chromatography eluting with hexane/EtOAc (4:1). Eluted solvent was evaporated to yield imidazole 121a as a brown crystal (1.56 g, 65%) from hexane/ethylacetate, mp 164-168 °C.
**1H-NMR** (400 MHz, DMSO-d$_6$) δ 8.22 (dd, $J = 1.5$ and 7.7 Hz, H6), 7.68 (d, $J = 3.1$ and 6.1 Hz, 2H, H7 and H10), 7.53 (m, H4), 7.38 (bd, $J = 8.3$ Hz, H3), 7.31 (dd, $J = 3.1$ and 6.1 Hz, 2H, H8 and H9), 7.20 (bt, $J = 7.7$ Hz H5), 5.08 (d, $J = 2.3$ Hz, 2H, H11), 3.07 (t, $J = 2.3$ Hz, H12);

**13C-NMR** (100 MHz, DMSO-d$_6$) δ 156.7, 150.2, 138.2, 133.2, 131.2, 124.5, 123.1, 118.4, 115.7, 114.9, 79.3, 78.0, 57.3; **IR** (cm$^{-1}$) 3301, 3288, 2119, 1684, 1603, 1581, 1462, 1438, 1216, 1091, 1006, 793, 667, 623.

### 4.14 Synthesis of 2-(5-bromo-2-(prop-2-yn-1-yloxy)phenyl)-1H-benzo[d]imidazole (121b)

Compound 120b (0.71 g, 3.0 mmol), o-phenylenediamine (91) (0.33 g, 3.0 mmol) and $p$-TsOH (0.114 g, 0.6 mmol) in DMF (10 mL) were reacted as described in section 4.10. The resulting residue was purified by column chromatography eluting with hexane/EtOAc (5:1). Eluted solvent was evaporated to yield imidazole 121b as white crystals (0.49 g, 50%), mp 130-131 °C

**1H-NMR** (400 MHz, CDCl$_3$) δ 10.50 (s, NH), 8.76 (d, $J = 2.5$ Hz, H6), 7.83 (bs, H7), 7.53 (dd, $J = 8.8$ and 2.5 Hz, H4), 7.53 (bs, H10), 7.29 (dd, $J = 3.0$ and 6.1 Hz, H8 and H9), 7.04 (d, $J = 8.8$ Hz, H3), 4.95 (d, $J = 2.4$ Hz, 2H, H11), 2.67 (t, $J = 2.4$ Hz, H12); **13C-NMR** (100 MHz, CDCl$_3$) δ 153.8, 147.9, 133.5, 132.8, 123.3, 122.9, 120.6, 119.6, 115.4, 114.8, 110.9, 77.2, 77.1, 57.2; **IR** (cm$^{-1}$) 3294, 2122, 1471, 1443, 1269, 1213, 1085, 1015, 800, 736.

### 4.15 Synthesis of 2-(3-methoxy-2-(prop-2-yn-1-yloxy)phenyl)-1H-benzo[d]imidazole (121c)

Compound 120c (1.75 g, 9.2 mmol), o-phenylenediamine (91) (0.99 g, 9.2 mmol) and $p$-TsOH (0.35 g, 1.84 mmol) in DMF (20 mL) were reacted as described in section 4.10. The resulting residue was purified by column chromatography eluting with hexane/EtOAc (5:1). Eluted solvent was evaporated to yield imidazole 121c as white crystals (1.50 g, 60%), mp 135-137 °C.
**1H-NMR** (400 MHz, CDCl$_3$) $\delta$ 10.82 (s, NH), 8.13 (d, $J$ = 1.2 and 8.1 Hz, H6), 7.77 (bs, H7), 7.58 (bs, H10), 7.27 (m, 3H, H8, H9 and H5), 7.02 (dd, $J$ = 1.2 and 8.1 Hz, H4), 4.90 (d, $J$ = 2.4 Hz, 2H, H11), 3.94 (s, 3H, OCH$_3$), 2.53 (t, $J$ = 2.4 Hz, H12);

**13C-NMR** (100 MHz, CDCl$_3$) $\delta$ 152.5, 151.1, 149.2, 144.6, 125.5, 123.6, 122.9, 121.7, 121.5, 115.1, 113.8, 113.5, 113.4, 78.2, 77.4, 61.0, 56.0; **IR** (cm$^{-1}$) 3278, 3260, 2938, 2836, 2117, 1478, 1428, 1277, 1124, 1059, 980, 745.

4.16 Synthesis of 2-(2-(but-2-yn-1-yloxy)phenyl)-1H-benzo[d]imidazole (121f)

Compound 120f (1.6 g, 9.2 mmol), o-phenylenediamine (91) (0.99 g, 9.2 mmol) and p-TsOH (0.35 g, 1.84 mmol) in DMF (20 mL) were reacted as described in section 4.10. The resulting residue was purified by column chromatography eluting with hexane/EtOAc (5:1). Eluted solvent was evaporated to yield imidazole 121f as a pale yellow solid (1.45 g, 60%), mp 156-158 °C.

