CHAPTER V

\[ \text{H}_2\text{NNOC} \quad \begin{array}{c} \text{N} \\ \text{N} \end{array} \quad \begin{array}{c} \text{H} \\ \text{O} \end{array} \]

\textit{p-hydrazinocarbonylphenylsydnone derivatives}
PURPOSE OF THE WORK

In the previous chapter we have demonstrated the use of 3-arylsydnones for the facile synthesis of so far unknown 1,3,4-oxadiazolin-5-ones. Now we thought of utilizing the sydnones with a potent functional group for the preparation of the 3-aryl-5-methyl-2-oxo-Δ^4^-1,3,4-oxadiazoles along with other heterocyclic systems.

PRESENT WORK

For this purpose we thought of using 3-(p-hydrazinocarbonyl)phenylsydnone as the starting material. In one of the experiment, the sydnone ring and the hydrazine carbonyl group of this compound have been used for the preparation of p-phenylene-1,3,4-oxadiazoles of the following type. The hydrazinocarbonyl group can also be used to prepare the 1,3,4-oxadiazoline ring, through its hydrazone derivatives.

The 3-(p-hydrazinocarbonyl) phenylsydnone is treated with aromatic aldehydes to get the corresponding hydrazone derivatives. These hydrazones have been converted to the title compound 3-[p-(p-(5’-phenyl-4’-N-acetyl-1’,3’,4’-oxadiazolin-2’-yl)phenyl oxadiazoles by two methods.

In the first method the hydrazone group on reaction with acetic anhydride forms 3-[p-(p-(5’-phenyl-4’-N-acetyl-1’,3’,4’-oxadiazolin-2’-yl)phenyl sydnones. In the next step the sydnone ring of these compound is subjected to ring conversion to the 3-[p-(p-(5’-phenyl-4’-N-acetyl-1’,3’,4’-oxadiazolin-2’-yl)phenyl oxadiazoles by reaction with bromine in acetic anhydride. Since acetic anhydride is used in both the steps, the same preparation can be carried out in the single step and with improved yield and purity.

The hydrazones derivatives of sydnones on reaction of bromine in acetic anhydride at 0°C gave only the 4-bromosydnone derivatives.
In another experiment we have introduced an isatin ring on the hydrazine carbonyl group to get the corresponding hydrazone derivative 3-[p-(2'-oxo-1'-indolo-3'-hydrazinocarbonyl)]phenyl sydnone. The sydnone ring of this compound was then subjected to ring conversion with bromine in acetic anhydride. The resulting bis heterocyclic compounds have the biological potential isatin ring coupled with the 1,3,4-oxadiazolin-2-ones and one can expect improved biological properties from this combination.
In the third experiment with the 3-(p-hydrazinocarbonyl) phenylsydnone we constructed the 3,5-disubstituted pyrazole rings using the hydrazine group to obtain the 3-[p-3',5'-disubstituted-pyrazole-N-1'-carbonyl) phenylsydnones. At this stage we thought of making use of one pot formation of tetrahydrocarbazoles by acid hydrolysis and reaction with cyclohexanone, so as to get the heterocyclic substitution on the tetrahydrocarbazole. However, the sydnone ring did undergo hydrolysis to give only the hydrazine, but failed to react with cyclohexanone.
The typical IR spectrum (No.20) of the above compound showed two $\nu_{\text{C}=\text{O}}$ peaks at 1783 and 1690 cm$^{-1}$ corresponding to the lactone carbonyl and amide carbonyl respectively. The $^1$H-NMR spectra was not resolved clearly, because of the poor solubility of the compounds. However, distinct signals appeared for all the protons. A typical spectrum (No.21) exhibited two singlets at $\delta$ 2.15 and 2.40 for the methyl protons of the acetyl group and the lactone respectively. The 4 protons of the $p$-disubstituted phenyl ring appear as two doublets at $\delta$ 7.2-7.5, while the 5 protons of the monosubstituted phenyl ring appear as a singlet at $\delta$ 7.99.

The IR spectrum of (No. 22) shows a broad peak for $\nu_{\text{NH}} \approx$3252, and the absence of the sydnone $\nu_{\text{CH}}$ at 3100 cm$^{-1}$. The sydnone $\nu_{\text{C}=\text{O}}$ appears at 1727 cm$^{-1}$, while the other $\nu_{\text{C}=\text{O}}$ at 1770 cm$^{-1}$. Two sharp peaks are observed at 1505 and 1330 for the $\nu_{\text{NO}_2}$.

The $^1$H-NMR spectrum (No. 23) of this compound shows the absence of a signal $\sim \delta$ 7.00 for sydnone C4 proton the signal at $\delta$ 10.1 is due to the $=\text{CH}$ (azine proton). The 8 aromatic protons and the amide protons appear in the region $\delta$ 7.02 and 8.4 ppm.
The IR spectrum (No. 24) of this compound showed two ν$_{\text{NH}}$ peaks at 3299-3227 cm$^{-1}$ for the two NH protons. Three ν$_{\text{C}=\text{O}}$ peaks were observed at 1712, 1739 and 1758 for isatin CO, amide CO and sydnone CO.

The proton NMR spectrum (No.25) shows a singlet at δ 7.2 for sydnone CH proton. The two NH protons are observed at δ 4.31 and δ 8.16 (isatin NH), both D$_2$O exchanged. All the aromatic protons (8H) appear in δ 7.9-7.1 with complex multiplicity.

