Journal of Advanced Zoology
ISSN: 0253-7214
Volume 45 Issue 2 Year 2024 Page 1230-1241

"An Overview On Biological Behavior Of Benzotriazole: Synthesis And Docking Study On Its Versatile Biological Activities"

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Abstract:

The practice of medicinal chemistry is devoted to the discovery and development of new chemical agents for treating diseases. Triazoles are obtained by a slight modification of azole ring and similar or improved activities as well as fewer adverse effects are reported for triazole derivatives several advantages are the notable attraction for using benzotriazole moiety-dependent methodologies, in my research work I synthesized various derivatives of n-(1h-benzotriazol-6-yl)-benzamide from Benzene 1,2,4-triamine and benzoic acid with high yield and the synthesized derivatives characterized by FT-IR spectrum, H^1 NMR spectrum, and mass spectrum data of synthesized derivatives compounds of benzotriazole Scheme analysis proves that resultant compounds n-(1h-benzotriazol-6-yl)-benzamide derivatives. The molecular docking studies validated the outcome results from the anti-inflammatory and antiarthritic agents and signifies the potential of these derivatives as crystal structure of C-terminus of voltage-gated sodium channel in complex (PDB ID:4DCK) and COX 2 Inhibitor (PDB ID:1CX2) inhibitors. So, these compounds can be modified further for the development of new anti-inflammatory and antiarthritic agents. This study strongly suggests that most of molecules synthesized in this study may indeed be promising drug candidates with interesting pharmacological profile and most of these derivatives could be a fruitful for further development of better anti-inflammatory and antiarthritic activity.

Keywords: Benzotriazole, Docking study, anti-inflammatory activity, antiarthritic activity.

INTRODUCTION:

The synthesis of novel benzotriazine heterocycles was developed independently around the same time by Bischler, Bamberger and Arndt. Over the years, different groups have reported the synthesis of benzotriazine based compounds. Benzo-condensed azole containing three heteroatoms, such as bezoxadiazole, benzothiazole and benzotriazole [1-5], have been extensively studied for their broad range

of biological activity. However, few reviews were focalized on a single nucleus. Indeed, this paper aims to provide an overview of the benzotriazole based systems and their relevance in medicinal chemistry.

Chemistry: 1H-1, 2, 3-Benzotriazole was synthesized by diazotization of ortho phenylene di amine using glacial acetic acid and sodium nitrate. 2-chloro-N- Alkyl/Aryl acetamide was synthesized by drop wise adding four equivalents of chloroacetyl chloride over one hour to the aqueous amine solution. Finally N-(Alkyl or Aryl)- 2-(1Hbenzotriazol-1-yl)-acetamide derivatives were synthesized by adding 2-chloro-N- Alkyl/Aryl acetamide to 1H-1, 2, 3-Benzotriazole and using anhydrous potassium carbonate as a base.
Rheumatoid arthritis (RA) is an immune-mediated inflammatory disease that is characterized by chronic progressive inflammation and subsequent destruction of peripheral joints, ligaments and tendons [6-8]. The pathogenesis of RA so far has not been fully elucidated. However, inflammatory involvement of the synovium, the lining tissue of diarthrodial joints, tendon sheaths and bursae represent the main process in RA pathology. The inflamed RA synovium is complex and characterized by synovial proliferation, neo angiogenesis and chronic inflammatory cell infiltration. Any of the numerous cell surface receptors, adhesion molecules and growth factors involved in the pathogenesis may serve as potential targets for therapeutic intervention [9-11].

MATERIALS AND METHODS:

All the chemicals used were produced from Sigma Aldrich, Merck and CDH laboratory chemical suppliers and purity of starting materials used for reactions was confirmed by checking their melting point or boiling point and by thin layer chromatography.

