SYNTHESIS OF 2, 5-DISUBSTITUTED INDOLES 
BY METAL MEDIATED REACTIONS

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January, 2011
DEDICATED

To

My Family
BANGLADESH UNIVERSITY OF ENGINEERING
AND TECHNOLOGY, DHAKA, BANGLADESH

DEPARTMENT OF CHEMISTRY

THESIS ACCEPTANCE LETTER

The thesis titled "Synthesis of 2, 5-disubstituted indoles by metal mediated reactions"
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Thesis title: **Synthesis of 2, 5-disubstituted indoles by metal mediated reactions.**

**Abstract**

Indole derivatives are one of the most privileged structure motifs frequently found in natural products, pharmaceuticals, functional materials, and agrochemicals. Synthesis and biological evaluation of indole derivatives have been a topic of special interest to organic and medicinal chemist. Here a convenient method for the synthesis of 2, 5-disubstituted indole derivatives through palladium catalyzed cross-coupling reaction followed by base catalyzed and palladium catalyzed intramolecular cyclization reaction is reported. In this purpose, 2-iodo-4-substituted-N-ethanoyl anilines 4, 7 were synthesized by the iodination of their parent 4-substituted anilines using I_2, (CH_3COO)_2Cu in CH_3COOH. The cross-coupling reaction of 2-iodo-4-substituted-N-ethanoyl anilines 4, 7 with terminal alkynes 11-13 were carried out in the presence of (Ph_3P)_2PdCl_2, CuI, and Et_3N in DMF at 60-80°C for 24-48 h under nitrogen atmosphere to yield 2-alkynyl-4-substituted-N-ethanoyl anilines 14-18. The condensed products 14, 15, 17 were subjected to base catalyzed cyclization by EtONa in EtOH at 80°C for 4-6 h to yield 2, 5-disubstituted-1H indoles 20, 22 along with a cyclic by products 2-alkynyl-4-substituted anilines 21, 23, 24. The condensed products 15-17 were also subjected to intramolecular cyclization by PdCl_2 in CH_3CN at 80°C for 0.5-2 h to yield 2, 5-disubstituted -N-ethanoyl indoles 25-27 only.

In *vitro* antimicrobial activities of the synthesized compounds 4, 7, 14-18, 25-27 were evaluated. None of the compound showed inhabitant activity against the gram positive and gram negative bacteria as well as human fungal pathogens.
SUMMARY

Investigation incorporated in this dissertation titled, “Synthesis of 2, 5–disubstituted indoles by metal mediated reactions” have been presented in four chapters. The first chapter is introductory section, in which the background, biological action and the important synthesis are presented. The chapter • deals with rationale, results and discussion, mechanism, and conclusion for the synthesis of 2, 5-disubstituted indoles. The chapter •• deals with the detailed methodologies and experimental procedure for the synthesis of the 2, 5-disubstituted indoles, spectra, and reference. The chapter ••• deals with the antimicrobial screening of the synthesized product.

Chapter •

It represents the important and synthesis of indole derivatives. Indoles are a class of fused heterocycles that are the constant interest in synthetic and pharmaceutical chemistry. In spite of their scarce presence of nature, indole derivatives have proved considerable interest due to their pharmacological activities. Various methods are known for the synthesis of indole derivatives but convenient palladium catalysed procedure for the synthesis of indole is limited in number.

Chapter ••

In this section the results and discussion are presented. Here a convenient approach for the synthesis of substituted indole derivatives through palladium catalyzed reaction of 4-disubstituted-2-iodo-N-ethanoyl aniline with terminal alkynes. The condensed products were subjected to base catalyzed and palladium catalyzed cyclization.

The yields (%) of the condensation reactions are slightly higher for phenyl acetylene and n-hexyne (65-70 %) compared with n-heptyne (60 %) with different aryl iodide. For the condensation reaction between aryl iodide and phenyl acetylene showed faster reaction compared with n-hexyne or n-heptyne in the identical condition. The cyclization of 4-substituted-2-(1-alkynyl)-N-ethanoyl aniline 16-18 using palladium chloride in acetonitrile to afford 2, 5-disubstituted-N-ethanoyl indole 25-27 in good yield. Base catalyzed cyclization of substituted-2-(1-alkynyl)-N-ethanoyl aniline 14, 15, 18 using sodium ethoxide in ethanol gave 2, 5-di substituted-1H indole 20, 22 along with 4-substituted-2-(1-alkynyl) aniline 21, 23, 24.
Chapter ***

In the experimental section the general procedure for the synthesis of indole is described. For this purpose first of all, different aryl iodide were synthesized from 4-substituted aniline using iodine-copper acetate in acetic acid. The palladium catalyzed reactions were carried out by stirring the mixture of 4-substituted-2-iodo-\(N\)-ethanoyl aniline 4, 7, terminal alkynes 11-13 (1.2 mol equiv.), bis(triphenylphosphine) palladium(\(\equiv\)) chloride (3.5 mol %), copper(\(\equiv\)) iodide (8 mol %) and triethylamine (4 mol equiv.) under nitrogen atmosphere in DMF(5-8 mL) at 60°-80°C for 24-48 hours. After usual workup condensed products 4-substituted-2-(1-alkynyl)-\(N\)-ethanoyl aniline 14-18 with 60-68% yields were obtained. Then the condensed products 14, 15, 17 were subjected to base catalyzed cyclization using sodium ethoxide (1.2-1.5 mol equiv.) in ethanol at 80°C under nitrogen atmospheres to afford 2, 5-disubstitued-1\(H\) indole derivatives 20, 21. The condensed product 15-17 were also subjected to palladium(\(\equiv\)) chloride(10 mol %) catalyzed cyclization in acetonitrile at 80°C to afford 2, 5-disubstitued-\(N\)-ethanoyl indole 25-27 in good yield.

Chapter **V**

In this chapter antimicrobial screening of the synthesized compound were reported. This contains introduction, methodology, results and discussion, conclusion and reference. In vitro antimicrobial activities of the synthesized compounds 4, 7, 14-18, 25-27 were evaluated. None of the compound showed inhabitant activity against the gram positive and gram negative bacteria as well as human fungal pathogens.
LIST OF ABBREVIATIONS

Ac        acetyl
aq.       aqueous
bp        boiling point
br        broad
d         doublet
dec.      decomposition
DMF       N, N-dimethyl formamide
equiv.    equivalent
Et        ethyl
Et₂O      diethyl ether
EtOAc     ethyl acetate
h         hour
hv        light
Hz        hertz
IR        infrared (spectrum)
J         coupling constant
m         multiplet or medium
M         mass or metal
min       minutes
mmol      mili mole
mol       mole
mol %     mole percent
mp.       melting point
NMR       nuclear magnetic resonance
OAc       acetate
Ph        phenyl
PhH       benzene
ppm       parts per million
quin.     quintet
rt  room temperature
s  singlet/ strong/ second
t  triplet
T  temperature
TLC  thin layer chromatography
TMS  tri methylsilyl
UV  ultra violet
W  weak
•  heat/ reflux
• H/ • c  chemical shift
• max  ultraviolet absorption in nm
• max  infrared absorption in cm⁻¹
INTRODUCTION
INTRODUCTION

1.1 General remarks

Indole derivatives are one of the most privileged structure motifs frequently found in natural products, pharmaceuticals, functional materials, and agrochemicals. Owing to the great structural diversity of biologically active indoles, indole ring system has become an important structural component in many pharmaceutical agents. This is exemplified by the amino acid tryptophan serves as a precursor for two chemically closely related hormones serotonin as vasconstrictor and neurotransmitter, melatonin exhibits a circadian rhythm, free radical scavenger & antioxidant.

1.2 Importance of indole derivatives

1.2.1 As Chemotherapeutic and pharmacological agents

Substituted indoles skeletons are widely found in bioactive compounds of medicinal interest. Indole derivatives have many fold uses. Some of them are mentioned bellow:

1.2.1.1 As antiviral agent.

i) The synthetic compound Arbidol has a bility to elicit protective broad-spectrum antiviral activity against a number of human pathogenic respiratory viruses.
Arbidol is used as antiviral treatment for influenza infection in Russia.\textsuperscript{10} Antiviral effects of Arbidol have also been reported against hepatitis C and hepatitis B viruses.\textsuperscript{11,12}

ii) Indolyl aryl sulfones \textsuperscript{6} bearing the 5-chloro-4-fluoro substitution pattern at the indole ring are potent inhibitors of HIV.\textsuperscript{13}

iii) S. Guo et al\textsuperscript{14} synthesized the indole derivatives \textsuperscript{7, 8, 9} displayed moderate inhibitory activities toward Bacillus anthracis and Mycobacterium tuberculosis.

iv) Merk NNRT agent L-737, 126\textsuperscript{15} \textsuperscript{10} has the antiviral activity against wt-HIV-1.

1.2.1.2 As anti cancer agent:

i) Vinblastine \textsuperscript{16,17} \textsuperscript{11} is used as the therapeutic agent to treat a variety of neoplastic diseases including Hodgkin’s disease, chronic carcinoma, acute and chronic leukemia’s, lymphosarcomas and a variety of other cancer.\textsuperscript{18}
ii) Dashwood et al.\textsuperscript{19} claimed the first direct evidence of pure anti-initiating activity by a natural anti-carcinogen indole-3-carbinol \textbf{12} found in human diet. The compound \textbf{12} has the potential therapeutic benefit against breast cancer.\textsuperscript{20} Tetramer \textbf{13} is about 5-fold more active than \textbf{12} in suppressing the growth of human breast cancer cell.\textsuperscript{21}

iii) N-Heterocyclic Indolyl Glyoxylamides \textbf{14} is an orally active anticancer agent,\textsuperscript{22} exhibited a broad spectrum of anticancer activity not only in murine leukemic cancer cells but also in human gastric, breast, and uterus cancer cell.

iv) The palladium complex \textbf{15} trans-[Pd (harmine) (DMSO) Cl\textsubscript{2}] exhibits a greater anticancer activity\textsuperscript{23} against different cancer cell line.
v) Pyrazolo [1, 5-a] indole derivatives 16 has growth inhibitory activities against human cancer cell lines.\textsuperscript{24}

\begin{align*}
15 & 16 \\
TfO^- & = \text{tri fluoro methane sulfonate}
\end{align*}

1.2.1.3 As antitumour agent:

i) Ellipticine 17 is used as antitumour agent.\textsuperscript{25}

ii) Antitumour 4-[1-(Arylsulfonyl-1H-indol-2-yl)]-4-hydroxycyclohexa-2, 5-dien-1-ones 18 showed selective in vitro inhibition of cancer cell lines of colon and renal.\textsuperscript{26}

\begin{align*}
17 & 18
\end{align*}

1.2.1.4 As antibacterial agent.

i) Antibacterial activity of ramiflorines 19 could be used against the most common Gram-positive pathogens.\textsuperscript{27}
ii) A novel Indole analogue 20 that inhibits the Gram negative bacteria *Pseudomonas aeruginosa* growth.  

iii) Indole-3-carboxylidine-DL-valine 21 has found to be sensitive against *E.coli*.  

1.2.1.5 As anti fungal agent  
The indole analogue 1-halogenobenzyl-3-imidazolylmethylindole derivative 22 exerted significant antifungal activity against *C. albicans* and 23 exhibited 16-fold higher than that of reference itraconazole.
1.2.1.6 As insecticidal agent
12-epi-Hapalindole J isonitrile 24 at 26 µM killed 100% of the larvae of the dipterans Chironomus riparius within 48 h.

24

1.2.1.7 As anti diabetics
i) The synthesized indole analogue 25 was found to be very potent insulin sensitizer comparable to clinically used drug rosiglitazone.

25

ii) Lidorestat 26 congeners as highly potent and selective inhibitors of aldose reductase for treatment of chronic diabetic complications.

26

iii) The indole analogue 27 which exhibits a novel selective for the treatment of type 2 diabetes Mellitus. 34
1.2.1.8 As anti-inflammatory drug

i) Indometacin 28 is a non-steroidal anti-inflammatory drug commonly used to reduce fever, pain, stiffness, and swelling. It works by inhibiting the production of prostaglandins, molecules known to cause these symptoms. It is an effective tocolytic agent. 36

ii) Etodolac 29 and Tenidap 30 are also non-steroidal anti-inflammatory drugs (NSAIDs). Tenidap is an inhibitor of prostaglandin interleukin-1 production in the body used for the treatment of rheumatoid arthritis and osteoarthritis.
1.2.1.9 As Psychotropic drug
Lysergic acid diethylamide 31 was used in psychiatry to enhance psychotherapy.\textsuperscript{40,41}

1.2.1.10 As Antidepressants
The synthesized indole analogue 32 is an efficient treatment of depression.\textsuperscript{42}

1.2.1.11 As antihypertensive
Ajmalicine 33 is an antihypertensive drug used in the treatment of high blood pressure.\textsuperscript{43,44}
1.2.1.12 As antihistamine

i) Latrepirdin 34 is an antihistamine drug used clinically in Russia.\textsuperscript{45}

ii) The indole analogue 35 is an antihistamine drug.\textsuperscript{46} It has anti-inflammatory effects\textsuperscript{47} and has been demonstrated to be superior to traditional antihistamines in the treatment of pruritus (itching).\textsuperscript{48}

1.2.2 As photolytic agent

The indole derivatives 5-methoxy-2-phenylindole 36 is used in photolysis study.\textsuperscript{49}

1.2.3 As indole alkaloids synthesis

The indole derivatives 2-ethoxycarbonyl-6-methoxy-3-methylindole 37 is used in indole alkaloids synthesis.\textsuperscript{50}
1.2.4 Used for synthesis of coenzyme

The indole derivatives 38, 39 is used in the synthesis of coenzyme PQQ (pyrroloquinoline quinone) analogs.51, 52
Indole synthesis
Indole synthesis

1.3 The indole nucleus is one of the most important heterocycles due to its presence in a vast number of bioactive natural products, pharmaceuticals, and agrochemicals. Synthesis and functionalization of indoles have been the subject of intensive research for over 100 years, and a variety of well-documented traditional and modern methods are now available. However, the development of general and efficient methods for preparation of functionalized indoles from simple and easily accessible starting materials remains an active research field. In this context the synthesis of indole derivatives have been categorized into three main types as follows:

- well established classical methods.
- metal-catalyzed indole synthesis without a Pd catalyst.
- Pd-catalyzed indole synthesis.

1.3.1 Classical methods
i) Fischer indole synthesis

Fischer indole synthesis produces indole from a (substituted) phenyl hydrazine and an aldehyde or ketone under acidic conditions.

Scheme-1

The venerable Fischer indole synthesis have been used both new and old, and to the large-scale production of pharmaceutical intermediates. A one-pot synthesis of indoles from phenylhydrazine hydrochloride and ketones in acetic acid with microwave irradiation.
The thermal cyclization of N-trifluoroacetyl eneydrazines leads to indoles (or indolines) under relatively mild conditions.\textsuperscript{64}

\textbf{Scheme-3}

ii) Bartoli indole synthesis

In Bartoli indole synthesis, ortho-substituted nitro arenes react with vinyl Grignard reagents to form substituted indoles.\textsuperscript{65-68}
Adrian Dobbs greatly enhanced the scope of the Bartoli indole synthesis by using an ortho-bromine as a directing group, which is subsequently removed by AIBN and tri butyltin hydride.  

Scheme-5

iii) The Madelung indole synthesis produces (substituted or unsubstituted) indoles by the intramolecular cyclization of N-phenylamides using strong base at high temperature.

Scheme-6

The Classical Madelung indole synthesis was modified by Houlihan which utilizes BuLi or LDA as bases under milder conditions. For example, benzylphosphonium salts such as undergo facile cyclization to indoles under thermal conditions. The basecatalyzed version of this reaction has been adapted to solid phase synthesis.
iv) Leimgruber–Batcho indole synthesis

The Leimgruber–Batcho indole synthesis involves the conversion of a n-o-nitrotoluene to a dialkylamino-o-nitrostyrene with dimethylformamide acetal, followed by reductive cyclization to an indole.

