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NOVEL 2 – AMINO - N' - (2-OXOINDOLIN – 3 - YLIDENE) BENZO [d] OXAZOL – 5 - CARBOHYDRAZIDES AS ANTI-INFLAMMATORY AGENTS

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Keywords:

Benzoxazole; Antiinflammatory; prostaglandin; Isatins; Indomethacin, carrageen

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ABSTRACT:

In the present work , novel 2-Amino-N'-(2-oxoindolin-3-ylidene) benzo[d]oxazole-5-carbohydrazides were synthesized and evaluated for *In-vivo* anti-inflammatory activity by carragenan induced rat paw edema method and were known to exhibit promising anti-inflammatory activity at a dose of 30mg/kg bw. Compounds **D₂**, **D₃**, **D₅** and **D₈** were found to be comparatively potent with the standard Indomethacin.

INTRODUCTION: Relief of pain and inflammation in human being is a major challenge for medicinal chemistry researchers. Non-steroidal anti-inflammatory agents currently in use are characterized by their ability to relieve the pain of both pathological and non-pathological inflammation associated with inflammatory disorders and to inhibit the synthesis of endogenous prostaglandins (PGs) which are the mediating factors for the inflammation process. They competitively inhibit cyclooxygenases (COXs) and elicit their therapeutic effects by inhibition of prostaglandin (PG) synthesis. Specifically by the enzymes that catalyze the synthesis of cyclic endoperoxides from arachidonic acid to form prostaglandins. Two COX isoenzymes have been identified: COX-1 and COX-2.

COX-1, expressed constitutively, is synthesized continuously and is present in all tissues and cell types, most notably in platelets, endothelial cells, the GI tract, renal microvasculature, glomerulus, and collecting ducts. COX-2 is considered an inducible isoenzyme, although there is some constitutive expression in the kidney, brain, bone, female reproductive system, neoplasias, and GI tract. The COX-2 isoenzyme plays an important role in pain and inflammatory processes ¹.

Among the heterocycles, Benzoxazoles occupy a unique place in the realm of natural and synthetic organic chemistry and it is considered as structural isosteres of the naturally occurring nucleic bases adenine and guanine, which allow them to interact easily with polymers of living systems and possess most remarkable and a wide range of biological activities. The substituted benzoxazoles have been shown to exhibit antitumor, antihistaminic, antiparasitic, and herbicidal, anti allergic, antihelmintic, COX-2inhibitory, antifungal, antibacterial, anticancer, antitubercular, anticonvulsant, diarrhoea-predominant irritable bowel syndrome, hypoglycaemic, HIV-1 reverse

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transcriptase inhibitor & insecticidal activities²⁻¹⁶. It has also been shown to have binding affinity to A β 42 fibrils. On the other hand, Isatins are an important group of heterocyclic compounds which are biologically active and of significant importance in medicinal chemistry.

A variety of biological activities are associated such as analgesic, anticonvulsant, antidepressant, anti-inflammatory, antimicrobial activity and effects on the central nervous system identified in animals as a major component of the endogenous monoamine oxidase inhibitor¹⁷⁻³⁴. In this communication we described the synthesis of hybrid molecules consisting of Benzoxazoles along with Isatin moiety highlighted their *in-vitro* anti-inflammatory activity.

Experimental:

Chemistry:

All chemicals used in this study were purchased from E. Merck, Aldrich companies. Melting points were recorded on VMP-AM melting point apparatus. Proton Nuclear Magnetic Resonance spectra were recorded on Varian Gemini 200, Avance 300 and Varian Unity 400 spectrometers using tetramethylsilane (TMS) as an internal standard and chemical shifts are shown in δ scale. Infrared spectra were recorded on Perkin-Elmer 1310 infrared spectrometer.

Electron Impact (EI) and Chemical ionization mass spectra (CIMS) were recorded on VG 7070 H ev instrument at 70 ev. Silica gel used for column chromatography was purchased from ACME chemical company. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F₂₅₄ (Merck); spots were visualized with UV light.

