

SYNTHESIS AND CHARACTERIZATION OF NOVEL QUINAZOLINE DERIVATIVES VIA REACTION OF ISATOIC ANHYDRIDE WITH SCHIFF'S BASE

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ABSTRACT

Novel 2, 3-dihydroquinazolin-4-one derivatives were synthesized by the reaction of isatoic anhydride with Schiff's bases in anhydrous dioxan with high yields. Schiff's bases were synthesized by the reaction of heteroaromatic aldehydes or ketones with primary heterocyclic amines. The resulting products were identified by their melting point and their molecular structures were confirmed by FT-IR, UV-Vis. and ¹HNMR spectroscopy and C.H.N. elemental analyses.

KEYWORDS: Quinazoline, Isatoic Anhydride, Schiff Bases, Synthesis

INTRODUCTION

Quinazoline is a class of heterocyclic compounds with two nitrogen atoms in one of the naphthalene fused rings system, the classification of quinazoline based on the substituens present on different positions of the basic structure given bellow.



A large number of reports, chemical abstracts and few patents on quinazoline derivatives of being potential anti-inflammatory and anti-allergic agents ⁽¹⁾ were puplished between 1975-2005.

The 2,3-dihydroquinazolinones is an interesting class of quinazoline system that possess a wide range of biological and pharmaceutical activities, and they are versatile intermediates in organic and bio-organic synthetic chemistry.⁽²⁻⁴⁾ They are exhibiting various medicinal and biological activities such as proteine Scr inhibition, anti-prolifrative anti-angiogenic and anti-tumor, ⁽⁵⁾ anticancer ,⁽⁶⁾ antitubercular,⁽⁷⁾ antibacterial ⁽⁸⁾ and antiviral activities⁽⁹⁾, examples of drug molecules having quinazolinone skeleton are given in Figure 1.



Figure 1: Some Marketed Drugs with Quinazolinone Skeleton

Several synthetic approaches have been reported for the synthesis of quinazolin-4-one derivatives by using

different catalytic systems.⁽¹⁰⁾ Thus, novel 3-aminoquinazolinones were synthesized from naproxenoyl chloride, anthranilic acid and hydrazine,⁽¹¹⁾ and from rearrangement of imidazoquinolinediones in boiling acetic acid. ⁽¹²⁾

Eco-friendly synthesis of 3-dihydroquinazolin-4(1H)-one derivatives was developed from various reaction systems such as, anthranilamides and aldehydes or ketones in water medium ⁽¹³⁾,isatoic anhydride, ammonium acetate, and aldehydes in ionic liquids ^{(14) (15)} and by a one-pot acetic acid- catalyzed reaction between isatoic anhydride, aromatic amines and aldehydes.⁽¹⁶⁾

A one-pot three-component domino approach for 2-arylquinazoline-4-amines, via the activation of sp³ C–H bond in a non-metal catalytic oxidation system by using I_2 in tert-butyl hydroperoxide (TBHP) was demonstrated.⁽¹⁷⁾ Other synthesis pathways include the cyclization-oxidation of anthranilamides with aldehydes, which is only useful for the synthesis of 2-substituted quinazolinones, and reductive cyclization of nitro-aromatic compounds ⁽¹⁸⁾ were reported.

Reports on solid-phase synthesis ⁽¹⁹⁾, palladium-catalyzed cyclocarbonylation of o-iodoanilines ⁽²⁰⁾ base-promoted ring closure of o-fluorobenzoyl guanidine's ⁽²¹⁾ ring closure of the N-protected guanidine's ⁽²²⁾ and functionalization reaction of cyclic amines ⁽²³⁾ are some additional inputs to explore the quinazolinone multifaceted importance. However, there are few reports on one-pot synthesis of 2,3- disubstituted quinazolinones using aldehydes as a starting material in which only preparation of 2-substituted analogues has been reported ⁽²⁴⁾.

