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Dengue virus fever controlling studies on derivatives of cytosine

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Abstract

Derivatives of cytosine**(I)**2-hydroxy-5-(((2-oxo-1,2-dihydropyrimidin-4-yl)imino)methyl)benzoic acid, **(II)**4-((4-hydroxybenzylidene)amino)pyrimidin-2(1H)-one,**(III)**4-((3-hydroxybenzylidene)amino)pyrimidin-2(1H)-one,**(IV)**4-((2-hydroxy benzylidene)amino)pyrimidin-2(1H)-one,**(V)**4-((4-chlorobenzylidene)amino)pyrimidin-2(1H)-one and **(VI)**4-((4-methoxy benzylidene)amino)pyrimidin-2(1H)-onewere prepared and characterized by physical and analytical data, FTIR , ^{1}H NMR, ^{13}C NMR spectra and were screened for larvicidal activity against *Aedes aegypti* and *Aedes albopictus.*

Keywords: *Aedes aegypti*, *Aedes albopictus,*antibacterial, antifungal, mosquito larvicidal, antiparasitic, anticancer lactic acid, Cytosine, 5-formyl-2-hydroxybenzoic acid, 4-Hydroxybenzaldehyde, 3-Hydroxybenzaldehyde, 2-Hydroxybenzaldehyde, 4-Chlorobenzaldehyde, 4-Methoxybenzaldehyde and octenol.

Introduction

Dengue virus[1] infected humans are the main carriers and multipliers of the virus, serving as a source of the dengue virus. When uninfected *Aedes aegypti* and *Aedes albopictus* bite infected human for blood meal to lay good healthy eggs dengue virus is transmitted to uninfected mosquitoes. After the dengue virus incubation for ten days an infected mosquitoes are capable of transmitting the virus to bite humans for blood meal in rest of their life time. To find a host, these mosquitoes are attracted to chemical compounds emitted by humans, including ammonia, carbon dioxide, lactic acid and octenol. The mosquitoes prefer to breed in areas of stagnant water. Currently *Aedes aegypti* and *Aedes albopictus* control is the best method for dengue fever prevention. When we control the growth of larvae of *Aedes aegypti* and *Aedes albopictus* the dengue virus transmission will be prevented Methoprene is a juvenile hormone[2] (JH) analog which acts as a growth regulator when used as an larvicides. Methoprene does not kill *Aedes aegypti* and *Aedes albopictus*.

Instead, it acts as mosquito's growth regulator, mimicking natural juvenile hormone. Juvenile hormone must be absent for a pupa to molt to an adult, so methoprene-treated larvae will be unable to successfully change from pupae to adults. This breaks the biological life cycle of *Aedes aegypti* and *Aedes albopictus*, preventing recurring infestation.

In recent years, derivatives of nucleic acid base were found to have potential non-toxic and non-antibiotic resistance of antibacterial, antifungal, mosquito larvicidal, antiparasitic and anticancer properties[3]. They have been prepared by starting from nucleic acid bases like cytosine or adenine and aldehydes or ketones. In the present study we have prepared

(I)2-hydroxy-5-(((2-oxo-1,2-dihydropyrimidin-4-yl)imino) methyl) benzoic acid, **(II)**4-((4-hydroxybenzylidene) amino) pyrimidin-2(1H)-one,**(III)**4-((3-hydroxy benzylidene) amino)pyrimidin-2(1H)-one, **(IV)**4-((2-hydroxy benzylidene)amino)pyrimidin-2(1H)-one, **(V)**4-((4-chlorobenzylidene)amino) pyrimidin-2(1H)-one and **(VI)**4-((4-methoxybenzylidene) amino) pyrimidin-2(1H)-oneand have been subjected to in vitro larvicidal activities against larvae of *Aedes aegypti* and *Aedes albopictus.*

