Abstract: Synthesis and biological activities of various 2° amides of some azoles have been discussed in this chapter.
Synthesis, characterization and antimicrobial screening of \( \text{N}'\text{-}(\text{substituted})-\text{2-}(1\text{H-azol-1-yl}) \) acetamides and \( \text{N-}[\text{2-}(1\text{H-azol-1-yl}) \text{ acetyl}]\text{-2-}(1\text{H-azol-1-yl})\text{-}\text{N (substituted) acetamides} \)

Abstract: Synthesis and biological activity of various 2\(^0\) amides of some azoles have been discussed in this chapter.

2.1 Introduction:

The acylation of ammonia or amines is a very general method of synthesis of amides. In which amine reacts with carboxylic acid derivatives generally acid halide, acid anhydride and the reaction is known as nucleophilic acyl substitution\(^1\).

It is well known that many bioactive compounds are found as amide derivatives\(^2\). Many natural products such as proteins and peptides are having linear structures of cyclic polyamides. Heterocyclic carboxamides are important bioactive agent showing activity as antimicrobial\(^3\), melatonin analogs, potential anti-HIV drugs\(^4\), antitumor agents\(^5\) and antipsychotic agents\(^6\).

Numbers of reports are present which showed the potential of amides as cytotoxic agents.

Hui-Po Wang et al. have synthesized series of α-azatyrosinamides and demonstrated selective toxicity against ras-mutated NIH3T3 cells also found active in inhibiting human prostate cancer cell lines\(^7\).

Bang-Chi Chen et al. have reported 2-aminothiazole-5-carboxamides in the synthesis of anti cancer drug, Dasatinib, which is novel multi-targeted kinase inhibitor use in treatment of chronic myelogenous leukemia\(^8\).

Yan Xia et al. have reported synthesis of 2-aminoisonicotinamide analogues displayed potent inhibition of hypoxia-induced accumulation of HIF-1α protein in human cancer cell lines\(^9\).

Chang-Hyun Oh et al. have reported synthesis of 3,4-diarylpyrazole-1-carboxamides and studied antiproliferative activity against A375 melanoma cell lines and shown some compounds are more potent than Sorafenib\(^10\).

Similarly Kyeong Lee et al. have reported novel inhibitors of Pgp with lower toxicity and higher efficacy 2-phenoxy-N-phenylacetamides. Pgp is associated with multidrug resistance of tumor cells to a number of chemotherapeutic drugs\(^11\).

Various substituted amide derivatives are associated with antimicrobial, analgesic\(^12\), anticonvulsant\(^13\), antiulcer\(^14\), cardiotonic\(^15\), MAO inhibitor, anti inflammatory\(^16\), sodium channel blockers\(^17\). They are also known to posses CNS activities such as antipsychotic, analgesic, anticonvulsants and antidepressant. Literature survey indicates that many anticonvulsants contain amide group as an important pharmacophore\(^18\) (1).
Nicotinamide analogue, pyrazinamide has been used for almost 50 years as a first-line drug to treat tuberculosis. It is bactericidal to semidormant mycobacterium and reduces total treatment time. Substituted amides are reported to mycobacterium tuberculosis active.

Manoj Kumar et al. have synthesized amide derivatives of Ibuprofen (2) with improved analgesic, gastro protective and anti inflammatory activity.

Aytemir Mutulu Delsiz et al. have reported a novel cephalosporin derivative 1,5-dihydroxy-4-pyridone-2-carboxyamide MT0703, which displayed excellent antibacterial activity against *P. aeruginosa* as well as *E. coli*, in both *in vitro* and *in vivo* conditions.

Marques J.V. et al. have reported a piper amide, piperine and several other amides having a variety of biological activity is such as antitumoral, efflux-pump inhibitor, insecticidal and antifungal activities.

The carboxamides such as carboxin, pyrocarboline and Mebenil (3) are well established fungicides and used as an active components of many plant-protecting agents to control crop smuts and rust diseases.
Amides of dicarboxylic acids are widely used as herbicides, defoliants, insecticides, fungicides and repellants\textsuperscript{25}.

Amides are known to play vital role in molecular recognition these works as DNA recognizing molecules through amide proton hydrogen bondings like synthetic analogues of distamycin and neutropsin\textsuperscript{26}.

The most of the natural polymers are optically active and have special chemical activities such as catalytic properties, shown by proteins and enzymes. These act as chiral media for asymmetric synthesis, chiral stationary phases for resolution of enantiomers in chromatographic separations\textsuperscript{27}.

The conversion of amines to stable amides is the technique of protecting group in multi-step synthetic process along with benzyloxycarbonyl group (Cbz) which is reported to be stable to basic and aqueous acidic conditions\textsuperscript{28}. Literature survey reveals that drugs such as penicillin (antibacterial), pyrazineamide (anti tubercular) possess specific activity due to presence of amide linkage in their structures\textsuperscript{29}. Amides are used as building blocks for many bioactive compounds such as vitamins, agrochemicals, xanthenes, combinatorial peptide synthesis, oligocarbamates, oligoamides, \( \beta \)-lactams, polyenamides, and benzodiazepines\textsuperscript{30}.

In view of the wide and variety of useful biological activities, therapeutic and agrochemical applications, various methods have been reported in the literature. Some of the important methods are summarized in the following schemes.

