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RESEARCH ARTICLE

EFFICIENT SYNTHESIS, ANTI-INFLAMMATORY AND ANTIBACTERIAL PROPERTIES OF 9-ARYL-6-(3-METHYLPHENYL)[1,2,4]TRIAZOLO[4,3-A]QUINOLINES

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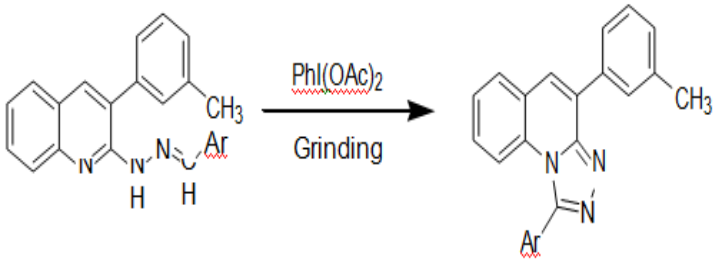
Abstract

A simple and highly efficiently method for the synthesis of 9-aryl-6- (3-methylphenyl)[1,2,4]triazolo [4,3-*a*]quinolines **8** by the oxidation of the corresponding aryl aldehyde 1-[3-(3-methylphenyl)quinolin-2-yl]hydrazones **7** using iodobenzene diacetate [PhI(OAc)$_2$] in the solid state at RT under grinding conditions is described. The yields are very good and purity is high. The structures of compounds **3-8** were confirmed by their spectroscopic (IR, ^{1}H NMR and MS) and analytical data. The compounds **8** have been tested for their antibacterial and anti-inflammatory activities.



Introduction:-

Fused 1,2,4-triazoles have emerged as an important class of nitrogen heterocycles attracting significant synthetic interest because of their pharmacological and biological activities. Though various methods for the synthesis of these compounds are known, some involve long reaction times, toxic oxidants and high reaction temperatures and even then may produced low yields. Therefore a convenient and eco-friendly method for the synthesis of fused 1,2,4-triazoles is highly desirable. quinolines are very interesting compounds with wide ranging biological properties. In recent years, iodobenzene diacetate [PhI(OAc)2] has emerged as a potential oxidizing agent in different areas of organic synthesis, because it is non-toxic and easy to handle. Solid state reactions without using harmful organic solvents is of great interest especially in relation to environmental concerns today. So, the grinding method has increasingly been used in organic synthesis in recent years. Compared to traditional methods, many organic reactions occur more efficiently in the solid state than in solution and in some cases even more selectively. Furthermore, the solid state reaction has many advantages: reduction pollution, low costs and simplicity in process and handling. These factors are beneficial to industry as well as to environment.

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Inspired by these facts and in continuation of our interest on solid state(solvent-free) organic transformations of quinoline derivatives, we report herein, a simple, efficient and convenient method for the 9-aryl-6- (3-methylphenyl)[1,2,4]triazolo[4,3-a]quinolines using iodobenzene diacetate [PhI(OAc)2] in the solid state.

Results and Discussion:-

Condensation of 2-aminobenzaldehyde 1 with 3-methylphenyl- acetonitrile 2 in the presence of solid KOH under solvent-free grinding conditions at RT afforded 3-(3-methylphenyl) quinoline-2-amine 3, which is converted into 3-(3-methylphenyl)-1,2-dihydro quinoline-2-one 4 by the reaction with HNO2. Treatment of 4 with POCl3 under microwave irradiation yielded 2-chloro-3-(3-methylphenyl) quinoline 5, which on hydrazinolysis with refluxing hydrazine hydrate furnished 2-hydrazino- 3- (3-methylphenyl) quinoline 6.

The hydrazine 6 on condensation with various aromatic aldehydes in the presence of catalytic amount of PTSA in solvent-free grinding conditions at RT afforded the corresponding aryl aldehyde 1-[3-(3-methylphenyl) quinoline-2-yl] hydrazones 7 in excellent yields.

Oxidative cyclization of hydrazones 7 with PhI(OAc)2 in the solid state at RT yielded the respective 9-aryl-6-(3-methylphenyl)[1,2,4]triazolo[4,3-a] quinolines 8 (Scheme I). The reaction is facile, clean, efficient and is devoid of any by-products. The reactions proceed efficiently in very good yields (85-94%) within a few minutes. Furthermore, it is to be noted highly pure products were obtained using this simple procedure and in most cases no further purification was needed. The process is enviro-friendly. The experimental procedure is very simple and avoids sophistication.

