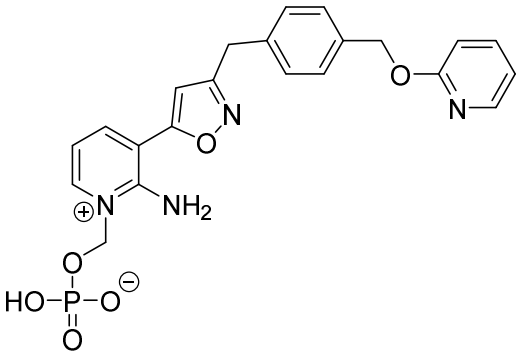
CLAIMS

WHAT IS CLAIMED IS:

1. Use of~~A method of treating a fungal infection in a subject, the method comprising administering to a subject with a fungal infection~~ a therapeutically effective amount of compound 1:



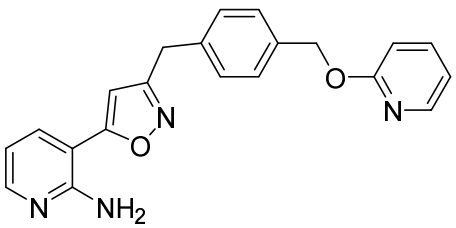
1,

or a pharmaceutically acceptable salt, solvate, or hydrate thereof, in the manufacture of a medicament for the treatment of a fungal infection in a subject;

wherein,

the fungal infection in the subject is caused by *Candida* spp., *Aspergillus* spp., *Scedosporium* spp., *Fusarium* spp., *Paecilomyces* spp., *Purpureocillium* spp., *Dematiaceous* spp., *Rhizopus, Mucor* spp., *Lichtheimia* spp., *Cunninghamella* spp., *Acremonium* spp., *Rasamsonia* spp., *Scedosporium* spp., *Schizophyllum* spp., *Trichoderma* spp., *Alternaria* spp., *Cladophialophora* spp., *Cladosporium* spp., *Exophiala* spp., *Fonsecaea* spp., *Lomentospora* spp., *Phialophora* spp., *Scopulariopsis* spp., *Magnusiomyces* (*Geotrichum)* spp., *Trichosporon* spp., *Malassezia* spp., *Saprochaete* spp., *Kodamaea* spp., *Rhodotorula* spp., *Saccharomyces* spp., *Pseudozyma* spp., *Sporobolomyces* spp., *Exophiala* spp., *Lacazia* spp., *Emmonsia* spp., *Wickerhamomyces (Pichia)* spp., *Emergomyces* spp., *Talaromyces* spp., or Emmonsia-like fungi, or a combination thereof;

the therapeutically effective amount of compound 1 provides a steady state 24-hr Area Under the Concentration-Time Curve (AUC_{0-24}) in the subject of at least about 100 µg×hr/mL of compound 1A:



1A;

wherein the subject has a contradiction to standard of care antifungal therapy; and

wherein the treatment comprises ~~administration of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, to the subject comprises a treatment regimen comprising the~~ daily administration of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, for at least 1-4 weeks.

2. The ~~method~~use of claim 1, wherein the contradiction to standard of care antifungal therapy is due to reduced kidney function.

3. The ~~method~~use of claim 1 or claim 2, wherein the contradiction to standard of care antifungal therapy is due to a kidney disease in the subject.

4. The ~~method~~use of claim 3, wherein the kidney disease is chronic kidney disease, metabolic syndrome, vesicoureteral reflux, tubulointerstitial renal fibrosis, IgA nephropathy, diabetic nephropathy, Alport syndrome, HIV associated nephropathy, glomerular nephritis (GN), focal segmental glomerulosclerosis, membranous glomerulonephritis, mesangiocapillary GN, interstitial fibrosis and tubular atrophy (IFTA), acute kidney injury (AKI), acute obstructive nephropathy, or drug induced fibrosis.

5. The ~~method~~use of claim 3, wherein the kidney disease is chronic kidney disease (CKD).

6. The ~~method~~use of claim 5, wherein chronic kidney disease (CKD) is Stage 1 CKD, Stage 2 CKD, Stage 3 CKD, Stage 4 CKD, or Stage 5 CKD.

