Section A -Research paper

SYNTHESIS OF QUINAZOLIN-4-ONE DERIVATIVES AND EVALUATE THEIR ANTI-INFLAMMATORY ACTIVITIES

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ABSTRACT

The inflammatory response is a critical component of tissues' reactions to harmful inflammogens. Heterocyclic compounds are among the most versatile organic molecules, with applications ranging from natural and biologically active synthetic materials to medicines and synthetic intermediates. Quinazolinone and its derivatives are an essential heterocyclic skeleton that plays an important role in many cellular processes and have been recognized for their remarkable therapeutic value. Thus, referring to it's widely range of biological activity this study deals with synthesis of quinazolin-4-one derivatives and evaluate their anti-inflammatory activities. Five different derivatives of quinazolin-4-one were synthesized & analysed for its chemical characterization & anti-inflammatory activity. Results showed that all the compounds exhibited dose dependent inhibition of albumin denaturation with 4b and 4c having the lowest capacity to cause the inhibition 26.65% and 34.28% at the concentration of 500µg/mL. The anti-protease action was also dose dependent and **4b** at 500µg/mL was able to inhibit only 19.84% of protease activity. The highest inhibition of albumin denaturation and anti-protease action was exhibited by **4d** with 61.78% and 42.27% inhibition respectively. The results signify the role of electron donating groups in anti-inflammatory action of the synthesized molecules. It was witnessed that electron donating substitution on the benzylidene ring was beneficial for the anti-inflammatory potential of the molecules whereas electron withdrawing substituents were detrimental for activity.

Keywords: Inflammation, quinazolin-4-one, Anti-protease, Albumin denaturation, benzylidene ring, Heterocyclic, Quinazolinone

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INTRODUCTION

The inflammatory response is a critical component of tissues' reactions to harmful inflammogens. This complicated response involves leukocytes, often known as inflammatory cells, such as macrophages, neutrophils, and lymphocytes. In response to the inflammatory process, these cells release specialised substances such as vasoactive amines and peptides, eicosanoids, pro-inflammatory cytokines, and acute-phase proteins, which mediate the nations, with low- and middle-income countries accounting for 80% of those affected (Shikata *et al*., 2013; Herman *et al*., 2017).

Drugs are generally utilised in diabetes to preserve lives and treat symptoms. Secondary goals of diabetes drugs include preventing long-term diabetic problems and increasing lifespan by removing various risk factors. All of these goals are met by the blood glucose-lowering capabilities of diabetes medications. Except for insulin, pramlintide, liraglutide, and exenatide, all diabetes medications are taken orally and are hence referred to as oral hypoglycemic agents or oral antihyperglycemic medicines. There are various types of diabetes medications, and their use is determined by the type of diabetes, the person's age and circumstances, as well as other consideration (Padhi *et al*., 2020. Contreras *et al*., 2000).

Established Drug Classes for the Treatment of Diabetes

Alpha-Glucosidase Inhibitors

Alpha-glucosidase is a glucosidic bond cleaving enzyme that is extensively expressed. Inhibiting alpha-glycosidase inhibits complex carbs from being broken down into monosaccharides in the small intestine. As a result, these compounds function as pseudo-carbohydrates (substrate mimics), inhibiting digestive enzymes and preventing oligo- and polysaccharide catabolization to monomers. This results in less sugar being absorbed, lowering postprandial glucose levels and lowering hyperglycemia. Because AGIs have been demonstrated to be equally effective as metformin, they are frequently recommended as first-line therapy or in combination with other antidiabetics (Bischoff, 1994; Lebovitz *et al*., 1997).

