BASE-PROMOTED SYNTHESIS OF NEW DIAZEPINE DERIVATIVES VIA ALKYNE CYCLIZATION

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ABSTRACT

BASE-PROMOTED SYNTHESIS OF NEW DIAZEPINE DERIVATIVES VIA ALKYNE CYCLIZATION

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A new methodology was developed for the synthesis of dipyrromethane and diazepine derivatives. In the first section of this thesis, synthesis of various dipyrromethanes from aromatic aldehydes was carried out. Dipyrromethanes were used as starting materials for the next step. In the second part of the study, introduction of a propargyl group to nitrogen atom to one of pyrrole units of dipyrromethane gave the expected mono-propargylated compounds which were the key compounds for further cyclization reactions. Base-supported cyclization resulted in the formation of the target compounds, new diazepine derivatives, via metal-free 7-exo-dig cyclization.

Keywords: Pyrrole, dipyrromethane, diazepine, alkyne cyclization
DIAZEPİN TÜREVLERİNİN BAZ DESTEKLİ ALKİN SİKLİZASYONU İLE SENETEZİ

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CHAPTER 1

INTRODUCTION

1.1 Pyrrole

Pyrrole (1) is a five-membered heterocyclic compound having four sp$^2$ hybridized carbon atoms and also one sp$^2$ hybridized nitrogen atom. The lone pair electrons of nitrogen are delocalized over the ring and contribute to the aromaticity.$^1$

\[ \text{Pyrrole} \]

Resonance structures of pyrrole are shown below (Scheme 1).$^1$

\[ \text{Scheme 1. Resonance structure of pyrrole} \]

Pyrroles are the one of the most significant molecule among heterocyclic compounds due to their current biological and pharmacological properties.$^2$ Many pyrrole derivatives show attracted biological properties for instance antibacterial,$^3$ antiinflammatory,$^4$ antioxidant,$^5$ antifungal,$^6$ and immune suppressant activities.$^7$ Pyrrole is quitey functionalized subunit of chlorophyll a (2), heme (3), ningalin A (4) and pyrrole alkaloids isolated from marine resource.$^8$
Atorvastatin (Lipitor) (5) is one of the example of pyrrole derived drugs and used to decrease cholesterol.⁹
1.2 Dipyrrromethanes

Dipyrrromethane is a heterocyclic compound in which two pyrroles are connected from the α-positions to a single sp\(^3\) hybridized carbon atom. Dipyrrromethane is called as β-substituted dipyrrromethane if the beta position(s) of pyrroles are substituted. Whereas, when the beta position(s) of pyrrole is lack of any substituent, dipyrrromethane is called as meso-substituted dipyrrromethane (Scheme 2).\(^{10}\)

![Scheme 2. Naming of dipyrrromethanes](image)

1.2.1. Importance of meso-substituted dipyrrromethane derivatives

Dipyrrromethanes substituted at C-5 position are significant initiator for the synthesis of meso-substituted porphyrins,\(^{11}\) corroles and porphyrins.\(^{12}\) Meso-porphyrin derivatives have implementation in phototherapeutics,\(^{13}\) biological processes,\(^{14}\) optoelectronics,\(^{15}\) catalysis,\(^{16}\) and material chemistry.\(^{17}\)

Two compounds have been approved for PDT (photo dynamic therapy) cancer treatment: porfimer (photofrin) (6) and foscan (7).\(^{18}\) Iron(III) complex of an amphipolar corrole (8) has been revealed to be a very potent catalytic antioxidant (Scheme 3).\(^{19}\)
Some dipyrromethane derivatives

1.2.2 Synthesis of dipyrromethanes

Lately, many procedure have been reported for the synthesis of dipyrromethanes.\textsuperscript{20} Most of the procedure include the condensation of an aldehyde and pyrrole in the presence of several acids like BF\textsubscript{3}•etherate, trifluoroacetic acid (TFA), propionic acid and p-toluenesulfonic acid. The purification of the dipyrromethanes is complicated because of oligomeric compounds which forms in the reaction media.\textsuperscript{21} Singh and co-workers reported solvent-free condensation of electron rich heterocycles with a variety of aldehydes using Amberlyst 15 catalyst. The condensations of pyrrole (1) with aldehydes (9) are catalyzed with Amberlyst 15 to afford corresponding dipyrromethane derivatives (10) (Scheme 4).\textsuperscript{22}
Temelli and Unaleroğlu developed a new synthetic method for the synthesis of dipyrromethanes substituted at C-5 position from the reaction of pyrrole and N-tosyl imine \( \text{11} \) in the presence of metal triflates (Scheme 5).\(^{21}\)

\[
\text{1} + \text{11} \xrightarrow{10\% \text{M(OTf)}_x} \text{12} + \text{13}
\]

\( M = \text{Cu, Gd} \)

\( R = \text{H, 4-CH}_3\text{O, 2-CH}_3\text{O, 4-CH}_3, 2-\text{OH, 4-NO}_2, 4-\text{CF}_3, 4-\text{F, 4-Cl, 4-Br} \)

**Scheme 5.** Synthesis of dipyrromethane by using metal triflate

Littler and co-workers developed a condensation reaction of an aldehyde with neat excess pyrrole catalyzed by TFA, followed by bulb-to-bulb distillation to remove oligomeric material and recrystallization to remove the N-confused dipyrromethane (Scheme 6).\(^{23}\)

\[
\text{1} + \text{PhCHO} \xrightarrow{1. \text{TFA (0.1 eq)}} \text{15} + \text{16} + \text{17}
\]

**Scheme 6.** Synthesis of dipyrromethane by using TFA
1.3. 1,4-Diazepines

Diazepine is a nitrogen containing, seven-membered heterocyclic structure. The ring numbering and nomenclature for some 1,4-diazepines are given below.

\[ \text{1H-1,4-Diazepine} \quad 18 \]
\[ 2H-1,4-Diazepine \quad 19 \]
\[ 6H-1,4-Diazepine \quad 20 \]
\[ 1H-2,3-Dihydro-1,4-Diazepine \quad 21 \]

1.3.1 Importance of 1,4-diazepines derivatives

Diazepine derivatives demonstrate a range of clinically important properties. Especially, benzodiazepines are used to treat anxiety disorders. They act on the central nervous system to produce a calming effect.

Clozapine (22) is an effective drug in decreasing psychopathology, improving some aspects of cognition, improving quality of life, decreasing hospitalisation, and decreasing suicide attempts and completions.\(^{25}\) Lorazepam (23) is used to treat irritable bowel syndrome, epilepsy, insomnia and to control tension caused by alcohol withdrawal. The compound causes slowing activity in the brain and allow for relaxation.\(^{26}\) Diazepam (24) is used to treat anxiety, acute alcohol withdrawal and seizures. It also used to relieve muscle spasm (Scheme 7).\(^{27}\)

\[ \text{Clozapine} \quad 22 \]
\[ \text{Lorazepam} \quad 23 \]
\[ \text{Diazepam} \quad 24 \]

Scheme 7. Some diazepine drugs
1.4. Base supported alkyne cyclization reactions

The ability to perform the key carbon-heteroatom bond formation step which transforms an acyclic precursor into the desired cyclic is a critical process to construct heterocycles. Particularly, forming a nitrogen functionality-alkyne bond via metal-free intramolecular cyclization is a precious synthetic strategy. It should be mentioned that a compact set of standards, known as ‘the Baldwin rules’, has been proven to be a useful tool for assessment the feasibility of ring closure reactions. Baldwin identified the cyclization processes in terms of three factors: (1) the ring size being formed (a numerical prefix); (2) the geometry of carbon atom undergoing the ring-forming reaction (sp = diagonal, sp\(^2\) = trigonal, and sp\(^3\) = tetrahedral); (3) the pattern of the breaking bond (exo, the breaking bond is outside of the formed ring, and endo, the breaking bond is inside of the new ring). (Scheme 8)

![Diagrams of ring closure for 6- and 7-membered rings](image)

**Scheme 8.** Patterns of ring closure for 6- and 7-membered rings

There are too many examples of metal-free alkyne cyclization reactions in literature. Balci and coworkers\(^30\) reported the formation of trizapine skeletons 27 via 7-exo-dig cyclization (Scheme 9).

---

7
Scheme 9. Metal-free 7-exo-dig cyclization reaction of product 25

Basceken and Balci\textsuperscript{31} reported the formation of 6-exo-dig cyclization product 29 starting from compound 28 by using NaH in DMF (Scheme 10).

Scheme 10. 6-exo-dig cyclization reaction of compound 29

Nagao et al. showed KOH-mediated cycloisomerization of propargylamides 30 into 4-carboxylated oxazoles 31\textsuperscript{32} (Scheme 11).

Scheme 11. Cycloisomerization of propargylamides 30

1.5. Aim of the study

This study focused on the synthesis of pyrrole-fused 1,4-diazepine derivatives 36 starting from dipyrromethane derivatives 34 by using base-supported reaction. Our aim was first to improve the methodology for the synthesis of dipyrromethane derivatives (34) and then control the propargylation step to get mono-propargylated products 35. Finally, we target to obtain 1,4 diazepine derivatives from mono-propargylated products via NaH as a base (Scheme 12).
Scheme 12. Synthesis of diazepines 36
CHAPTER 2

RESULTS AND DISCUSSION

2.1. Synthesis of compounds 38 and 40

Firstly, Vilsmeier Haack reaction\textsuperscript{33} was used to get pyrrole carbaldehyde 37. Pyrrole (1) was reacted with POCl\textsubscript{3} and DMF in dry ether at 0 °C. In order to get basic medium, the solution of NaHCO\textsubscript{3} was used and compound 37 was gained. Afterwards, pyrrole-2-carbaldehyde (37) in dry DMF was firstly reacted with NaH at 0 °C and then, solution of propargyl bromide in dry DMF was added to the reaction media to obtain compound 38 (Scheme 13).\textsuperscript{34, 35}

![Scheme 13. Synthesis of compound 38](image)

Structure 40 was synthesized in 97% yield from the reaction of indolecarbaldehyde 39, propargyl bromide and NaH at room temperature. After deprotonation of NH-proton with base, anionic nitrogen is formed. Then, anionic nitrogen attack propargyl bromide to generate structure 40 (Scheme 14).\textsuperscript{36}

![Scheme 14. Synthesis of structure 40](image)
2.2. Synthesis of 2-[phenyl(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41a) and other starting compounds (41b-i)

For the synthesis of 2-[phenyl(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41a), several methods were applied and the most appropriate one was modified and used for the synthesis of other derivatives 41b-i. According to the first procedure, excess pyrrole (1) and benzaldehyde (14) (40:1) were reacted at room temperature in the presence of TFA (0.1 equiv) as a catalyst for 15 minutes to obtain 2-[phenyl(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41a). Because of the fact that excess pyrrole usage was waste of resources and led to the formation of oligomers, the method was not preferred (Scheme 15).

