



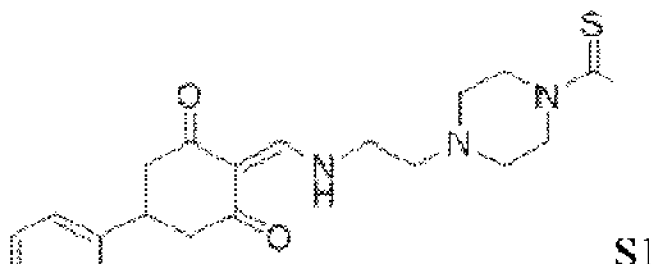
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(54) Titre : UTILISATION D'UN COMPOSE ARYLIQUE POLYCYCLIQUE DANS LA PREPARATION D'UN MEDICAMENT
ANTIFONGIQUE
(54) Title: APPLICATION OF POLYCYCLIC AROMATIC COMPOUND IN THE PREPARATION OF ANTIFUNGAL
DRUGS



(57) **Abrégé/Abstract:**

The present invention provides a polycyclic aryl compound S1 for preparing a drug for antifungal infection. The structural formula of the polycyclic compound is S1. The polycyclic aryl compound having the shell-core structure and represented by S1 in the present invention is suitable for preparing drugs for anti-Candida, Aspergillus, Mucor and other pathogenic fungal infections, and has the following beneficial effects: the compound S1 of the present application has a broad-spectrum antifungal effect on pathogenic fungi including, but not limited to, Candida, Aspergillus, Mucor, etc., is effective against azole resistant Candida, is low in toxicity to mammals, and can treat systemic fungal infection by oral administration, and can also be used locally to treat mucosal Candida infection.

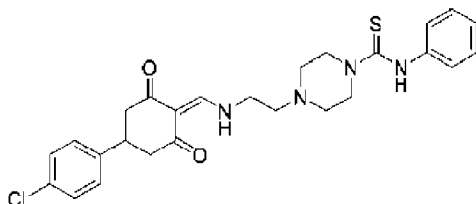


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ABSTRACT

The present invention provides a polycyclic aromatic compound S1 for the preparation of antifungal agents. The structural formula of the aforementioned polycyclic aromatic compound is as follows:



S1.

The polycyclic aromatic compound with the shell-core structure, represented by S1 in the present invention, is applicable for the preparation of drugs against pathogenic fungi such as *Candida*, *Aspergillus*, and *Mucormycetes*. It demonstrates the following beneficial effects: The compound S1 described in this application exhibits a broad-spectrum antifungal activity against pathogenic fungi, including but not limited to *Candida*, *Aspergillus*, and *Mucormycetes*. It is effective against azole-resistant *Candida* strains, and, simultaneously, it has low toxicity to mammals. The compound can be administered orally for the treatment of systemic fungal infections and can also be topically applied for treating mucosal *Candida* infections.

Application of a Polycyclic Aromatic Compound in the Preparation of Antifungal Drugs

Technical Field

The present invention relates to the pharmaceutical field. More specifically, the invention pertains to the application of a polycyclic aromatic compound S1 in the preparation of antifungal drugs against a range of pathogens, including but not limited to *Candida*, *Aspergillus*, *Mucormycetes*, *Cryptococcus*.

Background

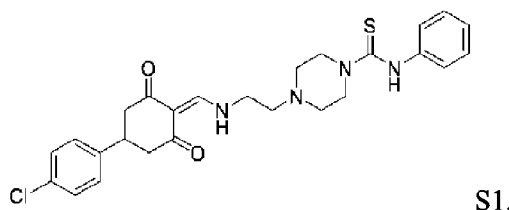
Fungal infections, including superficial and invasive fungal infections, pose a serious threat to human health. Invasive fungal infections, mainly caused by pathogenic fungi such as *Candida*, *Aspergillus*, *Mucormycetes*, and *Cryptococcus*, account for over 13 million infections and 1.6 million deaths annually. The number of deaths from fungal infections surpasses that from diseases such as malaria, tuberculosis, and breast cancer. Even with standard antifungal treatments, the mortality rate among immunocompromised patients can reach up to 67%.

Currently, drug therapy is the primary approach for treating invasive fungal infections, but the available drugs are limited to three classes: azoles (e.g., fluconazole, voriconazole), polyenes (amphotericin B), and echinocandins (caspofungin, micafungin). Each class has distinct advantages and disadvantages. While azoles exhibit high safety and oral bioavailability, their fungistatic action contributes to significant drug resistance. Polyenes offer broad-spectrum antifungal activity and proven efficacy but come with notable liver and kidney toxicity, with around 30% of adults treated with amphotericin B experiencing acute kidney injury, leading to increased mortality, hospitalization time and costs. Echinocandins represent a relatively new class of antifungal drugs approved in the last 30 years, but are limited by their low oral bioavailability. Consequently, the limited options available for treating invasive fungal infections fail to meet the growing clinical demand, highlighting the urgent need

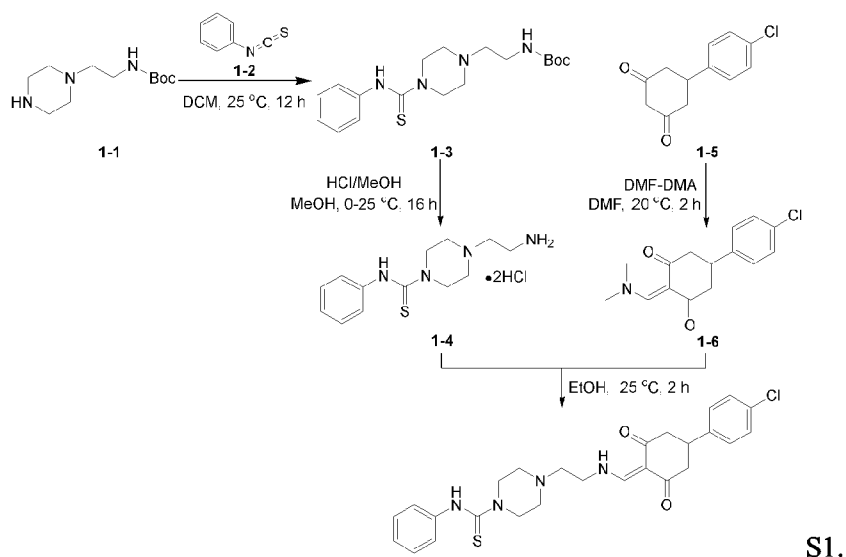
for the development of novel antifungal drugs.

