

**SYNTHESIS AND EVALUATION OF SOME NEW QUINOLINE DERIVATIVES FOR THEIR ANTI-INFLAMMATORY ACTIVITIES**

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**ABSTRACT**

The present research work is aimed to synthesize some novel substituted the 6-fluoro-quinolin-4(1*H*)-one compounds. The thirteen derivatives of Quinoline Scheme I synthesized during the course of research work. Structures of compounds have been established by means of IR, <sup>1</sup>H-NMR and elemental analysis.

All the compounds were evaluated for anti-inflammatory activity by Carrageenan Induced Rat hind Paw method. Out of seventeen compounds **V<sub>1</sub>**, **V<sub>3</sub>**, **V<sub>5</sub>**, **P<sub>4</sub>**, **P<sub>5</sub>** shows maximum anti-inflammatory activity.

**Key words:** Anti-inflammatory activity, 6-fluoro-quinolin-4(1*H*)-one, CHN analysis

**INTRODUCTION AND MATERIAL AND METHODS****INTRODUCTION**

Inflammation is defined as the local response to living mammalian tissues to injury due to any agent. Specifically it is a series of molecular and cellular responses acquired during evolution designed to eliminate foreign agents and promote repair of damaged tissues.

Cyclooxygenase (COX, also called prostaglandin H-Synthase or PGHS) is a bifunctional enzyme exhibiting both cyclooxygenase and peroxidase activities. The cyclooxygenase component converts arachidonic acid to a hydroperoxy endoperoxide (prostaglandin G<sub>2</sub>; PGG<sub>2</sub>), and the peroxidase component reduces the endoperoxide to the corresponding alcohol (prostaglandin H<sub>2</sub>; PGH<sub>2</sub>), the precursor of prostaglandins, thromboxanes, and prostacyclins.<sup>2</sup>

This inducible COX-2 is believed to be the target enzyme for the anti-inflammatory activity of nonsteroidal anti-inflammatory drugs.<sup>1</sup>

Conventional non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to treat pain and inflammation. The development of new agents with a safe profile, which are NSAIDs, is still popular.<sup>3</sup>

## MATERIAL AND METHODS

### Anti-Inflammatory Activity:

#### Materials:

Oedema was produced by using type IV lambda carrageenan from sigma laboratories. Foot volumes were measured in Plethysmometer by water displacement.

The instrument was calibrated before performing the experiment using standard calibrated probe number and standard drug used Indomethacin was obtained from Lincoln Pharmaceuticals Ltd. Ahmedabad.

#### Method:

#### Carrageenan Induced Rat hind Paw Edema:<sup>4</sup>

Anti-inflammatory activity was determined by Carrageenan Induced Rat hind Paw method of winter et al. wistar rats (120-150 g) was used for the experiment. The drugs were prepared as a suspension by triturating with water and 0.5% sodium CMC. The standard group received 50mg/kg body weight of Nimesulide, test group received 200mg/kg body weight of synthesized compounds and the control group received 1% w/v of CMC.

The difference between 0hour reading and one of the subsequent readings provides the actual edema volume at that time. The mean paw volume at different times was calculated and compared with the control. The percentage inhibition of inflammation after 4 hour was then calculated by using the formula.

## EXPERIMENTAL:

### A] Preparation of diethyl 2-((3-chloro-4-fluorophenylamino) methylene) malonate (I<sub>1</sub>).<sup>5</sup>

A mixture of 3-chloro-4-fluoro-aniline (0.01mol) and Diethyl ethoxy methylene malonate (0.01mol) was heated at 120-130<sup>0</sup>C for two hours the resulting ethanol was evaporated off. The crude solid was filtered, dried and recrystallized from n-hexane; Yield was found to be 88%. M.P. 54-55<sup>0</sup>C.