Ochi and co-workers have used this protocol to prepare 6-bromo-5-methoxyindole for use in the synthesis of marine bromoindoles. Showalter et al. synthesized 6-amino-5-ethoxycarbonylindole and 6-amino-7-ethoxycarbonylindole from the appropriate o-nitrotoluenes. The Leimgruber–Batcho method has been used to make C-4 substituted indoles for elaboration to conformationally-restricted analogs of indolomycin, and for the synthesis of arcyriacyanin A. It has been used in a large-scale synthesis of 6-bromoindole. An important extension of this indole ring synthesis is the functionalization of the intermediate dialkylamino-o-styrene. Clark and co-workers have acylated this intermediate enamine to yield which was converted to indole after reductive cyclization.
1.3.2 **Metal-catalysed indole synthesis without a Pd catalyst**

Among a variety of new synthetic transformations, transition-metal-catalyzed reactions are some of the most attractive methodologies for synthesizing heterocyclic compounds, since a transition-metal-catalyzed reaction can directly construct complicated molecules from readily accessible starting materials under mild conditions. This may be exemplified as follows:

i) Rhodium

The Rh-catalyzed hydroformylation of functionalized anilines leads to tryptophanols and tryptamine.\(^{83}\)

---

**Scheme-10**

The cationic Rh(I) dicarbonyl complex \([\text{Rh}(\text{mim}_2\text{-CH}_2\text{(CO)}_2)]^+\text{BPh}_4^-\), containing a bidentate bisimidazolymethane ligand (mim) \(N\)-methylimidazol-2-yl), was synthesized by Messerle et al.\(^{84}\) and proved to be an effective catalyst for the intramolecular hydroamination of aliphatic and aromatic alkynes.\(^{85}\)
ii) Titanium

Ti-induced reductive cyclization of oxo amides leading to an indole ring. This coupling reaction leads to the total syntheses of the indole alkaloids (-)aristoteline, camalexin, flavopereirine and other indolo[2,3-a]quinolizine alkaloids, and secofascaplysin. The reaction is general for simple indoles including highly strained examples (2,3-dibutyl-1-methylindole). It is also particularly useful for the preparation of 2-arylinodoles.

two new titanium complexes, Ti(NMe$_2$)$_2$- (dap)$_2$ and Ti(NMe$_2$)$_2$(SC$_6$F$_5$)$_2$(NHMe)$_2$, that catalyzed the hydroamination of terminal and some internal alkynes by 1,1-disubstituted hydrazines at 75-100°C.
iii) Zarconium

Intramolecular alkene insertion into a zirconium-stabilized aryne complex and subsequent oxidation has been used to prepare 3,4-disubstituted indoles, tryptophans and serotonin analogs and dehydrobufotenine.

iv) Copper

Castro et al. were the first to discover the metal-catalyzed cyclization of o-alkynylanilines to indoles using copper. Castro’s discoveries include the copper acetylide coupling with o-iodoanilines and the CuI-induced cyclization of o-alkynylanilines to yield indoles.

The Castro indole synthesis has been used to prepare -C-mannosylindole.
An interesting copper(I)-catalyzed cascade reaction for the synthesis of 2-(aminomethyl)indoles has been recently reported.\textsuperscript{101} This protocol implies the three-component coupling reaction of an N-protected o-ethynylaniline, paraformaldehyde and an amine in a process whereby a molecule of water is the only by-product.

\begin{center}
\textbf{Scheme-16}
\end{center}

Substituted indoles are formed from anilino-substituted Fischer chromium carbenes having o-alkenyl substituents on the benzene ring.\textsuperscript{102}
vi) Molybdenum: McDonald and Chatterjee have discovered the molybdenum promoted cyclization of 2-ethynylanilines to indoles.\textsuperscript{103}

\textbf{Scheme-19}

vi) Tin: Tin-mediated cyclization of 2-alkenylaryl isocyanides and tributyltinhydride on to the triple bond of the trimethylsilylacetylene produced the indole with no \textit{endo} cyclization to a quinoline.\textsuperscript{104,105}

\textbf{Scheme-20}

vii) Zinc:
A environmentally friendly and convenient one pot method for the synthesis of substituted indoles starting from commercially available arylhydrazines and terminal alkynes in a reaction promoted by Zn(OTf)\textsubscript{2} or ZnCl\textsubscript{2}.\textsuperscript{106}

\textbf{Scheme-21}
viii) Platinum
M. Malacria, L. Fensterbank, and co-workers devised an expedient route to 2,3-functionalized indoles from N-allyl 0-propargyl anilines using of PtCl₂ or a protic acid as catalyst.¹⁰⁷

Scheme-22

ix) Gold
Sodium-gold (III) complexes¹⁰⁸ catalysts reaction between 0-alkynylaniline derivatives and alkene containing unsaturated carbonyl compounds to get 2-substituted 3-alkylindoles.

Scheme-23

x) Tungsten
N. Iwasawa and co-workers¹⁰⁹ reported using a starting materials amines and [W(CO)₆] as catalyst under photo irradiation conditions leads to N-fused tri- and tetra cyclic indoles.
2.1.3 Pd-catalysed indole synthesis

Palladium catalyzed reactions, generally tolerant of a wide range of functionalities and therefore applicable to complex molecules, have achieved an important place in the arsenal of the practicing organic chemist. Almost every area of the organic synthesis has been deeply influenced by the profound potential of this versatile transition metal, modifying the way organic chemists design and realize synthetic processes.\textsuperscript{110,111} Because of its catalytic nature, palladium-catalyzed synthesis can provide access to fine chemicals, agrochemical and pharmaceutical intermediates, and active ingredients in fewer steps and with less waste than classical methods.

Pd(II)- and Pd(0)-Catalyzed Reactions, Phosphine Ligands, and Additives:

Both palladium(II) salts and palladium(0) complexes have been used in indole chemistry. Palladium(II) salts are fairly electrophilic species and tend to react with electron-rich compounds such as alkenes, alkynes, and arenes. The most commonly used palladium(II) salts in indole chemistry, are commercially available PdCl\(_2\) and Pd(OAc)\(_2\),\textsuperscript{112} very often utilized as complexes of the type PdX\(_2\)L\(_2\) (where L stands for a ligand) such as PdCl\(_2\)(PPh\(_3\))\(_2\), Pd(OAc)\(_2\)(PPh\(_3\))\(_2\),\textsuperscript{113} and PdCl\(_2\)(MeCN)\(_2\).\textsuperscript{114}

The typical reaction of palladium (II) salts with alkenes or alkynes affords $\pi$-complexes (Scheme 25) which because of the decreased electron density at the carbon-carbon multiple bond can undergo an intermolecular or intramolecular nucleophilic attack across the coordinated olefinic or acetylenic moiety. Intramolecular nucleophilic attack with nitrogen nucleophiles on $\pi$-palladium complexes close to the carbon-carbon multiple bond is particularly useful for the synthesis of indoles.

With arenes, palladium(II) salts typically Pd(OAc)\(_2\) can produce palladation intermediates (compounds containing carbon-palladium $\pi$-bonds) (Scheme 25). This palladation intermediates can give rise to homocoupling reactions,\textsuperscript{115} acetoxylation reactions,\textsuperscript{116} or in the presence of alkenes, vinylic substitution reactions.\textsuperscript{117}

Palladium(0) complexes contain a d\(^{10}\) palladium and are usually nucleophilic. Coordinatively unsaturated Pd(0) complexes react with covalent polar and nonpolar X-Y bonds (for example, N-H, C-H, C-X, or C-O) via an oxidative addition process producing X-Pd(II)-Y derivatives (containing an electrophilic palladium), which depending on reaction conditions, can undergo a variety of transformations. A great deal of indole chemistry is based on the oxidative addition of vinyl, aryl, heteroaryl halides, or triflates to generate addition intermediates containing $\pi$-carbon-palladium(II)
bonds (Scheme 25) in an initial step of their catalytic process, including the reactions involving indolyl halides and triflates. The reaction of palladium(0) complexes with allylic esters, typically acetates or carbonates, affords allylic palladium complexes (Scheme 25) which can undergo a nucleophilic attack at one of the allylic termini to afford allylation products.\textsuperscript{118}

\begin{center}
\textbf{Scheme-25}
\end{center}

Strategies in the palladium-catalyzed Synthesis of indole derivatives:

Cyclization reactions usually involve the assembly of the functionalized pyrrole nucleus on a benzenoid scaffold. Most of the alkyne-based palladium-catalyzed approaches to the assembly of the pyrrole ring and alkene-based precursors containing nitrogen nucleophiles and carbon-carbon double bonds are shown bellow. In addition to alkyne- and alkene-based procedures, strategies for the construction of the functionalized pyrrole nucleus are based on the intramolecular vinylation and the Buchwald/ Hartwig, N-arylation process.\textsuperscript{119}

Retro synthetic representation of the alkyne based palladium-catalyzed assembly of the pyrrole ring.
Retro synthetic representation of the alkene based palladium-catalyzed assembly of the pyrrole ring.

Assembly of the pyrrole nucleus contained in the indole system
i) Cyclization of o-alkynylanilines and o-alkynylanilides catalyzed by Pd(II) Salts.

Treatment of o-(phenylethynyl)acetanilides with PdCl$_2$ in acetonitrile results in smooth cyclization to N-acyl- 2-phenylindoles, from which free NH indoles are obtained by deacylation with alcoholic potassium hydroxide$^{120}$. The process occurs under conditions consistently milder than those described by Castro et al.$^{121}$ for the synthesis of indoles from o-iodoanilines and cuprous acetylides.
The versatility of the palladium-catalyzed cyclization was demonstrated in the synthesis of novel optically active tryptophan analogues from aniline-containing acetylenic amino acids.\textsuperscript{122}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{scheme-28.png}
\caption{Scheme-28}
\end{figure}

ii) Cyclization of 0-alkynylanilides

A broad range of 2, 3-disubstituted indoles can be prepared from 0 alkynyltrifluoroacetanilides and aryl, heteroaryl, and vinyl halides or triflates,\textsuperscript{123} allyl esters,\textsuperscript{124} alkyl halides,\textsuperscript{125} and alkynyl bromides\textsuperscript{126} by using Pd(0) catalyzed. With aryl, heteroaryl, and vinyl halides or triflates\textsuperscript{123} reactions were carried out according to the conditions shown in Scheme .
iii) Intermolecular cycloaddition of o-iodoanilines and o-iodoanilides with internal alkynes
2, 3-disubstituted indoles were isolated in good to excellent yields.\textsuperscript{127a,b} by treating o-iodoaniline or
the corresponding N-methyl, N-acetyl, and N-tosyl derivatives with an excess of the internal alkyne
and a sodium or potassium carbonate base and 1 equiv of LiCl or Bu\textsubscript{4}NCl and occasionally adding
5 mol % of PPh\textsubscript{3} at 100°C in DMF.

iv) Cyclization of o-alkynyl-N-alkylidene-anilines
Yamamoto et al.\textsuperscript{128} reported a palladium-catalyzed indole synthesis in which a new carbon-carbon
bond formed between the C-2 and the C-3. In this synthesis 2-(1-alkynyl)-N-alkylidene anilines
undergo a palladium-catalyzed cyclization to give 2-substituted 3-vinylindoles.

v) Cyclization of o-Halo-N-alkynylanilides and o-Iodo-N-propargylanilides
o-halo-N-alkynylanilides and o-halo-N-propargylanilides were employed as the starting alkynes to
construct the functionalized pyrrole ring. Witulsky and co-workers\textsuperscript{129} reported the palladium-catalyzed
reaction of o-halo-N-alkynylanilides with primary or secondary amines to give the interesting class of
2-aminoindoles.
vi) Grigg et al.\textsuperscript{130} reported a cascade process leading to indoles containing polycyclic substituents at the C-3 starting from o-iodo-N-propargylanilides and norbornene.

\textbf{Scheme-33}

Cyclization of Alkenes

i) o-Halo-N-allylaniline: The first synthesis of indoles based on the intramolecular Heck reaction was described by Mori et al.\textsuperscript{131} from o-halo-N-allylanilides containing the side-chain olefin conjugated to a carbonyl group.

\textbf{Scheme-34}

ii) o-Haloanilino enamines: Formation of indole derivatives from o-haloanilino enamines\textsuperscript{132} (derived from o-bromoanilines and 1,3-dicarbonyls) were subjected to cyclization conditions and afforded the desired products in low to moderate yields at high temperature.
iii) 0-Iodoanilines with an allene functionality connected to the nitrogen atom: 0-iodoanilines with an allene functionality connected to the nitrogen atom were indeed cyclized to indoles.$^{133}$

iv) 0-Allylanilines: Hegedus et al.$^{134}$ described an intramolecular version of the reaction in which 0-allylanilines underwent palladium-assisted cyclization to 2-methylindoles.

v) 0-Vinylanilines: Hegedus and co-workers reported the successful palladium-catalyzed preparation of indole from 0-vinylaniline.$^{135}$
vi) o-Nitrostyrenes: Watanabe et al.\textsuperscript{136} described the preparation of indoles via reductive N-heteroannulation in the presence of carbon monoxide, catalytic amounts of PdCl$_2$(PPh$_3$)$_2$ and an excess of SnCl$_2$ (Sn/Pd 10:1).

vii) o-Vinylphenyl Isocyanide: The three-component reaction of aryl iodides, o-vinyl isocyanide, and diethylamine was found to give 2, 3-disubstituted indoles according to Scheme.\textsuperscript{137}

Cyclization via intramolecular coupling of vinyl halides onto aromatic positions

In this type of cyclization the oxidative addition site is located in a vinylic fragment tethered to the benzenoid ring. This synthetic strategy was applied to the preparation of indole carbamates from phenolic carbamates containing a bromovinylic fragment bound to the nitrogen atom.\textsuperscript{138}
Cyclization via Intramolecular C-N Bond Forming Reactions

The C-N bond forming reaction to the direct formation of indole rings by intramolecular N-arylation were also reported. The conversion of o-(2,2-dibromovinyl)-phenylaniline and o-(2,2-dibromovinyl)-phenylacetanilide into 2-functionalized indoles through domino palladium-catalyzed coupling-cyclization reactions according to the conditions shown in Schemes.\textsuperscript{139}

1.4 Functionalization of the preformed indole system

Reaction with Pd(II) salts

Fujiwara and coworkers described a reaction in which the indolyl unit is involved in the regioselective addition to the carbon-carbon triple bonds of ethyl alkynoates.\textsuperscript{140}
Scheme-43

Reaction with organopalladium complexes
The selective targeting of C-H bonds in the presence of free NH functionality\textsuperscript{141} was carried out in the presence of the inexpensive and easy to handle MgO, which presumably affords an indolylmagnesium hydroxide.

Scheme-44

A mild, Pd(OAc)$_2$-catalyzed regioselective cross-coupling between indoles and potassium aryltrifluoroarylborates gives 2-aryl indoles in moderate yields in the presence of Cu(OAc)$_2$ in acetic acid at room temperature.\textsuperscript{142}
An efficient, practical, and highly regioselective direct palladium-catalyzed C-3 arylation of electron-rich free (NH)-indoles with various aryl bromides under ligand less conditions in refluxing toluene in the presence of K$_2$CO$_3$ as the base can be run outside a glove box without purification of solvent and reagents.$^{143}$

Scheme-46

Reaction with alkenes
Heck and co-workers$^{144}$ showed that 5-bromoindole reacted with methyl acrylate to give the corresponding vinylated indole in 53% yield. Hegedus et al.$^{145}$ showed that 4-bromo-1-tosylindole could be readily converted into a number of 4-substituted 1-tosylindoles via the Heck reaction with electron poor, neutral, and electron-rich olefins.

Scheme-47

Reaction with alkynes
Yamanaka et al.$^{146}$ described the palladium- catalyzed cross-coupling of 3-iodoindole derivatives with terminal alkynes under Sonogashira$^{147}$ conditions.
Hegedus et al.\textsuperscript{148} applied the Zn-based methodology, known as the Negishi reaction, to the selective functionalization of the C-3 position of a 3-iodo-4-bromo indole.

Gribble et al.\textsuperscript{149} prepared the triphenylphosphonium salt from 1-(phenylsulfonyl)-3-indolyl triflate and triphenyl phosphine.
Antimicrobial screening
INTRODUCTION

4.1 Bacteria and fungi are responsible for many infectious diseases. The increasing clinical implications of drug resistant fungal and bacterial pathogens have lent additional urgency to antimicrobial drug research. The deterioration of human population due to enhancement of prevalence of infectious diseases is becoming a global problem.

It was found from the literature that nitrogen and sulfur containing compounds showed marked microbial activities. In the vast heterocyclic structural space, the indole nucleus occupies a position of major importance. Many indole derivatives, including fused derivatives, form the basis of a range of pharmaceuticals and a high level of activity continues in the search for new indole-based medicinal agents. The known compound 5-nitro-2-phenyl-1H-indole (INF55) is an inhibitor of the NorA efflux pump in the human pathogenic bacterium Staphylococcus aureus.

Recently, our groups synthesized 2-substituted benzofurans, isoquinolinone and isoindonone and tested their antibacterial and antifungal activities.

In our present study, a total of two 4-substituted-2-iodo-N-ethanoyl aniline, five 4-substituted-2-(1-alkynyl)-N-ethanoyl aniline, and three 2,5-disubstituted indole derivatives have been tested for antimicrobial activity against five Gram positive and nine Gram negative bacteria as well as four human fungal pathogens.

4.2 Materials and methods

The antibacterial activities of furan derivatives were studied against thirteen bacteria and the activities of the same compounds were also studied against three fungi. For the detection of antibacterial activities the disc diffusion method was followed.

The antimicrobial screening which is the first stage of antimicrobial drug research is performed to ascertain the susceptibility of various fungi and bacteria to any agent. This test measures the ability of each test sample to inhibit the in vitro fungal and bacterial growth. This ability may be estimated by any of the following three methods.

a) Disc diffusion method
b) Serial dilution method
c) Bioautographic method

Among the above mentioned techniques the disc diffusion is a widely accepted in vitro investigation for preliminary screening of test agents which may possess antimicrobial activity. It is essentially a quantitative or qualitative test indicating the sensitivity or resistance of the microorganisms to the test materials. However, no distinction between bacteriostatic bactericidal activity and bactericidal activity can be made by this method.