Synthesis of Indole-2, 3-diones (isatins):

Isonitrosoacetanilides: In a 5 L R.B. Flask were placed 90g (0.54mol) of chloral hydrate and 1200 ml of water. To this solution, were then added crystallized sodium sulphate (1300 g) followed by a solution of appropriate aniline (0.5mol) in 300 ml of water, to which 51.2g (43ml, 0.52 mol) of concentrated Hydrochloric acid has been added to dissolve the aniline. Finally, a solution of hydroxylamine HCl, 110g (1.58mol) in 500 ml of water was added. The contents of the flask were

heated on water bath so that vigorous boiling began in about 40 to 45 minutes. After 1 to 2 minutes of vigorous boiling the reaction was completed. During the heating period, some crystals of isonitrosoacetanilide separated out. On cooling the solution in running water, the remaining crystallized. It was filtered under suction and air dried.

Indole-2, 3-diones – Sulphuric acid (600 g, 326 ml, sp.gr. 1.84) was warmed at 50°C in a 1 litre R.B. flask fitted with an efficient mechanical stirrer, and to this, 0.46mol of dry finely powdered appropriate isonitrosoacetanilide was added at such a rate so as to maintain the temperature between 60°C to 70°C but not higher. External cooling was applied at this stage so that the reaction could be carried out more rapidly.

After the addition of isonitrosoacetanilide was completed, the solution was heated to 80°C and maintained at that temperature for 10 minutes to complete the reaction. Then the reaction mixture was cooled to room temperature and poured up on 10 to 12 times the volume of crushed ice while stirring. After standing for about half-an-hour, the product separated was filtered, washed several times with small portions of cold water, several times to remove sulphuric acid. It was then air dried.

Synthesis of Methyl 4-hydroxy-3-nitrobenzoate

(2): To a solution of aluminium nitrate (40 g) in glacial acetic acid: acetic anhydride (1:1, v/v) mixture (160 ml) 40 g of Methyl-4-hydroxybenzoate (1) was added in small portions, while heating gently; cooling and shaking occasionally. The reaction mixture was left at room temperature for 1.5 h while shaking the contents intermittently to complete the nitration. The resulting brown solution was diluted with ice cold water (500 ml) to get a bulky yellow precipitate of methyl 4-hydroxy-3-nitrobenzoate. (mp= 73°C)

Synthesis of Methyl 3-amino-4-hydroxybenzoate

(3): Methyl 4-hydroxy-3-nitrobenzoate (2, 40 g) was dissolved in boiling ethanol (400 ml) and sodium dithionite was added to this boiling alcohol solution until it becomes almost colourless. Then the solvent was reduced to one third of its volume

by distillation and to the residual liquid, ice cold water was added. The resulting shiny product (3) was filtered, washed with cold water and dried. (mp= 143°C)

Synthesis of Methyl 2-aminobenzo[d]oxazol-5-carboxylate (4): 1.3 moles of methyl 3-Amino-4-hydroxybenzoate (3) was dissolved in 1L Methyl alcohol and cooled the solution to 5°C by adding chopped ice. A cold suspension of 1.5 moles of Cyanogen bromide in 1L of water was added over a period of 5min with rapid stirring. Continuing the stirring for 0.75h at room temperature, 1.3moles of solid Sodium bicarbonate in small portions over a period of 1.5 h was added to bring the pH 6.5 -7.0. Stirring was continued for another 1h. The solid was separated by filtration, washed with cold water and on recrystallization from ethyl alcohol has resulted white solid. (mp= 243°C)

Synthesis of 2-Aminobenzo[d]oxazol-5-carbohydrazide (5): A mixture of Methyl-2-aminobenzoate (4, 0.01mol) and hydrazine hydrate (99%) (0.01mol) were taken in 50ml of alcohol, heated under reflux on a water bath for 5hrs. The alcohol was reduced to half of its volume and cooled. The product separated was filtered and washed with small portions of cold alcohol first and then with cold water repeatedly and dried. The product purified by recrystallization from methanol has resulted white solid.

