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Synthesis and Anti-inflammatory Activities of some Pyrimidine Analogs derived from 1,3-diarylpropenones (Chalcones)

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Abstract : Claisen–Schmidt condensation of substituted aryl ketones (**1**) and benzaldehydes(**2**) in ethanol produced several 1,3-diarylpropenones (**3a-j**; 70–90%) which on further treatment with urea/thiourea in presence of ethanolic sodium hydroxide solution producedheterocyclic analogs of pyrimidine(**4a-j** and **5a-j**).All the synthesized compounds were screened for*in vivo* anti-inflammatory activity by using the carageenan-induced paw edema method in rats. The substituted pyrimidine derivatives **4e**, **4d** and **4b** showed remarkable reduction in inflammation. In addition, the structures of all the newly synthesized compounds were elucidated using ^{1}H NMR and ^{13}C NMR.
Keywords : Anti-inflammatory activity, 1,3-diarylpropenones, Pyrimidine, Claisen–Schmidt condensation

1.Introduction:

The search for the new and better drug in anti-inflammatory therapy is never ending process. The search for anti-inflammatory agent to relieve the swelling, redness, pain and fever associated with rheumatism dates back to antiquity [1]. At present, diverse classes of compounds were synthesized which possess analgesics and anti-inflammatory activities includes non steroidal anti-inflammatory drugs (NSAIDS), synthetic forms of natural cortisol (glucocorticoids), pharmaceutical biologics and many more. Although drug treatment has been improved to some extent yet, it is still a challenge for the pharmaceutical chemists to explore the more effective, potent, less toxic therapeutic agents to treat as well as reduce the signs and symptoms of acute inflammation and chronic inflammatory diseases. Thus, it is well evident from the literature and numerous studies that there is requirement for appropriate modification of the molecules to attenuate the toxicity and also ensure that the host immune defense against infection is not impaired [2].

The chemistry of chalcones has generated an intensive scientific interest due to their wide spectrum of biological properties such as antibacterial [3], antifungal [4], insecticidal [5], anticancer [6], antitubercular [7], anti-inflammatory [7-8], antioxidant [9], antimalarial [10], antileishmanial [11], ulcerogenic [12-13] etc.

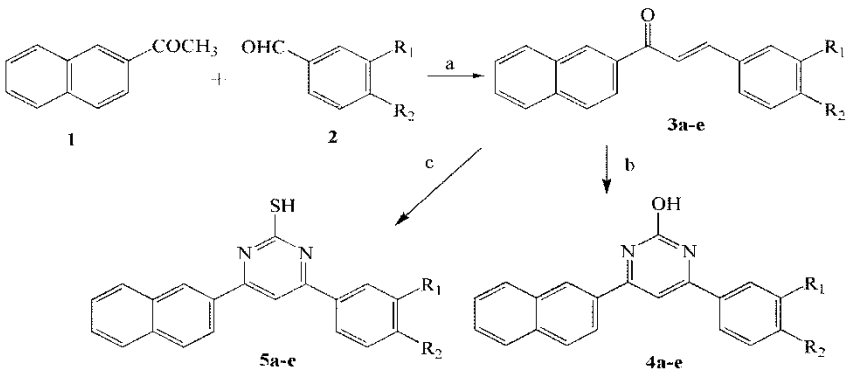
Chalcones have also been used as intermediates for the preparation various pharmacological active compounds [14-15]. Apart from this, a lot of pyrimidine analogs have also been used clinically for the treatment of diverse class of diseases that mainly includes 5-fluorouracil (anticancer),Idoxuridine and trifluoridine (antiviral), Zidovudine and stavudine (anti-HIV),Trimethoprim and sulphadiazine (antibacterial),Sulphadoxin (antimalarial),Minoxidil and prazocin (antihypertensive), Phenobarbitone(anticonvulsant), Propylthiouracil (antithyroid), Toxoflavin and fervennuline (antibiotics). The activity of pyrimidine analogs may be due to its presence in thiamine, cytosine and uracil, which are the essential building blockers of nucleic acids. In addition, substituted chalcones and their derivatives, including some of their heterocyclic analogues, have been reported to possess some interesting biological properties[16-19] which are detrimental to the growth of microbes tubercle bacilli, malarial parasites, acrus, Schistosoma, and intestinal worms.These findings prompt us to synthesize some novel pyrimidineanalogsderived fromchalcone and evaluate their anti-inflammatorypotential.

