Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry, 2019, *18*, 4-25

RESEARCH ARTICLE

Design and Development of Novel 2-(Morpholinyl)-*N*-substituted Phenylquinazolin-4-amines as Selective COX-II Inhibitor

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ARTICLE HISTORY

Received: April 09, 2018
Revised: August 29, 2018
Accepted: September 15, 2018

DOI:
10.2174/1871523017666181022144053

Abstract: ***Background*:** A novel series of 2-(Morpholin-4-yl)-*N*-phenylquinazolin-4-amine derivatives were synthesized and confirmed with spectral and elemental techniques.

***Methods*:** The compounds were tested for analgesic and anti-inflammatory activity by various pain models in rodents whereas the selectivity towards COX-2 receptor is determined by *in vitro* assay.

Results*:** Screening results of compounds exhibited comparable biological activity with that of standard compound Indomethacin used for study. Compound ***5d was found to be significantly potent with respect to its anti-inflammatory and analgesic activity with substantial COX-II selectivity.

Conclusion*:** *In silico* analysis by molecular docking and 3D-QSAR studies justifies activity profile of compound ***5d, suggesting that it may have potential for further evaluation and development as lead molecule for therapy in pain management.

Keywords: 3D-QSAR, analgesic, anti-inflammatory, COX II inhibitor, molecular docking, quinazoline.

1. INTRODUCTION

Prostaglandin-endoperoxide Synthase (PTGS) or Cyclo-oxygenase (COX) is the enzyme responsible for the formation of biological mediators such as prostaglandins, prostacyclins and thromboxanes. COX-1 and COX-2 are the isoenzymes that differ from each other at the catalytic site. COX-1 has isoleucine whereas COX-2 has valine at the position *523* in the catalytic site, comparatively, valine is small amino acid and allows for the access of molecules to the side pocket in enzyme but isoleucine hinders this access owing to its large size [1, 2]. The molecules from coxib series bind to this alternative site, leading to inhibition of enzyme activity and hence called as COX-2 inhibitors [3, 4]. Diaryl heterocycles have become the major class of selective COX-2 inhibitors, such as Celecoxib, Rofecoxib, Parecoxib and Valdecoxib, which display improved gastrointestinal safety profile compared to the traditional NSAIDs [5-7]. But the coxibs grieved from sharp criticism due to certain vascular events such as Myocardial Infarction (MI) and non-fatal stroke which may result in death. The other NSAID's also faced several clinical conditions like gastric irritation, bleeding, nephrotoxicity, dizziness and

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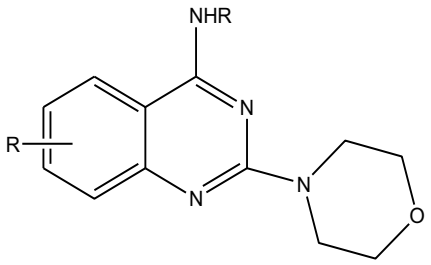
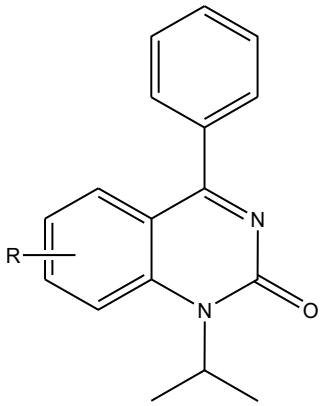


Proposed Derivatives
2-(Morpholin-4-yl)-*N*-phenylquinazolin-4-amine derivatives



Proquazone
4-phenyl-1-(propan-2-yl)quinazolin-2(1*H*)-one

Fig. (1). Proquazone and structurally analogous proposed.

nausea. The recent withdrawal of coxibs as selective COX-2 inhibitors from the market is due to their adverse cardiovascular condition and also gastric side-effects similar to conventional NSAIDs. There is considerable impetus to develop alternative anti-inflammatory agents with reduced gastric and cardiovascular side effects [8].

Quinazoline is a heteroatomic bicyclic nucleus that occurs widely in nature, present in number of natural molecules such as Samoquasine A, Neodichroine, Glycosminine, *etc*. [9]. Quinazoline possesses diverse biological activities like antineoplastic [1-3], antihypertensive [4], cardiac stimulant activity [5], antimalarial [6], anticonvulsant [7-9] and antimicrobial [10-12]. Proquazone (1-isopropyl-7-methyl-4-phenylquinazolin-2(1H)-one) is a synthetic quinazoline derivative with recognized anti-inflammatory and analgesic action (Fig. **1**). Derivatives of quinazoline are gaining importance in the development of potent, safe and selective COX-II inhibitors [13]. It gives the confidence to select such moiety with dual effect along with aryl amine and morpholine group as a major pharmacophoric substituent for the development of expectedly potent agent.

The arylamine derivatives are choice of pharmacophoric substituent as it is well reported for a similar set of activities such as analgesic, anti-inflammatory and anticonvulsant activity [14, 15] thus selected for enhancing the affectivity, whereas morpholine derivatives also possess cannabinoid receptor enhancing [16], neuroleptic activity [17] explaining its CNS activity. The result obtained from our last investigation [12] encourages making a sequel study explaining the significance of the next series of probable pharmacophoric groups on the various positions of quinazoline moiety. We present the design and synthesis of novel quinazoline derivatives, pharmacological evaluation, molecular docking and 3D QSAR study.

The synthesis of designed compounds includes simple nucleophilic substitution reaction, which starts with the addition of carboxamido group on to the morpholine group under inert condition followed by cyclization in between corresponding morpholin-4-carboxamide and anthranilic acid under acidic condition. The quinazolinones formed further undergoes displacement of ketonic group to arylamino group *via* chlorination gateway affording the title compounds. The purity and homogeneity of synthesized derivatives were checked by physical constant determination and chromatographic technique. These structures (Fig. **2**, Table **1**) were further confirmed by spectral and elemental analysis. The confirmed structures were further subjected to the extensive pharmacological screening on both *in vitro* and *in vivo* scales. The COX-II selectivity was ascertained by *in vitro* COX-II inhibition assay. Then further proceeds for *in vivo* by rat paw edema method induced by two well-known irritants *i.e*., carrageenan and egg albumin were employed to judge its ability to inhibit inflammation whereas, hot plate and tail flick

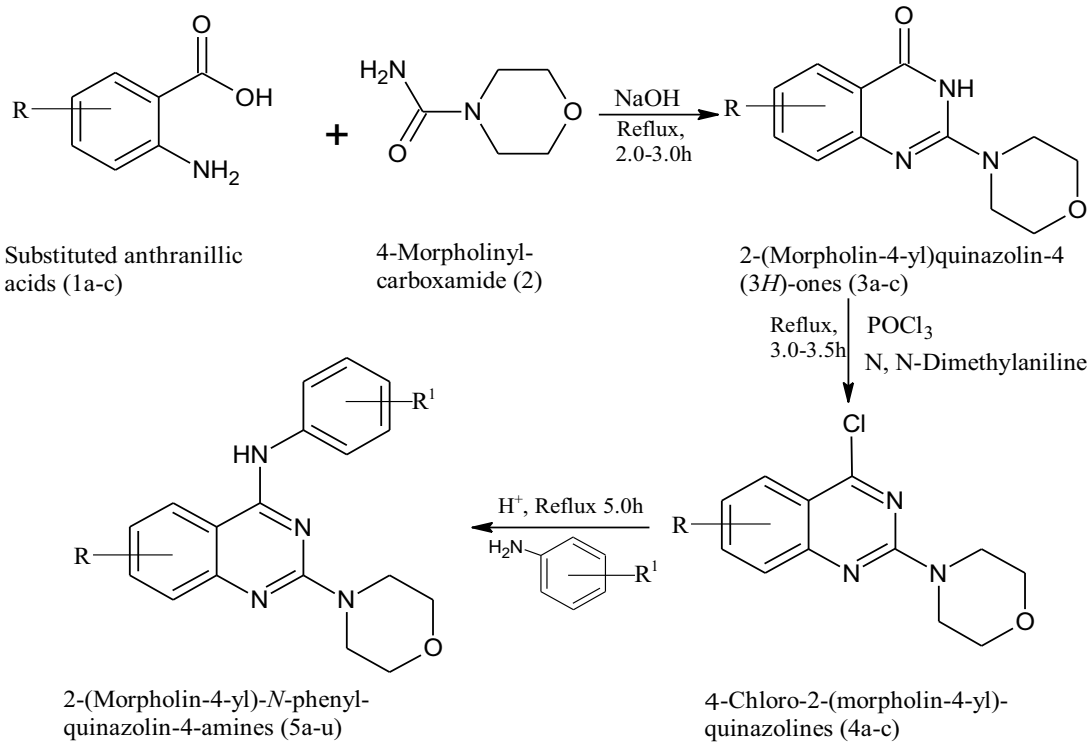


Fig. (2). Synthetic route for 2-(morpholin-4-yl)-N-phenylquinazolin-4-amine derivatives (***5a-u***).

Table 1. 2-(Morpholin-4-yl)-N-phenylquinazolin-4-amine derivatives (*5a-u*).

Comp. No.	R	R^1	Comp. No.	R	R^1
5a	H	H	**5l**	6,8-di Cl	*p*-OCH_3
5b	H	*p*-Cl	**5m**	6,8-di Cl	*p*-CH_3
5c	H	*p*-Br	**5n**	6,8-di Cl	*o*, *p*-di CH_3
5d	H	*p*-OH	**5o**	6,8-di Br	H
5e	H	*p*-OCH_3	**5p**	6,8-di Br	*p*-Cl
5f	H	*p*-CH_3	**5q**	6,8-di Br	*p*-Br
5g	H	*o*, *p*-di CH_3	**5r**	6,8-di Br	*p*-OH
5h	6,8-di Cl	H	**5s**	6,8-di Br	*p*-OCH_3
5i	6,8-di Cl	*p*-Cl	**5t**	6,8-di Br	*p*-CH_3
5j	6,8-di Cl	*p*-Br	**5u**	6,8-di Br	*o*, *p*-di CH_3
5k	6,8-di Cl	*p*-OH	-	-	-

methods discover the analgesic activity representing its capability to act on both central and peripheral system. To understand structure-activity relationship of synthesized compounds 3D QSAR study was carried out to outline the relationship between pharmacological activity and pharmacophoric substitutions on the basic moiety [18, 19].

2. RESULTS AND DISCUSSION

2.1. Chemistry

In continuation of our previous work [12], another set of simple chemical reactions was enrooted to synthesize 2-(morpholin-4-yl)-*N*-phenylquinazolin-4-amine derivatives (Fig. **2**). The reaction

starts with the substitution of urea on morpholine hydrochloride in the presence of strong hydrochloric acid under inert atmosphere, leading to the formation of the corresponding morpholine-4-carboxamide with the liberation of ammonia. The next step involves cyclization reaction between substituted anthranillic acids and morpholine-4-carboxamide to form a consequently 2-(morpholin-4-yl)-3, 4-dihydroquinazoline-4(3H)-one (***3 a-c***). The third step involves its chlorination in the presence of phosphorusoxytrichloride and N,N-dimethylamine followed by extraction with benzene, washed with 5% aqueous sodium bicarbonate solution and dried over magnesium sulfate to afford light brown colored 4-chloro-2-(morpholin-4-yl)quinazoline derivative (***4 a-c***), here simple replacement of 4-ketonic group with chloro group was carried out under the influence of N,N-dimethylamine. The last step engaged with the substitution of amino derivatives on to the 4- position of quinazoline moiety is achieved by refluxing the resulting chloro derivatives of quinazoline with different substituted aniline to yield title compounds (***5a-u***). All compounds synthesized were collected with good practical yield. The purity and homogeneity of compounds synthesized were determined by sharp melting points and TLC method. The structures were confirmed by FTIR, NMR, mass spectrum and C, H, N analysis. All derivatives showed a broad to variable absorbed peaks at 1708-1580 cm^{-1} showing the presence of C=C and C=N of quinazoline ring, the medium to weak peaks around 1370-1321 and 1147-1080 cm^{-1} indicates the attachment of morpholine ring. The secondary nitrogen of aniline group is confirmed by peaks of N-H deformation exhibiting at 1563-1612 cm^{-1}. Moreover, the presence of halogens in the compound is shown by different medium peaks exhibited in between 700-550 for C-Cl (compound ***5 h-n***), 600-500 for C-Br (compounds ***5o-u***). These groups were further confirmed by NMR studies showing a range of peaks in between 6.8-8.5 for aromatic protons present on quinazoline and aryl amines, it also exhibits variable peaks at 2.0-5.5 indicating the attachment of N-H group in aromatic condition, peaks at 2-3 also suggests for OCH_3 group as in compound ***5e, 5l*** and **5*s***, all compounds showed peaks around 1.8-3.5 may demonstrate the protons present on morpholine group. In MS spectra of the synthesized 2-(morpholin-4-yl)-*N*-phenylquinazolin-4-amine molecular peaks are weak (less than 10%). Instead, peaks M-1, M-2 and M-3 are intensive, the latter often being main ones. The peaks mentioned probably arise from a molecular radical cation by departures of hydrogen atoms. It may leave from the positions 1, 2 or 3 of the hetero-ring. There were also observed peaks probably identical with the molecular peaks and fragmentation routes of the corresponding title compounds. The values of elemental analysis are also within the range which gave further confirmation of correct synthesis of title compounds.

