Design synthesis and biological evaluation of some novel hybrid aurones

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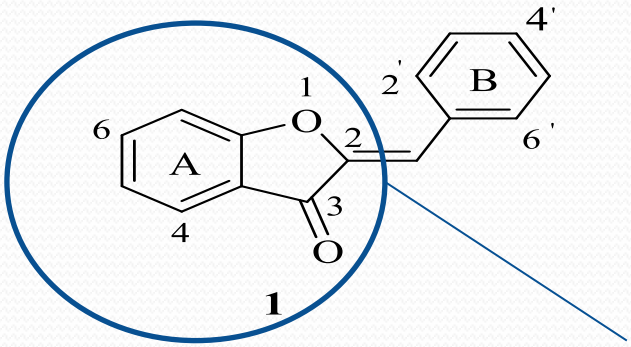
AURONES

❖Aurones are the yellow coloured compounds having 2-benzylidenebenzofuran-3-one structure (1) and are commonly known as 2-benzylidenecoumaran-3-ones.



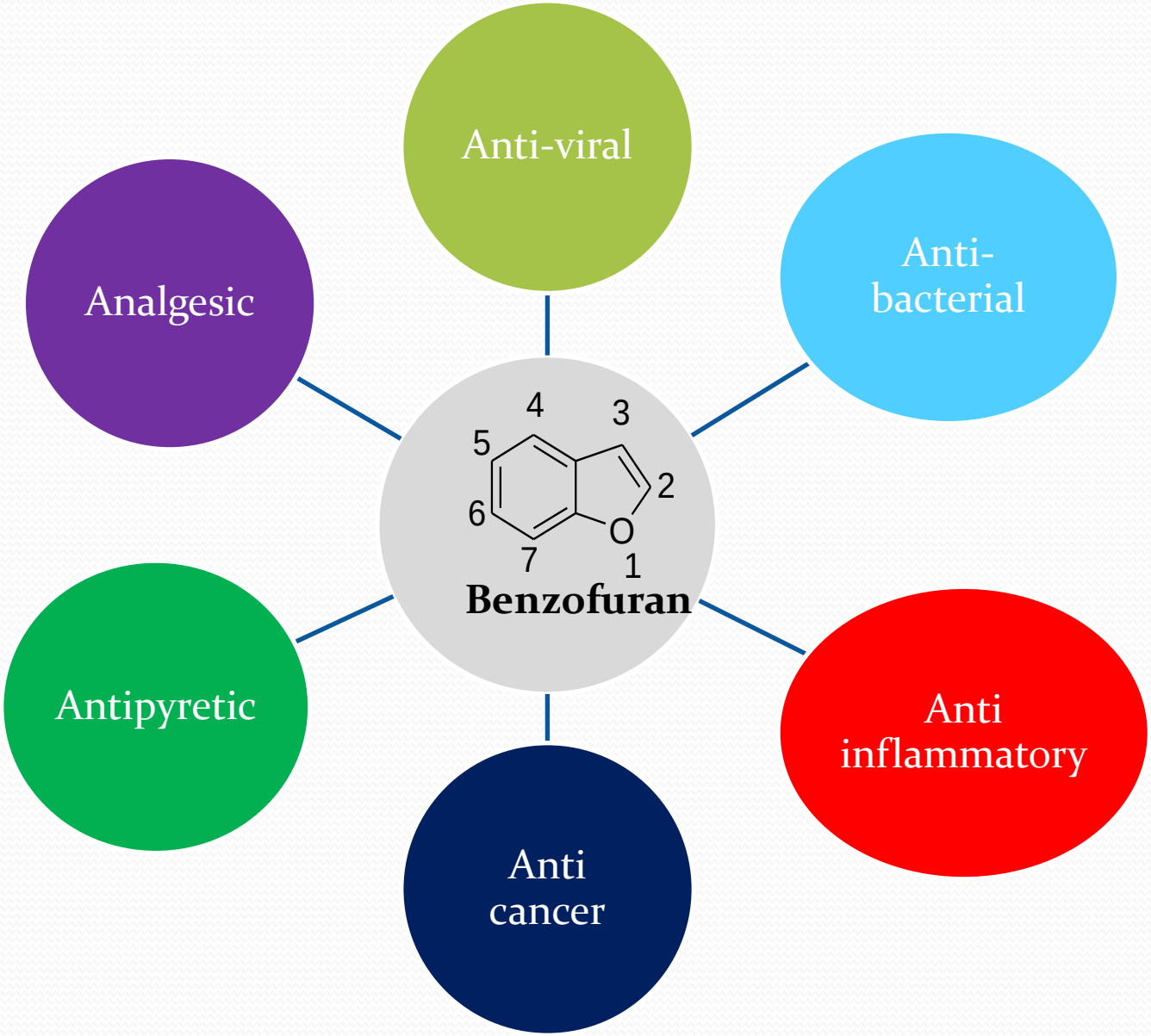
Benzofuran

❖They constitute a subclass of naturally occurring flavonoids which are structurally isomeric to flavones and biogenetically related to chalcones.

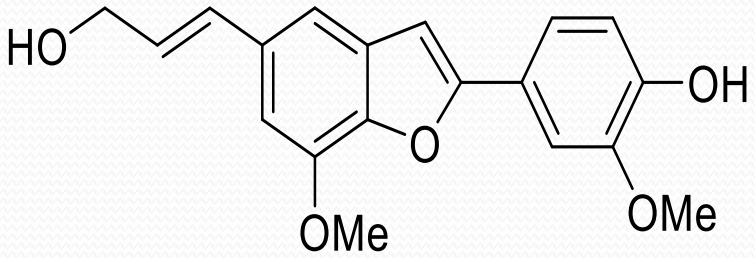
