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Design and Synthesis of 7-Chloro-3-Substituted Quinazolin-4(3H)-Ones as Potential Anti-inflammatory and Analgesic Agents

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ABSTRACT

In our effort to identify potent anti-inflammatory and analgesic agents a number of 7-chloro-3-substituted-2-phenylquinazolin-4(3H)-ones have been synthesized starting from 4-chloro anthranilic acid. Docking analysis of the quinazolinone derivatives were done with COX-II protein which was carried out by means of the AutoDock program. Their structures have been elucidated on the basis of elemental analyses and spectroscopic studies (IR, ^{1}H-NMR, MS). The synthesized compounds were tested for their analgesic activity by tail-flick method and anti-inflammatory activity by carrageenan induced rat paw oedema method. Preliminary evaluation of the anti-inflammatory and analgesic properties of the prepared compounds has indicated that some of them exhibit moderate to significant activity, compared to diclofenac standard.

Keywords: Quinazolinone, COX-II, Docking, anti-inflammatory, analgesic.

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INTRODUCTION

The chemistry of 4(3H)-quinazolinone has received an increasing interest because of its biological significance. Many derivatives of this system showed antifungal [1], antibacterial [2], anticancer [3], anti-inflammatory [4], anticonvulsant [5], hypolipidemic [6], antiulcer [7], analgesic [8] and antiproliferative [9] activities. Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed medicines for the treatment of pain, fever, inflammation and arthritis. [9] The classical NSAIDs produce their therapeutic benefit by inhibiting cyclooxygenase enzymes and thus reducing the formation of inflammatory mediator prostaglandins. [10-11] It has been reported that substitution of different aryl or heterocyclic moieties at

2 or 3 position of quinazolinone nucleus modulates the anti-inflammatory activity. [12]

Based on the above observations it was of interest to synthesize a series of novel quinazolinone derivatives with structure modifications involving incorporation of Schiff base at position 3 and phenyl moiety at position 2 of quinazolinone moiety to obtain safer and potent anti-inflammatory and analgesic agents.

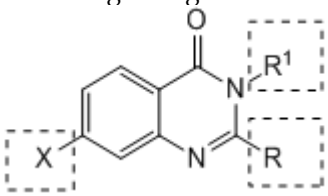

Fig. 1: Target for modification in quinazolinone structure

MATERIALS AND METHODS

Chemistry

2-amino-4-chloro benzoic acid was procured from Spectrochem, Mumbai. All other chemicals and reagents purchased from CDH and Rankem chemicals. Melting points of all the synthesized derivatives were determined by open-capillary tube method and values were uncorrected. IR spectra were recorded on Shimadzu FT/IR spectrometer in cm^{-1} values. ^1H NMR spectra were recorded on a Bruker 400 MHz NMR spectrometer using DMSO-d_6 / $CDCl_3$ as the solvent. (ESI-MS) spectra were recorded on Waters Micromass Q-TOF Micro. The progress of the reaction was checked by TLC in a solvent vapour saturated chamber on glass plates coated with Silica Gel G.

The following scheme (Fig. 2) was employed to synthesize ten novel quinazolinones derivatives. The steps involved reacting 4-chloro anthranilic acid with benzoyl chloride in presence of pyridine to yield 7-chloro-2-phenyl benzoxazin-4-one derivative, which is further refluxed with hydrazine hydrate to yield 3-amino-7-chloro2-phenylquinazolin-4-one derivative. This product was treated with various aromatic aldehydes in presence of ethanol and acetic acid to get the compounds Q 01 - Q 10.

