СЕКЦІЯ І
ХІМІЧНА НАУКА: СУЧАСНІСТЬ, ДОСЯГНЕННЯ ТА ПЕРСПЕКТИВИ

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NOVEL FLUORINATED IMIDAZO[1,2-*A*]AZINES AS POTENTIAL ANTICANCER COMPOUNDS

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Research Overview:

Imidazopyridine skeleton is an important part of various biologically active compounds in plants, pharmaceuticals and human enzymes. It forms the class of compounds, similar to purine and benzimidazole. Being organic heterocyclic compounds, they are used for synthesis of different chemical-biological tools and therapeutic agents *(1)*.

Imidazo[1,2-*a*]pyridines is a class of heterocyclic compounds that has recently received an increased attention. Little changes in the chemical structure of these compounds are responsible for the drastic variations in their biological effects. Imidazopyridines have broad spectrum biological activities such as antimicrobial and antiviral (2), antiprotozoal (3), and anticarcinogenic (4) activities. On the other hand, a considerable number of these compounds were reported as mutagens and carcinogens (6). Some of imidazopyridines were shown to strongly bind DNA minor grooves(6). They also act as orally active nonpeptide bradykinin B2 receptor antagonists, besides being prevalent as the core structure of several drug formulations such as alpidem, zolpidem, olprinone, zolimidine, and minodronic acid, which are available currently on the market (7).

Organo-fluorine chemistry is a unique branch of organic chemistry, as the fluorine incorporation in the organic molecules exhibits bizarre behaviors; hence, several applications are witnessed in medicines, electronics, agrochemicals, and catalysis. Since fluorine-containing compounds significantly affect pharmaceutical growth, they make up more than 50 percent of the best-selling drug molecules approved by the US Food and Drug Administration (FDA). The fluorine's electronegativity, size, electrostatic interactions, and lipophilicity are widely recognized factors that significantly impact the chemical reactivity, physico-chemical behavior, and biological activity. According to a recent study by Hagmann, about 15–20 percent of all licensed drugs introduced annually on the market contain fluorine/fluorine-containing functional groups (8)

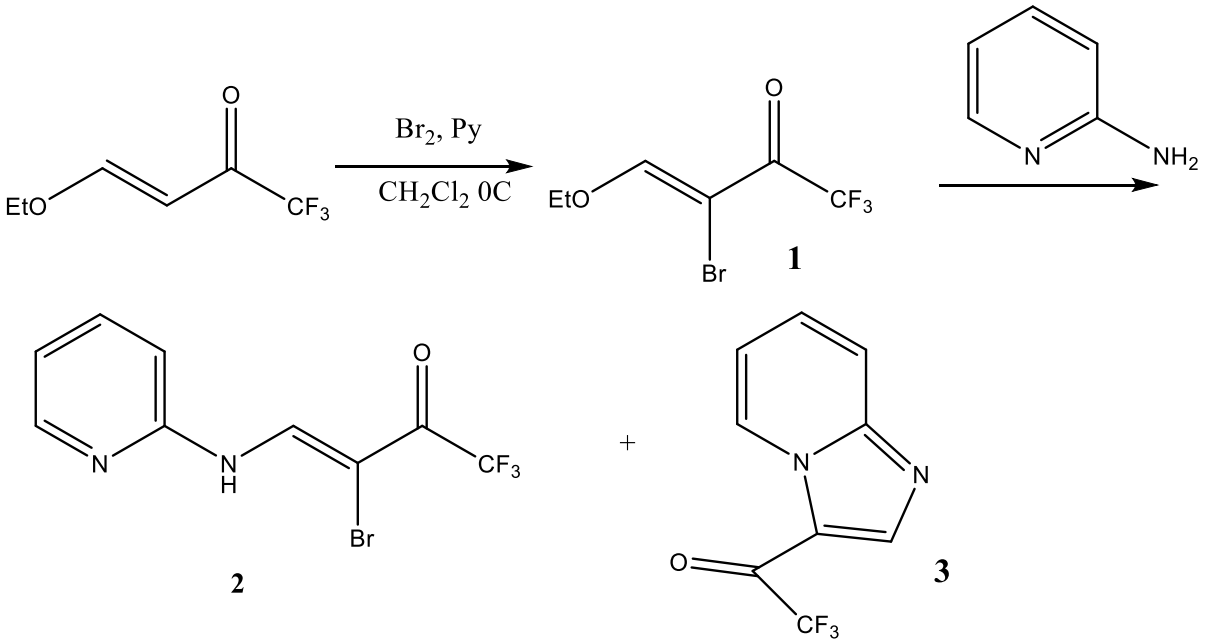
Previously, we have found that trifluoromethyl-3-haloenone **1** reacts with 2-aminopyridine and gives mixture of expected enaminone **2** and 3-trifluoroacetyl imidazo[1,2-*a*]pyridine **3** Pic **1**. The product ratio depends on the nature of 3-halogen atom and the solvent. In polar solvents main product is 3-trifluoroacetyl imidazo[1,2-*a*]pyridine **3**. Reaction in water and low polar solvents gives enaminone **2** as a major product (9).

