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Synthesis and Characterization of Substituted Azetidinonyl and Thiazolidinonyl Quinazolin-4 (3H) -ones as Potential NSAIDs

Deepak Kumar

Medicinal Chemistry Division, Department of Chemistry, D.N. (P.G.) College, Meerut 250002 (U.P), India

Abstract: ***A series of 2- ((2- (substituted benzylidene) hydrazinyl methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -ones (4a-4e) have been synthesized via condensation of 2- (hydrazinyl methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -one (3) with different aromatic aldehydes. Cycloaddition of thioglycolic acid with (4a-4e) yielded 3- (naphthalene-2-yl) -4-oxo-3, 4-dihydro-quinazolin-2-yl) methyl amino) -2- (substituted phenyl) thiazolidin-4- (3H) ones (5a-5e). While compound (4a-4e) on treatment with chloro-acetylchloride in the presence of triethylamine are converted into 2- ((3-chloro-2- (substituted phenyl) -4-oxoazetidin-1-ylamino) methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -ones (6a-6e). The structure of all the newly synthesized compounds have been confirmed by elemental analysis and spectral studies (IR, ^{1}H-NMR and mass spectroscopy).Compounds (4a-4e, 5a-5e and 6a-6e) have been evaluated for their anti-inflammatory and analgesic activity and were compared with the standard drug phenylbutazone. The most active compound of this series is 6e.***

Keywords: Thiazolidinonyl & Azetidinonyl quinazolinone; Naphthalene; anti-inflammatory activity; Analgesic activity; acute toxicity.

1. Introduction

Quinazolinone nucleus has been gaining prominence due to the fact that its derivatives have been found to possess wide spectrum of activities like anti-becterial [1], [2] analgesics [3], anticonvulsant [4] and anti-inflammatory [5-12]. However, we have also reported substituted quinazolinone [13], [14] derivatives as potent anti-inflammatory and analgesic inhibitors. Substitution pattern by different aryl or heteroaryl moieties at 2/3 position [15], [16] of quinazolinone nucleus markedly influence anti-inflammatory activities. Moreover, Thiazolidinones [17-19] Azetidinones [20], [21] and Naphthalene [22], [24] are other important pharmacodynamic heterocyclic nuclei which when incorporated in different heterocyclic templates have been reported to possess potent anti- inflammatory activity. In the light of the above observation we have synthesized a new series of quinazolinone derivatives by incorporating the Naphthalene moiety at 2nd while Thiazolidinone and Azetidinone moieties at 3rd position of the quinazolinone nucleus. All the compounds have been screened for their anti-inflammatory, analgesic and ulcerogenic activities.

Chemistry:

2-methyl-4H-benzo [d] [1, 3] oxazin-4-one on condensation with β-amino naphthalene give compound **1** which on brominating in the presence of glacial acetic acid resulted into the formation of **2**. The later compound on reaction with hydrazine hydrate yielded compound no. **3**, which on reaction with different substituted aromatic aldehyde in the presence of few drops of acetic acid, gives compound no. **(4a-4e).** Compound **(4a-4e)** on one hand when reacted with thioglycolic acid in presence of anhydrous $ZnCl_2$ resulted into, 3- (naphthalene-2-yl) -4-oxo-3, 4-dihydro-quinazolin-2-yl) methylamino) -2- (substituted phenyl) thiazolidin-4-(3H) ones **(5a-5e),** while compound **(4a-4e)** on cyclo-condensation with chloro acetyl chloride in the presence of few drops of triethyl amine gives 2- ((3-chloro-2-(substituted phenyl) -4-oxoazetidin-1-ylamino) methyl) -3-(naphthalene-2-yl) quinazolin-4 (3H) -ones **(6a-6e).**

Pharmacology

The experiment were performed with albino rats of Charles-Foster strain of either sex, excluding pregnant females, of 60 to 90 days weighing 100 to 120 g. Food (chaw pallet) and water was given to the animals ad libitum. The test compounds were dissolved in propylene glycol. Indomethacin and phenylbutazone were used as reference drugs for the comparison of anti-inflammatory, analgesic and ulcerogenic activity.

Anti-inflammatory activity against carrageenan-induced rat's paw oedema

This study was done by following the procedure of Winter et al. [1962]. The rats were divided into three groups (control, drug treated, and standard, drug of six animals each. A freshly prepared suspension of carrageenan (1% in 0.9% saline) 0.05 ml. was injected under the planter aponeurosis of the right hind paw of each rat. Test compounds and standard drug were administered orally to the animals of drug treated groups and the standard drug group, respectively 1h before the carrageen an injection. The paw volume of each rat was measured before 1 and after 3 h of carrageenan treatment with the help of a plethymometer. The percent anti-inflammatory activity was calculated according to the formula given below-

Percentage of inhibition of oedema = $(1-V_t/V_c) \times 100$

Where, V_t and V_c are the mean increase in paw volume of rats of the treated and the control group, respectively. Results obtained were statistically analyzed.