![Scheme 15. Synthesis of 5-phenyldipyrromethane 41a by using THF](image)

As reported by second procedure, mixing Amberlyst 15 ion exchange resin with pyrrole and benzaldehyde resulted in the formation of 2-[phenyl(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41a) in the absence of solvent in 30% yield after 1 hour and in 35% yield after 4 hours (Scheme 14). Due to low efficiency, this method was also not preferred (Scheme 16).

![Scheme 16. Synthesis of 41a by using Amberlyst 15](image)

The most appropriate procedure was applied for the synthesis of all starting compounds (41a-i) in high yields. The procedure published by Temelli and Unaleroglu where metal triflates were replaced by 0.18 M HCl, was used as an acid
to catalyzed reaction of pyrrole and benzaldehyde at the room temperature to get 2-[phenyl(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41a). Then, for testing scope of further reactions, additional derivatives 41b-i were synthesized (Scheme 17).

![Scheme 17](attachment:image.png)

The characterization of compounds 41a-i was done by using $^1$H-NMR and $^{13}$C-NMR spectra. The NH protons of structure 41a resonate at 7.88 ppm as broad singlet and the multiplet signals of protons belong phenyl group appear between 7.22-7.35 ppm as multiplet. In addition, the protons attached to C-4 position of pyrroles resonate at 6.14 ppm and the signal was split into doublet of doublets with coupling constants of $J = 5.9$ Hz and $J = 2.8$ Hz arising from the coupling with protons attached to the C-3 and C-5 carbon atoms of pyrrole (Figure 1).
2.3. Proposed mechanism for the formation of starting materials (41a-i)

Formation of the products 41a-i can be visualized through the mechanism proposed in Scheme 18. Thus, initial reaction of pyrrole with carbonyl substrate, activated through protonation by HCl, leads to the adduct 44a-i obtained from initially formed 43a-i. Similar nucleophilic attack of the C-2 position of pyrrole to the intermediate 45a-i results in the formation of adduct 46a-i which furnish products 41a-i after deprotonation.

Scheme 18. Proposed mechanism for the formation of dipyrrmethanes
2.4. Propargylation reaction of starting materials 41a, d-h

Propargylation reaction of starting materials was required for the synthesis of 47a and 47d-h which are key compounds for the final cyclization reactions (Scheme 19). According to the literature procedure,\textsuperscript{34} in the first try, 41a was reacted first with NaH in the presence of DMF and then a solution of propargyl bromide in dry DMF was added dropwise to the reaction media at 0 °C to obtain 47a and 48a. Because of the fact that, the yield of 47a (16%) was very low compared to the yield of 48a (45%), an alternative procedure was applied to increase the yields of desired mono-propargylated compounds 47a, d-h. According to the new procedure, after addition of propargyl bromide in dry DMF to the reaction mixture, NaH was added piecewise to the reaction media. As a result, yields of 47a was increased enormously.

Scheme 19. Propargylation reaction of dipyrrromethane derivatives
<table>
<thead>
<tr>
<th>Starting Compounds</th>
<th>Mono- Propargylated Products</th>
<th>Di- Propargylated Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="41a" alt="Image" /></td>
<td><img src="47a" alt="Image" /> 55%</td>
<td><img src="48a" alt="Image" /> 22%</td>
</tr>
<tr>
<td><img src="41d" alt="Image" /></td>
<td><img src="47d" alt="Image" /> 48%</td>
<td><img src="48d" alt="Image" /> 24%</td>
</tr>
<tr>
<td><img src="41e" alt="Image" /></td>
<td><img src="47e" alt="Image" /> 44%</td>
<td><img src="48e" alt="Image" /> 18%</td>
</tr>
<tr>
<td><img src="41f" alt="Image" /></td>
<td><img src="47f" alt="Image" /> 45%</td>
<td><img src="48f" alt="Image" /> 33%</td>
</tr>
<tr>
<td><img src="41g" alt="Image" /></td>
<td><img src="47g" alt="Image" /> 51%</td>
<td><img src="48g" alt="Image" /> 24%</td>
</tr>
<tr>
<td><img src="41h" alt="Image" /></td>
<td><img src="47h" alt="Image" /> 40%</td>
<td><img src="48h" alt="Image" /> 25%</td>
</tr>
</tbody>
</table>
Characterization of compound 47a and 48a was achieved by using $^1$H-NMR and $^{13}$C-NMR spectra. In the $^1$H-NMR spectrum of compound 47a the NH proton of pyrrole unit resonates at 7.91 ppm as a broad singlet and the terminal alkyne proton resonates at 2.36 ppm as triplet. This terminal alkyne proton can couple with CH$_2$ proton with a coupling constant of $J = 2.5$ Hz. Also, CH$_2$ protons appear as a doublet of doublets ($J = 1.6$ Hz and $J = 2.5$ Hz) at 4.39 ppm as shown in (Figure 2).

![Figure 2: $^1$H-NMR Spectrum of compound 47a in CDCl$_3$](image)

As one can see from the Figure 3, in the NMR spectrum of 48a there are no proton resonance arising from the NH-protons clearly indicating the attachment of two propargyl groups to the nitrogen atoms. Furthermore, the observed symmetry in the $^1$H- as well as in the $^{13}$C-NMR spectra also supports the symmetrical structure. The methylene protons are diastereotopic and they give rise to an AB-system with further splitting with the alkyne proton ($^4J = 2.5$ Hz). A-part of AB-system resonates at 4.36 – 4.35 ppm, whereas the B-part of AB-system appear at 4.32 – 4.27 ppm. The main coupling of the AB-system arising from the coupling of diastereotopic protons was measured as $J = 14.0$ Hz which is in the expected range. The high field signal at 2.33
ppm belongs to terminal alkyne protons and split into triplet with a coupling constant of $J=2.5$ Hz.

Figure 3: $^1$H-NMR Spectrum of compound 48a in CDCl$_3$

2.5. Cyclization reaction of mono-propargylated compound 47a

Reaction of mono-propargylated compounds 47a with AuCl$_3$ in the presence of acetonitrile was the first attempt to obtain diazepine derivative 49a. This reaction was carried out at room temperature as well as at reflux temperature. Unfortunately, the desired diazepine derivative 49a could not be obtained under these conditions. The starting material 47a was recovered, (Scheme 20).

Scheme 20. Reaction between compound 47a with AuCl$_3$
On the other hand, the intramolecular cyclization reactions of compounds 47a, d-g and 41b-c with NaH in DMF at room temperature afforded diazepine derivatives 49a-g in high yields (Scheme 21).

<table>
<thead>
<tr>
<th>R</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>a -Ph</td>
<td>76%</td>
</tr>
<tr>
<td>c -pyrrole</td>
<td>61%</td>
</tr>
<tr>
<td>d -p-MeOPh</td>
<td>87%</td>
</tr>
<tr>
<td>e -o-CIPh</td>
<td>61%</td>
</tr>
<tr>
<td>f -CH₃</td>
<td>85%</td>
</tr>
<tr>
<td>g -H</td>
<td>81%</td>
</tr>
</tbody>
</table>

Scheme 21. Cyclization reaction by using NaH

The structures of newly synthesized diazepine derivatives 49a-g are shown in the Scheme 22.

Scheme 22. Diazepine derivatives synthesized from mono-propargylated compounds
2.6. Proposed mechanism for the cyclization reaction

The mechanism of the alkyne cyclization reaction is mentioned in Scheme 21. In the first step, because of the basic reaction, 41a, c-g can easily give allene formation 50 which have an electropositive carbon center. Thus, the nitrogen atom of pyrrole with increased electron density on its, attacks the central carbon atom of allene unit to give 52 through the intermediate 51, which can form directly 49a, c-g or 52. The exo-cyclic products 52 can easily rearrange to 49a, c-g under the basic conditions by 1,3-H shifting.(Scheme 23).

Scheme 23. Proposed mechanism for the formation of diazepine derivatives 49a-g

The structure of 41c and 49c were proven by NMR studies as shown below (Figure 4). In the $^1$H-NMR spectrum of compound 41c, CH$_2$ protons resonate at 4.44 ppm as a doublet with a coupling constant of $J = 2.5$ Hz and alkyne proton resonate at 2.36 ppm as triplet with a coupling constant of $J = 2.5$ Hz because of long range coupling with CH$_2$ protons. In addition, two protons attached to the nitrogen atoms resonate at 7.93 ppm as a broad singlet (Figure 4). On the other hand, structure 41c is in agreement with 12 distinct signals in the $^{13}$C-NMR spectrum. (Figure 5).
The 1D and 2D NMR (HSQC, COSY, HMBC) spectra were used for characterization of cyclization product \(49c\). When the \(^1H\)-NMR spectra of \(49c\) and \(41c\) were compared, disappearance of alkyne protons and one of the nitrogen protons was very informative in view of the proposed structure. Furthermore, appearance of a singlet at 2.15 ppm
arising from the CH₃ protons in the ¹H-NMR spectrum of 49c clearly indicated the cyclization reaction (Figure 6). Moreover, the ¹³C-NMR spectrum with 16 distinct carbon resonance signals also supports the formation of product 49c (Figure 7).

In the HSQC spectrum of compound 49c, there are some significant heteronuclear correlations supporting the cyclic structure (Figure 8).

In COSY spectrum, we observe a correlation between the methyl protons and the newly formed double bond proton (Figure 9). The location of C-4 carbon atom was determined by the correlations between the C-4 carbon atom and H-8 olefinic proton and CH₃ protons observed in the HMBC spectrum.

The other correlations were in complete agreement with the proposed structure too.

![Figure 6: ¹H-NMR Spectrum of compound 49c in CDCl₃](image)

Figure 6: ¹H-NMR Spectrum of compound 49c in CDCl₃
Figure 7: $^{13}$C-NMR Spectrum of compound 49c in CDCl$_3$

Figure 8: HSQC Spectrum of compound 49c in CDCl$_3$
Figure 9: COSY Spectrum of compound 49c in CDCl$_3$

Figure 10: HMBC Spectrum of compound 49c in CDCl$_3$
2.7. An attempt for the cyclization reaction of 2-[(2-nitrophenyl)(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (47h)

2-[(2-Nitrophenyl)(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (47h) was another mono-propargylated derivative having a benzene group bearing a nitro-functionality at the ortho-position, which was synthesized in order to control the scope of the cyclization reaction. Unfortunately, expected cyclization product 54 was not obtained from the reaction of 47h with NaH in DMF even at high temperatures (Scheme 24).

