Synthesis of new pyrimidine and pyrrolopyrimidine derivatives as antitumor and antiinflammatory agents

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EMAN SAID ELSAYED ABDALLA
B. Sc. Ain-Shams University

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Synthesis of new pyrimidine and pyrrolopyrimidine derivatives as antitumor and antiinflammatory agents

THESIS ADVISORS **THESIS APPROVED**

Prof. Dr. Hassan Mohammed F. Madkour .....
Prof. of Organic Chemistry, Faculty of Science,
Ain Shams Univeristy.

Prof. Dr. Zeinab Mahmoud Nofal .....
Prof. of Therapeutical Chemistry,
National Research Centre.

Prof. Dr. Hoda Hanem Fahmy .....
Prof. of Pharmaceutical Chemistry,
National Research Centre.

Prof. Dr.
M. Y. El-Kady

.....

Head of Chemistry Department
Faculty of Science
Ain Shams University

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"The most beautiful thing one can experience is the mysterious. It is the source of all time, art, and science……."

Albert Einstein

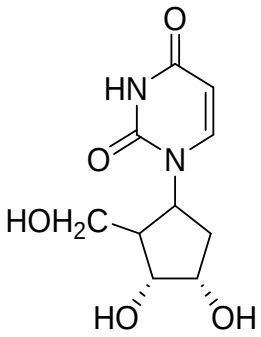
CONTENTS

GENERAL PART

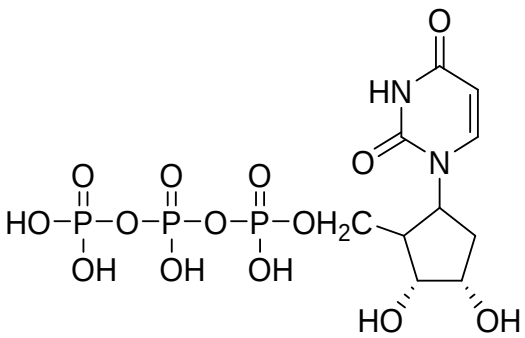
A- PYRIMIDINE DERIVATIVES

Chemotherapeutic Importance of Pyrimidine Derivatives

Uracils have represented, for more than 90 years ago,[134] a class of compounds which continually attracted photobiologists, organic chemists, biochemists and medicinal chemists. Uracils were first detected as constituents of ribonucleic acids, from which they were prepared by hydrolysis. Nucleosides derived from uracil are called uridine **(1)**, pseudouridine, and uridine phosphate **(2)**.



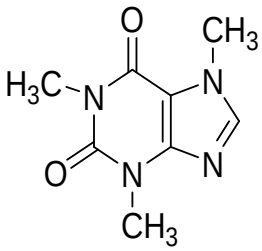
(1)



(2)

Pyrimidine derivatives, which constitute a partial structure of the purine base and many biologically active compounds, are involved widely in living organisms and have attracted much attention from the view point of medicinal chemistry.[61]

Furthermore, naturally occurring heterocondensed uracil derivatives are shown, Methyl xanthines, e.g., caffine[119] **(3)**, theophylline[120] **(4)** and theobromine[121] **(5)** show various pharmacological activities.



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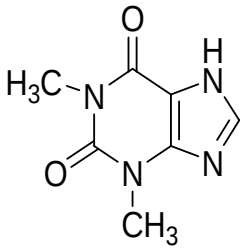

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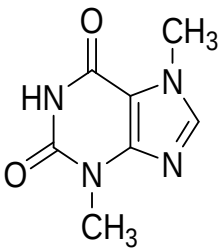
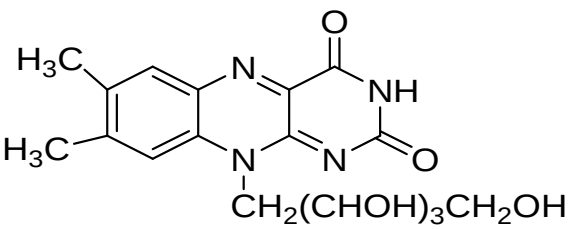


(5)

Riboflavine[122] (vitamin B_2) **(6)** acts as a coenzyme in bio-redox reactions. Uric acid **(7)** is a metabolite of purine nucleosides[123].



