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DICHLOROACETIC ACID DERIVATIVES AS POTENTIAL ANTI-TUMOR AND ANTI-INFLAMMATORY AGENTS

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The aim. *This review aims to provide a comprehensive understanding of dichloroacetic acid derivatives. We aim to cover all aspects of these compounds, including their chemical properties, various synthesis methods, and their wide range of applications in medicinal chemistry. By exploring their diverse roles in drug development, we aim to highlight their importance and potential in shaping future pharmaceutical innovation.*
Materials and methods. *Bibliosemantic and analytical methods are used in the research.*
Results*. Our studies confirm the potential effectiveness of dichloroacetic acid and its derivatives in the treatment of cancer and other diseases. These compounds can induce the apoptosis process, which is the programmed cell death, and inhibit the cancer cells' growth. This is particularly effective when dichloroacetic acid and its derivatives are used in combination with other therapeutic methods, as indicated in the patents cited in our study. Dichloroacetic acid and its derivatives have also shown the ability to lower blood glucose and cholesterol levels. This indicates the possibility of their use for diabetes, hyperlipidemia, and lactic acidosis treatment. Diabetes, hyperlipidemia, and lactic acidosis are serious conditions that can lead to significant health problems. Therefore, the possibility of using dichloroacetic acid and its derivatives for the treatment of these conditions opens new perspectives in medical science.*
Conclusions*. Our findings point to the prospects of further research in the field of new therapy methods development and the use of dichloroacetic acid derivatives as potential drugs to improve the effectiveness of cancer and other diseases treatment. We believe that these compounds have great potential for further study and may play an important role in future medical innovation*
Keywords*: dichloroacetate, dichloroacetic acid, dichloroacetamide, hybrid molecules, antitumor activity, anti-inflammatory activity, cholesterol, tumors, apoptosis, chemotherapy*

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1. Introduction

Dichloroacetic acid (DCA) derivatives represent the organic compounds class that have attracted considerable attention in medicinal chemistry due to their diverse chemical properties and applications in drug design and development. These compounds are basic building blocks in the various pharmaceutical agents and biologically active molecules' synthesis. DCA derivatives synthesis and manipulation offer medicinal chemists a reliable toolkit for fine-tuning the potential drug candidates' pharmacokinetic and pharmacodynamic properties. This literature review aims to provide a comprehensive overview of DCA derivatives, including their chemical properties, synthesis methods, and key applications in medicinal chemistry.

DCA derivatives, characterized by the chloroacetic functional group presence (-$ClCH_2COOH$), represent a valuable class of compounds that have found applications in many research areas, including drug discovery, herbicides, and speciality chemicals. The chloroacetic fragment's unique electrophilic properties offer several possibilities for chemical transformations, enabling the introduction of various substituents and functional groups into organic molecules. These chemical properties make DCA derivatives ideal candidates for modification and optimization in drug development.

The DCA derivatives synthesis has witnessed considerable progress over the years, with various methods and strategies developed to access these compounds efficiently. Traditional methods such as acetic acid chlorination or chloroacetyl chloride esterification have been complemented by more innovative and sustainable approaches, including environmental chemistry principles and the use of catalysts. This review will examine the synthetic methodologies' evolution and their impact on the various DCA derivatives availability.

The dichloroacetic acid derivatives application in medicinal chemistry is extensive and covers a wide range of therapeutic areas. These compounds have been precursors for nonsteroidal anti-inflammatory drugs (NSAIDs), herbicides, antimicrobial agents, and prodrugs' synthesis. In addition, dichloroacetic acid derivatives play a key role in the targeted drug delivery systems development, as they facilitate site-specific drug release and enhance the pharmaceuticals' bioavailability.

In this review, we delve into the structural diversity of dichloroacetic acid derivatives, exploring how sub-

tle modifications to their chemical structure can lead to profound changes in the drugs' biological activity and efficacy. In addition, we will consider the role of dichloroacetic acid derivatives in the prodrug design, which allows controlling the release of active compounds in the body. Also, we will discuss environmental and safety issues related to these compounds' synthesis and use, emphasizing the importance of sustainable and environmentally friendly chemistry in the development of modern medicines.

The aim of the study was the literature data analysis on dichloroacetic acid derivatives synthesis and the biological activity evaluation.

2. Materials and methods

Bibliosemantic and analytical methods were used in the study. To conduct the literature review, we used scientometric databases such as PubMed, Scopus, and Web of Science. Additionally, we used resources such as Google Scholar and free-access libraries to ensure the comprehensiveness of our search.

We also used Espacenet, an international patent database, to search and analyze relevant patents related to dichloroacetic acid and its derivatives. Espacenet provides access to information on more than 100 million patent documents from around the world, allowing us to explore the latest and most important patents in the field.

The main keywords used for the search included «dichloroacetate», «dichloroacetic acid», «dichloroacetamide», «hybrid molecules», «antitumor activity», «anti-inflammatory activity», «tumours» and «chemotherapy». These keywords were used to identify relevant sources that were analyzed in our study. With the help of these methods, we were able to collect and analyze a large amount of information, which allowed us to draw valid conclusions.

3. Results and discussion

3. 1. Dichloroacetic acid chemical properties, synthesis and transformation

Y. P. Singh and R. A. Singh confirmed the existence of two different dichloroacetic acid tautomers (**1a** and **1b**) (Fig. 1) [1].

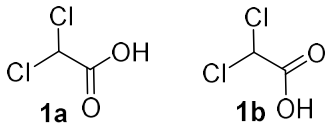

Fig. 1. Structure of DCA tautomers (**1a, b**)

The dichloroacetate tautomers' structure and relative energy were predicted by the Hartree-Fock method, and the infrared spectra of the two dominant ones were calculated using the density functional theory. A good agreement between the calculated and experimental harmonic oscillation frequencies is noted. Assuming Cs point symmetry, vibrational assignments for the observed frequencies were proposed. The spectra show distinct features originating from low-frequency vibrational modes caused by intermolecular motion. For DCA tautomer **1b**, the energy is minimal (Fig. 2). The dipole moment is large for DCA tautomer **1a**, and the polar surface area is slightly larger in the case of DCA tautomer **1b** (Fig. 2). The local ionization potential map and the lowest unoccupied molecular orbital map were compiled and analyzed. Linear regression data for both tautomers were also calculated, clearly demonstrating how DCA tautomer **1a** correlates more with experimental wavenumbers [1].

In Toxikologische Bewertungen from Berufsgenossenschaft Rohstoffe und Chemische Industrie (Germany), the dichloroacetyl chloride (**2**) hydrolysis is indicated to synthesize dichloroacetic acid (**3**) (Fig. 3) [2].

The work [3] describes the dichloroacetic acid **5** obtaining method by selective trichloroacetic acid (**4**) dichlorination (Fig. 4). According to the method, a fixed-bed catalytic reactor is used to convert trichloroacetic acid (**4**) into dichloroacetic acid (**5**) with a conversion degree of more than 99.5 % and a selectivity of more than 98 %, and the residue contains chloroacetic acid (**6**) and acetic acid (**7**) (Fig. 4). A catalyst based on a precious metal containing activated carbon was used; a trichloroacetic acid solution and hydrogen are preheated to the reaction temperature, they enter from the reactor top and come into contact with the catalyst, and the hydrodechlorination reaction takes place; hydrogen is constantly replenished during the reaction so that the hydrogen concentration in the reactor is maintained at the level of 10 % to 40 %; the formed liquid and gas phase products are removed from the reactor bottom, and the liquid phase products are distilled to obtain high purity dichloroacetic acid products after gas and liquid condensation and separation [3].

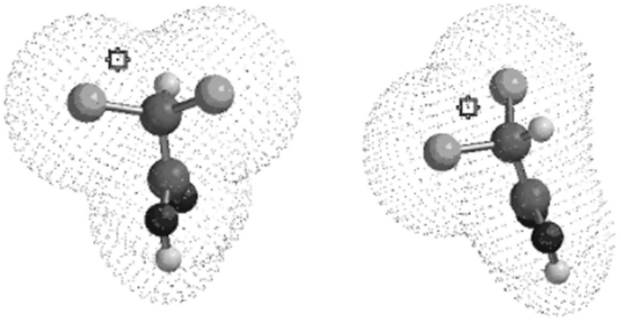

Fig. 2. DCA tautomers ionization potentials maps [1]

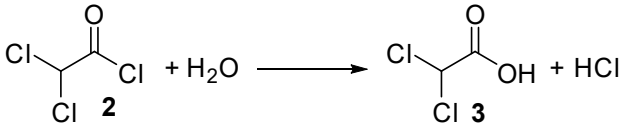

Fig. 3. Dichloroacetyl chloride (**2**) hydrolysis

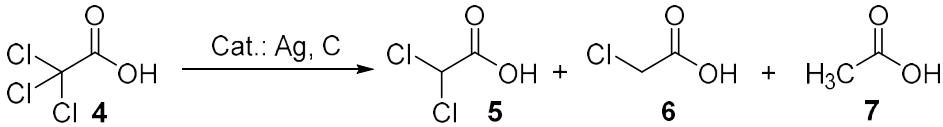

Fig. 4. Synthesis of dichloroacetic acid (**5**) by selective trichloroacetic (**4**) acid dechlorination

Alvin S. Wheeler and Samuel C. Smith investigated the direct dichloroacetic acid derivatives conversion into trichloroacetic acid derivatives, during which aniline, *o*- and *p*-toluidine, α-naphthylamine and *m*-nitroaniline trichloroacetates were obtained from dichloroacetic acid, and in the case of *o*-toluidine trichloroacetate – a complete analysis of the obtained compound was conducted. Trichloroacetates obtained from trichloroacetic acid served as compounds for comparison (Fig. 5) [4].

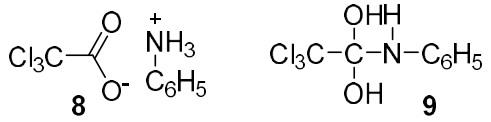

Fig. 5. Structure of obtained trichloroacetic acid derivatives (**8**, **9**)

In structure **8**, there is a pentavalent nitrogen atom and, therefore, an ammonium salt. Structure **9** contains a trivalent nitrogen atom and a chloral hydrate-type compound in which 2 hydroxyl groups are attached to one carbon atom. Such compound stability is due to the strong negative environment of three chlorine atoms. The decomposition products that were obtained did not give a clear understanding of how one is better than the other, but the researchers stopped their attention on formula **9** [4].

