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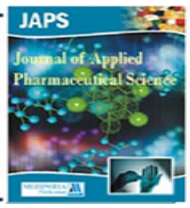

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Synthesis of novel Naphthalene COX inhibitors for anti-inflammatory activity

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ABSTRACT

Inflammation forms the part of various diseased conditions. To treat inflammation variet of anti inflammatory agents are synthesized, they showed undesirable side effects. In order to avoi these side effects, nonsteroidal anti-inflammatory drugs were developed. Research is a continuou and never ending process; efforts are being made to improve the present drug profile such tha present side effects can be eliminated. Syntheses of number of naphthalene derivatives wit pyrazole moiety were completed. The present classification records for numerous naphthalen derivatives (naproxen and nabumetone) and also many anti-inflammatory drugs containing diary heterocycle(celecoxib,rofecoxib) are available as reference, therefore some new non-vicinal 3,5 diaryl heterocycles,in which naphthalene as one of aryl ring and pyrazole as central scaffold wa prepared and evaluated for anti-inflammatory activity. The purity of all compounds has bee examined by the TLC and structure is confirmed by different analytical techniques like IR, Mas spectroscopy and NMR. Further, the synthesized drugs were evaluated for in vivo anti inflammatory activity by carrageenan induced rat paw edema test using Indomethacin as a standar drug. In conclusion, we have found that two compounds showed equipotent activity while othe two showed slightly more anti-inflammatory activity respectively.

Keywords: Naphthalene, pyrazole, non-vicinal 3, 5-diaryl heterocyclic, anti-inflammatory activity

INTRODUCTION

Inflammation is part of the complex biological response of vascular tissues to harmful stimuli , such as pathogens , damaged cells , or irritants . Inflammation is a protective attempt by the organism to remove the injurious stimuli and to initiate the healing process (Rang *et al*, 2003) . Inflammation is not a synonym for infection , even in cases where inflammation is caused by infection (Cuzzocrea *et al*, 2005) . To treat inflammation various treatment are available like glucocorticoid cortisol , Nonsteroidal anti-inflammatory drugs (NSAIDs) like aspirin , ibuprofen and a number of proteins produced by recombinant DNA technology . Naphthalene is important aryl ring in many active compounds such as anti-inflammatory , anti-bacterial , anti-microbial and anti-cancer . In recent trends , heterocycles plays a major role in drug synthesis (Joan.F *et al*, 2001, Kunal *et al*, 2011, Lake *et al*, 2011 and Sharma *et al*, 2011) . Pyrazole derivatives have been the subject of substantial attention by synthetic and medicinal chemists because of the role of this heteroaromatic ring in many biological activities such as anticancer , antiviral , anti-inflammatory , antifungal , antimicrobial , antihistaminic, antiplatelet and analgesic activities (Chauhan *et al*, 2011)

In particular some of naphthalene derivatives were in depth investigated as nonsteroidal anti inflammatory drugs (NSAIDs) . The mechanism of action of this class of compounds is linked to the nonselective or selective inhibition of two cyclooxygenase isoform , COX-1 & COX-2 (J.R.Vane et al,1998, Palwinder singh *et al,* 2008 and Anna Blobaum *et al,* 2007) . Even the literature survey supports that pyrazole containing moiety gave anti-inflammatory activity by acting on COX enzyme(Youssef *et al,* 2010, Sakya *et al,* 2006 , Amir *et al,* 2005, Dekhane *et al,* 2011, Kobayashi *et al,* 2009, Barsoum *et al,* 2009,Bechit *et al,* 2008, Engman *et al,* 1995, Nagarapu *et al,* 2011) etc . Thus synthesizing non-vicinal diaryl pyrazole is a novel approach. So the aim has been designed to synthesize 2-(5-substituted-1H-pyrazol-3-yl) naphthalen-1-ol for safer and potential anti-inflammatory agents .