2.2. Pharmacology

The working protocol for animals in these studies was approved by Committee for the Purpose of Control and Supervision of Experiments in Animal (CPCSEA) Nagpur and experiments were conducted in accordance with the standard guidelines. Preliminary pharmacological screening includes approximate toxicity testing (LD_{50}) on both rats and mice as per the OECD guidelines for selecting the dose. All the derivatives do not exhibit any toxicity up to 200mg/kg. The ED_{50} of synthesized compounds were determined by adopting the standard procedure. Acute toxicity studies of synthesized compounds were performed according to OECD guidelines No. 423, which showed a significant safety margin as indicated by a lack of systemic and behavioral toxicity up to 200 mg/kg. No adverse effects were observed at 200 mg/kg during the first 30 min, 24 h and even up to 14 days after oral administration. Therefore, random doses (10, 20, 50 and 100mg/Kg) were selected for *in vivo* anti-inflammatory and analgesic studies out of which best considerable results were obtained with 50 mg/Kg and thus considered for further study.

2.2.1. Anti-inflammatory Activity

The anti-inflammatory activity of test compounds was performed on the Albino rats of SD and Wistar strain. The anti-inflammatory activity of compounds was done by using Carrageenan-induced and egg albumin induce rat paw methods respectively [20, 21]. Test compounds (**5d**, **5e**, **5f**, **5h**, **5i**, **5k**, **5n**, **5m**, **5p** and **5t**) showed better and

Table 2. Anti-inflammatory activity of 2-(morpholin-4-yl)-N-phenyl-quinazolin-4-amine derivatives.

Comp. No.	UI	Carrageenan Induced			Egg Albumin Induced					
		Swelling in Thickness [x 10^{-2}mm]^a (% Inhibition) at Different Time Interval								
	TI	0.5 h	1.5 h	3.5 h	30 min	60 min	90 min	120 min	150 min	180 min
5a	0.52±0.1	3.2±0.2 (30.8)	5.6±0.5 (21.1)	12.5±1.0 (65.0)	1.2±0.8 (3.91)	2.3±0.5 (7.23)	4.6±0.5 (11.08)	5.8±0.2 (12.47)	7.1±0.2 (13.76)	11.5±0.5 (21.66)
5b	0.81±0.1	3.6±1.5 (34.6)	6.8±0.4 (25.7)	19.9±0.9 (44.3)	2.0±0.1 (6.51)	3.8±0.2 (11.95)	6.1±0.5 (14.70)	8.6±0.2 (18.49)	14.5±0.5 (28.10)	18.5±0.1 (34.84)
5c	0.48±0.2	1.5±0.5 (14.4)	3.4±0.5 (12.8)	10.5±0.5 (70.6)	0.5±0.1 (1.63)	1.1±0.1 (3.46)	4.8±0.1 (11.57)	7.1±0.8 (15.27)	10.2±0.9 (19.77)	12.9±0.1 (24.29)
5d	0.50±0.1	6.9±0.5 (66.3)	14.4±0.9 (45.7)	13.5±1.5 (62.2)	4.2±0.2 (13.68)	6.5±0.2 (20.44)	9.8±0.2 (23.61)	15.2±0.8 (32.69)	20.4±1.0 (39.53)	24.7±0.2 (46.52)
5e	0.36±0.2	4.8±0.6 (46.2)	6.1±0.2 (23.0)	21.6±0.2 (39.5)	2.6±0.6 (8.47)	5.1±0.1 (16.04)	5.8±0.8 (13.98)	6.5±0.1 13.98 ()	8.5±1.5 (16.47)	10.2±0.7 (19.21)
5f	0.51±0.2	6.3±0.3 (60.6)	12.5±0.2 (47.2)	22.5±0.2 (37.0)	4.5±0.8 (14.66)	6.5±0.4 (20.44)	7.8±0.5 (18.80)	8.2±0.5 (17.63)	10.5±0.8 (20.35)	14.8±1.0 (27.87)
5g	0.88±0.5	4.6±0.5 (44.2)	14.2±0.6 (53.6)	18.6±0.8 (47.9)	6.8±0.6 (22.15)	8.1±0.5 (25.47)	9.5±0.8 (22.89)	10.3±0.5 (22.15)	12.9±0.7 (25.00)	18.6±0.5 (35.03)
5h	0.45±0.2	7.5±1.2 (72.1)	9.5±0.5 (35.8)	30.2±0.5 (15.4)	3.4±0.2 (11.07)	4.2±0.1 (13.21)	6.8±0.4 (16.39)	9.1±0.8 (19.57)	11.4±1.5 (22.09)	19.5±0.3 (36.72)
5i	0.69±0.1	7.1±0.6 (68.3)	10.6±0.2 (40.0)	26.6±0.1 (25.5)	4.7±0.5 (15.31)	5.2±0.5 (16.35)	7.1±.5 (17.11)	9±0.5 (19.35)	13.4±0.1 (25.97)	17.6±0.1 (33.15)
5j	0.87±0.2	7.8±0.6 (75.0)	9.6±0.1 (36.2)	17.5±1.5 (51.0)	3.6±0.6 (11.73)	4.1±0.7 (12.89)	7.9±0.6 (19.04)	8.4±0.1 (18.06)	10.1±0.5 (19.57)	15.7±0.6 (29.57)
5k	0.45±0.2	7.6±0.5 (73.1)	15.5(±0.5 58.5)	22.9±0.2 (35.9)	4.1±0.5 (13.36)	6.4±0.2 (20.13)	7.1±0.8 (17.11)	8.5±0.5 (18.28)	10.5±0.6 (20.35)	18.1±0.1 (34.09)
5l	0.89±0.1	8.2±1.0 (78.8)	13.7±0.2 (51.7)	20.4±0.6 (42.9)	2.7±0.5 (8.79)	3.0±0.9 (9.43)	3.8±0.8 (10.83)	8.1±0.6 (17.42)	11.2±0.5 (21.71)	16.5±0.5 (31.07)
5m	0.78±0.5	9.5±0.2 (91.3)	18.5±0.6 (69.8)	28.6±0.8 (19.9)	4.9±0.2 (15.96)	5.7±0.5 (17.92)	7.2±0.5 (20.51)	10.5±0.5 (22.58)	16.8±1.5 (32.56)	25.6±0.9 (48.21)
5n	0.74±0.5	9.1±0.8 (87.5)	20.5±1.0 (77.4)	25.1±0.1 (27.7)	5.5±0.3 (17.92)	6.2±0.1 (19.50)	8.5±0.4 (24.22)	13.1±0.8 (28.17)	19.5±0.1 (37.79)	24.8±1.0 (46.70)
5o	0.22±0.1	4.5±0.5 (43.3)	9.3±0.2 (35.1)	17.5±0.5 (51.0)	1.9±0.2 (6.19)	3.5±0.5 (11.01)	6.8±0.1 (19.37)	7.5±0.8 (16.13)	8.9±0.5 (17.25)	17.4±0.5 (32.77)
5p	0.56±0.1	6.2±0.1 (59.6)	20.9±0.5 (78.9)	28.1±0.7 (21.3)	3.7±0.1 (12.05)	4.5±0.8 (14.15)	8.5±0.9 (24.22)	12.5±0.5 (26.88)	18.4±0.5 (35.66)	24.5±0.5 (46.14)
5q	0.69±0.1	8.2±0.2 (78.8)	12.8±1.5 (48.3)	17.8±0.1 (50.1)	3.8±0.2 (12.38)	5.1±0.5 (16.04)	7.1±0.4 (20.23)	8.2±0.7 (17.63)	12.8±0.1 (24.81)	15.6±1.0 (29.38)
5r	0.72±0.1	7.5±0.5 (72.1)	10.0±1.0 (37.7)	18.7±0.3 (47.6)	1.4±0.5 (4.56)	2.8±0.1 (8.81)	3.5±0.5 (9.97)	5.7±0.4 (12.26)	10±0.8 (19.38)	16.2±0.2 (30.51)
5s	0.78±0.5	7.5±0.6 (72.1)	11.5±0.3 (43.4)	22.5±0.5 (37.0)	2.7±0.8 (8.79)	3.6±0.4 (11.32)	4.5±0.5 (12.82)	6.4±0.2 (13.76)	11.5±0.5 (22.29)	18.5±0.5 (34.84)

(Table 2) contd….

Comp. No.	UI	Carrageenan Induced			Egg Albumin Induced					
		Swelling in Thickness [x 10^{-2}mm]^{a} (% Inhibition) **at Different Time Interval**								
	TI	**0.5 h**	**1.5 h**	**3.5 h**	**30 min**	**60 min**	**90 min**	**120 min**	**150 min**	**180 min**
5t	0.24±0.4	5.9±1.0 (56.7)	10.8±0.1 (40.8)	23.9±0.8 (33.1)	1.5±0.6 (4.89)	5.8±0.1 (18.24)	6.2±0.1 (17.66)	7.5±0.5 (16.13)	10.8±1.0 (20.93)	20.4±0.7 (38.42)
5u	0.56±0.1	5.4±0.3 (51.9)	12.5±0.7 (47.2)	20.2±0.6 (43.4)	1.2±0.8 (3.91)	3.6±0.4 (11.32)	5.8±0.5 (16.52)	9.2±0.9 (19.78)	11.5±0.4 (22.29)	17.3±0.5 (32.58)
Cntrl	1.1± 0.1	10.4±0.96	26.5±0.96	35.7 ± 1.1	30.7± 0.96	30.7±0.96	31.8 ±1.1	30.7± 0.96	30.7±0.9	31.8 ± 1.1
Std*	2.4± 1.1	8.2±1.2 (78.8)	16.2(61.1)	21.4±1.4 (40.1)	4.99±0.1 (16.25)	5.27±0.1 (16.57)	5.53±0.2 (16.43)	5.76±0.2 (24.30)	3.93±0.1 (25.58)	3.25± 0.1 (30.51)

*Indomethacin Number of animals used, n=6, Dose 50 mg/Kg body weight, Values are given in mean±SD (% inhibition). Percent inhibition is calculated using formula: Paw edema volume control-sample/control. All the test compounds are significant at $P < 0.001$ from the control. (Two way ANOVA followed by Bonferronipost test).

compounds (**5b**, **5g**, **5l**, **5s** and **5u**) possessed a good reduction of rat paw edema in both tests when compared with indomethacin as a standard drug, Since the inflammation is peripheral phenomena affected by synthesized compounds suggests its peripheral utility. The data for anti-inflammatory activity by both methods are summarized in Table **2**.

2.2.2. Analgesic Activity

The analgesic activity represents the effect of compounds on CNS as well as peripheral system were performed on Swiss Albino Mice by Eddy's Hot Plate and Wistar Albino rats by Tail Flick Method. Indomethacin and Tramadol were used in these methods for comparison. In the first method, the jumping and paw licking was noted at regular interval whereas the second one is about the measurement of tail flicking latency followed by percentage inhibition in analgesic activity was calculated. Out of twenty-one compounds, eleven (***5-a, b, c, d, f, h, l, o, p, q*** and ***s***) exhibited better activity and remaining derivatives showed good activity except for compound ***5-t*** when compared to standard drug using both methods, This exciting result elicits the distribution and action of our compounds on both systems. The results of analgesic activity are given in Table **3**.

2.2.3. COX-2 Inhibition Study

The compounds that displayed a better correlation with *in vivo* activity were further studied for *in vitro* selective COX-2 inhibition assay. Celecoxib being a selective inhibitor was used as a standard drug at a concentration of 1 μM. The results of the active compounds (Table **4**) showed moderate activity at a dose of 10, *20* and *50* μM. COX-2 inhibition activity of compound ***5d***, ***5k*** and ***5m*** was found to be fairly high as compared to others possibly through additional hydrogen bonding which increases binding affinity towards the isoenzyme.

