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Synthesis and Antiinflammatory Activity of N-(2-Methyl-4-Oxoquinazolin-3(4*H*)-yl)-3'-(Substituted Phenyl) Prop-2'-Enamides.

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ABSTRACT

A series of N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3'-(Substituted phenyl) prop-2'-enamides **(5a-i)** were synthesized by reaction of N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-acetamide **(4)** with substituted aromatic aldehydes in presence of absolute ethanol and 30% NaOH. The intermediate N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-acetamide was prepared by refluxing 3-amino-2-methylquinazolin-4(3*H*)-one **(3)** with acetic anhydride in presence of glacial acetic acid. A total of nine compounds were synthesized, purified and characterized by IR, ^{1}H NMR, and Mass spectral data. The title compounds **(5a-i)** were screened for antiinflammatory activity by carrageenan induced rat hind paw method. In carrageenan-induced paw edema test, Compounds with electron donating groups at 4th position such as 4-dimethyl amino **(5f)**, 4-hydroxy 3,5-dimethoxy **(5g)** and 4-methoxy **(5c)** derivatives exhibited significant antiinflammatory activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically potential compounds.

Keywords: 3-amino-2-methylquinazolin-4(3*H*)-one, Antiinflammatory activity, Cinnamides

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INTRODUCTION

Quinazolinone derivatives are found to show wide range of biological activities such as antiinflammatory [1], anticonvulsant [2], antitumor [3, 4], sedative-hypnotic [5], antibacterial and antifungal [6], anti-viral [7], anti-HIV [8, 9], anticancer [10, 11] and anticoccidal [12] activities etc. Cinnamides are reported to possess a wide spectrum of biological activities such as antiinflammatory [13], antitumor [14], antimicrobial [15] activities etc. The presence of a reactive α, β-unsaturated keto function in cinnamides is found to be responsible for their antiinflammatory activity, which may be altered depending on the type and position of substituent on the aromatic rings [16]. Curcumin, a natural constituent of Curcuma longa has also a styryl carbonyl moiety in its structure and displays antiinflammatory activity [17]. Curcumin and dehydrozingerone were reported to be potent scavengers of oxygen free radicals and also possess good antiinflammatory activity. Both are styryl ketones with similar substitution on the phenyl ring. In view of the potentiality of cinnamides which contain styryl ketone moiety, it has been planned to synthesize various substituted cinnamides containing other interesting structural feature such as quinazolinone moiety associated with antiinflammatory activity.

MATERIALS AND METHODS

Chemistry

Anthranilic acid was procured from Sigma Aldrich chemicals. All other chemicals and solvents are of AR grade. All the melting points reported in this series were determined in open capillaries using Thermonik precision melting point cum boiling point apparatus model C-PMB-2 and are uncorrected. The progress of all reactions was monitored by pre-coated TLC plates (E. Merck Kieselgel 60 F_{254}) using Toluene and Ethyl acetate (9:1 v/v) and the spots were visualized by iodine vapour. The IR spectra were recorded using KBr pellets on a Perkin-Elmer 1760 Spectropho-tometer (cm^{-1}). ^{1}H NMR spectra were recorded on GE Omega 400 MHz spectrometer or Bruker Avance 300 MHz spectrometer, using Tetramethylsilane (TMS) as an internal standard. Mass spectra were recorded on a JEOL-JMS-D-300 spectrometer.

Animal ethical committee approval number: SPMVV/IAEC/2014a/09.

Synthesis of 3-amino-2-methylquinazolin-4(3*H*)-one (3)

Anthranilic acid **(1)** (0.01 mol) and acetic anhydride were refluxed under anhydrous condition for 4 h. Excess of acetic anhydride was distilled off under reduced pressure **(2)**. To the mixture obtained hydrazine hydrate in glacial acetic acid was added and refluxed for 4 h. Obtained reaction mixture was poured into crushed ice and left overnight. The solid which was separated out was filtered, washed thoroughly with cold distilled water, dried and recrystallized from hot ethanol.

