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Synthesis of New Heterocyclic Compounds Derived From 4-Aminoantipyrine and its Biological Evaluation

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ABSTRACT

4-Aminoantipyrine is heterocyclic compound containing pyrazole ring. 4-Aminoantipyrine have attracted great attention in medicinal field due to its diversified biological activities such as antitumor, antimicrobial, antiviral, analgesic, and anti-inflammatory activity. Various synthetic methods have been developed to synthesize this novel heterocyclic nucleus.

Keywords: 4-Aminoantipyrine, Antipyretic, Quinoline, Anti-Malarial.

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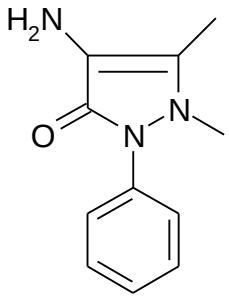
INTRODUCTION

4-Aminoantipyrine is a heterocyclic compound containing pyrazole ring. 4-Aminoantipyrine was 1st synthesized by Knorr [2]in 1883. It was the 1st pyarzolone derivative used in the management of pain and inflammation[1]. APDs having wide range of biological activities like antitumor [2-4], antimicrobial[5-7], antiviral [8-9], analgesic and anti-inflammatory activity [10-12]. With the above activities it attracted many researchers and many new 4-Aminoantipyrine derivatives were prepared with enhanced activities. 4-Aminoantipyrine was available in the brand names of Apirelina, Auralgan and Sedatine.

Antipyretics is a greek word anti means against, and pyreticus, pertaining to fever, are drugs or herbs that reduce fever. Antipyretics cause the hypothalamus to override an interleukin-induced increase in temperature. The body then works to lower the temperature, resulting in a reduction in fever.



4-Amino-1, 5-dimethyl-2-phenyl-1, 2-dihydro -3H-pyrazol-3-one

MATERIALS AND METHOD

All the chemicals used for the present work were of synthetic grade obtained SD fine and Research lab fine chemicals. Completion of the reaction was monitored time to time by thin layer chromatography (TLC) using E-Merck 0.52mm silica gel plates. Visualization was accomplished with UV light (256nm) and iodine chamber. Melting points were determined on BUCHI-535 melting point apparatus. All the ^{1}H NMR spectra have been recorded in $CDCl_3$ solvent unless otherwise mentioned. ^{1}H NMR chemical shifts are reported on Bruker 400MHz relative to Tetramethyl silane as internal standard scale. The I.R spectrum was recorded on Schimadzu FT-IR Spectrophotometer by using 1% Potassium bromide discs. The mass spectrum recorded on Quarttro Micro Spectrophotometer.

Scheme

The general scheme for the synthesis of Quinolin-8-yl 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(2-nitrobenzyl)amino)acetate derivative was mentioned in Figure 1.

