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# SYNTHESIS AND EVALUATION OF PYRAZOLINE DERIVATIVES AS ANTIBACTERIAL AGENTS

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## ABSTRACT

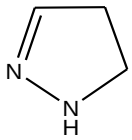
*Pyrazoline derivatives were found to exhibit broad spectrum of biological activity. Among all the pyrazolines, 2-pyrazoline has gained attraction and reported to possess wide range biological activities including antitumor, antibacterial, antifungal, antiviral, antiparasitic, anti-tubercular, anti-inflammatory, anti-diabetic, anesthetic, analgesic, insecticidal and potent selective activity such as nitric oxide synthase (NOS) inhibitors and cannaboid CB1 receptor antagonistic activity. Due to its wide range of biological activity, pyrazolines have received a considerable interest in the field of medicinal chemistry and drug discovery.*

## KEY WORDS

*Pyrazoline derivatives, Antiparasitic, anti-tubercular.*

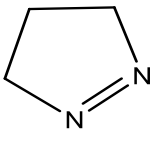
## INTRODUCTION

The Dihydro derivative of pyrazole is known as pyrazoline. It is having two adjacent nitrogen atoms, one endocyclic bond within the ring and basic in nature. The aromatic nature arises from the four electrons and the unshared pair of electrons on the –NH nitrogen. Pyrazolines are play important role in medicinal chemistry and also used as useful synthones in the field of organic, pharmaceutical and medicinal chemistry.

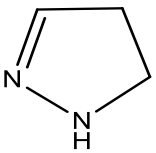



4,5-dihydro-2*H*-pyrazole

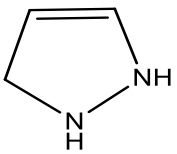
Three of them are possible structures depending on the position of double bond. These are 1-pyrazoline, 2-pyrazoline, 1, 3-pyrazoline out of these structures 1, 3-pyrazoline is most common.




