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Synthesis, Characterization and *In-vitro* Anti-Inflammatory Activity of Methoxydibenzofuran -1,3-Thiazole-Carboxamide Derivatives.

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Abstract
The dibenzofuranthiazole group encompasses a well-established array of molecules that have yielded pharmacologically and biologically active agents with diverse heterocyclic and linear structures. Despite the potency of existing drugs like Tetomilast, Oglemilast, and Ciliomilast as anti-inflammatory agents, they are associated with significant side effects such as nausea, vomiting, and gastric acid secretion. Moreover, many contemporary standard drugs exhibit undesirable effects, including drug resistance, highlighting the urgent need for newer agents with improved potency and fewer adverse reactions. This study aimed to explore a set of new compounds synthesized through a four-step procedure involving coupling reactions. The purity of all synthesized derivatives was verified primarily through melting point, thin-layer chromatography, and FTIR spectroscopy, complemented by 1HNMR and Mass spectra studies. Additionally, the anti-inflammatory activities of the synthesized compounds were assessed using the protein denaturation assay method. The yields of all synthesized compounds ranged from 54% to 87%, demonstrating a moderate inhibition effect. Notably, compounds 4c, 4d, 4e, 4f, 4g, and 4h exhibited promising activity compared to the standard drug diclofenac sodium at a low concentration (100 µg/ml), with inhibition percentages ranging from 26.70% to 38.54%, surpassing diclofenac sodium's inhibition rate of 25.31 µg/ml. Particularly, compound 4d demonstrated significant inhibitory properties across all concentrations tested. This experiment suggests that the anti-inflammatory activity of dibenzofuranthiazole carboxamide derivatives is primarily attributed to halogenic derivatives with para substitution. Fluoro and chloro substitutions were identified as key enhancers of activity, along with methoxy derivatives bearing meta substituents exhibiting moderate activity.

Keywords: dibenzofuranthiazole, FTIR spectroscopy, diclofenac sodium, protein denaturation assay, carboxamide derivatives.

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1. Introduction

"Inflammation is the reaction of vascular supporting elements to injury and results in formation of protein rich exudates provided the injury has not been so serious as to destroy the area". Inflammation is one of the most important mechanisms involved in the each disease. Inflammation is manifest by pain, swelling, redness, and loss of function in the affected tissue. The process is created by immune cells invading the tissue like an army in full battle mode. Cell-mediated immunity is initiated by several cell populations, including mast cells, macrophages, eosinophils, and neutrophils. The net effect of sustained immune activity in any target organ is inflammation with

local dysfunction, associated with systemic symptoms from immune mediators released into the bloodstream. And create systemic symptoms by mediator or mediator release.

Acute inflammation:

Acute inflammation is the initial response of the body to harmful stimuli and is achieved by the increased movement of plasma and leukocytes from the blood in to the injured tissues. A cascade of biochemical events propagates and matures the inflammatory response, involving the local vascular system, the immune system, and various cells within the injured tissue. Acute inflammation is a short-term process, usually appearing within a few minutes, hours or one or two days and ceasing upon the removal of the injurious stimulus (Jayakar B 2010).

The cardinal signs are produced by

- Changes in vascular flow
- Changes in vascular permeability
- Cellular events – Leucocytes exudation and phagocytes

Chronic inflammation:

Prolonged inflammation is known as chronic inflammation, known as chronic inflammation, leads to a progressive shift in the type of cells which are present at the site of inflammation and is characterized by simultaneous destruction and healing of the tissue from the inflammatory process. It is of longer duration and is associated with presence of lymphocytes, macrophages, proliferation of blood vessels and connective tissue.

The causes of chronic inflammation are

- Progression of acute inflammation
- Repeated bouts of acute inflammation
- Insidious low grade smoldering response

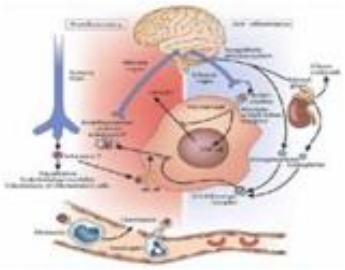

Fig.1. Different Stages Involved in Anti-inflammatory Cycle

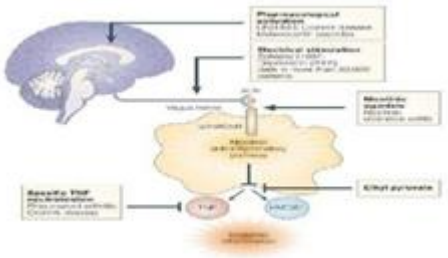

Fig.2. Mechanism of Acute inflammation

Anti-inflammatory activity:

Anti-inflammatory refers to the property of a substance or treatment that reduces inflammation. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids which affect the central nervous system. Anti-inflammatory medications are often used to treat medical conditions that cause swelling or inflammation in various areas of the body. Some of these medical conditions may include pulled muscles, arthritis, or lupus. Anti-inflammatory medications are available both with and without a prescription (Mohammed Ali 2001).