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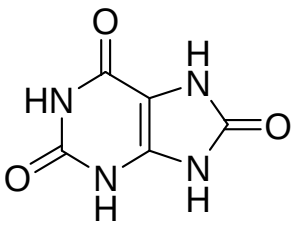
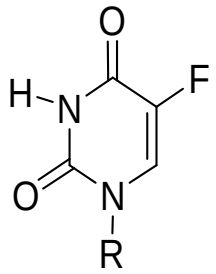


(7)

Moreover, a large number of pyrimidine derivatives are reported to exhibit antimycobacteral[64], antifolate[44], antiproliferative[49], and antihistaminic activities.[107]

They are also effective as antiplatelet agents with analgesic activity[18] and as a new drug for treatment of insomnia.[80]

Also, several uracil derivatives have been developed as drugs, thus, methyl thiouracil and propyl thiouracil are thyroid inhibitors[134] On the other hand, a large number of pyrimidine derivatives are reported to exhibit antitumor,[36] e.g. 5-flurouracil **(8)** which represent one of the most widely used antineoplastic agents.[51]



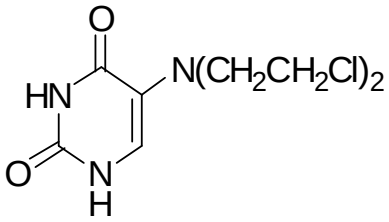
a, R= -H

b, R= -ribose

c, R= -deoxyribose

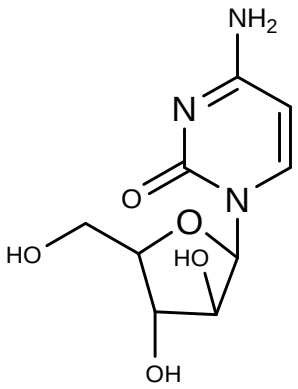
(8)

Uramustine[70] (uracil mustard) **(9)** was found to be anticancer agent.



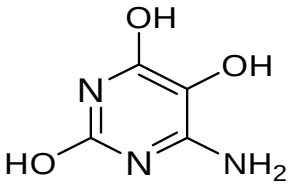
(9)

While Cytarabine **(10)** is used for the clinical treatment of leukemia. [48,106]



(10)

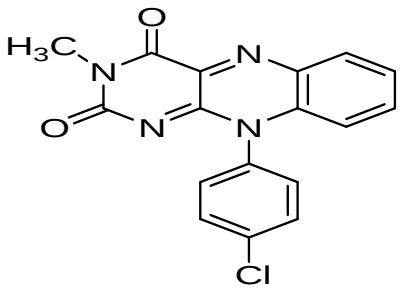
Furthermore, isouramil **(11)** was reported to have therapeutic effects in the treatment of malaria and cancer.[11]



(11)

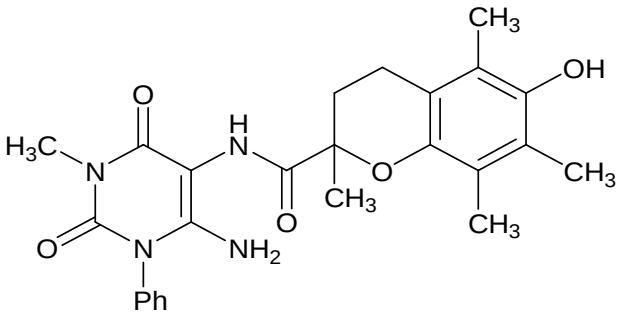
Moreover, it was reported that several 5-deazaflavins[25], Including 5-deazariboflavin, were found to be inactive in vivo, while 10-(4-chlorophenyl)-3-methylflavin **(12)** was very active against plasmodium uinckei malarial infection in mice by both oral and intraperitoneal **(Ip)** administration and against plasmodium in culture.

Jensen et al.,[45] finding that 5-deazariboflavin inhibits the growth of P.falciparum in culture.



(12)

In this respect, Yoshiaki Isobe et al.[53] reported that 5-substituted uracil derivative **(13)** are a new class of non- steroidal antiinflammatory agent possessing anti-oxidative activity.



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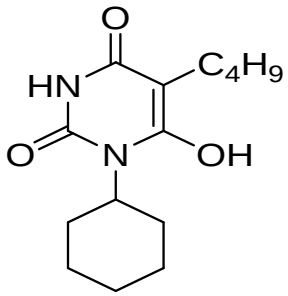
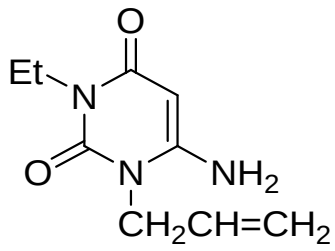
Senda et al.,[105] in 1967 found that Bucolome **(14)** is antiinflammatory agent.



(14)

Moreover, several uracil derivatives such as Aminometradine[124] **(15)** and Amisometradine[125] **(16)** are used clinically as diuretics.



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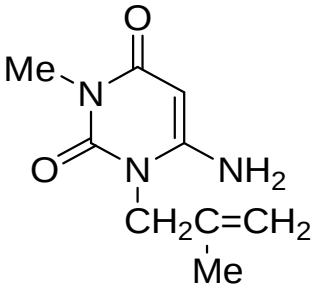

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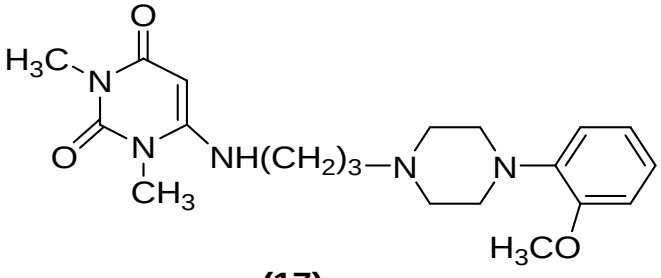
It was found that, Urapidil[60] **(17)** and Ketanserin[126] **(18)** are used as antihypertensives.