![Scheme 24. Reaction of structure 47h with NaH](image.png)

Intramolecular hydrogen-bonding can be attributed to this unexpected situation. Hydrogen-bonding is accepted as “strong, mostly covalent” with donor-acceptor distances of 2.2-2.5 Å; as “moderate, mostly electrostatic” if distance is between 2.5-3.2 Å and as “weak, electrostatic” with distance of 3.2 - 4.0 Å. The geometry of 50a was optimized by using B3LYP with 6-31+G(d,p) basis set in the gas phase to prove the formation of intramolecular hydrogen-bonding. As one can see from Figure 11, the distance between one of the oxygen atom of nitro group and hydrogen attached to the nitrogen atom of pyrrole is 2.40 Å. Thus, the intramolecular hydrogen-bonding of compound 50a is mostly covalent and this fact blocks the cyclization reaction.
2.8. An attempt for the propargylation reaction of 2-[(4-nitrophenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41i)

After failure of the cyclization reaction of 47h we decided to change to position of nitro group from the ortho-position to the para-position as in 55 to prove the intramolecular hydrogen-bonding in compound 47h which prevented the cyclization reaction. In designed structure 56, a similar hydrogen bonding will not be possible due to the distance between oxygen atom and NH hydrogen of pyrrole. For the synthesis of 55, dipyrrromethane derivative 41i was submitted to propargylation reaction under the same reaction conditions. For that reason, compound 2-[(4- nitrophenyl)(1H-pyrrol-2-yl)methyl]- 1H-pyrrole (41i) was reacted with NaH and propargyl bromide in the presence of DMF. Unlikely, instead of expected mono-propargylated product 55 or di- propargylated product 56, compound $57^{39}$ was produced under these reaction conditions (Scheme 25) and (Scheme 26).

![Figure 11. H bonding of compound 50a](image)
When compound 41i was reacted only with NaH in DMF, in the absence of propargyl bromide, 57 was again formed even in 1-2 minutes (Scheme 27). Thus, propargyl bromide does not effect the reaction. The spectral data ($^1$H-NMR, $^{13}$C-NMR, HRMS) of compound 57 is full-compatible with the literature data$^{39}$.

Due to the presence of a strong electron-withdrawing group such as nitro group, the acidity of methine proton is enhanced. Therefore, the base can easily abstract this proton forming an anion which can be stabilized due to the delocalization over the
benzene and pyrrole rings. This anion can undergo an oxidation reaction in the presence of air to form the oxidation product 57. Probably, a similar oxidation in the case of 41h due to the formation of strong hydrogen bonding is hindered (Figure 11). Because of the very fast tautomery in 57, two pyrrole rings are equal. This can be nicely seen in the symmetrical NMR spectra (Scheme 28).

![Scheme 28. Resonance structures of compound 57](image)

2.9. Synthesis of 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (58) with Sonagashira coupling reaction

Sonogashira cross-coupling reaction is used to form a new C-C bond between aryl or vinyl halide and a terminal alkyne by using cupper catalyst, palladium catalyst, bulky ligand and base (Scheme 29).

![Scheme 29. Sonogashira coupling reaction](image)

In order to test the scope of the cyclization reaction, additional derivative 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (58) was synthesized by using Sonagashira coupling reaction procedure. Desired coupling product 58 was obtain from the reaction of compound 41c with phenyl acetylene, Pd(OAc)$_2$, CuI and PPh$_3$ in dry DIPA and dry THF (Scheme 30).
Scheme 30. Synthesis of 57 by using Sonogashira coupling reaction

2.10. An attempt for the cyclization reaction of 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (58)

Coupling product 58 was reacted with NaH or AuCl₃ in the presence of DMF or THF at room temperature as well as at reflux temperature. However, desired cyclization product 59 did not form under these reaction conditions (Scheme 31).

Scheme 31. Reaction of compound 58 with NaH

2.11. Further propargylation of 5-methyl-11-(1H-pyrrol-2-yl)-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (49c)

The product 49c was reacted with of NaH in the presence of propargyl bromide in DMF. An SN2 reaction occur to give propargylated product 60 in 61% yield (Scheme 32). The compound 60 was suitable for further cyclization reactions. Therefore, the further cyclization reaction could be tried for compound 60.
2.12. An attempt for further cyclization reaction of 5-methyl-11-\((1\text{-}(\text{prop-2-yn-1-yl})\text{-}1H\text{-pyrrol-2-yl})\text{-}11H\text{-dipyrrrolo[1,2-d:2',1'-g][1,4]diazepine (60)\n
The key compound 60 was reacted with NaH with the expectation of the formation of derivative 61. Unfortunately, no trace of a cyclization product could be observed even at reflux temperature (Scheme 33).
CHAPTER 3

CONCLUSION

A novel synthetic methodology was improved for the synthesis of new diazepine derivatives which may show potential activities especially for psychological disorders. The method which is described starts with the synthesis of dipyrromethanes. In this step, some procedures were tried and the most favorable one was modified to obtain the starting dipyrromethane derivatives 41a-i (Scheme 34).

\[
\begin{align*}
\text{NH} & \quad + \\
& \quad R = -\text{O} - \underbrace{\text{O} - \text{Ph}}_{74\%} \\
& \quad R = -(\text{prop}-2-\text{yn}-1-\text{yl})-1\text{H}-\text{indole}, 59\% \\
& \quad R = -1-(\text{prop}-2-\text{yn}-1-\text{yl})-1\text{H}-\text{pyrrole}, 72\% \\
& \quad R = -3\text{-MeOPh}, 70\% \\
& \quad R = -3\text{-ClPh}, 89\% \\
& \quad R = -\text{CH}_3, 62\% \\
& \quad R = -\text{H}, 69\% \\
& \quad R = -3\text{-NO}_2, 79\% \\
& \quad R = -p\text{-NO}_2, 81\%
\end{align*}
\]

**Scheme 34.** Synthesis of starting compound 41a, d-h

Introducing propargyl group to nitrogen atom of pyrrole(s) gave the expected mono- and di-propargylated compounds 47a, d-h and 48a, d-h. The trouble for this step was that the yields of mono-propargylated compounds, which were much less than the yields of the di-propargylated compounds. So, this problem was solved by modification of the procedure (Scheme 35).
Scheme 35. Synthesis of propargylated compounds

Then, with the following simple cyclization reaction, desired diazepine derivatives 49a-g were obtained (Scheme 36).

![Scheme 36](image)

<table>
<thead>
<tr>
<th>R</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>-Ph</td>
</tr>
<tr>
<td>c</td>
<td>-pyrrole</td>
</tr>
<tr>
<td>d</td>
<td>-p-MeOPh</td>
</tr>
<tr>
<td>e</td>
<td>o-ClPh</td>
</tr>
<tr>
<td>f</td>
<td>-CH₃</td>
</tr>
<tr>
<td>g</td>
<td>-H</td>
</tr>
</tbody>
</table>


Moreover, attempt for the cyclization reaction of derivative 47h was done. The failure of cyclization reaction of 54 was attributed to the formation of intramolecular hydrogen-bonding between oxygen atom nitro group and pyrrole NH-hydrogen atom (Scheme 37). Surprisingly, the reaction of 41i with NaH gave an oxidation product 57 (Scheme 38).
Scheme 37. Reaction of 47h with NaH

Scheme 38. Reaction of 41i with NaH in the presence of air oxygen

Further, attempts with compounds having a benzene ring attached to the terminal carbon atom of alkyne functionality, was failed to give any cyclization product (Scheme 39).

Scheme 39. Synthesis of 59 by using Sonagahira reaction

Finally, we succeeded in the synthesis of 60, however, further cyclization to generate a new skeleton such as 61 was failed (Scheme 40).
Scheme 40. Reactions to get target compound 61

The characterization of newly synthesized compounds were succeeded by using $^1$H-NMR, $^{13}$C-NMR, IR and HRMS spectra.
CHAPTER 4

EXPERIMENTAL SECTION

4.1 General Methods

All reagents were acquired from commercial provider and additional purification was not done. $^1$H NMR spectra were recorded on an instrument 400 MHz and chemical shifts are shown in ppm. CDCl$_3$ and CD$_3$COCD$_3$ were used as internal standards. In addition, $^{13}$C-NMR spectra were recorded on an instrument 100 MHz and CDCl$_3$ and CD$_3$COCD$_3$ were used as internal standards. Also, $^{13}$C-NMR spectra were reported in ppm. IR were recorded in the range 4000-600 cm$^{-1}$ via ATR diamond. Melting point instrument was used to measure melting points.

Rotary vacuum evaporator was used for vaporisation of solvents at reduced pressure. Column chromatography was carried out on silica gel. TLC was performed on 0.2 mm silica gel aluminum plates. UV light ($\lambda = 254$ nm) was used to visualize the spots on TLC. LC-MS TOF electrospray ionization technique was used to record HRMS.

4.2. Synthesis of 1H-pyrrole 2-carbaldehyde(37)$^{33}$

To a stirred solution of POCl$_3$ (1.4 g, 9.1 mmol) and DMF (0.73 g, 9.7 mmol) was added pyrrole (0.6 g, 9.1 mmol) in dry ether (20 mL) dropwise at 0 °C. The composition was mixed at room temperature for 14h. Afterwards, the satiated solution of NaHCO$_3$ was added to media until a basic medium was beholded. Then, the composition was extracted with EtOAc (3 × 30 mL). DMF in extracts were removed with brine (3 × 15 mL) and the mixture dried over MgSO$_4$, and the solvent was vaporized. The crude composition was chromatographed eluting with hexane/EtOAc (10:1) to give (37) as a needle crystals (0.63 g, 73%), m.p. 44-45 °C.
1H-NMR (400 MHz, CDCl3) δ 10.47 (br s, 1H, -NH), 9.51 (d, J = 1.0, 1H, -H-1'), 7.18 (br s, 1H, H-3), 7.01 (ddd, J4,3 = 3.8 Hz, J5,4 = 2.3 Hz, 1H, H-4), 6.35 (ddd, J4,3 = 3.8 Hz, J4,5 = 2.4 Hz, 1H, H-4)

13C NMR (100 MHz, CDCl3) δ 179.4, 132.8, 126.9, 121.8, 111.3.

