Reviews

Synthesis and properties of fluorinated uracils as promising drugs for medicine*

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5-Fluorouracil is a well-known and widely used drug in medical practice for the treatment of cancer. However, there is no analytical review in the literature on the synthesis of 5-fluorouracil and its prodrugs, the properties of these compounds and the factors affecting their metabolism. In the present mini review, we made an attempt to summarize and analyze available material on these issues.

Key words: 5-fluorouracil, halogenation, halophilic reaction.

A large number of works are devoted to the synthesis and biological activity of pyrimidine derivatives, as well as their application in medicine and agriculture.[1—7] In the present review, we use the medical chemistry approach in an attempt to summarize the material on the synthesis and properties of fluorinated uracils and the development of drugs based on them for the treatment of oncological diseases.

The atomic radii of fluorine and hydrogen are close, however, the properties of these atoms are very different, therefore, fluorinated compounds often act as antimetabolites with respect to the corresponding non-halogenated compounds, including natural ones.[3,8—10]

5-Fluorouracil (**1**, 5-FU) was first synthesized in 1957[11] and later was found to possess antitumor activity.[2] In addition to 5-FU, the following compounds are efficient carcinostatic drugs: 5-fluoro-2′-deoxyuridine (**2a**, floxuridine),[12—14] 5-fluoro-5′-deoxyuridine (**2b**, doxifluridine),[15] 5′-deoxy-5-fluoro-*N*-[(pentyloxy)carbonyl]cytidine (**3**, capecitabine),[16] and 1-(2-tetrahydrofuryl)-5-fluorouracil (**4**, tegafur, ftorafur).[17] The following compounds are described as potential anticancer drugs: 1-(2′-oxopropyl)-5-fluorouracil,[18] which is a prodrug of 5-FU, and peptide-nucleic acid oligomers containing a 5-FU residue,[19] which are capable of binding to complementary DNA sequences and thus inhibiting key steps in gene expression in tumor cells.

It was found that the activity of 5-FU **1** and floxuridine **2a** largely depends on the method of their administration (intravenous injection and intravenous infusion), which, apparently, is explained by their interaction with the enzyme systems regulating their metabolism.[12] 5-Fluorouracil has a high toxicity; therefore, researchers are faced with the problem of developing 5-FU-based prodrugs, which could penetrate unchanged into the target cells and

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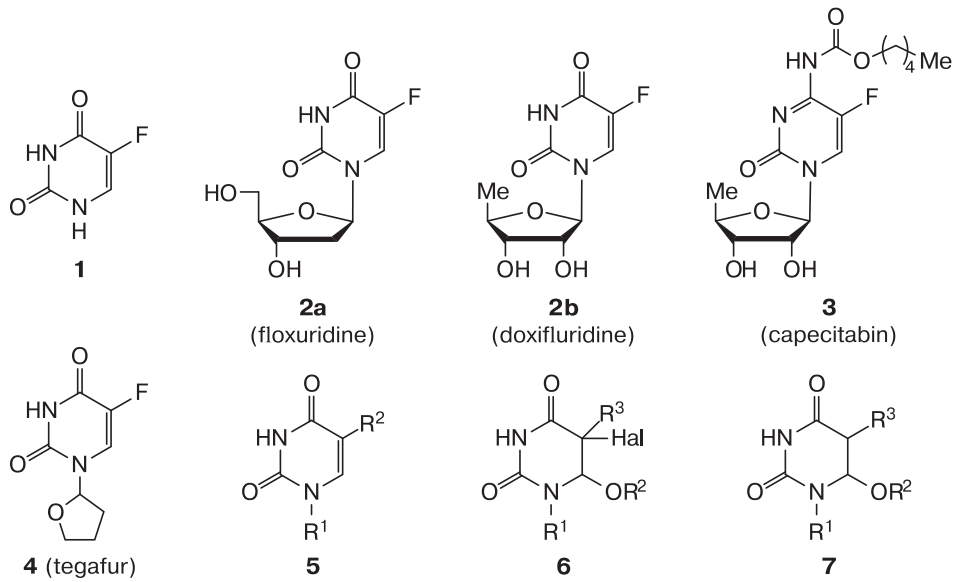


5: R^1 = H, 2′-deoxyribosyl; R^2 = H, Me
6: R^1 = H, 2′-deoxyribosyl; R^2 = Alk, Ac; R^3 = H, Me; Hal = Br, Cl, F
7: R^1 = H, 2′-deoxyribosyl; R^2 = Alk, Ac; R^3 = H, F, Me