The synthetic strategy for target molecules involves following sequence of reaction
SCHEME

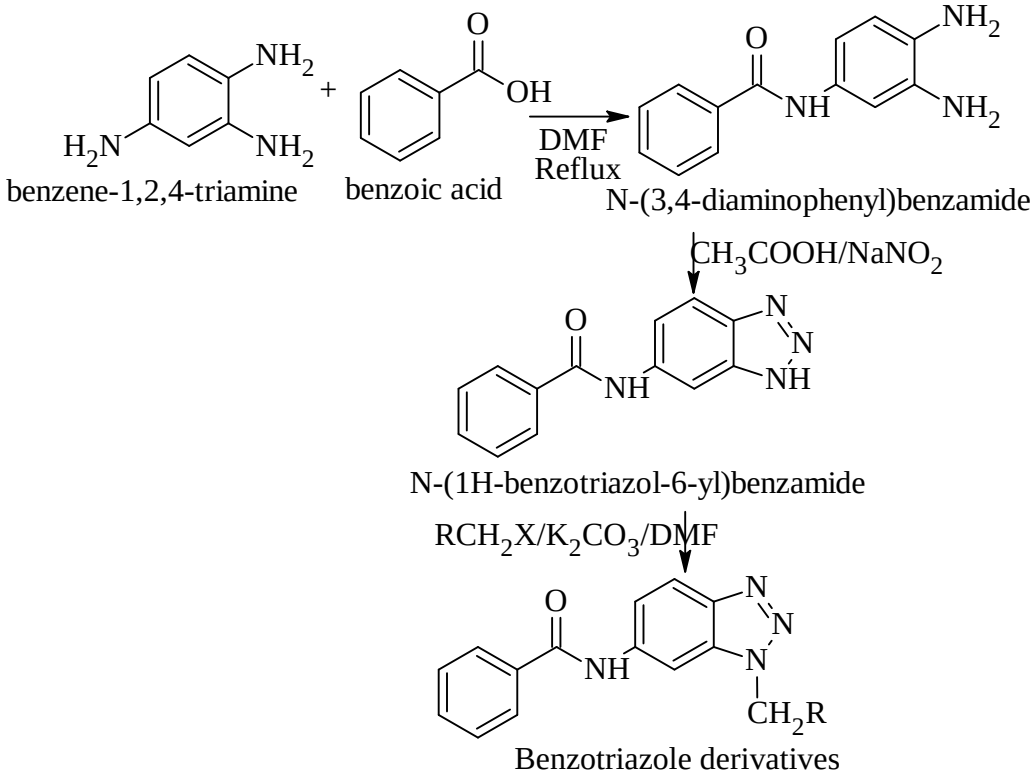


Figure no:1. **Scheme**

STEP-I: Synthesis of N-(3,4-diaminophenyl)benzamide
mol of Benzene 1,2,4-triamine treated with 0.01 mol of benzoic acid in presence of 25ml of DMF which is refluxed on water bath for 6hours and the purity of the product was confirmed by a single spot on TLC plate and recrystalized from methanol which gives the N-(3,4-diaminophenyl)benzamide the physicochemical properties of the compound given below table No 7.1.

Table No. 1: Physicochemical properties of N-(3,4-aminophenyl)benzamide

Sl. No	Parameter	N-(3,4-aminophenyl)benzamide
1	Molecular Formula	$C_{13}H_{13}N_3O$
2	Molecular weight	227.26
3	**T**heoretical yield	36.71gm
4	Practical yield	34.78gm
5	**%** yield	94.74%
6	Melting point	99-101^0 C
7	Recrystallization Solvent	Ethanol
8	Solvent for TLC	Cyclohexane: Chloroform 1:1
9	R_f Value	0.90

Step-II Synthesis of n-(1h-benzotriazol-6-yl)-benzamide

0.05mol of n-(3,4-diaminophenyl) benzamide refluxed with 15ml of acetic acid in 5gm of sodium nitrate stirred continuously with maintain constant temperature 15°C then the reaction mixture gives the brown color precipitate after cooling the purity of the product was confirmed by a single spot on TLC plate and recrysatlized from methanol which gives the N-(3,4-diaminophenyl)benzamide the physicochemical properties of the compound given below table No 2.

