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Synthesis of Quinazolinone Based Schiff Bases as Potential Anti-inflammatory and Analgesic Agents

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ABSTRACT

Quinazolinone is a an important heterocyclic compound possessing a wide range of biological activities such as anti-tumour, sedative, antidiabetic, analgesic, anti-inflammatory, antimicrobial and anticancer. It is a versatile lead molecule for the design of potential bioactive agents. They show anti-inflammatory and analgesic action by inhibiting the microsomal prostaglandin E2-synthase 1 (mPGES-1) which is a key enzyme of the arachidonic acid. The aim of the present study includes the synthesis of some novel Schiff bases of amino derivatives of quinazolinone as anti-inflammatory and analgesic agent. A new series of the title compounds incorporated into diverse N heterocyclic moieties. First step involves the synthesis of 6,8-diiodo-2-phenyl-4H-3,1-benzoxazin-4-one. In second step this compound reacts with hydrazine hydrate to form a new intermediate 6,8-diiodo-2-phenylquinazolin-4(3H)-one. Schiff bases (5a-5f) were synthesized by the reaction of 6,8-diiodo-2-phenylquinazolin-4(3H)-one with different aromatic aldehydes. Maximum yield of 79% was obtained from p-hydroxy derivative. Schiff bases formed were evaluated for anti-inflammatory and analgesic activities. O-hydroxy derivative showed maximum anti-inflammatory activity with percentage inhibition of 50.45%. It was proved to be good analgesic agent as well. It was concluded that Schiff bases containing hydroxyl group showed promising activity as compared to chloro derivatives.

Key words: Quinazolinone, anticancer, analgesic, anti-inflammatory, arachidonic acid

INTRODUCTION

Quinazolinone is an important heterocyclic compound with nitrogen as a part of the ring (Arora *et al*., 2011). 2-Quinazolinone and 4-Quinazolinone are the two structural isomers. Out of the two isomers, 4-isomer is present in most of the compounds (Kumar *et al*., 2012). The Quinazolin-4-(3H)-one and its analogues have shown a wide range of biological activities such as anti-tumour, sedative, antidiabetic, analgesic, anti-inflammatory, antimicrobial and anticancer (Wu *et al*., 2010; Kashaw *et al*., 2010; Levien and Baker, 2009; Yesilada *et al*., 2004; Fawzy *et al*., 2008; Khalil *et al*., 2003). They are frequently used in medicine for example Methaqualone, Afloqualone, Diproqualone, Fluproquazone, Tiacrilast, Halofuginone and Raltitrexed possessing different biological activities (Smyth *et al*., 1973; Ochiai and Ishida, 1982; Audeval *et al*., 1988; Wheatley, 1982; Welton *et al*., 1986; Sundrud *et al*., 2009; Widemann *et al*., 1999). It is a versatile lead molecule for the design of potential bioactive agents. They show their anti-inflammatory and analgesic action by inhibiting the microsomal prostaglandin E2-synthase 1 (mPGES-1) which is a

key enzyme of the arachidonic acid cascade. Its product PGE2 plays an important role in various inflammatory processes, pain, fever and cancer. Selective inhibition of mPGES-1 might be a promising step to avoid cyclooxygenase-related effects and reduction of PGE2 will make them a good anti-inflammatory and analgesic agents (Rorsch *et al.*, 2012).

Schiff base is also called as azomethine and secondary aldimines having general formula:

$$R_1R_2C = NR_3$$

where, R is an organic side chain. Reflux of mixture of aldehyde (or ketone) and amine in organic medium leads to synthesis of Schiff bases (Bendale *et al.*, 2011). Schiff bases that contain aryl substituents having effective conjugation are substantially more stable and more readily synthesized while those which contain alkyl substituent are relatively unstable. They have been found to possess various pharmacological activities such as antimalarial, anticancer, anti-microbial, antitubercular, anti-inflammatory and antiviral (Harpstrite *et al.*, 2008; Ghorab *et al.*, 2012; Saravanan *et al.*, 2010; Ferreira *et al.*, 2009; Jayakumarswamy *et al.*, 2011; Chinnasamy *et al.*, 2010). They are important not only in medical chemistry but also in organic synthetic chemistry. They are the important compound owing to their wide range of biological activities and industrial application (Wang *et al.*, 2008).

The past studies revealed that the Schiff bases of 2-phenylquinazolin-4-(3H)-one possess various biological activities. In this study some novel Schiff bases of 3-amino-6,8-diiodo-2-phenylquinazolin-4(3H)-one with anti-inflammatory and analgesic activities were synthesized. This work was based on the fact that several quinazolinone derivatives have potent anti-inflammatory and analgesic effect (Mariappan *et al.*, 2011; Mosaad *et al.*, 2010).