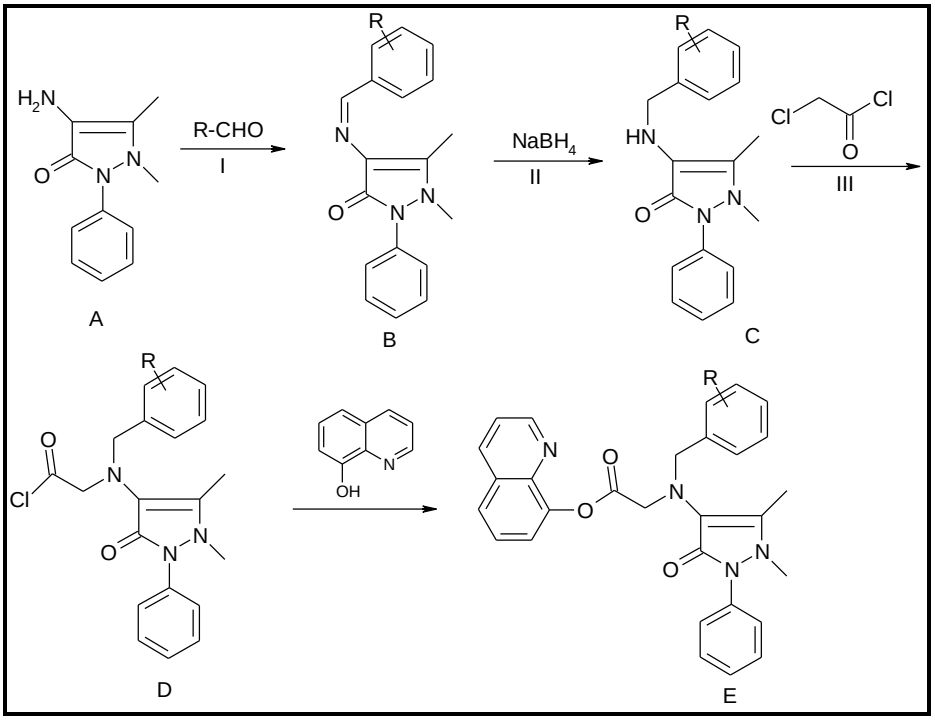


Figure 1: Synthesis of Quinolin-8-yl 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(2-nitrobenzyl)amino)acetate derivative

R= m-Nitrobenzaldehyde, p-Dimethylamino benzaldehyde, Vanilin, 3,4,5-Trimethoxy benzaldehyde, Anisaldehyde, Salicylaldehyde, F-Cl-Benzaldehyde, Indole-3-carbaldehyde

A=4-Amino-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazol-3-one

B= 4-(Benzylidene-amino)-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazole-3-one

C= 4-Benzylamino-1,5-dimethyl-2-phenyl-1,2-dihydro-pyrazole-3-one

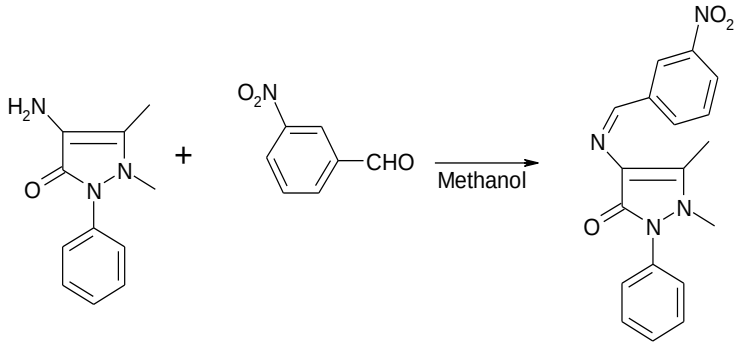
D= [Benzyl –(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-amino-acetylchloride

E= [Benzyl –(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-amino acetic acid quinoline-8yl-ester

Synthesis

Synthesis procedure for [Benzyl –(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-amino acetic acid quinoline-8yl-ester] derivative involves four steps, which are as follows:

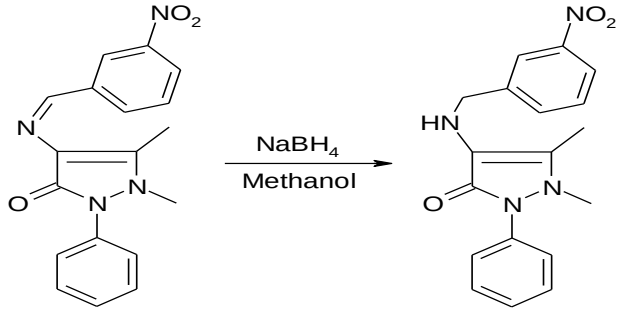
STEP 1: Preparation of 1, 5-Dimethyl-4-(3-Nitrobezyledeneamino)-2-phenyl-1H-pyrazole-3(2H)-one



PROCEDURE:

4-Aminoantipyrine (1g) was taken in round bottom flask and methanol was added. Then add m-Nitrobenzaldehyde (0.40g), few drops of glacial acetic acid and reflux for 6-8 hours at 45-50ºC. Yellow colour solid out during the reflux. Excess of methanol is distilled off and the reaction mixture was cooled. The solid product obtained was filtered and dried. Reaction mixture was monitored by TLC.

