

# PYRIMIDIN COMPOUNDS AND DERIVATES USEFUL FOR THEIR ANTI-CANCER ACTIVITY

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## INTRODUCTION

Pyrimidines have been used as medicines, especially barbiturates class, depression therapy, treatment of diseases such as AIDS, as anticancer drugs, an area where research has progressed a lot in recent years. They are typically used to reduce the cancer tumor by inhibiting the action of their enzymes. Some of them are already being used in commerce.

### I.1. Necessary materials and theoretical description:

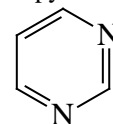
The pyrimidine ring occurs in nature isolated as a hydroxyl derivatives or fused with:

- benzene ring (quinazolines)
- imidazole ring (purine)
- pyrazine ring (pterine)
- quinoxaline nucleus (aloxazine)

Derivatives of these ring systems are found in many natural organic compounds like vitamins,

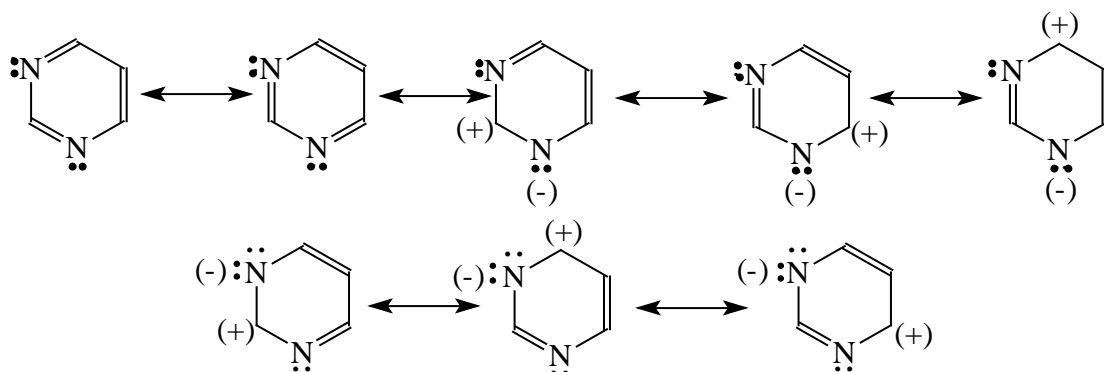
coenzymes, nucleic acids. Pyrimidine class includes many synthetic drugs.

The pyrimidine has two more isomeric diazines: pyridazine and pyrazine



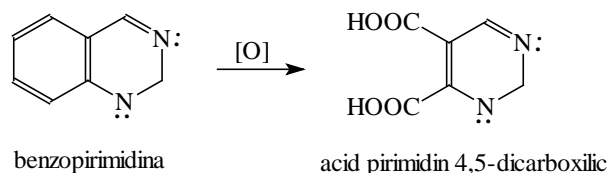
1,3-diazine  
Pyrimidine

Pyrimidine heterocyclic ring system consists of four carbon atoms and two sp<sup>2</sup> hybridized nitrogen atoms, bond together by σ sp<sup>2</sup>-sp<sup>2</sup>. The carbon atoms each form one σ sp<sup>2</sup> relation with a hydrogen atom. P-orbital electrons in the non-hybrid (four carbon atoms and two nitrogen atom) jointly form the electron cloud of extended molecular orbitals. Nitrogen atoms have unshared electron pairs of the sp<sup>2</sup> hybridized orbitals. The electron distribution can be represented as follows:



In the limit structures dipolar carbon atoms in positions 2, 4 and 6 have positive charges, which have an impact on the reactivity of the molecule. The pyrimidine has an aromatic character and is stable compared to oxidizing agents.