Sodium-Glucose Cotransporter Type 2 Inhibitors

SGLT2 inhibitors are the most recent and promising therapeutic class. Canagliflozin and dapagliflozin were the first SGLT2 inhibitors licenced in 2013, followed by other monotherapy drugs empagliflozin in 2014 and ertugliflozin in 2017. Furthermore, SGLT2 inhibitors are commonly used in combination regimens with metformin and DPP4 inhibitors, as well as combinations of all three plus TZD medications. After incretin treatments, SGLT2 inhibitors are the second largest group of antidiabetic medicines in clinical trials (12%). Other regulatory agencies have previously approved three of the twelve medications in phase II, III, and IV clinical trials. Five other medications are in phase III trials, indicating that new SGLT2 inhibitors may be approved in the near future (Milder *et al*., 2018).

amines, hydrazine hydrate, different carbohydrazide, Sen and Ray's synthesis, and also from 2-aminobenzylamine (Asif *et al*., 2014; Reddy and Sivaramakrishna, 2020).

Furthermore, quinazolinones have anticancer, antibacterial, anti-mutagenic, and antioxidant properties. Quinazolinone, which contains another natural alkaloid, luotonin A, was isolated from Peganum nigellastrum, a Chinese herbal medicinal plant, and shown to have cytotoxic effects against the murine leukaemia P388 cell line as well as antiviral and anti-phytopathogenic fungus properties. The quinazolinone medication idelalisib, marketed as Zydelig, was used to treat chronic lymphocytic leukaemia (Borah *et al*., 2022; Singha, 2020). Thus, referring to it’s widely range of biological activity this study deals with synthesis of quinazolin-4-one derivatives and evaluate their

anti-inflammatory activities.

Materials & Methods

Materials

Anthranilic acid, ethanol, hydrazine hydrate, sodium hydroxide, benzoyl chloride, glacial acetic acid and various aromatic aldehydes were procured from Oxford Fine Chemicals, and were used as obtained without any further purification or treatment. All other chemicals used in the study were of laboratory grade.

Scheme for synthesis of quinazolin-4-one

Step 1 Synthesis of 2-benzamidobenzoic acid

Step 2 Synthesis of 2-phenyl-4H-benzo[d][1,3]oxazin-4-one

Step 3 Synthesis of 3-amino-2-phenylquinazolin-4(3H)-one

Step 4 Synthesis of Quinazoline based schiffs base

Synthetic Procedure

Synthesis of 2-benzamidobenzoic acid

To the anthranilic acid (2 mmol) dissolved in 10% sodium hydroxide (10 mL), benzoyl chloride (2.2 mmol) was added with stirring at room temperature for over 1 h. Upon completion, reaction mixture was quenched with cold water to obtain solid residue, which was washed with dilute HCl followed by water and recrystallized from ethanol.

Synthesis of 2-phenyl-4H-benzo[d][1,3]oxazin-4-one

A solution of 2-benzamidobenzoic acid (2 mmol) in acetic anhydride (10 mL) was heated under reflux for 2 h and then poured into crushed ice. The solid residue thus obtained was filtered, dried, and recrystallized with ethanol.

Synthesis of 3-amino-2-phenylquinazolin-4(3H)-one

A mixture of benzoxazine (2 mmol) and hydrazine hydrate (2 mmol) in glacial acetic acid was heated under reflux for 3 h. The completion of reaction was monitored by TLC. On cooling a solid separated that was collected by filtration, washed with water, dried, and recrystallized from ethanol.

General procedure for synthesis of Quinazolinone based schiffs base

10 mmol of 3-amino-2-phenylquinazolin-4(3H)-one was dissolved in 25 ml of ethanol and to it was added 10 mmol of appropriate aromatic aldehyde. The mixture was stirred for 2-3h for the completion of reaction, as monitored by TLC and was evaporated under reduced pressure. The product obtained was filtered off and recrystallized from ethanol/acetone (Hussain *et al*., 2014).

Synthesis of (E)-2-phenyl-3-(pyridin-3-ylmethyleneamino)quinazolin-4(3H)-one

10 mmol of 3-amino-2-phenylquinazolin-4(3H)-one was dissolved in 25 ml of ethanol and to it was added 10 mmol of nicotinaldehyde. The mixture was stirred for 2-3h for the completion of reaction, as monitored by TLC and was evaporated under reduced pressure. The product obtained was filtered off and recrystallized from ethanol/acetone.