2.Materials and Method:

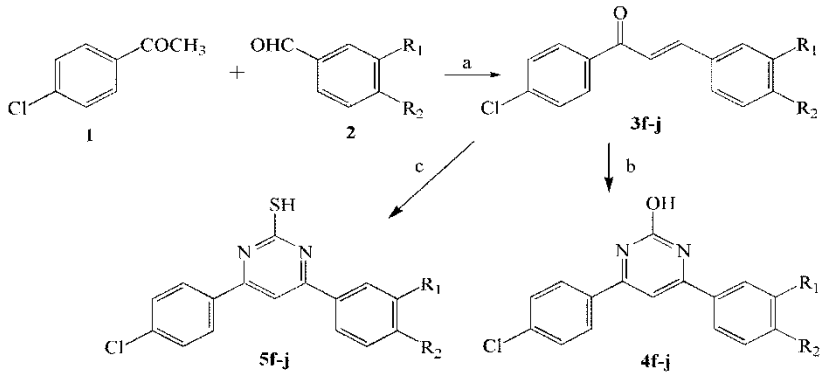
2.1. Chemistry:

All melting points were determined by open capillary tube method and are uncorrected. The ^{1}H NMR spectra were recorded on Brucker 300 MHz spectrometer in ($CDCl_3$) using TMS as an internal reference and chemical shifts is measured in δ ppm. The progress of the reaction was monitored by TLC using 0.2 mm thickness aluminium sheet precoated with silica gel Merck 60F 254 and visualization was done using iodine/UV lamp for detection of the spots. The solvent was removed under reduced pressure using Buchi rotary evaporator.

2.2. General procedure for the synthesis of 1,3-diarylpropenones (3a-j)



Scheme 1. Reagents and conditions: a. 20% NaOH, ethanol, 20-25 °C, stirring, 5% HCl; b. NH_2CONH_2, ethanolic NaOH solution, stirring; c. NH_2CSNH_2, ethanolic NaOH solution, stirring



Scheme 2. Reagents and conditions: a. 20% NaOH, ethanol, 20-25 °C, stirring, 5% HCl; b. NH_2CONH_2, ethanolic NaOH solution, stirring; c. NH_2CSNH_2, ethanolic NaOH solution, stirring.

Figure 1: Synthetic Methodology used for the preparation of Pyrimidine Analogs

An aqueous solution of sodium hydroxide (20%, 20 ml) was added slowly to the stirring solution of the appropriate aryl acetophenone(0.01 mol) and appropriate aldehyde (0.01mol) in ethanol(25 ml). The stirring

was continued, keeping the temperature of reaction mixture between 20-25 °C until the mixture is so thick that stirring is no more effective (3-4 hr). Remove the stirrer and kept the reaction mixture in refrigerator overnight. The reaction mixture was then poured into ice cold water (100 ml). It was then neutralized with hydrochloric acid (5%). A yellow solid was obtained after filtration which was re-crystallized from ethanol and was used further for the next step. The overall reaction scheme followed is depicted in **Figure 1**.

2.3. General procedure for the synthesis of pyrimidine derivatives (4a-j; 5a-j)

A mixture of chalcone(0.02 mol), urea/ thiourea (0.02 mol) were dissolved in ethanolic sodium hydroxide solution (10 ml) and the reaction mixture was stirred for 3 hrs on magnetic stirrer.This was then poured into 200 ml of cold water with continuous stirring of additional 1 hour and left overnight in refrigerator. The precipitate formed was filtered, washed and re-crystallized from ethanol. The structure of prepared analogs has been depicted in **Figure 2**.