1. **Method due to Gerhardt\textsuperscript{31}**.

\[
\begin{align*}
\text{RNH}_2 + \text{O} \quad \xrightarrow{\text{Base aprotic solvent}} \quad \text{O} \\
\text{acid halide or acid anhydride} \quad \xrightarrow{} \quad \text{O} \\
1^0/2^0 \text{ amine} \quad \xrightarrow{} \quad \text{HX}
\end{align*}
\]

(Scheme-1)
2. Method due to Schotten-Baumann\textsuperscript{32}.

\[
\text{RNH}_2 + R\text{-}X \xrightarrow{\text{aq. Base}} \text{aprotic solvent} \rightarrow R\text{-}NHR + HX
\]

\(1^\text{st}/2^\text{nd}\) amine, acid halide or acid anhydride

(Scheme-2)

3. Method due to Katritzky A. R. et al\textsuperscript{33}.

\[
\text{Bt Bt} \rightarrow \text{HN}_R^1 \rightarrow \text{THF reflux} \rightarrow \text{Bt}_R^1 \rightarrow R^2M
\]

R, R\textsuperscript{1} - alkyl, aryl. R\textsuperscript{2} - aryl, heteroaryl
M - Mg, Li

(Scheme-3)
4. Method due to Jeremy Schlarb\textsuperscript{34}

\[
R\overset{\text{O}}{\text{O}}\text{H} + \text{N-methylmorpholine} \rightarrow R\overset{\text{O}}{\text{O}}\text{.} \quad \overset{\text{N}}{\text{N}}\overset{\text{O}}{\text{O}}\text{.}
\]

\[
\text{Cl} + \text{Cl} \rightarrow 3 \text{N} + \text{N} + \text{Cl} + \text{Cl} \rightarrow \text{H}_3\text{C} - \overset{\text{N}}{\text{N}} \overset{\text{O}}{\text{O}} \rightarrow R\overset{\text{O}}{\text{O}}\text{.} \quad \overset{\text{N}}{\text{N}}\overset{\text{O}}{\text{O}}\text{.} \overset{\text{H}}{\text{O}}\overset{\text{H}}{\text{O}}\text{.} \quad \overset{\text{N}}{\text{N}}\overset{\text{O}}{\text{O}}\text{.} \overset{\text{H}}{\text{O}}\overset{\text{H}}{\text{O}}\text{.} + 3 \text{R'NH}_2 \quad \overset{\text{N}}{\text{N}}\overset{\text{O}}{\text{O}}\text{.} \overset{\text{H}}{\text{O}}\overset{\text{H}}{\text{O}}\text{.} + \text{Bt}
\]

(Scheme-4)

5. Method due to Katritzky A. R. \textit{et al}\textsuperscript{35}.

\[
R\overset{\text{O}}{\text{O}}\text{H} + 4 \text{Bt} \overset{\text{SOCl}_2}{\text{DCM, rt., 2hr.}} \rightarrow R\overset{\text{O}}{\text{O}}\text{.} \quad \overset{\text{N}}{\text{N}}\overset{\text{O}}{\text{O}}\text{.} \overset{\text{H}}{\text{O}}\overset{\text{H}}{\text{O}}\text{.} + \text{R'NH}_2 \quad \overset{\text{N}}{\text{N}}\overset{\text{O}}{\text{O}}\text{.} \overset{\text{H}}{\text{O}}\overset{\text{H}}{\text{O}}\text{.} + \text{Bt}
\]

(Scheme-5)
6. Method due to Katritzky A. R. et al\textsuperscript{36}.

(Scheme-6)

7. Method due to Chikhalia K. H. et al\textsuperscript{29}.

(Scheme-7)
8. Method due to Rogerio da C. R. et al\textsuperscript{37}.

\[
\begin{align*}
\text{Ph}_3P & + \text{Cl} - \text{N} &= \text{O} + \text{RCOOH} \\
\text{trichloroisocyanuric acid} & & \text{O} + \text{Ph}_3P \\
\neg & \neg & \neg \neg \\
\neg & \neg & \neg \neg \\
\neg & \neg & \neg \neg
\end{align*}
\]

(Scheme-8)

9. Method due to Joong-Gon Kim et al\textsuperscript{38}.

\[
\begin{align*}
\text{O} & \text{Cl} & \text{TEA} \\
\neg & \neg & \neg \\
\neg & \neg & \neg \\
\neg & \neg & \neg
\end{align*}
\]

(Scheme 9)

2.2 Present work:

An extensive literature survey reveals that the chemistry of 2-(1H-azole-1-yl)-N-(substituted phenyl) acetamide have not been reported so far. We have planned to synthesize novel amides using potential biological active substrate azoles. Numbers of synthetic approached have been reported for the synthesis of carboxamides, but these procedures suffers limitations such as harsh reaction condition, functional group tolerance and relatively low yield. We tried two methods namely A and B.

In the present work initially azoles were converted to azole-1-acetic acid which on activation and insitu N-acylation by various substituted aromatic amines afforded amides IIIa-d (i-vi). While N-acylation taking half moles of various substituted aromatic amines gave few disubstituted amides IVa (ii, v) and IVb (i, iv).
We planned to synthesize target amides using the following route-

**Method: A**

**Step I: Preparation of azole-1-yl-acetic acid**

**Step II: Activation of azole-1-yl-acetic acid by chlorination**

**Step III: In situ conversion of azole-1-acid chloride to amides**

The synthetic route applied is visualized in following scheme- 10

Similarly Ib, Ic and Id afforded III b (i-vi), III c (i-vi) and III d (i-vi) respectively.
Similarly III b gave disubstituted amide IV b (i, iv).

