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Der Pharma Chemica, 2012, 4 (1):383-391
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X
CODEN (USA): PCHHAX

COX-2 inhibitory and GABAergic activity of newly synthesized 2(3*H*)-furanone

Arvind Kumar[1], Bahar Ahmed[2], Birendra Srivastawa[3], Vaishali[1]

[1]*Department of Pharmaceutical Chemistry, S. D. College of Pharmacy & Vocational Studies, Muzaffarnagar, U. P.*
[2]*Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi, India*
[3]*School of Pharmaceutical Sciences, Jaipur National University, Jaipur, Rajasthan India*

ABSTRACT

A series of 5-(substituted-phenyl)-3-(substituted-arylidene)-2(3H)-furanones were synthesized by two step process. Molecular docking experiments were carried out to identify potential COX-2 inhibitor and GABA modulator among all synthesized furanone derivatives. Elemental analysis values were found within ±0.4% of the theoretical values. The IR spectra of compounds were recorded in KBr on Perkin Elmer BX-II FTIR spectrophotometer. The proton magnetic resonance spectra (^{1}H NMR) were recorded on Bruker 300MHz instrument in $CDCl_3$ using tetramethylsilane [$(CH_3)_4Si$] (TMS) as internal standard. All Synthesized furanones were screened for anti-inflammatory activity by Carrageenin induced rat paw edema method and by PTZ induced seizure method for anticonvulsant activity. Result indicate that tested compounds 5-(4-chloro-3methyl-phenyl)-3-(4-dimethylamino-benzylidene)-3Hfuran-2-one (15) and 3-Anthracen-9-ylmethylene-5-(4-chloro-3-methyl-phenyl)-3H-furan-2-one (16) possess the strongest anti-inflammatory activity, comparable to that of indomethacin, and the compound 16 also exhibits GABA modulator activity less comparable to diazepam.

Keywords: anti-inflammatory, COX-2, furanone, docking, GABA, anticonvulsant.

INTRODUCTION

Biological importance of unsaturated lactone is well known[1-4]. The γ-lactone ring is a part of variety of natural product like digitalis glycosides, sesquiterpene lactones, lignans like podophyllotoxin and antibiotics like patulin[5]. γ-lactone ring also a useful entity, present in natural product like fibrolides[6], dihydroxerulin[7] and protoanemonin[8].

Furanones are typical product of a polyketide biochemical synthesis pathway[9]. They are the constituents of various preprations. They also exist naturally like fissohamione from *Fissistigma oldhamii*[10]. Rofecoxib is used NSAID with a furanone core structure and is efficacious in treating rheumatoid arthritis[11]. The use of conventional NSAIDs has been restricted due to their adverse effect especially gastrointestinal toxicity and renal insufficiency [12, 13].

Cyclooxygenase (COX) also known as prostaglandin synthase is a potent mediator of inflammation. However, inhibition of COXs may lead to undesirable side effects. Nowadays it is well established that there are at least two COX isozymes, COX-1 and COX-2[14]. The prostaglandin series of bioactive compounds formed by the interaction of two distinct but related enzymes, cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) [15].

Recently several investigations has been described the design, synthesis and COX inhibitory activities of a novel class of compounds 3-(substituted-benzylidene)-5-(4-methoxy-phenyl)-3*H*furan-2-one possesses significant anti-inflammatory activity[16].

Epilepsy is the most frequent neurologic affection characterized by excessive temporary neuronal discharge[17]. γ-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian brain[18,19]. Fast synaptic inhibition in the fore brain is mediated mostly by the neutral aminoacid GABA intracting with post-synaptic $GABA_A$ receptors (GABARs). GABARs are heteromeric protein complexes composed of multiple subunit that form ligand-gated anion-selective channels that are modulated by barbiturates, benzodiazepines, ethanol, volatile anesthetics and the anesthetic steroids[20,21]. As GABA itself does not cross the blood-brain barrier, there is considerable interest in the development of systematically active GABA-mimetic agents[22]. The furanones ring system is also known as butyrolactone or butenolide, is a recognizable component of natural product[23]. The simpler butyrolactone, 3,3-diethylbutyrolactone, shows anticonvulsant activity[24]. While the furanones also reported to have cardiotonic[25,26], anti-inflammatory[27,28], antimicrobial[29-31], antiviral[32] and anticancer activity[33], platelet inhibitory activity[34]. Recently synthesized compounds 4,5-diaryl-3-hydroxy-2(5*H*)-furanone also reported to exhibits good anti-oxidant activity[35].