Synthesis of (E)-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one

10 mmol of 3-amino-2-phenylquinazolin-4(3H)-one was dissolved in 25 ml of ethanol and to it was added 10 mmol of benzaldehyde. The mixture was stirred for 2-3h for the completion of reaction, as monitored by TLC and was evaporated under reduced pressure. The product obtained was filtered off and recrystallized from ethanol/acetone.

Synthesis of (E)-3-(4-nitrobenzylideneamino)-2-phenylquinazolin-4(3H)-one

10 mmol of 3-amino-2-phenylquinazolin-4(3H)-one was dissolved in 25 ml of ethanol and to it was added 10 mmol of 4-nitrobenzaldehyde. The mixture was stirred for 2-3h for the completion of reaction, as monitored by TLC and was evaporated under reduced pressure. The product obtained was filtered off and recrystallized from ethanol/acetone.

Synthesis of (E)-3-(4-hydroxybenzylideneamino)-2-phenylquinazolin-4(3H)-one

10 mmol of 3-amino-2-phenylquinazolin-4(3H)-one was dissolved in 25 ml of ethanol and to it was added 10 mmol of 4-hydroxybenzaldehyde. The mixture was stirred for 2-3h for the completion of reaction, as monitored by TLC and was evaporated under reduced pressure. The product obtained was filtered off and recrystallized from ethanol/acetone.

Chemical Characterization

Melting point

The melting points were determined by open capillary method and are uncorrected using an electrically heated melting point determination apparatus.

Thin Layer Chromatography

The purity and homogeneity of the compounds was determined by thin layer chromatography.

Solubility

The solubility of all the synthesized compounds was qualitatively determined in different solvents.

Evaluation of *in vitro* anti-inflammatory activity

Inhibition of albumin denaturation

The technique of inhibition of albumin denaturation reported previously was used with slight modifications. The volume of each component of the reaction mixture was reduced to half its volume. The synthesized molecules were individually dissolved in DMSO and appropriately diluted to prepare solutions of 100, 200, 300, 400 and 500 µg/mL concentration. A solution of 1% BSA in deionized water was prepared for the test. The reaction vessel was filled with 200 µL of BSA, 1400 µL of PBS and 1000 µL of the test solutions. Ibuprofen solution (1 µg/mL) was used in the positive control and distilled water was used in the negative control vessels instead of test solution. The reaction mixtures were incubated at 37°C for 15 min and then heated at 70°C for 5 min. The mixtures were then allowed to cool to room temperature and the absorbance of constituent of each vessel were analyzed in UV-Visible

spectrophotometer at 660 nm (Singh and Mishra, 2020; Kumari *et al*., 2015).

Antiprotease action

Preparation of Tris-HCl buffer

An accurately weighed quantity of 121.44 g of Tris was dissolved in 800 mL of distilled water. The pH of the solution was adjusted to 7.0 by addition of appropriate volume of concentrated HCl and the final volume of the solution was made up to 1 L with distilled water. The technique of antiprotease action previously reported was used with slight modifications.[36,37] The reaction mixture was prepared with 0.06 mg trypsin, 1 mL 20 mM Tris-HCl buffer (pH 7.0) and 1 mL test sample of different concentrations (100 - 500 µg/mL). The mixture was incubated at 37°C for 5 min followed by the addition of 1 mL of 0.8% w/v solution of casein in water. The mixture was incubated additionally for 20 min. In order to stop the reaction, 2 mL of 70% perchloric acid was added to the mixture. The turbid suspension obtained after the reaction was centrifuged and the absorbance of the supernatant was recorded at 210 nm against buffer as blank (Oyedepo and Femurewa, 1995; Sakat *et al*., 2010).