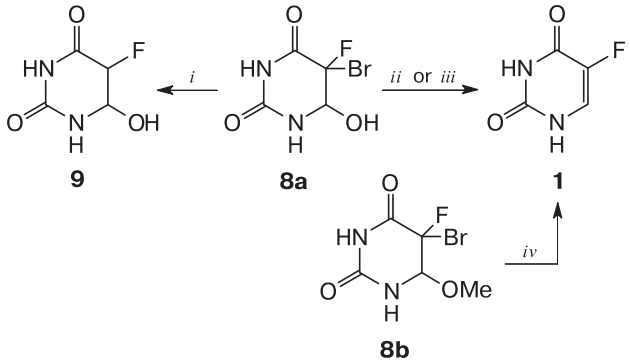
then metabolize into pharmacologically active compounds. One of the directions for the development of 5-FU prodrugs is the preparation of 5-fluoro-5,6-dihydropyrimidine derivatives.[12]

Pyrimidines **1** and **5**, as well as their *N*(1)-2′-deoxyribosyl derivatives react with hypohalites (ROBr or ROCl, R = Alk, Ac) to form 5-halogen derivatives **6**, some of which demonstrated antimicrobial and antileukemic activity. The introduced halogen atom can be removed either by catalytic hydrogenation or by treatment with hydrosulfides and some thiols (cysteine, glutathione) to give dihydro derivatives **7**, which spontaneously eliminate R^2OH to be converted into compounds **1** or **5**. Note that the possibility of restoration of the 5,6-double bond in dihydro-substituted uracils is very important in the development of prodrugs.[12]

There is evidence of a correlation between the ability of a prodrug to regenerate a double bond *in vitro* with the formation of 5-FU **1** or floxuridine **2a** and an antileukemic effect. Usually 5-FU prodrugs are less active than 5-FU itself **1**.[12] Dehalogenation and elimination processes can proceed *in vivo* due to the ubiquitous presence of glutathione in living organisms.[20]

Reductive debromination of 5-bromo-5-fluoro-6-hydroxy-5,6-dihydrouracil (**8a**) over Pd-catalyst at pH 3—7 gives 5-fluoro-6-hydroxy-5,6-dihydrouracil (**9**), while reflux of methyl ether **8b** in hydrobromic acid results in 5-FU **1** (90%)[12] (Scheme 1). Later, debromination of uracil derivatives was studied in more detail.[21,22] It was shown that 5-FU **1** can be obtained in high yield by heating compound **8a** in 50% H_2SO_4 at 80 °C.[22] Compound **1** was also formed by reflux of bromofluoro derivative **8a** in Ac_2O for 5 h, but in a lower yield.[23]

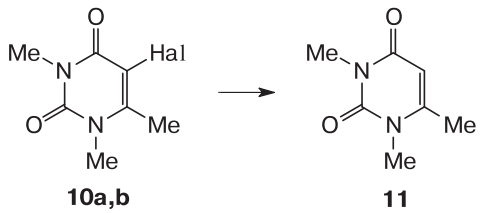
Scheme 1



Reagents, conditions, and yields: *i*. H_2, 10% Pd/C, AcONa (pH 3—7), H_2O, 1 h, 37%; *ii*. 50% H_2SO_4, 80 °C, 7 h, 93%; *iii*. Ac_2O, 80 °C, 5 h, 40%; *iv*. 36% HBr, reflux, 0.4 h, 90%.

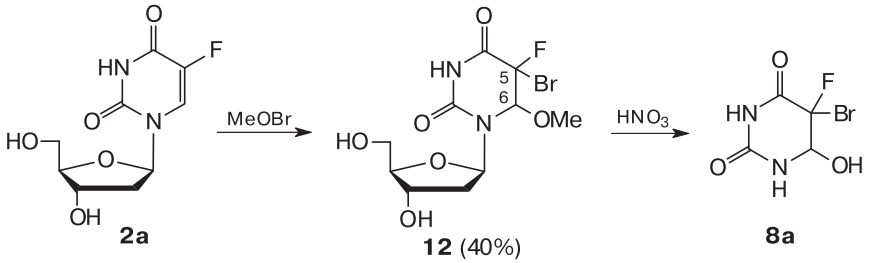
1,3,6-Trimethyluracil (**11**) (Scheme 2) can be obtained from 5-bromo- (**10a**) and 5-iodo-1,3,6-trimethyluracils (**10b**) by heating in 50% H_2SO_4 at 80 °C[21] or in 5% H_2SO_4 in the presence of excess of KI at 80 °C.[24]