MATERIALS AND METHODS

The purity of synthesized compounds were ascertained by thin layer chromatography on silica gel G in various solvent systems using iodine vapors and UV lamps for visualization of spots. Melting points of the compounds were determined in open glass capillaries using Kjeldahl flask containing liquid paraffin and are uncorrected. The elemental analysis was carried out on Vario-EL III CHNOS- Elemantar analyzer and the values were found within ±0.4% of the theoretical values. The IR spectra of compounds were recorded in KBr on Perkin Elmer BX-II FTIR spectrophotometer. The proton magnetic resonance spectra (^{1}H NMR) were recorded on Bruker 300MHz instrument in $CDCl_3$ using tetramethylsilane [$(CH_3)_4Si$] (TMS) as internal standard.

Synthesis of 4-(4-chloro-3-methyl-phenyl)-4-oxo-butyric acid (1)

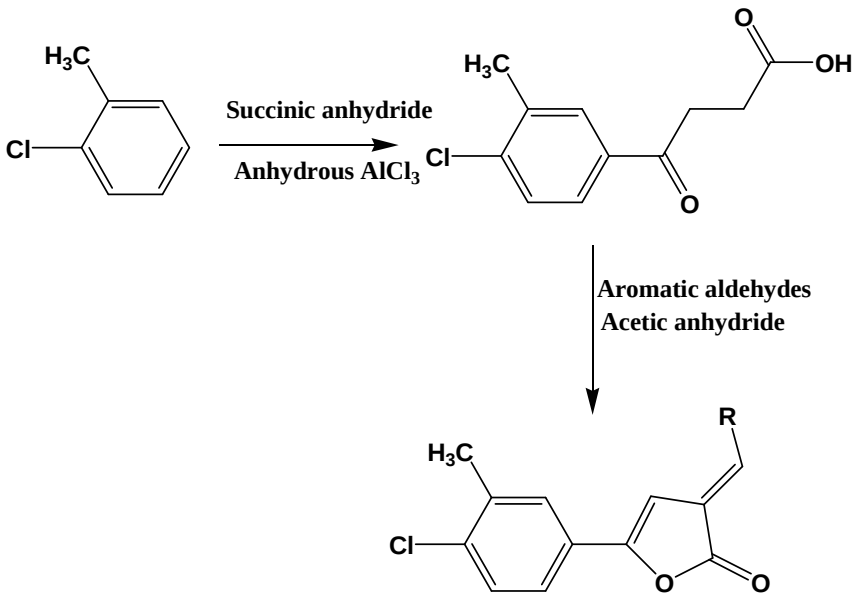
A mixture of succinic anhydride (0.1 mole; 10 gm) and dry 2-chlorotoluene (50 ml) was refluxed with anhydrous aluminium chloride (0.1125 mole; 15 gm) under anhydrous conditions for two hours. After completion of reaction dilute hydrochloric acid (2.5 % v/v, 50 ml) was added

slowly. Excess of solvent was removed by steam distillation and the hot solution was poured into beaker containing cold water (100 ml) when a solid mass separated out. It was purified by dissolving in sodium hydroxide solution (5% w/v), filtered followed by addition of hydrochloric acid. The compound so obtained was filtered, washed with cold water, dried and crystallized from methanol.

General procedure for Synthesis of 3-(substituted-arylidene) 5-(4-Chloro-3-methyl-phenyl)-3*H*-furan-2-one (2-13)

To a solution of 4-(4-chloro-3-methyl-phenyl)-4-oxo-butyric acid 1 (3mmole) and benzaldehyde (3mmole) in acetic anhydride (10ml) was added triethylamine (3-4 drops) and the reaction mixture was refluxed for four hour under anhydrous condition. After completion of reaction, the content was poured on to crushed ice in small portion while stirring. A colored solid mass so obtained was filtered, washed with water and recrystallized from methanol : chloroform mixture (1:1).