Statistical Analysis

All the experiments were performed in triplicate and the results are expressed as mean ± standard deviation. The difference between the experimental groups was compared by one way ANOVA followed by Dunnets multiple comparison test using Graph Pad Instat software.

***In silico* studies**

The 2D structures of the ligands were sketched on ChemDraw Ultra 8.0 and then transferred on Chem 3D to create the three dimensional structures. The canonical SMILES (simplified molecular-input line-entry system) were generated using ChemDraw and then submitted to SwissADME for the ADMET analysis, the prediction of physicochemical parameters and the drug-likeness using the Lipinski rule of five. The so-called Rule-of-five of Lipinski delineated the relationship between pharmacokinetic and physicochemical parameters.

Results & discussion

Five different type of compounds were synthesized with formulation code Q1 to Q5 by using different type of aldehydes. The maximum % yield of 75 % was obtained in Q2 which was made by using benzaldehyde and its colour was found to be brownish yellow. The lowest yield of 64% was noted in Q5 which was made using 2-chlorobenzaldehyde & having brown colour.

The formulation Q2 was having molecular formula $C_{21}H_{15}N_3O$ with molecular weight of 325.12 & Rf value of 0.72. The other formulations Q1, Q3, Q4 & Q5 was having molecular formula of $C_{20}H_{14}N_4O$, $C_{21}H_{14}N_4O_3$, $C_{21}H_{15}N_3O_2$, $C_{21}H_{14}ClN_3O$ respectively. The molecular weights ranged between 325.12 to 370.11. The Rf value was spanned between 0.61 to 0.72. The solubility pattern was found to be similar for all compounds. Each compounds was insoluble in water, soluble in chloroform & DMSO & sparingly soluble in methanol.

The IR and 1H NMR data of Q1 produced NMR signals of 8.4; 7.2-7.9 Ar H, 7.5 imine H, 7.7-9.3 pyridine H. the wave number for Q1 ranged between 1417.36 to 3104.67 $cm^{-1.}$

In case of Q2 the NMR signal was noted to be 7.2-7.9 Ar H, 8.1 imine H. The wave number ranged between 1477.79 to 3554.90. For the compound Q3 the NMR signal was obtained as 7.2-7.9 Ar H, 8.1 imine H, 8.2 H adj to NO2. The wave number ranged from 1289.17 to 3100.40 $cm^{-1.}$. The Q4 was found to have NMR signal as 7.2-7.9 Ar H, 8.1 imine H, 6.8 H adj to OH, 5.0 OH. The wave number ranged between 1082.70 to 3705.25 cm^{-1}. The last compound Q3 noted to have 7.2-7.69 Ar H, 8.1 imine H with wave number extending between 1015.34 to 3099.37 cm^{-1}.

Further, the anti -inflammatory activity was performed by albumin denaturation assay & inhibition of proteinase assay. All the compounds exhibited dose dependent inhibition of albumin denaturation with 4b and 4c having the lowest capacity to cause the inhibition 26.65% and 34.28% at the concentration of 500µg/mL. The antiprotease action was also dose dependent and **4b** at 500µg/mL was able to inhibit only 19.84% of protease activity. The highest inhibition of albumin denaturation and antiprotease action was exhibited by **4d** with 61.78% and 42.27% inhibition respectively. The results signify the role of electron dontating groups in anti-inflammatory action of the synthesized molecules. It was witnessed that electron donating substitution on the benzylidene ring was beneficial for the anti-inflammatory potential of the molecules whereas electron withdrawing substituents were detrimental for activity.

Further, We have used the Lipinski's rule that defines an orally active drug, which confirms to the number of hydrogen bonds acceptor (HBA) ≤ 10, hydrogen bonds donor (HBD) ≤ 5, molecular weight (MW) < 500 Da and Log P (the logarithm of octanol water partition coefficient) ≤ 5.