Analgesic activity

Following the method of Berkowitz et al. [1977] performed this activity. This method is based on the property of the test compound to antagonize the phenyl quinone-induced pain syndrome in mice. Groups of five mice were injected intraperitonely with 0.25 ml of a 0.02% solution of phenylquinone in ethanol (5%) 1 h after of oral administration of the test compound. The number of writhes induced in each mouse was counted for 5 min (between 5 and 10 min) after injection of an irritant. The analgesic effect was expressed as percent protection in comparison to control.

% protection = (1-mean no. of writhes in mice of test groups/mean number of writhes in mice of control group) x 100

Ulcerogenic activity

Ulcerogenic liabilities of newly synthesized compounds were checked with method of Verma et al [1981]. Albino rats were fasted for 24 h prior to drug administration. All animals were sacrificed 8 h after drug treatment, and their stomachs and small intestines were microscopically examined to assess the incidence of hyperemia, shedding of epithelium, Petechial and frank hemorrhages and erosion or discrete ulceration with or without perforation. The presence of any one of these criteria was considered to be an evidence of ulcerogenic activity.

Acute Toxicity study

The test compounds were investigated for their acute toxicity (ALD_{50}) in albino mice, according to the method of Smith [1960]. The test compounds were given orally at different dose levels in separate groups of animals. After 24 h of drug administration, percent mortality in each group was observed. ALD_{50} was calculated from the data obtained.

2. Pharmacological Result and Discussion

Compounds **(4a-4e)** have shown the varying range **(26.32-34.45%)** of anti-inflammatory activity. Out of these the compound which was substituted by 4-hydroxy, 3-methoxy phenyl **4e** was found to possess good activity **(34.56%).**

Compounds **(5a-5e),** having thiazolidinone ring along with β-amino naphthalene was found to possess varying degree of % of inhibition of oedema i.e. **(36.47-43.20%).** The compound **5e**, have exhibited **43.20%** of anti-inflammatory activity, which is quite more from its parent corresponding compound **4e**. The compounds **(6a-6e)** are characterized by the presence of azetidinone ring (β-lactum) have shown mild to moderate degree of % inhibition of carrageenan induced oedema. i.e. **(43.30-52.50%).**

The compounds, **(6a-6e)** which were characterized by naphthalene ring at 2^{nd} position of quinazolinone ring and azetidinoyl ring at 3^{rd} position of the same ring. However, it is interestingly enough, that substitution at phenyl ring plays a pivotal role to decide the anti inflammatory activity.

Moreover the compound which was substituted by 4-hydroxy, 3-methoxy group at phenyl ring, showed **52.50%** activity, which is better than phenyl butazone at a dose of 50 mg/kg p.o.

It is interesting to note that **6e** compound have shown better activity than phenyl butazone. Considering the potentiality of **6e** compound it is thought worthwhile to test these compounds were also studied at three graded doses and it was found that at all the three graded doses compound **6e** have shown much better activity than reference drug. It is evident from the data that out of these compounds compound **6e** have shown promising activity.

The analgesic activities of compounds **(4a-4e)** have shown the varying range **(24.05-32.10%)** of analgesic activity. Out of these, the compound which was substituted by 4-hydroxy, 3-methoxy group at phenyl ring was found to possess good activity **(32.10).** Compound **(5a-5e)** possesses varying degree of % of protection i.e. **(34.52-40.82%).** The compound **5e** have exhibited **40.82%** of analgesic activity, which is quite more than parent compound **4e**.

However the compounds **(6a-6e)** have shown range of **(41.18-50.10)** of analgesic activity. The only compound no. **6e** has shown better activity than reference drug. Considering the potentiality of these two later compounds have been screened at three graded doges and found to be better analgesic activity.

