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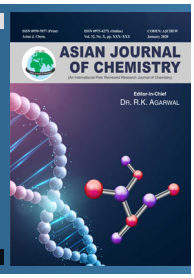

Synthesis, Anti-inflammatory Activity and *in silico* Studies of Some Novel Morpholine Based Carboxamides

PREMANAND M. HONAVAR[1,2], VASANTHA KUMAR[3], NIKHIL P.[4], NAVEEN KUMAR[3], S. SREENIVASA[2], VISHWANATHA P.[3], BOJA POOJARY[4] and B. SHIVARAMA HOLLA[3,*]

[1]Department of Chemistry, Sri Dharmasthala Manjunatheshwara College of Arts, Science, Commerce, BBA and P.G. Centre, Honavar-581334, India
[2]Department of Studies and Research in Organic Chemistry, Tumkur University, Tumkur-572103, India
[3]Department of Chemistry, Sri Dharmasthala Manjunatheshwara College (Autonomous), Ujire-574240, India
[4]Department of Studies and Research in Chemistry, Mangalore University, Mangalagangotri-574199, India

*Corresponding author: E-mail: hollabs@gmail.com

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Two series of carboxamides were synthesized from 3-fluoro-4-morpholinoaniline and different substituted aromatic/heterocyclic carboxylic acids. All the compounds were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The newly synthesized amide derivatives were screened for anti-inflammatory activity by following carrageenan induced rat paw edema method. Among the compounds screened, compound **6e** was found to be highly potent. Molecular docking interaction of active compounds revealed that effective binding was observed in the pocket of COX-I and COX-II proteins.

Keywords: Carboxamides, Morpholinyl, Pyridine, Antiinflammatory activity, Docking studies.

INTRODUCTION

Inflammation is referred as a complex biological process that happens when body tissues are exposed to hazardous stimuli, such as irritants and pathogens [1]. The process of inflammation threatens human health, and exaggerated and prolonged inflammation may cause various diseases, including arthritis, sepsis and even cancer [2]. Presently, 35% of the global medicinal prescription for the treatment of inflammation are non-steroidal anti-inflammatory drugs (NSAIDs) [3,4]. Aspirin and indomethacin are the common NSAIDs, that inhibit cyclo-oxygenases (COX-1 and COX-2) [5,6], which are involved in the catalyzation of converting arachidonic acid to prostaglandins. Considering the significant toxicity of NSAIDs to the gastro-intestinal tract and kidney [7], it is of great importance and urgent need to develop new anti-inflammation drugs [8].

Morpholine based compounds occupy pivotal place in medicinal chemistry owing their special features such as strong basic nature and participation in donor acceptor type of interaction [9]. From the literature, it is observed that morpholine moiety containing amide derivatives exhibited wide range of activities such as antimicrobial [10], anticonvulsant [11], analgesic [12], anticancer [13] and anticoagulant activities [14]. They also involved as intermediates in the synthesis of biologically important molecules. Carboxamides with conjugation of other aliphatic, aromatic and heterocyclic moieties produce various types of biological activities. A number of amides of aromatic and heterocyclic carboxylic acids have been synthesized in search for new antagonists of excitatory amino acids receptors with anticonvulsant activity. Amide functionality is also an important functional group which is responsible for binding with different protein molecules and as a result increases its pharmacological activity [15].

Amide derivatives exhibited anti-inflammatory [16,17], antimicrobial [18], antitubercular [19], anticancer [20] and anticonvulsant [21] activities. In the current study, morpholine containing aromatic amine and substituted aromatic/heterocyclic carboxylic acids were combined to synthesize a new series of amide derivatives and screened for *in vivo* anti-inflammatory activities by carrageenan induced paw edema method. Molecular docking studies was performed to understand the interaction of the molecules with COX-I (PDB code: 2OYE) and COX-II

protein (PDB code: 4COX) that are responsible for exhibiting anti-inflammatory activity.

EXPERIMENTAL

All the chemicals and solvents used were procured from Spectrochem and Sigma-Aldrich make in the appropriate grade and used without further purification; purity of the chemicals and solvents received was confirmed by TLC. Melting points were determined in open capillary and are uncorrected. IR spectra were recorded on Bruker alpha series in KBr (cm^{-1}). ^1H and ^{13}C NMR spectra were recorded on a BRUKER AV400, Agilent 400MR using TMS as internal standard, Mass data was recorded on Agilent Waters, USA and chemical shift values are reported in δ ppm.

General procedure for the synthesis of 4-(2-fluoro-4-nitrophenyl)morpholine (3): 3,4-Difluoronitrobenzene (10 mmol) was added dropwise to a mixture of morpholine (10 mmol) in dry dimethylformamide in presence of Hünig′s base DIPEA (30 mmol) and then the contents of the reaction mixture were heated at 90 ºC for 6 h. Reaction mass was poured to crushed ice to get solid product, filtered, washed with water and dried. The yellow solid obtained was recrystallized from ethanol to get pure product.

