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Microwave Assisted Synthesis, Characterization, Molecular Docking and Antiinflammatory Activity of *p*-Methoxy Cinnamic Acid Derivatives

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All the title compounds benzamido-(4-methoxy)-N^2-(arylidene)cinnamic acid hydrazide (**1-13**) were synthesized by the microwave irradiation of α-benzamido-(4-methoxy)cinnamalhydrazide (**II**) with different aromatic/hetero aromatic aldehydes and characterized by IR, ^{1}H and ^{13}C NMR, Mass spectral and elemental analysis. Furthermore, all the new derivatives were screened for antiinflammatory activity by Carrageenan induced rat paw edema method. Compound **3**, **6** and **12** exhibited highest activities, which are further supported by molecular docking studies showed -9.7, -8.1 and -8.6 as dock scores respectively. All the title compounds obey the Lipinski rule of five and devoid from toxicity assessed by Molinspiration and Osiris online predictors respectively.

Keywords: Cinnamamic acid derivatives, Microwave technique, Antiinflammatory activity, Molecular docking, Lipinski rule of five.

INTRODUCTION

Inflammation is the body's immune response to eliminates the harmful stimuli and begin the healing process. NSAIDS are the first drugs of choice to treat inflammation have several side effects. To overcome these drawbacks different specific COX-2 inhibitors were introduced. However these are also withdrawn from the market due to their potential side effects [1]. All these obstacles prompted us to introduce the newer agents, which are devoid from the side effects. On the other hand cinnamic acid and its derivatives possess wide range of biological activities such as antiinflammatory [2,3], antimicrobial [4,5], antioxidant [6], cytotoxicity [7], antihyperlipidemic [8.9] activities, *etc*. In addition to this, literature review more and more focused on another versatile molecule acylhydrazone exhibited number of biological activities which includes antiinflammatory [10,11], analgesic [12], antioxidant [13], antimicrobial [14,15], anticancer [16], antituberculosis [17,18], antiviral [19] and antiamoebic activities [20], *etc*. In the present era microwave chemistry plays an important role in synthetic chemistry and reduced the time from hours to minutes and also enhances the purity and yields [21].

In light of these facts we have planned to synthesize the *p*-methoxy cinnamic acid derivatives by hybridization between the two important pharmacophores such as cinnamic acid and hydrazone moieties in order to enhance their multi-target abilities. All the *p*-methoxy cinnamic acid derivatives were synthesized by using microwave technique completes the reaction with less reaction time and screened for antiinflammatory (*in vivo* and molecular docking studies against COX-2 protein (pdb code: 3LN1)) activity. Further the study was continued with the prediction of Lipinski rule of five, bioactive scores, drug likeness score and toxicity profile of synthesized compounds.

EXPERIMENTAL

All the melting points reported in this series were determined in open capillaries using Thermonik Pricision melting point cum boiling point apparatus C-PMB and are uncorrected. Homogeneity of the compounds was checked by using precoated TLC plates. The IR spectra were recorded using KBr pellets on a Perkin-Elmer 1760 spectrophotometer. ^{1}H, ^{13}C NMR spectra were recorded on Bruker Advance/Jeol 400 MHz spectrophotometer, using tetramethyl silane as internal standard. Mass spectra were recorded on an Apex Mass spectrophotometer, elemental analysis were performed using Flash EA1112 CHNS analyzer. Microwave irradiation was carried out in a domestic microwave oven (LGMS, 2.45 MHz). All the solvents and chemicals were procured from Sigma Aldrich and used without purification.

Synthesis of 2-phenyl-4-(4-methyl phenyl)oxazol-5-one (I): Synthesis of 2-phenyl-4-(4-methoxy phenyl)-oxazol-5-one was done accordance with the previously reported method [22].

Synthesis of α-benzamido-(4-methoxy)cinnamahydrazide (II): 2-Phenyl-4-(4-methoxy phenyl)oxazol-5-one (**2**) (0.02 mmol) was stirred with a solution of hydrazine hydrate

(0.04 mmol) in ethanol (30 mL) for 30 min. The bright yellow colour of oxazolone immediately changed to light yellow colour, which was filtered, washed, used in next step. Yield: 79 %; m.p. 155-157 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3228, 3242 (NH_2), 3073 (Ar C-H), 1651 (C=O), 1573 (C=C).

