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Microwave assisted synthesis and *in silico* molecular modeling studies some new derivatives of (Z)-N-(4-(4-(substituted-benzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide as lead compounds

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ABSTRACT

*COX-2 inhibitors are used to treat pain due to Rheumatoid arthritis. NSAID's is one such category but due to the ulcerogenic and thromboembolic effect of some of these drugs the search for new compound is always on. The present approach of synthesizing (Z)-N-(4-(4-(substituted-benzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide **(3.1-3.10)** as selective COX-2 inhibitors is directed towards the same. Ten compounds were synthesized using the principle of Erlenmeyer-Ploch synthesis for synthesis of oxadiazole and consequently imidazole derivatives. The synthesized compounds were analyzed using docking studies, for various parameters like hydrophobicity, hydrogen bonding, sitemap interactions. The structures of synthesized imidazole derivatives were proved by means of their IR, [1]H-NMR, (EI) mass. Among the synthesized compounds, **3.10** exhibited significant glide score as an analgesic using 5COX as receptor.*

Keywords: COX, docking, benzylidene, imidazolone, 5COX

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAID'S) are the main therapeutic agents for the treatment of Rheumatoid arthritis. It is understood that these drugs act by inhibition of enzyme cycloxygenase (COX) [1, 2]. Although these drugs are used globally, they are associated with one of the major side effects of GIT-ulceration [3] due to their non-selectivity. The existing therapy of NSAIDs is non-selective towards COX-2 inhibitors, which therefore gave rise to a new class of anti-inflammatory agents, in the form of coxibs (Celecoxib, Rofecoxib etc.), having selective activity towards COX-2 enzyme. Unfortunately, Rofecoxib was banned due to the thromboembolic adverse effect it produced. Lot of research is being done since then for the development of new agents which can lessen the sensation of pain, especially chronic pain, which is still undertreated. The following study is indented for the same.

Rationale

A large number of research studies aimed at finding selective COX-2 inhibitors have been reported [4-7]. Many of these have synthesized using CADD techniques to develop a new COX-2 inhibitor containing oxazoles, pyrazoles and imidazoles as core moiety [8-14]. In a Fujita-Ban modified *de Novo* approach, three series of diaryl heterocycles namely, diaryl imidazoles [15] diarylpyrazoles [16] and diaryloxazolones [17] were studied and it was inferred from the studies that diarylimidazoles posses better selective activity towards COX-2. Therefore, it was essential to

synthesize some new derivatives of diarylimidazoles and study those using computational techniques before performing related pharmacological studies.

Chemistry
Synthesis of oxazolone involves the condensation of aromatic aldehydes and hippuric acid with a stoichiometric amount of fused sodium acetate in the presence of acetic anhydride; as the dehydrating agent, this reaction is known as the Erlenmeyer Plöchl reaction. The method involves preparation of azlactones (oxazolones) in a Z configuration (originally assigned to the E configuration) by condensation of aromatic aldehyde with hippuric acid in the presence of acetic anhydride [18]. It is observed that aldehyde condenses under the influence of a base with reactive methylene group in the azlactone which is formed by the dehydration of benzoylglycine, when the latter reacts with acetic anhydride in the presence of sodium acetate [19, 20]. Synthesis of substituted imidazoles (**3.1-3.10**) was carried out according to scheme-2. The reaction proceeds when lone pair of nitrogen attacks carbonyl carbon. Upon restoration of carbonyl group as amide, the oxadiazole ring breaks and the oxygen accepts a proton from the reaction mixture. The hydroxyl was removed as water with closure of ring to form and imidazole. The imidazoles were characterized on the basis of IR, NMR and Mass spectral analysis

MATERIALS AND METHODS

Experimental

Synthesis
All the melting points were determined by open capillary tube method and are uncorrected. I. R. spectra were recorded on Perkin-Elmer-Spectrum RX-IFTIR spectrophotometer. ^{1}H-NMR spectra were recorded on Avance II (Bruker) (400 MHz) spectrometer in DMSO using TMS as internal standard and chemical shifts are indicated in δ (ppm). Mass Spectra were recorded using Waters Micromass Q-Tof Micro which is hybrid quadrupole time of flight mass spectrometer equppied with ESI. Chemicals were purchased from commercial suppliers and were used without any further purification.

