SYNTHESIS OF NEW ARYL IMIDAZOLE QUINOLINE-2-ONES

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Abstract: A series of some new aryl imidazole quinoline-2-ones have been synthesized by condensing N-[-(Z)-1-(Hydrazino carbonyl)-2-Phenyl vinyl]acetamide with simple and substituted coumarins in acetic acid by two step process (**method-A**) and one pot process (**method-B**). A comparative study of **method-A** and **method-B** is briefly discussed. The compounds **4g** showed marked activity against *S. aureus* bacteria and the compounds **4f, 4h** showed marked activity against *E.Coli* bacteria. The other compounds were moderately or weakly active against S. *aureus* and *E. Coli.* The compounds **4h, 4l** showed marked activity against *A. niger* and the compounds **4l** showed marked activity against *C. albicans*. The remaining compounds were moderately or weakly active against *A. niger* and *C. albicans*.

Introduction

Quinoline and quinolone compounds are having excellent biological activity like cardiotonic[1], anti-microbial[2] and anti-psychotic agents[3]. It has been proven that imidazole nucleus was a fertile source of medicinal agents such as a decongestants[4], anti-protozoal agents[5] and anti-fungal agents[6]. It is already reported that a wide range of pharmaceuticals properties of imidazolin-5-ones as anticonvulsants, sedatives, hypnotics and potent CNS depressants[7-8]. In view of these interesting biological activities, it appeared to be of great interest to synthesize unreported aryl imidazole quinoline-2-ones **4a-l** and assess their biopotential.

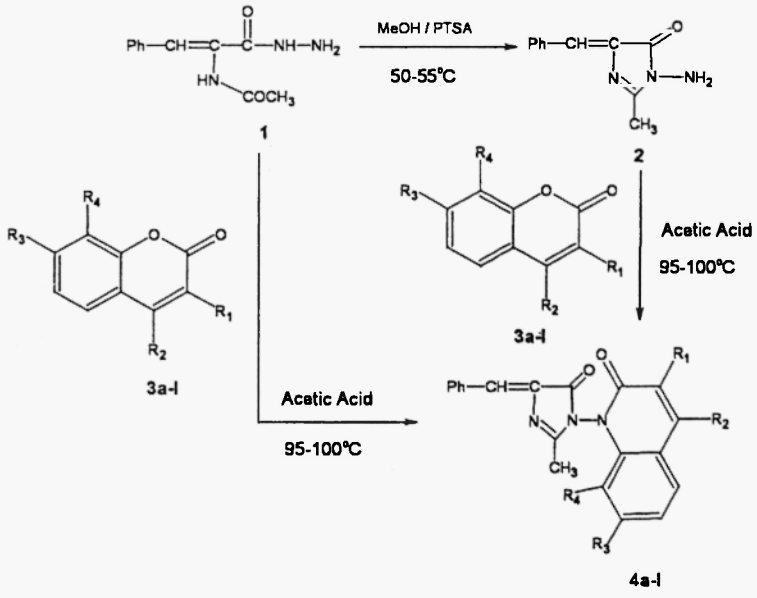
Results and Discussion

N-[(Z)-1-(hydrazinocarbonyl)-2-phenyl vinyl] acetamide[9] **1** is cyclized in methanol at 50-55° C in presence of catalytic amount (10% mol) of PTSA to give (5E)-3-amino-5-benzylidine-2-methyl-3,5-dihydro-4H-imidazole-4 one in 85% yield, which is treated further with various substituted coumarins **3a-l** in acetic acid at 95-100°C for 6-10 hr furnished imidazole quinoline-2-ones **4a-l** in 75-80%.

Alternatively these compounds **4a-l** were synthesized in one pot process by the reaction between N-[(z)-1-(hydrazinocarbonyl)-2-phenyl vinyl]acetamide **1** and various coumarin derivatives **3a-l** in acetic acid at 95-100°C for 8-12 hr furnished imidazole quinoline-2-ones **4a-l** in 50-60%. The results obtained in these two methods are tabulated in **Table-1**. The schematic diagram of the above two methods were depicted in **Scheme-1**. The compounds **4a-l** were characterized by IR, ^{1}H NMR and Mass spectral data. The IR spectra of the compounds **4a-l** shown absorption range at 1700-1600, 1600-1640 and 1570-1585 cm-1 which are characteristic of C=O, C=N and C=C stretching respectively.

