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RESEARCH ARTICLE

Synthesis and Biological Activity of Some Novel Pyrimidine Derivatives

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ABSTRACT

To synthesize and characterize novel pyrimidine derivatives and screen them for anti-inflammatory activity. A series of four 6, 7-dihydro-3-aceto substituted pentaleno [2, 1-d] pyrimidin-4-one derivatives (PM1-PM4) were synthesized from 2-amino-3, 4, 5, 6-tetra hydro pentalene-1-carboxamide. The synthesized compound, characterized on the basis of satisfactory analytical and spectral (H^1NMR, C^{13}Mass and Elemental) data. Studies were carried out for the synthesized compounds which were also evaluated for anti-inflammatory activity by Carrageenan induced rat paw edema method. Indomethacin is used as standard anti-inflammatory agents. The synthesized compounds showed good anti-inflammatory activity, compared to standard drugs. Two of the compounds PM1 and PM3 exhibited significant anti-inflammatory activity, as compared to standard drug Indomethacin. We report the successful synthesis of novel pyrimidine derivative, as well as their spectral characterization.

KEYWORDS

Anti-Inflammatory Activity, Pyrimidine, Indomethacin

INTRODUCTION

The growing appeal for biologically alive compounds fabricated multi component reactions attractive. The multi component abstract (MCC) access is abnormally appealing as the resulting products are formed in single step reactions and the assortment can be readily accomplished by varying the components. A array of heterocyclic compounds can be readily accumulated employing this access as approved by the amalgam of dihydro pyrimidine utilizing Biginelli reaction[1-2].

The consistent dihydro pyrimidines (DHPMs) accept been appear to accept antibacterial[3], antiviral[4], anti-inflammatory[5], analgesic[6], antihypertensive - calcium channel blocking agents[7-8] and antioxidants[9]. Recently, structurally simple DHPM acquired monastrol has emerged as a mitotic kinesin Eg5 motor protein inhibitor for the development of anticancer drugs[10]. Furthermore, the biological action of several afresh separated marine alkaloids has as well been attributed to the dihydro pyrimidinone atom in the structure.

Among them the batzelladine alkaloids A and B which arrest the binding of HIV envelope protein gp-120 to human CD4 cells are potential compounds in AIDS therapy[11].

Due to this, the enquiry of chemistry and biological research of these blends extend to appeal the synthetic and medicinal organic chemists.

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MATERIALS AND METHODS

Chemicals and Reagents

Cyclopentane, Cyanoacetamide, Diethyl amine, Absolute ethanol, Formamide.

Experimental

Melting points were determined on a Barnstead Electro thermal melting point apparatus, Mod. No. IA-9200 in open capillary tubes and are uncorrected. The ^{13}C (100 MHz) NMR spectra were measured in DMSO-*d6* on a Varian XL-400 spectrometer using tetramethylsilane as the internal standard. The IR spectra were recorded using a Nicolet 5 PC FT-IR instrument. Mass spectra (MS) were recorded on Jeol SX 102/DA-6000 mass spectrometer. Elemental analyses were performed on a Carlo-Erba CHNS-O EA 1108 Elemental analyzer. All reactions were monitored by thin layer chromatography on 0.2 mm silica gel 60 F254 (Merck) plates using UV light (254 and 366 nm) for detection.