By method A amides which are obtained in the range of 40% yields but when we used Method B then we found two fold in increase in the yields. The method B, visualized in scheme 12

Method B

Similarly IV b(iv, v), IV c (iv) and IV d (ii, v) were synthesized.

The literature survey suggested that synthesis of diacetylderivative always leads to mono acetyl one due to hydrolysis and steric effect. Fortunately we could succeed to obtain few derivatives but in poor yields.

2.3 Experimental work:

**General procedure for synthesis of azole-1-yl-acetic acid I a-d:**
Chloroacetic acid (0.05mol, 4.72g) was dissolved in dry chloroform (20ml). To which an equimolar amount of azole and pyridine (4ml) was added and reaction mixture was refluxed for 4hr. on water bath. After cooling to room temperature, viscous residue was obtained, it was then washed with DCM/acetone and recrystallized from ethanol.

**General procedure for synthesis of 2-(1H-azole-1-yl)-N-(substituted phenyl) acetamide IIIa(i-vi)- IIId(i-vi):**
To an azole-1-yl-acetic acid (0.05mol) I a-d in dry DMF (10ml), thionyl chloride (0.1 mol, 4ml) was added in drop wise fashion with occasional stirring and the refluxed for 1.5 hr. on water bath. The reaction mixture was allowed to cool and various substituted aromatic primary amines (0.05mol) dissolved in dry toluene/benzene were added in a drop wise fashion and reaction mixture refluxed for 2hr. which gave dark semisolid mass, solvent extraction, recrystallization gave the desired products.

**General procedure for synthesis of 2-(1H-azole-1-yl)-N-((1H-azole-1-yl) acetyl)-N-(substituted phenyl) acetamide IVa (ii, v), IVb (i, iv):**
To an azole-1-yl-acetic acid (0.05mol) I a-d in dry DMF (10ml), thionyl chloride (0.1 mol, 4ml) was added in a drop wise fashion with occasional stirring and then it was refluxed for 1.5 hr. on water bath. The reaction mixture was allowed to cool and various substituted aromatic primary amines (0.025mol) dissolved in dry toluene/benzene were added in a drop wise fashion and reaction mixture refluxed for 3-4 hr. which gave dark semisolid mass, solvent extraction, recrystallization gave the desired products.

**General procedure for synthesis of 2-(1H-azole-1-yl)-N-(substituted phenyl) acetamide III^B^ b(iv, v), III^B^ c(iv), and III^B^ d(ii, v):**
The reaction takes place in two steps-
Step I: Synthesis of N-chloroacetyl aryl amines
Step II: Synthesis of amides
General procedure for synthesis of N-chloroacetyl aryl amines:
Chloroacetylchloride (0.05mol, 4.0ml) was taken in dry benzene (30ml) and the clear solution was stirred on water bath for 15 min. Then solutions of various substituted aromatic primary amines (0.04mol) dissolved in dry toluene/benzene were added in a drop wise fashion and refluxed for 2hr. The reaction mixture was allowed to cool. It was then filtered and recrystallized from ethanol.

General procedure for synthesis of 2-(1H-azole-1-yl)-N-(substituted phenyl) acetamide III^B b(iv, v), III^B c(iv), and III^B d(ii, v):
A solution of azole I^a-d (0.05mol) in acetone/chloroform was slowly added to a solution of N-chloroacetyl aryl amines (0.045) and activated K_2CO_3 (0.015 mol, 2.0g) in acetone/chloroform (30ml).

The reaction mixture was refluxed for 10-14 hr. on water bath which was then allowed to cool and kept overnight. The residue obtained was filtered and recrystallized from suitable solvent to give III^B b(iv, v), III^B c(iv), and III^B d(ii, v).

Spectral characterization data:
2-(1H-imidazol-1-yl)-N-phenyl acetamide III^a(i):
azole-1-yl-acetic acid II^a on activation by thionyl chloride and insitu N-acylation of resulted acid chloride with aniline afforded colorless crystals of 2-(1H-imidazol-1-yl)-N-phenyl acetamide III^a(i) in 72% yield, Mol. Formula C_{11}H_{11}N_{3}O, m. p. 218-220^0C. The IR spectrum of this compound displayed bands at 3234, 1647 cm\(^{-1}\) corresponding to NH and C=O groups. The two bands at 754 and 696 cm\(^{-1}\) attributed to mono substituted phenyl moiety.

\(^1\)H NMR (Fig. N-1) spectrum showed a singlet at \(\delta 10.68\) due to NH of amide. The multiplet observed at \(\delta 7.60-7.05\) attributed to the presence of aromatic eight protons of imidazole and phenyl moiety. The -CH\(_2\) protons appeared at \(\delta 5.07\) as a singlet. \(^1^3\)C NMR (Fig. N-5) displayed peaks in three distinct regions, the peak at 165.48 attributed to C=O, the aromatic carbon atom displayed peak at \(\delta 139, 129, 124, 138, 122\) and 119 corresponding to C\(_2\), C\(_6\) and C\(_3\), C\(_5\) and C\(_4\) of phenyl while C\(_2\), C\(_4\) and C\(_5\) of imidazole moiety respectively. The singlet at \(\delta 40.63\) corresponds to –CH\(_2\) group. The Mass spectrum showed M\(^+\)-2 peak at 199.6.

Considering the spectral data the compound III^a(i) may be assigned the following structure.
2-(1H-imidazol-1-yl)-N-(2-methylphenyl) acetamide IIIa(ii).