2.3. Molecular Docking Studies

2.3.1. Docking Study

To study the interaction between ligands and COX-II receptor molecular docking was studied, the dock score was compared between various interactions. Biopredicta provides with hydrogen bonding, hydrophobic and Van der Wall interactions, results of specific ligand-receptor interaction are exhibited in Fig. (**3 a-f**) and Table **5**. Compound **5c** interacts with residues TYR359D, GLN360C and PRO113C by forming and hydrogen bond and exhibits a dock score of -2.2741, **5d** interacts with SER527D with a score of -1.6743, compound **5i** showed similar interactions but with SER327D at a score of -2.9175. The compound **5k** presented hydrogen bonding with GLN360D, ARG362C, **5n** forms a short distance hydrogen bond with SER129C with a dock score of -2.4532. Compound **5o** and **5r** interact with PRO113C and SER129C with dock score of -2.5328 and -2.5349 respectively. Compound **5t** exhibited only hydrogen bonding with ARG362 and a low dock score of -0.0239 however it exhibits a number of hydrophobic and Van der Waals interactions.

Table 3. Analgesic activity of 2-(morpholin-4-yl)-*N*-phenyl-quinazolin-4-amine derivatives.

Comp. No.	Hot Plate Method			Tail Flick Method		
	Latency in Seconds [Mean ± SE (% Inhibition of Analgesia)]					
Time Interval	0.5h	1.5h	3.0h	0.5h	1.5h	3.0h
5a	5.70±0.56 (35.44)	7.08±0.15 (40.11)	11.50±0.53 (46.26)	6.69±1.78 (37.52)	7.67±1.98 (40.29)	10.22±1.57 (38.65)
5b	4.43±0.43 (16.93)	5.41±0.19 (21.63)	7.36±0.89 (16.03)	8.98±1.25 (53.45)	9.68±1.75 (52.69)	10.51±151 (40.34)
5c	5.11±0.28 (27.98)	6.57±0.23 (35.46)	9.95±0.19 (37.89)	7.67±1.23 (45.50)	8.76±1.47 (47.72)	9.68±1.03 (35.23)
5d	4.97±0.75 (25.96)	6.03±0.79 (29.68)	9.36±0.24 (33.97)	6.69±1.54 (37.52)	8.76±1.54 (47.72)	9.68±0.98 (35.23)
5e	7.08±0.36 (48.02)	8.76±0.83 (51.60)	9.95±0.51 (37.89)	6.81±1.78 (38.62)	7.67±1.98 (40.29)	8.76±1.01 (28.42)
5f	5.94±0.52 (38.05)	8.00±0.19 (47.00)	12.27±0.85(49. 63)	8.98±1.45 (53.45)	10.22±1.22 (55.19)	11.87±1.50 (47.18)
5g	5.11±0.15 (27.98)	5.58±0.23 (24.01)	6.57±0.46 (5.94)	5.75±0.87 (27.30)	6.34±1.27 (27.76)	8.76±0.27 (28.42)
5h	7.22±0.46 (49.03)	8.76±0.27 (51.60)	13.14±0.75(52. 97)	7.67±1.54 (45.50)	9.20±0.50 (50.22)	10.82±1.04 (42.05)
5i	4.33±0.2 (15.01)4	6.69±0.57 (36.62)	8.00±0.68 (22.75)	5.94±1.52 (29.63)	6.57±1.40 (30.29)	7.67±1.22 (18.25)
5j	5.41±0.16 (31.98)	8.56±0.69 (50.47)	11.50±0.43(46. 26)	6.69±1.23 (37.52)	7.08±1.00 (35.31)	8.36±1.98 (25.00)
5k	4.72±0.38 (22.03)	5.04±0.81 (15.87)	8.36±0.29 (26.08)	5.66±1.59 (26.15)	6.57±1.02 (30.29)	9.20±0.74 (31.85)
5l	6.13±0.84 (39.97)	7.67±0.74 (44.72)	16.00±0.47(61. 38)	8.18±1.08 (48.90)	9.20±1.00 (50.22)	13.14±0.82 (52.28)
5m	4.91±0.56 (25.05)	5.58±0.15 (24.01)	7.08±0.53 (12.71)	7.08±1.42 (40.96)	8.00±1.42 (42.75)	9.60±1.62 (34.69)
5n	4.43±0.43 (16.93)	5.18±0.19 (18.15)	7.08±0.89 (12.71)	5.66±1.02 (26.15)	6.46±1.92 (29.10)	7.36±1.35 (14.81)
5o	5.11±0.28 (27.98)	8.18±0.23 (48.17)	9.20±0.19 (32.83)	5.75±1.05 (27.30)	6.46±0.50 (29.10)	8.36±1.75 (25.00)
5p	4.66±0.75 (21.03)	7.22±0.79 (41.27)	12.69±0.24 (51.30)	5.58±1.71 (25.09)	6.24±1.60 (26.60)	7.36±1.15 (14.81)
5q	4.38±0.36 (15.98)	4.66±0.83 (9.01)	7.08±0.51 (12.71)	6.69±0.90 (37.52)	8.56±1.41 (46.47)	9.95±1.25 (36.98)
5r	4.38±0.52 (15.98)	6.03±0.19 (29.68)	9.20±0.85 (32.83)	5.66±0.94 (26.15)	6.69±25 (31.54)	9.20±0.50 (31.85)
5s	5.11±0.1 (27.98)5	7.83±0.23 (45.85)	14.72±0.46 (58.02)	6.34±0.13 (34.07)	7.08±0.75 (35.31)	9.68±1.29 (35.23)

(Table 3) contd….

Comp. No.	Hot Plate Method			Tail Flick Method		
	Latency in Seconds [Mean ± SE (% Inhibition of Analgesia)]					
Time Interval	**0.5h**	**1.5h**	**3.0h**	**0.5h**	**1.5h**	**3.0h**
5t	4.28±0.46 (14.02)	5.26±0.27 (19.39)	6.81±0.75 (9.25)	5.84±1.65 (28.42)	6.69±1.87 (31.54)	8.84±1.20 (29.07)
5u	4.13±0.24 (10.90)	5.66±0.57 (25.09)	7.83±0.68 (21.07)	7.08±1.89 (40.96)	7.67±1.25 (40.29)	10.51±1.24 (40.34)
Control	3.68±0.21	4.24±0.98	6.18±0.42	4.18±0.33	4.58±0.23	6.27±0.45
Standard	4.91±0.93 (25.05)	8.76±0.34 (51.60)	10.22±0.25 (39.53)	7.08±1.23 (40.96)	7.67±1.06 (40.29)	9.20±1.64 (31.85)

Note: Tramadol (30mg/Kg) used as a standard. Number of animals used, n=6, Dose 50 mg/Kg for test compounds. All the test compounds are significant at $P < 0.001$. (Two way ANOVA followed by Bonferroni post test).

Table 4. COX-2 inhibition study of selective synthesized compound from *5*(*a-u*).

Comp. No.	*COX-2 Inhibition ± SD(%) at concentration of		
	10μM	**20μM**	**50μM**
5d	52.2±0.5	68.2±0.8	72.2±1.2
5e	22.2±1.3	29.5±1.0	38.7±0.5
5f	16.2±0.6	28.8±0.2	42.2±0.8
5h	21.1±0.3	36.8±1.2	48.2±0.5
5i	18.2±0.9	29.3±1.6	41.2±0.9
5k	32.2±1.4	53.6±0.5	64±0.9
5n	ns	13.1±1.1	19.1±0.5
5m	36.2±0.7	41.7±1.4	69.5±0.7
5p	25.2±1.0	31.5±0.9	46.5±0.4
5s	25.8±0.8	43.6±0.5	54±0.6
Celecoxib	80.1±2.7 at a concentration of 1 μM		

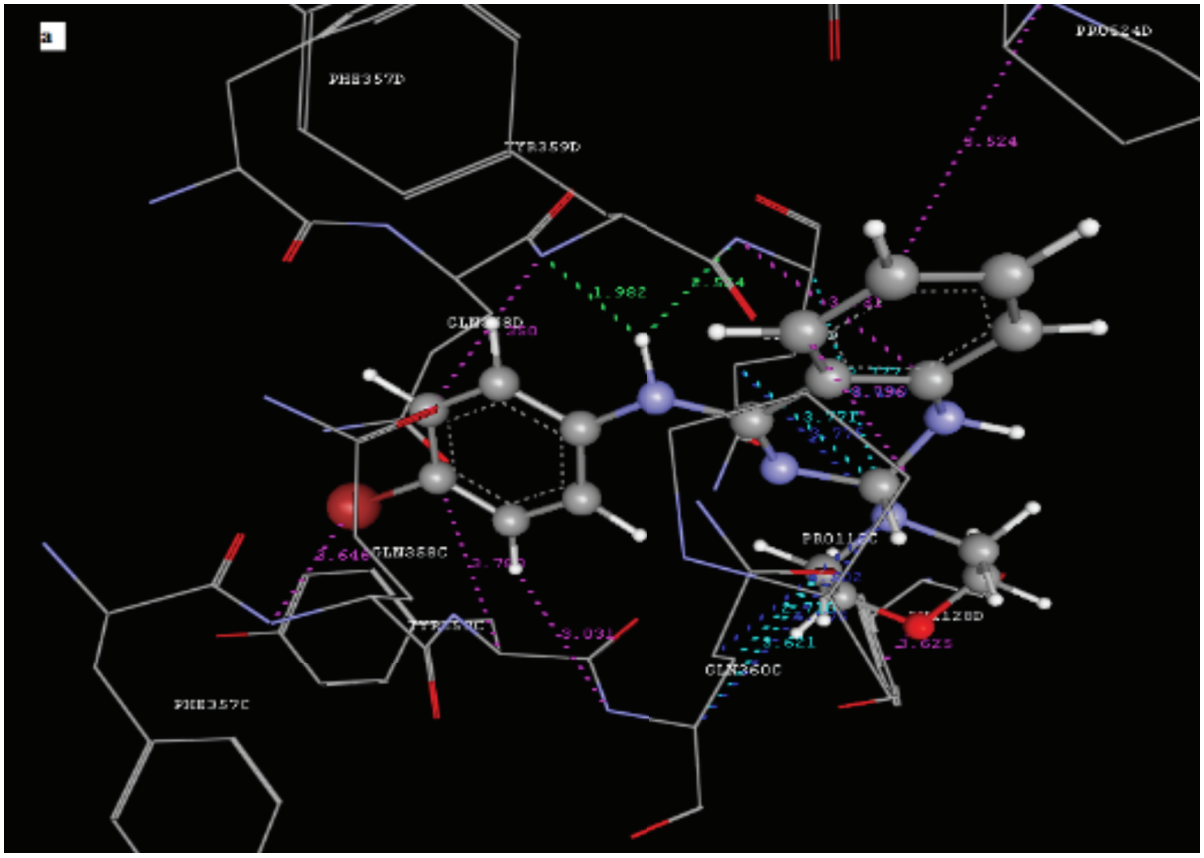
*Inhibition values are mean (n=3) ± Standard Deviation, ns = not significant *i.e*., inhibition below 10%.

2.3.2. 3D-QSAR Study

The three-dimensional quantitative structure activity relationship studies are useful in identifying and understanding the positional importance for the arrangement of pharmacophoric group in a structure of synthesized compounds explaining its behavior under *in vivo* or *in vitro* conditions. Thus, it helps to obtain a thoughtful mechanism of action of the title compound and can be useful in the development of newer potent analogues. The 3D QSAR study was done by obtained anti-inflammatory data of title compounds using various methods. The statistically significant results are achieved by multiple linear and partial least square regression methods and thus considered for further discussion. The actual and predicted anti-inflammatory data of the title compounds in the form of ED_{50} values are represented in Table **6** and the comparison between them is given in Table **7**.