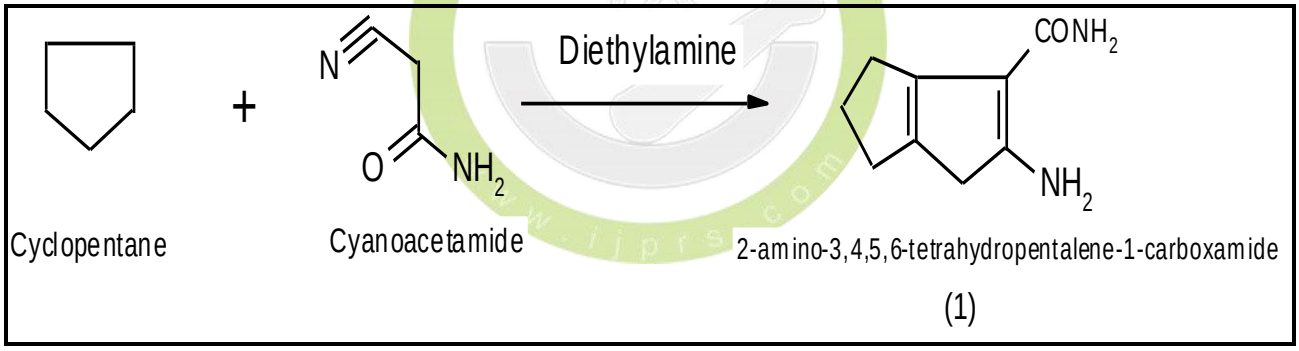
Method of Synthesis

Procedure

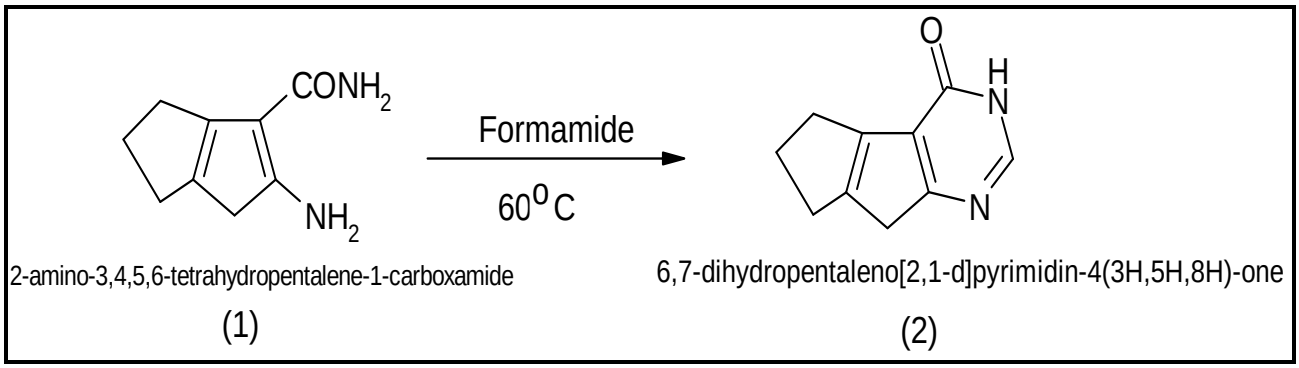
Synthesis of 2-amino, 3, 4, 5, 6-tetrahydropentalene – 1 - carboxamide (Scheme 1): Compound (1) was synthesized by mixing cyclopentane (0.1 mol. 8.4g), cyanoacetamide (0.01 mol, 0.84g) and refluxing for 1hr. To the resulting solution, 4.0 ml of diethyl amine, and 40 ml absolute ethanol were added, stirred in a round bottom flask for 3 hr. After the completion of the reaction time the mixture was poured on crushed ice. The separated solid was filtered, washed with water and recrystallised from alcohol to furnish compound (1). Yield: 68%: Melting Point: 496°C.

Synthesis of 6, 7-dihydropentaleno [2, 1-d] pyrimidin-4 (3H, 5H, 8H) -one (Scheme 2)

The compound (1) was heated with formamide (20 ml) in a round bottom flask in an oil bath at 60°C. The temperature was then gradually raised.



(Scheme-1)



(Scheme-2)

The reaction mixture gets dissolved completely with the formation of brown solution at 110°C. The temperature of the oil bath was raised to 180-200°C, then the reaction mixture was heated at the temperature for 3 hrs. After the completion of the reaction, reaction mixture was allowed to cool at room temperature. The product separated as yellow needles was collected by filtration and washed with water several times and finally with 25 ml of acetone and then dried. The product was recrystallised from alcohol. Yield: 72%, melting point: 492°C.

