Synthesis and antibacterial activity of benzimidazole amides based on computer-aided technology

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Abstract. Benzimidazole compounds are benzoheterocyclic compounds containing 2 nitrogen atoms. These compounds not only have broad-spectrum biological activities such as antihypertensive, antiparasitic, antibacterial and antifungal, but also play a great role in pharmacological activity and metal ligands. Therefore, the study of benzimidazole compounds has become one of the hot spots in recent years, especially in the field of medicinal chemistry. Benzimidazolamide compounds were synthesized from 2-mercaptobenzimidazole, 2-chloroacetamide, benzyl chloride, 2, 4-dichlorobenzyl chloride and 3-chlorobenzyl chloride by S-alkylation and n-alkylation reactions. The structure of the new compounds was determined by IR, MS and other modern analytical methods, and the antimicrobial activity was studied. And the basic methods of computer-aided drug design are introduced. This study has improved the heterocycles of such compounds, which will certainly be easier and more conducive to understanding its special function and drug activity mechanism, so as to provide a good research basis for the development of antimicrobials.

1. Introduction

Benzimidazole compounds contain a heterocyclic ring, the use of these compounds can mimic the effect of pure natural superoxide dismutase (SOD) and other similar enzymes to explore the biological activity, in addition, the benzimidazole ring-built drug molecules can show various activities. Benzimidazole ring can also be used as a linking group in a wide range of fields such as medical drugs, crop drugs, polymer materials, dyes, metal corrosion and supramolecular recognition. Because of its unique configuration and excellent characteristics such as physiological activity and reactivity that other items do not have, this kind of compound can be used in any field. The metal complex with this special group has become a special object of research, so this paper will also study this kind of compound and its derivatives [1].

2. Application of benzimidazole compounds

The research shows that benzimidazole compounds, their derivatives and their metal complexes are a class of important substances with great potential. It can not only show broad-spectrum biological activity in medicine and pesticide, but also be used as pharmaceutical intermediates. Therefore, it has considerable potential in the field of pharmaceutical chemistry research. Its special structure can form hydrogen bonds with enzymes and receptors in the organism, and can also coordinate with metals to form hydrophobic hydrophobic and π - π interactions. Many of our highly effective stomach drugs rely on this property, such as omeprazole. Of course, its derivatives and transition metal complexes also have unexpected biomolecular functions, which are used in health care drugs, such as vitamin B12. In addition, benzimidazole derivatives also have industrial corrosion resistance, and polybenzimidazole can also be used in aerospace technology [2-3].

In recent decades, people have continuously studied the relationship between the structure and performance of benzimidazole metal complexes. Their catalytic activities have been widely used in industrial production. Their complexes with special catalytic activities will become an important part of catalytic chemistry research. In terms of methyl elimination, the reason is that alkyl and hydrogen atoms must be eliminated in order to make the generated benzimidazole more stable. Benzimidazole and its derivatives have been the focus of research for many years and have high synthetic value. The research and development of new benzimidazole drugs will play an important role in the future drugs. There will be more highly effective, low toxic, and highly bioavailable drugs used in the clinic, bringing good news to people [4-5].

3. Computer Aided Drug Design

1) Introduction to computer-aided drug design methods

Computer-aided drug design is based on the mechanism of action of drug molecules. It covers fields such as quantum chemistry, medicinal chemistry, biology, computer graphics and information science. Currently

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more mature is structure-based drug design, which can be divided into direct drug design and indirect drug design. Computer-aided drug design is divided into direct drug design and indirect drug design according to whether the structure of the receptor is known. Molecular docking is a commonly used direct drug design method. The establishment of early molecular docking models for ARB drugs was based on the 3D structure of bacteriorhodopsin (BR). Recent studies have shown that bacteriorhodopsin has low homology with the G protein-coupled receptor superfamily, and some of its transmembrane regions are different, making it unsuitable for model construction. Nowadays, the 3D structure of rhodopsin (Rh) is mostly used for construction.