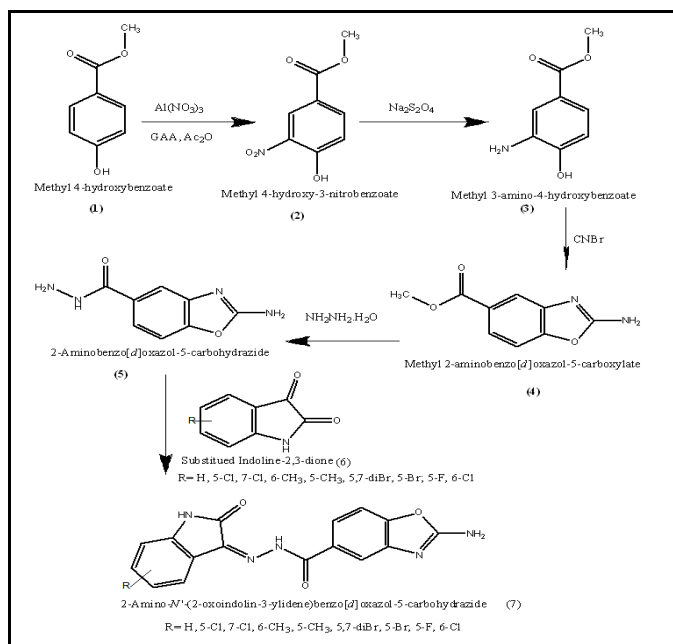


FIGURE: 1 Synthesis of 2--Amino-N'-(2-oxoindolin-3-ylidene) benzo [d] oxazol-5-carbohydrazide (7)

Synthesis of 2-Amino-N'-(2-oxoindolin-3-ylidene) benzo[d]oxazol-5-carbohydrazide (7):

The 2-aminobenzo[d]oxazole-5-carbohydrazide (5, 0.01mol) and appropriate isatin (6, 0.01mol) in methanol (20ml), 2 drops of glacial acetic acid heated under reflux on a water bath for 8 to 12 h. The product thus obtained was filtered, washed with water and air dried.

Pharmacological evaluation:

Plethysmograph, Carrageenan, Indomethacin, Test compounds, Normal saline, water, 1ml reusable glass syringe, needles for intraperitoneal injection, marker pens, cotton, 0.1% Sodium CMC suspension.

Animals:

All the experiments were carried out using male, Sprague-Dawley rats (300-350 g) were obtained from animal house, UCPSc, Kakatiya University, Warangal, India. On arrival the animals were placed at random and allocated to treatment groups in polypropylene cages with paddy husk as bedding. Animals were housed at a temperature of $24 \pm 2^\circ\text{C}$ and relative humidity of 30 – 70 %. A 12:12 light: day cycle was followed. All animals were allowed to free access to water and fed with standard commercial rat chew pellets. All the experimental procedures and protocols used in this study were reviewed by the Institutional Animal Ethics Committee, Kakatiya University, Warangal, India.

Preparation of carrageenan suspension:

1% w/v suspension of carrageenan was prepared by adding 100mg of carrageenan powder to 10ml of saline (0.9% NaCl) solution and set aside to soak for 1 hour. A homogenous suspension was then obtained by thorough mixing with a magnetic stirrer.

Experimental Procedure:

Sprague-Dawley strain Albino rats of either sex, weighing between 250-300 g, fasted overnight before the test and allowed water *ad libitum*, were divided into ten groups of six animals each. The volume of the right hind paw was measured using a plethysmograph. This constituted the initial reading. The test compounds were tested at a dose of 30mg/kg body weight. Indomethacin 5mg

(0.014mmoles)/kg body weight was used as standard. All these were administered as suspensions using sodium CMC (0.1% w/v) as suspending agent.