Step-1
Equimolar quantities of hippuric acid (2 g, 0.011 mol), redistilled benzaldehyde (0.011 mol) and acetic anhydride (1.12 g, 0.011 mol) were mixed together in a conical flask. To the above mixture anhydrous sodium acetate (2 g) was added and the flask was heated under microwave irradiation at 40W for 40-50 seconds. The liquefied mixture was then cooled, stirred well and heated again for 30 seconds at intervals, for a total of 3 minutes. Ethanol (q.s.) was then added to the above mixture in the conical flask and the mixture was then allowed to stand overnight. The crystalline product so obtained was filtered at suction and washed with boiling water and dried. The product was then recrystallized with benzene. The physical data of the compounds **(1.1-1.0)** are given in table 1.

Step-2
Two grams (0.005mol) of product obtained in step-1 (1.1) and acetanilide (1 g, 0.0066 mol) were taken in an Erlenmeyer flask with 1 ml of pyridine and dimethylformamide (DMF) (q.s.). The flask was heated initially for 50 seconds and then for total of 3 minutes at 40W, with intervals of stirring and cooling in between each pulse. The product formed was recovered by adding the reaction mixture to ice-water mixture. The product was filtered, dried and recrystallized with ethanol. The reaction scheme is shown as scheme-2 and the physical data of the compounds (3.1-3.10) are shown in table 2.

In silico molecular docking studies
Molecular docking studies were carried out using Suite 2012: Maestro, version 9.3, Schrödinger, LLC, New York, NY, 2012. The enzyme cycloxygenase, obtained from protein data bank was used as a receptor (ID: 5COX). Ligand preparation was done using LigPrep, version 2.5, Schrödinger, LLC, New York, NY, 2012. Docking studies were carried out using Glide, version 5.8, Schrödinger, LLC, New York, NY, 2012. For docking studies the energy minimized ligands were docked at the selected grid of the receptor having X, Y, Z scale at 60.3312, 44.6724 and 76.0573 A, respectively.

RESULTS AND DISCUSSION

Synthesis

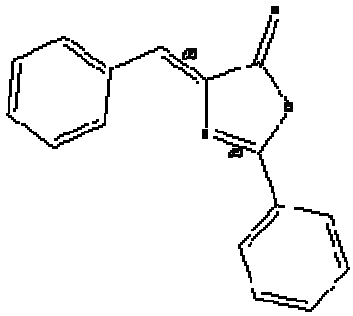
The IR spectra of the synthesized compounds revealed bands for different functional groups *viz.* aromatic, olefinic and ketonic. In the IR spectra of compounds **(1.1-1.10)** the presence of aromatic ring was confirmed by the presence of weak bands between 3188-3045 cm^{-1} due to aromatic C-H str. The olefinic double bond introduces very important bands in the spectra for confirmation of structure. In the structure of the synthesized compounds it can be visualized that the double bond is in conjugation with the aromatic ring as well as ketonic group of the oxazole ring. The olefinic bond stretching vibration for such a conjugated system, without a centre of symmetry, appears between 3090-3000 cm^{-1}. Apart from olefinic bond the important band which confirms the formation of azlactone ring is the band for ketonic functional group. The β-γ type azlactone ring; a five membered (γ) lactone ring with double bond at β to carbonyl functional group or α to –O- , obtains an intense carbonyl absorption band between 1782-1800 cm^{-1}. Lastly, the band for C=N str is obtained between 1689-1471 cm^{-1}, confirming the formation of oxazole ring. The results for individual compounds are discussed in table 2.

In the IR spectra of synthesized compounds **3.1-3.10,** apart from the peaks obtained for aromatic and olefinic functional groups, as seen above in step-1, several other peaks were obtained for confirmation of the compound. In the IR spectra of secondary amides free N-H stretching vibration is observed near 3500-3400 cm^{-1}, which was observed in all synthesized compounds (3.1-3.10) as given below in the description of individual compounds. Two other peaks for carbonyl functional groups were obtained at for acyclic (Amide I) band and cyclic imidazolone ring between 1780-1700 cm^{-1} and 1665-1650 cm^{-1}, respectively. The carbonyl absorption band of amides occurs at longer wavelengths than normal carbonyl absorption due to resonance effect. This also confirms the absence of band at 1790 cm^{-1} for azlactones. The other band for amides (Amide II) occurs due to N-H bending and is usually of half to one third the intensity of amide-I band. In secondary acyclic amides as with the synthesized compounds the peaks appeared in the region of 1570-1515 cm^{-1}. This band results from interaction between N-H bending and C-N stretching of the C-N-H group. Other individual peaks are discussed in table-3.