Mol. Formula: $C_{12}H_{13}N_{3}O$

Mol. Weight: 215.25

Physical Nature: Reddish crystals

$\text{m. p. (}^{\circ}\text{C)}$: 167-169

Yield (%): 63

$\text{IR (KBr) cm}^{-1}$ (Fig. I-1)

$\delta$ 3265 (NH), 3059, 2916, 1666 (C=O, amide), 748 (ortho sub.)

$^1\text{H NMR (DMSO-d6, 400MHz)}$: $\delta$ 10.18 (s, 1H, NH), 7.80 (s, 1H, imi.C$_2$-H), 7.42-7.07 (m, 6H, Ar-H), 5.37 (s, 2H, CH$_2$), 2.25 (s, 3H, Ar-CH$_3$).

$^{13}\text{C NMR (DMSO-d6, 400MHz)}$: $\delta$ 164.62 (C=O), Ar-C (139.29, 136.20, 132.53, 131.12, 126.65, 126.27, 125.52, 124.07), 51.85 (Ar-CH$_3$), 40.19 (N-CH$_2$-CO).

Mass (m/e, %): (Fig. M-1) 215.9 (M$^+$, 31), 148 (26), 118 (18), 117 (11).

2-(1H-imidazol-1-yl)-N-(4-methylphenyl) acetamide IIIa(iii).

Mol. Formula: $C_{12}H_{13}N_{3}O$

Mol. Weight: 215.25

Physical Nature: Creamy powder

$\text{m. p. (}^{\circ}\text{C)}$: 143-145

Yield (%): 61

$\text{IR (KBr) cm}^{-1}$

$\delta$ 3203 (NH), 3091, 2918, 1662 (C=O, amide), 1546, 1512, 815 (para disub.).
\[ {^1}H \text{ NMR (DMSO-d}_6\text{, 400MHz): } \delta \ 10.23 (s, 1H, NH), 7.76 (s, 1H, imi.C}_2\text{-H), 7.62-6.87 (m, 6H, Ar-H), 4.85 (s, 2H, CH}_2\text{), 2.23 (s, 3H, Ar-CH}_3\text{).} \]

\[ {^{13}}C \text{ NMR (DMSO-d}_6\text{, 400MHz): } \delta \ 166.12 (C=O), \text{ Ar-C (138.97, 136.86,}\]

\[ 133.51, 130.01, 129.88, 128.51, 124.13, \]

\[ 121.38, 119.84), 49.90 (\text{Ar-CH}_3\text{), 40.21 (N-CH}_2\text{-CO),} \]

Mass (m/e, %) : \(214.0 (\text{M}^+ - 1, 2), 201(2), 183(100), 148.2(8), 108.1(57)\)

2-(1H-imidazol-1-yl)-N-(2-chlorophenyl) acetamide IIIa(iv).

\text{Mol. Formula} : C_{11}H_{10}N_{3}OCl

\text{Mol. Weight} : 235.67

\text{Physical Nature} : Colorless crystals

\text{m. p. (°C)} : 240-243

Yield (%) : 59

\text{IR (KBr) cm}^{-1} : 3365 (NH), 3028, 2970, 1627 (C=O, amide), 756 (ortho disub.).

\[ {^1}H \text{ NMR (DMSO-d}_6\text{, 300MHz): } \delta \ 6.92 (\text{br, s, 1H, NH), 7.48-7.0 (m, 7H, Ar-H),}\]

\[ 5.20 (s, 2H, CH}_2\text{).} \]

2-(1H-imidazol-1-yl)-N-(4-chlorophenyl) acetamide IIIa(v).

\text{Mol. Formula} : C_{11}H_{10}N_{3}OCl

\text{Mol. Weight} : 235.67

\text{Physical Nature} : Curdy crystals

\text{m. p. (°C)} : 234-236

Yield (%) : 52
IR (KBr) cm$^{-1}$: 3527 (NH), 3180, 3120, 2962, 1674 (C=O, amide), 833 (para disub.).

$^1$H NMR (DMSO-d$_6$, 400MHz): $\delta$ 10.78(s, 1H, NH), 8.23(s, 1H, imi.C$_2$-H), 7.78-7.19(m, 6H, Ar-H), 5.04(s, 2H, CH$_2$).

$^{13}$C NMR (DMSO-d$_6$, 400MHz): $\delta$ 165.87 (C=O), Ar-C (139.45, 138.27, 129.46, 128.10, 127.89, 124.89, 124.13, 122.67, 121.41), 40.34(N-CH$_2$-CO).

**2-(1H-imidazol-1-yl)-N-(4-bromophenyl) acetamide** IIIa(vi).

Mol. Formula: C$_{11}$H$_{10}$N$_3$OBr

Mol. Weight: 280.12

Physical Nature: White powder

m. p. (°C): 160-161

Yield (%): 64

IR (KBr) cm$^{-1}$: 3262 (NH), 3107, 2966, 1695 (C=O, amide), 829 (para disub.).

$^1$H NMR (DMSO-d$_6$, 300MHz): $\delta$ 10.58(s, 1H, NH), 7.47-7.0(m, 7H, Ar-H), 5.30(s, 2H, CH$_2$).

$^{13}$C NMR (DMSO-d$_6$, 400MHz): $\delta$ 166.59(C=O), Ar-C (164.60, 139.48, 132.41, 124.16, 121.77, 116.14), 40.42(NCH$_2$-CO).