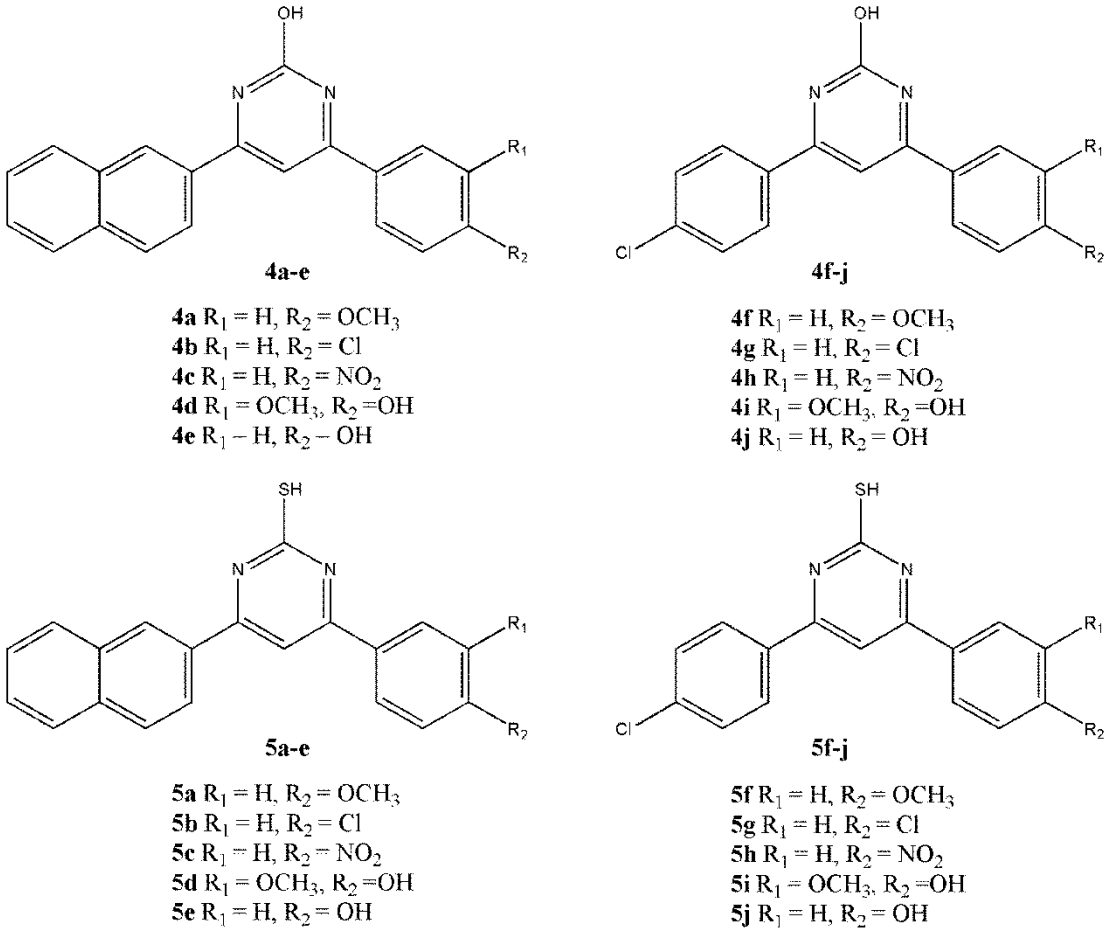


Figure 2: Chemical structures of pyrimidine analogs derived from chalcones

2.4. Spectral analysis of the synthesized compounds

2.4.1. 4-(4-methoxyphenyl)-6-(naphthalen-3-yl)pyrimidin-2-ol (**4a**): Molecular formula: $C_{21}H_{16}N_2O_2$; Melting point 146-147 °C; Yield 60%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 3.7 (s, 3H, OCH_3), 4.9 (s, 1H, OH), 6.8-7.6 (m, 12H, Ar-H). ^{13}CNMR (400 MHz, $CDCl_3$) δ: 160.2, 153, 134.2, 133.4, 132, 128.2, 126, 124.2, 114, 88, 55.2.

2.4.2. 4-(4-chlorophenyl)-6-(naphthalen-3-yl)pyrimidin-2-ol (**4b**): Molecular formula: $C_{20}H_{13}ClN_2O$; Melting point 155-156 °C; Yield 65%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 5.0 (s, 1H, OH), 6.7-7.7 (m, 12H, Ar-H).^{13}CNMR (400 MHz, $CDCl_3$) δ: 160.4, 153.2, 134.4, 133.4, 132.2, 131.2, 128.4, 126, 125.2, 124.2, 88.