EXPERIMENTAL PART

All solvents were distilled and dried on anhydrous CaCl₂ immeditely prior to use, and all non-equeous reaction were conducted in dried glass ware, the reflux condenser was equipped with anhydrous CaCl₂ guard tube. Schiff's bases and isatoic anhydride were purified before use.

Melting points were recorded on Electro thermal Melting Point (Stuart) model samp 30.AllFT-IR spectra were recorded at room temperature from 4000cm⁻¹ to 400cm⁻¹ with KBr disce on Shimadzu FT-IR 84005 spectrophotometer and UV-Vis. spectra were recorded at room temperature from 200nm to 400 nm in absolute ethanol on Shimadzu Double-Beam Spectrophotometer UV-210 A. The ¹H-NMR spectra were recorded on Bruker 500 MHz-Avance III spectrometer in DMSO-d6 as a solvent using δ (ppm) for chemical shift relative to tetramethylsilane (TMS) as an internal standard.

General Procedure for Synthesis of Schiffs Bases (3a-j)

A mixture of 3-Amino-1,2,4-triazole (0.002 mol) and 3-Indolcarbaldehyde (0.002 mol) and trace of glacial acetic acid in absolute ethanol (40ml) was placed in a(100ml) round-bottom flask equipped with condenser and stir bar. The mixture was allowed to react at reflux temperature for 4hr, then allowed to cool down to room temperature, where by a crystalline solid of Schiffs bas (3a) seprated out .The solid product was recrystallized twice from ethanol. Other Schiff's bases (3b-j) were synthesized by following the same procedure. The structural formulas, names, melting points, colures, and percentage yields for the synthesized Schiff's bases are given in table1.

General Procedure for Synthesis of 2, 3-Dihydroquinazolin-4-One (5a-j)

In well dried 100-ml round-bottom flask equipped with condenser and anhydrous calcium chloride tube guard a mixture of Schiff's bases (0.001mol) and isatoic anhydride (0.001mol) dissolved in (20ml) of anhydrous dioxan, the reaction mixture was refluxed for 8hr and left to stand for 24hr, then solid product of(5a) precipitated. The solid product was filtered off and recrystallized form ethanol.

Other derivatives (5b-j) were synthesized following the same procedure. The structural formulas, names, melting points, colures, and percentage yields for the synthesized 2, 3-dihydroquinazolin-4-ones are given in table 2.

RESULTS AND DISCUSSIONS

In this work the synthesis of novel 2, 3-dihydroquinazolin-4-one by direct reaction of Schiff's bases with isatoic anhydride in anhydrous dioxan is reported.

Schiff's bases were synthesized from the condensation reaction of commercially available heterocyclic aldehydes or ketones with primary heterocyclic amines of very well kwnon mechanism.⁽²⁵⁾



They were identified by their melting points and their molecular structures were confirmed by FT-IR, UV-Vis. spectroscopy, tables (1), (3) & (5).

Formation of the Schiffs bases products were followed up by the disappearance of both (C=O) absorption bands at (1670-1700) cm⁻¹ and (-NH₂) absorption bands at (3340-3420cm⁻¹) in the FT-IR spectra of the carbonyl compounds and the primary amines respectively, and the appearance of the absorbtion frequency of azomethine group (C=N) at (1630-1680) cm⁻¹ in the FT-IR spectra of the resulting imines.

The UV-Vis. Spectra of these imines show absorption maxima at (250- 430 nm) owing to the electronic transfers $\pi \rightarrow \pi *$ and $n \rightarrow \pi *$ characteristic of the structures of the synthesized Schiff's bases. The synthesis of novel 2, 3-dihydroquinazolin-4-ones were achieved by the polar cycloaddition reaction of imines to isatoic anhydride fairly anhydrous dioxin at reflux condition.



It may be concluded that the reaction takes place via concerted dipolar cycloaddition mechanism as in the following reaction scheme:

In the slow step of this mechanism, the nucleophilic azomethine group attacks the electrophilic carbon atom of the carbonyl group of the anhydride associated with CO_2 molecule expelsion to give dipolar reactive intermediate. Collapse of the reactive intermediate in an intramolcular cycloaddition in a fast step gives the taget molecule.

