Synthesis, characterization and antimicrobial screening of N’-(substituted) benzylidene-2-(1H-azol-1-yl) acetohydrazides and 1,3,4-oxadiazoles

Abstract: Various hydrazones, thioneoxadiazoles, 3-acetyl oxadiazoles and oxadiazoles derivatives of azoles have been included in this chapter.

Section 4.1- Synthesis N’-(substituted) benzylidene-2-(1H-azol-1-yl) acetohydrazides derived from some azoles

4.1.1- Introduction:

The reaction of primary amines with carbonyl compounds to give imines, also called Schiff bases or azomethine or hydrazone is well known synthetic transformation. Hydrazones and their derivatives are important and versatile class of compounds in organic chemistry for drug design, as possible ligands for metal complexes and organocatalysts.

These compounds have interesting biological properties such as antimicrobial, antiviral, vasodilator, antiinflammatory, analgesic, anticonvulsants, antidepressants, antitubercular, antitumor, antiparasitics, antimalerial, nematicidal, anti-HIV, diuretic, anti platelet, antioxidants and herbicidal.

Rollas, S. et al. have prepared 4-fluorobenzoic acid [(5-nitro-2-furyl)methylene]-hydrazide (1) and reported antibacterial activity against both Staphylococcus aureus ATCC 29213 and Mycobacterium tuberculosis H37Rv at a concentration of 3.13 µg/mL.

\[
\text{(1)}
\]

Gemma et al. have synthesized a series of 4-guinolhydrazones and reported most of the newly synthesized compounds displayed 100% inhibitory activity against Mycobacterium tuberculosis in cellular assay.

Sriram et al. have synthesized various isonicotinyl hydrazones and reported to shown good anti mycobacterial activity in vitro against Mycobacterium tuberculosis H37Rv and isonicotinyl hydrazide (INH) resistance Mycobacterium tuberculosis using the BACTEC 460 radiometric system.

Ali Tarik E. et al. have synthesized (substituted)-4-oxo-4H-chromene-3-carboxaldehyde and their Schiff bases derivatives, these molecules have attract considerable interest in human colon cancer and as potential topoisomerase inhibitors anticancer agents.
Zhang H. et al. have synthesized 5-methyl-3-phenylindole-2-carboxylic acid (4-methylbenzylidene) hydrazide (2) and found to induce apoptosis in T47D cells.\(^{21}\)

![Chemical Structure](image)

(2)

The generation of metal ion-induced radical intermediate has been proposed as the mechanism of action of hydrazone antitumors.\(^{22}\)

Schiff bases and their metal complexes also show biological activities such as antiviral, antitumor agents.\(^{23}\)

Hetero aryl Schiff bases having chloro, cyano group at C-2 position reported may show enhanced antibacterial effects, also reported to show biological activities such as antibiotics, anti cancer and active material against human immune virus.\(^{1c}\)

Schiff bases ligands derived from thiosemicarbazide are reported to show pharmacological properties as antibacterial, anticancer and show potential for recognition of anions and metals of biochemical, medical and environmental importance.\(^{24}\)

They are widely applied in enantioselective cyclopropanation, asymmetric addition of cyanide to aldehydes. Chiral Schiff bases reported as catalyst in asymmetric epoxidation of unfunctionalized olefins and widely used in synthesis of number of biological active molecules like oxadiazoles, 2-azetidinones, 4-thiazolidinones and various five membered heterocyclic compounds by 1,3-dipolar cycloaddition of azomethine imines.\(^{25}\)

Buu-Hoi et al. have synthesized hydrazide-hydrazone and reported hydrazone have lower toxicity than hydrazides because of the blockage of –NH\(_2\) group.\(^{26}\)

In view of wide and useful biological activities and applications of hydrazone, several methods have been reported in the literature. Few important methods are summarizes in following schemes.
1. Methods due to Bansal E. et al\textsuperscript{27}.

\[
\text{R} = \text{Ph, furfural}
\]

(Scheme-1)

2. Methods due to Jign Hai Yang et al\textsuperscript{25b}.

(Scheme-2)

3. Methods due to Gemma et al\textsuperscript{18}.
4. Methods due to Naqvi Arshi et al\textsuperscript{1b}.

\[
\text{R} = \text{water based synthesis} \\
\text{B} = \text{M. W. assisted synthesis} \\
\text{C} = \text{Solid state synthesis}
\]

(Scheme-4)

5. Methods due to Shelar M. D. et al\textsuperscript{25c}.

(Scheme-5)

6. Methods due to Wang Xiang-Shan et al\textsuperscript{28}.

(Scheme-6)
4.1.2 Present Work:

It is surprising to date that the chemistry of hydrazones of 1H-azoles has not been explored significantly. Literature survey reveals that the importance of Schiff bases. In view of this we planned to synthesize N’-(substituted benzylidene)-2-(1H-azol-1-yl) acetohydrazides Xa-d, XIa-d.