Quantitative structure-activity relationship (QSAR) is an important indirect drug design method. It plays an important role in the optimization of AngII receptor antagonist lead compounds. "Xu Jinyi" et al. conducted 2D-QSAR research on 42 AT receptor antagonists that have been marketed and are in the clinical research stage, and used the constructed QSAR equation to perform discriminant analysis on various AT receptor antagonists. The results show that there are three types of compounds with high AT receptor antagonistic activity, namely benzimidazole compounds, imidazopyridine compounds, and triazolinone compounds.

2) Characteristics and applications of computer-aided drug design technology

Due to the high costs, high cycle times, high risks and other shortcomings of drug research and development, the return on investment of drugs is getting lower year by year. Computational chemistry-based drug design (CADD) is a new drug design method based on the intersection of molecular mechanics, quantum mechanics and structural biology. It can be used to discover and optimize lead compounds, and conduct ADME/T of compounds. predict. As a large amount of omics data continues to accumulate, computer-aided drug design (CADD) has received more and more attention in new drug research and development with its powerful characterization, learning and classification capabilities, and has been used in every aspect of new drug research and development. stages have been widely used. As a classic computer-aided drug design method, virtual screening has achieved many successes in the development of new drugs. In the process of algorithm development, virtual screening technology has also made great progress. This article reviews the research status and development trends of virtual screening technology. Drug design is an effective drug design method that can be used for protein structure prediction, molecular design and optimization, target prediction, chemical reaction prediction, drug property prediction, etc. New drugs aimed at obtaining good drug efficacy are an important direction in drug research, and new drug design methods based on deep generation models have attracted much attention from domestic and foreign scholars and industries because of their unique advantages. Primary liver cancer is a common malignant tumor in my country, and the number of liver cancer deaths in China exceeds half of the global liver cancer deaths. Traditional chemotherapy for tumors not only causes severe side effects to patients, but also drug-induced DNA damage and mutations may lead to cancer recurrence. In contrast, molecular targeted therapy is significantly better than chemotherapy because the former kills tumor cells by targeting the promotion or inhibition of specific proteins or signaling pathways related to tumorigenesis, and this pathway has a smaller killing effect on normal cells. However, one of the most promising targets in molecular targeted therapy is tumor suppressor proteins.

4. Study on the Synthesis of Benzimidazole Compounds

4.1. Synthesis design of target compound

The essence of alkylation reaction is an electrophilic substitution reaction through a carbon cation intermediate. During the reaction, the alkyl group is transferred from one compound to another, thereby changing the chemical properties of the target compound. This reaction usually requires specific catalysts and conditions to ensure the smooth progress of the reaction. Carbon cations are formed by methods such as protonation or dehydrogenation, and they can be connected to many atoms, including carbon atoms, nitrogen atoms and oxygen atoms in the substrate molecule. Alkylating agents commonly used in industry include olefins, alkyl halides, alkyl sulfates, etc. The alkylation product of lead is alkyl lead, among which tetraethyl lead is often used as a gasoline additive and an anti-knock agent.

O-alkylation refers to the reaction of introducing an alkyl group onto an oxygen atom. Common O-alkylating agents include alcohols, phenols, ethers, etc. For example, alcohols and halogenated hydrocarbons can undergo O-alkylation reactions under alkaline conditions to produce ether compounds.

C-alkylation refers to the reaction of introducing an alkyl group onto a carbon atom. Common C-alkylating agents include olefins, alkynes, aromatic hydrocarbons, etc. For example, olefins and halogenated hydrocarbons can undergo C-alkylation reactions under the action of a catalyst to produce alkyl-substituted olefin compounds.

N-alkylation refers to the reaction of introducing an alkyl group onto a nitrogen atom. Common N-alkylating agents include amines, amides, nitriles, etc. For example, amines and halogenated hydrocarbons can undergo N-alkylation reactions under alkaline conditions to produce quaternary ammonium salt compounds. N-alkylation is an important reaction of introducing alkyl groups with saturated and unsaturated substituent groups onto N atoms. Common alkylating agents include alcohols, halogenated hydrocarbons, esters, olefins, ethylene oxide, and other compounds. Different alkylating agents have different reaction conditions. N-alkylation reaction is widely used, and N-alkylation products are important intermediates for compounds such as dyes, drugs, and surfactants. Under the catalysis of aluminum chloride, alkyl and acyl groups are introduced into the aromatic ring by the reaction of halogenated

hydrocarbons and acyl halides with aromatic compounds. The former is called F-C alkylation reaction, and the latter is called F-C acylation reaction.

