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SYNTHESIS AND EVALUATION OF PYRAZOLINE DERIVATIVES AS ANTIBACTERIAL AGENTS

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ABSTRACT

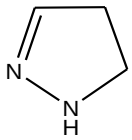
Pyrazoline derivatives were found to exhibit broad spectrum of biological activity. Among all the pyrazolines, 2-pyrazoline has gained attraction and reported to possess wide range biological activities including antitumor, antibacterial, antifungal, antiviral, antiparasitic, anti-tubercular, anti-inflammatory, 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.

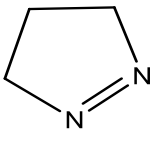
INTRODUCTION

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.

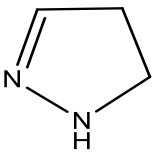


4,5-dihydro-2*H*-pyrazole

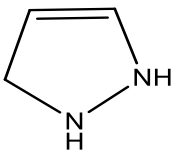
Three of them are possible structures depending on the position of double bond. These are 1-pyrazoline, 2-pyrazoline, 1, 3-pyrazoline out of these structures 1, 3-pyrazoline is most common.



1-pyrazoline

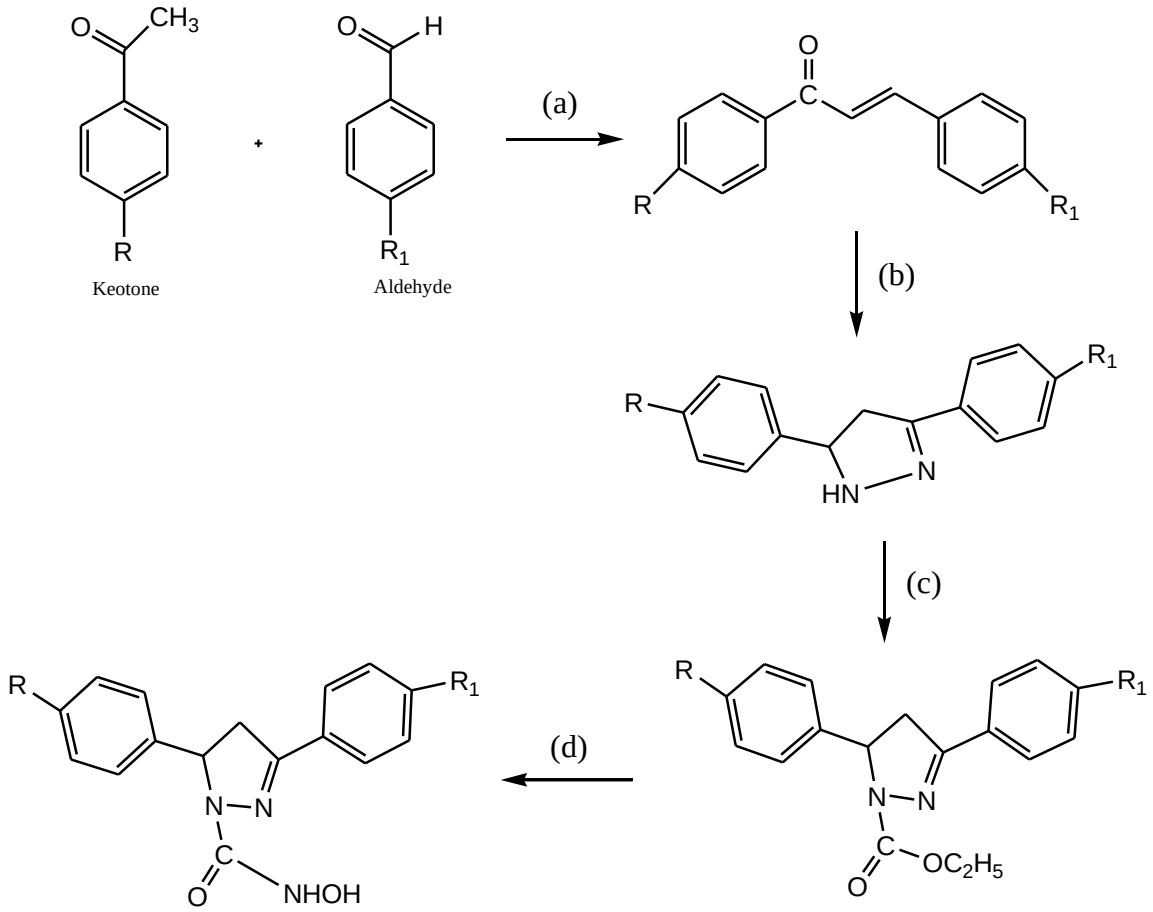


2-pyrazoline



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.

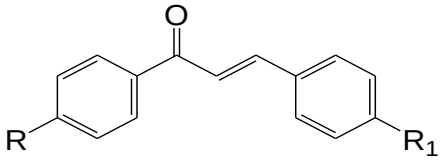
- H^1NMR spectra were recorded on BRUKER SPECTROSPIN-400MHz. Spectrometer using DMSO as solvent and TMS as an internal standard. The chemical shift data were expressed as values relative to TMS in ppm.
- MS data reports were recorded on GCMS – QP5050 SHIMADZU instrument.