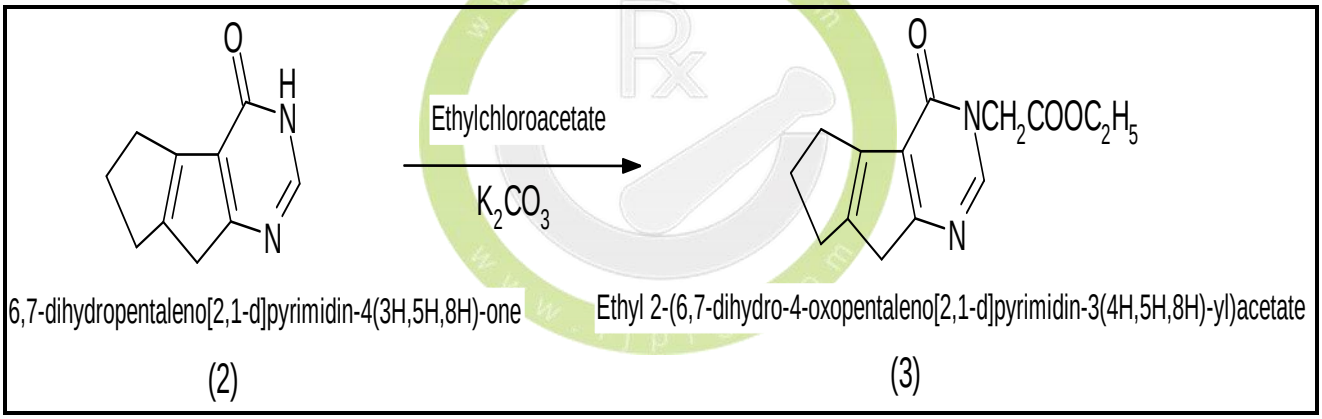
Synthesis of ethyl 2-(6,7-dihydro-4-oxopentaleno [2,1-d] pyrimidin-3 (4H, 5H, 8H) - yl) acetate (Scheme 3)

A mixture of compound 2 (0.01 mole), 25 ml ethyl chloro acetate and 85 g was refluxed for 8-10 hrs in round bottom flask.

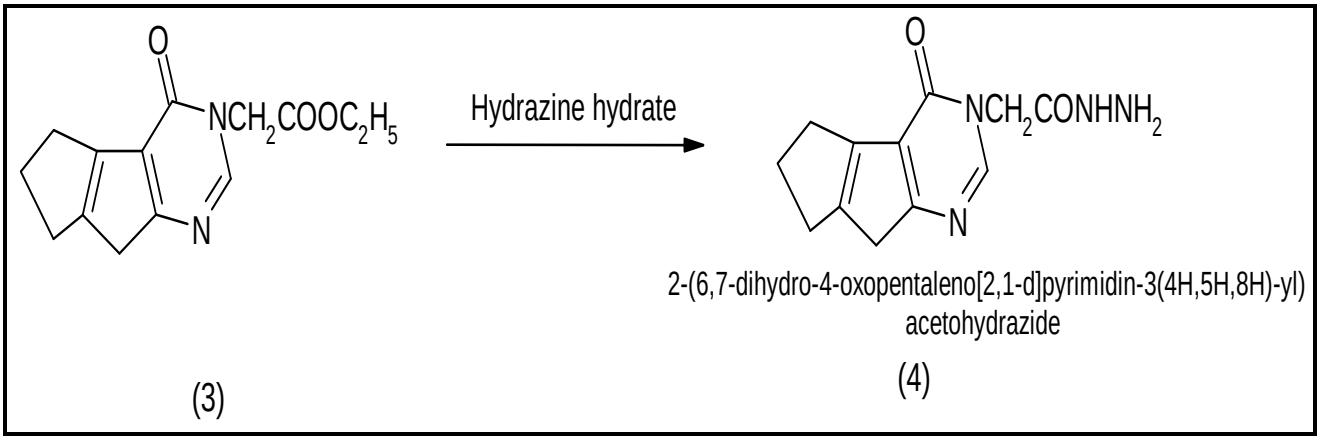
After completion of the reaction (monitored using TLC method), the resulting thick yellow liquid was poured over crushed ice, filtered washed with water and dried. The product was recrystallised from alcohol. Yield: 59%, melting point: 132°C.