The IR spectrum (No. 26) shows a broad band ~ 3300-3200 cm$^{-1}$ for the two ν$_{\text{NH}}$. The bands at 1783, 1740 and 1702 cm$^{-1}$ are due to lactone ν$_{\text{C}=\text{O}}$, isatin ν$_{\text{C}=\text{O}}$ and amide ν$_{\text{C}=\text{O}}$ respectively.

The evidence for the formation of the oxadiazolone ring is obtained in the $^1$H-NMR spectrum (No.27) which shows the absence of sydnone CH at δ 7.2. The two NH protons appear as singlets at δ 4.6 and δ 8.16 (isatin NH) both D$_2$O exchanged. The pattern for the aromatic protons is similar to the precursor. A singlet at δ 2.4 (3H) also confirms the presence of oxadiazolone ring.
SPCTRAL DATA

Schiff bases of 3-p-(hydrazino carbonyl)phenyl sydnone

IR SPECTRUM

SPECTRUM NO.19a

1739cm\(^{-1}\) : \(\nu_{c=0}\) of sydnone ring
1647cm\(^{-1}\) : \(\nu_{c=0}\)
3116cm\(^{-1}\) : \(\nu_{ch}\) of sydnone ring
3234cm\(^{-1}\) : \(\nu_{NH}\)
3302cm\(^{-1}\) : \(\nu_{ch}\) of side chain

IH-NMR SPECTRUM

SPECTRUM NO.19b

\[\delta\]
\begin{align*}
7.1\,(s.1H) & : CH\text{ proton of sydnone ring} \\
7.8\,(s.1H) & : CH\text{ proton} \\
7.9\,(d.2H \, J=7.8Hz) & : 4\text{ protons of aromatic ring A in AA' and BB' pattern} \\
8.0\,(d.2H \, J=7.9Hz) & \\
8.2\,(d.2H \, J=8.0Hz) & : 4\text{ protons of aromatic ring B in AA' and BB' pattern.} \\
8.3\,(d.2H \, J=8.1Hz) & \\
10.13 & : NH\text{ proton}
\end{align*}
SPECTRAL DATA

3-(5'-Pheny1-4'-N-acetyl-1',3',4'-oxadiazol-2'-yl)phenyl-5-methy1-2-oxa-1,3,4-oxadiazoles

IR SPECTRUM

SPECTRUM No.20

1783 cm\(^{-1}\) : \(\nu_{\text{C-O}}\) for oxadiazole ring
1690 cm\(^{-1}\) : \(\nu_{\text{C=O}}\) for COCH\(_3\) chain
3252 cm\(^{-1}\) : \(\nu_{\text{CH}}\)

\(^1\)H- NMR SPECTRUM

SPECTRUM No.21

2.1 (S, 3H) : C\(_5\) methyl protons
2.4 (S, 3H) : Acetyl protons
7.0 (S, 1H) : C\(_{5''}\) proton
7.3 (d.2H J 7.1 Hz) : 4 protons of aromatic ring A in AA'BB' pattern
7.4 (d.2H J 7.2 Hz)
8.1 - 7.9 (m, 5H) : 5 protons of aromatic ring B
SPECTRAL DATA

Schiff's bases of 4-bromo-3-[(p-hydrazinocarbonyl)] phenyl sydnone

IR SPECTRUM

SPECTRUM No.22

1760 cm\(^{-1}\) : \(v_{c=0}\) sydnone ring

1656 cm\(^{-1}\) : \(v_{c=0}\) Carbazide side chain

3221 cm\(^{-1}\) : \(v_{\text{NH}}\) for Carbazide side chain

\(^1\)H-NMR SPECTRUM

SPECTRUM No.23

7.9 (S, 1H) : CH proton

8.0 (d, 2H J 7.9 Hz) : 4 protons of Aromatic ring A in AA'BB'

8.1 (d, 2H J 8.0 Hz) : Pattern

8.3 (d, 2H J 8.1 Hz) : 4 protons of Aromatic ring B in AA'BB''

8.4 (d, 2H J 8.2 Hz) : Pattern

10.1 (S, 1H) : NH proton of hydrazone chain.
Spectra No. 23
$^1$H-NMR Spectrum

![NMR Spectrum Diagram]
SPECTRAL DATA

3-\([p(2'\text{-}\text{oxo-1'}\text{-}\text{Indalo-3'}\text{-}\text{hydrazinocarbonyl})]\) phenyl sydnone.

IR SPECTRUM
SPECTRUM No.24

\[1758 \text{ cm}^{-1} : \nu_{c=0} \text{ for sydnone ring.}\]
\[1739 \text{ cm}^{-1} : \nu_{c=0} \text{ for Isatin ring.}\]
\[1712 \text{ cm}^{-1} : \nu_{c=0} \text{ of Carbazide group.}\]
\[3295 \text{ cm}^{-1} : \nu_{\text{NH}} \text{ of NCHO}\]
\[3227 \text{ cm}^{-1} : \nu_{\text{NH}} \text{ for Isatin ring.}\]
\[3128 \text{ cm}^{-1} : \nu_{\text{CH}} \text{ for sydnone}\]

\(^1\text{H}\)-NMR SPECTRUM
SPECTRUM No.25

\[4.6 (S, 1H) : 1 \text{ proton of carbazide chain (D}_2\text{O exchanged})\]
\[7.2 (S, 1H) : C_4 - \text{proton}\]
\[7.3 - 7.9 (m, 8H) : \text{Aromatic protons of A and B ring}\]
\[8.1 (S, 1H) : 1 \text{ proton of Istatin}\]
SPECTRAL DATA