The compound is shown in Figure 1 below.

4.2. Experimental instruments and reagents

Raw materials and reagents used in the experiment include: Trichloromethane, 2-Chloroacetamide, Sodium hydroxide, 95% ethanol, THF, Sodium hydride, DMF, Benzyl chloride, Concentrated hydrochloric acid, 2-Mercapto-benzimidazole, 3-Chlorobenzyl chloride, 2,4-Dichlorobenzyl chlorlde [6-9].

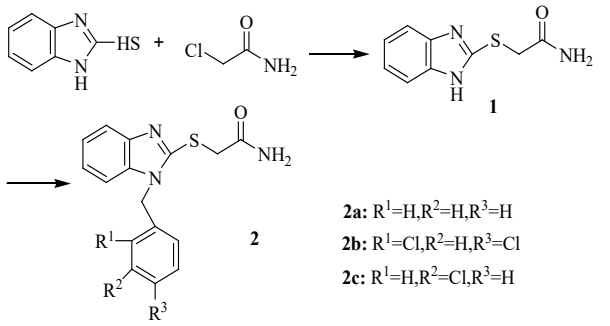

Figure 1. Design of target compound

The instruments used in the experiment include: three use ultraviolet instrument, rotary evaporator, collector type constant temperature heating magnetic stirrer, cryogenic coolant circulating pump, circulating water type multipurpose vacuum pump, electronic balance, electric blast drying oven, micro melting point tester, ultraviolet visible spectrophotometer.

Use the above reagents and equipment to conduct the experiment according to the specific experimental methods and steps [10-13].

4.3. Research methods and procedures

1) Synthesis of benzimidazolamide compound 1

After adding 2-chloroacetamide 2.8989g (0.031mol), concentrated HCl4ml and distilled water 5ml into a 50ml round-bottom three-mouth flask that had been cleaned and dried before the experiment, a reflux condensing device was set up with the condensing tube prepared before the experiment, and heating and stirring was performed at T=60~70℃. Keep the reaction until the liquid in the flask is clarified. If there is turbidity, add appropriate amount of water to dissolve it completely.

Weigh 3.4537g (0.023mol) 2-mercaptobenzimidazole and add it to the reaction solution, heat up, and after reflux for 4h, the reaction is tracked with TLC (developing agent: trichloromethane: acetone =10:1), and the reaction is allowed to continue until the reaction is completely finished. Pour the cooled reaction liquid into a 50ml beaker, add 20% NaOH solution, and measure the PH value with a test paper. When the PH value of the solution reaches 8 ~ 9, a lot of precipitation will be seen. The solution will be drained and filtered, washed and dried, and then recrystallized with 500ml distilled water and added activated carbon to make it fade. Let stand until no more crystals continue to precipitate, filter, wash with a small amount of water, dry, and obtain the final product. The calculated yield was: 80.19%; Melting range: 215.7℃ ~ 216.1℃.

2) Synthesis of benzimidazolamide compound 2a

Compound 1 of 0.5187g (0.005mol) was weighed and a reflux condensing device was constructed with a three-port flask and a condensing tube, and a stirring device was added during construction. Add the measured medicine to the three-mouth flask, and then add excess NaH to dissolve it fully. After completely dissolved, immediately add a little excess benzyl chloride, heating up the temperature to 40℃ ~ 60℃, maintain this temperature and stir reflux for 24 hours, use TLC to track the reaction (developing agent: ethanol) until the end of the reaction. The reaction liquid was removed, most of the solvent was removed by vacuum distillation, and then the product was washed with distilled water and extracted with chloroform (3×20mL). After combining the organic layer, the organic phase was dried and filtered with an appropriate amount of anhydrous sodium sulfate, and the filtered organic phase was rotatively evaporated to obtain a white solid. Yield: 51.52%, melting range: 218.4℃ ~ 219.3℃.