Synthesis of 2-(6,7-dihydro-4-oxopentaleno [2,1-d] pyrimidin - 3 (4H, 5H, 8H) - yl) aceto hydrazide (Scheme 4)

Compound 3 & Equimolar concentration of hydrazine hydrate and 3-5 drops Conc. HCl was refluxed with alcohol in Round bottom flask for about 6hrs. After the reaction is complete (monitored by TLC) the mixture is poured over crushed ice. The solid formed was filtered off and residue is washed with 10% dilute ammonium hydroxide (NH_4OH). The product is recrystallised from alcohol. Yield: 67%, melting point: 214°C.



(Scheme-3)



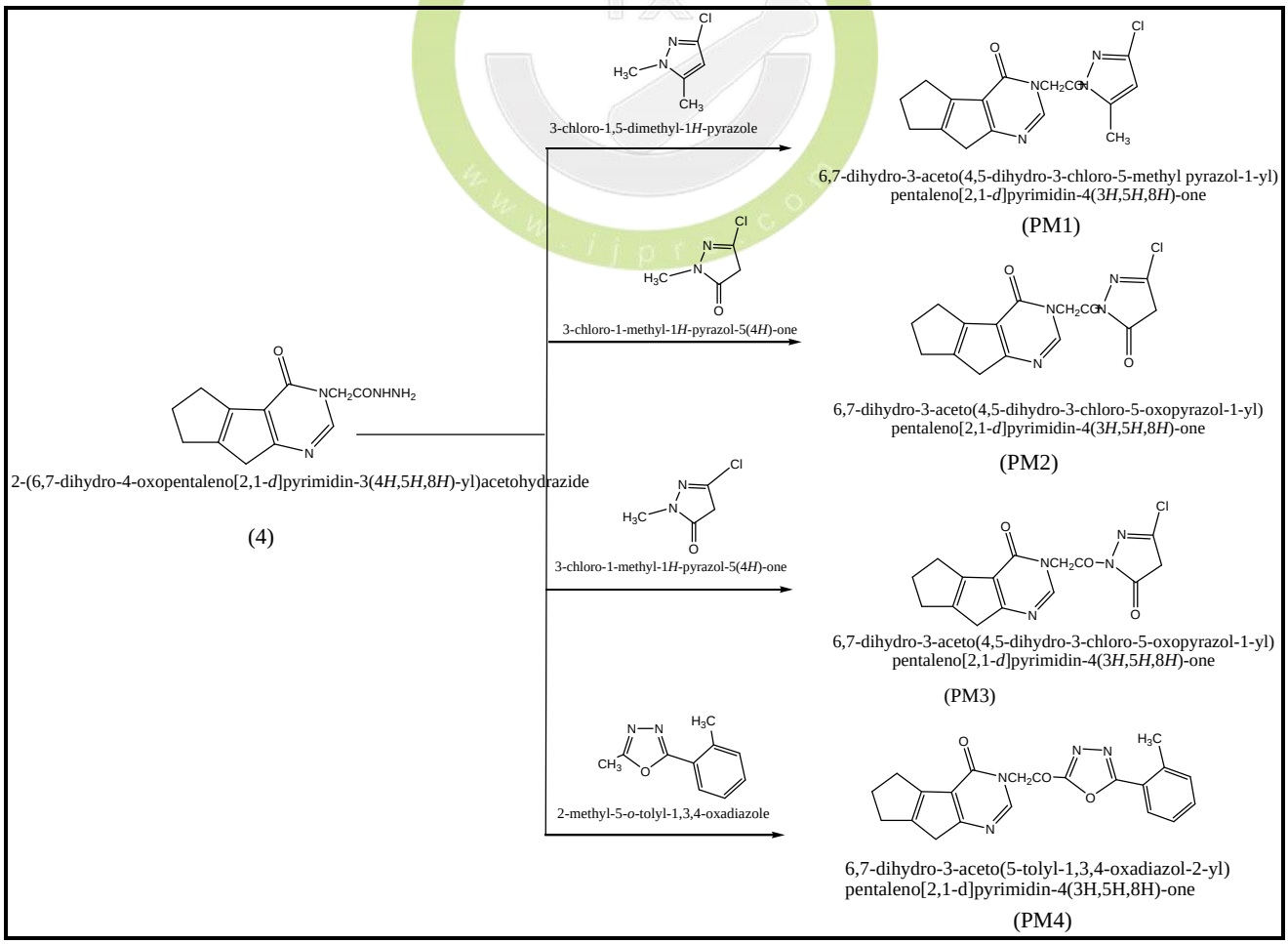
(Scheme-4)