General procedure for the synthesis of benzamido-(4-methoxy)-N²-(arylidene)cinnamic acid hydrazide (1-13): Equimolar ratios of α-benzamido-(4-methoxy)-cinnamahydrazide (**II**) and different benzaldehydes (0.01 mol) in absolute ethanol with few drops of glacial acetic acid were transferred in to reaction flask and allowed to microwave irradiation at 210 watts with 30 s of interval for about 60-210 s. The reaction was monitored by TLC and the mixture was allowed to cool at room temperature, filter and purified by recrystallization from methanol [23]. The physical data of all the *p*-methoxy cinnamic acid derivatives (**1-13**) were given below.

Benzamido-(4-methoxy)-N²-(benzylidene)cinnamic acid hydrazide (1) [24]**:** Yield: 71 %; m.p. 180-182 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3201 (N-H), 3044 (Ar C-H), 1634 (C=O), 1602 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.77 (s, 3H, OCH_3), 6.95-8.06 (m, 15H, Ar C-H, C=C), 8.42 (s, 1H, CH=N), 10.03 (s, 1H, CONH), 11.60 (s, 1H, CONHN); EI-MS *m/z*; 399 (M^+). Anal. calcd. for $C_{24}H_{21}N_3O_3$ (%): C, 72.16; H, 5.30; N, 10.52. Found: C, 72.25; H, 5.39; N, 10.30.

Benzamido-(4-methoxy)-N²-(4-methoxy benzylidene)-cinnamic acid hydrazide (2) [23]**:** Yield: 73 %; m.p. 184-186 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3244 (N-H), 3075 (Ar C-H), 1659 (C=O), 1599 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.77 (s, 3H, -OCH_3), 3.80 (s, 3H, -OCH_3), 6.95-8.05 (m, 14H, Ar-C-H, C=CH), 8.33 (s, 1H, CH=N), 10.02 (s, 1H, CONH), 11.49 (s, 1H, CONHN); EI-MS *m/z*; 429 (M^+). Anal. calcd. for $C_{25}H_{23}N_3O_4$ (%): C, 69.92; H, 5.40; N, 9.78. Found: C, 69.88; H, 5.48; N, 9.69

Benzamido-(4-methoxy)-N²-(3,4-dimethoxy benzylidene)cinnamic acid hydrazide (3): Yield: 69 %; m.p. 197-199 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3262 (N-H), 3023 (Ar C-H), 1662 (C=O), 1603 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.77-3.78 (s, 9H, -OCH_3), 6.85-8.07 (m, 13H, Ar C-H, C=C), 8.21 (s, 1H, HC=N), 10.06 (s, 1H, CONH), 11.52 (s, 1H, CONHN); ^{13}C NMR (100 MHz, DMSO-d_6): δ 55.9, 56.2, 114.2, 114.4, 115.4, 122.4, 122.5, 127.1, 127.4, 127.5, 128.9, 132.2, 134.2, 143.0, 149.9, 152.1, 159.9, 163.6, 168.Anal. calcd. for $C_{26}H_{25}N_3O_6$ (%): C, 67.96; H, 5.48; N, 9.14. Found: C, 67.84; H, 5.37; N, 9.25.

Benzamido-(4-methoxy)-N²-(3,4,5-trimethoxy benzylidene)cinnamic acid hydrazide (4): Yield: 65 %; m.p. 211-213 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3278 (N-H), 3011 (Ar C-H), 1652 (C=O), 1598 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.78-3.81 (s, 12H, -OCH_3), 6.91-8.02 (m, 12H, Ar C-H), 8.28 (s, 1H, HC=N), 10.01 (s, 1H, CONH), 11.38 (s, 1H, CONHN); EI-MS *m/z*; 489 (M^+). Anal. calcd. for $C_{27}H_{27}N_3O_6$ (%): C, 66.25; H, 5.56; N, 8.58. Found: C, 66.36; H, 5.48; N, 8.48.

Benzamido-(4-methoxy)-N²-(4-hydroxy benzylidene)-cinnamic acid hydrazide (5): Yield: 70 %; m.p. 189-191 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3207 (N-H), 3101 (Ar C-H), 1675 (C=O), 1612 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.74 (s, 3H, Ar-OCH_3), 6.91-8.20 (m, 14H, Ar C-H, C=C), 8.21 (s, 1H, HC=N), 9.62 (s, 1H, Ar-OH), 10.12 (s, 1H, CONH), 11.42 (s, 1H, CONHN); Anal. calcd. for $C_{24}H_{21}N_3O_4$ (%): C, 69.39; H, 5.10; N, 10.11. Found: C, 69.43; H, 5.17; N, 10.23.