4.3. Synthesis of 1-(Prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde (38)

To a solution of pyrrole-2-carbaldehyde (0.63 g, 6.7 mmol) (37) in DMF (10 mL) was added NaH (0.2 g, 11 mmol) at 0 °C portionwise over 1 h. The composition was mixed at 0 °C for 0.5 h, and to the reaction media was added propargyl bromide (0.11 mL, 8.5 mmol) in DMF (10 mL) dropwise over 0.5 h. The reaction mixture was mixed at room temperature for 16 h, and water addition (50 mL), the mixture was extracted with EtOAc (4 × 25 mL). DMF in media was removed with brine (6 × 15 mL), dried over MgSO4, and solvent in composition was evaporated. The crude product was chromatographed eluting with hexane/EtOAc (7/1) to give (38) as a yellow liquid (0.66 g 75%).

1H NMR (400 MHz, CDCl3) δ 9.49 (bd, J = 1.2 Hz, 1H, H-1'), 7.20–7.19 (m, 1H, H-5), 6.90 (dd, J3,4 = 4.0 and J3,5 = 1.6 Hz, 1H, H-3), 6.22 (dd, J4,5 = 2.4, J4,3 = 4.0 Hz, 1H, H-4), 5.14 (d, J = 2.6 Hz, 2H, H-1"), 2.39 (t, J = 2.6 Hz, 1H, H-3").

13C NMR (100 MHz, CDCl3) δ 179.5, 131.1, 130.4, 124.9, 110.1, 77.8, 74.4, 38.1.

4.4. Synthesis of 1-prop-2-ynyl-1H-indole-2-carbaldehyde (40)

Solid NaH was added (0.17 g, 7.1 mmol) piecewise at 0 °C to a stirred solution of 1H-indole-2-carbaldehyde (39) (0.94 g, 5.5 mmol) in dry DMF (10 mL). Then, propargyl bromide (0.85 mL, 7.8 mmol) was added to the stirring solution. After 7 hours, brine was added (50 mL) to remove DMF and ethyl acetate (3 × 50 mL) was used to extract product. The final composition were dried over MgSO4 and filtered. After vaporisation, the product (40) was obtained. Brown solid (0.91 g, 82%) from CH2Cl2, m.p. 101-103 °C.

1H NMR (400 MHz, CDCl3) δ 9.81 (s, 1H, H-8), 7.68 (dt, J4,5 = 8.0, J4,6 = J4,3 = 0.9 Hz, 1H, H-4), 7.47 (dd, J7,6 = 8.5, J7,5 = 1.0 Hz, 1H, H-7), 7.40 (ddd, J6,7 = 8.5, J6,5 = 7.0, J6,4 = 0.9 Hz, 1H, H-6), 7.22 (d, J3,4 = 0.9 Hz, 1H, H-3), 7.15 (ddd, J5,4 = 8.0, J5,6 =
7.0, $J_{5,7} = 1.0$ Hz, 1H, H-5), 5.39 (d, $J_{1',3'} = 2.5$ Hz, 2H, H-1’), 2.20 (t, $J_{3',1'} = 2.5$ Hz, 1H, H-3’).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 182.6, 140.1, 134.5, 127.4, 126.6, 123.5, 121.5, 118.7, 110.8, 78.2, 72.5, 33.9.

4.5. General procedure for synthesis of 5-substituted dipyrromethanes (41a-i)

Corresponding aldehydes (33a and 33d-i) and N-propargyl substituted aldehydes (38, 40) (5 mmol) were dissolved in pyrrole (15 mmol) and then HCl (0.18 M, 0.045 mmol, 250 mL) was added to media and the composition was mixed at room temperature for 3 hours. The reaction was followed with TLC and after completion of the reaction. The composition was extracted with EtOAc (3 × 50 mL) and dried over MgSO$_4$ and after evaporation, the residue was purified with gradient column chromatography eluting with hexane:ethyl acetate (10:1 to 5:1) and the product were crystallized from appropriate solvents.

4.6. Synthesis of 2-[phenyl(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41a)$^{21}$

Benzaldehyde (0.5 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) was reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above. (41a) was receipt as a pale yellow crystals (0.82 g, 74%), m.p. 105-106 °C from EtOAc/hexane.

4.7. Synthesis of 2-[(4-methoxyphenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41d)$^{21}$

HCl (0.18 M, 0.045 mmol, 250 mL) was added to a mixture of 4-methoxybenzaldehyde (0.75 g, 5 mmol) and pyrrole (1.005 g, 15 mmol). Then, procedure was continued as described above. 41d was obtain as pale yellow powder (0.88 g, 70%), m.p. 102-103 °C.
4.8. Synthesis of 2-[(2-chlorophenyl)\(1H\)-pyrrol-2-yl)methyl]-\(1H\)-pyrrole (41e)

4-chlorobenzaldehyde (0.70 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) was reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above (41e) was receipt as pale yellow powder (1.14 g, 89%), m.p. 108-109 °C.

4.9. Synthesis of 2-[di(\(1H\)-pyrrol-2-yl)methyl]-1-prop-2-ynyl-\(1H\)-pyrrole (41c)

1-(Prop-2-yn-1-yl)-1H-pyrrole-2-carbaldehyde (38) (0.665 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) was reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (41c). Yellow solid (0.89 g, 72%), m.p. 92-93 °C.
13C NMR (100 MHz, CDCl3) δ 132.1, 130.5, 121.5, 117.2, 108.7, 108.4, 107.4, 106.9, 78.3, 73.4, 36.2, 36.0.

IR (ATR, cm⁻¹) 3285, 1651, 1528, 1475, 1402, 1368, 1337, 1314, 1282, 1246, 1218, 1075, 1030, 939, 890, 785, 741, 641, 605.


Synthesis of 2-[di(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-indole (41b)

1-(Prop-2-yn-1-yl)-1H-indole-2-carbaldehyde (40) (0.916 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) were reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (41b). Yellow oil (0.88 g, 59%).

1H NMR (400 MHz, CDCl3) δ 7.90 (bs, 2H, H-1), 7.45 (d, J = 7.8 Hz, 1H, H-7’’), 7.29 (d, J = 8.2 Hz, 1H, H-6”), 7.20 – 7.12 (m, 1H, H-5”), 7.08 – 7.01 (m, 1H, H-4”), 6.62 – 6.60 (m, 2H, H-5), 6.17 (s, 1H, H-3”), 6.11 – 6.09 (m, 2H, H-4), 6.01 – 5.95 (m, 2H, H-3), 5.74 (s, 1H, H-1’), 4.63 (d, J1”’-3”’ = 2.5 Hz, 2H, H-1”’), 2.16 (t, J1”’-3”’ = 2.5 Hz, 1H, H-3””).

13C NMR (100 MHz, CDCl3) δ 139.7, 137.1, 129.7, 127.6, 122.0, 120.6, 120.2, 117.6, 109.2, 108.6, 107.3, 102.5, 78.3, 72.4, 36.5, 32.5.

IR (ATR, cm⁻¹) 3403, 2987, 1715, 1507, 1459, 1402, 1339, 1311, 1249, 1182, 1162, 1106, 1085, 1027, 907, 884, 770, 726, 646, 603.

HRMS calcd for C20H17N3 [M+H]+: 299.1542 found: 299.1553

4.11. Synthesis of 2-(1H-pyrrol-2-ylmethyl)-1H-pyrrole (41g)²¹

Formaldehyde (0.15 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) was reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (41g). Colorless needles from EtOAc/ hexane, m.p. 75 °C. (0.50 g, 69 %).

1H NMR (400 MHz, CDCl3) δ 7.63 (bs, 2H, H-1), 6.56 – 6.54 (m, 2H, H-5), 6.14 – 6.12 (m, 2H, H-4), 6.08 – 5.95 (m, 2H, H-3), 3.89 (s, 2H, H-1’).

13C NMR (100 MHz, CDCl3) δ 129.2, 117.5, 108.3, 106.6, 26.3.
4.12. Synthesis of 2-[1-(1H-pyrrol-2-yl)ethyl]-1H-pyrrole (41f)\(^{21}\)
Acetaldehyde (0.22 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) were reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (41f). Colorless sticky solid (0.49 g, 62%).

\[\begin{align*}
\text{H NMR (400 MHz, CDCl}_3) & \delta 7.60 (bs, 2H, H-1), 6.67 – 6.42 (m, 2H, H-5), 6.08 – 6.06 (m, 2H, H-4), 5.98 (bs, 2H, H-3), 4.06 (q, J_{2',1'} = 7.2 Hz, 1H, H-1'), 1.50 (d, J_{2',1'} = 7.2 Hz, 3H, H-2'). \\
\text{13C NMR (CDCl}_3) & \delta 20.6, 31.7, 105.0, 108.0, 117.2, 134.8.
\end{align*}\]

4.13. Synthesis of 2-[(2-nitrophenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41h)\(^{22}\)
2-Nitrobenzaldehyde (0.75 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) were reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (41h). Yellow needle crystals from CH\(_2\)Cl\(_2\) (1.05 g, 79%), m.p. 145-147 °C.

\[\begin{align*}
\text{H NMR (400 MHz, CDCl}_3) & \delta 8.16 (bs, 2H, H-1), 7.90 (dd, J_{4', 3'} = 8.1 and J_{3', 5'} = 1.2 Hz, 1H, H-3''), 7.54 (td, J_{4', 5'} = 7.7 and J_{4', 6'} = 1.2 Hz, 1H, H-4'') 7.46 – 7.35 (m, 1H, H-5''), 7.30 (dd, J_{6', 5'} = 8.1 and J_{6', 4'} = 1.5 Hz, 1H, H-6''), 6.75 – 6.71 (m, 1H, H-5), 6.22 (s, 1H, H-1'), 6.18 (m, 1H, H-4), 5.89 – 5.84 (m, 1H, H-3). \\
\text{13C NMR (100 MHz, CDCl}_3) & \delta 148.8, 137.2, 133.0, 131.0, 130.7, 127.8, 124.5, 117.6, 108.6, 107.4, 38.9.
\end{align*}\]

4.14. Synthesis of 2-[(4-nitrophenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41i)\(^{21}\)
4-Nitrobenzaldehyde (0.75 g, 5 mmol) and pyrrole (1.005 g, 15 mmol) were reacted in HCl (0.18 M, 0.045 mmol, 250 mL) as described above to give compound (41i) as light yellow needles from hexane/ethyl acetate, m.p. 161 °C. (1.08 g, 81%).
**4.15. Synthesis of 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (58)**

A mixture of CuI (20 mg, 0.10 mmol), PPh<sub>3</sub> (40 mg, 0.15 mmol), and PdCl<sub>2</sub> (20 mg 0.10 mmol) was mixed under the nitrogen atmosphere for 2 min. After that, 2-[phenyl(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (0.2 g, 1.42 mmol), iodobenzene (0.34 g, 1.70 mmol) and DIPA (2 mL) in dry THF (20 mL) was added to the reaction mixture. The reaction was monitored with thin-layer chromatography and was completed after 1.5 h. After evaporation, the crude product was purified by column chromatography (silica gel/hexane-EtOAc 10:1) to give 2-(phenyl(1H-pyrrol-2-yl)methyl)-1-(3-phenylprop-2-yn-1-yl)-1H-pyrrole (58) as brown viscous oil (0.303 g, 60%).