Materials and Methods

Materials

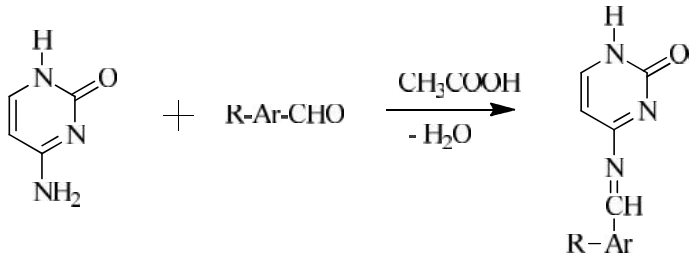
All the reagents used were of AR grade. Commercially available rectified spirit was dried over anhydrous quicklime for 24 hours, filtered and distilled before use (BP 78^{o}C). Dimethylsulphoxide (sigma) and N,Ndimethylformamide (sigma) were used as such. Cytosine with5-formyl-2-hydroxybenzoic acid, 4-Hydroxybenzaldehyde, 3-Hydroxybenzaldehyde, 2-Hydroxybenzaldehyde, 4-Chlorobenzaldehyde and 4-Methoxybenzaldehyde were purchased from Alfa Aesar.

Instruments

Melting points were determined using Elico melting point apparatus. Elemental analyses were performed using Elementar Vario EL III. IR spectra of the compounds were recorded with KBr pellets with carry 630 FTIR Spectrometer in the 4000-400 cm-1range. The 1HNMR and 13CNMRspectra were recorded on a Bruker 400 MHz FT- PMR Spectrometer.

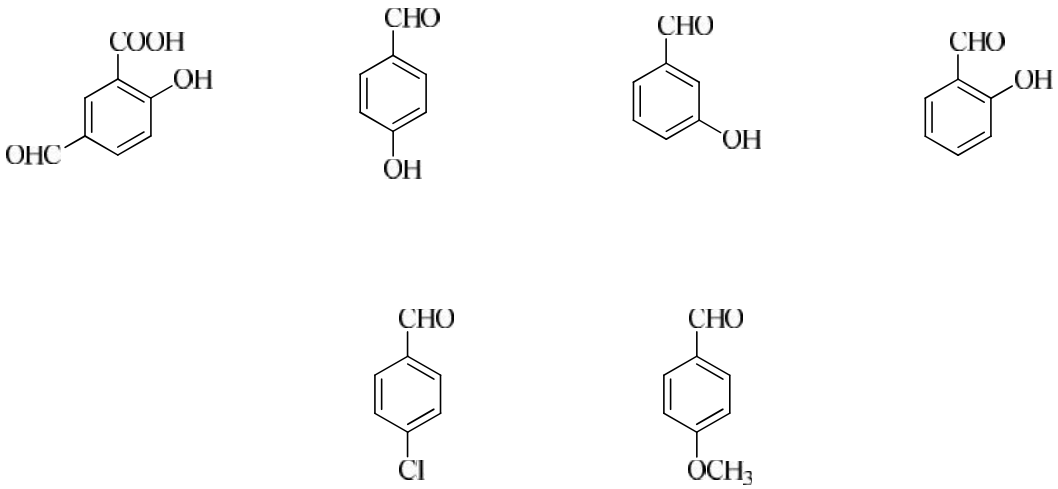
General preparation of derivatives of cytosine

All the azomethine compounds of derivatives of cytosine were prepared as reported in the literature by the following scheme – 1



Scheme 1

Where, R-Ar-CHO =



Preparation of (I)2-hydroxy-5-(((2-oxo-1,2-dihydropyrimidin-4-yl)imino)methyl)benzoic acid[4,11]

25ml of ethanolic solution of cytosine (1.11 g 0.01mol) was added to 25ml of ethanolic solution of 5-formyl-2-hydroxybenzoic acid(1.66 g 0.01mol).Then three drops of acetic acid was added to the reaction mixture. The reaction mixture was heated and refluxed for about 5 hours at 90°C. The resulting solution was further concentrated by water bath. The product 2-hydroxy-5-(((2-oxo-1,2-dihydropyrimidin-4-yl)imino)methyl)benzoic acid obtained was precipitated, cooled and collected after filtration. The precipitate was purified by washing with distilled water and then with ethanol. The 2-hydroxy-5-(((2-oxo-1,2-dihydropyrimidin-4-yl)imino)methyl)benzoic acid was again recrystallized in ethanol and then dried over vacuum desiccator.