Benzamido-(4-methoxy)-N²-(3,4-dihydroxy benzylidene)cinnamic acid hydrazide (6): Yield: 63 %; m.p. 196-198 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3365 (Ar-OH), 3274 (N-H), 3051 (Ar C-H), 1678 (C=O), 1594 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.76 (s, 3H, -OCH_3), 6.80-7.93 (m, 13H, Ar C-H, HC=C), 8.13 (s, 1H, HC=N), 9.60 (s, 2H, Ar-OH), 10.00 (s, 1H, CONH), 11.37 (s, 1H, CONHN); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.9, 114.2, 122.4, 127.4, 127.5, 128.9, 132.2, 134.2, 143.0, 147.4, 149.6, 163.6. Anal. calcd. for $C_{24}H_{21}N_3O_5$ (%): C, 66.81; H, 4.91; N, 9.74. Found: C, 66.74; H, 4.85; N, 9.70;

Benzamido-(4-methoxy)-N²-(4-chlorobenzylidene)-cinnamic acid hydrazide (7): Yield: 76 %; m.p. 170-172 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3221 (N-H), 3091 (Ar C-H), 1665 (C=O), 1601 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.76 (s, 3H, -OCH_3), 7.01-8.24 (m, 14H, Ar C-H), 8.27 (s, 1H, HC=N), 10.17 (s, 1H, CO-NH), 11.48 (s, 1H, CO-NHN); ^{13}C NMR (100 MHz, DMSO-d_6) δ 55.9, 114.2, 122.4, 127.4, 127.5, 127.8, 128.9, 129.0, 130.6, 131.9, 132.2, 134.2, 143.0, 159.9, 163.6, 168.0. EI-MS *m/z*; 433 (M^+). Anal. calcd. for $C_{24}H_{20}N_3O_3Cl$ (%): C, 66.44; H, 4.65; N, 9.68. Found: C, 66.51; H, 8.21; N, 9.57.

Benzamido-(4-methoxy)-N²-(2,4-dichlorobenzylidene)-cinnamic acid hydrazide (8): Yield: 74 %; m.p. 207-209 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3234 (N-H), 3078 (Ar C-H), 1681 (C=O), 1603 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ:3.73 (s, 3H, -OCH_3), 7.10-8.13 (m, 13H, Ar C-H, HC=C), 8.26 (s, 1H, HC=N), 10.36 (s, 1H, CONH), 11.51 (s, 1H, CONHN); Anal. calcd. for $C_{24}H_{19}N_3O_3Cl_2$ (%): C, 61.55; H, 4.09; N, 8.97. Found: C, 61.62; H, 4.13; N, 8.90.

Benzamido-(4-methoxy)-N²-(3-nitrobenzylidene)-cinnamic acid hydrazide (9): Yield: 78 %; m.p. 164-167 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3210 (N-H), 3061 (Ar C-H), 1656 (C=O), 1599 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.76 (s, 3H, -OCH_3), 7.11-8.21 (m, 14H, Ar C-H, HC=C), 8.28 (s, 1H, HC=N), 10.21 (s, 1H, CONH), 11.65 (s, 1H, CONHN); ^{13}C NMR (100 MHz, DMSO-d_6) δ55.9, 114.2, 122.4, 122.9, 126.2, 127.4, 127.5, 127.8, 128.9, 129.8, 132.2, 134.2, 134.7, 135.3, 143.0, 148.1, 163.6, 168, 169.9. Anal. calcd. for $C_{24}H_{20}N_4O_5$ (%): C, 64.86; H, 4.54; N, 12.61. Found: C, 64.84; H, 4.65; N, 12.48.

Benzamido-(4-methoxy)-N²-(3,4-dimethoxy-4-hydroxy benzylidene)cinnamic acid hydrazide (10): Yield: 65 %; m.p. 214-216 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3243 (N-H), 3031 (Ar C-H), 1683 (C=O), 1603 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.72-3.75 (s, 9H, OCH_3), 6.90-8.13 (m, 12H, Ar C-H, HC=C), 8.17 (s, 1H, HC=N), 9.46 (s, 1H, OH), 10.10 (s, 1H, CO-NH), 11.48 (s, 1H, CONHN); Anal. calcd. for $C_{26}H_{25}N_3O_6$ (%): C, 65.67; H, 5.30; N, 8.84. Found: C, 65.80; H, 5.54; N, 8.61.

