Journal of Applied Pharmaceutical Research
Volume 6, Issue 1, Year of Publication 2018, Page 11 – 15
DOI: 10.18231/2348-0335.2018.0003

Research Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | ***JOAPR***
www.japtronline.com ***ISSN: 2348 – 0335***

SYNTHESIS OF SOME DIHYDROPYRIMIDINONE DERIVATIVES AND STUDY OF THEIR ANTI-INFLAMMATORY ACTIVITY

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Article Information
Received: 12th December 2017
Revised: 24th December 2017
Accepted: 19th January 2018

Keywords
Dihydropyrimidinones derivative synthesis, toxicity study, anti inflammatory activity study

ABSTRACT
This research revealed that the numbers of available heterocyclic compounds are mainly focused on nitrogen containing compounds, such as quinazolines, indoles, benzimidazole, quinoxalines, coumarins and pyrimidines etc. A mixture of substituted aldehydes (0.01 mol) like acetyl acetone (method 1) or ethyl acetoacetate (method 2), urea or thiourea (0.01 mol) and lemon juice (0.5 ml) were taken into a round bottom flask and reflux for 1 hour at 80^0C under continuous stirring. After completion of the reaction the final product was recrystalized for purification. Simultaneously toxicity and anti-inflammatory activity were performed. But in case of using ethyl acetoacetate in method 2, the percentage yield was more as compare to using of acetyl acetone in method 1. So the derivatives obtained from method 2 were selected for further toxicity and anti- inflammatory activities.

INTRODUCTION

Medicinal chemistry is an applied science with fundamental roots originating from all branches of chemistry and biology. The term "pharmaceutical chemistry" is often substituted for "medicinal chemistry" where the compounding of drugs to materials useful in pharmacy commands considerable attention [1–3]. Dihydropyrimidinones are useful targets in chemical synthesis as they have been associated with a diverse range of therapeutic and medicinal properties [4–6]. The dihydro-pyrimidinone scaffold is also found in various marine alkaloids, which have been shown to possess antiviral, antitumor, antibacterial and antioxidant activities [7–9]. In particular, the batzelladine alkaloids are known to be potent HIV gp-120-CD4 inhibitors. In general dihydropyrimidinones act as anticancer, calcium channel blockers, antibacterial, α1a-adrenergic receptor antagonist such as monestrol, oxomonestrol etc. Because of heterocyclic moiety these compounds producing pharmacological activity [10 – 13] as per the

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literature survey dihyropyrimidinone derivatives are synthesized in different methods. Members of the pyrimidinone family had a wide range of application in medicinal chemistry those are used as antimalarial, anticancer, antibacterial, antihypertensive, calcium channel blockers, potassium channel antagonists [14, 15]

Aims of our research work is to

- Synthesize some new dihydropyrimidinones derived aldehydes
- Perform oral toxicity study and
- Evaluate the anti-inflammatory activities of those derivatives

MATERIALS & METHODS

Materials

Ethyl acetoacetate was purchased from Finar Chemical, Hyderabad, India. Urea and Thiourea were purchased from SDFCL, Mumbai, India.Wistar rats were purchased from NIN, Hyderabad, India. Tween 80 and Sodium Chloride were purchased from Asian Chemicals, Hyderabad, India. Carrageenan was purchased from Sigma India, Mumbai, India. Lemon juice. Water for injection and Distilled water were purchased from local market. Reference standard, Indomethacin was purchased from Sterkem Pharna (Pvt.) Ltd., Mumbai, India.

Synthesis of Dihydropyrimidinones Derivatives

Method 1: Mixture of substituted aldehydes (0.01 mol) like Acetyl acetone (0.01 mol), urea or thiourea (0.01 mol) and lemon juice (0.5 ml) were taken into a round bottom flask. Then this mixture was refluxed for 1½ hours (90 minutes) at 120°C under continuous stirring. Completion of the reaction was monitored by TLC. Then cold water was added into the reaction mixture with continuous shaking for 10 minutes. Then it was filtered, washed with water and dried in vacuum. The obtained product was further recrystallized by ethanol (Figure 1).

Method 2: In a typical experimental procedure, a mixture of substituted aldehydes (0.01 mol), Ethyl acetoacetate (0.01 mol), urea or thiourea (0.01 mol) and lemon juice (0.5 ml) were taken into a round bottom flask. Then this mixture was refluxed for 1 hour at 80^0 C under continuous stirring. Completion of the reaction was monitored by TLC. Then cold water was added into the reaction mixture and stirring continuously for 10 minutes. Then it was filtered, washed with water and dried in vacuum. The obtained product was further recrystalized by ethanol (Figure 2).