1-pyrazoline

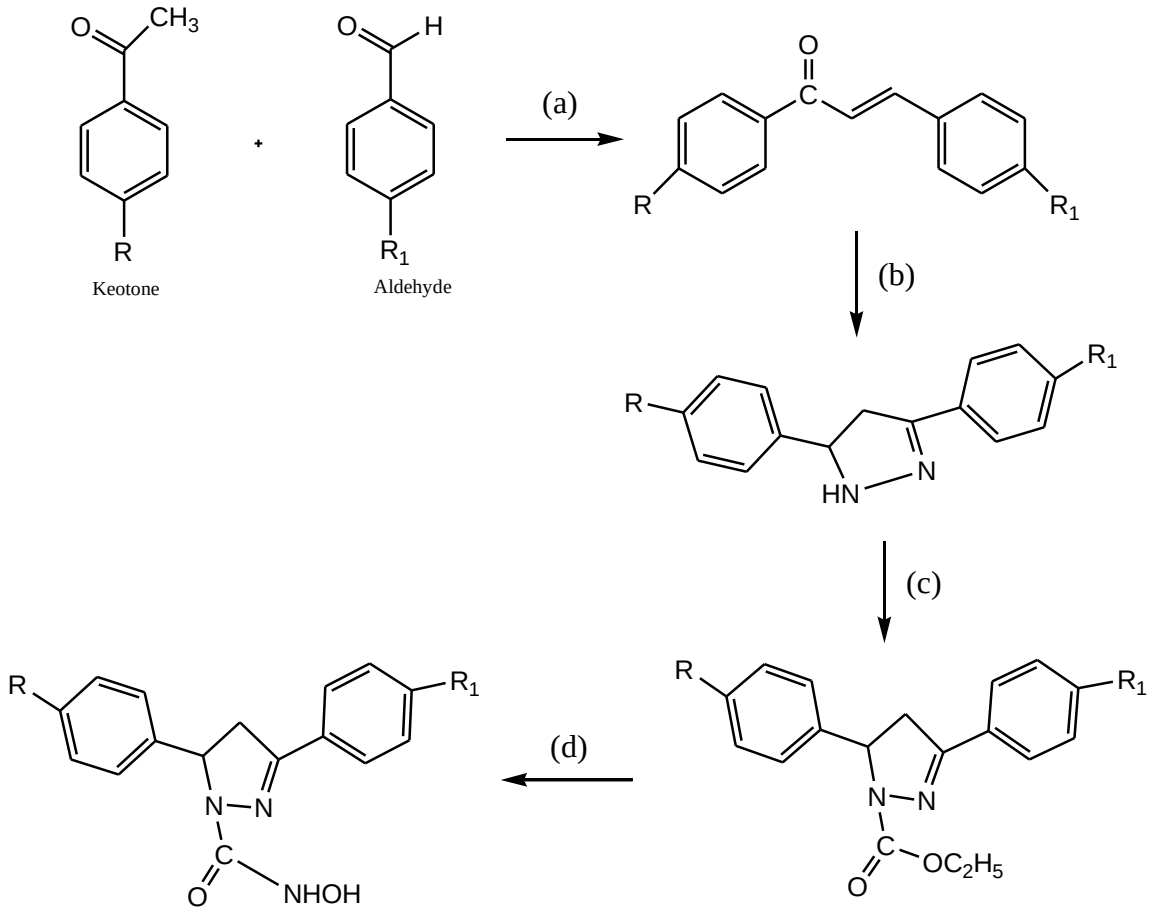



2-pyrazoline




1, 3-pyrazoline

**Scheme:**




**Reagent and conditions:**

(a) 40% NaOH, EtOH, 6-8h stirring,

(b) $NH_2NH_2H_2O$, EtOH, 75°C, 6-8 hrs reflux,

(c) Et3N, Ethylchloroformate, EtOH, 1-3 hrs reflux,

(d)Hydroxyl amine Hcl, KOH, $CH_3OH$, 70°C, 8-12 h, reflux.

## EXPERIMENTAL:

### Chemistry:

### Materials

Chemicals used in synthetic work were Aetophenone, *p*-chloroacetophenone, *p*-methoxy acetophenone, *p*-nitro-acetophenone, Benzaldehyde, *p*-Chloro-benzaldehyde, *p*-methoxy-benzaldehyde, *p*-nitro-benzaldehyde, hydrazine hydrate (80%), ethyl chloroformate, tri ethyl amine, potassium hydroxide, Hydroyl amine, ethanol, methanol, sodium hydroxide, chloroform, Hexane and ethyl acetate.

Chemicals were purchased from HIMEDIA Laboratories Pvt ltd, Mumbai. All the solvents used were Analytical grades were obtained from FINAR Chemicals ltd Ahmedabad.

### Instruments and apparatus

- All the reactions were performed in dried Borosil glass beakers, round bottom flasks, conical flasks.
- Pre-coated silica gel plates (MERCK) was used for TLC (Silica gel 60 $F_{254}$.)
- Compounds melting points were determined by open capillary method.
- JASCO UV Chamber was used for detection of spots in TLC.
- IR Spectra were recorded on BRUKER FTIR Spectrophotometer.

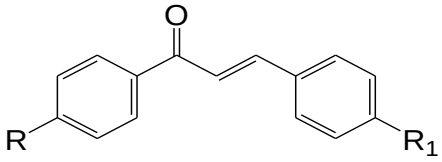
- $H^1$NMR spectra were recorded on BRUKER SPECTROSPIN-400MHz. Spectrometer using DMSO as solvent and TMS as an internal standard. The chemical shift data were expressed as values relative to TMS in ppm.
- MS data reports were recorded on GCMS – QP5050 SHIMADZU instrument.