General procedure for the synthesis of 3-fluoro-4-morpholinoaniline (4): 4-(2-Fluoro-4-nitrophenyl)morpholine (**3**) (10 mmol) was taken in round bottom flask containing 10 mL of 6 M HCl, stirred the mixture for 0.5 h, then (30 mmol) of Sn granules were added during stirring. The stirring was continued for another 2.5 h and after completion of the reaction, 50 mL of distilled water was added with 20 % NaOH. The product was extracted with ethyl acetate. The organic layer was evaporated to dryness to get product **4**.

General procedure for the synthesis of amide derivatives (6a-e and 11a,b): To a solution of different acids **5a-e** (2.54 mmol) in DMF and N-methylmorpholine (7.64 mmol), added 3.81 mmol of TBTU (N,N,N′,N′-tetramethyl-O-(benzotriazol-1-yl)uronium tetrafluoroborate). Reaction mass was stirred at room temperature for 1 h. Added 3-fluoro-4-morpholinoaniline (**4**) (2.54 mmol) and stirring continued for 12 h. Completion of the reaction was monitered by TLC (3:2 hexane: ethyl acetate). After the completion, reaction mass was poured onto crushed ice, solid obtained was filtered off, washed with cold water and dried. All the products were recrystallized using DMF.

Spectral data

3-Fluoro-*N*-(3-fluoro-4-morpholinophenyl)-4-methylbenzamide (6a): Yield: 86 %; m.p.: 178-180 ºC; IR (KBr, ν_{max}, cm^{-1}): 3292 (N-H), 2964 (-C-H), 1641 (C=O), 1592 (C=C), 1116 (C-F); ^1H NMR (400 MHz, DMSO-*d*6, δ in ppm): 10.23 (s, 1H, N-H), 7.698-7.642 (m, 3H, Ar-H), 7.449-7.401 (m, 2H, Ar-H), 7.026-6.980 (t, 1H, Ar-H, *J* = 9.2Hz), 3.715-3.694 (t, 4H, O-CH_2, *J* = 4.2Hz), 2.946-2.925 (t, 4H, N-CH_2, *J* = 4.2 Hz), 2.277(s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ in ppm): 164.2, 161.9, 159.5, 155.9, 153.5, 136.0, 134.7, 134.5, 134.4, 132.1, 128.8, 128.6, 124.0, 119.4, 119.3, 116.8, 114.6 114.3, 109.1, 108.9, 66.6, 51.2, 14.6; MS (*m/z*): calculated: 332.1336, found 333. 0410 (M+1).

***N*-(3-Fluoro-4-morpholinophenyl)thiophene-2-carboxamide (6b):** Yield: 82 %; m.p.: 186-188 ºC; IR (KBr, ν_{max}, cm^{-1}): 3306 (N-H), 3086, 2952 (-C-H), 2848, 2820, 1633 (C=O), 1589 (C=C), 1116 (C-F); ^1H NMR (400 MHz, DMSO-d_6, δ in ppm): 10.22 (s, 1H, NHCO), 7.956 (d, 1H, *J* = 3.2 Hz, thiophene-H), 7.824 (d, 1H, *J* = 3.2Hz, thiophene-H), 7.635-7.591 (dd, 1H, *J* = 2.4 Hz & 15.2Hz, Ar-H), 7.406-7.381 (dd, 1H, *J* = Hz, Ar-H), 7.191 (t, 1H, *J* = 4.5 Hz, thiophene-H), 7.003 (t, 1H, *J* = 9.6 Hz, Ar-H), 3.702 (t, 3H, O-CH_2), 2.935 (t, 4H, N-CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, δ in ppm): 160.1, 155.9, 153.5, 140.2, 136.0, 134.2, 132.3, 129.5, 128.4, 119.4, 116.7, 109.0, 66.6, 51.1; MS (*m/z*): calculated 306.0838, found: 306.9971.

5-Chloro-*N*-(3-fluoro-4-morpholinophenyl)thiophene-2-carboxamide (6c): Yield: 84 %; m.p.: 194-196 ºC; IR (KBr, ν_{max}, cm^{-1}): 3291 (N-H), 2983, 2961 (-C-H), 1631 (C=O), 1576 (C=C), 1118 (C-F); ^1H NMR (400 MHz, DMSO-d_6, δ in ppm): 10.29 (s, 1H, NH), 7.843 (d, 1H, *J* = 4 Hz, thiophene-H), 7.572 (d, 1H, *J* = 16Hz, Ar-H), 7.359 (d, 1H, *J* = 9Hz, Ar-H), 7.230 (d, 1H, *J* = 4Hz, thiophene-H), 7.002 (t, 1H, *J* = 9Hz, Ar-H), 3.699 (t, 3H, J = 4Hz, O-CH_2), 2.933 (t, 4H, *J* = 4.2Hz, N-CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, δ in ppm): 160, 155.9, 153.5, 139.3, 136.25, 134.3, 133.78, 129.4, 128.6, 119.5, 116.8, 109.1, 66.6, 51.1; MS (*m/z*): calculated 340.8003, found 340.9494 (M+) and 342.9491 (M+2).