Synthesis of N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl) acetamide (4)

A solution of compound **3** (0.01 mol) and acetic anhydride (0.03 mol) in glacial acetic acid was heated under reflux for 3 h. The reaction mixture was allowed to cool and diluted with water, the solid which separated out was filtered off, dried and recrystallized from ethanol.

General method of synthesis of N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3'-(substituted phenyl) prop-2'-enamides (5a-i)

A solution of compound **4** (0.01 mol) in absolute ethanol (50 ml) was refluxed with various aromatic aldehydes in the presence of 30% NaOH for 6 hours, concentrated, cooled and poured on to ice. The solid thus obtained were recrystallized from methanol. The various N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3'-(substituted phenyl) prop-2'-enamides **(5a-i)** were prepared by similar procedure.

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Spectral data

N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3'-phenylprop-2'-enamide (5a)

IR (KBr) v_{max}: 3410 (N-H stretch), 1720 (C=O of quinazolinone), 1670 (C=O of NHCO), 1630 (CH=CH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H, CH_3), 6.80 (d, 1H,-CO-CH=), 7.20-8.15 (m, 9H, Ar-H), 7.60 (d, 1H, =CH-Ar), 8.82 (s, 1H, NH).

N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3'-(4-methylphenyl) prop-2'-enamide (5b)

IR (KBr) v_{max}: 3408 (N-H), 1710 (C=O of quinazolinone), 1665 (C=O of NHCO), 1625 (CH=CH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.14 (s, 3H, CH_3), 2.40 (s,3H,Ar-CH_3), 6.84 (d,1H,-CO-CH=), 6.92-7.70 (m,8H,Ar-H), 7.55 (d,1H,=CH-Ar), 8.60 (s,1H,NH). MS m/z: 319 [M^+].

3'-(4-Methoxyphenyl)-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)prop-2'-enamide (5c)

IR (KBr) v_{max}: 3410 (N-H), 1720 (C=O of quinazolinone), 1670 (C=O of NHCO), 1630 (CH=CH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.25 (s, 3H, CH_3), 3.76 (s,3H,Ar-OCH_3), 6.84 (d,1H,-CO-CH=), 7.20-8.15 (m,8H,Ar- H), 7.75 (d,1H, =CH-Ar), 8.85 (s,1H,NH).

3'-(4-Hydroxyphenyl)-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)prop-2'-enamide (5d)

IR (KBr) v_{max}: 3409(NH), 1720 (C=O of quinazolinone), 1668 (C=O of NHCO), 1630 (CH=CH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.14 (s, 3H, CH_3), 5.82 (s,1H,Ar-OH), 6.86 (d,1H,-CO-CH=), 6.76-7.58 (m,8H,Ar-H), 7.70 (d,1H,=CH-Ar), 8.45 (s,1H,NH).

3'-(4-Hydroxy-3-methoxyphenyl)-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)prop-2'-enamide (5e)

IR (KBr) v_{max}: 3420 (N-H), 1740 (C=O of quinazolinone), 1672 (C=O of NHCO), 1625 (CH=CH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.18 (s,3H,CH_3), 3.75 (s,3H,Ar-OCH_3), 5.52 (s,1H,Ar-OH), 6.79 (d,1H,-CO-CH=), 6.74-7.52 (m,7H,Ar-H), 7.59 (d,1H,=CH-Ar), 8.63 (s,1H,NH).

3'-[4-(Dimethyl amino)phenyl]-*N*-(2-methyl-4-oxoquinazolin- 3(4*H*)-yl)prop-2'-enamide (5f)

IR (KBr) v_{max}: 3412 (N-H), 1730 (C=O of quinazolinone), 1663 (C=O of NHCO), 1610 (CH=CH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.20 (s, 3H, CH_3), 2.90 (s, 6H,-N(CH_3)$_2$), 6.85 (d,1H,-CO-CH=), 6.86-7.60 (m,8H,Ar-H), 7.60 (d,1H,=CH-Ar), 8.24 (s,1H,NH).