**1H-NMR** (400 MHz, CDCl$_3$) $\delta$ 10.70 (s, NH), 8.60 (dd, $J$ = 1.7 and 7.8 Hz, H6), 7.82 (bs, H9), 7.49 (bs, H7), 7.42 (m, H4), 7.26 (dd, $J$ = 3.1 and 5.8 Hz, 2H, H8 and H10), 7.17 (m, 2H, H3 and H5), 4.90 (m, 2H, H11), 1.89 (qt, 3H, CH$_3$); **13C-NMR** (100 MHz, CDCl$_3$) $\delta$ 155.2, 149.7, 131.0, 131.0, 130.3, 122.5, 122.5, 118.5, 113.1, 85.2, 73.3, 57.4, 3.66; **IR** (cm$^{-1}$) 3202, 2919, 2851, 2161, 1587, 1488, 1471, 1259, 1224, 994, 737. **HRMS-TOF** [M + H]$^+$ Calcd for C$_{17}$H$_{14}$N$_2$O 263.12055, found: 263.11789.

4.17 Synthesis of 2-(2-((3-phenylprop-2-yn-1-yl)oxy)phenyl)-1H-benzo[d]imidazole (121d)

Compound 120d (0.64 g, 2.7 mmol), o-phenylenediamine (91) (0.29 g, 2.7 mmol) and p-TsOH (0.1 g, 0.52 mmol) in DMF (10 mL) were reacted as described in section 4.10. The resulting residue was purified by column chromatography eluting with hexane/EtOAc (7:1). Eluted solvent was evaporated to yield imidazole 121d as white crystals (0.26 g, 30%), mp 178-180 °C.
4.18 Synthesis of 1-(2-oxopropyl)-1H-pyrrole-2-carbaldehyde (143)

To a solution of 1H-pyrrole-2-carbaldehyde (142) (0.50 g, 5.25 mmol) in DMF (10 mL) was added NaH (0.126 g, 5.25 mmol) at 0 °C. After stirring for 20 min, chloroacetone (0.42 mL, 5.25 mmol) was added and the resulting mixture was stirred overnight at 50 °C. After the completion of the reaction, ethyl acetate (30 mL) was added and the organic phase was washed with water (3 × 50 mL) and then dried over MgSO₄. Removal of solvent gave the product 143 as white needles (0.51 g, 65%) from chloroform/hexane, mp 60-62 °C (lit. mp = 60-62 °C). 1H-NMR (400 MHz, CDCl₃) δ 8.60 (s, NH), 8.60 (d, J = 1.6 and 7.8 Hz, H6), 7.68-7.15 (m, other phenyl protons), 5.15 (m, 2H, H7); 13C-NMR (100 MHz, CDCl₃) δ 155.2, 149.4, 131.8, 131.8, 131.3, 130.4, 129.1, 128.4, 128.4, 122.8, 122.5, 121.7, 113.2, 88.5, 82.8, 57.8; IR (cm⁻¹) 3327, 3051, 2238, 1604, 1455, 1309, 1207, 1001, 744, 712; HRMS-TOF [M + H]+ Calcd for C₂₂H₁₆N₂O 325.13444, found: 325.13354.

4.19 Synthesis of 1-(prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde (144)

To a solution of 1H-pyrrole-2-carbaldehyde (142) (1.00 g, 10.5 mmol) in DMF (10 mL) was added NaH (0.27 g, 10.5 mmol) at 0 °C. After stirring for 20 min, propargyl bromide (1.17 mL, 11 mmol) was added and the resulting mixture was stirred overnight at rt. The residue was extracted with EtOAc and the organic phase was washed with water (3 × 50 mL) and then dried over MgSO₄. The crude product was purified by column chromatography eluting with hexane/EtOAc (5:1). Eluted solvent was evaporated to give 144 as a brown liquid (1.1 g, 85%).
1^H-NMR (400 MHz, CDCl₃) δ 9.50 (d, J = 0.9 Hz, H8), 7.23 (m, H5), 6.92 (dd, J = 1.7 and 4.0 Hz, H3), 6.24 (dd, J = 2.6 and 4.0 Hz, H4), 5.15 (d, J = 2.6 Hz, 2H, H6), 2.33 (t, J = 2.6 Hz, H7); 13C-NMR (100 MHz, CDCl₃) δ 179.4, 131.0, 130.4, 124.8, 110.1, 77.7, 74.5, 38.0; IR (cm⁻¹) 3202, 2919, 2851, 2161, 1587, 1488, 1471, 1259, 1224, 994, 737.

4.20 Synthesis of 2-(1-(prop-2-yn-1-yl)-1H-pyrrol-2-yl)-1H-benzo[d]imidazole (145)

Compound 144 (1.3 g, 10.0 mmol), o-phenylenediamine (91) (1.08 g, 10.0 mmol) and p-TsOH (0.34 g, 2.00 mmol) in DMF (10 mL) were reacted as described in general procedure. The resulting residue was purified by column chromatography eluting with hexane/EtOAc (10:1). Eluted solvent was evaporated to give benzimidazole 145 as a brown solid (0.6 g, 30%), mp 160-162 °C.

1^H-NMR (400 MHz, CD₂OD) δ 7.56 (br s, 2H, H8 and H11), 7.22 (m, 2H, H9 and H10), 7.15 (dd, J = 3.8 and 1.7 Hz H3), 6.81 (dd, J = 2.6 and 1.7 Hz, H5), 6.27 (m, H4), 5.43 (d, J = 2.5 Hz, 2H, H6), 2.75 (t, J = 2.5 Hz, H7); 13C-NMR (100 MHz, CD₂OD) δ 147.8, 126.6, 123.8, 123.5, 113.6, 110.0, 79.8, 74.6, 38.6; IR (cm⁻¹) 3296, 3284, 2162, 1583, 1452, 1397, 1284, 1096, 782, 729, 665; HRMS-TOF [M + H]+ Calcd for C₁₄H₁₁N₃ 222.10171, found: 222.10257.