Control group of animals received a suspension of sodium CMC only. All these were administered intraperitoneally 1h before the injection of carrageenan. 0.1 ml of 1% w/v carrageenan suspension in normal saline was injected in to the plantar region of the right hind paw.

The swelling produced after injection of the carrageenan was measured at 2hour intervals for 8 hours. Percentage inhibition of edema was calculated using the formula given below:

$$\% \text{inhibition of oedema} = \frac{\text{Mean oedema of control group} - \text{Mean oedema of test group}}{\text{Mean oedema of control group}} \times 100$$

RESULTS AND DISCUSSION:

Synthesis:

Methyl-4-hydroxy benzoate upon nitration with aluminium nitrate in presence of glacial acetic acid and acetic anhydride produces methyl-4-hydroxy-3-nitrobenzoate and undergoes reduction in presence of sodium dithionate to form methyl 3-amino-4-hydroxy benzoate (3) which undergoes cyclization in presence of cyanogenbromide to form methyl - 2 - amino- benzo [d] oxazol - 5 - carboxylate (4) upon treatment with hydrazine hydrate produces 2-Aminobenzo [d] oxazol - 5 - carbohydrazide upon reaction with substituted Isatins (6) yields 2 - Amino - N' - (2-oxoindolin-3-

ylidene) benzo [d] oxazol - 5 - carbohydrazide (7) Yields and Melting point of the intermediates (Table 2) and 2-Amino-N'-(2-Oxoindolin-3-Ylidene) Benzo [D]Oxazol - 5 Carbohydrazides (Table 1). The structures of the compounds were confirmed by spectral studies such as IR, ¹H NMR and MS³⁵⁻³⁷.

Acute toxicity³⁸:

All the compounds are evaluated for acute toxicity and well tolerated by the experimental animals and it has been found to be non-toxic and safe even up to a dose of 300mg/kg bodyweight orally.

Anti-inflammatory activity³⁹:

All the synthesized compounds (D1-D6) were subjected for *in-vivo* anti-inflammatory activity by carrageenan induced rat paw odema method at a dose of 30 mg/kg body weight using Indomethacin as a reference standard. 2-Amino-N'-(2-oxoindolin-3-ylidene) benzo [d] oxazole - 5 - carbohydrazides showed promising anti-inflammatory activity The Percentage Inhibition was determined (Table 4).

Among the synthesized compounds **D₂** (R= 5-chloro), **D₃** (R= 7-chloro), **D₅** (R= 5-methyl) and **D₈** (R= 5-fluoro, 6-chloro) were found to be comparatively potent with 36.76 (6h), 31.77(8h), 31.37(6h), 32.60(6h) percentage inhibition of paw edema respectively and the compounds **D₄** (R= 6-methyl) and **D₆** (5, 7-dibromo) showed weak anti-inflammatory activity with 15.76 (4h), 7.84 (6h) percentage inhibition of paw edema respectively and are shown in Table 3 and Figure 2.

TABLE 1: PHYSICAL DATA OF 2-AMINO-N'-(2-OXOINDOLIN - 3 - YLIDENE) BENZO [d] OXAZOL - 5 - CARBOHYDRAZIDES:

Compound	R	Molecular formula	Molecular weight	Melting point (°C)	Percentage yield
D ₁	H	C ₁₆ H ₁₁ N ₅ O ₃	321.9	315	73
D ₂	5-Cl	C ₁₆ H ₁₀ ClN ₅ O ₃	355.74	320	75
D ₃	7-Cl	C ₁₆ H ₁₀ ClN ₅ O ₃	355.74	310	70
D ₄	6-CH ₃	C ₁₇ H ₁₃ N ₅ O ₃	335.32	325	76
D ₅	5-CH ₃	C ₁₇ H ₁₃ N ₅ O ₃	335.32	305	82
D ₆	5,7-diBr	C ₁₆ H ₉ Br ₂ N ₅ O ₃	479.08	310	75
D ₇	5-Br	C ₁₆ H ₁₀ BrN ₅ O ₃	399.18	330	77
D ₈	5-F, 6-Cl	C ₁₆ H ₉ FCIN ₅ O ₃	373.73	350	76