3) Synthesis of benzimidazolamide compounds 2b

Compound 1 was weighed at 0.5177g (0.005mol) and added into a three-port flask equipped with a stirring device and a reflux condensing device, and then excess NaH was added to dissolve it fully. After the dissolution was complete, slightly excess 2, 4-dichlorobenzyl chloride was added quickly, heated up, and the temperature was controlled at 40℃ ~ 60℃. After stirring and reflow for 24h, TLC was used to track the reaction (developing agent: ethanol) until the end of the reaction. Most of the solvent was removed by vacuum distillation, the product was washed with distilled water, and then extracted with chloroform (3×20mL). After combining the organic layer, the organic phase was dried and filtered with an appropriate amount of anhydrous sodium sulfate, and the filtered organic phase was rotatively evaporated to obtain a white solid. Yield: 45.14%, melting range: 249.7℃ ~ 250.9℃.

4) Synthesis of benzimidazolamide compound 2c

Weigh 0.5177g (0.005mol) of compound 1 and add it to a three-port flask equipped with a stirring device and a reflux condensing device, then add excess NaH and let it dissolve fully. Wait until completely dissolved, immediately add a little excess of 3-chlorobenzyl chloride, heating to increase the temperature to 40℃ ~ 60℃, maintain this temperature and stir reflux for 24 hours, use TLC to track the reaction (development agent: ethanol) until the end of the reaction. Most of the solvent was removed by vacuum distillation, the product was washed with distilled water, and then extracted with chloroform (3×20mL). After combining the organic layer, the organic phase was dried and filtered with an appropriate amount of anhydrous sodium sulfate, and the filtered organic phase was rotatively evaporated to obtain a white solid. Yield: 58.66%, melting range: 212.5℃ ~ 213.2℃.

4.4. Research results

1)UV spectrum analysis Dissolve the above products in DMF, and measure the following UV spectrum (UV) **Figure 2** at room temperature, with DMF as reference.

c,1.0×10-4mol.L-1; d1,1.0×10-4mol.L-1; d2,1.0×10-4mol.L-1; d3,1.0×10-4mol.L-1.

When a heteroatom is serially attached to an unsaturated bond, the n electrons on the heteroatom can transition to the π * orbital, and thus the n → π * transition occurs. This transition requires the least energy, and the corresponding absorption band is generally located at 270-300nm, which will become longer with the increase of conjugated system. From the UV spectrum analysis, Maxc=286, Abs=2.239; Maxd1=290, Abs=2.238; Maxd2=296, Abs=2.258; Maxd3=285, Abs=2.254. It can be seen that the above compounds contain unsaturated bonds and heteroatoms, which are speculated to be consistent with the target products.

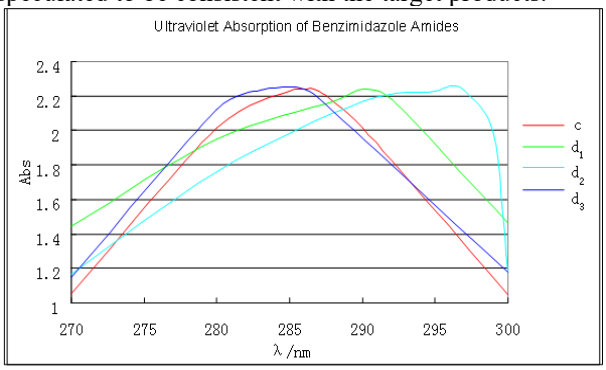

Figure 2. Ultraviolet Spectrum (UV)

2)Spatial structure of target compounds

The spatial structure of the target compound is shown in Figures 3 below:

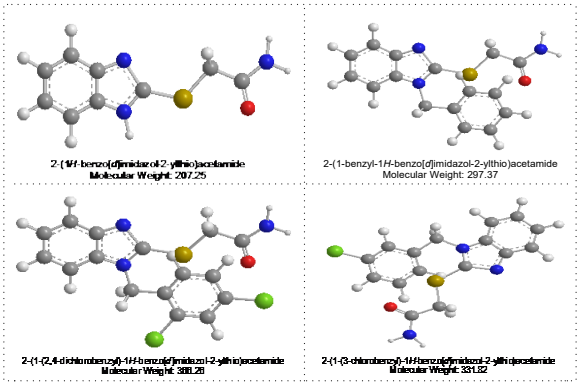

Figure 3. Spatial structures of target compounds

5. Antimicrobial activity analyses

5.1. Antibacterial activity

At present, the determination of microbial activity is mostly focused on the quantification of metabolic activity. The main methods include carbon respiration, ATP analysis, enzyme analysis, and incorporation of radiolabeled tracers into cell macromolecules. The most commonly used enzyme analysis methods are dehydrogenase analysis and esterase analysis. Among them, esterase analysis has been widely used in the determination of a series of microbial activities because of its simplicity, rapidity, economy, and high sensitivity. Fluorescein diacetate (FDA) is easily hydrolyzed by non-specific enzymes (esterases, proteases, lipases) in bacteria and fungi, and the final product of the reaction is fluorescein. The generation of fluorescein can quantitatively monitor the hydrolysis of FDA, and then be used for the analysis of enzyme activity or microbial activity. This paper uses this method to conduct activity analysis research.

Fluorescein diacetate (FDA) is connected to two conjugated acetate radicals. It is a non-polar substance that can freely penetrate the cell membrane and is easily hydrolyzed by non-specific enzymes (esterases, proteases, lipases) in bacteria and fungi. FDA is a colorless compound and has no fluorescence itself. The reaction product, fluorescein, is a polar and fluorescent substance that is stable and difficult to decompose. It is difficult to pass through the cell membrane and accumulate in the cell. When the amount stored in the cell exceeds a certain amount, it is released into the environment. Since the fluorescence properties of the reactants and products are different, even if the reactants are in excess, it does not interfere with the determination of the products. Using acetone as a terminator can, on the one hand, terminate the hydrolysis reaction, and on the other hand, it can dissolve the cell membrane and help the leaching of fluorescein in the cell membrane. At the same time, the use of fluorescence photometry avoids the disadvantage of high background absorbance of soluble organic matter in acetone-dissolved samples.

The antibacterial activities of the four benzimidazole amides obtained were compared with those of ciprofloxacin and norfloxacin, as shown in Table 1 below.

Table 1. Comparison of in vitro antibacterial activities of benzimidazole amide compounds

Chemical compound	Gram positive bacteria				Gram negative bacteria			
	Micrococcus luteus	MRSA	staphylococcus aureus	Bacillus subtilis	Pseudomonas aeruginosa	Escherichia coli	Proteus	Salmonella typhi
1	256	256	256	4	256	256	256	128
2b	256	256	16	256	64	128	64	128
2a	256	256	>256	256	>256	256	256	256
2c	256	256	256	64	>256	256	256	256
Ciprofloxacin	8	16	16	32	32	32	32	32
Norfloxacin	2	8	0.5	1	16	16	8	4

1)Anti-Gram-positive bacteria

(1) Micrococcus luteus resistant

It can be seen from Table 1 that compounds 1, 2a, 2b and 2c have certain antibacterial activity against Micrococcus luteus, and the MIC values of these three benzimidazoles are 256 μ G/mL, while the MIC value of ciprofloxacin is 8 μ G/mL, the MIC value of norfloxacin is 2 μ G/mL, so it can be seen that the antibacterial activity of benzimidazole compounds against Micrococcus luteus is weaker than that of chloramphenicol and norfloxacin.

(2) Anti MRSA (methicillin-resistant Staphylococcus aureus)

It can be seen from Table 1 that compounds 1, 2a, 2b and 2c all exhibit certain antibacterial activity against MRSA, and the MIC values of these three benzimidazole compounds are 256 μ G/mL, while MIC value of ciprofloxacin is 16 μ G/mL, the MIC value of norfloxacin is 8 μ G/mL, so it can be seen that the antibacterial activity of benzimidazole compounds against Micrococcus luteus is weaker than that of chloramphenicol and norfloxacin.

(3) Staphylococcus aureus resistant

It can be seen from Table 1 that the antibacterial activities of compounds 1, 2a, 2b and 2c against MRSA are different. Compound 2a has the weakest antibacterial activity and 2b has the strongest antibacterial activity. MIC values of compound 1 and compound 2c are the same, both of which are 256 μ G/mL, MIC value of compound 2a is greater than 256 μ G/mL, MIC value of compound 2b is 16 μ G/mL, the MIC value is the same as that of ciprofloxacin, and the MIC value of norfloxacin is 0.5 μ g/mL. Therefore, the antibacterial activity of compound 2b against Staphylococcus aureus is equal to that of ciprofloxacin and much weaker than that of norfloxacin; Compounds 1,2a and 2c are much weaker than ciprofloxacin and norfloxacin.