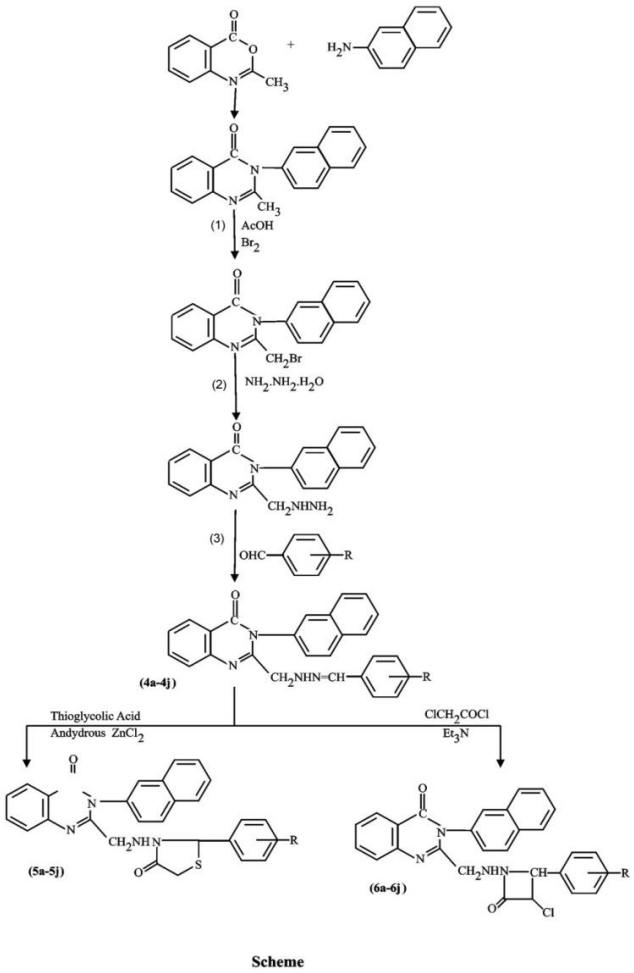
The UD_{50} of compound **6e** is 168 mg/kg p.o., while UD_{50} of phenyl butazone is 66.6. As the UD_{50} of compound **6e** is quite high then standard drug, which suggest that these two compounds is less ulcerogenic than phenyl butazone.

The ALD_{50} of all the compounds were >800 mg/kg i.p. except that of compound **6e**, which > 1200. As the values of ALD_{50} is quite high which suggest their good safety margin, **table-V, VI &VII.**

Experimental

All reagents and solvents were generally used as received from the commercial supplier. Reactions were routinely performed in oven-dried borosil glassware. The melting points of compounds were determined in open capillaries with the help of thermionic melting point apparatus and were uncorrected. The progress of the reaction is monitored by TLC and product are purified through recrystallization and purity of the compounds was checked by thin layer chromatography (TLC) performed on silica gel G coated plate of 0.5 mm thickness. The eluent was a mixture of different polar and nonpolar solvents in different proportions, and spots were visualized under iodine chamber. The IR spectra were recorded on Perkin Elmer 881 FTIR spectrophotometer (λ max in cm.). The H-NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 on Brucker DRX-400/300. FTNMR instrument. Mass spectra were determined on JEOL JMS-D-300 instrument.

Elemental and spectral analyses of the compounds were obtained from sophisticated, Analytical Instrumentation Facility Chandigarh, Punjab and CDRI, Lucknow, India.



Scheme

2-Methyl-3- (naphthalene-2-yl) -quinazolin-4 (3H) -one (1):

A mixture of 2-methyl benzoxazin-4-one (0.01 mole) and 2-amino naphthalene (0.01 mole) in ethanol (50 ml.) were heated under reflux for 2 hr. The excess of solvent was distilled off. The reaction mixture poured onto crushed ice. The solid which was obtained, washed with water, filtered and recrystallized from Ethanol to yield the compound 1.

Compound 1: M.P: 141ºC, yield 90%, mol. formula: $C_{19}H_{14}N_2O$

Elemental analysis;

% C	: Calcd. :	79.70	: Found :	79.88
% H	: Calcd. :	04.93	: Found :	04.95
% N	: Calcd. :	09.79	: Found :	09.82

Spectral analysis:

IR (KBr) $\lambda_{max.}$ in cm^{-1}: 2920 (CH_3, C-H stretching), 3155 (CH-Ar), 1710 (C=O of quinazolinone), 1580 (C⎓C of aromatic ring), 1240 (C-N).

^{1}H-NMR ($CDCl_3$) □ in ppm: 7.99-6.89 (m, 11H, Ar-H), 2.10 (s, 3H, CH_3).

MS: $[M]^+$ at m/z 286.

2- (Bromomethyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -one (2)

To a solution of compound 1a (0.01 mole) in acetic and to this solution bromine (0.04 mole) was added slowly and the mixture was stirred for 8 hr., during this period the solid was separated. The reaction mixture was poured into ice water and the solid thus obtained was filtered, washed with excess of water. The solid was dried and recrystallized from methanol to yield the compound 2.