2.4.3. 4-(naphthalen-3-yl)-6-(4-nitrophenyl)pyrimidin-2-ol (**4c**): Molecular formula: $C_{20}H_{13}N_3O_3$; Melting point 151-152 °C; Yield 75%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 5.0 (s, 1H, OH), 6.7-7.7 (m, 10H, Ar-H), 8.1-8.2 (m, 2H, Ar-H).

2.4.4. 4-(4-hydroxy-3-methoxyphenyl)-6-(naphthalen-3-yl)pyrimidin-2-ol (**4d**):Molecular formula $C_{21}H_{16}N_2O_3$; Melting point 145-146 °C; Yield 70%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 3.7 (s, 3H, OCH_3), 5.0 (s, 2H, OH), 6.7-7.7 (m, 11H, Ar-H).^{13}CNMR (400 MHz, $CDCl_3$) δ: 160.2, 153, 151.2, 145.2, 134.4, 133.2, 132.6, 128.1, 126.2, 125.2, 121.4, 117, 112.2, 88.2, 56.2.

2.4.5. 4-(4-hydroxyphenyl)-6-(naphthalen-3-yl)pyrimidin-2-ol (**4e**): Molecular formula $C_{20}H_{14}N_2O_2$; Melting point 140-141 °C; Yield 65%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 5.0 (s, 2H, OH), 6.7-7.7 (m, 12H, Ar-H).^{13}CNMR (400 MHz, $CDCl_3$) δ: 160.2, 158.4, 153, 134.2, 133.4, 132.2, 131.2, 128.1, 126.2, 124.4, 116.4, 88.2.

2.4.6. 4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-ol (**4f**): Molecular formula $C_{17}H_{13}ClN_2O_2$; Melting point 145-146 °C; Yield 60%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 3.7 (s, 3H, OCH_3), 4.9 (s, 1H, OH), 6.7-7.3 (m, 9H, Ar-H).

2.4.7. 4,6-bis(4-chlorophenyl)pyrimidin-2-ol (**4g**): Molecular formula $C_{16}H_{10}Cl_2N_2O$; Melting point 153-154 °C; Yield 70%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 4.9 (s, 1H, OH), 6.7-7.4 (m, 9H, Ar-H).

2.4.8. 4-(4-chlorophenyl)-6-(4-nitrophenyl)pyrimidin-2-ol (**4h**): Molecular formula $C_{16}H_{10}ClN_3O_3$; Melting point 152-153 °C; Yield 65%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 5.0 (s, 1H, OH), 6.7-7.7 (m, 7H, Ar-H), 8.1-8.2 (m, 2H, Ar-H).

2.4.9. 4-(4-chlorophenyl)-6-(4-hydroxy-3-methoxyphenyl)pyrimidin-2-ol (**4i**): Molecular formula $C_{17}H_{13}ClN_2O_3$; Melting point 148-149 °C; Yield 70%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 3.7 (s, 3H, OCH_3), 5.0 (s, 2H, OH), 6.7-7.4 (m, 8H, Ar-H).

2.4.10. 4-(4-chlorophenyl)-6-(4-hydroxyphenyl)pyrimidin-2-ol (**4j**): Molecular formula $C_{16}H_{11}ClN_2O_2$; Melting point 144-145 °C; Yield 65%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 5.0 (s, 2H, OH), 6.7-7.4 (m, 9H, Ar-H).

2.4.11. 4-(4-methoxyphenyl)-6-(naphthalen-3-yl)pyrimidine-2-thiol (**5a**): Molecular formula $C_{21}H_{16}N_2OS$; Melting point 154-155 °C; Yield 65%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 2.8 (s, 1H, SH), 3.7 (s, 3H, OCH_3), 6.8-7.8 (m, 12H, Ar-H).

2.4.12. 4-(4-chlorophenyl)-6-(naphthalen-3-yl)pyrimidine-2-thiol (**5b**): Molecular formula $C_{20}H_{13}ClN_2S$; Melting point 150-151 °C; Yield 60%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 2.9 (s, 1H, SH), 7.3-7.8 (m, 12H, Ar-H).