Invention Content

To address the limitations of existing antifungal drugs, the present invention provides a polycyclic aromatic compound S1 for the preparation of antifungal agents. The structural formula of the aforementioned polycyclic aromatic compound is as follows:



The present invention pertains to a method for preparing the polycyclic aromatic compound S1: compound **1-1** reacts with compound **1-2** to form thiourea compound **1-3**. The latter then undergoes Boc protection group removal under hydrochloric acid conditions to form hydrochloride compound **1-4**. Subsequently, compound **1-5** reacts with N,N-dimethylformamide dimethyl acetal to produce dione compound **1-6**. Finally, under ethanol solvent conditions, the reaction of compound **1-4** with compound **1-6** yields the target compound S1.



The present invention further relates to a pharmaceutical composition, which

comprises a therapeutically effective amount of the disclosed polycyclic aromatic compound S1 or its pharmaceutically acceptable salts, and one or more pharmaceutically acceptable carriers.

The term "pharmaceutically acceptable salt" as used in this application refers to salts of the compounds of the present invention that are safe and effective when administered to mammals and exhibit the desired biological activity, typically in the form of free acids. Pharmaceutically acceptable salts of the free amino compounds of the present invention can be prepared using methods known in the art and can be derived from organic and inorganic acids. Suitable organic acids include maleic acid, fumaric acid, benzoic acid, ascorbic acid, succinic acid, methanesulfonic acid, acetic acid, trifluoroacetic acid, oxalic acid, propionic acid, tartaric acid, salicylic acid, citric acid, gluconic acid, lactic acid, mandelic acid, phenylacetic acid, aspartic acid, stearic acid, palmitic acid, ethylenediaminetetraacetic acid (EDTA), glutamic acid, p-toluenesulfonic acid, and benzenesulfonic acid. Suitable inorganic acids include hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, and nitric acid. Therefore, the "pharmaceutically acceptable salts" of the compounds of the present invention should encompass all acceptable salt forms.

The present invention further pertains to the application of a therapeutically effective amount of the polycyclic aromatic compound as indicated by S1, or its pharmaceutically acceptable salts, or its pharmaceutical compositions, in the preparation of drugs for the treatment of pathogenic fungal infections caused by *Candida*, *Aspergillus*, *Mucormycetes*, *Cryptococcus*, and the like.

The present invention further pertains to the application of a therapeutically effective amount of the polycyclic aromatic compound as indicated by S1, or its pharmaceutically acceptable salts, or its pharmaceutical compositions, in the preparation of drugs for the treatment of both superficial and invasive fungal infections caused by fungal pathogens.

The term "pharmaceutical composition" as described in this application refers to a mixture containing one or more of the compounds described herein or their

physiologically/pharmaceutically acceptable salts or prodrugs, along with other chemical components such as physiologically/pharmaceutically acceptable carriers and excipients. The purpose of pharmaceutical compositions is to facilitate administration to a biological organism, promoting the absorption of active ingredients and thereby exerting biological activity.

The beneficial effects of the present application include:

- a) The compound S1 described in this application exhibits broad-spectrum antifungal activity against pathogenic fungi, including but not limited to *Candida*, *Aspergillus*, *Mucormycetes*, *Cryptococcus*, and the like.
- b) The compound S1 described in this application is effective against azole-resistant strains of *Candida*.
- c) The compound S1 described in this application has low toxicity to mammals.
- d) The compound S1 described in this application can be administered orally to treat systemic fungal infections.
- e) The compound S1 described in this application can be topically applied for treating mucosal *Candida* infections.

Figure Descriptions

Figure 1: ¹H-NMR spectrum of compound S1.

Figure 2: The survival rate of *Galleria mellonella* infected by fungus and treated with S1.

Figure 3: The fungal load after topical treatment of vulvovaginal candidiasis with compound S1.

Figure 4: The survival rate of mice systemic infected with fungus and treated with compound S1 orally.

Figure 5: The organ fungal load of mice systemic infected with fungus and treated with compound S1 orally.

Figure 6: Kidney histopathology of mice systemic infected with fungus and treated with compound S1 orally.

Specific embodiments

The structure of the S1 compound described in this application was determined through nuclear magnetic resonance (NMR) and/or mass spectrometry (MS).

NMR shifts (δ) are expressed in units of 10^{-6} (ppm). NMR measurements were conducted using a Bruker AVANCE-400 NMR spectrometer, with deuterated chloroform (CDCl_3) as the solvent and tetramethylsilane (TMS) as the internal standard.

Column chromatography typically employs Yantai HuangHai silica gel with a particle size of 200-300 mesh as the support.

The known starting materials for the present invention can be synthesized using methods known in the art or obtained from companies such as Aldrich Chemical Company, Accela ChemBio Inc, and others.

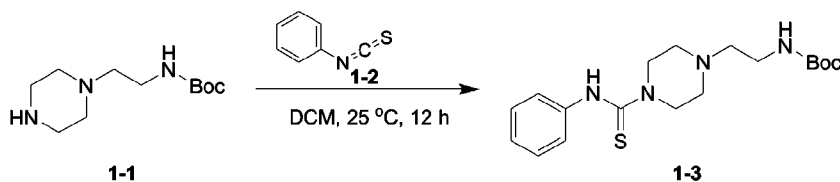
Unless otherwise specified in the examples, reactions were conducted under an argon or nitrogen atmosphere.

The term "argon or nitrogen atmosphere" refers to a reaction vessel connected to a gas balloon containing approximately 1L volume of argon or nitrogen.