TABLE 2: PHYSICAL DATA OF INDOLE 2, 3 DIONES

S.no.	Compound	R	Molecular formula	Molecular weight	Melting point (°C)	Percentage yield
1	I ₁	H	C ₈ H ₅ NO ₂	147.10	200	70
2	I ₂	5-Cl	C ₈ H ₄ ClNO ₂	181.58	255	65
3	I ₃	7-Cl	C ₈ H ₄ ClNO ₂	181.58	190	68
4	I ₄	6-CH ₃	C ₉ H ₇ NO ₂	161.16	170	72
5	I ₅	5-CH ₃	C ₉ H ₇ NO ₂	161.16	184	75
6	I ₆	5,7-diBr	C ₈ H ₃ Br ₂ NO ₂	305.00	250	-
7	I ₇	5-Br	C ₈ H ₄ BrNO ₂	225.03	248	-
8	I ₈	5-F, 6-Cl	C ₈ H ₃ FCINO ₂	199.57	240	62

TABLE 3: SHOWING THE MEAN PAW EDEMA VOLUME (n=6) OF 2-AMINO-N'-(2-OXOINDOLIN-3-YLIDENE) BENZO[d] OXAZOL-5-CARBOHYDRAZIDES (30mg/kg bw) COMPARED TO STANDARD DRUG INDOMETHACIN (5mg/kg bw)

Compound	R	Mean paw edema Volume(ml) ± SD				
		0h	2h	4h	6h	8h
D ₁	H	0.400±0.00	0.720±0.075	0.650±0.055	0.616±0.041	0.533±0.052
D ₂	5-Cl	0.434±0.052	0.650±0.075	0.566±0.086	0.516±0.041	0.500±0.000
D ₃	7-Cl	0.399±0.075	0.650±0.058	0.667±0.052	0.600±0.063	0.466±0.052
D ₄	6-CH ₃	0.417±0.04	0.700±0.00	0.716±0.041	0.766±0.041	0.600±0.00
D ₅	5-CH ₃	0.417±0.04	0.566±0.057	0.65±0.05	0.560±0.045	0.530±0.051
D ₆	5,7-diBr	0.434±0.08	0.75±0.055	0.816±0.075	0.75±0.084	0.63±0.052
D ₇	5-Br	0.450±0.054	0.583±0.026	0.78±0.04	0.65±0.082	0.60±0.040
D ₈	5-F, 6-Cl	0.483±0.09	0.60±0.054	0.60±0.119	0.55±0.093	0.50±0.098
Indomethacin		0.416±0.04	0.596±0.083	0.526±0.134	0.480±0.092	0.447±0.080
Control		0.434±0.05	0.780±0.098	0.850±0.055	0.816±0.075	0.683±0.041

Spectral data:**2 - Amino - N' - (2-oxoindolin - 3 - ylidene) benzo [d] oxazol - 5 - carbohydrazide (D₁)**

IR (KBr, cm⁻¹): 3392.12, 3167.50 (NH₂ str.), 1685.77(C=O str.), 1139.28 (C-O str.);

¹H NMR (DMSO-d₆, 400 MHz) δ = 13.85 (s, 1H, NH), 11.38 (s, 1H, NH), 7.75(s, 2H, NH₂), 7.68-7.54 (m, 4H, Ar-H), 7.43-7.38(t, 1H, Ar-H), 7.14-7.10(t, 1H, Ar-H), 6.98(s, 1H, Ar-H) ppm; Mass spectrum (ESI): (M⁺) 321.9 m/z ;HRMS: 321.90

2 - Amino -N'- (5-chloro-2-oxoindolin-3-ylidene) benzo[d]oxazol-5-carbohydrazide (D₂):

IR (KBr, cm⁻¹): 3392.12, 3167.50 (NH₂ str.), 1685.77(C=O str.), 1139.28 (C-O str.)