3-\([p(2'-\text{o xo}-1'\text{-Indolo-3'}\text{-hydrazinocarbonyl})\text{ phenyl oxadiazole}]

IR SPECTRUM

SPECTRUM No.26

1783 cm\(^{-1}\) : \(\nu_{\text{C=O}}\) oxadiazole ring
1750 cm\(^{-1}\) : \(\nu_{\text{C=O}}\) Isatin ring
1702 cm\(^{-1}\) : \(\nu_{\text{C=O}}\) Carbazide side chain
3259 cm\(^{-1}\) : \(\nu_{\text{NH}}\)
2925 cm\(^{-1}\) : \(\nu_{\text{CH}_3}\) Oxadiazole ring

\(^1\)H-NMR SPECTRUM

SPECTRUM No.27

2.4 (S, 3H) : \(\text{C}_5\) protons
4.3 (S, 1H) : Side chain proton (\(\text{D}_2\text{O}\) exchanged)
7.2 - 7.9 (m, 8H) : Aromatic protons of A and B ring
8.1 (S, 1H) : Isatin ring proton (\(\text{D}_2\text{O}\) exchanged)
Spectra No. 26
IR Spectrum

[Chemical Structure Image]

695.33
795.00
917.56
1135.40
1265.55
1369.47
1604.12
1672.04
1783.19
1702.92
2851.46
2295.66
3259.01
Spectra No. 27

$^1$H-NMR Spectrum
SPECTRAL DATA

H3C NHNH
4-[3',5'-dimethyl-pyrazol-1'yl-carbonyl] phenyl-1-hydrazine hydrate.

IR SPECTRUM

SPECTRUM No.29

1684 cm\(^{-1}\) : \(\nu_{C=O}\) for C=O group

3401 cm\(^{-1}\) : \(\nu_{\text{NH}_2}\) for NH\(_2\) group

3326 cm\(^{-1}\) : \(\nu_{\text{NH}}\) for NH group

\(^1\text{H}-\text{NMR SPECTRUM}\)

SPECTRUM No.30

2.7 (\(\delta\, 6H\)) : 6 protons of 2-CH\(_3\) groups

4.3 (d, 2H) : protons of NH\(_2\)

7.8 (d, 2H J 7.6) : 4 Protons of Aromatic ring in AA' BB' Pattern

7.9 (d, 2H J 7.8)

8.2 (s, 1H) : NH proton
BIOLOGICAL PROPERTIES OF OXADIAZOLES, ISATIN AND PYRAZOLES.

Oxadiazoles are five membered heterocycles with two nitrogen and one oxygen atoms. Depending upon the position of nitrogen atoms they are classified as 1,2,3-, 1,2,4-, 1,2,5- and 1,3,4- oxadiazoles – A to D, respectively.

\[ \text{\begin{array}{c}
\text{N}\\
\text{O}^X
\end{array}} \]

1,3,4-Oxadiazoles find a wide variety of use such as dyestuff, biologically active compounds both in medicine and agriculture, fluorescent materials and heat resistant polymers.

Smith et. al., (1) screened various substituted 1,3,4-oxadiazoles for antituberculosis property and found that compound (E) possessed good tuberculosis properties.

\[ \text{\begin{array}{c}
\text{N}\\
\text{O}\\
\text{X}
\end{array}} \]

\((E)\) Where, \(X = O, S\)

Several derivatives of 5-substituted-1,3,4-oxadiazoles (F) synthesised by Kurihara et. al., (2) were reported to possess hypoglycemic activity. These compounds are also found to be less toxic than the corresponding hydrazides.
Hypotensive, analgesic, anti-inflammatory, anticonvulsant, tranquilising, muscle relaxant, bronchodilatory and anticholinergic activities were shown by 2,5-disubstituted-1,3,4-oxadiazoles (G) (3).

Singh, H., et. al., synthesised some amido/imido ethyl derivatives of 2-amino/mercapto-5-aryl-1,3,4-oxadiazoles (H and I). These compounds exhibited fungicidal activity comparable with Dithane M-45 at 1000 ppm (4).

Some N-dialkylamino methyloxadiazolones and oxadiazole thiones (J) were reported to possess tuberculostatic and antiinflammatory activities (5).
Various 2,5-diaryl substituted-1,3,4-oxadiazoles (K) were screened for antiinflammatory, sedative and analgesic activities (6).

A German patent (7) gives the synthesis of imino oxadiazole carboxylate (L) derivatives which act as drugs and agrochemicals.

Where, R = un/subt.phenyl

Herbicidal activity of 2-amino-5-substituted - 1,3,4 oxadiazoles (M) was reported by a German patent (8).
5-Substituted-1,3,4-oxadiazole-2-hydrazines (N-1) and their corresponding hydrazones (N-2) synthesised by Kalluraya et. al., (9), were tested for both gram-positive and gram-negative bacteria.

\[
\begin{align*}
(N-1) & \quad & (N-2) \\
\text{R} & \quad \text{O} \quad \text{NHNH}_2 & \quad \text{R} & \quad \text{O} \quad \text{NHN=CHR'} \\
\end{align*}
\]

Anticonvulsant, antiinflammatory, bactericidal and fungicidal activity of a number of 2,5-disubstituted-1,3,4-oxadiazoles (O) were reported (10).

\[
\begin{align*}
(O) & \\
\text{R'} & \quad \text{HC} \quad \text{O} \quad \text{R} & \\
\end{align*}
\]

Where, \( R = -\text{NH}_2, -\text{NHHSO}_2 -\text{R} \) and \(-\text{NHCO-R}\)

Misra, U. et. at., synthesised indolymethyl-1,3,4-oxadiazoles and studied their antiinflammatory and CNS activity (11).