**2-(1H-benzimidazol-1-yl)-N-phenyl acetamide** IIIb(i).

Mol. Formula: C$_{15}$H$_{13}$N$_3$O

Mol. Weight: 251.28

Physical Nature: White crystals

m. p. (°C): 244-246

Yield(%): 68

IR (KBR) cm$^{-1}$: 3302 (NH), 3032, 2914, 1637 (C=O, amide), 760, 710 (mono sub.).

$^1$H NMR (DMSO-d$_6$, 300MHz): $\delta$ 9.80(br s, 1H, NH), 7.10-7.39(m, 10H, Ar-H), 3.40(s, 2H, CH$_2$).
2-[(1H-benzimidazol-1-yl)-N-(2-methylphenyl) acetamide IIIb(ii).

**Mol. Formula**: \( C_{16}H_{15}N_3O \)

**Mol. Weight**: 265.31

**Physical Nature**: White crystals

**m. p. \(^{\circ}C\)**: 138-140

**Yield (%)**: 62

**IR (KBR) cm\(^{-1}\)** (Fig. I-2): 3263 (NH), 3138, 3057, 2935, 1662 (C=O, amide), 746 (ortho disub.)

2-[(1H-benzimidazol-1-yl)-N-(4-methylphenyl) acetamide IIIb(iii).

**Mol. Formula**: \( C_{16}H_{15}N_3O \)

**Mol. Weight**: 265.31

**Physical Nature**: Colorless crystals

**m. p. \(^{\circ}C\)**: 240-242

**Yield (%)**: 42

**IR (KBR) cm\(^{-1}\)**: 3321 (NH), 3030, 2912, 1695 (C=O, amide), 815 (para disub.)

**\(^1\)H NMR (DMSO-d\(_6\), 300MHz):**

\( \delta \) 8.68 (br s, 1H, NH), 7.43-6.90 (m, 9H, Ar-H), 3.37(s, 2H, CH\(_2\)), 2.50(s, 3H, Ar-CH\(_3\)).

**Mass (m/e, %):**

264.0(M+-1,2), 240.9(100), 148(10), 134(2), 106(11).

2-[(1H-benzmidazol-1-yl)-N-(2-chlorophenyl)acetamide IIIb(iv).

**Mol. Formula**: \( C_{15}H_{12}N_3OCl \)

**Mol. Weight**: 285.73

**Physical Nature**: Straw color crystals

**m. p. \(^{\circ}C\)**: 230-232

**Yield (%)**: 46

**IR (KBR) cm\(^{-1}\)**: 3435 (NH), 3161, 3059, 2972, 1687 (C=O amide), 748 (ortho disub.)
$^1$H NMR (DMSO-d6, 300MHz): $\delta$ 7.54 (br s, 1H, NH), 7.50-7.20 (m, 9H, Ar-H), 5.62 (s, 2H, CH$_2$).

2-(1H-benzimidazol-1-yl)-N-(4-chlorophenyl) acetamide IIIb(v).

Mol. Formula : C$_{15}$H$_{12}$N$_3$OCl
Mol. Weight : 285.73
Physical Nature : White crystals
m. p. (°C) : 110-112
Yield(%) : 49
IR (KBR) cm$^{-1}$ : 3402 (NH), 3016, 2777, 1643 (C=O, amide), 840 (para disub.)

$^1$H NMR (DMSO-d6, 300MHz): $\delta$ 10.65 (s, 1H, NH), 8.23 (d, 1H, benzimi.C-2 H), 7.67-7.17(m, 8H, Ar-H), 5.18(s, 2H, CH$_2$).

$^{13}$C NMR (DMSO-d6, 400MHz): $\delta$166.37 (C=O), Ar-C (145.71, 138.29, 129.45, 127.94, 123.16, 122.30, 121.46, 120, 111.08),40.63(N-CH$_2$-CO).

2-(1H-benzotriazol-1-yl)-N-phenyl acetamide IIIc(i).

Mol. Formula : C$_{14}$H$_{12}$N$_4$O
Mol. Weight : 252.27
Physical Nature : White needles
m. p. (°C) : 202-204
Yield(%) : 72
IR (KBR) cm$^{-1}$ (Fig. I-3) : 3281 (NH), 3084, 1689 (C=O, amide), 752, 698 (mono sub.)

$^1$H NMR (DMSO-d6, 300MHz): $\delta$ 8.70(s, 1H, NH), 7.46-6.90 (m, 9H, Ar-H), 3.40(s, 2H, CH$_2$).
2-(1H-benzotriazol-1-yl)-N-(2-methylphenyl) acetamide IIIc(ii).

Mol. Formula : C_{15}H_{14}N_{4}O  
Mol. Weight : 266.30  
Physical Nature : Brown crystals  
m. p. (°C) : 156-158  
Yield(%) : 46  
IR (KBR) cm\(^{-1}\) : 3352 (NH), 3090, 2929, 1642 (C=O, amide), 1288, 752(ortho disub.)  
\(^1\)H NMR (DMSO-d\(_6\), 300MHz) : \(\delta\) 6.80(br s, 1H, NH), 7.90-7.39(m, 8H, Ar-H), 2.56 (s, 3H, Ar-CH\(_3\)), 2.40(s, 2H, CH\(_2\)).  
Mass (m/e, %):  
266.0(M\(^+\), 3), 265(M\(^+\)-1, 2), 174.1(13), 138.1(43), 120.1(100), 106(11).