**1H NMR (400 MHz, CDCl<sub>3</sub>)** δ 7.86 (bs, 1H, H-1''), 7.39 – 7.06 (m, 12H, arom), 6.81 – 6.72 (m, 1H, H-5), 6.62 (dd, J<sub>4,3</sub> = 4.1 and J<sub>4,5</sub> = 2.5 Hz, 1H, H-4), 6.08 – 6.06 (m, 1H, H-4''), 6.04 – 6.02 (m, 1H, H-3''), 5.81 – 5.75 (m, 1H, H-3), 5.65 5.57 (s, 1H, H-1''), 4.54 (s, 2H, H-1''').

**13C NMR (101 MHz, CDCl<sub>3</sub>)** δ 141.6, 133.5, 131.9, 131.7, 128.6, 128.5, 128.5, 128.3, 126.9, 122.3, 121.3, 117.14, 109.4, 108.3, 107.4, 107.1, 85.0, 83.6, 42.6, 37.2.

**IR (ATR, cm<sup>-1</sup>)** 3375, 2919, 1682, 1597, 1489, 1442, 1386, 1342, 1284, 1233, 1115, 1071, 1027, 968, 915, 883, 845, 755, 689, 602.

**HRMS** calcd for C<sub>24</sub>H<sub>20</sub>N<sub>2</sub> [M+H]<sup>+</sup>: 337.1699 found: 337.1720
4.16. General procedure for propargylation of dipyrromethanes substituted at C-5 position

To a stirred solution of 5-substituted dipyrromethanes (40a and 40d-h) (3 mmol) in DMF (30 mL) was added propargyl bromide (3.6 mmol) in DMF (5 mL) dropwise at 0 °C over a period of 30 min. The process was followed by portionwise addition of NaH (3.6 mmol) at 0 °C over a period of 30 min. The reaction was monitored with thin-layer chromatography and completed after 12-17 h. After completion of the reaction, the composition was extracted with EtOAc (4 × 40 mL). Then, DMF in media was removed with brine (8 × 50 mL) and mixture dried over MgSO₄. The eluent was removed under reduced pressure and the residue was purified with gradient column chromatography on silica gel eluted with hexane:ethyl acetate (20:1 to 7:1) and crystallized appropriate solvent.

4.17. Synthesis of 2-[phenyl(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (47a) and 2-[phenyl(1-prop-2-ynyl-1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (48a)

To a stirred solution of 2-[phenyl(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41a) (0.82 g, 3.9 mmol) in DMF (30 mL) was added propargyl bromide (0.384 mL, 4.6 mmol) in DMF at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.112 g, 4.6 mmol). The reaction was completed after 12 h and the further procedure was applied as described above. Mono-propargylated product (47a) was isolated as light yellow oil (0.49 g, 55%) and di-propargylated product (48a) was isolated as light yellow solid (0.20 g, 22%) m.p. 73-74 °C from EtOAc/ hexane.

**1H NMR** (400 MHz, CDCl₃) δ 7.91 (bs, 1H, H-1’’), 7.39 – 7.10 (m, 5H-arom), 6.79 – 6.72 (m, 1H, H-5), 6.68 (dd, J₄,₃ = 4.1 and J₄,₅ = 2.5 Hz, 1H, H-4’’), 6.14 – 6.12 (m, 1H, H-4’’), 5.10 – 6.06 (m, 1H, H-5’’), 5.83 – 5.82 (m, 1H, H-3’’), 5.70 – 5.68 (m, 1H, H-3’’), 5.56 (s, 1H, H-1’’), 4.39 – 4.36 (m, 2H, H-1’’’’), 2.35 (t, J₁’’’’-₃’’’’ = 2.5 Hz, 1H, H-3’’’’).

**13C NMR** (101 MHz, CDCl₃) δ 141.5, 133.5, 131.8, 128.5, 128.4, 126.9, 121.2, 117.1, 109.5, 108.3, 107.4, 107.3, 78.3, 73.4, 36.3, 29.6

**IR (ATR, cm⁻¹)** 1662, 1510, 1416, 1381, 1342, 1287, 1272, 1252, 1118, 1094, 1043, 1002, 935, 909, 845, 808, 773, 714, 638, 593, 575.
HRMS calcd for C$_{18}$H$_{16}$N$_2$ [M+H]$^+$: 259.1151 found: 259.1158

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.28 – 7.06 (m, 5H-arom), 6.71 – 6.66 (m, 2H-H-5), 6.03 – 5.94 (m, 2H-H-4), 5.54 (s, 1H-H-1'), 5.50 – 5.41 (m, 2H-H-3), 4.33 (dd, $J_{geminal}$ = 14.0 Hz and $J_{1''',3'''}$ = 2.5 Hz, 4H, H-1''), 2.33 (t, $J_{1''',3'''}$ = 2.5 Hz, 2H, H-3''').

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 140.6, 132.9, 128.7, 128.5, 126.9, 121.1, 109.9, 107.3, 78.7, 73.3, 41.2, 36.3.

IR (ATR, cm$^{-1}$) 3283, 3243, 3025, 2116, 1704, 1598, 1477, 1449, 1434, 1340, 1226, 1197, 1124, 1071, 1027, 1016, 962, 896, 821, 789, 778, 751, 710, 697, 656, 609.

HRMS calcd for C$_{21}$H$_{18}$N$_2$ [M+H]$^+$: 299.1542 found: 299.1553

4.18. Synthesis of 2-[(4-methoxyphenyl)(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (47d) and 2-[(4-methoxyphenyl)(1-prop-2-ynyl-1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (48d)

To a stirred solution of 2-[(4-methoxyphenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41d) (0.88 g, 3.48 mmol) in DMF (30 mL) was added propargyl bromide (0.36 mL, 4.18 mmol) in DMF at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.10 g, 4.18 mmol). After 10 h. reaction was completed. The further procedure was done as described above. Mono-propargylated product (47d) was isolated as yellow oil (0.15 g, 48%) and di-propargylated product (48d) was isolated as yellow needles (0.12 g, 24%) from EtOAc/ hexane, m.p. 72-73 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.90 (bs, 1H, H-1''), 7.13 – 6.81 (m, 4H-arom), 6.78 – 6.74 (m, 1H, H-5), 6.69 (dd, $J_{4,3}$ = 4.1 and $J_{4,5}$ = 2.6 Hz, 1H, H-4), 6.14 – 6.12 (m, 1H, H-4''), 6.08 (t, $J$ = 3.2 Hz, 1H, H-5''), 5.82 (m, 1H, H-3''), 5.71 – 5.69 (m, 1H, H-3), 5.51 (s, 1H, H-1'), 4.38 (d, $J_{1''',3'''}$ = 2.5 Hz, 3H, H-1''), 3.79 (s, 3H-OMe), 2.36 (t, $J_{1''',3'''}$ = 2.5 Hz, 1H, H-3'').

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 158.5, 133.8, 133.6, 133.5, 132.2, 129.4, 121.1, 117.0, 113.9, 109.3, 108.3, 107.2, 78.4, 73.3, 55.2, 41.7, 36.2.

IR (ATR, cm$^{-1}$) 3372, 3289, 1681, 1607, 1583, 1508, 1479, 1463, 1439, 1342, 1300, 1284, 1243, 1173, 1108, 1090, 1072, 1028, 936, 884, 842, 790, 707, 667,645, 592.
HRMS calcd for C_{19}H_{18}N_{2}O [M+H]^+: 291.1491 found: 291.1507.

1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.09 – 7.04 (m, 2H, H-3''), 6.86 – 6.82 (m, 2H, H-2''), 6.76 – 6.74 (m, 2H, H-5), 6.06 – 6.04 (m, 2H, H-4), 5.55 (s, 1H, H-1''), 5.52 – 5.49 (m, 1H, H-3''), 3.79 (s, 3H, OMe), 2.39 (t, $J_{1'''',3''''} = 2.5$ Hz, 2H, H-3'').

IR (ATR, cm$^{-1}$) 3289, 3256, 1680, 1603, 1577, 1507, 1478, 1454, 1420, 1390, 1319, 1299, 1281, 1256, 1242, 1196, 1172, 1159, 1127, 1104, 1072, 1028, 956, 936, 898, 856, 826, 732, 721, 707, 687, 668, 644, 610, 571.

HRMS calcd for C_{22}H_{20}N_{2}O [M+H]^+: 329.1648 found: 329.1684.

4.19. Synthesis of 2-[(2-chlorophenyl)(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (47e) and 2-[(2-chlorophenyl)(1-prop-2-ynyl-1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (48e)

To a stirred solution of 2-[(2-chlorophenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41e) (1.14 g, 4.44 mmol) in DMF (30 mL) was added propargyl bromide (0.46 mL 5.3 mmol) in DMF at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.10 g, 5.3 mmol). The reaction was completed after 16 h. and the further procedure was done as described above. Mono- propargylated (47e) product was isolated as colorless oil (0.35 g, 44 %) and di- propargylated (48e) product was isolated as light yellow needles from EtOAc/ hexane (0.21 g, 18%).

1H NMR (400 MHz, CDCl$_3$) $\delta$ 7.94 (bs, 1H, H-1''), 7.40 – 7.35 (m, 1H, H-3'''), 7.22 – 7.15 (m, 1H, arom), 7.01 – 6.96 (m, 1H, arom), 6.81 – 6.77 (m, 1H, H-5), 6.70 (dd, $J_{4,3} = 4.2$ and $J_{4,5} = 2.6$ Hz, 1H, H-4), 6.15 – 6.13 (m, 1H, H-4''), 6.11 – 6.07 (m, 1H, H-5''), 5.93 (s, 1H, H-1''), 5.81 – 5.80 (m, 1H, H-3'), 5.68 – 5.61 (m, 1H, H-3''), 4.41 (d, $J_{1'''',3''''} = 2.5$ Hz, 2H, H-1'''). 2.33 (t, $J_{3'''',5''''} = 2.5$ Hz, 1H, H-3''').

13C NMR (101 MHz, CDCl$_3$) $\delta$ 139.5, 133.7, 132.3, 130.4, 130.0, 129.5, 128.2, 127.0, 121.2, 117.2, 109.4, 108.8, 107.7, 107.4, 77.9, 73.5, 39.9, 36.2.
IR (ATR, cm⁻¹) 3376, 3291, 1723, 1571, 1468, 1434, 1285, 1235, 1115, 1072, 1046, 1029, 936, 884, 847, 751, 712, 663, 609.