Hiremath, S.P., et al., screened 5-(2\(^1\)-phenylindol-3\(^1\)-yl) amino-2-phenoxymethyl-1,3,4-oxadiazoles (P) for their antibacterial, antifungal, oxytoxic and catatonic activities (12).

\[
\begin{align*}
(P) \\
\end{align*}
\]
Menon et al synthesised 2-methyl-5-(4-acetoxycinnolin-3-yl)-1,3,4-oxadiazoles (Q) and found them to be moderately active against antimicrobials (13).

\[
\text{(Q)}
\]

Where, R\textsubscript{1}, R\textsubscript{2} & R\textsubscript{3} = H, Me & Cl

2-Amino-5-(3\textsuperscript{1}-pentadecylaryloxy isopropyl)-1,3,4-oxadiazoles (R) exhibited the antiinflammatory activity (14).

\[
\text{(R)}
\]

Where, R\textsubscript{2} = C\textsubscript{15} H\textsubscript{31}, CH\textsubscript{3} and R\textsubscript{1} = H or Cl

Simmons, K.A., et al., identified 2-(2\textsuperscript{1}-nitrophenyl)-1,3,4-oxadiazoles (S) as herbicides through random screening (15). Based upon whole plant symptoms, these compounds are thought to be inhibiting plant growth in a fashion analogous to paraguat.
BIOLOGICAL PROPERTIES OF ISATIN

Isatin (2,3-dioxindole) is an endogenous compound which is distributed throughout the central nervous system. Recent studies suggest that isatin may be an endogenous modulator of food intake. Isatin, a postulated anxiogenic endocoid is found to inhibit the memory-facilitating effect of centrally administered arterial natriuretic peptide (ANP) in rats.

Shailaja. Rani et al, prepared various isatin derivatives and screened them for their biological activity. Some isatin derivatives were found to exhibit potential anticonvulsant activity.

Silberman, Sandra, L. synthesised certain 3-substituted-2-oxindole-1-carboxamides (A) and the pharmaceutically-acceptable base salts thereof which were found to be useful for inhibition of viral replication.

![Chemical structure of isatin derivatives](image)

3-(Arylmethylene) oxindoles (B) and analogs have found to be gastrin releasing antagonists.
Joshi, et al.,\textsuperscript{24} have reported antibacterial activity for fluorinated isatins (C).

Srivastava, et. al, synthesised many hydrazone derivatives of isatin (D) and evaluated them against various strains of fungi, virus and bacteria, both in vitro and in vivo.\textsuperscript{25}

1,3-Diacyl-2-oxindoles (E) and 3-acyl-2-oxaindole-1-carboxamides (F) have shown analgesic and anti-inflammatory activity.\textsuperscript{26,27}
Joshi, et al.,\textsuperscript{28} have reported the insecticidal activity of some novel indole derivatives (G).

Pyridyl methylene-2-indolinones (H) have shown to possess cardiotonic activity.\textsuperscript{29}

Tang, Peng. Cho. Et. al., have reported the treatment of diseases for some indolinone (I) combinational libraries and related products\textsuperscript{30}.
Some of the 2-hydrazinoquinoline derivatives of isatin have found to possess antidiuretic and antimicrobial activities\textsuperscript{31}.

Badami and Kavali have recently reported the synthesis and antimicrobial activity of some 3-aryl-4-[(2',3'-dihydrospiro-1',4'-benzodiazepine-5'-[3''-3"H]-2''-oxindol]-1''-H]-7'-yl]Sydnones, from this laboratory.\textsuperscript{31a}
PYRAZOLES:

Pyrazole is a five membered heteroaromatic possessing a wide spectrum of biological activities. Some of the derivatives of pyrazoles have been used in chemotherapy, these include antipyrine (C) an antipyretic agent, aminopyrine (D) – an antipyretic and analgesic agent, phenylbutazone (E)-an antiinflammatory agent and oxyphenbutazone (F) – an antiinflammatory agent

Antiinflammatory, (32) antipyretic, analgesic (33), bactericidal, (34) vasodilating, respiration stimulating bronchdilating and hypotensive activities (35) of pyrazolopyridines have been reported in the literature.

Fluorinated derivatives of propyphenazone (E) have found to exhibit analgesic, antipyretic and antiinflammatory activities (36).
Reudiger et. al., (37) have reported cardiovascular property of pyrazolylxy alkyl carboxamide (F).

4-Carboxyalkylamino-1,3-dimethyl pyrazolo (3,4-b) quinolines (G) are found to be useful as antiviral agents against influenza, A2-Hongkong strain and encephalomyocarditis virus (38).

A German patent (39) describes the aryl (dichloro acetamido) nitropyrazoles (H) as herbicides and plant growth regulators.
Patel et al., prepared pyrazolyl methylene-1,2,4-triazoles (I) and have been screened for bactericidal activity (40).

Pyrazolo (4,3-e)pyrrolo(1,2-a)(1,4) Diazepinone was found to possess appreciable in vitro cytotoxic activity (41).

Manfredin et al., synthesized 4-iodo-1-B-D-ribofuranosyl pyrazole-3-carboxylates (J) and found them to show wide spectrum of antiproliferative activity and low cytotoxicity activity against resting peripheral blood lymphocytes (42). Though (J) did not show any antiviral activity it was able to potentiate the anti-HIV-1 activity of dideoxyinosine (ddI).
3-Pyrazolyl-α α α-trifluorotolyl ethers were found to possess herbicidal activity (43).