For example, the oxidation of benzo-pyrimidine, the pyrimidine nucleus remains untouched:



### I.2. The aromatic character

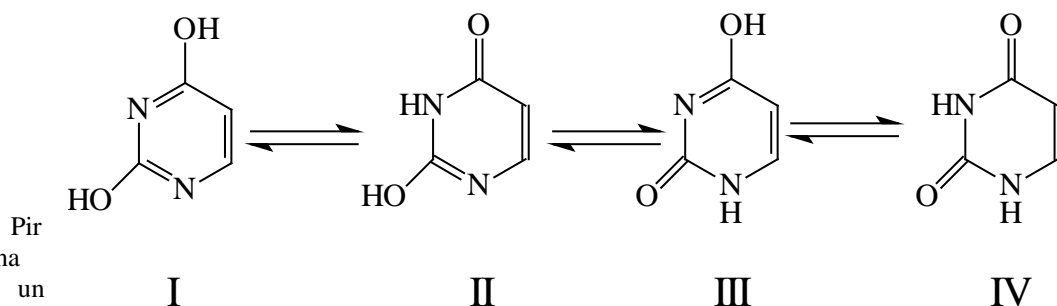
The aromatic character of the pyrimidine and its simple derivatives (substituted with alkyl, aryl, halo, nitro) decreases gradually as they introduce hydroxyl or amino groups in the positions 2, 4 and 6, thus the electrophilic substitution takes longer and only in the 5 position.

The substituents bound to the ring in positions 2, 4 and 6 are much more reactive than those in position 5, thereby the groups-Cl, -OC<sub>2</sub>H<sub>5</sub> or -SC<sub>2</sub>H<sub>5</sub>, in positions 2, 4 and 6 may be substituted by hydroxyl or

amino group by acid hydrolysis or ammonolysis (ammonia in EtOH).

The thio group at the 2ns position may be replaced by hydrogen by treatment with H<sub>2</sub>O<sub>2</sub>, causing perhaps the oxidation to the sulfone group followed by the removal of this group by hydrolysis.

The Oxygenated compounds of the pyrimidine is characterized by a tautomerism lactam (amide) Lactima (enol).



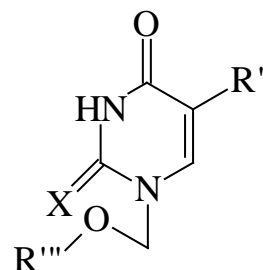
Pirimidina este un produs stabil, incolor cu  $p_t = 22.5^\circ$ ,  $p_f = 124^\circ$  și solubil în apă, cu acizii tari formează săruri. Acidul conjugat pirimidinic are  $pK_a = 1.3$ .

As noted above 3'-azido-3'-deoxythymidine, AZT is one of the drugs used in the treatment of AIDS, perhaps the most used. It is true that AZT prolongs the lives of patients, but has serious side effects like anemia and isolated cases have been reported to reduce susceptibility to AZT [25, 26].

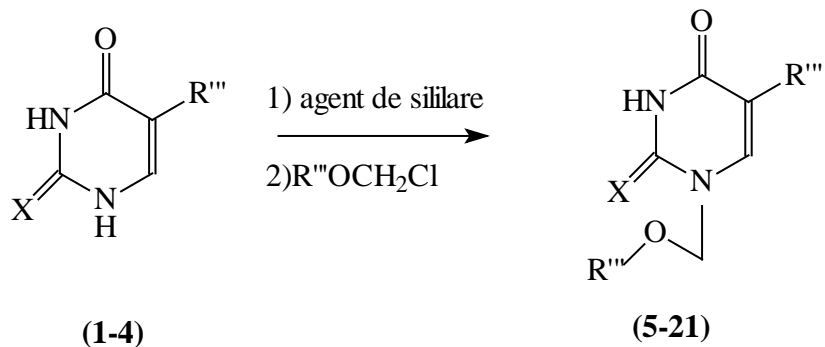
These results emphasize the need for new classes of compounds with potential anti-HIV-1 activity, lower toxicity and better to work by a different mechanism.

The class brought into question is that of the compounds 1 - [(2-hydroxyethoxy) methyl] -6 - (phenylthio) thymine, heptyl.

The first discussed are the compounds 1 - [(alkyloxy) methyl] -6 - (phenylthio) thymine and 5-alkyl-1-[(alkyloxy) methyl] uracil, which are used for the preparation of heptyl. General formula:



These compounds were characterized by elemental analysis, melting point and the recrystallization solvent.