Scheme1



Molecular docking

To identify potential COX-2 inhibitor and GABA modulator lead among compounds **2-13**, docking calculations were performed using using EXHZ Version 1.4 and Auto Dock 4.0 on Fedora Linux WS 3.0 into the 3D structure of the catalytic site of COX-2 enzyme (pdb code: 3NT1) and GABA receptor (pdb code: 3IP9).

The conversion of available ligands to 3-dimensional format carried out with the help of Marvin View and Binding site analysis carried out for 'the identification and visualization of possible binding sites and the distribution of surrounding residues in the active sites'.

Parameters have been chosen for docking of compounds with the chosen receptor (PDB Id: 3NT1) were Gridcenter as: -38.416 -49.518 -22.262, (xyz-coordinates), number of grid point: 110 110 110, spacing: 0.375 (spacing-A°), dielectric constant -0.1465 and the parameter for

GABA receptor (PDB Id: 3IP9) were Gridcenter as: 23.357 19.489 18.247 (xyz-coordinates), number of grid point: 110 110 110 spacing: 0.375A°, dielectric constant -0.1465. The Lamarckian Genetic Algorithm were used for GABA as well as COX-2.

Each docking experiment consisted of 10 docking runs with 150 individuals and 500,000 energy evaluations. The identification of interactions between projected potential compounds and the receptor PDB coordinates and 3D coordinates of top 10 conformations were taken as input. The Cut off value of parameter used was 4.5 Angstrom (Distance between protein receptor and ligand atom).

The obtained results were evaluated in terms of binding energy and docking positioning into the catalytic site of COX-2 and GABA receptor.

Anti-inflammatory evaluation

The anti-inflammatory activity of the synthesized compounds was carried out by the method of Winter, C.A., et al. (1962)*. Pedal inflammation in albino rats was induced by carrageenin in rat hind paw and the edema volume was measured by mercury displacement in a plethysmograph. The studies were carried out on healthy rats weighing between 120-200 gm, divided in groups of 5 animals each and housed in polypropylene cages. They were fed on standard pellet diet, water ad. libitum. The drug used as standard was Indomethacin in dose of 10 mg/kg body weight. The doses of test compounds were 20 mg/kg body weight. The standard and test compound were administered through oral route in the form of (0.5% CMC) suspensions. The control group was administered 0.2 ml of normal saline orally. Carrageenin was injected subcutaneously, 0.1ml of a 1% w/v carrageenin suspension (in 0.5% CMC) to hind paw of each of the rats.

Anticonvulsant evaluation

The anticonvulsant activity was carried out by pentylenetetrazole (PTZ) induced convulsion model on male albino mice weighing between 25-30g for grandmal type of epileptic condition. They were housed under standard laboratory conditions maintained at 25°c and humidity at 45-60% for one week before anticonvulsant activity was carried out. Food and water were withdrawn prior to the experiment. The animals were divided in to 12 groups of five mice in each group. PTZ was introduced intraperitonialy to all groups at the dose of 80mg/kg body weight. Test compounds were injected IP 50mg/kg body weight and one group received standard drug diazepam in dose of 8mg/kg 30 minute before PTZ injection. The control group was received normal saline. Time of onset of seizure was recorded and the number of convulsion and mortality rate was counted of all groups. All the result was statistically analyzed and expressed as mean ± SEM.