Synthesis of 6,7-dihydro-3-aceto(4,5-dihydro-3,5-dimethylpyrazol-1-yl) pentaleno[2,1-d]pyrimidin-4(3H,5H,8H)-one (PM1)

1, 3, 5, trimethyl-*1H*-pyrazole (0.11g, 0.001 mol) and compound 4 (0.35g, 0.001 mol) in absolute ethanol (20 ml) was heated in round bottom flask under reflux for 6 hrs. After cooling, the reaction mixture was poured onto ice, filtered and the precipitate was crystallized from $CHCl_3$/n-heptane. Yield: 58%, melting point: 764°C. **^{1}HNMR [δ ppm]**: 2.28 (m, -C_5H_6-), 2.79 (d,-CH_3-), 2.9 (m, -C_5H_6-), 4.07 (d, -CH_2-), 5.9 (m,-$C_3H_4N_2$-), 7.50 (d, -CH-N-). **^{13}CNMR [δ ppm]**: 17 (s, -CH_3), 21.26 (s, -CH_2-), 36.7 (s, -CH_2-), 36.8 (s,-CH_2-), 38.5(s, -CH_2-), 43.9 (s, -CH_2), 105 (m, -$C_3H_4N_2$), 127 (d, -C_2H_4-), 134 (d, -C_2H_4-), 135 (d,-C_2H_4-), 143(m, -$C_3H_4N_2$), 144 (m, -C3H_4N_2), 146 (d, -C_2H_4 -), 148.3(d, -NH_3), 161(s, -NH), 200 (s, -CO), **Mass (m/z):** 310.14 (100.00%), 311.15 , 43 (s, -CH_2), 200 (s, -C) (18.7%), 312.15 (18.7%), 311.14 (1.5%).

Synthesis of 6,7-dihydro-3-aceto(4,5-dihydro-3-methyl-5-oxopyrazol-1-yl)pentaleno[2,1-d]pyrimidin-4(3H,5H,8H)-one (PM2)

1, 3, dimethyl-*1H*-pyrazol-5(4*H*)-one (0.001 mol) and solution of compound 4 (0.35g, 0.001 mol) in absolute alcohol (10ml) containing KOH (10%, 1 ml) was heated under reflux for 5 hours. The reaction mixture was then cooled, poured into ice cold water (20ml), filtered and the precipitate was crystallized from the Benzene or Petroleum Ether. Yield: 82%, melting point: 856°C. **^{1}HNMR [δ ppm]**: 2.9 (m -C_5H_6-), 2.28 (m-C_5H_8-), 1.90(m -C_5H_8-), 2.28 (m -C_5H_8-), 7.5 (d-CH-N-), 2.2(s, -CN-), 0.9 (s, -CH_3-), 3.85 (s, -CH_2-).**^{13}CNMR [δ ppm]**: 134 (d -C_2H_4-), 135 (d,-C_2H_5-), 127 (d-C_2H_5-), 146 (d -C_2H_5-), 368 (s,-CH_2), 38.5(s, CH_2), 21.2 (s -CH_2-), 36.7 (s -CH_2-), 148.3(s -NH_3), 161.6(s -NH), 162(s, -NH), 42.3(s -CH_2), 159.56 (s -NH_3), 47.6(s, -CH_2), 170 (s, NH) **Mass (m/z):** 312.12 (100%), 313.13 (17.6%), 314.13(2.1%), 313.12(1.5%).



