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PROSPECTS FOR THE CHEMISTRY OF IMIDAZOLE DERIVATIVES (Review)

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Abstract. *Introduction.* The problem of creating new effective domestic pharmacological preparations, including the development of the methods for obtaining biologically active substances in compliance with the "green chemistry" principles, are among the priority areas for the development of chemical science. The choice of an initial molecule, which carries the potential of biological activity, is the guarantor of a successful experimental search. Imidazole derivatives occupy a unique place in the medicinal chemistry. An imidazole cycle is part of the natural compounds such as histamine, biotin, some alkaloids and nucleic acids, and is a structural fragment of medicinal preparations. *The goal* of the present review is to analyze the publications on the chemistry of imidazole derivatives with an emphasis on the methods of obtaining biologically active and other practically useful molecules with an obligatory imidazole cycle. *The objects of the study:* imidazole derivatives. The examples of the routes of synthesizing imidazole derivatives, as well as the compounds of interest for the medicinal chemistry, agriculture, and other fields, which have been published in the scientific and technical literature since 2000, have been presented. *Conclusion.* The studies in the field of searching for new highly effective preparations among imidazole derivatives are relevant and promising. The most important stage in this search is the directed synthesis of the substances with the specified, practically useful properties. The range of new practically useful substances in the series of imidazole derivatives has been significantly expanded and replenished thanks to the modern modifications of the classical methods of their obtaining.

Key words: imidazole, imidazole derivatives, synthesis, structure, biological activity

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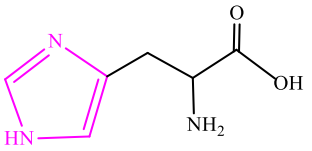
1. Introduction

Imidazole is an organic compound with the formula C_3H_4N. The imidazole ring is a valuable component of many important molecules, including natural products, bioactive molecules, ionic liquids, and imidazoliums. An imidazole fragment is part of the most important amino acids, i.e. histidine (1) and histamine (2).



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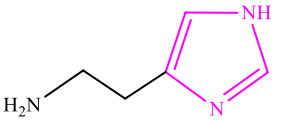
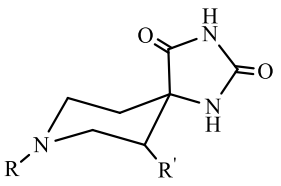


2

The pK_a of imidazole is 14.5 and the pK_b is 8.8. These indicators contribute to the widespread use of the derivatives of this class in various fields [1]. The literature describes a huge potential for the broad-spectrum pharmacological activities, in particular, antiviral [2], antifungal and antibacterial [3], anti-inflammatory and analgesic [4], anti-stress, anti-cancer, anti-tuberculosis [5] activities.

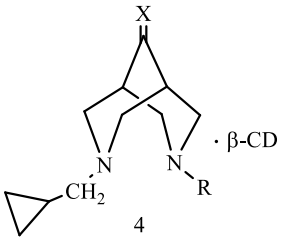
The substances (3-5), possessing an obligatory N-alkoxyalkylpiperidine fragment in the molecular structure, and a high pharmacological activity, have been discovered at the Laboratory of Chemistry of Synthetic and Natural Medicinal Substances of JSC «A.B. Bekturov Institute of Chemical Sciences» [6-8].



3

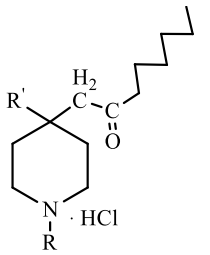
R = $CH_2CH_2OCH_2CH_3$, $CH_2CH_2CH_2OCH_2CH_2CH_3$, $CH_2CH_2CH_2OCH_2CH_2CH_2CH_3$;
R' = H, CH_3

Myelostimulators



4

X = 2H, $NOCOC_6H_5$;
R = $CH_2CH_2CH_2OCH(CH_3)_2$



5

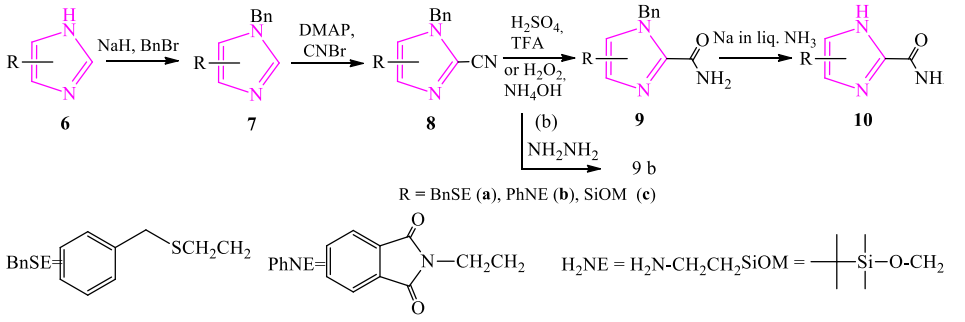
R = $C_3H_6OC_2H_5$;
R' = OH, $OCOCH_3$, $OCOC_2H_5$, $OCOC_6H_5$

Local anesthetics

The idea of "marrying" N-alkoxyalkylpiperidine with the imidazole ring seems to be quite logical. Prior to starting an experimental research, we have set a goal to analyze the scientific literature for the period starting from 2000 on the chemistry of imidazole derivatives with an emphasis on the methods for obtaining biologically active molecules with an obligatory imidazole cycle.

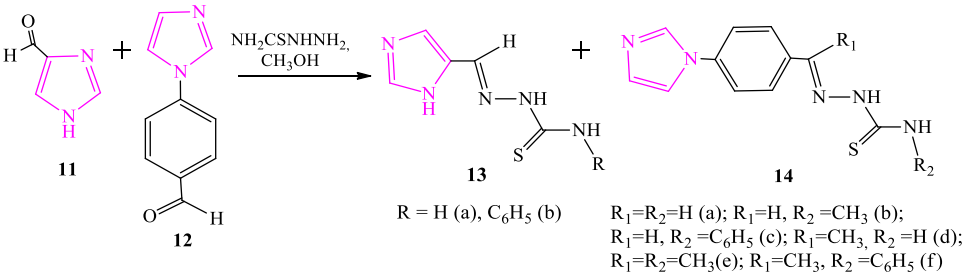
2. Synthesis of biologically active imidazole derivatives