Unless otherwise specified in the examples, the term "solution" refers to an aqueous solution.

Unless otherwise specified in the examples, the reaction temperature is at room temperature, which is 20°C to 30°C .

Example 1: Synthesis of Compound 1-3

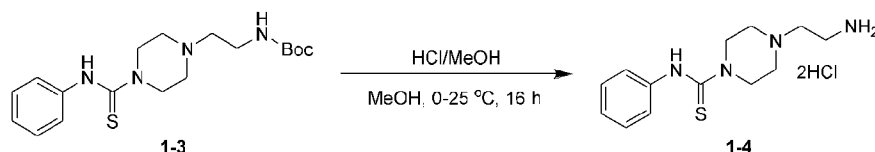


At room temperature, compound 1-1 (5.00 g, 21.8 mmol, 1.00 eq) was dissolved in dichloromethane (25 mL), followed by the addition of compound 1-2 (3.54 g, 26.2 mmol, 3.13 mL, 1.20 eq). After stirring the reaction mixture for 12 hours, the reaction solution was filtered, and the product was obtained by concentration. The product was

purified by silica gel column chromatography (DCM: MeOH = 8:1) to yield the white crystalline compound 1-3.

Compound 1-3: $^1\text{H-NMR}$ (400MHz, CDCl_3), δ 7.42 (s, 1H), 7.34-7.30 (t, $J = 7.8$ Hz, 2H), 7.16 (s, 1H), 7.14-7.10 (t, $J = 7.6$ Hz, 2H), 4.91 (s, 1H) 3.83-3.80 (t, $J = 4.8$ Hz, 4H), 3.22-3.21 (d, $J = 5.2$ Hz, 2H), 2.50-2.46 (m, 6H), 1.45 (s, 9H); LC-MS m/z .

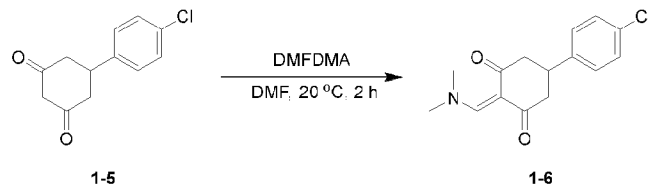
Example 2: Synthesis of Compound 1-4



Compound 1-3 (12.0 g, 32.9 mmol, 1.00 eq) was dissolved in methanol (60.0 mL), and at 0 degrees Celsius, a methanolic hydrochloric acid solution (32.9 mmol, 48.0 mL, 1.00 eq) was added. Subsequently, the reaction was allowed to reach room temperature. After 16 hours of reaction, the reaction mixture was concentrated under reduced pressure to obtain a white solid crude hydrochloride compound 1-4 (13.1 g).

Compound 1-4: LC-MS m/z 265.2 $[\text{M}+\text{H}]^+$.

Example 3: Synthesis of Compound 1-6

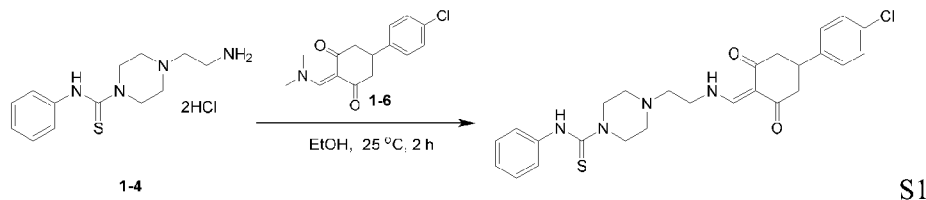


At room temperature, compound 1-5 (8.00 g, 35.9 mmol, 1.00 eq) was dissolved in N,N-dimethylformamide (100 mL), and then N,N-dimethylformamide dimethyl acetal (35.9 g, 301 mmol, 40.0 mL, 8.38 eq) was added. After stirring the reaction for 2 hours, the reaction mixture was filtered to obtain the filtrate. The filtrate was concentrated under reduced pressure to yield a light yellow solid compound 1-6 (8.50 g, 30.6 mmol, yield: 85.2%).

Compound 1-6: $^1\text{H NMR}$ (400MHz, CDCl_3), δ 8.08 (s, 1H), 7.32-7.30 (m, 2H), 7.19-7.17 (d, $J = 8.4$ Hz, 2H), 3.43 (s, 3H), 3.37-3.32 (m, 1H), 3.22 (s, 3H), 2.77-2.62

(m, 4H); LC-MS m/z 278.1 $[M+H]^+$.

Example 4: Synthesis of Compound S1



At room temperature, hydrochloride compound 1-4 (13.1 g, 38.8 mmol, 1.20 eq) was dissolved in ethanol (52.0 mL), followed by the addition of compound 1-6 (8.99 g, 32.4 mmol, 1.00 eq) for the reaction. After stirring for 2 hours, the mixture was extracted three times with chloroform (100 mL x 3), and washed with saturated brine solution (100 mL x 1). The organic phase was combined, filtered, and the crude product was obtained by concentration under reduced pressure. The product was purified by silica gel column chromatography to yield the white solid compound S1 (11.2 g, 22.5 mmol, yield: 69.6%). The ^1H -NMR spectrum of compound S1 is shown in Figure 1.

Compound S1: ^1H NMR (400 MHz, CDCl_3), δ 11.24-11.21 (brs, 1H), 8.20-8.16 (d, $J = 14.4$ Hz, 1H), 7.36-7.30 (m, 5H), 7.18-7.16 (m, 3H), 7.11-7.10 (d, $J = 7.6$ Hz, 2H), 3.88-3.86 (t, $J = 4.4$ Hz, 4H), 3.54-3.51 (m, 2H), 3.36 (m, 1H), 2.73-2.72 (m, 3H), 2.66-2.64 (m, 3H), 2.59-2.56 (t, $J = 4.8$ Hz, 4H), 2.05-2.02 (t, $J = 6.4$ Hz, 1H); LC-MS m/z 497.2 $[M+H]^+$.