5-Bromo-*N*-(3-fluoro-4-morpholinophenyl)furan-2-carboxamide (6d): Yield: 78 %; m.p.: 190-192 ºC; IR (KBr, ν_{max}, cm^{-1}): 3302 (N-H), 3129 (=C-H), 2961, 2887, 2845 (-C-H), 1654 (C=O), 1592 (C=C), 1120 (C-F); ^1H NMR (400 MHz, DMSO-d_6, δ in ppm): 10.23 (s, 1H, NH), 7.622-7.580 (dd, 1H, *J* = 2 & 14.2 Hz, Ar-H), 7.423-7.398 (dd, 1H, *J* = 1.4 & 8.6 Hz, Ar-H), 7.308 9 (d, 1H, *J* = 3.6 Hz, furyl-H), 6.992 (t, 1H, *J* = 9 Hz, Ar-H), 6.801 (d, 1H, *J* = 3.2 Hz, furyl-H), 3.699 (t, 4H, *J* = 4.4 Hz, O-CH_2), 2.930 (t, 4H, *J* = 4.4 Hz, N-CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, δ in ppm): 160.6, 160.1, 158.2, 154.3, 140.9, 138.5, 130.5, 124.12, 122.34, 121.6, 119.5, 113.9, 71.3, 55.8; MS (*m/z*): calculated 368.0172, found 368.9220 (M+) and 370.9177 (M+2).

2-Chloro-*N*-(3-fluoro-4-morpholinophenyl)nicotinamide (6e): Yield: 85%; m.p.: 202-204 ºC; IR (KBr, ν_{max}, cm^{-1}): 3356 (N-H), 2946, 2917, 2846 (C-H), 1663 (C=O), 1611 (C=N), 1584 (C=C), 1115 (C-F); ^1H NMR (400 MHz, DMSO-d_6, δ in ppm): 10.65 (s, 1H, NH), 8.50 (s, 1H, pyridyl-H), 8.03 (d, *J* = 6.4 Hz, 1H, pyridyl-H), 7.607-7.530 (m, 2H, Ar-H), 7.31 (d, *J* = 7.6 Hz, pyridyl-H), 7.016 (t, 1H, *J* = 8.8 Hz, Ar-H), 3.703 (s, 4H, O-CH_2), 2.932 (s, 4H, N-CH_2); ^{13}C NMR (100 MHz, DMSO-d_6, δ in ppm): 163.8, 156.0, 153.6, 151.0, 146.9, 138.6, 136.4, 134.1, 133.4, 123.6, 119.7, 116.1, 108.2, 66.6, 51.1; MS (*m/z*): calculated 335.0837, found 335.9958 (M+) and 337.9890 (M+2).

6-(3,5-Difluorophenyl)-*N*-(3-fluoro-4-morpholinophenyl)-2-methylnicotinamide (11a): Yield: 76 %; m.p.: 212-214 ºC; IR (KBr, ν_{max}, cm^{-1}): 3262 (N-H), 2968, 2918, 2845 (C-H), 1641 (C=O), 1118 (C-F); ^1H NMR (400 MHz, DMSO-d_6, δ in ppm): 10.51 (s, 1H, NH), 8.035-7.964 (dd, 2H, *J* = 8.4 & 20 Hz, Ar-H), 7.862-7.840 (m, 2H, pyridyl-H), 7.665-7.622 (dd, 1H, *J* = 2.2 & 15Hz, Ar-H), 7.387-7.302 (m, 2H, Ar-H), 7.017 (t, 1H, *J* = 9.4Hz, Ar-H), 3.712 (t, 4H, *J* = 3.6Hz, O-CH_2), 2.61 (s, 3H, CH_3), 2.469 (t, 4H, *J* = 4.6 Hz, N-CH_2); ^{13}C NMR

(100 MHz, DMSO-d_6, δ in ppm): 166.4, 164.65, 162.1, 156.01, 153.6, 142.0, 137.2, 136.2, 134.5, 132.0, 119.5, 118.2, 116.1, 110.2, 108.38, 105.1, 66.6, 51.2, 23.3. MS (*m/z*): calculated (427. 1508), found, 428.0576 (M+1).