To understand why a trichloro- and not a dichloro-compound was obtained, one should visualize the rearrangement of two molecules of dichloroacetic acid (**10**) into one molecule of trichloroacetic acid (**11**) and one molecule of chloroacetic acid (**12**) under the amine influence, which has a basic character (Fig. 6) [4].

J. E. Katon, T. H. Stout, and G. G. Hess conducted a study of the dichloroacetic acid derivatives infrared spectra, in which the infrared spectra of seven compounds containing the -$CHCl_2$ group attached to various carbonyl functional groups were recorded under various conditions. As a result, group frequency ranges were developed for the CH, CC, and CCl (two) stretching modes and the two CH bending modes. Except for the CC valence mode, these oscillations fall into narrow spectrum regions. Conformational equilibria present in chlorine-substituted acetic acid derivatives are reflected in their infrared spectra in several ways. The situation regarding the observed carbonyl stretching frequencies related to conformational equilibria was also considered [5].

In work [6], a proprietary method of obtaining dichloroacetic acid ester derivatives was patented. It was proposed to obtain dichloroacetic acid esters by reacting a glyoxylic acid ester of the general formula R_1-CO-$COOR_2$, where R_1 is an optionally substituted aryl or heteroaryl group, and R_2 is an alkyl, cycloalkyl or aryl group with phosphorus pentachloride in the dispersant presence suitable for distribution phosphorus pentachloride [6].

Of pharmaceutical interest is the new dichloroacetic acid amidophosphine, which can function as an active ligand for metals. Thus, 3,7-bis(dichloroacetyl)-1,3,7-triaza-5-phosphabicyclo[3.3.1]nonane (DCP) (**14**) was synthesized by double *N*-acylation of 1,3,5-triaza-7-phosphadamantane (PTA) (**13**), which occurs with the CH_2 loss, under appropriate conditions (Fig. 7) [7–9].

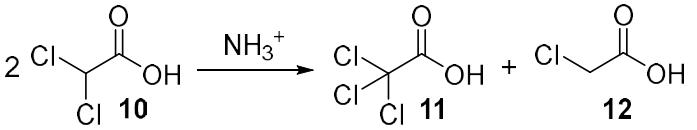

Fig. 6. Scheme of dichloroacetic acid (**10**) rearrangement into trichloroacetic acid (**11**) and chloroacetic acid (**12**)

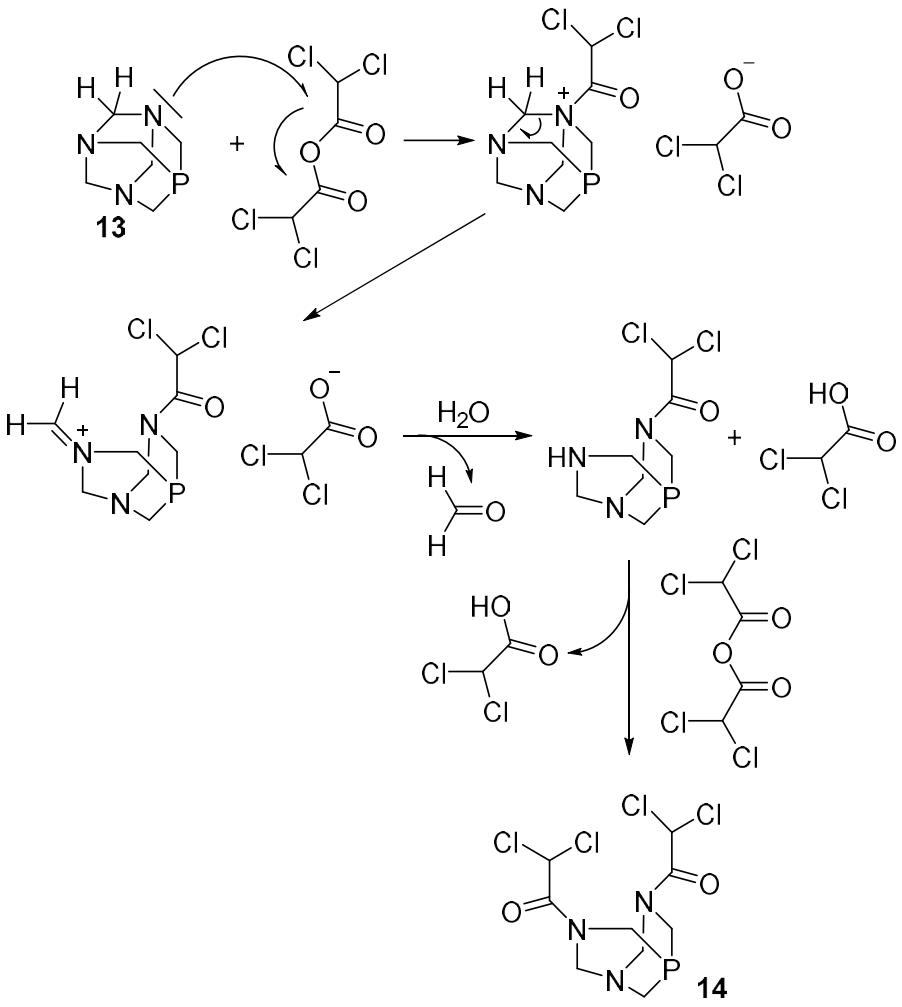

Fig. 7. Synthesis of 3,7-bis(dichloroacetyl)-1,3,7-triaza-5-phosphabicyclo[3.3.1] nonane (**14**)

As a result of hindered rotation around CN amide bonds, three rotameric forms of DCP were observed, the ratio of which depended on the solvent in the solution. In contrast, the DCP X-ray crystal structure showed the opposite orientation of the two amide carbonyl groups (anti-rotamer). It was found that the lipophilic, air-thermally stable DCP can act regiospecifically as a P-donor ligand towards soft metal ions. By replacing the ligands on the corresponding precursors, complexes 1–9 were obtained, where pro-apoptotic dichloroacetic acid is associated with metal ions with known cytotoxic activity on cancer cells (Pt^{2+}, Pd^{2+}, Ru^{2+}, Re^{+}, Au^{+}). The DCP and its complexes' antiproliferative activity was evaluated *in vitro* compared to cisplatin on three human tumour cell lines: A2780 (ovarian cisplatin-sensitive), A2780cis (ovarian cisplatin-resistant), and K562 (erythroleukemia) [10, 11]. The results showed that the simultaneous presence of DCP and Pt (II) provides the best performance concerning non-platinum complexes. Experiments on proapoptotic activity showed that the antiproliferative activity of the most active DCP-Pt (II) complexes is associated with apoptosis induction [12].

V. Arjunan, S. Senthilkumari, P. Ravindran, and S. Mohan conducted a study focusing on the synthesis, FTIR, and FT-Raman spectral analysis, as well as the establishment of the structure-activity relationships for *N*-(4-bromophenyl)-2,2-dichloroacetamide. The *N*-(4-bromophenyl)-2,2-dichloroacetamide (4BNPA) (**17**) was prepared through a procedure outlined in reference [13], involving the 4-bromoaniline (**15**), dichloroacetic acid (**16**), and phosphorus oxychloride use (Fig. 8). The 4-bromoaniline (**15**), dichloroacetic acid (**16**), and phosphorus oxychloride were employed as received, without any additional purification, while all other chemicals utilized were of analar (AR) grade. The synthesized crude compound underwent multiple recrystallizations from ethanol, resulting in a product yield of approximately 70 % [14–16].

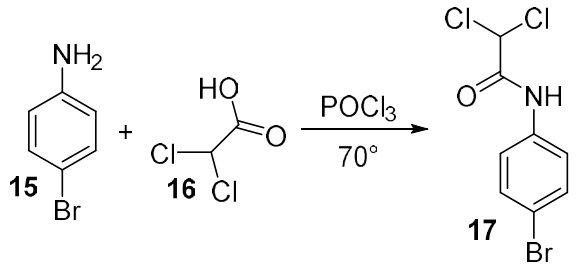

Fig. 8. Synthesis of *N*-(4-bromophenyl)-2,2-dichloroacetamide (**17**)

Tianwen Li and his research team investigated the synthesis and biological assessment of *N*-arylphenyl-2,2-dichloroacetamide analogues as potential anticancer agents. The synthesis involved employing a Suzuki coupling reaction between heterocyclic bromide (**19**) and 3-aminophenylboronic acid (**18**) to yield 3-heteroaniline intermediates (**20**). Subsequently, these intermediates underwent a reaction with 1.3-mole equivalents of dichloroacetyl chloride (**21**) in toluene, resulting in the desired compounds (**22**) (Fig. 9) [17].

The *N*-biphenyl-2,2-dichloroacetamide derivatives (**25**) synthesis was achieved through the Suzuki coupling reaction, combining 2,2-dichloro-*N*-(3-iodophenyl)acetamide (**23**) with substituted phenylboronic acid (**24**) (Fig. 10) [17].

A similar methodology was employed to produce *N*-terphenyl-2,2-dichloroacetamide derivatives (**27**) (Fig. 11). Notably, 2,2-dichloro-*N*-(3-iodophenyl)acetamide and 2,2-dichloro-*N*-(3,5)-diiodophenyl)-acetamide (**26**), integral to the synthesis process, were prepared following established procedures (Fig. 11) [17–19].

All synthesized compounds' cytotoxicity was evaluated *in vitro* using the MTT assay on human epidermoid carcinoma cell line (KB-3-1), non-small cell lung cancer (A549), and large cell lung cancer cell line NCI-H460 (H460). Given the enhanced activity of *N*-arylphenyl-2,2-dichloroacetamide derivatives against the A549 cell line, the IC50 value concerning A549 cells was selected as the activity index for subsequent structure-activity relationship (SAR) discussions. The substituted *N*-([1,1':3',1"-terphenyl]-5'-yl)-2,2-dichloroacetamide derivatives displayed robust cytotoxicity not only against A549 cells but also H460 and KB-3-1 cells. Remarkably, *N*-(3,5-bis(benzo[d][1,3]dioxol-5-yl) phenyl)-2,2-dichloroacetamide exhibited an IC_{50} value of 1.04 μM against H460 cells, 2.40 μM against KB3-1 cells, and 1.73 μM against A549 cells. Consequently, the mentioned compound exhibits considerable promise in the realm of drug development [17].