**General procedure for the synthesis of chalcones ($A_1$-$A_6$):**

To a cold solution of solution of ethanol & sodium hydroxide (40%) was placed in a conical flask provided with a mechanical stirrer. Acetophenone (0.01M) was poured with constant stirring, then benzaldehyde (0.01M) was added drop wise to the solution. The progress of the reaction was monitored by TLC. The reaction mixture was kept at refrigerator overnight. Filter the product &washed with cold water until the washings were neutral to litmus and then with ice cold ethanol. The crude product was recrystallized from ethanol.[37]

The physical properties of prepared chalcones**($A_1$-$A_6$)** given in Table 1.

**Table: 1. The physical data for chalcone derivatives ($A_1$-$A_6$)**




| Code | R | $R_1$ | MF | M.W | % Yield | *$R_f$ | M.P°C |
|---|---|---|---|---|---|---|---|
| $A_1$ | -Cl | -H | $C_{15}H_{12}ClO$ | 242 | 75.2 | 0.58 | 80-83 {Lit. MP 120ºC}[38] |
| $A_2$ | -Cl | -Cl | $C_{15}H_{10}Cl_2O$ | 276 | 80.8 | 0.52 | 95-97 |
| $A_3$ | -H | - $OCH_3$ | $C_{15}H_{11}O_2$ | 238 | 76.5 | 0.6 | 112-114 {Lit M. P85°C}[39] |
| $A_4$ | -$OCH_3$ | -$OCH_3$ | $C_{17}H_{16}O_3$ | 268 | 72.3 | 0.54 | 120-123 {Lit MP160ºC}[39] |
| $A_5$ | - $NO_2$ | -H | $C_{15}H_{11}NO_3$ | 253 | 80.2 | 0.46 | 114-117 |
| $A_6$ | -Cl | -$NO_2$ | $C_{15}H_{10}ClNO_3$ | 287 | 78.6 | 0.58 | 123-125 |

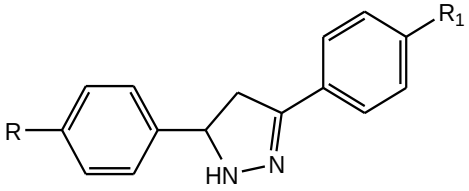
**Solvent system: Hexane: Ethylacetate (2:1)*

**Synthesis of Pyrazoline derivatives ($B_1$-$B_6$):**

To excess quantity of hydrazine hydrate added chalcone derivatives (**$A_1$-$A_6$**, 0.01mol) and refluxed for 6-8hrs.The progress of the reaction was monitored by TLC. The mixture were poured into crushed ice and the solid mass which separated out was filtered dried and recrystallized from appropriate solvents.[33]

The physical properties of pyrazoline derivatives(**$B_1$-$B_6$**) given in Table 2.

**Table: 2: The physical data of pyrazoline derivatives ($B_1$-$B_6$)**

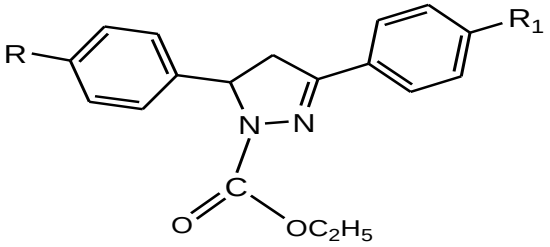



| Code | R | $R_1$ | MF | M.W | % Yield | *$R_f$ | M.P°C |
|---|---|---|---|---|---|---|---|
| $B_1$ | -Cl | -H | $C_{15}H_{13}N_2Cl$ | 256 | 72 | 0.46 | 121-125 {Lit MP} |
| $B_2$ | -Cl | -Cl | $C_{15}H_{12}N_2Cl$ | 290 | 76 | 0.48 | 132-136 |
| $B_3$ | -H | - $OCH_3$ | $C_{16}H_{16}N_2O_2$ | 252 | 70 | 0.52 | 141-145 |
| $B_4$ | -$OCH_3$ | -$OCH_3$ | $C_{17}H_{18}N_2O_2$ | 282 | 76 | 0.5 | 148-152 |
| $B_5$ | -$NO_2$ | -H | $C_{15}H_{13}N_3O_2$ | 262 | 60 | 0.43 | 158-162 |
| $B_6$ | -Cl | - $NO_2$ | $C_{15}H_{12}N_3ClO_2$ | 301 | 64 | 0.4 | 165-169 |