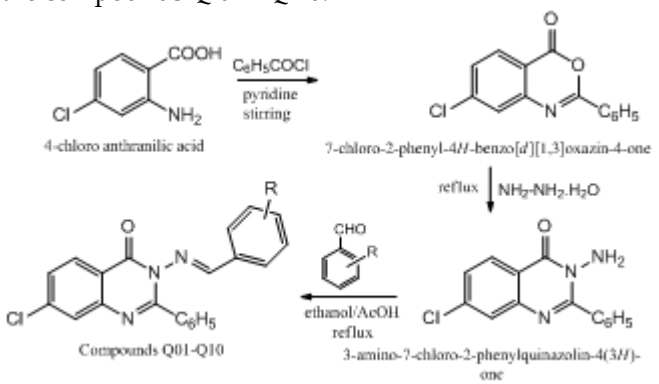

Fig. 2: Synthetic scheme

Pharmacological Studies

The pharmacological studies were done at the Pharmacology Division of Teena Biolabs Pvt. Ltd., Hyderabad. The experimental protocol used in the present study was approved by Institutional Animal Ethics Committee of Teena Biolabs Pvt. Ltd., Hyderabad (Study no. TBLSTPRJ0252013).

Anti-inflammatory activity

Anti-Inflammatory activity was performed by paw oedema method by using Wistar Rats (100-150 g) of either sex. The animals were divided into 3 groups with 5 mice in each group (control, standard drug and test compounds). The dose of test and standard was kept at 10 mg/kg body weight of rats. Percentage inhibition by the standard or the test compound was calculated by applying the following formula:

$$\% \, Inhibition = \frac{P_c - P_t}{P_c} \times 100$$

Where P_c is mean paw inflammation of control group and P_t is mean paw inflammation of test group.

Analgesic activity

The analgesic activity of the test compounds was done by tail flick method using (swiss albino) mice (23-35 g) of either sex. The animals were divided into 3 groups with 5 mice in each group (control, standard drug and test compounds). The dose of test and standard was kept at 10 mg/kg body weight of mice. The percentage analgesic activity (PAA) was calculated using the formula:

$$PAA = \left[\frac{T_2 - T_1}{10 - T_1}\right] \times 100$$

Where T_1 is the reaction time before treatment and T_2 is the reaction time after treatment.

Molecular Docking Studies

All the molecular modeling studies were carried out on an Intel Pentium 1.6 GHz processor, 512MB RAM memory with Windows XP operating system using AutoDockTools (ADT) v 1.5.4 and AutoDock v 4.2. The target sequences of COX-2 for anti-inflammatory activity were incurred from UniProt/Swiss-Prot protein knowledge base (ID: P0A0K8a).

RESULTS AND DISCUSSION

Chemistry

Compounds synthesized had a Schiff base in position 3 of quinazolinone ring. The IR spectra of all compounds displayed the characteristic peaks in the region 1440-1520 cm^{-1} indicating the formation of the Schiff base (-H-C=N). The appearance of peak in the region 1600-1740 cm^{-1} confirmed the presence of C=O of 4-keto-quinazolinone in the compounds which further confirms the formation of the title compounds. Halogen group in the quinazolin-4(3H)-ones showed the characteristic absorption bands at 590–760 cm^{-1}. The structural assignments were further supported by their ^1H NMR spectra. The multiplets at 6.5-8.2 ppm ascertained the presence of aromatic protons. The relatively downfield multiplet at 8.19-8.3 ppm which integrates up to 2H protons in the vicinity of the halogen (Cl) attached to the quinazolinone ring or phenyl ring. The singlet at around 9 ppm appeared due to the proton attached to the imine carbon. In ESI-MS spectra, molecular ion [M+] peaks, which appeared at

different intensities, confirmed the molecular weights of the synthesized compounds.

The physical data of the synthesized compounds are shown in Table 1.

Table 1: Physical data of synthesized compounds

Compound	R/Aldehyde	R′	Molecular Weight	Melting Point (°C) (uncorrected)	R_f Value*	% yield
Q 01	furfural dehyde	-	349.77	180-181	0.65	45
Q 02	H	H	359.81	167-169	0.72	54
Q 03	4-Cl	H	394.25	175-176	0.61	23
Q 04	2-Cl	H	394.25	178-180	0.76	67
Q 05	2-OH	H	375.81	201-202	0.56	51
Q 06	2-NO_2	H	404.81	205-207	0.59	54
Q 07	3-NO_2	H	404.81	179-181	0.62	59
Q 08	3-OCH_3	4-OCH_3	419.86	180-182	0.87	60
Q 09	4-CH_3	H	373.83	197-199	0.43	69
Q 10	4-OH	H	375.81	203-205	0.55	32

The following are the spectral data of the synthesized compounds.