Figure 1. Synthesis of Dihydropyrimidinones Derivatives by Method 1

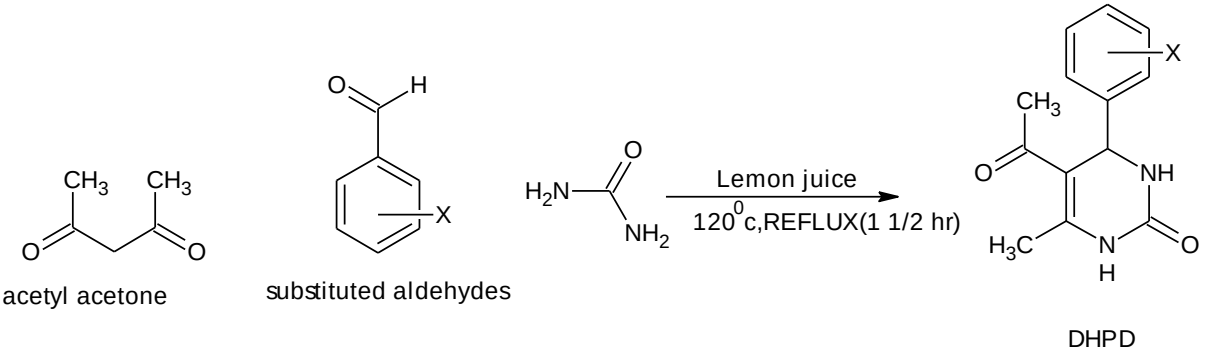
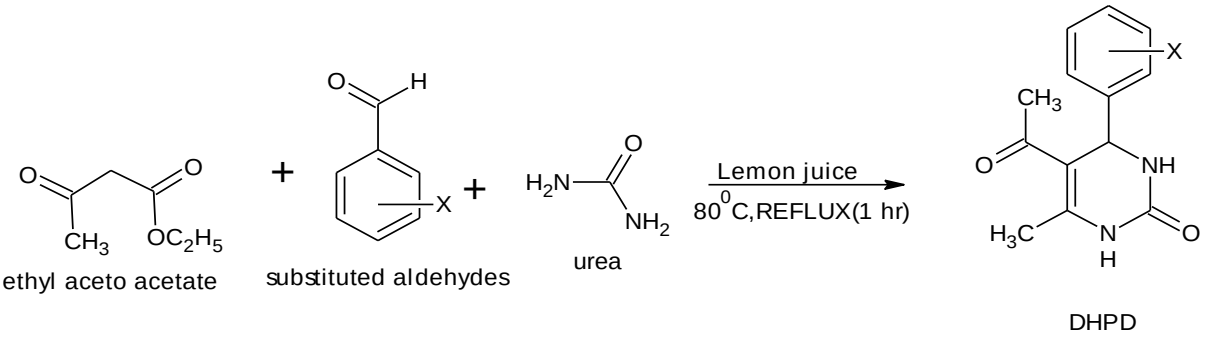


Figure 2. Synthesis of Dihydropyrimidinones Derivatives by Method 2



Anti Inflammatory Study of Dihydropyrimidinones Derivatives

Acute inflammatory model-carrageen an induced rat paws edema assay[16–17]

The anti-inflammatory activity of the test compounds was evaluated in Wistar male albino rats employing the method. Male wistar rats were used for the study. Animals were kept in fasting condition for overnight and were divided into control, standard and different test groups each consisting of six animals. The different test compounds were administered to the animals in the test group at the dose of 100 mg/kg by oral route. Animals in the standard set acknowledged indomethacin at the dose of 10 mg/kg by oral route. All test and standard compounds were administered through vehicle (1% sodium carboxy methyl cellulose). The control group rats were received the vehicle solution without drugs. After One hour test drugs were administrated to all the groups of rats were observed with 0.1 ml of 1% carrageenan in the sub plantar region of right hind paw. By using digital plethysmometer to measure at zero hour paw volume for the rats after administration. The percentage inhibition of paw volume for each groups were calculated by comparing with mean paw volume of control group. It was articulated as mean percent inhibition of paw volume for each test group.

Percent oedema inhibition = $100(1-V_t/V_c)$

V_c = Volume of oedema in the control group

V_t = Volume of oedema in the treated group

Acute oral toxicity- acute toxic class method [17–18]

Toxicity study was performed stepwise by using five male rats. The rats were fasted earlier before administration of dose. The synthesized compounds were suspended in Tween-80. Then it was administered orally in a dose of up to 150 mg/kg body weight. The animals were kept under observation for 14 days. No transience was reported up to the dose of 100 mg/kg body weight of individual rat and a toxicity activity was reported in case of dose for 150 mg/kg body weight of individual rat.