MATERIALS AND METHODS

The chemicals employed in the synthetic work were purchased from Chemco Fine Chemicals Factory, Mumbai. The solvents AR grades were obtained from *Qualikems Fine Chemicals Pvt. Ltd.*, New Delhi**.** Thin layer chromatography was performed on aluminium sheet (2x5cm) coated with silica gel 60 F_{254},marketed by Merck Specialities Private Ltd. and spots were visualized under UV light and by exposure to iodine vapour. FTIR spectra were recorded in KBr powder on a Jasco V460 IR Specrmeter by diffused reflectance technique. Mass spectra were recorded on a prostar binary-410 LC with 500 IT PDA detector and spectrum was taken by direct infusion mass with ESI and APCI positive and negative mode ionization ranging from 500-2000 m/e. Elemental (C, H, N) analyses were obtained on Vario EL III Elementar^{1}H- NMR spectra were measured in d_6-DMSO on a Bruker II Avance 400 MHz NMR spectrometer. The reported chemical shifts were against TMS.

Chemistry

General procedure Synthesis of 2-(5-substituted-1H-pyrazol-3-yl) naphthalen-1-ol was carried out by Friedal Craft α-naphthol proceeded to esterification by various benzoic acid derivatives to yield various naphthyl esters. Naphthyl esters underwent base catalysed Baker-venkatraman rearrangement reaction to give 1, 3-diketones. Further 1, 3-diketones were refluxed with hydrazine hydrate gave 3, 5-disubstituted pyrazole as shown in the synthetic scheme.

Synthesis of 1-(1-hydroxynaphthalen-2-yl) ethanone

(Vyawhare *et al,* 2010) was carried out by the following procedure: In 80ml hot glacial acetic acid, 50gm zinc chloride was added and the reaction mixture was refluxed till it dissolved. Then 30 gm of 1-naphthol was added to reaction mixture and was refluxed for 8 hrs. The reaction mixture was cooled and poured in acidulated water. The crude product was filtered, washed with water and recrystallized from ethanol to obtain pure product of 93.5 %w/w yield having m.p.82-85 ºC. (Table: 1)

Table. 1: Analysis for 1-(1-hydroxynaphthalen-2-yl) ethanone.

PARAMETERS	RESULT
Molecular formula	$C_{12}H_{10}O_2$
Molecular weight	186.21 gm/mole
Percentage Yield	93.5 %w/w
Melting Point	82-85°C
Recrystallization solvent	Ethanol
Rf value	0.70
Mobile phase	Chloroform

Synthesis of 2-acetylnaphthalen-1-yl substituted benzoate

(Yadav *et al,* 2012) In 100-ml of two necked RBF having dropping funnel and calcium guard tube, place 1.86 gm(0.01 mole) of 1-(1-hydroxynaphthalen-2-yl) ethanone and 0.015 mole of substituted benzoic acid in 3.72 ml of dry pyridine.Stirr the mixture at 0º-5º C for near about 15 minutes. Add 1.49 ml (2.46 gm, 0.016 moles) of dry phosphorus oxychloride drop wise during 2 hours. When the addition was over, the mixture was poured with good stirring into ice-cold hydrochloric acid, followed by small volume of ice-cold water. The product was collected on a Buchner funnel with the help of vacuum pump. Washing was continued till no more pyridine smell was present. The product was dried at room temperature and recrystallized from methanol. (Table: 2)

Table 2: Analysis 2-acetylnaphthalen-1-yl substituted benzoate.

Compound Code	-X	Molecular Formula	Molecular Weight (gm/mole)	Melting Point(ºC)	% Yield(w/w)	Rf value
5a	-H	$C_{19}H_{14}O_3$	290.3	70-72	94.35	0.73
5b	-Br	$C_{19}H_{13}BrO_3$	368.0	176-178	76.53	0.75
5c	-F	$C_{19}H_{13}FO_3$	308.1	170-175	78.89	0.77
5d	-Cl (ortho)	$C_{19}H_{13}ClO_3$	324.6	100-103	56.78	0.74
5e	$-CH_3$	$C_{20}H_{16}O_3$	304.1	75-78	84.56	0.68
5f	$-NO_2$ (meta)	$C_{19}H_{13}NO_5$	335.5	150-154	70.85	0.79
5g	3,5-dinitro	$C_{19}H_{13}N_2O_7$	380.1	180-182	65.5	0.71
5h	-OH (ortho)	$C_{19}H_{14}O_4$	306.1	115-118	60.70	0.74

Mobile phase:-Chloroform:Benzene(7:3)

Table. 3: Analysis for 1-(1-hydroxynaphthalen-2-yl)-3-substituted propane-1, 3-Dione.