Compound 2: M.P.: 182ºC, yield 88%, mol.formula: $C_{19}H_{13}BrN_2O$

Elemental analysis:

% C	: Calcd. :	62.48:	Found :	62.62
% H	: Calcd. :	03.59 :	Found :	03.60
% N	: Calcd. :	07.67 :	Found :	07.70

Spectral analysis:

IR (KBr) $\lambda_{max.}$ in cm^{-1}: 3155 (Ar-CH), 2930 (CH_3, C–H Stretching), 1710 (C=O of quinazolinone ring), 1540 (C⎓C of aromatic ring). 1230 (C-N) 705 (C-Br),

^{1}H-NMR ($CDCl_3$) □ in ppm: 7.95-6.85 (m, 11H, Ar-H), 2.25 (s, 2H, CH_2Br)

MS: $[M]^+$ at m/z 365.

2- (Hydrazinyl methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -one (3)

A solution of 2- (bromo methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -one (0.01 mole), hydrazine hydrated (0.01 mole), were taken in acetone (50 ml), The reaction mixture was heated under reflux for 6hr. After cooling it was poured in water and the solid thus obtained was washed with excess of water and recrystallized from ethanol to yield compound 3.

Compound 3: M.P.: 202ºC, yield 90%, mol. formula: $C_{19}H_{16}N_4O$

Elemental analysis:

% C	: Calcd. :	72.13	: Found:	72.42
% H	: Calcd. :	05.10	: Found:	05.23
% N	: Calcd. :	17.71	: Found:	17.95

Spectral analysis:

IR (KBr) $\lambda_{max.}$ in cm^{-1}: 3300 (N-H), 3165 (Ar-CH), 2925 (CH_3, C–H Stretching), 1545 (C⎓C of aromatic ring) 1240 (C-N)

^{1}H-NMR ($CDCl_3$) □ in ppm: 7.90-6.85 (m, 11H, Ar H) 4.80 (brs, 3H, $NH.NH_2$ exchangeable with D_2O), 3.25 (d, 2H, CH_2 NH)

MS: $[M]^+$ at m/z 316.

2- ((2- (2-Methyl benzylidene) hydrazinyl) methyl) -3- (naphthalene-2-yl) -quinazolin-4 (3H) -one (4a):

A mixture of 2- (hydrazinyl methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -one (0.01 mole) and 2-methyl

benzaldehyde (0.01 mole) in methanol (50 ml) were heated under reflux for 4hr. The excess of solvent was distilled off. The reaction mixture poured onto crushed ice. The solid which was obtained was washed with water, filtered and recrystallized from mixture of ethanol-water to afford the compound (4a).

Compound 4a: M.P.: 210°C, yield: 85%, mol. Formula: $C_{27}H_{22}N_4O$

Elemental analysis;

% C	: Calcd. :	77.49	: Found	:	77.73
% H	: Calcd. :	05.30	: Found	:	05.31
% N	: Calcd. :	13.39	: Found	:	13.36

Spectral analysis:

IR (KBr) $\lambda_{max.}$ in cm^{-1}: 3310 (N-H), 3155 (Ar-CH), 2920 (CH_3, C-H Stretching), 1720 (C=O of quinazolinone ring), 1585 (C=N), 1540 (C⎓C of aromatic ring), 1244 (C-N).

^{1}H-NMR ($CDCl_3$) □ in ppm: 9.50 (brs, 1H, $NHCH_2$ exchangeable with D_2O), 8.26 (ss, 1H, N=CH-Ar), 7.85-6.80 (m, 15H, Ar-H), 3.28 (d, 2H, CH_2NH), 2.15 (s, 3H, CH_3).
MS: $[M]^+$ at m/z 418.

Compounds **(4b-4e)** were prepared similarly and their physical and analytical data are given in **table-I**, while spectral data i.e. IR, ^{1}H-NMR and mass and given in **table-IV.**

3- (Naphthalene-2-yl) -4-oxo-3, 4-dihydroquinazolin-2-yl) methyl amino) -2-o-tolyl thiazolidin-4 (3H) -one (5a).

To a mixture of 2- (2- (3-methyl benzylidene) hydrazinyl) methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -one (0.01 mole) and 2-methyl benzaldehyde (0.01 mole) in methanol (50 ml), thioglycolic acid (0.02 mole) was added drop wise in the presence of anhydrous $ZnCl_2$ and the reaction mixture was refluxed for 10hr. The reaction mixture was concentrated, cooled and poured into ice water, and filtered. The resulting solid was recrystallized from acetic acid to yield the compound (5a.)