Feng Liang et al. [9] synthesized a number of 1*H*-imidazole-2-carboxamides, which could be used for the DNA recognition. From 4(5)-(2-(benzylthio)ethyl)-1*H*-imidazole (6 a),N-phthaloylhistamine (6 b), and 4(5)-(2-thioethyl)-1*H*-imidazole-2-carboxamides (10 a-c) were obtained, which (thiol and amine) served for the attachment of a molecule to the metal or carbon electrodes. 4(5)-(Tertbutyldimethylsilyloxymethyl)-1*H*-imidazole (6 c) was synthesized in a similar way, and used as a sample in the NMR studies. The two different methods for obtaining 1*H*-imidazole-2-carboxamides were studied, and it was shown that the 2nd position of imidazole could be converted into an ether or cyano group, and subsequently into an amide. The bonding with the protected nitrogen atom 1-N in compounds (7 a-c) was carried out by the interaction of sodium salt and benzyl bromide. By comparing different protecting groups such as the trityl and Boc groups, the benzyl group was found to be the most effective protecting group for the subsequent reaction of cyanation. The cyano group was introduced into the 2nd position of the imidazole ring by treating thereof with 1-cyano-4-(dimethylamino)pyridinium bromide (CAP). CAP was obtained by the reaction of the equivalent amounts of cyanogen bromide and 4-(dimethylamino)pyridine (8 a) in dimethylformamide. The cyano group was converted into the amide group (9 a) with the yield of 46% upon the hydrolysis in the presence of a mixture of 20% sulfuric acid and 18% triphosphate. Because of hydrogen peroxide, (8 b) is changed to (9 b) and (8 c) to (9 c). The final products (10 a-c)were obtained by removing the sodium and benzyl groups by the treatment with liquid ammonia.

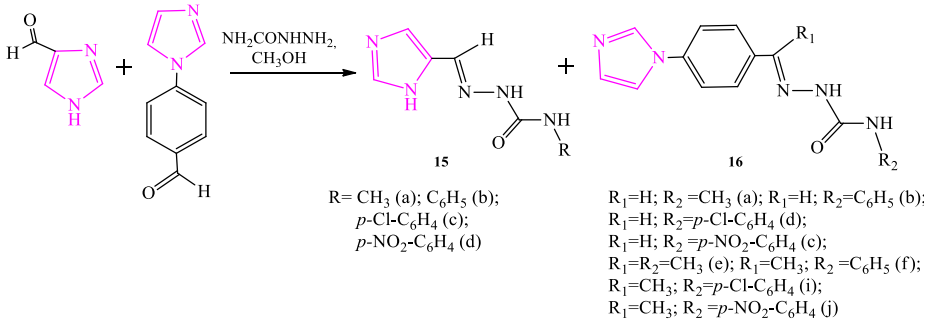


6 **7** **8** **9** **10**

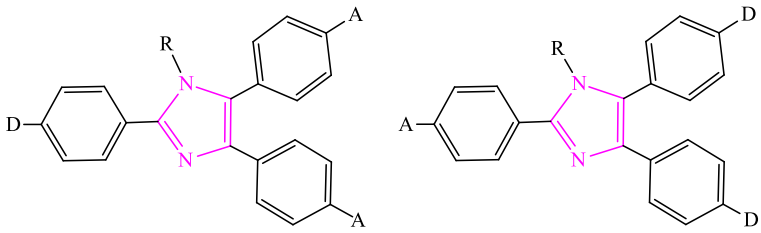
The potential of imidazole derivatives of thiosemicarbazones and hydrazones [10] as the antifungal agents against *A. flavus* and *C. cladosporioides* was demonstrated. An interaction of the equimolar amounts of 4(5)-imidazole-carboxyaldehyde and 4-(1*H*-imidazol-1-yl) benzaldehyde (11) and 4-(1*H*-imidazol-1-yl) acetophenone (12) in the presence of thiosemicarbazides in methanol provided thiosemicarbazone derivatives (13 a-b, 14 a-h). The reaction mixture was stirred for 6 h, cooled to the r.t., the resulting solid was filtered off, washed with ethanol and ether, and dried in vacuum.



Imidazolyl hydrazone derivatives (15 a-d, 16 a-j) were synthesized by the reaction of an equimolar dose (2 mmol) of 4(5)-imidazole-carboxyaldehyde and 4-(1*H*-imidazol-1-yl)benzaldehyde or 4-(1*H*-imidazol-1-yl)hydrazide in the presence of hydrazide in methanol, upon adding 3 drops of acetic acid as a catalyst [10]:

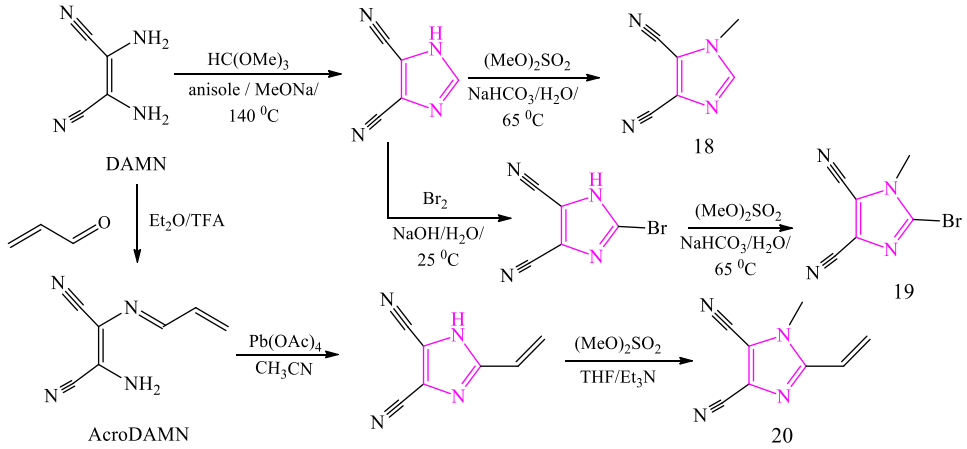


A simultaneous condensation of α-diketones and aldehydes in the presence of ammonia or ammonium salts (the Debus-Radziszewski synthesis) is one of the oldest, most versatile, and frequently used methods for the synthesis of imidazole derivatives. This simple synthetic method is widely used for obtaining chromophores - 2,4,5-triarylimidazole derivatives, which are used as an optical carrier for data storage or switching in modulating devices.There are possible two principalorientations to generate Y-shaped imidazole chromophores (17) as shown bottom. The first classof chromophores (D-π-IM-(π-A)2 systems) are generated by the donor which is appended through an additional π-linker (aryl) to the imidazole C_2, completed with two peripheral acceptorslinked at the imidazole C_4/C_5 positions. The second class(A-π-IM-(π-D)2 systems) possesses one acceptor and twodonors in the reversed orientation[11-15].