3'-(4-Hydroxy-3,5-dimethoxyphenyl)-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)prop-2'-enamide (5g)

IR (KBr) v_{max}: 3415 (N-H), 1710 (C=O of quinazolinone), 1664 (C=O of NHCO), 1624 (CH=CH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.15 (s, 3H, CH_3), 2.35 (s,6H,Ar-OCH_3), 5.3 (s,1H,OH), 6.84 (d,1H,-CO-CH=), 6.76-7.55 (m,6H,Ar-H), 7.52 (d,1H,=CH-Ar), 8.62 (s,1H,NH). MS m/z: 381 [M^+].

N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3'-(3,4,5-trimethoxyphenyl) prop-2'-enamide(5h)

IR (KBr) v_{max}: 3420 (N-H), 1720 (C=O of quinazolinone), 1675 (C=O of NHCO), 1615 (CH=CH). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.16 (s, 3H, CH_3), 3.73 (s,9H,$(OCH_3)_3$), 6.82 (d,1H,-CO-CH=), 6.28-7.54 (m,6H,Ar-H), 7.50 (d,1H,=CH-Ar), 8.54 (s,1H,NH). MS m/z: 395 [M^+].

3'-(3,4-Dimethoxyphenyl)-*N*-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)prop-2'-enamide (5i)

IR (KBr) v_{max}: 3414 (N-H), 1716 (C=O of quinazolinone), 1668 (C=O of NHCO), 1625 (CH=CH). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.14 (s, 3H, CH_3), 3.75 (s, 6H, $(OCH_3)_2$), 6.89 (d, 1H,-CO-CH=), 6.80-7.62 (m,7H,Ar-H), 7.66 (d,1H,=CH-Ar), 8.62 (s,1H,NH).

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BIOLOGICAL EVALUATION

Antiinflammatory activity

The *in vivo* antiinflammatory activity of all title compounds was evaluated using carrageenan induced hind paw edema test in male albino rats (150–180 g) of Wistar strain at 100 mg/kg body weight [18].

The rats were divided into groups of six animals. Control group received 0.5 % sodium carboxy methylcellulose, the standard group received standard drug phenylbutazone 100 mg/kg body weight, and the test groups received the synthesized compounds at the dose of 100 mg/kg body weight. The volume of the injected paw was measured by water displacement in a plethysmograph immediately after carrageenan injection. The paw volume was again measured after 3 h. A mark was made at the lateral maleolus, and the foot was dipped to the same distance into the arm of the plethysmograph.

Average edema volumes for test compound treated and positive control rats were compared statistically with those of the vehicle treated control animals and expressed as the present edema inhibition which was calculated using the formula.

$$\text{Percent edema inhibition} = 100\ (1- V_t/V_c)$$

Where, V_c volume of the edema in the control group, and V_t volume of the edema in the treated group.

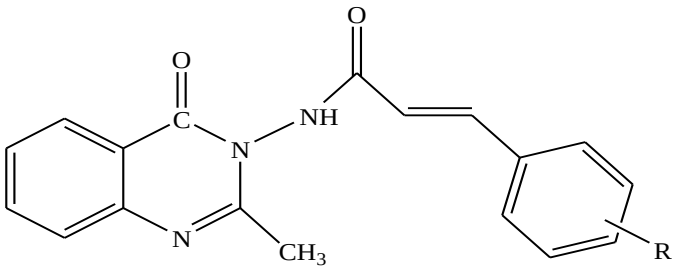
RESULTS AND DISCUSSION

Chemistry

Synthesis of N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3'-(substituted phenyl) prop-2'-enamides (5a-i)

The intermediate N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-acetamide **(scheme)** was prepared by refluxing 3-amino-2-methylquinazolin-4(3*H*)-one with acetic anhydride in presence of glacial acetic acid. The intermediate N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-acetamide upon nucleophilic addition with substituted benzaldehydes in absolute ethanol and 30% NaOH yielded the title compounds. A total of nine compounds were synthesized in this series. The compounds were obtained in good yield ranging from 60-80%, **Table 1**.