In a typical case, a mixture of hydrazone 7a (Ar = C6H5) and PhI(OAc)2 was ground in a mortar by pestle at RT for 7.0 min. The solid was combined with cold water and filtered to give 6-(3-methylphenyl)-9-phenyl [1,2,4]triazolo[4,3-a] quinoline 8a (Ar = C6H5) in 87% yield.The generality of this oxidative transformation was established by treating other hydrazones 7b-j with PhI(OAc)2 under solid state grinding conditions and in all cases respective 9-aryl-6-(3-methylphenyl)[1,2,4]triazolo [4,3-a] quinolines 8b-j were obtained in 84-94% yields (Table II).

The structural assignment of compounds 3-8 were based on their elemental analysis and spectral (IR, 1H NMR and MS) data (Table I and II). The advantages of this protocol include a simple reaction set-up not requiring specialized equipment, short reaction times, non-toxicity of the reagent, mild reaction conditions and high product yields with excellent purity.

Antibacterial activity

All the compounds 8 were screened for their antibacterial activity against Escherichia coli and Bacillus subtilis using Gentamycin as standard drug. The activity was determined using filter paper disc technique of Vincent and Vincent at 250 and 500 □ g/discconcentrations. The results are given inTable-III. All the compounds were active against both the bacteria at the concentration of 250 □ g/disc. The activity of the compound depends upon the nature and position of the substituent at the phenyl group. Compounds 8b, 8d, 8e and 8f promising significant antibacterial activity and the remaining compounds exhibited either good or moderate antibacterial activity. Introduction of nitro group at aryl moiety decreases the activity of the compounds. The compound 8e showed significant activity against both the organisms comparable with that of Gentamycin.

Anti-inflammatory activity

The anti-inflammatory activity of the compounds 8 were tested by applying carrageenan induced rat paw edema method, using Diclofenac sodium as reference drug for comparison. The results are presented in Table IV. The screening data indicate that all the compounds 8a-j exhibited interesting activity, however with a degree of variation. The compounds 8c, 8d, 8e, 8i and 8j exhibited significant anti-inflammatory activity. Rest of the compounds showed moderate anti-inflammatory activity.

Experimental Section

Melting points were measured on a Cintex melting point apparatus and are uncorrected. Homogeneity of the compounds was checked using precoated TLC plates (Merk, 60F-254). IR spectra (KBr) were recorded on a Perking-Elmer FT-IR spectrophotometer, 1H NMR spectra on a Varian Gemini 300 MHz spectrometer (chemical shifts in δ ppm) and mass spectra on a PE-SCIEX API 3000 LC-MS/MS System. The 3-methylphenylacetonitrile 2 was purchased from Aldrich Chemical Company.

3-(3-Methylphenyl) quinolin-2-amine 3

A mixture of 2-aminobenzaldehyde 1 (0.01 mol), 3-methylphenylacetonitrile 2 (0.01 mol) and solid KOH (0.01 mole) was ground by pestle and mortar at RT for 2.0 min. After completion of the reaction, as monitored by TLC, the reaction mixture was treated with cold water. The solid obtained was filtered, washed with water and purified by recrystallization from methanol to afforded 3, yield 97%; m.p. 195oC. Anal. Calcd for C15H13N2: C, 76.57; H, 5.57; N, 17.86. Found: C, 76.68; H, 5.58; N, 17.90%. IR (KBr): 3466, 3076 (NH2), 1634 (C-NH2), 1591 cm-1 (C=N); 1H NMR (300 MHz, CDCl3): □ 2.42 (s 3H, CH3),5.46 (s, 2H, NH2), 7.40 (m, 1H, C6-H), 7.74 (s, 1H, C4-H), 7.96 (m, 1H, C5-H), 8.83
(m, 1H, C7-H), 7.18-7.32 (m, 4H, Ar-H); LC-MS: m/z 222.1568 [M+H]+
3-(3-Methylphenyl)-1,2-dihydro quinolin-2-one 4