* *Solvent system: Hexane: Ethyl acetate (2:3).*

**Synthesis of ethyl 3,5-substituted-diphenyl-4,5-dihydro-pyrazole-1-carboxylate derivatives ($C_1$-$C_6$):**
The pyrazoline derivatives (**$B_1$-$B_6$**, 0.01mol) were added to ethylchloro formate (0.02mol), triethylamine (0.02mol) taken in methanol and stirred for 3-6 hours. The progress of the reaction was monitored by TLC. The resulting solid products were filtered dried and recrystallized from appropriate solvents[40].The products obtained from ethyl chloro formate are named as **$C_1$-$C_6$**. The physical properties of ethyl 3, 5- substituted-diphenyl- 4, 5- dihydro-pyrazole - 1 - carboxylate derivatives**($C_1$-$C_6$)** given in Table 3.

**Table: 3.** The physical data of ethyl 3, 5-substituted-diphenyl-4, 5-dihydro-pyrazole-1-carboxylate derivatives**($C_1$-$C_6$)**




| Code | R | $R_1$ | MF | M.W | % Yield | *$R_f$ | M.P.°C |
|---|---|---|---|---|---|---|---|
| $C_1$ | -Cl | -H | $C_{18}H_{17}N_2O_2$ | 328 | 64 | 0.52 | 142-145 |
| $C_2$ | -Cl | -Cl | $C_{18}H_{16}N_2ClO_2$ | 362 | 72.6 | 0.56 | 152-155 |
| $C_3$ | -H | -$OCH_3$ | $C_{19}H_{20}N_2O_3$ | 324 | 75.7 | 0.6 | 168-172 |
| $C_4$ | -$OCH_3$ | -$OCH_3$ | $C_{20}H_{22}N_2O_4$ | 354 | 69 | 0.58 | 172-176 |
| $C_5$ | -$NO_2$ | -H | $C_{18}H_{18}N_3O_4$ | 340 | 67.6 | 0.52 | 188-193 |
| $C_6$ | -Cl | -$NO_2$ | $C_{18}H_{16}N_3ClO_4$ | 373 | 63.8 | 0.49 | 191-195 |

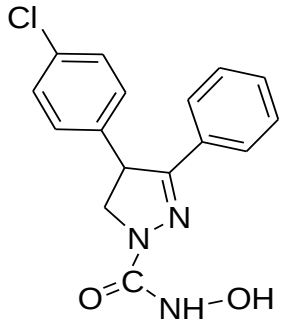
* *Solvent system: Hexane: Ethylacetate (3:2).*

**Synthesis of substituted Hydroxyl amine derivatives($D_1$-$D_6$):**

The ethylchloro formate derivatives (0.001mol) were dissolved in methanol and to that equimolar quantity of Hydroxyl amine(0.001mol) and potassium hydroxide (0.001mol) were and reflexed for overnight. The progress of the reaction was monitored by TLC. After completion of reaction, mixture was evaporated, solid obtained was washed with water to get the product and recrystallized from ethanol.