- (1) X = O; R'' = Me
- (2) X = S; R'' = Et
- (3) X = S; R'' = Pr-i
- (4) X = S; R'' = Bu

### I.3. HEPT derivatives with anti - HIV activities

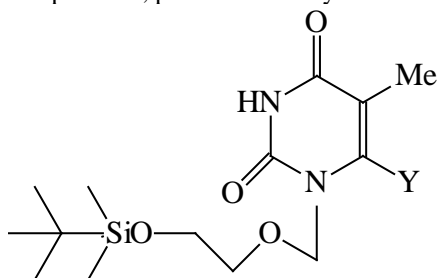
#### I.3.1 Obtaining HEPT derivative substituted in

C-6

As has been shown, HEPT has a potential anti-HIV-1 activity and lower cytotoxicity than the other substances currently in use for the treatment of AIDS. But is just a start. There have been studies and tried to obtain the derivatives of HEPT in an effort to obtain compounds with high activity as anti-HIV-1 as low cytotoxicity.

Next we will describe some of the classes of derivatives to HEPT, the method of their production and their anti-HIV-1.

The synthesis of the compounds containing a halogen atom from position C-6, the reaction involves two steps. In the first step an activation of the substituted occurs in C-6 position, which is achieved by reaction with lithium diisopropylamine (LDA), and in the second step is reacted with a halide. To obtain the 6-iodo derivatives (22) using the iodide [31], and 6 to yield the brominated (23) and 6-chlorine (24) is used bromoacetophenone, p-toluenesulfonyl chloride.



(22) Y = I

(23) Y = Br

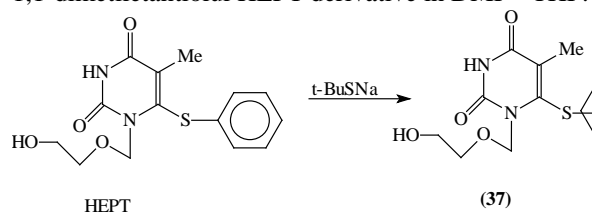
(24) Y = Cl

For the introduction in the C-6 position of the ring pirimidimic the functions of oxygen and nitrogen is required following reaction scheme:

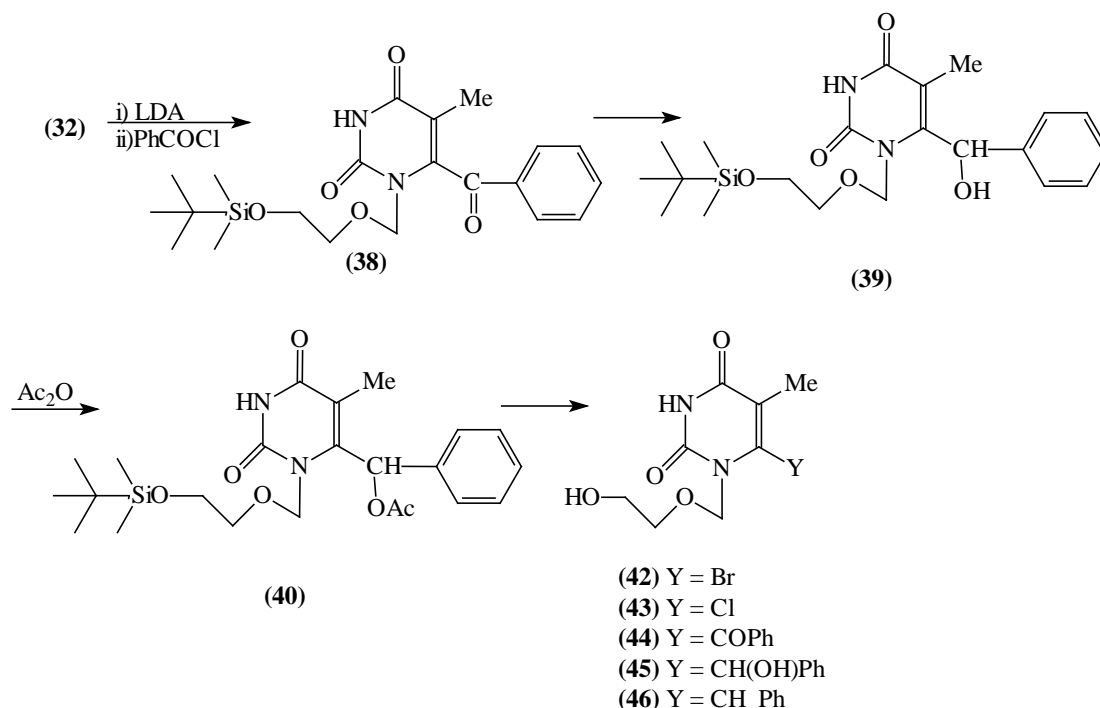
Using as a base material 6-phenylsulfanyl derivative (25), that will react with nucleophile (NaOMe, NaOC<sub>6</sub>H<sub>11</sub>, NaOPh, or LiNHPh C<sub>6</sub>H<sub>11</sub>NH<sub>2</sub>) in tetrahydrofuran (THF) to give compounds (26-30).