MATERIALS AND METHODS

The study was started on 1st of September, 2011 and was carried out till 30th June, 2012.

Chemicals: Carrageenan and 3,5-diiodoanthranillic acid were obtained from HiMedia Labs, Mumbai. All other chemical reagents were used of analytical grade which were procured from different companies (Loba Chem, Merck Limited and S D Fine). The progress of the reaction was monitored on readymade silica gel plates (Merck) using chloroform-methanol (6:4) as a solvent system. Iodine was used as a developing agent. Melting points were determined with a Buchi 530 melting point apparatus in open capillaries. IR spectra details as mentioned in experimental part below were recorded on KBr discs, using a Perkin-Elmer Model 1600 FT-IR spectrometer. The proton magnetic resonance spectra (^{1}H-NMR) were recorded on Perkin Elmer Spectrophotometer-300 MHz in DMSO-d6 using TMS as an internal standard. Elemental analysis was performed by CHNS (O) Analyzer.

Animals: The Wistar albino rats (150-200 g) of either sex were obtained from Zoin Co. Biologicals, Ambala. They were kept at standard laboratory diet, environmental temperature and humidity. A 12 h light and dark cycle was maintained throughout the experimental protocol. The experimental protocol was duly approved by Committee for the Purpose of Control and Supervision of Experiments on Animals.

Synthesis: Synthesis of 6, 8-diiodo-2-phenyl-4H-3, 1-benzoxazin-4-one (3): 3,5-diiodoanthranilic acid (1) (3.88 g, 0.01 mol) was reacted with benzoyl chloride (1.17 mL,

0.01 mol)(2) in presence of pyridine and stirred for 3 h and the resulting mixture was treated with 5% sodium bicarbonate solution to get 2-phenylbenzoxazin-4-one (3). The precipitate was filtered, dried and recrystallized from ethanol. The percentage yield obtained was 73%, m.p. 231°C, FTIR: 525 cm^{-1} (-I), 1689 cm^{-1} (-C = O), 1610 cm^{-1} (-C = N-), 1201 (C-O), ^{1}H-NMR (DMSO-d6, δ ppm): 8.5612 (2H, s, fused Ar-H), 7.9201-7.9413 (2H, d, Ar-H), 7.3801-7.5403 (3H, t, Ar-H).

Synthesis of 3-Amino-6,8-diiodo-2-phenylquinazolin-4(3H)-one (4): Compound (3) (4.75 g, 0.01 mol) was treated with hydrazine hydrate (0.64 g, 0.02 mol) in presence of ethanol and refluxed for 2-3 h to form 6,8-diiodo-2-phenylquinazolin-4(3H)-one (4). The content was then cooled, filtered off and recrystallized from ethanol. The percentage yield obtained was 69%, m.p. 239°C, FTIR: 513 cm^{-1} (-I), 1700 cm^{-1} (-C = O), 1617 cm^{-1} (-C = N), 3431 and 3337 cm^{-1} (-NH_2), 1102 cm^{-1} (C-N), ^{1}H-NMR (DMSO-d6, δ ppm): 2.5537 (2H, s, NH_2), 8.0284 (2H, s, fused Ar-H), 7.1360-7.9563 (5H, m, Ar-H).

General Synthesis of Schiff bases of 6, 8-Diiodo-2-phenylquinazolin-4(3H)-one (5a-5f): Different aromatic aldehydes (0.01 mol) were treated with compound (4) (4.89 g, 0.01 mol) in presence of ethanol and refluxed for 3-4 h. After that the reaction mixture was cooled and the product was filtered off. All the compounds were recrystallized from ethanol. The physicochemical data of synthesized Schiff bases are represented in Table 1.

3-{[(E)-(2-chlorophenyl)methylidene]amino}-6,8-diiodo-2-phenylquinazolin-4(3H)-one (5a): FTIR: 546 (-I), 1679 (-C = O), 1629 (-C = N), 713 (-Cl); ^{1}H-NMR (DMSO-d6, δ ppm): 8.1710 (2H, s, fused Ar-H), 7.1803-7.9460 (5H, m, Ar-H), 8.1272 (1H, s, H-C = N), 7.3489-7.7757 (4H, m, subst. Ar-H). Anal Calcd. for $C_{21}H_{12}ClI_2N_3O$ (%): C, 41.21; H, 1.98; N, 6.87; O, 2.62. Found: C, 41.03; H, 1.93; N, 6.89; O, 2.41.