In the present work some azoles were converted to ethyl esters which on hydrazinolysis using hydrazine hydrate formed hydrazides VIIIa-d. The condensation of hydrazides with benzaldehyde in acidic medium formed hydrazones Xa-d. Similarly reaction of 4-chlorobenzaldehyde afforded XIa-d.

The reaction methodology applied given in following scheme 7.

(Scheme-7)
4.1.3-Experimental Work:

**General procedure for the synthesis of azole-1-yl acetic acid ethyl ester IIa-d:**
To a solution of azole 1a-d (0.05mol) in dry ethanol (30ml), ethyl bromoacetate (0.05mol) was slowly added in presence of 06 g of anhydrous potassium carbonate. The resulting solution was refluxed for 18-20 hr. on water bath. Then the reaction mixture was cooled to room temperature and filtered. The products obtained were used in next step without further purification.

**General procedure for the synthesis of azole-1-yl acetic acid hydrazides VIIIa-d:**
To a solution of azole-1-yl acetic acid ester IIa-d (0.05mol) in ethanol (30ml), hydrazine hydrate (0.1mol) was added with stirring. The reaction mixture was refluxed for 18-20 hr. on water bath. The products obtained were used for next step without further purification.

**General procedure for the synthesis of hydrazones Xa-d, XIa-d:**
To azole-1-yl acetic acid hydrazides VIIIa-d (0.02mol) in dry ethanol (50ml) was added benzaldehyde and 4-chlorobenzaldehyde (0.02mol) in presence of acid catalyst. The reaction mixture was refluxed for about 14-16 hr. It was cooled to room temperature and added on crushed ice. The residue obtained which was washed with cold water for two/three times and recrystallized from suitable solvent in moderate to good yields of Xa-d, XIa-d.

**Spectral Characterization Data:**

**N'-benzylidene-2-(1H-imidazol-1-yl) acetohydrazide Xa:**
1H-imidazol-1-yl acetic acid hydrazide on condensation with benzaldehyde in ethanol afforded yellow crystals N'-benzylidene-2-(1H-imidazol-1-yl) acetohydrazide Xa in 62% yield, m. p. 68-70°C. The IR spectrum of this compound reveals bands at 3250, 1654 and 1629 cm\(^{-1}\) corresponding to NH, C=O, and C=N groups respectively. The band at 752, 690 cm\(^{-1}\) attributed to mono substituted phenyl ring. \(^1\)H NMR spectrum of this compound showed two singlet at δ 10.92 and at δ 8.67 which were attributed to the NH and N=CH protons respectively. The multiplate between δ 7.86 and 7.25 corresponding to aromatic protons of imidazole and phenyl moiety. The methylene protons displayed a singlet at δ 4.84.

Considering the spectral data the compound Xa may be assigned the following structure.
N’-(4-chlorobenzylidene)-2-(1H-imidazol-1-yl) acetohydrazide XIa:
Mol. Formula : C_{12}H_{11}N_{4}OCl
Mol. Weight : 262.69
Physical Nature: Silvery plates
m. p.(°C) : 47-49
Yield(%) : 58
IR (KBr) cm\(^{-1}\) (Fig.I-1) : 3360 (NH), 3198, 1656 (C=O amide), 1595, (C=N), 823 (para disub).
\(^1\)H NMR (CDCl\(_3\), 400MHz) : \(\delta\) 9.80 (s, 1H, NH), 8.59 (s, 1H, HC=N), 7.78-7.76 (m, 3H, Ar-H Imi.C\(_2\)-H), 7.47-7.29 (m, 4H, Ar-H), 5.56 (s, 2H, CH\(_2\)).