In order to obtain 6-alkylthio derivatives is started from the compound (31) which protects the hydroxyl group lock tert-butyldimethylsilyl chloride (TBDMS-Cl) and imidazole, thereby obtaining the compound (32) [32]. This compound will be reacted with LDA, in a first step, and then a series of dialkyl disulfides to provide compounds (33-36).

I.3.2 An alternative method to obtain alkylthio compounds is based on the fact that the group of HEPT-6-phenylthio site can be regarded as a position in the enol system using such an addition reaction - removal between HEPT and thiolated alkane [33]. This will yield the 6 - (tert-butylthio) (37) by treatment with 1,1-dimethylethanethiol HEPT derivative in DMF - THF.

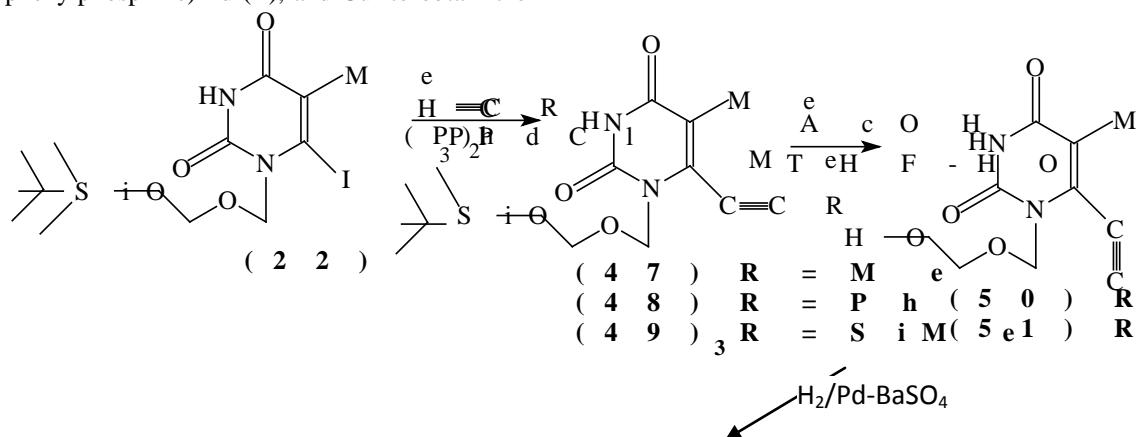


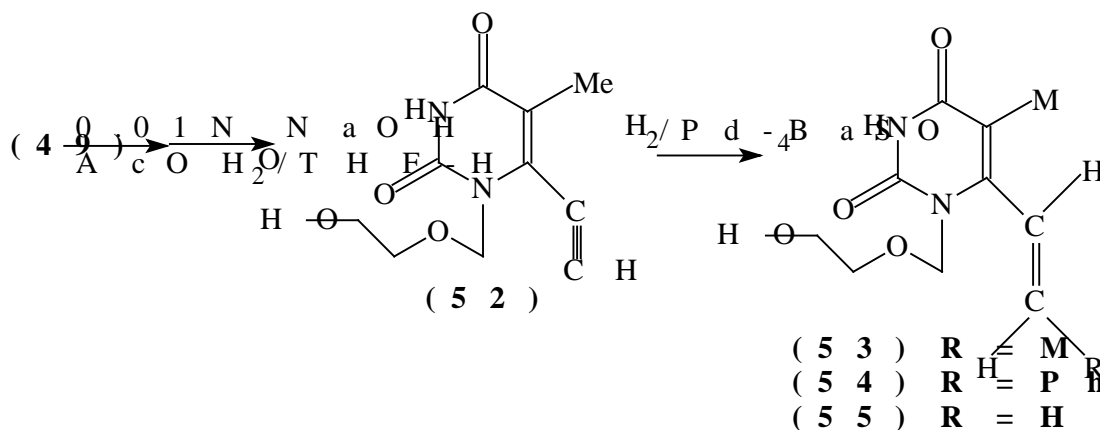
To introduce the benzyl group at C-6 we choose a synthetic route because reaction with benzyl bromide at C-6 activated did not work. The reaction of the activated species C-6 of the compound (32) with a benzoyl chloride produces (38), which is converted into the compound (39) by treatment with NaBH<sub>4</sub> in EtOH. Acetylation of (39) gives the compound (40). Compound (40) distilled in the presence of Pd-substituted occurs in C catalyst giving free aciclotimidinele (42-46).



I.3.3. Another modification from position C-6 was made using a Pd catalyst, and carrying out a coupling between a terminal alkyne and iodine nucleolizidă [34, 35]. By treating compound (22) with an alkyne (propyne, phenyl-acetylene, (trimethylsilyl) acetylene) located in MeCN-Et<sub>3</sub>N in the presence of bis (triphenylphosphine) Pd (II), and CuI to obtain the

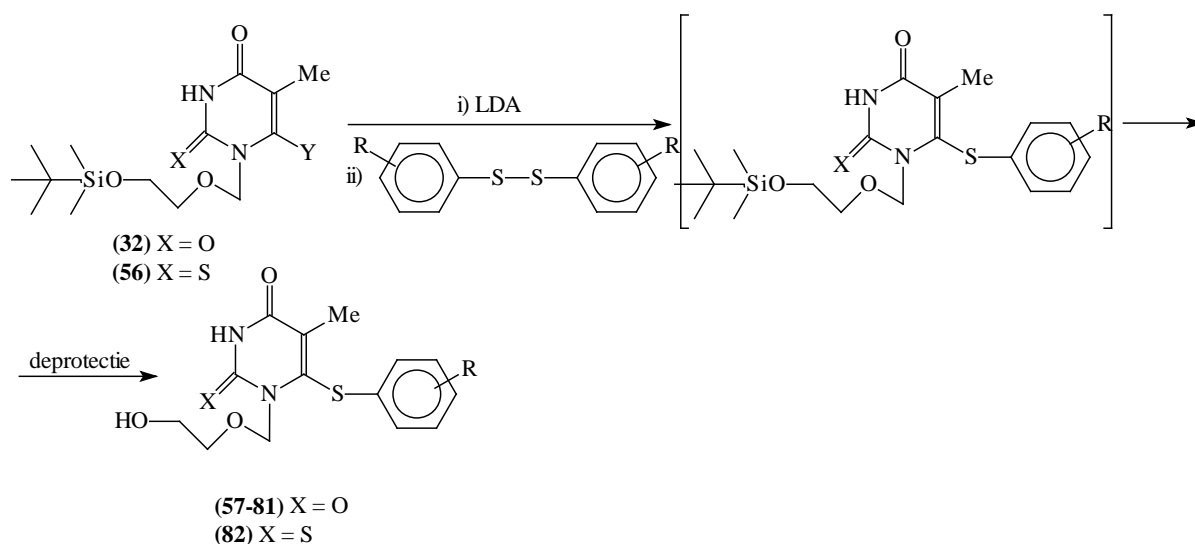
compounds (47-49). Deprotection of compounds (47, 48) give the compounds (50, 51). Deprotection of (49) takes place in two steps to afford compound (52). 6-vinyl derivatives (53-55) are produced by partial hydrogenation of the compounds (50-52) in the presence of Pd-BaSO<sub>4</sub>.