Yongchong Yang and colleagues conducted an inquiry into the novel derivatives of *N*-phenyldichloroacetamide synthesis and bioactivity. The process for synthesizing *N*-phenyl-2,2-dichloroacetamide derivatives (**30**) involved the reaction of a substituted aniline (**28**) with 1.3 equivalents of dichloroacetyl chloride (**29**) in dry toluene (Fig. 12). This reaction resulted in the formation of *N*-phenyl-2,2-dichloroacetamide derivatives (**30**) after refluxing for 1-5 hours, yielding a range of 90–99 % [19, 20].

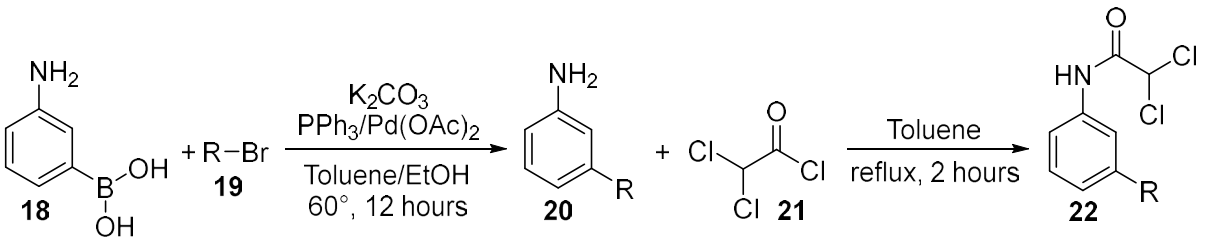

Fig. 9. Synthesis of *N*-phenyl-2,2-dichloroacetamide derivatives (**22**)

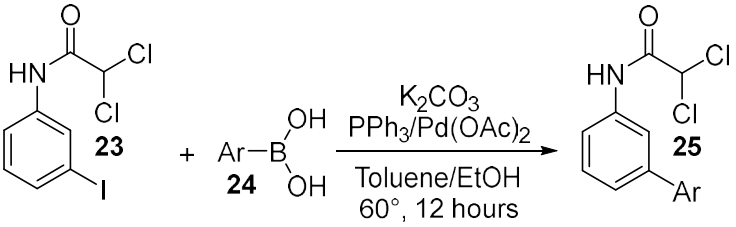

Fig. 10. Synthesis of *N*-([1,1'-biphenyl]-3-yl)-2,2-dichloroacetamide derivatives (**25**)

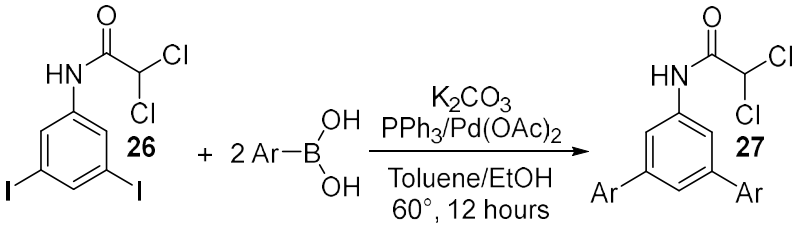

Fig. 11. Synthesis of *N*-([1,1':3',1''-terphenyl]-5'-yl)-2,2-dichloroacetamide derivatives (**27**)

M. Fereidoonnezhad, Z. Faghih, A. Mojaddami, S. M. H. Tabaei, and Z. Rezaei employed a similar approach in their investigation of the dichloroacetates synthesis. They also detailed the 2,2-dichloro-*N*-(3 or 4-((trifluoromethyl)sulfonyl)phenyl)acetamide (**32**) synthesis (Fig. 13). To achieve this, *N*-(3-(trifluoromethylthio)-phenyl)-2,2-dichloroacetamide (**31**) was oxidized by 30 % H_2O_2 in acetic acid at 35 °C (Fig. 13). The reaction blend analysis via TLC (n-hexane/ethyl acetate 4:1) demonstrated its completion after 48 hours. The purified 2,2-dichloro-N-(3 or 4-((trifluoromethyl)sulfonyl)phenyl)acetamide (**32**), was obtained through chromatography on a short silica gel column with elution using n-hexane/ethyl acetate (8/1) as the solvent [20, 21].

In a previous stage of our investigation, amides of interest were synthesized by employing dichloroacetyl chloride and methyl dichloroacetate, taking into consideration the respective amines' properties. The amides, derived from substituted ethylamines (**34**–**37**) and aminobenzoic acids (**38**–**41**), were successfully produced using methyl dichloroacetate (**33**) as the acylating agent (Fig. 14). During this reaction, aliphatic amines exhibited reactivity at room temperature, whereas aromatic amino acid derivatives necessitated prolonged heating in the reagent excess [22].

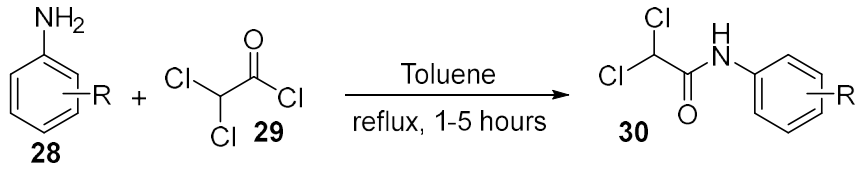

Fig. 12. Synthesis of *N*-phenyl-2,2-dichloroacetamide derivatives (**30**)

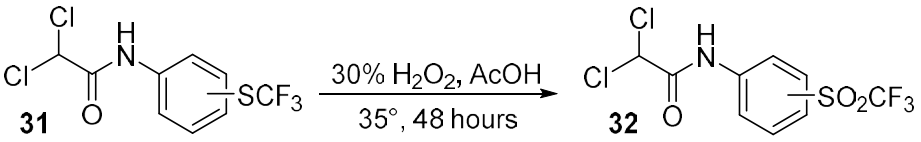

Fig. 13. Synthesis of 2,2-dichloro-*N*-(3 or 4-((trifluoromethyl)sulfonyl)phenyl)acetamide (**32**)

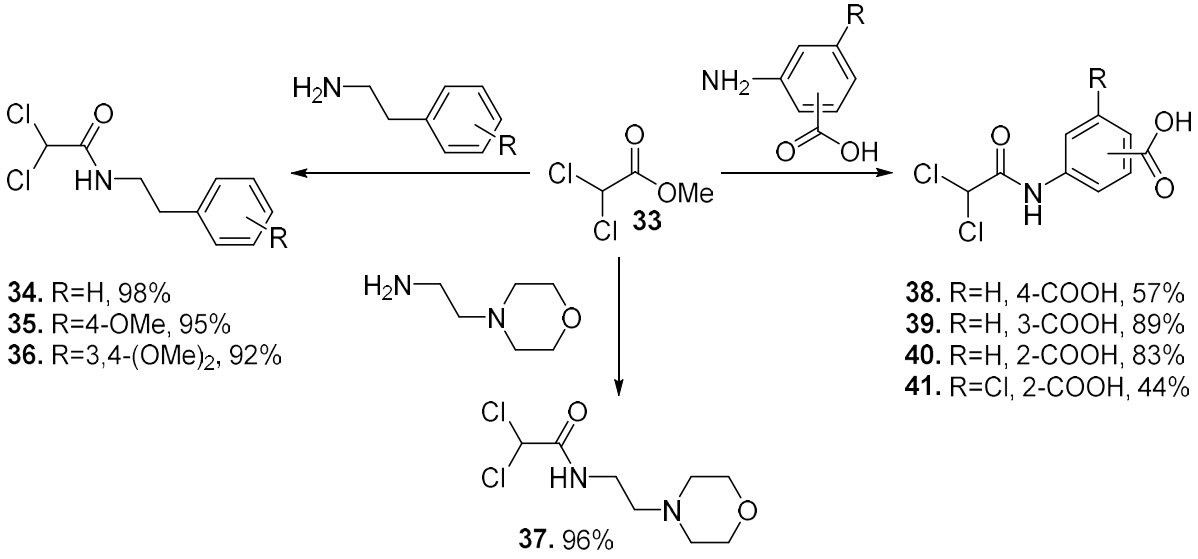

Fig. 14. Synthesis of dichloroacetamides (**34-41**) using methyl dichloroacetate (**33**) as an acylating agent

Furthermore, the aminohydroxybenzoic acids amides (**43**, **44**) were synthesized by employing dichloroacetyl chloride (**42**) in a dioxane medium with the triethylamine presence, which facilitated the hydrogen chloride neutralization released during the reaction (Fig. 15). The synthesized compounds' structural composition and purity were meticulously validated through elemental analysis, LC-MS, and ^{1}H NMR spectroscopy techniques [22].

In the scientific study [23], an investigation was conducted regarding the synthesis and biological assessment of DCAcAm pyrimidines as pyruvate dehydrogenase kinase inhibitors, aimed at reducing the cancer cells' growth. The target DCAcAm pyrimidines synthesis commenced with the commercially available material **45** utilization (Fig. 16). Compound **45** underwent a reaction with nitric acid (90 % aqueous solution), resulting in the formation of compound **46**, which was subsequently subjected to chlorination with phosphorus oxychloride, yielding 2,6-dichloropyrimidine (**47**) (Fig. 16) [24]. This intermediate was further reduced in the iron and acetic acid presence, leading to the formation of 4,6-dichloro-5-aminopyrimidines (48) (Fig. 16) [25]. The final steps involved the compound **48** amidation in dichloromethane with dichloroacetyl chloride to produce dichloroacetamides **49a** and **49b** (Fig. 16). Subsequently, mono-substituted DCAcAm pyrimidines (**50-67**) were synthesized by subjecting intermediates **49a** and **49b** to alkylation with various aliphatic amines at room temperature (Fig. 16). The reaction temperature was elevated to 60 °C to successfully synthesize bis-substituted pyrimidines (**68-81**) (Fig. 16) [23].

Finally, the bis-piperazine pyrimidine (**82**) *N*-Boc protection was removed, resulting in the compound **83**, which was further subjected to treatment with either bromethanol or glycolic acid to obtain the target compounds **84** and **85**, with yields of 64.7 % and 24.7 %, respectively (Fig. 17). All compounds obtained underwent characterization through ^{1}H NMR, ^{13}C NMR, and HRMS spectra analysis [23].

