

Introduction

The Research Institute of Pharmaceutical Sciences (RIPS), within the School of Pharmacy, was established in 1964 to discover and disseminate knowledge of natural drug products, develop and commercialize new products, improve public health and stimulate the economy. The major research component of RIPS is the National Center for Natural Products Research (NCNPR). The NCNPR is the nation's only university-affiliated research center devoted to discovering, developing and commercializing new pharmaceuticals and agrochemicals derived from natural products.



Facilities and Resources

The NCNPR is located in the Thad Cochran Research Institute, a modern, well-equipped research building (151,000 gsf). Centralized resources include:

- A repository of samples including extracts and column fractions from plants, marine organisms and micro-organisms as well as purified compound (natural, synthetic and semisynthetic).
- Isolation, purification and screening laboratories including Biosafety Level 2 laboratories.
- 600, 500, and 400 MHz NMR spectrometers; LC, GC, MS and CE instrumentation.
- Culture facilities for fermentation/isolation.
- Genomics research laboratories.

R&D Focus and Opportunity

The NCNPR is focused on the discovery and development of bioactive, novel chemical molecules for use in a variety of therapeutic areas. Drug discovery efforts have historically focused on antiinfective and anti-cancer compounds but have been expanded to include CNS, inflammation and immune modulation. The University of Mississippi is currently seeking commercial partners to accelerate early stage pharmaceutical R&D studies.

The NCNPR's drug discovery efforts have resulted in a number of lead compounds with antiinfective activity as summarized in Table 1.

Development Capabilities

- Bioassay Guided Isolation
 - o Targeted screening (including drug-resistant isolates and azole reversal)
 - Opportunistic Infections (*Candida albicans*, *Cryptococcus neoformans*, *Mycobacterium intracellulare* and *Aspergillus fumigatus*)
 - Antimicrobial (Methicillin-resistant *Staphylococcus aureus*, *Pseudomonas aeruginosa*)
 - Antiparasitic (*Plasmodium falciparum*; *Leishmania donovan*)
 - o Anti-inflammatory
 - Inhibition of nuclear factor kappa B (NF-kappa B) mediated transcription
 - Inhibition of Cox-2 activity
 - Antioxidant activity
 - o Anti-cancer/Cytotoxicity
 - SK-MEL, KB, BT-549, SK-OV-3, HepG2/VERO, LLC-PK1
 - o CNS
 - *In vitro* receptor binding assays; *In vivo* neurobehavioral assays (selective for anxiety and/or depression)
 - Neurodegeneration and cholesterol homeostasis
- Development of molecular mechanism-targeted bioassays
 - o Inhibition of hypoxia-inducible factor 1 (HIF-1)
 - o Activation of Peroxisome Proliferator Activated Receptor-gamma (PPAR)
 - o Inhibition of VEGF expression
- Structural Characterization; Lead Optimization, SAR and Synthesis
- *In vivo* models
 - o *C. albicans* (systemic and topical)
 - o *Cr. neoformans*
 - o MRSA (systemic)
 - o *Trichophyton mentagrophytes* (Athlete's foot)



Funding

Research is funded from a variety of sources including CDC, FDA, NIH/NIAID/NCI, DOD, NSF, EPA, NOAA/Sea Grant, USDA, WHO and industry. The School of Pharmacy has been in the top 5 in the nation among U.S. Schools of Pharmacy in total federal funding for the last five years.

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Table 1. Lead Antiinfective Compounds Under Development by the NCNPR

UM No.	Compound ID	<i>C. albicans</i>			<i>Cr. neoformans</i>			<i>A. fumigatus</i>			MRSa			<i>M. intracellulare</i>		
		IC ₅₀	MIC	MFC	IC ₅₀	MIC	MFC	IC ₅₀	MIC	MFC	IC ₅₀	MIC	MBC	IC ₅₀	MIC	MBC
UM1740	18545	0.80	2.08	2.08	2.04	8.33	8.33	19.00	20.00	20.00	-	-	-	6.50	15.63	31.25
	52287	0.95	2.50	2.50	1.50	5.00	5.00	-	-	-	-	-	-	6.50	10.00	20.00
	52289	0.80	2.50	2.50	2.50	5.00	5.00	7.00	20.00	20.00	-	-	-	1.50	5.00	10.00
	52290	0.80	2.50	2.50	2.00	5.00	5.00	10.00	20.00	20.00	-	-	-	3.00	10.00	20.00
UM3800	9402	1.50	5.00	-	1.50	5.00	-	-	-	-	1.50	-	-	10.00	20.00	-
	9403	<0.05	0.05	6.25	0.80	6.25	-	25.00	-	-	0.50	1.56	3.13	-	-	-
	14844	0.05	0.12	7.50	0.95	3.75	-	9.50	15.00	-	0.30	1.88	30.00	9.50	15.00	30.00
UM3630	51365	15.00	-	-	0.80	1.25	1.25	0.45	0.63	0.63	1.50	2.50	10.00	2.00	5.00	20.00
	51367	15.00	-	-	0.40	0.63	1.25	3.00	5.00	-	0.35	1.25	5.00	0.90	2.50	20.00
UM4080	58267	1.50	2.50	2.50	0.40	0.63	0.63	3.50	5.00	5.00	1.50	5.00	-	10.00	20.00	-
	71514	3.00	5.00	5.00	0.25	0.63	1.25	3.50	5.00	5.00	1.50	5.00	-	7.00	10.00	-
Amphotericin B (AmpB)		0.20	0.63	1.25	0.80	1.25	2.50	1.00	2.50	5.00	NA			NA		
Ciprofloxacin		NA			NA			NA			0.10	0.31	-	0.35	0.50	-

"-" = not active; NA = not applicable

IC₅₀ = concentration in µg/ml that affords 50% inhibition of growth

MIC = Minimum Inhibitory Concentration; the lowest test concentration in µg/ml that allows no detectable growth

MFC/MBC = Minimum Fungicidal/Bactericidal Concentration; the lowest test concentration (µg/ml) that kills the organism

UM1740

- This class of compounds has exhibited potent *in vitro* antifungal activity with no toxicity in VERO cells. Preliminary *in vivo* data in a rodent model has shown compound 18545 to be efficacious against *C. albicans* infection in the kidney.
- Cost effective synthesis achievable in 6 steps starting with commercially available material.

UM3800

- Compounds 9403 and 14844 have been shown to exhibit superior activity against *C. albicans in vitro* and comparable activity against *Cr. neoformans*. Compound 9403 has exhibited *in vivo* activity against *C. albicans* infection during preliminary studies.
- Compounds have been prepared synthetically utilizing published methodology. *In vitro* SAR of analogs reveals selectivity among fungal isolates.

UM3630

- Compound 51367 has exhibited potent broad spectrum activity against *Cr. neoformans*, and *M. intracellulare* and MRSa. *In vivo* data against *Cr. neoformans* infection in the brain (rodent model) has shown compound 51367 to be efficacious and non-toxic in preliminary studies. *In vivo* studies in a systemic model for MRSa are ongoing.
- Domestic source readily available with simple methodology for isolation and purification.

UM4080

- This class of compounds has exhibited potent and selective *in vitro* activity against *Cr. neoformans* with no toxicity in VERO cells.
- Synthesis achievable in 3 steps starting with commercially available intermediate. Analogs are currently being developed for SAR.

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