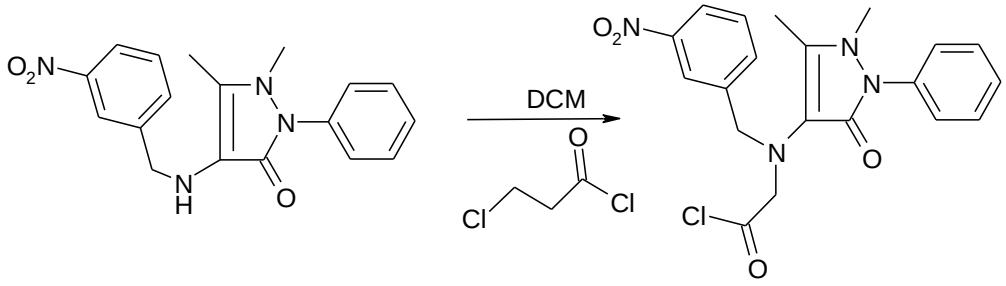
STEP 2: Preparation of 1, 5-Dimethyl-4-(3-nitrobezylamino)-2-phenyl-1H-pyrazol-3(2H)-one



PROCEDURE:

The solid of 1st step (0.75g) was dissolved in methanol and $NaBH_4$ was added at 0ºC. Then the reaction mixture was stirred for 5-6hours at room temperature. The mixture was evoperated to 1/3rd of its volume then quenched with ice cold water and extracted with (3*25ml) ethylacetate. The combined organic layers were washed with water and brine solution, evoperated under reduced pressure to afford (3). Reaction mixture was monitored by TLC.

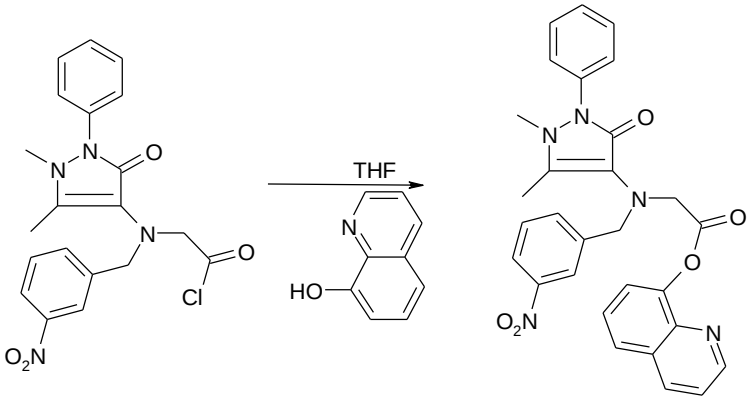
STEP 3: Preparation of 2-chloro-N-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)-N-(3-nitrobenzyl)acetamide



PROCEDURE:

Compound (2) is dissolved in DCM and chloroacetyl chloride (0.38ml), triethylamine (1.37ml) was added at 0ºC. The reaction mixture was stirred for 3-4 hours at room temperature. Then cool the reaction mixture and evaporate the solvent under reduced pressure by using Rota evaporator. The solid product was dried. Reaction mixture was monitored by TLC.

STEP 4: Preparation of Quinolin-8-yl 2-((1, 5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(2-nitrobenzyl)amino)acetate



PROCEDURE:

Take 8-hydroxy quinoline (0.040g) and dissolve it in THF (10ml), add 60% NaOH solution, then stir the mixture for 1 hour. To a stirred mixture compound (3) was added and stirring continued for 6-8 hours at 45ºC. After completion of the reaction, it was treated with crushed ice and neutralized by dil. HCl. The precipitate thus obtained was filtered, dried and recrystalised from THF.

Characterization

Completion of the reaction was monitored time to time by thin layer chromatography (TLC) using E-Merck 0.25mm silica gel plates. Visualization was accomplished with UV light (256nm) and iodine chamber. Melting points were determined on BUCHI-535 melting point apparatus. All the ^{1}H NMR spectra have been recorded in $CDCl_3$ solvent unless otherwise mentioned. ^{1}H NMR chemical shifts are reported on Bruker 400MHz relative to Tetramethyl silane as internal standard scale. The I.R spectrum was recorded on Schimadzu FT-IR Spectrophotometerby using

1% Potassium bromide discs. The mass spectrum recorded on Quarttro Micro Spectrophotometer.