Table 1: Physicochemical data of N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3'- (substituted phenyl) prop- 2'-enamides (5a-i)



Compound	R	Molecular Formula	Molecular weight	M.P ^{0}C	Yield in %
5a	H	$C_{18}H_{15}N_3O_2$	305	185-187	70
5b	4-CH_3	$C_{19}H_{17}N_3O_2$	319	188-190	75
5c	4-OCH_3	$C_{19}H_{17}N_3O_3$	335	175-177	72
5d	4-OH	$C_{18}H_{15}N_3O_3$	321	130-132	76
5e	4-OH,3-OCH_3	$C_{19}H_{17}N_3O_4$	351	125-127	75
5f	4-$N(CH_3)_2$	$C_{20}H_{20}N_4O_2$	348	115-117	80
5g	4-OH, 3,5-$(OCH_3)_2$	$C_{20}H_{19}N_3O_5$	381	195-197	75
5h	3,4,5- $(OCH_3)_3$	$C_{21}H_{21}N_3O_5$	395	200-202	65
5i	3,4- $(OCH_3)_2$	$C_{20}H_{19}N_3O_4$	365	195-197	70

Recrystallization Solvent: Methanol

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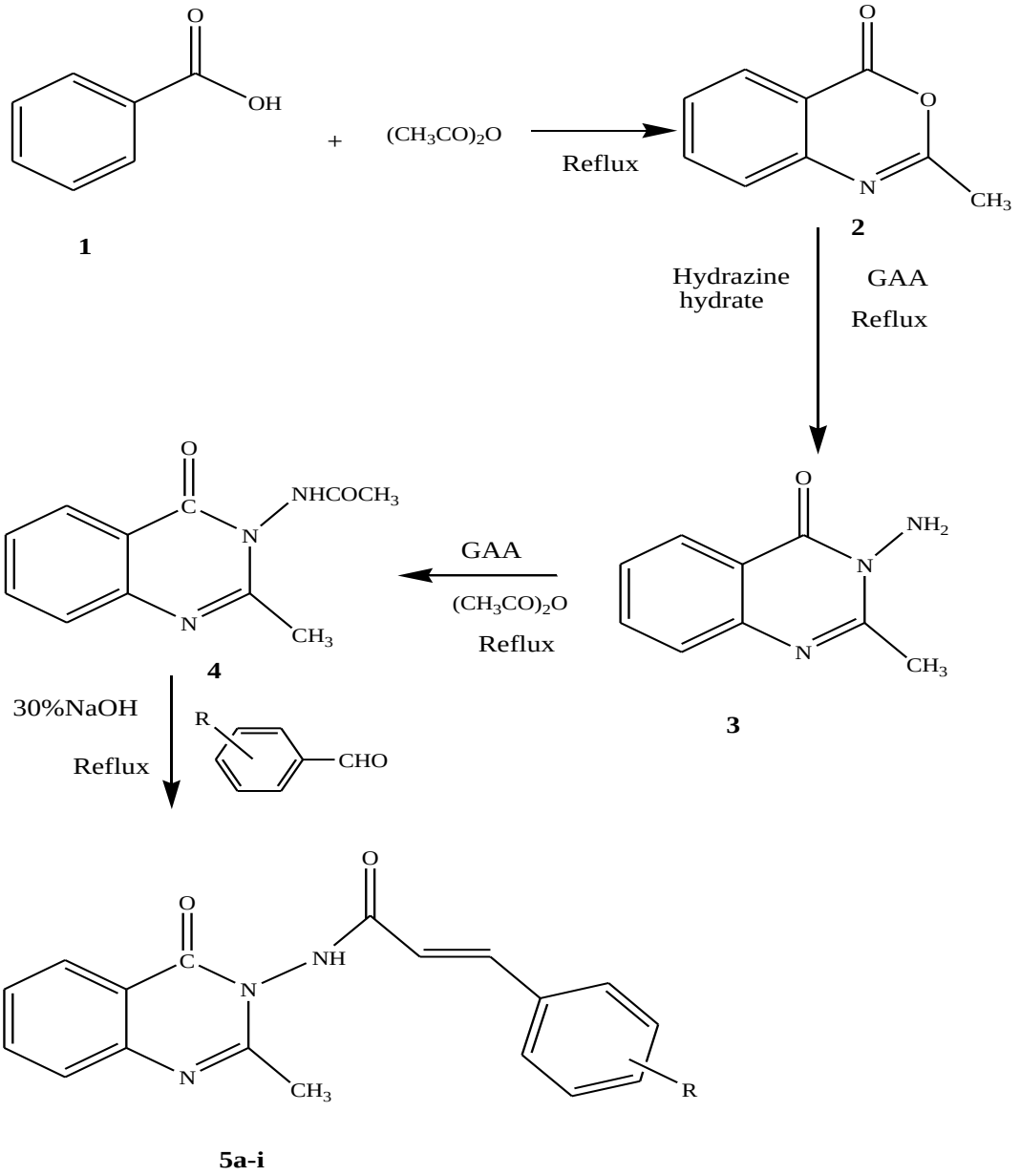