To a cold solution of 3 (0.01 mol) in 2 M HCl (25 mL) was added NaNO2 solution (0.01 mol in 25 mL water) and the reaction mixture was stirred at RT for 0.5 hr and treated with chilled water. The precipitated solid was filtered, washed with water and purified by recrystallization from methanol to obtain 4, yield 96%; m.p. 182oC. Anal. Calcd for C15H12NO: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.35; H, 5.14; N, 11.89%. IR (KBr): 3163 (NH), 1649 (C=O),
1598 cm-1 (C=N); 1H NMR (300 MHz, CDCl3): □ □ 2.43 (s 3H, CH3), 7.55 (m, 1H, C6-H), 7.81 (s, 1H, C4-H), 7.96 (m,
1H, C5-H), 8.70 (m, 1H, C7-H), 7.20-7.42 (m, 4H, Ar-H), 9.75 (brs, 1H, NH); LC-MS: m/z 213.1849 [M+H]+
2-Chloro-3-(3-methylphenyl) quinoline 5

A mixture of 4 (0.01 mol) and POCl3 (10 mL) was refluxed for 1.5 hr. The reaction mixture was cooled and poured onto a mixture of crushed ice and NaHCO3. The separated solid was filtered, washed with water and purified by recrystallization from ethanol to afford 5, yield 95%; m.p. 142oC. Anal. Calcd for C15H11ClN: C, 70.73; H, 4.35; N, 11.00. Found: C, 70.84; H, 4.37; N, 11.04%. IR (KBr): 1593 cm-1 (C=N); 1H NMR (300 MHz, CDCl3): □ 2.44 (s 3H, CH3), 7.55 (m, 1H, C6-H), 8.12 (s, 1H, C4-H), 8.23 (m, 1H, C5-H), 9.15 (m, 1H, C7-H), 7.22-7.42 (m, 4H, Ar-H); LC-MS: m/z 241.1691 [M+H]+

2-Hydrazino-3-(3-methylphenyl) quinoline 6
A mixture of 5 (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 mL) was refluxed on a water bath for 4.0 hr. The reaction mixture was cooled and poured into ice-cold water. The solid separated was filtered, washed with water and purified by recrystallization from ethanol to yield 6, yield: 96%; m.p. 108oC. Anal. Calcd for C15H14N3: C, 71.98; H, 5.64; N, 22.38. Found: C,
72.09; H, 5.65; N, 22.42%. IR (KBr): 3433, 3328, 3171 (NHNH2), 1616 (C-NHNH2),
1560 cm-1 (C=N); 1H NMR (300 MHz, CDCl3): □ □ 2.40 (s 3H, CH3), 6.15 (brs, 2H, NH2), 7.62 (m, 2H, C4H, C6-H), 7.98 (m, 1H, C5-H), 8.83 (m, 1H, C7-H), 7.18-7.38 (m, 5H, NH, 4Ar-H); LC-MS: m/z 247.1852[M+H]+
General procedure for the synthesis of aryl aldehyde 1-[3- (3-methylphenyl) quinolin-2-yl]hydrazones 7

A mixture of 6 (0.01 mole), aromatic aldehyde (0.01 mol) and PTSA (0.015 mol) was ground by pestle and mortar at RT for the specified time (Table II). On completion of the reaction (monitored by TLC), the reaction mixture was treated with ice-cold water. The product which separated was filtered, washed with water and purified by recrystallization from ethanol to give 7 (Table II).

General procedure for the synthesis of 9-aryl-6-(3-methylphenyl) [1,2,4]triazolo[4,3-a] quinolines 8

A mixture of appropriate hydrazone 7 (0.01 mol) and PhI(OAc)2 (0.01 mol) was ground in a mortar by pestle at RT for the period indicated in Table II. After complete conversion as indicated by TLC, the reaction mixture was digested with cold water. The separated solid was filtered, washed with water and purified by recrystallization from ethanol to furnish 8 (Table II).

Conclusion:-

We have demonstrated a simple and efficient procedure for the synthesis of quinolines By employing Oxidative cyclization of hydrazones with PhI(OAc)2 in the solid state at RT .

The salient features of this method include operational simplicity, improved reaction rates, high yields of products.