Medications:

1. Steroids

Steroid medications such as cortisone are man-made or synthetic versions of natural hormones produced by the human body. These medications are often prescribed as anti-inflammatory medications. Steroid creams or ointments are often used externally to reduce swelling and inflammation associated with muscle, skin, or joint issues. Cortisone injections may be given by a doctor for deeper muscle or joint problems, including conditions such as arthritis. Many steroids, specifically glucocorticoids, reduce inflammation or swelling by binding to glucocorticoid receptors. These drugs are often referred to as corticosteroids (Kokate CK 2001).

Non-steroidal anti-inflammatory drugs:

Non-steroidal anti-inflammatory drugs, commonly referred to as NSAIDs, are the most commonly prescribed anti-inflammatory medications for conditions such as arthritis and muscle pain. Many of these medications are available over the counter and can be found in most drug stores. Non-steroidal anti-inflammatory drugs (NSAIDs) alleviate pain by counteracting the cyclooxygenase (COX) enzyme. On its own COX enzyme synthesizes prostaglandins, creating inflammation. In whole the NSAIDs prevent the prostaglandins from ever being synthesized, reducing or eliminating the pain. Some common examples of NSAIDs include aspirin, ibuprofen, and naproxen. The newer specific COX-inhibitors, although probably sharing a similar mode of action, are not classified together with the traditional NSAIDs. On the other hand, there are analgesics that are commonly associated with anti- inflammatory drugs but that have no anti-inflammatory effects. An example is paracetamol, called acetaminophen in the U.S. and sold under the brand name of Tylenol. As opposed to NSAIDS, which reduce pain and inflammation by inhibiting COX enzymes, paracetamol has recently been shown to block the reuptake of cannabinoids. And which only reduces pain, likely explaining why it has minimal effect on inflammation.(Ashok D et al 2017).

2. Immune Selective Anti-Inflammatory Derivatives (ImSAIDs):

Early work in this area demonstrated that the sub-mandibular gland released a host of factors which regulate systemic inflammatory responses and modulate systemic immune and inflammatory reactions. It is now well accepted that the immune, nervous and endocrine systems communicate and interact to control and modulate inflammation and tissue repair. One of the neuro-endocrine pathways, when activated, results in the release of immune regulating peptides from the submandibular gland upon neuronal stimulation from sympathetic nerves. This pathway or communication is referred to as the cervical

sympathetic trunk- submandibular gland (CST-SMG) axis, a regulatory system that plays a role in the systemic control of inflammation.

2. Materials and Methods

The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on FT-IR spectrometer- 4100 type A with potassium bromide pellets. The 1H-NMR and spectra of the synthesized compounds were recorded on a JOEL 500 MHz NMR spectrometer in CHCl3 / DMSO. Mass spectra were recorded on Shimadzu GCMS QP 5000. The purity of the compounds was checked by TLC on pre – coated SiO2 gel (HF254 200 mesh) aluminum plates (E-merk) using ethyl acetate: n-hexane as eluent and visualized in UV- chamber. (Harbone JB 2005). The IR, 1H-NMR, and mass spectra were consistent with the assigned structure.

In-vitro anti-inflammatory activity

Anti-denaturation assay method

The denaturation of protein as one of the causes as inflammation is well documented. Production of auto-antigen in certain rheumatic diseases may be due to in vivo denaturation of proteins. A number of anti inflammatory drugs are known to inhibit the denaturation of protein. Based on that we have employed protein denaturation as in vitro screening model for anti-inflammatory compounds. (Sangita C et al 2012).