### B] Preparation of ethyl 7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate(I<sub>2</sub>).<sup>6</sup>

Diphenyl ether was heated under stirring at 240<sup>0</sup>C. 0.158 mol of ethyl anilinomethylene malonate was added slowly to the boiling diphenyl ether for about 15 minutes after adding the mixture was refluxed in oil bath for two hours. The mixture was cooled, filtered and washed twice with 200 ml pet ether. The crude solid obtained was dried and purified by recrystallization twice from DMF; Yield was found to be 78%. M.P. >270<sup>0</sup>C.

### C] Preparation of 7-chloro-6-fluoro-4-oxo-1, 4-dihydroquinoline-3-carbo hydrazide (I<sub>3</sub>).<sup>7</sup>

Ethyl 7-chloro-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylate I<sub>2</sub> (0.035 mol) in ethanol (20mL), DMF (10mL) was added to 99% hydrazine hydrate (0.035mol) and was refluxed for 12 hours. Excess solvent was removed by distillation and the mixture was poured into crushed ice. The solid separated was filtered, washed with water and dried. The crude solid was purified by recrystallized from ethanol dioxan mixture (1:1) to give whitish-brown solid; Yield was found to be 80%. M.P. 245-247<sup>0</sup>C.

**D] Preparation of 7-chloro-6-fluro-3-(3-methyl-5-oxo-4, 5 dihydropyrazole-1-carbonyl) quinolin-4(IH)-one (I<sub>4</sub>).**<sup>7</sup>

7-chloro-6-fluro-4-oxo-1,4-dihydroquinoline-3-carbohydrazide I<sub>3</sub> (0.018 mol) in ethanol (20 mL) was added to ethyl acetoacetate (0.02 mol) and refluxed for 4 hours. To this mixture 2mL of acetic acid was added and further refluxed for two hours. Excess of solvent was removed and the mixture was poured into ice-water. The solid separated was filtered, washed with water and dried. It was purified by recrystallized from ethanol to afford whitish amorphous solid; Yield was found to be 67%. M. P 218-220<sup>0</sup>C.

**E] Preparation of 6-fluro-3-(3-methyl-5-oxo-4, 5-dihydro- H-pyrazole-1-carbonyl)-7-(substituted) quinolin-4(IH)-one (V<sub>1</sub>-V<sub>5</sub>).**<sup>8</sup>

The mixture of 7-chloro-6-fluro-3-(3-methyl-5-oxo-4, 5 dihydropyrazole-1-carbonyl) quinolin-4(IH)-one (0.005 mole), Piperazine (0.01 mole), Pyridine (10 mL) and Triethyl amine (3mL) was stirred at 120-130<sup>0</sup>C for 10 hours. After completion of the reaction, the reaction mixture was cooled to room temperature. The mixture was poured into crushed ice and neutralized with dilute HCl. The solid product was filtered dried and recrystallized from DMF and Ethanol (2:1). Similarly V<sub>2</sub>, V<sub>3</sub>, V<sub>4</sub> and V<sub>5</sub> were prepared by using Morpholin, Imidazole, Piperadine and Pyrollidine. Analytical data's were given in the table.

**F] Preparation of 7-chloro-6-fluro-3-(5-substituted-1, 3, 4-oxadiazole-2-yl) quinolin-4(IH)-one (P<sub>1</sub>-P<sub>7</sub>).**<sup>8,9</sup>

A mixture of an equimolar quantity of 7-chloro-6-fluro-4-oxo-1, 4-dihydroquinoline-3-carbohydrazide I<sub>3</sub> (0.006mol) and substituted aromatic acids (0.006) in 15 mL of phosphorus oxychloride was refluxed for 8 hours. The progress of the reaction was monitored by TLC using ethyl acetate: acetone (9:1) as eluent. The reaction mixture was cooled and poured carefully on to crushed ice (200g) with constant stirring and neutralized with sodium bicarbonate solution (10% w/v). The resulting solid thus obtained was collected by filtration, washed well with cold water, dried and recrystallized from ethanol: DMF (2:1) to give (P<sub>1</sub>-P<sub>7</sub>). Analytical data was given in the table.