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

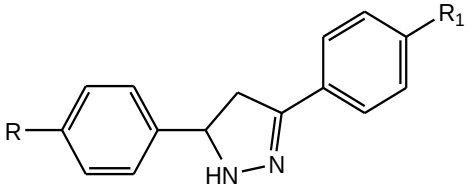
**Solvent system: Hexane: Ethylacetate (2:1)*

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)

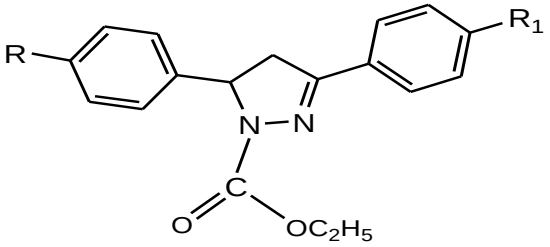


Code	R	R_1	MF	M.W	% Yield	*R_f	M.P°C
B_1	-Cl	-H	$C_{15}H_{13}N_2Cl$	256	72	0.46	121-125 {Lit MP}
B_2	-Cl	-Cl	$C_{15}H_{12}N_2Cl$	290	76	0.48	132-136
B_3	-H	- OCH_3	$C_{16}H_{16}N_2O_2$	252	70	0.52	141-145
B_4	-OCH_3	-OCH_3	$C_{17}H_{18}N_2O_2$	282	76	0.5	148-152
B_5	-NO_2	-H	$C_{15}H_{13}N_3O_2$	262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

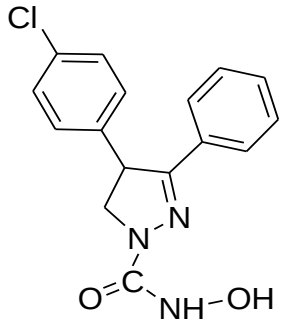
* *Solvent system: Hexane: Ethylacetate (3:2).*

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.

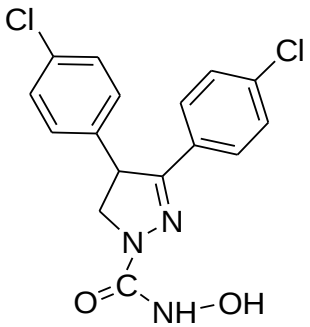
4-(4-chlorophenyl)-4,5-dihydro-N-hydroxy-3-phenylpyrazole-1-carboxamide (D_1)

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)



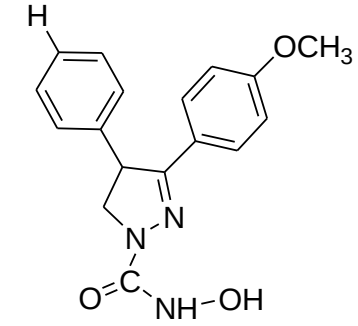
3,4-bis(4-chlorophenyl)-4,5-dihydro-N-hydroxypyrazole-1-carboxamide (D_2)

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)

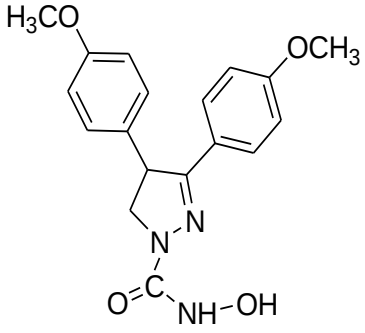
Molecular formula	$C_{17}H_{17}N_3O_3$
Molecular weight	311
Solubility	Chloroform, C_2H_5OH
Percentage yield	60
Melting Point	190-194°C



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)

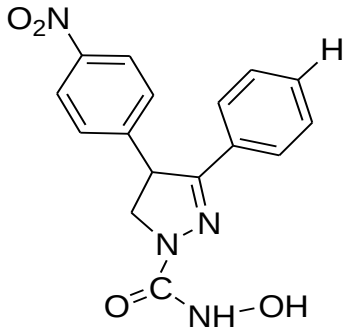
Molecular formula $C_{23}H_{22}N_4O_3$
Molecular weight 341
Solubility Chloroform, C_2H_5OH
Percentage yield 54.5
Melting Point 205-209°C



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)

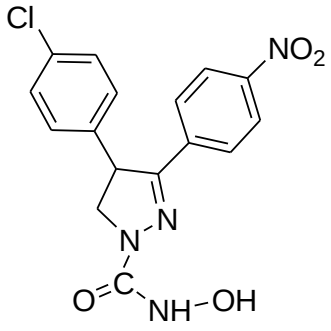
Molecular formula $C_{17}H_{14}N_2O_4$
Molecular weight 280
Solubility Chloroform, C_2H_5OH
Percentage yield 42
Melting Point 215-218°C



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.

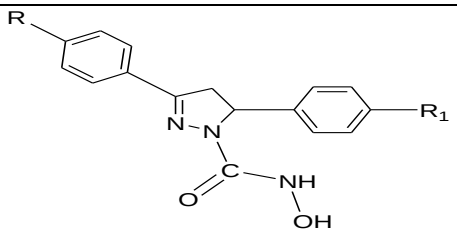
ANTIFUNGAL ACTIVITY

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.

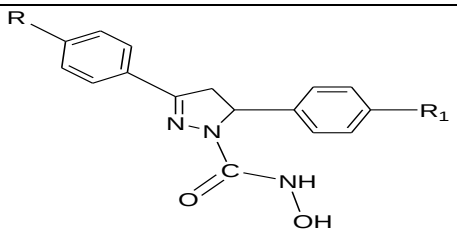
All the compounds showed mild activity against B. subtilis, K. pneumonia and **D_9, D_{10}** compounds showed moderate activity against S. aureus, **D_8, D_{10}** showed moderate activity against E. Coli. Among all derivatives **(D_1-D_6),** compound **D_{10}**were exhibited potent activity against bacteria, 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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