HRMS calcd for C₂₁H₁₇ClN₂ [M+H]^+: 333.1153 found: 333.1168

1H NMR (400 MHz, CDCl₃) δ 7.41 – 7.37 (m, 1H, H-3′′′), 7.23 – 7.16 (m, 2H, arom), 7.00 – 6.95 (m, 1H, arom), 6.79 – 6.77 (m, 2H, H-5), 6.07 – 6.05 (m, 2H, H-4), 6.01 (s, 1H, H-1′), 5.52 – 5.49 (m, 2H, H-3), 4.42 (dd, J_geminal = 7.9 Hz and J₁''',3''' = 2.5 Hz, 4H, H-1''′), 2.37 (t, J₁''',3''' = 2.5 Hz, 2H, H-3''′).

13C NMR (101 MHz, CDCl₃) δ 138.2, 133.9, 131.6, 130.4, 129.5, 128.2, 126.9, 121.2, 110.0, 107.4, 78.2, 73.4, 37.0, 36.3.

IR (ATR, cm⁻¹) 3295, 1475, 1434, 1339, 1306, 1291, 1254, 1233, 1130, 1071, 1044, 1029, 1016, 936, 846, 819, 787, 777, 734, 706, 666, 628, 607, 574.

HRMS calcd for C₂₁H₁₇ClN₂ [M+H]^+: 333.1153 found: 333.1168

4.20. Synthesis of 1-prop-2-ynyl-2-(1H-pyrrol-2-ylmethyl)-1H-pyrrole (47g) and 1-prop-2-ynyl-2-[(1-prop-2-ynyl-1H-pyrrol-2-yl)methyl]-1H-pyrrole (48g)

To a stirred solution of 2-(1H-pyrrol-2-ylmethyl)-1H-pyrrole (0.50 g, 3.42 mmol) (41g) in DMF (30 mL) was added propargyl bromide (3.5 mL, 4.1 mmol) in DMF at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.09 g, 4.1 mmol). The reaction was completed after 11 h. and the further procedure was done as described above. Mono-propargylated (47g) product was isolated as colorless liquid (0.12 g, 51%) and di-propargylated (48g) product was isolated as light yellow oil (0.14 g, 24%).

1H NMR (400 MHz, CDCl₃) δ 7.84 (bs, 1H, H-1′′′), 6.72-6.70 (m, 2H, H-5, H-5′′′), 6.61 (dd, J₄,₃ = 4.0 and J₄,₅ = 2.5 Hz, 1H, H-4), 6.16 – 6.15 (m, 1H, H-4′′′), 6.02 – 5.98 (m, 2H, H-3′′′), 4.42 (d, J₁'',₃''′ = 2.5 Hz, 2H, H-1′″), 3.99 (s, 2H, H-1′), 2.33 (t, J₁'',₃''′ = 2.5 Hz, 1H, H-3''″).

13C NMR (101 MHz, CDCl₃) δ 129.3, 128.5, 121.1, 117.0, 108.6, 108.4, 107.5, 106.0, 78.8, 73.2, 36.1, 25.3.
IR (ATR, cm⁻¹) 3377, 3282, 1698, 1567, 1482, 1420, 1311, 1286, 1240, 1205, 1180, 1115, 1088, 1071, 935, 883, 775, 707, 640.


4.21. Synthesis of 1-prop-2-ynyl-2-[1-(1H-pyrrl-2-yl)ethyl]-1H-pyrrole (47f) and 1-prop-2-ynyl-2-[1-(1-prop-2-ynyl-1H-pyrrl-2-yl)ethyl]-1H-pyrrole (48f)

To a stirred solution of 2-[1-(1H-pyrrl-2-yl)ethyl]-1H-pyrrole (0.49 g, 3.05 mmol) (41f) in DMF (30 mL) was added propargyl bromide (0.31 g, 3.66 mmol) in DMF at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.08 g, 3.6 mmol). After 10 h. reaction was completed. The further procedure was done as described above. Mono-propargylated product (47f) was isolated as colorless liquid (0.08 g, 33%) and di-propargylated compound (48f) was isolated as colorless liquid (0.26 g, 45%).
HRMS calcd for C_{13}H_{14}N_{2}[M+H]^+: 199.1229 found: 199.1238.

1H NMR (400 MHz, CDCl₃) δ 6.66 – 6.63 (m, 2H, H-5), 6.04 – 6.01 (m, 2H, H-4), 5.83 – 5.81 (m, 2H, H-3), 4.39 (d, J₁''',3''' = 2.5 Hz, 2H, H-1'''), 4.24 (q, J₁',2''' = 6.9 Hz, 1H, H-1'), 2.29 (t, J₁''',3''' = 2.5 Hz, 1H, H-3'''), 1.55 (d, J₁',2''' = 6.9 Hz, 3H, H-2''').

13C NMR (101 MHz, CDCl₃) δ 134.6, 120.9, 107.4, 107.0, 78.7, 73.13, 36.0, 29.5, 20.8.

IR (ATR, cm⁻¹) 3286, 2927, 2851, 1712, 1479, 1420, 1373, 1340, 1283, 1234, 1202, 1128, 1077, 1011, 934, 789, 759, 706, 637, 572.

HRMS calcd for C_{16}H_{16}N_{2}[M+H]^+: 237.1386 found: 237.1395.

4.22. Synthesis of 2-[(2-nitrophenyl)(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (47h) and 2-[(2-nitrophenyl)(1-prop-2-ynyl-1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (48h)

To a stirred solution of 2-[(2-nitrophenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41h) (1.05 g, 3.9 mmol) in DMF (20 mL) was added propargyl bromide (0.384 mL, 4.6 mmol) in DMF (5 mL) at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.112 g, 4.6 mmol). The reaction was completed after 12 h. and the further procedure was done as described above. Mono-propargylated (47h) product was isolated as yellow sticky solid (0.24 g, 44%) and di-propargylated product (48h) was isolated as colorless cubic crystals (0.10 g, 12%) from CHCl₃, m.p. 143-144 °C from EtOAc/hexzane.

1H NMR (400 MHz, CDCl₃) δ 7.98 (bs, 1H, H-1''), 7.93 (dd, J₄''', 3'' = 8.1 and J₃''', 5'' = 1.2 Hz, 1H, H-3''''), 7.51 (td, J₄''', 3''-5'' = 7.6 and J₄''', 6'' = 1.2 Hz, 1H, H-4'''') 7.43 – 7.38 (m, 1H, H-5''''), 7.13 (dd, J₆'', 5'' = 7.8 and J₆'', 4'' = 1.0 Hz, 1H, H-6''''), 6.87 – 6.77 (m, 1H, H-5), 6.73 – 6.71 (m, 1H, H-4), 6.38 (s, 1H, H-5''), 6.17 – 6.15 (m, 1H, H-4''), 6.09 – 6.03 (m, 1H, H-3), 5.85 (s, 1H, H-1'), 5.61 – 5.58 (m, 1H, H-3''), 4.49 (d, J₁'',3'' = 2.6 Hz, 2H, H-1''''), 2.33 (t, J₁'',3'' = 2.6 Hz, 1H, H-3'''').

13C NMR (101 MHz, CDCl₃) δ 148.6, 136.8, 133.0, 131.5, 130.9, 129.7, 127.8, 124.8, 121.6, 117.6, 109.3, 108.8, 107.9, 107.4, 77.2, 73.7, 37.5, 36.2.
IR (ATR, cm\(^{-1}\)) 3286, 2914, 2849, 1669, 1605, 1520, 1472, 1423, 1397, 1342, 1285, 1183, 1117, 1073, 834, 784, 713, 657, 604.

HRMS calcd for C\(_{18}\)H\(_{15}\)N\(_3\)O\(_2\) [M+H]+: 306.1237 found: 306.1237

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.96 (dd, \(J_{4''}, 3'' = 8.1\) and \(J_{3''}, s'' = 1.2\) Hz, 1H, H-3''), 7.51 (td, \(J_{4''}, 3''-5'' = 7.6\) and \(J_{4''}, 6'' = 1.2\) Hz, 1H, H-4'') 7.47 – 7.37 (m, 1H, H-5''), 7.15 (dd, \(J_{6''}, 5'' = 7.6\) and \(J_{6''}, 4'' = 1.2\) Hz, 1H, H-6''), 6.81 – 6.75 (m, 2H, H-5), 6.50 (s, 1H), 6.08 – 6.02 (m, 2H, H-4''), 5.50 – 5.48 (m, 2H, H-3''), 4.36 (dd, \(J_{\text{geminal}} = 13.9\) Hz and \(J_{1'\text{-},3''} = 2.5\) Hz, 4H, H-1''), 2.36 (t, \(J_{1'\text{-},3''} = 2.5\) Hz, 2H, H-3'').

\(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 148.8, 135.5, 133.0, 131.3, 131.0, 128.0, 124.9, 121.5, 110.3, 107.5, 77.8, 73.7, 36.3, 36.0.

IR (ATR, cm\(^{-1}\)) 3300, 3281, 1519, 1477, 1355, 1301, 1288, 1253, 1131, 1071, 1178, 937, 864, 836, 819, 742, 719, 687, 638, 606, 572.

HRMS calcd for C\(_{21}\)H\(_{17}\)N\(_3\)O\(_2\) [M+H]+: 344.1393 found: 344.1418

### 4.23. General procedure for NaH-supported cyclization reactions of N-propargyl dipyrromethane derivatives

To a stirred solution of N-propargyl dipyrromethane derivatives (47a-g) (1 mmol) in DMF (10 mL) was added solid NaH (1.2 mmol) portionwise at room temperature and the reaction composition was mixed for 1 h. After completion of the reaction, the composition was extracted with EtOAc (3 × 50 mL). Afterwards, DMF in media was removed with brine (3 × 25 mL) and the mixture was dried over MgSO\(_4\). Evaporation of solvent gave the residue which was purified with gradient column chromatography eluted with hexane:ethyl acetate (10:1 to 4:1) and crystallized appropriate solvent.

### 4.24. Synthesis of 5-methyl-11-phenyl-11\(H\)-dipyrrrolo[1,2-d:2',1'-g][1,4]diazepine (49a)

A stirred solution of 2-[phenyl(1\(H\)-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1\(H\)-pyrrole (47a) (0.49 g, 1.88 mmol) in DMF (20 mL) was reacted with NaH (0.05 g, 2.25 mmol) as described above to give cyclization product (49a). White tiny needles (0.37 g, 76%) from EtOAc/ hexane, (m.p. 106-107 °C).
49

1H NMR (400 MHz, CDCl3) δ 7.24 – 7.15 (m, 4H, arom), 6.90 (bs, 1H, arom), 6.89 – 6.86 (m, 1H, H-3), 6.64 – 6.60 (m, 1H, H-8), 6.29 – 6.25 (m, 1H, H-2), 6.23 (s, 1H, H-6), 6.23 – 6.18 (m, 1H, H-9), 6.10 – 6.07 (m, 1H, H-1), 6.06 – 6.05 (m, 1H, H-10), 5.40 (s, 1H, H-11), 2.08 (s, 3H, H-1').