Preparation of (II)4-((4-hydroxybenzylidene) amino)pyrimidin-2(1H)-one

Cytosine (1.11 g 0.01mol) was dissolved in 5ml of hot glacial acetic acid, 1.22 g (0.01mol) of 4-hydroxybenzaldehyde was dissolved in 5ml of glacial acetic acid and were mixed. The reaction mixture was refluxed with stirring for 5 hours. The mixture was allowed to cool, and poured onto ice. The crude solid4-((4-hydroxybenzylidene)amino)pyrimidin-2(1H)-one was filtered off and washed with distilled water, then re-crystallized from acetic acid and then dried over vacuum desiccator.

Preparation of (III)4-((3-hydroxybenzylidene) amino)pyrimidin-2(1H)-one

The 4-((3-hydroxybenzylidene)amino)pyrimidin-2(1H)-one was prepared by stirring a methanolic solution of cytosine (1.11 g 0.01mol)with 3-hydroxybenzaldehyde (1.22 g 0.01mol) in 1:1stoichiometric ratio at room temperature over 24hours.The precipitate obtained were filtered and washed with methanol and recrystallized from methanol and then dried over vacuum desiccator.

Preparation of (IV)4-((2-hydroxybenzylidene) amino)pyrimidin-2(1H)-one

A mixture of 2-hydroxybenzaldehyde (1.22 g 0.01mol) and cytosine (1.11 g 0.01mol) were grained with a pestle in an open mortar at room temperature for 3minutes. To this reaction mixture sulphuric acid 2drops and 20ml DMF were added and grained for 5minutes. On completion of reaction as monitored by TLC, the light greenish-colored solid 4-((2-hydroxybenzylidene)amino)pyrimidin-2(1H)-one was separated out. The obtained solid was isolated by simple Buchner filtration and was recrystallized from DMF and then dried over vacuum desiccator.

Preparation of (V)4-((4-chlorobenzylidene) amino)pyrimidin-2(1H)-one

4-((4-chlorobenzylidene)amino)pyrimidin-2(1H)-one was prepared from equimolar quantity of cytosine (1.11 g 0.01mol)and 54-Chlorobenzaldehyde(1.40 g 0.01mol) in 30 ml of methanol were heated at 70oC on water bath for 4-hrs in presence of few drops of glacial acetic acid. The crude product was obtained after removal of methanol under reduced pressure. The products were recrystallized from methanol and then dried over vacuum desiccator.

Preparation of (VI)4-((4-methoxybenzylidene) amino)pyrimidin-2(1H)-one

Equimolar quantities of 0.01 mole of cytosine (1.11 g 0.01mol) and4-Methoxybanzaldehyde (1.36 g 0.01mol) were dissolved in 20 ml of DMSO and 3 drop of glacial acetic acid was added and refluxed for 3 hours. After completion of the reaction(monitored by TLC), some solvent was distilled out, the reaction mixture was poured on ice cold water and the solid 4-((4-methoxybenzylidene)amino)pyrimidin-2(1H)-one came out which was filtered and then recrystallized by DMSO and then dried over vacuum desiccator.

***Aedes aegypti* rearing**

The larvae of *Aedes aegypti* and *Aedes albopictus* were collected from National Centre for disease control, Government of India ministry of health and family welfare, Southern India branch, field station, Mettupalayam, Coimbatore district, Tamilnadu, India. The larvae were kept in the plastic buckets half filled with tap water and fed with dog biscuit once a day initially and twice during the later stages of development. Water in rearing container was refreshed every day by removing a little quantity of water from the rearing buckets and replacing with fresh water. This was aimed at preventing scum from forming on the water surface.