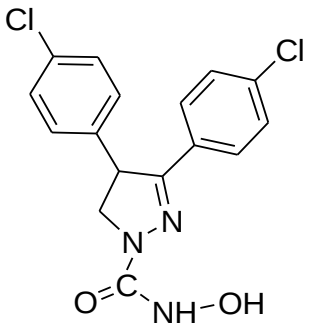
**4-(4-chlorophenyl)-4,5-dihydro-N-hydroxy-3-phenylpyrazole-1-carboxamide ($D_1$)**

| | |
|---|---|
| Molecular formula | $C_{16}H_{14}N_3ClO_2$ |
| Molecular weight | 315 |
| Solubility | Chloroform, $C_2H_5OH$ |
| Percentage yield | 54.6 |
| Melting Point | 175-178°C |
| $R_f$ value | 0.42 (Pet ether: Ethylacetate : Chloroform- 2:1:2) |



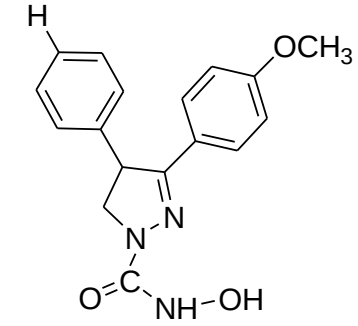

**3,4-bis(4-chlorophenyl)-4,5-dihydro-N-hydroxypyrazole-1-carboxamide ($D_2$)**

| | |
|---|---|
| Molecular formula | $C_{16}H_{13}N_3Cl_2O_2$ |
| Molecular weight | 350 |
| Solubility | Chloroform, $C_2H_5OH$ |
| Percentage yield | 52.4 |
| Melting Point | 182-186 |
| $R_f$ value | 0.42(Hexane: Ethylacetate: Chloroform- 2:1:2) |
| IR spectrum (KBr, $cm^{-1}$) | N-H stretch amide (3397 $cm^{-1}$), Ar-H stretch (3069 $cm^{-1}$), (C-H stretchin $CH_2$(2346 $cm^{-1}$), C=O stretch in amides (1746 $cm^{-1}$), C=N stretch (1561 $cm^{-1}$), N-Odef (1476 $cm^{-1}$), C-C def parade substituted (802 $cm^{-1}$). |
| $^1H$ NMR (DMSO, δ, ppm) | 8.4(d,1H,pyri-H),7.8(d,1H,Ar-H),7.4(d,1H,Ar-H),7.4(d,1H,pyri-H),7.2(d,1H,Ar-H),7.06(d,1H,Ar-H), 6(s,1H,NH), 4.9(t, 1H, pyr-H), 3.8(s,3H,$CH_3$). |
| Mass(m/z) | 374$[M+2]^+$ |




**4,5-dihydro-N-hydroxy-3-(4-methoxyphenyl)-4-phenylpyrazole-1-carboxamide ($D_3$)**

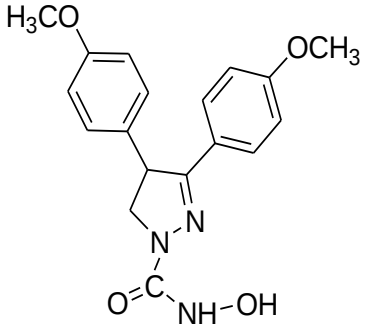
| | |
|---|---|
| Molecular formula | $C_{17}H_{17}N_3O_3$ |
| Molecular weight | 311 |
| Solubility | Chloroform, $C_2H_5OH$ |
| Percentage yield | 60 |
| Melting Point | 190-194°C |



$R_f$ value 3.2(Pet ether: Ethylacetate : Chloroform- 2:1:2)

**4,5-dihydro-N-hydroxy-3,4-bis(4-methoxyphenyl) pyrazole-1-carboxamide ($D_4$)**

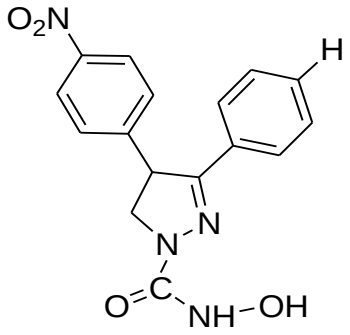
Molecular formula $C_{23}H_{22}N_4O_3$
Molecular weight 341
Solubility Chloroform, $C_2H_5OH$
Percentage yield 54.5
Melting Point 205-209°C