4.3 Principle of disc diffusion method

In this classical method, antibiotics diffuse from a confined source through the nutrient agar gel and create a concentration gradient. Dried and sterilized filter paper discs (6 mm diameter) containing the test samples of known amounts are placed on nutrient agar medium uniformly seeded with the test microorganisms. Standard antibiotic (Doxacilina) discs and blank discs are used as positive and negative control. These plates are kept at low temperature (4°C) for 24 hours to allow maximum diffusion of the test materials to the surrounding media. The plates
are then inverted and incubated at 37°C for 24 hours for optimum growth of the organisms. The test materials having antimicrobial property inhibit microbial growth in the media surrounding the discs and thereby yield a clear, distinct area defined as zone of inhibition. The antimicrobial activity of the test agent is then determined by measuring the diameter of zone of inhibition expressed in millimetre.

In the present study the crude extracts, fractions as well as some pure compounds were tested for antimicrobial activity by disc diffusion method. The experiment is carried out more than once and the mean of the readings is required.

4.4 Experimental
4.4.1 Apparatus and reagents:
Filter paper discs          Petri dishes          Inoculating loop
Sterile cotton             Sterile forceps        Spirit burner
Micropipette               Screw cap test tubes   Nose mask and Hand gloves
Laminar air flow booth     Autoclave               Incubator
Refrigerator               Nutrient agar medium   Ethanol
Chloroform

4.4.2 Test materials

Table 1: List of compounds used for antimicrobial activities

<table>
<thead>
<tr>
<th>Comp. No</th>
<th>Name of the test chemicals</th>
<th>Molecular structure</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>2-iodo-4-methyl-n-ethanoyl aniline</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>4-chloro-2-iodo-N-ethanoyl aniline</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>4-methyl-2-(phenyl ethynyl)-N-ethanoylaniline</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>4-methyl-2-(1-hexynyl)-N-ethanoyl aniline</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>----------------------------------------------------------------</td>
<td>----------------------------------------------------------------</td>
</tr>
<tr>
<td>16</td>
<td>4-methyl-2-(1-heptynyl)-N-ethanoyl aniline</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>4-chloro-2-(1-hexynyl)-N-ethanoyl aniline</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>4-chloro-2-(phenylethynyl)-N-ethanoyl aniline</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>2-butyl-5-methyl-N-ethanoyl indole</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>2-pentyl-5-methyl-N-ethanoyl indole</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>2-butyl-5-chloro-N-ethanoyl indole</td>
<td></td>
</tr>
</tbody>
</table>

### 4.4.3 Test organisms

The microbial strains used for the experiment were collected as pure cultures from the Institute of Nutrition and Food Science (INFS), University of Dhaka. Both gram positive and gram-negative organisms were taken for the test and they are listed in the **Table 2**.
List of test microorganisms

<table>
<thead>
<tr>
<th>Gram positive Bacteria</th>
<th>Gram negative Bacteria</th>
<th>Fungi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus cereus</td>
<td>Escherichia coli</td>
<td>Candida albicans</td>
</tr>
<tr>
<td>Bacillus megaterium</td>
<td>Pseudomonas aeruginosa</td>
<td>Aspergillus niger</td>
</tr>
<tr>
<td>Bacillus subtilis</td>
<td>Salmonella paratyphi</td>
<td>Sacharomyces cerevaceae</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>Salmonella typhi</td>
<td></td>
</tr>
<tr>
<td>Sarcina lutea</td>
<td>Shigella boydii</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Shigella dysenteriae</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vibrio mimicus</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Vibrio parahemolyticus</td>
<td></td>
</tr>
</tbody>
</table>

Composition of culture medium

Nutrient agar medium (DIFCO) (Table 14) was used in the present study for testing the sensitivity of the organisms to the test materials and to prepare fresh cultures.

4.4.4 Composition of nutrient agar medium.

a. Nutrient agar medium

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacto peptone</td>
<td>0.5 gm/litter</td>
</tr>
<tr>
<td>sodium chloride</td>
<td>0.5 gm/litter</td>
</tr>
<tr>
<td>Bacto yeast extract</td>
<td>1.0 gm/litter</td>
</tr>
<tr>
<td>Bacto agar</td>
<td>2.0 gm/litter</td>
</tr>
<tr>
<td>Distilled water q.s.</td>
<td>100 ml</td>
</tr>
<tr>
<td>pH</td>
<td>7.2-7.6 at 25°C</td>
</tr>
</tbody>
</table>

b. Nutrient broth medium

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacto beef extract</td>
<td>0.3 gm/litter</td>
</tr>
<tr>
<td>Bacto peptone</td>
<td>0.5 gm/litter</td>
</tr>
<tr>
<td>Distilled water q.s.</td>
<td>100 ml</td>
</tr>
<tr>
<td>pH</td>
<td>7.2±0.2 at 25°C</td>
</tr>
</tbody>
</table>

c. Mulet-Hunton medium

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beef infusion</td>
<td>30 gm/litter</td>
</tr>
<tr>
<td>Casamino acid</td>
<td>1.75 gm/litter</td>
</tr>
<tr>
<td>Starch</td>
<td>1.15 gm/litter</td>
</tr>
<tr>
<td>Bacto agar</td>
<td>1.70 gm/litter</td>
</tr>
<tr>
<td>Distilled water q.s.</td>
<td>100 ml</td>
</tr>
<tr>
<td>pH</td>
<td>7.3±0.2 at 25°C</td>
</tr>
</tbody>
</table>
d. **Tryptic soya broth medium**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Amounts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacto tryptone</td>
<td>1.7 gm/litter</td>
</tr>
<tr>
<td>Bacto soytone</td>
<td>0.3 gm/litter</td>
</tr>
<tr>
<td>Bacto dextrose</td>
<td>0.25 gm/litter</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>0.5 gm/litter</td>
</tr>
<tr>
<td>Di potassium hydrogen phosphate</td>
<td>0.25 gm/litter</td>
</tr>
<tr>
<td>Distilled water q.s</td>
<td>100 ml</td>
</tr>
<tr>
<td>pH</td>
<td>7.3 ± 0.2 at 25°C</td>
</tr>
</tbody>
</table>

Nutrient agar medium (DIFCO) is the most frequently used and also used in the present study for testing the sensitivity of the organisms to the test materials and to prepare fresh cultures.

**4.5 Preparation of medium**

Amount of each of the constituents was taken in a conical flask and distilled water was added to it to make the required volume. The contents were heated in a water bath to make a clear solution. The pH (at 25°C) was adjusted at 7.2 - 7.6 using NaOH or HCl 10 ml and 5 ml of the medium was then transferred in screw cap test tubes to prepare plates and slants respectively. The test tubes were then capped and sterilized by autoclaving at 15-lbs pressure at 121°C for 20 minutes. The slants were used for making fresh culture of microorganisms that were in turn used for sensitivity study.

**4.6 Sterilization procedure**

To avoid any type of contamination and cross contamination by the test organisms, the antimicrobial screening was done in Laminar Hood and all types of precautions were strictly maintained. UV light was switched on an hour before working in the Laminar hood. Petridishes and other glassware were sterilized by autoclaving at a temperature of 121°C and a pressure of 15-lbs./sq. inch for 20 minutes. Micropipette tips, cotton, forceps, blank discs etc. were also sterilized by UV light.

**4.7 Preparation of subculture**

In an aseptic condition under laminar air cabinet, the test organisms were transferred from the pure cultures to the agar slants with the help of a transfer loop to have fresh pure cultures. The inoculated strains were then incubated for 24 hours at 37°C for their optimum growth. These fresh cultures were used for the sensitivity test.

**4.8 Preparation of the test plates**

The test organisms were transferred from the subculture to the test tubes containing about 10 ml of melted and sterilized agar medium with there of a sterilized transfer loop in an aseptic area. The test tubes were shaken by rotation to get a uniform suspension of the Organisms. The microbial suspension was immediately transferred to the sterilized Petridishes. The petridishes were rotated several times clockwise and anticlockwise to assure homogenous distribution of the test organisms in the media.
4.9 Preparation of discs

Three types of discs were used of antibacterial screening. They were:
(a) Standard Discs
(b) Blank Discs and
(c) Sample Discs

The descriptions of these discs were given below:

(a) Standard Discs
These were used as positive control to ensure the activity of standard antibiotic against the test organisms as well as for comparison of the response produced by the known antibacterial agent with that of produced by the test sample. In this investigation, (30 µg/disc) standard disc was used as the reference.

(b) Blank Discs
These were used as negative control which ensures that the residual solvents (left over the discs even after air-drying) and the filter paper were not active themselves.

(c) Preparation of Sample Discs with Test Sample
Measured amount of each test sample was dissolved in specific volume of solvent to obtain the desired concentrations in an aseptic condition. Then discs were soaked with solution of test samples and dried.

4.10 Diffusion and incubation
The sample discs, the standard antibiotic discs and the control discs were placed gently on the previously marked zones in the agar plates pre-inoculated with test microorganisms. The plates were then kept in a refrigerator at 4°C for about 24 hours upside down to allow sufficient diffusion of the materials from the discs to the surrounding agar medium. The Plates were then inverted and kept in an incubator at 37°C for 24 hours.

4.11 Determination of the zone of inhibition
The antimicrobial potency of the test agents are measured by their activity to prevent the growth of the microorganisms surrounding the discs which gives clear zone of inhibition.

After incubation, the antimicrobial activity of the test materials was determined by measuring the diameter of the zones of inhibition in millimeter with transparent scale.

4.12 RESULTS AND DISCUSSION

The antimicrobial activities of the twelve synthesized compounds derivatives were examined in the present study. The antibacterial activities of 2-iodoaniline and a cetanilide derivatives were studied against thirteen bacteria such as Bacillus cereus, Bacillus megaterium, Bacillus subtilis, Staphylococcus aureus, Sarcina lutea, Escherichia coli, Pseudomonas aeruginosa, Salmonella paratyphi, Salmonella typhi, Shigella boydii, Shigella dysenteriae, Vibrio mimicus, Vibrio parahemolyticus and the activities of the same compounds were also...
studied against three fungi such as Candida albicans, Aspergillus niger, Sacharomyces cerevaceae. All compounds were soluble in chloroform and only one compound was showed no inhibitory activity against microbial growth.

The antibacterial activities were measured in terms of diameters of zone of inhibition in (mm). All experiments were performed thrice to minimize the experimental plus individual errors. The mean value of the diameters of zone inhibition (M.DIZ) was taken as disc for determining antimicrobial spectra. Sensitivity test results are and were compared with a standard antibiotic doxacilin (30µg/disc).

Table 5.3: Antimicrobial activities of test samples of B. daigremontianum

<table>
<thead>
<tr>
<th>Test microorganisms</th>
<th>Diameter of zone of inhibition (mm)</th>
<th>4</th>
<th>7</th>
<th>14</th>
<th>15</th>
<th>16</th>
<th>17</th>
<th>18</th>
<th>25</th>
<th>26</th>
<th>27</th>
<th>Doxacilin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram positive bacteria</strong></td>
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<td></td>
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<tr>
<td>Bacillus cereus</td>
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<td>42</td>
</tr>
<tr>
<td>Bacillus megaterim</td>
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<td>43</td>
</tr>
<tr>
<td>Bacillus subtilis</td>
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<td>-</td>
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<td>43</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
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<td>-</td>
<td>-</td>
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<td>43</td>
</tr>
<tr>
<td>Sarcina lutea</td>
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<td>-</td>
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<tr>
<td><strong>Gram negative bacteria</strong></td>
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<td>Escherichia coli</td>
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<td>Pseudomonas aeruginosa</td>
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<td>Salmonella paratyphi</td>
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<td>Salmonella typhi</td>
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<td>Shigella boydii</td>
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<td>Shigella dysenteriae</td>
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<tr>
<td>Vibrio mimicus</td>
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**Antimicrobial activities of test samples**

* potency per disc 250µg
**Interpretation of sensitivity test results:**

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<th>Gram (+) Bacteria:</th>
<th>Gram (-) bacteria</th>
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<td>18mm (M.DIZ) = Sensitive</td>
<td>&gt;16mm (M.DIZ) = Sensitive</td>
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<tr>
<td>14-18 mm (M.DIZ) = Intermediate</td>
<td>13-16 mm (M.DIZ) = Intermediate</td>
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<tr>
<td>&gt;14mm (M.DIZ) = resistant</td>
<td>&gt;13mm (M.DIZ) = resistant</td>
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**Conclusion**

Nine synthesized compound have been tested for in antimicrobial activity against five gram-positive and eight gram-negative bacteria as well as three human fungal pathogens. None of these compound demonstrated antimicrobial activity against the test organism.
REFERENCES

Experimental
Experimental

3.0 General Experimental

Melting points were determined in open capillary tubes on Gallenkamp (England) melting point apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR spectrophotometer. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker D PX-400 spectrophotometer (400 MHz) using tetramethysilane as internal reference. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel 60F-254 (E. Merck), and the spots were visualized with UV light. Column chromatography was performed on silica gel (60–120 mesh). Bis(triphenylphosphine)palladium(II) chloride and other reagents were purchased from E. merck (Germany) and Fluka (Switzerland).

3.1 Synthesis of starting materials

3.1.1 Iodination of 4-methyl aniline 1
In a 250 mL round bottom flask, provided with a reflux condenser, a mixture of 5 g (46.65 mmol) of 4-methyl aniline 1, 9.313 g (46.65 mmol) of granulated iodine and 11.84g(46.65 mmol) copper(II) acetate was stirred in 70 mL of glacial acetic for 30 min. The reaction mixture was refluxed for 12 hr with constant stirring at 120°C. The progress of the reaction was monitored by TLC. At the end of the reaction, the reaction mixture was allowed to cool at room temperature. The precipitate of copper (II) iodide was removed by filtration and the filtrate was poured into water and extracted with chloroform (3×50 mL), the combined chloroform extracts washed with sodium hydrogen carbonate solution, sodium thiosulfate solution, distilled water, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel using n-hexane/ethyl acetate (4:1) as eluant and three compounds 3, 4, 5 were isolated.
2, 6-di iodo-4-methyl aniline 3

Physical state: Yellow solid.
mp. 110° C.
Rf Value: 0.85 (n-hexane/ethyl acetate = 4:1)
IR (KBr): $\nu_{\text{max}}$ 3406.1 & 3317.3 (-NH$_2$), 3037.7 (sp$^2$C-H), 2898.8 (sp$^3$C-H), 1608.5 & 1460.0 (C=C) cm$^{-1}$.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.45 (s, 2H, C-3 & C-5), 4.19 (s, 2H, -NH$_2$), 2.15 (s, 3H, Ar-CH$_3$)

2-iodo-4-methyl-N-ethanoyl aniline 4

Physical state: brown crystalline solid.
mp. 125-130°C.
Rf Value: 0.6 (n-hexane/ethyl acetate = 4:1)
IR (KBr): $\nu_{\text{max}}$ 3265.3(-NH), 1654.8(C=O), 1290.3(C-N) cm$^{-1}$.
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.99 (d, 1H, $J$ =8.0 Hz, C-6), 7.59 (s, 1H, C-3), 7.32 (br s, 1H, -NH), 7.12 (d, 1H, $J$ =8.0 Hz, C-5), 2.26(s, 3H, -CO- CH$_3$), 2.10(s, 3H, Ar-CH$_3$).
4-methyl-N-ethanoyl aniline 5

Physical state: Brownish crystalline solid.
mp. 148-151°C
Rf Value: 0.40 (n-hexane/ethyl acetate = 4:1)
IR (KBr): •max 3292.3(-NH), 3255.6, 1662.5 (C=O), 1602.7, 1550.7, 1510.2, 1454.2, 1402.2, 1365.5, 1321.1 and 819.7 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): •H 7.52 (br s, 1H, -NH), 7.35 (d, 2H, J=8.4 Hz, C-2 & C-6), 7.08 (d, 2H, J=8.4 Hz, C-3 & C-5), 2.28(s, 3H, -CO-CH₃), 2.12 (s, 3H, Ar-CH₃).

3.1.2 Iodination of 4-Chloro aniline 2

In a 250 mL round bottom flask, provided with a reflux condenser, a mixture of 5 g (39.21 mmol) of 4-chloro aniline 2, 9.95 g (39.21 m mol) of granulated iodine, 7.828 g (39.21 m mol) of copper(II) acetate was stirred in 70 mL of acetic acid for 30 min. The reaction mixture was refluxed for 12 hr with constant stirring at 120°C. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was allowed to cool at room temperature. The precipitate of copper (II) iodide was removed by filtration and the filtrate was poured into water and extracted with chloroform (3×50 mL). The chloroform layer was washed with sodium hydrogen carbonate solution, sodium thiosulfate solution, water, dried with anhydrous sodium sulfate and concentrated under reduced pressure. The crude product was
purified with column chromatography on silica gel using n-hexane/ethyl acetate (4:1) as eluant, three compounds 6, 7, 8 were isolated.

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4-chloro-2, 6-di-iodo aniline 6

Physical state: Yellow powder.

mp. 127-129°C.

Rf Value: 0.9 (n-hexane/ethyl acetate = 4:1)

IR (KBr): • max 3408.0 & 3317.3 (-NH₂), 1604.7 & 1442.7 (C=C), 1402.2, 860.2 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): • H 7.60 (s, 2H, C-3 & C-5), 4.59 (s, 2H, NH₂).

