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Design, Synthesis and Studies of Structure Activity Relationship of γ-butyrolactones for Evaluation of Analgesic Activity

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ABSTRACT

Substituted Phenyl acetic acids have been used for the synthesis of various γ-butyrolactone. γ-butyrolactone compounds were designed by docking studies with cycloxygenase II active site. Thirteen compounds of γ-butyrolactone have been synthesized, characterized and subjected for analgesic activity in mice by hot plate method. Some of the compounds have been found to show better hydrogen and hydrophobic interactions with the cyclooxygenase enzyme. Out of 13 compounds 05 compounds have shown significant analgesic activity and can serve as future potential to be active as analgesic agents by inhibiting cyclooxygenase II enzyme. It has been observed that the analgesic activity of the compounds depends on the structure activity relationship of certain functional group. Structure activity relationship studies shows that by introduction of groups like halogens, hydroxyl and methoxy group plays a prominent role in enhancing analgesic activity of the substituted butyrolactones.

Key words: Analgesic, γ-butyrolactones, Cyclooxygenase, Hot plate method, Phenyl acetic acid

INTRODUCTION

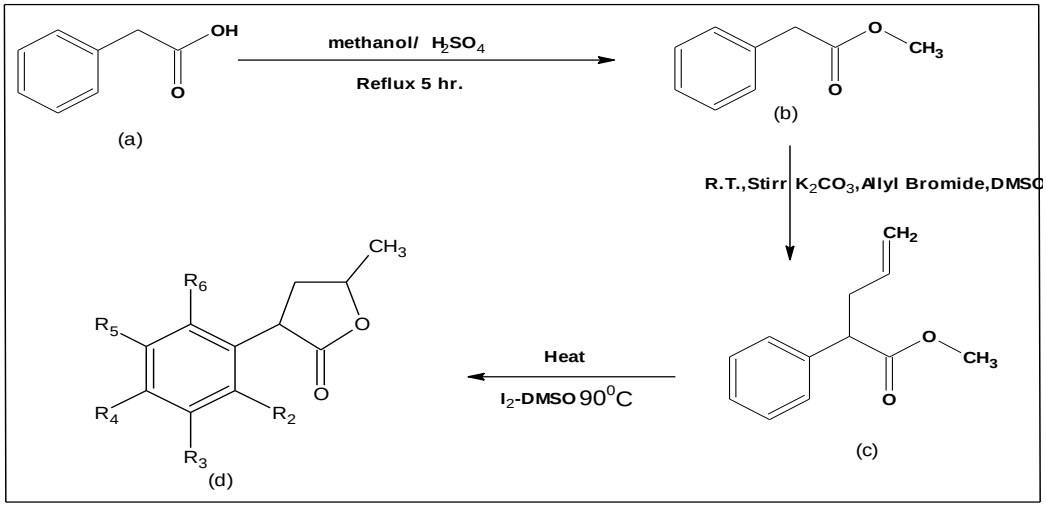
Gamma-Butyrolactone (GBL) is a well known class of natural products showing significant biological activities like anticancer [1], antimycobacterial [2], anti-inflammatory, analgesic [3], antiproliferative, vasoralxing activities [4]. Some of the structurally similar compounds to GBL like Gamma Hydroxy Butyric Acid (GHB) have exhibited anticonvulsant activity used for the tratment of cataplexy in patients with narcolepsy [5,6]. Some derivatives of GBL possess anticonvulsant and analgesic activity [7-9]. Many mono-, bi- and tri-substituted monocyclic γ-butyrolactones are known, to occur naturally. Presently available Non Steroidal Anti-inflammatory (NSAIDs) drugs are commonly used as analgeics for the treatment of mild to moderate pain. However extensive use of NSAIDs has certain disadvantages like GI irritation, bleeding and ulceration. In case of opioids analgesics dependence and serious adverse effects are observed. Hence there is a need to find the new compounds which can be used as alternative to existing drug molecules [10]. Litearture studies shows that very few data is available on analgesic activity of butyrolactones. GBL is a precurrsor for GHB and in literature it has been mentioed that some substituted γ-butyrolactone may be involved in the analgesic activity [11]. However very few work has been carried out on exploring the analgesic activity of γ-butyrolactones. In view of the reported diverse range of pharmacological activities of γ-butyrolactones and their role as analgesic agent we have decided to design and synthesize novel γ-butyrolactone derivatives to explore their potential analgesic activity. Present work deals with structure activity relationship studies of various phenyl substituents at positin 3 of γ-butyrolactone and analysis of their docking interactions with the cyclooxygenase enzyme. Analgesic activity is evaluated by hot plate method in mice.