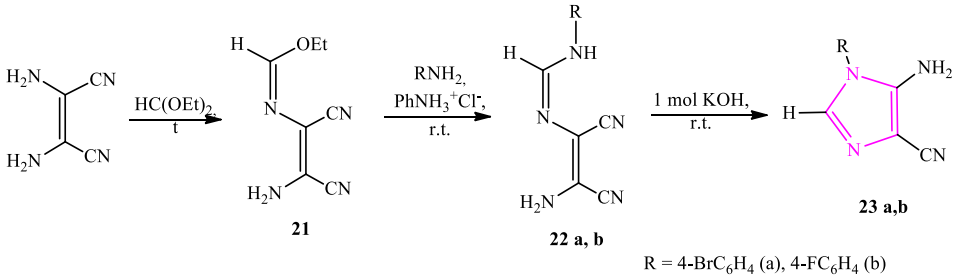
17 D = NMe_2, OMe, H
A = NO_2, SO_2, CN
R = H, alkyl, aryl, etc.

It turned out that the synthesis of 4,5-dicyanimidazole “opened” a convenient preparative way of obtaining diverse imidazole derivatives as popular components with the acceptor properties. 1-Methylimidazole-4,5-dicarbonitrile (18), 2-bromomethylimidazole-4,5-dicarbonitrile (19), and 1-methyl-2-vinylimidazole-4,5-dicarbonitrile (20), which were both acceptor fragments and donors, expanding π-conjugated bonds, were obtained in different reactions from diaminomaleonitrile(DAMN) [16–17].



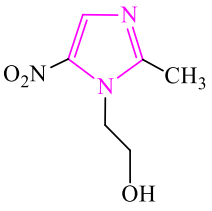
Significant contributions to obtaining imidazole-containing chromophores with excellent thermal stability in the guest environment (the host systems), and good miscibility with high-performance polymers, were made by Bu X.R. et al. [18-21]. Besides, the fragments of thiophene or thiazole were introduced into the structure of the synthesized imidazoles. The studies in the field of imidalozol chromophores were continued in the works [22–26], where it was shown that the nitro-, dimethylamino-groups performed the function of an acceptor and a donor, in polarizing the π-bonds with the release of blue light.

Imidazole derivatives were synthesized as synthons for obtaining purines, widely used in the pharmaceutical industry[27]:



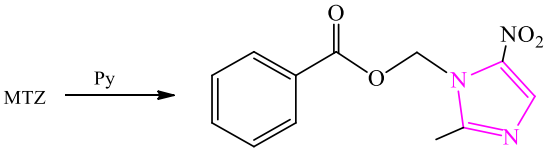
New 5-amino-1-phenyl-1*H*-imidazole-4 carbonitriles (23 a-b) were formed during the cyclization of formamidine in the presence of a strong base KOH by way of multi-stage synthesis, including the stage of interaction of ethanol with phenylalanine in the molar ratio of 1:1 into new formamidines (22 a-b). And thenthe reaction followed by their interaction with the primary amines upon the catalysis by hydrochloride of ethyl (Z) -N- (2-amino-1,2-diacyaninyl) aniline formimidate (21). Purines were further obtained by treating 5-amino-1-phenyl-1*H*-imidazole-4 carbonitriles with ammonia.

The preparation metronidazole refers to 5-nitroimidazoles (24), and has a wide spectrum of activity against anaerobic microorganisms[28]:



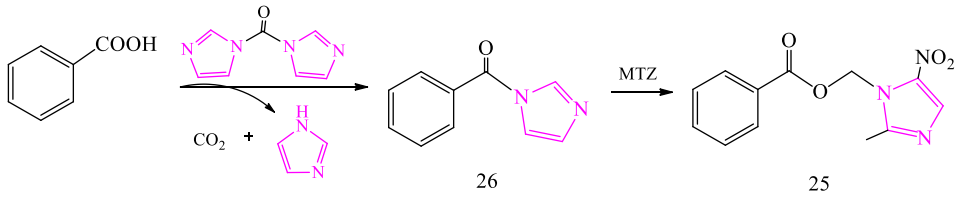
24

Its use may result in changing the patients' taste sensations, including a "metallic" taste. In order to eliminate this shortcoming, benzoylmetronidazole (HPLC)(25) was created by way of a two-stage synthesisfrommetronidazole(MTZ)[29]:



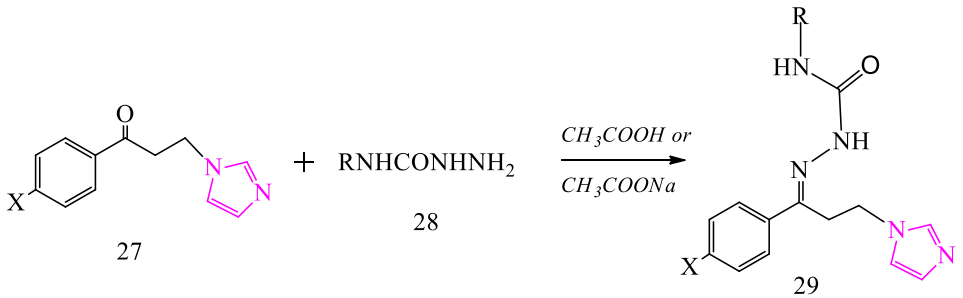
25

An alternative method for obtaining MTZ included carrying out the two consecutive one-pot steps through the formation of benzoylimidazole (26) with the use of N,N-carbonyldiimidazole:



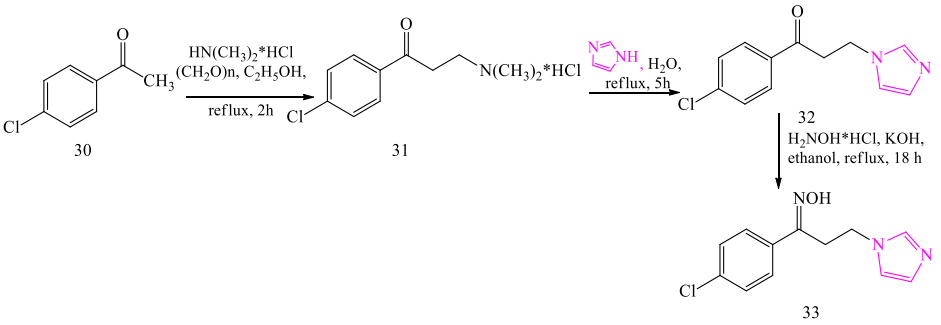
Huang Q.,etal.[29]found that the by-product of the first stage, imidazole, played the role of a catalyst, contributing to obtaining the target benzoylmetronidazole. Besides, it was shownthat β-cyclodextrin could be a pharmaceutical solvent for benzoylmetronidazole, and could improve its bioavailability, since it was found that the solubility of benzoylmetronidazole (S=0.1435 g/l) in water with the formation of 1:1 benzoylmetronidazole/β-cyclodextrin complexes significantly, by 9.7 times, (S=1.3881 g/l), increased its solubility.