To obtain derivatives of, HEPTor HEPT substitutes in the phenyl group in C-6 the treated compounds (32) and (56) with LDA in THF below -70 °C generating the active species that can react with various diaryl disulfides.

The compounds (57-82) were prepared as follows, with a yield of 16-87%. By this method we were able to use, the diaryl disulfides which carry the function of cyano or nitro, as an electrophile agent.



R: (57) 2-Me; (58) 2-Cl; (59) 2-NO<sub>2</sub>; (60) 2-OMe; (61) 3-Me; (62) 3-Et; (63) 3-t-Bu; (64) 3-CH<sub>2</sub>OH; (65) 3-CF<sub>3</sub>; (66) 3-F; (67) 3-Cl; (68) 3-Br; (69) 3-I; (70) 3-NO<sub>2</sub>; (71) 3-OH; (72) 3-OMe; (73) 4-Me; (74) 4-F; (75) 4-Cl; (76) 4-NO<sub>2</sub>; (77) 4-CN; (78) 4-OH; (79) 4-OMe; (80) 3,5-Me<sub>2</sub>; (81) 3,5-Cl<sub>2</sub>; (82) 3,5-Me<sub>2</sub>

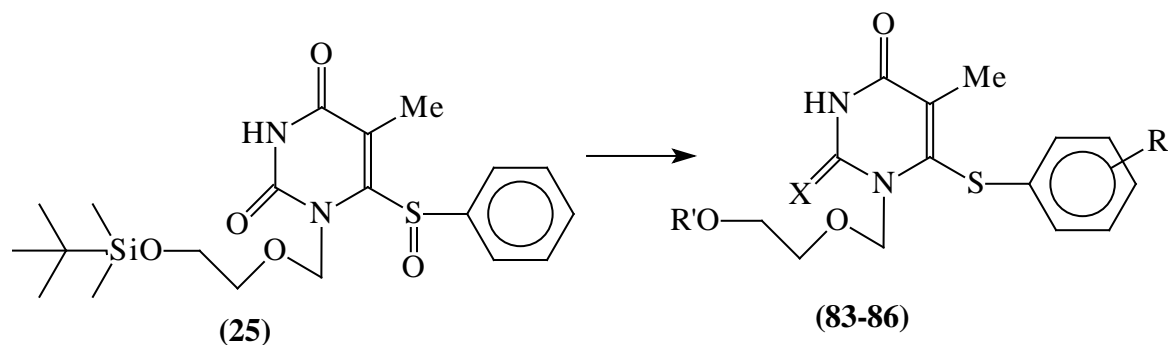
Through this reaction scheme you can not enter the phenyl group substituents of the type COOMe, or-COMe.

In order to obtain these substances starts with the compound (25). This was treated with 3 -

(methoxycarbonyl) in DMF benzotriazol formed compound (83) in a yield of 48%.

After the extract of the TBDMS group we obtained aciclotimidina (84).

The compounds (85, 86) have been prepared starting with the compound (25) by a similar method.



- (83) **R = 3-COOMe, R' = TBDMS**  
 (84) **R = 3-COOMe, R' = H**  
 (85) **R = 3-COMe, R' = H**  
 (86) **R = 4-COMe, R' = H**

By turning methoxycarbonyl group of the compound (83) by basic hydrolysis, we obtain the compound (87) which is distilled off to give 6 - [(3-carboxyphenyl) thio] acicotimidina (88).