$R_f$ value 3.6(Pet ether: Ethylacetate : Chloroform- 2:1:2)

**4,5-dihydro-N-hydroxy-4-(4-nitrophenyl)-3-phenylpyrazole-1-carboxamide ($D_5$)**

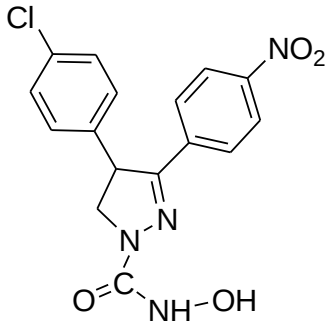
Molecular formula $C_{17}H_{14}N_2O_4$
Molecular weight 280
Solubility Chloroform, $C_2H_5OH$
Percentage yield 42
Melting Point 215-218°C



$R_f$ value 0.32(Hexane: Ethylacetate : Chloroform- 2:1:2

**4-(4-chlorophenyl)-4,5-dihydro-N-hydroxy-3-(4-nitrophenyl) pyrazole-1-carboxamide ($D_6$)**

Molecular formula $C_{16}H_{13}N_4ClO_4$
Molecular weight 360
Solubility Chloroform, $C_2H_5OH$
Percentage yield 39
Melting Point 218-222°C



$R_f$ value 0.38 (Pet ether: Ethylacetate : Chloroform- 2:1:2)

The compounds were synthesized as shown in Scheme. The chalcones **($A_1$-$A_6$)** were prepared through Claisen-Schmidt condensation of substituted acetophenones with substituted benzaldehydes in alcoholic sodium hydroxide by conventional method. Among the synthesized chalcones, **$A_2$** has given high yield (82.8%) and **$A_4$** given low yield (72.3%). The pyrazoline derivatives **($B_1$-$B_6$)** were synthesized by the reaction of excess hydrazine hydrate (80%) with **$A_1$-$A_6$** in ethanol by conventional method. Out of synthesized compounds **$B_2$ &** $B_4$ has given high yield (76.0%) and **$B_5$** has given low yield (60. 0%).The synthesized Pyrazolines derivatives were treated with ethylchloro formate and the resulted compounds **($C_1$-$C_6$)** were then reacted with

Hydroxylamine yielding pyrazoline derivatives **($D_1$-$D_6$)**. All the newly synthesized final products were characterized based on their physical and spectral data.

**Characterization data**

The purified final compounds were characterized as pyrazoline derivatives on the basis of their spectral data (IR, $^1$H NMR, and Mass).

**IR spectrum** of the respective compound $D_{10}$ has shown characteristic peak of N-H stretch (3397 $cm^{-1}$), aromatic C-H stretch (3069 $cm^{-1}$), C-O stretch in amide (1746 $cm^{-1}$), C=N stretch (1576 $cm^{-1}$) and N-O bending (1476 $cm^{-1}$).

**$^1$H NMR spectrum** (DMSO, δ ppm) of the respective compound **$D_{10}$** shows a specific pattern of signals. It shows singlet at 6.1 which is corresponds to the one proton of amine group, seven doublets at 8.5 which corresponds to the one proton of pyridine, 8.4, 8.1, 7.9 corresponds to three protons on aromatic ring,7.4 corresponds to one proton on pyridine ring, 3.94 corresponds at one proton on pyridine ring and 3.7 corresponds to the one proton on pyrazole ring. One triplet at 4.9 corresponds to one proton on pyrazole ring.

Further, presence of molecular ion peak [M+2] at m/e 424 with **40%** abundance in mass spectrum confirms the structure of **$D_{10}$**

The peaks obtained in the IR $^1$NMR and Mass spectra confirmed the structure of compound **$D_{10}$** as 3,5-bis(4-nitrophenyl)-N-(pyridin-2-yl)-4,5-dihydro-1H-pyrazole-1-carboxamide.