Larvicidal bioassay

The larvicidal activity of six novel derivatives of cytosine were assessed by using the standard method as prescribed by WHO. From the stock solution, five different test concentrations (150, 200, 250 and 300 ppm was prepared and tested against the freshly molted (0 – 6 hrs) 4th instar larvae of *Aedes aegypti* and *Aedes albopictus* DMSO (emulsifier) in water was treated as control. Ten larvae of these *Aedes aegypti* species was introduced in 250-ml plastic cups containing 100 ml of aqueous medium (99 ml of dechlorinated water + 1ml of emulsifier) and the required amount of six novel derivatives of cytosine was added. The larval mortality was observed and recorded after 24 hrs. of post treatment. For each experiment, five replicates were maintained at a time. The percentage of mortality was calculated by using Abbott's formula[12] (Abbott, 1925). The LC_{50}, LC_{90}, 95% confidence limit of Lower Confidence Limit (LCL) and Upper Confidence Limit (UCL), chi-square values and the degrees of freedom was calculated by using Probit analysis with Statistical Package for Social Sciences (SPSS) 16.0 Version in MS-Excel, 2007.

Results

The physical and analytical data of the derivatives of cytosine **(I)** 2-hydroxy-5- (((2-oxo- 1,2-dihydropyrimidin-4-yl)imino)methyl)benzoic acid, **(II)**4- ((4-hydroxybenzylidene) amino) pyrimidin-2(1H)-one, **(III)**4-((3-hydroxybenzylidene) amino) pyrimidin-2(1H)-one,**(IV)**4-((2-hydroxybenzylidene) amino) pyrimidin-2(1H)- one, **(V)**4-((4-chloro benzylidene) amino)pyrimidin-2(1H)-one and**(VI)**4-((4-methoxybenzylidene)amino)pyrimidin-2 (1H)-one are compared with reported in the literature values[4,5].

[I] 2-hydroxy-5-(((2-oxo-1,2-dihydropyrimidin-4-yl)imino)methyl)benzoic acid

FTIR (cm^{-1}): 3630 & 680 cm^{-1} (—O—H), 3380 & 850 cm^{-1} (—N—H), 3220 cm^{-1} (—C—OH), 1650 cm^{-1} (—N=CH), 1540 cm^{-1} (—N—C—), 1270 cm^{-1} (Acid >C=O) & (—N=C—) and 1090 cm^{-1} (Ar—COOH)

^{1}HNMR δ (ppm): 11.0 (s, 1H), 8.53 (s, 1H), 8.48 (s, 1H), 8.43 (d, 1H), 8.12 (d, 1H), 8.00 (s, 1H), 7.23 (d, 1H) 5.40 (d, 1H) & 5.35 (s, 1H)

^{13}CNMR δ (ppm): 171.8 (s), 164.5 (s), 163.7 (s), 160.1 (s), 156.3 (s), 135.8 (s), 130.9 (s), 127.4 (s), 126.2 (s), 118.0 (s), 112.1 (s) & 104.8 (s)

[II] 4-((4-hydroxybenzylidene)amino)pyrimidin-2(1H)-one

FTIR (cm^{-1}): 3560 & 680 cm^{-1} (ArO-H), 3170 & 880 cm^{-1} (-N-H), 1730 cm^{-1} (>C=O),1670 cm^{-1} (-N=CH-), 1540 cm^{-1} (-N=C<), 1230 cm^{-1} (-N-C-) & 1090 cm^{-1} (Ar-O)

^{1}HNMR δ (ppm): 8.48 (s, 1H), 8.43 (d, 1H), 8.00 (s, 1H), 7.78 (d, 2H), 6.85 (d, 2H), 5.40 (d, 1H), & 5.35 (s, 1H)