Benzamido-(4-methoxy)-N²-(isopropyl benzylidene)-cinnamic acid hydrazide (11): Yield: 66 %; m.p. 207-209 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3237 (N-H), 3027 (Ar C-H), 1680 (C=O), 1610 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 1.2 (d, 6H, $(CH_3)_2$), 2.9 (s, 1H, $CH(CH_3)_2$), 3.73 (s, 3H, -OCH_3), 6.90-8.13 (m, 14H, Ar C-H, CH=C), 8.12 (s, 1H, CH=N), 10.09 (s,

1H, CO-NH), 11.52 (s, 1H, CONHN); Anal. calcd. for $C_{27}H_{27}N_3O_3$ (%): C, 73.45; H, 6.16; N, 9.52. Found: C, 73.55; H, 6.22; N, 9.78.

Benzamido-(4-methoxy)-N²-[(indol-3-yl)methylene]-cinnamic acid hydrazide (12): Yield: 73 %; m.p. 161-163 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3310 (N-H), 3061 (Ar-CH), 1682 (C=O), 1608 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.76 (s, 3H, -OCH_3), 6.96- 8.32 (m, 15H, Ar CH, CH=C), 10.06 (s, 1H, CO-NH), 10.51 (s, 1H, CO-NHN), 11.61 (s, 1H, NH); EI-MS *m/z*; 439 $(M+1)^+$. Anal. calcd. for $C_{26}H_{22}N_4O_3$ (%): C, 70.89; H, 5.49; N, 12.72. Found: C, 70.61; H, 5.36; N, 12.71.

Benzamido-(4-methoxy)-N²-[(fur-2-yl)methylene]-cinnamic acid hydrazide (13): Yield: 68 %; m.p. 177-179 °C; IR (KBr, $\nu_{max,}$ cm^{-1}): 3256 (N-H), 3019 (Ar C-H), 1678 (C=O), 1588 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6) δ: 3.78 (s, 3H, -OCH_3), 6.70-7.96 (m, 13H, Ar C-H, HC=C), 8.09 (s, 1H, HC=N), 10.08 (s, 1H, CONH), 11.48 (s, 1H, CONHN); Anal. calcd. for $C_{22}H_{19}N_3O_4$ (%): C, 67.86; H, 4.92; N, 10.79. Found: C, 67.81; H, 4.88; N, 10.72.

Pharmacological screening

***in vivo* Antiinflammatory activity** [24]**:** The *in vivo* anti-inammatory activity of all title compounds was evaluated using carrageenan-induced rat paw edema in male albino rats (150-180 g) of Wistar strain. The rats were divided into groups of six animals. Control group received 0.5 % sodium carboxy methylcellulose, the standard group received standard drug indomethacin 5 mg/kg body weight and the test groups received the title compounds at the dose of 100 mg/kg body weight. The volume of paw was measured by plethysmograph immediately after carrageenan injection. The paw volume was again measured after 3 h. A mark was made at the lateral malleolus and the foot was dipped to the same distance into the arm of the plethysmograph. Average edema volumes for test compound treated and positive control rats were compared statistically and the percentage of edema inhibition was calculated using the formula:

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

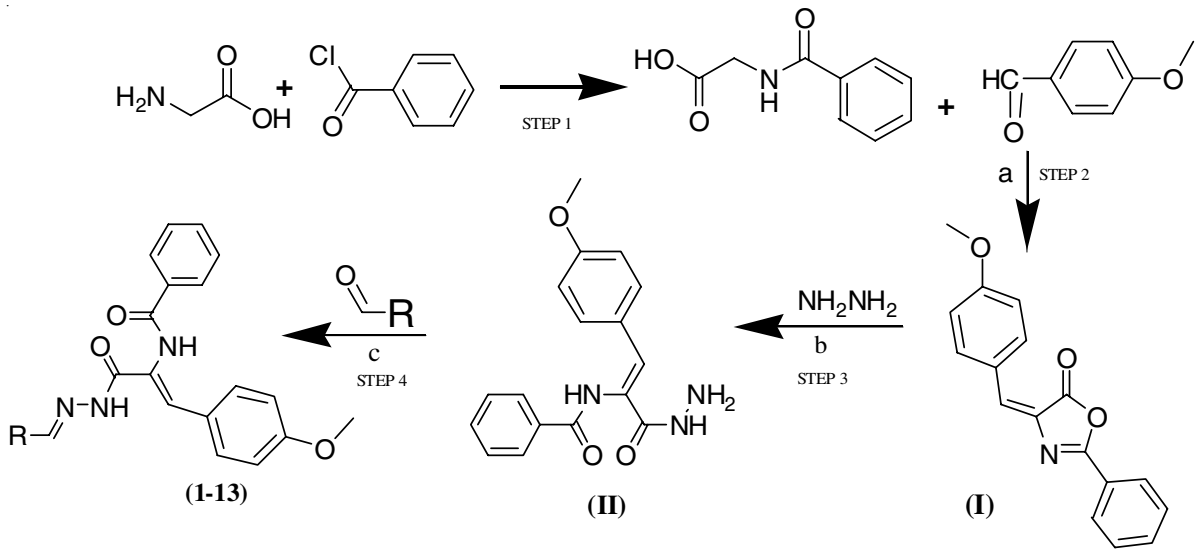
where, V_c volume of the edema in the control group and V_t volume of the edema in the treated group. Statistical significance of the results was tested by Dunnet's test.