In the proton NMR spectra different types of protons can be accounted *viz.* aromatic, olefinic and amine and protons of acetanilide moiety. A singlet was obtained for olefinic proton between δ6.66-7.4, as there are no neighboring protons to couple. A weak singlet is also obtained for the proton attached to heterocyclic nitrogen which is attributed to the proton-exchange rate on nitrogen atom. The aromatic protons appear as a multiplet as there are three aromatic rings, with different substitutions. Compound 3.1 is only mono substituted, compound 3.4 and 3.5 are ortho-para substituted and meta-para disubstituted while other are substituted at both the para positions. Multiplets are also obtained for the third aromatic ring, containing only four protons, of acetanilide group. The calculated values appeared in the region of δ 6.47-7.17 which are in agreement with the observed values obtained from the spectra.

Stereochemistry

It was discussed previously that the compounds were synthesized in Z configuration. It can be visualized that both the high priority groups in the synthesized compounds lie on one side of the double bond i.e. on left side, directly attached to carbon and having priority over H (C>H) and on the right side, double-bonded nitrogen having priority over carbon (N>C), according to the Cahn-Ingold-Prelog convention for a given stereocenter.



Docking Studies

Molecular docking studies were carried out using synthesized compounds as ligands' and enzyme cycloxygenase as receptor (PDB ID: 5COX). It was found that only one of the compounds **(3.10)** could be docked at the binding pocket of the receptor, obtaining a high glide score of = 9.9, the ligand-receptor interaction can be visualized in figure 1. The ligand forms hydrogen bonds with leucine and arginine with a bond distance of 2.222 and 2.216 A˚ and it was rewarded for hydrophobic enclosure of its aromatic and double bond linkage by residues of valine (523, 349), tyrosine (355, 348), phenylalanine (518, 381), isoleucine (517), tryptophan (387), leucine (384) and alanine (527) as seen in figure 2. Hydrophobic atoms on the protein that are necessary for recognition of hydrophobic enclosure are displayed in CPK representation in gray. The molecule was penalized for having two free rotatory bonds at aromatic positions which increase the entropy of the system and hence the G score (figure 3).