Table 1.

The ratio of enamine (**2**) and 3-trifluoroacetylimidazo[1,2-a]pyridine (**3**) in different solvents.

Solvent / Enone	$CHCl_3$	MeCN	DMF	DMSO	H_2O
1	25 / 75	12 / 88	8 / 92	7 / 93	<99 / >1

Increasing the polarity of the solvent, in the case of the interaction of bromoenone (**1**) with 2-aminopyridine, leads to an increase in the yield of the cyclic product. Carrying out the reaction in DMF and DMSO allows to increase the selectivity of the reaction in the direction of the imidazopyridine (**3)** formation and obtain it with a yield of more than 90%.

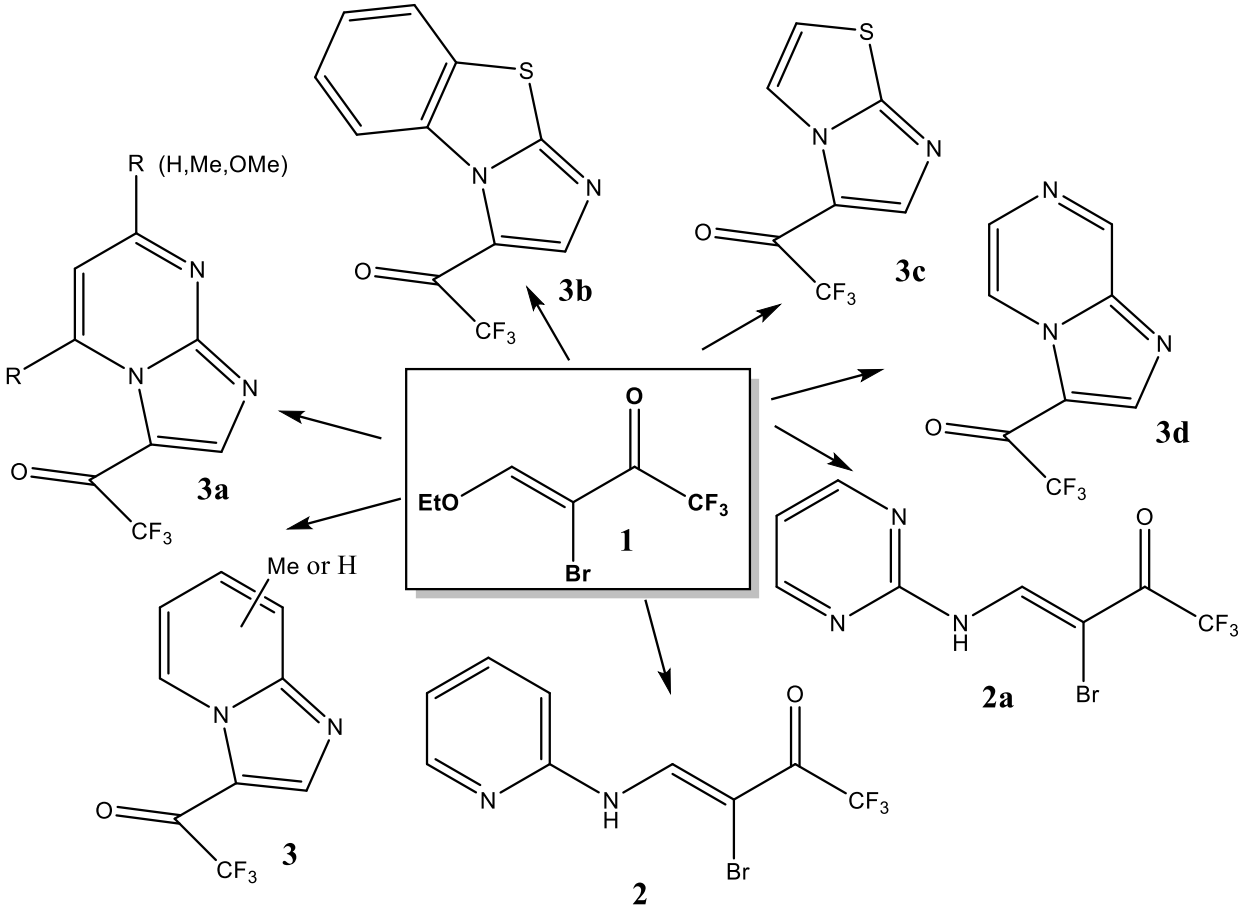


Pic 1. Reaction of trifluoromethyl-3-bromoenone **1** with 2-aminopyridine.

Research Goal:

The goal of this research project was synthesis, separation and purification of new trifluoromethyl heterocycles **3** and explore their biological application in cancer cells.

Reaction of α-bromoenone **1** with corresponding 2-aminopyridines and 2-aminotiazols where carried out in DMA at 80 ˚C for 4-5 hrs. Imidazo[*1,2a*]azines **3,3b,3c** were obtained with high yield and high purity. Reaction of α-bromoenone **1** with corresponding 2-aminopyrimidines requires longer heating time (8-10hrs) and gives corresponding imidazo[*1,2a*]pyrimidenes with lower yield (50-60%) and purity. All fluorinated imidazopyrimidines and imidazoazoles were purified by column chromatography and recrystallization. Anticancer activity tests are in progress now.



Pic **2.** Synthesis of trifluoromethyl enaminones **2** and 3-trifluoroacetyl imidazo[1,2-*a*]azines **3.**

Experimental part:

(E)-3-Bromo-4-(2-pyridinilamino)-1,1,1-trifluoro-3-buten-2-one (**2**).

