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Synthesis and biological evaluation of some new quinazolone fused azetidine analogs as potential anti-inflammatory agents

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ABSTRACT

In view of potent antimicrobial and anti-inflammatory activities exhibited by quinazoline-4-(3H)-one, an efficient synthesis of novel quinazolone analogs fused with azetidin-2-ones ***4a-j*** *has been established. Thus, condensation of 2-phenyl-3-amino quinazolin-4-one* ***2*** *with various aromatic aldehydes afforded quinazolone fused Schiff bases* ***3a-j*** *which on further cycloaddition with chloroacetyl chloride in the presence of triethylamine catalyst yielded title compounds. All the synthesized compounds were screened for in vivo anti-inflammatory activity using the carrageenin-induced paw edema method in rats.*

Keywords: Anti-inflammatory, Azetidine, Schiff bases, Quinazolone.

INTRODUCTION

Inflammation is a complex biological response of vascular tissues against aggressive agents such as pathogens, irritants, or damaged cells. It is a dynamic process and can be classified as either acute or chronic [1]. At present, although diverse classes of compounds were synthesized which posse's analgesics and anti-inflammatory activities includes non steroidal anti-inflammatory drugs (NSAIDS), synthetic forms of natural cortisol (glucocorticoids), pharmaceutical biologics and many more. Although drug treatment has been improved to some extent yet, it is still a challenge for the pharmaceutical chemists to explore the more effective, potent, less toxic therapeutic agents to treat as well as reduce the signs and symptoms of acute inflammation and chronic inflammatory diseases. Thus, it is well evident from the literature and numerous studies that there is requirement for appropriate modification the molecules to attenuate the toxicity and also ensure that the host immune defense against infection is not impaired [2].

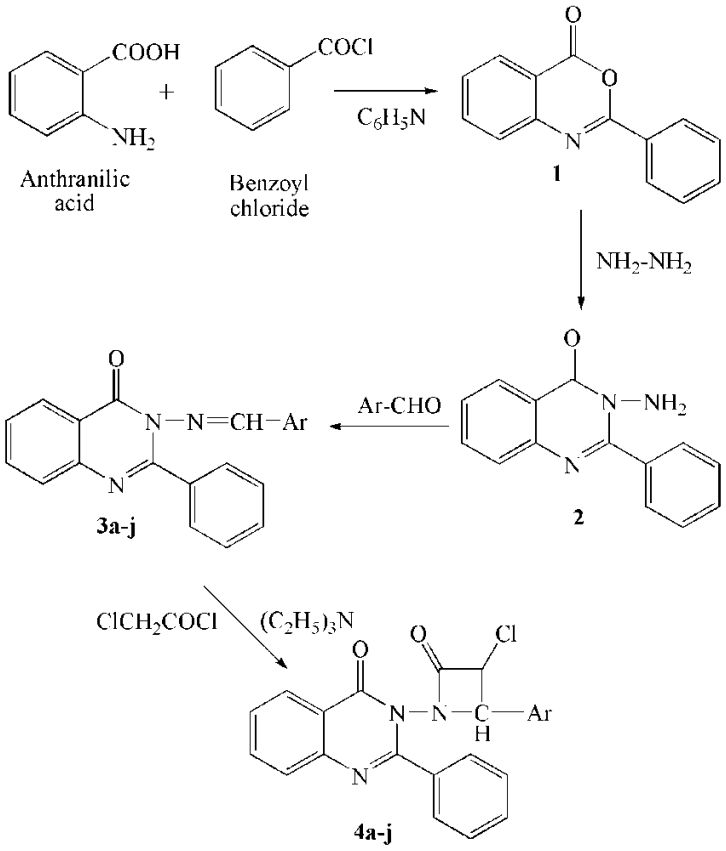
In light of the growing number of applications in recent years, there has been an enormous increase in the interest among biologists and chemists in their synthesis and bioactivity of quinazoline derivatives. Quinazolones have been frequently used in medicine because of their wide spectrum of biological activities such as antibacterial [3-4], anti-HIV [4], antimicrobial [5-7], antifungal activities [4, 8], anthelmintic [9], CNS depressant [10], antitubercular [11], antineoplastic [11-14] and antiviral [15] activities. Moreover, quinazolin-2,4 (1H, 3H)-diones, quinazolin-4(3H)-ones and 1,2,3- benzotriazin-4(3H)-ones is used for thromboxane synthase inhibitors and antihypertensive agents [16]. On the other side, literature survey revealed that 2-azetidinones are also associated with various pharmacological activities like antimicrobial, antiviral, anesthetic, anticonvulsant [17-19], etc. These findings

prompted us to synthesize novel quinazolone analogs fused with 2-azetidinones. Each of the quinazoline analogues prepared has been tested for their *in vivo* anti-inflammatory activity and the results are reported in this paper.