Compound 5a: M.P.: 255°C, yield: 82%, mol. formula: $C_{29}H_{24}N_4O_2S$

Elemental analysis:

% C	: Calcd. :	70.71	: Found	:	70.55
% H	: Calcd. :	04.91	: Found	:	04.93
% N	: Calcd. :	11.37	: Found	:	11.40

Spectral analysis:

IR (KBr) $\lambda_{max.}$ in cm^{-1}: 3310 (N-H), 3150 (Ar-CH), 2925 (CH_3, C-H Stretching), 1735 (C=O of thiazolidinone), 1720 (C=O of quinazolinone ring), 1580 (C=N), 1525 (C⎓C of aromatic ring), 1250 (C-N), 680 (C-S-C)

^{1}H-NMR ($CDCl_3$) □ in ppm: 9.52 (brs, 1H, $NHCH_2$ exchangeable with D_2O), 7.86-6.83 (m, 15H, Ar-H), 4.52 (s, 1H, CH-Ar), 3.65 (s, 2H, CH_2 of thiazolidinone), 3.29 (d, 2H, CH_2NH), 2.17 (s, 3H, CH_3).
MS: $[M]^+$ at m/z 492.

Compounds **(5b-5e)** were prepared similarly and their physical and analytical data are given in **table-II**, while spectral data i.e. – IR, 1H-NMR and mass and given in **table-IV**

2- ((3-Chloro-2- (2-o-tolyl azetidin-1-ylamino) methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -one (6a);

To a solution of 2- (2- (2-methyl benzylidene) hydrazinyl) methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -one (0.01 mole) and 2-methyl benzaldehyde (0.01 mole) in ethanol (100 ml.), 2-3 drops of triethyl amine and chloracetyl chloride (0.02 mole) were added under stirring for 1hr. The reaction mixture were stirred and refluxed for 8hr. After refluxing, the reaction mixture was distilled off, cooled and poured onto ice. Solid thus obtained was filtered and recrystallize from acetone to afford compound (6a).

Compound 6a: M.P.: 248°C, yield 70%, mol. formula: $C_{29}H_{23}ClN_4O_2$

Elemental analysis:

% C	: Calcd. :	70.37	: Found:		70.48
% H	: Calcd. :	04.68	: Found:		04.66
% N	: Calcd. :	11.32	: Found:		11.30

Spectral analysis:

IR (KBr) $\lambda_{max.}$ in cm^{-1}: 3345 (N-H), 3164 (Ar-CH), 3032 (CH-Ar), 2945 (CH_3, C-H Stretching), 1745 (C=O of thiazolidinone), 1723 (C=O of quinazolinone ring), 1570 (C=N), 1546 (C⎓C of aromatic ring), 1225 (C-N), 760 (C-Cl).

^{1}H-NMR ($CDCl_3$) □ in ppm: 9.65 (brs, 1H, $NHCH_2$ exchangeable with D_2O), 7.90-6.88 (m, 15H, Ar-H), 6.64 (s, 1H, CH-Cl), 4.60 (s, 1H, CH-Ar), 3.33 (d, 2H, CH_2NH), 2.22 (s, 3H, CH_3).
MS: $[M]^+$ at m/z 495.

Compounds **(6b-6e)** were prepared similarly and their physical and analytical data are given in **table-III**, while spectral data i.e.-IR, 'H-NMR and mass and given in **table-IV.**

Acknowledgment

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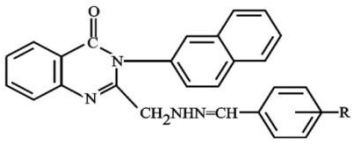
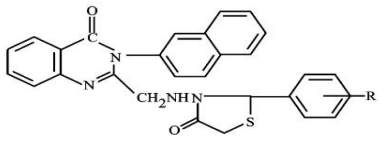
Table I: Physical and analytical data of 6-substituted-2- ((2- (substituted benzylidene) hydrazinyl methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -ones (4b-4e)



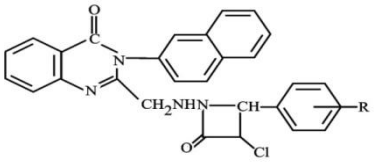
Comp.	R	M.P °C	Yield %	Recrysta -llization solvent	Molecular formula	Elemental analysis					
						% C		% H		% N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
4b	4-CH_3	218	80	Methanol	$C_{27}H_{22}N_4O$	77.49	77.70	05.30	05.29	13.39	13.37
4c	2-OCH_3	215	85	Acetone	$C_{27}H_{22}N_4O_2$	74.64	74.45	05.10	05.12	12.89	12.92
4d	4-OCH_3	223	78	Methanol	$C_{27}H_{22}N_4O_2$	74.64	74.78	05.10	05.11	12.89	12.85
4e	4-OH 3-OCH_3	230	82	Ethanol	$C_{27}H_{22}N_4O_3$	71.99	71.76	04.92	04.90	12.44	12.48