4-chloro-2-iodo-N-ethanoyl aniline 7
Physical state: White crystalline solid.
R_f Value: 0.5 (n-hexane/ethyl acetate = 4:1)
IR (KBr): •_{\text{max}} 3274.9 (-NH), 1658.7 (C=O), 1577.7, 1568.0, 1521.7, 1463.9, 1375.2, 1288.4 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): •\(^1\)H 8.15 (d, 1H, J = 8.0 Hz, C-6), 7.74 (d, 1H, J = 2.0 Hz, C-3), 7.36 (br s, 1H, -NH), 7.30 (dd, 1H, J = 8.0 & 2.0 Hz, C-5), 2.22 (s, 3H, -CO- CH\(_3\)).

4-chloro-2-iodo aniline 8

Physical state: Light brown crystalline solid.
mp. 40-42°C
R_f Value: 0.70 (n-hexane/ethyl acetate = 4:1)
IR (KBr): •_{\text{max}} 3408.1 & 3317.3 (-NH\(_2\)), 1604.7 & 1442.7 (C=C), 1402.2, 868.0 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): •\(^1\)H 7.58 (d, 1H, J = 2.3 Hz, C-3), 7.08 (dd, 1H, J = 2.3 & 8.4 Hz, C-5), 6.64 (d, 1H, J = 8.4 Hz, C-6), 4.07 (s, 2H, -NH\(_2\)).

3.1.3 Iodination of 4-methyl aniline 1 in propanoic acid.

In a 50 mL round bottom flask, provided with a reflux condenser, a mixture of 1.008 g (9.33 mmol) of 4 -methyl aniline 1, 2.369 g (9.33 mmol) of granulated iodine and 1.862 g (9.33 mmol) copper(••)acetate were stirred in 15 mL propanoic acid for 30 min. The reaction mixture was refluxed for 12 hr with constant stirring at 130°C. The progress of the reaction was monitored by TLC. At end of the reaction, the reaction mixture was allowed to cool at room temperature. The precipitate copper (••) iodide was removed by filtration and the filtrate was poured into water and extracted with chloroform (3×25 mL). The combined chloroform extract was washed with sodium hydrogen carbonate solution, sodium thiosulfate solution, distilled water, dried with anhydrous
sodium sulfate and concentrate under reduced pressure. The crude product was purified with column chromatography on silica gel using n-hexane/ethylacetate(4:1) as eluent, two compounds 3, 9 were isolated.

$\begin{align*}
1 & 3 & 9 \\
\end{align*}$

4-methyl-N-propanoyl aniline 9

Physical state: White crystalline solid.

$R_f$ Value: 0.6 (n-hexane/ethyl acetate= 4:1)

IR (KBr): \text{$\nu_{max}$} 3303.8(-NH), 1664.5(C=O), 1610.5, 1544.9, 1521.1, 1309.6(C-N), 813.9cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): \text{$\nu$} 7.37 (d, 2H, C-2 & C-6), 7.22 (br s, 1H, -NH), 7.09(d, 2H, $J$=8.0 Hz, C-3 & C-5), 2.35 (quart, 2H, -CO-CH$_2$-), 2.29 (s, 3H, Ar-CH$_3$), 1.22(t, 3H, -CH$_3$).

3.1.4 Preparation of 2, 6-di iodo-4-methyl-N-eyhanoyl aniline 10

In a 100 mL round bottom flask equipped with a reflux condenser, a mixture of 3.2g 2, 6-diiodo-4-methyl aniline 3, acetic acid, acetic anhydride (1:1:1) mol ratio and small amount of zinc dust were stirred at room temperature for half an hour. The reaction mixture was refluxed for 3 hours with constant stirring at 80$^\circ$ C. The hot reaction mixture was poured in a thin stream into a 500 mL beaker containing 200 mL of cold water with constant stirring. The crude product was
filtered and washed with a little cold water and dried upon filter paper in air. The product 10 was purified by crystallization process using ethanol.

2, 6-diiodo-4-methyl-N-ethanoyl aniline 10

Physical state: white solid
mp. 135-138°C
Rf Value: 0.6 (n-hexane/ethyl acetate= 4:1)
IR (KBr): 3159.2(-NH), 2997.2, 2916.2(C-H), 1676.0(C=O) 1579.6 & 1452.3 (C=C)cm⁻¹.
¹H NMR (400 MHz, CDCl₃): •H 7.68(s, 2H, C-3 & C-5), 6.99(-NH), 2.26(s, 3H, -CO-CH₃), 2.22 (s, 3H, Ar-CH₃).

3.2 Synthesis of 2-alkynyl-4-substituted -N-ethanoyl aniline 14-18

3.2.1 Synthesis of 4-methyl-2-phenylethynyl-N-ethanoyl aniline 14

In a 50 mL round bottom flask equipped with a reflux condenser, a mixture of 2-Iodo-4-methyl-N-ethanoyl aniline 4 (0.5gm, 1.818 mmol), bis(triphenylphosphine) palladium(••)chloride (0.044g, 0.063 mmol), copper(•)iodide (0.027 g, 0.145 mmol), triethylamine(0.734 g, 7.272 mmol) was stirred in 7 ml DMF under nitrogen atmosphere for 1 hour at room temperature. Then Phenyl acetylene 11(0.222 g, 2.186 mmol) was added drop wise and the solution was heated at 80-85°C for 23 hours. The mixture was then evaporated to dryness under reduced pressure, the residue extracted with chloroform (3×50 mL), the combined chloroform extracts washed with distilled water (3×50 mL), dried over a nhydrous Na₂SO₄, filtered and concentrated under reduced pressure.
pressure. The residue was purified by column chromatography on silica gel using n-hexane:ethyl acetate (5:1) to yield the pure 4-Methyl-2-phenylethynyl-N-ethanoyl aniline 14.

4-Methyl-2-phenylethynyl-N-ethanoyl aniline 14

Physical state: White crystal

mp.128-129°C

Rf Value: 0.75 (n-hexane/ethyl acetate = 5:1)

IR (KBr): \( \nu_{\max} \) 3296.1 (-NH-), 3041.5, 2214.1 (C\( \cdot \)C), 1654.8 (C=O), 1583.4, 1533.3, 1492.8, 1396.4, 823.5, 756.0 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta \) 8.27(s, 1H, C-6), 7.89(s, 1H, –NH), 7.52-7.30, 7.15 (m, 7H, Ar-H), 2.30(s, 3H, -CO-CH\(_3\)), 2.22 (s, 3H, Ar-CH\(_3\)).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta \) 167.96(C=O), 136.49(Ar-NH), 133.00, 132.97, 131.85, 131.55 130.47, 128.82, 128.55, 122.40,119.66, 118.11, 111.70(Ar-C), 95.96 & 84.45(C\( \cdot \)C), 24.83(ethanoyl-CH\(_3\)), 20.50 (Ar-CH\(_3\)).

3.2.2 Synthesis of 2-(1-Hexynyl)-4-methyl-N-ethanoyl aniline 15

In a 50 mL round bottom flask equipped with a reflux condenser, a mixture of 2-iodo-4-methyl-N-ethanoyl aniline 4 (0.5gm, 1.818 mmol), bis(triphenylphosphine) palladium(II)chloride (0.044g, 0.063 mmol), copper(II)iodide (0.027 g, 0.145 mmol), triethylamine (0.734 g, 7.272 mmol) was stirred in 7 ml DMF under nitrogen atmosphere for 1 hour at room temperature. Then 1-Hexyne
12 (0.178 g, 2.181 mmol) was added and the solution heated at 60°C for 48 hours. The mixture was then evaporated to dryness under reduced pressure, the residue extracted with chloroform (3×50 mL). The combined chloroform extracts washed with distilled water (3×50 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using n-hexane/ethyl acetate (8:1) to yield the pure 2-(1-Hexynyl)-4-methyl-N-ethanoyl aniline 15.

\[ \text{2-(1-Hexynyl)-4-methyl-N-ethanoyl aniline 15} \]

Physical state: Brown crystalline solid.

mp. 84-86°C

R$_f$ Value: 0.80 (n-hexane/ethyl acetate = 5:1)

IR (KBr): • $\text{max}$ 3274.9 (-NH-), 2956.7, 2933.5, 2223.8 (C•C), 1664.5(C=O), 1587.3, 1525.6, 1488.9, 1363.6, 1301.9, 829.3 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): • H 8.21 (d, 1H, $J$ =8.4 Hz, C-6), 7.84(br s, 1H, –NH), 7.15(s, 1H, C-3), 7.07(d, 1H, $J$ =8.4 Hz, C-5), 2.49(t, 2H, $J$ =7.2 Hz, C-3•), 2.25(s, 3H, -CO-CH$_3$), 2.17 (s, 3H, Ar-CH$_3$), 1.63(quin, 2H, $J$ =7.2 and 6.8 Hz, C-4•), 1.50 (sex, 2H, $J$ = 7.2 & 6.8 Hz, C-5•), 0.96 (t, 3H, $J$ =7.2 Hz, -CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$): • c 167.91(C=O), 136.54(Ar-NH), 132.74, 131.81, 129.59, 118.99, 112.46(Ar, C), 97.33 & 76.17 (C•C), 30.83(C-3•), 24.83(ethanoyl-CH$_3$), 22.08 (C-4•), 20.63 (Ar-CH$_3$), 19.25(C-5•), 13.59(-CH$_3$).
3.2.3 Synthesis of 2-(1-Heptynyl)-4-methyl-N-ethanoyl aniline 16

In a 50 mL round bottom flask equipped with a reflux condenser, a mixture of 2-iodo-4-methyl-N-ethanoyl aniline 4 (0.5gm, 1.818 mmol), bis(triphenylphosphine) palladium(••)chloride (0.044g , 0.063 mmol), copper(•)iodide (0.027 g, 0.145 mmol), triethylamine (0.734 g, 7.272 mmol) was stirred in 7 ml DMF under nitrogen atmosphere for 1 hour at room temperature. Then 1-Heptyne 13 (0.178 g, 2.181 mmol) was added and the solution was heated at 60°C for 48 hours. The mixture was then evaporated to dryness under reduced pressure. The residue extracted with chloroform (3×50 mL), the combined chloroform extracts washed with distilled water (3×50 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using n-hexane/ethyl acetate (8:1) to yield the pure 2-(1-Heptynyl)-4-methyl-N-ethanoyl aniline 16.

2-(1-Heptynyl)-4-methyl-N-ethanoyl aniline 16

Physical state: Brown crystalline solid.

mp. 64-65°C

R$_f$ Value: 0.80 (n-hexane/ethyl acetate = 5: 1)

IR (KBr): • max 3274.9 (-NH), 2933.5, 2219.9 (C• C), 1662.5 (C=O), 1522.5 cm$^{-1}$.

$^1$H NMR (400 MHz, CDCl$_3$): • H 8.21 (d, 1H, J=8.4 Hz, C-6), 7.84 (br s, 1H, –NH), 7.16(s, 1H, C-3), 7.07(d, 1H, J=8.0 Hz, C-5), 2.48(t, 2H, J = 6.8 Hz, -C• C-CH$_2$-),
2.25 (s, 3H, -CO-CH₃), 2.18 (s, 3H, Ar-CH₃), 1.64 (quin, 2H, J = 7.2 & 6.8 Hz, C-4•), 1.49-1.24 (m, 4H, C-5• & C-6•), 0.92 (t, J = 7.2 Hz, 3H, -CH₃).

¹³C NMR (100 MHz, CDCl₃): C 167.94 (C=O), 136.48 (Ar-NH), 132.73, 131.80, 129.59, 118.91 & 112.38 (Ar-C), 97.42 & 76.09 (C• C), 31.18 (C-3•), 28.47 (C-4•), 24.90 (ethanoyl-CH₃), 22.24 (C-5•), 20.64 (Ar-CH₃), 19.55 (C-6•), 14.01 (-CH₃).

3.2.4 Synthesis of 4-chloro-2-(1-hexynyl)-N-ethanoyl aniline 17

In a 50 mL round bottom flask equipped with a reflux condenser, a mixture of 4-chloro-2-iodo-N-ethanoyl aniline 7 (0.5g, 1.69 mmol), bis(triphenylphosphine) palladium(••)chloride (0.041g, 0.059 mmol), copper(•)iodide (0.025 g, 0.135 mmol), triethylamine (0.682 g, 6.76 mmol) were stirred in 7 ml DMF under nitrogen atmosphere for 1 hour at room temperature. Then 1-Hexyne 12 (0.166g, 2.028 mmol) was added and the solution was heated at 60°C for 48 hours. The mixture was then evaporated to dryness under reduced pressure. The residue extracted with chloroform (3×50 mL), the combined chloroform extracts washed with distilled water (3×50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using n-hexane/ethyl acetate (6:1) to yield the pure 4-chloro-2-(1-hexynyl)-N-ethanoyl aniline 17.
4-Chloro-2-(1-hexynyl)-N-ethanoyl aniline

Physical state: white crystalline solid.
mp. 80-82°C
Rf Value: 0.68 (n-hexane/ethyl acetate = 5: 1)
IR (KBr): 3294.2(-NH), 2956.7, 2927.7, 2232.8(C=C), 1662.5(C=O), 1598.9 & 1473.5 (C=C) cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 8.31(d, 1H, J=8.8 Hz, C-6), 7.85(br s, 1H, -NH),
7.31(d, 1H, J=2.0 Hz, C-3), 7.21(dd, 1H, J=8.8 & 2.0 Hz, C-5), 2.49 (t, 2H, J=6.8 Hz, C•C-CH₂-),
2.18(s, 3H, -CO-CH₃), 1.62(quin, 2H, J=6.8 & 7.2 Hz, C-4•),
1.50(sex, 2H, J= 7.2 & 7.6 Hz, C-5•), 0.96 (t, 3H, J=7.6 Hz, -CH₃).

¹³C NMR (100 MHz, CDCl₃): 168.01(C=O), 137.50(Ar-NH), 131.05, 128.87, 127.98, 120.12,
& 114.09(Ar, C), 99.07 & 74.94 (C•C), 30.63(C-3•), 24.82(ethanoyl-CH₃), 22.06 & 19.22( C-4• &
C-5•), 13.55(-CH₃).

3.2.5 Synthesis of 4-Chloro-2-phenylethynyl-N-ethanoyl aniline

In a 50 mL round bottom flask equipped with a reflux condenser, a mixture of 4-chloro-2-iodo-N-ethanoyl aniline 7 (0.5gm, 1.69 mmol), bis(triphenylphosphine) palladium(••)chloride (0.041g, 0.059 mmol), copper(•)iodide (0.025 g, 0.135 mmol), triethylamine(0.682 g, 6.76 mmol)
was stirred in 7 ml DMF under nitrogen atmosphere for 1 hour at room temperature. Then Phenyl acetylene 11 (0.206 g, 2.028 mmol) was added dropwise and the solution heated at 80-85°C for
23 hour s. Then the reaction mixture was vaporated to dryness undre reduced pressure, the residue extracted with chloroform (3×50 mL), the combined chloroform extracts washed with (3×50 mL) of 95% ethanol, dried over ahydrous Na₂SO₄ and concentrated under reduced
pressure. The residue was purified by column chromatography on silica gel using hexane/ethylacetate (6:1) to yield 18.

4-Chloro-2-phenyl ethynyl-N-ethanoyl aniline 18

Physical state: Brown crystalline solid
mp. 178-180°C
R_f Value: 0.65 (n-hexane/ethyl acetate = 5:1)
IR (KBr): •max 3300.00 (-NH), 2210.3 (C= C), 1660.6(C=O), 1521.7, 1400.2 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): •H 8.36(d, 1H, J=8.8Hz, C-6), 7.90(br s, 1H, -NH),
7.53-7.15(Ph, 2H), 7.45(s, 1H, C-3), 7.40-7.39 (m, 3H, Ph), 7.29(d, 1H, J=8.8 Hz, C-5), 2.22 (s, 3H, -CO-CH₃).
¹³C NMR (100 MHz, CDCl₃): •c 168.09(C=O), 137.51(Ar-NH), 131.59, 131.10, 129.72, 129.32, 128.69, 121.86, 120.53, & 113.41 (Ar-C), 97.42 & 83.04 (C= C), 24.91(ethanoyl-CH₃).

1, 4-di phenyl-1, 3-buta-di-yne 19
Physical state: white crystalline solid.  
R$_f$ Value: 0.9 (n-hexane)  
IR (KBr): $\nu_{max}$ 2135.1, 1483.2, 1434.9, 912.3, 754.1, 684.7 cm$^{-1}$.  
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.52 (d, 4H), 7.35 (m, 6H)  
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ c 132.58, 129.28, 128.51, 121.90, 81.63, 73.99.