Based on the principle of bioisosterism a series of 4-(1-phenyl-3-methyl[3,4-b]pyridine) hydrazone derivatives were synthesised. These compounds showed promising analgesic activity (44).

5-[4-(4-Methylphenyl)-3-(trifluoromethyl)-1-H-pyrazole-1-yl] benzene sulfonamide (K) was synthesised by Penning et al., (45). This compound is currently in phase III clinical trials for the treatment of rheumatoid arthritis and osteoarthritis.
EXPERIMENTAL:

These compounds were prepared by the following steps:

1. Preparation of Schiff’s bases of 3-[(p-hydrazinocarbonyl) phenyl] sydnone.
   a) preparation of 3-[p-(5’-phenyl-4’-N-acetyl-1’2’4’-oxadiazolin-2’-yl] phenyl sydnone.
   b) Preparation of 4-Bromoderivatives of Schiff’s bases of 3-[(p-hydradzinocarbonyl)] phenyl sydones.


3. 3-[p(2’-Oxo-1’-Indolo-3’-hydrazinocarbonyl)] phenyl sydnone.

4. 3-[p(2’-Oxo-1’-Indolo-3’-hydrazinocarbonyl)] phenyl oxadiazole.

5. 4-[3’,5’-Disubstituted-pyrazol-1’yl-carbonyl] phenylhydrazine.

1. Preparation of Schiff’s bases of 3-[(p-hydrazinocarbonyl) phenyl] sydnones.

   A mixture of 3-[p-(hydrazinocarbonyl)] phenylsydnone (2.20g, 0.01 mole) and benzaldehyde (1.06g, 0.01 mole) in 50ml dry alcohol was refluxed on a water bath for 2 hr. The solvent was evaporated and the solid separated was crystallised from ethanol.

   Similarly were prepared the other derivatives are listed in Table No.25.
(a) Preparation of 3-[p-(5'-phenyl-4'-N-acetyl-1'3'4'-oxadiazolin-2'-yl] phenyl sydnone.

Schiff's base (0.01 mole) in 50ml acetic anhydride was stirred at 120-30°C for 1 hr. The reaction mixture was then poured into ice-cold water and neutralised with ammonia. The solid separated was filtered, washed with water, air dried and recrystallised from ethanol.

(b) Preparation of 4-Bromoderivatives of Schiff's bases of 3-[p-hydrazino carbonyl] phenyl sydnone.

Schiff's base (1g) was suspended in acetic anhydride (5ml) and bromine(0.5ml) was added with stirring and cooling. The 4-bromoderivative of 3-[p-hydrazinocarbonyl] phenylsydnone which separated was filtered, dried and crystallised from ethanol.

2. Preparation of 3-[p-(5'-phenyl-4'-N'-acyetyl-1'3'4'-oxadiazolin-2'-yl] phenyl oxadiazoles.

These compounds were prepared by two routes:

(a) 3-[p-(5'-Phenyl-4'-N-acetyl-1'3'4'-oxadiazolin-2'-yl)]phenylsydnone was suspended in acetic anhydride (5ml) at 60° and an ice-cold solution of bromine (0.5ml) in acetic anhydride (5ml) was added with stirring and cooling. 4-Bromo sydnone began to separate after stirring for 30 minutes at RT. The reaction mixture was then heated on water bath for 30 minutes, gradually increasing the temperature to 50-70°. Vigorous evolution of CO₂ was observed. The solution was then diluted with water and the solid obtained was filtered and washed with
water. Crystallisation from ethanol furnished 3-[p-(5'-phenyl-4'-N-acetyl-1'3'4'-oxadiazolin-2'-yl)] phenyloxadiazoles.

(b) The above compounds were prepared by following the above procedure from Schiff’s bases of 3-[(p-hydrazino carbonyl)] phenyl sydnones.

Similarly were prepared the other derivatives and are listed in Table No.26

3. Preparation of 3-[p-(2'-oxo-1'-Indolo-3'-hydrazinocarbonyl)] phenyl sydnone.

A mixture of 3-[p-(hydrazinocarbonyl)] phenyl sydnone (2.20g, 0.01 mole) and isatin (1.47g, 0.01 mole) in 50ml dry alcohol was refluxed on a water bath for 4 hr.

The reaction mixture was cooled and poured into water. The pale yellow solid separated was filtered and washed with water. Crystallised from alcohol.

Similarly prepared the other derivatives are listed in Table No.27

4. Preparation of 3-[p-(2'-oxo-1'-Indolo-3'-hydrazinocarbonyl)] phenyl oxadiazole.

3-[4'-(3''-Hydrazino carbonyl)isatino] phenyl sydnone (1g) was suspended in AC₂O (5ml) at 0° and an ice-cold solution of bromine (0.5ml) in AC₂O (5ml) was added with stirring and cooling 4-Bromosydnone began to separate after stirring the solution for 30 minutes at RT. The reaction mixture was then heated on a water bath for 30 minutes gradually increasing the temperature to 60-70°.
Vigorous evolution of CO₂ was observed. The solution was then with diluted water and the solid obtained was filtered and washed with water. Crystallisation from ethanol. Table No. 28.