¹H NMR (DMSO-d₆, 400 MHz) δ = 13.85 (s, 1H, NH), 11.38 (s, 1H, NH), 7.75(s, 2H, NH₂), 7.68-7.54 (m, 2H, Ar-H), 7.46-7.50(s,1H,Ar-H),7.43-7.38(t, 1H, Ar-H), 7.14-7.10(t, 1H, Ar-H), 6.98(s, 1H, Ar-H) ppm; Mass spectrum (ESI): 355; HRMS:355.15

2 - Amino - N' - (7-Chloro - 2 - oxoindolin - 3 - ylidene) benzo[d]oxazol- 5-carbohydrazide (D₃):

IR (KBr, cm⁻¹): 3392.12, 3167.50 (NH₂ str.), 1685.77(C=O str.), 1139.28 (C-O str.)

¹H NMR (DMSO-d₆, 400 MHz) δ = 13.85 (s, 1H, NH), 11.38 (s, 1H, NH), 7.75(s, 2H, NH₂), 7.68-7.54 (m, 3H, Ar-H), 7.43-7.38(t, 1H, Ar-H), 7.14-7.10(t, 1H, Ar-H), 6.98(s, 1H, Ar-H) ppm;Mass spectrum (ESI): 355; HRMS: 355.10

2 - Amino - N'- (6-methyl-2-oxoindolin - 3-ylidene) benzo[d] oxazol-5-carbohydrazide (D₄):

IR (KBr, cm⁻¹): 3392.12, 3167.50 (NH₂ str.), 1685.77(C=O str.), 1139.28 (C-O str.)

¹H NMR (DMSO-d₆, 400 MHz) δ = 13.85 (s, 1H, NH), 11.38 (s, 1H, NH), 7.75(s, 2H, NH₂), 7.68-7.54 (m, 2H, Ar-H), 7.43-7.38(t, 1H, Ar-H),7.23-7.32(s,1H,Ar-H) 7.14-7.10(t, 1H, Ar-H), 6.98(s, 1H, Ar-H),2.0 (s,3H,CH₃) ppm.; Mass spectrum (ESI):335;HRMS: 335.12

2-Amino-N'- (5 - methyl - 2-oxoindolin - 3 - ylidene) benzo[d] oxazol-5-carbohydrazide (D₅):

IR (KBr, cm⁻¹): 3392.12, 3167.50 (NH₂ str.), 1685.77(C=O str.), 1139.28 (C-O str.)

¹H NMR (DMSO-d₆, 400 MHz) δ = 13.85 (s, 1H, NH), 11.38 (s, 1H, NH), 7.75(s, 2H, NH₂), 7.68-7.54 (m, 2H, Ar-H), 7.43-7.38(t, 1H, Ar-H),7.23-7.32(s,1H,Ar-H) 7.14-7.10(t, 1H, Ar-H), 6.98(s, 1H, Ar-H),2.0 (s,3H,CH₃) ppm.

Mass spectrum (ESI): 335

2 - Amino - N' - (5, 7- dibromo - (2-oxoindolin -3-ylidene) benzo [d] oxazol – 5 - carbohydrazide (D₆): IR (KBr, cm⁻¹): 3404.46, 3247.59 (NH₂ str.), 1690.05 (C=O str.), 1141.28 (C-O-C str.)