RESULTS AND DISCUSSION

4-(4-Chloro-3-methyl-phenyl)-4-oxo-butyric acid (1)

White cream colored flakes, Yield: 67%, M.p.: 96-98ºC, IR (KBr, cm^{-1}) υ: 3367(O-H), 2932(C-H), 1726 (C=O), 1679(ArC=C), ^{1}HNMR($CDCl_3$): δ, ppm 2.30(s,3H,-CH_3), 2.80, 2.52, (t, each, 4H, 2xCH_2), 6.90, 7.31(m, each, 2H, Ar-H), 7.61(s,1H,Ar-H),10.61(s,1H,-OH)

3-Benzylidene 5-(4-Chloro-3-methyl-phenyl)-)- 2(3*H*)-furanone (2)
Dark brown colored crystals, Yield: 52%, m.p. 155-156ºC. Anal. Calcd. for $C_{18}H_{13}Cl\ O_2$: C,72.85; H, 4.42. Found: C, 72.75; H, 4.38. IR (KBr, cm^{-1}) υ: 2939(C-H), 1763 (C=O), 1621(ArC=C). ^{1}HNMR ($CDCl_3$): δ, ppm 2.44(s, 3H, -CH_3), 6.50(s, 1H, furanone ring), 6.80, 7.50(d, each, 2H, Ar-H), 6.92, 7.09(m, each, 3H, Ar-H), 7.26(s, 1H, olefinic H), 7.41(s, 1H, Ar-H), 7.65(d, 2H, Ar-H)

5-(4-chloro-3-methyl-phenyl)-3-(2-nitro-benzylidene)-2(3*H*)-furanone (3)
Dark brown colored needles Yield: 59%, m.p.: 180-183°C. Anal. Calcd. for $C_{18}H_{12}ClN\ O_4$: C, 63.26; H, 3.54; N, 4.10. Found: C, 63.20; H, 3.49; N, 4.06. IR (KBr, cm^{-1}) υ: 2933(C-H), 1777 (C=O), 1594(ArC=C), ^{1}HNMR ($CDCl_3$): δ,ppm 2.44(s, 3H, -CH_3), 6.80(s, 1H, furanone ring), 6.85, 7.61(d, each, 2H, Ar-H), 7.50, 8.10(d, each, 2H, Ar-H), 7.26(s, 1H, olefinic H), 7.68, 7.70(m, 2H, Ar-H), 7.11(s, 1H, Ar-H)

5-(4-Chloro-3-methyl-phenyl)-3-(3-nitro-benzylidene)-2(3*H*)-furanone (4)
Dark brown colored crystals Yield: 61%, m.p.: 191-193°C. Anal. Calcd. for $C_{18}H_{12}ClN\ O_4$: C, 63.26; H, 3.54; N, 4.10. Found: C, 63.22; H, 3.51; N, 4.07. IR (KBr, cm^{-1}) υ: 2935(C-H), 1770 (C=O), 1610(ArC=C), ^{1}HNMR ($CDCl_3$): δ, ppm 2.36(s, 3H, -CH_3), 6.75(s, 1H, furanone ring), 7.01, 7.16(d, each, 2H, Ar-H), 7.09(s, 1H, Ar-H), 7.59(m, 1H, Ar-H), 7.89, 8.10(d, each, 2H, Ar-H), 8.27(s, 1H, Ar-H) 7.26(s, 1H, olefinic H).

5-(4-Chloro-3-methyl-phenyl)-3-(4-nitro-benzylidene)-3*H*-furan-2-one (5)
Dark brown crystals, Yield: 56%, m.p.: 125-128°C. Anal. Calcd. for $C_{18}H_{12}ClN\ O_4$: C, 63.26; H, 3.54; N, 4.10. Found: C, 63.24; H, 3.50; N, 4.09. IR (KBr, cm^{-1}) υ: 2835(C-H), 1775 (C=O), 1600(ArC=C), ^{1}HNMR ($CDCl_3$): δ, ppm 2.35(s, 3H, -CH_3), 6.76(s, 1H, furanone ring), 7.08, 7.19(d, each, 2H, Ar-H), 7.01(s, 1H, Ar-H), 7.29, 8.29(d, each, 4H, Ar-H), 7.26(s, 1H, olefinic H).