5. Preparation of 4-[(3',5'-dimethyl-2'-2-3'-2-pyrazol-1'-yl carbonyl)] phenylhydrazine.

p-[(3',5'-Dimethyl-pyrazol-1'-yl-carbonyl)] phenylsydnone (2.78g, 0.01 mole) in a mixture of 10ml alcohol, 10 ml H₂O, 10ml of HCl was refluxed on a water bath for half hour. To this was added 0.98ml of cyclohexanone and the heating was continued for another hour. The reaction mixture was cooled and poured into water, filtered and washed with water. Crystallised absolute alcohol.

Similarly were prepared the other derivatives and are listed in Table No.29.
CHARACTERISATION DATA OF COMPOUNDS

Schiff bases of 3-\(p\)-(hydrazino carbonyl)phenyl sydnones

Table No.25

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield %</th>
<th>M.P (°C)</th>
<th>Molecular formula</th>
<th>Elemental analysis Found (Calc)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C%</td>
</tr>
<tr>
<td>H</td>
<td>4-NO(_2)</td>
<td>68</td>
<td>250-252</td>
<td>(C_{16}H_{11}N_{5}O_{4})</td>
<td>56.99 (56.97)</td>
</tr>
<tr>
<td>2-OCH(_3)</td>
<td>4-OH</td>
<td>70</td>
<td>254-55</td>
<td>(C_{17}H_{14}N_{4}O_{4})</td>
<td>60.41 (60.35)</td>
</tr>
<tr>
<td>II</td>
<td>3-NO(_2)</td>
<td>61</td>
<td>253-55</td>
<td>(C_{16}H_{11}N_{5}O_{4}C)</td>
<td>56.35 (56.97)</td>
</tr>
<tr>
<td>2-Cl</td>
<td>5-Cl</td>
<td>63</td>
<td>243-245</td>
<td>(C_{16}H_{10}N_{4}O_{2}Cl)</td>
<td>53.22 (53.20)</td>
</tr>
<tr>
<td>3-Cl</td>
<td>4-CH(_3)</td>
<td>65</td>
<td>258-60</td>
<td>(C_{17}H_{13}N_{4}O_{2}Cl)</td>
<td>60.1 (59.92)</td>
</tr>
<tr>
<td>H</td>
<td>4-OCH(_3)</td>
<td>64</td>
<td>251-53</td>
<td>(C_{17}H_{14}N_{4}O_{3})</td>
<td>63.31 (63.35)</td>
</tr>
</tbody>
</table>
CHARACTERISATION DATA OF COMPOUNDS

\[
\begin{align*}
H_3C\overset{\text{O}}{\text{C}}\overset{\text{N}}{\text{N}}\overset{\text{O}}{\text{O}}\overset{-\text{N}}{\text{O}}\overset{\text{O}}{\text{O}}\overset{\text{N}}{\text{N}}\overset{\text{O}}{\text{O}}
\end{align*}
\]

3-(5\(^\prime\)-Aryl-4\(^\prime\)-N-acetyl-1\(^\prime\),3\(^\prime\),4\(^\prime\)-oxadiazo-2\(^\prime\)-yl)phenyl-5-methy-2-oxa-\(\Delta^4\)-1,3,4-oxadiazoles

Table No.26

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield</th>
<th>M.P</th>
<th>Molecular formula</th>
<th>Elemental Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td>°C</td>
<td></td>
<td>Calc &amp; (Found)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C%</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>50</td>
<td>138-40</td>
<td>C(<em>{19})H(</em>{16})N(_4)O(_4)</td>
<td>62.70</td>
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<td>(62.64)</td>
</tr>
<tr>
<td>H</td>
<td>4-Cl</td>
<td>53</td>
<td>105-07</td>
<td>C(<em>{19})H(</em>{15})N(_4)O(_4)Cl</td>
<td>57.29</td>
</tr>
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<td>(57.22)</td>
</tr>
<tr>
<td>H</td>
<td>4-OCH(_3)</td>
<td>51</td>
<td>195-97</td>
<td>C(<em>{20})H(</em>{18})N(_4)O(_3)</td>
<td>60.66</td>
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<td>(60.61)</td>
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<tr>
<td>H</td>
<td>2-OCH(_3)</td>
<td>50</td>
<td>102-03</td>
<td>C(<em>{20})H(</em>{18})N(_4)O(_3)</td>
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<td>(60.61)</td>
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<td>2-Cl</td>
<td>5-Cl</td>
<td>52</td>
<td>135-38</td>
<td>C(<em>{19})H(</em>{14})N(_4)O(_4)Cl(_2)</td>
<td>52.71</td>
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<td>(52.67)</td>
</tr>
<tr>
<td>3-Cl</td>
<td>4-CH(_3)</td>
<td>51</td>
<td>151-53</td>
<td>C(<em>{20})H(</em>{18})N(_4)O(_4)Cl</td>
<td>58.15</td>
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<td>(58.10)</td>
</tr>
<tr>
<td>H</td>
<td>4-NO(_2)</td>
<td>53</td>
<td>161-63</td>
<td>C(<em>{19})H(</em>{15})N(_5)O(_5)</td>
<td>55.70</td>
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<td>(55.75)</td>
</tr>
<tr>
<td>4-OH</td>
<td>2-OCH(_3)</td>
<td>50</td>
<td>167-69</td>
<td>C(<em>{20})H(</em>{18})N(_4)O(_6)</td>
<td>57.24</td>
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<td>(57.29)</td>
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</tbody>
</table>
CHARACTERISATION DATA OF COMPOUNDS