6-(4-Chlorophenyl)-*N*-(3-fluoro-4-morpholinophenyl)-2-methylpyridine-3-carboxamide (11b) : Yield: 80 %; m.p.: 224-226 ºC; IR (KBr, ν_{max}, cm^{-1}): 3268 (N-H), 2998, 2964, 2919, 2881 (C-H), 1643 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6, δ in ppm): 10.48 (s, 1H, NH), 8.14 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.91-7.95 (m, 2H, pyridyl-H), 7.64 (d, 1H, *J* = 14 Hz, Ar-H), 7.55 (d, 2H, *J* = 8.4 Hz, Ar-H), 7.38 (d, 1H, *J* = 8.4Hz, Ar-H), 7.01 (t, 1H, *J* = 9 Hz, Ar-H), 3.71 (t, 4H, O-CH_2), 2.94 (t, 4H, N-CH_2), 2.47 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6, δ in ppm): 166.6 (C=O), 156.0, 155.8, 155.2,153.6, 137.2, 137.0, 136.2, 136.1, 134.7, 134.5, 134.4, 131.2, 129.4, 128.9, 119.5, 117.5, 116.2, 108.5, 108.2, 66.0, 51.1, 23.3; MS (*m/z*): calculated (425. 1306), found, 426.0310 (M+1) and 428.0305 (M+3)

Anti-inflammatory activity: The effect of test drug on carrageenan induced paw edema in rats was studied as per the method described by Winter *et al.* [22]. Wistar albino rats of either sex weighing between 160-230 gwere selected for the experimentation andthey were randomly divided into three groups: Group 1: Water control, Group 2: Diclofenac -- (100 mg/kg), Group 3 to 16: CODED drugs.

To a first group, tap water was administered to serve as control. Second group was taken as standard and administered with the standard drug diclofenac (100 mg/kg) and group 3 to 16 would be treated with the test drugs. The test drug was administered once daily for seven consecutive days. On 7th day prior to carrageenan injection the initial paw volume of left hind paw was measured using a plethysmometer (Electronic-Orchid) as follows: after 1 h, drug administration, paw edema would be produced by injecting 0.1 mL freshly prepared 1 % carrageenan in sterile saline solution to the sub-plantar aponeurosis of the left hind limb. The rats was administered with the tap water in the dose of 2 mL/100g body weight to ensure uniform hydration. This is supposed to minimize the variation in edema formation. The intensity of edema formation was recorded after 1, 3 and 6h after carrageenan injection. Results was expressed as percentage increase in paw volume in comparison to the initial values. Percentage increase in paw volumes was calculated by subtracting the initial paw volumes from the paw volumes obtained after the injection of the phlogistic agent. The figure was divided by the initial paw volume and multiplied by hundred. Also percentage of inhibition was calculated by using the following equation:

$$\text{Inhibition } (\%) = 1 - \frac{V_t}{V_c} \times 100$$

where V_t is edema volume in drug treated group and V_c is edema volume in the control group.

Molecular docking

Ligands preparation: The Chemdraw was used to draw the structures of the synthesized compounds. Optimization of the ligands was carried out using macromolecular force field (MMF) followed by energy minimization protocol [23]. Several ligand conformations were generated, based on CHARM energy, bond energy, dihedral energy, initial potential energy, electrostatic energy values, the drug likeliness was evaluated using the Lipinski rule of 5 *via* Lipinski drug filter protocol [24] these studies were performed using Discovery studio 3.5 (Accelrys).

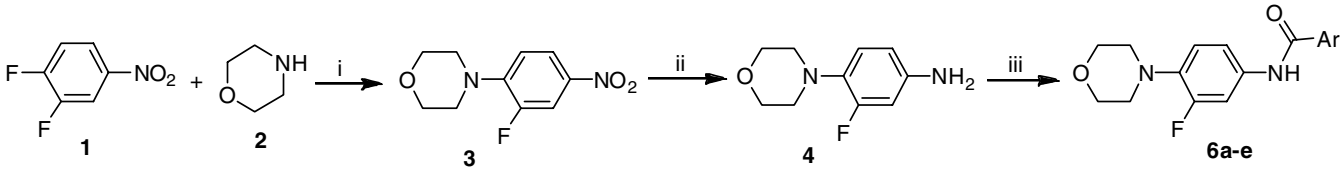
Protein preparation: In this study, COX-1, COX-2 proteins (PDB ID: 2OYE, 4COX) were selected as target proteins for anti-inflammatory activity [25,26]. The 3D structures were retrieved from protein data bank to study the binding mode of inhibitors. Prior to protein preparation, the inhibitors, other ligand and water molecules were deleted from the protein to obtain clean protein. The structures thus obtained were optimized classically using CHARM force field implemented in the Autodock suite [27], minimized with conjugate gradient energy minimization protocol followed by convergence energy minimization (0.001 kcal/mol) that arrange the structures for docking and simulations.