4.21 Synthesis of 7-(4-nitrobenzylidene)-6,7-dihydrobenzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepine (122e)

Compound 120e (2.2 g, 13.7 mmol), o-phenylenediamine (91) (1.48 g, 13.7 mmol) and p-TsOH (0.47 g, 2.74 mmol) in DMF (15 mL) were reacted as described in section 4.10. The resulting residue was purified by column chromatography eluting with hexane/EtOAc (10:1). Eluted solvent was evaporated to give benzimidazo-oxazepine 122e as a pale yellow solid (1.51 g, 30%), mp 194-196 °C.
\[ ^1{\text{H}}\text{-NMR} \ (400 \text{ MHz, CDCl}_3) \delta \ 8.76 \ (d, J = 1.4 \text{ and } 8.1 \text{ Hz, H1}), \]
\[8.37 \ (d, J = 8.7 \text{ Hz, 2H, H2'} \text{ and H2''}), \ 7.93 \text{(m, H6')}, \ 7.71 \text{(d, J = 8.7 \text{ Hz, 2H, H3' and H3'''})}, \ 7.71 \text{(bs, H9')}, \ 7.45 \text{(m, H3)}, \ 7.41 \text{(m, 2H, H7' and H8'}), \ 7.28 \text{(s, H8)}, \ 7.23 \text{(t, J = 8.1 Hz, H2'),} \]
\[7.18 \text{(d, J = 8.3 Hz, H4)}, \ 4.99 \text{(s, 2H, H6');} \]
\[^{13}{\text{C}}\text{-NMR} \ (100 \text{ MHz, CDCl}_3) \delta \ 156.5, \ 147.6, \ 143.8, \ 140.3, \ 134.5, \ 132.2, \]
\[132.1, \ 130.0, \ 124.1, \ 123.9, \ 123.8, \ 123.1, \ 120.6, \ 120.2, \ 110.6, \ 68.3; \]
\[\text{IR} \ (\text{cm}^{-1}) \ 3060, \ 1597, \ 1454, \ 1310, \ 1209, \ 1022, \ 753, \ 734, \ 700, \ 683; \]
\[\text{HRMS-TOF} \ [\text{M} + \text{H}]^+ \text{ Calcd for C}_{22}\text{H}_{15}\text{N}_3\text{O}_3 \ 370.12176, \text{ found: 370.11862}.\]

4.22 Synthesis of benzof][benzo[4,5]imidazo[1,2-d][1,4]oxazepin-7(6H)-imine (122g)

Compound 120g (1.01 g, 6.3 mmol) was dissolved in DMF (10 mL). To this solution
o-phenylenediamine (91) (0.67 g, 6.3 mmol) and p-TsOH (0.24 g, 1.26 mmol) were
added at room temperature and the resulting mixture was heated at 80 ºC for 2-3 hours.
The reaction was controlled by TLC. When the reaction was finished, the solution was
cooled to room temperature. The reaction mixture was added dropwise with vigorous
stirring into a mixture of Na\textsubscript{2}CO\textsubscript{3} (1.26 mmol) and H\textsubscript{2}O (100 mL). The product was
precipitated as a free flowing solid in the solution and it was collected by filtration,
washed with H\textsubscript{2}O and dried to give benzimidazo-oxazepine 122g as a white solid (0.94
g, 60%), mp 178-180 ºC.

\[ ^1{\text{H}}\text{-NMR} \ (400 \text{ MHz, DMSO-\text{d}_6}) \delta \ 12.30 \ (\text{bs, NH}), \ 8.35 \text{(dd, J = 1.6 \text{ and } 7.6 \text{ Hz, H1}), 7.64} \text{(bs, 2H, H6' and H9'}), \ 7.57 \text{(m, H3)}, \ 7.41 \text{(qd, J = 8.3 Hz, H4)}, \ 7.26 \text{(t, J = 7.6 Hz, H2)}, \ 7.22 \]
\[(dd, J = 3.1 \text{ and } 6.0 \text{ Hz, 2H, H7'} \text{ and H8'}), \ 5.41 \text{(s, 2H, H6');} \]
\[^{13}{\text{C}}\text{-NMR} \ (100 \text{ MHz, DMSO-\text{d}_6}) \delta \ 153.5, \ 148.1, \ 134.7, \ 131.2, \ 130.4, \ 122.7, \ 122.0, \ 119.2, \ 117.4, \ 116.5, \]
\[114.6, \ 113.1, \ 53.7; \]
\[\text{IR} \ (\text{cm}^{-1}) \ 2995, \ 2882, \ 1742, \ 1580, \ 1470, \ 142, \ 1392, \ 1210, \ 1091, \ 1035, \ 746; \]
\[\text{HRMS-TOF} \ [\text{M} + \text{H}]^+ \text{ Calcd for C}_{15}\text{H}_{11}\text{N}_3\text{O} \ 250.10058, \text{ found: 250.09749}.\]
4.23 General procedure of cyclization with NaH

To a solution of benzimidazole derivative (1.51 mmol) in DMF (10 mL) was added NaH (60% suspension in oil) (0.12 g, 3.02 mmol) and the resulting mixture was stirred at room temperature overnight. After completion of the reaction (controlled by TLC), the solvent was evaporated and water (10 mL) was added into reaction vessel. The mixture was extracted with EtOAc (2 × 10 mL), and organic extracts were washed with water (5 × 20 mL) and dried over MgSO₄ and evaporated. The residue was purified by column chromatography using hexane/ethylacetate.

