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## “GREENING” OF AMIZONE SYNTHESIS WHEN MANUFACTURING

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*The principles of “green chemistry” have been introduced into the procedure of manufacturing synthesis of Amizone. All starting raw materials as solvents have been assessed in accordance with their human toxicity, danger in production, as well as the possible impact on the environment and cost. According to the results of the analysis isonicotinic acid has been chosen as a starting substance for the synthesis at the first step, and the synthetic procedure without solvents has been proposed. The replacement of acetone with isopropanol has been proposed for the alkylation step according to the data concerning toxicity and manufacturing safety. Aqueous ethanol has been chosen as a solvent for recrystallisation. To reduce the impact on the environment the process of conversion of the benzylamine excess into less toxic and flammable hydrochloride has been recommended.*

The quality of a pharmaceutical drug is affected by many factors. However, the main of them is the quality of its components, and above all – the quality of the active pharmaceutical ingredient/ingredients (APIs). For a long period manufacturers have had to choose for themselves the manufacturer of API with reliable results on the quality of the API. Today, the main suppliers of pharmaceutical substances are India and China. In some cases, they are the monopolists for production of certain substances.

Unfortunately, only some plants commercially produce APIs in Ukraine. They are, for example, “Farmak” JST, “InterChem” JLC PJSC, SIC “Borshchahivskiy CPP”. As a rule, it is the synthesis of the original substances, which are manufacturers’ “brands”, for example “Thio-triazoline”, “Amizone” and others. One of the problems associated with reduction of the API synthesis by industrial enterprises in developed countries is a difficult environmental situation and high requirements to the producers to waste and their control [7, 10, 11].

One of the ways to reduce the impact on the atmosphere during the process of API industrial synthesis is widespread adoption of the principles of “green chemistry” by the leading pharmaceutical companies in the world [5, 8, 9]. These principles can not only reduce the risk of the environmental pollution, but decrease the effect of hazardous reagents on the health of employees engaged in the API manufacture.

The aim of our work was to implement the principles of “green chemistry” into the industrial synthesis of Amizone by “Farmak” JST.

### Materials and Methods

The synthesis of Amizone was carried out according to the general principles of organic synthesis. When preparing to the re-registration of Amizone substance associated with the organization of a new production site for the API synthesis in Shostka we carried out the pre-

liminary experimental studies to improve the methods of synthesis allowing to increase the yield of the end product and decrease the amounts of related impurities [2, 3].

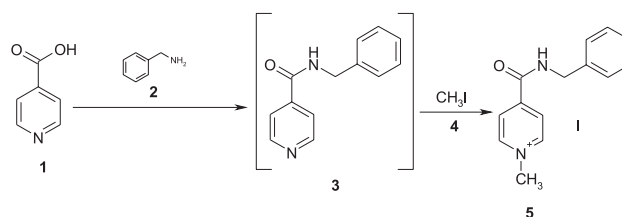
For evaluation the modern international classification – Globally Harmonized System of Classification and Labelling of Chemicals (GHS) [6] applied all over the world when working with chemicals was used. The relative cost of reagents was given according to the data of the Sigma-Aldrich company.

### Results and Discussion

As a result of our previous research [2, 3] we recommend to carry out the synthesis according to Scheme.

When introducing this Scheme into the industrial synthesis we paid attention to the maximum “greening” of the procedure developed. Due to the main chemical rules we can use different starting substances such as isonicotinic acid, its esters and chloranhydride and different solvents during both stages of synthesis. The principles of “green chemistry” include 12 basic ones [4]. We analyzed these principles and tried to assess the compliance of the new methodology, as well as offer additional improvements to meet these requirements.

Firstly, toxicity and properties of possible reagents and solvents (Tab. 1) were analysed. While developing the synthetic technology [2, 3] the choice of starting materials, mainly focusing on their cost and reaction yields, was evaluated. Due to the combination of “cost-yield-purity” parameters the advantage was given to the synthesis from isonicotinic acid. When studying the “greening” synthesis,