Table No. 2: Physicochemical properties of n-(1h-benzotriazol-6-yl)-benzamide

Sl. No	Parameter	n-(1h-benzotriazol-6-yl)-benzamide
1	Molecular Formula	$C_{13}H_{10}N_4O$
2	Molecular weight	238.24
3	**T**heoretical yield	34.78gm
4	Practical yield	31.66gm
5	**%** yield	91.02%
6	Melting point	110-112^0 C
7	Recrystallization Solvent	Ethanol
8	Solvent for TLC	Cyclohexane: Chloroform 1:1
9	R_f Value	0.96

Step-III Synthesis of derivatives of n-(1h-benzotriazol-6-yl)-benzamide

A mixture of n-(1h-benzotriazol-6-yl)-benzamide (6gm, 1 mol) in DMF (25ml) and various substituted aromatic halides (RCH2X) (3.3ml, 0.5 mol) was refluxed on a water bath for 6-8 hrs. Excess of halides was removed by distillation under reduced pressure Collected product was recrystallized from ethanol. The purity of the product was confirmed by a single spot-on TLC plate and physicochemical properties of *Derivatives* n-(1h-benzotriazol-6-yl)-benzamide given below table No 3 to 4

IR N-H Stretch of 3^0 amine -3323.81 cm^{-1}**,** N-H Stretch Of 2^0 amine 2956.69 cm^{-1}, Aromatic C-H Stretch 2923.27 cm^{-1}, Aliphatic C-H Stretch 2810.52 cm^{-1}, C = O Stretch 1633.10 cm^{-1}, -NO2 Stretch 1269.64 cm^{-1}, -CH3 stretch 959.14 cm^{-1}.

Table No 3: physicochemical properties of Derivatives of n-(1h-benzotriazol-6-yl)-benzamide (D13, D16, and D21)

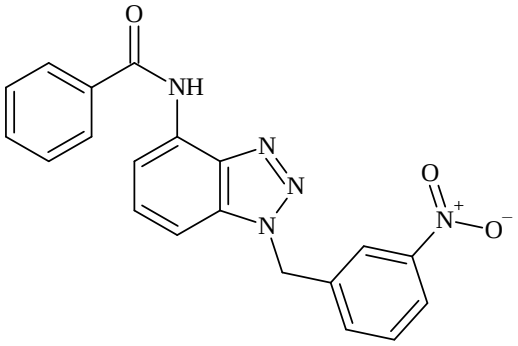
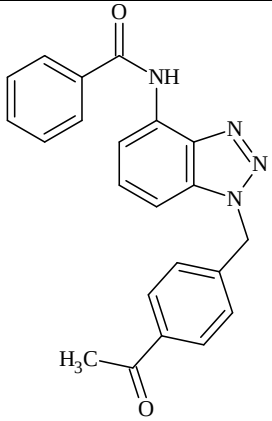
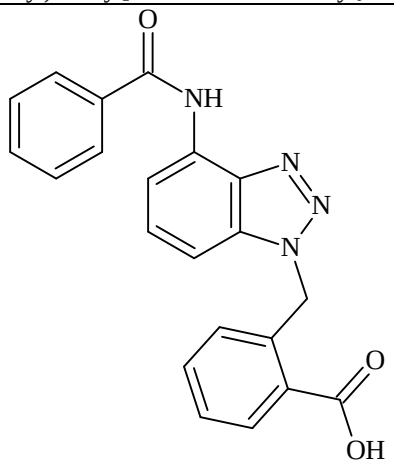
Sl. No	Parameter	D13	D16	D21
1	Molecular Formula	$C_{20}H_{15}N_5O_3$	$C_{22}H_{18}N_4O_2$	$C_{21}H_{16}N_4O_3$
2	Molecular weight	373.36	370.40	372.37
3	**T**heoretical yield	5.00gm	5.00gm	5.00gm
4	Practical yield	3.68gm	3.87gm	3.94gm
5	**%** yield	73.60%	77.40%	78.80%
6	Melting point	112-114^0 C	116-118^0 C	108-110^0 C
7	Recrystallization Solvent	Ethanol	Ethanol	Ethanol
8	TLC	Benzene: n-butanol 1:5	Benzene: n-butanol 1:5	Benzene: n-butanol 1:5
9	R_f Value	0.90	1.02	0.88