The ^{1}H NMR spectrum of **4a** shows a singlet at δ 7.28 due to C-9H of quinolone, two doublets are obtained at δ 7.20 and 7.1 due to C-7H and C-6H of the quinolone, a multiple at δ 7.0-7.50 for the aromatic protons, one singlet is observed at δ 6.19 due to C-H vinylic proton, one singlet is observed at δ 6.04 due to C-3H of quinolone, one singlet is obtained at δ 2.23 due 4 CH_3 group of imidazole, one singlt is observed at δ 2.07 due to 12 CH_3 of quinolone.

The sharp signal (D_2O exchangeable) at δ 10.12 is assigned to O-H proton. ^{1}H NMR spectra details of the compounds **4a-l** is depicted in **Table-2**. The mass spectrum of **4a** shows



Scheme-1

Compd	R_1	R_2	R_3	R_4
4a	H	CH_3	OH	H
4b	H	H	H	H
4c	H	C_6H_5	OH	H
4d	CH_3	CH_3	OH	H
4e	H	CH_3	H	CH_3
4f	H	H	NH_2	H
4g	Cl	Cl	H	H
4h	Br	Br	H	H
4i	H	Cl	OH	H
4j	H	Br	OH	H
4k	CH_3	C_6H_5	OH	H
4l	H	CH_3	NH_2	H

Table-1: Analytical and spectral data of compounds **4a-l**

Compd	M. Formula (Mol. Wt.)	M^+	M..P (°C)	Method-A		Method-B		Calcd / (found) (%)		
				Yield (%)	Time (hrs)	Yield (%)	Time (hrs)	C	H	N
4a	$C_{21}H_{17}N_3O_3$ (359)	360	209-214° C	78	6	51	8	70.194 (71.04)	4.73 (4.60)	1169 (10.98)
4b	$C_{20}H_{15}N_3O_2$ (329)	330	212-215° C	75	8	55	8	72.94 (73.00)	4.55 (4.50)	12.77 (12.78)
4c	$C_{26}H_{19}N_3O_3$ (421)	422	220-225° C	75	10	53	11	74.10 (74.00)	4.51 (4.50)	11.41 (11.52)
4d	$C_{22}H_{19}N_3O_3$ (374)	375	215-218° C	75	7	54	9	70.59 (70.60)	5.35 (5.36)	12.83 (12.81)
4e	$C_{22}H_{19}N_3O_2$ (357)	358	220-222° C	79	8	59	10	73.94 (73.90)	5.32 (5.37)	11.76 (11.75)
4f	$C_{20}H_{16}N_4O_2$ (344)	345	220-225° C	80	8	52	11	69.77 (69.82)	4.65 (4.70)	16.28 (16.18)
4g	$C_{20}H_{13}Cl_2N_3O_2$ (398)	399	210-212° C	76	9	51	11	60.30 (60.28)	3.26 (3.27)	10.55 (10.56)
4h	$C_{20}H_{13}Br_2N_3O_2$ (489)	490	220-225° C	78	7	50	10	49.07 (49.06)	2.66 (2.65)	8.59 (8.62)
4i	$C_{20}H_{14}ClN_3O_3$ (379.5)	381	218-222° C	76	8	53	11	63.24 (63.20)	3.69 (3.68)	11.06 (11.11)
4j	$C_{20}H_{14}BrN_3O_3$ (425)	426	214-218° C	77	8	52	10	56.48 (56.46)	3.29 (3.30)	9.89 (9.90)
4k	$C_{27}H_{21}N_3O_3$ (435)	436	216-218° C	75	9	52	12	74.48 (74.49)	4.83 (4.80)	9.65 (9.69)
4l	$C_{21}H_{18}N_4O_2$ (358)	359	220-222° C	76	9	57	10	70.39 (70.40)	5.03 (5.04)	15.64 (15.62)