MATERIALS AND METHODS

Molecular modeling is performed on a Pentium IV computer (CPU at 2.8 GHz) with Windows XP operating system using V-Life Sciences MDS Software. Melting points were determined with Veego melting point apparatus. R_f value was calculated for compounds using n-hexane: Ethyl acetate (9.0:1.0) as mobile phase. IR spectra in KBr were recorded on a FTIR Spectrophotometer with Diffuse Reflectance Attachment (Varian 680). ^{1}H-NMR spectra were obtained using Varian Mercury YH 300 Spectrometer. Analgesic activity was performed on Mvtex Analgesiometer.

Chemistry

Compounds have been synthesized as per the Scheme 1 for 5-(methyl)-3- phenyldihydrofuran-2-(3H)-one (d). (0.01 mol) of compound (a) was refluxed with 10 ml methanol and 2-3 drops of sulfuric acid for 5 h to (b) Followed by addition reaction with the help of allyl bromide and potassium bicarbonate at room temperature to form intermediate (c) followed by cyclisation reaction with Dimethyl Sulfoxide (I2-DMSO) solution and heating it to give 5-(methyl)-3-phenyldihydrofuran-2-(3H)-one (d). The synthesis starts with esterification of phenyl acetic acids (a) with methanol in presence of sulfuric acid. The esters of phenyl acetic acid were alkylated by using allyl bromide in the presence of anhydrous potassium carbonate at room temperature. Final step is the lactonisation of allyl esters by using catalytic amount of molecular iodine in DMSO solvent at 90°C which affords substituted γ-butyrolactone (d). It was found that the first step of reaction proceed well at 60°C with concentrated sulfuric acid. After each step, washing of the product was done with ethyl acetate and water. Product was found in organic layer after evaporation. Compounds have been characterized by spectral analysis like IR, ^{1}H-NMR and Mass spectra (Table 1).



Scheme 1: Synthesis of 5-(methyl)-3-phenyldihydrofuran-2-(3H)-one derivatives

Table 1: Physical data of synthesized derivatives

Sr. No.	Comp. Code	R_2	R_3	R_4	R_5	R_6	Mol. Wt.	% Yield	Boiling point (°C)	R_f value
1.	B1	H	H	H	H	H	176.21	80.00	204-206	0.59
2.	B14	OH	H	H	H	H	192.21	83.71	178-180	0.56
3.	B15	H	Cl	H	H	H	210.65	73.95	192-194	0.48
4.	B16	H	CH_3	H	H	H	190.23	71.46	164-166	0.61
5.	B17	H	OH	H	H	H	192.21	81.16	182-184	0.55
6.	B18	OCH_3	H	H	H	H	206.23	78.26	200-202	0.63
7.	B19	H	OCH_3	OCH_3	H	H	236.26	68.21	196-198	0.54
8.	B20	CH_3	H	CH_3	H	CH_3	218.29	74.33	176-178	0.49
9.	B21	H	H	Br	H	H	255.10	82.23	186-188	0.58
10.	B22	Br	H	H	H	H	255.10	84.25	194-196	0.62
11.	B23	H	OCH_3	H	H	H	206.23	80.51	202-204	0.53
12.	B24	H	H	H	C_2H_5O	H	220.26	69.79	168-170	0.59
13.	B25	H	OCH_3	OCH_3	OCH_3	H	266.28	68.89	172-174	0.57

Pharmacological studies

Acute toxicity studies

The animals were fasted for 24 h prior to the experiment and up and down procedure [12]. Organisation for Economic Co-operation and Development (OECD) guideline no. 425 Newly synthesized compounds suspended in 0.5% w/v Carboxy Methyl Cellulose (CMC) suspension and administered to groups of mice (n=6) upto a dose level of 2000 mg/kg b.w. p.o. Animals were placed individually in plastic cages and observed at least once daily for the first 30 min and periodically for 24 h to observe for signs of toxicity, compounds have been found to be safe upto dose level of 2000 mg/kg. From the acute toxicity studies the doses of 100 mg/kg was selected for further evaluation analgesic activity.