3-[(2'-oxo-1'-Indalo-3'-hydrazinocarbonyl) phenyl sydnone

Table No.27

<table>
<thead>
<tr>
<th>Yield %</th>
<th>M.P °C</th>
<th>Molecular formula</th>
<th>Elemental Analysis Calc &amp; (Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>65</td>
<td>281-83</td>
<td>C\textsubscript{15}H\textsubscript{11}N\textsubscript{5}O\textsubscript{3}</td>
<td>C% 58.25 (58.09)  H% 3.55 (3.60)  N% 22.65 (22.63)</td>
</tr>
</tbody>
</table>

CHARACTERISATION DATA OF COMPOUNDS

3-[(p(2'-oxo-1'-Indalo-3'-hydrazinocarbonyl)] phenyl oxadiazole

Table No.28

<table>
<thead>
<tr>
<th>Yield %</th>
<th>M.P °C</th>
<th>Molecular formula</th>
<th>Elemental Analysis Calc &amp; (Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>61</td>
<td>205-07</td>
<td>C\textsubscript{16}H\textsubscript{13}N\textsubscript{5}O\textsubscript{4}</td>
<td>C% 56.63 (56.60)  H% 3.83 (3.85)  N% 20.64 (20.65)</td>
</tr>
</tbody>
</table>
CHARACTERISATION DATA OF COMPOUNDS

4-Bromoderivatives of Schiffs bases of 3-[(p-hydrazinocarbonyl) phenyl] sydnone

Table No.29

<table>
<thead>
<tr>
<th>R</th>
<th>R'</th>
<th>Yield %</th>
<th>M.P.</th>
<th>Molecular Formula</th>
<th>Elemental analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>C%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
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<td>Calc</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H</td>
<td>4-NO₂</td>
<td>58</td>
<td>242-44</td>
<td>C₁₆H₁₀N₅O₄Br</td>
<td>46.15</td>
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<tr>
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<td></td>
<td></td>
<td>(46.12)</td>
</tr>
<tr>
<td>2-OCH₃</td>
<td>4-OH</td>
<td>60</td>
<td>250-52</td>
<td>C₁₇H₁₃N₅O₄Br</td>
<td>52.03</td>
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<td></td>
<td>(52.00)</td>
</tr>
<tr>
<td>H</td>
<td>3-NO₂</td>
<td>53</td>
<td>249-51</td>
<td>C₁₆H₁₀N₅O₄Br</td>
<td>46.17</td>
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<tr>
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<td></td>
<td>(46.13)</td>
</tr>
<tr>
<td>2-Cl</td>
<td>5-Cl</td>
<td>51</td>
<td>240-42</td>
<td>C₁₆H₉O₂Cl₂Br</td>
<td>43.63</td>
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<td>(43.58)</td>
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<td>3-Cl</td>
<td>4-OCH₃</td>
<td>50</td>
<td>245-47</td>
<td>C₁₇H₁₂N₄O₂Cl₂Br</td>
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<td>(48.65)</td>
</tr>
<tr>
<td>H</td>
<td>4-OCH₃</td>
<td>57</td>
<td>251-53</td>
<td>C₁₇H₁₃N₄O₃Br</td>
<td>50.82</td>
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<td>(50.78)</td>
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</table>
CHARACTERISATION DATA OF COMPOUNDS

4-[3',5'-disubstituted-pyrazol-1'yl-carbonyl] phenyl—hydrazines

Table No.30

<table>
<thead>
<tr>
<th>Sl.No.</th>
<th>R</th>
<th>R'</th>
<th>Yield %</th>
<th>M.P</th>
<th>Molecular Formula</th>
<th>Elemental analysis Calc &amp; (Found)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃</td>
<td>CH₃</td>
<td>56</td>
<td>168</td>
<td>C₁₂H₁₄N₄O</td>
<td>C% 58.25  (58.28)  H% 6.79  (6.70)  N% 27.18  (27.15)</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>C₆H₅</td>
<td>62</td>
<td>171</td>
<td>C₁₇H₁₆N₄O</td>
<td>C% 69.86  (69.81)  H% 5.47  (5.41)  N% 19.17  (19.18)</td>
</tr>
<tr>
<td>3</td>
<td>CH₃</td>
<td>C₆H₅</td>
<td>60</td>
<td>162</td>
<td>C₂₂H₁₈N₄O</td>
<td>C% 74.57  (74.58)  H% 5.08  (5.02)  N% 15.81  (15.78)</td>
</tr>
</tbody>
</table>
RESULTS OF ANTIMICROBIAL SCREENING

All these compounds tested for their antimicrobial activity exhibited moderate antibacterial activity against E. coli only. But they were more active against the fungi and in particular Pencillium, when compared with the drug Griseofulvin.

ANTIMICROBIAL ACTIVITY OF COMPOUNDS

Schiff bases of 3-p-(hydrazino carbonyl)phenyl sydnones

Table No.31

<table>
<thead>
<tr>
<th>Sl.No</th>
<th>R</th>
<th>R’</th>
<th>Antimicrobial activity</th>
<th>E.Coli</th>
<th>C.Bacillus</th>
<th>Pencillium</th>
<th>A.Candida</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
</tr>
<tr>
<td>1</td>
<td>H</td>
<td>4-NO₂</td>
<td></td>
<td>14</td>
<td>13</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>2</td>
<td>2-OCH₃</td>
<td>4-OH</td>
<td></td>
<td>15</td>
<td>12</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>3-NO₂</td>
<td></td>
<td>12</td>
<td>11</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>4</td>
<td>2-Cl</td>
<td>5-Cl</td>
<td></td>
<td>15</td>
<td>-</td>
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<td>4-CH₃</td>
<td></td>
<td>14</td>
<td>-</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>4-OCH₃</td>
<td></td>
<td>13</td>
<td>-</td>
<td>20</td>
<td>18</td>
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</tbody>
</table>