Example 5: *In vitro* antifungal activity evaluation of compound S1

The following is provided in conjunction with Example 5 to further describe and explain the present invention, but these examples are not meant to limit the scope of the invention.

(1) Strains and Media

The fungal strains used include *Candida albicans* (SC5314), *Candida albicans* clinical strain (CA1-3), *Candida parapsilosis* (ATCC 22019), *Candida glabrata* (ATCC 28870), *Candida tropicalis* (ATCC 750), *Aspergillus fumigatus* (ATCC 1022),

Aspergillus fumigatus clinical strain (AF1-3), *Mucormycetes* (NRRL3631), *Cryptococcus neoformans* (ATCC 32609), and *Pneumocystis carinii* (ATCC PRA-159). The strains are stored at -80°C in YPD+glycerol culture medium, cultured on YPD agar plates, and activated in YPD liquid medium.

(2) Methods

The minimum inhibitory concentration (MIC_{50}) of compound S1 against the aforementioned fungi was determined using the micro-broth dilution method. Fungal strains were cultured on YPD agar medium at 35°C for 24 hours and activated twice. The activated *Candida albicans* was picked with an inoculation loop, diluted in RPMI 1640 culture medium, and the concentration of the fungal suspension was adjusted to the working concentration $(2.0\sim 2.5) \times 10^3$ cells/ml. The compound S1 solution was freshly prepared by diluting the stock solution in RPMI 1640 liquid culture medium to a 2-fold working concentration. Next, 100 μ L of the serially diluted drug solution was added to columns 2-11 of a 96-well plate; column 1 served as the growth control well (no drug added, replaced with 100 μ L of RPMI 1640 culture medium), and column 12 was the blank control well (only 200 μ L of RPMI 1640 culture medium added). Columns 1-11 of the 96-well plate were inoculated with 100 μ L of the fungal suspension at the working concentration. After incubation at 35°C for 48 hours, the OD values at a wavelength of 490 nm were measured using a microplate reader. Background readings were subtracted from each well, and the lowest drug concentration inhibiting 50% fungal growth was determined as the final MIC_{50} result. The experiment was repeated three times.

(3) Results

The antifungal activity of the compounds in the present invention was determined using the experimental method described above. The results of the *in vitro* antifungal activity of compound S1 are shown in Table 1, indicating that compound S1 possesses broad-spectrum antifungal activity.

Table 1. The MIC_{50} of S1 against fungi (μ g/ml)

Strains	S1	FLC
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SC5314	2	0.25
CA1	2	0.25
CA2	8	>64
CA3	1	2
ATCC 22019	1	0.25
ATCC28870	8	16
ATCC 750	0.5	1
ATCC 1022	1	1
AF1	2	1
AF2	1	4
AF3	8	>64
ATCC 32609	2	1
ATCC PRA-159	64	>64
NRRL3631	16	>64

Example 6: Cytotoxicity assessment of compound S1.

(1) Methods

The LO-2 and RAW264.7 cells were cultured in DMEM + 10% FBS + 1% penicillin/streptomycin medium. HK-2 cells were cultured in DMEM/F-12 + 10% FBS + 1% penicillin/streptomycin medium.

Cell viability was assessed using the CCK-8 assay: 5×10^4 cells/ml cells (100 μ l) were added to each well of a 96-well plate and pre-cultured at 37°C, 5% CO₂ for 24 hours. Different concentrations of small molecule compounds were added to each well and the plate was incubated for an additional 6 hours. After 6 hours, 10 μ l of CCK-8 solution was added to each well, and the plate was further incubated at 37°C, 5% CO₂ for 1-4 hours. Absorbance at 450 nm was measured using a multi-function microplate reader. The results represent the average of three independent experiments.

Cell damage was assessed using the LDH assay: 5×10^4 cells/ml cells (100 μ l) were

added to each well of a 96-well plate and incubated overnight at 37°C, 5% CO₂. The medium was then replaced with 100 µl of fresh medium. Different concentrations of small molecule compounds were added to each well and incubated for 24 hours. Positive control wells were treated with 10 µl of Lysis Buffer and incubated for 30 minutes at 37°C, 5% CO₂. After adding 100 µl of Working Solution to each well, the plate was incubated for an additional 30 minutes in the dark at room temperature. Finally, 50 µl of Stop Solution was added to each well, and absorbance at 490 nm was immediately measured using a multi-function microplate reader. LDH release percentage was calculated according to the formula. The results represent the average of three independent experiments.

(2) Results

The results were presented in Table 2. The growth inhibitory concentrations (IC₅₀) of small molecule S1 on LO-2, HK-2, and RAW264.7 cells were 78.44 µg/ml, 73.61 µg/ml, and 86.57 µg/ml at 24 h, respectively. And the IC₅₀ were 53.91, 105.21, and 35.64 µg/ml at 48 h, respectively. These values are significantly higher (exceeding 10 times) than the MIC₅₀ values of S1 against pathogenic fungi. The cytotoxicity results indicate that S1 causes 50% cell damage at doses significantly higher than those required for growth inhibition. The concentrations needed for 50% cell damage in LO-2, HK-2, and RAW264.7 cells are 131.91, 106.1, and 68.74 µg/ml, respectively. These results suggest that this small molecule exhibits selectivity between fungi and mammalian cells.

Table 2. The IC₅₀ of S1 on LO-2, HK-2, and RAW264.7 cells (µg/ml)

	24h		48h	
	CCK-8	LDH	CCK-8	LDH
LO-2	78.44	58.21	53.91	131.91
HK-2	73.61	110.2	105.21	106.1
RAW264.7	86.57	219.7	35.64	68.74

Example 7: Evaluation of *in vivo* antifungal activity of compound S1 against *Galleria mellonella*.