Table No 4: physicochemical properties of Derivatives of n-(1h-benzotriazol-6-yl)-benzamide (D13, D16, and D21)

Sl. No	Parameter	D27	D38	D43
1	Molecular Formula	$C_{21}H_{17}N_5O_3$	$C_{20}H_{15}N_4O_2F$	$C_{23}H_{20}N_4O_3$
2	Molecular weight	387.39	362.35	400.42
3	**T**heoretical yield	5.00gm	5.00gm	5.00gm
4	Practical yield	3.98gm	3.87gm	3.74gm
5	**%** yield	79.60%	77.40%	74.80%
6	Melting point	102-104^0 C	106-108^0 C	100-102^0 C
7	Recrystallization Solvent	Ethanol	Ethanol	Ethanol
8	TLC	Benzene:Methanol 1:5	Benzene:Methanol 1:5	Benzene:Methanol 1:5
9	R_f Value	0.89	0.88	0.90

SYNTHESIZED DERIVATIVES

Table No:5. Synthesized *Derivatives of* n-(1h-benzotriazol-6-yl)-benzamide

D13	 *N*-[1-(3-nitrobenzyl)-1*H*-benzotriazol-4-yl]benzamide
D16	 *N*-{1-[(4-acetylphenyl)methyl]-1*H*-benzotriazol-4-yl}benzamide
D21	 2-[(4-benzamido-1*H*-benzotriazol-1-yl)methyl]benzoic acid

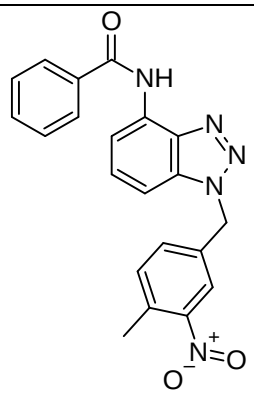
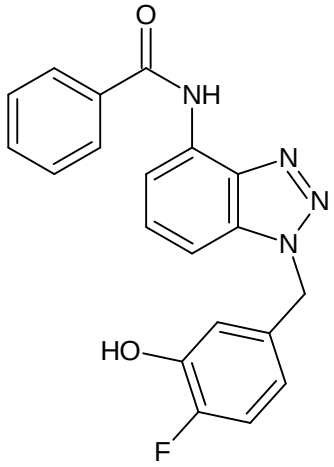
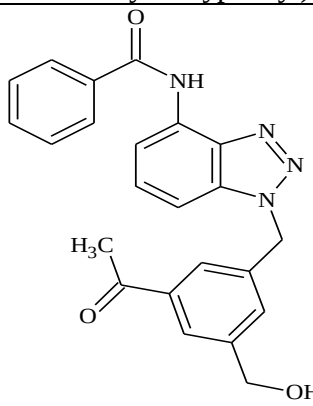
D27	 *N*-{1-[(4-methyl-3-nitrophenyl)methyl]-1*H*-benzotriazol-4-yl}benzamide
D38	 *N*-{1-[(4-fluoro-3-hydroxyphenyl)methyl]-1*H*-benzotriazol-4-yl}benzamide
D43	 *N*-(1-{[3-acetyl-5-(hydroxymethyl)phenyl]methyl}-1*H*-ben zotriazol-4-yl)benzamide

Table no: 6. Molecular Docking scores of selected compounds with COX 2 Inhibitor (PDB ID:1CX2)

Ligand	Binding Affinity
D1	-9.8
D2	-10.3
D3	-9.4
D4	-9.6
D5	-10.5
D6	-10.6
D7	-8.9
D8	-9.9
D9	-9.7
D10	-10.9
D11	-10.5