Molecular docking: Molecular docking of compounds **1-13** with the 3D X-ray crystal structure of human COX-2 retrieved from the Protein Data Bank (PDB code: 3LN1) was imported in to MCULE, the online drug discovery plat form. The structure of title compounds were drawn using chem sketch 12.0 software available in MCULE and run the docking for a selected target. Consequently it generates the different pose of ligands with the target and among those we can select the best pose of ligand, which gained the good dock score.

Molecular property prediction: Molecular properties like log P (lipophilicity), total polar surface area (TPSA), number of hydrogen bond donors (HBD) and acceptors (HBA), number of rotatable bonds and as well as prediction of bioactivity score for the important drug targets like GPCR ligands, kinase inhibitors, ion channel modulators, enzymes and nuclear receptors were assessed by the online tool kit Molinspiration (www.molinspiraton.com) [25]. The Osiris Property Explorer is an integral part of Actelion's in-house substance registration system. It calculate the various drug relevant properties such as log S (solubility), drug likeness score and toxicity such as mutagenicity, tumorogenicity, irritant and reproductive effects [26].

RESULTS AND DISCUSSION

All the *p*-methoxy cinnamic acid derivatives (**1-13**) were synthesized by the reaction between the α-benzamido-(4-methoxy)-cinnamalhydrazide (**II**) and aromatic/hetero aromatic aldehydes under microwave irradiation with less reaction time (60-210 s) and yields were good (63-78 %) (**Scheme-I**). Compound **II** has been synthesized from



(a): $(CH_3CO)_2O$/zinc oxide; (b): Absolute ethanol, stirring; (c): MW at 210 watts; R = Phenyl (**1**); 4-methoxy phenyl (**2**); 3,4,-Dimethoxy phenyl (**3**); 3,4,5-Trimethoxy phenyl (**4**); 4-Hydroxy phenyl (**5**); 3,4-Dihydroxy phenyl (**6**); 4-Chloro phenyl (**7**); 2,4-Dichloro phenyl (**8**); 3-Nitro phenyl (**9**); 3,5-Dimethoxy-4-hydroxy phenyl (**10**); 4-Isopropyl phenyl (**11**); Indol-3-yl (**12**); 2-Furyl (**13**)

Scheme-I: General sequence of reactions for the synthesis of title compounds **1-13**

compound **I** by the action of hydrazine hydrate which attacks the oxazole ring at the highly susceptible carbonyl site. Compound **I** was prepared according to the procedure given in literature. All the title compounds were characterized by the spectral data IR, ^{1}H NMR, ^{13}C NMR, Mass and elemental analysis. The IR spectral data of title compounds **(1-13)** revealed bands at 3278-3201 cm^{-1} and 1681-1634 cm^{-1} due to the presence of NH and C=O peaks respectively. Appearance of two more bands between 3101-3011 cm^{-1} and 1612-1588 cm^{-1} regions indicated the presence of aromatic -C-H, C=C- groups in all the cinnamic acid hydrazides. ^{1}H NMR spectra data showed a singlet at δ 8.09-8.42 region due to CH=N indicates the formation of title compounds. Appearance of singlet at δ 10.00-10.36, δ 11.37-11.60 and δ 3.72-3.81 is due to the CONHC-, CONHN- and aromatic OCH_3 groups, respectively. Singlet at δ 1.2 and multiplet at δ 6.70-8.32 region due to the methyl (**11**) and aromatic protons of title compounds. Additional support for the structures of title compounds was provided by ^{13}C NMR spectra revealed two peaks at δ 163-169 and around δ 143-due to -CONH and HC=N, respectively. Appearance of peaks between δ 114-159 due to the presence of aromatic/heroaromatic carbons and also appearance of signal around δ 55 indicated the presence of-OCH_3. The mass spectral data revealed the presence of molecular ion peaks at *m/z* 399, 429, 489, 433 and 439 indicates the formation of title compounds **1**, **2**, **4**, **7** and **12**, respectively.