Table I:- IR, ^{1}H NMR and mass spectral data of compounds **7** and **8**

Compd	IR (KBr) max in cm^{-1}

		^{1}H NMR (300 MHz, CDCl3) (□, ppm)	LC-MS $[M+H]^+$ m/z
7a	3344 (NH), 1619 (C=N)	2.40 (s, 3H, CH_3), 7.65 (m, 1H, C_6-H), 7.80 (m, 2H, C_4-H, C_5-H), 8.30 (m, 1H, C_7-H), 8.47 (s, 1H, N=CH), 6.98-7.60 (m, 9H, Ar-H) 10.28(s, 1H, NH).	339.223
7b	3353 (NH), 1618(C=N)	2.40 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 7.68(m, 1H, C_6-H), 7.75 (m, 2H, C_4-H, C_5-H), 8.32 (m, 1H, C_7-H), 8.43 (s, 1H, N=CH), 6.97-7.65 (m, 8H, Ar-H), 10.26 (s, 1H, NH).	353.260
7c	3346 (NH), 1614 (C=N)	2.42 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.76(m, 2H, C_4-H, C_6-H), 8.03 (m, 1H, C_5-H), 8.30 (m, 1H, C_7-H), 8.45 (s, 1H, N=CH), 6.90-7.65 (m, 8H, Ar-H), 10.25 (s, 1H, NH).	369.256
7d	3352 (NH), 1621 (C=N)	2.43 (s, 3H, CH_3), 7.70 (m, 2H, C_4-H, C_6-H), 8.00 (m, 1H, C_5-H), 8.38 (m, 1H, C_7-H), 8.43 (s, 1H, N=CH), 6.98-7.65 (m, 8H, Ar-H), 10.24 (s, 1H, NH).	373.225
7e	3343 (NH), 1619 (C=N)	2.45 (s, 3H, CH_3), 7.72 (m, 2H, C_4-H, C_6-H), 8.02 (m, 1H, C_5-H), 8.36 (m, 1H, C_7-H), 8.42 (s, 1H, N=CH), 7.00-7.63 (m, 8H, Ar-H), 10.27 (s, 1H, NH).	373.22
7f	3349 (NH), 1623 (C=N)	2.43 (s, 3H, CH_3), 7.76 (m, 1H, C_6-H), 7.97 (m, 2H, C_4-H, C_5-H), 8.40 (m, 1H, C_7-H), 8.53 (s, 1H, N=CH), 7.08-7.52 (m, 8H, Ar-H), 10.35 (s, 1H, NH).	357.24
7g	3334 (NH), 1620 (C=N)	2.44 (s, 3H, CH_3), 7.76 (m, 1H, C_6-H), 8.00 (m, 2H, C_4-H, C_5-H), 8.40 (m, 1H, C_7-H), 8.50 (s, 1H, N=CH), 7.04-7.48 (m, 8H, Ar-H), 10.28 (s, 1H, NH).	384.21
7h	3350 (NH), 1623 (C=N)	2.43 (s, 3H, CH_3), 7.73 (m, 1H, C_6-H), 8.02 (m, 2H, C_4-H, C_5-H), 8.36 (m, 1H, C_7-H), 8.48 (s, 1H, N=CH), 7.02-7.46 (m, 8H, Ar-H), 10.35 (s, 1H, NH).	384.21
7i	3342 (NH), 1622 (C=N)	2.45 (s, 3H, CH_3), 7.75 (m, 1H, C_6-H), 7.95 (m, 2H, C_4-H, C_5-H), 8.38 (m, 1H, C_7-H), 8.52 (s, 1H, N=CH), 7.07-7.50 (m, 8H, Ar-H), 10.32 (s, 1H, NH).	384.21
7j	3353 (NH), 1619 (C=N)	2.41 (s, 3H, CH_3), 3.93 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 7.50 (m, 2H, C_4-H, C_6-H), 7.65 (m, 1H, C_5-H), 8.32 (m, 1H, C_7-H), 8.40 (s, 1H, N=CH), 6.85-7.36 (m, 7H, Ar-H), 10.17 (s, 1H, NH).	399.2

Table I:- IR, ^{1}H NMR and mass spectral data of compounds **7** and **8 -** Contd..