❖Are responsible for imparting beautiful yellow colours to some of the flower petals and fruits.

❖ They have been shown to have Z-stereochemistry.

PHARMACOLOGICAL ACTIVITIES OF BENZOFURAN ANALOGS



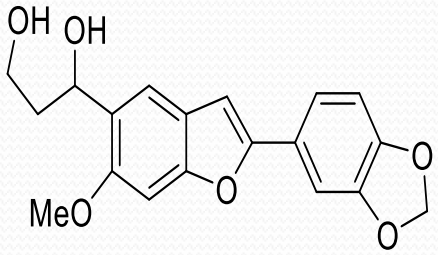
❑ Most recognized benzofuran drug



Ailanthoidol

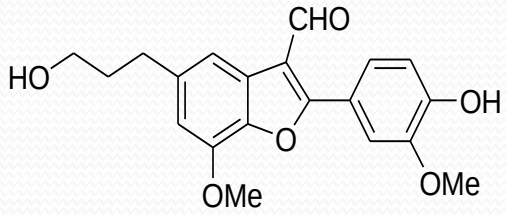
- ❖ Anticancer
- ❖ Antiviral
- ❖ Immunosuppressive
- ❖ Antioxidant
- ❖ Antifungal
- ❖ Antifeedant

- **Benzofuran is an integral part of many of natural products which are physiologically and pharmacologically active.**