**ANTIBACTERIAL ACTIVITY**

All the six derivatives **($D_1$-$D_6$)** were screened for their antibacterial activity by following standard protocol against different gram +ve, gram –ve bacteria and compared with the standard (given in Table 4). Results of the study indicated that all compounds exhibited mild to moderate antibacterial activity against the test organisms. The degree of inhibition varied with test compound and test bacterium.

All the compounds showed mild activity against B. subtilis, K. pneumonia and **$D_9$, $D_{10}$** compounds showed moderate activity against S. aureus, **$D_8$, $D_{10}$** compounds showed moderate activity against E. Coli. Among all derivatives **($D_1$-$D_{10}$), $D_{10}$**compound is having potent activity against bacteria, the increased potency may be the presence electron withdrawing group (-$NO_2$) on $R_1$, $R_2$ position of the phenyl ring. Apart from nitro groups, the mild electron withdrawing group (-Cl) also influenced and showed significant activity but the phenyl ring substituted with electron donating groups (-$OCH_3$) showed decrease in activity.

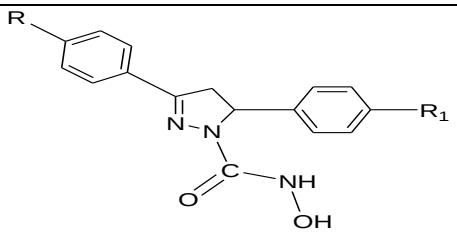
**ANTIFUNGAL ACTIVITY**

All the six derivatives **($D_1$-$D_6$)** were screened for their antifungal activity by following standard protocol against different pathogenic fungal organisms and compared with the standard (given in Table 5). Results of antifungal study indicated that all compounds exhibited mild to moderate antifungal activity against the test organisms. The degree of inhibition varied with test compound and test fungal.

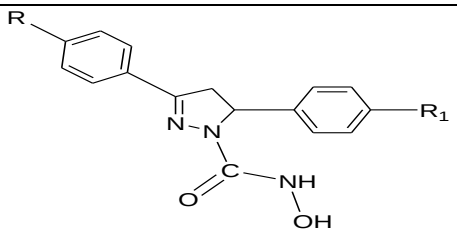
All the compounds showed mild activity against B. subtilis, K. pneumonia and **$D_9$, $D_{10}$** compounds showed moderate activity against S. aureus, **$D_8$, $D_{10}$** showed moderate activity against E. Coli. Among all derivatives **($D_1$-$D_6$),** compound **$D_{10}$**were exhibited potent activity against bacteria, the increased potency may be the presence electron withdrawing group (-$NO_2$) on $R_1$, $R_2$ position of the phenyl ring. Apart from nitro groups, the mild electron withdrawing group (-Cl) also influenced and showed significant activity but the phenyl ring substituted with electron donating groups (-$OCH_3$) showed decrease in activity.

All the compounds mild activity against albicans, Malassezia furfur and **$D_8$, $D_{10}$**showed moderate activity against A. niger. Among all the derivatives **($D_1$-$D_6$)**, compound **$D_{10}$**were shown potent activity, the increased potency may be the presence electron withdrawing group (-$NO_2$) on $R_1$, $R_2$ position of the phenyl ring. Apart from nitro groups, the mild electron withdrawing group (-Cl) also influenced and showed significant activity but the phenyl ring substituted with electron donating groups (-$OCH_3$) showed decrease in activity.