3-(2-Chloro-benzylidene)-5-(4-Chloro-3-methyl-phenyl)-3*H*-furan-2-one (6)
Dark brown colored crystals, Yield: 60%, M.p.: 157-158°C. Anal. Calcd. for $C_{18}H_{12}Cl_2\ O_2$: C, 65.28; H, 3.65. Found: C, 65.24; H, 3.60. IR (KBr, cm^{-1}) υ: 2941(C-H), 1776 (C=O), 1603(ArC=C), ^{1}HNMR ($CDCl_3$): δ, ppm 2.36(s, 3H, -CH_3), 6.76(s, 1H, furanone ring), 7.03, 7.10(d, each, 2H, Ar-H), 7.00(s, 1H, Ar-H), 7.27, 7.32(d, each, 2H, Ar-H), 7.38, 7.49(m, each, 2H, Ar-H), 7.26(s, 1H, olefinic H).

Synthesis of 3-(4-Chloro-benzylidene)-5-(4-Chloro-3-methyl-phenyl)-3*H*-furan-2-one (7)
Brown colored crystals Yield: 56%, m.p.: 175-176°C. Anal. Calcd. for $C_{18}H_{12}Cl_2\ O_2$: C, 65.28; H, 3.65. Found: C, 65.21; H, 3.62. IR (KBr, cm^{-1}) υ: 2938(C-H), 1769 (C=O), 1594(ArC=C), ^{1}HNMR ($CDCl_3$): δ, ppm 2.36(s, 3H, -CH_3), 6.74(s, 1H, furanone ring), 7.00, 7.12(d, each, 2H, Ar-H), 7.08(s, 1H, Ar-H), 7.42, 7.55(d, each, 4H, Ar-H), 7.26(s, 1H, olefinic H).

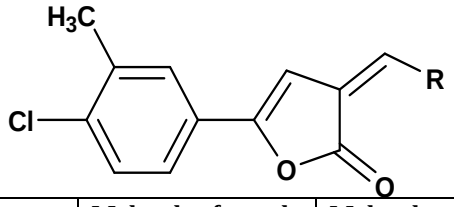
5-(4-Chloro-3-methyl-phenyl)-3-(4-fluoro-benzylidene)-3*H*-furan-2-one (8)
Dark brown solid, Yield: 63%, m.p.: 179-180°C. Anal. Calcd for $C_{18}H_{12}Cl\ F\ O_2$: C, 68.69; H, 3.84. Found: C, 68.61; H, 3.82. IR (KBr, cm^{-1}) υ: 2945(C-H), 1760 (C=O), 1626(ArC=C), ^{1}HNMR ($CDCl_3$): δ, ppm 2.34(s, 3H, -CH_3), 6.75(s, 1H, furanone ring), 6.98, 7.11(d, each, 2H, Ar-H), 7.06(s, 1H, Ar-H), 7.16, 7.65(d, each, 4H, Ar-H), 7.32(s, 1H, olefinic H).

5-(4-Chloro-3methyl-phenyl)-3-(4-dimethylamino-benzylidene)-3*H*-furan-2-one (9)
Dark brown crystals, Yield: 56%, m.p.: 161-162°C. Anal. Calcd for $C_{20}H_{18}Cl\,N\,O_2$: C, 70.69; H, 5.34; N, 4.12. Found: C, 70.64; H, 5.32; N, 4.08. IR (KBr, cm^{-1}) υ: 2941(C-H), 1752(C=O), 1583(ArC=C), ^{1}HNMR ($CDCl_3$): δ, ppm 2.35(s, 3H, -CH_3), 3.07, (s, 6H, -$N(CH_3)_2$), 6.74(s, 1H, furanone ring), 6.98, 7.10(d, each, 2H, Ar-H), 7.04(s, 1H, Ar-H), 672, 7.55(d, each, 4H, Ar-H), 7.32(s, 1H, olefinic H).

3-Anthracen-9-ylmethylene-5-(4-chloro-3-methyl-phenyl)-3*H*-furan-2-one (10)
Dark brown crystals, Yield: 67%, m.p.: 203-205°C. IR (KBr, cm^{-1}) υ: 2940(C-H), 1772(C=O), 1610(ArC=C), ^{1}HNMR ($CDCl_3$): δ, ppm 2.35(s, 3H, -CH_3), 6.74(s, 1H, furanone ring), 7.00, 7.12(d, each, 2H, Ar-H), 7.08(s, 1H, Ar-H), 7.34(s, 1H, olefinic H), 7.40(m, 4H, Ar-H), 8.01(m, 4H, Ar-H), 8.50(s,1H,Ar-H)