N’-benzylidene-2-(1H-benzimidazol-1-yl) acetohydrazide Xb:
Mol. Formula : C\(_{16}\)H\(_{14}\)N\(_4\)O
Mol. Weight : 278.31
Physical Nature : Yellow needles
m. p.(°C) : 60-62
Yield(%) : 74
IR (KBr) cm\(^{-1}\) : 3190 (NH), 3055, 2949, 1665 (C=O amide), 1620, (C=N), 752, 686.
\(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) 10.25 (s, 1H, NH), 8.65 (s, 1H, HC=N), 7.86-7.83 (m, 5H, benzimi-H), 7.45 (s, 5H, Ar-H), 5.40 (s, 2H, CH\(_2\)).
LCMS (m/z, %): (M+1) 279.2 (4), 211.1 (13), 210.1 (18), 209.1 (100).
N’-(4-chlorobenzylidene)-2-(1H-benzimidazol-1-yl) acetohydrazide XIb:

Mol. Formula : C_{16}H_{13}N_{4}O Cl
Mol. Weight : 312.75
Physical Nature : Curdy plates
m. p. (°C) : 198-200
Yield(%) : 61

IR (KBr) cm\(^{-1}\) : 3267 (NH), 2941, 1640 (C=O amide), 1593 (C=N), 817.
\(^1\)H NMR (CDCl\(_3\), 400MHz): \(\delta\) 10.39 (s, 1H, NH), 8.60 (s, 1H, HC=N), 7.83 - 7.79 (m, 5H, benzimi-H), 7.78 - 7.41 (m, 4H, Ar-H), 5.30(s, 2H, CH\(_2\)).

LCMS (m/z, %) : 281.2 (M+2, 19), 280.2 (100), 100.1 (4).

N’-benzylidene-2-(1H-benzotriazol-1-yl) acetohydrazide Xc:

Mol. Formula : C_{15}H_{13}N_{5}O
Mol. Weight : 279.30
Physical Nature : White thready
m. p. (°C) : 208-210
Yield(%) : 78

IR (KBr) cm\(^{-1}\) (Fig. I-2) : 3184 (NH), 3095, 2956, 1678 (C=O amide), 1500, (C=N), 819, 744.
\(^1\)H NMR (DMSO-d\(_6\), 400MHz) : \(\delta\) 11.91 (s, 1H, NH), 8.25 (s, 1H, HC=N), 8.07 - 7.37 (m, 9H, Ar-H), 6.04 (s, 2H, CH\(_2\)).
LCMS (m/z, %) : 281.2 (M+2, 19), 280.2 (100), 100.1 (4).
N’-(4-chlorobenzylidene)-2-(1H-benzotriazol-1-yl) acetohydrazide XIc:

Mol. Formula : C_{15}H_{12}N_{5}OCl

Mol. Weight : 313.75

Physical Nature : Yellow plates

m. p.(°C) : 196-199

Yield(%) : 67

IR (KBr) cm⁻¹ : 3200 (NH), 3095, 2978, 1647 (C=O amide), 1587 (C=N), 823.

¹H NMR (DMSO-d₆, 400MHz): δ 11.90 (s, 1H, NH), 8.72 (s, 1H, HC=N), 8.25-7.37 (m, 8H, Ar-H), 5.78 (s, 2H, CH₂).

N’-benzylidene-2-(1H-4-methylpiperazine-1-yl) acetohydrazide Xd:

Mol. Formula : C_{14}H_{20}N_{4}O

Mol. Weight : 260.33

Physical Nature : White crystals

m. p.(°C) : 108-110

Yield(%) : 56

IR (KBr) cm⁻¹ : 3210 (NH), 3070, 2980, 1690 (C=O amide), 1582 (C=N), 706, 667.

¹H NMR (CDCl₃, 400MHz): δ 11.16 (s, 1H, NH), 8.14 (s, 1H, HC=N), 7.64-7.46 (m, 5H, Ar-H), 4.64 (s, 2H, CH₂), 2.24 (s, 3H, N-CH₃), 2.18 (m, 8H, 4CH₂).
N’-(4-chlorobenzylidene)-2-(1H-4-methylpiperazine-1-yl)acetohydrazide XId:

**Mol. Formula**: $C_{14}H_{19}N_{4}OCl$

**Mol. Weight**: 294.78

**Physical Nature**: Yellow plates

**m. p.($^\circ$C)** : 199-200

**Yield(%)** : 86

**IR (KBr) cm$^{-1}$**: 3200 (NH), 2939, 1627 (C=O amide), 1585 (C=N), 862, 817.

**$^1$H NMR (DMSO-$d_6$, 400MHz)**: $\delta$ 10.21 (s, 1H, NH), 8.70 (s, 1H, HC=N), 7.89-7.55 (m, 4H, Ar-H), 4.82 (s, 2H, CH$_2$), 2.27 (s, 3H, N-CH$_3$), 2.21 (m, 8H, 4CH$_2$).