3-{[(E)-(3-chlorophenyl)methylidene]amino}-6,8-diiodo-2-phenylquinazolin-4(3H)-one (5b): FTIR: 545 (-I),1700 cm^{-1} (-C = O), 1624 cm^{-1} (-C = N), 710 cm^{-1} (-Cl); ^{1}H-NMR (DMSO-d6, δ ppm): 8.6361(2H, s, fused Ar-H), 7.4164-7.7850 (5H, m, Ar-H), 8.1491(1H, s, H-C=N), 7.5311-7.6848 (4H, m, subst. Ar-H). Anal. Calcd. for $C_{21}H_{12}ClI_2N_3O$ (%): C, 41.21; H, 1.98; N, 6.87; O. Found: C, 40.95; H, 2.1; N, 6.76; O, 2.64.

3-{[(E)-(4-chlorophenyl)methylidene]amino}-6,8-diiodo-2-phenylquinazolin-4(3H)-one (5c): FTIR: 553 (-I), 1703 cm^{-1} (-C = O), 1624 cm^{-1} (-C = N), 705 cm^{-1} (-Cl); ^{1}H-NMR (DMSO-d6, δ ppm): 8.6041(2H, s, fused Ar-H), 7.3911-7.9181(5H, m, Ar-H), 8.0317 (1H, s, H-C = N), 7.2305-7.8056 (4H, m, subst. Ar-H). Anal. Calcd. for $C_{21}H_{12}ClI_2N_3O$ (%): C, 41.21; H, 1.98; N, 6.87; O, 2.62. Found: C, 41.89; H, 1.95; N, 6.65; O, 2.84.

Table 1: Physicochemical parameters of some Novel 6,8-Diiodo-2-phenylquinazolin-4(3H)-one Schiff bases (5a-5f)

Compound	Arachidonic acid	Molecular formula	MW (g mol^{-1})	Yield (%)	M.p. (°C)	R_f
5a	o-chlorophenyl	$C_{21}H_{12}ClI_2N_3O$	611.06	76	220-224	0.65
5b	m-chlorophenyl	$C_{21}H_{12}ClI_2N_3O$	611.06	74	234-238	0.63
5c	p-chlorophenyl	$C_{21}H_{12}ClI_2N_3O$	611.06	71	232-236	0.67
5d	2-hydroxyphenyl	$C_{21}H_{13}I_2N_3O_2$	593.15	77	250-254	0.72
5e	p-hydroxyphenyl	$C_{21}H_{13}I_2N_3O_2$	593.15	79	241-245	0.60
5f	3-hydroxy-4-methoxyphenyl	$C_{22}H_{15}I_2N_3O_3$	623.18	75	253-257	0.72

3-{[(E)-(2-hydroxyphenyl)methylidene]amino}-6,8-diiodo-2-phenylquinazolin-4(3H)-one (5d): FTIR: 564 (-I), 1702 (-C = O), 1623 (-C = N), 730 (-Cl), 3432 (-OH); ^{1}H-NMR (DMSO-d6, δ ppm): 8.9158 (2H, s, fused Ar-H), 8.0901 (1H, s, -C=N), 7.3215-7.5807 (5H, m, Ar-H), 6.9040-7.5617 (4H, m, subst. Ar-H), 5.1494 (1H, s, O-H). Anal. Calcd. for $C_{21}H_{12}ClI_2N_3O$ (%): C, 42.52; H, 2.21; N, 7.08; O, 5.39. Found: C, 41.39; H, 2.20; N, 6.9; O, 5.27.

3-{[(E)-(4-hydroxyphenyl)methylidene]amino}-6,8-diiodo-2-phenylquinazolin-4(3H)-one (5e): FTIR (cm^{-1}): 551 (-I), 1701 (-C = O), 1625 (-C = N), 742 (-Cl), 3466 (-OH); ^{1}H-NMR (DMSO-d6, δ ppm): 8.2123 (2H, s, fused Ar-H), 7.2926-7.9983 (5H, m, Ar-H), 7.1951-7.8537 (4H, d, subst. Ar-H), 5.4381 (1H, s, O-H). Anal. Calcd. for $C_{21}H_{12}ClI_2N_3O$ (%): C, 42.52; H, 2.21; N, 7.08; O, 5.39; I, 42.79. Found: C, 42.63; H, 2.01; N, 7.26; O, 5.47.