Table-2 : NMR spectral data of compounds **4a-l.**

Compd.	^{1}H NMR (δ ppm)
4a	δ 10.12 (s, 1H, OH), 7.28 (s, 1H C-9H quinolone), 7.20 (d, 1H, J=8.25Hz, C-7H quinolone), 7.0-7.5 (m, 5H, Ar-H), 7.1 (d, 1H, J=8.25Hz, C-6H quinolone), 6.19 (s, 1H, vinylic), 6.04 (s, 1H, C-3H quinolone), 2.27 (s, 3H-4^1-CH_3 imidazole), 2.07 (s, 3H, CH_3 quinolone).
4b	δ 7.5-7.0 (m, 9H, Ar-H), 6.20 (s, 1H vinylic), 5.98 (d, 1H, C-3H, J=8.25Hz, quinolone), 5.5 (d, 1H, J=8.25Hz, C-4H, quinolone), 2.0 (s, 3H, CH_3 imdazole).
4c	δ 10.80 (s, 1H, OH), 7.26 (s, 1H, C-9H quinolone), 7.20 (d, 1H, J=8.25Hz, C-7H quinolone), 7.11 (s, 1H C-6H quinolone), 7.20-6.80 (m, 10H, Ar-H), 6.04 (s, 1H, vinylic), 5.90 (s, 1H, C-3H quinolone), 2.12 (s, 3H, CH_3, imidazole).
4d	δ 10.50 (s, 1H, OH), 7.30 (s, 1H, C-9H quinolone), 7.20 (d, 1H, J=8.25Hz, C-7H quinolone), 7.18 (d, 1H, J=8.25Hz, C-6H quinolone), 7.10-7.00 (m, 5H, Ar-H), 6.01 (s, 1H, vinylic), 2.29 (s, 3H, CH_3 imidazole), 2.12 (s, 3H, C-4 CH_3 quinolone), 2.02 (s, 3H, C-3 CH_3 quinolone).
4e	δ 7.29-7.08 (m, 8H, Ar-H), 6.28 (s, 1H, vinylic), 5.90 (s, 1H C-3H quinolone), 2.20 (s, 3H C-9H CH_3 quinolone), 1.90 (s, 3H C-4 CH_3 imidazole), 1.70 (s, 3H, CH_3 quinolone).
4f	δ 7.22 (s, 1H, C-9H quinolone), 7.15 (d, 1H, J=8.25Hz, C-7H quinolone), 7.05 (d, 1H, J=8.25Hz, C-6H) quinolone), 7.10-7.00 (m, 5H, Ar-H), 6.10 (s, 1H, vinylic), 5.90 (d, 1H, J=8.25Hz, C-3H quinolone), 5.5 (d, 1H, J=8.25Hz, C-4H quinolone), 4.90 (s, 2H NH_2), 2.03 (s, 3H CH_3 imidazole).
4g	δ 7.20-6.90 (m, 9H, Ar-H), 6.10 (s, 1H, vinylic), 1.99 (s, 3H, CH_3 imidazole).
4h	δ 7.19-7.01 (m, 9H, Ar-H), 6.09 (s, 1H, vinylic), 2.08 (s, 3H, CH_3 imidazole).
4i	δ 10.90 (s, 1H, OH), 7.21 (s, 1H, C-9H quinolone), 7.11 (d, 1H, J=8.25Hz, C-7H quinolone), 7.01 (d, 1H, J=8.25Hz, C-6H quinolone), 7.10-7.00 (m, 5H, Ar-H), 5.90 (s, 1H, vinylic), 5.60 (s, 1H, C-3H quinolone), 2.00, (s, 3H, CH_3, imidazole).
4j	δ 10.55 (s, 1H, OH), 7.32 (s, 1H, C-9H quinolone), 7.20 (d, 1H, J=8.25Hz, C-7H quinolone), 7.11 (d, 1H, J=8.25Hz, C-6H quinolone), 7.10-6.90 (m, 5H, Ar-H), 5.90 (s, 1H vinylic), 5.78 (s, 1H, C-3H quinolone), 2.10 (s, 3H, CH_3 imidazole).
4k	δ 10.4 (s, 1H, OH), 7.30 (s, 1H, C-9H quinolone), 7.22 (d, 1H, J=8.25Hz, C-7H quinolone), 7.11 (d, 1H, J=8.25Hz, C-6H, quinolone), 7.10-6.92 (m, 10H, Ar-H), 5.89 (s, 1H vinylic), 2.01 (s, 3H, C-3 CH_3 imidazole), 1.90 (s, 3H, CH_3 quinolone).
4l	δ 7.25 (s, 1H, C-9H quinolone), 7.15 (d, 1H, J=8.25Hz, C-7H quinolone), 7.10 (d, 1H, C-6H), 7.10-6.90 (m, 5H, Ar-H), 5.98 (s, 1H vinylic), 5.60 (s, 1H C-3H imidaozle), 4.5 (s, 2H NH_2), 2.09 (s, 3H CH_3 C-4H), 2.01 (s, 3H, CH_3 quinolone).

molecular ion peak at m/z 360 (30%), which is consistent with its molecular formula $C_{21}H_{17}N_3O_3$. The M^+ values of the compounds **4a-l** were depicted in **Table-1**. Simple and substituted coumarins were prepared by the pechmann reaction of an appropriately substituted phenols and β-keto esters in presence of an acid[10].