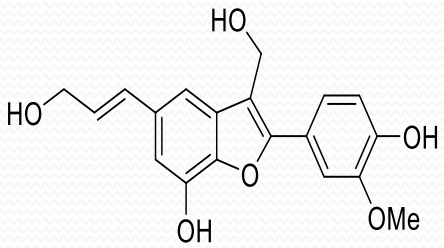
Machicendiol

Traditional medicine for asthma and ulcer



XH14

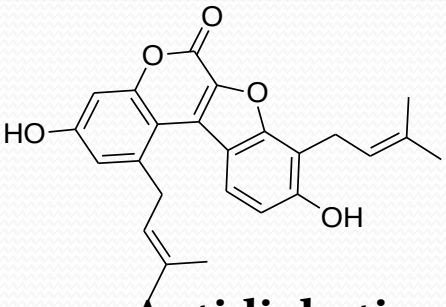
Antagonist against adenosine receptor



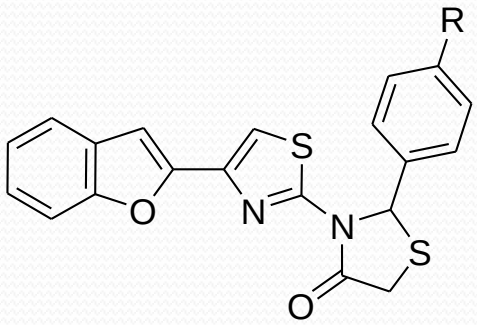
Vibsanol

Fish poison

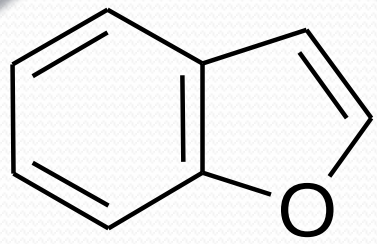
BIOLOGICALLY ACTIVE BENZOFURAN DERIVATIVES



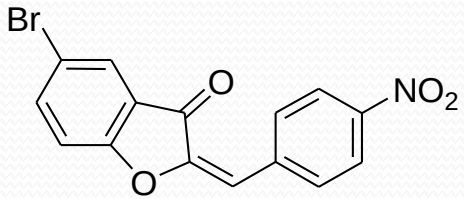
Antidiabetic



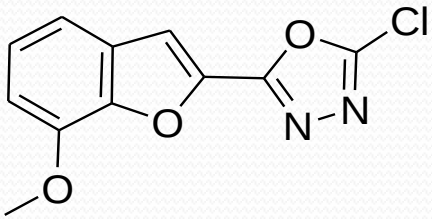
Antimicrobial



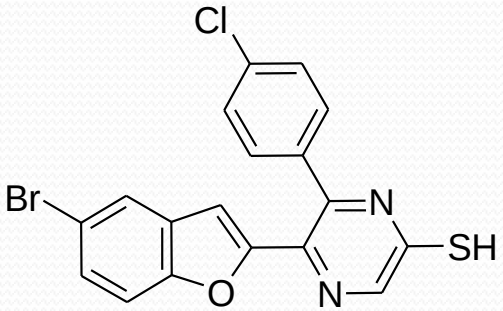
Benzofuran



Anticancer

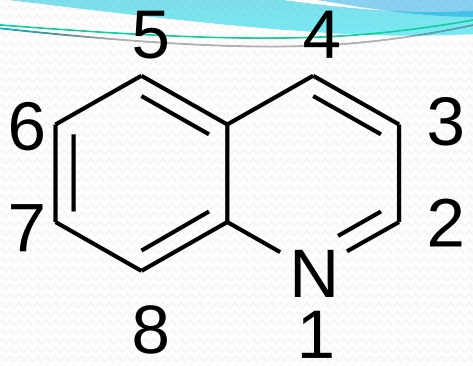


Antibacterial



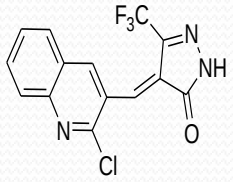
Anti-Inflammatory

QUINOLINE

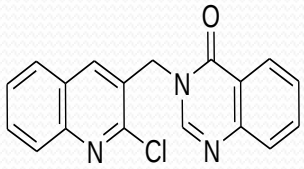


- 1st isolated from cinchona tree
- Pharmacologically active molecule

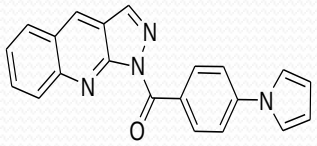
BIOLOGICALLY ACTIVE QUINOLINE DERIVATIVES