Scheme

Table 1

## Information about reagents and solvents

Substance, CAS number	Toxicity (GHS Classification)	Hazard statement(s)	Cost/100 g
Isonicotinic acid 55-22-1	Acute toxicity, Oral (4) Skin irritation (2)	H302: Harmful if swallowed. H315: Causes the skin irritation.	36
Ethyl isonicotinate 1570-45-2	GHS – None found Xi – Irritant	H315: Causes the skin irritation. H319: Causes a serious eye irritation. H335: May cause the respiratory irritation.	63.10
Methyl isonicotinate	Flammable liquids (4) Skin irritation (2) Eye irritation (2A) Specific target organ toxicity – single exposure (3), Respiratory system	H315: Causes the skin irritation. H319: Causes a serious eye irritation. H335: May cause the respiratory irritation.	78.10
Isonicotinyl chloride	GHS – None found	No information	81.90*
Isonicotinyl chloride hydrochloride 39178-35-3	Skin corrosion (1B) Serious eye damage (1)	H314: Causes severe skin burns and eye damage.	381
Benzylamine 100-46-9 221-943-6	Flammable liquids (3) Skin corrosion/irritation (1) Serious eye damage/eye irritation (1) Health hazards not otherwise classified (corrosion) (1)	H314: Causes severe skin burns and eye damage. H318: Causes a serious eye damage. H226: Flammable liquid and vapour.	30.70
Benzylamine hydrochloride 3287-99-8	Acute toxicity, Oral (4) Skin irritation (2) Serious eye damage/eye irritation (2) Specific target organ systemic toxicity (3)	H302: Harmful if swallowed. H315: Causes the skin irritation. H318: Causes a serious eye damage. H335: May cause the respiratory irritation.	95.10
Iodomethane 74-88-4	Acute toxicity (Oral) (3) Acute toxicity (Inhalation: Vapours) (3) Skin corrosion/irritation (2) Serious eye damage/eye irritation (1) Specific target organ toxicity – Single exposure (3) (drowsiness and dizziness, respiratory irritation) Specific target organ toxicity – Repeated exposure (2) (thyroid gland, respiratory)	H301 + H331: Toxic if swallowed or if inhaled. H312: Harmful in contact with the skin. H315: Causes the skin irritation. H319: Causes a serious eye irritation. H335: May cause the respiratory irritation. H351: Suspected of causing cancer. H410: Very toxic to aquatic life with long lasting effects.	88
Acetone 67-64-1	Flammable liquids (2) Skin irritation (3) Eye irritation (2A) Specific target organ toxicity – single exposure (3)	H225: Highly flammable liquid and vapour. H316: Causes a mild skin irritation. H319: Causes a serious eye irritation. H336: May cause drowsiness or dizziness.	
Propanol-2 67-63-0	Flammable liquids (2) Eye irritation (2) Specific target organ toxicity – single exposure (3)	H225: Highly flammable liquid and vapour. H319: Causes a serious eye irritation. H336: May cause drowsiness or dizziness.	
Ethanol 64-17-5	Flammable liquids (2) Skin irritation (2) Eye irritation (2B) Specific target organ toxicity – single exposure (3) Acute aquatic toxicity (2)	H225: Highly flammable liquid and vapour. H315 + H320: Causes the skin and eye irritation. H335: May cause the respiratory irritation. H401: Toxic to aquatic life.	

\* For 25 mg.

Table 2

## The principles of “green chemistry” in the synthesis of Amizone

The “green chemistry” principles [4]	The synthetic steps and parameters controlled	Result and decision
It is better to prevent waste than to treat or clean up waste after it is formed.	Development of an optimal synthetic procedure.	Pharmacopoeial purity after recrystallization.
Synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product.	The total yield after all synthetic stages and recrystallization.	Intermediate yield – 92% End product yield – 87% After recrystallisation – 87%
Wherever practicable, synthetic methodologies should be designed to use and generate substances that possess little or no toxicity to human health and the environment.	The choice of the starting raw materials and solvents.	Safety class of the reagent is taken into account.
Chemical products should be designed to preserve efficacy of function while reducing toxicity.	The product is not novel.	–
The use of auxiliary substances (e.g. solvents, separation agents, etc.) should be made unnecessary wherever possible and innocuous when used.	Decrease in use of auxiliary substances.	Development of the synthetic procedure without a solvent.
Energy requirements should be recognized for their environmental and economic impacts and should be minimized. Synthetic methods should be conducted at ambient temperature and pressure.	Development of the procedure at normal pressure and the minimal temperature.	Isonicotinic acid as a starting raw material is more economical; the synthesis without solvents at normal pressure (high temperature).
A raw material or feedstock should be renewable rather than depleting wherever technically and economically practicable.		Yields are very high. There is not need in reagents recycling. Acidifying of the uterine solution for benzylamine hydrochloride formation.
Reduce derivatives – Unnecessary derivatization (blocking group, protection/deprotection, temporary modification) should be avoided whenever possible.		An intermediate is not isolated, blocking groups are not used.
Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.	Studying the possibility and expediency of the use of catalysts in the synthesis.	The synthesis with high yields without any catalysts (the cost is reasonable).
Chemical products should be designed so that at the end of their function they do not persist in the environment and break down into innocuous degradation products.	Development of approaches to waste management.	Conversion of the benzylamine residue into less toxic hydrochloride.
Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.	Development of in-process monitoring procedures.	Chromatographic control of the benzylamine residue when manufacturing [1].
Substances and the form of the substance used in a chemical process should be chosen to minimize potential for chemical accidents, including releases, explosions, and fires.	Revision of the starting raw materials and the solvents according to their fire and explosion properties.	Replacing of isonicotinoyl chloride with the acid. Avoiding the use of acetone in the synthesis during amidation – carrying out the synthesis without solvents; replacing ethanol in recrystallisation processes by aqueous ethanol.