Compound Code	-X	Molecular Formula	Molecular Weight (gm/mole)	Melting Point (ºC)	% Yield (w/w)	Rf value
6a	-H	$C_{19}H_{14}O_3$	290.3	72-75	74.8	0.67
6b	-Br	$C_{19}H_{13}BrO_3$	368.0	180-182	84.2	0.65
6c	-F	$C_{19}H_{13}FO_3$	308.1	170-172	56.2	0.71
6d	-Cl (ortho)	$C_{19}H_{13}ClO_3$	324.6	90-94	70.5	0.70
6e	$-CH_3$	$C_{20}H_{16}O_3$	304.1	80-85	65.4	0.65
6f	$-NO_2$ (meta)	$C_{19}H_{13}NO_5$	335.5	160-163	74.87	0.74
6g	3,5-dinitro	$C_{19}H_{13}N_2O_7$	380.1	190-194	66.5	0.65
6h	-OH (ortho)	$C_{19}H_{14}O_4$	306.1	118-120	58.8	0.72

Mobile phase:-Chloroform:Benzene(7:3)

Table. 4: Analytical Table for 2-(5-substituted-1*H*-pyrazol-3-yl) naphthalen-1-ol.

Compound Code	-X	Molecular Formula	Molecular Weight (gm/mole)	Melting Point (ºC)	% Yield (w/w)	Rf value
7a	-H	$C_{19}H_{14}N_2O$	286.3	160-162	60.74	0.70
7b	-Br	$C_{19}H_{13}N_2BrO$	365.2	187-190	75.65	0.74
7c	-F	$C_{19}H_{13}N_2FO$	304.3	170-172	74.88	0.78
7d	-Cl (ortho)	$C_{19}H_{13}N_2ClO$	320.8	140-143	48.5	0.69
7e	$-CH_3$	$C_{20}H_{16}N_2O$	300.4	160-163	79.8	0.65
7f	$-NO_2$ (meta)	$C_{19}H_{13}N_3O_3$	331.3	180-182	35.6	0.77
7g	3,5-dinitro	$C_{19}H_{12}N_4O_5$	376.4	191-193	39.74	0.76
7h	-OH (ortho)	$C_{19}H_{14}N_2O_2$	302.3	130-132	40.4	0.64

Mobile phase:-Chloroform:Benzene(7:3)

Table. 5: Spectral characteristics for 2-(5-substituted-1*H*-pyrazol-3-yl) naphthalene-1-ol .