(4) Bacillus subtilis resistance

It can be seen from Table 1 that the antibacterial activities of compounds 1, 2a, 2b and 2c against Bacillus subtilis are different. The antibacterial activity of compound 1 is the strongest, followed by compound 2c, and the MIC value is 256 μ 2a and 2b of g/mL. MIC value of compound 1 is 4 μ G/mL, MIC value of compound 2c is 64 μ G/mL, while MIC values of ciprofloxacin and norfloxacin are 32 μ G/mL and 1 μ G/mL, so it can be seen that compound 1 has a stronger anti Bacillus subtilis activity than ciprofloxacin and a weaker anti Bacillus subtilis activity than norfloxacin; The antibacterial activity of compound 2c was weaker than that of compounds 1, ciprofloxacin and norfloxacin, but stronger than that of compounds 2a and 2b.

2)Anti Gram negative bacteria

(1) Anti Pseudomonas aeruginosa and Proteus

Table 2 shows that compound 1 has the same antibacterial activity against Pseudomonas aeruginosa and Proteus, and its MIC value is 256 μ G/mL, compound 2b has the same antibacterial activity as compound 1 against Pseudomonas aeruginosa and Proteus, and its MIC values are 64 μ g/mL. Compound 2b and 2c have the same antibacterial activity against Pseudomonas aeruginosa, and their MIC values are greater than 256 μ G/mL, the antibacterial activity against Proteus is the same, and its MIC value is 256 μ g/mL. The antibacterial activity of ciprofloxacin against Pseudomonas aeruginosa and Proteus was the same, with 256 μ G/mL, while the antibacterial activity of norfloxacin against Pseudomonas aeruginosa is weaker than that against Proteus, and its MIC value against Pseudomonas aeruginosa is 16 μ G/mL, MIC value of anti Proteus is 8 μ g/mL. It can be seen that compound 2b has stronger anti Pseudomonas aeruginosa and proteus activity than compounds 1, 2a and 2c, and weaker anti proteus activity than ciprofloxacin and norfloxacin. Norfloxacin has the strongest anti proteus activity.

(2) Anti Escherichia coli and Salmonella typhimurium

It can be seen from Table 1 that compounds 1, 2a and 2c have the same anti coliform activity, and their MIC values are 256 μ G/mL, the anti-coliform activity of compound 2b is stronger than that of the first three compounds, and its MIC value is 128 μ g/mL. The anti-Salmonella typhimurium activity of compounds 1 and 2b is stronger than that of compounds 2a and 2c, and the MIC values of the former two compounds are 128 μ G/mL, MIC value of the latter two is 256 μ g/mL. The activity of ciprofloxacin against Escherichia coli and Salmonella typhimurium is the same, and its MIC value is 32 μ G/mL, Norfloxacin is more active against Escherichia coli and Salmonella typhimurium than ciprofloxacin, and its MIC value against Escherichia coli is 16 μ G/mL, while MIC value of anti- Salmonella typhimurium is 4 μ g/mL. Therefore, the antibacterial activity of compound 2b against Escherichia coli is obviously stronger than that of compounds 1, 2a and 2c, but also weaker than ciprofloxacin and norfloxacin; For the anti-Salmonella typhimurium activity, the antibacterial activity of compounds 1 and 2b was significantly stronger than that of compounds 2a and 2c, but also significantly weaker than that of ciprofloxacin and norfloxacin. Norfloxacin has the strongest antibacterial activity among the five compounds.

5.2. Antifungal activity

The comparison of antifungal activities of benzimidazole amide compounds in vitro is shown in Table 2 below.

1)Candida albicans resistant

It can be seen from Table 2 that among the four compounds synthesized, compound 2b has the strongest activity against Candida albicans, and its MIC value is 32 μ G/mL, compound 2c has the weakest antibacterial activity, and its MIC value is greater than 256 μ g/mL. Compound 1 and 2a have the same antibacterial activity, with MIC values of 256 μ G/mL, the antibacterial activity of conazole is far stronger than compounds 1, 2a, 2b and 2c, and its MIC value is only 1 μ g/mL. It can be seen that the anti-Candida albicans activities of benzimidazole amide compounds 1, 2a, 2b and 2c obtained are far weaker than those of conazole.