3-{[(E)-(4-hydroxy-3-methoxyphenyl)methylidene]amino}-6,8-diiodo-2-phenylquinazolin-4(3H)-one. (5f): FTIR: 588 (-I), 1669 (-C = O), 1621 (-C = N), 732 (-Cl); 3479 (-OH); ^{1}H-NMR (DMSO-d6, δ ppm): 3.8563(3H, s, CH_3), 8.5408 (2H, s, fused Ar-H), 8.0995 (1H, s, H-C=N), 7.338-7.9238 (5H, m, Ar-H), 6.8484-7.1965 (3H, m, subst. Ar-H), 4.9315(1H, s, O-H). Anal Calcd. for $C_{21}H_{12}ClI_2N_3O$ (%): C, 42.40; H, 2.43; N, 6.74; O, 7.70; I, 40.73. Found: C, 42.31; H, 2.22; N, 6.43; O, 7.90.

Anti-inflammatory activity: Carrageenan-induced rat paw edema: The carrageenan-induced rat paw edema assay was carried out according to Winter *et al.* (1962). Wistar rats were divided into 8 groups each consisting of 6 animals (Gill *et al.*, 2010):

- **Group I: Disease control:** Carrageenan (1%) was administered in the plantar surface of rat (p.o.)
- **Group II: Standard:** Suspension of Diclofenac sodium (10 mg kg^{-1}) in 1% gum acacia (p.o.)+ Carrageenan
- **Group III to VIII: Test:** Suspension of test compounds 5a-5f, respectively (200 mg kg^{-1}) in 1% Gum acacia (p.o.)+carrageenan

Edema was induced on the left hind paw of the rats by subplantar injection of 0.1 mL of a solution of 1% (w/v) carrageenin in a 0.9% NaCl (w/v). The paw volume was measured at intervals of 60, 120, 180 min by the mercury displacement method using a plethysmograph after administration of the suspension of test compounds in 1% Gum acacia orally. The average paw edema volume of all the groups were calculated and compared with that of control. The percentage inhibition of paw edema in drug treated group was compared with the carrageenan control group and calculated according to the following equation:

$$\text{Inhibition of drug (\%)} = \left(\frac{V_c - V_t}{V_c}\right) \times 100$$

where, V_c is the inflammatory increase in paw volume of control group of animals and V_t is the inflammatory increase in paw volume of drug-treated animals.

Analgesic activity: Swiss albino mice of either sex were divided into 8 groups each consisting of 6 animals:

- **Group I: Control:** One percent gum acacia (p.o.)
- **Group II: Standard:** Suspension of Diclofenac sodium (10 mg kg^{-1}) in 1% gum acacia (p.o.)
- **Group III-VIII: Test:** Suspension of test compounds 5a-5f, respectively (200 mg kg^{-1}) in 1% gum acacia (p.o.)

Eddy's Hot plate method: The analgesic activity of the test compounds (5a-5f) were measured by hot-plate method. The rats were placed on a hot plate maintained at 55±0.5°C. The reaction time was taken as the interval from the instant animal reached the hot plate until the moment animal licked its feet or jumped out (Zakaria *et al.*, 2006; Franzotti *et al.*, 2001; Sahu *et al.*, 2012). The reaction time was recorded before and after 0, 30, 60 and 90 min following oral administration of tests compounds (5a-5f) and standard drug in the form 1% Gum acacia suspension. Following groups were made and latency period in which rat responded to hot plate was calculated.

Statistical analysis: All the results were expressed as Standard Error of Means (SEM). The data was statistically analyzed by one way Analysis of Variance (ANOVA) followed by Tukey using GraphPad Prism 5 Software. The p-value <0.05 was considered to be statistically significant.

RESULTS

Anti-inflammatory activity: The positive control, Diclofenac and test compounds (5a-5f) significantly inhibited the paw edema response in comparison to control group. Diclofenac showed an inhibition of 66.7% after 3 h. Compound 5d showed maximum activity with an inhibition of 50.45% and compound 5a showed minimum activity with an inhibition of 38.9% after 3 h as shown in Table 2.

Analgesic activity: Diclofenac showed marked analgesic response. All the test compounds (5a-5f) also showed good analgesic activity with compound 5d having maximum activity and compound 5f with minimum analgesic activity. All values were significant with p-value <0.05 as compared to standard and control as shown in Table 3.