Analgesic activity by Hot plate test

For the analgesic activity, adult female Albino Swiss mice weighing 25-30 g were used [13]. The animals were kept in group of 6 mice in cages at temperature conditions of 22 ± 2°C, under a light/dark cycle and feeded well during storage. Each experimental group contained 6 animals and animals were kept on starvation for 20 h before experiment. The protocol for experiments was approved by Institutional Ethics Committee. In hot plate test mice were treated orally with the synthesized compounds (dose 100 mg/kg) and Standard group with standard Pentazocine (10 mg/kg; i. p.) and the control group with vehicle 15 min before being placed on a hot plate apparatus Mvtex Analgesiometer with temperature controlled at 55 ± 0.5°C. The latency to first sign of hind paw licking or jump response to avoid heat nociception was taken as an index of

nociceptive threshold with cut off time of 15 sec with the help of stop watch. The nociceptive threshold was observed at 15, 30, 60, 90, 120, 180 and 240 min after administration. Analgesic activity of the test compounds were compared with respect to control. Data was analyzed by Student's *t*-test for n=6 (P value<0.01).

Docking method

Cyclooxygenase-2 (COX-2) Protein Data Bank (PDB Code: 4COX) co-crystallized with Indomethacin as reference ligand was retrieved from the PDB. GRIP docking is done further on selected minimize energy conformers. V-life sciences software was used for the docking studies.

RESULTS AND DISCUSSION

The binding energy studies show favorable binding of selected ligands to the COX-2 enzymes. All the amino acids residues present in the active site of COX-2 enzyme were involved in the interactions with ligand. Compounds B15, B18 and B19 showed hydrogen bond interactions with Tyr355a, ARG120a residues. Reference ligand also exhibited interaction with similar amino acids residues at approximately similar inter atomic distances. Compound B15 shows binding of one hydrogen bond between O from C=O and Tyr355a with distance 2.231. Compound B18 forms 2 hydrogen bond interactions (Figure 1). One between methoxy group and ARG120a of distance 2.812 and another between O from C=O and Tyr355a of distance 2.127. Similarly Compound B19 (Figure 2) showed 2 hydrogen bond interactions of which one is between ARG120a and one methoxy group of distance 2.231 and one hydrogen bond between O from C=O and Tyr355a of distance 2.458.