The resulting products were identified by their melting points and their molecular structures were confirmed by FT-IR, UV-Vis.and ¹HNMR spectroscopy, tables (2),(4),(6) & (7).

The FT-IR spectra of the products show characteristic absorption band at $(1649-1741 \text{cm}^{-1})$ indicative of C=O group formation of lactones beside the characteristic bands of the residual groups in the structure, table (6).

The UV-Vis. spectra show absorption maxima at (205-455nm) owing to the electronic transfers $\pi \rightarrow \pi *$ and $n \rightarrow \pi *$ characteristic of the structure of the synthesized 1,3-quinazolin-4-one,table,(4).

Comp. No.	Structural Formula	Name Yi		m.p.°C	Colour
3a		<i>N</i> -[(<i>E</i>)-1 <i>H</i> -indol-3- ylmethylidene]-1 <i>H</i> -1,2,4- triazol-3-amine		193-195	Pale yellow
3b		(3Z)-3- [(4-chlorophenyl)imino]- 1,3-dihydro-2 <i>H</i> -indol-2- one 74		264	Golden
3с	H ₃ C N CH ₃ N O CH ₃ O CH ₃	4-{[(<i>E</i>)- (4-methoxyphenyl) methylidene]amino} -1,5-dimethyl-2-phenyl- 1,2-dihydro-3 <i>H</i> -pyrazol- 3-one	91	164-167	Yellow
3d	S C CI	<i>N</i> -[(<i>E</i>)- (4-chlorophenyl) methylidene]-1, 3-benzothiazol-2-amine	83	87-89	Pale yellow
Зе	HO	(3Z)-3-(4- hydroxybenzylidene)-1,3- dihydro-2 <i>H</i> -indol-2-one	78	202-204	Orange
3f		2-{(Z)-[(4- hydroxyphenyl)imino]met hyl}phenol	88	237-240	White
3g	N S NH	<i>N</i> -[(<i>E</i>)-1 <i>H</i> -indol-3- ylmethylidene]-1,3- benzothiazol-2-amine	85	178-180	Yellow
3h	Br NH	3,5-dibromo- <i>N</i> -[(<i>E</i>)-1 <i>H</i> - indol-3- ylmethylidene]pyridin-2- amine	81	136-143	Pale yellow
3i	HO O	4-{[(Z)-(2- hydroxyphenyl)methylide 71 ne]amino}benzoic acid		269-270	Dark yellow
3j	CI N OH	2-{(Z)-[(4- chlorophenyl)imino]meth yl}phenol	77	98-101	Golden

Table 1: Structural Formulas, Names, Melting Points, Coloures, and % Yields of Schiff's Bases (3a-j)

Comp.No.	Structural Formula	Name	Yield%	m.p.°C	Colour
5a		2-(1 <i>H</i> -indol-3-ylmethyl)-3- (1 <i>H</i> -1,2,4-triazol-3-yl)-2,3- dihydroquinazolin-4(1 <i>H</i>)- one	69	243-247	Brown
5b		3'-(4-chlorophenyl)-1' <i>H</i> - spiro[indoline-3,2'- uinazoline]-2,4'(3' <i>H</i>)-dione	78	263	Orange
5c	N H ₃ C H ₃ C C H ₃ C	3-(1,5-dimethyl-3-oxo-2- phenyl-2,3-dihydro-1 <i>H</i> - pyrazol-4-yl)-2-(4- methoxyphenyl)-2,3- dihydroquinazolin-4(1 <i>H</i>)- one	91	148-152	Pale yellow
5d		3-(1,3-benzothiazol-2-yl)-2- (4-chlorophenyl)-2,3- dihydro quinazolin-4(1 <i>H</i>)- one	88	201	White
5e	HO O N NH	3'-(4-hydroxyphenyl)-1' <i>H</i> - spiro[indoline-3,2'- quinazoline]-2,4'(3' <i>H</i>)-dione	84	221-226	Yellow
5f		2-(2-hydroxyphenyl)-3-(4- hydroxyphenyl)-2,3- dihydroquinazolin-4(1 <i>H</i>)- one	89	239	Brown
5g		3-(1,3-benzothiazol-2-yl)-2- (1 <i>H</i> -indol-3-yl)-2,3- dihydroquinazolin-4(1 <i>H</i>)- one	60	249-251	Green Light