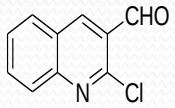
Antimalerial



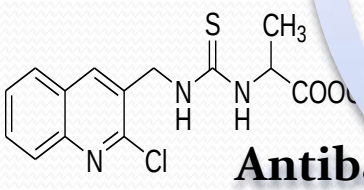
Antimicrobial



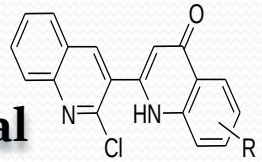
Antitubercular



Quinoline

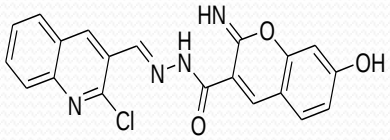


Antibacterial



Antifungal

Analgesic



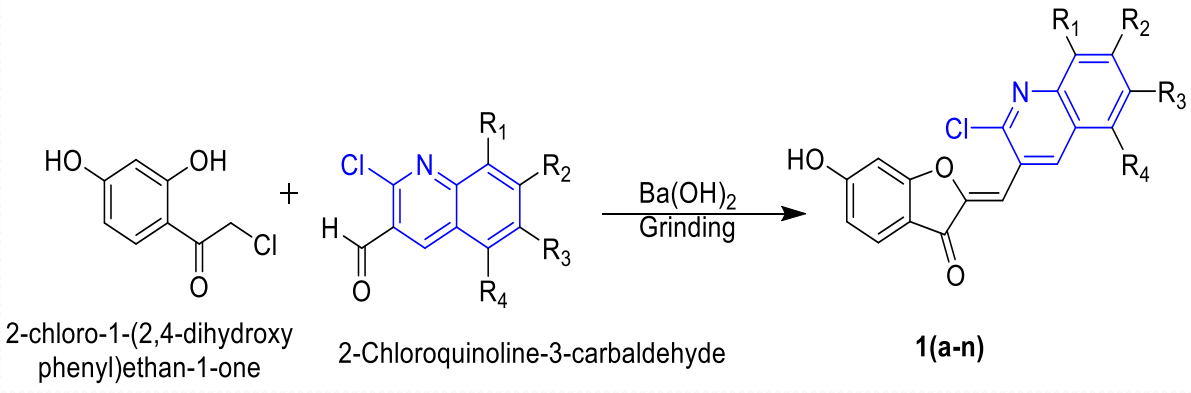
OBJECTIVES

❖ The spectrum of biological activities of this class of compounds has not been extensively studied so far. The existing data on the bioactivity of natural and synthetic aurones i.e. 2-benzylidenebenzofuran-3-one is very promising. So these heterocyclic compounds can be considered as an attractive scaffold for drug design and development.

❖ Pyrazole, quinoline, Coumarin, Chromone nuclei are the well known for their potency in various biological activities and are the part of many existing drugs.

❖ It is proposed to adopt a hybrid approach to adopt above mentioned nuclei in the aurone skeleton with a hope to have synergized action of both the unit towards antibacterial potential of the compound synthesized.

Synthesis of quinoline based aurone anologues



2-chloro-1-(2,4-dihydroxy phenyl)ethan-1-one

2-Chloroquinoline-3-carbaldehyde

1(a-n)

Comp.	R_1	R_2	R_3	R_4
1a	H	H	H	H
1b	CH_3	H	H	H
1c	H	CH_3	H	H
1d	H	H	H	CH_3
1e	CH_3	CH_3	H	H
1f	CH_3	H	CH_3	H
1g	H	CH_3	H	CH_3
1h	H	H	OCH_3	H
1i	H	OCH_3	H	H
1j	H	Cl	H	H
1k	H	H	F	H
1l	H	H	Br	H
1m	H	H	Bu	H
1n	C_2H_5	H	H	H

Optimization of reaction conditions

Sr.No.	Catalyst	Time	Temperature	Yield (%)
1	KOH/Grinding	1h	Room temperature	45-60
2	NaOH/Grinding	1h	Room temperature	40-60
3	KOH/Ethanol	8h	Refluxing	70-85
4	Al_2O_3/CH_2Cl_2	16h	Refluxing	No reaction
5	$Ba(OH)_2$/Ethanol	8h	Refluxing	No reaction
6	$Ba(OH)_2$/DMSO	16h	Room temperature	65-80
7	$Ba(OH)_2$/DMSO	4h	90 ^oC	65-85
8	K_2CO_3/Water	12h	Room temperature	60-70
9	K_2CO_3/Water	6h	60 ^oC	60-70
10	Al_2O_3/Grinding	1h	Room temperature	No reaction
11	$CaCl_2$/Grinding	1h	Room temperature	No reaction
12	$ZnCl_2$/Grinding	1h	Room temperature	No reaction
13	Activated $Ba(OH)_2$/Grinding	15+10 min	Room temperature	72-93