2-(1H-benzotriazol-1-yl)-N-(4-methylphenyl) acetamide IIIc(iii).

Mol. Formula : C_{15}H_{14}N_{4}O  
Mol. Weight : 266.30  
Physical Nature : Colorless crystals  
m. p. (°C) : 230-232  
Yield(%) : 52  
IR (KBR) cm\(^{-1}\) : 3437(NH), 3110, 2928, 1645 (C=O, amide), 1037, 824 (para disub.)  
\(^1\)H NMR (DMSO-d\(_6\), 300MHz) : \(\delta\) 8.67(s, 1H, NH), 7.35-7.0(m, 8H, Ar-H), 3.40(s, 2H, CH\(_2\)), 2.20(s, 3H, CH\(_3\)).  
Mass (m/e, %):  
266.0(M\(^+\), 5), 263(100), 235(8), 134(13).

2-(1H-benzotriazol-1-yl)-N-(2-chlorophenyl) acetamide IIIc (iv).

Mol. Formula : C_{14}H_{11}N_{4}OCl  
Mol. Weight : 286.72  
Physical Nature : Curdy crystals  
m. p. (°C) : 218-221  
Yield (%) : 43
IR (KBR) cm\(^{-1}\) : 3269 (NH), 3089, 2945, 1667 (C=O, amide), 758 (ortho disub.)

2-(1H-benzotriazol-1-yl)-N-(4-chlorophenyl) acetamide IIIc(v).

Mol. Formula : C\(_{14}\)H\(_{11}\)N\(_{4}\)OCl
Mol. Weight : 286.72
Physical Nature : Reddish crystals
m. p. (\(^\circ\)C) : 244-245
Yield (%) : 46
IR (KBR) cm\(^{-1}\) : 3192 (NH), 3047, 2841, 1650 (C=O, amide), 821 (para disub.)

\(^1\)H NMR (DMSO-d\(_6\), 300MHz): \(\delta\) 9.10(br s, 1H, NH), 7.55-7.35(m, 8H, Ar-H), 2.50(s, 2H, CH\(_2\)).

Mass (m/e, %): 263.1(100), 168.1(24), 154(3).

2-(4-methylpiperazin-1-yl)-N-phenyl acetamide IIId(i).

Mol. Formula : C\(_{13}\)H\(_{19}\)N\(_{3}\)O
Mol. Weight : 233.31
Physical Nature : Colorless needles
m. p. (\(^\circ\)C) : 234-236
Yield (%) : 69
IR (KBR) cm\(^{-1}\) : 3367 (NH), 3003, 2974, 2943, 2796, 1630 (C=O, amide), 777, 675 (mono sub.)

\(^1\)H NMR (CDCl\(_3\), 300MHz): \(\delta\) 9.55(s, 1H, NH), 7.38(m, 5H, Ar-H), 2.73(s, 2H, CH\(_2\)), 2.30(s, 3H, N-CH\(_3\)), 1.63(s, 8H, 4CH\(_2\)).
2-(4-methylpiperazin-1-yl)-N-(2-methylphenyl) acetamide IIId(ii).

Mol. Formula: C_{14}H_{21}N_{3}O
Mol. Weight: 247.34
Physical Nature: Colorless crystals
m. p. (°C): 87-88
Yield (%): 42

IR (KBR) cm\(^{-1}\): 3375 (NH), 2943, 2821, 1629 (C=O, amide), 752 (ortho disub.)

\(^1\)H NMR (CDCl\(_3\), 300MHz): δ 10.43 (br s, 1H, NH), 7.47-7.22(m, 4H, Ar-H), 3.39(s, 2H, CH\(_2\)), 2.73(s, 3H, Ar-CH\(_3\)), 2.48(s, 3H, N-CH\(_3\)), 2.35(s, 8H, 4CH\(_2\)).

\(^{13}\)C NMR (DMSO-d\(_6\), 400MHz): δ 168.90 (C=O), Ar-C (132.50, 131.88, 128.41, 127.57, 123.77, 121.90), 49.77(N-CH\(_3\)), 40.13(N=CH\(_2\)-CO), 34.68(Ar-CH\(_3\)), 17.90(aliph.CH\(_2\)).

2-(4-methylpiperazin-1-yl)-N-(4-methylphenyl) acetamide IIId(iii).

Mol. Formula: C_{14}H_{21}N_{3}O
Mol. Weight: 247.34
Physical Nature: Colorless crystals
m. p. (°C): 50-52
Yield(%): 67

IR (KBR) cm\(^{-1}\): 3225 (NH), 3175, 2945, 2823, 1689 (C=O, amide), 1292, 819 (para disub.)

2-(4-methylpiperazin-1-yl)-N-(2-chlorophenyl) acetamide IIId(iv).

Mol. Formula: C_{13}H_{18}N_{3}OCl
Mol. Weight: 267.75
Physical Nature: Colorless crystals
m. p. (°C): 106-108
Yield(%): 60
2-(4-methylpiperazin-1-yl)-N-(4-chlorophenyl) acetamide IIId(v).

Mol. Formula : $C_{13}H_{18}N_3OCl$

Mol. Weight : 267.75

Physical Nature : Reddish crystals

m. p. ($^\circ$C) : 78-80

Yield(%) : 41

IR (KBR) cm$^{-1}$ (Fig. I-4) : 3423(NH), 2951, 2853, 1664 (C=O, amide), 1186, 829 (para disub.)