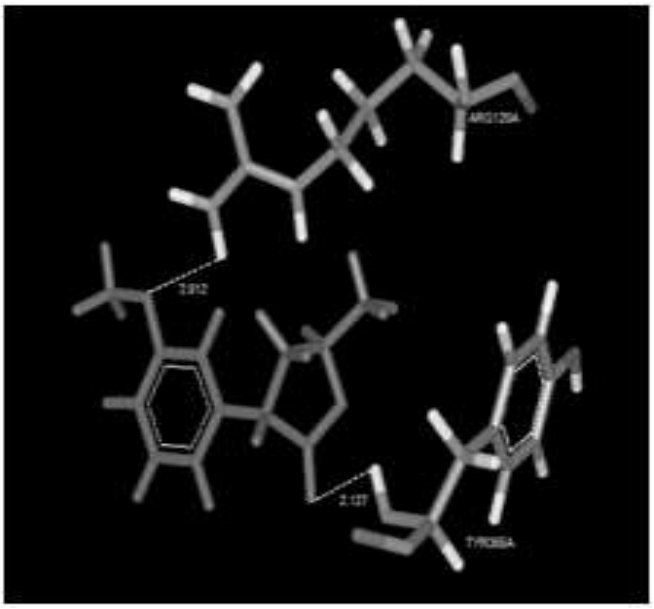


Figure 1: H-bond interactions of B18

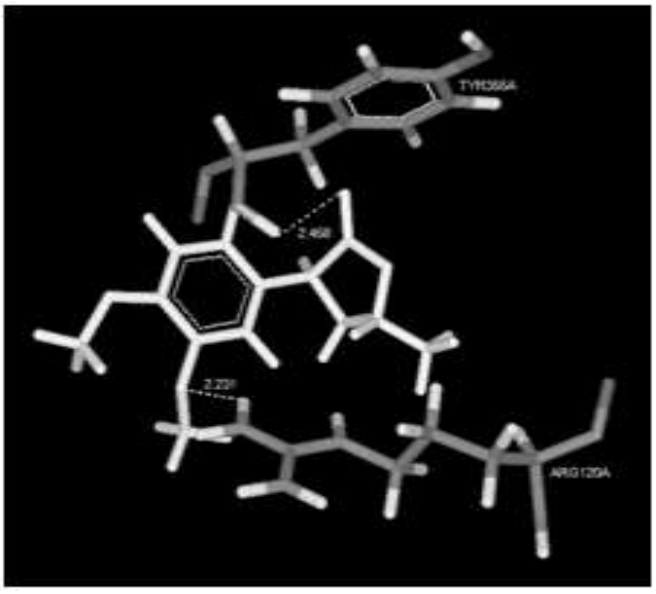


Figure 2: H-bond interactions of B1

Compound No. B17 and B22 also showed better binding with hydrophobic interaction and exhibited favorable interactions with the amino acid residues. The docking interactions suggests that introduction or substitution of halogens at position 2nd (B22) and 3rd (B15) shows better binding to active site. Similarly substitution of hydroxy group at 3rd position (B17) is important for interaction with amino acids residues. Substitution of methoxy group at 2nd, 3rd and 4th position (B18 and B19) also exhibited better binding in docking studies.

Docking studies were used to design the compounds for studying their docking interaction with cyclooxygenase enzyme. Synthesis was performed by using various substituted phenyl acetic acid derivatives. It was found that the first step of reaction proceed well at 60°C with concentrated sulfuric acid. In the final step the temperature conditions were 80°C to get the single product. After each step, washing of the product was done with ethyl acetate and water. Product was found in organic layer after evaporation. Compounds have been characterized by spectral analysis like IR, ^{1}H-NMR, Mass spectra and elemental analysis (Table 1).

All of the synthesized derivatives contain characteristic functional groups for IR in the ranges of 3010-3100 cm^{-1} for CH stretching in aromatic ring, 2200-2500 cm^{-1} for methyl group on cyclopentanone ring, 1690-1760 cm^{-1} for C=O group, 1500-1600 cm^{-1} for C=C and 1050-1300 cm^{-1} for C-O group in cyclopentanone ring**.** The synthesized derivative shows NMR values in the ranges of δppm=7-8 for aromatic ring and δppm=2-5 for cyclopentanone ring.

In the analgesic studies (Figure 3) it has been observed that the compounds substituted with halogens, hydroxyl and methoxy group shows significant analgesic activity. The compounds are found to increase in reaction time to the pain stimulus. The results are significant at P<0.01 (Table 2). Compounds may act by inhibiting the COX enzymes by blocking the synthesis of prostaglandins which evoke inflammatory responses. The compounds are thus useful as analgesics in pain management. Structure activity relationship studies are thus helpful in designing the compounds for better analgesic properties.