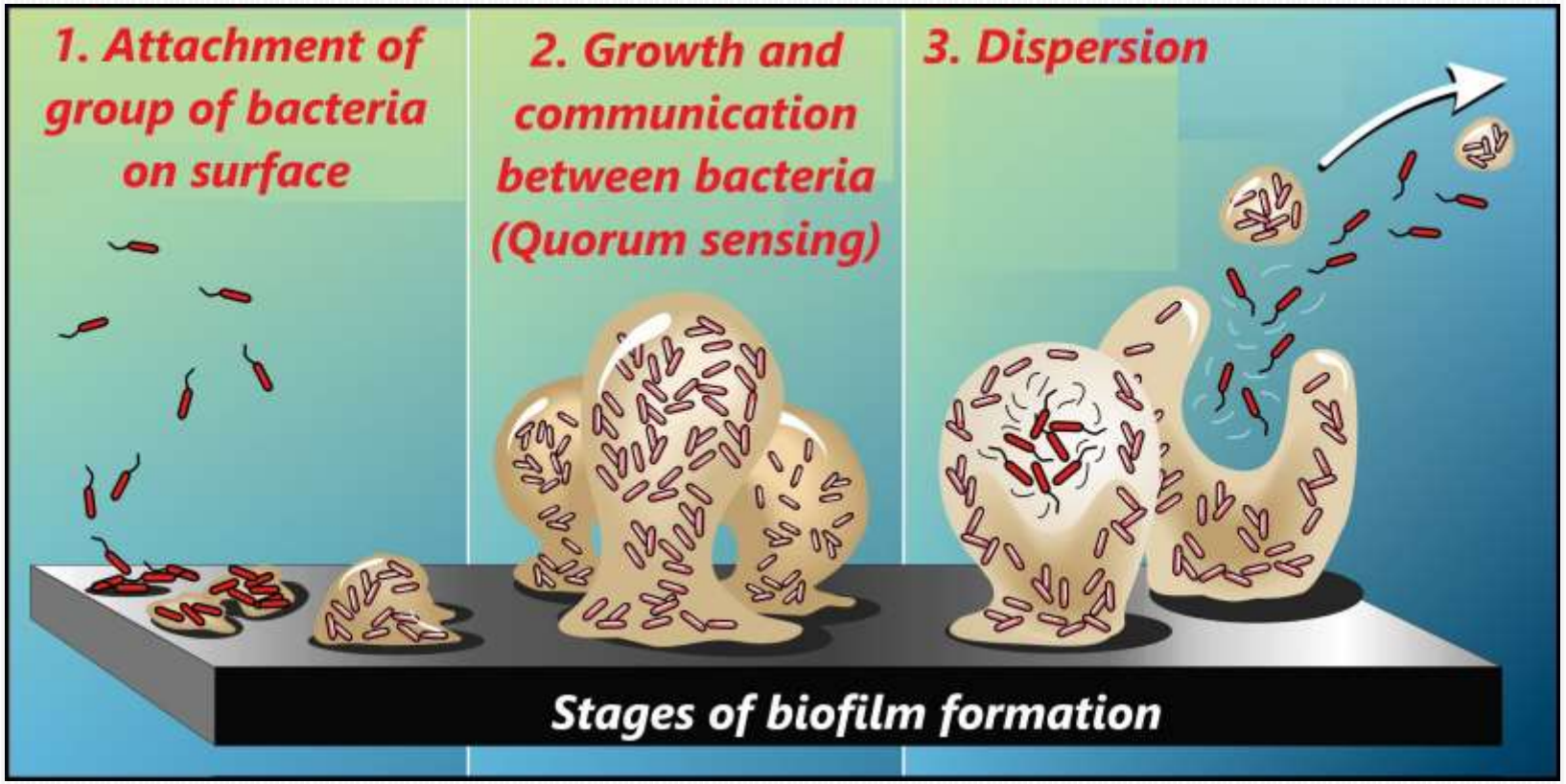
Biological Activity

Table :- In vitro antibacterial and antifungal activities with minimum inhibitory concentration (mg/mL) of compounds **6(a-n)**.