2.4.13. 4-(naphthalen-3-yl)-6-(4-nitrophenyl)pyrimidine-2-thiol (**5c**): Molecular formula $C_{20}H_{13}N_3O_2S$; Melting point 157-158 °C; Yield 55%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 2.8 (s, 1H, SH), 7.3-7.8 (m, 10H, Ar-H), 8.1-8.2 (m, 2H, Ar-H).

2.4.14. 4-(2-mercapto-6-(naphthalen-3-yl)pyrimidin-4-yl)-2-methoxyphenol (**5d**): Molecular formula $C_{21}H_{16}N_2O_2S$; Melting point 148-149 °C; Yield 58%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 2.8 (s, 1H, SH), 3.7 (s, 3H, OCH_3), 5.0 (s, 1H, OH), 6.7-7.7 (m, 11H, Ar-H).

2.4.15. 4-(2-mercapto-6-(naphthalen-3-yl)pyrimidin-4-yl)phenol (**5e**): Molecular formula $C_{20}H_{14}N_2OS$; Melting point 144-145 °C; Yield 60%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 3.0 (s, 1H, SH), 4.9 (s, 1H, OH), 6.7-7.8 (m, 12H, Ar-H).

2.4.16. 4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyrimidine-2-thiol (**5f**): Molecular formula $C_{17}H_{13}ClN_2OS$; Melting point 154-155 °C; Yield 65%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 3.0 (s, 1H, SH), 3.7 (s, 3H, OCH_3),6.8-7.4 (m, 9H, Ar-H).

2.4.17. 4,6-bis(4-chlorophenyl)pyrimidine-2-thiol (**5g**): Molecular formula $C_{16}H_{10}Cl_2N_2S$; Melting point 152-153 °C; Yield 60%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 2.8 (s, 1H, SH), 7.3-7.5 (m, 9H, Ar-H).

2.4.18. 4-(4-chlorophenyl)-6-(4-nitrophenyl)pyrimidine-2-thiol (**5h**): Molecular formula $C_{16}H_{10}ClN_3O_2S$; Melting point 147-148 °C; Yield 55%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 2.9 (s, 1H, SH), 7.3-7.7 (m, 7H, Ar-H), 8.2-8.3 (m, 2H, Ar-H).

2.4.19. 4-(6-(4-chlorophenyl)-2-mercaptopyrimidin-4-yl)-2-methoxyphenol (**5i**): Molecular formula $C_{17}H_{13}ClN_2O_2S$; Melting point 154-155 °C; Yield 55%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 2.8 (s, 1H, SH), 3.6 (s, 3H, OCH_3), 5.0 (s, 1H, OH), 6.8-7.4 (m, 8H, Ar-H).

2.4.20. 4-(6-(4-chlorophenyl)-2-mercaptopyrimidin-4-yl)phenol (**5j**): Molecular formula $C_{16}H_{11}ClN_2OS$; Melting point 156-157 °C; Yield 60%; ^{1}HNMR (300 MHz, $CDCl_3$, TMS=0) δ: 2.9 (s, 1H, SH), 4.9 (s, 1H, OH), 6.7-7.4 (m, 9H, Ar-H).

2.5. Biological Activity:

2.5.1. Anti-inflammatory Activity

Adult wistar rats (150–180g) of either sex from the animal house of Guru Gobind Singh College of Pharmacy, Yamuna Nagar (**Regn. No. 873/PO/ac/05/CPCSEA**) were used throughout the work. They were kept under standard conditions of light and temperature with free access to food and water. The animals were randomly divided into groups of six rats each. The paw edema was induced by sub-plantar injection of 50mL of 1% carrageenan solution in saline (0.9%).Indomethacin and the testcompounds (**4a-j** and **5a-j**) were suspended in DMSOand injected subcutaneously at a dose level of 1mg/kg and 10 mg/kg body weight respectively, 1 h prior to the carrageenan injection.DMSO was injected to the control group. The volume of paw edema (in mL) was determined by means of a water plethysmometer immediately after the injection of carrageenan and 4 h later. The difference between these two values was taken as edema volume. The percentage protection against inflammation was calculated as follows: (Vc – Vd)/Vc × 100, where Vc is the increase in paw volume in the absence of the test compound (control) and Vd is the increase of paw volume after injection of the test compound.