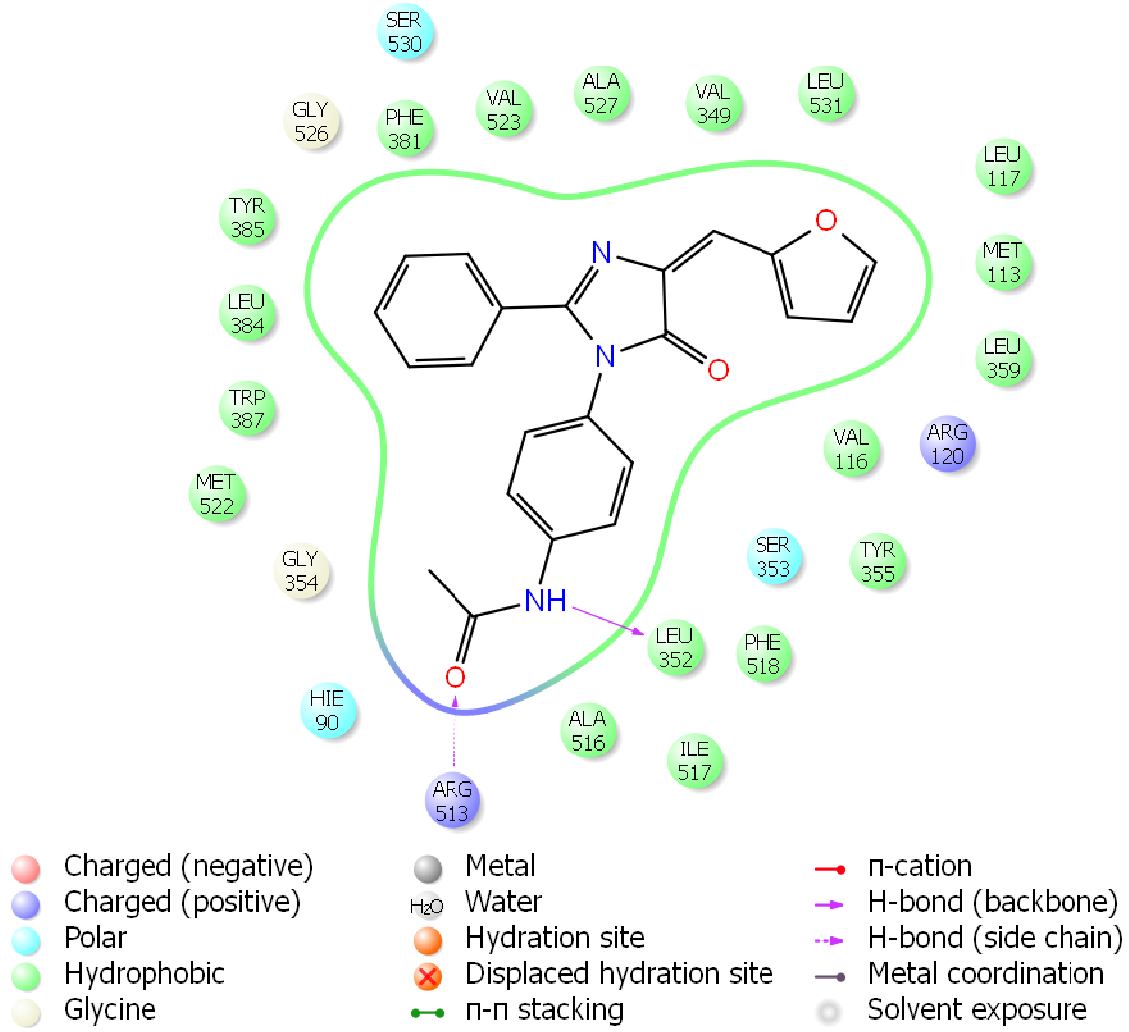


Figure 1: Ligand interaction diagram for receptor and compound (3.10)