Compound	*B. subtilis*	*S. aureus*	*K. pneumoniae*	*M. smegmatis*	*F. oxysporum*	*C. albicans*
1a	0.020	1.25	-	0.625	0.625	-
1b	1.25	2.5	-	-	-	-
1c	1.25	2.5	-	-	-	-
1d	1.25	1.25	-	-	-	-
1e	0.625	1.25	-	-	-	-
1f	1.25	1.25	-	-	-	-
1g	0.156	2.5	-	0.078	0.313	0.078
1h	1.25	1.25	0.625	-	-	-
1i	1.25	1.25	-	0.625	-	-
1j	1.25	1.25	0.625	-	-	0.156
1k	1.25	2.5	-	-	-	0.156
1l	0.313	1.25	-	-	-	0.156
1m	1.25	2.5	-	-	-	-
1n	1.25	1.25	-	0.625	-	-

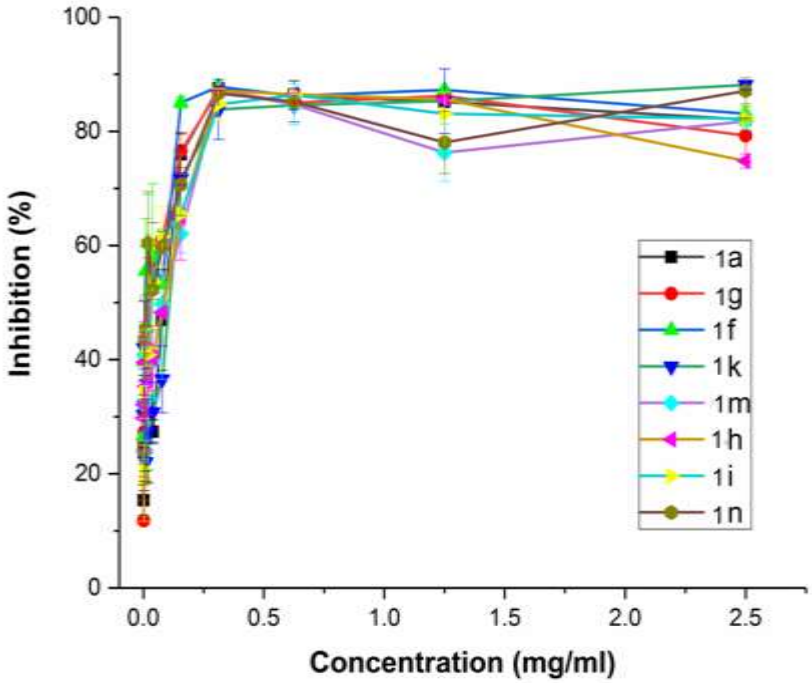
– no inhibition

Bacterial Biofilms :- The City of Microbes

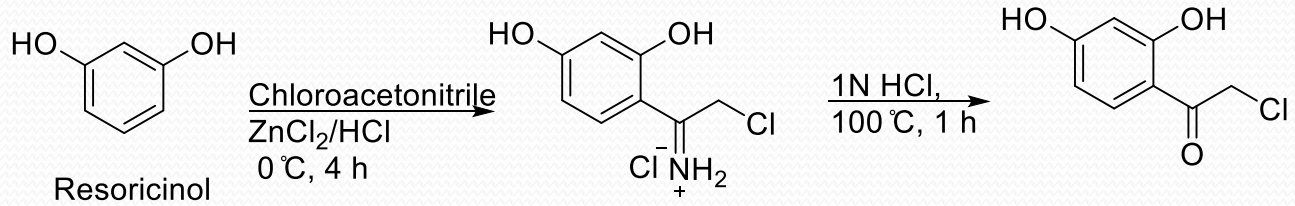


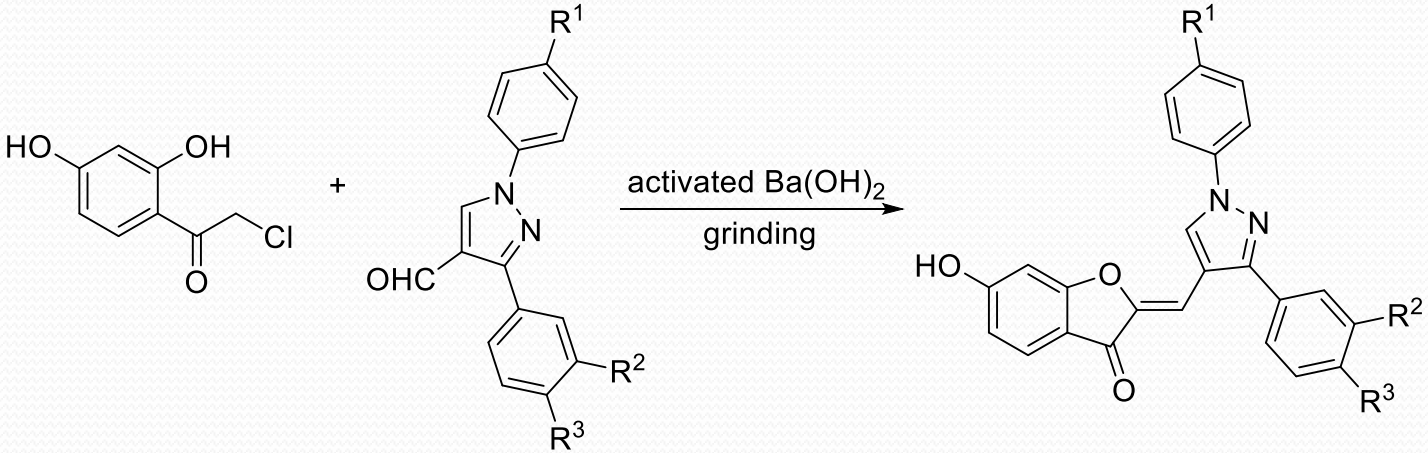
- Out of the all test compounds **1a**, **1g**, **1f**, **1k**, **1m**, **1h**, **1i** and **1n** showed the negative impact on violacein production. Even at very low concentration, test compound have significantly reduced (~50%) violacein production describing their potential anti quorum sensing or anti biofilm activity.