Table II: Physical and analytical data of 6-substituted-3- (naphthalene-2-yl) -4-oxo-3, 4-dihydro-quinazolin-2-yl) methyl amino) -2- (substituted phenyl) thiazolidin-4- (3H) ones (5b-5e)



Comp.	R	M.P °C	Yield %	Recrysta -llization Solvent	Molecular formula	Elemental analysis %					
						% C		% H		% N	
						Calcd.	Found	Calcd.	Found	Calcd.	Found
5b	4-CH_3	250	76	Methanol	$C_{29}H_{24}N_4O_2S$	70.71	70.62	4.91	4.92	11.37	11.39
5c	2-OCH_3	255	80	Methanol	$C_{29}H_{24}N_4O_3S$	68.49	68.36	4.76	4.79	11.02	11.06
5d	4-OCH_3	252	75	Ethanol	$C_{29}H_{24}N_4O_3S$	68.49	68.38	4.76	4.78	11.02	11.05
5e	4-OH, 3-OCH_3	260	78	DMF- water	$C_{29}H_{24}N_4O_4S$	66.40	66.53	4.61	4.59	10.68	11.64

Table III: Physical and analytical data of 6-substituted-2- ((3-chloro-2- (substituted phenyl) -4-oxoazetidin-1-ylamino) methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) –ones (6b-6e)

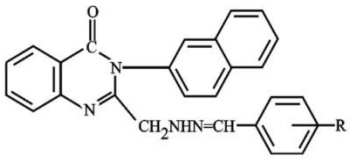


Comp.	R	M.P °C	Yield %	Recrysta -llization solvent	Molecular formula	Elemental analysis %					
						% C		% H		% N	
						Calcd	Found	Calcd	Found	Calcd	Found
6b	4-CH_3	256	73	Methanol	$C_{29}H_{23}ClN_4O_2$	70.37	70.50	04.68	04.67	11.32	11.30
6c	2-OCH_3	251	77	Ethanol	$C_{29}H_{23}ClN_4O_3$	68.17	68.04	04.54	04.56	10.96	10.98
6d	4-OCH_3	268	70	Acetone	$C_{29}H_{23}ClN_4O_3$	68.17	68.09	04.54	04.52	10.96	10.99
6e	4-OH, 3-OCH_3	254	75	Acetic Acid	$C_{29}H_{23}ClN_4O_4$	66.10	66.02	04.40	04.41	10.63	10.65

Table IV: Spectral Data of compounds (4b-4e), 5b-5e), & (6b-6e)