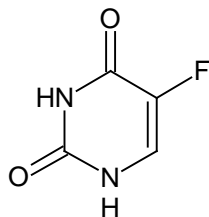
Amidation of (87) is achieved via an active ester intermediate, following published method [36].

After the TBDMS group was replaced, we obtained the derivative 6 - [(3-carbamoylphenyl) thio], (89).

Dehydration of the carbamoyl group is achieved using the O-acetyl derivative (90), to give 6 - [(3-cyanophenyl) thio] acicotimidina (91)

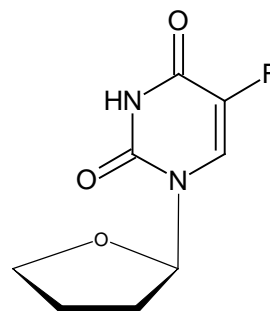
Pyrimidines have been used as medicinal products, in particular the class of barbiturates, in the treatment of depression, the treatment of diseases such as AIDS.

## II. ANTICANCER DRUGS COMMONLY USED TO REDUCE CANCEROUS TUMOR BY INHIBITION OF ENZYMES. SOME OF THESE ARE ALREADY USED COMMERCIALY.



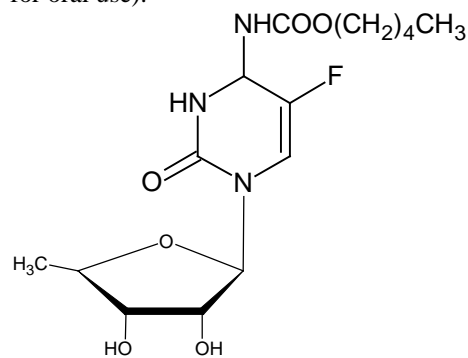
5-fluorouracil (5-fluoro-2, 4 - (1H, 3H)-pyrimidine-dione)

Antimetabolite of uracil, inhibits thymidylate-sinteteza. Indications in solid tumors, warts, epidermal tumors.

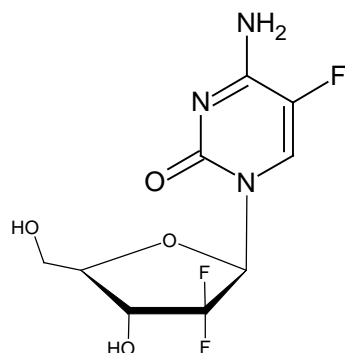


Ftorafur = Tegafur

For advanced colorectal cancer (bioprecursor of 5-FU for oral use).



For the colo-rectal cancer , and metastatic breast cancer in combination with docetaxel (XELODA-cp).



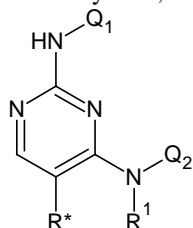
Analog difluoro of 2-deoxy-cytidine.  
 Pancreatic cancer, lung, bladder and metastatic breast under the name of Gemzar.

### III. RESEARCH AND INVENTIONS OF SOME ANTITUMOR DRUGS

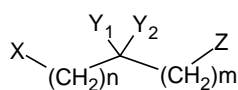
Other studies have started from formula I, wherein R<sup>\*</sup> is defined as the optional substituent R<sup>\*</sup>, one of following groups: halo-, hydroxy-, nitro-, cyano-, mercapto-, carboxy-, sulafanoil-, ureido-, carbamoyl or a group from formula I b

A, B, C are defined as well. Q1 and Q2 are independently selected from the arena monocyclic with 5 or 6 carbon atoms and bicyclic heterocycles with 9 or 10 carbon atoms (in 50%).

One, or both (Q1, or Q2) contain available carbon atom to be substituted with I a. Optionally, these Q1 and Q2 may be substituted further with a salt from a pharmaceutically acceptable or in-vivo hydrolysable ester; their use as anti-cancer agents and processes for preparation and pharmaceutical production has been described in an invention made by AstraZeneca UK Ltd. (United Kingdom - Robert Bradbury et al, 1998).