For molecular docking studies, a flexible docking approach was employed using the LeadIT software in which COX proteins were considered as receptor proteins. The docking results for receptor-ligand complex comprised intermolecular interaction energies, namely, hydrogen bonding and hydrophobic and electrostatic interaction. Receptor-ligand complex with least binding energy was used to infer the best binding compound. The best conformations were selected based on the least docking energy value [28].

RESULTS AND DISCUSSION

Synthesis of *N*-(3-fluoro-4-morpholinophenyl) substituted arylamides (**6a-e**) is depicted in **Scheme-I**. Initially, 3,4-difluoronitrobenzene (**1**) was treated with morpholine in the presence of DIPEA base in DMF solvent to yield compound **3**. Nitro group of compound **3** was then reduced with Sn in HCl to yield amine **4**. Finally, different carboxamides **6a-e** were synthesized by the condensation of amine **4** with substituted aromatic acids (**5a-e**) using TBTU as coupling agent in the presence of NMM base in DMF medium at room temperature.

Synthesis of *N*-(3-fluoro-4-morpholinophenyl)-2-methyl-6-substituted-arylpyridine-3-carboxamides was depicted in **Scheme-II**. Initially, substituted acetophenones (**7a-b**) were reacted with *N*,*N*-dimethyl formamide dimethylacetal to yield



6a: 3-F-4-Me-phenyl, **6b**: 2-Thienyl, **6c**: 5-Cl-2-thienyl, **6d**: 5-Br-2-furyl, **6e**: 2-Cl-3-pyridyl

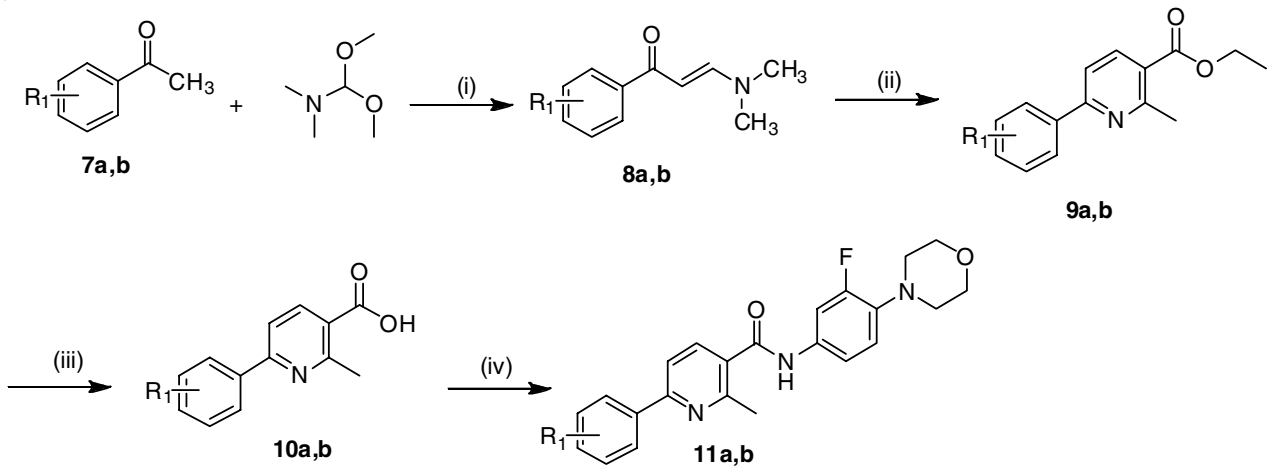
Scheme-I: Synthesis of *N*-(3-fluoro-4-morpholinophenyl)substituted arylamides (**6a-e**); Reagents and conditions: (i) DIPEA, DMF, 90 °C (ii) Sn/conc. HCl (iii) Ar-CO_2H (**5a-e**), HBTU, NMM, DMF, RT, 12 h

3-(dimethylamino)-1-aryllprop-2-en-1-ones (**8a-b**), which were then subjected to cyclization with ammonium acetate and ethyl-acetoacetate in ethanolic medium to yield ethyl-2-methyl-6-arylpyridine-3-carboxylates (**9a-b**) [29]. These esters were then hydrolyzed with aqueous NaOH in ethanol to obtain the corresponding carboxylic acids (**10a-b**). These acids were then coupled with 3-fluoro-4-morpholinobenzenamine (**4**) in the presence of coupling agent (TBTU) in DMF medium and N-methylmorpholine base to yield compound **11a-b**.