2.3.3. Linear Regression Analysis Models

The 3D-QSAR models were generated using stepwise forward-backward multiple linear regressions (MLR_SWFB) (Model-1) and stepwise forward backward partial least square regression (PLSR_SWFB) (Model-2) methods:



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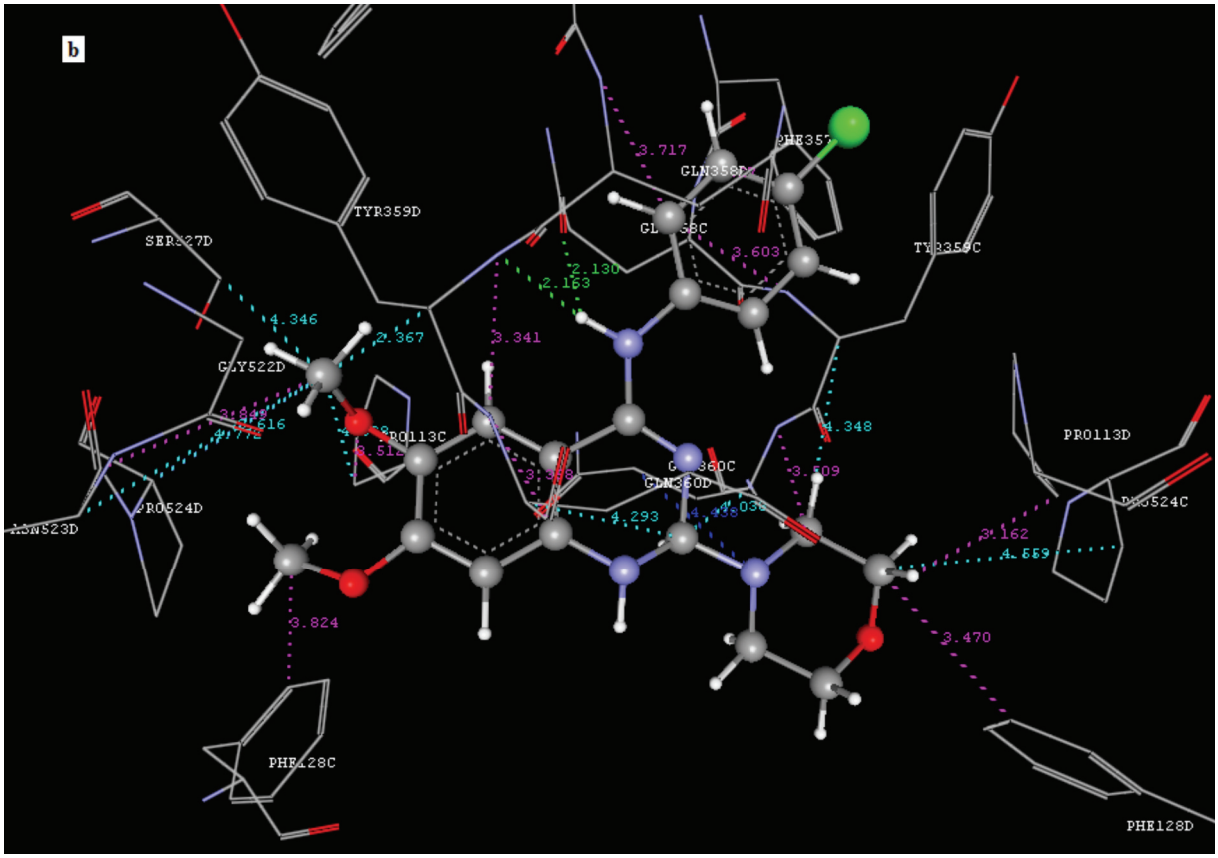

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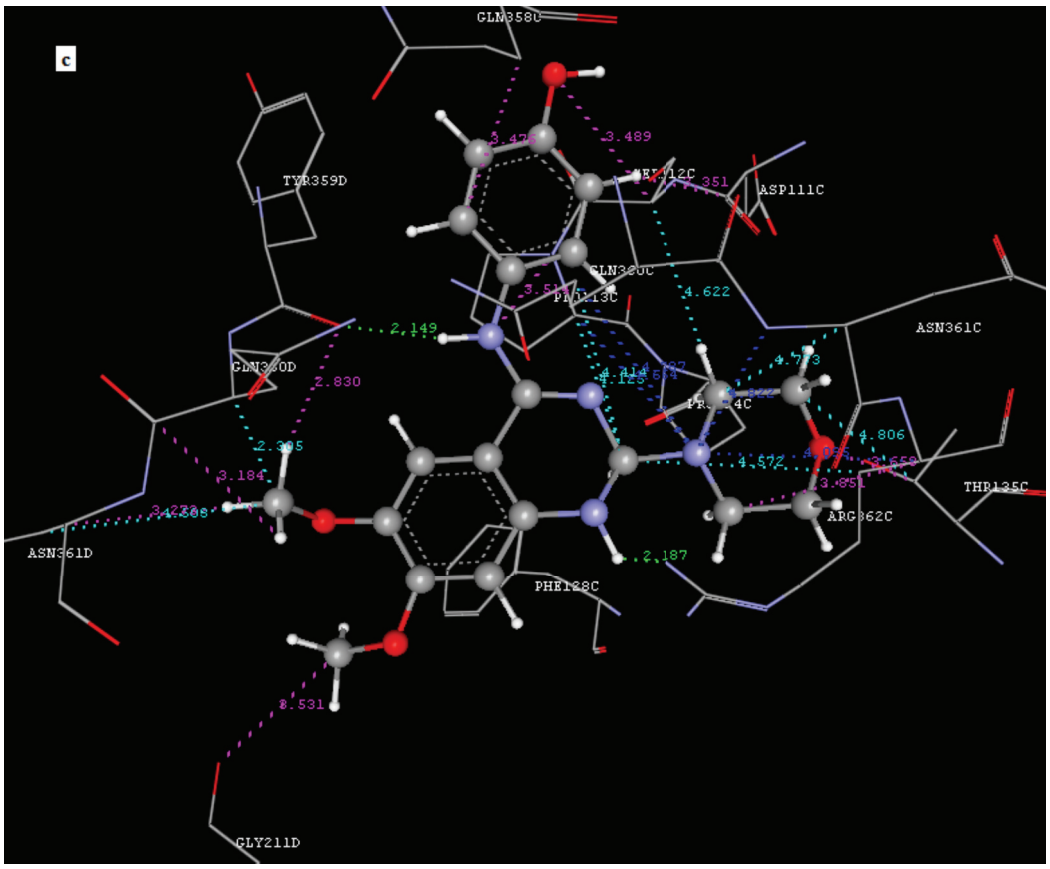
Fig. (3) contd…



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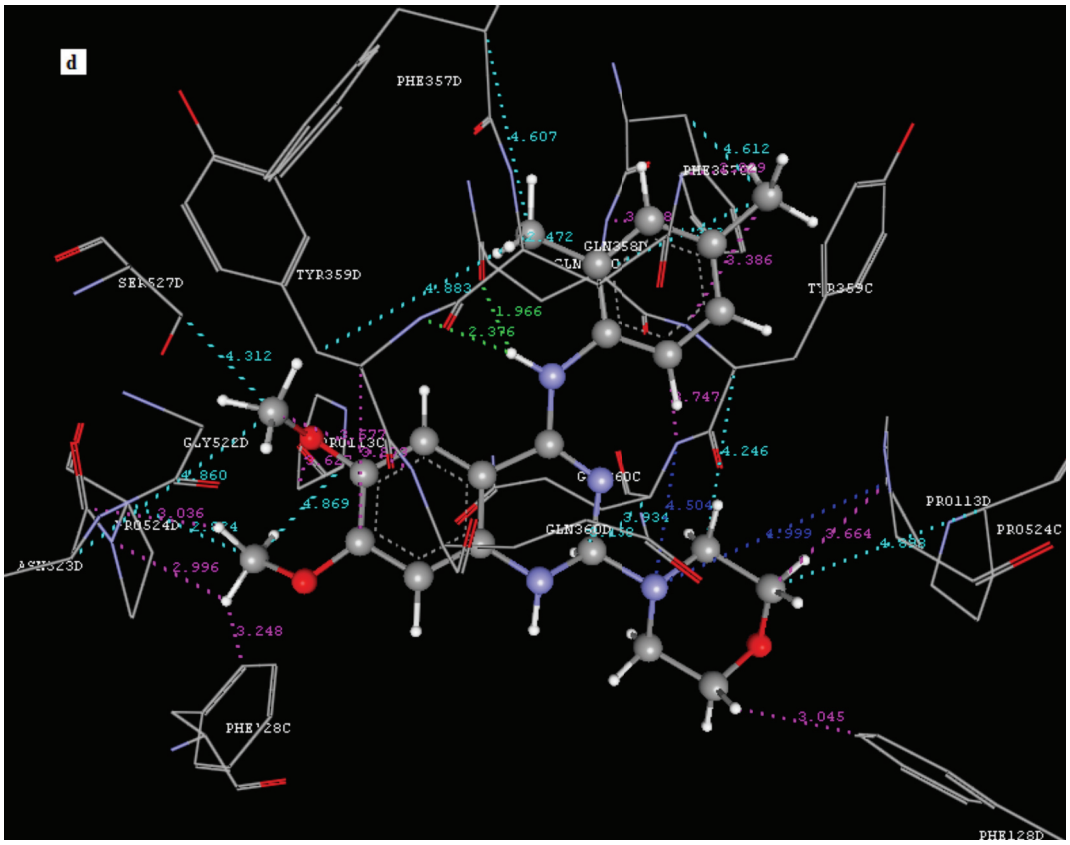
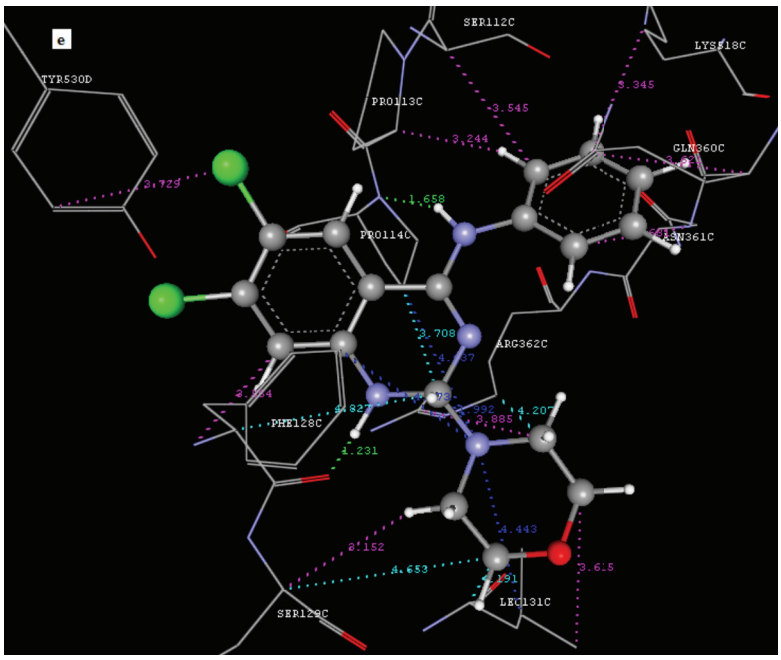
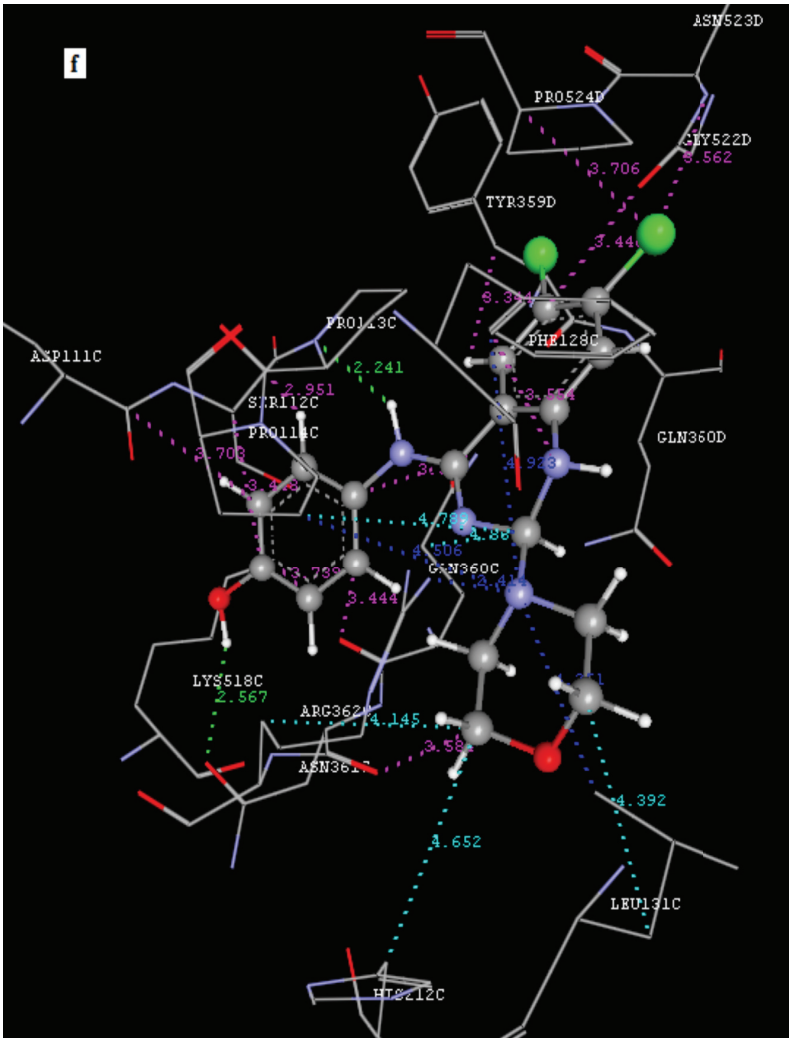


d

Fig. (3) contd…



e



f

Fig. (3a-f). Molecular docking poses of synthesized compounds **5d**, **5k**, **5n**, **5o**, **5r** and **5t** on the COX-II receptor.