Biological Evaluation

Antipyretic Activity Studies

Male albino rats of (200-250g weight) were used for antipyretic study were purchased from Mahavir Agencies Ltd. (Hyderabad, India). All the procedures were conducted in compliance with guidelines established by the National Institute of Laboratory Animals Welfare. The study has approval from Institutional Animal Ethical Committee. In the antipyretic activity study, male albino rats administered with the synthesized compounds upto a maximum dose of 200mg/kg, 0.60ml/kg orally.

In-vivo Study

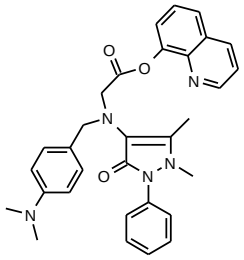
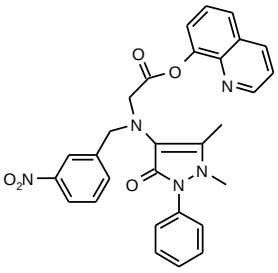
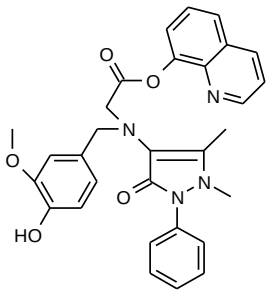
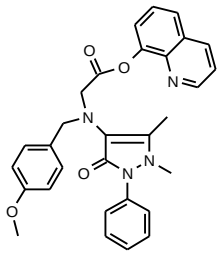
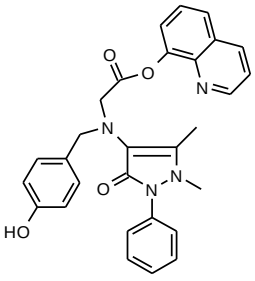
Animals

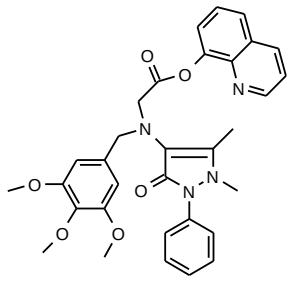
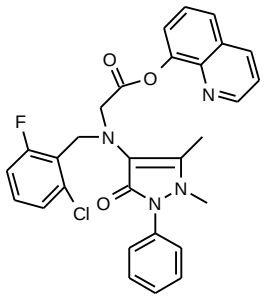
Specific pathogen-free male albino rats (200-250g weight) were used. The rats were fed standard cow pellets water. All rats were acclimated for one week before commencing the experiments. All the animals were treated according to the Guide for care and Use of Laboratory. Animals published by the National institute of Health (NIH, 1996).

Treatments

The synthesized compounds were screened for antipyretic activity by using Wister albino rats. Twelve rats were divided into four groups comprising three rays in each group. The normal body temperature of each rat was measured with digital thermometer rectally at predetermined intervals and recorded. The rats were trained to remain quiet in a restraint cage. Fever was induced by subcutaneous injection of 10ml/kg 20% (w/v) yeast suspended in 0.5% (w/v) methylcellulose solution. Rats were then returned to their housing cages. After 19h of yeast injection rectal temperature was measured, the third and fourth group of animals received synthetic derivatives orally at dose 200mg/kg respectively. The first group received 5ml/kg body weight of 2% (v/v) aqueous Tween-80 solution orally (vehicle control group). The second group received standard drug paracetamol (150mg/kg). Temperature was recorded at 1 h intervals upto 3 h after drug injection.

Table 1: Derivatives of 4-Aminoantipyrine

Compound	IUPAC Name
E_1 	Quinolin-8-yl 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(2-nitrobenzyl)amino)acetate
E_2 	Quinolin-8-yl 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(4-(dimethylamino)benzyl)amino)acetate
E_3 	Quinolin-8-yl 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(4-hydroxy-3-methoxybenzyl)amino)acetate
E_4 	Quinolin-8-yl 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(4-methoxybenzyl)amino)acetate
E_5 	Quinoline-8-yl-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-yl)(4-hydroxy benzyl)amino)acetate

E_6		Quinoline-8-yl-2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-yl)-3,4,5-trimethoxybenzyl)amino)acetate
E_7		Quinoline-8-yl-2-((2-chloro-6-fluorobenzyl) -((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-yl)amino)acetate

RESULTS AND DISCUSSION

The structures of the newly synthesized compounds were established by spectroscopic interpretation as discussed below. Melting range of the synthesized compounds, percentage yield, R_f value, molecular formula, molecular weight were established (Table. 2).