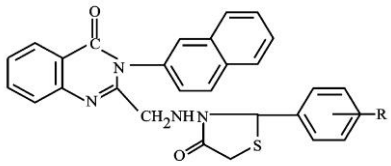
Comp	IR (KBr) $\square_{max}$ in cm^{-1}	^{1}H-NMR ($CDCl_3$) $\square$ $\square$in ppm	MS: [M]$^+$ m/z
4b	3320 (N-H), 3165 (Ar-CH), 2925 (CH_3, C-H stretching), 1725 (C=O of quinazolinone ring), 1580 (C=N), 1525 (C⎓C of aromatic ring), 1240 (C-N).	9.48 (brs, 1H, $NHCH_2$), 8.23 (ss, 1H, N=CH-Ar), 7.83-6.82 (m, 15H, Ar-H), 3.26 (d, 2H, CH_2NH), 2.11 (s, 3H, CH_3),	418
4c	3325 (N-H), 3160 (Ar-CH), 2925 (CH_3, C-H stretching), 1720 (C=O of quinazolinone ring), 1585 (C=N), 1535 (C⎓C of aromatic ring), 1250 (C-N).	9.54 (brs, 1H, $NHCH_2$), 8.29 (ss, 1H, N=CH-Ar) 7.87-6.78 (m, 15H, Ar-H), 3.31 (d, 2H, CH_2NH), 3.80 (s, 3H, CH_3)	339
4d	3320 (N-H), 3160 (Ar-CH), 2930 (CH_3, C-H stretching), 1720 (C=O of quinazolinone ring), 1580 (C=N), 1530 (C⎓C of aromatic ring), 1240 (C-N).	9.51 (brs, 1H, $NHCH_2$), 8.26 (ss, 1H, N=CH-Ar) 7.85-6.76 (m, 15H, Ar-H), 3.29 (d, 2H, CH_2NH), 3.76 (s, 3H, CH_3)	339
4e	3310 (N-H), 3160 (Ar-CH), 2920 (CH_3, C-H stretching), 1720 (C=O of quinazolinone ring), 1580 (C=N), 1525 (C⎓C of aromatic ring), 1240 (C-N).	9.55 (brs, 1H, $NHCH_2$), 9.21 (ss, 1H, OH), 8.29 (SS, 1H, N=CH-Ar), 7.88-6.80 (m, 14H, Ar-H), 3.32 (d, 2H, CH_2NH), 2.18 (s, 3H, OCH_3)	434
5b	3320 (N-H), 3150 (Ar-CH), 2930 (CH_3, C-H stretching), 1720 (C=O of quinazolinone ring), 1735 (C=O of thiazolidinone), 1575 (C=N), 1535 (C⎓C of aromatic ring), 1245 (C-N), 675 (C-S-C).	9.52 (brs, 1H, $NHCH_2$), 7.87-6.81 (m, 15H, Ar-H), 3.65 (s, 2H, CH_2 of thiazolidinone), 4.51 (s, 1H, CH-Ar), 3.28 (d, 2H, CH_2NH), 2.16 (s, 3H, CH_3)	492
5c	3320 (N-H), 3165 (Ar-CH), 2935 (CH_3, C-H stretching), 1735 (C=O of thiazolidinone), 1725 (C=O of quinazolinone ring), 1580 (C=N), 1540 (C⎓C of aromatic ring), 1240 (C-N), 680 (C-S-C).	9.53 (brs, 1H, $NHCH_2$), 7.86-6.83 (m, 14H, Ar-H), 3.67 (s, 2H, CH_2 of thiazolidinone), 3.30 (d, 2H, CH_2NH), 3.82 (s, 3H, OCH_3), 4.56 (s, 1H, CH-Ar),	509
5d	3325 (N-H), 3155 (Ar-CH), 2930 (CH_3, C-H stretching), 1730 (C=O of thiazolidinone), 1720 (C=O of quinazolinone ring), 1575 (C=N), 1535 (C⎓C of aromatic ring), 1230 (C-N), 675 (C-S-C).	9.52 (brs, 1H, $NHCH_2$), 7.84-6.80 (m, 15H, Ar-H), 3.65 (s, 2H, CH_2 of thiazolidinone), 3.28 (d, 2H, CH_2NH), 3.79 (s, 3H, OCH_3), 4.55 (s, 1H, CH-Ar),	509
5e	3340 (N-H), 3155 (Ar-CH), 2935 (CH_3, C-H stretching), 1730 (C=O of thiazolidinone), 1715 (C=O of quinazolinone ring), 1570 (C=N), 1535 (C⎓C of aromatic ring), 1220 (C-N), 665 (C-S-C)	9.63 (brs, 1H, $NHCH_2$), 9.25 (ss, 1H, OH), 7.92-6.90 (m, 14H, Ar-H), 3.74 (s, 2H, CH_2 of thiazolidinone), 3.80 (s, 3H, OCH_3), 3.30 (d, 2H, CH_2NH), 4.60 (s, 1H, CH-Ar)	525
6b	3340 (N-H), 3155 (Ar-CH), 3025 (CH-Ar), 2940 (CH_3, C-H stretching), 1740 (C=O of Azetidinone), 1730 (C=O of quinazolinone ring), 1560 (C=N), 1520 (C⎓C of aromatic ring), 1225 (C-N), 775 (C-Cl).	9.64 (brs, 1H, $NHCH_2$), 7.88-6.85 (m, 15H, Ar-H), 6.63 (s, 1H, CH-Cl), 4.57 (s, 1H, CH-Ar), 3.30 (d, 2H, CH_2NH), 2.20 (s, 3H, CH_3)	495
6c	3335 (N-H), 3150 (Ar-CH), 3025 (CH-Ar), 2935 (CH_3, C-H stretching), 1740 (C=O of Azetidinone), 1720 (C=O of quinazolinone ring), 1565 (C=N), 1530 (C⎓C of aromatic ring), 1220 (C-N), 755 (C-Cl).	9.67 (brs, 1H, $NHCH_2$), 7.92-6.87 (m, 15H, Ar-H), 6.68 (s, 1H, CH-Cl), 4.63 (s, 1H, CH-Ar), 3.35 (d, 2H, CH_2NH), 3.83 (s, 3H, CH_3)	511
6d	3360 (N-H), 3140 (Ar-CH), 3020 (CH-Ar), 2935 (CH_3, C-H stretching), 1740 (C=O of Azetidinone), 1715 (C=O of quinazolinone ring), 1555 (C=N), 1530 (C⎓C of aromatic ring), 1215 (C-N), 750 (C-Cl).	9.65 (brs, 1H, $NHCH_2$), 7.90-6.86 (m, 15H, Ar-H), 6.67 (s, 1H, CH-Cl), 4.62 (s, 1H, CH-Ar), 3.34 (d, 2H, CH_2NH), 3.81 (s, 3H, OCH_3)	511
6e	3360 (N-H), 3155 (Ar-CH), 3035 (CH-Ar), 2955 (CH_3, C-H stretching), 1755 (C=O of Azetidinone), 1730 (C=O of quinazolinone ring), 1570 (C=N), 1545 (C⎓C of aromatic ring), 1230 (C-N), 765 (C-Cl).	9.69 (brs, 1H, $NHCH_2$), 9.28 (ss, 1H, OH), 7.96-6.92 (m, 14H, Ar-H), 6.68 (s, 1H, CH-Cl), 4.66 (s, 1H, CH-Ar), 3.37 (d, 2H, CH_2NH), 3.86 (s, 3H, OCH_3)	527