The substitution and physical data given in Table-1

Table-01 Physical data of all synthesized compounds



Compounds	R	Molecular formula	Molecular weight	Melting point	%Yield
C-2	-phenyl	$C_{18}H_{13}Cl\,O_2$	296.75	155-156ºC	52
C-3	-2-nitrophenyl	$C_{18}H_{12}ClN\,O_4$	341.75	180-182°C	59
C-4	-3-nitrophenyl	$C_{18}H_{12}ClN\,O_4$	341.75	191-193°C	61
C-5	-4-nitrophenyl	$C_{18}H_{12}ClN\,O_4$	341.75	125-128°C	56
C-6	-2-chlorophenyl	$C_{18}H_{12}Cl_2\,O_2$	331.19	157-158°C	60
C-7	-4-chlorophenyl	$C_{18}H_{12}Cl_2\,O_2$	331.19	175-176°C	56
C-8	4-fluorophenyl	$C_{18}H_{12}Cl\,F\,O_2$	314.74	179-180°C.	63
C-9	-4-dimethyl aminophenyl	$C_{20}H_{18}Cl\,N\,O_2$	339.82	161-162°C	56
C-10	-9-anthryl	$C_{26}H_{17}Cl\,O_2$	396	203-205°C	67
C-11	-4-methoxyphenyl	$C_{20}H_{18}Cl_2\,O_3$	326	149-150°C	61
C-12	-3,4-dimethoxyphenyl	$C_{20}H_{17}Cl\,O_4$	356	160-162°C	54
C-13	-3,4,5-trimethoxyphenyl	$C_{21}H_{19}Cl\,O_5$	386	171-173°C	70

5-(4-Chloro-3-methyl-phenyl)-3-(4-methoxy-benzylidene)-3*H*-furan-2-one (11)
Dark brown solid, Yield: 61%, M.p.: 149-150°C. IR (KBr, cm^{-1}) υ: 2949 (C-H), 1721(C=O), 1597(ArC=C), ^{1}HNMR ($CDCl_3$): δ, ppm 2.36(s, 3H, -CH_3), 3.88, (s, 3H, -OCH_3), 6.78(s, 1H, furanone ring), 7.01, 7.12(d, each, 2H, Ar-H), 7.05(s, 1H, Ar-H), 691, 7.60(d, each, 4H, Ar-H), 7.33(s, 1H, olefinic H).

5-(4-Chloro-3-methyl-phenyl)-3-(3,4-methoxy-benzylidene)-3*H*-furan-2-one (12)
Dark brown crystals, Yield: 54%, m.p.: 160-162°C. IR (KBr, cm^{-1}) υ: 2953 (C-H)1771(C=O), 1607(ArC=C), ^{1}HNMR ($CDCl_3$): δ, ppm 2.33(s, 3H, -CH_3), 3.86, (s, 6H, -OCH_3), 6.82(s, 1H, furanone ring), 7.00, 7.12(d, each, 2H, Ar-H), 7.09(s, 1H, Ar-H), 6.55, 6.65(m, each, 2H, Ar-H), 6.70(s, 1H, Ar-H) 7.35(s, 1H, olefinic H).

5-(4-Chloro-3-methyl-phenyl)-3-(3,4,5-trimethoxy-benzylidene)-3*H*-furan-2-one (13)
Brown crystals, Yield: 70%, m.p.: 171-173°C. IR (KBr, cm^{-1}) υ: 2952 (C-H), 1770(C=O), 1610(ArC=C), ^{1}HNMR ($CDCl_3$): δ, ppm 2.36(s, 3H, $-CH_3$), 3.77, (s, 9H, $-OCH_3$), 6.80(s, 1H, furanone ring), 7.00, 7.10(d, each, 2H, Ar-H), 7.06(s, 1H, Ar-H), 6.45,(s, 2H, Ar-H), 7.33(s, 1H, olefinic H).