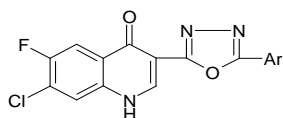
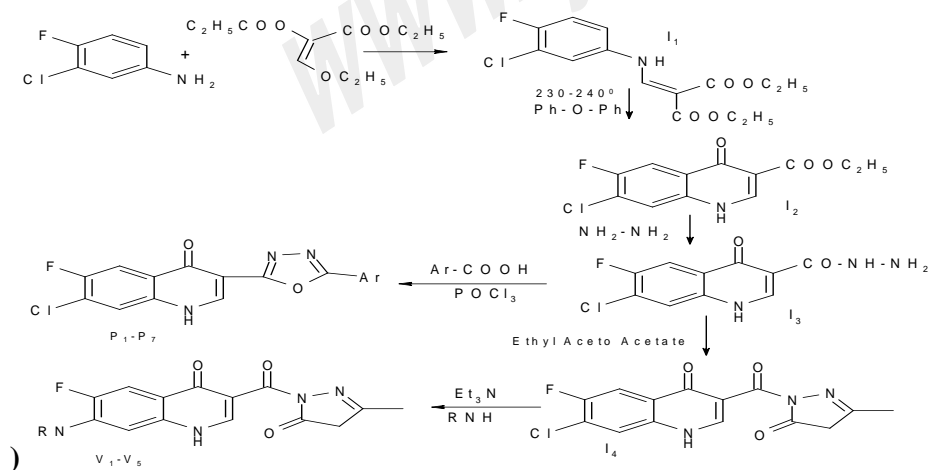
## RESULT AND DISCUSSION

In the present research work about thirteen new Quinoline derivatives were synthesized as mentioned in the scheme and experimental work.

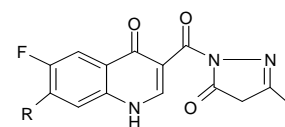
All these compounds were tested for their purity by TLC and melting point. The structure of these quinolones were confirmed by IR NMR and CHN analysis All these were found to be satisfactory.

The synthesized compounds were evaluated for anti-inflammatory activity by Paw edema method using carragenan. The inflammation was measured by PM these compounds were given by IM . There was significant reduction in the inflammation. Compounds V<sub>1</sub>, V<sub>3</sub>, V<sub>5</sub>, P<sub>4</sub>, P<sub>5</sub> shows promising anti-inflammatory activity. The readings were calculated by One way ANOVA followed by Dunnet’s t test. Indomethacin is used as standard drug with suitable molecular modification and manipulations, these compounds may be excellent anti-inflammatory agents in future.


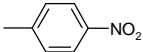
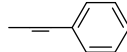
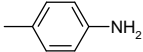
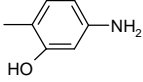
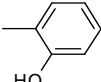
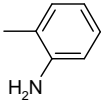
**SCHEME- (P<sub>1</sub>-P<sub>7</sub>, V<sub>1</sub>-V<sub>5</sub>)**



Compound	-Ar
P <sub>3</sub>	
V <sub>1</sub>	
V <sub>4</sub>	
V <sub>2</sub>	
V <sub>5</sub>	



Compound	-Ar
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<b>P<sub>1</sub></b>	
<b>P<sub>2</sub></b>	
<b>P<sub>3</sub></b>	
<b>P<sub>4</sub></b>	
<b>P<sub>5</sub></b>	
<b>P<sub>6</sub></b>	
<b>P<sub>7</sub></b>	