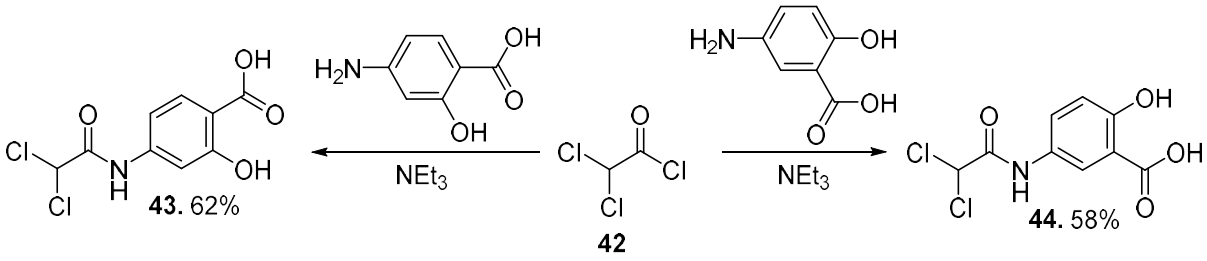

Fig. 15. Synthesis of aminohydroxybenzoic acids amides (**43-44**) using dichloroacetyl chloride (**42**) as an acylating agent

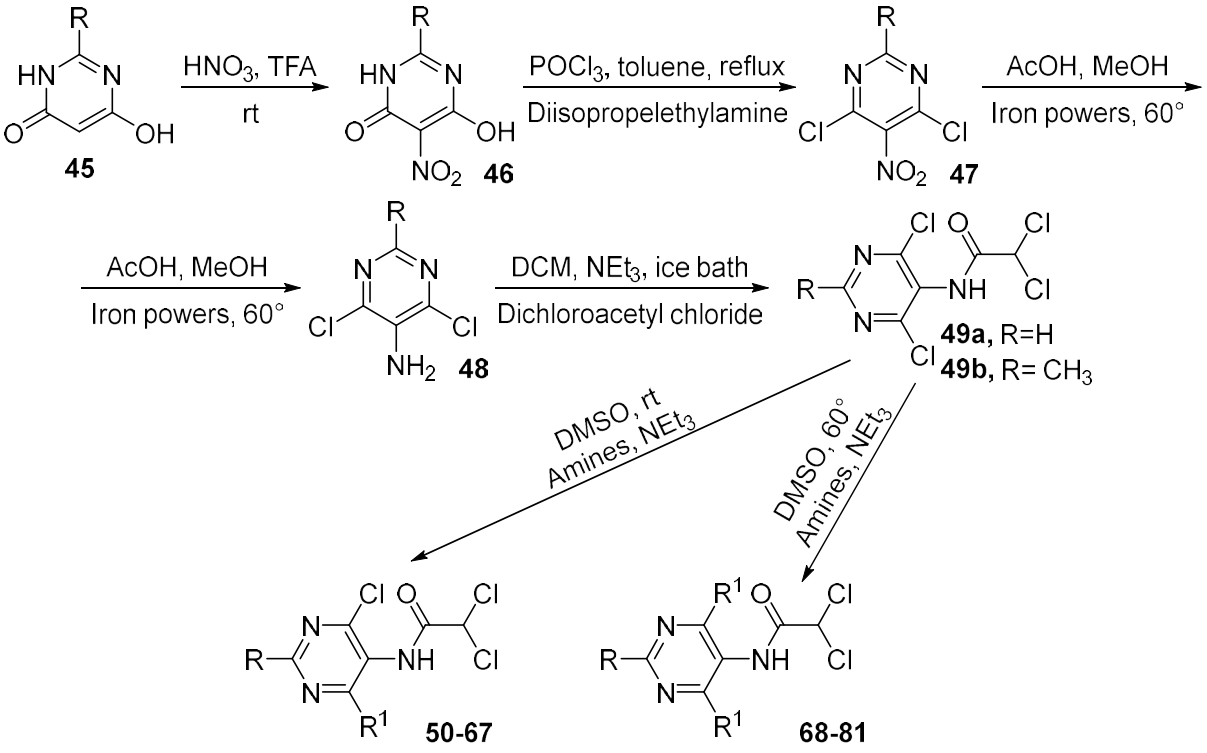

Fig. 16. Synthesis of mono-substituted dichloroacetamide pyrimidines (**50-67**) and bis-substituted dichloroacetamide pyrimidines (**68-81**)

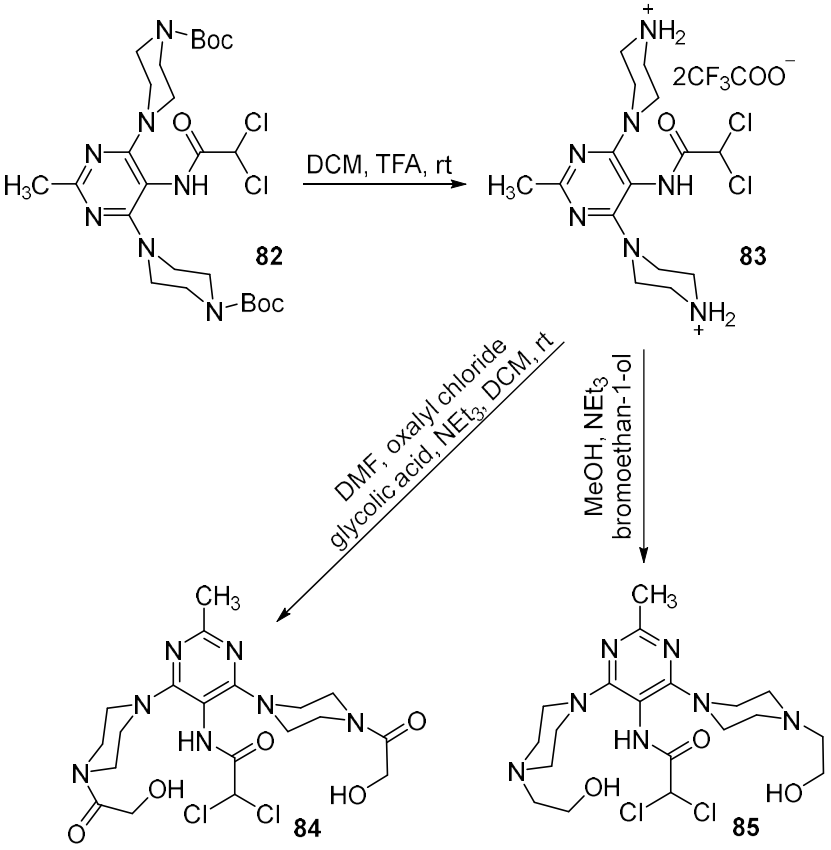

Fig. 17. Synthesis of bis-piperazine pyrimidines (**82-85**)

3. 2. Biological activity of dichloroacetic acid derivatives

Peter W. Stacpoole (1998) and colleagues investigated the clinical pharmacology and toxicological effects of dichloroacetate, which is a product of water chlorination and various drugs and industrial chemicals metabolism [26, 27]. Its accumulation in groundwater and in some areas designated by the US federal environmental restoration program called Superfund was considered a potential health hazard. However, concerns about the toxicity of DCA have been based on data from inbred lines of rodents administered DCA at doses thousands of times higher than those normally exposed to humans. In these animals, chronic DCA administration caused hepatotoxicity and neoplasia. The DCA doses used in animal toxicology experiments are remarkably like those used clinically for the chronic or acute treatment of several acquired or inherited metabolic or cardiovascular diseases. As a drug, DCA is usually well tolerated and stimulates the mitochondrial pyruvate dehydrogenase enzyme complex activity, which leads to increased glucose and lactate oxidation and lactic acidosis relief. Using this mechanism, the drug can also enhance cellular energy metabolism. DCA is dehalogenated *in vivo* to monochloroacetate and glyoxylate, from which it can be further catabolized to glycolate, glycine, oxalate, and carbon dioxide [28]. Differences in its metabolism and toxicology in humans between ecologically and clinically relevant doses remain an open question [29].

In 2018, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area re-evaluated dichloroacetic acid to obtain information on the maximum workplace concentration (MAK value) and to revise its carcinogenicity classification. Critical effects are irritation, carcinogenicity in the rats and mice liver, and neurotoxicity. After oral administration, dichloroacetic acid or its sodium salt has a tumor-promoting effect and is carcinogenic in rats and mice liver. The NOAEL (No Obvious Adverse Effect Level) for carcinogenic effects in rats is 3.6 mg/kg body weight [30]. No NOAEL can be obtained in mice. Dichloroacetic acid is not mutagenic in most *in vitro* and *in vivo* tests. Mechanisms involved in tumor development in the liver include interference with energy metabolism, oxidative stress, and apoptosis inhibition. Since the primary action mode is not genotoxic, dichloroacetic acid and its salts are classified as carcinogenic category 4. Dichloroacetic acid is corrosive to the rabbits' eyes and skin as there are no inhalation studies available to assess possible respiratory tract irritation; the structurally similar trichloroacetic acid was used for cross-reading. Thus, a MAK value of 0.2 ml/m^3 was obtained, which corresponds to 1.1 mg/m^3 for dichloroacetic acid. Accordingly, an MAK value of 1.1 mg/m^3 for the respirable fraction measured as acid has been established for salts. Because the local effect is critical, the acid and its salts are classified as peak limitation category I with a deviation factor of 1. Because skin contact with dichloroacetate can significantly contribute to systemic toxicity, the salts are designated by the letter "H". Skin contact is not expected to contribute to the dichloroacetic acid systemic toxicity. From the available data, sensitization is not expected [31].

Albert L. Shroads and colleagues investigated the dichloroacetate kinetics and metabolism dependence on the patient's age. DCA is biotransformed by the glutathione transferase ζ-1 isoform (GSTz1), also known as maleyl acetoacetate isomerase, which catalyzes the tyrosine catabolism penultimate step [32]. DCA causes reversible peripheral neuropathy in several species, including humans. The study evaluated the DCA kinetics, biotransformation, and its effect on tyrosine metabolism in nine patients treated with 25 mg/kg/day for 6 months and in rats treated with 50 mg/kg/day for 5 days. The hepatic maleyl acetoacetate isomerase activity and expression were also measured. Chronic DCA administration causes a significant age-dependent decrease in plasma clearance and an increase in plasma half-life in patients and rats. Unchanged DCA urinary excretion in rats increases with age, whereas oxalate, the DCA metabolism end product, shows the opposite trend. Monochloroacetate (MCA) low concentrations, known to be neurotoxic, increased with age in the dosed rats' urine. MCA was detected in the old

animals' plasma only. Hepatic GSTz1-specific activity was similarly inhibited by DCA treatment among all age groups, whereas plasma and urinary levels of maleylacetone, the natural substrate for this enzyme, increased with age. The obtained further allowed us to conclude that age is an important variable in the *in vivo* DCA metabolism and elimination and that it may partially explain this compound neurotoxicity in humans and other species [33].