Alkylimidazole anticonvulsants (nafimidone and denzymol), containing both the imidazole fragments and arylsemicarbazone pharmacophores, and arylsemicarbazone antacids [30-32], related to the derivatives of (2*E*)-2-[3-(1*H*-imidazol-yl)-1-phenylpropylidene]hydrazine-carboxamide (29) [33]. The compounds were synthesized by the interaction of the solutions of the corresponding ketones (27) in acetic acid or sodium acetate in ethanol for 18 h with semicarbazide and/or semicarbazide hydrochloride (28):



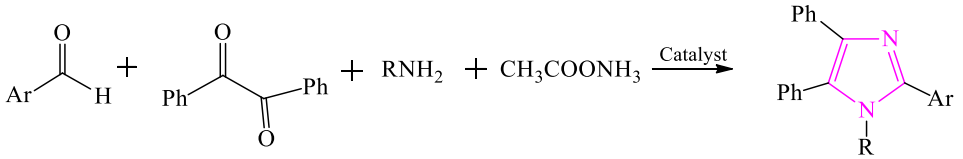
X = H, Br or OCH_3; R = H or Ar

Attia M.I. et al. [34] proposed to synthesize the Mannich base (31) for obtaining antifungal agents by the reaction of 4-chloroacetophenone (30) with paraformaldehyde, dimethylamine hydrochloride with the addition of a catalytic amount of hydrochloric acid. Further, imidazole was alkylated with the obtained Mannich base (31) in water for 5 h. The oxime (33) was obtained by the reaction of imidazole-ketone (32) with hydroxylamine hydrochloride and potassium hydroxide in ethanol.



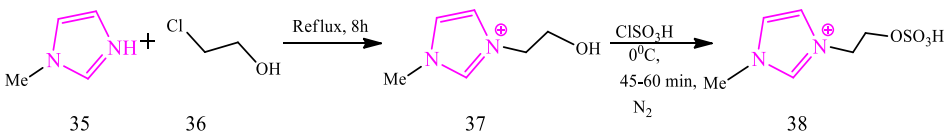
An interest in the chemistry of tetrasubstituted imidazoles was aroused due to their wide range of pharmacological properties - they were structural fragments of the preparations for the treatment of psychosis, anxiety, depression, attention deficit, memory disorders, cognitive impairment, appetite disorders, obesity etc.[34].

The synthesis of tetrasubstituted imidazole derivatives was carried out only under the catalytic conditions [35]. The condensation of benzyl, benzylamine, benzaldehyde, and ammonium acetate was carried out in many solvents in the presence of various amounts ofcatalyst$K_7Na_3P_2W_{18}Cu_4O_{68}$. But when the reaction was carried out without a solvent at 140^oC, imidazole 1,2,4,5-tetraazole (34) was obtained with the yield of 92%.As a result of the study of the fungicidal action of substance against 9 strains of phytopathogen fungi, compoundwas identified with a high level of fungicidal activityin for glioma cells.

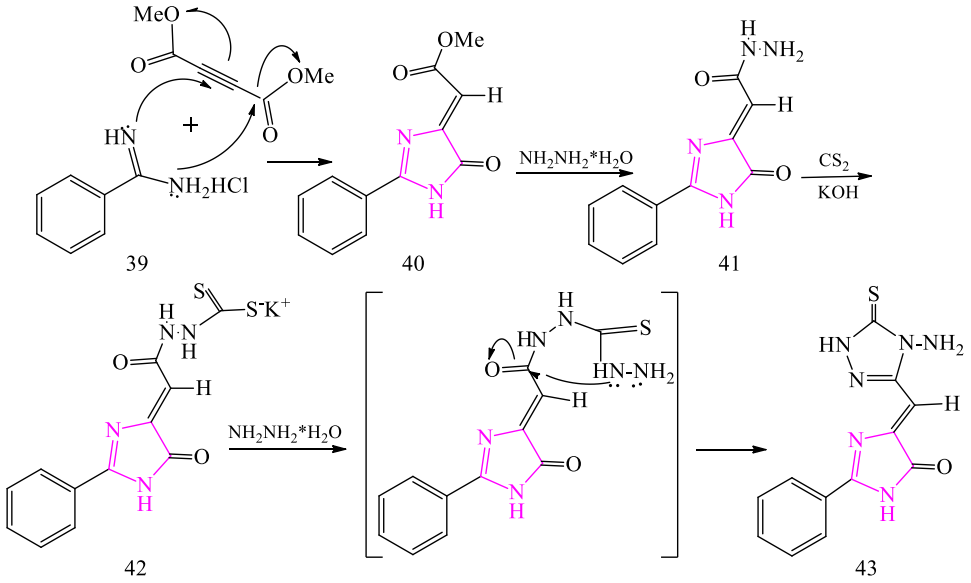


The research chemists under the leadership of Ali Javid [36] carried out this reaction in the presence of the Preisler catalyst ($H_{14}[NaP_5W_{30}O_{110}]$), and 1,2,4,5-tetrasubstituted imidazoles (34) were obtained with the yield of 48-97%.

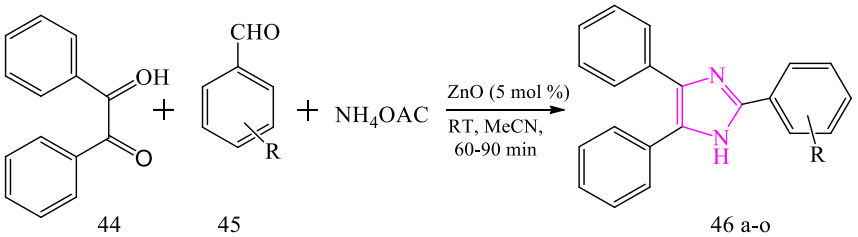
To obtain biologically active substances, imidazoles were synthesized under the conditions of the Biginelli reaction in the presence of the Bronsted acids [37]. Thus, 1-methylimidazole (35) and 2-chloroethanol (36) were subjected to chloroformation by dropping 97% stoichiometric amount of chlorosulfonic acid (37) at 0°C for 45–60 min in vacuum to form 1-methyl-3-(2-hydroxyethyl)imidazole chloride (38):



The paper [38] described the synthesis of new imidazole and triazole derivatives with antifungal, antibacterial, antiparasitic, hypocholesterolemic, hypotensive, and anti-inflammatory activities. Benzimidinium chloride (39) was mixed with dimethylacetylenedicarboxylate (DMAD) in methanol. After heating the mixture, 2-phenyl-4-methoxycarbonylmethylene-1(3*H*)-imidazol-5-one (40) was formed. The latter reacts with hydrazine hydrate in methanol to yield 2-phenyl-4-hydrazinecarbonylmethylene-1(3*H*)-imidazol-5-one (41). Carbon disulfide and potassium hydroxide were added to 2-phenyl-4-hydrazinecarbonylmethylene-1(3*H*)-imidazol-5-one (41) in ethanol to synthesize N-[(2-phenyl-1(3*H*)-imidazol-5-on-4-ylidene)acetyl]hydrazine potassium carbodithioate (42). Following this, carbodithioate without further purification, and hydrazine hydrate in water refluxed while stirring to furnish 4-(4-amino-5-thioxo-4,5-dihydro-1*H*-1,2,4-triazol-3-ylmethylen)-2-phenyl-1(3*H*)-imidazol-5-one (43).