besides these factors, the attention was paid to the human toxicity and danger in production, as well as the possible impact on the environment.

Analyzing the data giving in Tab. 1 concerning toxicity of reagents and their cost it can be concluded that the best starting material is isonicotinic acid, and chloranhydride is unacceptable in manufacturing even when it is introduced into the reaction as a hydrochloride. Ethyl and methyl esters of isonicotinic acid are slightly more toxic; moreover, they are classified as potentially flammable liquids unlike isonicotinic acid.

The same principles were taken into account when analysing the choice of solvents for both synthesis and recrystallisation. During our previous investigation it was found that the reaction of amination between isonicotinic acid and benzylamine could be carried out without any solvents. Previously the conditions for the best yields and optimal purity were discussed. Such procedure is consistent with the principles of “green chemistry”. The next step of the synthesis is alkylation of the key intermediate – isonicotinic acid benzylamide with methyl iodide. There is no choice of reagents because of the structure

of the end product. The replacement of acetone with isopropanol is reasonable at this stage according to the data of toxicity and manufacturing safety (Tab. 1). Due to the "green chemistry" principles water is an optimal reagent for any process. When choosing a solvent for recrystallisation of Amizone in its manufacturing, unfortunately, the replacement of aqueous ethanol with water is not reasonable because it reduces purity and yields to the limit of pharmacopoeial requirements on the content of impurities [3].

In addition to achieving high yield of the synthesis development of methods for unreacted substances recyc-

ling is important to reduce the impact on the environment. Among reagents used for the synthesis of Amizone it is necessary to convert benzylamine into less toxic and flammable hydrochloride.

The summary of the steps for "greening" the synthesis of Amizone is given in Tab. 2.

#### CONCLUSIONS

The procedure for "green" manufacturing synthesis of Amizone has been developed. The use of the starting raw materials and solvents has been substantiated in accordance with their safety and toxicity, as well as recycling of residues of the reagents.

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#### «ОЗЕЛЕНЕННЯ» СИНТЕЗУ АМІЗОНУ В ПРОЦЕСІ ПРОМИСЛОВОГО ВИРОБНИЦТВА

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**Ключові слова:** амізон; промисловий синтез; «зелена хімія»

Принципи «зеленої хімії» впроваджені в процес промислового синтезу субстанції Амізон. Оцінювання всіх вихідних речовин та розчинників здійснювали у відповідності з їх токсичністю для людини, безпекою у виробництві, а також можливим впливом на навколишнє середовище та вартістю. За результатами аналізу для синтезу на першій стадії як вихідний реагент було обрано ізонікотинову кислоту та запропонована синтетична методика без використання розчинників. У відповідності з даними про токсичність для стадії алкілювання запропонована заміна ацетону ізопропанолом. Як розчинник для перекристалізації амізону-сирцю запропоновано водний етанол. Для зменшення впливу на навколишнє середовище рекомендовано перетворення надлишку бензиламіну на менш токсичний та займистий гідрохлорид.

#### «ОЗЕЛЕНЕНИЕ» СИНТЕЗА АМИЗОНА В ПРОЦЕССЕ ПРОМЫШЛЕННОГО ПРОИЗВОДСТВА

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**Ключевые слова:** амизон; промышленный синтез; «зеленая химия»

Принципы «зеленой химии» внедрены в процесс промышленного синтеза субстанции Амизон. Оценивание всех исходных веществ и растворителей осуществляли в соответствии с их токсичностью для человека, опасностью в производстве, а также возможным влиянием на окружающую среду и стоимостью. По результатам анализа для синтеза на первой стадии в качестве исходного реагента была выбрана изоникотиновая кислота и предложена синтетическая методика без использования растворителей. В соответствии с данными о токсичности и для стадии алкилирования предложена замена ацетона изопропанолом. В качестве растворителя для перекристаллизации амизона-сырца предложен водный этанол. Для снижения влияния на окружающую среду рекомендовано превращение избытка бензиламина в менее токсичный и воспламеняющийся гидрхлорид.