4.23.1 Cyclization of 121a with NaH

To a solution of benzimidazole derivative (121a) (1.0 g, 4 mmol) in DMF (10 mL) was added NaH (60% suspension in oil) (0.32 g, 8 mmol) and the resulting mixture was reacted as described in general procedure. The residue was purified by column chromatography using hexane/ethylacetate (10:1) to give 122a as a white solid (NMR ratio: 64%, isolated yield 20%, 0.19 g) (mp 176-178 ºC) and 140b as a white solid (NMR ratio: 27%, isolated yield 15%, 0.14 g) (mp 102-104 ºC).

4.23.2 Synthesis of 7-methylene-6,7-dihydrobenzo[j]benzo[4,5]imidazo[1,2-d][1,4]oxazepine (122a)

\[ \text{H-NMR (400 MHz, CDCl}_3\text{) } \delta 8.69 (d, J = 8.0 Hz, H1), 7.77 (d, J = 7.7 Hz, H9), 7.54 (d, J = 7.5 Hz, H6), 7.27 (m, 3H, H3, H7 and H8'), 7.11 (t, J = 8.0 Hz, H2), 7.03 (d, J = 8.2 Hz, H4), 5.64 (s, H8), 5.45 (s, H9), 4.73 (s, 2H, H6); \text{C-NMR (100 MHz, CDCl}_3\text{) } \delta 156.2, 149.9, 143.6, 138.1, 134.6, 132.0, 132.7, 123.4, 123.4, 122.8, 120.6, 120.0, 117.6, 111.2, 110.1, 72.7; \text{IR (cm}^{-1}\text{) } 2918, 2849, 1652, 1606, 1452, 1387, 1213, 1044, 744.\]
4.23.3 Synthesis of 6-methylbenzo/[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepine (140b)

\[ \begin{align*}
{^1H-NMR} (400 \text{ MHz, CDCl}_3) \delta & \quad 8.21 \text{ (dd, } J = 8.1 \text{ and } 1.6 \text{ Hz, H1), 7.83 \text{ (m, H9'), 7.45 \text{ (m, H3), 7.39 \text{ (m, H6'), 7.31 \text{ (m, 3H, H7', H8' and H2), 7.13 \text{ (d, } J = 8.1 \text{ Hz, H4), 6.50 \text{ (s, H7), 2.15 \text{ (s, 3H, CH}_3);}} \quad {^{13}C-NMR} (100 \text{ MHz, CDCl}_3) \delta & \quad 157.9, 150.0, 148.8, 142.7, 134.4, 132.1, 130.7, 125.5, 123.4, 123.3, 122.9, 121.3, 120.0, 109.4, 108.3, 18.4; \quad \text{IR} (\text{cm}^{-1}) 3300, 3287, 3047, 1684, 1439, 1394, 1216, 1091, 1006, 738, 622. \quad \text{HRMS-TOF [M + H]}^+ \quad \text{Calcd for C}_{16}H_{12}N_2O 249.10288, \quad \text{found: 249.10224.} \end{align*} \]

4.23.4 Cyclization of 121b with NaH

To a solution of benzimidazol derivative 121b (1.3 g, 4 mmol) in DMF (10 mL) was added NaH (60% suspension in oil) (0.32 g, 8 mmol) and the resulting mixture was reacted as described in general procedure. The residue was purified by column chromatography using hexane/ethylacetate (15:1) to give 122b\textsuperscript{95} as a white crystal (NMR ratio: 10%, isolated yield 10%, 0.13 g) (mp 166-168 °C) and 141b as a white crystal (NMR ratio: 70%, isolated yield 15%, 0.19 g) (mp 143-145 °C) from hexane/ethylacetate.

4.23.5 Synthesis of 2-bromo-7-methylene-6,7-dihydrobenzo/[f] benzo[4,5]imidazo [1,2-d][1,4] oxazepine (122b)

\[ \begin{align*}
{^1H-NMR} (400 \text{ MHz, CDCl}_3) \delta & \quad 8.95 \text{ (d, } J = 2.4 \text{ Hz, H1), 7.86 \text{ (m, H9'), 7.62 \text{ (m, H6'), 7.45 \text{ (dd, } J = 2.4 \text{ and } 8.7 \text{ Hz, H3), 7.36 \text{ (m, 2H, H7' and H8'}, 6.98 \text{ (d, } J = 8.7 \text{ Hz, H4), 5.75 \text{ (s, H8), 5.56 \text{ (s, H9), 4.73 \text{ (s, 2H, H6);}} \quad {^{13}C-NMR} (100 \text{ MHz, CDCl}_3) \delta & \quad 155.3, 148.2, 143.3, 138.1, 134.6, 134.4, 134.0, 123.9, 123.7, 122.4, 120.2, 119.2, 115.3, 111.3, 110.6, 72.6; \quad \text{IR} (\text{cm}^{-1}) 3062, 2986, 2914, 1490, 1444, 1409, 1309, 1007, 812, 726, 704. \end{align*} \]
4.23.6 Synthesis of 2-bromo-6-methylbenzo[\f]benzo[4,5]imidazo[1,2-d][1,4] oxazepine (141b)