**LCMS (m/z, %)**: 279.1 (72), 277.1 (100), 159.2 (12), 143.1 (67), 100.1 (14).
Section 4.2.1- Synthesis of 1,3,4-oxadiazoles derived from some azoles

4.2.1-Introduction:

1,3,4-oxadiazoles and their derivatives are important class of N-heterocyclic compounds having valuable biological properties\(^{29}\), considerable attention have been received in recent years in medicine, pesticide chemistry.

1,3,4-oxadiazoles are known to have broad spectrum of biological activities in number of biological targets such as antimicrobial\(^{30}\), anti inflammatory\(^{31}\), human β-tryptase inhibitors\(^{32}\), anticonvulsants\(^{33}\), analgesic\(^{34}\), antitumor\(^{35}\), hypoglycemic\(^{36}\). Number of oxadiazole derivatives reported to possess pharmacological properties such as antimicrobial, antimalerial\(^{37}\), anticonvulsant\(^{38}\), anticancer\(^{39}\), cyclooxygenase inhibitors (COX)\(^{40}\), anti HIV\(^{41}\), anti inflammatory\(^{42}\), antiviral\(^{42}\), antihelmintic\(^{44}\), antioxidants\(^{45}\) hypoglycemic\(^{46}\) and herbicidal\(^{47}\).

It is reported that 1,3,4-oxadiazoles analogues are equipotent with phenylbutazone, naproxen and other NSAIDs by virtue of a dual mechanism, inhibiting both COX and LOs to reduce gastric ulcer formation\(^{48}\). Their utility as muscle relaxant, antibacteriostatic and anti inflammatory are well known\(^{49}\) and extensively used in the symptomatic treatment of rheumatic fever, arthritis\(^{50}\).

Katritzky et al. reported that 2-amino-1,3,4-oxadiazoles are possess antidiabetic, antiarthritics, analgesic, ulcerogenic and lipid peroxidation activities\(^{51}\).

Joshi S. D. et al. synthesized and shown that 3-acetyl oxadiazoles (1) are better against *Mycobacterium tuberculosis* H\(_{37}\)Rv\(^{52}\).

![Diagram](image)

(1)

Pattan Shashikant R. et al. reported synthesis and antitubercular activity of substituted 1,3,4-oxadiazoles\(^{53}\).

2-aryl substituted oxadiazoles have been reported to show antimicrobial, anti inflammatory, analgesic and hypoglycemic activity\(^{54}\). Substituted 1,3,4-oxadiazoles have been found to possess HIV integrase and angiogenesis inhibitors\(^{55}\). Symmetrically substituted 2,5-dihalophenyl-1,3,4-oxadiazoles (2) have been shown to insecticidal activity\(^ {56}\).
Substituted 1,3,4-thione oxadiazoles and their derivatives possess CNS depressant, anti tubercular and pesticide activity\(^5\).

The capacity of 1,3,4-oxadiazoles nucleus to undergo variety of chemical reaction including aromatic electrophilic substitution, nucleophilic substitution, thermal and photochemical, which made it medicinal backbone on which number of potential molecules can be constructed\(^5\). 1,3,4-oxadiazoles are frequently used as ester or amide substitutes in medicinal chemistry\(^5\).

As a result of useful and wide applications number of oxadiazoles derivatives and methods of synthesis have been reported in literature. Some of the important methods of synthesis are given in following schemes.

1. **Method due to Wadodkar K. N. et al\(^6\)**.

\[
\text{HET} \longrightarrow \text{CONHNH}_2 \quad \overset{\text{KNCS / PhNCS}}{\longrightarrow} \quad \text{HET} \longrightarrow \text{CONHNH} - \text{CS} - \text{NH}_4
\]

\[
\text{I}_2 / \text{KI} \\
\text{R}_4 = \text{H, Ar}
\]

(Scheme-8)
2. Method due to Awadallah Adel M. et al\textsuperscript{61}.

\[ \text{Ph. Ar} + \text{Ph} \rightarrow \text{(Scheme-9)} \]

3. Methods due to Farghaly Abdel-Rahman et al\textsuperscript{51}.

\[ \text{(Scheme-10)} \]