(1) Methods

Healthy *Galleria mellonella* larvae without black spots were selected (approximately 3 cm in length, weighing about 0.5 g). The larvae were randomly divided into groups of 20 larvae each, and placed in petri dishes with a diameter of 10 cm. *Candida albicans* SC5314 was cultured in YPD liquid medium until reaching the logarithmic growth phase, and the fungal cells were collected and washed twice with PBS. The fungal suspension was adjusted to a concentration of 1×10^8 cells/ml with physiological saline. The *Galleria mellonella* larvae were immobilized, positioned with the abdomen facing up, and the injection site was disinfected with alcohol. Holding the larvae, a Hamilton microsyringe was used to gently puncture the right lower second leg, injecting 10 μ l of the fungal suspension into the midsection of the larvae. After successful modeling, the larvae were placed on a clean tissue for 1 min. The drug S1 (25, 50, 100 mg/kg) was injected into the left lower second leg, and the control group (WT) was injected with an equal volume of physiological saline. The larvae were observed and dead individuals were removed daily. The survival time of each group was recorded, and the survival rate of *Galleria mellonella* larvae was calculated after 3 days.

(2) Results

The results were shown in Figure 2. *Galleria mellonella* larvae infected with WT died on the fourth day after infection. Compound S1 (25 mg/kg) showed no significant impact on the survival rate of *Galleria mellonella* larvae. Compound S1 (50 and 100 mg/kg) increased the survival rates of *Galleria mellonella* larvae to 18.3% and 45%, respectively ($P < 0.05$).

Example 8: The efficacy of compound S1 in the topical treatment of vulvovaginal candidiasis.

(1) Methods

Female BALB/c mice weighing 18-20 g were intraperitoneally injected with 100 μ l of estrogen (sesame oil containing 0.5 mg β -estradiol) and 100 μ l of

cyclophosphamide (100 mg/kg) for three consecutive days prior to infection, and subsequently every three days. On the day of infection, overnight-activated *Candida albicans* SC5314 in YPD liquid medium was collected, washed twice with PBS, and adjusted to a concentration of 1×10^7 cells/ml. Mice were anesthetized with chloral hydrate, and 10 μ l of the fungal suspension was intravaginally administered. Mice were then positioned with elevated hindquarters for half an hour. On the second day post-infection, each corresponding group (3 mice per group) received 5 μ l of compound S1 (0.1, 0.5, 2.5 mg), administered consecutively for three days. On the fourth day, mice were vaginally washed with PBS, and the lavage was diluted and plated on YPD agar for counting after 48 hours of cultivation.

(2) Results

The results, as shown in Figure 3, indicate that after three days of topical treatment with S1 (2.5 mg), the fungal burden in the vaginal lavage decreased by 2 logs.

Example 9: The efficacy of compound S1 in the oral treatment of systemic fungal infection in mice.

(1) Methods

Inoculate *Candida albicans* SC5314 in YPD liquid medium and culture to the logarithmic growth phase, collect the cells, and wash them twice with PBS. Adjust the cell concentration to 2×10^6 cells/ml with saline. Female BALB/c mice weighing 18-22 g were randomly divided into groups: NS (intravenous injection of saline), WT (intravenous injection of SC5314), WT + different concentrations of drug treatment groups (oral administration), and a separate drug control group. Inject the fungal suspension into the tail vein of different mice, each with 100 μ l (inoculum dose of 2×10^5 cells/mouse), and inject an equal volume of saline in the NS group.

Survival rate: The survival of each group of mice was observed and recorded daily. After 30 days, the survival rate was calculated, and the surviving mice were euthanized. Survival curves were plotted, and statistical analysis was performed using the Log-rank test.

Fungal burden: On the 3rd and 7th days after modeling, the left kidneys, brains, livers, and spleens of each group of mice (3 mice/group) were collected, weighed, ground, and the tissue homogenate was serially diluted and spread on YPD agar plates. After 48 hours of incubation at 30 °C, the colony-forming units (CFUs) were counted. Statistical analysis was conducted using the Student *t* Test.

Histopathology: The right kidneys used for the microbiological assessment were fixed in 10% formalin. Pathological sections were prepared, including HE staining and PAS staining.

(2) Results

Survival rate were presented in Figure 4, indicating a notable 60% increase in the survival of mice with systemic infection upon treatment with Compound S1 at 100 mg/kg ($P < 0.05$). Additionally, Compound S1 at 50 mg/kg demonstrated a prolongation of survival time in mice with systemic infection.

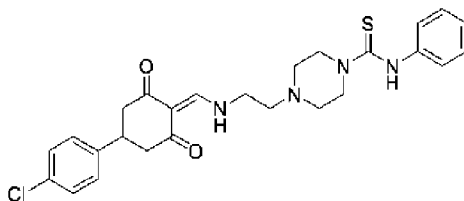
Figure 5 presented the organ fungal burden results after 7 days of Compound S1 treatment. A substantial reduction ($P < 0.05$) of fungal burden by two logs was observed in the liver, kidneys, and brain of mice.

Histopathological findings in Figure 6 exhibited no discernible distinctions in kidney, liver, spleen, and brain pathology between mice treated with Compound S1 and the NS control. No evidence of tissue damage, hyphae, pseudohyphae, spores, or inflammatory cell infiltration was noted.

Finally, it is important to note that the detailed description provided above for specific embodiments of the present invention is exemplary only. The invention is not limited to the specific embodiments described above. For those skilled in the art, any equivalent modifications and substitutions made to the present invention fall within the scope of the invention. Therefore, all equivalent transformations and modifications made without departing from the spirit and scope of the present invention should be considered as encompassed within the scope of the invention.