Table 2: Anti-inflammatory effect of some novel 6,8-Diiodo-2-phenylquinazolin-4(3H)-one Schiff bases (5a-5f) on carrageenan induced paw edema

		Mean paw volume (mL)			
Treatment	Dose (mg kg^{-1}) orally	60 min	120 min	180 min	Inhibition (%)
Control	-	0.62±0.014	0.66±0.034	0.72±0.012	-
Standard	10	0.46±0.01^{a}	0.34±0.015^{a}	0.24±0.012^{a}	66.70
5a	200	0.52±0.012^{ab}	0.49±0.012^{ab}	0.44±0.015^{ab}	38.90
5b	200	0.53±0.005^{ab}	0.47±0.023^{ab}	0.40±0.008^{ab}	43.51
5c	200	0.54±0.015^{ab}	0.46±0.010^{ab}	0.37±0.020^{ab}	48.15
5d	200	0.56±0.006^{ab}	0.43±0.011^{ab}	0.35±0.088^{ab}	50.45
5e	200	0.55±0.008^{ab}	0.43±0.024^{ab}	0.36±0.066^{ab}	49.07
5f	200	0.53±0.012^{ab}	0.47±0.014^{ab}	0.39±0.010^{ab}	45.83

Values are Mean±SEM, All values are significant at $^{a}p<0.05$ when compared to control and at $^{b}p<0.05$ when compared to diclofenac (Tukey's test)

Table 3: Analgesic activity of some novel 6,8-diiodo-2-phenylquinazolin-4(3H)-one Schiff bases (5a-5f) on Eddy's hot plate

		Lapse time (sec)			
Treatment	Dose (mg kg^{-1}) orally	0 min	30 min	60 min	90 min
Control	-	3.30±0.083	3.32±0.19	3.40±0.062	3.35±0.053
Standard	10	3.33±0.15[a]	5.77±0.06[a]	7.45±0.12[a]	9.45±0.28[a]
5a	200	3.04±0.095[ab]	4.24±0.14[ab]	4.77±0.25[ab]	5.63±0.18[ab]
5b	200	3.10±0.069[ab]	4.10±0.10[ab]	4.68±0.29[ab]	5.61±0.13[ab]
5c	200	3.16±0.030[ab]	4.24±0.12[ab]	4.80±0.23[ab]	5.75±0.15[ab]
5d	200	3.27±0.083[ab]	4.28±0.10[ab]	4.90±0.17[ab]	6.30±0.22[ab]
5e	200	3.17±0.049[ab]	4.29±0.12[ab]	4.79±0.10[ab]	5.85±0.09[ab]
5f	200	3.10±0.066[ab]	4.17±0.20[ab]	4.71±3.89[ab]	5.52±0.10[ab]

Values are Mean±SEM, All values are significant at [a]$p<0.05$ when compared to control and at [b]$p<0.05$ when compared to diclofenac (Tukey's test)

DISCUSSION

Past literature revealed that quinazolinone nucleus and Schiff bases of 3-aminoquinazolinone derivatives possessed anti-inflammatory and analgesic agent (Venkataraman *et al.*, 2010; Mosaad *et al.*, 2010; Babu and Nadendla, 2011; Tyagi *et al.*, 1998; Mohamed *et al.*, 2011; Saravanan *et al.*, 2010, 2012; Mariappan *et al.*, 2011). In accordance with the results of past studies, the present study revealed that the Schiff bases of 6,8-diiodo derivatives were also active as anti-inflammatory and analgesic agent.

Anti-inflammatory activity: Action of carrageenan takes place as a biphasic event. Presence of edema takes place in two phases. First phase involves the release of histamine, serotonin and kinin like substances. Second phase is the accelerating phase of swelling with a release of prostaglandins. Inhibition of edema may be occurred due to the suppression of any of these chemical mediators (Emma *et al.*, 2010). Hydroxyl derivatives showed good anti-inflammatory activity with o-hydroxy derivative showing maximum activity of 50.45%. Chloro derivatives were seem to be less potent as compared to hydroxyl derivatives with p-chloro derivative showing maximum activity of 48.15%.

Analgesic activity: The mechanism of pain transmission is very complex and many different neuromodulators and receptors could be involved. The central analgesic activity of the synthetic compounds were studied using Eddy's Hot plate method and significantly increased reaction time was observed. Again o-hydroxy derivative showed maximum central analgesic activity.

It may be considered that Schiff bases of quinazolinone showed their anti-inflammatory and analgesic activity by inhibiting the microsomal prostaglandin E2-synthase 1 (mPGES-1) like other quinazol-4-(3H)-ones derivatives.

The maximum activity was shown by o-hydroxy phenyl derivative of quinazololinone with 6.30±0.22 retention time. Chloro substituents too showed moderate analgesic activity.

It may be concluded that Schiff bases containing hydroxyl group showed promising ant-inflammatory and analgesic activity as compared to chloro derivatives. Inhibition of microsomal prostaglandin E2-synthase 1 (mPGES-1) may be involved in their mechanism of action.

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