Table V: Biological data of 2- ((2- (substituted benzylidene) hydrazinyl methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) -ones (4a-4e)



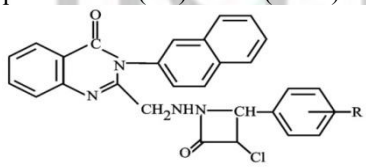
Comp.	R	Anti-inflammatory Activity		Analgesic Activity		UD_{50} (mg./kg. i.p)	Acute Toxicity ALD_{50} (mg./kg.p.o)
		Dose (mg./kg. p.o)	% Inhibition of Oedema	Dose (mg./kg.p.o)	% Protection		
4a	2-CH_3	50	26.32*	50	24.05*		>800
4b	4-CH_3	50	26.83*	50	24.35*		>800
4c	2-OCH_3	50	30.51*	50	28.10*		>800
4d	4-OCH_3	50	31.77*	50	29.25*		>800
4e	4-OH, 3-OCH_3	50	34.45*	50	32.10*		>800

Table VI: Biological data of 3- (naphthalene-2-yl) -4-oxo-3, 4-dihydro-quinazolin-2-yl) methyl amino) -2- (substituted phenyl) thiazolidin-4- (3H) ones (5a-5e)



Comp.	R	Anti-inflammatory Activity		Analgesic Activity		UD_{50} (mg./kg.i.p)	Acute Toxicity ALD_{50} (mg./kg.p.o)
		Dose (mg./kg.p.o)	% Inhibition of oedema	Dose (mg./kg.p.o)	% Protection		
5a	2-CH_3	50	36.47*	50	34.52*	-	>800
5b	4-CH_3	50	37.24*	50	35.10*	-	>800
5c	2-OCH_3	50	39.66*	50	37.15*	-	>800
5d	4-OCH_3	50	40.51**	50	38.28*	-	>800
5e	4-OH, 3-OCH_3	50	43.20**	50	40.82**	-	>800

Table VII: Biological data of 2- ((3-chloro-2- (substituted phenyl) -4-oxoazetidin-1-ylamino) methyl) -3- (naphthalene-2-yl) quinazolin-4 (3H) –ones (6a-6e)



Comp.	R	Anti-inflammatory Activity		Analgesic Activity		UD_{50} (mg./kg.i.p)	Acute Toxicity ALD_{50} (mg./kg.p.o)
		Dose (mg./kg.p.o)	% Inhibition of Oedema	Dose (mg./kg.p.o)	% Protection		
6a	2-CH_3	50	43.30**	50	41.18*	-	>800
6b	4-CH_3	50	44.08**	50	41.73*	-	>800
6c	2-OCH_3	50	50.12**	50	48.25**	-	>800
6d	4-OCH_3	50	50.88**	50	48.50**	-	>800
6e	4-OH, 3-OCH_3	50	52.50***	50	50.10***	168	>1200
Pheny butazone		25 50 100	17.50** 38.80*** 68.60***	25 50 100	15.80** 36.50*** 60.50***	66.6	
*P<0.05, **P<0.01.***<0.001 Propylene glycol standard for control group.							