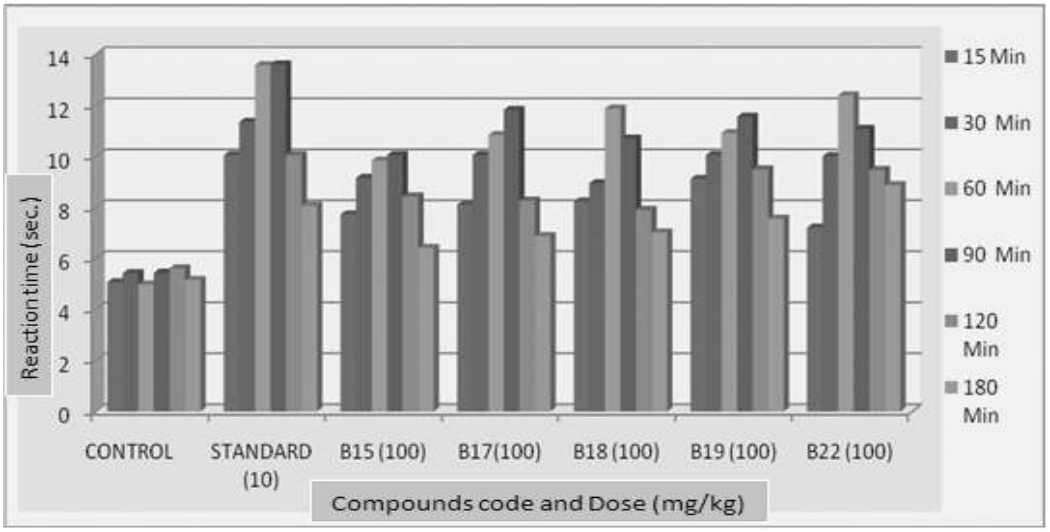


Figure 3: Analgesic activity of γ-butyrolactone by hot plate method

Table 2: Analgesic activity of γ-butyrolactone

Comp Code/Dose (mg/kg)	Basal reaction time (s)	Reaction time(sec)					
		15 min	30 min	60 min	90 min	120 min	180 min
Control	4.068 ± 0.3420	5.073 ± 0.3404	5.427 ± 0.0799	4.982 ± 0.1557	5.441 ± 0.1407	5.615 ± 0.1349	5.163 ± 0.2383
Standard (Pentazocine) (10)	5.180 ± 0.1233	10.065 ± 0.1780**	11.368 ± 0.5459 **	13.583 ± 0.3220	13.617 ± 0.3385**	10.063 ± 0.1117 **	8.077 ± 0.3338**
B15 (100)	5.434 ± 0.4768	7.732 ± 0.7036**	9.168 ± 0.6119**	9.843 ± 0.1607	10.062 ± 0.3798**	8.445 ± 0.5020**	6.422 ± 0.2276
B17 (100)	4.892 ± 0.2342	8.117± 0.683**	10.063 ± 0.2636**	10.842± 0.7279	11.832± 0.7655**	8.278 ± 0.2732**	6.880 ± 0.1643**
B18 (100)	5.064 ± 0.3123	8.240± 0.2863**	8.952 ± 0.2249**	11.883± 0.5778	10.702± 0.1370**	7.915± 0.3529**	7.027 ± 0.2096**
B19 (100)	5.145 ± 0.2454	9.120 ± 0.0575**	10.067 ± 0.2712**	10.925 ± 0.2119	11.565 ± 0.2935**	9.540 ± 0.2543**	7.565 ± 0.3867**
B22 (100)	5.342 ± 0.3650	7.215 ± 0.1051**	10.012 ± 0.3832**	12.400 ± 0.5987	11.082 ± 0.5596**	9.472 ± 0.3893**	8.887 ± 0.4539**

Values are expressed as ± SEM n=6; **P value=P<0.01

5-(methyl)-3- phenyldihydrofuran-2-(3H)-one (B1): Yield: 80%; b. p. 204-206°C. IR (KBr) 3028.51 (N–H); 1721.93 (C=O, cyclic); 1456.13 (C-H, CH_3, def); 1153.76 (C-O, cyclic). ^{1}H-NMR (300 MHz, $CDCl_3$, *d* ppm): 1.224-1.242 (d, 3H, J=7.2Hz); 2.485-2.479, 2.901-2.921 (dd, 1H, J1=8.4, J2=8.0, Cyclopentanone ring); 3.715-3.734 (t, 1H, J=7.6, Cyclopentanone ring); 4.381-4.585 (sixlet, 5H, Cyclopentanone ring); 7.217-7.459 (m, 4H, Ar). Mass spectra of compound exhibited molecular ion peak at *m/z* 176(M+). Anal. Cal. for $C_{11}H_{11}O_2$ (176.21): C, 74.911; H, 6.243; O, 18.16%, found: C, 76.721; H, 6.30; O, 18.011%.

3-(2-hydroxyenyl)-5-methyldihydrofuran-2(3H)-one (B14): Yield: 83.71%; b. p. 178-180°C. IR (KBr) 3458.53 (Ar-OH); 3040.13 (C-H Ar, str.); 2943.73 (C-H, CH_3, str.); 1736.08 (C=O, cyclic); 1435.72 (C-H, CH_3, def); 1148.67 (C-O, cyclic). ^{1}H-NMR (300 MHz, $CDCl_3$, *d* ppm): 1.399-1.420 (d, 3H, J=8.4 Hz); 2.324-2.344, 2.415-4.434 (dd, 1H, J1=8.0, J2=7.6, Cyclopentanone ring); 3.991-4.013 (t, 1H, J=8.8, Cyclopentanone ring); 4.419-4.651 (sixlet, 5H, Cyclopentanone ring); 5.192(s, Ar-OH); 6.791-6.981 (m, 4H, Ar). Mass spectra of compound exhibited molecular ion peak at *m/z* 192(M+). Anal. Cal. for $C_{11}H_{11}O_3$ (192.21): C, 68.675; H, 5.723; O, 24.972%, found: C, 70.771; H, 5.673; O, 24.072%.