7-chloro-3-(furan-2-ylmethyleneamino)-2-phenylquinazolin-4(3H)-one ***(Q 01)*** **Spectral Data:** IR (KBr) cm^{-1}: 3093 (ArH), 1678 (C=O), 1516 (C=N). ^1H NMR ($CDCl_3$, δ ppm): 9.05 (s, 1H, N=CH), 7.79-8.27 (m, 7H, Ar-H), 7.70-7.74 (m, 3H, furan H). MS (m/z): M^+ 351. Anal. calcd. for $C_{19}H_{12}ClN_3O_2$: C, 65.24; H, 3.46; N, 12.01. Found: C, 65.37; H, 3.52; N, 12.15.

3-(benzylideneamino)-7-chloro-2-phenylquinazolin-4(3H)-one ***(Q 02)*** **Spectral Data:** IR (KBr) cm^{-1}: 3021 (ArH), 1654 (C=O), 1586 (C=N). ^1H NMR ($CDCl_3$, δ ppm): 9.21 (s, 1H, N=CH), 7.28-8.12 (m, 13H, Ar-H). MS (m/z): M^+ 359. Anal. calcd. for $C_{21}H_{14}ClN_3O$: C, 70.10; H, 3.92; N, 11.68. Found: C, 70.78; H, 3.82; N, 11.65.

3-(4-chlorobenzylideneamino)-7-chloro-2-phenylquinazolin-4(3H)-one ***(Q 03)*** **Spectral Data:** IR (KBr) cm^{-1}: 3059 (ArH), 1644 (C=O), 1566 (C=N). ^1H NMR ($CDCl_3$, δ ppm): 9.03 (s, 1H, N=CH), 7.33-8.31 (m, 12H, Ar-H). MS (m/z): M^+ 394. Anal. calcd. for $C_{21}H_{13}Cl_2N_3O$: C, 63.98; H, 3.32; N, 10.66. Found: C, 63.68; H, 3.48; N, 10.86.

3-(2-chlorobenzylideneamino)-7-chloro-2-phenylquinazolin-4(3H)-one ***(Q 04)*** **Spectral Data**: IR (KBr) cm^{-1}: 3032 (ArH), 1626 (C=O), 1559 (C=N). ^1H NMR ($CDCl_3$, δ ppm): 9.33 (s, 1H, N=CH), 7.05-8.12 (m, 12H, Ar-H). MS (m/z): M^+ 394. Anal. calcd. for $C_{21}H_{13}Cl_2N_3O$: C, 63.98; H, 3.32; N, 10.66. Found: C, 63.41; H, 3.78; N, 10.96.

3-(2-hydroxybenzylideneamino)-7-chloro-2-phenylquinazolin-4(3H)-one ***(Q 05)*** **Spectral Data**: IR (KBr) cm^{-1}: 3385 (OH), 1662 (C=O), 1552 (C=N). ^1H NMR ($CDCl_3$, δ ppm): 10.45 (s, 1H, ArOH), 9.18 (s, 1H, N=CH), 7.16-8.02 (m, 12H, Ar-H). MS (m/z): M^+ 375. Anal. calcd. for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18. Found: C, 67.98; H, 3.88; N, 10.86.

3-(2-nitrobenzylideneamino)-7-chloro-2-phenylquinazolin-4(3H)-one ***(Q 06)*** **Spectral Data:** IR (KBr) cm^{-1}: 3039 (ArH), 1624 (C=O), 1556 (C=N). ^1H NMR ($CDCl_3$, δ ppm): 9.08 (s, 1H, N=CH), 7.11-8.12 (m, 12H, Ar-H). MS (m/z): M^+ 404. Anal. calcd. for $C_{21}H_{13}ClN_4O_3$: C, 62.31; H, 3.24; N, 13.84. Found: C, 63.12; H, 3.71; N, 13.98.