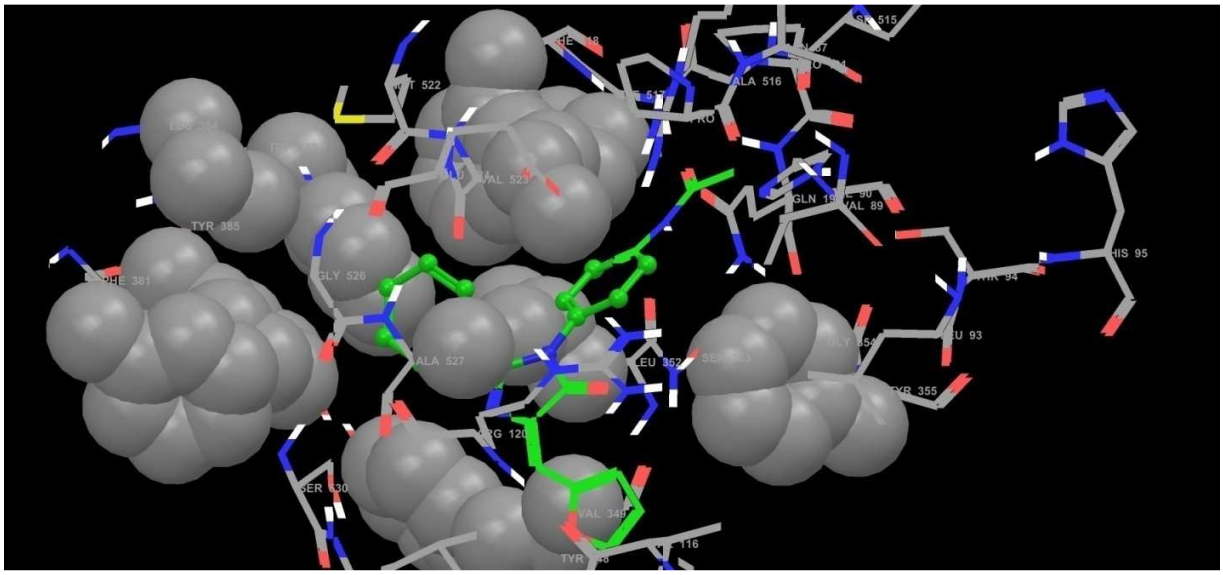


Figure 2: Hydrophobic enclosure of ligand

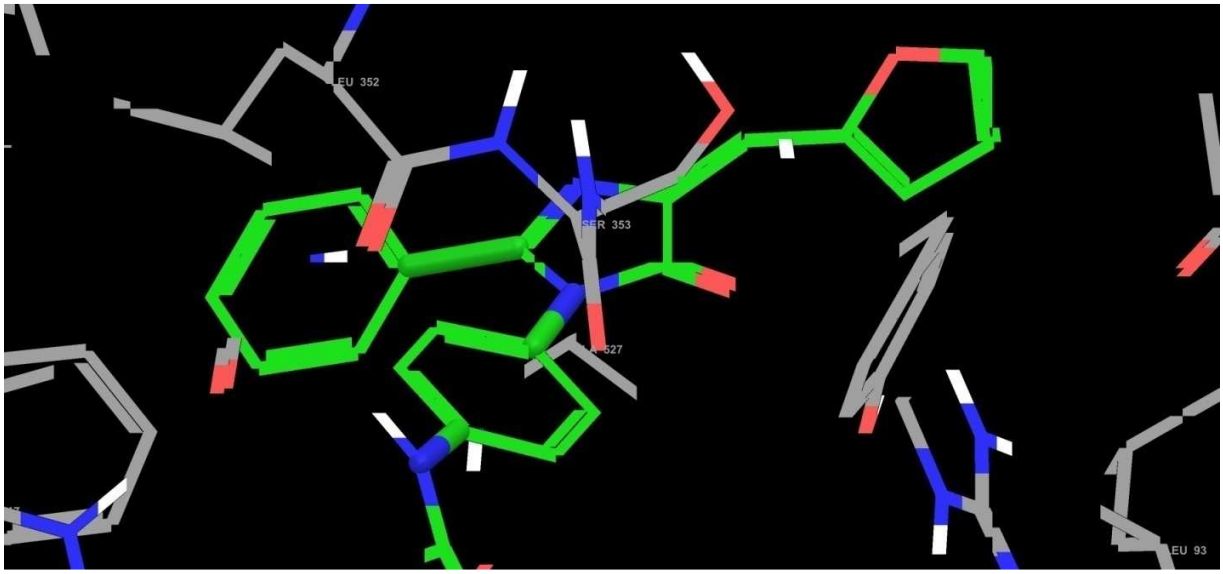
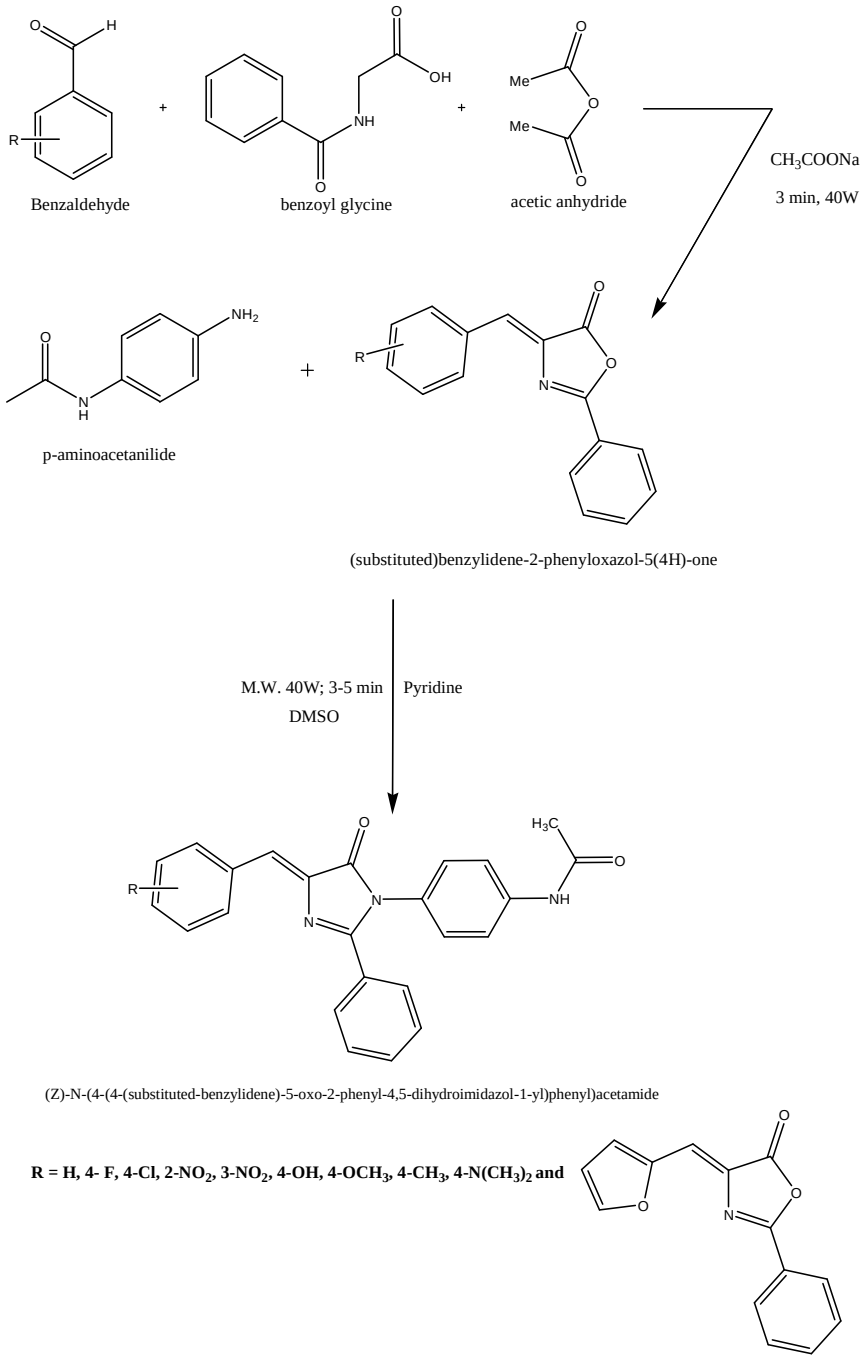