4. Methods due to Rajak Harish et al\textsuperscript{62}.

\[ \text{Ph. D. Thesis, Mr. Rambhau P. Gore  Z. B. Patil College, Deopur, Dhule} \]
5. Methods due to Nesterova et al\textsuperscript{63}.

\begin{center}
(Scheme-11)
\end{center}

\begin{center}
(Scheme-12)
\end{center}

6. Methods due to Joshi S. D. et al\textsuperscript{52}.

\begin{center}
(Scheme-13)
\end{center}

7. Methods due to Sidhaye R. V. et al\textsuperscript{40}.

\begin{center}
(Scheme-14)
\end{center}
8. Methods due to Singh R. K. P. et al.\textsuperscript{64}

R\textsuperscript{\textcircled{-}} \text{CHO} + H\textsubscript{2}N\text{HNN} \xrightarrow{\text{Electrocyclization}} R\textsuperscript{\textcircled{-}} \text{CH=NN} \text{HNN} \\
H\textsubscript{2}N\text{NNHNH}_{2} \xrightarrow{\text{O}} \text{O} \text{N} \text{N}\text{NH}_{2} \text{NH}_{2}

4.2.2-Present Work:

In the events of multi-drug resistance microbes and problems associated with multi-drug therapy, the needs of new antimicrobial agents are can be justified. Worldwide researchers are trying to synthesize new drugs with better pharmacokinetics and dynamic properties with less adverse effect. Literature survey realizes the importance of 1,3,4-oxadiazole derivatives.

In continuation of our studies of Schiff bases we are reporting the synthesis of novel series of thioneoxadiazoles, 3-acetyl oxadiazoles and oxadiazoles.

The carbohydrazides \text{VIIIa-d} proved to be versatile key intermediate for the synthesis of thioneoxadiazoles, 3-acetyl oxadiazoles and oxadiazoles.

The thioneoxadiazoles \text{IXa-d} were synthesized by Young-Wood’s method. In which hydrazides \text{VIIIa-d} were treated with CS\textsubscript{2} and potassium hydroxide in ethanol. The cyclocondensation of Schiff bases \text{Xa-d, Xla-d} with acetic anhydride afforded 3-acetyl 1,3,4-oxadiazoles\textsuperscript{25} \text{XIIa-d} and \text{XIVa-d}. While the reaction with bromine in acetic acid in presence of anhydrous sodium acetate gave 1,3,4-oxadiazoles\textsuperscript{11} \text{XIIa-d} and \text{XVIIa-d}. The synthetic strategy is summarized in following scheme 15.
4.2.3-Experimental Work:

**General procedure for the synthesis of 1,3,4-thioneoxadiazoles IXa-d:**

To carbohydrazides **VIIIa-d** (0.02 mol) in ethanol (20ml) was added a solution of potassium hydroxide (0.025mol, 1.40 g) in ethanol (20ml) and stirred for 15 minutes, followed by excess of CS$_2$ (0.08 mol, 1.5ml) was added in portions. The reaction mixture was heated under reflux for 10-14 hr. cooled to room temperature, acidified
with dilute hydrochloric acid and resulting solid was filtered, washed with water and recrystallized from suitable solvent.

**General procedure for the synthesis of 3-acetyl-1, 3, 4-oxadiazoles XIIa-d, XIVa-d:**

A mixture of hydrazones Xa-d, XIa-d (0.005mol) and acetic anhydride (15ml) was heated under reflux for 10-12 hr. It was cooled to room temperature and then added on crushed ice. The separated product was filtered, washed with water and recrystallized from suitable solvent.

**General procedure for the synthesis of 1, 3, 4-oxadiazoles XIIIa-d, XVa-d:**

A mixture of hydrazones Xa-d, XIa-d (0.005 mol), anhydrous sodium acetate (0.01 mol) and acetic acid (5ml) was stirred for 15 minutes at room temperature. Bromine (0.006mol, 0.3ml) in acetic acid (5ml) was added drop by drop using separating funnel while stirring. Reaction mixture was stirred for further 3 hr., and added on crushed ice. The separated product was filtered, washed with water and recrystallized from suitable solvent.