Scheme 2

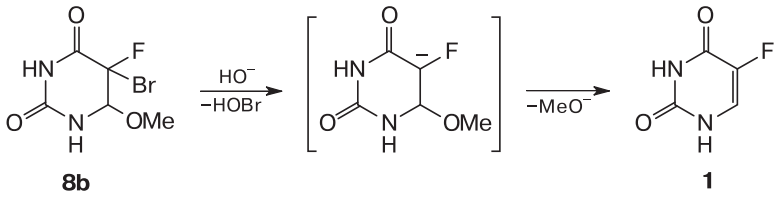


10: R = Br (**a**), I (**b**)

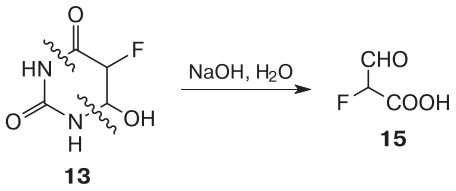
Scheme 3



Scheme 4



Scheme 5



Addition of methyl hypobromite MeOBr to floxuridine **2a** (Scheme 3) and its *O*,*O*-diacetates leads to a mixture of two optically active stereoisomers *dl*-**12**, which were separated.[12] Treatment of compounds *d*-**12** and *l*-**12** with fuming nitric acid gave two optically active aglycons *d*-**8a** and *l*-**8a**, respectively, but the absolute configurations of chiral centers at C(5) and C(6) were not established.

In contrast to methyl hypobromite, which undergoes addition to floxuridine **2a** at 0 °C or at room temperature in the reaction with equimolar amounts of reagents, methyl hypochlorite reacts with **2a** under similar conditions only being in a large excess and in an acidic medium.[12]

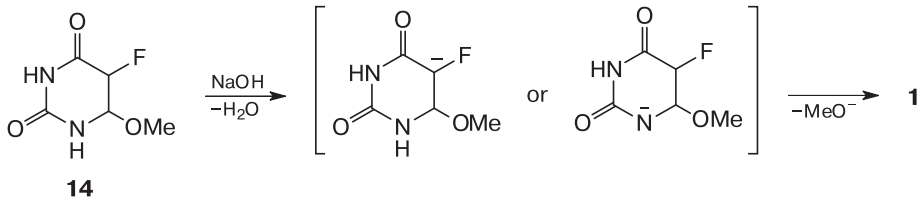
Treatment of 5-bromo-5-fluoro-6-methoxy-5,6-dihydrouracil (**8b**) with 1 *M* NaOH for 20 h gives 5-FU **1**. It is possible that this transformation proceeds as a halophilic reaction (Scheme 4).[12]

The products of addition of water (compound **13**, Scheme 5) and methanol (compound **14**, Scheme 6) to 5-FU are unstable in aqueous solutions at any pH values and transform into 5-FU (Scheme 5). Under alkaline conditions, compounde **13** undergoes deeper destruction with the formation of 2-fluoro-3-oxopropionic acid (**15**), probably, as a result of the amide bond hydrolysis and the decomposition of α-carbinolamine to aldehyde (see Scheme 5).[25]

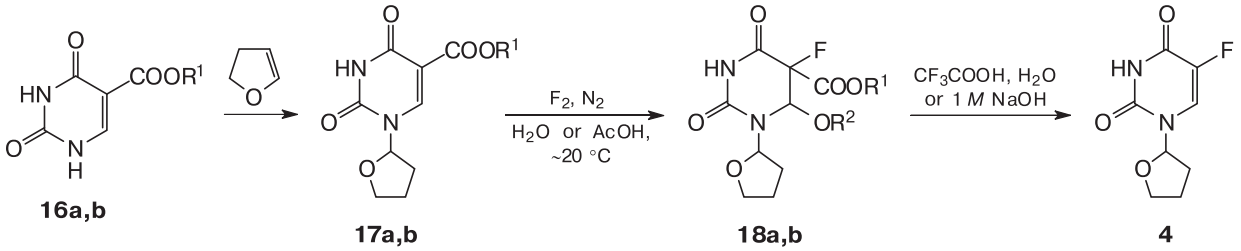
In contrast to 5-hydroxy derivative **13**, compound **14** under alkaline conditions undergoes quantitative conversion to 5-FU **1** without deeper destruction.[12] Probably, this transformation follows the mechanism shown in Scheme 6.