Figure 3: Rotatory penalty for –CH_2- molecule attached to pyridine ring

Scheme-2



R = H, 4- F, 4-Cl, 2-NO_2, 3-NO_2, 4-OH, 4-OCH_3, 4-CH_3, 4-$N(CH_3)_2$ and

Table 1 Physical data of compounds synthesized in Step-1 (1.1-1.10)

C. No.	Name	M.P. (˚C)	IR
1.1	*(Z)-4-benzylidene-2-phenyloxazol-5(4H)-one*	167-169	3078 cm^{-1} (Ar-H), 3090 (Ar-CH=C-), 1790 cm^{-1} (C=O oxazole), 1652 cm^{-1}(C=N oxazole), 1630, 1591 cm^{-1} (conjugated olefins).
1.2	*(Z)-4-(4-fluorobenzylidene)-2-phenyloxazol-5(4H)-one*	179-182	3073 cm^{-1} (Ar-H), 3015 cm^{-1} (Ar-CH=C-), 1795 cm^{-1} (C=O oxazole), 1652 cm^{-1} (C=N oxazole), 1628 , 1594 cm^{-1} (conjugated olefins), 1235 cm^{-1} (C-F).
1.3	*(Z)-4-(4-chlorobenzylidene)-2-phenyloxazol-5(4H)-one*	187-188	3088cm^{-1} (Ar-H), 3015 cm^{-1} (Ar-CH=C-), 1800 cm^{-1} (C=O oxazole), 1655 cm^{-1} (C=N oxazole), 1632, 1597 cm^{-1} (conjugated olefins) 1090 cm^{-1} (C-Cl).
1.4	*(Z)-4-(2-nitrobenzylidene)-2-phenyloxazol-5(4H)-one*	135-140	3085 cm^{-1} (Ar-H), 850 cm^{-1} (C-N, $ArNO_2$), 1550, 1335 cm^{-1} (N=O, $ArNO_2$), 3020 (Ar-CH=C-), 1638 cm^{-1}, 1594 cm^{-1} (conjugated olefins), 1790 cm^{-1} (C=O oxazole), 1655 cm^{-1} (C=N oxazole).
1.5	*(Z)-4-(3-nitrobenzylidene)-2-phenyloxazol-5(4H)-one*	163-165	3045 cm^{-1} (Ar-H), 3016 cm^{-1} (Ar-CH=C-), 1625, 1600 cm^{-1} (conjugated olefins), 1792 cm^{-1} (C=O oxazole), 1650 cm^{-1} (C=N oxazole), 1520, 1345 cm^{-1} (N=O, $ArNO_2$), 855 cm^{-1} (C-N, $ArNO_2$).
1.6	*(Z)-4-(4-hydroxybenzylidene)-2-phenyloxazol-5(4H)-one*	170-172	3215 cm^{-1} (*br*, O-H str, Ar-OH), 3045 cm^{-1} (Ar-H), 3020 (Ar-CH=C-), 1792 cm^{-1} (C=O oxazole), 1650 cm^{-1} (C=N oxazole), 1630, 1596 cm^{-1} (conjugated olefins).
1.7	*(Z)-4-(4-methoxybenzylidene)-2-phenyloxazol-5(4H)-one*	158-160	3062 cm^{-1} (Ar-H), 3010 cm^{-1} (Ar-CH=C-), 2950, 2830 cm^{-1} (C-H, CH_3), 1790 cm^{-1} (C=O oxazole), 1652 cm^{-1} (C=N oxazole), 1632, 1600 cm^{-1} (conjugated olefins), 1245, 1030 cm^{-1} (Ar-O-CH_3 asym and sym str).
1.8	*(Z)-4-(4-methylbenzylidene)-2-phenyloxazol-5(4H)-one*	138-140	3068 cm^{-1} (Ar-H), 3000 cm^{-1} (Ar-CH=C-), 2910, 2860 cm^{-1} (Ar-CH_3), 1785 cm^{-1} (C=O oxazole), 1650 cm^{-1}(C=N oxazole), 1630, 1600 cm^{-1} (conjugated olefins).
1.9	*(Z)-4-(4-(dimethylamino)benzylidene)-2-phenyloxazol-5(4H)-one*	158-160	3070 cm^{-1} (Ar-H), 3012 cm^{-1} (Ar-CH=C-), 1782 cm^{-1} (C=O oxazole), 1655 cm^{-1} (C=N oxazole), 1628, 1598 cm^{-1} (conjugated olefins), 1325 cm^{-1} (Ar-N-$(CH_3)_2$).
1.10	*(Z)-4-(furan-2-ylmethylene)-2-phenyloxazol-5(4H)-one*	158-162	3057 cm^{-1} (Ar-H), 3010-3000 cm^{-1} (multiple bands for Furan), 3015 cm^{-1} (Ar-CH=C-), 1640, 1594 cm^{-1} (conjugated olefins), 1785 cm^{-1} (C=O oxazole ring), 1655 cm^{-1}(C=N oxazole).