D12	-10.5
D13	-9.4
D14	-9.1
D15	-10.8
D16	-10
D17	-10.4
D18	-11.1
D19	-11.1
D20	-10.5
D21	-10.3
D22	-9.5
D23	-10
D24	-11.3
D25	-9.9
D26	-9.8
D27	-11.1
D28	-9.7
D29	-10.1
D30	-10.8
D31	-9.5
D32	-9.7
D33	-9.8
D34	-11.2
D35	-9.6
D36	-9.7
D37	-9.9
D38	-10.8
D39	-9.5
D40	-10.3
D41	-10
D42	-10.4
D43	-9.6
D44	-9.7
D45	-10.2
D46	-9.7
D47	-8.4
D48	-10.9
D49	-9.5
D50	-10.4
Indomethacin	-9.8

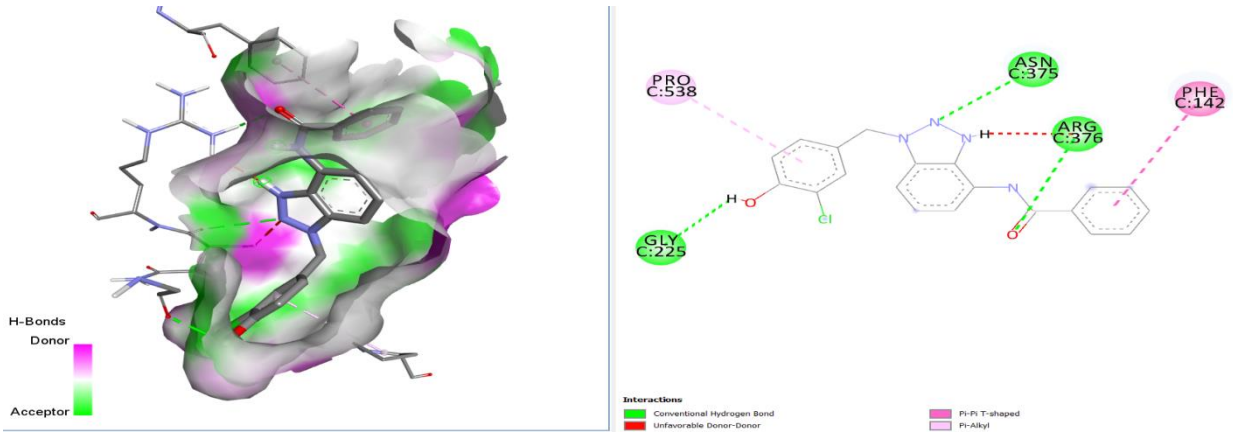


Figure No 2. 3D and 2D Interactions of D32 with COX 2 Inhibitor (PDB ID:1CX2)

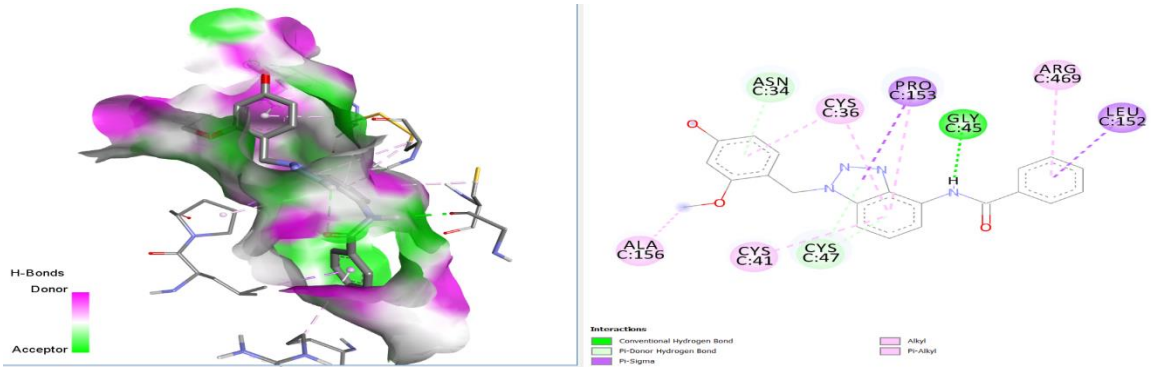


Figure No 3. 3D and 2D Interactions of D33 with COX 2 Inhibitor (PDB ID:1CX2)