In addition to anticancer activity, dichloroacetate compounds have proven efficacy in the treatment of diseases caused by a glycolytic parasite. Spanish scientists patented this invention and described a pharmaceutically acceptable dichloroacetate compound obtained from a dichloroacetic acid salt, a dichloroacetic acid complex ester with C1-C6 alkanol, C1-C6 acyloxymethanol or C1-C6 alkoxycarbonyloxymethanol and its mixtures. The compound inhibits the parasites' growth, while the host cells' growth is not inhibited or less inhibited [34].

B. M. Madhok and others investigated the DCA possibility to induce apoptosis and cell cycle arrest in colorectal cancer cells. The study aimed to determine whether a metabolic switch from glycolysis to mitochondrial respiration would reduce the growth of colorectal cancer cells compared to normal cells. In the study, representative colorectal cancer and non-cancerous cell lines were treated with DCA. The study found that DCA (20 mM) did not reduce the non-cancerous cells' growth but caused a significant decrease in the cancer cells' proliferation (P=0.009), which was associated with apoptosis and cell cycle arrest in the G2 phase. The greatest apoptotic effect was evident in metastatic LoVo cells (metastatic left supraclavicular lymph node from colorectal adenocarcinoma), in which DCA induced up to a tenfold increase in the apoptotic cells' number after 48 hours. The most pronounced G2 arrest was evident in well-differentiated HT29 cells, in which DCA induced an eightfold increase in cells in the G2 phase after 48 hours. Dichloroacetate reduced lactate levels in growth media and induced the pyruvate dehydrogenase complex E1a subunit dephosphorylation in all cell lines. Still, the inner mitochondrial membrane potential was reduced only in cancer cells (P=0.04). As a result, it was concluded that pyruvate dehydrogenase kinase inhibition weakens glycolysis and facilitates mitochondrial oxidative phosphorylation, which leads to a decrease in colorectal cancer cells' growth but not non-cancerous cells [35].

Research by Luke H. Stockwin et al. (2010) demonstrates that sodium dichloroacetate selectively acts on cells with defects in mitochondrial electron transport chains, in which the DCA anticancer activity mechanistic basis was reevaluated *in vitro* using biochemical, cellular, and proteomic approaches. Research results showed that DCA is inactive, induces apoptosis only at high concentrations (25 mM, 48 hours), and is not selective for cancer cells. Further 2DPAGE proteomic analysis confirmed DCA-induced growth inhibition without apoptosis induction. In addition, DCA depolarizes mitochondria and promotes reactive oxygen species (ROS) formation in all cell types. However, DCA was found to have selective activity against Rho (0) cells and to synergize with 2-deoxyglucose in complex IV-deficient HCT116 p53 (2/2) cells [36].

Korean scientists patented erlotinib dichloroacetate as a compound with antitumor activity (Fig. 18) [37].

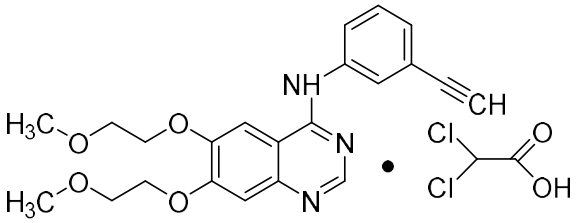

Fig. 18. Structure of erlotinib dichloroacetate

According to the present invention, erlotinib dichloroacetate can inhibit the epidermal growth factor receptor and induce cancer cells to self-destruct by apoptosis, thereby inhibiting the cancer cells' growth, leading to its destruction, and exhibiting significantly enhanced anticancer effects due to the constructive collaboration between erlotinib and dichloroacetic acid [37].

Monica Abdelmalak and colleagues investigated the dichloroacetate long-term safety in congenital lactic acidosis, following 8 patients (four of whom were male) with biochemically and/or molecularly proven deficiencies of the pyruvate dehydrogenase complex (PDC) E1α subunit (3 patients) or respiratory chain complexes I (1 patient), IV (3 patients) or I+IV (1 patient) treated with oral dichloroacetate (12.5 mg/kg/12 hours) for 9.7–16.5 years. All subjects initially participated in randomized controlled trials of DCA and continued in an open-label chronic safety study. The patients' age (1 adult) ranged from 3.5 to 40.2 years at the DCA introduction beginning, and at the time of summing up the study results – from 16.9 to 49.9 years (mean±SD: 23.5±10.9 years). Subjects were normal or underweight for age and sex. 3 patients with MPC deficiency did not adhere to a high-fat (ketogenic) diet. DCA maintained a normal lactate concentration in the blood even in children with MPC deficiency who followed unlimited diets. Hematological, electrolyte, renal, and hepatic status remained stable. Nerve conduction was either unchanged or moderately decreased, leading to a DCA reduction or temporary cessation in 3 patients, although peripheral neuropathy symptomatic worsening did not occur. As a result of the study, it was concluded that chronic DCA administration is usually well tolerated by patients with lactic acidosis congenital causes and is effective in maintaining normal blood lactate levels even in children with MPC deficiency who do not follow a strict ketogenic diet [38].

Robert I. Misbin studied the dichloroacetate effect on lipid metabolism in isolated rat liver cells. The study showed that the DCA administration to normal rats leads to a decrease in the glucose and triglycerides levels in the blood serum and an increase in the number of ketone bodies with the insulin and cholesterol at constant levels [39]. The DCA effect on lipid metabolism was studied on isolated rat hepatocytes [40]. At a DCA dose of 10 mM, the tritiated water incorporation into fatty acids

was inhibited by 33±4 %. No effect on cholesterol incorporation (measured as unsaponifiable lipids) was observed. DCA inhibited the ^{14}C-glucose incorporation into lipids but did not affect glucose oxidation. Fatty acid oxidation was increased by 76±7 %. However, DCA did not affect the newly synthesized lipid recovery. Thus, tritiated water incorporation inhibition into fatty acids means a decrease in synthesis, not an increase in turnover. DCA did not affect the 14C-palmitate incorporation into triglycerides or phospholipids. DCA did not affect cell viability, which was assessed by incorporating 3H-isoleucine into the protein and excluding trypan blue. These results suggest that DCA lowers serum triglyceride levels by inhibiting fatty acid synthesis and stimulating fatty acid oxidation in the liver [41].

In 2007, a scientific team led by S. Bonnet conducted experimental studies in which sodium dichloroacetate acted on human tumour cells implanted in experimental rats. During the experiment, a change in the tumour cells' metabolism under the sodium dichloroacetate influence was proven due to the free radical processes' activation, proliferative and angiogenic transcription factors inhibition (rats treated with sodium dichloroacetate had smaller tumours with reduced vascularization and tumour perfusion compared to the control), which is an explanation of the positive effect in the treatment of several tumours [42–44].

In a small, uncontrolled clinical trial of five glioblastoma patients reported by E. D. Michelakis et al. in 2008, three received dichloroacetate and palliative care, and two received dichloroacetate and standard therapy. After 15 months after the treatment started, three patients had glioblastoma regression, which was confirmed by the MRI results, and one patient remained clinically stable. Eighteen months after the treatment started, four patients remained alive without any signs of hematological or hepatorenal toxicity. The data we obtained allow us to consider dichloroacetate as an agent affecting the cancer cells' metabolism [45].

In 2010, Dana F. Flavin published a clinical case report on the non-Hodgkin's lymphoma treatment with dichloroacetate, describing the story of a 48-year-old patient with stage 4 non-Hodgkin's follicular lymphoma. The patient underwent 3 months of conventional chemotherapy, which resulted in complete remission, after which the tumours recurred in the nasopharynx and cervical lymph nodes a year later. Refusing all proposed chemotherapy, the patient began dichloroacetate self-administration at a dose of 900 mg per day, which eventually led to complete remission after four months [46, 47]. One year after the last positron emission tomography, the tumours' absence was noted [48].

Akbar Khan (2012) presented a case of complete long-term remission in a 72-year-old female patient with kidney metastatic squamous cell carcinoma. A nephrectomy was performed, during which the tumour invasion into the renal vein and numerous metastases in the abdominal lymph nodes were revealed. After palliative radiation therapy completion, the patient received oral dichloroacetate for three months. During the next five years from the moment of remission, the patient showed no signs of disease progression [49].

In 2013, Japanese scientists Ohashi T. et al. presented a publication that revealed the topic of the dichloroacetate effect on immune dysfunction caused by excessive secretion of lactic acid by a tumor. The study found that treatment with dichloroacetate reduced the arginase I expression in tumour-infiltrating immune cells and increased the interferon-c-producing CD81 T cells and killer cells number in the tumour-bearing mice spleen [50]. Although dichloroacetate treatment alone did not inhibit tumour growth, it enhanced the Poly (I:C) antitumor immunotherapeutic activity in both CD81 T-cell-sensitized and killer cell tumour models [51, 52]. Thus, dichloroacetate acts not only on tumor cells by inhibiting glycolysis but also on immune cells, improving the immune status modulated by lactic acid and increasing the antitumor immunotherapy effectiveness [53, 54].

Yu. Duan and co-authors investigated the dichloroacetate antitumor activity on C6 glioma cells *in vitro* and *in vivo* in an experiment on laboratory animals. The study found that dichloroacetate is a small molecule that can penetrate the blood-brain barrier, revealing a potential therapeutic effect on brain tumours [55]. Dichloroacetate inhibits C6 glioma cell proliferation, induces C6 cell apoptosis, and arrests C6 cells [12, 56]. *In vivo,* antitumor effects showed that dichloroacetate markedly inhibited the C6 glioma tumours' growth in both C6 brain tumour-bearing rats and C6 tumour-bearing nude mice. Dichloroacetate significantly induced the production of the oxygen-reactive forms and reduced the mitochondrial membrane potential in tumour tissues. *In vivo* antitumor activity results also indicated that dichloroacetate has potential antiangiogenic activity, making it a promising therapeutic agent in glioma treatment. In summary, it may be a viable therapeutic agent in the treatment of gliomas [57].

This topic was also studied by domestic scientists, including Kolesnik D. L., who investigated the possibility of enhancing the dichloroacetate effect in combination with metformin and hypoxia conditions. The conducted studies showed that hypoxia enhances the DCA cytostatic and cytotoxic effects in C6 glioma cells due to an elevated level of tumour cell necrosis and reactive oxygen species hyperproduction. The study of the sodium dichloroacetate anti-glioma activity in combination with metformin turned out to be promising since the obtained data proved the synergism of the dichloroacetate and metformin anti-glioma effect, which can be considered as a starting point for the development of effective treatment schemes for malignant brain tumours based on the agents mentioned above' combined use [58–60].