Compd	IR (KBr) max in cm^{-1}	^{1}H NMR (300 MHz, CDCl3) (□ , ppm)	LC-MS $[M+H]^+$ m/z
8a	1608 (C=N)	2.45 (s, 3H, CH_3), 7.88 (m, 2H, C_3-H, C_5-H), 8.18 (m, 1H, C_4-H), 8.42(m, 1H, C_2-H), 7.23-7.60 (m, 9H, Ar-H).	337.1918
8b	1610(C=N)	2.46(s,3H,CH_3)2.48 (s, 3H, CH_3), 7.80 (m, 2H, C_3-H, C_5-	351.2147

		H), 8.30 (m, 1H, C4-H), 8.45 (m, 1H, C2-H), 7.25-7.58 (m, 8H, Ar-H)	
8c	1611 (C=N)	2.45 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 7.85 (m, 2H, C3-H, C5-H), 8.16 (m, 1H, C4-H), 8.43 (m, 1H, C2-H), 7.00-7.60 (m, 8H, Ar-H).	367.2282
8d	1606(C=N)	2.48(s, 3H, CH_3), 7.83 (m, 2H, C3-H, C5-H), 8.18 (m, 1H, C4-H), 8.42 (m, 1H, C2-H), 7.23-7.62 (m, 8H, Ar-H).	371.1838
8e	1608(C=N)	2.46 (s, 3H, CH_3), 7.86 (m, 2H, C3-H, C5-H), 8.24 (m, 1H, C4-H), 8.40 (m, 1H, C2-H), 7.20-7.58 (m, 8H, Ar-H).	371.1838
8f	1607(C=N)	2.49 (s, 3H, CH_3), 7.85(m, 2H, C3-H, C5-H), 8.16(m, 1H, C4-H), 8.42 (m, 1H, C2-H), 7.18-7.60 (m, 8H, Ar-H).	355.2121
8g	1606 (C=N)	2.46 (s, 3H, CH_3), 7.87 (m, 2H, C3-H, C5-H), 8.20 (m, 1H, C4-H), 8.46 (m, 1H, C2-H), 7.24-7.62 (m, 8H, Ar-H).	382.2120
8h	1604 (C=N)	2.45 (s, 3H, CH_3), 7.85 (m, 2H, C3-H, C5-H), 8.18 (m, 1H, C4-H), 8.43 (m, 1H, C2-H), 7.22-7.63 (m, 8H, Ar-H).	382.2120
8i	1601 (C=N)	2.48 (s, 3H, CH_3), 7.86 (m, 2H, C3-H, C5-H), 8.16 (m, 1H, C4-H), 8.45 (m, 1H, C2-H), 7.20-7.60 (m, 8H, Ar-H).	382.2120
8j	1610 (C=N)	2.45 (s, 3H, CH_3), 3.92 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 7.87 (m, 2H, C3-H, C5-H), 8.18 (m, 1H, C4-H), 8.45(m, 1H, C2-H), 6.98-7.58 (m, 7H, Ar-H).	397.2562

Table II:- Physical and analytical data of compounds **7** and **8**

Compd	Reaction time (min)	m.p. ^oC	Yield (%)	Mol. formula	Found (%) (Calcd) C	H	N
7a	1.5	76	96	$C_{22}H_{18}N_3$	78.19	5.37	16.
					78.08	5.36	16.
7b	2.0	91	97	$C_{23}H_{20}N_3$	78.48	5.74	15.
					78.38	5.72	15.
7c	2.0	95	94	$C_{23}H_{20}N_3O$	75.09	5.49	15.
					74.98	5.47	15.
7d	1.5	103	95	$C_{22}H_{17}ClN_3$	70.97	4.62	15.
					70.87	4.60	15.
7e	2.0	165	97	$C_{22}H_{17}ClN_3$	70.98	4.61	15.
					70.87	4.60	15.
7f	1.5	105	96	$C_{22}H_{17}FN_3$	74.25	4.83	15.
					74.14	4.81	15.
7g	2.0	143	94	$C_{22}H_{17}N_4O_2$	69.03	4.48	18.
					68.92	4.47	18.
7h	1.5	112	96	$C_{22}H_{17}N_4O_2$	69.01	4.49	18.
					68.92	4.47	18.
7i	2.0	156	97	$C_{22}H_{17}N_4O_2$	69.02	4.48	18.
					68.92	4.47	18.
7j	2.0	178	96	$C_{24}H_{22}N_3O_2$	78.78	6.07	15.