Procedure: The experiment was carried out with minor modification. The standard drug and extract was dissolved in minimum quantity of Dimethyl Formamide (DMF) and diluted with phosphate buffer (0.2 M, PH 7.4). Final concentration of DMF in all solution was less than 2.5%. Test Solution (4ml) containing different concentrations of drug was mixed with 1 ml of 1mM albumin solution in phosphate buffer and incubated at 37°C in incubator for 15 min. Denaturation was induced by keeping the reaction mixture at 70°C in water bath for 15 min. After cooling, the turbidity was measured at 660 nm. Percentage of Inhibition of denaturation was calculated from control where no drug was added. The diclofenac sodium was used as standard drug. The percentage inhibition of denaturation was calculated by using following formula.(*Banerjee M et al* 2011)

$$\text{Percentage of inhibition} = \frac{(A_{\text{Test}} - A_{\text{Control}})}{(A_{\text{Test}})} \times 100$$

At = O.D. of test solution
Ac = O.D. of control

3. Results and Discussion

Table: 1 Anti inflammatory activity of Compounds (4 - 4i)

Compound code	Concentrations in µg/ml					
	100	200	300	400	500	1000
4	4.06	21.85	43.26	49.57	63.91	80.30
4a	7.08	8.52	26.70	29.76	35.16	51.63
4b	9.92	29.34	44.07	46.11	58.59	71.77
4c	26.70	44.60	61.68	66.85	72.99	80.36
4d	35.86	54.96	70.71	76.30	79.37	89.06
4e	27.16	30.99	47.08	51.83	52.61	67.03
4f	27.60	28.91	46.11	47.08	48.91	65.49
4g	38.54	44.60	62.30	64.98	66.85	79.96
4h	32.57	41.87	52.03	63.00	67.58	78.38
4i	5.60	7.08	9.92	14.49	29.76	59.16
Diclofinac sodium	25.31	51.44	64.77	72.49	77.22	84.94

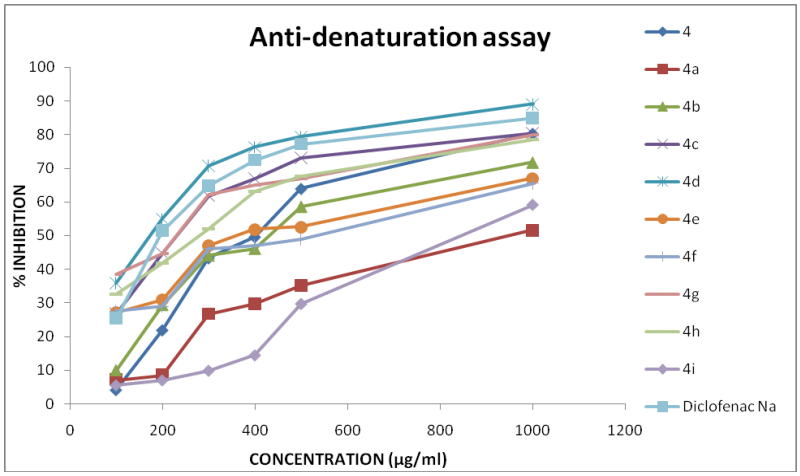

Fig:3 Anti-denaturation Assay

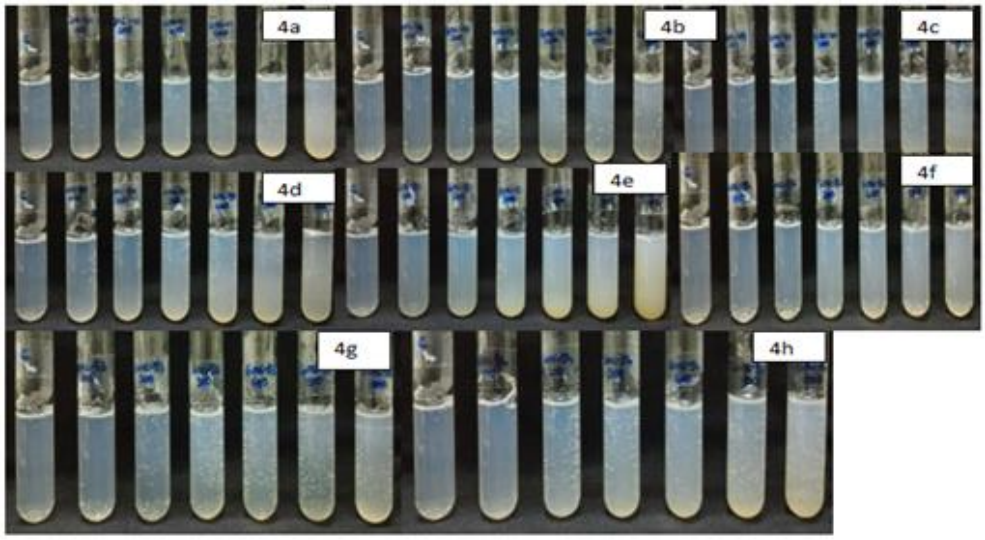

Fig.4. Photocopies representing anti inflammatory activity screening

Discussion:

A well-known derivative, dibenzofuran carboxamide, was synthesized via a four-step procedure involving conversion of methoxydibenzofuran to various intermediates, culminating in the parent compound. Aryl amine groups were introduced through coupling reactions. Purity of synthesized derivatives was confirmed using melting point, thin layer chromatography, and FTIR spectroscopy. Additional 1H NMR and Mass spectra studies were conducted. Yields ranged from 54-87%, with all compounds being non-hygroscopic. Spectral data indicated characteristic absorption bands corresponding to specific functional groups. Anti-inflammatory activity was evaluated using a protein denaturation assay, with results demonstrating moderate inhibition effects for all synthesized compounds. Compounds 4c, 4d, 4e, 4f, 4g, and 4h exhibited promising activity compared to diclofenac sodium, particularly compound 4d showing superior inhibitory properties across all concentrations.

4. Conclusion

The study titled "Synthesis, Characterization, and Biological Activity of Methoxydibenzofuran-1,3-Thiazole Carboxamide Derivatives" presents the synthesis of ten compounds. The presence of dibenzofuranthiazole in molecules has led to pharmacologically active agents, including potent anti-inflammatory drugs such as Tetomilast, Oglemilast, and Ciliomilast, albeit with significant side effects. To address this, new compounds with improved potency and fewer side effects were synthesized. Inspired by existing drugs like Tetomilast containing a thiazole moiety and Oglemilast with a dibenzofuran nucleus, the study focused on synthesizing dibenzofuran thiazole carboxamide derivatives. All compounds were synthesized in the laboratory and purified via crystallization. Structural confirmation was achieved through various analytical techniques including melting point, FTIR, 1H-NMR, and High-Resolution Mass Spectroscopy. Cyclic nucleotide phosphodiesterases (PDEs) play a crucial role in inflammation by regulating intracellular cAMP levels. Inhibition of PDEs can suppress the release of inflammatory mediators, making them potential targets for anti-inflammatory drugs. Biological evaluation of the synthesized compounds showed moderate inhibitory effects against protein denaturation, with compounds 4c, 4d, 4e, 4f, 4g, and 4h exhibiting promising activity compared to diclofenac sodium. Compound 4d demonstrated particularly strong inhibition across all concentrations tested, suggesting its potential as a novel anti-inflammatory agent. Halogenic derivatives with para substitution, especially fluorine and chlorine, were identified as key groups enhancing activity, along with methoxy derivatives with meta substituents showing moderate activity.

5. References

[1] Jayakar B., (2010). In vitro antioxidant evaluation of Pseudarthria viscid. International Journal of current pharmaceutical research 2, 21-23.

[2] Mohammed Ali. (2001) Objective type Pharmacy. 2nd Ed. Delhi, Birla publication 567-568.

[3] Kokate CK., Gokhale SB (2001) Pharmacognosy. Pune, Nirali Prakashan. 16th Edn 134.

[4] Ashok D., SreeKanth S., Sarasija M., Vijiulatha M., (2017).Synthesis biological evalution and molecular docking of spirofurochromanone derivative as anti-inflammatory and anti oxidant agents.Royal Society of Chemistry 7,25710-25724.

[5] Harborne JB., (2005). Phytochemical Methods. A guide to modern techniques of plant analysis. 3rd Edn, Springer (India) Pvt. Ltd. New Delhi. 5-16, 22.

[6] Sangita C., Priyanka C., Protapaditya D., Sanjib B., (2012).Evalution of invitro anti- inflammatory activity of coffee against the denaturation of protein.Asian Pacific Journal of Tropical Biomedicine s178-s180.

[7] Banerjee M., Sundeepp H.K., Sahu S.K., Das A., (2011).Synthesis and invitro protein denaturation screening of novel substituted Isoxazole /Pyrazole derivatives. Rasayan. J. Chem 4(2),413-417.