Table 5. V-life Sciences MDS: Biopredicta module generated, amino acid residues which form hydrogen bonds and length of hydrogen bond (A) with ligand for compounds and receptor 3LN1.

S. No.	Compound No.	Dockscore	Amino Acid Residues which form Hydrogen Bonds with Ligand	Length of Hydrogen Bond (A)
1	**5a**	-1.3464	PRO113C: 9710N- 30H	2.458
2	**5c**	-2.2741	TYR359D: 16210N- 31H	1.982
			GLN360D: 16222N- 31H	2.524
3	**5d**	-1.6743	SER527D: 17571O- 44H	2.487
4	**5i**	-2.9175	GLN358C: 1734O- 33H	2.130
			TYR359D: 16210N- 33H	2.163
5	**5k**	-2.0034	ARG362C: 11774N- 32H	2.187
			TYR359D: 1621O-33H	2.149
6	**5l**	-1.6756	SER112C: 9709O- 33H	2.096
7	**5m**	-1.2398	PRO113C: 9710N- 33H	2.045
8	**5n**	-2.4532	GLN358C: 11734O-34H	1.966
			TYR359D: 16210N- 34H	2.376
9	**5o**	-2.5328	PRO114C: 9717N- 3OH	1.658
			PHE128C: 9842O- 29H	1.231
10	**5q**	-2.1427	TYR359D: 16213O- 31H	2.061
11	**5r**	-2.5349	PRO113C: 9710N- 31H	2.241
			ASN361C: 11763O- 44H	2.567
12	**5s**	-1.0241	SER112C: 9709O- 31H	2.234
13	**5t**	-0.0239	ARG362C: 11772N- 30H	1.992
			ARG362C: 11775N- 30H	2.029

Table 6. The actual and predicted anti-inflammation data of 2-(morpholin-4-yl)-*N*-phenylquinazolin-4-amine derivatives.

Comp. No.	R	R1	Actual ED_{50}	Predicted ED_{50}	
				MLR (SWFB)	PLSR (SWFB)
5a	H	H	0.6476	1.8984***	1.8963
5b	H	*p*-Cl	0.5727	1.7026	1.7060
5c	H	*p*-Br	0.6810	1.8935	1.8915***
5d	H	*p*-OH	0.5318	0.5600***	0.5510
5e	H	*p*-OCH_3	0.5612	1.9020	1.8998
5f	H	*p*-CH_3	0.5557	1.8955	1.8935
5g	H	o, *p*-di CH_3	0.5825	1.7389	1.7412***

(Table 6) contd….

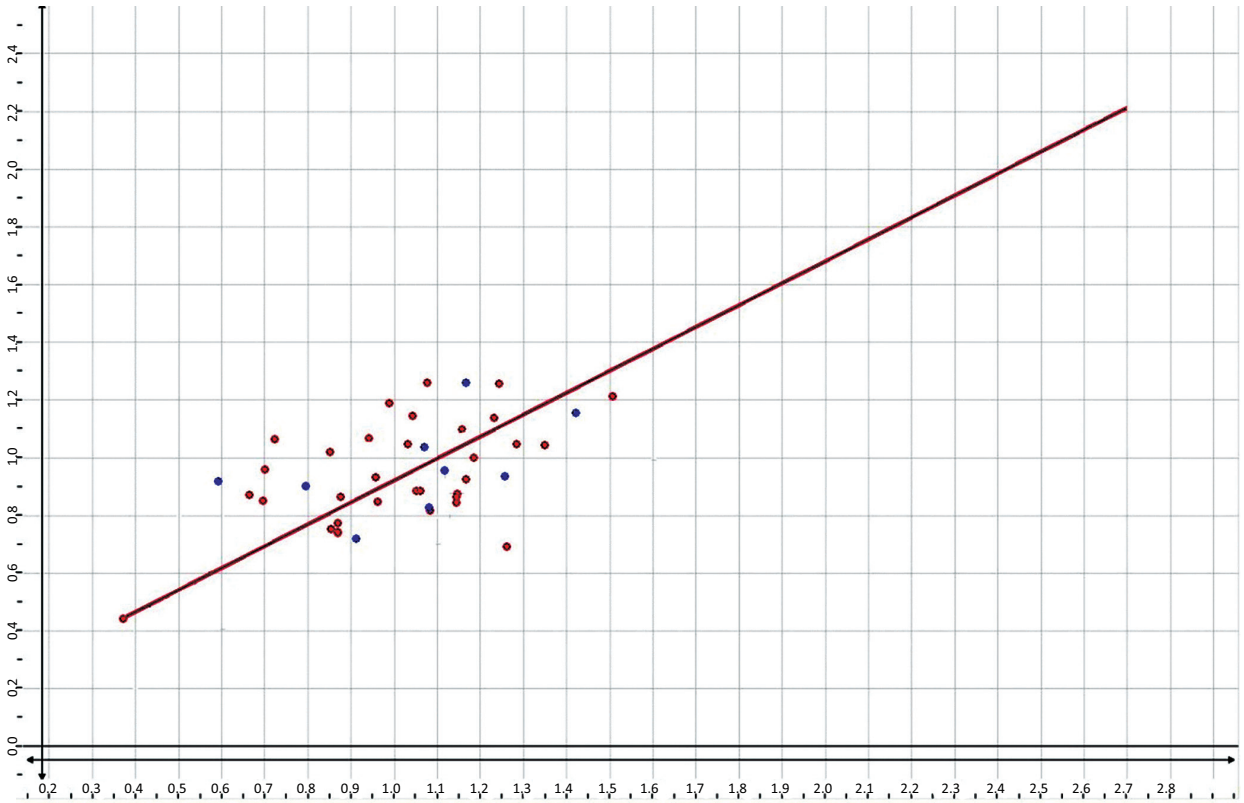
Comp. No.	R	R1	Actual ED_{50}	Predicted ED_{50}	
				MLR (SWFB)	PLSR (SWFB)
5h	6, 8-di Cl	H	0.5189	1.8635	1.8623
5i	6, 8-di Cl	*p*-Cl	0.5341	1.8986	1.8965
5j	6, 8-di Cl	*p*-Br	0.5916	1.7016	1.7050***
5k	6, 8-di Cl	*p*-OH	0.5534	2.0514	2.0498
5l	6, 8-di Cl	*p*-OCH_3	0.5692	1.4424	1.4531***
5m	6, 8-di Cl	*p*-CH_3	0.5253	1.8944	1.8924
5n	6, 8-di Cl	o, *p*-di CH_3	0.5414	1.8931	1.8912
5o	6, 8-di Br	H	0.5916	1.9250	1.9231
5p	6, 8-di Br	*p*-Cl	0.5274	1.8946	1.8926
5q	6, 8-di Br	*p*-Br	0.5890	2.7655***	1.7661
5r	6, 8-di Br	*p*-OH	0.5817	1.8934	1.8914
5s	6, 8-di Br	*p*-OCH_3	0.5557	1.6473	1.6522
5t	6, 8-di Br	*p*-CH_3	0.5477	1.4434***	1.4540
5u	6, 8-di Br	o, *p*-di CH_3	0.5706	1.8960	1.8940

***Test set molecules (using random selection method); MLR_SWFB: Stepwise forward-backward multiple linear regression method; PLSR_SWFB: Stepwise forward-backward partial least square regression method.

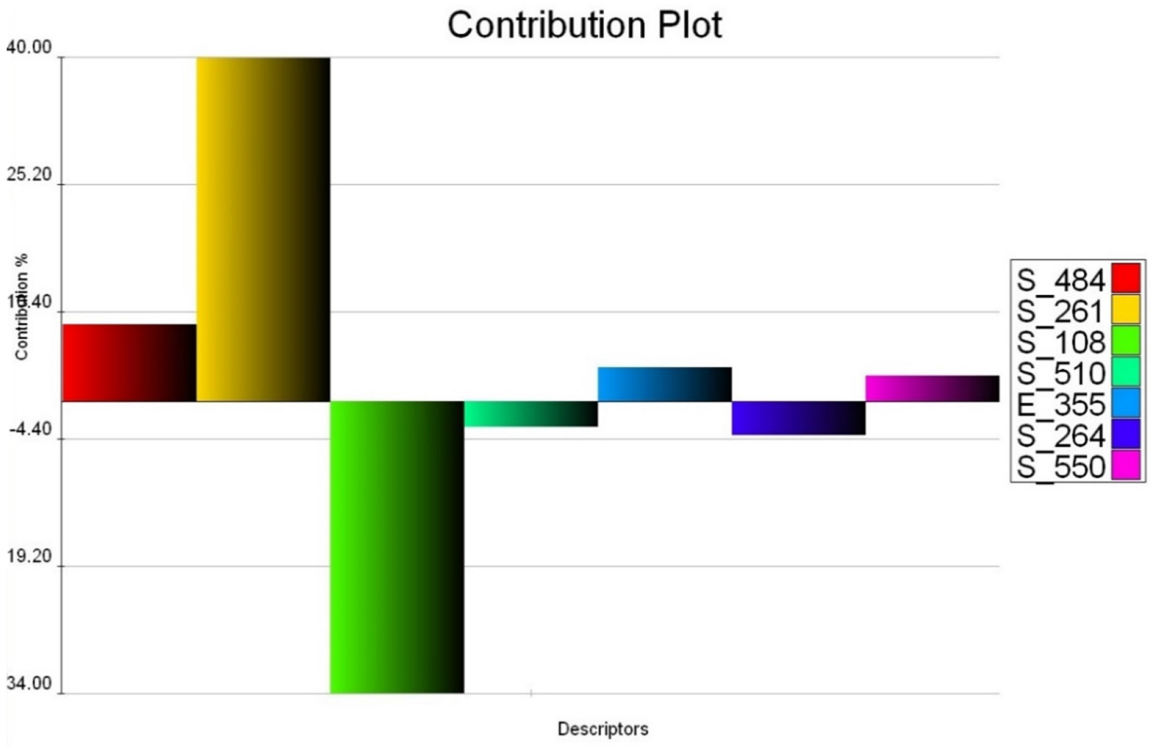
Table 7. Comparative results of statistical analysis generated by 3D QSAR method.

Statistical Parameter	Model 1 - MLR (SWFB)	Model 2 - PLSR (SWFB) (4)
n (Training/Test)	17/4	17/4
D	13	16
r^2	0.9365	0.7910
q^2	0.7282	0.4885
F-test	67.40	38.18
r^2se	0.7337	0.4694
q^2se	0.6970	0.6926
Pred r^2	0.7146	0.9694
`Pred r^2se	0.8817	0.8255
Descriptor	S_484 (9.09) S_261 (40.24) S_108 (-34.68) S_510 (-3.76) E_355 (4.58) S_264 (-4.15) S_550 (3.51)	S_577 (36.68) S_605 (23.64) S_596 (22.98) E_190 (16.71)

MLR_SWFB:= Stepwise forward-backward multiple linear regression method; PLSR_SWFB= Stepwise forward-backward partial least square; n= number of training set molecules; D= degree of freedom; r^2 = correlation coefficient; q^2 = test set prediction (crossed validated r^2); pred_r^2 = r^2 for external test set; pred_r^2 se = correlation coefficient of predicted data set.



A: Actual vs Predicted activity graph



B: Contribution Plot

Fig. (4). 3D-QSAR study of 2-(Morpholin-4-yl)-N-phenylquinazolin-4-amine derivatives (***5a-u***).

The most statistically significant MLR_SWFB model exhibited correlation coefficient (r^2) of 0.9365, cross validated correlation coefficient (q^2) of 0.7282, F test of 67.40, r^2 for external test set(pred_r^2) 0.7337, coefficient of correlation for predicted data set (pred_r^2 se) of 0.7146. The fitness plot of actual *vs* predicted activity and the plot of various contributing parameters is shown in Fig. (**4**). PLSR_SWFB model showed correlation coefficient (r^2) of 0.7910, cross validated correlation coefficient (q^2) of 0.0.4885, F test of 67.40, r^2se 0.4694for external test set (pred_r^2) of 0.6926 and 0.8255 Pred r^2se. Following are the models generated found significant during 3D QSAR study by using different methods.