MATERIALS AND METHODS

2.1. Chemistry:

All melting points were determined by open capillary method and are uncorrected. IR spectra recorded on Elmer RX1 spectrophotometer using KBr pellets and are expressed in cm^{-1}. The ^1H NMR spectra were recorded on Brucker 300 MHz spectrometer in $CDCl_3$ using TMS as an internal reference (chemical shift in δ ppm). The progress of the reaction was monitored by TLC using 0.2 mm thickness aluminium sheet pre-coated with silica gel Merck 60F 254 and visualization was done using iodine/UV lamp for detection of the spots. The solvent was removed under reduced pressure using Buchi rotary evaporator. All other organic solvents used were of LR grade, dried over anhydrous sodium sulfate and used as received.



Scheme 1: Synthesis of azetidine fused quinazolone analogs

2.2. Synthesis of 2-Phenyl benzoxazin-4-one **1** [20]

Anthranilic acid (0.01mol) was treated with benzoyl chloride (0.01mol) in presence of pyridine and stirred for 3 hour and the resulting mixture was treated with 5% sodium bicarbonate solution to get 2-Phenyl benzoxazin-4-one. The precipitate was filtered, dried and recrystallized from ethanol. Molecular formula $C_{14}H_9NO_2$, Yield 84%, m.p. 121-122°C. IR (KBr), 1650 (C= O); 1530 (C=N); 3200, 3050 (Ar-H).

*2.3. 2-phenyl-3-amino quinazolin-4-one **2***

Compound **1** (0.01mol) was treated with hydrazine hydrate (0.02mol) in presence of ethanol and refluxed for 2-3 h to form 2-Phenyl-3-amino quinazolin-4-one. The content was then cooled, filtered off and re-crystallized from

ethanol. Molecular formula $C_{14}H_{11}N_3O$, Yield 70 %, m.p.191-192 °C. IR (KBr), 1670 (C=O); 1520 (C=N); 3350 (NH); 3100 (Ar-H).

2.4. *General procedure for synthesis of Quinazolone fused Schiff bases* ***3a-j***

Different aromatic aldehydes (0.01 mol) were treated with compound **2** (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 re-crystallized from ethanol.

2.4.1. *3-(benzylideneamino)-2-phenylquinazolin-4(3H)-one* ***3a***:

Molecular Formula: $C_{21}H_{15}N_3O$, Yield: 77%; mp: 223-224 °C; IR (KBr): 1520 (C=N), 3050 (C=C), 1660 (C=O) cm^{-1}. ^{1}HNMR ($CDCl_3$) δ: 7.2-7.8 (m, 14H, Ar-H), 8.0 (s, 1H, -CH).

2.4.2. *3-(2-nitrobenzylideneamino)-2-phenylquinazolin-4(3H)-one* ***3b****:*

Molecular Formula: $C_{21}H_{14}N_4O_3$, Yield: 65%; mp: 225-226 °C; IR (KBr): 1525 (C=N), 3300 (Ar-CH), 1650 (C=O) cm^{-1}. ^{1}HNMR ($CDCl_3$) δ: 7.2-7.9 (m, 12H, Ar-H), 8.1 (s, 1H, -CH), 8.3 (d, 1H, Ar-CH).

2.4.3. *3-(3,4-dimethoxybenzylideneamino)-2-phenylquinazolin-4(3H)-one* ***3c****:*

Molecular Formula: $C_{23}H_{19}N_3O_3$, Yield: 70%; mp: 214-215 °C. ^{1}HNMR ($CDCl_3$) δ: 3.8 (s, 6H, $-OCH_3$), 6.8-7.7 (m, 11H, Ar-H), 8.1 (s, 1H, -CH), 7.9 (d, 1H, Ar-CH).