**Spectral Characterization Data:**

5-((1H-benzimidazol-1-yl) methyl)-1,3,4-oxadiazole-2(3H)-thione IXb:

The (1H-benzimidazol-1-yl)-acetohydrazide, VIIIb on treatment with potassium hydroxide and followed by excess of carbon disulphide afforded yellow crystals of 5-(1H-(benzimidazol-1-yl) methyl)-1,3,4-oxadiazole-2 (3H)-thione IXb in 56% yield, m. p. 150-152°C. The IR spectrum of this compound showed the bands at 3176, 2611 and 1141 cm\(^{-1}\) indicates thiol-thione tautomerism, which were due to NH, SH and C=S. The band at 2966 and 1447 cm\(^{-1}\) displayed CH\(_2\) and C=N stretching. \(^1\)H NMR spectrum of this molecule showed multiplets in the range \(\delta 7.58-7.32\) corresponding to the SH and five protons of benzimidazole moiety. The singlet at \(\delta 4.80\) attributed to methylene protons.

Considering the spectral data the compound IXb may be assigned the following structure.
5-((1H-imidazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione IXa:

Mol. Formula : C₆H₆N₄OS
Mol. Weight : 182.20
Physical Nature : Yellow solid
m. p. (⁰°C) : 146-148
Yield(%) : 56

IR (KBr) cm⁻¹ (Fig. I-3) : 3209 (NH), 2887, 1481 (C=N), 1118 (C=S).

5-((1H-benzotriazol-1-yl)methyl)-1,3,4-oxadiazole-2(3H)-thione IXc:

Mol. Formula : C₉H₇N₅OS
Mol. Weight : 233.25
Physical Nature : White plates
m. p. (⁰°C) : 192-194
Yield(%) : 47

IR (KBr) cm⁻¹ : 3184 (NH), 2897, 2618 (SH), 1496 (C=N), 1163 (C=S).

¹H NMR (DMSO-d₆, 400MHz): δ 7.91-7.43 (m, 5H, Ar-H and SH), 6.24 δ (s, 2H, CH₂).

LCMS (m/z, %) : (M+1) 234.0 (5), (M⁺) 233.1 (8), 232.0 (100).
5-((4-methylpiperazin-1-yl) methyl)-1,3,4-oxadiazole-2(3H)-thione IXd:

Mol. Formula : C₈H₁₄N₄O₅S
Mol. Weight : 214.29
Physical Nature : light yellow plates
m. p. (°C) : 141-142
Yield(%) : 49

IR (KBr) cm⁻¹ : 3209 (NH), 2982, 2860, 1489 (C=N), 1110 (C=S).

Spectral Characterization Data:
1-(2-(4-chloro phenyl)-5-((imidazol-1-yl) methyl)-1,3,4-oxadiazole-3(2H)-yl) ethanone XIVa:
N’-(4-chlorobenzylidene)-2-(1H-imidazol-1-yl) acetohydrazide XIa, hydrazone on reaction with acetic anhydride under reflux afforded colorless crystals of 1-(2-(4-chloro phenyl)-5-((imidazol-1-yl) methyl)-1,3,4-oxadiazol-3(2H)-yl) ethanone, XIVa in 52% yield, m. p. 192-195 °C. The IR spectrum of this compound displayed band at 1670 cm⁻¹ due to acetyl group. The presence of C=N and C-O-C stretching bands at 1627 and 1089 cm⁻¹ indicates the oxadiazole ring. The band at 817 cm⁻¹ due to para substituted phenyl moiety. ¹H NMR spectrum showed a singlet at δ 2.3 due -CH₃ of acetyl group. The singlet at observed at δ 7.2 accounted for C₂-H of oxadiazole ring. The resonance at δ 7.93-7.53 corresponding to the seven protons of imidazole and phenyl ring. The singlet at δ 4.90 due to –CH₂ protons.

Considering the spectral data the compound XIVa may be assigned the following structure.
1-(5-((1H-benzimidazol-1-yl) methyl)-2-(4-chlorophenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone XIVb:

**Mol. Formula**: C_{18}H_{15}N_{4}O_{2}Cl

**Mol. Weight**: 354.80

**Physical Nature**: Yellow plates

**m. p. (°C)**: 208-210

**Yield(%)**: 46

**IR (KBr) cm^{-1}** (Fig. I-4): 3091, 1703 (acetyl C=O), 1600 (C=N), 1317, 1089 (C-O-C), 817(para disub.).

**^1H NMR (DMSO-d_6, 400MHz)**: δ 8.60 (s, 1H, benzimi-C_2-H), 7.79-7.42(m, 9H, Ar-H and oxadiazole -C_2-H), 4.52(s, 2H, CH_2), 2.23 (s, 3H, CH_3).