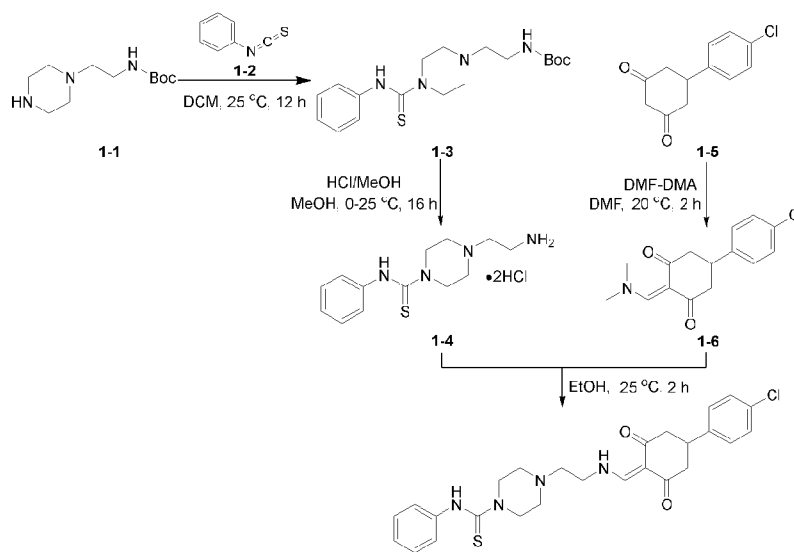
Claims

1. The application of a polycyclic aromatic compound or its pharmaceutically acceptable salt in the preparation of antifungal drugs, characterized by the structural formula of the aforementioned polycyclic aromatic compound:



S1.

2. A method for preparing the compound as shown in the structural formula of claim 1, comprising:



S1,

wherein compound **1-1** reacts with compound **1-2** to generate thiourea compound **1-3**, the latter undergoes Boc protection group removal under hydrochloric acid conditions to form hydrochloride compound **1-4**; compound **1-5** reacts with N,N-dimethylformamide dimethyl acetal to produce dione compound **1-6**, and under ethanol solvent conditions, the reaction of compound **1-4** with compound **1-6** yields the target compound S1.

3. A pharmaceutical composition comprising the polycyclic aromatic compound or its pharmaceutically acceptable salt as shown in claim 1, and one or more pharmaceutically acceptable carriers.

4. The use of the polycyclic aromatic compound or its pharmaceutically acceptable salt as described in claim 1 or 3, or its pharmaceutical composition, in the preparation of drugs for treating pathogenic fungal infections caused by *Candida*, *Aspergillus*, *Mucormyces*, *Cryptococcus*, and the like.
5. The use of the polycyclic aromatic compound or its pharmaceutically acceptable salt as described in claim 1 or 3, or its pharmaceutical composition, in the preparation of drugs for treating superficial and invasive fungal infections caused by fungal pathogens.