					78.66	6.05	15.
8a	7.0	162	87	$C_{22}H_{16}N_3$	78.65	4.80	16.
					78.55	4.79	16.
8b	7.5	179	90	$C_{23}H_{18}N_3$	79.02	5.20	16.
					78.83	5.18	15.
8c	8.0	195	88	$C_{23}H_{18}N_3O$	75.49	4.96	15.
					75.39	4.95	15.
8d	7.5	221	92	$C_{22}H_{15}ClN_3$	71.35	4.09	15.
					71.25	4.08	15.
8e	7.0	255	94	$C_{22}H_{15}ClN_3$	71.34	4.10	15.
					71.25	4.08	15.
8f	7.5	209	92	$C_{22}H_{15}FN_3$	74.66	4.28	15.
					74.56	4.27	15.
8g	7.5	235	84	$C_{22}H_{15}N_4O_2$	69.37	3.98	18.
					69.28	3.96	18.
8h	8.0	223	85	$C_{22}H_{15}N_4O_2$	69.39	3.97	18.
					69.28	3.96	18.
8i	8.0	278	88	$C_{22}H_{15}N_4O_2$	69.38	3.98	18.
					69.28	3.96	18.
8j	7.5	217	86	$C_{24}H_{20}N_3O_2$	72.82	5.09	14.
					72.71	5.08	14.

Table III:- Antibacterial screening results of compounds **8.**
Inhibition zone (in mm)

Compd	E. coli at			B. subtilis at	
	250 □ g/disc	500 □ g/disc		250 □ g/disc	500 □ g/dis
8a	9.0	15.5		6.0	9.5
8b	10.0	16.5		6.5	12.5
8c	9.0	15.0		5.5	9.0
8d	10.5	17.5		6.5	13.0
8e	11.0	20.0		7.0	13.5
8f	10.0	17.0		6.5	12.5
8g	6.5	9.0		5.0	8.0
8h	7.5	10.5		5.5	9.0
8i	8.0	12.0		6.5	11.5
8j	9.5	16.0		6.0	9.0
Gentamycin	12.0	22.0		8.0	15.0

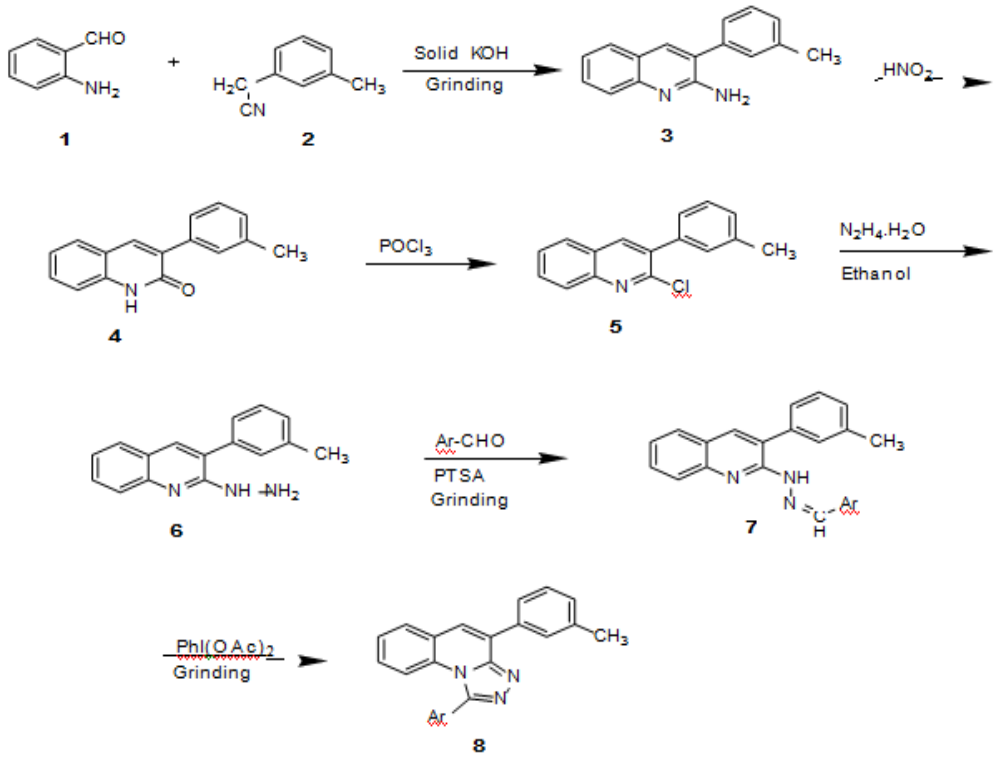
Table IV:- Anti-inflammatory activity date of compounds **8.** (Carrageenan-induced paw edema test in rats) Compd[a] Rat paw edema in mL[b] (Treatment in hours)