I. V. Prokhorova continued research on this topic, setting herself the goal of investigating metformin, DCA, and their combined effect on the survival of rats with C6 glioma and the main blood hematological and biochemical indicators. DCA and metformin were administered orally to inbred female rats for 11 days, starting on the second day after tumour cell transplantation, at a total dose of 1.1 and 2.6 g/kg, respectively. The administered dosages of all the pharmacological agents investigated in

this study fell within the established range of therapeutic doses for rats. It is important to note that these dosages were deliberately maintained below the maximum tolerated levels for enhanced safety and relevance to clinical scenarios [61]. In combined treatment, metformin was administered 3 hours after DCA administration. The obtained results showed that the DCA administration did not significantly affect the lifespan of rats with C6 glioma. The life expectancy of rats administered only metformin was significantly longer (by 19.1 %, $p<0.01$). Combined DCA+metformin administration prolonged the lifespan of animals with glioma by 50 % ($p<0.001$). A positive result of the antitumor activity of metformin alone and in combination with DCA correlated with a decrease in the ratio of mean platelet volume/platelet count (MPV/PLT) by 75.0 % ($p<0.05$) compared to the tumour control. In addition, the pronounced antitumor effect of combined therapy with DCA and metformin was associated with a decrease ($p<0.05$) in plasma glucose and lactate levels of rats with C6 glioma by 10 % and 41.4 %, respectively, compared to tumour controls. The blood parameters study showed that the C6 glioma growth is accompanied by leukopenia, anaemia, and thrombocytopenia development. The DCA introduction caused the anaemia and leukopenia manifestations correction but did not affect the platelet level in the blood of animals with glioma. Metformin alone and in combination with DCA had a positive effect on leukocyte counts and caused complete thrombocytopenia correction, increasing platelet counts by more than 200 % ($p<0.001$). As a result, the metformin ability, both alone and in combination with DCA, to affect the C6 glioma development, which is manifested in increasing the rats' life span, was revealed. The most pronounced antitumor effect was recorded against the background of these drugs' combined use, which may be related to its ability to reduce the lactate and glucose levels in the blood of tumour-bearing rats. It has been proven that metformin, both in monotherapy and in combination with DCA, provides anaemia and thrombocytopenia correction, which occur against the background of C6 glioma growth [62].

Moises Armides Franco-Molina and others (2020) conducted an *in vivo* assessment of the silver and sodium dichloroacetate combination antitumor and immunogenic properties against melanoma, the use of which in a complex is aimed at achieving synergism and increasing both compounds' activity, the action mechanism of which is to affect the DNA and mitochondria integrity at various levels [63, 64]. During the antitumor efficacy determination, the tumour volume, the tumour necrosis factor-α, nuclear factor κB production (both factors were determined by the enzyme immunoassay method), and the nitric oxide level (by the nitrate/nitrite colourimetric analysis method) were evaluated; for immunogenic cell death, the danger-associated molecular structures release was assessed using immunohistochemistry and flow cytometry. The obtained results showed that the colloidal silver and sodium dichloroacetate combination is more effective than each of the components separately and that the antitumor mechanism is not related to immunogenic cell death [65].

Honokiol bis-dichloroacetate (**85**) also shows activity against vemurafenib-resistant melanoma during *in vivo* studies, which was synthesized by Michael Y. Bonner and team to increase the honokiol lipophilicity (Fig. 19) [66].

In parallel, a new fluorinated honokiol analogue, bis-trifluoromethyl-bis-(4-hydroxy-3-allylphenyl) methane (hexafluoro) (86), was synthesized (Fig. 20) [66].

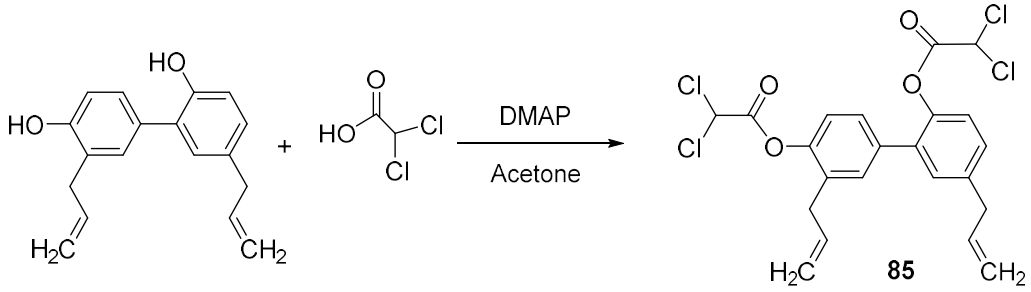

Fig. 19. Synthesis of hoquinol (**85**)

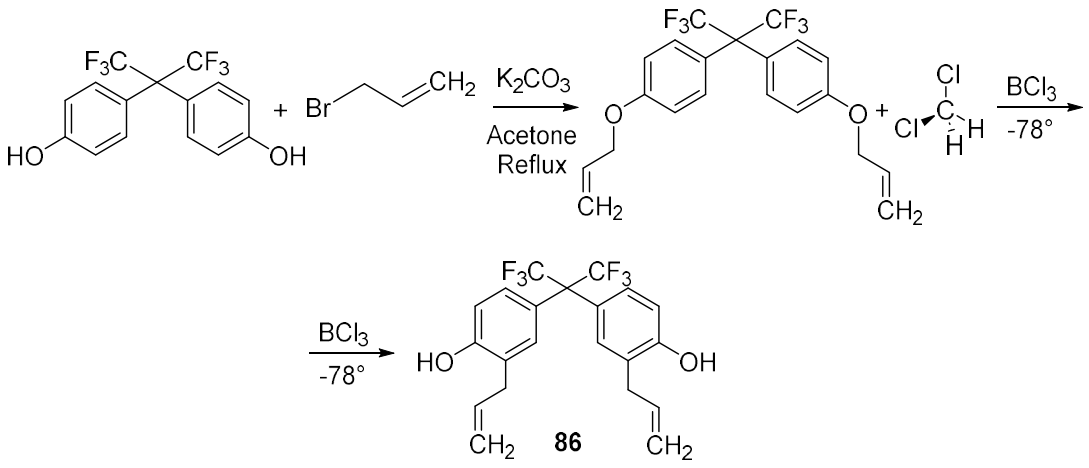

Fig. 20. Synthesis of hexafluoride (**86**)

Both compounds showed activity against A375 melanoma *in vivo*, but honokiol DCA was more active [67]. Honokiol DCA can act on vemurafenib-resistant melanomas by enhancing both respiration and reactive oxygen generation, leading to activity against aggressive melanoma *in vivo* [66].

Simultaneous treatment with dichloroacetate and omeprazole reveals a synergistic antiproliferative effect on malignant tumours, which was studied by Japanese scientists. The study showed that the DCA and omeprazole combination showed more potent antitumor activity than DCA alone in HT1080 fibrosarcoma cells and differentiated colon carcinoma cells. At the same time, the drugs did not affect the WI-38 human fibroblast proliferation [68, 69]. Since omeprazole and DCA can be administered orally and used clinically for several years without serious side effects, this combination therapy can be recommended for use in the treatment of malignant tumours' treatment [70, 71].

There is also a synergistic antitumor effect of dichloroacetate in combination with 5-fluorouracil in colorectal cancer, which was studied by scientists from China. The study treated four human colorectal cancer cell lines with DCA or 5-fluorouracil or the DCA and 5-fluorouracil combination. Cell viability was determined by reaction with 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide. The results showed that DCA suppresses colorectal cancer cells' viability and has a synergistic antiproliferative effect in combination with 5-fluorouracil [72, 73].

Xiao Lu and colleagues investigated the possibility of enhancing the anticancer chemotherapy agents' effect in combination with dichloroacetate by inhibiting autophagy in non-small cell lung cancer. This study aimed to examine the dichloroacetate effects on autophagy regulation and chemosensitization in non-small cell lung cancer (NSCLC) cells using laser confocal microscopy and Western blotting in A549 and H1975 cell lines. As a result, it was found that dichloroacetate, which demonstrated antitumor properties in various carcinoma models, induced NSCLC cells' apoptosis by suppressing cancer cells' autophagy [74–76].

The research (Mohammad Usman et al., 2017) was conducted with the aim of the copper/dichloroacetic acid cocrystals binuclear complex biological evaluation against human breast cancer [77]. A dinuclear copper (II) co-crystal (**89**) was synthesized from the H_2valdien skeleton (**87**) and the anticancer drug «Dichloroacetic acid» (**88**) pharmacophore embedded in two Cu (II) connected by a hydrogen bonds network (Fig. 21) [78, 79].