Table 2: Structural Formulas, Names, Melting Points, Colours, and % Yields of 2,3-Dihydroquinazolin-4-One (5a-j)

	Table 2: Contd.,					
5h	HN HN HN H H H	3-(3,5-dibromopyridin-2- yl)-2-(1 <i>H</i> -indol-3-yl)-2,3- dihydroquinazolin-4(1 <i>H</i>)- one	74	255	Light Orange	
5i		4-[2-(2-hydroxyphenyl)-4- oxo-1,4-dihydroquinazolin- 3(2 <i>H</i>)-yl]benzoic acid	62	251-256	Yellow	
5j	CI N H HO	3-(4-chlorophenyl)-2- (2-hydroxyphenyl)-2,3- dihydroquinazolin-4(1 <i>H</i>)- one	78	234-237	Peggy	

Table 3: The UV-Visible Absorption 3 Max (nm) in Ethanol of Shiffs Bases (3a-j)

Comp.	Max (nm) λ						
3a	225	250	300				
3b	228	250	307	405			
3c	214	258	305	356			
3d	225	267	305				
3e	205	244	303				
3f	214	255	310				
3g	214	245	270	298			
3h	212	246	310				
3i	220	250	288	335			
3j	225	260	320				

Table 4: The UV-Visible Absorption of 3 Max in Ethanol of 2, 3-Disubustituted-1, 3-Quinazoline-5-One (5a-j)

Comp.	$\lambda \max(nm)$					
5a	235	250	350			
5b	225	278	380	448		
5c	220	265	340			
5d	235	255	305	408		
5e	205	250	340			
5f	210	246	320			
5g	212	250		414		
5h	228	278	310	405		
5i	218	268	305			
5j	205	265	310	387		

Comp.	$v_{\rm s}$ N-H	v _s C-H	v_{s} C-H	v_s C=O	$v_s C = N$	$v_s C = C$	V _s	δ_w N-H	С-Н
Code	Lactam	Aromatic	Aliphatic	Lactam	Imine	Aromatic	C-N	Lactam	Bending
3a	3446	3043	2931	-	1633	1600	1243	761	1334
3b	3446	3085	-	1728	1645	1595	1238	756	1336
3c	-	3049	2962	1645	1610	1580	1245	-	1305
3d	-	3058	2931	-	1637	1540	1240	-	1346
3e	3446	3016	-	1731	1618	1560	1271	734	1330
3f	-	3056	2995	-	1693	1541	1280	-	1350
3g	3442	3045	2931	-	1633	1493	1242	759	1390
3h	3463	3045	2931		1631	1502	1242	759	1388
3i	-	3045	2995	-	1679	1566	1286	-	1365
Зј	-	3012	2930	-	1612	1540	1272	-	1359

Table 5: The Majer FT-IR Absorptions (cm⁻¹) of the Prepared Imine (3a-j)

Table 6: The Majer FT-IR Absorptions (cm⁻¹) of the Prepared 2, 3-Dihydroquinazolin-4-One (5a-j)

Comp.	v_s N-H	v _s C-H	<i>v</i> _s C-H	v_s C=O	$v_s C = C$	<i>v</i> _s	δ_w N-H	С-Н
Code	Lactam	Aromatic	Aliphatic	Lactam	Aromatic	C-N	Lactam	Bending
5a	3427	3008	2939	1729	1568	1265	763	1363
5b	3448	3010	-	1741	1460	1263	748	1334
5c	3421	3049	2935	1726	1593	1245	761	1305
5d	3409	3058	2941	1691	1531	1282	756	1313
5e	3446	3068	-	1731	1514	1265	763	1363
5f	3423	3070	2945	1726	1600	1265	794	1326
5g	3392	3114	2923	1726	1579	1274	744	1369
5h	3448	3053	2939	1649	1583	1244	740	1359
5i	3446	3066	2991	1735	1598	1286	754	1321
5j	3296	3101	2941	1726	1512	1265	761	1363