2.3.4. Model-1

pED_{50} = 0.9854 + 16.2030 (S_484) + 10.2030 (S_261) - 6.2030 (S_108) - 16.2030 (S_510)+ 12.2030 (E_355) - 10.2030 (S_264) + 18.2030 (S_550)

2.3.5. Model-2

pED_{50} = 10.8884 + 9.2030 (S_577) + 18.2565 (S_605) +12.5486 (S_596) + 8.2030 (E_190)

The **Model-1** exhibited better internal and external predictions, so it was considered for further discussions and explanations of SAR. The data set was subjected under stepwise multiple linear regression methods to generate selected model which includes the contribution of six steric and one electronic parameter. Its fitness plots of actual versus predicted activities (pED$_{50}$) for above mentioned model are shown in Fig. (**4a**). This model highlighted the steric properties which usually explains the stability of molecule based on their spatial arrangement of substituents as well as also play an important role in receptors studies thus found to be important structural property of interest, this parameter in above said model was found to be balancing the molecular structure of the compound, such as S_484 and S_550 as in compound **5a, 5c** and **5d** suggest the substitution of relatively smaller groups at second and fourth positions of phenyl group which are also adjacent to the heteroatoms, S_261 suggests the substitution of activating group to 6th and 8th position of quinazoline ring, bulkier as in compound **5l, 5r** and **5s** may also affect the activity. Seventh position of quinazoline and third on of N-aryl group are susceptible to bulkier group substitution suggested by negative values of S_108 and S_510 respectively. The nitrogen on fourth position of parent moiety may be further substituted and converted from secondary to tertiary however attachment of longer aliphatic group may produce the adverse effect on anti-inflammatory activity. The Fig. (**4b**) illustrates the contribution of various parameters in elucidating anti-inflammatory activity. Compounds **5a**, **5d**, **5h**, **5m**, **5p** and **5s** were found possess better analgesic and anti-inflammatory agent when subjected to several couple of models for both activities. Most active compound with respect to various described parameters are depicted in Fig. (**3d**).

3. EXPERIMENTAL PROCEDURES

3.1. Chemistry

The chemicals used in the present work were of AR and LR grade, purchased from Loba, Merck and Fisher scientific fine chemicals. Synthesized compounds were scaled for good yield and purified by recrystallization with suitable solvent system. Purified compounds were assigned for physical constant determination was carried out by open capillary method using LABHOSP melting point apparatus and recorded without correction. The structures were further confirmed by elemental (C,H,N) and spectral analysis like Infrared spectroscopy, Nuclear Magnetic Resonance Spectroscopy and Mass Spectroscopy. The schematic representation of preparation for title compound was highlighted in Fig. (**2**) and general procedures are as follows:

3.2. General Synthetic Procedure

3.2.1. Synthesis of 4-Morpholinyl Carboxamide (2)

The mixture of morpholine (8.7g, 0.1 mol) and urea (6.0g, 0.1 mol) was heated under nitrogen atmosphere for 1.5h. to yield a 4-morpholinyl carboxamide. It was further recrystallized with ethanol to remove the impurity or unreacted product present. Yield (%):83; mp(°C): 184-185; R_f: 0.68, IR (KBr)cm^{-1}:1660(C=O), 3536 (N-H), 1104 (C-O-C); ^{1}HNMR ($CDCl_3$) δppm: 4.5 (s, 2H, NH_2), 1.88-4.5(m, 8H, 1,4-oxazinane); MS (m/z): 130.1;

Found(%): C 45.79, H 7.53, N 21.56, MF: $C_5H_{10}N_2O_2$, Calculated(%): C 46.14, H 7.74, N 21.56.

3.2.2. Synthesis of 2-(Morpholin-4-yl)quinazolin-4(3H)-one (3a-c)

A mixture of various derivatives of 2-aminobenzoic acid (**1 a-c**) (13.7g, 0.1 mol) with compound **2** (13.0g, 0.1 mol) was refluxed in ethanol for approx. 1.5 h and cooled. The resultant mixture was treated with aqueous solution of sodium bicarbonate in order to dissolve the unreacted acid, which could be ensured by cessation of carbon dioxide effervescence. The solid separated was washed with water, dried and recrystallized with ethanol as a white crystalline mass. **3a**: Yield (%): 64; m.p. (°C): 204-206; R_f: 0.77, IR (KBr) cm^{-1}:1600(C=C), 1632 (C=N),1730 (C=O), 1340 (tert. C-N), 1109 (C-O-C); ^{1}HNMR ($CDCl_3$) δppm: 7.79-7.96(q, 4H Ar-H of quinazoline), 1.58-3.92(m, 8H, 1,4-oxazinane); MS (m/z): 231.2; Anal. Calcd. C 62.33, H 5.67, N 18.17, O 13.84, found. C 61.46, H 5.29, N 18.14, O 14.12.

3.2.2.1. 3b: 6, 7-dichloro-2-(morpholin-4-yl) quinazolin-4(3H)-one

Yield (%): 52; m.p. (°C): 234-236; R_f : 0.80, IR (KBr) cm^{-1}:1580(C=C), 1640 (C=N), 1705 (C=O), 1350 (tert. C-N), 639 (C-Cl), 1100 (C-O-C); ^{1}HNMR ($CDCl_3$) δppm: 7.79-8.12(d, 2H Ar-H of quinazoline, J=4.02), 1.88-4.50(m, 8H, 1,4-oxazinane); MS (m/z): 300.1; Anal. Calcd. C 48.20, H 3.69, Cl 23.62, N 14.0, O 10.66, found. C 48.01, H 3.74, Cl 23.22, N 13.98, O 10.52.

3.2.2.2. 3c: 6, 7-dibromo-2-(morpholin-4-yl) quinazolin-4(3H)-one

Yield (%): 62; m.p. (°C): 204-206; R_f : 0.77, IR (KBr) cm^{-1}:1600(C=C), 1659 (C=N),1710 (C=O), 1312 (tert. C-N), 516 (C-Br), 1121 (C-O-C); ^{1}HNMR ($CDCl_3$) δppm: 7.89-8.10(d, 2H Ar-H of quinazoline, J=3.89), 1.90-5.20(m, 8H, 1,4-oxazinane); MS (m/z): 389.0; Anal. Calcd. C 37.05, H 2.85, Br 41.08, N 10.80, O 8.23, found. C 37.18, H 2.82, Br 40.85, N 10.50, O 8.35.

3.2.3. Synthesis of 4-chloro-2-(morpholin-4-yl)-3,4-dihydroquinazoline(4a-c)

The equimolar quantity of **3a-c** (0.0647 mol, 15.0g)**,** N, N-dimethylaniline and phosphorous pentachloride were taken in dry benzene and refluxed in for 3 h. The reaction mixture was then cooled and filtered. The filtrate was diluted with benzene(30ml) then washed with 20% sodium hydroxide solution finally with water and dried over magnesium sulphate, the final organic layer get evaporated. The final product was recrystallized in heptane. **4a:** Yield (%): 49; m.p. (°C): 222-224; R_f : 0.72, IR (KBr) cm^{-1}: 1625(C=C), 1602 (C=N), 619 (C-Cl), 1340 (tert. C-N), 1109 (C-O-C); ^{1}HNMR ($CDCl_3$) δppm: 7.50-7.96(q, 4H Ar-H of quinazoline), 1.98-5.0(m, 8H, 1,4-oxazinane); MS (m/z): 251.7; Anal. Calcd. C 57.26, H 5.61, Cl 14.08, N 16.69, O 6.36, found. C 57.20, H 5.60, Cl 13.80, N 16.56, O 6.32.

3.2.3.1. 4b: 4,6,7-Trichloro-2-(morpholin-4-yl)-3,4-dihydroquinazoline

Yield (%): 52; m.p. (°C): 248-250; R_f : 0.78, IR (KBr) cm^{-1}:1630(C=C), 1570 (C=N), 1345 (tert. C-N), 682 (C-Cl), 1121 (C-O-C); ^{1}HNMR ($CDCl_3$) δppm: 7.46-7.86(d, 2H Ar-H of quinazoline, J=4.89), 1.88-4.50(m, 8H, 1,4-oxazinane); MS (m/z): 320.6; Anal. Calcd. C 44.96, H 3.77, Cl 33.17, N 13.11, O 4.99, found. C 48.01, H 3.74, Cl 33.50, N 13.23, O 5.20.

3.2.3.2. 4c: 6,7-Dibromo-4-chloro-2-(morpholin-4-yl)-3,4-dihydroquinazoline

Yield (%): 64; m.p. (°C): 204-206; R_f : 0.77, IR (KBr) cm^{-1}:1580(C=C), 1614 (C=N), 1320 (tert. C-N), 604 (C-Br), 1132 (C-O-C); ^{1}HNMR ($CDCl_3$) δppm: 7.80-8.15(d, 2H Ar-H of quinazoline, J=4.56), 1.65-4.55(m, 8H, 1,4-oxazinane); MS (m/z): 409.5; Anal. Calcd. C 35.20, H 2.95, Br 39.02, Cl 8.66, N 10.26, O 3.91, found. C 35.18, H 2.98, Br 39.10, Cl 8.60, N 10.24, O 4.10.

3.2.4. Synthesis of N,2-Diphenylquinazolin-4-amine Derivative (5a-u)

A mixture of **4a-c** (12.0g, 0.05mol) and substituted anilines (0.05mol) was taken in 95% ethanol and refluxed for approx. 1.5 to 3.0 h. The reaction mixture was poured in a blend of 100 ml ice cold water with 20 ml of concentrated hydrochloric acid followed by vigorous continuous stirring gave pale white colored precipitate. Solvent methanol was used for recrystallization. The physical characterization, elemental and spectral analysis data of the synthesized compounds were given below.

3.2.4.1. 5a: 2-(Morpholin-4-yl)-N-phenylquinazolin-4-amine

Yield (%): 78; m.p. (°C): 188-190; R_f : 0.66, IR (KBr) cm^{-1}:1610(C=C), 1640 (C=N), 3480 (N-H), 1324 (tert. C-N), 1245 (C-O-C); ^{1}HNMR ($CDCl_3$) δppm: 7.1(q, 4H Ar-H of quinazoline), 4.0(NH), 2.9-3.67(m, 8H, 1,4-oxazinane); MS (m/z):[M^+] 308.7; Anal. Calcd. C 70.11, H 6.54, N 18.17, O 5.19, found. C 70.30, H 6.58, N 18.14, O 5.25.

3.2.4.2. 5b: N-(4-Chlorophenyl)-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-amine

Yield (%): 72; m.p. (°C): 220-222; R_f : 0.79, IR (KBr) cm^{-1}:1590(C=C), 1660 (C=N), 3500 (N-H), 1340 (tert. C-N), 640 (C-Cl) 1230 (C-O-C); ^{1}HNMR ($CDCl_3$) δppm: 7.3(q, 4H Ar-H of quinazoline), 4.0(NH), 6.37-7.05 (q, 4H, Ar-H), 2.5-3.5(m, 8H, 1,4-oxazinane); MS (m/z):[M^+] 342.8; Anal. Calcd. C 63.6, H 5.59,Cl 10.34, N 16.34, O 4.67, found. C 63.56, H 5.52, Cl 10.40, N 16.38, O 5.02.

3.2.4.3. 5c: N-(4-Bromophenyl)-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-amine

Yield(%):71; m.p. (°C): 188-190; R_f: 0.74; IR(KBr) cm^{-1}: 1459(C=C), 1614 (C=N), 1341 (C-N tertiary), 1114 (C-O), 1612 (N-H), 541 (C-Br); ^{1}HNMR ($CDCl_3$) δppm: 7.1 (q,4H,Ar-H of quinazoline), 2.1 (s, C-N), 4.0 (s, 1H,NH), 6.32-7.21 (q, Ar-H), 2.9-3.67 (m, 8H 1,4-oxazinane); Mass (m/z): 387.3; Anal. Calcd: C 65.82, H 4.5, Br 20.63, N 14.47, O 4.13, found: C 65.75, H 4.87, Br 20.56, N 14.47, O 4.12.