7. The ~~method~~use of claim 2, wherein the subject has high levels of protein in his or her urine (proteinuria).

~~8. The method of any one of claims 1-7, wherein the therapeutically effective amount of compound 1 provides a steady state 24-hr Area Under the Concentration-Time Curve (AUC_{0-24}) of at least 150 µg×hr/mL of the compound 1A.~~

~~9. The method of any one of claims 1-8, wherein the contradiction to standard of care antifungal therapy comprises an azole antifungal, an allylamine antifungal agent, echinocandin antifungal, or polyene antifungal.~~

~~10. The method of any one of claims 1-8, wherein the contradiction to standard of care antifungal therapy comprises amphotericin B, candicidin, filipin, hamycin, natamycin, nystatin, rimocidin, bifonazole, butoconazole, clotrimazole, econazole, fenticonazole, isavuconazole, ketoconazole, luliconazole, miconazole, omoconazole, oxiconazole, sertaconazole, sulconazole, tioconazole, albaconazole, efinaconazole, epoxiconazole, fluconazole, isavuconazole, itraconazole, posaconazole, propiconazole, ravuconazole, terconazole, voriconazole, abafungin, amorolfin, butenafine, naftifine, or terbinafine, anidulafungin, caspofungin, micafungin, rezafungin, or a pharmaceutically acceptable salt of any of the preceding antifungal agents.~~

11. The method of any one of claims 1-10, wherein the fungal infection is caused by *Candida* spp., *Aspergillus* spp., *Scedosporium* spp., *Fusarium* spp., *Paecilomyces* spp., *Purpureocillium* spp., *Dematiaceous* spp., or Mucorales fungi, or a combination thereof.

12. The method of any one of claims 1-11, wherein the subject is immunocompromised.

13. The method of any one of claims 1-12, wherein the subject is infected with HIV/AIDS or has cancer.

14. The method of claim 13, wherein the cancer is acute myeloid leukemia or acute lymphoid leukemia.

15. The method of any one of claims 1-14, wherein the subject has neutropenia.

16. The method of any one of claims 1-15, wherein the subject has lymphopenia.

17. The method of any one of claims 1-16, wherein the subject is undergoing or has undergone cancer chemotherapy treatment.

18. The method of any one of claims 1-17, wherein the subject is undergoing or has undergone corticosteroid treatment.

19. The method of any one of claims 1-18, wherein the subject is undergoing or has undergone TNF inhibitor treatment.

20. The method of any one of claims 1-19, wherein the subject is an organ transplant recipient.

21. The method of any one of claims 1-16, wherein the subject is a hematopoietic stem cell transplant recipient.

22. The method of any one of claims 1-16, wherein the subject has graft-versus-host disease.

23. The method of any one of claims 1-22, wherein the fungal infection is superficial, locally invasive, or disseminated throughout the subject.

24. The method of any one of claims 1-23, wherein the fungal infection is a cutaneous infection, lung infection, sinus infection, central nervous system infection, brain infection, eye infection, heart infection, kidney infection, gastrointestinal tract infection, stomach infection, pelvic infection, blood infection, or a combination thereof.

25. The method of any one of claims 1-24, wherein the fungal infection comprises a fungal disease or condition that is candidiasis, aspergillosis, blastomycosis, coccidioidomycosis (Valley Fever), cryptococcosis, histoplasmosis, mucormycosis, Pneumocystis pneumonia (PCP), ringworm, sporotrichosis, talaromycosis, allergic bronchopulmonary aspergillosis, allergic sinusitis, azole-resistant *A. fumigatus*, aspergilloma, pulmonary aspergillosis, invasive aspergillosis, cutaneous aspergillosis, fusariosis, scedosporiosis, rhinocerebral mucormycosis, pulmonary mucormycosis, disseminated mucormycosis,

abdominal-pelvic mucormycosis, gastric mucormycosis, cutaneous mucormycosis, or a combination thereof.

26. The method of any one of claims 1-25, wherein the treatment regimen comprises a loading dose of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, and a maintenance dose of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

27. The method of claim 26, wherein the treatment regimen comprises a loading dose of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, of about 2000 mg compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

28. The method of claim 26 or claim 27, wherein the loading dose of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, is administered to the subject by intravenous (I.V.) infusion.

29. The method of claim 26 or claim 27, wherein the loading dose of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprises the administration of two doses of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, to the subject by intravenous (I.V.) infusion.

30. The method of claim 26 or claim 27, wherein each loading dose of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, is administered to the subject by intravenous (I.V.) infusion over about 30 minutes to about 4 hours.

31. The method of claim 26 or claim 27, wherein each dose of the loading dose comprises about 1000 mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

32. The method of claim 26 or claim 27, wherein the loading dose comprises administration of about 1000 mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, to the subject by intravenous (I.V.) infusion followed by a second administration of about 1000 mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, to the subject by intravenous (I.V.) infusion within about 24 hours of the first infusion.

33. The method of any one of claims 26-32, wherein the maintenance dose is administered once daily starting on the second day of treatment.

34. The method of claim 33, wherein the maintenance dose comprises once daily administration of about 600 mg to about 1500 mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

35. The method of any one of claims 26-34, wherein the maintenance dose of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof is administered over a

period of about 30 minutes to about 4 hours by I.V. infusion starting on the second, third, or fourth day of treatment.