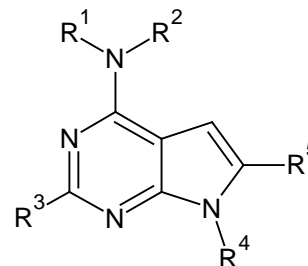
(I)



(Ia)

This invention is based on the discovery of 2,4-pyrimidine compounds with inhibitory effects on cellular enzymes that show surprising selectivity for CDK2, CDK4, and CDK6, and also inhibit FAK, and thus has anti-cancer properties (against cell migration, proliferation and apoptosis thereof). These properties can be used in the treatment of diseases associated with cancer (tumors, leukemias), fibroproliferative disorders (psoriasis, rheumatoid arthritis, Kaposi's sarcoma, hemangioma, arteroscleeroză, etc.).

Synthesis and use of pyrrole-pyrimidine compounds 2b as selective antagonists.



The invention was made by an American team consisting of Arlindo Castelhamo and his collaborators, 2007.

R1 can be a substituted or unsubstituted alkyl, where the substituent may be hydroxyl, dihydroxy, carboxyl, amino, amido.

R2 is hydrogen or a substituted or unsubstituted alkyl, where the substituent may be hydroxyl, dihydroxy, carboxyl.

R1, R2 and the nitrogen together form a substituted piperazine, substituted azetidine or pyrrolidine ring substituted with saturated or unsaturated alcohols.

R3 is phenyl or aromatic hydrocarbon with 5 or 6 carbon atoms of which substituents may be hydroxyl, cyano, alkyl, alkoxy or amino groups.

R4 is hydrogen or a substituted or unsubstituted alkyl (C1-C15)

R5 is ether, substituted or unsubstituted alkyl (C1-C30) or (C3-C10) cycloalkyl, or 4-6 membered heterocyclyl.

### IV. ANTI-INFLAMMATORY DRUGS

Adenosine is usually modulator of numerous physiological activities, particularly for the nervous and cardiovascular system. It acts on the induction of sedation, vaso-dilation, inhibition of heart rate, stimulating gluconeogenesis and lipolysis inhibition. It opens ion channels K Ca channels reduce flow, and inhibits or stimulates circuit mechanism fosfoizoinosidei receptor mediation. It is divided into P1, and P2 adenosine (ATP, ADP and other nucleotide receptor). Found four subtypes of adenosine receptors, two of them (A1 and A2) shows the affinity for adenosine in the nanomolar range, while the other two provide for the low affinity receptors (A2b and A3), micromolecular order.

Adenosinieni receptors were observed in the retinas of various mammals, including cattle, pigs, monkeys, rats, rabbits, and humans. Therefore compounds that treats adenosine have been suggested as potential therapeutic agents in the treatment of optic nerve and retinal.

And other receptors adenosine antagonists are required as pharmacological tools and are considered



of great interest in different stages of disease and different conditions.

The subject of the invention shows that a method for the treatment of diseases associated with the A2b adenosine receptorin which each treatment is required to contain a treatment to be administered to the subject before the compound of structure I, to thereby treat the disease associated with the A2b receptor adeniozin , especially asthma, urticaria, arthritis sclerodermice, myocardial infarction, diabetic retinopathy, proliferative tumors, etc.

## V. CONCLUSIONS

The interest towards chemistry of pyrimidine compounds is related to the presence of natural biological products, such as nucleic acids, some vitamins and coenzymes, fundamental components of living cells.

A large number of synthetic pyrimidine compounds are used as medicine and agriculture and pesticides. The pyrimidine compounds are known antibacterial (sulfamethazine, Sulphamerazine), antimicrobial (bucolome), antimalarials (pyrimethamine), antiviral (madu, floxuridine), antihypertensives (minoxidil), antihistamines (tonzilamina), anticancer (fluorouracil, diazouracilul, uracil mustard ) special sedative barbiturate type, natural antibiotics (bacimetrim) etc.. We also note the fused pyrimidine compounds that have found use in many areas.

**This paper aims to find new applications of pyrimidine compounds in the treatment of cancerous tumors.**

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