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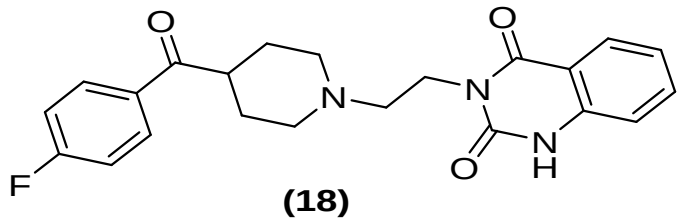
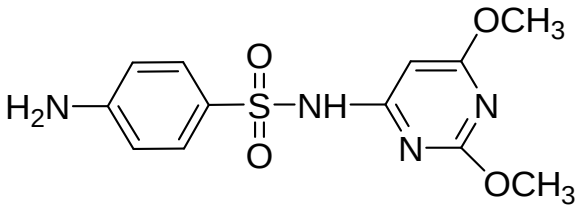


(18)

Also, it was found that trivial sulfadimethoxine[76] **(19)** is known as a potent antibiotic developed by Hoffman –La Roche Inc., in 1955 as a lasting sulfonamide for humans as well as animals.



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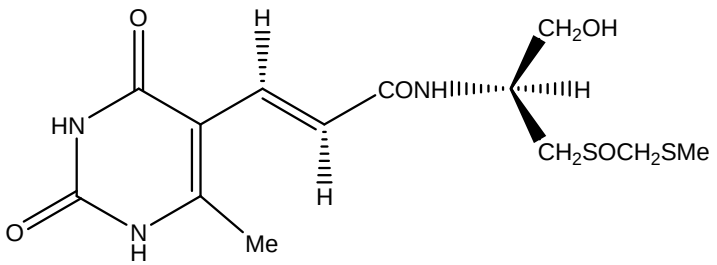
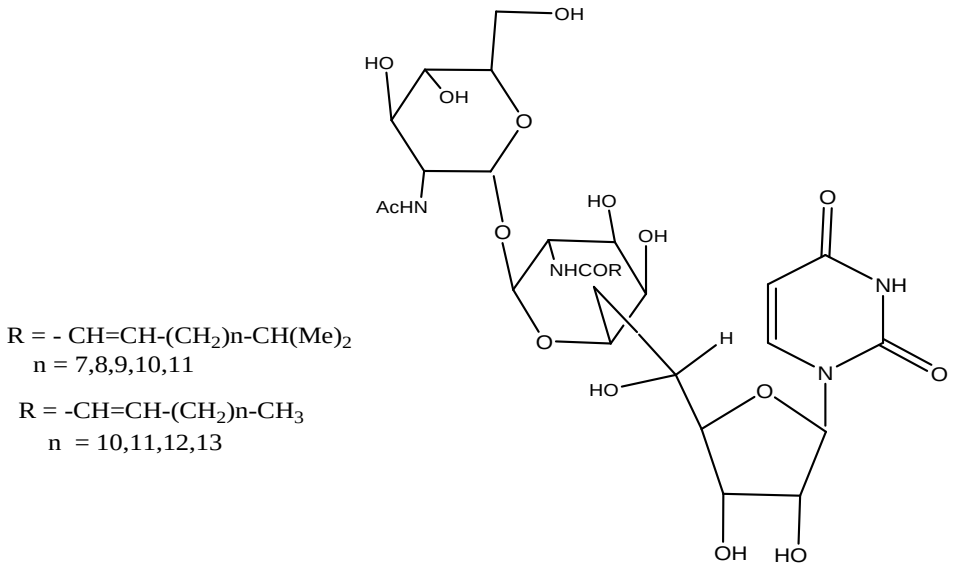
Sparsomysin **(20)** is known as naturally occurring antibiotic and antitumor substance[90].



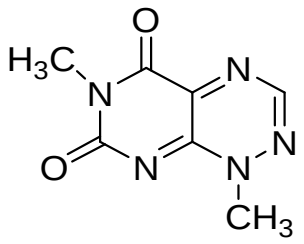
(20)

Furthermore, it was found that the Tunicamycins **(21)** form a family of closely related nucleosides of novel structure with demonstrater antibiotic and antiviral capabilities[26].



(21)

On the other hand, naturally occurring heterocondensed uracil derivatives are shown in toxoflavin[30]**(22)** and fervenuline[29] **(23)** are antibiotics .



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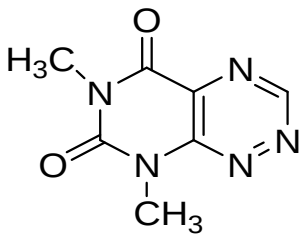

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