3-(3-chlorophenyl)-5-methyldihydrofuran-2(3H)-one (B15): Yield: 73.95%; b. p. 192-194°C. IR (KBr) 2949.50 (C-H, Ar, str.); 1736.02

(C=O, cyclic, str.); 1432.29 (C-H, CH_3, def); 1155.33 (C-O, cyclic, str.); 810.36 (Ar-Cl). ^{1}H-NMR (300 MHz, $CDCl_3$, *d* ppm): 1.271-1.291 (d, 3H, J=8.0 Hz); 2.423-2.441, 2.502-2.521 (dd, 1H, J1=7.2, J2=7.6, Cyclopentanone ring); 3.639-3.660 (t, 1H, J=8.4, Cyclopentanone ring); 4.253-4.365 (sixlet, 5H, Cyclopentanone ring); 7.211-7.434 (m, 4H, Ar). Mass spectra of compound exhibited molecular ion peak at *m/z* 210 (M+). Anal. Cal. for $C_{11}H_{11}O_3Cl_1$ (210.65): C, 62.663; H, 4.474; O, 15.191; Cl, 16.853%, found: C, 66.211; H, 3.547; O, 14.782; Cl, 16.788%.

5-methyl -3-(2-methylphenyl) dihydrofuran-2(3H)-one (B16): Yield: 71.46%; b. p. 164-166°C. IR (KBr) 3025(C-H, Ar, str.); 2947.86 (C-H, CH_3, str); 1735.42 (C=O, cyclic, str.); 1438.19 (C-H, CH_3, def); 1155.13 (C-O, cyclic, str.). ^{1}H-NMR (300 MHz, $CDCl_3$, *d* ppm): 1.610-1.628 (d, 3H, J=7.2Hz); 2.371-2.390, 2.405-2.425 (dd, 1H, J1=7.6, J2=8.0, Cyclopentanone ring); 3.519-3.540 (t, 1H, J=8.4, Cyclopentanone ring); 4.421-4.612 (sixlet, 5H, Cyclopentanone ring); 7.112-7.214 (m, 4H, Ar). Mass spectra of compound exhibited molecular ion peak at *m/z* 190 (M+). Anal. Cal. for $C_{12}H_{10}O_2$ (190.23): C, 75.698; H, 6.834; O, 16.822%, found: C, 77.478; H, 6.612; O, 16.844%.

3-(3-hydroxyphenyl)-5-methyldihydrofuran-2(3H)-one (B17): Yield: 81.16%; b. p. 182-184°C. IR (KBr) 3459.38 (Ar-OH); 3035.28 (C-H Ar, str.); 2949.50 (C-H, CH_3, str.); 1736.02 (C=O, cyclic); 1432.29 (C-H, CH_3, def); 1155.33 (C-O, cyclic). ^{1}H-NMR (300 MHz, $CDCl_3$, *d* ppm): 1.670-1.689 (d, 3H, J=7.6 Hz); 2.481-2.500, 2.544-2.562 (dd, 1H, J1=7.6, J2=7.2, Cyclopentanone ring); 2.649-2.671 (t, 1H, J=8.8, Cyclopentanone ring); 4.480-4.581 (sixlet, 5H, Cyclopentanone ring); 5.104 (s, 1H, Ar-OH); 6.800-6.200 (d, 1H, J=8.0, Aromatic ring); 6.841(s, 1H, Aromatic ring); 7.182-7.201(d, 1H, J=7.6, Aromatic ring); 7.239-7.260 (t, 1H, J=8.4, Aromatic ring). Mass spectra of compound exhibited molecular ion peak at *m/z* 192(M+). Anal. Cal. for $C_{11}H_{11}O_3$ (192.21): C, 68.675; H, 5.723; O, 24.972%, found: C, 69.581; H, 5.861; O, 24.994%.