- All these results clearly indicate about the potential of these molecules as antibacterial, antifungal and quorum sensing inhibitors.



SYNTHESIS OF PYRAZOLE BASED AURONE ANALOGUES





2(a-n)

2a:R^1 =H, R^2 =H, R^3 =H, **2b**:R^1 =H, R^2 =H, R^3 =CH_3, **2c**:R^1 =H, R^2 =H, R^3 =OCH_3, **2d**:R^1 =H, R^2 =H, R^3 =Cl, **2e**:R^1 =H, R^2 =H, R^3 =Br, **2f**:R^1 =H, R^2 =NO_2, R^3 =H, **2g**:R^1 =H, R^2 =H, R^3 =NO_2, **2h**: R^1 =NO_2, R^2 =H, R^3 =H,**2i**:R^1 =NO_2, R^2 =H, R^3 =CH_3, **2j**:R^1 =NO_2, R^2 =H, R^3 =OCH_3, **2k**:R^1 =NO_2, R^2 =H, R^3 =Cl, **2l**:R^1 =NO_2, R^2 =H,R^3 =Br, **2m**:R^1 =NO_2, R^2 =NO_2, R^3 =H, **2n**:R^1 =NO_2, R^2 =H, R^3 =NO_2

Table. Comparison of the results of catalyst used for the synthesis of pyrazole based aurones as per scheme -B