Synthesis of 6,7-dihydro-3-aceto(4,5-dihydro-3-hydroxy-5-oxopyrazol-1-yl)pentaleno[2,1-d]pyrimidin-4(3H,5H,8H)-one (PM3)

Compound 4 (0.001 mol) and 3-hydroxy,1-methyl-*1H*-pyrazol-5(4*H*)-one (0.001 mol) was refluxed with alcohol for about 10 hours then the reaction is completed, the reaction mixture was cooled and the poured on crushed ice. The solid found was filtered off, recrystallised from alcohol**.** Yield: 67%, melting point: 906^{o}C. **^{1}HNMR [δ ppm]**: 2.9 (s, -C_5H_6-), 2.28 (d,-C_5H_8-), 1.90(d -C_5H_8-), 2.28 (d -C_5H_8-), 7.50 (s,-CH-N-), 2.2(s, -CN-), 2.0 (d, -OH-), 3.85 (s -CH_2-). **^{13}CNMR [δ ppm]**: 134 (d -C_2H_4-), 135 (d,-C_2H_4-), 127.7(d -C_2H_4-), 146 (d-C_2H_4-), 36.8 (s,-CH_2-), 38.5(s, -CH_2-), 21.2 (s -CH_2-), 36.7 (s -CH_2-), 148.3(s -NH_3), 161.6 (s, -NH), 62.8(s, -NH), 36.2 (s, -CH_2-), 155 (s, -NH_3-), 47.6 (s, -CH_2), 170.7(s, -NH). **Mass (m/z):** 314.10 (100%), 315.10 (17.7%), 316.11(2.1%).

Synthesis of 6,7-dihydro-3-aceto(5-phenyl-1,3,4-oxadiazol-2-yl)pentaleno[2,1-d]pyrimidin-4(3H,5H,8H)-one (PM4)

Equimolar quantity of Compound 4 (0.01 mol) and 0.01 mol of 2-methyl, 5-phenyl-1,3,4-oxadiazole are taken. To this mixture 5 mol of ethanol was added and refluxed for 5 hours. The reaction mixture was cooled and filtered, and then the compound obtained was dried and recrystallised using ethanol. Yield: 72%, melting point: 886^{o}C. **^{1}HNMR [δ ppm]**: 2.9 (d, -C_5H_6-), 2.28 (d,-C_5H_8-), 1.90(d, -C_5H_8-), 2.28 (d, -C_5H_8 -), 7.50 (d,-CH-N-), 7.48 (s, -C_6H_6), 7.32 (s, C_6H_6-), 7.22 (s, -C_6H_6-), 7.32(s, -C_6H_6, 7.48 (s,-C_6H_6), 4.07(s, -CH_2). **^{13}CNMR [δ ppm]**: 134 (d, -C_2H_4-), 135(d,-C_2H_4-), 127.7(d, -C_2H_4-), 146.2(d, -C_2H_4-), 36.8 (s,-CH-), 38.5(s, -CH-), 21.2(s, -CH-), 36.7(s, -CH_2-), 148.3(s, -NH_3), 161.6(s, -NH), 26.5(s, -C_6H_6), 129.3(s, -C_6H_6), 128.8(s, -C_6H_6), 129.3(s, -C_6H_6), 127.3(s, -C_6H_6), 46.0(s, -NC), 46.0(s, -CO) **Mass (m/z):** 360.12 (100%), 361.13 (21.9%), 361.13(2.9), 361.12(1.5%).

RESULTS AND DISCUSSION

All the synthesized compounds were characterized on the base of their ^{1}HNMR, Mass and basal or elemental analysis. The abstraction was aimed at evaluating the anti-inflammatory effect of compounds on mice.

Biological Activity

Anti-Inflammatory Activity[12]

Carrageenan Induced Rat Paw Edema Method

Animals

Adult Wistar rats of both sexes weighing between 150-220 g were used for experiment. They were housed in accepted ecological conditions like, ambient temperature (25^{0}C ± 10C), relative humidity (55±5%) and 12/12h light dark cycle. Animals had free access to standard pellet diet and water ad libitum. All animal experiments were carried out in accordance with the guidelines of CPCSEA. The institute animal ethical committee gave the approval for conducting animal experiments.