3-(3-nitrobenzylideneamino)-7-chloro-2-phenylquinazolin-4(3H)-one ***(Q 07)*** **Spectral Data:** IR (KBr) cm^{-1}: 3012 (ArH), 1662 (C=O), 1541 (C=N). ^1H NMR ($CDCl_3$, δ ppm): 8.88 (s, 1H, N=CH), 7.08-8.35 (m, 12H, Ar-H). MS (m/z): M^+ 404. Anal. calcd. for $C_{21}H_{13}ClN_4O_3$: C, 62.31; H, 3.24; N, 13.84. Found: C, 63.95; H, 3.81; N, 13.71.

3-(3,4-dimethoxybenzylideneamino)-7-chloro-2-phenylquinazolin-4(3H)-one ***(Q 08)*** **Spectral Data**: IR (KBr) cm^{-1}: 3010 (ArH), 1665 (C=O), 1545 (C=N). ^1H NMR ($CDCl_3$, δ ppm): 8.95 (s, 1H, N=CH), 7.18-8.25 (m, 11H, Ar-H) 3.35-3.84 (m, 6H, Ar–OCH_3). MS (m/z): M^+ 419. Anal. calcd. for $C_{23}H_{18}ClN_3O_3$: C, 65.79; H, 4.32; N, 10.01. Found: C, 65.15; H, 4.81; N, 10.71.

3-(4-methylbenzylideneamino)-7-chloro-2-phenylquinazolin-4(3H)-one ***(Q 09)*** **Spectral Data**: IR (KBr) cm^{-1}: 3019 (ArH), 1654 (C=O), 1588 (C=N). ^1H NMR ($CDCl_3$, δ ppm): 9.13 (s, 1H, N=CH), 7.28-8.35 (m, 12H, Ar-H) 2.51 (S, 3H, CH_3). MS (m/z): M^+ 373. Anal. calcd. for $C_{22}H_{16}ClN_3O$: C, 70.68; H, 3.75; N, 11.18. Found: C, 71.15; H, 3.31; N, 10.79.

3-(4-hydroxybenzylideneamino)-7-chloro-2-phenylquinazolin-4(3H)-one ***(Q 10)*** **Spectral Data**: IR (KBr) cm^{-1}: 3369 (OH), 3093 (ArH), 1668 (C=O), 1577 (C=N). ^1H NMR ($CDCl_3$, δ ppm): 10.56 (s, 1H, ArOH), 9.33 (s, 1H, N=CH), 7.25-8.31 (m, 12H, Ar-H). MS (m/z): M^+ 375. Anal. calcd. for $C_{21}H_{14}ClN_3O_2$: C, 67.12; H, 3.75; N, 11.18. Found: C, 68.15; H, 3.39; N, 10.95.

Pharmacological Studies

Statistical significance of anti-inflammatory and analgesic activity of the compounds were analyzed using one-way analysis of variance (ANOVA) followed by Dunnett's multiple comparison test. A significance level of $P<0.05$ was considered as acceptable in all cases.

Anti-inflammatory activity

It was observed that there was a gradual increase in the volume of the paw of the rats in the control (0.5% of sodium carboxyl methyl cellulose treated) as the group did not receive any anti-inflammatory agent. The anti-inflammatory effect induced by Diclofenac sodium progressively increased and reached a maximum at 1 h and it was maintained up to 4 h while the synthesized compounds reached to their maximum anti-inflammatory activity between 2-4 h. Compounds Q 02, Q 03, Q 05, Q07 and Q 09 showed comparable % inhibition (after 4 h) when compared to Diclofenac.

Analgesic activity

It was observed that there was a gradual increase in the reaction time to respond to the heat in almost all the compounds. In the standard group (Diclofenac) the response time did not decrease even after 3 h of drug administration. While in the test compounds mostly the response time started decreasing after 2 h. Compounds Q 04 and Q 05 showed comparable PAA (after 3 h) when compared to Diclofenac.