2.4.4. *3-(3,4,5-trimethoxybenzylideneamino)-2-phenylquinazolin-4(3H)-one* ***3d****:*

Molecular Formula: $C_{24}H_{21}N_3O_4$, Yield: 68%; mp: 215-216 °C. ^{1}HNMR ($CDCl_3$) δ: 3.7 (s, 9H, $-OCH_3$), 6.7 (d, 2H, Ar-H), 7.2-7.6 (m, 8H, Ar-CH), 7.9 (d, 1H, Ar-CH), 8.2 (s, 1H,-CH).

2.4.5. *3-(4-hydroxybenzylideneamino)-2-phenylquinazolin-4(3H)-one* ***3e****:*

Molecular Formula: $C_{21}H_{15}N_3O$, Yield: 70%; mp: 211-212 °C. ^{1}HNMR ($CDCl_3$) δ: 5.0 (s, 1H, -OH), 6.8-7.6 (m, 12H, Ar-H), 7.8 (d, 1H, Ar-CH), 8.1 (s, 1H,-CH).

2.4.6. *3-(3-nitrobenzylideneamino)-2-phenylquinazolin-4(3H)-one* ***3f****:*

Molecular Formula: $C_{21}H_{14}N_4O_3$, Yield: 66%; mp 229-230 °C. ^{1}HNMR ($CDCl_3$) δ: 7.1-7.7 (m, 9H, Ar-CH), 7.9 (m, 2H, Ar-CH), 8.1 (s, 1H, -CH), 8.2-8.5 (m, 2H, Ar-CH).

2.4.7. *3-(4-chlorobenzylideneamino)-2-phenylquinazolin-4(3H)-one* ***3g****:*

Molecular Formula: $C_{21}H_{14}ClN_3O$, Yield: 60%, mp: 210-211 °C. IR (KBr): 1570 (C=N), 3220 (Ar-CH), 1655 (C=O) cm^{-1}. ^{1}HNMR ($CDCl_3$) δ: 7.2-7.7 (m, 12H, Ar-CH), 8.0 (d, 1H, Ar-CH), 8.2 (s, 1H, -CH).

2.4.8. *3-(3-methoxy-4-hydroxybenzylamino)-2-phenylquinazolin-4(3H)-one* ***3i****:*

Molecular Formula: $C_{22}H_{17}N_3O_2$, Yield: 65%; mp: 245-246 °C. IR (KBr): 1550 (C=N), 3300 (Ar-CH), 3200 (-OH), 1650 (C=O) cm^{-1}. ^{1}HNMR ($CDCl_3$) δ: 3.6 (s, 3H, $-OCH_3$), 4.5 (s, 1H, -OH), 6.8-7.7 (m, 11H, Ar-CH), 7.9 (d, 1H, Ar-CH), 8.1 (s, 1H, -CH).

2.4.9. *3-(4-methoxybenzylideneamino)-2-phenylquinazolin-4(3H)-one* ***3i****:*

Molecular Formula: $C_{22}H_{17}N_3O_2$, Yield: 74%; mp: 215-216 °C. ^{1}HNMR ($CDCl_3$) δ: 3.5 (s, 3H, $-OCH_3$), 6.8-7.7 (m, 12H, Ar-CH), 8.0 (d, 1H, Ar-CH), 8.2 (s, 1H, -CH).

2.4.10. *3-((furan-2-yl)methyleneamino)-2-phenylquinazolin-4(3H)-one* ***3j****:*

Molecular Formula: $C_{19}H_{13}N_3O_2$, Yield: 75%; mp: 245-246 °C. IR (KBr): 1530 (C=N), 3200 (Ar-CH), 1670 (C=O) cm^{-1}. ^{1}HNMR ($CDCl_3$) δ: 6.5 (m, 2H, furan), 7.2-7.6 (m, 8H, Ar-CH), 7.5 (s, 1H, -CH), 7.8 (d, 1H, Ar-CH), 7.6 (s, 1H, -CH).

2.5. General procedure for the synthesis of compounds 4a-j

To a stirred solution of the particular Quinazolone fused Schiff bases **3a-j** (0.02 mol) and triethylamine (0.01 mol) in dioxan (50 ml), chloroacetyl chloride (0.01 mol) was added drop wise at 0-5°C. The reaction mixture stirred for 3 h and the separated solid was crystallized from methanol to give the title compounds.