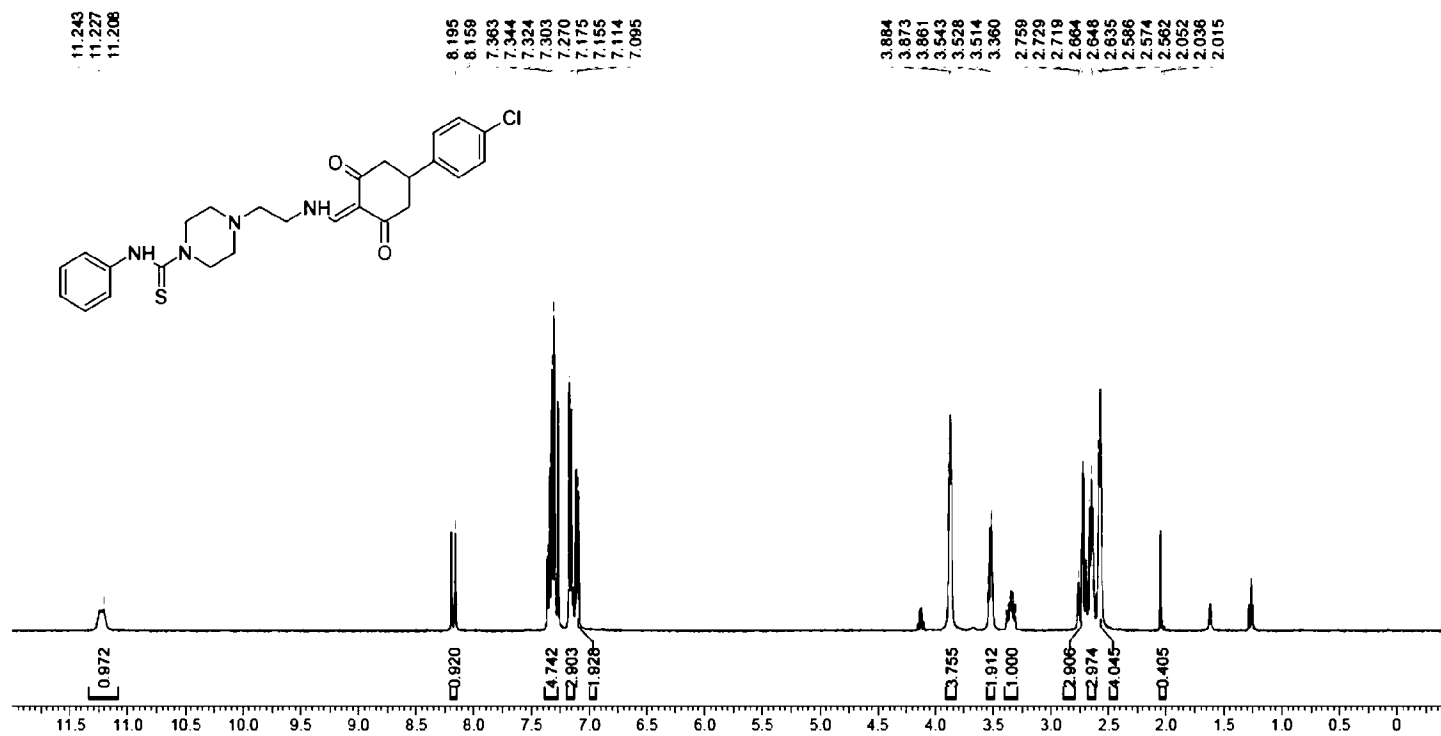


Figure 1

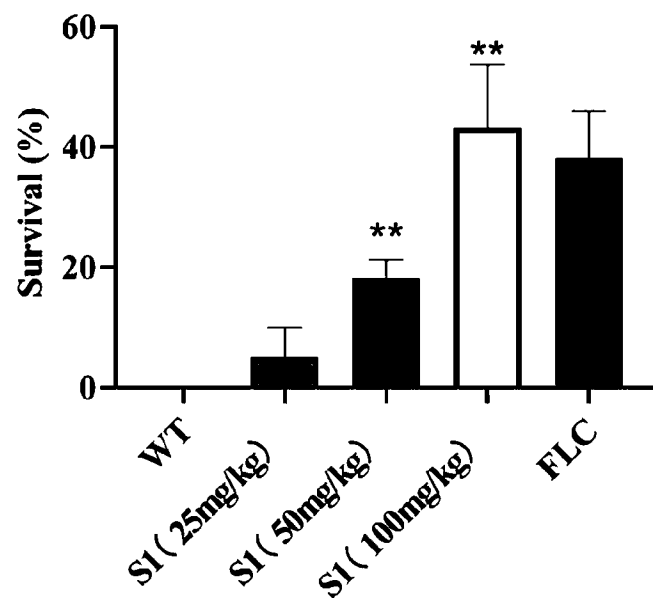


Figure 2

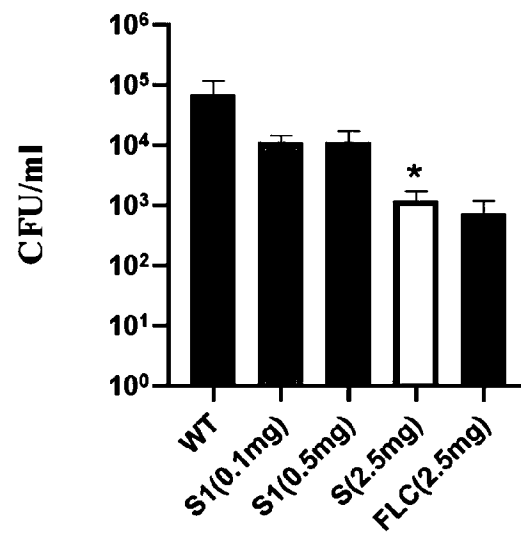


Figure 3

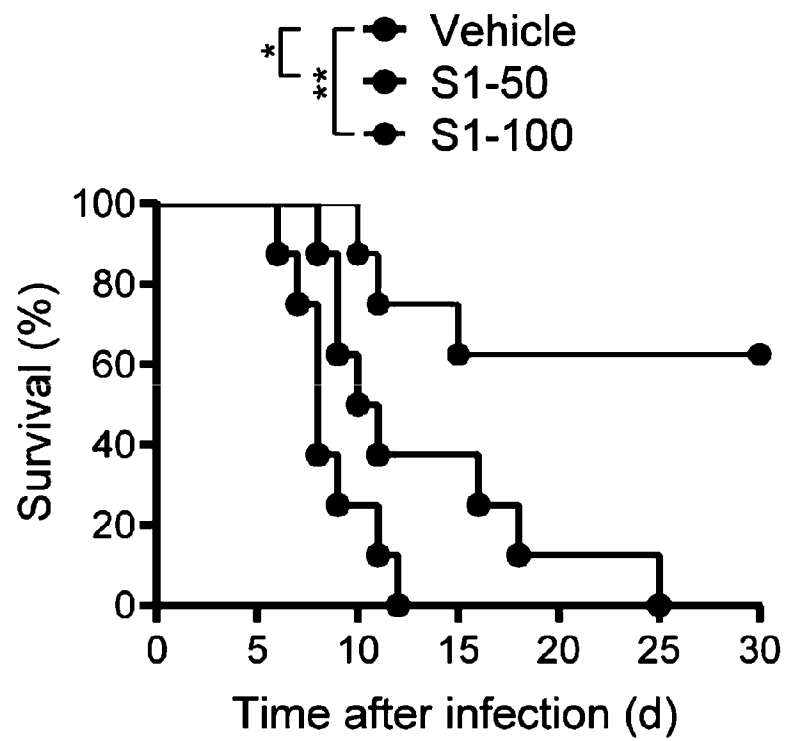