Results for anti-inflammatory activity
Among the all synthesized compounds the c-10, was found in best conformation with **3NT1** receptor having least mean binding energy -10.78 (**Figure-01**), other compounds c-12, c-2, c-9 and c-13 were also found comparable in their conformation with least mean binding energies -10.33, -9.91, -9.81 and -9.79 respectively.

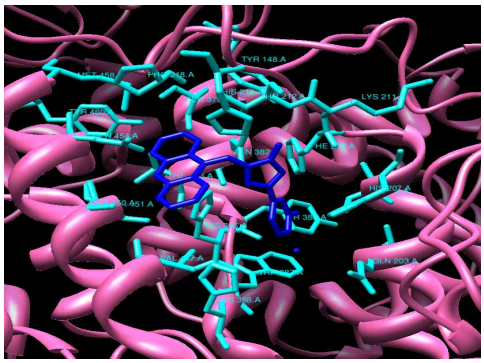


Figure 01: 3NT1 (COX-2) Receptor with atoms interacting with test compound no. 10

Table-2: Docking and biological activity result of synthesized compounds

Compounds	Least Mean Binding energies with receptor 3NT1	Least Mean Binding energies with receptor 3IP9	% Inhibition For Anti-inflammatory Activity			% of Mortality Protection for anticonvulsant activity
			1 Hour	2 Hour	3 Hour	
Control	-	-	-	-	-	-
C-2	-9.91	-7.15	66.2	50.6	24.8	60
C-3	-9.05	-7.45	61.4	47.9	27.1	40
C-4	-8.44	-5.88	58.2	40.6	8.6	20
C-5	-7.67	-7.72	53.4	47.6	5.1	60
C-6	-7.56	-6.40	57.4	40.7	6.0	20
C-7	-8.40	-6.07	61.8	45.0	30.0	20
C-8	-8.62	-7.56	63.0	45.2	05.6	60
C-9	-9.81	-7.35	67.8	50.3	27.4	40
C-10	-10.78	-8.16	74.3	59.2	39.1	80
C-11	-9.24	-6.34	64.7	56.1	22.4	40
C-12	-10.33	-6.64	75.9	59.2	22.5	20
C-13	-9.79	-7.17	63.9	50.2	10.2	40
Indomethacin	-	-	77.5	63.7	41.9	-
Diazepam (8 mg/kg)	-	-	-	-	-	100

The selected test compounds inhibited carrageenin-induce rat paw edema, the effect was found to be significant upto 3 hrs observation. Moreover the anti-inflammatory effect of synthesized product (c-10 and c-12) was found to be comparable to that of indomethacin (used as standard drug). Table-2

Result for Anticonvulsant Activity

Among the all synthesized compounds the c-10, was found in best conformation with **3IP9** receptor having least mean binding energy -8.16(**Figure-02**), other compounds c-5 and c-8 were also found comparable in their conformation with least mean binding energies -7.72 and -7.56 respectively.

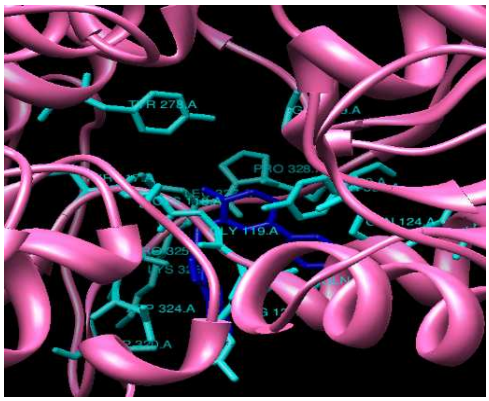


Figure 02: 3IP9 (GABA) Receptor with atoms interacting with test compound no. 10

Some selected test drugs could suppress the onset and duration of the chronic seizure in PTZ model. As we could observe that the test agent's c-10, c-5 and c-8 reduced the convulsion rate and percentage of mortality protection. Table-2

Acknowledgement

We are Thanks to Manager, Mascon Global ltd. for support of molecular docking study. Thanks to Jamia Hamdard for helping me in recording the NMR spectra of the synthesized compounds. We are thankful to in-charge animal house S. D. College of Pharmacy & Vocational studies Muzaffarnagar for conduct of animal activity.

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