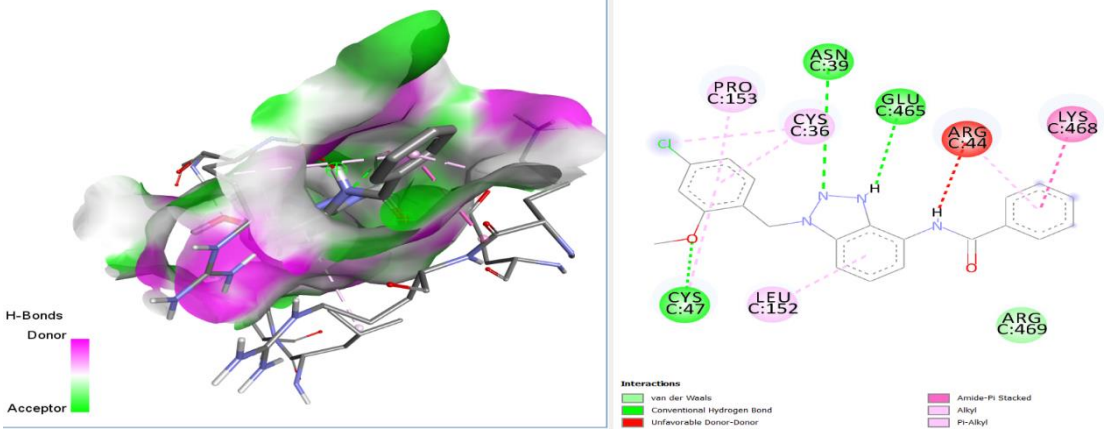


Figure No 4. 3D and 2D Interactions of D34 with COX 2 Inhibitor (PDB ID:1CX2)

However, the study showed that all the compounds synthesised are potential for the anticancer activity and can be selected based on further *in-vitro* and *in-vivo* activity studies.

In vitro antiarthritic activity

Protein Denaturation Method

- Test solution (0.5ml): It consist of 0.05ml of test solution of various concentrations (500µg/ml) and 0.45 ml of Bovine serum albumin (5% aqueous solution)
- Test controlsolution (0.5ml): It consist of 0.05ml of distilled water and 0.45ml of Bovine serum albumin (5% aqueous solution).
- Product control (0.5ml): It consist of 0.05ml test solution of concentration (500µg/ml) and 0.45ml o f distilled water.
- Standard solution (0.5ml): It consist of 0.05ml of Diclofenac sodium (500µg/ml) and 0.45ml of Bovine serum albumin (5%aqueous solution). PH was adjusted to 6.3 to all above solution by using 1N HCl.
- All the sample solution was incubated at 37℃ for 20 minutes and the temperature was increased to 57℃ for 3 minutes. Allow the solution to cool for some time then add 2.5ml of Phosphate buffer to all above s olution.
- Absorbance of the resulting solution is measured at 660 nm using UV visible spectrophotometer. Th e Percentage inhibition of protein denaturation was calculated as per the given

formula

$$\%\ inhibition = 100 - \frac{(OD\ of\ test\ solution - OD\ of\ product\ control)}{OD\ of\ test\ control} \times 100$$

***In-vitro* anti-inflammatory Activity of derivatives of n-(1h-benzotriazol-6-yl)-benzamide**

Table No. 7*: In-vitro* anti-inflammatory Activity of derivatives of n-(1h-benzotriazol-6-yl)-benzamide