\[ \text{\H-NMR (400 MHz, CDCl}_3 \text{) } \delta 8.36 (\text{d, } J = 2.5 \text{ Hz, H1}), 7.83 (\text{m, H9'}), 7.45 (\text{dd, } J = 2.5 \text{ and } 8.6 \text{ Hz, H3}), 7.40 (\text{m, H6'}), 7.35 (\text{m, 2H, H7' and H8'}), 7.01 (\text{d, } J = 8.6 \text{ Hz, H4}), 6.50 (\text{d, } J = 0.9 \text{ Hz, H7}), 2.14 (\text{d, } J = 0.9 \text{ Hz, 3H, CH}_3); \text{\C-NMR (100 MHz, CDCl}_3 \text{) } \delta 156.2, 148.6, 142.4, 134.8, 134.3, 133.0, 124.5, 123.8, 123.6, 123.0, 120.2, 118.3, 109.5, 108.3, 18.4; \text{ IR (cm}^{-1}\text{)} 3300, 3287, 3047, 1704, 1521, 1427, 1333, 1221, 1197, 931, 727, 715. \text{ HRMS-TOF [M + H]+ Calcd for C}_{16}\text{H}_{11}\text{BrN}_2\text{O 327.01481, found: 327.01275.} \]

4.23.7 Cyclization of 121c with NaH

1. To a solution of benzimidazole derivative 121c (1.1 g, 4 mmol) in DMF (10 mL) was added NaH (60% suspension in oil) (0.32 g, 8 mmol) and the resulting mixture was reacted as described in general procedure. The residue was purified by column chromatography using hexane/ethylacetate (15:1) to give 122c\textsuperscript{05} as a pale yellow solid, mp 164-166 °C (NMR ratio: 40%, isolated yield 30%, 0.32 g), 135a as a pale yellow solid (NMR ratio: 20%, isolated yield 10%, 0.10 g), and 135b as white solid (NMR ratio: 40%).

2. To a solution of benzimidazole derivative 121c (1.1 g, 4 mmol) in DMF (10 mL) was added NaH (60% suspension in oil) (0.32 g, 8 mmol) and the resulting mixture was heated to 85 °C and stirred over night to afford 135b (NMR ratio: 50%) and 123c (NMR ratio: 50%) as white solid mixture.

4.23.8 Synthesis of 4-methoxy-7-methylene-6,7-dihydrobenzo[\f]benzo[4,5] imidazo[1,2-d][1,4] oxazepine (122c) and 4-methoxy-6-methylene-6,7-dihydrobenzo [\f]benzo [4,5] imidazo[1,2-d][1,4]oxazepine (135a)
\[ ^1\text{H-NMR} \quad (400 \text{ MHz, CDCl}_3) \quad \delta \quad 8.28 \text{ (dd, } J = 8.1 \text{ and 1.5 Hz, } H1), \quad 7.85 \text{ (m, } H9'), \quad 7.61 \text{ (m, } H6), \quad 7.34 \text{ (m, 2H, } H8' \text{ and } H7), \quad 7.14 \text{ (t, } J = 8.1 \text{ Hz, } H2), \quad 7.03 \text{ (dd, } J = 8.1 \text{ and 1.5 Hz, } H3), \quad 5.69 \text{ (s, } H8), \quad 5.52 \text{ (s, } H9), \quad 4.93 \text{ (s, 2H, } H6), \quad 3.94 \text{ (s, 3H, OCH}_3); \quad ^{13}\text{C-NMR} \quad (100 \text{ MHz, CDCl}_3) \quad \delta \quad 150.8, \quad 149.7, \quad 146.4, \quad 143.2, \quad 138.4, \quad 134.6, \quad 123.6, \quad 123.4, \quad 123.1, \quad 122.8, \quad 119.3, \quad 120.1, \quad 113.1, \quad 111.2, \quad 110.3, \quad 73.6, \quad 56.3. \]

\[ ^1\text{H-NMR} \quad (400 \text{ MHz, CDCl}_3) \quad \delta \quad 7.87 \text{ (m, } H9'), \quad 7.72 \text{ (dd, } J = 8.0 \text{ Hz, } H1), \quad 7.42 \text{ (m, } H6'), \quad 7.34 \text{ (m, 2H, } H8' \text{ and } H7'), \quad 7.25 \text{ (t, } J = 8.0 \text{ Hz, } H2), \quad 7.10 \text{ (dd, } J = 8.0 \text{ and 1.4 Hz, } H3), \quad 4.87 \text{ (d, } J = 1.8 \text{ Hz, } H8), \quad 4.81 \text{ (bs, 2H, } H7), \quad 4.59 \text{ (d, } J = 1.8 \text{ Hz, } H9), \quad 3.95 \text{ (s, 3H, OCH}_3); \quad ^{13}\text{C-NMR} \quad (100 \text{ MHz, CDCl}_3) \quad \delta \quad 156.7, \quad 151.9, \quad 150.3, \quad 142.1, \quad 141.6, \quad 134.1, \quad 124.6, \quad 123.1, \quad 122.8, \quad 122.2, \quad 121.6, \quad 120.1, \quad 114.4, \quad 108.6, \quad 94.2, \quad 55.9, \quad 44.7; \quad \text{IR (cm}^{-1}) \quad 3009, \quad 2834, \quad 1658, \quad 1578, \quad 1525, \quad 1478, \quad 1435, \quad 1235, \quad 1048, \quad 851, \quad 744, \quad 732. \]

