A convenient synthesis of novel pyrimidine analogues of o-hydroxy chalcones and pyrano [2,3-*d*]pyrimidines and their biological activities

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Vinod K. Ahluwalia, Madhu Chopra* and Ramesh Chandra

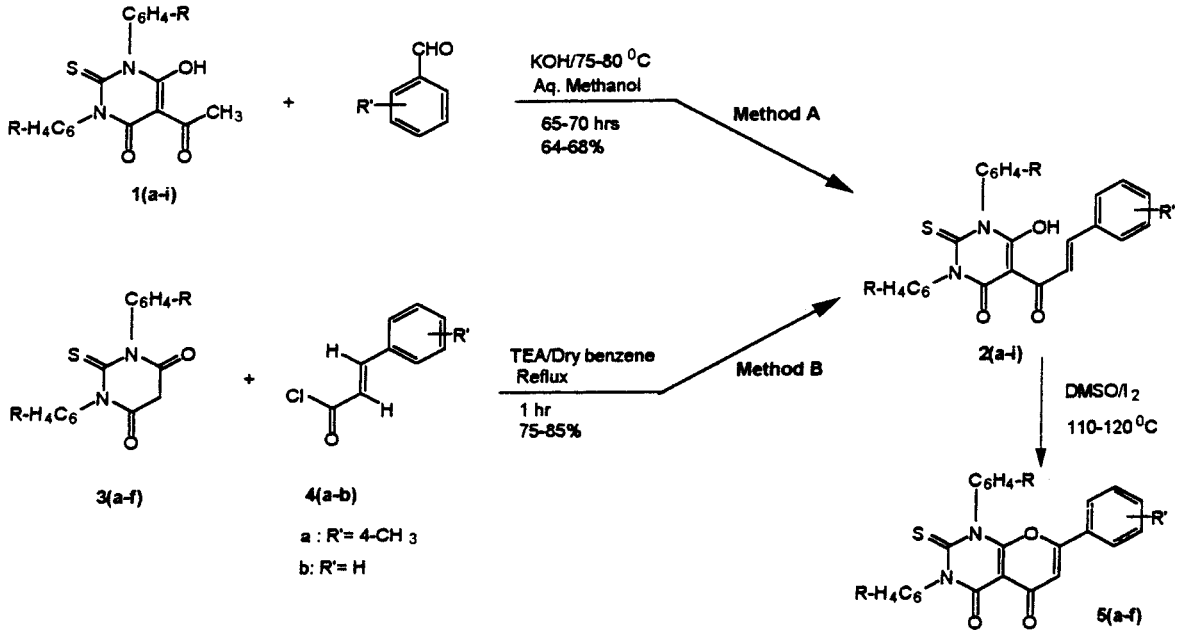
Dr B.R. Ambedkar Center for Biomedical Research, University of Delhi, Delhi 110007, India

A convenient method for the synthesis of new pyrimidine analogues of chalcones by condensation of 5-acetyl-1,3-diaryl-1,2,3,4-tetrahydro-6-hydroxy-4-oxo-2-thioxopyrimidines with aromatic aldehydes in aqueous methanolic potassium hydroxide (method A) and by condensation of 1,3-diaryl-2-thiobarbituric acids with cinnamoyl chlorides in presence of triethylamine (method B) is reported which on subsequent oxidative cyclization afforded 1,3,7-triaryl-1,2,3,4-tetrahydro-4,5-dioxo-2-thioxo-5*H*-pyrano[2,3-*d*]pyrimidines which were evaluated for their antimicrobial activity.

Synthetic studies on hetero atom containing chalcones and pyrano[2,3-*d*]pyrimidines have been extensively investigated in view of their structural diversity and a wide spectrum of biological activity. Hetero atoms containing chalcones and pyrano[2,3-*d*]pyrimidines play important role in medicinal chemistry as antiulcer, herbicidal, antibacertial, analgesic, sedative and antiphlogistic, virucidal, *etc*. activities.

We report an efficient, inexpensive and mild method for the synthesis of pyrimidine analogues of *o*-hydroxychalcones viz. (E)-1-3-aryl[1,3-diaryl-1,2,3,4-tetrahydro-6-hydroxy-4-oxo-2-thioxopyrimidin-5-yl]-2-propen-1-one (**2a–f**) have been synthesized by condensation of 5-acetyl-1,3-diaryl-1,2,3,4-tetrahydro-6-hydroxy-4-oxo-2-thioxopyrimidines[8] (**1a–f**) with aromatic aldehydes in aqueous methanolic potassium hydroxide by stirring at 75–80°C for 65–70 h in 64–68% yield (Scheme 1) (Method A). Another method, requiring shorter reaction time (2 h) and proceeding in better yield (75–80%) has been developed. It involves condensation of 1,3-diaryl-thiobarbituric acid[9] (**3a–f**) with cinnamoyl chloride[10] (**4a–b**) in presence of triethylamine in dry benzene at reflux temperature to give (**2a–f**), (Scheme 1) (method B).

Oxidative cyclization of **2a–f** was carried out in dimethyl sulfoxide in the presence of catalytic amounts of iodine to give 1,3-diaryl-1,2,3,4-tetrahydro-4,5-dioxo-7-phenyl (or 4-methyl phenyl)-2-thioxo-5*H*-pyrano[2,3-*d*]pyrimidines (**5a–f**) (Scheme 1).



1,2,3,5	R	R'
a	2-OCH_3	4-CH_3
b	2-CH_3	H
c	4-CH_3	4-CH_3
d	2-OCH_3	H
e	H	4-CH_3
f	H	H
g	3-OCH_3	4-CH_3
h	2-CH_3	4-CH_3
i	4-OCH_3	H

Scheme 1

* To receive any correspondence. E-mail: Madhu-India@hotmail.com

Biological activity

The compounds **5a–f** were tested for antifungal, antibacterial and antimycobacterial activities by M/s Ranbaxy Laboratories Ltd., New Delhi.

Ciprofloxacin was used as standard for antibacterial and antimycobacterial activities while antifungal activity was evaluated using Amphotericin B and Fluconazole as standards. The compounds were tested at 5–10 times higher concentration as compared to standard antimicrobial agents employed.

All compounds except **5d** showed weak antimycobacterial activity against *Mycobacterium vaccae* ATCC 5483, *M. xenopi* and *M. smegmatis* ATCC 14468 at much higher concentration than Ciproflaxacin. At concentration (50 µg) several times higher than Ciprofloxacin (1.25 µg), all compounds **5a–f** were feebly active against gram positive organisms. The compound 1,2,3,4-tetrahydro-7-(4-methylphenyl)-4,5-dioxo-1,3-diphenyl-2-thioxo-5*H*-pyrano[2,3-*d*]pyrimidine (**5e**) showed weak antifungal activity at 12.5-50 µg/well against *Candida kefyr* R-34 and *Cryptococcus neoformans* and weaker activity against *Staphylococcus cerevisiae*.

Our method is noteworthy owing to the easy availability of the starting materials, the experimental simplicity of procedure and high yield of the products in a short time. Also it provides a new entry into a new variety of pyrano[2,3-*d*] pyrimidines as antimicrobial agents substituted at 1,3 and 7 positions.

Techniques used: 1H NMR, IR, mass spectrometry

References: 10

Scheme: 1

Table 1: Physical data, comparison of reaction time and yields for **2a–i** and **5a–f**

Table 2: spectral data for **2a–i** and **5a–f**

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