Compound Code	-X	IR(cm^{-1})	Mass Spectra	^{1}H NMR(ppm)
7a	-H	-OH(3610-3620) -C-H str(3050) -C=C- Aromatic(1470 & 1600) -C=N(1650)	287.3(M^++1) 286.1 (M^+)	7.2-8.3(m,12H,Ar) 9.82(w,1H,-OH) 13.2(w,1H,-NH)
7b	-Br	-OH(3620-3640) -C-H str(3090) -C=C- Aromatic(1470 & 1590) -C=N(1650) -C-Br(600)	366.2(M^++1) 367.3(M^++2)	6.8-8.1(m,11H,Ar) 8.89(w,1H,-OH) 13.1(w,1H,-NH)
7c	-F	-OH(3640-3650) -C-H str(3100) -C=C- Aromatic(1470 & 1610) -C=N(1655) -C-F(1200)	305.9(M^++1) 306.2(M^++2)	6.8-8.3(m,11H,Ar) 8.92(w,1H,-OH) 12.9(w,1H,-NH)
7d	-Cl (ortho)	-OH(3520-3495) -C-H str(3110) -C=C- Aromatic(1470 & 1590) -C=N(1645) -C-Cl(800)	321.6(M^++1) 322.1(M^++2)	6.7-8.4(m,11H,Ar) 9.73(w,1H,-OH) 13.7(w,1H,-NH)
7e	$-CH_3$	-OH(3310-3290) -C-H str(3070) -C=C- Aromatic(1470 & 1600) -C=N(1655)	301.5(M^++1) 300.4 (M^+) 284.9(M-15)	6.6-8.3(m,11H,ArOH) 9.82(w,1H,-OH) 13.2(w,1H,-NH) 2.89(s,2H,$-CH_3$)
7f	$-NO_2$ (meta)	-OH(3610-3620) -C-H str(3050) -C=C- Aromatic(1470 & 1600) -C=N(1650) - NO_2 (1485)	332.4(M^++1)	7.2-8.3(m,10H,Ar) 3.2-3.8(s,1H,$-CH_2$-) 9.72(w,1H,-OH) 13.1(w,1H,-NH)
7g	3,5-dinitro	-OH(3610-3620) -C-H str(3050) -C=C- Aromatic(1470 & 1600) -C=N(1650) - NO_2 (1490)	376.4(M^++1)	7.1-8.8(m,10H,Ar) 3.1-3.9(s,1H,$-CH_2$-) 9.88(w,1H,-OH) 13.3(w,1H,-NH)
7h	-OH (ortho)	-OH(3610-3620) -C-H str(3050) -C=C- Aromatic(1470 & 1600) -C=N(1650) -C-OH(3200-3210)broad peak	303.6(M^++1)	7.2-8.3(m,12H,Ar) 9.81(w,1H,-OH) 13.2(w,1H,-NH)

Table. 6: Screening of Anti-inflammatory Activity in Albino Wistar Rat.

Compound Code	Inhibition of inflammation (cm)					% inhibition			
	0hr	1hr	2hr	3hr	4Hr	1hr	2hr	3hr	4Hr
Control	0.36±0.02	0.33±0.02	0.31±0.02	0.30±0.02	0.29±0.02	-	-	-	-
Standard Indomethacin	0.33±0.02	0.30±0.02	0.26±0.02	0.23±0.02	0.20±0.02	9.09	16.12	23.33	31.03
7a	0.32±0.02	0.28±0.02	0.21±0.02	0.18±0.02	0.15±0.02	15.15	32.25	40.00	48.27
7b	0.33±0.02	0.26±0.02	0.19±0.02	0.15±0.02	0.09±0.02	21.21	38.70	50.00	68.96
7c	0.32±0.02	0.28±0.02	0.21±0.02	0.18±0.02	0.14±0.02	15.15	32.25	40.00	51.72
7d	0.31±0.02	0.27±0.02	0.20±0.02	0.15±0.02	0.11±0.02	18.20	35.48	50.00	62.06
7e	0.33±0.02	0.30±0.02	0.26±0.02	0.21±0.02	0.19±0.02	9.09	16.12	30.00	34.48
7f	0.33±0.02	0.30±0.02	0.28±0.02	0.25±0.02	0.22±0.02	9.09	9.67	16.66	24.13
7g	0.34±0.02	0.31±0.02	0.29±0.02	0.26±0.02	0.24±0.02	6.06	6.45	13.33	17.24
7h	0.31±0.02	0.28±0.02	0.26±0.02	0.23±0.02	0.20±0.02	15.16	16.12	23.33	31.03

Synthesis of 1-(1-hydroxynaphthalen-2-yl)-3-substituted propane-1, 3-dione (β-diketone synthesis (Base-catalyzed Baker-Venkataraman Rearrangement)

(Nopporn *et al*, 2002*) :* A solution of 0.01 mole of 2-acetylnaphthalen-1-yl substituted benzoate in 11 ml of dry pyridine was prepared in 100 ml RBF and warmed to 50ºC.To this solution 1 gm of pulverized or fused KOH was added. The mixture was stirred for 15-30 minutes, during which time a copius precipitates of the yellow potassium salt of 1-(1-hydroxynaphthalen-2-yl)-3-substituted propane-1, 3-dione(β-diketone) formed. The mixture was cooled to room temperature and acidified with ice cooled 100 ml of 10 % hydrochloric acid .The diketone separated which was collected on a filter paper , dried and recrystallized with methanol .(Table : 3)