**4.23.9 Synthesis of 4-methoxy-6-methylbenzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepine and 4-methoxy-7-methylbenzo[f]benzo[4,5]imidazo[1,2-d][1,4]oxazepine (135b and 123c)**

\[ ^1\text{H-NMR} \quad (400 \text{ MHz, CDCl}_3) \quad \delta \quad 7.92 \text{ (m, } H1), \quad 7.81, \quad 7.58, \quad 7.40 \text{ (m, } H8' \text{ and } H7'), \quad 7.35 \text{ (m, } H6' \text{ and } H9) \quad 7.26 \text{ (m, } H2), \quad 7.09 \text{ (m, } H3), \quad 6.61, \quad 6.55 \text{ (bd, } H6 \text{ and } H7'), \quad 2.28 \text{ (d, } J = 0.8 \text{ Hz, CH}_3), \quad 2.20 \text{ (d, } J = 1.4 \text{ Hz, CH}_3); \quad ^{13}\text{C-NMR} \quad (100 \text{ MHz, CDCl}_3) \quad \delta \quad 151.4, \quad 151.1, \quad 150.7, \quad 150.1, \quad 149.3, \quad 149.1, \quad 147.3, \quad 141.9, \quad 140.1, \quad 137.6, \quad 133.7, \quad 133.6, \quad 125.9, \quad 125.6, \quad 125.5, \quad 124.1, \quad 124.0, \quad 123.6, \quad 123.5, \quad 123.0, \quad 122.1, \quad 121.9, \quad 115.3, \quad 114.8, \quad 112.9, \quad 109.8, \quad 108.8, \quad 56.3, \quad 56.3, \quad 18.4, \quad 14.9; \quad \text{IR (cm}^{-1}) \quad 2923, \quad 1679, \quad 1519, \quad 1480, \quad 1436, \quad 1267, \quad 1208, \quad 1172, \quad 1049, \quad 739; \quad \text{HRMS-TOF [M + H]}^+ \quad \text{Caled for } C_{17}H_{14}N_2O_2 \quad 279.11541, \quad \text{found: 279.11280.} \]
4.23.10 Cyclization of 121d with NaH

To a solution of benzimidazole derivative 121d (1.05 g, 4 mmol) in DMF (10 mL) was added NaH (60% suspension in oil) (0.32 g, 8 mmol) and the resulting mixture was reacted as described in general procedure. The residue was purified by column chromatography using hexane/ethylacetate (20:1) to give 122d-E as white crystals (NMR ratio: 50%, isolated yield 10%, 0.12 g) (mp 194-196 °C) from hexane/ethylacetate and 122d-Z as a pale yellow solid (NMR ratio: 50%).

\[\text{H-NMR (400 MHz, CDCl}_3\right) \delta 8.63 \text{ (dd, } J = 8.0 \text{ and } 1.6 \text{ Hz, H1), 7.82 \text{ (d, } J = 8.0 \text{ Hz, H9'), 7.42 \text{ (m, H3), 7.20 \text{ (m, 2H, H7 and H8'), 7.12 \text{ (m, 4H, H10, H11, H6'), 6.97 \text{ (m, 3H, H2 and H9), 6.82 \text{ (s, H8), 6.66 \text{ (d, } J = 8.2 \text{ Hz, H4), 5.12 \text{ (bs, 1H, H6), 4.67 \text{ (bs, 1H, H6); 13C-NMR (100 MHz, CDCl}_3\right) \delta 155.4, 150.5, 143.5, 133.1, 132.5, 132.0, 129.3, 129.0, 128.8, 128.5, 127.4, 123.0, 122.8, 122.4, 120.8, 119.7, 116.9, 112.2, 99.8, 74.7; IR (cm}^{-1}\right) 3202, 2919, 2851, 1587, 1488, 1471, 1259, 1224, 994, 737 \text{ HRMS-TOF [M + H]+ Calcd for C}_22\text{H}_{16}\text{N}_2\text{O 325.13392, found: 325.13354.}}

\[\text{H-NMR (400 MHz, CDCl}_3\right) \delta 8.69 \text{ (dd, } J = 8.1 \text{ and } 1.6 \text{ Hz, H1), 7.88 \text{ (m, H9'), 7.71 \text{ (m, H6'), 7.50-7.39 \text{ (m, 5H, H9, H10, H11), 7.41 \text{ (m, H3) 7.36 \text{ (m, 2H, H7 and H8'), 7.22 \text{ (s, H8), 7.19 \text{ (m, 2H, H2 and H4), 5.03 \text{ (s, 2H, H6); 13C-NMR (100 MHz, CDCl}_3\right) \delta 156.1, 150.5, 143.6, 134.6, 133.8, 131.9, 131.8, 131.7, 129.1, 128.8, 128.6, 127.3, 123.3, 122.7, 120.7, 120.1, 117.6, 110.7, 68.8.}}