3.2.4.4. 5d: 4-{[2-(Morpholin-4-yl)-3,4-dihydroquinazolin-4-yl]amino}phenol

Yield(%):59; m.p. (°C): 202-204; R_f: 0.80; IR(KBr) cm^{-1}: 1648 (heterocyclic-C=N), 1350 (C-N tertiary), 1164 (C-O, cyclic ether), 1325(C-OH, Ar); ^{1}HNMR ($CDCl_3$) δppm: 5.41 - 6.93 (m, Ar-H), 1.8 (s, NH,) 4.81 (s, Ar C-NH), 6.26-6.51 (q, Ar-H), 2.96-3.67 (q,), 5.0 (s, OH); Mass (m/z): 352.16; Anal. Calcd: C 64.76, H 5.72, N 15.90, O 13.62; found: C 64.12, H 5.96, N 15.23, O 14.01.

3.2.4.5. 5e:N-(4-Methoxyphenyl)-2-(morpholin-4-yl)-3,4-dihydro-quinazolin-4-amine

Yield(%):64; m.p. (°C): 232-234; R_f: 0.68; IR(KBr) cm^{-1}: 1658(C=C), 1607 (C=N), 1382 (C-N), 1115 (C-O), 1563 (N-H), 1248 (OCH_3); ^{1}HNMR ($CDCl_3$) δppm: 5.04 - 7.41 (q, 4H, Ar-H), 2.0 (s, 1H, C-N) 4.0 (s,1H, C-NH), 6.32-6.55 (q, 4H,Ar-H), 3.00 -3.59 (m, 8H 1,4-oxazinane), 3.73 (s, 3H,OCH_3).; Mass (m/z): 338.4; Anal. Calcd: C 67.44 H 6.55 N 16.56 O 9.46, found: C 66.84 H 6.75 N 16.46 O 10.16.

3.2.4.6. 5f: N-(4-Methylphenyl)-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-amine

Yield(%):71 m.p. (°C): 252-254; R_f: 0.73; IR(KBr) cm^{-1}: 1623(C=C), 1587 (C=N), 1342 (C-N), 1095 (C-O), 1576 (N-H), 2950 (CH_3); ^{1}HNMR ($CDCl_3$) δppm: 5.04 - 7.1 (q, 4H Ar-H), 2.0(s, 1H C-N,) 4.0 (s, 1H Ar C-NH), 6.31-6.84 (q, 4HAr-H), 3.12 -3.50 (m, 8H 1,4-oxazinane), 2.35 (s, CH_3).; Mass (m/z): 322.40; Anal. Calcd: C 70.78, H 6.88, N 17.38, O 4.96, found: C 70.64, H 5.01, N 17.20, O 5.41.

3.2.4.7. 5g: N-(2,4-Dimethylphenyl)-2-(morpholin-4-yl)-3,4-dihydro-quinazolin-4-amine

Yield(%):58 m.p. (°C): 225-227; R_f: 0.78; IR(KBr) cm^{-1}: 1601(C=C), 1612 (C=N), 1355 (C-N), 1100 (C-O,), 1576 (N-H), 2946 (CH_3); ^{1}HNMR ($CDCl_3$) δppm: 5.04 - 7.1 (q,4H, Ar-H), 2.0 (s, 1H,C-N) 4.0 (s,1H, C-NH), 6.31-6.84 (q, 4H,Ar-H), 3.12 -3.50 (m, 8H 1,4-oxazinane), 2.35 (s, 3H,CH_3).; Mass (m/z): 336.43 Anal. Calcd: C 71.40, H 7.19, N 16.65 O 4.76, found: C 71.83, H 7.20, N 16.70, O 4.80.

3.2.4.8. 5h: 6,7-Dibromo-2-(morpholin-4-yl)-N-phenylquinazolin-4-amine

Yield(%):68; m.p. (°C): 204-206; R_f: 0.64; IR(KBr) cm^{-1}: 1568(C=C), 1651 (C=N), 1342 (C-N tertiary), 1121 (C-O), 1610 (N-H), 565 (C-Br); ^{1}HNMR ($CDCl_3$) δppm: 7.4-7.5 (d,2H,Ar-H, J=3.89), 3.0 (s, C-N), 5.5 (s, 1H,NH), 6.20-7.50 (q, Ar-H), 3.0-3.80 (m, 8H 1,4-oxazinane); Mass (m/z): 468.12; Anal. Calcd: C 46.38, H 89, Br 34.28, N 12.02, O 3.43, found: C 46.30, H 4.10, Br 34.50, N 12.00, O 3.50.

3.2.4.9. 5i: 6,7-Dibromo-N-(4-chlorophenyl)-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-amine

Yield(%):70; m.p. (°C): 210-212; R_f: 0.78; IR(KBr) cm^{-1}: 1565(C=C), 1610 (C=N), 1326 (C-N tertiary), 1090 (C-O), 1640 (N-H), 570 (C-Br), 630 (C-Cl); ^{1}HNMR ($CDCl_3$) δppm: 7.1-7.2 (d,2H,Ar-H, J=4.12), 3.0 (s, C-N), 5.5 (s, 1H,NH),

6.20-7.50 (q, Ar-H), 3.0-3.80 (m, 8H 1,4-oxazinane); Mass (m/z): 545.5; Anal. Calcd: C 43.19, H 3.42, Br31.92,Cl 7.08 N 11.19, O 3.20, found: C 43.30, H 3.40, Br 32.04,Cl 7.10 N 11.20, O 3.10.

3.2.4.10. 5j: 6,7-Dibromo-N-(4-bromophenyl)-2-(morpholin--4-yl)-3,4-dihydroquinazolin-4-amine

Yield(%):70; m.p. (°C): 224-226; R_f: 0.80; IR(KBr) cm^{-1}: 1540(C=C), 1600 (C=N), 1350 (C-N tertiary), 1120 (C-O), 1670 (N-H), 542 (C-Br); ^{1}HNMR ($CDCl_3$) δppm: 7.1-7.2 (d,2H,Ar-H, J=4.57), 3.2 (s, C-N), 5.0 (s, 1H,NH), 6.20-7.50 (q, Ar-H), 3.0-3.80 (m, 8H 1,4-oxazinane); Mass (m/z): 545.5; Anal. Calcd: C 39.66, H 3.14, Br 43.98, N 10.28, O 2.94, found: C 40.0, H 4.80, Br 44.21, N 10.25, O 2.98.

3.2.4.11. 5k: 4-{[6,7-Dibromo-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-yl]amino}phenol

Yield(%):58; m.p.(°C): 212-214; R_f: 0.65; IR(KBr) cm^{-1}: 1528(benzene-C=C), 1724 (heterocyclic-C=N), 1361 (C-N tertiary), 1101 (C-O, cyclic ether), 1582 (N-H deformation), 541 (Ar -Br), 700 (Ar-OH); ^{1}HNMR ($CDCl_3$) δppm: 7.0-7.3 (d, Ar-H of quinazoline, J=4.57), 2.0 (s, C-N, quinazoline), 4.4 (s, Ar C-NH), 6.37-.7.05 (q, Ar-H of aniline), 2.9-3.67 (m, 8H 1,4-oxazinane); Mass (m/z): 482.2; Anal. Calcd: C 44.84, H 3.76, Br 33.14 N 11.62, O 6.64 found: C 44.54, H 3.79, Br 33.10 N 11.63, O 6.10.

3.2.4.12. 5l: 6,7-dibromo-N-(4-methoxyphenyl)-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-amine

Yield(%):56; m.p. (°C): 234-236; R_f: 0.73; IR(KBr) cm^{-1}: 1478(C=C), 1754 (C=N), 1341 (C-N), 1114 (C-O), 1612 (N-H), 1266(C-O), 541 (Br); ^{1}HNMR ($CDCl_3$) δppm: 7.1-7.2 (d, 2H,Ar-H, J=4.01), 2.0 (s,1H, C-N), 4.4 (s,1H,NH), 6.32-6.55 (q, 4H,Ar-H), 2.9-3.67 (m, 8H 1,4-oxazinane), 3.7-3.9 (t, 3H,OCH_3, J=2.41); Mass (m/z): 496.2; Anal. Calcd C 45.99, H 4.06, Br 32.21, N 11.29, O 6.45, found: C 45.75, H 4.07, Br 32.24, N 11.34, O 6.34.

3.2.4.13. 5m: 6,7-Dibromo-N-(4-methylphenyl)-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-amine

Yield(%):48; m.p. (°C): 236-238; R_f: 0.66; IR(KBr) cm^{-1}: 1437(C=C), 1652 (C=N), 1336 (C-N), 1112 (C-O,), 1623 (N-H), 1357 (Ar-OH), 557 (C-Br); ^{1}HNMR ($CDCl_3$) δppm: 5.68 - 7.5 (d, Ar-H,J=3.59), 2.0 (s,1H, C-N), 4.0 (s, 1H,C-NH), 6.31-6.84 (q, Ar-H of aniline), 2.57-3..40 (m, 8H 1,4-oxazinane), 2.35 (s, Ar C-CH_3).; Mass (m/z): 480.20; Anal. Calcd C 47.52 H 4.20 Br 33.28 N 11.67 O 3.33, Found: C 48.10, H 4.51, Br 33.08, N 11.45, O 3.52.

3.2.4.14. 5n:6,7-Dibromo-N-(2,4-dimethylphenyl)-2-(morpholin-4-yl)-1,2-dihydroquinazolin-4-amine

Yield(%):50; m.p. (°C): 242-244; R_f: 0.62; IR(KBr) cm^{-1}: 1490(C=C), 1727 (C=N), 1331 (C-N), 1147 (C-O), 1612 (N-H), 3054 (CH_3), 557 (C-Br); ^{1}HNMR ($CDCl_3$) δppm: 6.5-8.02 (d, 2H, Ar-H, J=4.01), 2.0 (s,1H C-N), 4.0 (s, 1H,NH), 6.19-6.65 (t, Ar-H, J=4.12), 2.57-3..40 (m, 8H 1,4-oxazinane), 2.35 (s, 3H, CH_3); Mass (m/z): 494.2; Anal. Calcd.: C 48.60, H 4.49, Br32.34, N 11.34, O 3.24, found: C 48.15, H 4.87, Br 32.34, N 11.74, O 3.34.

3.2.4.15. 5o:6,7-Dichloro-2-(morpholin-4-yl)-N-phenylquinazolin-4-amine

Yield(%):58; m.p. (°C): 236-238; R_f: 0.59; IR(KBr) cm^{-1}: 1550(C=C), 1670 (C=N), 1340 (C-N tertiary), 1120 (C-O), 1610 (N-H), 755 (C-Cl); ^{1}HNMR ($CDCl_3$) δppm: 7.4-7.5 (d,2H,Ar-H, J=4.56), 3.0 (s, C-N), 5.5 (s, 1H,NH), 6.20-7.50 (q, Ar-H), 3.0-3.80 (m, 8H 1,4-oxazinane); Mass (m/z): 377; Anal. Calcd: C 57.30, H 4.81, Cl18.79, N 14.85, O 4.24, found: C 57.50, H 4.50, Cl17.89, N 14.50, O 4.40.

3.2.4.16. 5p: 6,7-Dichloro-N-(4-chlorophenyl)-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-amine

Yield(%):52; m.p. (°C): 246-248; R_f: 0.68; IR(KBr) cm^{-1}: 1525(C=C), 1640 (C=N), 1325 (C-N tertiary), 1120 (C-O), 1665 (N-H), 680 (C-Cl); ^{1}HNMR ($CDCl_3$) δppm: 7.0-7.4 (d,2H,Ar-H, J=4.69), 3.6 (s, 1H, C-N), 5.0 (s, 1H,NH), 5.75-6.95 (q,4H, Ar-H), 2.9-4.21 (m, 8H 1,4-oxazinane); Mass (m/z): 411.71; Anal. Calcd: C 52.51, H 4.16, Cl 25.83, N 13.61, O 3.89, found: C 52.39, H 4.02, Cl 25.60, N 13.87, O 4.05.

3.2.4.17. 5q: N-(4-Bromophenyl)-6,7-dichloro-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-amine

Yield(%):45; m.p. (°C): 266-268; R_f: 0.56; IR(KBr) cm^{-1}: 1521 -C=C), 1647(C=N), 1325 (C-N), 1122 (C-O), 1550 (N-H), 700 (C-Cl), 560 (Br);

^{1}HNMR ($CDCl_3$) δppm: 6.8-7.2 (d,2H,Ar-H, J=3.89), 4.01 (s, 1H, C-N), 6.4 (s, 1H,NH), 6.0-7.32 (q,4H, Ar-H), 2.87-3.41 (q, 8H morpholine); Mass (m/z): 456.16; Anal. Calcd: C 47.39, H 3.76, Br 17.52, Cl5.54, N 12.28, O 3.51 found: C 47.36, H 3.80, Br 17.48, Cl 15.60, N 12.32, O 3.85.