Reference

<table>
<thead>
<tr>
<th></th>
<th>E.coli</th>
<th>C.bacillus</th>
<th>Pencillium</th>
<th>A-candida</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>22</td>
<td>34</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>-</td>
<td>-</td>
<td>17</td>
<td>18</td>
</tr>
</tbody>
</table>
ANTIMICROBIAL ACTIVITY OF COMPOUNDS

3-(5'-Aryl-4'-N-acetyl-1',3',4'-oxadiazolin-2'-yl)phenyl-5-methy-2-oxa-1',3,4-oxadiazoles

Table No.32

<table>
<thead>
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<th>R</th>
<th>R'</th>
<th>Antimicrobial Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>E.Coli mm</td>
</tr>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>4-Cl</td>
<td>11</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>4-OC\textsubscript{3} \textsuperscript{2}</td>
<td>10</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>2-OC\textsubscript{3} \textsuperscript{2}</td>
<td>11</td>
</tr>
<tr>
<td>5</td>
<td>2-Cl</td>
<td>5-Cl</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>3-Cl</td>
<td>4-CH\textsubscript{3} \textsuperscript{2}</td>
<td>14</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>4-NO\textsubscript{2}</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>4-OH</td>
<td>2-OC\textsubscript{3} \textsuperscript{2}</td>
<td>13</td>
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</table>

ANTIMICROBIAL ACTIVITY OF COMPOUNDS

3-\{p(2'-oxo-1'-Indelo-3'-hydrazinocarbonyl)] phenyl sydnone.

Table No.33

<table>
<thead>
<tr>
<th>Antimicrobial Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.coli mm</td>
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<tr>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference</th>
<th>E.coli mm</th>
<th>C.bacillus mm</th>
<th>Penicillium mm</th>
<th>A.candida mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>22</td>
<td>34</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>-</td>
<td>-</td>
<td>17</td>
<td>18</td>
</tr>
</tbody>
</table>

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ANTIMICROBIAL ACTIVITY OF COMPOUNDS

3-[p(2'-oxo-1'-indalo-3'-hydrazinocarbonyl)] phenyl oxadiazoles.

Table No.34

<table>
<thead>
<tr>
<th></th>
<th>E. coli</th>
<th>C. bacillus</th>
<th>Penicillin</th>
<th>A. Candida</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
</tr>
<tr>
<td>12</td>
<td>10</td>
<td>13</td>
<td>19</td>
<td>17</td>
</tr>
</tbody>
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ANTIMICROBIAL ACTIVITY OF COMPOUNDS

4-Bromoderivatives of Schiff's bases of 3-[(p-hydrazinocarbonyl)] phenyl sydnones

Table No.35

<table>
<thead>
<tr>
<th>Sl. No.</th>
<th>R</th>
<th>R'</th>
<th>Antimicrobial Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E.Coli</td>
<td>C.bacillus</td>
<td>Penicillin</td>
</tr>
<tr>
<td></td>
<td>mm</td>
<td>mm</td>
<td>mm</td>
</tr>
<tr>
<td>1</td>
<td>H</td>
<td>4-NO₂</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>2-OCH₃</td>
<td>4-OH</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>3-NO₂</td>
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</tr>
<tr>
<td>4</td>
<td>2-Cl</td>
<td>5-Cl</td>
<td>15</td>
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<tr>
<td>5</td>
<td>3-Cl</td>
<td>4-CH₃</td>
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<tr>
<td>6</td>
<td>H</td>
<td>4-OCH₃</td>
<td>13</td>
</tr>
</tbody>
</table>

Reference

<table>
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<tr>
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<th>C.bacillus</th>
<th>Penicillin</th>
<th>A-candida</th>
</tr>
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<tbody>
<tr>
<td></td>
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<td>mm</td>
<td>mm</td>
<td>mm</td>
</tr>
<tr>
<td>Norfloxacin</td>
<td>22</td>
<td>34</td>
<td>-</td>
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</tr>
<tr>
<td>Griseofulvin</td>
<td>-</td>
<td>-</td>
<td>17</td>
<td>18</td>
</tr>
</tbody>
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ANTIMICROBIAL ACTIVITY OF COMPOUNDS

4-[3',5'-disubstituted-pyrazol-1'yl-carbonyl] phenyl-1-hydrazines.

Table No.36

<table>
<thead>
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<th>Sl.No.</th>
<th>R</th>
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<th>Antimicrobial Activity</th>
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</thead>
<tbody>
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<td></td>
<td></td>
<td></td>
<td>E.coli</td>
</tr>
<tr>
<td>1</td>
<td>CH₃</td>
<td>CH₃</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>C₆H₆</td>
<td>16</td>
</tr>
<tr>
<td>3</td>
<td>C₆H₆</td>
<td>C₆H₆</td>
<td>17</td>
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</tbody>
</table>

Reference

<table>
<thead>
<tr>
<th></th>
<th>E.coli</th>
<th>C.bacillus</th>
<th>Pencillium</th>
<th>A.candida</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norfloxacin</td>
<td>22</td>
<td>34</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Griseofulvin</td>
<td>-</td>
<td>-</td>
<td>17</td>
<td>18</td>
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REFERENCES

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   *Tohoku Yakka Diagaku Kenkyu Nempo*, 17, 43, 1970;

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23. Nakanishi, Susumu,


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