**Table No. 1 Analytical data of 6-fluro-quinolin-4(1H)-one compounds  
(scheme-I).**

Comp.	Mol. Formula	Mol. Wt.	M.P °C	Yield %	Elemental analyses			LogP	CLogP	CMR
					Calcd. (Found)					
					C	H	N			
<b>I<sub>4</sub></b>	C <sub>14</sub> H <sub>9</sub> ClFN <sub>3</sub> O <sub>3</sub>	322.	218	67	52.27	2.82	13.06	0.65	-0.513	7.810
<b>V<sub>1</sub></b>	C <sub>18</sub> H <sub>18</sub> FN <sub>5</sub> O <sub>3</sub>	371	182-183	78	58.22	4.89	18.86	-0.25	-1.717	9.734
<b>V<sub>2</sub></b>	C <sub>18</sub> H <sub>17</sub> FN <sub>4</sub> O <sub>4</sub>	372	>270	67	58.06 (58.03)	4.60 (4.57)	15.05 (15.04)	-0.03	-1.703	9.518
<b>V<sub>3</sub></b>	C <sub>17</sub> H <sub>12</sub> FN <sub>5</sub> O <sub>3</sub>	353	264	66	57.79	3.42	19.82	-0.71	-1.349	9.048

<b>V<sub>4</sub></b>	C <sub>19</sub> H <sub>19</sub> FN <sub>4</sub> O <sub>3</sub>	370	166-168	75	61.61 (61.54)	5.17 (5.14)	15.13 (15.8)	1.11	-0.321	9.829
<b>V<sub>5</sub></b>	C <sub>18</sub> H <sub>17</sub> FN <sub>4</sub> O <sub>3</sub>	356	238-240	61	60.67 (60.28)	4.81 (4.76)	15.72 (15.58)	0.69	-0.880	9.365
<b>P<sub>1</sub></b>	C <sub>17</sub> H <sub>9</sub> ClFN <sub>3</sub> O <sub>2</sub>	342	106	29	59.75	2.65	12.30	3.08	1.600	8.699
<b>P<sub>2</sub></b>	C <sub>17</sub> H <sub>8</sub> ClFN <sub>4</sub> O <sub>4</sub>	387	183-184	60	52.80 (52.74)	2.09 (1.92)	14.49 (14.42)	--	1.393	9.311
<b>P<sub>3</sub></b>	C <sub>19</sub> H <sub>11</sub> ClFN <sub>3</sub> O <sub>2</sub>	368	94-96	35	62.05	3.01	11.43	3.87	2.194	9.905
<b>P<sub>4</sub></b>	C <sub>17</sub> H <sub>10</sub> ClFN <sub>4</sub> O <sub>2</sub>	357	233	63	57.24	2.83	15.71	2.28	0.643	9.068
<b>P<sub>5</sub></b>	C <sub>17</sub> H <sub>10</sub> ClFN <sub>4</sub> O <sub>3</sub>	373	258-260	44	54.78 (54.66)	2.70 (2.64)	15.03 (14.87)	1.89	-0.037	9.221
<b>P<sub>6</sub></b>	C <sub>17</sub> H <sub>9</sub> ClFN <sub>3</sub> O <sub>3</sub>	358	100-102	58	57.08	2.54	11.75	2.69	0.919	8.852
<b>P<sub>7</sub></b>	C <sub>17</sub> H <sub>10</sub> ClFN <sub>4</sub> O <sub>2</sub>	357	138-140	38	57.24 (57.18)	2.83 (2.80)	15.71 (15.67)	2.28	0.643	9.068

The combustion analysis of compounds synthesized was found to be within the limits of permissible errors

**Table No. 2: Spectral data of 6-fluro-quinolin-4(1H)-one compounds:**

Compound	IR Bands (cm <sup>-1</sup> )	Types of Vibrations	δ ppm	Proton nature
<b>I<sub>4</sub></b>	1691,115,987 801,2795,1290	-C=O str.-N-H str. -C-H Ar. str.-C-Cl str.-C-H Alkyl. str. -C-F str.		
<b>V<sub>1</sub></b>	1697,428, 3385 3109,038,262 1036,53, 899	-C=O str.-N-H str. -C-H Ar. str.-C-H Alkyl. str.-C-F str. -C-N Piperazine -C-H def.		
<b>V<sub>2</sub></b>	1666,34323057, 2990,2856,1260 1174,798, 806	-C=O str.-N-H str. -C-H Ar. str.-C-H Alkyl. str.-C-F str.-C-O strMorpholine -C-H def.	1.23-1.28 2.4859 3.24-3.31 7.00-7.73	3H, -CH <sub>2</sub> H, -CH <sub>2</sub> Pyrazole 4H, Morpholine 3H, -Ar-CH
<b>V<sub>3</sub></b>		-C=O str.-N-H str.		