Antiinflammatory activity: All the title compounds **1-13** screened for *in vivo* antiinflammatory activity by carrageenan induced rat paw edema method and the results were given in Table-1. Among all, compound **3** exhibited highest activity which is equal to the standard drug indomethacin (74 %). Compounds **6** and **12** showed equal activities (72 %) which are comparable to the standard. The good activity of compound **12** might be due to the presence of additional electron rich heterocyclic ring at the hydrazone end of the molecule. This result is in accordance with the previous report stated that the presence of indole moiety in the acylhydrazone framework enhances the antiinflammatory activity [27,28]. Compounds **11** (4-isopropyl phenyl derivative), **7** (4-chloro phenyl derivative) and **1** (phenyl derivative) exhibited significant activities followed by 2-furyl, 4-methoxy and 4-hydroxy derivatives. The results suggested that the type of substitution at the hydrazone end played an important role such as presence of activating groups on the aromatic ring (compounds such as **2**, **3**, **5** and **11**) enhances the activity profile compared to the other substitutions (compound **9**, **13** and **7**) [19]. It is interesting to note that increases the number of methoxy group on the phenyl ring (at the imine end) increases the activity up to dimethoxy groups (compound **1 < 2 < 3 > 4** derivatives).

TABLE-1
in vivo ANTI-INFLAMMATORY ACTIVITY AND MOLECULAR DOCK SCORES OF TITLE COMPOUNDS **1-13**

S. No.	Compd.	Edema volume (± SD)[a]	Edema inhibition (%)[c]	Dock score (Kcal/mol)
1	**1**	0.17 (0.10)	68.5 *	-8.5
2	**2**	0.22 (0.04)	59.2	-8.0
3	**3**	0.14 (0.04)	74.0 *	-9.7
4	**4**	0.39 (0.02)	27.7 *	-6.6
5	**5**	0.25 (0.05)	53.7	-4.9
6	**6**	0.15 (0.04)	72.2*	-8.6
7	**7**	0.16 (0.08)	70.3*	-8.3
8	**8**	0.28 (0.22)	48.1	-7.8
9	**9**	0.33 (0.10)	38.8	-7.4
10	**10**	0.30 (0.01)	44.4 *	-7.7
11	**11**	0.16 (0.12)	70.3	-7.9
12	**12**	0.15 (0.06)	72.2 *	-8.1
13	**13**	0.19 (0.03)	64.8*	-8.2
14	**Std**	0.14 (0.02)	74.0*	-8.7

Significant levels *p < 0.001 by Dunnet's test; [a]Edema volume was measured 3 h after carrageenan injection and expressed as mean ± standard deviation; [b]Control edema volume = 0.54 ± 0.03; [c]At 100 mg/kg (p.o) percent edema inhibition was calculated by comparing edema volume of test/std with that of the respective control animals

Molecular docking: Further all the title compounds **1-13** were docked into COX-2 (PDB code: 3LN1) protein and the results were depicted in Table-1. Docking results revealed that the aromatic substitution at the hydrazide end is responsible for binding of ligand with the hydrophobic cavity of target protein, which alters the activity profile of compounds. All the derivatives showed good to moderate affinity towards the target assessed by using one click molecular docking tool. Among all compound **3** (-9.7) showed highest docking score

TABLE-2
MOLECULAR DESCRIPTORS OF TITLE COMPOUNDS **1-13**

Compd.	log P	log S	TPSA	% ABS	*n*-HBA	*n*-HBD	*n*-ROTB	MW	MUT	TUM	IRR	REPE	DL
1	4.7	-5.4	79.7	81.6	6	2	7	399	G	G	G	G	6.35
2	4.6	-5.5	89.0	78.3	7	2	8	429	G	G	G	G	6.35
3	4.6	-5.5	98.2	75.2	8	2	9	459	G	R	G	G	6.35
4	4.5	-5.5	107.5	72.0	9	2	10	489	G	G	G	G	6.35
5	4.4	-5.1	100.0	74.5	7	3	7	415	G	G	G	G	6.34
6	4.0	-5.8	120.2	67.6	8	4	7	431	G	G	G	G	6.34
7	5.3	-6.2	79.7	81.6	6	2	7	433	G	G	G	G	6.38
8	5.9	-6.9	79.7	81.6	6	2	7	468	G	G	G	G	6.38
9	4.1	-6.2	125.6	65.7	8	1	8	444	G	G	G	R	0.63
10	4.0	-4.8	118.4	68.3	8	2	9	475	G	G	G	G	4.72
11	5.9	-6.3	79.7	81.6	6	2	8	441	G	G	G	G	6.09
12	4.0	-5.6	95.5	76.1	7	3	7	438	G	G	G	G	7.16
13	3.9	-5.1	92.9	77.0	7	2	7	389	R	G	G	G	6.01