3.3 Base catalyzed cyclization of 2-alkynyl-4-substituted-N-ethanoyl aniline

3.3.1 Synthesis of 2-Butyl-5-chloro-1H indole 20

In a 50 mL round bottom flask equipped with a reflux condenser, a mixture of 4-chloro-2-(1-Hexynyl)-N-ethanoyl aniline 17 (0.100gm, 0.37 mmol) and sodium ethoxide (0.050g, 0.74 mmol) in ethanol (10 mL) and was stirred under a nitrogen atmosphere for 4 hours at 80°C. At end of the reaction the mixture was evaporated to dryness under reduced pressure. Distilled water (200 mL) was added to the residue and it was neutralized with 6N HCl, extracted with chloroform (3×50 mL). The combined chloroform extract was washed with distilled water (3×50 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using n-hexane/ethyl acetate (6:1) as eluant to yield 2-Butyl-5-chloro-1H indole 20 and 2-butyl-4-chloro aniline 21.
Physical state: Brown liquid.
Rf Value: 0.7 (n-hexane/ ethyl acetate = 6:1)
IR (KBr): 3421.5(-NH), 2958.6, 2929.7, 1488.9 cm$^{-1}$

$^1$H NMR (400 MHz, CDCl$_3$): $^\cdot_\text{H}$ 7.87(s, 1H, -NH), 7.46(s, 1H, C-4), 7.17(d, 1H, $^J = 8.4$ Hz, C-7), 7.04(d, 1H, $^J = 8.4$ Hz, C-6), 6.13(s, 1H, vinylic H), 2.73(t, 2H, $^J = 7.6$ Hz, C-1$^\cdot$), 1.69(quin, 2H, $^J = 7.2$ & 7.6 Hz, C-2$^\ast$), 1.39(sex, 2H, $^J = 7.2$ & 7.6 Hz, C-3$^\ast$), 0.95 (t, 3H, $^J = 7.2$ Hz, -CH$_3$).

Physical state: Brown liquid.
IR (KBr) $^\ast_{\text{max}}$ 3585.4 & 3544.9 (–NH$_2$), 2958.6 & 2929.7 (C-H), 2235.0 (C• C) cm$^{-1}$. 

2-Butyl-5-chloro-1H indole 20

2-butyl-4-chloro aniline 21
\[ ^1H \text{ NMR (400 MHz, CDCl}_3\text{):} \quad \cdot H \ 7.20 (d, 1H, J = 2.0 \text{ Hz C-3}), \ 7.01 (dd, 1H, J = 2.0 \text{ & 8.4 Hz, C-5}), \]
\[ 6.58 (d, 1H, J = 8.4 \text{ Hz, C-6}), \ 4.14 (br, s, 2H, -NH), \ 2.45 (t, 2H, J = 6.8 \text{ Hz, C-3•}), \ 1.59 (\text{quin, 2H, J = 6.8 & 7.2 Hz, C-4•}), \ 1.36 (\text{sex, 2H, J = 7.2 and 7.6 Hz, C-5•}), \ 0.90 (t, 3H, J = 7.2 \text{ Hz, -CH}_3). \]

3.3.2 Synthesis of 2-Butyl-5-methyl-1H indole 22

In a 50 mL round bottom flask equipped with a reflux condenser, a mixture of 2-Butyl-4-methyl-N-ethanoyl aniline 15(0.102gm, 0.46 mmol) and sodium ethoxide (0.055g, 0.82 mmol) in ethanol(10 mL) was stirred under a nitrogen atmosphere for 4 hours at 80°C. At the end of the reaction the mixture was evaporated to dryness under reduced pressure. Distilled water (200 mL) was added to the residue and neutralized with 6N HCl, extracted with chloroform (3×50mL). The combined chloroform extract was washed with distilled water (3×50 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using n-hexane/ethyl acetate (6:1) to yield 2-Butyl-4-methyl-1H indole 22 and 2-(1-hexynyl)-4-methyl aniline 23.

15 22 23

2-Butyl-4-methyl-1H indole 22
Physical state: Brown liquid.

IR (KBr): 3408.0(-NH), 2956.7, 2929.7, 1618.2, 1502.4, 1458.1 cm.\(^{-1}\)

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\cdot\)\(_7\) 7.75(br s, 1H, -NH), 7.29(s, 1H, C-4), 7.16(d, 1H, \(J = 8.0\) Hz, C-7), 6.91(d, 1H, \(J = 8.0\) Hz, C-6), 6.13(s, 1H, vinylic H), 2.72(t, 2H, \(J = 7.6\) Hz, C-1\(_\cdot\)), 2.41(s, 3H, Ar-CH\(_3\)), 1.68(quin, 2H, \(J = 7.6 \& 7.2\) Hz, C-2\(_\cdot\)), 1.39(sex, 2H, \(J = 7.2\) and 7.6 Hz, C-3\(_\cdot\)), 0.87 (t, 3H, \(J = 7.2\) Hz, -CH\(_3\)).

2-(1-hexynyl)-4-methyl aniline 23

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\cdot\)\(_6\) 7.05(s, 1H, C-3), 6.85(d, 1H, \(J = 8.0\) Hz, C-6 ), 6.59 (d, 1H, \(J = 8.0\) Hz, C-5 ), 4.21(br, s, 2H, -NH), 2.45(t, 2H, \(J = 6.8\) H, C-3\(_\cdot\)), 2.18(s, 3H, Ar-CH\(_3\)), 1.60(quin, 2H, \(J = 6.8 \& 7.6\) Hz, C-4\(_\cdot\)), 1.49(sex, 2H, \(J = 7.2\) \& 7.6 Hz, C-5\(_\cdot\)), 0.93 (t, 3H, \(J = 7.2\) Hz, -CH\(_3\) ).

3.3.3 Synthesis of 4-Methyl-2-phenylethynylaniline 24

In a 50 mL round bottom flask equipped with a reflux condenser, a mixture of 4-Methyl-2-phenylethynyl-N-ethanoyl aniline 14 (0.45gm, 0.19 mmol) and sodium ethoxide (0.008g, 0.38 mmol) in ethanol(10 mL) and the mixture stirred under a nitrogen atmosphere for 4 hours at 80°C.
At the end of the reaction, the mixture was evaporated to dryness under reduced pressure. Distilled water (200 mL) was added to the residue and it was neutralized with 6N HCl, extracted with chloroform (3×50 mL). The combined chloroform extract was washed with distilled water (3×50 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using n-hexane/ethylacetate (6:1) to yield the 4-methyl-2-phenylethynyl aniline 24.

4-Methyl-2-phenyl aniline 24

Physical state: white crystalline solid.

IR (KBr): \( \nu_{max} 3473.6 \text{ and } 3379.1 (-\text{NH}_2), 2185.2 (\text{C} = \text{C}) , 1595.0, 1505.5, 1311.5, 756.0 \text{ cm}^{-1} \)

\(^1\text{H NMR} (400 \text{ MHz, CDCl}_3): 7.52-7.49 (m, 2H, Ph), 7.36-7.29 (m, 3H, Ph), 7.17(s, 1H, C-3), 6.95(d, 1H, \text{ J = 8.0 Hz, C-6}), 6.64(d, 1H, \text{ J = 8.0 Hz, C-5}), 4.13(s, 2H, -\text{NH}_2) \).

3.4 Palladium chloride catalyzed synthesis of 2, 5-disubstituted indole derivatives 25-27

3.4.1 Synthesis of 2-Butyl-5-methyl-N-ethanoyl indole 25

In a 50 mL round bottom flask equipped with a reflux condenser, a mixture of palladium (**) chloride (0.008 gm, 0.045 mmol) and acetonitrile (5 mL) was refluxed at 80°C with constant
stirring. The solid was dissolved after 20 min and the reaction mixture was allowed to cool at room temperature. In this solution 0.102 gm (0.445 mmol) of 2-(1-hexynyl)-4-methyl-N-ethanoyl aniline 15 was added and the mixture was refluxed at 80°C. The progress of the reaction was monitored by TLC. The starting material disappeared after 40 min and the reaction mixture was evaporated to dryness under reduced pressure. The product was purified by column chromatography on silica gel using n-hexane/ethylacetate (5:1) to yield 0.071 g of the pure 5-methyl-2-butyl-N-ethanoyl indole 25.

2-Butyl-5-methyl-N-ethanoyl indole 25

Physical state: White crystalline solid
mp. 68-69°C
R_f Value: 0.72 (n-hexane/ethylacetate = 5:1)
IR (KBr): • max 2958.6 & 2935.5(C-H), 1679.9 (C=O), 1591.2 & 1469.7(C=C) 1379.4, 1317.3 cm⁻¹.
1H NMR (400 MHz, CDCl₃): • H 7.68(d, 1H, J=8.4 Hz, C-7), 7.25(s, 1H, C-4), 7.04 (d, 1H, J=8.4 Hz, C-6), 6.32(s, 1H, C-3), 2.98(t, 2H, J=7.6 Hz, C-1•), 2.72(s, 3H, -CO-CH₃), 2.41(s, 3H, Ar-CH₃), 1.68(quin, 2H, J=7.2 & 7.6 Hz, C-2•), 1.44 (sex, 2H, C-3•), 0.95 (t, 3H, J=7.2 Hz, -CH₃).
$^{13}$C NMR (100 MHz, CDCl$_3$): \textbullet 170.19(C=O), 143.18(Ar-NH), 134.60, 132.49, 130.31, 124.59, 120.20, 114.48 & 108.03 (Ar-C), 31.07(C-1\bullet), 30.30(C-2\bullet), 27.57(C-3\bullet), 22.56((ethanoyl-CH$_3$), 21.11(Ar-CH$_3$), 13.97(-CH$_3$).

### 3.4.2 Synthesis of 5-methyl-2-pentyl-N-ethanoyl indole 26

In a 50 mL round bottom flask equipped with a reflux condenser a mixture of palladium (\bullet\bullet) chloride (0.006 g, 0.032 mmol) and acetonitrile (5 mL) was refluxed at 80°C with constant stirring. The solid dissolved after 20 min and the reaction mixture was allowed to cool at room temperature. In this solution 0.076 g (0.315 mmol) of 2-(1-Heptynl)-4-methyl-N-ethanoyl aniline\textsuperscript{16} was added and the mixture was refluxed at 80°C. The progress of the reaction was monitored by TLC. The starting material disappeared after 40 min and the reaction mixture was evaporated to dryness under reduced pressure. The product was purified by column chromatography on silica gel using n-hexane/ethyl acetate (5:1) to yield 0.056 g of the pure 5-methyl-2-pentyl-N-ethanoyl indole 26.

Physical state: White crystalline solid. mp. 50-51°C

R$_f$ Value: 0.77 (n-hexane/ethyl acetate = 5:1)

IR (KBr): \textbullet max 2921.9(C-H), 1687.6 (C=O), 1591.2 & 1460.70(C=C), 1373.2, 1315.4, 815.8 cm$^{-1}$. 

2-Pentyl-5-methyl-N-ethanoyl indole 26
1H NMR (400 MHz, CDCl3): \( \delta \) 7.68 (d, 1H, \( J = 8.4 \) Hz, C-7), 7.25 (s, 1H, C-4), 7.04 (d, 1H, \( J = 8.4 \) Hz, C-6), 6.32 (s, 1H, vinylic H), 2.97 (t, 2H, \( J = 7.6 \) Hz, C-1\•), 2.72 (s, 3H, -CO-CH\(_3\)), 2.41 (s, 3H, Ar-CH\(_3\)), 1.69 (quin, 2H, \( J = 7.2 \) and 7.6 Hz, C-2\•), 1.42-1.28 (m, 4H, C-3\•& C-4\•), 0.96 (t, \( J = 7.2 \) Hz, 3H, -CH\(_3\)).

13C NMR (100 MHz, CDCl3): \( \delta \) 170.19 (C=O), 143.21 (Ar-NH-), 134.61, 132.49, 130.31, 124.59, 120.20, 114.48, 108.03 (Ar-C), 31.67, 30.55, 28.62 (C-1\•, C-2\•& C-3\•), 27.57 (ethanoyl -CH\(_3\)), 22.56 (C-4\•), 21.12 (Ar-CH\(_3\)), 14.05 (-CH\(_3\)).

3.4.3 Synthesis of 2-Butyl-5-chloro-N-ethanoyl indole 27

In a 50 mL round bottom flask equipped with a reflux condenser a mixture palladium (••) chloride 0.006g (0.033 mmol) and acetonitrile 5 mL was refluxed at 80°C with constant stirring. The solid dissolved after 20 min in the reaction mixture was allowed to cool at room temperature. In this solution 4-chloro-2-(1-hexynyl) -N-ethanoyl aniline 18 (0.075g, 0.327 mmol) was added and the mixture was refluxed at 80°C. The progress of the reaction was monitored by TLC. The starting material was disappeared after 2 hr and the reaction mixture was evaporated to dryness under reduced pressure. The product was purified by column chromatography on silica gel using n-hexane/ethyl acetate (5:1) to yield 0.051 g of the pure 2-butyl-5-chloro-N-ethanoyl indole 27.

Physical state: white crystalline solid.
mp. 51-52°C

Rf Value: 0.75 (n-hexane/ethyl acetate = 5:1)

IR (KBr): \( \bullet \max \) 2937.4, 1685.7 (C=O), 1591.2 & 1448.4 (C=C), 1371.3, 1317.3, 829.3 cm\(^{-1}\).

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \bullet \) H 7.80 (d, 1H, \( J = 9.2 \) Hz, C-7), 7.42 (d, 1H, \( J = 2.0 \) Hz, C-4), 7.17 (dd, 1H, \( J = 9.2 \) & \( 2.0 \) Hz, C-6), 6.34 (s, 1H, vinylic H), 2.96 (t, 2H, \( J = 7.2 \) Hz, C-1\( \bullet \)), 2.72 (s, 3H, -CO-CH\(_3\)), 1.69 (quin, 2H, \( J = 7.2 \) & \( 7.6 \) Hz, C-2\( \bullet \)), 1.44 (sext, 2H, \( J = 7.2 \) and \( 7.6 \) Hz, C-3\( \bullet \)), 0.96 (t, 3H, \( J = 7.6 \) Hz, -CH\(_3\)).

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \( \bullet \) c 170.05 (C=O), 144.13 (Ar-NH-), 134.90, 131.20, 128.63, 123.47, 119.63, 115.94, 107.52 (Ar-C), 30.96 & 30.22 (C-1\( \bullet \) & C-2\( \bullet \)), 27.48 (ethanoyl -CH\(_3\)), 22.55 (C-3\( \bullet \)), 13.93 (-CH\(_3\)).
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References

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Results and discussion
2.0 Present work: Synthesis of 2, 5-disubstituted indoles by metal mediated reactions.

2.1 Rationale

The indole ring system is probably the most ubiquitous heterocycle in nature. Owing to the great structural diversity of biologically active indoles, the indole ring system has become an important structural component in many pharmaceutical agents. Substituted indoles have been referred to as “privileged structures” since they are capable of binding to many receptors with high affinity. For over a hundred years, the synthesis and functionalization of indoles has been a major area of focus for synthetic organic chemists, and numerous methods for the preparation of indoles have been developed.

Palladium catalyzed reactions have been extensively used for carboannulation and heteroannulation processes. Several research groups have reported the synthesis of aromatic heterocycles via palladium-catalyzed annulation of internal alkynes. Others have shown that palladium catalyzed cyclizations are valuable synthetic tools for the preparation of a wide variety of heterocycles using vinyl compounds, terminal alkynes, allenes and other substrates. In recent years, our group has developed methods for the synthesis of benzofused heterocyclic compounds, for example, isobenzofurans and isoidolinones by palladium-catalyzed reactions with terminal alkynes and acid chloride.

Due to the presence of indole moiety in natural products and molecules with biological activity, we were interested in developing a convenient method for the synthesis of 2, 5-disubstituted indoles from 4-substituted-2-iodo-N-ethanoyl aniline and terminal alkynes catalyzed by (PPh$_3$)$_2$PdCl$_2$ and CuI as co-catalyst followed by base catalyzed and PdCl$_2$ cyclization in different solvents and bases at variable temperatures under nitrogen atmosphere.

2.2 Results and discussion

Here a convenient approach for the synthesis of 2, 5-disubstituted indoles through palladium catalyzed reaction followed by base catalyzed and palladium catalyzed cyclization is reported.

The required starting materials 4-substituted-2-iodo-N-ethanoyl aniline 4, 7 were prepared by a convenient procedure using iodine-copper acetate in acetic acid from their parent 4-substituted anilines 1, 2 (Scheme-1). After usual workup, the crude product was purified by column chromatography on silica gel using n-hexane/ethyl acetate (4:1) as eluent and products 3-8 were isolated.
Iodination of 4-methyl aniline 1 and 4-chloroaniline 2 were carried out using iodine and copper(II) acetate in acetic acid to yield 4-substituted-2-iodo-N-ethanoyl aniline 4, 7 (major yield), along with 4-substituted-2, 6-diiodo aniline 3, 6, and 4-substituted-2-iodo aniline 8. A little amount of 4-substituted-N-ethanoyl 5 aniline was also obtained.