**Table 4: Antibacterial activity of compounds $D_1$-$D_6$ (MIC)**




| Code | $R_1$ | $R_2$ | *B.subtilis* | | *S.aureus* | | *E.coli* | | *K. pneumonia* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *µg/ml* | *µM* | *µg/ml* | *µM* | *µg/ml* | *µM* | *µg/ml* | *µM* |
| **$D_1$** | -H | -H | 195 | 0.56 | 150 | 0.43 | 175 | 0.51 | 225 | 0.67 |
| **$D_2$** | -H | $-OCH_3$ | 180 | 0.48 | 130 | 0.34 | 160 | 0.42 | 190 | 0.51 |
| **$D_3$** | $-OCH_3$ | - H | 150 | 0.38 | 125 | 0.32 | 135 | 0.34 | 170 | 0.43 |
| **$D_4$** | $-OCH_3$ | $-OCH_3$ | 185 | 0.45 | 150 | 0.37 | 150 | 0.37 | 200 | 0.49 |
| **$D_5$** | -Cl | $-OCH_3$ | 115 | 0.27 | 125 | 0.37 | 100 | 0.24 | 150 | 0.36 |
| **$D_6$** | $-CH_3$ | $-NO_2$ | 120 | 0.28 | 140 | 0.33 | 115 | 0.27 | 160 | 0.38 |
| **$D_7$** | -H | $-NO_2$ | 150 | 0.38 | 125 | 0.32 | 135 | 0.34 | 170 | 0.43 |
| **$D_8$** | -Cl | $-NO_2$ | 120 | 0.29 | 110 | 0.26 | 95 | 0.22 | 135 | 0.32 |
| **$D_9$** | $-NO_2$ | -Cl | 115 | 0.23 | 90 | 0.21 | 100 | 0.23 | 120 | 0.28 |
| **$D_{10}$** | $-NO_2$ | $-NO_2$ | 90 | 0.28 | 85 | 0.19 | 75 | 0.17 | 115 | 0.26 |
| **Std** | Ciprofloxacin | | 10 | 0.03 | 15 | 0.04 | 10 | 0.03 | 20 | 0.06 |




| Code | $R_1$ | $R_2$ | *B.subtilis* | | *S.aureus* | | *E.coli* | | *K. pneumonia* | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | *µg/ml* | *µM* | *µg/ml* | *µM* | *µg/ml* | *µM* | *µg/ml* | *µM* |
| **$D_1$** | -H | -H | 195 | 0.56 | 150 | 0.43 | 175 | 0.51 | 225 | 0.67 |
| **$D_2$** | -H | $-OCH_3$ | 180 | 0.48 | 130 | 0.34 | 160 | 0.42 | 190 | 0.51 |
| **$D_3$** | $-OCH_3$ | - H | 150 | 0.38 | 125 | 0.32 | 135 | 0.34 | 170 | 0.43 |
| **$D_4$** | $-OCH_3$ | $-OCH_3$ | 185 | 0.45 | 150 | 0.37 | 150 | 0.37 | 200 | 0.49 |
| **$D_5$** | -Cl | -Cl | 115 | 0.27 | 125 | 0.37 | 100 | 0.24 | 150 | 0.36 |
| **$D_6$** | $-CH_3$ | $-NO_2$ | 120 | 0.28 | 140 | 0.33 | 115 | 0.27 | 160 | 0.38 |
| **$D_7$** | -H | $-NO_2$ | 150 | 0.38 | 125 | 0.32 | 135 | 0.34 | 170 | 0.43 |
| **$D_8$** | -Cl | $-NO_2$ | 120 | 0.29 | 110 | 0.26 | 95 | 0.22 | 135 | 0.32 |
| **$D_9$** | $-NO_2$ | -Cl | 115 | 0.23 | 90 | 0.21 | 100 | 0.23 | 120 | 0.28 |
| **$D_{10}$** | $-NO_2$ | $-NO_2$ | 90 | 0.28 | 85 | 0.19 | 75 | 0.17 | 115 | 0.26 |
| **Std** | Ciprofloxacin | | 10 | 0.03 | 15 | 0.04 | 10 | 0.03 | 20 | 0.06 |

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