13C NMR (101 MHz, CDCl3) δ 140.4, 134.6, 134.5, 128.0, 127.3, 126.3, 123.2, 120.2, 118.2, 113.0, 109.5, 109.5, 107.7, 107.0, 42.1, 19.6.

IR (ATR, cm⁻¹) 3095, 1689, 1599, 1480, 1445, 1424, 1377, 1348, 1333, 1300, 1290, 1279, 1247, 1215, 1198, 1169, 1152, 1116, 1074, 1031, 1023, 889, 849, 828, 811, 776, 726, 713, 704, 694, 611, 591.


4.25. Synthesis of 11-(4-methoxyphenyl)-5-methyl-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (49d)

A stirred solution of 2-[(4-methoxyphenyl)(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (47d) (0.15 g, 0.5 mmol) in DMF (15 mL) was reacted with NaH (0.01 g, 0.6 mmol) as described above to give cyclization product (49d). Yellow needles (0.12 g, 87%) from EtOAc/hexane, (m.p. 65-68 °C).

1H NMR (400 MHz, CDCl3) δ 6.86 – 6.84 (m, 1H, H-3), 6.83 – 6.81 (m, 2H, H-3'), 6.75 – 6.73 (m, 2H, H-2''), 6.59 (dd, J₈,₉ = 2.8 and J₈,₁₀ = 1.4 Hz, 1H, H-8), 6.26 – 6.23 (m, 2H, H-9 and H-6), 6.20 – 6.16 (m, 1H, H-2), 6.05 – 6.02 (m, 1H, H-1), 6.02 – 6.00 (m, 1H, H-10), 5.32 (s, 1H, H-11), 3.73 (s, 3H, H-1'''), 2.07 (s, 3H, H-1').

13C NMR (101 MHz, CDCl3) δ 158.2, 135.0, 134.9, 132.5, 128.5, 123.8, 120.2, 118.2, 113.4, 113.0, 109.6, 109.5, 107.6, 106.9, 55.2, 41.5, 19.7.

IR (ATR, cm⁻¹) 2922, 1693, 1605, 1507, 1481, 1424, 1379, 1348, 1333, 1281, 1243, 1199, 1175, 1114, 1082, 1028, 889, 829, 789, 766, 700, 635, 609, 585, 562.

4.26. Synthesis of 11-(2-chlorophenyl)-5-methyl-11H-dipyrrrolo[1,2-d:2',1'-g][1,4]diazepine (49e)
A stirred solution of 2-[(2-chlorophenyl)(1H-pyrrol-2-y1)methyl]-1-prop-2-ynyl-1H-pyrrole (47e) (0.35 g, 1.2 mmol) in DMF (15 mL) was reacted with NaH (0.03 g, 1.44 mmol) as described above to give cyclization product (49e). Light orange liquid (0.21 g, 61%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (dd, $J_{3'',4''} = 7.6$ and $J_{3'',5''} = 1.8$ Hz, 1H, H-3''), 7.41 (dd, $J_{6'',5''} = 7.7$ and $J_{6'',4''} = 1.6$ Hz, 1H, H-6''), 7.32 – 7.21 (m, 2H, arom), 6.87 (dd, $J_{3,2} = 2.9$ and $J_{3,1} = 1.8$ Hz, 1H, H-8), 6.54 (s, 1H, H-6), 6.17 – 6.15 (m, 1H, H-9), 6.12 – 6.11 (m, 1H, H-2), 5.77 (s, 1H, H-11), 5.74 – 5.68 (m, 2H, H-10 and H-1), 2.33 (s, 3H, H-1').

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 136.5, 134.7, 134.4, 133.8, 131.3, 129.9, 128.4, 126.3, 123.4, 120.3, 118.3, 113.2, 109.4, 109.4, 107.5, 106.9, 39.1, 20.1.

IR (ATR, cm$^{-1}$) 2924, 1732, 1694, 1570, 1474, 1434, 1418, 1380, 1347, 1316, 1288, 1242, 1160, 1197, 1115, 1084, 1041, 895, 857, 808, 782, 748, 698, 641, 562.

HRMS calcd for C$_{18}$H$_{15}$ClN$_2$ [M+H$^+$]: 295.0996 found: 295.1000.

4.27. Synthesis of 5-methyl-11H-dipyrrrolo[1,2-d:2',1'-g][1,4]diazepine (49g)
A stirred solution of 1-prop-2-ynyl-2-(1H-pyrrol-2-ylmethyl)-1H-pyrrole (47g) (0.12 g, 0.65 mmol) in DMF (15 mL) was reacted with NaH (0.01 g, 0.78 mmol) as described above to give cyclization product (49g). Light yellow solid (0.09 g, 81%) m.p. 58-60 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.80 (dd, $J_{3,2} = 3.0$ and $J_{3,1} = 1.7$ Hz, 1H, H-3), 6.58 (dd, $J_{8,9} = 2.7$ and $J_{8,10} = 1.7$ Hz, 1H, H-8), 6.47 (s, 1H, H-6), 6.19 (t, $J = 3.2$ Hz, 1H, H-9), 6.13 (t, $J = 3.1$ Hz, 1H, H-2), 5.96 – 5.85 (m, 2H, H-1 and H-10), 3.85 (s, 2H, H-11), 2.29 (s, 3H, H-1').

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 132.8, 132.6, 123.2, 119.4, 117.5, 112.7, 109.7 (2C), 105.3, 104.4, 26.0, 19.9.

IR (ATR, cm$^{-1}$) 2916, 2849, 1715, 1507, 1480, 1417, 1378, 1331, 1235, 1180, 1114, 1024, 885, 826, 747, 695, 610, 546.

HRMS calcd for C$_{12}$H$_{12}$N$_2$ [M+H$^+$]: 185.1084 found:185.1073. 

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4.28. Synthesis of 5,11-dimethyl-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (49f)
A stirred solution of 1-prop-2-ynyl-2-[1-(1H-pyrrol-2-yl)ethyl]-1H-pyrrole (47f) (0.08 g, 0.4 mmol) in DMF (15 mL) was reacted with NaH (0.01 g, 0.78 mmol) as described above to give cyclization product (49f) as colorless liquid (0.06 g, 85%).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 6.81 (dd, $J_{3,2} = 2.7$ and $J_{3,1} = 1.7$ Hz, 1H, H-3), 6.60 – 6.57 (m, 1H, H-8), 6.52 (s, 1H, H-6), 6.22 – 6.21 (m 1H, H-9), 6.15 – 6.14 (m, 1H, H-2), 5.92 – 5.84 (m, 2H, H-1 and H-10), 3.85 (q, $J_{11,1''} = 7.0$ Hz, 1H, H-11), 2.29 (d, $J = 1.0$ Hz, 3H, H-1').

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 138.0, 137.8, 123.7, 119.2, 117.3, 113.0, 109.4 (2C), 103.2, 102.5, 30.1, 19.8, 15.0.

IR (ATR, cm$^{-1}$) 3100, 2973, 1686, 1556, 1482, 1432, 1418, 1379, 1261, 1186, 1170, 1157, 1114, 1087, 1051, 1038, 971, 884, 791, 730, 691, 622, 591, 579.

HRMS calcd for C$_{13}$H$_{14}$N$_2$ [M+H]$^+$: 198.1157 found: 199.1236.

4.29. Synthesis of 5-methyl-11-(1H-pyrrol-2-yl)-11H-dipyrrolo[1,2-d:2',1'-g][1,4]diazepine (49c)
A stirred solution of 2-[di(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-pyrrole (41c) (0.89 g, 3.6 mmol) in DMF (15 mL) was reacted with NaH (0.1 g, 4.2 mmol) as described above to give cyclization product (49c). Brown solid (0.5 g, 65%) m.p. 130-131 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.73 (s, 1H, H-1''), 6.87 (dd, $J_{3,2} = 3.1$ and $J_{3,1} = 1.8$ Hz, 1H, H-3), 6.66 – 6.59 (m, 2H, H-5'' and H-8), 6.30 (s, 1H, H-6), 6.24 (t, $J = 3.2$ Hz, 1H, H-9), 6.18 (t, $J = 3.1$ Hz, 1H, H-2), 6.07 – 6.03 (m, 3H, H-10, 4'',1''), 5.59 – 5.55 (m, 1H, H-3''), 5.43 (s, 1H, H-11), 2.15 (s, 3H, H-1').

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 133.5, 133.3, 130.3, 122.9, 120.6, 118.5, 116.7, 112.6, 109.5, 109.5, 108.3, 107.3, 106.4, 105.9, 36.9, 19.8.

IR (ATR, cm$^{-1}$) 3285, 1651, 1528, 1475, 1402, 1368, 1337, 1314, 1282, 1246, 1218, 1075, 1030, 953, 939, 890, 785, 741, 641, 605.
4.30. Synthesis of 5-methyl-13-(1H-pyrrol-2-yl)-13H-pyrrrolo[1',2':4,5][1,4]diazepino[1,7-a]indole (49b)

A stirred solution of 2-[di(1H-pyrrol-2-yl)methyl]-1-prop-2-ynyl-1H-indole (41b) (0.91 g, 3 mmol) in DMF (20 mL) was reacted with NaH (0.09 g, 3.6 mmol) as described above to give cyclization product (49b). Yellow sticky oil (0.61 g, 72%).

\[ \text{HRMS calcd for C}_{20}H_{17}N_3 [\text{M+H}]^+ : 300.1495 \text{ found: 300.1507} \]

\[ \text{IR (ATR, cm}^{-1}) 3396, 2917, 1715, 1556, 1480, 1458, 1426, 1373, 1350, 1314, 1243, 1175, 1087, 1024, 937, 884, 767, 746, 735, 707, 666, 604. \]

4.31. Synthesis of (Z)-2-((4-nitrophenyl)(2H-pyrrol-2-ylidene)methyl)-1H-pyrrole (57)\(^\text{39}\)

To a stirring solution of 2-[(4-nitrophenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole (41i) (0.5 g, 1.8 mmol) in DMF (10 mL), sodium hydride was added (0.04 g mL, 2 mmol) portionwise and stirred for 2-3 minutes at room temperature. After completion of the reaction which was monitored by using TLC, solvent was removed and water (10 mL) was added. The resulting composition was extracted with ethyl acetate (3 × 20 mL). The organic mixture dried over MgSO\(_4\), then filtered. After vaporisation of the solvent, the compound 57 was chromatographed on silica gel column eluting with hexane/EtOAc (7:1) to give (Z)-2-((4-nitrophenyl)(2H-pyrrol-2-ylidene)methyl)-1H-pyrrole (57) (0.32 g, 64%) as yellow sticky solid.
H NMR (400 MHz, CDCl₃) δ 8.30 – 8.21 (m, 2H, H-3''), 7.63 – 7.62 (m, 2H, H-2''), 7.63 – 7.59 (m, 2H, H-5), 6.41 (dd, J = 4.2 Hz and J = 1.0 Hz, 2H, H-3), 6.36 (dd, J = 4.2 Hz and J = 1.5 Hz, 2H, H-4).