Table 7: The¹HNMR Spectra of Compounds 5a . j in DMSO-d6 Relative to TMS

Comp.	Chemical Shift ð ppm
5a	13.2(1H,-NH-), 10.2(1H,-NH-)5.26(1H,C-NH-)6.8-7.8 (8H,Ar)2.53,3.09(2H,=CH ₂ .Het).
5b	11.00 (1H,-CO-NH), 6.64-7.85 (8H,Ar.), 6.03(2H,=CH ₂ .Het.), 2.51(1H,-NH).
50	5.29(1H,-NH), 6.08(2H,=CH ₂ .Het), 6.82-7.69(12H,Ar.), 3.86(3H,O-CH ₃), 3.11(3H,N-CH ₃), 2.19
50	(3H,=C-CH ₃).
5d	5.38(1H,-NH -),6.05(2H,=CH ₂ .Het), 6-90-8.10(12H,Ar.).
5e	11.72 (1H,-CO-NH-),6.91-7.93 (8H,Ar.), 5.84 (1H,-OH), 2.51(1H,-NH-),
5f	5.97 (2H,=CH ₂ .Het), 5.19 (1H,-NH-),5.38 (1H,-OH), 6.82.89(9H,Ar.).
5g	9.94(1H,C-NH-),6.72-8.91 (7H,Ar.), 6.51 (2H,CH ₂ . Het.), 5.41(1H,C-NH-),
5h	10.01 (1H,C-NH-),5.33 (1H,C-NH-) 6.19 (1H,CH ₂ . Het.),6.89 -8.11(9H,Ar.).
5;	5.21(1H,-NH-),11.09(1H,-OH carboxylic acid), 5.40 (1H,-OH),6.09 (2H,=CH ₂ .Het), 6.92-8.98
51	(9H,Arom.).
5j	5.39 (1H, -OH), 5.14 (1H,C-NH-),6.93-7.95 (11H,Arom.).

Table 8: The C.H.N (⁰/₀) Analyses for the Compounds (5a-j)

Comp No	Formula	Cal./ Fou.			
Comp. No	rormula	C%	H%	N%	
50	СЧИО	66.27	4.68	24.40	
Ja	$C_{19} \Pi_{16} \Pi_{6} O$	66.08	4.11	23.95	
5h		67.12	3.75	11.18	
50	$C_{21}\Pi_{14}C\Pi N_3O_2$	66.43	3.08	10.23	
5c	СЧИО	70.89	5.49	12.72	
	$C_{26}\Pi_{24}\Pi_4O_3$	69.93	5.11	12.19	
5d		64.36	3.60	10.72	
	$C_{21}\Pi_{14}CIN_{3}OS$	64.93	3.89	11.01	
50	CHNO	70.58	4.23	11.76	
56	$C_{21}\Pi_{15}\Pi_{3}O_{3}$	69.73	3.91	11.02	

Table 8: Contd.,							
55	CHNO	72.28	4.85	8.43			
51	$C_{20}\Pi_{16}\Pi_{2}O_{3}$	71.88	4.01	7.92			
5 a	CHNOS	69.68	4.07	14.13			
Jg	$C_{23}\Pi_{16}\Pi_{4}OS$	69.80	4.59	14.71			
5h	$C_{21}H_{14}Br_2N_4O$	50.63	2.83	11.25			
		49.56	2.11	10.79			
5;		69.99	4.48	7.77			
51	$C_{21}H_{16}N_2O_4$	70.89	5.01	8.33			
5:		68.48	4.31	4.31			
5]	$C_{20}\Pi_{15}CIN_{2}O$	69.79	4.79	4.73			

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