N-[2-(1H-imidazol-1-yl) acetyl]-2-(1H-imidazol-1-yl)-N-(2-methylphenyl) acetamide IVa(ii):

azole-1-yl-acetic acid IIa on activation by thionyl chloride and insitu N-acylation of resulting acid chloride with 2-methylaniline afforded brown powder of N-[2-(1H-imidazol-1-yl) acetyl]-2-(1H-imidazol-1-yl)-N-(2-methylphenyl) acetamide IVa(ii) in 18% yield, Mol. Formula $C_{17}H_{17}N_5O_2$ m. p. 92-94$^\circ$C. The IR spectrum of this compound displayed band at 3140 and 3070 cm$^{-1}$ corresponding to Ar-H. The absence of band in the region of NH confirmed the absence of NH group and indicated the conversion to diacetylderivative. The bands at 1650 cm$^{-1}$ attributed to C=O of disubstituted amide. The ortho disubstitution phenyl moiety displayed by band at 750 cm$^{-1}$. $^1$H NMR spectrum showed two singlets at $\delta$ 2.5 and 3.37 corresponding to Ar-CH$_3$ and two –CH$_2$ group respectively. The ten aromatic protons observed as a multiplate in the range $\delta$ 7.2-7.5. The Mass spectrum showed M$^+$ peak at 323.0 and M$^+$ -1 peak as a base peak at 322.0.

Considering the spectral data the compound IVa(ii) may be assigned the following structure.
N-[2-(1H-imidazol-1-yl) acetyl]-N-(4-chlorophenyl)-2-(1H-imidazol-1-yl) acetamide IVa(v).

**Mol. Formula**: C_{16}H_{14}N_{5}O_{2}Cl

**Mol. Weight**: 343.77

**Physical Nature**: Light yellow crystals

**m. p. (°C)**: 138-140

**Yield (%)**: 20

**IR (KBr) cm\(^{-1}\) (Fig.I-5)**:

\[3120, 3072, 2974, 1695 (C=O, amide), 1550, 833 \text{ (para sub.)}\]

**\(^1\)H NMR (DMSO-d\(_6\), 400MHz)**: \(\delta\) 8.22-7.31(m, 6H, Imi. H\(_2\), H\(_4\), H\(_5\)), 7.26(t, 2H, Ar-H), 6.94(t, 2H, Ar-H), 3.1(s, 4H, 2CH\(_2\)).

**Mass (m/e, %)**:

\[343(M^+, 2), 293(100), 277(2), 263(15), 233(7)\].

N-[2-(1H-benzimidazol-1-yl) acetyl]-N-phenyl-2-(1H-benzimidazol-1-yl)-acetamide IVb(i).

**Mol. Formula**: C_{24}H_{19}N_{5}O_{2}

**Mol. Weight**: 409.44

**Physical Nature**: Colorless crystals

**m. p. (°C)**: 196-199

**Yield (%)**: 16

**IR (KBr) cm\(^{-1}\) (Fig. I-6)**:

\[3032, 2740, 1689 (C=O, amide), 1477, 1174, 759, 642 \text{ (mono sub)}\]
1H NMR (DMSO-d6, 400MHz): δ 8.87(s, 2H, B.Imi. H2), 7.74(s, 5H, Ar-H), 9.95(d, 4H, B. Imi. H3, H6), 7.27(t, 4H, B. Imi. H4, H5), 3.40(s, 4H, 2CH2).

Mass (m/e, %): (Fig. M-2) 409(M+, 37), 413(100), 147.9(40), 133(4), 119(2).

N-[2-(1H-benzimidazol-1-yl) acetyl]-2-(1H-benzimidazol-1-yl)-N-(2-chlorophenyl) acetamide IVb(iv).

Mol. Formula : C24H18N5O2Cl
Mol. Weight : 443.89
Physical Nature : Reddish crystals
m. p. (°C) : 208-210
Yield (%) : 15

IR (KBr) cm⁻¹ : 3128, 3032, 2978, 2868, 1690 (C=O, amide amide), 684 (ortho disub.)

1H NMR (DMSO-d6, 400MHz): δ 7.70(s, 2H, B. Imi. H2), 7.4-7.2(m, 12H, Ar-H), 2.50(s, 4H, 2CH2),

Mass (m/e, %): 443(M⁺, 5), 441(M⁺-2, 12), 343.8(7), 234.9(20), 167(100), 131(45), 117(25).

2.4 Antimicrobial activity:

The synthesized compounds IIIa(i-vi), IIIb(i-v), IIIc(i-v) and IIIId(i-v) were screened for their in vitro antimicrobial activities against *Escherichia coli*, *Staphylococcus aureus*, *Candida albicans* and *Aspergillus niger* by Disc diffusion method(Well method, Disc size 6mm, Hi media) using nutrient agar, Potato dextrose agar and MGYP(Hi media). The compounds were tested at the concentration of 100µg/ml in DMF. The results were compared with respective standard Streptomycin and Amphotericin-B. The zones of inhibition were measured in mm and the data is presented in Table 1, 2, 3 and 4.

All the compounds showed moderate to good activity against bacterial strain while benzimidazole compounds, IIIb(i-v) found inactive against fungal strain A. niger. Imidazole and benzimidazole compounds with chloro, bromo substituents found more potent antibacterial than standard Streptomycin.
Table 1. Results of antimicrobial activity of the compounds IIIa(i-vi).