3.2.4.18. 5r: 4-{[6,7-Dichloro-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-yl]amino}phenol

Yield(%):40; m.p. (°C): 228-230; R_f: 0.59; IR(KBr) cm^{-1}: 1510(C=C), 1687 (C=N), 1321 (C-N), 1174 (C-O), 1579 (N-H), 1357 (OH), 747 (Cl); ^{1}HNMR ($CDCl_3$) δppm: 5.04 - 7.1 (d, Ar-H, J=5.69), 1.8 (s,1H, C-N), 4.81 (s, 1H,NH), 6.26-6.51 (q, 4HAr-H), 2.86-3.57 (m, 8H,morpholine), 5.9 (s, 1H, OH); Mass (m/z): 392.1; Anal. Calcd C 54.97, H 4.61, Cl 18.03, N 14.25, O 8.14, Found - C 55.17, H 4.51, Cl 17.83, N 14.45, O 8.44.

3.2.4.19. 5s: 6,7-Dichloro-N-(4-methoxyphenyl)-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-amine

Yield(%):56; m.p. (°C): 280-282; R_f: 0.78; IR(KBr) cm^{-1}: 1561(C=C), 1754 (C=N), 1341 (C-N), 1114 (C-O,), 1612 (N-H), 1266(C-O), 632 (Cl); ^{1}HNMR ($CDCl_3$) δppm: 6.8-7.2 (d,2H, Ar-H, J=4.01), 2.0 (s,1H, C-N), 4.4 (s,1H,NH), 6.32-6.55 (q,4H, Ar-H), 2.9-3.67 (m, 8H morpholine), 3.73 (s, 3H, OCH_3); Mass (m/z): 407.3; Anal. Calcd C 56.03, H 4.95, Cl 17.41, N 13.76, O 7.86, found: C 56.03, H 4.97 Cl 17.40, N 13.75, O 7.86.

3.2.4.20. 5t: 6,7-Dichloro-N-(4-methylphenyl)-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-amine

Yield(%):52; m.p. (°C): 236-238; R_f: 0.68; IR(KBr) cm^{-1}: 1552(C=C), 1754 (C=N), 1341 (C-N), 1114 (C-O), 1612 (N-H), 2952(CH_3), 721 (Cl); ^{1}HNMR ($CDCl_3$) δppm: 7.0-7.1 (d, 2H,Ar-H, J=4.24), 2.0 (s,1H, C-N), 4.4 (s, 1H, NH), 6.31-.6.84 (q, 4H, Ar-H), 2.9-3.67 (m, 8H morpholine), 2.35 (s, 3H, CH_3); Mass (m/z): 391.3; Anal. Calcd.: C 58.32, H 5.15, Cl 18.12, N 14.32, O 4.09, found: C 58.02, H 5.26, Cl 18.15, N 14.42, O 4.12.

3.2.4.21. 5u: 6,7-Dichloro-N-(2,4-dimethylphenyl)-2-(morpholin-4-yl)-3,4-dihydroquinazolin-4-amine

Yield(%):51; m.p. (°C): 226-228; R_f: 0.74; IR(KBr) cm^{-1}: 1578(C=C), 1754 (C=N), 1341 (C-N), 1114 (C-O), 1612 (N-H), 2956 (CH_3), 621 (Cl); ^{1}HNMR ($CDCl_3$) δppm: 7.0-7.1 (d,2H, Ar-H, J=3.51), 1.9 (s,1H, C-N), 4.0 (s,1H, NH), 6.32-.6.55 (q,4H Ar-H), 2.9-3.67 (m, 8H, morpholine), 2.54 (s,3H, CH_3); Mass (m/z): 405.3; Anal. Calcd.: C 59.27, H 5.47, Cl 17.49, N 13.82, O 3.95, found: C 58.96, H 4.18, Cl 17.41, N 13.84, O 3.94.

3.3. Pharmacological Studies

3.3.1. In vitro Studies: Cyclooxygenase-2 (COX-2) Inhibition Assays

The selective compounds from 5 *a-u* was screened according to the manufacturer's instructions to inhibit the ability of COX-2 in catalysis of arachidonic acid to prostaglandin H_2 (PGH_2) conversion using a COX inhibitor screening assay kit (catalog No. 560131, Cayman Chemical Co., USA). Celecoxib was used as reference compound. The test compounds were dissolved in DMSO and added 20 µL to COX reaction tube to get final concentration mentioned at Table **5**.

3.3.2. In-vivo Studies

Local breed Albino mice and Wistar rats of either sex weighing between 20 to 25g and 150-200g respectively, obtained from Biological E. limited, Hyderabad (India) were used in the present studies. All animals were housed in wired mesh cages under the laboratory conditions (23 ± 2 C, 12 hr light and maintained on a standard pellet diet (Hindustan Lever Ltd., Mumbai, India) and water *ad libitum* before the day of the experiment. On the last day food was withdrawn and they were given water only. During the course of experiment, the general behavior of animals was normal. All the experimental protocols were approved by the institutional and local animal ethical committee. The experiments were conducted in accordance with standard guidelines. The animals were divided into three groups (control, standard test) and each experimental group consisted of six animals [19-21].

3.3.2.1. Acute Toxicity Study

The acute oral toxicity study was carried out on synthesized compounds, as per the limit dose test of up and down system mentioned in OECD test guidelines No. 423 at a limit dose of 2 g/kg body weight (*p.o.*). Three rats (one male and two female) were selected for each group, in such a way that the weight differences were not exceeding 10% of the mean initial weight of the population.

Rats were fasted for food but water was provided *ad libitum* overnight prior to test compound administration (200mg/kg, *p.o.*), suspended in 1.0%, w/v, carboxymethyl cellulose (CMC) and the access to food was reinstated after 3-4 h. After dosing, individual rat was observed at least once during the first 30 min, periodically during the initial 24 h, with special attention given during the first 4 h and daily thereafter, for a total of 14 days. The systemic and behavioral toxicity patterns were studied as described in OECD test guidelines [13].

3.3.2.2. Carrageenan Induced Rat Paw Edema Method

Rats were divided in groups of six animals each. A mark was made on both the hind paws just below the tibio-tarsal junction so that each time the paw could be dipped in the mercury column of plethysmograph up to the mark to ensure constant paw volume. To each group, except the control group, test compounds were administered orally in a dose level 50 mg/kg. The control group received an equivalent amount of vehicle only. One group received Diclofenac (50 mg/kg). After one hour, carrageenan (0.1 mL, 1% w/v solution in saline) was injected into the sub plantar tissue of the left hind paw of control and Diclofenac-treated group as well. The same volume of saline solution was injected into that of the right hind paw to serve as reference non-inflamed paw for comparison. The initial paw volume was measured immediately after injection. The difference in paw volume was measured in control, standard and treated group after 3h of carrageenan injection. The percent reduction in paw volume was calculated from the equation % anti-inflammatory = [(n - n')/n]*100, where n was the average difference in thickness between the left and the right hind paw of control group and n' was that of the test group of rats [15].

3.3.2.3. Egg Albumin Induced Rat Paw Edema

Egg albumin is reported to induce inflammation in the hind paw of rats and therefore, this model was employed to evaluate the anti-inflammatory activity of synthesized derivatives. Acute inflammation was induced by injecting 0.1 mL/kg of fresh egg albumin into the plantar region of the hind paw of rats. Separate sets of rats (n = 6) were employed for control, standard and treatment groups as described in carrageenan induced inflammation experiment. The change in paw volume (mm) was measured by digital Vernier Caliper up to 120 min, at 20 min intervals after egg albumin injection [15].

3.3.2.4. Hot Plate Method

Swiss albino mice of either sex were divided into twenty one different groups each containing six animals, the animals were marked on tail individually. Food was withdrawn 12 h prior to drug administration till completion of experiment. The animals were weighed and numbered appropriately. To control group (0.3 mL) 2% v/v solution of Tween 80 was given by oral route and after 0min and 90 min behavioral changes count. Tramadol was used as a standard drug. The jumping and paw liking was noted 0 min, 90 min. The percentage inhibition in analgesic activity was evaluated using the following formula [15]:

% Inhibition = 1- [latency before treatment/latency after treatment] x 100

3.3.2.5. Tail-flick Method

Swiss albino mice (25-30 g) of either sex (reaction time: 3-4 sec) were divided into groups of six each. Tramadol (50 mg/kg, p.o.) was used as a standard. The tail-flick latency was assessed by the analgesiometer (Techno, India). The magnitude of the current which was passing through the naked nichrome wire was kept constant at 6 ampere. The tail skin was kept at a distance of 1.5 cm from the heat source. The radiant heat (55°C±2) in the tail was applied and maintained at 2.5 cm measured from the root of the tail. In order to avoid the tissue damage, the cut of reaction time was kept at 10-13 sec. The mean scores in control, standard, and test groups were recorded [15].

3.3.2.6. Ulceration Study

Groups of six male Wistar rats with a weight between 150 and 200 g are used. They were starved for 48 h (water *ad libitum*) prior to drug administration. The test drugs are administered orally in 10 ml/kg as aqueous solution or suspension. Doses are chosen which are highly active in the anti-inflammatory tests in rats. The animals are sacrificed 3, 5 or 7 h post drug. Control animals are sacrificed after 7 h. Stomachs are removed and placed on saline-soaked filter paper until inspec-

tion. A longitudinal incision along the greater curvature is made with fine scissors. The stomach is inverted over the index finger and the presence or absence of gastric irritation is determined. The presence of a single or of multiple lesions (erosion, ulcer or perforation) is considered to be positive. The number of ulcers and the occurrence of hyperemia are noted [15].

3.4. Molecular Docking

To analyze the anti-inflammatory data of synthesized compounds molecular docking studies were carried out using Vlife Science MDS software program with version 4.3 [21]. The dock score functions and hydrogen bonds formed within the reference cavity are used to predict their binding modes, affinities and orientation of synthesized compounds within active site of the COX-2 enzyme. A homology modeling was run in the Biopredicta module of Vlife Science program to obtain COX-2 receptor. The receptor was optimized and water molecules and hydrogen were removed. Ligands were optimized from 2D to 3D moiety and then optimized for further docking process. The protein ligand complex was constructed based on the X ray crystal structure of COX-2 (prostaglandin-endoperoxide synthase 2) from the RCSB Protein Data Bank (PDB entry 3LN1). A batch docking was run under Gasteiger-Marseille algorithm with flexible molecules and receptor, dock score function was calculated and tabulated. The scoring functions were based on minimized ligand protein complexes, results were obtained in form of hydrogen bonding, hydrophobic and Van der Waal interactions which are mentioned in Table **5**.

3.5. 3D-QSAR

3.5.1. Chemical Data

A series of twenty one molecules belonging to 2-(morpholin-4-yl)-*N*-phenylquinazolin-4-amine derivatives as an anti-inflammatory agents were used to generate 3D QSAR using the Molecular Design Suite (VLife MDS software package, version 3; from VLife Sciences, Pune, India) [22].

The data set of 21 compounds were divided into training and test set using random selection method with 80% as training and 20% as test set compounds and various methodologies were applied to the descriptors generated over the grid. The linear and non-linear regression analysis methods were used to deduce the 3D-QSAR models. The 3D pharmacophoric features were generated using MolSign module of VLife with aligned compound ***5a***.

3.5.2. Pharmacological Activities

The negative logarithm of the measured ED_{50} (μM) against inflammation as *p* ED_{50} [pED_{50}=-log ($ED_{50}\times10^{-6}$)] was used as the dependent variable, thus correlating the data linear to the free energy change. Since some compound exhibited insignificant/no inhibition, such compounds were excluded from the present study.

CONCLUSION

A series of 2-(Morpholin-4-yl)-*N*-phenylquinazolin-4-amine derivatives were synthesized and tested for their analgesic and anti-inflammatory activity with selectivity towards COX-2 receptor by various pain models in rodents. Screening results of compounds exhibited comparable biological activity with that of standard compounds used for the study. Compound **5d** was found to be significantly potent with respect to its anti-inflammatory and analgesic activity. *In silico* analysis by molecular docking and QSAR studies justifies activity profile of compound **5d**, suggesting that it may have the potential for further evaluation and development as a lead molecule for therapy in pain management.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was approved by Committee for the Purpose of Control and Supervision of Experiments in Animal (CPCSEA), Nagpur, India. (OECD guidelines No. 23).

HUMAN AND ANIMAL RIGHTS

No humans were used in this study. All the reported experiments on animals were performed in accordance with the Guide for the Care and Use of Laboratory Animals, 8th Edition, published by the National Academy of Sciences, The National Academies Press, Washington DC, USA.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

ACKNOWLEDGEMENTS

Declared none.

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