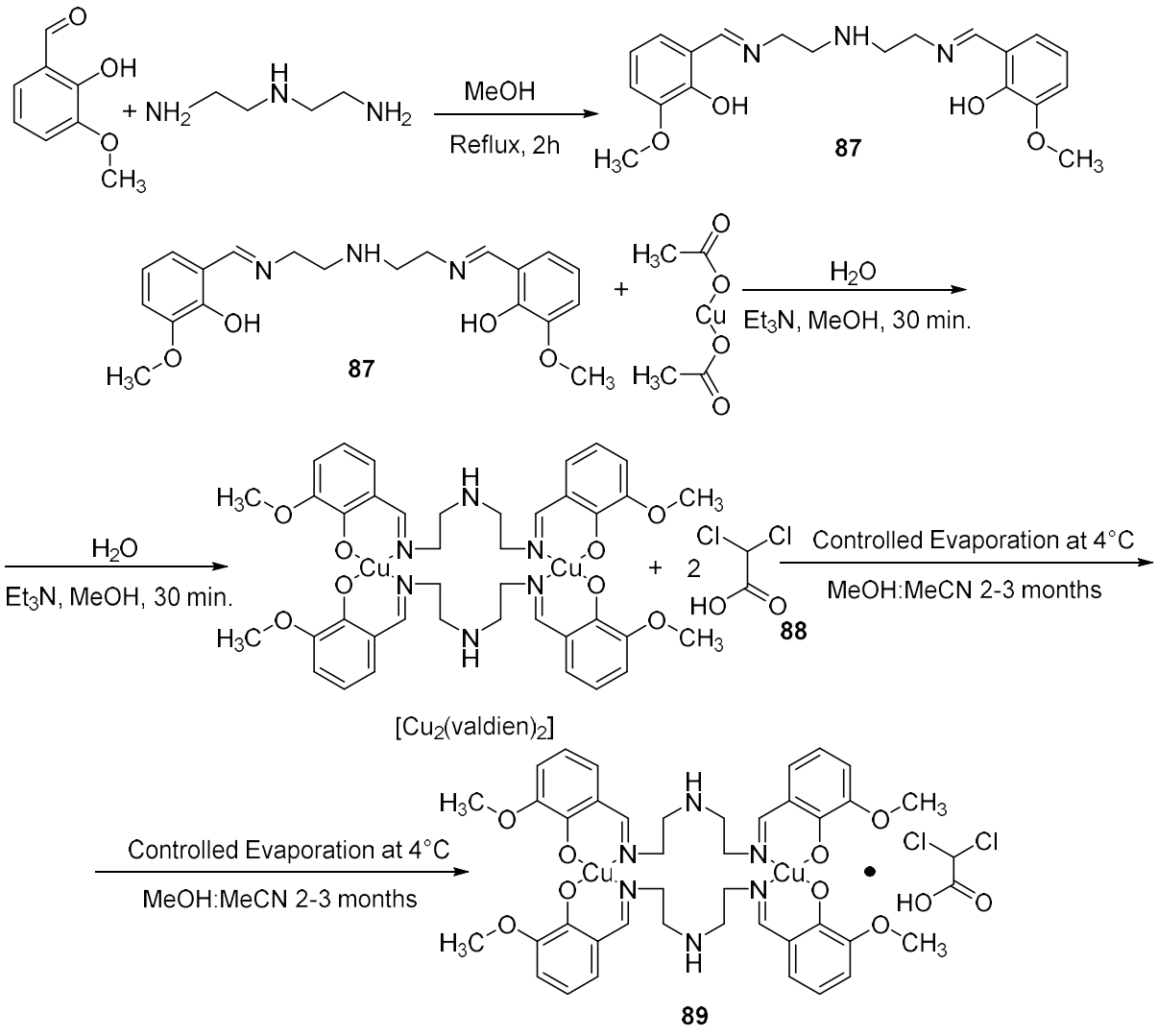

Fig. 21. Synthesis of copper/dichloroacetic acid cocrystal dinuclear complex

[Cu_2(valdien)$_2$···2Cl_2CHCOOH] (**89**) was confirmed as a potential anticancer drug by studying its DNA binding profile, cleavage mechanism with pBR322 by gel electrophoretic analysis, and *in vitro* cytotoxicity on MCF-7 cancer cell lines [77].

Dichloroacetic acid metabolic reprogramming has also been shown to potentiate MCF-7 human breast adenocarcinoma cells photodynamic therapy (PDT) [77].

At the start of their study, Zeiyad Alkarakooly and colleagues hypothesized that when dichloroacetic acid and PDT were combined, they could exacerbate mitochondrial dysfunction and induce apoptosis through a reactive oxygen species-dependent pathway. To evaluate the hypothesis, they used MCF-7 cells as an *in vitro* model of PDT dependent on 5-aminolevulinic acid (5-ALA) [80]. As a result of the experiment, it was found that MCF-7 treated with PDT and dichloroacetic acid not only increased the cell growth inhibition but also affected the mitochondrial membrane integrity through the reactive oxygen species production and increased apoptosis [81].

Streeter Jackson's patent described a similar cancer treatment method, which describes the available therapeutic efficacy in the dichloroacetic acid and electromagnetic radiation combination [82].

In their research, Mohammad Hossain and his research team delved into the examination of the cytotoxic impacts associated with 3,5-bis(benzylidene)-4-piperidones. Their findings revealed a notable metabolic shift in several tumours, wherein glycolysis emerged as the predominant method for energy production, as opposed to oxidative phosphorylation [83]. This shift is a well-documented occurrence referred to as the Warburg effect [84]. One of the key players in facilitating glycolysis is pyruvate dehydrogenase kinase 1 (PDK1), and this enzyme inhibition holds the potential to reverse the Warburg effect. Among the compounds under investigation, dichloroacetic acid, the PDK1 inhibitor, has been thoroughly assessed for its anti-tumor properties [85, 86]. Subsequently, a novel category of hybrid molecules (**92**) with the potential to function as anti-tumour agents were conceived, uniting the features of 3,5-bis(benzylidene)-4-piperidones (**90**) and dichloroacetic acid (**91**) (Fig. 22) [87].

These novel hybrid molecules are potent cytotoxic agents against HCT116 human colon cancer cells [87].

Margaret O. James et al. investigated the therapeutic use of dichloroacetate based on its pharmacological property to inhibit pyruvate dehydrogenase kinase and the glutathione transferase zeta-1 role. The first step in DCA metabolism is conversion to glyoxylate, catalyzed by glutathione transferase zeta-1 (GSTZ1), for which DCA is a mechanism-based inactivator [88]. The GSTZ1 inactivation rate by DCA depends on age, GSTZ1 haplotype, and cellular chloride concentration, and the DCA effect on its metabolism makes it difficult to select an effective dose with minimal side effects [89].

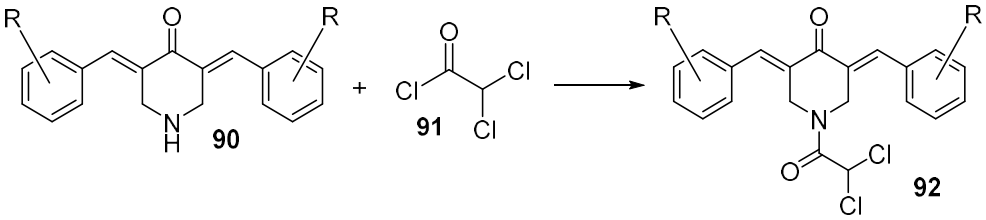

Fig. 22. Synthesis of novel 3,5-bis(benzylidene)-4-piperidones hybrid molecules (**92**)

Shanta Dhara and Stephen J. Lippar investigated the possibility that metaplatin (**93**) might influence the Warburg effect, which explains most solid tumors' resistance to apoptosis, by inhibiting pyruvate dehydrogenase kinase (Fig. 23) [84]. In the metaplatin molecule (**93**), two DCA units are attached to the axial positions of the six-coordinate Pt (IV) center [90].

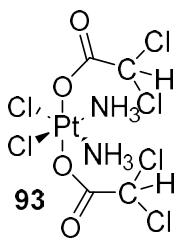

Fig. 23. Structure of metaplatin (**93**)

Through a unique mechanism, metaplatin selectively attacks nuclear DNA with cisplatin and mitochondria with DCA in cancer cells. The metaplatin cytotoxicity in various cancer cell lines equals or exceeds the cytotoxicity of all known Pt (IV) compounds and is comparable to the cisplatin cytotoxicity. Metaplatin alters the cancer cells' mitochondrial membrane potential gradient (Δψm), promoting apoptosis by releasing cytochrome C and translocating apoptosis-inducing factor from the mitochondria to the nucleus. Cisplatin, which is generated by the metaplatin cellular reduction, enters the nucleus and targets DNA, forming 1,2-intrachain d (GpG) cross-links characteristic of its antitumor efficacy. These metaplatin properties are manifested in its ability to selectively kill cancer cells co-cultured with normal fibroblasts and partially overcome resistance to cisplatin [90].

Stacpoole and co-authors (1983) studied the dichloroacetate and related carboxylic acids' potential on the enzymes' activity. DCA markedly reduces the circulating cholesterol level in animals and patients with combined hyperlipoproteinemia or homozygous familial hypercholesterolemia. To investigate its cholesterol-lowering action mechanism, the DCA and its hepatic metabolites, glyoxylate and oxalate effect on the activity of 3-hydroxy-3-methylglutaryl coenzyme A reductase obtained from the healthy rats' liver with a reverse light cycle was studied. Oral DCA administration for 4 days reduced the HMG-CoA reductase activity by 46 % at a dose of 50 mg/kg per day and by 82 % at a dose of 100 mg/kg per day. The drug inhibitory effect is due to a decrease in both the expressed enzyme activity and the total number of reductase molecules present [91].

In further studies, Stacpoole and colleagues attempted to modify the dichloroacetic acid pharmacokinetics and bioavailability by synthesizingy various derivatives containing dichloroacetic acid esters with polyols and dichloroacetic acid ionic complexes. Studies were conducted on laboratory animals: rats without diabetes received single orogastric doses of the DCA physiological solution (control, 100 mg/kg) or the following derivatives (D1–4) within 24 hours: D1–D3 esters: potassium tetra(dichloroacetyl)glucuronate (D1), inositol monophosphate tetradichloroacetate (D2), inositol hexadichloroacetate (D3), and inositol hexa[*N*-methylnicotinate] hexadichloroacetate (D4). Each derivative was administered at a dose that would provide 100 mg/kg of DCA as an anion. All derivatives were effective when administered orally, significantly lowering blood glucose and lactate levels. D4 had the strongest and longest-lasting glucose- and lactate-lowering effects but increased plasma DCA concentrations less than the sodium salt equivalent dose. When administered to rats with a reverse light cycle, D4 markedly inhibited the tritiated water incorporation into cholesterol and triglycerides [39, 91]. As a result, it was concluded that dichloroacetic acid derivatives retain the original compound's biological activity but may exhibit different pharmacokinetics. Eventually, they may prove useful in diabetes, hyperlipidemia, and lactic acidosis treatment in humans [92].

Dichloroacetates can be presented in various dosage forms. In the literature review presented by K. Zh. Kasenov, the possibility of creating transdermal therapeutic systems containing dipromonium (diisopropylammonium dichloroacetate) for the treatment of such a common disease as hypercholesterolemia is mentioned, with the possibility of depriving patients of such drug side effects as nausea and vomiting, which are often observed in the oral drug administration [93].

The drugs' precise delivery to the cell's mitochondria in anticancer therapy was investigated by scientists Shanta Dhar and Rakesh Pathak, who, in their patent, characterized a targeted molecular framework (**94**) for the construction of a metabolic inhibitor that has specific activity against cancer cells and antitumor immunity. Incorporation of a mitochondrial-targeting moiety, such as a triphenylphosphonium cation, through a biodegradable linker has enabled mitochondrial targeting of certain metabolic inhibitors, such as dichloroacetic acid (Fig. 24) [94].