^{13}CNMR δ (ppm): 163.7 (s), 160.8 (s), 160.1 (s), 156.3 (s), 130.6 (s), 127.4 (s), 126.3 (s), 116.0 (s) & 104.8 (s)

[III] 4-((3-hydroxybenzylidene)amino)pyrimidin-2(1H)-one

FTIR (cm^{-1}): 3580 & 680 cm^{-1} (—O—H), 3390 & 710 cm^{-1} (—N—H), 1690 cm^{-1} (>C=O),1640 cm^{-1} (—N=CH), 1610 cm^{-1} (—N=C—), 1230 cm^{-1} (—N—C—) & 960 cm^{-1} (Ar—OH)

^{1}HNMR δ (ppm): 8.48 (s, 1H), 8.43 (d, 1H), 8.00 (s, 1H), 7.46 (s, 1H), 7.39 (d, 1H), 7.25 (t, 1H), 7.02 (d, 1H), 5.40 (s, 1H) & 5.35 (s, 1H)

^{13}CNMR δ (ppm): 163.7 (s), 160.1 (s), 158.6 (s), 156.3 (s), 135.1 (s), 130.2 (s), 127.4 (s), 121.8 (s), 118.2 (s), 114.9 (s) & 104.8 (s)

[IV] 4-((2-hydroxybenzylidene)amino)pyrimidin-2(1H)-one

FTIR (cm^{-1}): 3532 & 787 cm^{-1} (—O—H), 3235 & 904 cm^{-1} (—N—H), 1642 cm^{-1} (—N=CH),1606 cm^{-1} (—N=C—), 1219 cm^{-1} (Ar—OH) & 1120 cm^{-1} (—N—C—)

^{1}HNMR δ (ppm): 8.48 (s, 1H), 8.43 (d, 1H), 8.00 (s, 1H), 7.66 (d, 1H), 7.52 (t, 1H), 7.08 (t, 1H), 7.02 (d, 1H), 5.40 (d, 1H) & 5.35 (s, 1H)

^{13}CNMR δ (ppm): 163.7 (s), 161.1 (s), 160.1 (s), 156.3 (s), 132.4 (s), 132.1 (s), 127.4 (s), 121.4 (s), 118.5 (s), 117.8 (s) and 104.8 (s)

[V] 4-((4-chlorobenzylidene)amino)pyrimidin-2(1H)-one

FTIR (cm^{-1}): 3250 & 800 cm^{-1} (—N—H), 1640 cm^{-1} (—N=CH), 1630 cm^{-1} (—N=C—), 1250 cm^{-1} (—N—C—) & 780 cm^{-1} (Ar—Cl)

^{1}HNMR δ (ppm): 8.48 (s, 1H), 8.43 (d, 1H), 8.00 (s, 1H), 7.77 (d, 2H), 7.52 (d, 2H) & 5.40 (d, 1H)

^{13}CNMR δ (ppm): 163.7 (s), 160.1 (s), 156.3 (s), 136.6 (s), 131.8 (s), 130.6 (d), 128.9 (s), 127.4 (s) & 104.8 (s)

[VI] 4-((4-methoxybenzylidene)amino)pyrimidin-2(1H)-one

FTIR (cm^{-1}): 3250 & 870 cm^{-1} (—N—H), 1740 cm^{-1} (Ar—OR), 1690 cm^{-1} (>C=O), 1640 cm^{-1} (—N=CH), 1540 cm^{-1} (—N=C—), 1200 cm^{-1} (—N—C—) & 1120 cm^{-1} (ArO—R)

^{1}HNMR δ (ppm): 8.48 (s, 1H), 8.43 (d, 1H), 8.00 (s, 1H), 7.84 (d, 2H), 7.06 (d, 2H), 5.40 (d, 1H) & 3.83 (s, 3H)

^{13}CNMR δ (ppm): 163.7 (s), 162.9 (s), 160.1 (s), 156.3 (s), 130.2 (d), 127.4 (s), 126.0 (s), 114.4 (s), 104.8 (s) & 55.8 (s)