Table 2: Anti-inflammatory activity of synthesized compounds

Group	Paw volume (mL)[$]					% Inhibition (after 4 h)
	Initial	1 h	2 h	3 h	4 h	
Control	0.72 ± 0.04	0.92 ± 0.04	1.12 ± 0.04	1.32 ± 0.04	1.36 ± 0.04	-
Diclofenac	0.72 ± 0.04****	0.72 ± 0.04****	0.72 ± 0.04****	0.72 ± 0.04****	0.72 ± 0.04****	47.06
Q 01	0.72 ± 0.04**	0.86 ± 0.04**	0.92 ± 0.04**	0.86 ± 0.04**	0.84 ± 0.04**	38.24
Q 02	0.68 ± 0.04****	0.78 ± 0.04****	0.78 ± 0.04****	0.80 ± 0.04****	0.80 ± 0.04****	41.18
Q 03	0.72 ± 0.04***	0.84 ± 0.04***	0.80 ± 0.06***	0.80 ± 0.04***	0.80 ± 0.04***	41.18
Q 04	0.72 ± 0.04**	0.96 ± 0.04**	0.92 ± 0.04**	0.92 ± 0.04**	0.84 ± 0.04**	38.24
Q 05	0.72 ± 0.04****	0.80 ± 0.04****	0.78 ± 0.04****	0.72 ± 0.04****	0.72 ± 0.04****	47.06
Q 06	0.72 ± 0.04***	0.76 ± 0.04***	0.84 ± 0.04***	0.84 ± 0.06***	0.84 ± 0.04***	38.24
Q 07	0.68 ± 0.04****	0.78 ± 0.04****	0.74 ± 0.04****	0.78 ± 0.04****	0.76 ± 0.04****	44.12
Q 08	0.72 ± 0.04***	0.78 ± 0.04***	0.86 ± 0.04***	0.84 ± 0.04***	0.84 ± 0.04***	38.24
Q 09	0.72 ± 0.04***	0.84 ± 0.04***	0.82 ± 0.04***	0.80 ± 0.04***	0.80 ± 0.04***	41.18
Q 10	0.72 ± 0.04**	0.88 ± 0.04**	0.94 ± 0.04**	0.90 ± 0.04**	0.82 ± 0.04**	39.71

[$]Paw volume is expressed as mean with standard error (n=5); **** p<0.0001, *** and ** p<0.05

Table 3: Analgesic activity of synthesized compounds

Group	Reaction time (sec)[$]					PAA (after 3 h)
	Initial	30 min	1 h	2 h	3 h	
Control	2.4 ± 0.24	2.4 ± 0.24	2.4 ± 0.24	2.4 ± 0.24	2.4 ± 0.24	-
Diclofenac	2.4 ± 0.24***	7.4 ± 0.24***	10.0 ± 0.00***	10.0 ± 0.00***	10.0 ± 0.00***	100
Q 01	2.4 ± 0.24	6.2 ± 0.04	7.2 ± 0.04	7.8 ± 0.04	5.6 ± 0.20	42.10526
Q 02	2.4 ± 0.24	3.8 ± 0.24	4.6 ± 0.24	5.2 ± 0.24	3.8 ± 0.24	18.42105
Q 03	2.4 ± 0.24	4.4 ± 0.24	7.6 ± 0.24	10.0 ± 0.00	6.2 ± 0.37	50
Q 04	2.4 ± 0.24	4.6 ± 0.24	6.8 ± 0.24	9.0 ± 0.24	7.8 ± 0.24	71.05263
Q 05	2.4 ± 0.24**	6.6 ± 0.04**	7.6 ± 0.04**	9.2 ± 0.04**	10.0 ± 0.00**	100
Q 06	2.4 ± 0.24	3.4 ± 0.24	6.4 ± 0.24	6.6 ± 0.24	5.2 ± 0.24	36.84211
Q 07	2.4 ± 0.24	5.2 ± 0.24	7.4 ± 0.24	5.8 ± 0.24	3.7 ± 0.24	17.10526
Q 08	2.6 ± 0.24	5.6 ± 0.20	6.8 ± 0.24	5.6 ± 0.24	5.0 ± 0.24	34.21053
Q 09	2.4 ± 0.24	4.2 ± 0.24	5.6 ± 0.24	4.4 ± 0.24	3.6 ± 0.24	15.78947
Q 10	2.4 ± 0.20	2.8 ± 0.24	3.8 ± 0.24	4.6 ± 0.24	5.6 ± 0.24	42.10526