2.5.1.*3-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-2-phenylquinazolin-4(3H)-one* **4a**:
Molecular Formula: $C_{23}H_{16}ClN_3O_2$, Yield: 50%; mp: 195-196 °C. ^{1}HNMR ($CDCl_3$) δ: 4.5 (d, 1H, -CH), 5.0 (d, 1H, -CH), 7.2-7.6 (m, 13H, Ar-CH), 7.8 (d, 1H, Ar-CH).

2.5.2.*3-(3-chloro-2-(2-nitrophenyl)-4-oxoazetidin-1-yl)-2-phenylquinazolin-4(3H)-one* ***4b****:*
Molecular Formula: $C_{23}H_{15}ClN_4O_4$, Yield: 60%; mp: 192-193 °C. ^{1}HNMR ($CDCl_3$) δ: 4.6 (d, 1H, -CH), 5.2 (d, 1H, -CH), 7.2-7.6 (m, 11H, Ar-CH), 7.8 (d, 1H, Ar-CH), 8.0 (d, 1H, Ar-CH).

2.5.3.*3-(3-chloro-2-(3,4-dimethoxyphenyl)-4-oxoazetidin-1-yl)-2-phenylquinazolin-4(3H)-one* ***4c****:*
Molecular Formula: $C_{25}H_{20}ClN_3O_4$, Yield: 62 %; mp: 178-179 °C. ^{1}HNMR ($CDCl_3$) δ: 3.7 (s, 6H, $-OCH_3$), 4.8 (d, 1H, -CH), 5.4 (d, 1H, -CH), 6.7-7.6 (m, 11H, Ar-CH), 7.8 (d, 1H, Ar-CH).

2.5.4.*3-(3-chloro-2-(3,4,5-trimethoxyphenyl)-4-oxoazetidin-1-yl)-2-phenylquinazolin-4(3H)-one* ***4d****:*
Molecular Formula: $C_{26}H_{22}ClN_3O_5$, Yield: 65%; mp: 185-186 °C. ^{1}HNMR ($CDCl_3$) δ: 3.6 (s, 9H, $-OCH_3$), 4.7 (d, 1H, -CH), 5.4 (d, 1H, -CH), 6.2 (s, 2H, Ar-CH), 7.2-7.8 (m, 9H, Ar-CH).

2.5.5.*3-(3-chloro-2-(4-hydroxyphenyl)-4-oxoazetidin-1-yl)-2-phenylquinazolin-4(3H)-one* ***4e****:*
Molecular Formula: $C_{23}H_{16}ClN_3O_3$, Yield: 55%; mp: 202-203 °C. ^{1}HNMR ($CDCl_3$) δ: 4.8 (d, 1H, -CH), 5.0 (s, 1H, -OH), 5.4 (d, 1H, -CH), 6.7-7.8 (m, 13H, Ar-CH).

2.5.6.*3-(3-chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-yl)-2-phenylquinazolin-4(3H)-one* ***4f****:*
Molecular Formula: $C_{23}H_{15}ClN_4O_4$, Yield: 64%; mp: 178-179 °C.^{1}HNMR ($CDCl_3$) δ: 4.7 (d, 1H, -CH), 5.2 (d, 1H, -CH), 7.2-8.2 (m, 13H, Ar-CH).

2.5.7.*3-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)-2-phenylquinazolin-4(3H)-one* ***4g****:*
Molecular Formula: $C_{23}H_{15}Cl_2N_3O_2$, Yield: 56%; mp: 187-188 °C. ^{1}HNMR ($CDCl_3$) δ: 4.8 (d, 1H, -CH), 5.4 (d, 1H, -CH), 7.0-7.8 (m, 13H, Ar-CH).

2.5.8.*3-(3-chloro-2-(4-hydroxy-3-methoxyphenyl)-4-oxoazetidin-1-yl)-2-phenylquinazolin-4(3H)-one****4h****:*
2.5.9. Molecular Formula: $C_{24}H_{18}ClN_3O_4$, Yield: 55%; mp: 210-211 °C. ^{1}HNMR ($CDCl_3$) δ: 3.6 (s, 3H, $-OCH_3$), 4.7 (d, 1H, -CH), 5.1 (s, 1H, -OH), 5.4 (d, 1H, -CH), 6.5-6.8 (m, 3H, Ar-CH), 7.2-7.8 (m, 9H, Ar-CH).