Statistical analysis

Data were expressed as means ± SEM. Significant differences between the control and the treated groups were obtained using Student's t-test. The differences in results were considered significant when $p < 0.001$.

2.5.2. Ulcerogenic activity

Adult wistar rats (120–150 g) were fasted for 12 h prior to theadministration of the compounds. The animals were divided intofive equal groups, of four animals. The control group received0.2 mL DMSO orally, reference groups received 5 mg/kg indomethacinand test groups received 10 mg/kg tested compounds orallyfor three successive days. Animals were sacrificed by diethyl ether6 h after the last dose and the stomach was removed. An opening atthe greater curvature was made and the stomach was cleaned bywashing with cold saline and examined for ulceration. The numberand diameter of discrete areas of damage in the glandular mucosawere scored. The ulcer score was calculated as: 0.0—normal (noinjury); 0.5—latent injury; 1.0—slight injury (two to three dottedlines); 2.0—severe injury (continuous lined injury or five to sixdotted injuries); 3.0—very severe injury (several continuous linedinjuries); 4.0—widespread lined injury.

3.Result and Discussion:

3.1. Chemistry

The synthetic pathway leading to the title compounds is given in **Figure 1**. 1,3-diarylpropenones prepared by Claisen–Schmidt condensation of substituted aryl ketones (**1**) and benzaldehydes(**2**), on treatment with urea/thiourea in presence of ethanolic sodium hydroxide solution under stirring conditions afforded the target pyrimidine derivatives (**Figure 1**; **4a-j**; 60–75%, **5a-j**; 55–65%,). The purity and structures of all the synthesized compounds have been characterized on the basis of their ^{1}H NMR spectral data.

Anti-inflammatory Activity

The *in-vivo* anti-inflammatory activity of the prepared analogs (**4a-j** and **5a-j**) was studied using the carrageenan-induced rat paw edema model [20]. The anti-inflammatory activity of the test compounds was compared with a standard drug indomethacin and as depicted in **Table 1**.

The test and standard drug produced significant inhibition of paw edema as compared to control.The pyrimidine analogs obtained by treating urea with substituted chalcone showed remarkable reduction in inflammation as compared with the standard drug indomethacin, after 4 h of carrageenan administration, whereas pyrimidine analogs obtained by treating thiourea with substituted chalcone doesn't showed remarkable anti-inflammatory activity. Out of all prepared analogs, three compounds**4e**, **4d** and **4b**exhibit significant anti-inflammatory activity 97.4%, 97.4%and 92% respectively, relative to standard drug indomethacin. In addition, the compounds**4a**, **4i** and **4j**also showed moderate anti-inflammatory activity with percentage inhibition of 92%, 88% and 88%respectively.

3.2. Ulcerogenic activity

Selected synthesized compounds (**4e**, **4d** and **4b**) were alsoevaluated for their ulcerogenic potential relative to indomethacinas a reference drug in rats [21]. Compound **4e** revealed a good ulcernindex (0.96 ± 0.2) when compared with that of indomethacin(0.98 ± 0.3) while compounds **4d** and **4b** showed ulcer indexes of(1.10 ± 0.3) and (1.56 ± 0.2) respectively.

Conclusions

The present investigation describes the synthesis of some novel pyrimidine analogs with comparable anti-inflammatory potencies, obtained by treating urea/thiourea with 1,3-diarylpropenonesprepared from Claisen–Schmidt condensation of substituted aryl ketones and benzaldehydes. All spectral data (^{1}H NMR and ^{13}C NMR) of the prepared analogs were in accordance with assumed structures.From this research it can be concluded that pyrimidine class of compounds synthesized from chalcones certainly holds great promise towards good active leads in medicinal chemistry. Further study to acquire more information concerning pharmacological activity is in progress. The promising activity of these compounds along with the other activity data obtained during the study can also be useful for establishing the structure activity relationship studies and for the development of newer and potent anti-inflammatory compounds.

List of Abbreviations

TMS: Tetramethylsilane, $CDCl_3$: Deuterated chloroform, TLC: Thin layer chromatography, DMSO: Dimethyl sulfoxide.

Conflict of Interest

There is no Conflict of Interest.

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