Figure 4

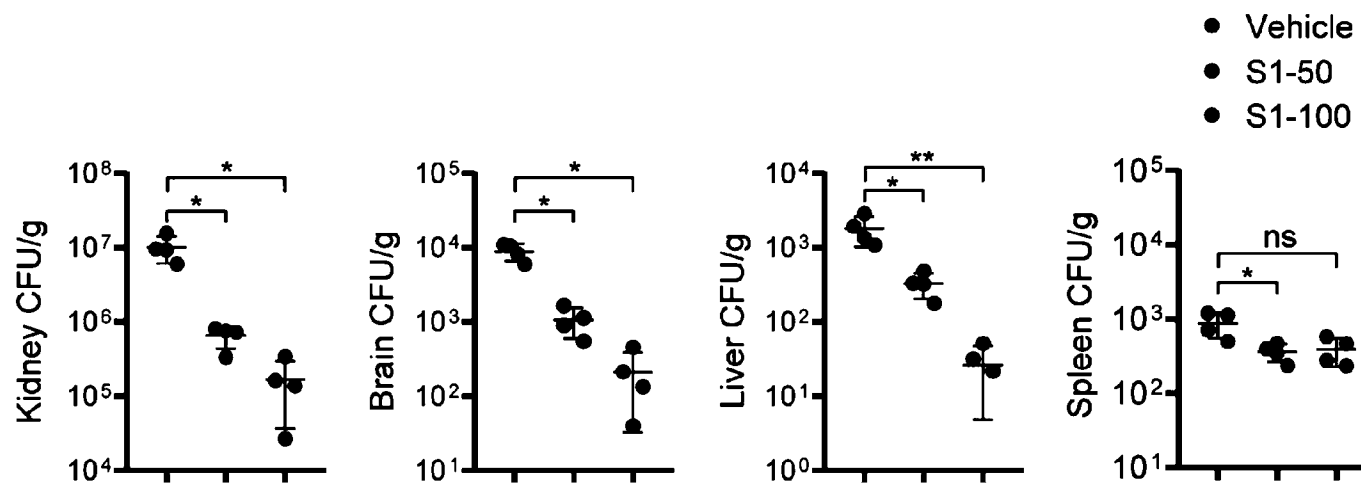


Figure 5

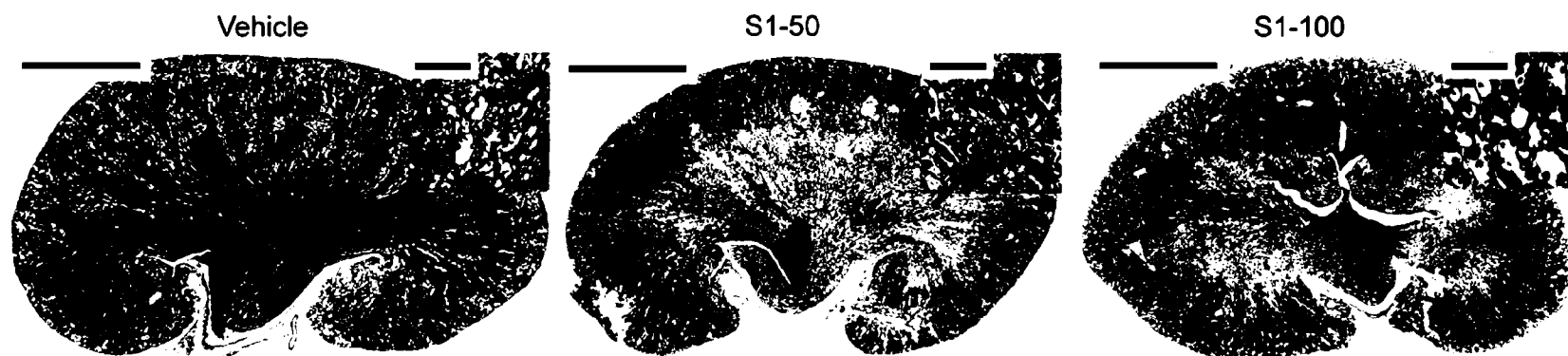
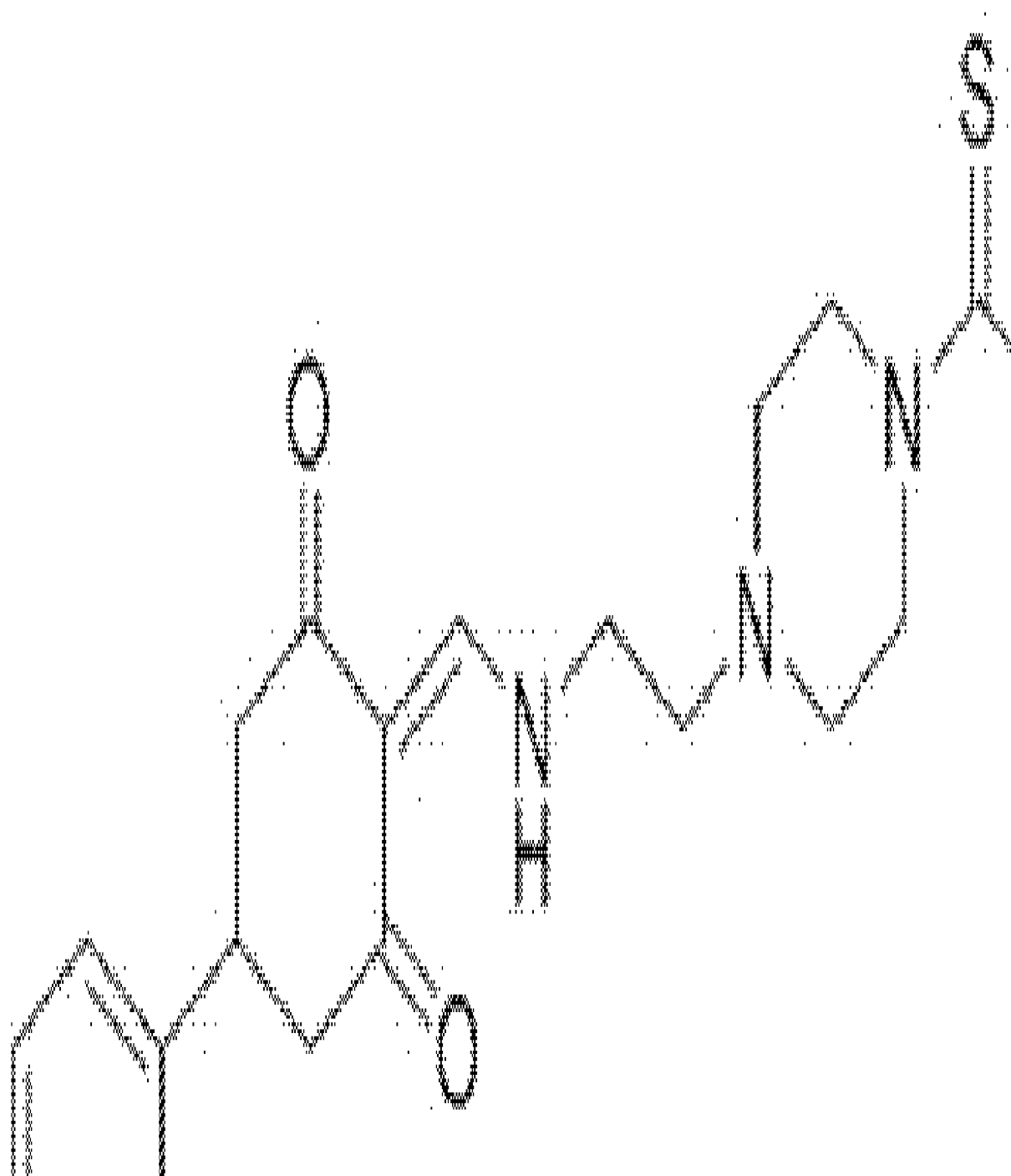


Figure 6



S1