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Antimicrobial activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
</tr>
<tr>
<td>IIIa(i)</td>
<td>8.43</td>
</tr>
<tr>
<td>IIIa(ii)</td>
<td>11.61</td>
</tr>
<tr>
<td>IIIa(iii)</td>
<td>26.44</td>
</tr>
<tr>
<td>IIIa(iv)</td>
<td>8.1</td>
</tr>
<tr>
<td>IIIa(v)</td>
<td>20.92</td>
</tr>
<tr>
<td>IIIa(vi)</td>
<td>20.45</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>18.22</td>
</tr>
<tr>
<td>Amphotericin-B</td>
<td>NA</td>
</tr>
</tbody>
</table>

Diameter in mm calculated by digital Vernier Calliper. * Zone of inhibition in mm. ‘_’ means no zone of inhibition. NA- Not applicable.

Graph 1. The comparative antimicrobial activity of compounds IIIa(i-vi)
Table 2. Results of antimicrobial activity of the compounds IIIb(i-v).

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Antimicrobial activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>S. aureus</td>
</tr>
<tr>
<td>IIIb(i)</td>
<td>9.16</td>
</tr>
<tr>
<td>IIIb(ii)</td>
<td>10.46</td>
</tr>
<tr>
<td>IIIb(iii)</td>
<td>9.49</td>
</tr>
<tr>
<td>IIIb(iv)</td>
<td>12.19</td>
</tr>
<tr>
<td>IIIb(v)</td>
<td>17.38</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>18.22</td>
</tr>
<tr>
<td>Amphotericin-B</td>
<td>NA</td>
</tr>
</tbody>
</table>

Diameter in mm calculated by digital Vernier Caliper. *Zone of inhibition in mm. ‘_’ means no zone of inhibition. NA- Not applicable.

Graph 2. The comparative antimicrobial activity of compounds IIIb(i-v)
Table 3. Results of antimicrobial activity of the compounds IIIc(i-v).

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Antimicrobial activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
</tr>
<tr>
<td>IIIc(i)</td>
<td>12.19</td>
</tr>
<tr>
<td>IIIc(ii)</td>
<td>22.98</td>
</tr>
<tr>
<td>IIIc(iii)</td>
<td>10.78</td>
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<tr>
<td>IIIc(v)</td>
<td>11.71</td>
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<tr>
<td>Streptomycin</td>
<td>18.22</td>
</tr>
<tr>
<td>Amphotericin-B</td>
<td>NA</td>
</tr>
</tbody>
</table>

Diameter in mm calculated by digital Vernier Caliper * Zone of inhibition in mm. ‘_’ means no zone of inhibition. NA- Not applicable.

Graph 3. The comparative antimicrobial activity of compounds IIIc(i-v)
Table 4. Results of antimicrobial activity of the compounds IIId(i-v).

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Antimicrobial activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
</tr>
<tr>
<td>IIId(i)</td>
<td>9.65</td>
</tr>
<tr>
<td>IIId(ii)</td>
<td>14.09</td>
</tr>
<tr>
<td>IIId(iii)</td>
<td>13.25</td>
</tr>
<tr>
<td>IIId(iv)</td>
<td>_</td>
</tr>
<tr>
<td>IIId(v)</td>
<td>9.66</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>18.22</td>
</tr>
<tr>
<td>Amphotericin-B</td>
<td>NA</td>
</tr>
</tbody>
</table>

Diameter in mm calculated by digital Vernier Caliper * Zone of inhibition in mm. ‘_’ means no zone of inhibition. NA- Not applicable.

Graph 4. The comparative antimicrobial activity of compounds IIId(i-v)
2.5 Conclusions:
In summary, the four series of novel azole amides have been synthesized by applying two different methods. The amides which were obtained in low yield by method A, but when B was used then improvement in % yield was observed.

Our attempt of synthesis of N, N-disubstituted amides found limited success, only in few cases we got product with poor yield. It might be due to less reactivity of azole-1-acid chloride due to electronic and steric effects.

The antimicrobial study of new compounds was carried out. The preliminary microbial screening results revealed that all the synthesized compound possess moderate to good activity. They are more active against bacteria than fungal strains. The compounds IIIa (iii, v, vi), IIIb(v), IIIc(ii) are found more potent than standard against bacterial strain and compound IIIa(v, vi) and IIIb(i) against fungal strain. These can be used as an antibacterial agent against E. coli and S. aureus.

The study reports the synthesis and antimicrobial screening of novel azole derivatives and supports the antimicrobial nature of azoles for further study.
Fig. I-1: IR Spectrum of compound IIIa(ii)

Fig. I-2: IR Spectrum of compound IIIb(ii)
Fig. 1-3: IR Spectrum of compound IIIc(i)

Fig. 1-4: IR Spectrum of compound IIId(v)
Fig. I-5: IR Spectrum of compound IVa(v)

Fig. I-6: IR Spectrum of compound IVb(i)
Fig. N-1: $^1$H NMR Spectrum of compound IIIa(i).
Fig. N-2: $^1$H NMR Spectrum of compound IIIb(iii).
Fig. 3: $^1$H NMR Spectrum of compound IIIc(ii).
Fig. N-4: $^1$H NMR Spectrum of compound IIId(ii).
Fig. N-5: $^1$H NMR Spectrum of compound IIIa(i)
Fig. N-6: $^{13}$H NMR Spectrum of compound IIIb(v).
Fig. M-1: Mass Spectrum of compound IIIa(ii).
Fig. M-2: Mass Spectrum of compound IVb(i).


2.7 References:


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