In order to optimize the iodination reaction condition, 4-methyl aniline 1 was used as a model and temperature was varied from 25°C to 130°C better yields were obtained at higher temperature. To find out the role of solvent and the origin of the acid part present in the amide 4, 5, 7 three solvents acetic acid, propanoic acid and trifluoroacetic acid were used as a reaction medium. In propanoic acid a moderate yield of 4-methyl-N-propanoyl aniline 9 was obtained along with other products (scheme-2). No yield was obtained when the reaction was carried out in trifluoro acetic acid at the same condition. It was observed that the 4-substituted acetonilide was formed from carboxylic acid and trifluoro acetic acid (strong carboxylic) was not suitable for this reaction.
The 4-substituted-2, 6-di iodo aniline 3 was converted to it’s corresponding acetonilide derivatives 10 using acetic anhydried in acetic acid (Scheme-3). Compound 10 was found unsuitable for palladium catalyzed cross-coupling reaction with terminal alkyne.

Scheme-3

The palladium catalyzed cross-coupling reactions were carried out by stirring the mixture of 4-substituted-2-iodo-N-ethanoyl aniline 4, 7 with terminal alkynes 11-13 (1.2 mol equiv.), bis(triphenylphosphine) palladium(••) chloride (3.5 mol %), copper(•) iodide (8 mol %) and triethylamine(4 mol equiv.) under nitrogen atmosphere in DMF(5-8 mL) at 60-80°C for 24-48 hours. After usual workup, the crude product was purified by column chromatography on silica gel using n-hexane /ethyl acetate as eluant in different ratio to afford 4-substituted-2-(1-alkynyl)-N-ethanoyl aniline14-18 in good yield (Scheme-4).

Then the condensed products 15, 17 were subjected to base catalyzed cyclization using sodium ethoxide(1.2-1.5 mol equiv.) in ethanol at 80°C under nitrogen atmospheres for 4 h to afford 2, 5-disubstitued-1H indoles 20, 22 along with acyclic 4-substituted-2-alkynyl anilines 21, 23. In the same procedure, compound 14 yielded only acyclic compound 24 (Scheme-4).

The condensed products 15-17 were also subjected to palladium (••) chloride (10 mol %) catalyzed cyclization in acetonitrile at 80°C for 0.5-2 h to afford 2, 5-disubstitued-N-ethanoyl indoles 25-27 in good yield (Scheme-4).
2.3.1 Synthesis of starting materials

Commercially available 4-methyl aniline 1 and 4-chloro aniline 2 were used to prepare the required starting materials. Iodination of reaction of the aromatic nucleus was done as shown in the *scheme-1*. After usual work up the crude product was purified by column chromatography on silica gel with hexane/ethyl acetate (4:1) as eluent.

The results are given in the *Table-1*. 

<table>
<thead>
<tr>
<th>Compounds</th>
<th>X</th>
<th>R</th>
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</thead>
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<tr>
<td>4</td>
<td>CH₃</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>Cl</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>-</td>
<td>Ph</td>
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<td>-</td>
<td>C₄H₉</td>
</tr>
<tr>
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<td>-</td>
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<td>CH₃</td>
<td>Ph</td>
</tr>
<tr>
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<td>CH₃</td>
<td>C₄H₉</td>
</tr>
<tr>
<td>16, 26</td>
<td>CH₃</td>
<td>C₅H₁₁</td>
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<tr>
<td>17, 20, 21, 27</td>
<td>Cl</td>
<td>C₄H₉</td>
</tr>
<tr>
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<td>Cl</td>
<td>Ph</td>
</tr>
<tr>
<td>19</td>
<td>-</td>
<td>Ph</td>
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### Table 1: Iodination of 4-substituted aniline

<table>
<thead>
<tr>
<th>Entry</th>
<th>4-substituted aniline</th>
<th>Reagents &amp; condition</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>15</td>
</tr>
</tbody>
</table>

Yield (%) was calculated on the base of amount of the compounds 1 and 2.
2.3.2 Characterization of 4-substituted 2-iodoacetanilide/aniline 3-10

The structure of the compounds were established by spectral data-

2, 6-diiodo-4-methylaniline 3

A white crystalline solid. mp.119-121°C.

In the IR spectrum the compound showed the stretching frequency of N-H at $\nu_{\text{max}}$3406.1 and 3317.3 cm$^{-1}$ due to –NH$_2$. The absorption band was found at $\nu_{\text{max}}$3037.7 and 2898.8 cm$^{-1}$ due to the stretching of methyl and aromatic C-H. The absorption band at 1608.5 and 1460.0 cm$^{-1}$ indicated the presence of C=C stretching vibration in the aromatic ring.

In the $^1$H NMR spectrum of the compound the chemical shift was found at $\delta_H$ 7.45 (s, 2H) owing to the presence of C-3 and C-5 aromatic proton. The chemical shift at $\delta_H$ 4.19 (br s, 2H) and 2.15 (s, 3H) for presence of primary amine group –NH$_2$ and Ar-CH$_3$ respectively.

2-iodo-4-methyl-N-ethanoyl aniline 4

A brownish crystalline solid, mp.122-125°C.

In the IR spectrum (fig-1a) of the compound the absorption band was found at $\nu_{\text{max}}$ 3265.3 cm$^{-1}$ due to –NH stretching. The stretching vibration frequency of C=O was found at 1654.8 cm$^{-1}$. The absorption band at 1290.3 cm$^{-1}$ represented C-N bending vibration.

In the $^1$H NMR spectrum (fig-1b) of the compound one doublet was found at $\delta_H$ 7.99(1H, $J$=8.0 Hz) for the presence of C-6 proton, a singlet at $\delta_H$ 7.59 because of C-3 proton. A broad singlet was found at $\delta_H$ 7.32 due to –NH proton. A doublet at $\delta_H$ 7.12(1H, $J$=8.0 Hz) was found as a result of C-5 proton. Two sharp singlets at $\delta_H$ 2.26 and 2.10 were found in favor of –CO-CH$_3$ and Ar-CH$_3$ respectively.

4-methyl-N-ethanoyl aniline 5

A brown crystalline solid, mp.148-151°C.

In the IR spectrum of the compound the absorption band was found at $\nu_{\text{max}}$3292.3 cm$^{-1}$ due to –NH stretching vibration. A sharp band at $\nu_{\text{max}}$ 1662.5 cm$^{-1}$ recognized the stretching vibration of C=O. The bands at 1602.7 and 1454.2 cm$^{-1}$ indicated the presence of C=C stretching vibration in the aromatic ring.

In the $^1$H NMR spectrum the chemical shift of the compound a broad singlet was found at $\delta_H$ 7.52 in consequence of –NH, one doublet at $\delta_H$ 7.35(2H, $J$=8.4 Hz) due to C-2 and C-6 protons, another
doublet at $\delta_H$ 7.08 (2H, $J$ = 8.4 Hz) due to C-3 and C-5 protons respectively. Two sharp singlets at 2.28 and 2.12 were found in favor of –CO-CH$_3$ and Ar-CH$_3$ respectively.

4-Chloro-2,6-diiodoaniline 6

Yellowish amorphous solid, mp.127-129°C.

In the IR spectrum of the compound the absorption band at $\delta_{\text{max}}$ 3408.0 and 3317.3 cm$^{-1}$ represented stretching vibration of primary amine –NH$_2$. The absorption band at 1604.7 and 1442.7 cm$^{-1}$ was caused by C=C stretching vibration in the aromatic ring.

In the $^1$H NMR spectrum of the compound the chemical shift was found at $\delta_H$ 7.60 (s, 2H) for C-3 and C-5 protons of the in aromatic ring. The chemical shift at $\delta_H$ 4.59 (s, 2H) was designed for presence of Ar–NH$_2$.

4-Chloro-2-iodo-N-ethanoyl aniline 7

White crystalline solid, 125-127°C.

In the IR spectrum (fig-2a) of the compound the absorption band at $\delta_{\text{max}}$ 3274.9 cm$^{-1}$ represented -NH stretching vibration. The absorption frequency at 1658.7 cm$^{-1}$ indicated the presence of C=O stretching vibration. The absorption band at 1577.7 and 1463.9 cm$^{-1}$ were caused by C=C stretching vibration in the aromatic ring.

In the $^1$H NMR spectrum (fig-2b) of the compound one doublet was found at $\delta_H$ 8.15 (1H, $J$ = 8.0 Hz) for C-6 proton, an other doublet at $\delta_H$ 7.74 (1H, $J$ = 2.0 Hz) due to C-3 proton. A broad singlet was found at $\delta_H$ 7.36 due to –NH proton. A double doublet at $\delta_H$ 7.30 (dd, 1H, $J$ = 2.0 & 8.0 Hz) was because of C-5 proton. One sharp singlet at $\delta_H$ 2.22 was found on behalf of –CO-CH$_3$.

4-Chloro-2-iodoaniline 8

Brown crystalline solid, mp. 40-42°C.

In the IR spectrum of the compound the absorption band was found at $\delta_{\text{max}}$ 3408.0 and 3317.3 cm$^{-1}$ because of –NH$_2$ stretching vibration. The absorption band at 1604.7 and 1442.7 cm$^{-1}$ indicated the presence of C=C stretching vibration in the aromatic ring.
In the $^1$H NMR spectrum of the compound the chemical shift was found at $\delta_{H} 7.58$ (d, 1H, $J=2.3$ Hz) for C-3 proton. One doublet at $\delta_{H} 7.08$ (dd, 1H, $J=2.3$ Hz, 8.4 Hz) for C-5 proton. One doublet at $\delta_{H} 6.64$ (1H, $J=8.4$ Hz) for C-6 proton. One singlet was found at $\delta_{H} 4.07$ as a result of $-\text{NH}_2$.

4-methyl-N-propanoyl aniline 9
White crystalline solid

In the IR spectrum (fig-3a) of the compound the absorption band was found at $\nu_{\text{max}} 3303.8$ cm$^{-1}$ due to $-\text{NH}$ stretching vibration. The absorption band at 1664.5 cm$^{-1}$ represented the stretching vibration of C=O. The band at 1309.6 cm$^{-1}$ represented C-N bending vibration.

In the $^1$H NMR spectrum (fig-3b) of the compound the chemical shift was found as a doublet at $\delta_{H} 7.37$ (2H, $J=8.0$) due to C-2 and C-6 proton a broad, a broad singlet was found at $\delta_{H} 7.22$ on account of $-\text{NH}$, and another doublet at $\delta_{H} 7.09$ (2H, $J=8.0$) due to C-3 and C-5 respectively. One quartet at $\delta_{H} 2.35$ due to $-\text{CO-CH}_2$-. One sharp singlet at 2.29 originated for Ar-CH$_3$ and one triplet at 1.22 due to terminal -CH$_3$ protons.

2, 6-diiodo-4-methyl-N-ethanoyl aniline 10
White amorphous solid. mp.135-138°C.

In the IR spectrum of the compound the absorption band was found at $\nu_{\text{max}} 3159.2$ cm$^{-1}$ due to $-\text{NH}$ stretching vibration. The bands at 2997.2 and 2916.2 cm$^{-1}$ were due to C-H stretching vibration. The absorption band at 1676.0 cm$^{-1}$ recognized the stretching vibration of C=O. The absorption band at 1579.6 and 1452.3 cm$^{-1}$ indicated the presence of C=C stretching vibration in the aromatic ring.

In the $^1$H NMR spectrum of the compound the chemical shift was found at $\delta_{H} 7.68$ (s, 2H) as a result of C-3 and C-5 aromatic protons, abroad singlet at $\delta_{H} 6.99$ for the existence of $-\text{NH}$ group. Two sharp singlets at $\delta_{H} 2.26$ and 2.22 were caused by $-\text{CO-CH}_3$ and Ar-CH$_3$ correspondingly.
2.4.1 Synthesis of 4-substituted-2-alkynyl-N-ethanoyl aniline and dialkyne 14-19

A mixture of 4-substituted-2-iodo-N-ethanoyl aniline 4 or 7 (1 m mol), bis(triphenylphosphine) palladium(II)chloride (3.5 mol%), copper(I)iodide (8 mol%), and triethylamine (4 mmol) was stirred in DMF (5-7 mL) under nitrogen atmosphere for 1 h. Then alkynes 11, 12, or 13 (1.2 mmol) was added and the solution was heated at 60-80°C for 24-48 h. The mixture was then evaporated to dryness under reduced pressure. After usual workup, the crude product was purified by column chromatography on silica gel using n-hexane/ethyl acetate as eluant to afford the pure compounds 14-19.

<table>
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<th>R</th>
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</thead>
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<tr>
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<td>7</td>
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<td>Ph</td>
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<td>C₄H₉</td>
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<td>Cl</td>
<td>Ph</td>
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The results are given in the Table-2.

**Table 2: Synthesis of 4-substituted-2-alkynyl-N-ethanoyl aniline**

<table>
<thead>
<tr>
<th>Entry</th>
<th>4-Substituted-2-iodo-N-ethanoyl aniline</th>
<th>Terminal alkyne</th>
<th>Condition</th>
<th>Product</th>
<th>Yield (%)</th>
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<td>7</td>
<td>11</td>
<td></td>
<td>18</td>
<td>70</td>
</tr>
</tbody>
</table>
Yield (%) was calculated on the base of the amount of compounds 4 and 7

2.4.2 Characterization of 4-substituted-2-alkynyl-N-ethanoyl aniline and dialkyne 14-19

4-methyl-2-phenyl-N-ethanoyl aniline 14

White crystalline solid, mp. 127-128°C

In the IR spectrum (fig-4a) of the compound the absorption band was found at $\nu_{\text{max}}$ 3296.1 cm$^{-1}$ as a result of –NH stretching vibration. The absorption band at 2214.1 cm$^{-1}$ was found in support of the stretching vibration of carbon-carbon triple bond, where as the band at 1654.8 cm$^{-1}$ was in favor of C=O stretching vibration. The absorption band at 1583.4 and 1492.8 cm$^{-1}$ indicated the presence of C=C stretching vibration in the aromatic ring.

In the $^1$H NMR spectrum (fig-4b) the compound demonstrated the chemical shifts in form of singlet at $\delta_H$ 8.27 caused by C-6 proton, another singlet at $\delta_H$ 7.89 indicated the presence of –NH proton. The chemical shifts at $\delta_H$ 7.52-7.30 and 7.15(m, 7H) represented protons of the both benzene ring. Two sharp singlets at $\delta_H$ 2.30 and 2.22 indicated the existence of the protons of –CO-CH$_3$ and Ar-CH$_3$ respectively.

In the $^{13}$C NMR spectrum (fig-4c, d) the compound showed the chemical shift at $\delta_c$ 167.96 was caused by carbonyl carbon, at $\delta_c$ 136.49 in support of (Ar-NH). The chemical shifts at $\delta_c$ 133.00, 132.97, 131.85, 131.55, 130.47, 128.82, 128.55, 122.40, 119.66, 118.11, and 111.70 were on account of Ar-C. The chemical shifts at $\delta_c$ 95.96 & 84.45 were in support of C=C. The chemical shifts at $\delta_c$ 24.83 and 20.50 were caused by -CH$_3$ of ethanoyl and Ar-CH$_3$ correspondingly.

4-Methyl-2-(1-hexynyl)-N-ethanoyl aniline 15

Brown crystalline solid, mp. 84-86°C

In the IR spectrum (fig-5a) of the compound the absorption band was found at $\nu_{\text{max}}$ 3274.9 cm$^{-1}$ as a result of –NH stretching vibration. The absorption band at $\nu_{\text{max}}$ 2956.7 and 2933.5 cm$^{-1}$ were due to stretching vibration of C-H. The stretching vibration of carbon-carbon triple bond was found at 2223.8
The band at 1664.5 cm\(^{-1}\) was on account of C=O stretching vibration. The absorption band at 1587.3 and 1488.9 cm\(^{-1}\) indicated the presence of C=C stretching vibration in the aromatic ring.

In the \(^1\)H NMR spectrum (fig-5b) the compound showed a doublet at \(\delta_H 8.21(1H, J=8.4 \text{ Hz})\) caused by C-6 proton. One broadened singlet at \(\delta_H 7.84\) indicated the existence of –NH proton. One singlet at \(\delta_H 7.15\) was on account of C-3 proton. The chemical shift at \(\delta_H 7.07(1H, J=8.4 \text{ Hz})\) was attributable to C-5 proton. One triplet at \(\delta_H 2.49(2H, J=7.2 \text{ Hz})\), one quintet at \(\delta_H 1.63(2H, J=7.2 \text{ and } 6.8 \text{ Hz})\), one sextet at 1.50(2H, \(J=7.2 \text{ and } 6.8 \text{ Hz}\)) indicated the presence of three -CH\(_2\)- groups positioned at C-3\(\text{•}\), C-4\(\text{•}\), and C-5\(\text{•}\) of the chain. A triplet at 0.96 (3H, \(J=7.2 \text{ Hz}\)) established the presence of terminal -CH\(_3\).

Two sharp singlets at \(\delta_H 2.25\) and 2.17 indicated the presence of protons of –CO-CH\(_3\) and Ar-CH\(_3\) respectively.

In the \(^13\)C NMR spectrum (fig-5e) of the compound the chemical shift was originated at \(\delta_c 167.91\) caused by carbonyl carbon. The chemical shift at \(\delta_c 136.54\) was as a result of Ar-NH. The chemical shifts at \(\delta_c 132.74, 131.81, 129.59, 118.99\), and 112.46 were on behalf of the aromatic carbon. The chemical shifts at \(\delta_c 97.33\) & 76.17 were found caused by C\(\text{•}\)C. The chemical shifts were at \(\delta_c 30.83\) on behalf of C-3\(\text{•}\), 24.83 for ethanoyl-CH\(_3\), 22.08 designed for C-4\(\text{•}\), 20.63 in support of Ar-CH\(_3\), 19.25 for C-5\(\text{•}\) and 13.59 was in favor of terminal -CH\(_3\).