¹HNMR (DMSO-d₆, 400 MHz): δ = 13.8 (s, 1H, NH), 11.25 (s, 1H, NH), 7.87 (s, 1H, Ar-H), 7.8 (s, 1H, Ar-H), 7.74 (s, 1H, Ar-H), 7.65 (s, 2H, NH₂), 7.56(d, 1H, Ar-H), and 7.52 (d, 1H, Ar-H) ppm.; Mass spectrum: ESI- 479.7; HRMS: 479.9

2 – Amino - N' - (5-bromo-2-oxoindolin-3-ylidene) benzo[d]oxazol-5-carbohydrazide (D₇):

IR (KBr, cm⁻¹): 3392.12, 3167.50 (NH₂ str.), 1685.77(C=O str.), 1139.28 (C-O str.)

¹H NMR (DMSO-d₆, 400 MHz) δ = 13.85 (s, 1H, NH), 11.38 (s, 1H, NH), 7.75(s, 2H, NH₂), 7.68-7.54 (m, 2H, Ar-H), 7.46-7.50(s,1H,Ar-H),7.43-7.38(t, 1H, Ar-H), 7.14-7.10(t, 1H, Ar-H), 6.98(s, 1H, Ar-H) ppm.Mass spectrum:ESI-400;HRMS: 400.09

2-Amino- N - 5 Fluoro-7-dibromo-2-oxoindolin-3-ylidene) benzo [d] oxazol - 5 - carbohydrazide (D₈):

IR (KBr, cm⁻¹): 3404.46, 3247.59 (NH₂ str.), 1690.05 (C=O str.), 1141.28 (C-O-C str.); ¹H NMR (DMSO-d₆, 400 MHz): δ = 13.8 (s, 1H, NH), 11.25 (s, 1H, NH), 7.87 (s, 1H, Ar-H), 7.8 (s, 1H, Ar-H), 7.74 (s, 1H, Ar-H), 7.65 (s, 2H, NH₂), 7.56(d, 1H, Ar-H), and 7.52 (d, 1H, Ar-H) ppm. Mass spectrum: ESI-373; HRMS: 373.73

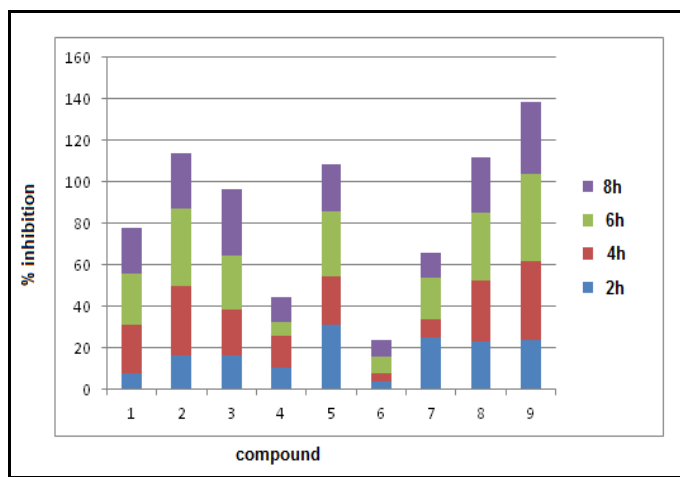


FIGURE2: GRAPHICAL REPRESENTATION OF PERCENTAGE INHIBITION OF PAW ODEMA METHOD

CONCLUSIONS: 2 – Amino - N' - (2-oxoindolin-3-ylidene) benzo [d] oxazole – 5 - carbohydrazides showed promising anti-inflammatory activity. At a

dose of 30mg/kg bw, compounds **D₂** (R= 5-chloro), **D₃** (R= 7-chloro), **D₅** (R= 5-methyl) and **D₈** (R= 5-fluoro, 6-chloro) were found to be comparatively potent with 36.76 (6h), 31.77(8h), 31.37(6h), 32.60(6h) percentage inhibition of paw edema respectively and the compounds **D₄** (R= 6-methyl) and **D₆** (5, 7-dibromo) showed weak anti-inflammatory activity with 15.76 (4h), 7.84 (6h) percentage inhibition of paw edema respectively.

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