Synthesis of 2-(5-substituted-1H-pyrazol-3-yl) naphthalen-1-ol

(Alhuwalia *et al*, 2006)A mixture of the 0.0174 mole respective diketone, 0.022 mole hydrazine hydrochloride was refluxed in 15 ml ethanol for 12 hours. After the completion of the reaction, the mixture was poured on to crushed ice acidify drop wise with acetic acid to check whether solution gets acidic pH. The solid obtained was filtered, washed with water and recrystallized from methanol to give pure product. Table: 4 and Table: 5

SCREENING OF ANTI-INFLAMMATORY ACTIVITY

Anti-inflammatory activity for the prepared compounds was determined in vivo by the acute carrageenan induced paw edema standard method in rats. Wister albino rats of either sex (pregnant female animals were excluded) weighing 160–190 g were divided into 8 groups of 3 rats each. Administration of indomethacin (reference standard at a dose of 3 mg/kg of body weight) and the tested compounds dissolved in 1% tween 80, at a dose of 3 mg/kg (body weight) was given intraperitoneally 1 h before induction of inflammation. The control group was given saline only. Carrageenan paws edema was induced by subcutaneous injection of 1% solution of carrageenan in saline (0.1 ml/rat) into the right hind paw of rats. Paw volumes were measured volumetrically after 1h, 2h, 3h and 4 h of inflammation induction with Plethysmometer and compared with the initial hind paw volume (Table:6) of each rat for determining the edema volume (Vogel *et al*, 2008 and Winter *et al*, 1962). Data were collected, checked, revised and analyzed. Quantitative variables from normal distribution were expressed as means of SE ‘‘standard error’’.

The % inhibition of edema was calculated at the end of 4 hrs by using the formula

$$\text{Percent (\%) inhibition} = 1 - V_t/V_c \times 100$$

Where V_t- edema volume in test group,

V_c-edema volume in control group

Results were expressed as mean ± standard deviation

RESULTS AND DISCUSSIONS

The purity of all the compounds were examined by TLC and structure confirmation was carried out by IR, Mass and 1H-NMR spectroscopy. Further the compounds were evaluated for in-vivo anti-inflammatory activity by acute carrageenan induced paw edema method in rats. It is concluded that target molecules, non-vicinal diaryl heterocycles have naphthalene moiety as one of the aryl group and substituted phenyl as the other aryl group with pyrazole as the central scaffold. Credible mechanism of action is predicted as same as that of vicinal diaryl heterocycles in NSAID class as in pyrazolone derivatives that acts by inhibiting COX-1 enzymes or by inhibiting selective COX-2 enzyme as in celecoxib, rofecoxib etc .As a result , it is predicted that the novel synthesized compounds acts by inhibiting either of the cyclooxygenase enzymes non-selectively. The pharmacological screening of the synthesized compounds showed anti-inflammatory activity ranging from 17.24% to 68.96% inhibition of rat paw edema volume after 4hr, whereas the standard drug Indomethacin showed 31.03% inhibition of rat paw edema volume after 4hr. Compound 7a, 7b, 7c and 7d were more potent than that of standard drug where as compound 7e and 7h were equipotent and compound 7f and 7g were less potent that than the standard drug.