Also, it was reveled s that all compounds meet every single criterion of Lipinski's rule of five and thus fully obey the rule. Consequently, all the investigated compounds present a good drug-likeness profile, since they are predicted to be easily absorbed and have good permeability and bioavailability.

The solubility characteristic of the compounds is defined as insoluble if more negative than -10. It ranges from poorly soluble to highly soluble corresponding to the value of -10 to greater than zero, respectively. The values of the poorly soluble compounds lie in between -10 and - 6. The higher than -6 and less than -4 is classified as moderately soluble.

Table 1: Yield and color of synthesized compound

Compound code	Aldehyde Used	Yield (%)	Color
Q1	Nicotinaldehyde	68	Yellow
Q2	Benzaldehyde	75	Brownish Yellow
Q3	4-nitrobenzaldehyde	71	Yellow
Q4	4-hydroxybenzaldehye	69	Yellow
Q5	2-chlorobenzaldehyde	64	Brown

Table 2 Physical Properties of the synthesized compounds

Compound code	Molecular Formula	Molecular Weight	R_f Value	Melting point (°C)
Q1	$C_{20}H_{14}N_4O$	326.12	0.69	283-285
Q2	$C_{21}H_{15}N_3O$	325.12	0.72	196-198
Q3	$C_{21}H_{14}N_4O_3$	370.11	0.61	247-249
Q4	$C_{21}H_{15}N_3O_2$	341.12	0.62	268-270
Q5	$C_{21}H_{14}ClN_3O$	359.08	0.71	271-274

Table 3: Solubility characteristics of the synthesized compounds

Compound code	Water	Methanol	Chloroform	DMSO
Q1	Insoluble	Sparingly Soluble	Soluble	Soluble
Q2	Insoluble	Sparingly Soluble	Soluble	Soluble
Q3	Insoluble	Sparingly Soluble	Soluble	Soluble
Q4	Insoluble	Sparingly Soluble	Soluble	Soluble
Q5	Insoluble	Sparingly Soluble	Soluble	Soluble

Table 4: IR and 1H NMR data of Q1

S. No.	NMR signals (ppm relative to TMS)	Wave number (cm^{-1})	Due to…
1	8.4; 7.2-7.9 Ar H, 7.5 imine H, 7.7-9.3 pyridine H	3104.67	Ar/Het C-H Str
2		2970.38	Ar C-C Str
3		1639.00	C=N Str
4		1456.90	N=N Str
5		1417.36	C-N Str

Table 5: IR and 1H NMR data of Q2

S. No.	NMR signals (ppm relative to TMS)	Wave number (cm^{-1})	Due to…
1	7.2-7.9 Ar H, 8.1 imine H	3554.90	N-H stretching
2		3107.54	Ar/Het C-H Str
3		3039.13	Ar C-C Str
4		1653.56	C=N Str
5		1477.79	N=N Str
6		1393.03	C-N Str

Table 6: IR and 1H NMR data of Q3

S. No.	NMR signals (ppm relative to TMS)	Wave number (cm^{-1})	Due to…
1	7.2-7.9 Ar H, 8.1 imine H, 8.2 H adj to NO_2	3100.40	Ar/Het C-H Str
2		2970.97	Ar C-C Str
3		1639.54	C=N Str
4		1456.90	N=N Str
5		1289.17	C-N Str

Table 7: IR and 1H NMR data of Q4

S. No.	NMR signals (ppm relative to TMS)	Wave number (cm^{-1})	Due to…
1	7.2-7.9 Ar H, 8.1 imine H, 6.8 H adj to OH, 5.0 OH	3705.25	O-H str
2		3104.67	Ar/Het C-H Str
3		2970.38	Ar C-C Str
4		1639.00	C=N Str
5		1456.90	N=N Str
6		1289.63	C-N Str
7		1082.70	C-O Str