Antimicrobial activity

All the compounds **4a-l** were screened in vitro antibacterial activity by cup-plate diffusion method against *Staphylococcus aureus* and *Escherichia coli* bacteria. The concentration of the compounds was 1 µg/ml in DMF, the zone of inhibition measured in mm. *Ciprofloxacin* was used as a standard drug. The compounds **4g** showed marked activity against *S. aureus* bacteria and the compounds **4f, 4h** showed marked activity against *E. Coli* bacteria. The other compounds were moderately or weakly active against *S. aureus* and *E. Coli*. The results are presented in **Table-3**.

Table-3 : Results of Antimicrobial activity and Antifungal activity

Compd	Zone of inhibition in mm*			
	Antibacterial		Antifungal	
	S. aureus	***E.Coli***	***A. Niger***	***C. albicans***
4a	06	03	10	10
4b	04	05	06	04
4c	10	09	04	03
4d	08	04	02	01
4e	02	05	04	03
4f	12	15	07	06
4g	15	10	12	11
4h	15	16	18	10
4i	09	03	10	09
4j	13	15	09	07
4k	07	06	11	14
4l	01	04	19	18
Ciproflxacin	20	21	-	-
Griseofulvin	-	-	26	25
Control DMF	Nil	Nil	Nil	Nil

Including diameter of the well – 8mm.

Antifungal activity

All the compounds **4a-l** were tested for their anti-fungal activity against *A. niger* and *Candida albicans* at a concentration 1 µg/ml using *Griseofulvin* as a standard by cup-plate diffusion method. The compounds **4h, 4l** showed marked activity against *A. niger* and the compounds **4l** showed marked activity against *C. albicans*. The remaining compounds were moderately or weakly active against *A. niger* and *C. albicans*. The results are tabulated in **Table-3**.

Experimental Section

All the melting points were determined in open capillary in liquid paraffin bath and are uncorrected. The purity of the compounds was checked by TLC. IR spectra (KBr) were recorded

on Shimadzu FTIR Model 8010 spectrophotometer and the ^{1}H NMR spectra in $CDCl_3$ on Varian 200 MHz NMR spectrophotometer using TMS as an internal standard. The C, H and N analysis of the compounds was done on a carlo Erba Model EA 1108, C, H and N elemental analyzer. The mass spectra were recorded on EIMS, 70 eV spectrophotometer.

***Synthesis of (5E)-3-amino-5-benzylidine-2-methyl-3,5-dihydro-4H-imidazole-4-one* 2**

N-[(z)]-1-(hydrazinocarbonyl)-2-phenyl-vinyl]acetamide **1** (2.19g, 0.01 mole) was refluxed in methanol with a catalytic amount of PTSA (0.001 mole) for 6 hours. The reaction was monitored over TLC. Then reaction mixture was cooled to room temperature and stirred over night. Filtered the crystallized material yield 85% m. p: 175-178°C.

***Synthesis of 1-[(4z)-4-benzylidene-2-methyl-5-oxo-4,5-dihydro-1-H-imidazole-1yl]-7-hydroxy-4-methyl quinoline-2(1H)-one* 4a.**

Method-A (*Two step process*): The compound **2** (2.01g, 0.01 mole) and 4-methyl-7-hydroxy-coumarin (1.76g, 0.01mole) in acetic acid (10ml) were maintained at 95-100° C for 6 hours. Then the reaction mass was cooled to ambient temperature and poured in crushed ice, the mixture extracted with methylene chloride, and the solvent was then removed under reduced pressure. This crude product was purified by column chromatography using 50:50 hexane and ethyl acetate as elutent.

Compounds **4b-l** were prepared similarly.

Method-B (*one pot-process*): The compound N-[(z)]-1-(hydrazinocarbonyl)-2-phenyl vinyl]acetamide **1** (2.19g, 0.01 mole) and 7-hydroxy-4-methyl-coumarin (1.76g, 0.01 mole) were mixed in Acetic acid (10 ml) and maintained at 95-100° C for 8 hours. Upon completion of the reaction, monitored by TLC, the mixture was poured in ice and extracted with methylene chloride. The solvent was then removed under reduced pressure. This crude product was purified by chromatography by using 50:50 Hexane and Ethyl acetate as a mobile phase.

Compounds **4b-l** were prepared similarly.

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