Procedure

Anti-inflammatory activity was assessed by the method described by (Winter et al., 1962[12]). Albino rats of either sex weighing 150 – 220 g were divided in 3 groups. Group-1 received 0.5% CMC suspension (control), Group- 2 accustomed accepted biologic Indomethacin (10 mg kg^{-1}, p.o) respectively. Group -3 received test compounds through the same route. Animals were treated with drugs by oral route and subsequently 1 h after treatment; 0.1ml of 1% suspension of carrageenan in normal saline was injected into the sub planter region of left hind paw to induce edema. The paw volume was again measured after the time interval of 2 hr and 4 hr after carrageenan injection using digital paw edema meter. The difference between the initial and subsequent values gave the actual edema volume which was compared with control. The inhibition of inflammation was calculated using the formula, % inhibition = 100 (Vc-Vt/Vc), Where 'Vc' represents edema volume in control and 'Vt' edema volume in group treated with test compounds.

Statistical Analysis

Data analysis was carried out using one-way analysis of variance (ANOVA) followed by

Dunnett's multiple comparison tests. $P < 0.05$ was considered statistically significant.

Clinical study for anti-inflammatory activity of 6, 7-dihydro-3-aceto substituted pentaleno [2, 1-d] pyrimidin-4-one (PM1-PM4) revealed that the compound PM1 and PM4 exhibited significant 50 % anti-inflammatory activity as compared to standard drug Indomethacin after 2hr. All the compounds showed negligible activity after 4 hr.

Table 1:Anti-inflammatory activity of 6, 7-dihydro-3-aceto substituted pentaleno [2, 1-d] pyrimidin-4-one (PM1-PM4)

Compound	% Age Inhibition of Rat Paw Edema (Dose= 10 $mgkg^{-1}$)	
	2hr	4hr
Indomethacin	68.81±0.03	75.40±0.04
PM1	34.70±0.008**	21.63±0.02
PM2	28.30±0.03*	8.10±0.03
PM3	26.10±0.18	15.10±0.01
PM4	32.20±0.002**	14.17±0.01

*p<0.05, **p<0.01, ***p<0.001

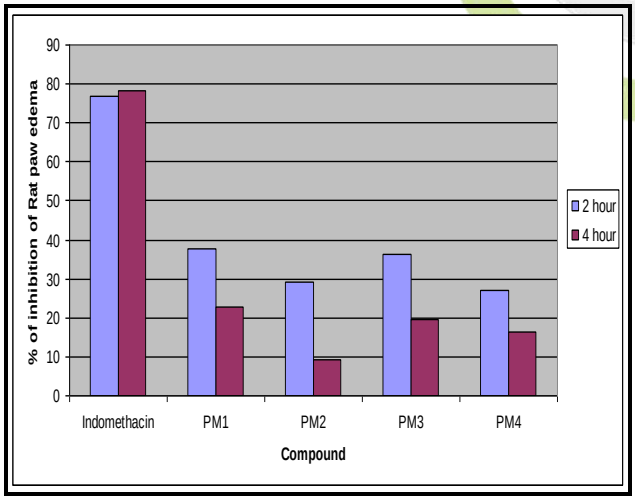


Figure 1: Anti-inflammatory activity of Anti-inflammatory activity of 6, 7-dihydro-3-aceto substituted pentaleno [2, 1-d] pyrimidin-4-one (PM1-PM4)

CONCLUSION

In conclusion, highly functionalized 6, 7-dihydro-3-aceto substituted pentaleno [2, 1-d] pyrimidin-4-one (PM1-PM4) are synthesized from 2-amino-3, 4, 5, 6-tetra hydro pentalene-1-carboxamide. The anti-inflammatory activity is measured. In this study, the synthesized compounds may be used as lead compounds for anti-inflammatory activity and may further be evaluated for toxicological contour in approaching research.

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