Comp code	% Inhibition		
	250µgm	**500 µgm**	**Average**
D13	42.15	57.39	56.29
D16	48.13	62.66	58.66
D21	44.21	60.45	58.70
D27	**60.16**	**72.63**	**66.54**
D38	56.60	65.33	63.78
D43	42.10	56.38	55.60
IBUPROFEN	78.18	86.36	85.22

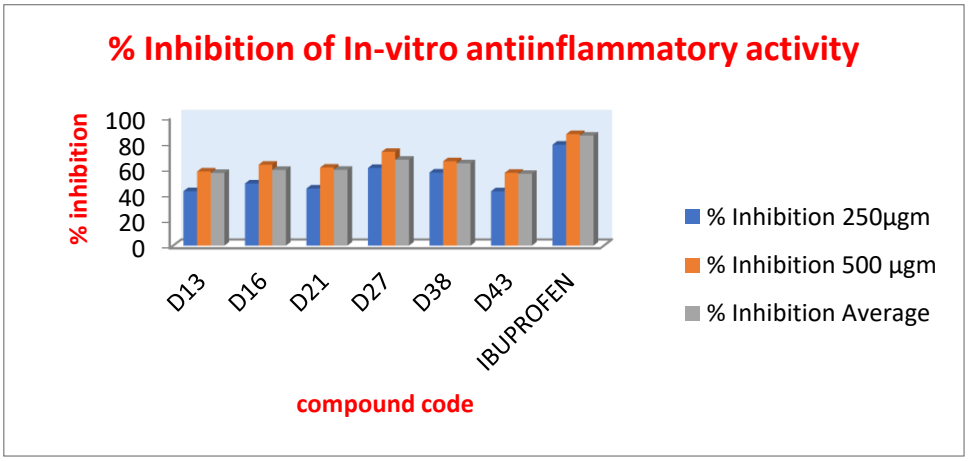


Figure No. 5*: In-vitro* anti-inflammatory Activity of derivatives of n-(1h-benzotriazol-6-yl)-benzamide

In-vitro Anti-inflammatory activity was carried out using Bovine Serum albumin denaturation method. All the title compounds (D13, D16, D21, D27, D38 and D43) were screened for anti-inflammatory activity. The results of the anti-inflammatory activity of the compounds are shown in the table No. 9.1 and Figure No. 9.1. D27 showed good activity. whereas other compounds showed mild to poor anti-inflammatory activity.

***In-vitro* antiarthiritc Activity of derivatives of n-(1h-benzotriazol-6-yl)-benzamide**

Table No. 8*: In-vitro* anti-arthiritc Activity of derivatives of n-(1h-benzotriazol-6-yl)-benzamide

Comp code	% Inhibition		
	250µgm	**500 µgm**	**Average**
D13	24.12	46.79	36.41
D16	29.41	55.28	42.02
D21	31.45	59.74	45.16
D27	**55.67**	**76.92**	**66.13**
D38	30.64	58.73	44.59
D43	42.94	66.74	54.67
DICLOFENAC SODIUM	78.67	90.46	84.63