log P: Lipophilicity; log S: Solubility; TPSA: Total polar surface area; *n*-HBA: No of hydrogen bond acceptors; *n*-HBD: No of hydrogen bond donors; *n*-VIO: *n*-Violations; *n*-ROTB: No of rotatable bonds; MW: Molecular weight; MUT: Mutagenic; TUM: Tumerigenic; IRR: Irritant; REPE: Reproductive effect; DL: Drug-likeness score; G: No Risk; R: High Risk.

than standard indomethacin (-7.18) followed by compound **6** (-8.6), **1** (-8.5) and **7** (-8.3). Amino acids VAL 492, GLU493, GLY 495, ALA496, VAL 318, SER 322, LEU321, HIS 63, GLY 323, TYR 359, THR 356, GLU161, ASN 484, LEU 353, HIS 320, MET 491, LEU353, HIS 320, HER 322 and PHE 430 were found at the active site of human COX-2 with title compounds and illustrated in Figs. 1-4. Docking results of the active compounds were further supported by *in vivo* antiinflammatory results.

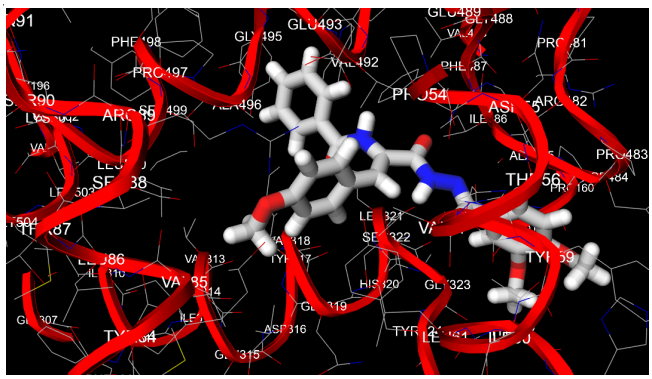


Fig. 1. Interaction of compound **3** with COX-2

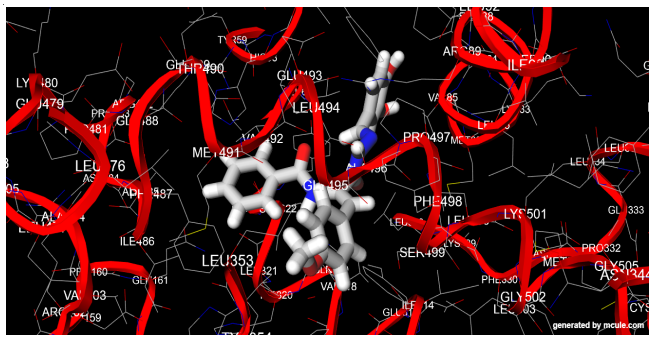


Fig. 2. Interaction of compound **6** with COX-2

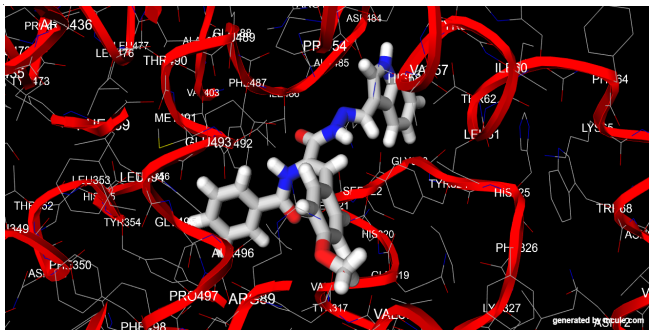


Fig. 3. Interaction of compound **12** with COX-2

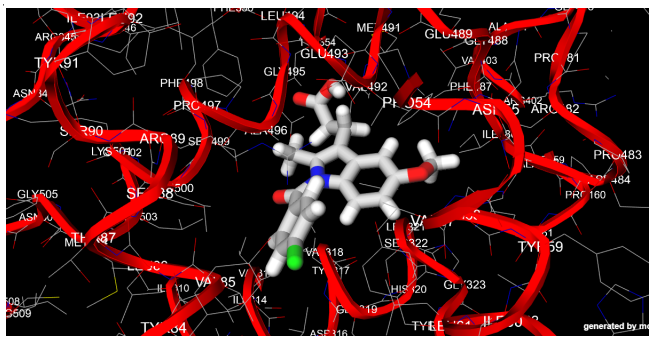


Fig. 4. Interaction of standard with COX-2

Molecular properties predictions: The efficacy of any drug depends on its high oral bioavailability in human beings. For any compound to become a successful drug candidate it should satisfy the Lipinski's rule of five which stated that any compound to become orally active drug, if it should have molecular weight not more than 500, partition coefficient (log P) below 5, number of hydrogen bond donors not more than 5 and number of hydrogen bond acceptors not more than 10. Topological polar surface area is another descriptor used to assess the drug transporter properties. TPSA is the sum of surfaces of polar atoms such as oxygen, nitrogen and attached hydrogen. The % of absorbance was calculated by the following equation [29]:

$$\% \text{ ABS} = (109\text{-}0.345) \times \text{TPSA}$$

The predicted values revealed that log P, TPSA, % absorption and log S found between 3.9 to 5.9; 79.2 to 125.6; 65.7 to 81.6 % and-4.82 to -6.90, respectively, Table-2. For a potent compound to be orally effective it should show no more than one violation of Lipinski's rule of five. The bioactivity scores of the title compounds **1-13** towards GPCR, kinase inhibitor, protease inhibitor and enzyme inhibitor