13C NMR (101 MHz, CDCl₃) δ 148.2, 144.6, 143.8, 139.8, 139.7, 131.5, 128.6, 122.9, 118.3.

4.32. Synthesis of 5-methyl-11-(1-(prop-2-yn-1-yl)-1H-pyrrol-2-yl)-11H-dipyrrrolo[1,2-d:2',1'-g][1,4]diazepine (60)
To a stirred solution of 5-methyl-11-(1H-pyrrol-2-yl)-11H-dipyrrrolo[1,2-d:2',1'-g][1,4]diazepine (49c) (0.5 g, 1.7 mmol) in DMF (20 mL) was added propargyl bromide (0.170 mL, 2.04 mmol) in DMF (5 mL) at 0 °C over a period of 30 min and the reaction was followed by portionwise addition of NaH (0.05 g, 2.04 mmol). The reaction was completed after 12 h. and the mixture was extracted with EtOAc (3 × 50 mL). Then the organic extracts were washed with brine (8 × 50 mL) and dried over MgSO₄. The eluent was removed under reduced pressure and the residue was purified with gradient column chromatography eluted with hexane:ethyl acetate (20:1 to 7:1). Compound 60 product was isolated as brown sticky solid (0.44 g, 61 %).

H NMR (400 MHz, CDCl₃) δ 6.91 (bs, 1H, H-5''), 6.74 (bs, 1H, H-4''), 6.64 (bs, 1H, H-8), 6.44 (bs, 1H, H-3), 6.26 (m, 1H, H-2), 6.20 (m, 1H, H-9), 6.07 (m, 3H, H-1, 10, 3'') 5.69 (s, 1H, H-11), 5.61 (s, 1H, H-11), 4.57 (dd, J_{geminal} = 8.7 and J_{1''',3'''} = 2.3 Hz, 2H, H-1''), 2.43 (t, J_{1''',3'''} = 2.3 Hz, 1H, H-3''), 2.27 (s, 3H, H-1').

13C NMR (101 MHz, CDCl₃) δ 133.8, 133.2, 129.5, 123.3, 121.4, 120.3, 118.3, 113.0, 109.7, 109.6, 109.1, 107.1, 107.1, 106.4, 78.6, 73.5, 37.0, 36.1, 19.9.

IR (ATR, cm⁻¹) 3264, 1698, 1480, 1424, 1394, 1266, 1250, 1237, 1225, 1184, 1163, 1120, 1087, 1075, 1033, 1019, 938, 909, 886, 852, 793, 771, 714, 701, 647, 617, 609.

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(24) Meanwell, N. A.; Walker, M. A. 1,4-Diazepines The Bristol Myers Squibb Pharmaceutical Research Institute, **2008**, p. 2.


APPENDIX A

SPECTRAL DATA

Figure 12 $^1$H-NMR Spectrum of Compound 41a in CDCl$_3$

Figure 13 $^{13}$C-NMR Spectrum of Compound 41a in CDCl$_3$
Figure 14 $^1$H-NMR Spectrum of Compound 41d in CDCl$_3$

Figure 15 $^{13}$C-NMR Spectrum of Compound 41d in CDCl$_3$
Figure 16 $^1$H-NMR Spectrum of Compound 41e in CDCl$_3$

Figure 17 $^{13}$C-NMR Spectrum of Compound 41e in CDCl$_3$
Figure 18 IR Spectrum of Compound 41e

Figure 19 ¹H-NMR Spectrum of Compound 41c in CDCl₃
Figure 20 $^{13}$C-NMR Spectrum of Compound 41c in CDCl₃

Figure 21 IR Spectrum of Compound 41c
Figure 22 $^1$H-NMR Spectrum of Compound 41b in CDCl$_3$

Figure 23 $^{13}$C-NMR Spectrum of Compound 41b in CDCl$_3$
Figure 24 IR Spectrum of Compound 41b

Figure 25 $^1$H-NMR Spectrum of Compound 41g in CDCl$_3$
Figure 26 $^{13}$C-NMR Spectrum of Compound 41g in CDCl$_3$

Figure 27 $^1$H-NMR Spectrum of Compound 41f in CDCl$_3$
Figure 28 $^{13}$C-NMR Spectrum of Compound 41f in CDCl$_3$

Figure 29 $^1$H-NMR Spectrum of Compound 41h in CDCl$_3$
Figure 30 $^{13}$C-NMR Spectrum of Compound 45h in CDCl$_3$

Figure 31 $^1$H-NMR Spectrum of Compound 41i in CD$_3$COCD$_3$
Figure 32 $^{13}$C-NMR Spectrum of Compound 41i in CD$_3$COCD$_3$

Figure 33 $^1$H-NMR Spectrum of Compound 58 in CDCl$_3$
Figure 34 $^{13}$C-NMR Spectrum of Compound 58 in CDCl$_3$

Figure 35 IR Spectrum of Compound 58
Figure 36 $^1$H-NMR Spectrum of Compound 47a in CDCl$_3$

Figure 37 $^{13}$C-NMR Spectrum of Compound 47a in CDCl$_3$
Figure 38 $^1$H-NMR Spectrum of Compound 48a in CDCl$_3$

Figure 39 $^{13}$C-NMR Spectrum of Compound 48a in CDCl$_3$
Figure 40 IR Spectrum of Compound 48a

Figure 41 $^1$H-NMR Spectrum of Compound 47d in CDCl$_3$
Figure 42 $^{13}$C-NMR Spectrum of Compound 47d in CDCl$_3$

Figure 43 IR Spectrum of Compound 47d
Figure 44 $^1$H-NMR Spectrum of 48d in CDCl$_3$

Figure 45 $^{13}$C-NMR Spectrum of Compound 48d in CDCl$_3$
Figure 46 IR Spectrum of Compound 48d

Figure 47 $^1$H-NMR Spectrum of Compound 47e in CDCl$_3$
Figure 48 $^{13}$C-NMR Spectrum of Compound 47e in CDCl$_3$

Figure 49 IR Spectrum of Compound 47e
**Figure 50** $^1$H-NMR Spectrum of Compound 48e in CDCl$_3$

**Figure 51** $^{13}$C-NMR Spectrum of Compound 48e in CDCl$_3$
Figure 52 IR Spectrum of Compound 48e

Figure 53 $^1$H-NMR Spectrum of Compound 47g in CDCl$_3$
Figure 54 $^{13}$C-NMR Spectrum of Compound 47g

Figure 55 IR Spectrum of Compound 47g
Figure 56 $^1$H-NMR Spectrum of Compound 48g in CDCl$_3$

Figure 57 $^{13}$C-NMR Spectrum of Compound 48g
Figure 58 IR Spectrum of Compound 48g

Figure 59 $^1$H-NMR Spectrum of Compound 47f in CDCl$_3$
Figure 60 $^{13}$C-NMR Spectrum of Compound 47f in CDCl$_3$

Figure 61 IR Spectrum of Compound 47f
Figure 62 $^1$H-NMR Spectrum of Compound 48f in CDCl$_3$

Figure 63 $^{13}$C-NMR Spectrum of Compound 48f in CDCl$_3$
Figure 64 IR Spectrum of Compound 48f

Figure 65 $^1$H-NMR Spectrum of Compound 47h in CDCl$_3$
Figure 66 $^{13}$C-NMR Spectrum of Compound 47h in CDCl$_3$

Figure 67 IR Spectrum of Compound 47h
Figure 68 $^1$H-NMR Spectrum of Compound 48h in CDCl$_3$

Figure 69 $^{13}$C-NMR Spectrum of Compound 48h in CDCl$_3$
Figure 70 IR Spectrum of Compound 48h

Figure 71 $^1$H-NMR Spectrum of Compound 49a in CDCl$_3$
Figure 72 $^{13}$C-NMR Spectrum of Compound 49a in CDCl$_3$

Figure 73 IR Spectrum of Compound 49a
Figure 74 $^1$H-NMR Spectrum of Compound 49d in CDCl$_3$

Figure 75 $^{13}$C-NMR Spectrum of Compound 49d in CDCl$_3$
Figure 76 IR Spectrum of Compound 49d

Figure 77 $^1$H-NMR Spectrum of 49e in CDCl$_3$
Figure 78 $^{13}$C-NMR Spectrum of Compound 49e in CDCl$_3$

Figure 79 IR Spectrum of Compound 49e
**Figure 80** $^1$H-NMR Spectrum of Compound 49g in CDCl$_3$

**Figure 81** $^{13}$C-NMR Spectrum of Compound 49g in CDCl$_3$
Figure 82 IR Spectrum of Compound 49g

Figure 83 $^1$H-NMR Spectrum of 49f in CDCl$_3$
Figure 84 $^{13}$C-NMR Spectrum of Compound 49f in CDCl$_3$

Figure 85 IR Spectrum of Compound 49f
Figure 86 $^1$H-NMR Spectrum of 49c in CDCl$_3$

Figure 87 $^{13}$C-NMR Spectrum of Compound 49c in CDCl$_3$
Figure 88 IR Spectrum of Compound 49c

Figure 89 1H-NMR Spectrum of 49b in CDCl₃
Figure 90 $^{13}$C-NMR Spectrum of Compound 49b in CDCl$_3$

Figure 91 IR Spectrum of Compound 49b
Figure 92 $^1$H-NMR Spectrum of 57 in CDCl$_3$

Figure 93 $^{13}$C-NMR Spectrum of Compound 57 in CDCl$_3$
Figure 94 $^1$H-NMR Spectrum of 60 in CDCl$_3$

Figure 95 $^{13}$C-NMR Spectrum of Compound 60 in CDCl$_3$
Figure 96 IR Spectrum of Compound 60

Cartesian Coordinates for the Optimized Structure 50a

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