2.5.10. *3-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-2-phenylquinazolin-4(3H)-one* ***4i****:*
Molecular Formula: $C_{24}H_{18}ClN_3O_3$, Yield: 65%; mp: 205-206 °C. ^{1}HNMR ($CDCl_3$) δ: 3.7 (s, 3H, $-OCH_3$), 4.7 (d, 1H, -CH), 5.5 (d, 1H, -CH), 6.9-8.0 (m, 13H, Ar-CH).

2.5.11. *3-(3-chloro-2-(furan-2-yl)-4-oxoazetidin-1-yl)-2-phenylquinazolin-4(3H)-one* ***4j****:*
Molecular Formula: $C_{21}H_{14}ClN_3O_3$, Yield: 60%; mp: 188-189 °C. ^{1}HNMR ($CDCl_3$) δ: 4.7 (d, 1H, -CH), 5.2 (d, 1H, -CH), 6.0-6.3 (m, 2H, furan), 7.1 (d, 1H, furan), 7.2-7.8 (m, 9H, Ar-CH), .

2.6. Biological Activity:

2.6.1. Animals and Instruments used

Adult wistar rats of either sex weighing between 150–180g were used throughout the work. The selected animals were kept under standard conditions of light and temperature with free access to food and water. All experimental procedures were carried out in strict accordance with the guidelines prescribed by the committee for the purpose of control and supervisions on experimentation on animals (CPCSEA) and were approved by the Institutional Animal Ethics Committee of Guru Gobind Singh College of Pharmacy, Yamuna Nagar, Haryana (Regn. No. 873/PO/ac/05/CPCSEA). The paw edema was induced by sub-plantar injection using carrageenan and the increased foot volumes were measured in a Plethysmograph by water displacement.

2.6.2. Anti-inflammatory Activity

The anti-inflammatory activity was carried out by the Winter *et. al*. method [21]. The apparatus used for the measurement of rat paw volume was that of Buttle *et. al*. modified by Singh and Ghosh [22-23]. The animals were randomly divided into twenty two groups of four rats each. Test compounds (**3a-j** and **4a-j**) and standard drug

aspirin were suspended in 0.5% *w/v* of sodium carboxyl methylcellulose (CMC), which was used as a vehicle for the control group. The rats were dosed with test drugs orally (100 mg/kg body weight) including the reference standard with help of oral catheter. After 30 minutes drug administration, 50 µl of 1% w/v carrageenan solution in saline (0.9%) was injected in the sub plantar region of the left hind paw of control as well as standard and test groups. The volume of paw edema (in ml) was determined by means of a water plethysmometer immediately after injection of carrageenan and 4 h later. The percentage protection against inflammation was calculated as follows: (Vc – Vd)/Vc × 100, where Vc is the increase in paw volume in the absence of the test compound (control) and Vd is the increase of paw volume after injection of the test compound. Data were expressed as means ± SEM. Significant differences between the control and the treated groups were obtained using Student's t-test and *p*-values. The differences in results were considered significant when $p < 0.001$.

RESULT AND DISCUSSION

2.7. Chemistry

A series of some quinazolone fused azetidine analogs has been synthesized in an attempt to find new compounds with promising anti-inflammatory activities. The synthesis pathway leading to the title compounds is given in **Scheme 1**. The purity and structures of all the synthesized compounds have been elucidated on the basis of their spectral data including IR and ^{1}H NMR. In IR spectra, all the compounds displayed the characteristic peaks in the region 1440-1514 cm^{-1} indicated the formation of Schiff base (–H-C=N). The appearance of peaks in the region 1550-1687 cm^{-1} confirmed the presence of C=O in all the compounds. The structural assignments were further supported by their ^{1}H NMR spectra and all the synthesized compounds were in conformity with the structures envisaged. The molecular properties of the title compounds such as logP, Topological polar surface area (TPSA), natom, nON, nOHNH were calculated by http://www.molinspiration.com and given in **Table 1**.

Table 1 Molecular properties of the compounds 3a-j and 4a-j.