mechanisms were calculated using Molinspiration programme and depicted in Table-3. If the bioactivity score for a molecule is more than 0 then it is active; between -0.5 to 0 then moderately active [30]. The results revealed that all the compounds displayed more selectivity towards enzyme inhibition (in the range of -0.30 to -0.54), which gave additional support to the result of predicted antiinflammatory activities [31]. It is interesting to note that compound **12** exhibited good affinity towards enzyme inhibition.

TABLE-3
BIOACTIVE SCORES OF TITLE COMPOUNDS **1-13**

Compd.	GPCRL	ICM	KI	NRL	PI	EI
1	-0.47	-0.77	-0.54	-0.82	-0.48	-0.41
2	-0.44	-0.72	-0.51	-0.77	-0.45	-0.38
3	-0.43	-0.70	-0.49	-0.74	-0.46	-0.37
4	-0.42	-0.71	-0.46	-0.74	-0.45	-0.35
5	-0.41	-0.70	-0.48	-0.70	-0.45	-0.35
6	-0.41	-0.69	-0.49	-0.70	-0.45	-0.34
7	-0.46	-0.75	-0.54	-0.81	-0.50	-0.42
8	-0.47	-0.75	-0.54	-0.84	-0.52	-0.42
9	-0.56	-0.75	-0.60	-0.83	-0.56	-0.47
10	-0.41	-0.67	-0.45	-0.68	-0.43	-0.31
11	-0.42	-0.70	-0.52	-0.71	-0.45	-0.37
12	-0.28	-0.65	-0.38	-0.72	-0.42	-0.30
13	-0.61	-0.86	-0.73	-1.07	-0.60	-0.54

GPCRL: G protein coupled receptor ligand; ICM: Ion channel modulators; KI: Kinase inhibitor; NRL: Nuclear receptor ligand; PI: Protease inhibitor; EI: Enzyme inhibitor.

However, toxicity is also one of the important issue could be addressed for all the lead compounds before its selection. All the title compounds **1-13** free from risk of toxicity (mutagenicity, tumorogenicity, irritability and reproductive effects) except compounds **9** and **13** predicted by OSIRIS. Drug likeness score may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs and positive scores are desirable. All the title compounds showed positive

drug likeness scores 0.63-7.16 and compound **12** scored the highest drug likeness score assessed by OSIRIS tool.

Conclusion

All the *p*-methoxy cinnamic acid derivatives (**1-13**) were synthesized in good yields with less reaction time by using microwave technique. Compound **3** exhibited good anti-inflammatory activity, which is comparable to the standard drug indomethacin. Further, the docking results of active compounds were correlated with the molecular docking results. Title compounds obey the Lipinski rule of five, good percentage of oral absorption and free from toxicity accessed by using different tools.

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