Quinolin-8-yl 2-((1, 5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(2-nitrobenzyl)amino)acetate (compound 1)

^{1}H NMR**:** 8.90(d,1H-CH),8.41(d,1H-CH),7.96(d,1H-CH),7.90(T,1H -CH), 7.56(d,1H-CH),7.51(T,3H-CH), 7.37(T,2H-CH), 7.35(d,2H-CH),7.05(d,2H-CH), 6.90(T,1H-CH),6.64(d,2H-CH),4.26(s,1H-CH), 4.25(s,1H-CH), 3.11(s,3H-N-CH_3),3.06(s,6H-CH_3),2.26(S,3H,CH_3).

Quinolin-8-yl 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(4-(dimethylamino)benzyl)amino)acetate (compound 2)

^{1}H NMR: 8.90(d,1H-CH),8.41(d,1H-CH),7.96(d,1H-CH),7.90(T,1H -CH), 7.56(d,1H-CH),7.51(T,3H-CH), 7.37(T,2H-CH), 7.35(d,2H-CH),7.05(d,2H-CH), 6.90(T,1H-CH),6.64(d,2H-CH),4.26(s,1H-CH), 4.25(s,1H-CH), 3.11(s,3H-N-CH_3),3.06(s,6H-CH_3),2.26(S,3H,CH_3).

Quinolin-8-yl 2-((1, 5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(4-hydroxy-3-methoxybenzyl)amino)acetate (compound 3)

^{1}H NMR:8.90(d,1H-CH),8.41(d,1H-CH),7.96(d,1H-CH),7.90(T,1H -CH), 7.56(d,1H-CH),7.51(T,3H-CH), 7.37(T,2H-CH), 7.35(d,2H-CH), 6.97(s.1H-CH), 6.90(T,1H-CH),

6.75(d,1H-CH), 6.72(s,1H-CH), 5.35(s,1H-OH), 4.26(s,2H-CH_2), 4.25(s,2H-CH_2), 3.83(s,3H-CH_3), 3.11(s,3H-CH_3), 2.26(s,3H-CH_3).

Quinolin-8-yl 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(4-methoxybenzyl)amino)acetate (compound 4)

^{1}H NMR: 8.90(d,1H-CH),8.41(d,1H-CH),7.96(d,1H-CH),7.90(T,1H -CH), 7.56(d,1H-CH),7.51(T,3H-CH), 7.37(T,2H-CH), 7.35(d,2H-CH), 7.25(d-2H-CH), 6.90(T,1H-CH), 6.87(d,2H-CH), 4.26(s,2H-CH_2), 4.25(s,2H-CH_2), 3.83(s,3H-CH_3), 3.11(s,3H-CH_3), 2.26(s,3H-CH_3).

Quinolin-8-yl 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(3,4,5-trimethoxyoxybenzyl)amino)acetate (compound 5)

^{1}H NMR: 8.90(d,1H-CH),8.41(d,1H-CH),7.96(d,1H-CH),7.90(T,1H -CH), 7.56(d,1H-CH),7.51(T,3H-CH), 7.37(T,2H-CH), 7.35(d,2H-CH), 7.19(d-2H-CH), 6.90(T,1H-CH), 6.63(d,2H-CH),5.35(s,-OH) 4.26(s,2H-CH_2), 4.25(s,2H-CH_2), 3.11(s,3H-CH_3), 2.26(s,3H-CH_3).