Table 8: IR and 1H NMR data of Q5

S. No.	NMR signals (ppm relative to TMS)	Wave number (cm^{-1})	Due to…
1	7.2-7.69 Ar H, 8.1 imine H	3099.37	Ar/Het C-H
2		2992.19	Ar C-C
3		1687.76	C=N
4		1439.83	N=N
5		1299.77	C-N
6		1015.34	C-Cl

Table 9: Inhibition of albumin denaturation by test compounds

Treatment	Inhibition of albumin denaturation (%)					
	100 µg/mL	200 µg/mL	300 µg/mL	400 µg/mL	500 µg/mL	10 µg/mL
4a	8.1	16.38	28.26	38.91	48.76	-
4b	3.12	8.24	14.8	18.72	26.65	-
4c	3.81	9.26	20.73	25.11	34.28	-
4d	15.63	23.43	34.64	54.83	61.78	-
4e	8.37	18.79	28.69	40.21	50.39	-
Ibuprofen	-	-	-	-	-	64.18

Table 10: Percent inhibition of proteinase action by test compounds

Treatment	Inhibition of Protease Action (%)					
	10 µg/mL	100 µg/mL	200 µg/mL	300 µg/mL	400 µg/mL	500 µg/mL
Ibuprofen	63.18	-	-	-	-	-
4a	-	6.36	10.56	17.82	32.11	41.8
4b	-	2.51	5.06	10.95	13.18	19.84
4c	-	3.68	7.01	11.62	15.92	20.65
4d	-	8.16	12.94	20.78	34.69	42.27
4e	-	5.51	8.85	15.76	29.42	37.81

Table 11: SMILES and IUPAC names of Q1-Q5

Compound Code	IUPAC Name	SMILES
Q1	(E)-2-phenyl-3-(pyridin-3-ylmethyleneamino)quinazolin-4(3H)-one	O=C1N(/N=C/C3=CC=CN=C3)C(C4=CC=CC=C4)=NC2=C1C=CC=C2
Q2	(E)-3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one	O=C1N(/N=C/C4=CC=CC=C4)C(C3=CC=CC=C3)=NC2=C1C=CC=C2
Q3	(E)-3-(4-nitrobenzylideneamino)-2-phenylquinazolin-4(3H)-one	O=C1N(/N=C/C4=CC=C([N+]([O-])=O)C=C4)C(C3=CC=CC=C3)=NC2=C1C=CC=C2
Q4	(E)-3-(4-hydroxybenzylideneamino)-2-phenylquinazolin-4(3H)-one	O=C1N(/N=C/C4=CC=C(O)C=C4)C(C3=CC=CC=C3)=NC2=C1C=CC=C2
Q5	(E)-3-(2-chlorobenzylideneamino)-2-phenylquinazolin-4(3H)-one	O=C1N(/N=C/C4=CC=CC=C4Cl)C(C3=CC=CC=C3)=NC2=C1C=CC=C2

Table: Physicochemical properties predicted by Swiss ADME

Compound Code	MW	HBD	HBA	Log P	NRB	PSA	MR	Log S	Violations	BS
Q1	326.35	0	4	3.32	3	60.14	98.67	-4.27	0	0.55
Q2	325.36	0	3	4.05	3	47.25	100.87	-4.94	1	0.55
Q3	370.36	0	5	3.26	4	93.07	109.69	-4.97	0	0.55
Q4	341.36	1	4	3.61	3	67.48	102.9	-4.78	0	0.55
Q5	359.81	0	3	4.5	3	47.25	105.88	-5.52	1	0.55

Conclusion

It can be determined that compounds containing the quinazolin-4-one moiety have stronger anti-inflammatory activity. The anti-protease action was also dose dependent and 4b at 500µg/mL was able to inhibit only 19.84% of protease activity. The highest inhibition of albumin denaturation and anti-protease action was exhibited by 4d with 61.78% and 42.27% inhibition respectively. The results signify the role of electron donating groups in anti-inflammatory action of the synthesized molecules. Consequently, these compounds can be considered as potential targets that can be further investigated for developing novel anti-inflammatory drugs.

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