Table 1.The physical and analytical data of derivatives of cytosine

Derivatives of Cytosine	Molecular Weight	Nature of Appearance	% of yield	Elemental Analysis (in %)				
				C	H	O	N	Cl
[I] $C_{12}H_9N_3O_4$	259.2176	Yellow Crystalline Solid	85	55.60	3.50	24.69	16.21	-
[II] $C_{11}H_9N_3O_2$	215.2081	Yellow Crystalline Solid	87	61.39	4.22	14.87	19.53	-
[III] $C_{11}H_9N_3O_2$	215.2081	Yellow Crystalline Solid	68	61.39	4.22	14.87	19.53	-
[IV] $C_{11}H_9N_3O_2$	215.2081	Yellow Crystalline Solid	79	61.39	4.22	14.87	19.53	-
[V] $C_{11}H_8ClN_3O$	233.6537	Yellow Crystalline Solid	80	56.54	3.45	6.85	17.98	15.17
[VI] $C_{12}H_{11}N_3O_2$	229.2346	Yellow Crystalline Solid	84	62.87	4.84	13.96	18.33	-

Larvicidal activity

Larvicidal activity[13] of all azomethine compounds are determined as recommended by WHO in 150,200,250 and 300ppm concentration in dimethyl sulfoxide(DMSO) solvent. The results of**(I)**2-hydroxy-5-(((2-oxo-1,2-dihydropyrimidin-4-yl)imino)methyl) benzoic acid, **(II)**4-((4-hydroxybenzylidene) amino) pyrimidin-2(1H)-one, **(III)**4-((3-hydroxybenzylidene) amino) pyrimidin - 2(1H) - one, **(IV)**4-((2-hydroxybenzylidene)amino)pyrimidin-2(1H)-one, **(V)**4-((4-chlorobenzylidene)amino)pyrimidin-2(1H)-one and**(VI)**4-((4-methoxybenzylidene) amino) pyrimidin-2(1H)-oneare given in the Table 2.

The larvicidal activity of azomethine compounds I-VI (Table. 2) clearly indicate that all the compounds (I-VI) control the growth of larvae. The nature of bonding[14], and structure of azomethine organic compounds are elucidated by the elemental analysis, melting point, FTIR, ^{1}HNMR,^{13}CNMR spectral analysis, chromatography and molar ratio methods. In accordance with the data obtained in the present investigation, it is found that the larvicidal activity of **(I)**2-hydroxy-5-(((2-oxo-1,2-dihydropyrimidin-4-yl) imino)methyl)benzoic acid, **(II)**4-((4-hydroxy benzylidene)amino)pyrimidin-2(1H)-one, **(III)**4-((3-hydroxybenzylidene)amino)pyrimidin-2 (1H)-one, **(IV)** 4-((2-hydroxybenzylidene) amino) pyrimidin-2(1H)-one, **(V)**4-((4-chlorobenzylidene)amino) pyrimidin-2(1H)-one and**(VI)**4-((4-methoxy benzylidene) amino)pyrimidin-2(1H)-one increases depend upon the functional groups present in the Schiff bases (I<II<IV<III<VI<V). Table.2.

Table.2 Larvicidal activity[15-18] of derivatives of cytosine against *Aedes aegypti*