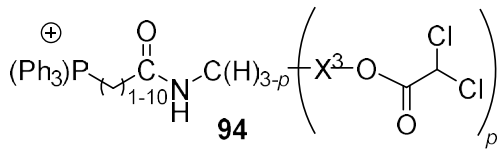

Fig. 24. Structure of proposed molecular framework (**94**) (in this formula, *p* is from 1 to 3, and X^3 is a linker [94])

Worthy of attention is the anticancer drug imatinib dichloroacetate (**95**), which, according to the invention of Korean scientists (Kim Kyoung Soo et al., 2012) and experiments, can inhibit tyrosine kinase and induce cancer cells to self-destruct by apoptosis, thereby inhibiting the cancer cells growth and leading to their destruction, and demonstrates significantly enhanced anticancer effects due to the synergy between imatinib and dichloroacetic acid (Fig. 25) [95].

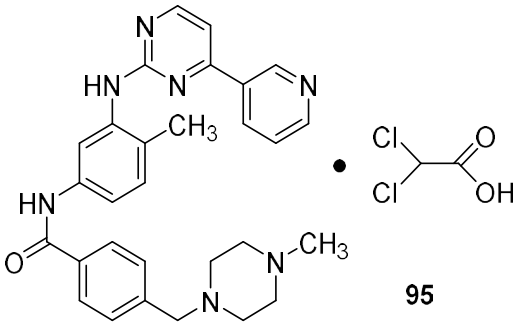

Fig. 25. Structure of imatinib dichloroacetate (**95**)

Another invention discloses a combined mangaporphyrin-dichloroacetic acid drug for tumor treatment. The medicinal product contains a manganese porphyrin and dichloroacetic acid or a pharmaceutically acceptable dichloroacetic acid salt and may contain one or more pharmaceutically acceptable carriers (optional). Baoqiu Li's experiments demonstrated the following: after the combined administration of mangaporphyrin and dichloroacetic acid, which do not have antitumor effects, the tumour treatment effect can be improved; toxicity can be reduced; the experimental animals' lifespan can be extended [96].

Evangelos Michelakis and Stephen Archer were granted a patent for the dichloroacetate and its chemical counterparts' utilization in cancer treatment, specifically for apoptosis induction or apoptosis resistance restoration within the cell. DCA is recognized as the mitochondrial enzyme pyruvate dehydrogenase kinase prototype inhibitor, thereby facilitating the pyruvate dehydrogenase activation and the glucose oxidation promotion. Consequently, DCA enhances the $NADH^+$ supply, leading to a complex alteration in electron transport. This intricate process results in an AOS escalated generation within mitochondrial complex I and mitochondria subsequent depolarization, thereby initiating apoptosis, as elucidated in the proposed mechanism (Fig. 26) [97].

To establish that the DCA effects are not random and non-specific but rather metabolic and have a regulatory impact on apoptotic pathways, a comprehensive analysis, encompassing gene chip and Gene Ontology (GO) analysis, was conducted on both treated and untreated cells. By scrutinizing these effects on both the A549 cell line and a glioblastoma cell line, which represents a tumour type significantly distinct from lung cancer due to the epithelial versus glial cell differentiation, and by focusing on the shared alterations prompted by DCA therapy, it was possible to identify consistent shifts in gene expression due to DCA, thus distinguishing them from any unique, tumour-specific genetic alterations [97].

Para-dichloroacetate phenformin (**96**) is a compound that exhibits antitumor activity (Fig. 27) [98, 99].

Its properties were patented in 2017 by Chinese scientists Du Jianping and Lan Quan [98].

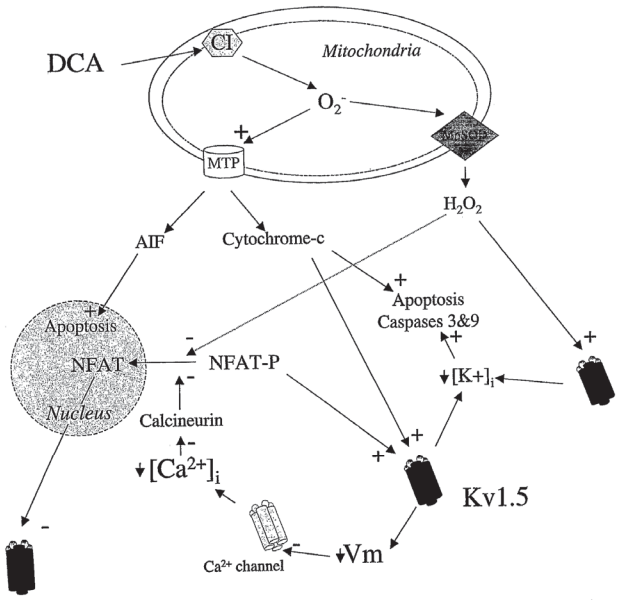

Fig. 26. Dichloroacetate's proposed action mechanism [97]

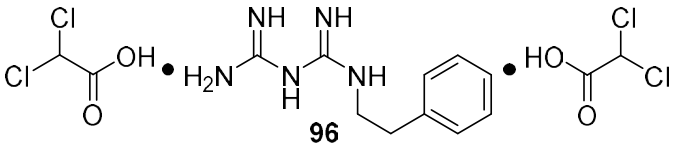

Fig. 27. Structure of para-dichloroacetate phenformin (**96**)

Additionally, our research encompassed the biological activity assessment of synthesized compounds [22].

To evaluate the compounds' **97–99** antitumor activity, *in vitro* studies were conducted at a concentration of 10^{-5} mol/l (Fig. 28). The experiments encompassed 60 cancer cell lines representing a broad human oncological disease spectrum, including lung, breast, ovarian, leukaemia, colon cancer lines, kidney, melanoma, prostate, and CNS cancer [100–102]. The results indicated that compounds **97–99** exhibited moderate effects on specific melanoma, leukaemia, and kidney cancer cell lines (Table 1) [22].

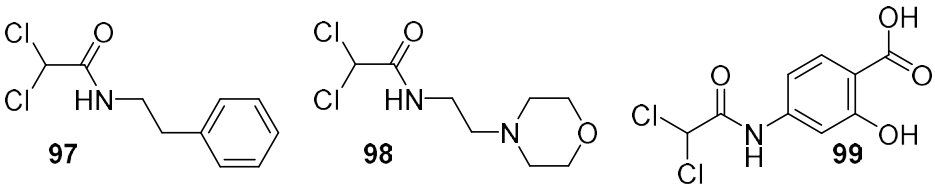

Fig. 28. Structure of synthesized amides (**97–99**)

Table 1

Compounds 97–99 antitumor activities at a concentration of 10–5 mol/l *in vitro* on 60 cancer cell lines

Compound	Average mitotic activity, %	The mitotic activity range, %	The most sensitive cancer cell lines and their mitotic activity when using compounds (GP, %)
97	104.58	91.45÷118.12	UO-31 (91.45) kidney cancer
98	102.11	90.51÷120.72	UO-31 (90.51) kidney cancer SR (90.70) leukemia
99	104.54	45.83÷122.08	LOX IMV (45.83) melanoma A498 (82.74) kidney cancer

Under the 4-(2,2-dichloroacetylamino)-2-hydroxybenzoic acid 9 influence, the LOX IMV melanoma cell line mitotic activity decreased to 45.83 %. This compound also demonstrated a moderate cytostatic effect on the A498 kidney cancer cell line. In summary, the preliminary findings from the antitumor activity assessment suggest promising prospects for the development of potential anticancer agents within the dichloroarylacetamides group [22].

Limitations of the study. Despite the considerable effort that went into this study, it has several limitations that should be considered. First, our literature review is limited to those sources that were available in scientometric databases such as PubMed, Scopus, Web of Science, Google Scholar, and Espacenet. Although these databases provide a wide information range, other potentially relevant sources may have been missed.

Second, although we used different keywords to find relevant sources, there may be other keywords that could lead to other relevant sources.

Third, our conclusions are based on an available data analysis. Since we have not conducted our own experiments or clinical trials, our conclusions depend on the quality and reliability of the data presented in the primary sources.

Finally, although our results support the potential efficacy of dichloroacetic acid and its derivatives in cancer and other disease treatments, further studies are needed to fully understand the mechanisms of these compounds' action and their potential side effects. Our results serve as a starting point for further research in this area.

These limitations do not diminish our study's significance, but they do highlight the need for further research on dichloroacetic acid derivatives.

Prospects for further research. Our findings indicate the great potential of dichloroacetic acid derivatives in medical science, but they also open up new directions for further research. First, more research is needed to fully understand the action mechanisms of these compounds. This includes the study of their interaction with biological molecules and their influence on various biological processes.

Second, more clinical trials are needed to evaluate the efficacy and safety of these compounds in humans. This includes studying their potential side effects and interactions with other medications.

Third, the development of new compounds based on dichloroacetic acid that may have improved therapeutic properties or reduced side effects should be considered.

Finally, more research needs to be done on the possibility of using dichloroacetic acid and its derivatives to treat diseases other than cancer. This may include studying their potential use in the treatment of neurodegenerative diseases, cardiovascular diseases, and infectious diseases.

These prospects for further research emphasise the significance of our study and the importance of further study of dichloroacetic acid derivatives in medical science. We hope that our review will stimulate further research in this area.

4. Conclusion

In this literature review, we investigated the importance of dichloroacetic acid derivatives in medicinal chemistry. In summary, dichloroacetate derivatives are an invaluable asset in the medicinal chemist's toolbox, offering unparalleled versatility in drug development. These compounds facilitate the precise chemical modifications that underlie the pharmacokinetics and pharmacodynamics fine-tuning required to create new therapeutics. The evolution of sustainable synthesis methods is expanding its availability, promoting more efficient and environmentally responsible drug development practices. Its applications cover a wide range of therapeutic areas, making them indispensable in drug development, including nonsteroidal anti-inflammatory drugs, antimicrobial agents, and the synthesis of prodrugs. In addition, these derivatives have an excellent ability to influence biological activity through small structural adjustments, which is promising for the creation of more effective drug candidates.

The potential for controlled drug release of dichloroacetate derivatives opens new avenues for improving therapeutic outcomes and patient compliance, particularly in the context of targeted drug delivery systems. Applying green chemistry principles in its synthesis and application is not only an ethical imperative but also a strategic necessity for solving regulatory requirements and environmental problems. In this light, DCA derivatives continue to play a key role in medicinal and pharmaceutical chemistry development, offering a sustainable and innovative path to pharmaceutical development and the search for new therapeutic solutions.

Conflict of interest

The authors declare that they have no conflict of interest concerning this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

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Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

Data availability

Manuscript has no associated data.

Use of artificial intelligence

The authors confirm that they did not use artificial intelligence technologies when creating the current work.

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