	1690,3156, 3121 2988,2899,2876 1263,1111,844, 893	-C-H Ar. str.C-H Alkyl. str.-C-F str. -C-N str. Imidazole -C-H def.		
<b>V<sub>4</sub></b>	1699,3106,2989 2857,1284,1101 787, 808	-C=O str.-N-H str. -C-H Ar. str.-C-H Alkyl. str.-C-F str. -C-N str.Piperidine -C-H def.	1.23-1.28 2.4-2.7 3.24-3.31 7.93-7.96 12.41	3H , -CH <sub>3</sub> 2H , - CH <sub>2</sub> Pyrazole 8H, Piperidine 3H, -Ar-CH 1H, -N-H
<b>V<sub>5</sub></b>	1678,3284,3049 2852,2920,1256 1164,1516	-C=O str.-N-H str. -C-H Ar. str.-C-H Alkyl. str.-C-F str. -C-N str. Pyrollidine-C-N Ar. str.	13.24,1.22 3.74,7.92	1H, -N-H3H,CH <sub>3</sub> 8H,Pyrollidine3 H, -Ar-CH
<b>P<sub>1</sub></b>	33431628,3102, 2911,740,1537 1007	-N-H str.-C=O str. -C-H Ar. Str-C-Cl str.-C=N Ar str. -C-O Ether str.		
<b>P<sub>2</sub></b>	3123,1696,3000, 2918,1274,1620 1539	-N-H str.-C=O str. -C-H Ar. str.-C-F str.-C=N Ar str. -N=O str.	10.9 7.87-7.91 6.97-7.37	1H, -N-H3H, Quinolone 3H, -Ar-CH
<b>P<sub>3</sub></b>	3451,1697,3071, 2866,1259,1603, 1588,810,3079, 3071	-N-H str.-C=O str.- C-H Ar. str.-C-F str.-C=N Ar str. -C-H def.CH=CH-.		
<b>P<sub>4</sub></b>	3422,1585,3310, 2928,1240,1516 684	-N-H str.-C=O str. -C-H Ar. str.-C-F str.-C=N Ar str. C-Cl str.		
<b>P<sub>5</sub></b>	3437,1586,3063, 3003,1240,1528 1086,3387	-N-H str.-C=O str. -C-H Ar. str.-C-F str.-C=N Ar str.-C- O Ether str-OH str	5.03,9.94 6.41 8.14-8.17 13.78	2H, -NH21H, OH3H, -Ar-CH 3H, Quinolone 1H, -N-H
<b>P<sub>6</sub></b>	3304,1665,3053, 3011,1220,1555 1138,3113,675	-N-H str.-C=O str. -C-H Ar. str.-C-F str.-C=N Ar str.-C- O Ether str-OH str. -C-Cl str.		
<b>P<sub>7</sub></b>	3427,1703,3061, 2925,1257,1613 1227,691,758	-N-H str.-C=O str. -C-H Ar. str.-C-F str.-C=N Ar str. -C-O Ether str-C- Cl str.-C-H def.	13.86,4.98 7.93-8.16 7.35-7.37	1H, -N-H2H, - NH23H,Quinolo ne4H, -Ar-CH