**4-M ethyl-2-(heptyn-1-yl)-N-ethanoyl aniline 16**

Brown crystalline solid, mp. 64-65°C

In the IR spectrum (fig-6a) of the compound the absorption band was found at \(\nu_{\max} 3274.9 \text{ cm}^{-1}\) as a result of –NH stretching vibration. The absorption band at 2219.9 \text{ cm}^{-1} represented the stretching vibration of carbon- carbon triple bond, whereas the band at 1662.5 cm\(^{-1}\) was caused by stretching vibration of C=O.

In the \(^1\)H NMR spectrum (fig-6b) of the compound showed a doublet at \(\delta_H 8.21(1H, J=8.4 \text{ Hz})\) caused by C-6 proton. One broadened singlet at 7.84 indicated the presence of –NH proton. One singlet originated at \(\delta_H 7.16\) due to C-3 proton, one doublet at \(\delta_H 7.07(1H, J=8.0 \text{ Hz})\) because of C-5 proton. One triplet at \(\delta_H 2.48(2H, J=6.8 \text{ Hz})\), one quintet at 1.64 (2H, \(J=7.2 \text{ and } 6.8 \text{ Hz}\)), a multiplet at 1.49-1.24(m, 4H) indicated the presence of four -CH\(_2\)- groups positioned at C-3\(\text{•}\), C-4\(\text{•}\), C-5\(\text{•}\) & 6\(\text{•}\) of the chain respectively. A triplet at \(\delta_H 0.92(3H, J=7.2 \text{ Hz})\) established the presence of terminal-CH\(_3\). Two sharp singlets at \(\delta_H 2.25\) and 2.18 indicated the presence of –CO-CH\(_3\) and Ar-CH\(_3\) protons correspondingly.
In the $^{13}$C NMR spectrum (fig-6e) the compound showed the chemical shift at $\delta_{c} 167.94$ caused by carbonyl carbon. The chemical shift at $\delta_{c} 136.48$ was in support of Ar-NH. The chemical shift at $\delta_{c} 132.73, 131.80, 129.59, 118.91$ & $112.38$ were in favor of Ar-C. The chemical shifts at $\delta_{c} 97.42$ & $76.09$ were caused by carbon carbon triple bond. The chemical shifts at $\delta_{c} 31.18, 28.47$ were designed for C-3$\cdot$ & C-4$\cdot$. The chemical shift at $\delta_{c} 24.90$ for ethanoyl-CH$_{3}$ and $22.24$ designed for C-5$\cdot$. The chemical shifts at $\delta_{c} 20.64, 19.55,$ and $14.01$ were as a result of Ar-CH$_{3}$, C-6$\cdot$ and terminal -CH$_{3}$.

4-Chloro-2-(hexyn-1-yl)-N-ethanoyl aniline 17

White crystalline solid, mp. 80-82°C

In the IR spectrum (fig-7a) of the compound the absorption band was found at $\nu_{\text{max}} 3294.2$ cm$^{-1}$ due to -NH stretching vibration. The absorption band at $\nu_{\text{max}} 2956.7$ and $2927.7$ cm$^{-1}$ were due to stretching vibration of C-H. The absorption band at $2223.8$ cm$^{-1}$ characterized the stretching of carbon carbon triple bond, where as the absorption band at $1662.5$ cm$^{-1}$ was in support of stretching vibration of C=O. The absorption band at $1598.9$ and $1473.5$ cm$^{-1}$ indicated the presence of C=C stretching vibration in the aromatic ring.

In the $^1$H NMR spectrum (fig-7b-d) the compound showed the chemical shift at $\delta_{H} 8.31$ (d, 1H, $J=8.8$ Hz,) caused by C-6 proton. One broadened singlet at $\delta_{H} 7.85$ indicated the presence of –NH proton. The chemical shift at $\delta_{H} 7.31$ (d, 1H, $J=2.0$ Hz,) indicated the presence of C-3 proton. One double doublet at $\delta_{H} 7.21$ (1H, $J=8.8$ & $2.0$ Hz) was as a result of C-5 proton of the aromatic ring. One triplet at $\delta_{H} 2.49$ (2H, $J=6.8$ Hz), one quintet at $\delta_{H} 1.62$ (2H, $J=6.8$ Hz and $7.2$ Hz), one sextet at $1.50$ (2H, $J=7.2$ and $7.6$ Hz) indicated the existence of three -CH$_{2}$- groups positioned at C-3$\cdot$ C-4$\cdot$, and C-5$\cdot$ of the chain respectively. A triplet at $\delta_{H} 0.96$ (3H, $J=7.6$ Hz) recognized the presence of terminal -CH$_{3}$ of the chain. A sharp singlet at $\delta_{H} 2.18$ was for the presence of -CO-CH$_{3}$.

In the $^{13}$C NMR spectrum (fig-7e) of the compound showed chemical shift at $\delta_{c} 168.01$ due to presence of carbonyl group C=O, the peak at $\delta_{c} 137.50$ was in favor of Ar-NH. The chemical shifts at $\delta_{c} 131.05, 128.87, 127.98, 120.12$ & $114.09$ were in support of aromatic carbon. The chemical shift position at $\delta_{c} 99.07$ & $74.94$ were due to C$\cdot$C, at 30.63 was in favor of C-3$\cdot$, at 24.82 was due to -CH$_{3}$ of the ethanoyl group. The chemical shift value at $\delta_{c} 22.06$ & $19.22$ were as a result of C-4$\cdot$ & C-5$\cdot$. The chemical shift was found at $\delta_{c} 13.55$ in consequence of terminal –CH$_{3}$.
4-Chloro-2-phenylethynyl-N-ethanoyl aniline 18
Brown crystalline solid, 178-180°C
In the IR spectrum (fig-8a) of the compound the absorption band was found at $\nu_{\text{max}}$ 3300.0 cm$^{-1}$ due to $\text{–NH}$ stretching vibration. The band at 2210.3 cm$^{-1}$ represented the stretching vibration of carbon carbon triple bond, where as the band at 1660.6 cm$^{-1}$ was correspond to stretching vibration of C=O.

In the $^1$H NMR spectrum (fig-8b-c) the compound showed a doublet at $\delta_{\text{H}}$ 8.36( 1H, $J=8.8$ Hz) caused by C-6 proton of the aromatic ring. One broadened singlet at 7.90 indicated the presence of $\text{–NH}$ proton. One singlet at 7.45 was a sign of C-3 proton and a doublet at $\delta_{\text{H}}$ 7.29(1H, $J=8.8$ Hz,) as a result of C-5 proton. The chemical shift position at $\delta_{\text{H}}$ 7.53-7.15(2H, Ph) and 7.40-7.39 (m, 3H, Ph) correspond to protons of one phenyl group. One sharp singlet at $\delta_{\text{H}}$ 2.22 indicated the presence of $\text{–CO-CH}_3$ proton.

In the $^{13}$C NMR spectrum (fig-8d) the compound showed the chemical shift at $\delta_{\text{C}}$ 168.09 caused by C=O. The chemical shift at $\delta_{\text{C}}$ 137.51 was supporting to Ar-NH. The peaks at 131.59 was caused by C-2 & C-6 of the phenyl group. The chemical shift at $\delta_{\text{C}}$ 131.10, 129.72 & 129.32 were due to Ar-C, at 128.69 was due to C-3 & C-5 of the phenyl group. The chemical shift at $\delta_{\text{C}}$ 121.86, 120.53 & 113.41 were supporting rest of the aromatic carbon. The chemical shifts at $\delta_{\text{C}}$ 97.42 & 83.04 were caused by C•C and at 24.91 was on behalf of ethanoyl-CH$_3$.

1, 4-di phenyl-1, 3-buta-di-yne 19
White crystalline solid
In the IR spectrum of the compound the absorption band was found at $\nu_{\text{max}}$ 2135.1 cm$^{-1}$ because of C•C bond present in the compound.

In the $^1$H NMR spectrum of the compound the chemical shift was found at $\delta_{\text{H}}$ 7.52(d, 4H) as a result of C-2 & C-6 of the both phenyl groups. The chemical shift position at $\delta_{\text{H}}$ 7.35 (m, 6H) as a result of coupling of the protons at C-3, C4, and C-5 in the aromatic.

2.4.3 Mechanism of $\text{(PPh}_3)_2\text{PdCl}_2$ catalyzed cross-coupling reaction of 4-substituted-2-iodo-N-ethanoyl aniline with terminal alkyne.

The cross-coupling reaction of 4-substituted-2-iodo-N-ethanoyl aniline with terminal alkyne was catalyzed by $\text{(PPh}_3)_2\text{PdCl}_2$, where CuI acted as a co-catalyst$^{157}$. The catalytic process can be divided into two catalytic cycles.
The palladium cycle:

The active palladium catalyst is the 14 electron compound Pd(0)L₂ A which reacts with the aryl halide in an oxidative addition to Pd(II) complex B. This complex reacts in a rate limiting transmetallation with the copper acetylide produced in the copper cycle to complex C expelling the copper halide CuX G. Both organic ligands are trans oriented and transfer to cis in a trans-cis isomerization to complex D. In the final step the product is released in a reductive elimination with regeneration of Pd(0)L₂.

The copper cycle:

CuI form a pi-alkyne complex E. The organocopper compound F forms after reaction with the base and continues to react with palladium intermediate B with regeneration of copper halide G. The copper acetylide is assumed to be involved in the reduction of Pd (II) catalysts, first forming a dialkyne-PdL₂ complex and then by reductive elimination Pd (0)L₂ and a diacetylene.
2.5.1 Base catalyzed synthesis of 2, 5-disubstituted-1H indole and 4-substituted-2-alkynyl aniline 20-24

A mixture of 4-substituted-2-alkynyl-N-ethanoyl aniline (1 mmol), sodium ethoxide (1.2-1.5 mmol) in 20 mL ethanol was stirred under a nitrogen atmosphere for 4 h at 80°C. At the end of the reaction the mixture was evaporated to dryness under reduced pressure. After usual workup, the residue was purified by column chromatography on silica gel using n-hexane/ethylacetate as eluant to yield 2, 5-disubstitued-1H indole 20, 22 along with acyclic 4-substituted-2-alkynyl aniline 21, 23, 24.

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<th>Compounds</th>
<th>X</th>
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<tr>
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<td>C₄H₉</td>
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<td>17, 20, 21</td>
<td>Cl</td>
<td>C₄H₉</td>
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The results are given in the Table-3.

**Table 3: Base catalyzed synthesis of 2, 5-disubstituted indoles.**

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<thead>
<tr>
<th>Entry</th>
<th>4-substituted-2-Alkynyl Acetanilide</th>
<th>Reagents &amp; condition</th>
<th>2,5-disubstituted indoles(a)</th>
<th>4-substituted-2-alkynyl anilines(b)</th>
<th>Yields % (a/b)</th>
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</table>


2.5.2 Characterization of 2, 5-disubstitued-1H indole/ 4-substituted-2-alkynyl aniline 20-24

2-butyl-5-chloro-1H -indole 20

Brown liquid

In the IR spectrum (fig-9a) of the compound the absorption band was found at $\nu_{\text{max}}$ 3421.5 cm$^{-1}$ caused by –NH stretching vibration of the indole. The absorption band at 2958.6 & 2929.7 cm$^{-1}$ were due to stretching vibration of C-H.

In the $^1$H NMR spectrum(fig-9b) of the compounds chemical shift was found in the form of a broad singlet at $\delta_{\text{H}}$ 7.87 due to -NH of indole, an other singlet at $\delta_{\text{H}}$ 7.46 was due to C-4 proton, one doublet at $\delta_{\text{H}}$ 7.17(1H, $J = 8.4$Hz) as a result of C-7 proton, an other doublet at $\delta_{\text{H}}$ 7.04(1H, $J = 8.4$) because of C-6 proton, a singlet at $\delta_{\text{H}}$ 6.13 due to C-3 proton. The chemical shift at $\delta_{\text{H}}$ 2.73(t, 2H, $J = 7.6$ Hz), at $\delta_{\text{H}}$ 1.69(quint, 2H, $J =7.2$ and 7.6 Hz), and 1.39(sex, 2H, $J = 7.2$ and 7.6 Hz) were due to the presence of -CH$_2$- groups located at C-1, C-2 and C-3 respectively of the chain. The chemical shift at $\delta_{\text{H}}$ 0.95(t, 3H, $J =7.2$ Hz) was in support of terminal -CH$_3$.

2-butyl-4-chloro aniline 21

In the IR spectrum of the compound the absorption band was found at $\nu_{\text{max}}$ 3585.4 and 3544.9 cm$^{-1}$ due to stretching vibration of –NH$_2$. The absorption band at 2958.6 & 2929.7 cm$^{-1}$ were due to C-H stretching vibration, where as the band at 2235.0 cm$^{-1}$ was as a result the stretching vibration of C•C.

In the $^1$H NMR spectrum the compound showed a doublet at $\delta_{\text{H}}$ 7.20(1H, $J =2.0$ Hz) due to C-3 proton, one double doublet at $\delta_{\text{H}}$ 7.01(1H, $J =2.0$ & $8.4$ HZ) due to C-5 proton, another doublet at 6.58 (1H, $J = 8.4$ Hz) due to C-6 proton. One broadened singlet at $\delta_{\text{H}}$ 4.14 was attributable to -NH$_2$. One triplet at $\delta_{\text{H}}$ 2.5.2 Characterization of 2, 5-disubstitued-1H indole/ 4-substituted-2-alkynyl aniline 20-24

2-butyl-5-chloro-1H -indole 20

Brown liquid

In the IR spectrum (fig-9a) of the compound the absorption band was found at $\nu_{\text{max}}$ 3421.5 cm$^{-1}$ caused by –NH stretching vibration of the indole. The absorption band at 2958.6 & 2929.7 cm$^{-1}$ were due to stretching vibration of C-H.

In the $^1$H NMR spectrum(fig-9b) of the compounds chemical shift was found in the form of a broad singlet at $\delta_{\text{H}}$ 7.87 due to -NH of indole, an other singlet at $\delta_{\text{H}}$ 7.46 was due to C-4 proton, one doublet at $\delta_{\text{H}}$ 7.17(1H, $J = 8.4$Hz) as a result of C-7 proton, an other doublet at $\delta_{\text{H}}$ 7.04(1H, $J = 8.4$) because of C-6 proton, a singlet at $\delta_{\text{H}}$ 6.13 due to C-3 proton. The chemical shift at $\delta_{\text{H}}$ 2.73(t, 2H, $J = 7.6$ Hz), at $\delta_{\text{H}}$ 1.69(quint, 2H, $J =7.2$ and 7.6 Hz), and 1.39(sex, 2H, $J = 7.2$ and 7.6 Hz) were due to the presence of -CH$_2$- groups located at C-1, C-2 and C-3 respectively of the chain. The chemical shift at $\delta_{\text{H}}$ 0.95(t, 3H, $J =7.2$ Hz) was in support of terminal -CH$_3$.

2-butyl-4-chloro aniline 21

In the IR spectrum of the compound the absorption band was found at $\nu_{\text{max}}$ 3585.4 and 3544.9 cm$^{-1}$ due to stretching vibration of –NH$_2$. The absorption band at 2958.6 & 2929.7 cm$^{-1}$ were due to C-H stretching vibration, where as the band at 2235.0 cm$^{-1}$ was as a result the stretching vibration of C•C.

In the $^1$H NMR spectrum the compound showed a doublet at $\delta_{\text{H}}$ 7.20(1H, $J =2.0$ Hz) due to C-3 proton, one double doublet at $\delta_{\text{H}}$ 7.01(1H, $J =2.0$ & $8.4$ HZ) due to C-5 proton, another doublet at 6.58 (1H, $J = 8.4$ Hz) due to C-6 proton. One broadened singlet at $\delta_{\text{H}}$ 4.14 was attributable to -NH$_2$. One triplet at $\delta_{\text{H}}$
2.45(2H, J = 6.8 Hz) was in favor of C•C–CH$_2$–, one quintet at $\text{H} 1.59(2H, J = 6.8 \& 7.2 \text{ Hz})$ was due to –CH$_2$– of C-4•, one sextet at $\text{H} 1.36(\text{sex}, 2H, J = 7.2 \text{ and } 7.6 \text{ Hz})$ was by reason of -CH$_2$– of C-5•, one triplet at $\text{H} 0.90 (t, 3H, J = 7.2 \text{ Hz})$ was caused by terminal -CH$_3$.

**2-Butyl-4-methyl-1H indole 22**

Brown liquid.

In the IR spectrum of the compound the absorption band was found at 3408.0 cm.$^{-1}$ due to –NH of the indole, 2956.& 2929.7 cm.$^{-1}$ due to C-H stretching vibration, the absorption band at 1618.2 and 1458.1 cm.$^{-1}$ were due to aromatic C=C stretching vibration.