**LCMS (m/z, %)**: (M^+2) 357.3 (5), 322.2 (6), 279.2 (74), 277.1 (100), 242.6 (7).

5-(1-(4-methylpiperazine-1-yl) methyl)-2-phenyl-1,3,4-oxadiazole-3(2H)-thione XIId:

**Mol. Formula**: C_{16}H_{22}N_{4}O_{2}

**Mol. Weight**: 302.37

**Physical Nature**: Yellow needle

**m. p. (°C)**: 76-78

**Yield(%)**: 53

**IR (KBr) cm^{-1}** (Fig. N-4): 3051, 2829, 1689 (C=O, ester), 1622 (C=N), 1072(C-O-C), 752, 692 (mono sub.).

**^1H NMR (CDCl_3, 400MHz)**: δ 7.45 (s, 5H, Ar-H), 7.12 (s, 1H, oxadiazole -C_2-H), 2.28 (s, 3H, CH_3), 2.23(s, 3H, N-CH_3), 2.10 (s, 2H, CH_2), 1.55 (s, 8H, 4CH_2).

**LCMS (m/z, %)**: 211.2 (12), 210.1 (16), 209.1 (100).
Spectral Characterization Data:

5-(4-chloro phenyl)-2-((imidazol-1-yl) methyl)-1,3,4-oxadiazole XVa:

N’-(4-chlorobenzylidene)-2-(1H-imidazol-1-yl) acetohydrazide XIa, hydrazone on reaction with bromine in acetic acid afforded yellow solid of 5-(4-chloro phenyl)-2-((imidazol-1-yl) methyl)-1,3,4-oxadiazole XVa, in 48% yield, m. p. 200-202°C. The IR spectrum (Fig. I-5) of this molecule displayed a band at 1587 cm\(^{-1}\) due to C=N stretching while the absence of band in the range of carbonyl group indicates its unsubstituted nature. The bands at 1089 and 815 cm\(^{-1}\) were indicates the C-O-C and para substitution pattern of phenyl moiety. \(^1\)H NMR spectrum showed aromatic resonance at δ 7.90-7.41 as multiplet corresponding to seven protons of imidazole and phenyl moiety. The singlet at δ 4.84 indicates CH\(_2\) protons.

Considering the spectral data the compound XVa may be assigned the following structure.

![Structure XVa](image)

2-((benzimidazo-1-yl) methyl)-5-phenyl-1,3,4-oxadiazole XIIIb:

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mol. Formula</td>
<td>C(<em>{16})H(</em>{12})N(_4)O(_2)</td>
</tr>
<tr>
<td>Mol. Weight</td>
<td>276.29</td>
</tr>
<tr>
<td>Physical Nature</td>
<td>Reddish crystals</td>
</tr>
<tr>
<td>m. p. (°C)</td>
<td>54-56</td>
</tr>
<tr>
<td>Yield(%)</td>
<td>42</td>
</tr>
</tbody>
</table>

IR (KBr) cm\(^{-1}\): 1622 (C=N), 1065 (C-O-C), 752, 690.

\(^1\)H NMR (CDCl\(_3\), 400MHz): δ 7.85-7.25(m, 10H, Ar-H), 5.32(s, 2H, CH\(_2\)).
2-((benzotriazo-1-yl)methyl)-5-phenyl-1,3,4-oxadiazole XIIIc:

Mol. Formula  : $C_{15}H_{11}N_5O$
Mol. Weight   : 277.28
Physical Nature : Reddish crystals
m. p. ($^0$C)  : 193-195
Yield(%)      : 59

IR (KBr) cm$^{-1}$ (Fig. I-6) : 3051, 2947, 1622 (C=N), 1300, 1072 (C-O-C), 752, 692 (mono sub.).
$^1$H NMR (CDCl$_3$, 400MHz) : $\delta$ 8.20-7.30(m, 9H, Ar-H), 5.31(s, 2H, CH$_2$).

4.3 Antimicrobial Activity:
The synthesized compounds IXa-d, Xa-d, XIa-d, XII, XIII, XIV and XVa-d 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 and Potato dextrose agar. 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 and 2.