Synthesis of tegafur **4**, which turned out to be an efficient prodrug of 5-FU, was first described in the work.[26] The key stages of the synthesis (Scheme 7) are the heating of compounds **16a,b** with dihydrofuran in pyridine at 155 °C to generate intermediate products **17a,b** and further

Scheme 6



Scheme 7

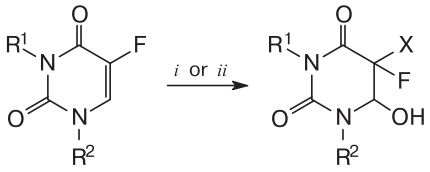


16, 17: R^1 = Me (**a**), Et (**b**)
18: R^1 = Me, R^2 = H (**a**), R^1 = Et, R^2 = Ac (**b**)

transformation of the latter to fluorinated derivatives **18a,b** (Scheme 7) Hydrolysis of compound **18a** in aqueous CF_3COOH for 46 h gives the target compound **4** in 84% yield.[27] Hydrolysis of derivative **18b** with 1 *M* aqueous NaOH for 1 h at room temperature also results in product **4** in 63% yield.[27]

A scheme for the synthesis of 5-substituted fluorouracils was proposed, which uses 5-FU **1** and its derivatives **19** and **20** as substrates. Oxidative halogenation of 5-FU **1** and compounds **19** and **20** with the system KHal—H_2O_2 in 20% aqueous H_2SO_4 gives the corresponding 5-chloro- and 5-bromo-5-fluoro-6-hydroxy-5,6-dihydrouracils (X = Cl, Br) in high yields (Scheme 8). 5-Fluoro-6-hydroxy-5-nitro-5,6-dihydrouracils (X = NO_2) were synthesized by nitration of the starting substrates **1**, **19**, and **20** with a mixture of nitric and sulfuric acids (see Scheme 8).[22,28,29]

Scheme 8



$R^1 = R^2 = H$ (**1**); $R^1 = R^2 = Me$ (**19**); $R^1 = H$, $R^2 = CH_2COOH$ (**20**)

Reagents and conditions: *i*. KCl or KBr, 33% H_2O_2, 20% H_2SO_4, ~20 °C, 5 h; *ii*. HNO_3, H_2SO_4, 0—10 °C, 5 h.

Pharmacokinetic studies show[30] that the main metabolite of the known 5-fluorouracil carcinostatics, which belong to the group of antimetabolites, is 5-FU.

It is known that uracil widely spread in living systems[31—33] can undergo oxidative chlorination with chlorine anions, which are present in significant amounts in the human circulatory system, and active oxygen, which is generated in sufficient concentration at chronic inflammatory processes in various organs. The formed 5-chlorouracil, due to the similarity of its structure to the structure of thymine (the steric volumes of a chlorine atom and a Me group are close), can replace the latter in the biosynthesis of nucleic acids, which can lead to oncological diseases.[31—33] 6-Methyluracil, which, unlike uracil, is not a biogenic amine, undergoes oxidative chlorination 2500 times more readily than uracil,[34] therefore, its presence in significant amounts in areas of chronic inflammation will prevent uracil chlorination, inhibiting the above undesirable processes of uracil conversion, and, therefore, will reduce the risk of cancer. Our experiment on the oxidative chlorination of an equimolar mixture of uracil and 6-methyluracil led to the complete chlorination of the latter to 5-chloro-6-methyluracil, with 5-chlorouracil being absent in the reaction mixture.[35]

As indicated above, 5-FU readily undergoes oxidative chlorination to form 5-chloro-5-fluoro-6-hydroxy-5,6-dihydrouracil in high yield.[22] In our opinion, used as a carcinostatic agent 5-FU in the human body can easily undergo chlorination to be converted to an inactive metabolite.

It is interesting to note that, in contrast to the oxidative chlorination of a mixture of 6-methyluracil and uracil, in which only 6-methyluracil is completely chlorinated,[35] the chlorination of an equimolar mixture of 6-methyluracil and 5-halouracils (Hal = F, Cl, Br) proceeds much less readily.[36] Most of the starting compounds were recovered from the reaction mixture unchanged and only 5-chloro-6-methyluracil was obtained in small amounts (~25% from 5-FU **1**, ~40% from 5-chlorouracil, and ~10% from 5-bromouracil).[36] The observed result is practically independent of the molar ratio substrate : KCl : H_2O_2 (1 : 1 : 2). Taking into account that the individual 5-halouracils (F, Cl, Br) undergo chlorination readily and in good yields,[22,37] it can be assumed that oxidative halogenation is inhibited in mixtures of 5-halogenated uracils and 6-methyluracil, with the main accent on 5-halogenated uracils. Perhaps this is due to the formation of a complex between 6-methyluracil and the indicated

5-halouracils, which we observed earlier for some uracil derivatives.[38]

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No human or animal subjects were used in this research.

The authors declare no competing interests.

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