CONCLUSION

In conclusion we have reported a facile route for the synthesis of 2-(5-substituted-1H-pyrazol-3-yl) naphthalen-1-ol which is a non vicinal diaryl heterocycle a novel moiety that was employed for the anti-inflammatory activity. The procedure for synthesizing 2-acetylnaphthalen-1-yl substituted benzoate is a critical one, as it is an exothermic reaction it is important to maintain the reaction temperature between 0-5ºC and as the esters are water liable, the reaction condition must be anhydrous to aid in ester synthesis. Further it is advisable to use all the solvent in the freshly distilled and pure form. In final step of cyclization the reaction completion can be monitored by TLC and further structure can be confirmed by spectroscopic data. Further the compounds were evaluated for in-vivo anti-inflammatory activity by acute carrageenan induced paw edema standard method in rats. The pharmacological screening of the synthesized compounds showed wide range of anti-inflammatory activity. Comparatively the standard drug Indomethacin showed 31.03% inhibition of rat paw edema volume after 4hr. Compound 7a, 7b, 7c and 7d were more potent than that of standard drug where as compound 7e and 7h were equipotent and compound 7f and 7g were less potent that than the standard drug. Results of various compounds containing electron donating groups like methyl and halogen functional group are showed more activity than that of electron withdrawing groups nitro and dinitro functional group. From the obtained results, we can conclude that compound 7b exhibited maximum activity. In future study, further detailed investigation on the mechanism of action and toxicity studies will be carried out and therapeutic index would be revealed for the synthesized drugs.

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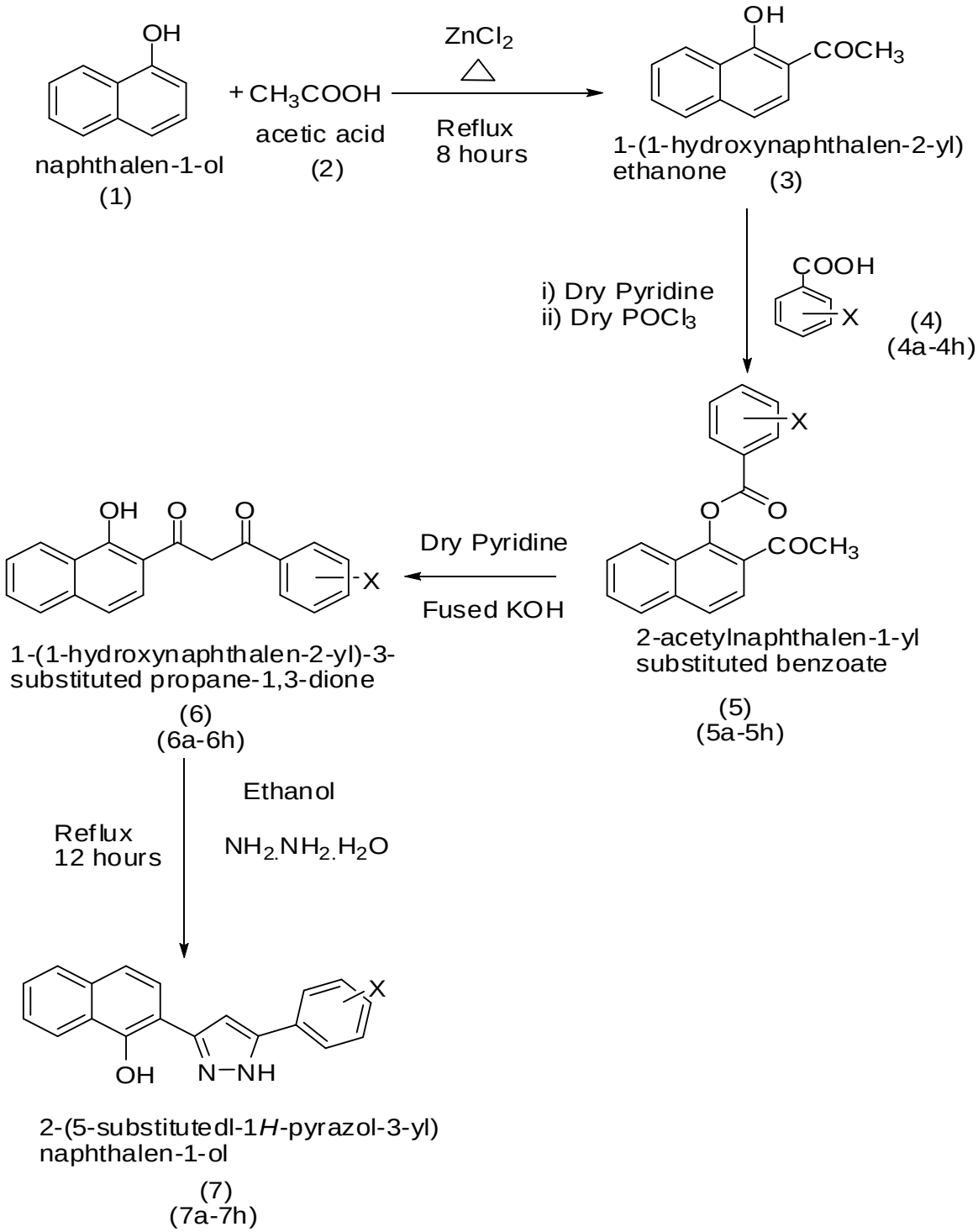
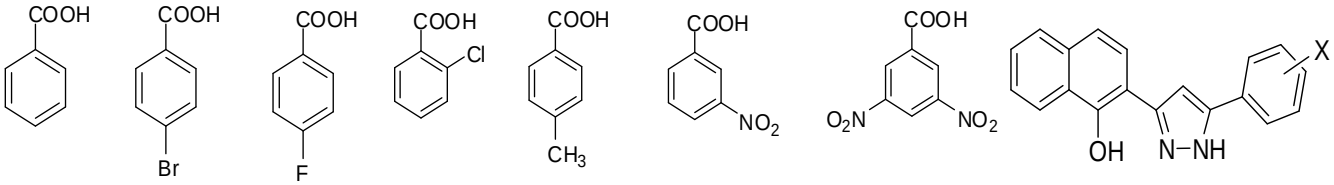