5a-i

The IR spectra of the compounds displayed bands at 3408-3420 cm^{-1} due to N-H, a band at 1710-1740 cm^{-1} due to C=O group of Quinazolinone and a band at 1663-1675 cm^{-1} due to CO stretching of NHCO. The compounds also exhibited band at 1610-1645 cm^{-1} due to the C=C (styryl) stretching.

The ^{1}H NMR spectral data of compounds showed doublet at δ 7.50-7.75 due to $C_6H_5CH=$, multiplet at 6.28-8.15 due to aryl protons, doublet at 6.79-6.89 due to -COCH= and singlet at 8.24-8.85 due to –NHCO.

Pharmacology studies

The antiinflammatory activity was evaluated *in vivo* by measuring the inhibition of carrageenan induced edema in the hind paw of the rat at 100 mg/kg. The data is given in **Table 2**. Among the series, the compounds with electron donating groups at 4^{th} position such as 4-dimethyl amino **(5f)** and 4-methoxy **(5c)** exhibited significant antiinflammatory activity [16] whereas, the lower alkyl analogue, 4-methyl derivative showed insignificant activity. Sterically hindered phenolic compound containing dimethoxy groups at both the *ortho* positions to the phenolic hydroxyl group **(5g)** also showed significant activity. It is in agreement with the earlier literature reporting that the presence of sterically hindered phenolic group has a substantial effect on antiinflammatory activity and the double bond of the styrene skeleton enhances this activity [19].

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Table 2: Antiinflammatory activity of N-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-3'- (substituted Phenyl) prop-2'-enamides (5a-i)

Compound	R	Edema volume ml (±SD)[a]	% of Edema Inhibition at 100mg/kg [c]
5a	4-H	0.31 (0.016) [b]	26
5b	4-CH_3	0.26 (0.02) [b]	38
5c	4-OCH_3	0.25 (0.01) [b]	40*
5d	4-Cl	0.28 (0.03) [b]	33
5e	4-NO_2	0.29 (0.12) [b]	31
5f	4-$N(CH_3)_2$	0.23 (0.015) [b]	45*
5g	4-OH, 3,5-$(OCH_3)_2$	0.23 (0.01) [b]	45*
5h	3,4,5- $(OCH_3)_3$	0.27 (0.02) [b]	36
5i	3,4- $(OCH_3)_2$	0.30 (0.02) [b]	28
	Phenylbutazone	0.13 (0.01) [b]	69*

[a] Edema volume was measured 3 h after carrageenan injection and expressed as mean ± standard deviatio
[b] Control edema volume= 0.42 (0.02)
[c] At 100 mg/kg (p.o) percent edema inhibition was calculated by comparing edema volume with that of the respective vehicle-treated control animals
* Statistically Significant ($p < 0.05$, Mann–Whitney)

The present study leads to a convenient method for the synthesis of new compounds. Among the series of compounds, three compounds showed significant antiinflammatory activity. Further investigation with appropriate structural modification of the above compounds may result in therapeutically potential compounds.

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