[$]Paw volume is expressed as mean with standard error (n=5); **** p<0.0001, *** and ** p<0.05

Table 4: Docking results of quinazolinones with COX-2

Compound	H bond	Binding energy	Ligand efficiency	Inhibitory constant (uM)	Electrostatic energy	Amino acids
Q 01	2	-9.79	-0.39	67.14	-0.09	HIS42,GLN43
Q 02	2	-7.99	-0.31	1.38	-0.01	GLN41,HIS42
Q 03	2	-9.15	-0.34	195.15	-0.03	GLN41,HIS42
Q 04	-	-8.52	-0.32	571.67	0.01	-
Q 05	3	-8.75	-0.32	383.28	-0.05	GLN43,HIS42,GLN41
Q 06	2	-8.96	-0.31	271.61	-0.83	GLN41,LYS472
Q 07	2	-10.1	-0.35	39.3	-1.45	LYS472,GLN41
Q 08	2	-7.32	-0.24	4.28	-0.22	GLN43,ARG82
Q 09	1	-8.7	-0.37	416.84	-0.04	GLN43
Q 10	1	-8.23	-0.3	921.16	-0.1	GLN43,ARG82

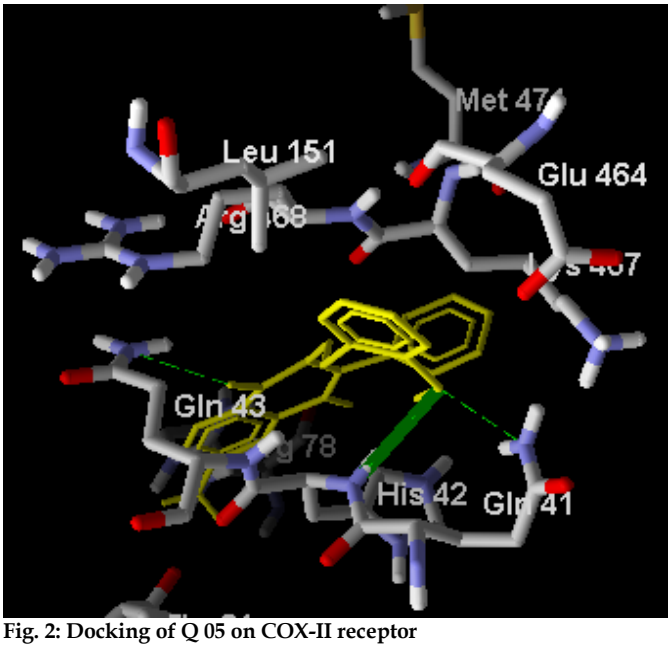

Fig. 2: Docking of Q 05 on COX-II receptor

Molecular Docking Studies

All the synthesized quinazolinone derivatives when docked with COX-2 protein (for anti-inflammatory activity) showed strong interactions except compound Q 04. The resultant docking scores shows best interaction with cluster formation in active site amino acids. The predicted docking results with COX-2 are tabulated in Table 4. Docking study reveals that compound Q 05 binds well with COX-II receptor with 3 hydrogen bonds and is found to me most active.

From the obtained results it can be concluded that the lead compound, 7-chloro-3-substituted-2-phenylquinazolin-4(3H)-ones can be further exploited for arriving at a pharmacophore for a more potent anti-inflammatory and analgesic agent.

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