Compounds	Ar	MW	logP	TPSA	natom	nON	nOHNH
3a	-C_6H_5	325.37	4.60	47.26	25	4	0
3b	-2$NO_2C_6H_4$	370.37	4.51	93.08	28	7	0
3c	-3,4-di$OCH_3C_6H_3$	385.42	4.25	65.73	29	6	0
3d	-3,4,5-tri$OCH_3C_6H_2$	415.45	4.23	74.96	31	7	0
3e	-4OHC_6H_4	341.37	4.12	67.49	26	5	1
3f	-3$NO_2C_6H_4$	370.37	4.54	93.08	28	7	0
3g	-4ClC_6H_4	359.82	5.28	47.26	26	4	0
3h	-4OH,3-$OCH_3C_6H_3$	371.40	3.94	76.72	28	6	1
3i	-4$OCH_3C_6H_4$	355.40	4.66	56.49	27	5	0
3j	-Furfuraldehyde	315.33	3.86	60.40	24	5	0
4a	-C_6H_5	401.85	4.53	55.21	29	5	0
4b	-2$NO_2C_6H_4$	446.85	4.44	101.03	32	8	0
4c	-3,4-di$OCH_3C_6H_3$	461.90	4.18	73.67	33	7	0
4d	-3,4,5-tri$OCH_3C_6H_2$	491.93	4.16	82.91	35	8	0
4e	-4OHC_6H_4	417.85	4.05	75.43	30	6	1
4f	-3$NO_2C_6H_4$	446.85	4.46	101.03	32	8	0
4g	-4ClC_6H_4	436.30	5.21	55.21	30	5	0
4h	-4OH,3-$OCH_3C_6H_3$	447.88	3.87	84.67	32	7	1
4i	-4$OCH_3C_6H_4$	431.88	4.59	64.44	31	6	0
4j	-Furfuraldehyde	391.81	3.79	68.35	28	6	0

2.8. Anti-inflammatory Activity

The *in-vivo* anti-inflammatory activity was studied using carrageenan-induced rat paw edema model. The anti-inflammatory activity of the test compounds was compared with standard drug aspirin as depicted in **Table 2**. The test and standard drug produced significant inhibition of paw edema as compared to control. Out of all prepared analogs **3h, 3e, 3a** and **3g** exhibit more activity than standard drug aspirin.

Table 2. Anti-inflammatory potential of compounds 3a-j and 4a-j on carrageenan-induced rat paw edema (ml), % protection, relative activity to aspirin

Tested Compounds	Increase in paw edema (ml) ± SEM[a,b]	% Protection	Activity relative to aspirin
Control	0.94 ± 0.021	0.0	0.0
Aspirin	0.25 ± 0.018	73.4	100
3a	0.23 ± 0.025	75.5	102
3b	0.72 ± 0.023	23.4	32
3c	0.27 ± 0.026	71.3	97
3d	0.27 ± 0.024	71.3	97
3e	0.20 ± 0.019	78.7	107
3f	0.69 ± 0.028	26.6	36
3g	0.24 ± 0.024	74.5	101
3h	0.20 ± 0.025	78.7	107
3i	0.31 ± 0.026	67.0	91
3j	0.75 ± 0.022	20.2	27
4a	0.37 ± 0.021	60.6	83
4b	0.76 ± 0.030	19.1	26
4c	0.43 ± 0.022	54.3	74
4d	0.34 ± 0.023	63.8	87
4e	0.32 ± 0.024	65.9	90
4f	0.77 ± 0.028	18.0	24
4g	0.68 ± 0.029	27.6	38
4h	0.34 ± 0.016	63.8	87
4i	0.76 ± 0.024	19.1	26
4j	0.82 ± 0.030	12.8	17

[a]SEM denotes the standard error of the mean. [b]All data are significantly different from control ($p < 0.001$).

CONCLUSION

In summary, the present investigation describes synthesis of quinazolones fused azetidine analogs with comparable anti-inflammatory potencies which are characterized by suitable methods such as spectroscopic evaluation like IR and ^{1}H NMR. All spectral data were in accordance with assumed structures. The compounds **3h, 3e, 3a** and **3g** show remarkable reduction in inflammation, after 4 h of carrageenan administration. The promising activity of these compounds along with the other activity data obtained during the study can also be useful for establishing the structure activity relationship studies and for the development of newer and potent anti-inflammatory compounds.

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