Table 2. Comparison of in vitro antifungal activities of benzimidazole amide compounds

Chemical compound Fungus	Candida albicans	Candida resistant
1	256	256
2b	32	256
2a	256	>256
2c	>256	>256
Conazole	1	4

2)Candida resistant

It can be seen from Table 2. The antibacterial activity of compounds 1 and 2b is stronger than that of compounds 2a and 2c. The MIC values of the first two compounds are 256 μ G/mL, MIC values of the latter two are greater than 256 μ G/mL, MIC of conazole is 4 μ g/mL. It can be seen that the anti-candida activity of conazole is the strongest, and it is far stronger than the synthesized benzimidazole amide compounds 1, 2a, 2b and 2c.

6. Prospects of computer-aided drug design

This research not only lays a solid research foundation for the development of antibacterial drugs, but also has far-reaching potential impact and practical significance in the field of computational-aided drug design in the context of medicinal chemistry and engineering. First, by integrating the latest advances in the pharmaceutical field and engineering technology, this study provides a unique perspective and method for the design of new antibacterial drugs. Secondly, by introducing advanced engineering concepts into computational-aided drug design, we not only improve the efficiency of drug development but also broaden its application scope. This will be the research direction later in this article.

In mature industrial fields such as aerospace, papermaking, and steelmaking, most quality control is carried out through mechanism modeling or first through mechanism modeling and then combined with data-driven quality control, especially for industries with very strict control requirements. For pharmaceuticals, the first task of intelligence is to integrate intelligent technology with lean management methods, pharmaceutical equipment with intelligent control technology, the digital world with the physical world, and create a technical model for manufacturing high-quality pharmaceuticals, and This technical model has been applied and studied through the actual production of Xuesaitong for injection (lyophilized), Yiqi Fumai for injection (lyophilized), and Guanxinning tablets, and has achieved good results. Therefore, for pharmaceutical quality control, we can also try to combine data-driven process modeling with mechanism process modeling. That is, using the existing actual production data, using a simplified method to initially establish a suitable model, and forming some corresponding equations for material, energy and mass conservation. Then, on the basis of the mechanism model, a large amount of data learning is carried out according to the changes in process parameters, and neural networks are used for data mining to correct the preliminary model. Then, the model is verified based on the actual process production, and the physical space and the information space are combined. Combined, pharmaceutical factory production can be controlled in real time to achieve intelligent optimal control of the pharmaceutical process.

"One system, grasp dual attributes, adhere to the trinity, and strengthen the four major manufacturing" layout to form a strategic path for the healthy and sustainable development of artificial intelligence. The development of intelligent enterprises, intelligent workshops, and intelligent factories has become a trend. The pharmaceutical production process is transparent Unmanned production sites and intelligent production management have become inevitable trends. Judging from the current development status of pharmaceutical production, pharmaceutical production can already achieve automated production, that is, some production sites are transparent and unmanned, but from the perspective of automation The gradual and complete transformation to intelligence will take some time. The reason is the time-varying nature of the pharmaceutical production process and the particularity and instability of the products produced, which makes it different from traditional shipbuilding, metallurgy, steelmaking and other process industries. Certain differences. From the perspective of the pharmaceutical production process, due to the lack of linkage of data between various production departments, information between various operating units cannot be effectively communicated in actual production, and a closed-loop information exchange circle cannot be formed, resulting in A lot of "useless" data has been collected, resulting in the hidden information behind a lot of data being buried, resulting in the loss of a large amount of information and restricting the development of the pharmaceutical digital factory. In addition, the difficulty of its intelligent transformation lies in the fact that each How to construct a mechanism model of unit operations, how to mine the information behind a large amount of industrial data, and how to effectively interact with the mined information with actual production to form a digital twin workshop, etc. Therefore, the later research of this article will draw on the relatively mature data-driven technology. The applied research experience in the fields of process industry, discrete industry and biological fermentation, combined with research methods in the food fields such as boiled sugar and toffee production, based on the inherent laws of the pharmaceutical process, provides insights into how data-driven technology can be intelligently optimized in pharmaceutical process control. , how to dig out the information contained in the production site data, how to interact and integrate the information space and the physical space through digital twin technology, etc., provide certain direction suggestions, and lay the foundation for subsequent in-depth research.