All the compounds were characterized by IR, ^{1}H & ^{13}C NMR and LC-MS spectral data. IR spectra of compounds **6a-e** and **11a-b** showed a strong absorption band for the N-H stretching in the range 3330-3260 cm^{-1} and a strong carbonyl stretching band in the region 1650-1630 cm^{-1}. The ^{1}H NMR spectrum of all the target compounds showed a broad singlet for the N-H proton of the amide in the region 10.2-10.6 ppm, which clearly indicated the formation of products. Also this is confirmed by the presence of a carbony carbon signal in the ^{13}C NMR spectrum in the region 160-167 ppm. LC-MS spectrum of all the target compounds is in agreement with the molecular weight of the products.

The antiinflammatory activity of the synthesized compounds **6a-e** and **11a-b** is given in Table-1. It is clearly noted that compound **6e**, which is 2-chloro-3-pyridyl substituted derivative emerged as highly potent candidate in the series. This compound has shown considerable inhibition from the 1st h to 24 h and is found to be equipotent to indomethacin drug. However other two pyridine derivatives, **11a** and **11b** were found to be less potent compared to compound **6e**. Compound from the thiophene series **6b** and **6c** were found to be active molecule as they showed considerable inhibition at the end of 24 h. Compound **6a** with 3-fluoro-4-methylphenyl derivative was emerged as second potent compound in the series with considerable inhibition. Compound **6d** with 5-bromofuryl substitution was least potent aming all the compounds. From the study it is clear that, compound **6e** emerged as highly promising antiinflammatory compound.

Molecular docking: Molecular docking studies was performed on COX-I (PDB code: 2OYE) and COX-II protein (PDB code: 4COX) to understand the possible mode of action of the potent compounds **6e** and **6a**. The results are depicted in Figs. 1 and 2, respectively. Fig. 1 shows the interaction of compounds **6a** and **6e** with the COX-I protein. The morpholine oxygen involves in hydrogen bonding with ARG 67 residue. The N-H and C=O of amide functionality involves in hydrogen bonding with GLN106 and ASN143, respectively. The additional H-bonding interaction in compound **6e** appears between the nitrogen of pyridine with GLN144. This could gives more stability to compound **6e** in the pocket of 2OYE protein. Fig. 2 shows the interaction of compounds **6a** and **6e** with COX-II



11a: 3,5-F_2; **11b**: 4-Cl

Scheme-II: Synthesis of *N*-(3-fluoro-4-morpholinophenyl)-2-methyl-6-substituted-arylpyridine-3-carboxamides **11a,b**; Reagents and conditions: (i) Neat reflux (ii) Ethyl acetoacetate, ammonim acetate, EtOH, reflux (iii) 20 % NaOH, ethanol, reflux (iv) TBTU, NMM, DMF, RT

TABLE-1
ANTIINFLAMMATORY ACTIVITY OF THE COMPOUNDS **6a-e** AND **11a, b**

Compd.	Afetr 1 h		Afetr 2 h		Afetr 3 h		Afetr 24 h	
	Swelling	Inhibition (%)	Swelling	Inhibition (%)	Swelling	Inhibition (%)	Swelling	Inhibition (%)
Cont.	18.95 ± 1.56	–	22.88 ± 1.66	–	26.68 ± 1.34	–	22.31 ± 2.17	–
6a	27.55 ± 3.83	-45.38	20.15 ± 3.80	11.94	14.79 ± 3.64**	44.56	5.91 ± 3.22**	73.50
6b	22.00 ± 3.43	-16.09	18.63 ± 3.29	18.58	12.91 ± 2.23**	51.61	6.37 ± 0.90**	71.44
6c	35.66 ± 10.98	-98.11	32.83 ± 9.72*	-43.48	19.66 ± 5.53*	26.32	6.88 ± 1.06	69.17
6d	35.89 ± 8.15	-89.39	32.38 ± 8.95	41.52	27.21 ± 11.21	-1.98	20.85 ± 15.73	6.54
6e	10.95 ± 1.73	42.22	8.21 ± 1.86	64.12	6.05 ± 1.47**	77.32	2.15 ± 1.60**	90.36
11a	41.58 ± 11.02	-119.41	37.49 ± 12.52	-63.85	33.57 ± 11.20	-25.82	16.08 ± 8.52	27.92
11b	36.61 ± 8.78	-93.19	52.14 ± 9.83*	-127.88	36.65 ± 5.53*	-37.36	14.68 ± 1.06	34.19
Indomethacin	19.34 ± 3.17	-2.05	11.42 ± 3.09	50.09	7.00 ± 2.51**	73.77	1.43 ± 0.35**	93.59