To a solution of benzimidazole derivative 145 (1.1 g, 5 mmol) in DMF (10 mL) was added NaH (60% suspension in oil) (0.4 g, 10 mmol) and the resulting mixture was reacted as described in general procedure. The residue was purified by column chromatography using hexane/ethylacetate (3:1) to give 146 as a brown crystal
(isolated yield: 92%, 1.02 g) from hexane/ethylacetate, (mp 147-149 °C). (lit. mp = 158 °C\textsuperscript{103}).

\begin{align*}
{\text{\textsuperscript{1}H-NMR}} (400 \text{ MHz, CD}_3\text{OD}) & \delta 7.91 (m, 2H, H9' and H6'), 7.41 (td, J = 7.4 and 1.0 Hz, H8'), 7.37 (bs, H5), 7.30 (td, J = 1.0 and 7.4 Hz, H7'), 7.23 (dd, J = 1.3 and 2.5 Hz, H3), 7.14 (bs, H1), 6.71 (dd, J = 2.5 and 4.0 Hz, H2) 2.86 (d, J = 1.1 Hz, 3H, CH₃);

{\text{\textsuperscript{13}C-NMR}} (100 \text{ MHz, CD}_3\text{OD}) & \delta 144.0, 143.0, 131.1, 124.0, 122.0, 120.6, 120.2, 119.4, 117.2, 112.7, 109.9, 106.2, 17.7; \text{IR (cm}^{-1}) 3103, 1614, 1566, 1501, 1445, 1354, 1269, 1223, 1073, 737.
\end{align*}
REFERENCES


Figure 51. $^1$H-NMR spectrum of compound 37
Figure 52. $^{13}$C-NMR spectrum of compound 37

Figure 53. IR spectrum of compound 37
Figure 54. $^1$H-NMR spectrum of compound 59

Figure 55. $^{13}$C-NMR spectrum of compound 59
Figure 56. IR spectrum of compound 59

Figure 57. $^1$H-NMR spectrum of compound 40
Figure 58. $^{13}$C-NMR spectrum of compound 40

Figure 59. IR spectrum of compound 40
Figure 60. $^1$H-NMR spectrum of compound 38

Figure 61. $^{13}$C-NMR spectrum of compound 38
Figure 62. IR spectrum of compound 38

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

Figure 65. IR spectrum of compound 63
Figure 66. $^1$H-NMR spectrum of compound 41

Figure 67. $^{13}$C-NMR spectrum of compound 41
Figure 68. IR spectrum of compound 41

Figure 69. $^1$H-NMR spectrum of compound 70
Figure 70. $^{13}$C-NMR spectrum of compound 70

Figure 71. IR spectrum of compound 70
Figure 72. $^1$H-NMR spectrum of compound 42a

Figure 73. $^{13}$C-NMR spectrum of compound 42a
Figure 74. IR spectrum of compound 42a

Figure 75. $^1$H-NMR spectrum of compound 42b
Figure 76. $^{13}$C-NMR spectrum of compound 42b

Figure 77. IR spectrum of compound 42b
**Figure 78.** $^1$H-NMR spectrum of compound $42c$

**Figure 79.** $^{13}$C-NMR spectrum of compound $42c$
Figure 80. IR spectrum of compound 42c

Figure 81. $^1$H-NMR spectrum of compound 45a
Figure 82. $^{13}$C-NMR spectrum of compound 45a

Figure 83. IR spectrum of compound 45a
Figure 84. $^1$H-NMR spectrum of compound 45b

Figure 85. $^{13}$C-NMR spectrum of compound 45b
Figure 86. IR spectrum of compound 45b

Figure 87. $^1$H-NMR spectrum of compound 45c
Figure 88. $^{13}$C-NMR spectrum of compound 45c

Figure 89 IR spectrum of compound 45c
Figure 90. $^1$H-NMR spectrum of compound 74

Figure 91. $^{13}$C-NMR spectrum of compound 74
Figure 92. IR spectrum of compound 74

Figure 93. $^1$H-NMR spectrum of compound 43a
Figure 94. $^{13}$C-NMR spectrum of compound 43a

Figure 95. IR spectrum of compound 43a
Figure 96. $^1$H-NMR spectrum of compound 44

Figure 97. IR spectrum of compound 44
Figure 98. $^1$H-NMR spectrum of compound 43b

Figure 99. $^{13}$C-NMR spectrum of compound 43b
Figure 100. IR spectrum of compound 43b

Figure 101. $^1$H-NMR spectrum of compound 43c
Figure 102. $^{13}$C-NMR spectrum of compound 43c

Figure 103. IR spectrum of compound 43c
Figure 104. $^1$H-NMR spectrum of compound 46a

Figure 105. $^{13}$C-NMR spectrum of compound 46a
Figure 106. IR spectrum of compound 46a

Figure 107. $^1$H-NMR spectrum of compound 47
Figure 108. $^{13}$C-NMR spectrum of compound 47

Figure 109. HMBC spectrum of compound 47
Figure 110. HSQC spectrum of compound 47

Figure 111. IR spectrum of compound 47
Figure 112. $^1$H-NMR spectrum of compound 46b

Figure 113. $^{13}$C-NMR spectrum of compound 46b
Figure 114. IR spectrum of compound 46b

Figure 115. $^1$H-NMR spectrum of compound 46c
Figure 116. $^{13}$C-NMR spectrum of compound 46c

Figure 117. IR spectrum of compound 46c
Figure 118. $^1$H-NMR spectrum of compound 116

Figure 119. $^{13}$C-NMR spectrum of compound 116
Figure 120. IR spectrum of compound 116