7. Conclusion

Because of the special structure of benzimidazole amides and their derivatives, they have shown a variety of pharmacological and biological activities, and the research on metal complex catalysts and corrosion resistance has also received more and more attention. In general, as long as the special structure of benzimidazole ring exists in the compound, the action of benzimidazolyl group is only to coordinate with one-nitrogen. However, because there are many hydrogen bond donors in benzimidazole, it shows rich hydrogen bonds and π - π stacking in the compound. In the process of future operational research, if we do our best to analyze and design this class of compounds containing benzimidazole, and make favorable improvements in the heterocycles of this class of compounds, it will certainly be easier and more conducive to the study of its special functions and the mechanism of drug activity, thus promoting the development of pharmaceutical chemistry and adding a touch of color to scientific research.

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Reference

1. Meng JP, Geng RX, Zhou CH.2009.Research progress of benzimidazoles [J]. Chinese Journal of New Drugs, 18 (16): 1505-1514.
2. He GN, Yuan B, Jia QP, Lv S.2022.Synthesis of new benzimidazole derivatives [J]. Synthetic Chemistry, 30 (02): 107-112.
3. Feng YZ, Dai WZ, Liu GY, Lian JX.2022.Preliminary study on the synthesis and antibacterial activity of 2-aminobenzimidazole derivatives [J]. World Pesticide, 44 (03): 47-52.
4. Tang YC, Li M, Dai KM, Xiang XX, Huang HG.2022.Synthesis of benzimidazole [2,1-a] isoquinoline-6 (5H) - one derivatives [J] via fluorescein catalyzed oxidative coupling reaction under visible light. Fine Chemicals, 39 (07): 1501-1506.
5. Wang YB, Guo C, Tao S, Liu JC, Zhao JG, Liu N.2022.Dai Bin Selectivity of basic regulation: synthesis of benzimidazolone and benzodiazepines by N-alkyl-N - (2 - (pyridin-2-yl amino) phenyl) formamide [J]. Organic Chemistry, 42 (04): 1146-1162.
6. Jiang Z, Hu J, Li YP, Li YH, Li ZR.2015.Synthesis of diaryl cyclic amides and benzimidazoles and their anti Coxsackie virus activities [J]. Chinese Journal of Pharmaceutical Chemistry, 25 (04): 261-268.
7. Zhang XW.2019.Synthesis and activity study of piperidyl benzimidazole formamide PARP-1 inhibitors [D]. Tsinghua University.
8. Liu X.2022.Synthesis of benzimidazole compounds and their antiseptic and bacteriostatic activities [J]. Chemical Engineering and Equipment, (08): 21-23.
9. Mou J, Chen NH, Pei DS.2021.Study on anti-tumor activity and structure-activity relationship of benzimidazole derivatives [J]. Chinese Journal of Pharmaceutical Industry, 52 (03): 283-298.
10. Cao JM, Zhang LJ, Li CY, Sun BW, Sun YQ.2021.Synthesis of benzimidazole derivatives and evaluation of their endothelial lipase inhibitory activity [J]. Chinese Journal of Pharmaceutical Chemistry, 31 (07): 489-497.
11. Jadhav RI, Kedar NA, Chavan.2022.KHSynthesis and antimicrobial activity of novel 1H-benzo[d]imidazole-aryl sulfonamide/amide derivatives[J].Indian Journal of Chemistry,61 (02):184-191.
12. Fonkui TY , Ikhile MI, Njobeh PB , Ndinteh DT.2019.Benzimidazole Schiff base derivatives: synthesis, characterization and antimicrobial activity[J]. BMC CHEMISTRY,13 (01):127-185.
13. El-Sayed A A , Abu-Bakr S M , Swelam S A ,et al. 2022.Applying Nanotechnology in the Synthesis of Benzimidazole Derivatives: A Pharmacological Approach[J].Biointerface Research in Applied Chemistry.DOI:10.33263/BRIAC121.9921005.