Compounds	Con .(ppm)	Larval mortality	95% Confidence Limits (ppm)		
			LC_{50} (LCL-UCL)	LC_{90} (LCL-UCL)	χ^2
I	150	25.33±2.20	191.54 (167.88-213.90)	412.02 (361.23-499.75)	3.010
	200	47.21±3.24			
	250	61.20±2.34			
	300	73.48±3.20			
II	150	21.28±1.30	215.08 (126.26-353.61)	391.97 (294.20-1255.72)	5.076
	200	39.20±4.20			
	250	51.30±4.33			
	300	79.00±1.23			
III	150	23.20±1.30	195.24 (177.94-212.23)	357.48 (325-57-406.32)	2.302
	200	37.20±3.20			
	250	61.10±3.30			
	300	83.20±4.14			
IV	150	21.30±1.23	210.48 (101.29-370.07)	381.19 (284.07-1523.71)	5.997
	200	34.20±2.33			
	250	52.30±2.32			
	300	81.20±2.20			
V	150	29.00±2.20	192.17 (166.47-227.87)	418.26 (341.85-598.21)	0.179
	200	42.20±2.30			
	250	64.00±1.20			
	300	91.20±2.40			
VI	150	20.20±3.20	187.03 (172.03-201.45)	322.54 (298.15-356.54)	0.184
	200	38.50±2.40			
	250	67.40±3.50			
	300	88.67±2.20			

Values are mean ± S.D of five replication; Number of larvae =10; LC_{50}=Lethal concentration 50 and LC_{90}=Lethal concentration 95; Values with different alphabet in column are statistically significant (p<0.05 level; DMRT).

Discussion

Derivatives of cytosine (1-6) act as a Juvenile Hormone like methoprene[19-21] analog against larvae of a *Aedes aegypti* growth regulator when used as an larvicides. Derivatives of cytosine (I-VI)do not kill *Aedes aegypti* and *Aedes albopictus*. Instead, they act as a *Aedes aegypti* growth regulator, mimicking[19-21] natural juvenile hormone. Juvenile hormone must be absent for a pupae to molt to an adult, so derivatives of cytosine (I-VI) treated larvae will be unable to successfully change from pupae to adults. This breaks the biological life cycle of *Aedes aegypti* and *Aedes albopictus*[19-21]Juvenile hormone is a key growth regulator of development and reproduction in *Aedes aegypti*.

Juvenile hormone delays metamorphosis until larvae have attained an appropriate stage and size. At that point, a drop in Juvenile hormone permits a metamorphic molt.

As the antimetamorphic role of Juvenile hormone comes to an end, the late pupae becomes again "competent" to synthesize Juvenile hormone, which plays an essential role orchestrating reproductive maturation. Juvenile hormone synthesis is controlled by the rate of flux of isoprenoid precursors, with a complex interplay of changes in precursor pools, enzyme levels and nutritional and developmental modulators, such as 20-hydroxyecdysone 20E, ecdysiast-triggering hormone, insulin and allatostatin-C. Juvenile hormone uses multiple molecular mechanisms to exert its pleiotropic functions at different stages of the mosquito life cycle. Juvenile hormone acts via an unidentified membrane receptor. Here derivatives of cytosine treated larvae of *Aedes aegypti* died[22-26] without growth regulator, Juvenile hormone.

Conclusion

The derivatives of cytosine**(I)**2-hydroxy-5-(((2-oxo-1,2-dihydropyrimidin-4-yl)imino)methyl)benzoic acid, **(II)**4-((4-hydroxybenzylidene)amino)pyrimidin-2(1H) -one, **(III)** 4-((3-hydroxybenzylidene)amino) pyrimidin-2(1H)-one,**(IV)**4-((2-hydroxybenzylidene) amino)pyrimidin-2(1H)-one,**(V)**4-((4-chlorobenzyl idene)amino)pyrimidin-2(1H)-one and**(VI)**4-((4-methoxybenzylidene)amino)pyrimidin-2(1H)-onewere prepared by the condensation of 5-formyl-2-hydroxybenzoic acid, 4-Hydroxybenzaldehyde, 3-Hydroxybenzaldehyde, 2-Hydroxybenzaldehyde, 4-Chlorobenzaldehyde and 4-Methoxybenzaldehyde with cytosine and were screened against *Aedes aegypti* and *Aedes albopictus.* It was concluded that theincrease in the larval mortality of *Aedes aegypti* and *Aedes albopictus* depend upon the functional groups present in the Schiff bases.

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