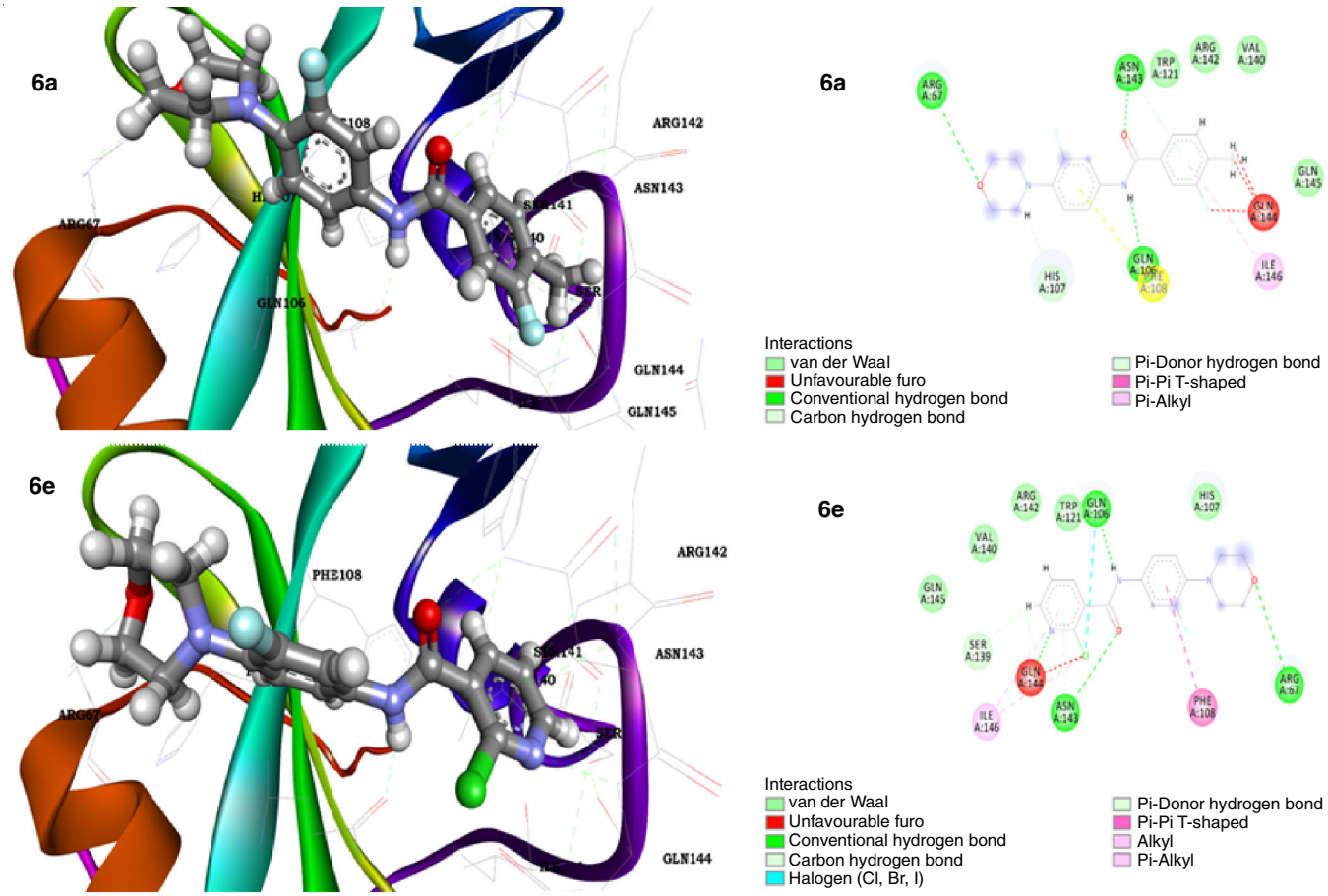


Fig. 1. 3D and 2D docking poses of compounds **6a** and **6e** with COX-I protein 2OYE