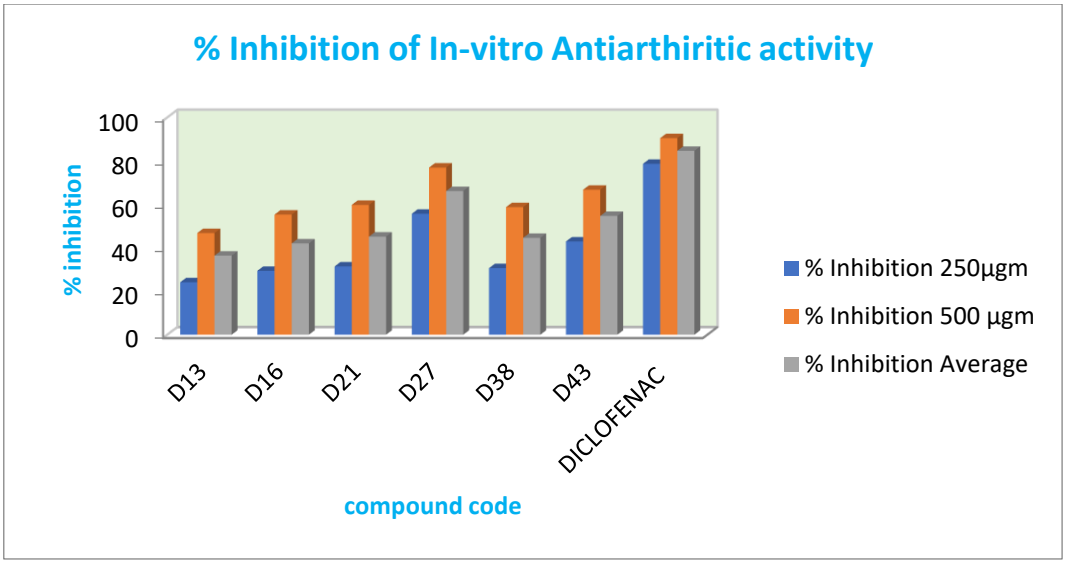


Figure No. 6*: In-vitro* anti-arthiritc Activity of derivatives of n-(1h-benzotriazol-6-yl)-benzamide

In vitro antiarthiritc activity Protein Denaturation method the production of auto antigen in certain arthritic disease may be due to denaturation of protein. Percentage inhibition was found to be 66.13% and the effect was compared with standard drug (Diclofenac sodium). In-vitro studies which were carried out by the above-mentioned methods proved that the D27 compound possess anti-inflammatory and antiarthritic activity which was similar to that of standards.

RESULTS AND DISCUSSION:

The intermediates converted into corresponding derivatives and they were obtained in high purity with good yield. The FT-IR studies show peeks at 1600-1790 cm^{-1} C=O stretch proves formation of derivatives of corresponding structure n-(1h-benzotriazol-6-yl)-benzamide derivatives and these derivatives will be tested for their biological activities.

Docking studies were carried out to analyse the different types of biomolecular interactions and ligand receptor binding affinities. The docking studies were carried out by means of Autodock vina, Biovia Discovery Studio 2020, PyRX, and PyMOL. The docking study was performed on proteins namely crystal structure of C-terminus of voltage-gated sodium channel in complex (PDB ID:4DCK) and COX 2 Inhibitor (PDB ID:1CX2) proteins. The computational work was performed on a HP 15s-eq0132au Laptop running on AMD Ryzen 7 3700U processor.

Compounds D13, D16, D21, D27, D38 and D43 reported the excellent docking score with crystal structure of C-terminus of voltage-gated sodium channel in complex (PDB ID:4DCK) and COX 2 Inhibitor (PDB ID:1CX2) proteins as anti-inflammatory and antiarthritic agents

In-vitro Anti-inflammatory activity was carried out using Bovine Serum albumin denaturation method. All the title compounds (D13, D16, D21, D27, D38 and D43) were screened for anti-inflammatory activity. The results of the anti-inflammatory activity of the compounds are shown in the table No. 9.1 and Figure No. 9.1. D27 showed good activity. whereas other compounds showed mild to poor anti-inflammatory activity.

CONCLUSION:

In vitro antiarthiritc activity Protein Denaturation method the production of auto antigen in certain arthritic disease may be due to denaturation of protein. Percentage inhibition was found to be 66.13% and the effect was compared with standard drug (Diclofenac sodium). In-vitro studies which were carried out by the above-mentioned methods proved that the D27 compound possess anti-inflammatory and antiarthritic activity which was similar to that of standards.

Acknowledgment: The author acknowledgment the BLDEA's SSM College of Pharmacy and Research Centre, Vijayapura, BLDE Deemed University, Karnataka for providing the opportunity and resources necessary for me to complete my research work and for encouraging us throughout the research project.

Conflict of interests:
None

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