	1H	2H	3h	4h
8 a	2.42±0.295	2.08±0.310**	1.42±0.254**	1.02±0.265**
	11.67	27.52	54.48	67.61
8 b	2.24±0.278	1.82±0.297**	1.12±0.309**	0.98±0.284**
	18.24	36.58	64.10	68.88
8 c	2.26±.0267	1.91±0.281**	1.21±0.302***	0.85±0.262**

	17.51	33.44	61.21	73.01
8d	2.21±0.285	1.88±0.292***	1.18±0.275***	0.82±0.270***
	19.34	34.49	62.17	73.96
8e	2.11±0.264	1.68±0.289***	1.06±0.284***	0.72±0.308***
	22.99	41.46	66.02	77.14
8f	2.14±0.289	1.96±0.276***	1.09±0.266***	0.81±0.254***
21.89		31.70	65.06	74.28
8g	2.22±0.254	1.87±0.263***	1.15±0.255**	0.96±0.268**
	18.97	38.84	63.14	69.52
8h	2.30±0.305	1.78±0.304***	1.13±0.249**	0.93±0.302***
	16.05	37.97	63.78	70.47
8i	2.18±0.308	1.72±0.295***	1.11±0.278***	0.75±0.249***
	20.40	40.06	64.42	76.19
8j	2.16±0.310	1.69±0.306***	1.10±0.256***	0.78±0.251***
	21.16	41.11	64.74	75.23
control	2.74±0.242	2.87±0.254	3.12±0.289	3.15±0.291
	NA	NA	NA	NA
Diclofenac sodium	1.84±0.251***	1.32±0.254***	0.91±0.257***	0.52±0.309***
	32.84	54.01	70.83	83.49

[a]Dose level: test compounds (100mg/kg b.wt), Diclofenac sodium (10mg/kg b.wt)

[b]Values are expressed as mean± SD (number of animals N= 6 rats) Statistically significant compared to respective control values, ***P<0.001,
**P<0.01, *P<0.05 (Dunnet's test)



Ar	Ar
a : C_6H_5	**f :** 4-F C_6H_4
b : 4-$CH_3C_6H_4$	**g :** 2-NO_2 C_6H_4
c : 4-$CH_3OC_6H_4$	**h :** 3-NO_2 C_6H_4
d : 2-Cl C_6H_4	**i :** 4-NO_2 C_6H_4
e : 4-Cl C_6H_4	**j :** 3,4-$(CH_3O)_2C_6H_3$

Scheme I

References:-

1. Runge FF. Ann Physik Und Chem. 1834;31:65.
2. Gerhrdt Ch. Ann Chemi Phys. 1842;7:25.
3. Bharate JB, Vishwakarma RA, Bharate SB. RSC Adv. 2015;5:42020–42053.
4. Afzal O, Kumar S, Haider MR, et al. Eur J Med Chem. 2015;97:871–910.
5. Batista VF, Pinto DCGA, Silva AMS. ACS Sustain Chem Eng. 2016;4:4064–4078.
6. Jain S, Chandra V, Kumar JP, Pathak K, Pathak D, Vaidya A. Arabian J Chem. 7. 2016; 12:4920–4946.
7. Hu Y-Q, Gao C, Zhang S, et al. Eur J Med Chem. 2017;139:22–47.
8. Mandewale MC, Patil UC, Shedge SV, Dappadwad UR, Yamgar RS. Beni-Suef
9. Univ J Basic Appl Sci. 2017;6:354–361. 1
10. Kukowska M. Eur. J. Pharm. Sci. 2017;109:587–615.
11. Casal JJ, Asís SE. Austin Tuberc Res Treat. 2017;2:1007–1010.
12. Bhongade MA, Yeole MP. Eur J Biomed Pharm Sci. 2019;6:180–188.
13. Jain S, Chandra V, Jain PK, Pathak K, Pathak D, Vaidy A. Arab J Chem. 2019;12: 15. 4920–4946.
14. Dorina AM, Mangalagiu I, Antoci V. Med Analy Chem Int J. 2019;3, 000133.
15. Nainwal LM, Tasneem S, Akhtar W, et al. Eur J Med Chem. 2019;164:121–170. 18. Weyesa A, Muluget E. RSC Adv. 2020;10:20784–20793.
16. Murauer A, Ganzera M. J Chromatogr A. 2018;1554:117–122.