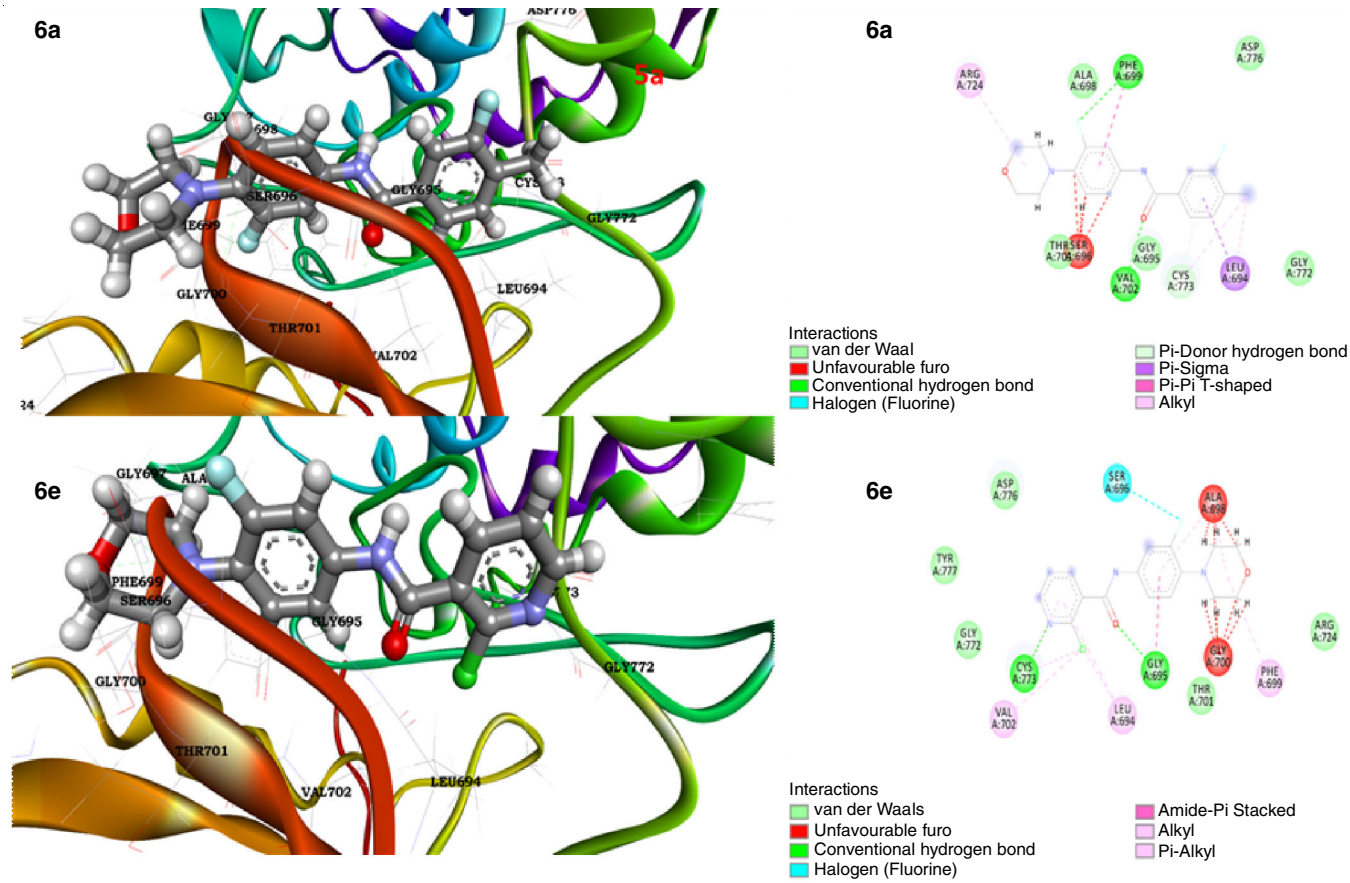


Fig. 2. 3D and 2D docking poses of compounds **6a** and **6e** with COX-II protein 4COX

TABLE-2
DOCKING RESULTS OF TARGET MOLECULES ON COX-I AND COX-II PROTEINS

Compd.	PDB 2OYE			PDB 4COX		
	Docking score	Hydrogen bond interaction residue	π-π interactionon residues	Docking score	Hydrogen bond interaction residue	π-π interactionon residues
6a	-10.098	ARG67, ASN143, GLN106	PHE108	-12.146	PHE699, VAL702	PHE699
6b	-11.203	ARG67, ARG86, SER88, SER90, LYS109	–	-16.603	GLN695, VAL702, GLY695	PHE699
6e	-8.853	ARG67, ASN143, GLN144, GLN106	PHE108	-10.898	GLY695, CYS773	GLN695
Indomethacin	-30.583	–	–	-22.299	–	–

protein. Both the compounds binds with different residues in the pocket. Compound **6a** involves in hydrogen bonding with fluorine atom with PHE699 and carbonyl oxygen with VAL702. It also involves in π-π interaction with PHE699. Pyridine nitrogen of compound **6e** involves in hydrogen bonding with CYS773 and its carbonyl oxygen involves in hydrogen bonding with GLY695 residue. The phenyl ring involves in π-π interaction with GLY695. All the interactions and docking scores of potent compounds are given in Table-2.

Conclusion

In the present investigation, a series of novel morpholine based carboxamides with different aryl and heterocyclic units in good yields were efficiently synthesized. Anti-inflammatory activity of these compounds identified a highly potent compound **6e**, which is equipotent to indomethacin drug. Also, compounds **6a** and **6b** emerged as good inhibitors of inflammation. Docking score and binding of the most active compounds into the crystal structure of COX proteins is in compatible with the *in vivo* antiinflammatory study.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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