Quinolin-8-yl 2-((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)(3,4,5-trimethoxyoxybenzyl)amino)acetate (compound 6)

^{1}H NMR: 8.90(d,1H-CH),8.41(d,1H-CH),7.96(d,1H-CH),7.90(T,1H -CH), 7.56(d,1H-CH),7.51(T,1H-CH), 7.37(T,2H-CH), 7.35(d,2H-CH), 6.90(T,1H-CH), 6.59(s,2H-CH), 4.26(s,2H-CH_2), 4.25(s,2H-CH_2), 3.83(s,9H-CH_3), 3.11(s,3H-CH_3), 2.26(s,3H-CH_3).

Quinoline-8-yl-2-((2-chloro-6-fluorobenzyl) -((1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazole-4-yl)amino)acetate (compound 7)

^{1}H NMR: 8.90(d,1H-CH),8.41(d,1H-CH),7.96(d,1H-CH),7.90(T,1H -CH), 7.56(d,1H-CH),7.51(T,1H-CH),7.42(d,1H-CH) 7.37(T,2H-CH),7.36(d,1H-CH) 7.35(d,2H-CH), 7.07(T,1H-CH), 6.90(T,1H-CH), 6.87(d,2H-CH), 4.26(s,2H-CH_2), 4.25(s,2H-CH_2), 3.11(s,3H-CH_3), 2.26(s,3H-CH_3).

Table 2: Physical Data of Synthesized Compounds

Mol. Formula	Mol. Weight	Melting Point	% Yield
$C_{31}H_{31}N_5O_3$	521	218-222	45
$C_{29}H_{25}N_5O_5$	523	219-220	61
$C_{30}H_{28}N_4O_5$	524	220-221	53
$C_{30}H_{28}N_4O_4$	508	212-213	49
$C_{29}H_{26}N_4O_4$	494	207-208	45
$C_{32}H_{32}N_4O_6$	568	227-228	52
$C_{29}H_{24}ClFN_4O_3$	530	212-213	45

Antipyretic Activity:

The synthesized 4-Aminoantipyrine derivatives are purified, characterized and screened for antipyretic activity by using Wister albino rats. The activity of the derivatives was performed at a concentral level of subcutaneous injection of 10ml/kg of 15 %(w/v) yeast suspended in 0.5%(w/v) methylcellulose solutions for all groups. Paracetamol was used as standard drug at a concentration of 150mg/kg for second group, tween-80 (2%v/v) 5ml/kg orally for first group. The 3rd and 4th groups were received with synthesized derivatives.

Derivative	Group	Body Weight (ml/kg)	Temperature (ºC) Before Yeast	Temperature(ºC) After 19hrs	Dose(ml/kg) Sample-1 (200mg/kg)	Temperature(ºC) After drug		
						1hr	2hr	3hr
p-Dimethylaminobenzaldehyde	III	240	34.8	35.4	0.60	35.0	34.3	34.1
		240	34.5	34.9	0.60	34.5	34.5	34.3
		200	35.2	35.4	0.50	35	34.6	34.5
Vanilin	IV	200	33.9	34.6	0.50	34.3	34.6	34.6
		180	34.6	35.1	0.45	33.9	33.2	33.1
		220	35.1	35.3	0.45	34.5	33.9	33.6
m-Nitrobenzaldehyde	V	170	34.8	35.1	0.42	35.1	35.0	35.0
		180	35.1	35.4	0.45	35.3	35.1	34.9
		160	35.0	35.3	0.40	35.0	34.8	34.5
Salicylaldehyde	VI	200	34.9	35.0	0.50	34.7	34.6	34.5
		160	34.4	34.7	0.40	34.4	34.3	34.2
		170	34.2	34.5	0.42	34.2	34.0	34.0
Anisaldehyde	VII	170	34.5	34.9	0.42	34.9	34.8	34.7
		200	34.9	35.3	0.50	35.1	35.0	34.8
		180	34.6	34.8	0.45	34.7	34.6	34.6

CONCLUSION:

The present synthetic work is carried by incorporating different aldehydes and quinoline moiety to synthesize 4-Aminoantipyrine derivatives. Reduction was done in presence of $NaBH_4$ and then cyclization in presence of TEA& chloroacetyl chloride in presence of methanol as solvent. The anti-pyretic activity of the synthesized 4-Aminoantipyrine derivatives revealed that the compounds E_1 shown E_3 showed good antipyretic activity on Wister Albino Rats.

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