3-(2-methoxyphenyl)-5-methyldihydrofuran-2(3H)-one (B18): Yield: 78.26%; b. p. 200-202°C. IR (KBr) 3025 (C-H Ar, str.); 2947.86 (C-H, CH_3, str.); 1735.42 (C=O, cyclic); 1438.19 (C-H, CH_3, def); 1155.13 (C-O, cyclic). ^{1}H-NMR (300 MHz, $CDCl_3$, *d* ppm): 1.589-1.611 (d, 3H, J=8.8Hz); 2.423-4.443, 2.621-2.639 (dd, 1H, J1=8.0, J2=7.6, Cyclopentanone ring); 3.636-3.655 (t, 1H, J=7.6, Cyclopentanone ring); 5.124-5.381 (sixlet, 5H, Cyclopentanone ring); 7.181-7.266 (m, 4H, Aromatic ring). Mass spectra of compound exhibited molecular ion peak at *m/z* 206 (M+). Anal. Cal. for $C_{12}H_{13}O_3$ (206.23): C, 69.825; H, 6.304; O, 23.274%, found: C, 71.235; H, 6.102; O, 23.024%.

3-(3-4-dimethoxyphenyl)-5-methyldihydrofuran-2(3H)-one (B19): Yield: 68.21%; b. p. 196-198°C. IR (KBr) 2998.14 (C-H Ar, str.); 2948.06 (C-H, CH_3, str.); 1718.25 (C=O, cyclic); 1437.15 (C-H, CH_3, def); 1155.19 (C-O, cyclic). ^{1}H-NMR (300 MHz, $CDCl_3$, *d* ppm): 1.399-1.421 (d, methyl, 3H, J=8.4 Hz); 1.411-1.431, 1.610-1.630 (dd, 1H, J1=8.4, J2=8.0, Cyclopentanone ring); 3.648-3.670 (t, 1H, J=8.8, Cyclopentanone ring); 5.137-5.291 (sixlet, 5H, Cyclopentanone ring); 3.201 (s, 1H, Ar-OCH_3); 6.872-6.891 (d, 1H, J=7.6, Aromatic ring); 6.951 (s, 1H, Aromatic ring); 6.963-6.981 (d, 1H, J=7.2, Aromatic ring). Mass spectra of compound exhibited molecular ion peak at *m/z* 236 (M+). Anal. Cal. for $C_{13}H_{12}O_4$ (236.26): C, 66.029; H, 5.079; O, 27.089%, found: C, 66.213, H, 6.114; O, 29.231%.

3-mesityl-5-methyldihydrofuran-2(3H)-one (B20): Yield: 74.33%; b. p. 176-178°C. IR (KBr) 2916.39 (C-H, CH_3, str.); 1694.68 (C=O, cyclic); 1413.85 (C-H, CH3, def); 1253.41 (C-O, cyclic). ^{1}H-NMR (300 MHz, $CDCl_3$, *d* ppm): 2.261-2.281 (d, 3H, J=8.0 Cyclopentanone-CH_3); 2.173-2.192, 2.203-2.223 (dd, 1H, J1=7.6, J2=7.2, Cyclopentanone ring); 2.391(s, 3H, methyl); 3.611-3.632 (t, 1H, J=8.4, Cyclopentanone Ring); 4.549-4.657 (sixlet, 5H, Cyclopentanone ring); 6.831 (s, 3H, Ar-H). Mass spectra of compound exhibited molecular ion peak at *m/z* 218 (M+). Anal. Cal. for $C_{14}H_{17}O_2$ (218.29): C, 76.962; H, 7.788; O, 14.659%, found: C, 71.235; H, 6.102; O, 23.024%.