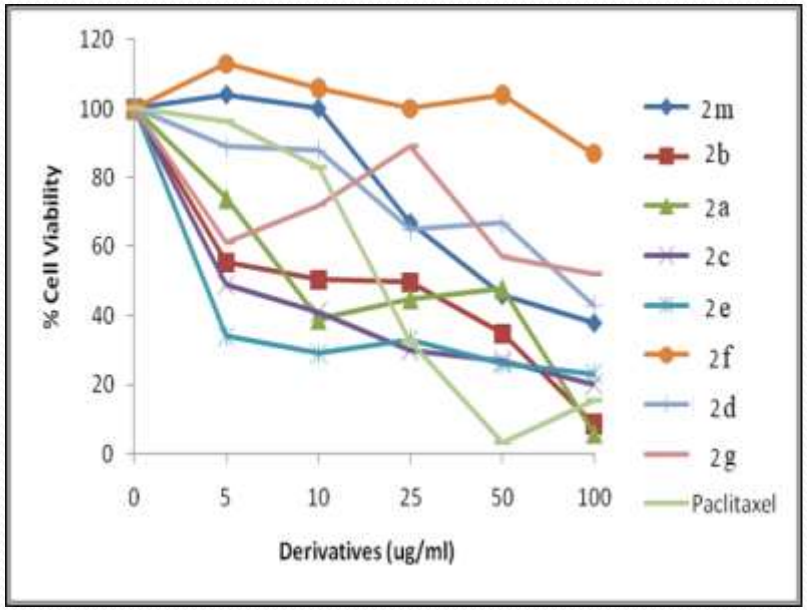
Entry	Catalyst	Time	Temp. (℃)	Yield(%)*
1	KOH/Ethanol	10 h	Refluxing	60-70
2	NaOH/Ethanol	12 h	Refluxing	55-65
3	$Ba(OH)_2$/Ethanol	6 h	Refluxing	70-80
4	Asl_2O_3/CH_2Cl_2	15 h	Refluxing	60-67
5	KOH/ Grinding	1 h	Room temp.	No product
6	NaOH/Grinding	1 h	Room temp.	No product
7	$Ba(OH)_2$/DMSO/stirring	12 h	Room temp.	70-80
8	$Ba(OH)_2$/DMSO	2-4 h	90℃	70-90
9	Activated $Ba(OH)_2$ /grinding	10 min.	Room temp.	70-92

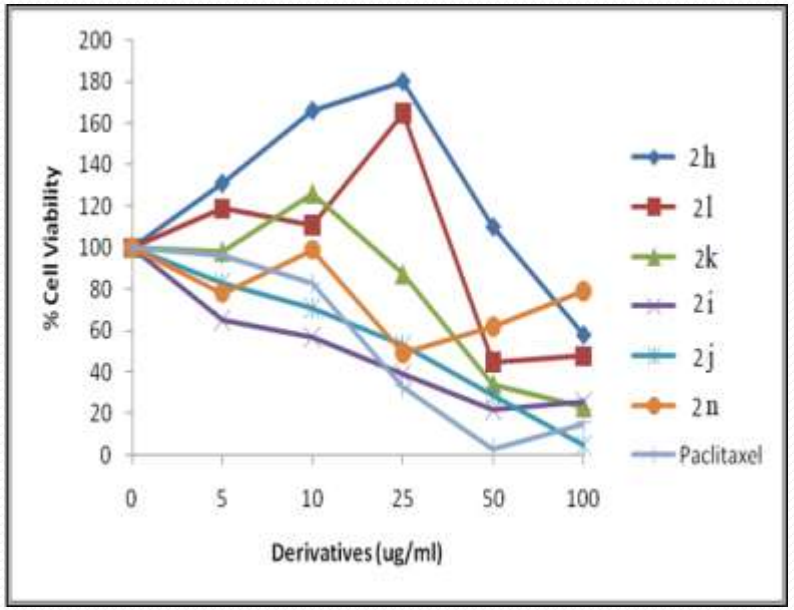
*isolated yields

IC_{50} values of aurone analogs.

Compounds	2a	2b	2c	2d	2e	2f	2g	2h	2i	2j	2k	2l	2m	2n	Paclitaxel
IC_{50}[a] value (µg/ml)	13.8	15.8	4.3	81.6	2.7	142.3	180.0	86.4	12.9	24.0	41.4	61.8	47.6	15.5	18.5

[a]The IC_{50} value represents the concentration of each compounds that inhibits MCF-7 activity by 50%





% cell viability after aurone analogs derivatives treatment in MCF-7 cells. These derivatives showed highly cytotoxic effect against MCF-7 cells.

❖ Novel quinoline based and pyrazole based aurone have been synthesized based on hybrid approach.

❖All the novel compounds have been Characterized by IR, NMR (^{1}H, ^{13}C), and mass Spectrometry.

❖Biological screening of these compounds has been done.

❖We have published two research papers on quinoline based and pyrazole based novel aurones.

Thank You