RESULTS & DISCUSSIONS

The yield percentage of Dihydropyrimidinones derivatives were found 56.5% and 88.3% respectively by Method 1 and Method 2. Hence better results were observed in method 2 than method 1 and so method 2 was considered for further investigation. The acute Oral toxicity study of Dihydropyrimidinones derivatives prepared by method 2 was carried out by as per the OECD guidelines-423. The initial dose was 5 mg per kg and maximum dose was 150 mg/kg body weight of rat. After toxicity studies it was observed that when dose was 150 mg/kg body weight, the toxic effects were observed in the body of rats. So the dose of 100 mg/kg body weight was considered as maximum dose for anti-inflammatory activity studies. The toxicity study report was given in table 1.

Table 1: Rats used for toxicity studies

Testing animals	Dose of the test drug	Toxicity
Head marking	5mg/kg	No
Body marking	10 mg/kg	No
Tail marking	50 mg/kg	No
Head and body marking	100 mg/kg	No
Head and tail marking	150 mg/kg	Yes

Anti-inflammatory activity of Dihydropyrimidinones derivatives obtained by method 2. As per the % yield Method 2 was selected for the animal study. All 7 newly synthesized compounds (DP-1 to 7) were evaluated accurately with maintaining the proper conditions. Among them some compounds (dP-3, 6, 7) had shown significant reduction in paw oedema which are shown in table 2.

The Dihydropyrimidinones derivatives obtained by method 2 were found to be economic (Percentage of yield was 88.3%) as well as less time consuming. Toxicity study was performed using male rats.Anti-inflammatory studies were performed for those synthesized compounds by carrageenan induced paw oedema method and compared with standard indomethacin drug. It was confirmed that potent to moderately potent anti-inflammatory activities were observed by those synthesized compounds obtained from method 2. Among those compounds, DP 3, 6 and 7 using standard dose 100 mg per kg body weight of male rats had significant reduction activity in paw oedema as compare to compounds P 2, 4 and 5. The compounds DP 3, 6 and 7 showed 76-79% protection and compounds P1, 2, 4, and 5 showed 64-74 % protection in our present investigation.

It was concluded that prominent activity has been shown the compounds bearing nitro and chloro groups as compare to other Dihydropyrimidinones derivatives where those groups were absent. It was also confirmed that the groups in para position showed better activity as compare to the groups in ortho position.

Table 2. Carrageenan induced Paw Oedema method

Group	**1 hr.**	**2 hr.**	**3 hr.**	**4 hr.**	**5 hr.**
Control 1% Water (1 ml/kg)	0.32±0.01	0.58±0.04	0.64±0.02	0.72±0.01	0.84±0.02
dP-1 (100 mg/kg)	0.30±0.02 (7.28%)	0.46±0.01 (20.26%)	0.57±0.03 (38.06%)	0.26±0.04 (52.24%)	0.22±0.02 (64.38%)
dP-2 (100mg/kg)	0.29±0.03 (8.26%)	0.48±0.02 (20.86%)	0.57±0.03 (38.42%)	0.21±0.01 (66.46%)	0.16±0.04 (72.64%)
dP-3 (100mg/kg)	0.26±0.02 (8.42%)	0.52±0.04 (09.10%)	0.56±0.02 (40.48%)	0.28±0.03 (65.29%)	0.19±0.02 (79.42%)
dP-4 (100mg/kg)	0.31±0.01 (06.52%)	0.50±0.03 (28.46%)	0.52±0.04 (34.28%)	0.26±0.02 (58.14%)	0.21±0.01 (75.28%)
dP-5 (100 mg/kg)	0.28±0.02 (10.24%)as p	0.52±0.03 (28.21%)	0.34±0.02 (47.60%)	0.28±0.01 (64.64%)	0.18±0.02 (73.84%)
dP-6 (100mg/kg)	0.28±0.03 (10.86%)	0.53±0.04 (29.64%)	0.35±0.02 (40.52%)	0.29±0.02 (63.86%)	0.17±0.03 (76.52%)
dP-7 (100mg/kg)	0.30±0.01 (10.64%)	0.50±0.03 (32.10%)	0.42±0.04 (41.48%)	0.27±0.03 (64.29%)	0.16±0.01 (78.22%)
Standard (10 mg/kg) Indomethacin	0.26±0.01 (15.55%)	0.52±0.02 (36.92%)	0.32±0.01 (62.40%)	0.24±0.03 (76.66%)	0.15±0.02 (82%)

- Dp = Dihydropyrimidinone derivatives

ACKNOWLEDGMENT

The authors are very much grateful to Dr. M. Shivarama Krishnaiah, Chairman, Dr. Vijaya Lakshmi, Secretary, Dr. Ranabir Chanda, Principal, Mr. Naveen (Ph.d), faculty, Pratishta Institute of Pharmaceutical Sciences for providing the enough research facility and guidelines.

FINANCIAL ASSISTANCE

Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest

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