Table 2 Physical data of compounds synthesized in Step-2 (3.1-3.10)

C. No.	Name	M. F.	Yield	M.P. (°C)	R_f
3.1	*(Z)-N-(4-(4-benzylidene-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide*	$C_{24}H_{19}N_3O_2$	98%	198-202	0.56
3.2	*(Z)-N-(4-(4-(4-fluorobenzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide*	$C_{24}H_{18}FN_3O_2$	92%	222-224	0.56
3.3	*(Z)-N-(4-(4-(4-chlorobenzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide*	$C_{24}H_{18}ClN_3O_2$	94%	220-222	0.58
3.4	*(Z)-N-(4-(4-(2-nitrobenzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide*	$C_{24}H_{18}N_4O_4$	82%	108-110	0.58
3.5	*(Z)-N-(4-(4-(3-nitrobenzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide*	$C_{24}H_{18}N_4O_4$	86%	154-156	0.56
3.6	*(Z)-N-(4-(4-(4-hydroxybenzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide*	$C_{24}H_{19}N_3O_3$	89%	190 (decompose) 230 (melts)	0.5
3.7	*(Z)-N-(4-(4-(4-methoxybenzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide*	$C_{25}H_{21}N_3O_3$	92%	138-142	0.57
3.8	*(Z)-N-(4-(4-(4-methylbenzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide*	$C_{25}H_{21}N_3O_2$	90%	108-110	0.6
3.9	*(Z)-N-(4-(4-(4-(dimethylamino)benzylidene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide*	$C_{26}H_{24}N_4O_2$	92%	---	0.6
3.10	*(Z)-N-(4-(4-(furan-2-ylmethylene)-5-oxo-2-phenyl-4,5-dihydroimidazol-1-yl)phenyl)acetamide*	$C_{22}H_{17}N_3O_3$	97%	120-122	0.8