SYNTHETIC SCHEME



4(a) 4(b) 4(c) 4(d) 4(e) 4(f) 4(h) (7)

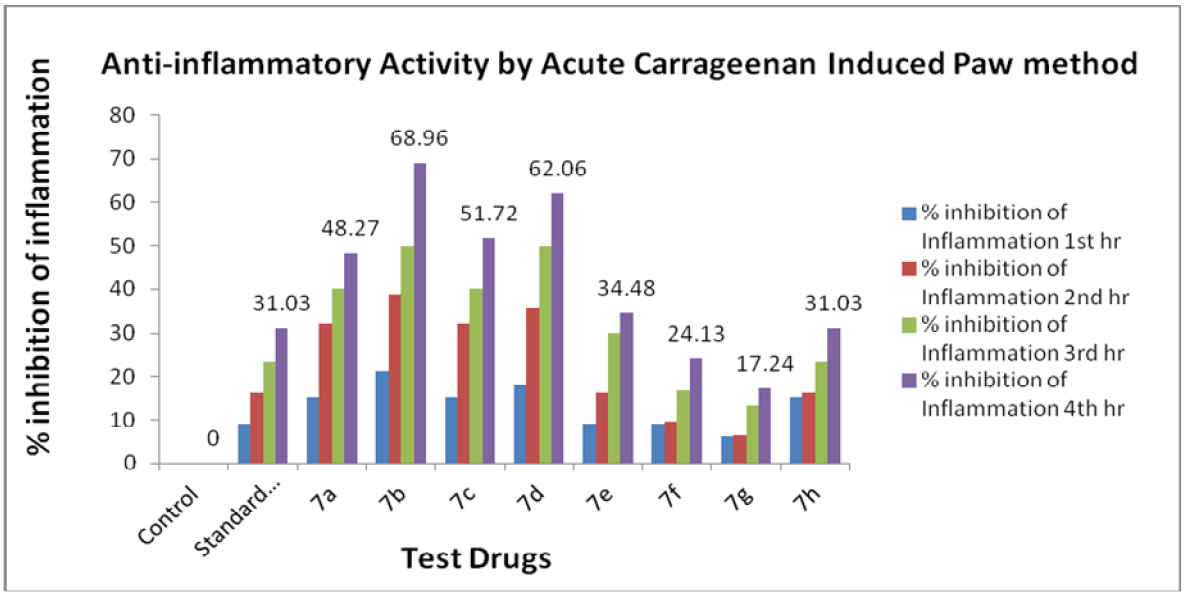


Fig. 1: Comparison of Anti-inflammatory activity between Indomethacin & Test Drugs.

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