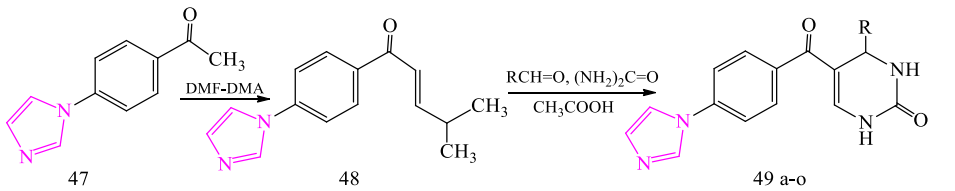
An accelerated and improved one-pot synthesis of 2,4,6-triphenyl-1*H*-imidazoles (46 a-o) was carried out by the reaction of benzyl (44), aromatic aldehydes (45), and ammonium acetate (NH_4OAc) in the presence of ZnO. The indicated route of synthesis represented an environmentally friendly, sparing reaction, leading within a short time to new imidazole derivatives with the yield of 60-93% [40].



44 45 46 a-o

R=H (a); R=4-Me (b); R=4-Br (c); R=2-Cl (d);
R=4-Cl (e); R=3-NO_2 (f); R=2-OH (g); R=4-OMe (h);
R=4-OH (i); R=3,4-$(OMe)_2$ (j); R=2-NO_2 (k);
R=4-NO_2 (l); R=2-F (m); R=4-F (n); R=2-Me (o)

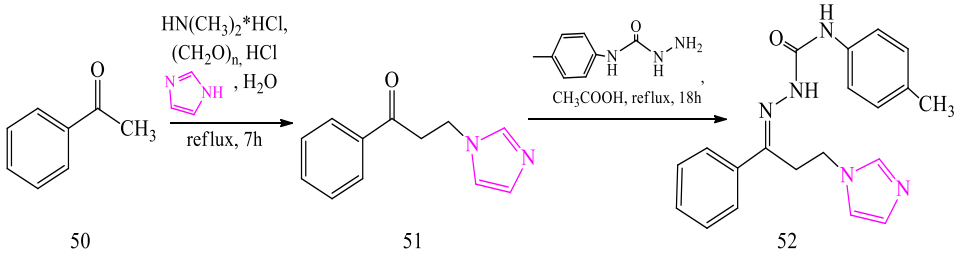
The compounds, containing two important frameworks, imidazole and dihydropyrimidinone, looked attractive from the point of view of the therapeutic potential. Bhat M.A. et al. [41] synthesized imidazole derivatives of dihydropyrimidinone. (2E)-1-[4-(1*H*-Imidazol-1-yl)phenyl]-4-methylpent-2-en-1-one (48) was synthesized by refluxing 1-[4-(1*H*-imidazol-1-yl)phenyl]ethan-1-one (47) with dimethylformamide-dimethylacetal (DMF-DMA) for 12 h without a solvent. Further, dihydropyrimidinone derivatives (49 a-o) with an imidazolyl fragment were obtained by the interaction of the obtained enaminone with urea and various substituted benzaldehydes in the presence of glacial acetic acid.



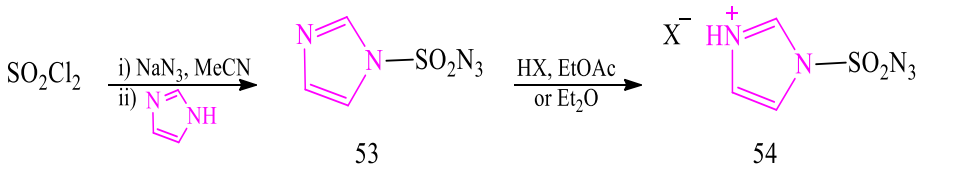
47 48 49 a-o

R=C_6H_5 (a); R=2-NO_2-C_6H_4 (b); R=4-NO_2-C_6H_4 (c); R=3-NO_2-C_6H_4 (d);
R=4-Cl-C_6H_4 (e); R=2,4-$(Cl)_2$-C_6H_3 (f); R=2-OCH_3-C_6H_4 (g);
R=4-OH-C_6H_4 (h); R=3-OH-C_6H_4 (i); R-OCH_3-C_6H_4 (j); R=2,4,5-$(OCH_3)_3$-C_6H_2 (k);
R=2,3,4-$(OCH_3)_3$-C_6H_2 (l); R=3,4,5-$(OCH_3)_3$-C_6H_2 (m);
R=2,4,6-$(OCH_3)_3$-C_6H_2 (n); R=3,4-$(OCH_3)_2$-C_6H_3 (o)

To obtain the preparations for the treatment of neurological disorders, (2E)-2-[3-(1*H*-imidazol-1-yl)-1-phenylpropylidene]-N-(4-methylphenyl)hydrazinecarbo-xamide (52) was synthesized by the interaction of N-(4-methylphenyl)hydrazine-carboxamide, which obtained from acetophenone (50),with 3-(1*H*-imidazol-1-yl)-1-phenylpropan-1-one (51) in the presence of glacial acetic acid in alcohol [42].

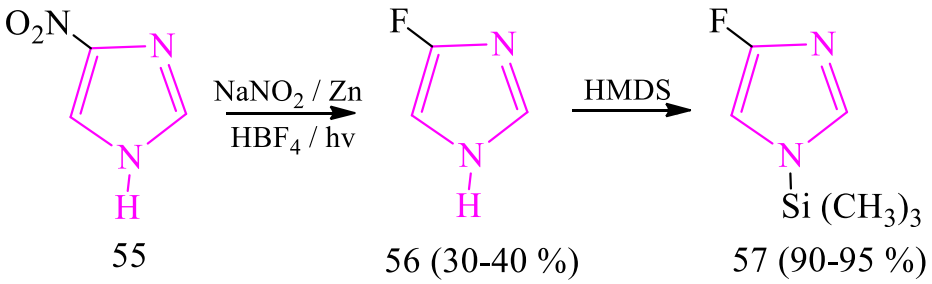


It was found that imidazole-1-sulfonylazide hydrochloride [43] was an effective reagent, sensitive to shocks, heat, and friction. It was shown that imidazole-1-sulfonyl azide (53) was easily formed by adding an equimolar amount of sodium azide in acetonitrile to sulfofuryl chloride, followed by dropping 2 moles of imidazole into the reaction mixture. The salts (54) of the target product were obtained by the reaction of the corresponding acid in ethyl acetate or diethyl ether:



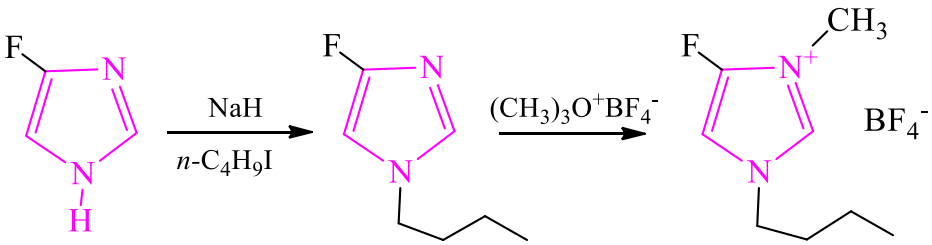
A review of the chemistry of fluoroimidazoles and their heteroannelated derivatives was published in 2014 by Nossova et al. [44]. The review considered the syntheses, chemical properties, biological significance, and other properties of the fluoroimidazole class of heterocycles.

For the studies [45], aimed at changing the basicity of the axial ribonucleoside coenzyme residue, 5'-deoxyadenosycobalamine, a fluoroimidazole-substituted ribonucleoside was synthesized. The choice of fluoroimidazole as a heterocyclic component of the ribonucleoside was necessitated by the requirement to a fragment, which could be easily glycosylated into a ribosyl unit. 4-Fluoro-N-trimethylsilylimidazole (57) acted as the required heterocyclic component. The latter was obtained by the reduction-diazotization of 4-nitro-1*H*-imidazole (55) with the $NaNO_2$/Zn mixture, followed by the photolysis in the presence of aqueous tetrafluoroboric acid to form 4-fluoro-1*H*-imidazole (56) with the yield of 30–40%. The fluorine derivative was treated with hexamethyldisilazide(HMDS) /reflux for 10 h to yield the desired N-TMS derivative (90-95%) as an intermediate product for glycosylation.



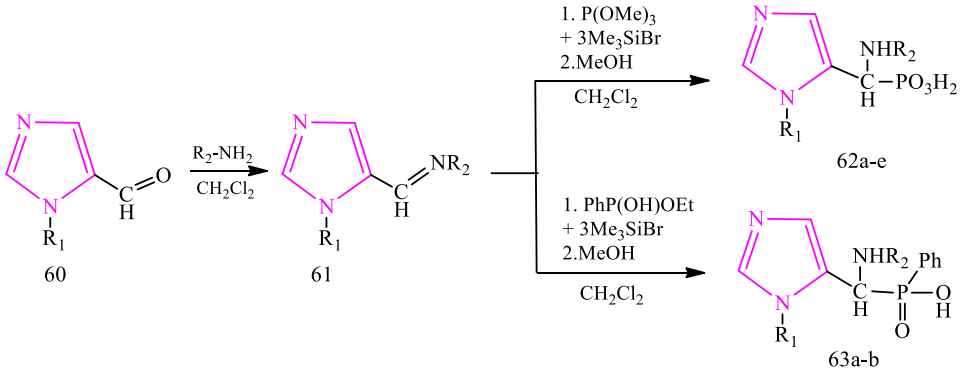
55 56 (30-40 %) 57 (90-95 %)

Lingsheid Y., Paul M., Breohl A., Giernoth R. proposed a scheme for obtaining the fluoroimidazole analogues [46]. 1-Butyl-4-fluoro-1*H*-imidazole (58)was obtained by deprotonation, using sodium hydride in N,N-dimethylformamide, followed by alkylation with 1-iodobutane. The process proceeded selectively. The subsequent treatment of N-butylfluoroimidazole with trimethyloxonium fluoroborate in dichloromethane resulted1-butyl-4-fluoro-3-methyl-1*H*-imidazol-3-ium tetrafluoroborate(BMIMBF4)(59)in an ionic liquid:



58 59

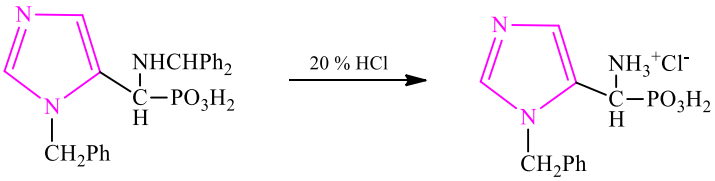
With the purpose to obtain new biologically active imidazole derivatives, and test their binding ability in relation to metal ions, Boduszek et al. [47-49] synthesized a number of imidazole-containing aminophosphonic and aminophosphinic acids, proving that imidazole aldehydes (60) reacted with the primary amines with the formation of the corresponding aldimines (61). The aldimines (61) reacted without isolation with a mixture of trimethyl phosphite (or ethylphenyl phosphinate) and bromotrimethylsilane to form phosphonic (or phosphinic) silylated intermediates, which, after treating with methanol yielded the final aminophosphonic (62 a-e) or aminophosphinic acid (63 a-b).



60 61

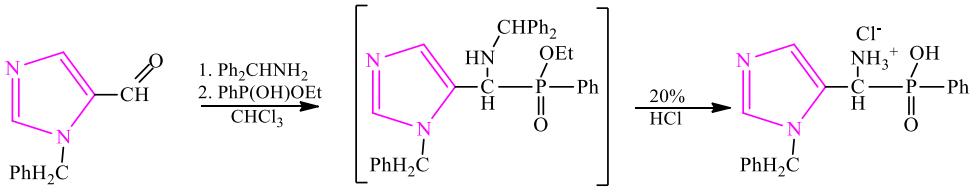
R_1 = H, R_2 = CH_2Ph (a); R_1 = CH_2Ph, R_2 = CH_2Ph (b); R_1 = H, R_2 =Bu (c);
R_1 = CH_2Ph, R_2 = Bu (d); R_1 = CH_2Ph, R_2 = $CHPh_2$ (e)

1-Benzylimidazole-5-(amino)methylphosphonic acid (62f) was obtained by heating the N-benzidryl derivative (62e) with hydrochloric acid. During the hydrolysis, the benzhydryl group was removed, forming aminophosphonic acid (62 f) in the form of a hydrochloride.



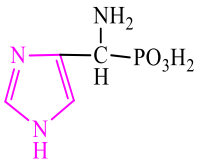
62 e 62 f

1-Benzylimidazole-5-(amino)methylphosphinic acid (64) was obtained in the one-pot reaction as shown below:

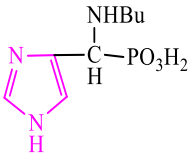


64

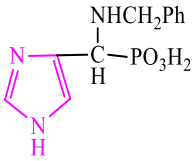
Sobek et al. [50] showed, using the potentiometric titration and spectroscopic data, that the introduction of imidazole into the aminophosphonate fragments (65-68) resulted in a very powerful ligand for Cu (II) and Ni (II) ions, and also increased anantimetabolites activity of the modified molecules.