Table 3 Spectral data of compounds synthesized in Step-2

C. No.	IR	NMR	Mass
3.1	IR (KBr): 3400 cm^{-1} (N-H str), 1710 cm^{-1} (acyclic >C=O), 1650 cm^{-1} (cyclic-C=O), 1555cm^{-1} (-N-H bend).	^{1}H NMR (DMSO): δ 2.13 (s, 3H, -CO-C*H*$_3$), δ 6.92 (s, 1H, ArC=C*H*-), δ 7.28-7.79 (m, 14H, Ar*H*), δ 8.04 (s, 1H, -N*H*).	MS (m/e): 381.15 (100.0%), 382.15 (26.3%)
3.2	3420 cm-1 (N-H str), 1703 cm-1 (acyclic >C=O), 1652 cm-1 (cyclic-C=O), 1515cm-1 (-N-H bend).	1H NMR (DMSO): δ 2.10 (s, 3H, -CO-CH3), δ 7.0 (s, 1H, ArC=CH-), δ 6.9-7.61 (m, 13H, ArH), δ 8.0 (br, s, 1H, -NH).	
3.3	IR (KBr): 3423 cm-1 (N-H str), 1700 cm-1 (acyclic >C=O), 1654 cm-1 (cyclic-C=O), 1512 cm-1 (-N-H bend).	1H NMR (DMSO): δ 2.09 (s, 3H, -CO-CH3), δ 7.07 (s, 1H, ArC=CH-), δ 7.22-7.67 (m, 13H, ArH), δ 8.2 (br, s, 1H, -NH).	
3.4	IR (KBr): 3430 cm-1 (N-H str), 1690 cm-1 (acyclic >C=O), 1652 cm-1 (cyclic-C=O), 1520 cm-1 (-N-H bend).	1H NMR (DMSO): δ 2.06 (s, 3H, -CO-CH3), δ 7.7 (s, 1H, ArC=CH-), δ 7.28-8.12 (m, 13H, ArH), δ 8.16 (br, s, 1H, -NH).	MS (m/e): 426.13 (100.0%)
3.5	IR (KBr): 3430 cm-1 (N-H str), 1690 cm-1 (acyclic >C=O), 1652 cm-1 (cyclic-C=O), 1520 cm-1 (-N-H bend).	1H NMR (DMSO): δ 2.11 (s, 3H, -CO-CH3), δ 7.07 (s, 1H, ArC=CH-), δ 7.3-8.23 (m, 13H, ArH), δ 8.16 (br, s, 1H, -NH).	
3.6	IR (KBr): 3402 cm-1 (N-H str), 3205 (br –O-H str), 1790 cm-1 (acyclic >C=O), 1656 cm-1 (cyclic-C=O), 1528 cm-1 (-N-H bend).	1H NMR (DMSO): δ 2.06 (s, 3H, -CO-CH3), δ 6.97 (s, 1H, ArC=CH-), δ 6.8-7.62 (m, 13H, ArH), δ 8.16 (br, s, 1H, -NH), δ 12.9 (br, 1H, Ar-OH).	MS (m/e): 397.14 (100.0%), 398.15 (26.3%)
3.7	IR (KBr): 3435 cm-1 (N-H str), 1704 cm-1 (acyclic >C=O), 1652 cm-1 (cyclic-C=O), 1520 cm-1 (-N-H bend), 1240 cm-1 (asym Ar-O-CH3 str), 1023 (sym Ar-O-CH3 str).	1H NMR (DMSO): δ 2.12 (s, 3H, -CO-CH3), δ 3.89 (s, 3H, Ar-O-CH3), δ 7.7 (s, 1H, ArC=CH-), δ 6.79-7.69 (m, 13H, ArH), δ 8.12 (br, s, 1H, -NH).	
3.8	IR (KBr): 3432 cm-1 (N-H str), 1692 cm-1 (acyclic >C=O), 1653 cm-1 (cyclic-C=O), 1520 cm-1 (-N-H bend).	1H NMR (DMSO): δ 2.06 (s, 3H, -CO-CH3), δ 2.39 (s, H, Ar-CH3), δ 6.98 (s, 1H, ArC=CH-), δ 7.26-7.59 (m, 13H, ArH), δ 8.10 (br, s, 1H, -NH).	
3.9	IR (KBr): 3430 cm-1 (N-H str), 1702 cm-1 (acyclic >C=O), 1660 cm-1 (cyclic-C=O), 1517cm-1 (-N-H bend), 1320 cm-1 (Ar-N-(CH3)2).	1H NMR (DMSO): δ 2.09 (s, 3H, -CO-CH3), δ 3.06 (s, H, Ar-N-(CH3)2), δ 7.01 (s, 1H, ArC=CH-), δ 6.7-7.67 (m, 13H, ArH), δ 8.02 (br, s, 1H, -NH).	
3.10	IR (KBr): 3430 cm-1 (N-H str), 1695 cm-1 (acyclic >C=O), 1658 cm-1 (cyclic-C=O), 1510cm-1 (-N-H bend).	1H NMR (DMSO): δ 2.09 (s, 3H, -CO-CH3), δ 7.27-8.12 (m, 3H, 2-furyl), δ 6.66-7.67 (m, 10H, ArH), δ 8.15 (br, s, 1H, -NH).	MS (m/e): 371.13 (100.0%).

Table 4 Docking scores of compound (3.10) with its isomers

ligand	Isomer	Gscore[a]	Lipophilic EvdW[b]	PhobEn[c]	HBond[d]	Electro[e]	Sitemap[f]	LowMW[g]	Penalties[h]	RotPenal[i]
3.10	1	-9.91	-5.74	-2.44	-0.53	-0.35	-0.77	-0.26	0	0.18
	2	-9	-5.87	-2.24	-0.62	-0.37	-0.81	-0.26	1	0.18
	3	-3.89	-6.49	-2.42	0	0	-0.9	-0.26	6	0.18

[a]Glide Score; [b]LipophilicEvdW- Lipophilic term derived from hydrophobic grid potential and fraction of the total protein-ligand vdW energy [c]PhobEn- Hydrophobic enclosure reward; [d]HBond- Chem core H bond term; [e]Electro- electrostatic reward; [f]Sitemap- ligand complementarity terms; [g]LowMW- reward for ligand with low molecular weight; Penalties[h]- Penalty for polar atom burial ; RotPenal[i]- Penalty for roation about C-C bond

CONCLUSION

Ten imidazole derivatives were successfully synthesized as COX-2 inhibitors and it was found that only one of the compounds could be docked at the receptor site of 5COX. The docking studies revealed that the docked compound **3.10** scores well and could be used for further for designing potent analgesic agents.

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