Figure 121. $^1$H-NMR spectrum of compound 129
**Figure 122.** $^{13}$C-NMR spectrum of compound 129

**Figure 123.** IR spectrum of compound 129
Figure 124. $^1$H-NMR spectrum of compound 117

Figure 125. $^{13}$C-NMR spectrum of compound 117
Figure 126. IR spectrum of compound 117

Figure 127. $^1$H-NMR spectrum of compound 118
Figure 128. $^{13}$C-NMR spectrum of compound 118

Figure 129. IR spectrum of compound 118
Figure 130. $^1$H-NMR spectrum of compound 120a

Figure 131. $^{13}$C-NMR spectrum of compound 120a
Figure 132. IR spectrum of compound 120a

Figure 133. $^1$H-NMR spectrum of compound 120b
Figure 134. $^{13}$C-NMR spectrum of compound 120b

Figure 135. IR spectrum of compound 120b
Figure 136. $^1$H-NMR spectrum of compound 120c

Figure 137. $^{13}$C-NMR spectrum of compound 120c
Figure 138. IR spectrum of compound 120c

Figure 139. $^1$H-NMR spectrum of compound 120f
Figure 140. $^{13}$C-NMR spectrum of compound 120f

Figure 141. $^1$H-NMR spectrum of compound 120g
Figure 142. $^{13}$C-NMR spectrum of compound 120g

Figure 143. IR spectrum of compound 120g
Figure 144. $^1$H-NMR spectrum of compound 120d

Figure 145. $^{13}$C-NMR spectrum of compound 120d
Figure 146. IR spectrum of compound 120d

Figure 147. $^1$H-NMR spectrum of compound 120e
Figure 148. $^{13}$C-NMR spectrum of compound 120e

Figure 149. IR spectrum of compound 120e
Figure 150. $^1$H-NMR spectrum of compound 121a

Figure 151. $^{13}$C-NMR spectrum of compound 121a
Figure 152. IR spectrum of compound 121a

Figure 153. $^1$H-NMR spectrum of compound 121b
Figure 154. $^{13}$C-NMR spectrum of compound 121b

Figure 155. IR spectrum of compound 121b
Figure 156. $^1$H-NMR spectrum of compound 121c

Figure 157. $^{13}$C-NMR spectrum of compound 121c
Figure 158. IR spectrum of compound 121c

Figure 159. $^1$H-NMR spectrum of compound 121f
Figure 160. $^{13}$C-NMR spectrum of compound 121f

Figure 161. IR spectrum of compound 121f
Figure 162. $^1$H-NMR spectrum of compound 121d

Figure 163. $^{13}$C-NMR spectrum of compound 121d
Figure 164. IR spectrum of compound 121d

Figure 165. $^1$H-NMR spectrum of compound 143
Figure 166. $^{13}$C-NMR spectrum of compound 143

Figure 167. $^1$H-NMR spectrum of compound 144
Figure 168. $^{13}$C-NMR spectrum of compound 144

Figure 169. IR spectrum of compound 144
Figure 170. $^1$H-NMR spectrum of compound 145

Figure 171. $^{13}$C-NMR spectrum of compound 145
Figure 172. IR spectrum of compound 145

Figure 173. $^1$H-NMR spectrum of compound 122e
Figure 174. $^{13}$C-NMR spectrum of compound 122e

Figure 175. IR spectrum of compound 122e
Figure 176. $^1$H-NMR spectrum of compound 122g

Figure 177. $^{13}$C-NMR spectrum of compound 122g
Figure 178. IR spectrum of compound 122g

Figure 179. $^1$H-NMR spectrum of compound 122a
**Figure 180.** $^{13}$C-NMR spectrum of compound 122a

**Figure 181.** IR spectrum of compound 122a
Figure 182. $^1$H-NMR spectrum of compound 140b

Figure 183. $^{13}$C-NMR spectrum of compound 140b
Figure 184. IR spectrum of compound 140b

Figure 185. $^1$H-NMR spectrum of compound 122b
Figure 186. $^{13}$C-NMR spectrum of compound 122b

Figure 187. IR spectrum of compound 122b
Figure 188. $^1$H-NMR spectrum of compound 141b

Figure 189. $^{13}$C-NMR spectrum of compound 141b
Figure 190. IR spectrum of compound 141b

Figure 191. $^1$H-NMR spectrum of compound 122c
Figure 192. $^{13}$C-NMR spectrum of compound 122c

Figure 193. $^1$H-NMR spectrum of compound 135a
Figure 194. $^{13}$C-NMR spectrum of compound 135a

Figure 195. IR spectrum of compound 135a
Figure 196. $^1\text{H}$-NMR spectrum of compound 123c and 135b

Figure 197. $^{13}\text{C}$-NMR spectrum of compound 123c and 135b
Figure 198. IR spectrum of compound 123c and 135b

Figure 199. $^1$H-NMR spectrum of compound 122d-Z
Figure 200. $^{13}$C-NMR spectrum of compound 122d-Z

Figure 201. $^1$H-NMR spectrum of compound 122d-E
Figure 202. $^{13}$C-NMR spectrum of compound 122d-E

Figure 203. $^1$H-NMR spectrum of compound 146
Figure 204. $^{13}$C-NMR spectrum of compound 146

Figure 205. IR spectrum of compound 146
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TUBITAK-SAGE-Ankara

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