36. The method of any one of claims 26-35, wherein the maintenance dose of about 600 mg to about 1200 mg compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof is administered over a period of about 30 minutes to about 4 hours by I.V. infusion starting on the second, third, or fourth day of treatment.

37. The method of any one of claims 26-34, wherein the maintenance dose of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof is administered orally to the subject starting on the second, third, or fourth day of treatment.

38. The method of any one of claims 26-34, wherein the maintenance dose of about 800 mg to about 1000 mg compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof is administered orally once daily to the subject starting on the second, third, or fourth day of treatment.

39. The method of any one of claims 26-34, wherein, starting on the second, third, or fourth day of treatment:

a) about 600 mg to about 900 mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof is administered over a period of about 30 minutes to about 3 hours by I.V. infusion; or

b) about 700 mg to about 1000mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof is administered orally once daily.

40. The method of any one of claims 26-34, wherein:

starting on the second day of treatment, about 600 mg to about 900 mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof is administered over a period of about 30 minutes to about 3 hours by I.V. infusion; and

starting on the fourth day of treatment:

a) about 600 mg to about 900 mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof is administered over a period of about 30 minutes to about 3 hours by I.V. infusion; or

b) about 700 mg to about 1000mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof is administered orally once daily.

41. The method of any one of claims 1-40, wherein:

the compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof is administered in combination with an additional therapeutic agent.

42. The method of any one of claims 1-41, wherein:

the treatment regimen comprises the daily administration of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, for about 4 weeks to about 6 weeks.

43. The method of any one of claims 1-42, wherein:
the treatment regimen comprises the daily administration of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, for about 4 weeks to about 12 weeks.

44. The method of any one of claims 1-25, wherein:
the treatment regimen comprises a loading dose of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, and maintenance doses of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof;
wherein the loading dose of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, comprises the administration of two doses of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, to the subject by intravenous (I.V.) infusion on the first day of therapy, wherein each dose comprises about 1000 mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof;
followed by maintenance doses comprising once daily administration of about 600 mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof by intravenous (I.V.) infusion for at least two days, followed by either:
once daily administration of about 600 mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, by intravenous (I.V.) infusion; or
once daily oral administration of about 700 mg of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

45. The method of claim 44, wherein the treatment regimen comprises up to 14 days of administration of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof.

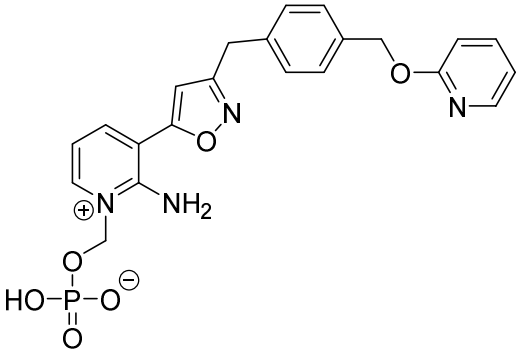
46. The method of any one of claims 1-45, wherein the fungal infection in the subject is caused by *Candida* spp.

47. The method of any one of claims 1-46, wherein:
the treatment regimen increases the chances of survival for the subject, decreases galactomannan levels in the subject, decreases β-d-glucan levels in the subject, or a combination thereof.

48. The method of any one of claims 1-47, wherein:

~~a dose adjustment of the compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof that is administered to the subject is not required based on the kidney status of the subject.~~

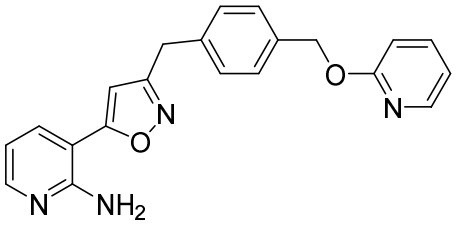
~~49.~~8. ~~A method of treating a fungal infection in a subject, the method comprising administering to a subject with a fungal infection~~ Use of a therapeutically effective amount of compound 1:



1,

or a pharmaceutically acceptable salt, solvate, or hydrate thereof, in the manufacture of a medicament for the treatment of a fungal infection in a subject;

wherein, the therapeutically effective amount of compound 1 provides a steady state 24-hr Area Under the Concentration-Time Curve (AUC_{0-24}) in the subject of at least about 100 µg×hr/mL of compound 1A:



1A;

wherein the treatment comprises ~~administration of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, to the subject comprises a treatment regimen comprising the~~ daily administration of compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof, for at least 1-4 weeks;

wherein a dose adjustment of the compound 1, or a pharmaceutically acceptable salt, solvate, or hydrate thereof that is to be administered to the subject is not required based on the kidney status of the subject.