**Table No.3: Anti-inflammatory activity of Quinolin-4(1H)-one compounds:**

Comp	Mean paw oedema volume $\pm$ SE					% inhibition at 4 <sup>th</sup> hr
	0 hour	1 hour	2 hour	3 hour	4 hour	
<b>Ct.</b>	0.975 $\pm$ 0.025	1.475 $\pm$ 0.025	1.650 $\pm$ 0.028	1.775 $\pm$ 0.025	1.842 $\pm$ 0.012	
<b>Std.</b>	0.975 $\pm$ 0.025	1.225 $\pm$ 0.025*	1.325 $\pm$ 0.025**	1.350 $\pm$ 0.028**	1.275 $\pm$ 0.025**	<b>44.47</b>
<b>I<sub>4</sub></b>	1.10 $\pm$ 0.040	1.225 $\pm$ 0.025*	1.480 $\pm$ 0.040*	1.575 $\pm$ 0.025**	1.625 $\pm$ 0.025**	13.35
<b>V<sub>1</sub></b>	<b>1.000<math>\pm</math>0.021</b>	<b>1.350<math>\pm</math>0.028</b>	<b>1.425<math>\pm</math>0.045</b> **	<b>1.500<math>\pm</math>0.040</b> **	<b>1.425<math>\pm</math>0.047</b> **	<b>29.26</b>
<b>V<sub>2</sub></b>	1.040 $\pm$ 0.0	1.400 $\pm$ 0.042	1.575 $\pm$ 0.025 ns	1.600 $\pm$ 0.0**	1.635 $\pm$ 0.025*	12.266
<b>V<sub>3</sub></b>	<b>1.060<math>\pm</math>0.0</b>	<b>1.375<math>\pm</math>0.025</b>	<b>1.435<math>\pm</math>0.028</b> **	<b>1.440<math>\pm</math>0.025</b> **	<b>1.320<math>\pm</math>0.040</b> **	<b>39.54</b>
<b>V<sub>4</sub></b>	0.975 $\pm$ 0.025	1.350 $\pm$ 0.028	1.575 $\pm$ 0.025 ns	1.575 $\pm$ 0.025**	1.675 $\pm$ 0.028*	9.97
<b>V<sub>5</sub></b>	<b>0.975<math>\pm</math>0.025</b>	<b>1.400<math>\pm</math>0.041</b>	<b>1.490<math>\pm</math>0.025</b> *	<b>1.420<math>\pm</math>0.025</b> **	<b>1.364<math>\pm</math>0.028</b> **	<b>35.04</b>
<b>P<sub>1</sub></b>	0.950 $\pm$ 0.0	1.350 $\pm$ 0.029	1.575 $\pm$ 0.025	1.660 $\pm$ 0.025	1.610 $\pm$ 0.025	14.40

	28		ns	ns	*	
<b>P<sub>2</sub></b>	1.000±0.1 2	1.425±0.063	1.550±0.028 ns	1.575±0.025 ns	1. 59±0.025ns	15.84
<b>P<sub>3</sub></b>	0.975±0.0 25	1.375±0.047	1.475±0.047 **	1.610±0.120 *	1.575±0.025 *	16.95
<b>P<sub>4</sub></b>	<b>0.950±0.0 28</b>	<b>1.350±0.029</b>	<b>1.475±0.025 **</b>	<b>1.500±0.040 **</b>	<b>1.402±0.028 **</b>	<b>31.38</b>
<b>P<sub>5</sub></b>	<b>0.975±0.0 25</b>	<b>1.350±0.028</b>	<b>1.500±0.040 *</b>	<b>1.600±0.0**</b>	<b>1.370±0.025 *</b>	<b>34.45</b>
<b>P<sub>6</sub></b>	0.975±0.0 25	1.445±0.063	1.560±0.028 ns	1.525±0.025 **	1.570±0.025 *	17.32
<b>P<sub>7</sub></b>	0.950±0.0 28	1.375±0.048	1.580±0.040 ns	1.575±0.025 ns	1.525±0.025 ns	20.78

One way ANOVA followed by Dunnett's 't' test      \*\*P<0.01

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