In the $^1$H NMR spectrum of the compound the chemical shift at $\text{H} 7.75(\text{br s}, 1H)$ was in support of –NH of indole. The chemical shifts at $\text{H} 7.29(s, 1H), 7.16(d, 1H, J = 8.0 \text{ Hz}), 6.91(d, 1H, J = 8.0 \text{ Hz}),$ and 6.13( s, 1H ) were in consequence of the protons positioned at C-4, C-7, C-6, and C-3 respectively. The chemical shift at $\text{H} 2.72(t, 2H, J = 7.6 \text{ Hz})$ was caused by C-1•. The chemical shift at $\text{H} 2.41(s, 3H)$ was due to Ar-CH$_3$. The chemical shifts at $\text{H} 1.68 (\text{quint}, 2H, J = 7.6 \text{ and } 7.2 \text{ Hz})$ and 1.39(\text{sex}, 2H, J = 7.2 \text{ and } 7.6 \text{ Hz}) were in consequence of the protons positioned at C-2• and C-3• respectively. The chemical shift at $\text{H} 0.87 (t, 3H, J = 7.2 \text{ Hz})$ was in favor of terminal -CH$_3$.

**2-(1-hexynyl)-4-methyl aniline 23**

In the $^1$H NMR spectrum of the compound the chemical shifts were found as a singlet at $\text{H} 7.05$, one doublet at $\text{H} 6.85(1H, J = 8.0 \text{ Hz})$, another doublet at 6.59 (1H, J = 8.0 Hz) were in support of protons positioned at C-3, C-6, and C-5 respectively. One broadened singlet at $\text{H} 4.21$ was caused by -NH$_2$. One triplet at $\text{H} 2.45(2H, J = 6.8 \text{ Hz})$ for -C•C-CH$_2$– and one singlet at $\text{H} 2.18$ was due to Ar-CH$_3$. The chemical shifts in the form a quintet at 1.60(2H, J = 6.8 & 7.6 Hz), one sextet at 1.49(2H, J = 7.2 and 7.6 Hz) were on behalf of protons positioned at C-4• and C-5• respectively. One triplet at $\text{H} 0.93 (t, 3H, J = 7.2 \text{ Hz})$ was in favor of terminal -CH$_3$.

**4-Methyl-2-phenyl aniline 24**

White crystalline solid

In the IR spectrum (fig-10a) of the compound the absorption band was found at $\text{max} 3473.6 \& 3379.1 \text{ cm}^{-1}$ were in support of -NH$_2$. The stretching vibration of C•C was found at 2185.2 cm$^{-1}$. 
In the $^1$H NMR spectrum (fig-10b) the compound showed chemical shift at $\cdot H$ 7.52-7.49(m, 2H) and at $\cdot H$ 7.36-7.29(m, 3H) were due to the protons of phenyl group. The chemical shifts at 7.17(s, 1H), at $\cdot H$ 6.95(d, $J=8.0$ Hz), and at $\cdot H$ 6.64(d, 1H, $J=8.0$ Hz) were in favor of the protons situated at C-3, C-6, and C-5 of the aromatic ring. The chemical shift at 4.13(s, 2H) was caused by $-\text{NH}_2$. 
2.5.3 Mechanism of base catalyzed cyclization of 2-Alkynyl-4-substituted-N-ethanoyl aniline

The cyclization of 2-Alkynyl-4-substituted-N-ethanoyl aniline was carried out by sodium ethoxide in ethanol. The plausible mechanism for the base catalyzed cyclization was shown in the following scheme.

In the initial step of the catalytic reaction ethoxide ion extract the proton from nitrogen and nitrogen bears the negative charge. The nitrogen attacks the partially positive carbon of alkyne and partially negative carbon attacks the proton of the alcohol available in the solvent system. In the final step ethanoyl group is removed by hydrolysis during workup.
2.6.1 PdCl$_2$ catalyzed synthesis of 2, 5-disubstituted-N-ethanoyl indole 25-27

In a round bottom flask equipped with a reflux condenser 0.1 mmol of palladium (**) chloride in 8 mL acetonitrile was refluxed at 80°C with constant stirring. The solid dissolved after 20 min and the mixture was allowed to cool at room temperature. In this solution 1.0 mmol of 2-alkynyl-4-substituted-N-ethanoyl aniline was added and the mixture was refluxed at 80°C with continuous stirring for 0.5-2h. At the end of the reaction, the mixture was evaporated to dryness under reduced pressure. The product was purified by column chromatography on silica gel using n-hexane/ethyl acetate (5:1) as eluant to yield pure 2, 5-disubstituted-N-ethanoyl indole.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>X</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>15, 25</td>
<td>CH$_3$</td>
<td>C$_4$H$_9$</td>
</tr>
<tr>
<td>16, 26</td>
<td>CH$_3$</td>
<td>C$<em>5$H$</em>{11}$</td>
</tr>
<tr>
<td>17, 27</td>
<td>Cl</td>
<td>C$_4$H$_9$</td>
</tr>
</tbody>
</table>

The results are given in the Table-4.
Table 4: PdCl$_2$ catalyzed synthesis of 2, 5-disubstituted-N-ethanoyl indole.

<table>
<thead>
<tr>
<th>Entry</th>
<th>2-alkynyl-4-substituted-N-ethanoyl aniline.</th>
<th>Reagents &amp; Condition.</th>
<th>2, 5-disubstituted-N-ethanoyl indole.</th>
<th>Yields (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16</td>
<td></td>
<td>25</td>
<td>71</td>
</tr>
<tr>
<td>2</td>
<td>17</td>
<td></td>
<td>26</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>18</td>
<td></td>
<td>27</td>
<td>68</td>
</tr>
</tbody>
</table>

Yield (%) was calculated on the base of amount of compounds 16, 17 and 18.

2.6.2 Characterization of 2, 5-disubstituted-N-ethanoyl indole 25-27

2-Butyl-5-methyl-N-ethanoyl indole 25

White crystalline solid
mp. 68-69°C
In the IR spectrum (fig-11a) of the compound the absorption band was found at $\lambda_{\text{max}}$ 2958.6 & 2935.5 cm$^{-1}$ due to C-H stretching. The absorption band at 1679.9 cm$^{-1}$ indicated the existence of C=O stretching vibration. The band at 1591.2 & 1469.7 cm$^{-1}$ represented stretching vibration of C=C in the aromatic ring.

In the $^1$H NMR spectrum (fig-11b-e) of the compound the chemical shifts were found in the form of doublet at $\delta_H$ 7.68(1H, $J$=8.4 Hz), one singlet at $\delta_H$ 7.25, another doublet at $\delta_H$ 7.04 (1H, $J$=8.4 Hz) and another singlet at $\delta_H$ 6.32 indicated the presence of one proton at C-7, C-4, C-6, and C-3 position respectively of the indole ring. A triplet at $\delta_H$ 2.98 (2H, $J$=7.6 Hz) was due to the protons of C-1, two singlet at $\delta_H$ 2.72 and 2.41 were due to protons of -CO-CH$_3$ and Ar-CH$_3$ correspondingly. The chemical shift at $\delta_H$ 1.68(quin, 2H, $J$=7.2 & 7.6 Hz) and 1.44 (sex, 2H, $J$=7.2 & 7.6 Hz) indicated the presence of the protons at C-2 and C-3 respectively. A triplet at $\delta_H$ 0.95 (3H, $J$=7.2 Hz) recognized the presence of terminal -CH$_3$.

In the $^{13}$C NMR spectrum (fig-11f) of the compound the chemical shift at $\delta_c$ 170.19 was due to C=O of the ethanoyl group. The chemical shift at $\delta_c$ 143.18 was in support of Ar-NH. The chemical shift at $\delta_c$ 134.60, 132.49, 130.31, 124.59, 120.20, 114.48 and 108.03 were due to aromatic carbon. The chemical shifts were found at $\delta_c$ 31.07, 30.30 and 27.57 for C-1, C-2 and ethanoyl-CH$_3$ respectively. The chemical shift at $\delta_c$ 22.56, 21.11 and 13.97 were due to the presence of C-3, Ar-CH$_3$ and terminal -CH$_3$ accordingly.

2-pentyl-5-methyl-N-ethanoyl indole 26

White crystalline solid. mp. 50-51°C

In the IR spectrum(fig-12a) of the compound the absorption band was found at $\lambda_{\text{max}}$ 2921.9 cm$^{-1}$ due to C-H stretching vibration, another band at 1687.6 cm$^{-1}$ recognized the presence of the C=O group. The absorption bands at 1591.2 & 1460.7 cm$^{-1}$ represented stretching vibration of C=C in the aromatic ring.

In the $^1$H NMR spectrum (fig-12b-d) of the compound the chemical shift $\delta_H$ at 7.68(d,1H, $J$=8.4 Hz) owing to the proton of C-7, at $\delta_H$ 7.25(s, 1H) on a count of the proton of C-4, at $\delta_H$ 7.04 (d, 1H, $J$=8.4 Hz) as a result of the proton of C-6 and at $\delta_H$ 6.32(s, 1H) because of the proton of C-3. The chemical shift at $\delta_H$ 2.97(t, 2H, $J$=7.6 Hz) caused by C-1, at $\delta_H$ 2.72(s, 3H) owing to protons of -CO-CH$_3$, at $\delta_H$ 2.41(s, 3H) because of Ar-CH$_3$. The chemical shift at $\delta_H$ 1.69(quin, 2H, $J$=7.2 & 7.6 Hz),
1.42-1.28 (m, 4H), and 0.91 (t, 3H, J=7.2 Hz) in consequence of the protons of C-2•, C-3• & 4• and terminal -CH₃ accordingly.

In the ¹³C NMR spectrum (fig-12e) of the compound showed the chemical shift at •c 170.19 because of C=O of the ethanoyl group. The chemical shift at 143.21 is in support of Ar-NH. The chemical shifts at •c 134.61, 132.49, 130.31, 124.59, 120.20, 114.48 & 108.03 were in consequence of aromatic carbon. The chemical shifts at •c 31.67, 30.55, 28.62, caused by four carbons C-1•, C-2• & 3• of the chain. The chemical shifts were found at •c 27.57 by reason of ethanoyl-CH₃ and at •c 22.56 due to C-4•. The chemical shift at •c 21.12 and 14.05 Ar-CH₃ and terminal -CH₃ correspondingly.

2-Butyl-5-chloro-N-ethanoyl indole 27
White crystalline solid mp. 51-52°C

In the IR spectrum(fig-13a) of the compound the absorption band was originated at •max 2937.4 cm⁻¹ as a result of C-H stretching vibration, another band at 1685.7 cm⁻¹ on a count of C=O stretching vibration of the ethanoyl group. The absorption bands at 1591.2 and 1448.4 cm⁻¹ represented stretching vibration of C=C in the aromatic ring.

In the ¹H NMR spectrum (fig-13b-d) of the compound chemical shift at •H 7.80(d, 1H, J=9.2 Hz) due to proton of C-7, at •H 7.42(d, 1H, J=2.0 Hz) because of proton of C-4, at •H 7.17 (dd, 1H, J=9.2 & 2.0 Hz) due to proton of C-6, at •H 6.34(s, 1H) due to proton of C-3. The chemical shift was found at •H 2.96(t, 2H, J=7.2 Hz) by reason of C-1•, at •H 2.72(s, 3H) caused by proton of -CO-CH₃, at •H 1.69(quin, 2H, J=7.2 and 7.6 Hz) by reason of proton of C-2•; at •H 1.44 (sex, 2H, J=7.2 & 7.6 Hz) due to proton of C-3•, and a triplet at •H 0.96 (3H, J=7.6 Hz) as a consequence of terminal -CH₃.

In the ¹³C NMR spectrum (fig-13e) of the compound demonstrated the chemical shift at •c 170.05 caused by C=O of the ethanoyl group. The chemical shift at •c 144.13 was in support of Ar-NH. The chemical shifts at 134.90, 131.20 & 128.63, 123.47, 119.63, 115.94 & 107.53 were caused by aromatic carbon. The chemical shifts were found at •c 30.96 30.22, 27.48 for C-1•, C-2• and ethanoyl-CH₃ of the chain correspondingly. The chemical shifts at •c 22.55, 13.93 were as a result of C-3• and terminal -CH₃.

2.6.3 Mechanism of palladium (••) chloride catalyzed cyclization of 2-alkynyl-4-substituted-N-ethanoyl aniline.

The proposed reaction mechanism for the palladium- catalyzed cyclization, in analogy with the
mechanism proposed by Utimoto et al. for the palladium (II)-catalyzed intramolecular cyclization of alkynylamines.\textsuperscript{121b}

The catalytic process consists of the following basic steps:

(a) Initial formation of a pi-alkynepalladium complex, (b) Intramolecular nucleophilic attack of the nitrogen nucleophile across the activated carbon-carbon triple bond to give the sigma-indolylpalladium complex, (c) Proton transfer with loss of Pd(II), which enters a new catalytic cycle, and formation of 2, 5-disubstituted-N-ethanoyl indole.

2.7 Conclusion

Here we developed a convenient method for the synthesis of 2, 5-disubstituted indole through palladium and base catalyzed reactions.

The most important features of the synthesis were that –

1) Readily available inexpensive starting materials were used under relatively mild conditions.

2) The approach of synthesis of indole from 2, 6-di iodo aniline or acetanilide by palladium-catalyzed cross-coupling reaction was found to be unsuitable.

3) 2, 5-disubstituted-1H indole was obtained by base catalyzed cyclization.

4) 2, 5-disubstituted-N-ethanoyl indole was obtained by PdCl\textsubscript{2} catalyzed cyclization.
Spectrum
Figure 1a: IR spectrum of the compound 4
Figure 1c: $^1$H NMR spectrum of the compound 4
Figure 2b: IR spectrum of the compound 7
Figure 2(c): $^1$HNMR spectrum of compound 7
Figure 2(d): $^1$HNMR spectrum of compound 7
Figure 3(a): IR spectrum of compound 9
Figure 3(b): $^1$HNMR spectrum of compound 9
Figure 3(c): $^1$H-NMR spectrum of compound 9
Figure 4(a): IR spectrum of compound 14
Figure 4(b): $^1$H-NMR spectrum of compound 14
Figure 4(c): $^{13}$C NMR spectrum of compound 14
Figure 4(d): $^1$H NMR spectrum of compound 14
Figure 5(b): $^1$HNMR spectrum of compound 15
Figure 5(c): $^1$HNMR spectrum of compound 15
ARD, BGSIR, 1H spectrum, MAZ-49 in CDCl₃, Mazharul Haque, BUET.

Figure 5(d): ¹HNMR spectrum of compound 15
Figure 6(a): IR spectrum of compound 16
ARD, BCSIR, 1H spectrum, MAZ-60 C in CDCl₃, Mazharul Haque, BUET

Figure 6(b): ¹H NMR spectrum of compound 16
Figure 6(c): $^1$H-NMR spectrum of compound 16
Figure 6(d): $^1$H-NMR spectrum of compound 16
Figure 6(a). $^{13}$CNMR spectrum of compound 16
Figure 7(a): IR spectrum of compound 17
Figure 7(b): $^1$HNMR spectrum of compound 17
Figure 7(c): ^1^H NMR spectrum of compound 17
Figure 7(d): $^1$HNMR spectrum of compound 17
Figure 8(a): IR spectrum of compound 18
Figure 8(b): $^1$HNMR spectrum of compound 18
Figure 8(c): $^1$HNMR spectrum of compound 18
Figure 8(d): $^{13}$C NMR spectrum of compound 18
Figure 9(a): IR spectrum of compound 20
Figure 9(b): $^1$HNMR spectrum of compound 20
Figure 9(c): $^1$HNMR spectrum of compound 20
Figure 9(d): $^1$HNMR spectrum of compound 20
Figure 9(e): $^1$HNMR spectrum of compound 20
Figure 9(f): $^1$HNMR spectrum of compound 20
Figure 10(a): IR spectrum of compound 24
Figure 10(b): $^1$HNMR spectrum of compound 24.
Figure 10(c): $^1$HNMR spectrum of compound 24
Figure 11(b): $^1$HNMR spectrum of compound 25
ARD, BCSIR, 1H spectrum, MAZ-65 in CDCl₃, Mazharul haque, BUET

Figure 11(c): ¹H NMR spectrum of compound 25
Figure 11(d): $^1$HNMR spectrum of compound 25

ARD, BCSIR, 1H spectrum, MAZ-65 in CDCl$_3$, Mazharul haque, BUET
Figure 11(e): $^1$HNMR spectrum of compound 25
Figure 11(f). $^{13}$CNMR spectrum of compound 25.

140
Figure 12(a): IR spectrum of compound 26
Figure 12(b): $^1$HNMR spectrum of compound 26
ARD, BCSIR, 1H Spectrum, 71 in CDCl₃, Mazhar

Figure 12(c): ¹H NMR spectrum of compound 26
Figure 12(d): $^1$H NMR spectrum of compound 26
Figure 13(a): IR spectrum of compound 27
Figure 13(b): $^1$HNMR spectrum of compound 27
Figure 13(c): $^1$HNMR spectrum of compound 27
Figure 13(d): $^1$HNMR spectrum of compound 27.
Figure 13(e): $^{13}$C NMR spectrum of compound 27