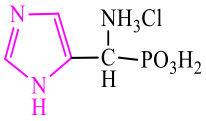
65
(amino)(1H-imidazol-4-yl)methyl phosphonic acid



66
imidazole-4-methyl-(N-buthylamino) phosphonic acid



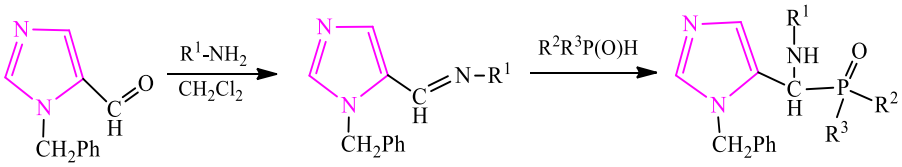
67
imidazole-4-methyl-(N-benzhylamino) phosphonic acid



68
1-benzylimidazole-5-methyl(amino) phosphonic acid

It was established that the phosphonic function was the main donor system in the media with pH below 6, and above this pH value the ligand was coordinated with a metal ion, with the participation of nitrogens of the amino and imidazole groups.

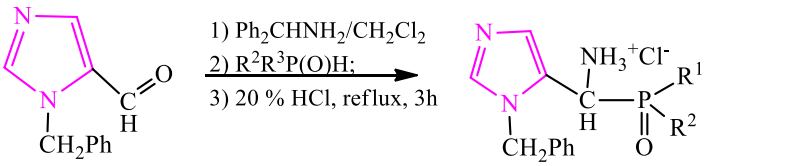
The authors [51] studied the effect of the imidazole fragment in 1-benzylimidazole-5-carboxaldehyde with the primary amines, with the formation of the corresponding aldimines, using the standard procedure under the mild conditions, followed by the reaction of aldimines with phosphine oxides at the r.t.in the inert solvent (CH_2Cl_2) to obtain imidazole aminophosphine oxides (69 a-d) in high yields:



69 a-d, 52-65 %

R_1 = Bu; R_2 = Ph, R_3=Ph (a):
R_1 = CH_2Ph, R_2 = Ph, R_3=Ph (b);
R_1 = Bu, R_2 =Bu, R_3 =Bu (c);
R_1 = CH_2Ph, R_2 = CH_3, R_3 =Bu (d)

It was established that the use of benzhydrylamine (Ph_2CHNH_2) in the reaction with an aldehyde made it possible to obtain some imidazolaminophosphine oxides with a free amino group. The benzhydryl group in the intermediate N-benzhydryl derivatives (70 a-d) were removed by the hydrolysis with hydrochloric acid, resulting in the final products in the form of hydrochlorides.

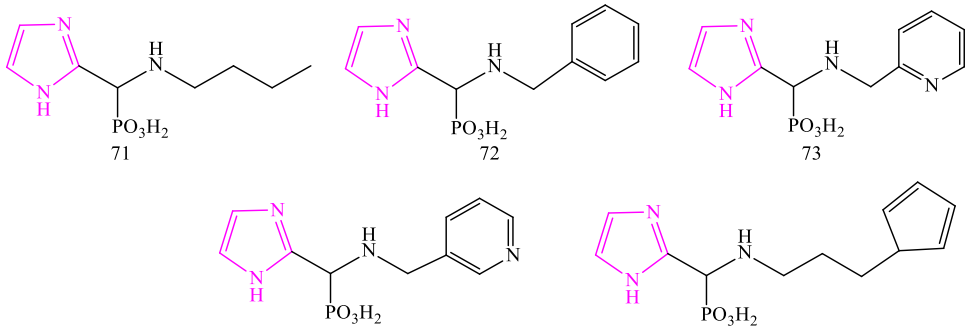


70 a-d, 51-58 %

R^1 = Ph, R^2 = Ph (a);
R^1 = Bu, R^2 = Bu (b);
R^1 = Bu, R^2 =Ph (c);
R^1 = CH_3, R^2 =Ph (d)

Some of the synthesized imidazolamine phosphine oxides were studied as new binding reagents for the transition metal ions [51].

It was shown [52–55], that the presence of the imidazole ring made phosphonates (71-75) much more effective chelating ligands with nickel (II) ions than the previously developed 4-substituted imidazoles. Further, M. Pirkosz et al. [62] studied the solutions of Cu (II) and Ni (II) complexes of a new N-substituted imidazol-2-yl (amino)methylphosphonate for using as a chelating agent in the analytical chemistry, for the industrial purification, removal of toxic metal ions from the environment, or as the inhibitors of corrosion.