All the compounds have shown moderate to good activity against bacterial strains. The compound XIa is found equally or more potent than standard against *Escherichia coli* and *Staphylococcus aureus*. While compound IXb against *Escherichia coli* and *A. niger*. The activity data reveals that most of the compounds are inactive against fungal strains except XIVb and XIIId which are equally potent against antifungal drug Amphotericin-B against *A. niger*.
Table 1. Results of antimicrobial activity of the compounds Xa-d, XIa-d:

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Antimicrobial activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
</tr>
<tr>
<td>Xa</td>
<td>8.27</td>
</tr>
<tr>
<td>XIa</td>
<td>17.45</td>
</tr>
<tr>
<td>Xb</td>
<td>8.08</td>
</tr>
<tr>
<td>XIb</td>
<td>9.15</td>
</tr>
<tr>
<td>Xc</td>
<td>12.14</td>
</tr>
<tr>
<td>XIc</td>
<td>13.34</td>
</tr>
<tr>
<td>Xd</td>
<td>7.23</td>
</tr>
<tr>
<td>XIId</td>
<td>8.27</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 1: Biological activities of compounds Xa-d, XIa-d.
Table 2. Results of antimicrobial activity of the compounds IXa-d, XII, XIII, XIV, XVa-d:

<table>
<thead>
<tr>
<th>Compound No.</th>
<th>Antimicrobial activity*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E. coli</td>
</tr>
<tr>
<td>IXa</td>
<td>17.87</td>
</tr>
<tr>
<td>IXb</td>
<td>21.22</td>
</tr>
<tr>
<td>IXc</td>
<td>8.14</td>
</tr>
<tr>
<td>IXd</td>
<td>13.65</td>
</tr>
<tr>
<td>XIVa</td>
<td>9.78</td>
</tr>
<tr>
<td>XIVb</td>
<td>13.10</td>
</tr>
<tr>
<td>XIIId</td>
<td>8.49</td>
</tr>
<tr>
<td>XVa</td>
<td>8.17</td>
</tr>
<tr>
<td>XIIIb</td>
<td>9.27</td>
</tr>
<tr>
<td>XIIIc</td>
<td>_</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: Biological activities of the compounds IXa-d, XII, XIII, XIV, XVa-d.
4.4 Conclusions:
In conclusion this research study reports the successful synthesis of novel series of Schiff’s bases, thioneoxadizoles, 3-acetyl oxadiazoles and oxadiazoles. The key intermediate azole carbohydrazides $\text{VIIIa-d}$ were prepared by hydrazinolysis of corresponding esters.

The hydrazides were converted to thioneoxadizoles $\text{IXa-d}$ by reported Young-Wood method and Schiff’s bases $\text{Xa-d, XIa-d}$. 3-acetyl oxadiazoles $\text{XII, XIV}$ and oxadiazoles $\text{XIII, XVa-d}$ by respective methods.

During synthesis whenever possible we tried greener approach with the use of less hazardous solvents such as ethanol, methanol in place of benzene, 1,4-dioxane and catalyst.

The antimicrobial study of synthesized compounds reveals that imidazole, benzimidazole, Schiff bases and thioneoxadiazole are more active against bacteria while benzimidazole only shows activity against fungal strain, *Aspergillus niger*. In the series of oxadiazoles benzimidazole and N-methyl piperazine derivatives are found more active.
Fig. I-1: IR Spectrum of compound XIa

Fig. I-2: IR Spectrum of compound Xc
Fig. I-3: IR Spectrum of compound IXa

Fig. I-4: IR Spectrum of compound XIVb
Fig. I-5: IR Spectrum of compound XVa

Fig. I-6: IR Spectrum of compound XIIIc
Fig. N-1: $^1$H NMR Spectrum of compound XIa
Fig. N-2: $^1$H NMR Spectrum of compound Xc
Fig. N-3: $^1$H NMR Spectrum of compound IXc
Fig. N-4: $^1$H NMR Spectrum of compound XIId
Fig. M-1: Mass Spectrum of compound Xb
Fig. M-2: Mass Spectrum of compound IXc
Fig. M-3: Mass Spectrum of compound XIVb
4.2.8-References:

   (b) Arshi, Naqvi.; Mohd. Shahnawaaz.; Rao, Arikatla V.; Seth, Daya S.; Nawal, K. E. Journal of Chem. 2009, 6, S1, S75.
   (c) Belskaya, Nataliya P.; Dehaen, Wim.; Bakulev, V. A. Arkivoc, 2010, (i), 275.


   (b) Parashar, Bharat.; Bharadwaj, Sudhir.; Sharma, V. K.; Punjabi, P.B. Der Pharma Chemica, 2010, 2, 2, 229.

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