To emulsion of 1.6 mmol 3-Bromo-4-ethoxy-1,1,1-trifluoro-3-ен-2-one **1** in 20 ml of water a solution of 1.6 mmol of 2-aminopyridine in 5 ml of H_2O was added while stirring at 0 ˚C. Reaction mixture was stirred at r. t. for 2 hours. The precipitate was filtered off, washed with water, dried and purified by recrystallization from hexane.

Yield 70%, melting point 128-129˚C.

IR spectrum (CCl_4), ν, cm-1: 1698.4 (C=O), 1625.6 (C=C).

^{1}H NMR 300 MHz, ($CDCl_3$), δ, ppm.: 9.13 (d, 1H, J_{HH} = 12.2 Hz), 8.38 (d, 1H, J_{HH} = 4.7 Hz), 7.80 (br.s, 1H), 7.72 (m, 1H), 7.11 (m, 1H), 6.95 (d, 1H, J_{HH} = 8.2 Hz).

^{19}F NMR ($CDCl_3$), δ, м.ч.: -68.6 (c, 3F).

Found, %: C 36.72; H 2.01; N 9.56. $C_9H_6F_3BrN_2O$. Calculated, %: C 36.64; H 2.05; N 9.49.

1-Imidazo[1,2-a]pyridin-3-yl-2,2,2-trifluoro-1-ethanone (3).

To solution of 8 mmol 2-aminopyridine in 2 ml DMF a solution of 4 mmol of 3-bromo-4-ethoxy-1,1,1-trifluorobut-3-en-2-one (**1**) in 2 мл DMF was added at r. t. Reaction mixture was stirred 30 min at r. t., then heated 4 hrs. at 80˚C. Reaction was monitored by TLC. R. m. was cooled

to r. t. and 100 ml of water was added. The precipitate was filtered off, washed with water, dried and recrystallized from hexane.

Yield 85 %, M. p. 133-134˚C.

IR spectrum (CCl_4), ν, $см^{-1}$: 1666.6 (C=O).

^{1}H NMR ,300 MHz, ($CDCl_3$), δ, ppm.: 9.63 (d, 1H, J_{HH} = 6.8 Hz), 8.60 (br.s, 1H), 7.92 (d, 1H, J_{HH} = 8.9 Hz), 7.71 (m, 1H), 7.29 (m, 1H).

^{19}F NMR ($CDCl_3$), δ, ppm.: –72.8 (s, 3F).

Found, %: C 50.57; H 2.50; N 13.05. $C_9H_5F_3N_2O$. Calculated, %: C 50.48; H 2.35; N 13.08.

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