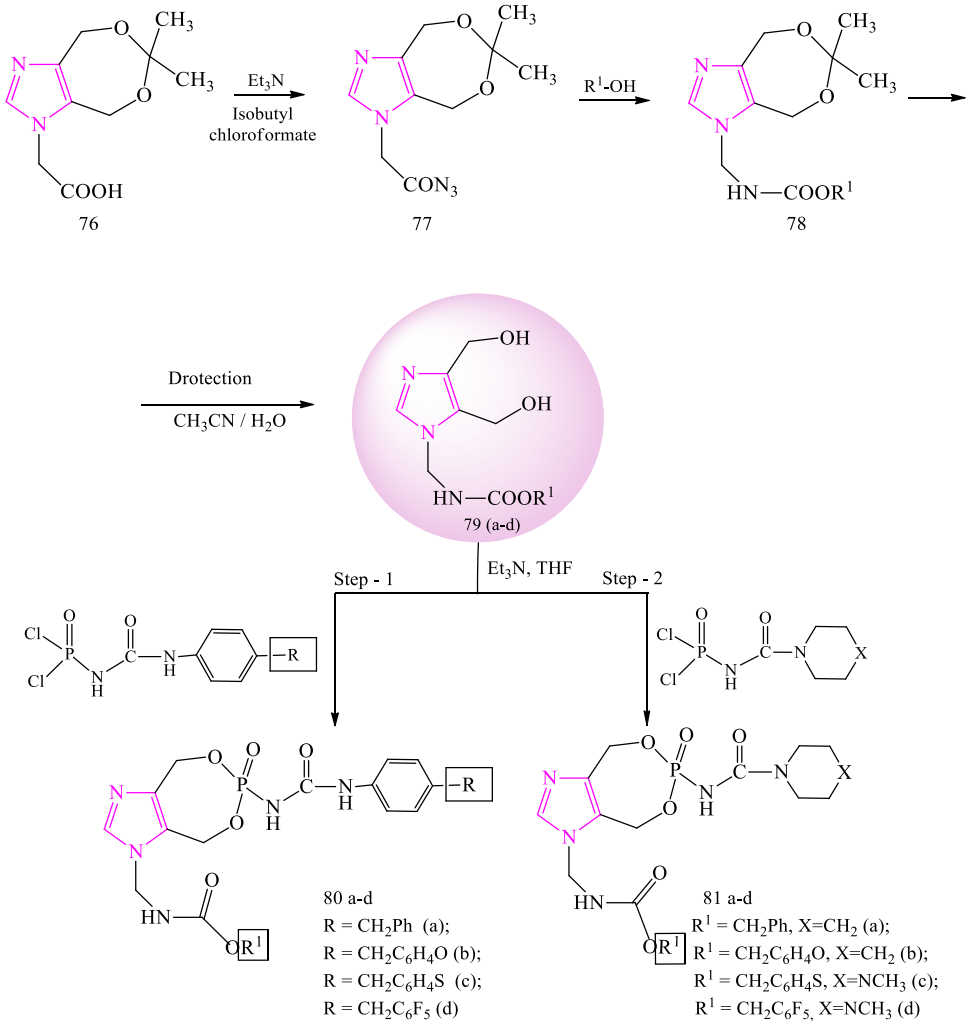
71 72 73

74 75

The study [56] showed, that the introduction of pyridine as an additional donor into the side chain further increased a binding capacity of the ligand. The efficiency of this compound was due to the chelation of metal ions through the nitrogens of imidazole, imino group and pyridine.

It is well known that imidazole derivatives have a wide spectrum of pharmacological activity, including valuable vasodilators and vasoconstrictors [57].The chemistry of nitrogen-containing heterocyclic phosphorus compounds attracts great attention of chemists due to their wide range of application in agriculture, medicine and industry. For example, the authors [58] synthesized imidazole substituted carbamate ureido/carboxamides via the Curtius rearrangement.These newly synthesized compounds were showed antibacterial

and antifungal activities.The antibacterial activity of carbamates containing imidazole ureas/caboxamides dioxaphosphepinoes were screened against the *Staphylococcus aureus*, *Bacillus cerus* and *Escherichia coli*. Antifungal activity of compounds were screened against *Aspergillus niger* and *Candida albicans*. Ketoconazole and Amoxicillin are tested as references compound to compare the activities.



3. Conclusion

The performed analysis of the literature shows that imidazole derivatives are widely used in various fields as the medicinal preparations against microbes and bacteria, for the treatment of the nervous system diseases, seizures, etc., as well as anti-corrosion agents and dyes, catalysts, polymerizing agents, herbicides, fungicides, etc.

The most important step in this search is the targeted synthesis of the substances with the pre-set practically useful properties, associated with the identification issues, physicochemical characteristics and biological activity. Thanks to the modern modifications of the classical methods of obtaining, the range of new practically useful substances in the series of imidazole derivatives is significantly expanded and replenished.

The studies in the field of searching for new highly effective preparations among imidazoles is relevant, and is being intensively developed.

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Conflict of Interest: No conflict of interest.

ИМИДАЗОЛ ТУЫНДЫЛАРЫ ХИМИЯСЫНЫҢ БОЛАШАҒЫ (ШОЛУ)

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Түйіндеме. *Кіріспе.*Жаңа тиімді отандық фармакологиялық препараттарды құру мәселесі, оның ішінде «жасыл химия» қағидаттарын сақтай отырып, биологиялық белсенді заттарды алу әдістерін әзірлеу химия ғылымын дамытудың басым бағыттарының бірі болып табылады. Сәтті эксперименттік ізденістің кепілі биологиялық белсенділік потенциалы бар бастапқы молекуланы таңдау. Имидазол туындылары медициналық химияда ерекше орын алады. Имидазол циклі гистамин, биотин, кейбір алкалоидтар және нуклеин қышқылдары сияқты табиғи қосылыстардың бөлігі және дәрілік заттардың құрылымдық фрагменті болып есептелінеді. Бұл шолудың *мақсаты* міндетті имидазол циклі бар биологиялық белсенді молекулаларды алу жолына баса назар аудара отырып, имидазол туындыларының химиясы бойынша жарияланымдарды талдау. *Зерттеу нысандары:* имидазол туындылары. *Нәтижелері.* Имидазол туындыларын синтездеу жолдары ұсынылған, сонымен қатар 2000 жылдан бастап ғылыми және ғылыми-техникалық әдебиеттерде жарияланған дәрілік химия, ауыл шаруашылығы және басқа салалар үшін қызығушылық тудыратын қосылыстар келтірілген. *Қорытынды.* Имидазол туындылары арасында жаңа жоғары тиімді препараттарды іздеу саласындағы зерттеулер өзекті және мақсатты. Бұл ізденістің маңызды кезеңі-берілген пайдалы қасиеттері бар заттардың бағытталған синтезі. Өндірудің классикалық әдістерінің заманауи модификацияларының арқасында имидазол туындылары қатарында іс жүзінде жаңа пайдалы заттардың ауқымы едәуір кеңейеді және толықтырылады.

Түйінді сөздер: имидазол, имидазол туындылары, синтез,құрылыс, биологиялық белсенділік.

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ПЕРСПЕКТИВЫ ХИМИИ ПРОИЗВОДНЫХ ИМИДАЗОЛА (ОБЗОР)

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Резюме. *Введение.* Проблема создания новых эффективных отечественных фармакологических препаратов, включая разработку методов получения биологически активных веществ со соблюдением принципов «зеленой химии», входит в число приоритетных направлений развития химической науки. Выбор исходной молекулы, несущий потенциал биологической активности, служит гарантом успешного экспериментального поиска. Производные имидазола занимают уникальное место в медицинской химии. Имидазольный цикл входит в состав природных соединений, таких как гистамин, биотин, некоторые алкалоиды и нуклеиновые кислоты, и является структурным фрагментом лекарственных препаратов. Анализ публикаций по химии производных имидазола с акцентом на пути получения биологически активных и других практически полезных молекул с обязательным имидазольным циклом определен как *цель* данного обзора. *Объекты исследования:* производные имидазола. Приведены примеры путей синтеза производных имидазола, а также представлены соединения, представляющие интерес для медицинской химии, сельского хозяйства и других областей, опубликованных в научной и научно-технической литературе с 2000 г. *Заключение.* Исследования в области поиска новых высокоэффективных препаратов среди производных имидазола актуальны и перспективны. Важнейшим этапом этого поиска является направленный синтез веществ с заданными практически полезными свойствами. Благодаря современным модификациям классических методов получения значительно расширяется и пополняется круг новых практически полезных веществ в ряду производных имидазола.

Ключевые слова: имидазол, производные имидазола, синтез,строение, биологическая активность

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