3-(4-bromophenyl)-5-methyldihydrofuran-2(3H)-one (B21): Yield: 82.23%; b. p. 186-188°C. IR (KBr) 3021.21 (C-H, Ar, str.); 2946.48 (C-H, CH_3, str.); 1736.41 (C=O, cyclic); 1435.39 (C-H, CH3, def); 1014.97 (C-O, cyclic); 745.30 (Ar-Br). ^{1}H-NMR (300 MHz, $CDCl_3$, *d* ppm): 1.249-1.269 (d, 3H, J=8.0, methyl); 2.481-2.502, 2.621-2.641 (dd, 1H, J1=8.4, J2=8.0, Cyclopentanone ring); 3.571-3.590 (t, 1H, J=7.6, Cyclopentanone ring); 4.428-4.631 (sixlet, 5H, Cyclopentanone ring); 7.121-7.142 (d, 1H, J=8.4, Aromatic ring); 7.441-7.459 (d, 1H, J=7.2, Aromatic ring). Mass spectra of compound exhibited molecular ion peak at *m/z* 255 (M+). Anal. Cal. for $C_{11}H_{10}O_2Br_1$ (255.10): C, 51.744; H, 3.920; O, 12.544; Br, 31.321%, found: C, 51.211; H, 3.547; O, 14.782; Br, 32.004%.

3-(2-bromophenyl)-5-methyldihydrofuran-2(3H)-one (B22): Yield: 84.25%; b. p. 194-196°C. IR (KBr) 3025.12 (C-H, Ar, str.); 2946.48 (C-H, CH_3, str.); 1736.41 (C=O, cyclic); 1435.39 (C-H, CH_3, def); 1014.99 (C-O, cyclic); 745.30 (Ar-Br). ^{1}H-NMR (300 MHz, $CDCl_3$, *d* ppm): 1.358-1.371 (d, 3H, J=7.2, methyl); 2.581-2.602, 2.263-2.265 (dd, 1H, J1=8.4, J2=8.0, Cyclopentanone ring); 2.728-2.749 (t, 1H, J=8.4, Cyclopentanone ring); 4.423-4.581 (sixlet, 5H, Cyclopentanone ring); 7.184-7.371 (m, 1H, Aromatic ring). Mass spectra of compound exhibited molecular ion peak at *m/z* 255 (M+). Anal. Cal. for $C_{11}H_{10}O_2Br_1$ (255.10): C, 51.744; H, 3.920; O, 12.544; Br, 31.321%, found: C, 51.211; H, 3.547; O, 14.782; Br, 32.004%.

3-(3-methoxyphenyl)-5-methyldihydrofuran-2(3H)-one (B23): Yield: 80.51%; b. p. 202-204°C. IR (KBr) 3034.23 (C-H, Ar, str.); 2940.34 (C-H, CH3, str.); 1736.45 (C=O, cyclic); 1450.45 (C-H, CH_3, def); 1155.13 (C-O, cyclic). Anal. Cal. for $C_{12}H_{13}O_3$ (206.23), C, 64.006; H, 4.848; O, 15.516%, found: C, 67.771; H, 5.673; O, 12.544%.

3-(4-ethoxyphenyl)-5-methyldihydrofuran-2(3H)-one (B24): Yield: 69.79%; b. p. 168-170°C. IR (KBr) 3079.93 (C-H, Ar, str.); 2946.58 (C-H, C_2H_5, str.); 1738.49 (C=O, cyclic); 1471.79 (C-H, CH_3, def); 1325.46 (C-H, CH_2, def); 1155.13 (C-O, cyclic). Anal. Cal. for $C_{13}H_{15}O_3$ (220.26): C, 70.825; H, 6.810; O, 21.792%, found: C, 69.581; H, 5.861; O, 24.994%.

5-methyl-3-(3-4-5-trimethoxyphenyl)dihydrofuran-2(3H)-one (B25): Yield: 69.79%; b. p. 168-170°C. IR (KBr) 3025.12 (C-H, Ar, str.); 2939.82 (C-H, CH_3, str.); 1734.53 (C=O, cyclic); 1428.71 (C-H, CH_3, def); 1127.92 (C-O, cyclic). Anal. Cal. for $C_{14}H_{17}O_5$ (266.28): C, 63.091; H, 6.384; O, 30.043%, found: C, 66.213, H, 6.114; O, 29.231%.

CONCLUSION

Docking studies of γ-butyrolactone derivatives showed significant binding interactions with cyclooxygenase target. Compounds have been found to exert prominent interaction with the target protein. Five compounds have shown significant analgesic activity when compared with standard drug. Compounds B15, B18 and B19 were found to be potent analgesics from the series of prepared γ-butyrolactone derivatives. Compounds B17 and B22 also showed significant activity and hydrophobic interaction. These compounds may act as COX-inhibitors and exhibit analgesic activity with lesser side effects and enhanced potency.

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