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表1. わが国で深在性真菌症の治療薬として承認されている抗真菌薬

クラス	一般名	商品名	剤型	製造承認年	備考
ポリエン系 (Polyene)	アムホテリシB (Amphotericin B)	ファンギゾン〔ブリストル・マイヤーズ　スクイブ〕	注射液	1962	シロップ剤は口腔カンジダ症の治療、腸管内 *Candida* 抑制（予防投与）など適用
フロロピリミジン系 (Fluoropyrimidine)	フルシトシン (Flucytosine)	アンコチル 〔日本ロシュ〕	錠剤・顆粒剤	1979	
アゾール系 (Azole)	ミコナゾール (Miconazole)	フロリード 〔持田製薬〕	静注液	1985	ゲル剤は口腔咽頭カンジダ症および食道カンジダ症の治療に適用
アゾール系 (Azole)	フルコナゾール (Fluconazole)	ジフルカンカプセル 〔ファイザー製薬〕	カプセル	1989	
		ジフルカン静注 〔ファイザー製薬〕	静注液	1989	
アゾール系 (Azole)	イトラコナゾール (Itraconazole)	イトリゾールカプセル 〔ヤンセン協和〕	カプセル	1993	

表2. アゾール系薬剤の耐性機序

耐性機序	備　考
(1) 薬剤標的分子($P450_{14DM}$)の過剰産生	・$P450_{14DM}$分子数の増加によってエルゴステロール合成が亢進 ・FLCZ, ITCZを含むすべてのアゾール系薬剤に耐性化（交叉耐性） ・確認されている耐性臨床株は *C. glabrata* のみ（*C. albicans* の報告例はない）
(2) 薬剤標的分子($P450_{14DM}$)の変化	・$P450_{14DM}$遺伝子(ERG11)の点変異によって薬剤親和性が低下した酵素が生成 ・この修飾酵素の正常基質に対する活性は保持される場合と失われる場合とがある(点変異の部位によって) ・臨床分離株では見つかっていない
(3) ステロール合成系の変化	・エルゴステロールは合成されず、その代替機能をもち、しかも薬剤親和性の低いステロール（14α-methylfecosterolなど）が蓄積 ・$P450_{14DM}$とsterol△5,6 desaturaseがともに欠失または不活化 ・AMPHに対しても耐性を示す ・FLCZ耐性*C. albicans* 臨床分離株に見出されている
(4) 薬剤細胞透過性の低下	・細胞内への薬剤移入が阻止されることによる細胞内薬剤濃度の低下 ・細胞膜脂質組成の変化と関連 ・KTZ または ITCZ 耐性 *C. albicans* のほか*C. krusei*, *C. glabrata* の臨床分離株での報告があるが確証は困難
(5) 薬剤細胞外排出の亢進	・以下の2種の薬剤排出ポンプの過剰発現によって細胞内薬剤を汲み出して細胞内薬剤濃度を低下させる：(ⅰ)ABCトランスポーター(CDRIなど)(ⅱ)MFSトランスポーター(CaMDRI) ・(ⅰ)はすべてのアゾール系薬剤の耐性に、(ⅱ)はFLCZ耐性に関与 ・*C. albicans* その他の*Candida* spp.の臨床分離株で最も高頻度にみられる耐性機序

FLCZ, fluconazole; ITCZ, itraconazole; KCZ, ketconazole

表3. 日本および欧米諸国で臨床開発中の新規抗真菌薬

(2000年12月現在)

Drug	Class	Form	Status	
			Japan	Other countries
UK-292,663 [phosphatyl fluconazole]	Triazole	intravenous	P-Ⅱ/Ⅲ	P-Ⅲ(US)
JK 1211 [β -hydroxydextrin-itraconazole]	〃	oral	P-Ⅱ	P-Ⅲ, launched (EU)
ITR-IV [〃]	〃	intravenous	P-Ⅰ	P-Ⅲ, launched (EU)
UK-109,496 [voriconazole]	〃	oral & intravenous	P-Ⅰ	P-Ⅲ(US, EU)
SCH-56592 [posaconazole]	〃	oral	P-Ⅰ	P-Ⅱ(US)
ER-30346/BMS-207147 [ravuconazole]	〃	oral & intravenous	—	P-Ⅱ/Ⅲ(US)
NS-718 [lipid nanosphere-amphotericin B]	Polyene	intravenous	P-Ⅱ	
SM-26000 [liposomal amphotericin B]	〃	intravenous	P-Ⅱ/Ⅲ	Launched (EU, US)
AR-121 [liposomal nystatin]	〃	intravenous	—	P-Ⅲ(US),
FK463	Lipopeptide	intravenous	P-Ⅱ/Ⅲ	P-Ⅲ(EU, US)
L-743872 [caspofungin]	〃	intravenous	—	P-Ⅲ(US)
LY-303,366	〃	oral & intravenous	P-Ⅰ	P-Ⅱ(US, EU)

US : United States ; EU : European countries

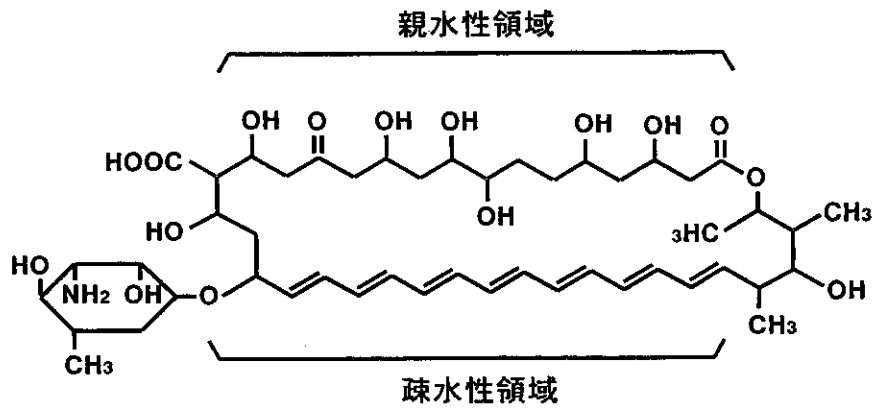
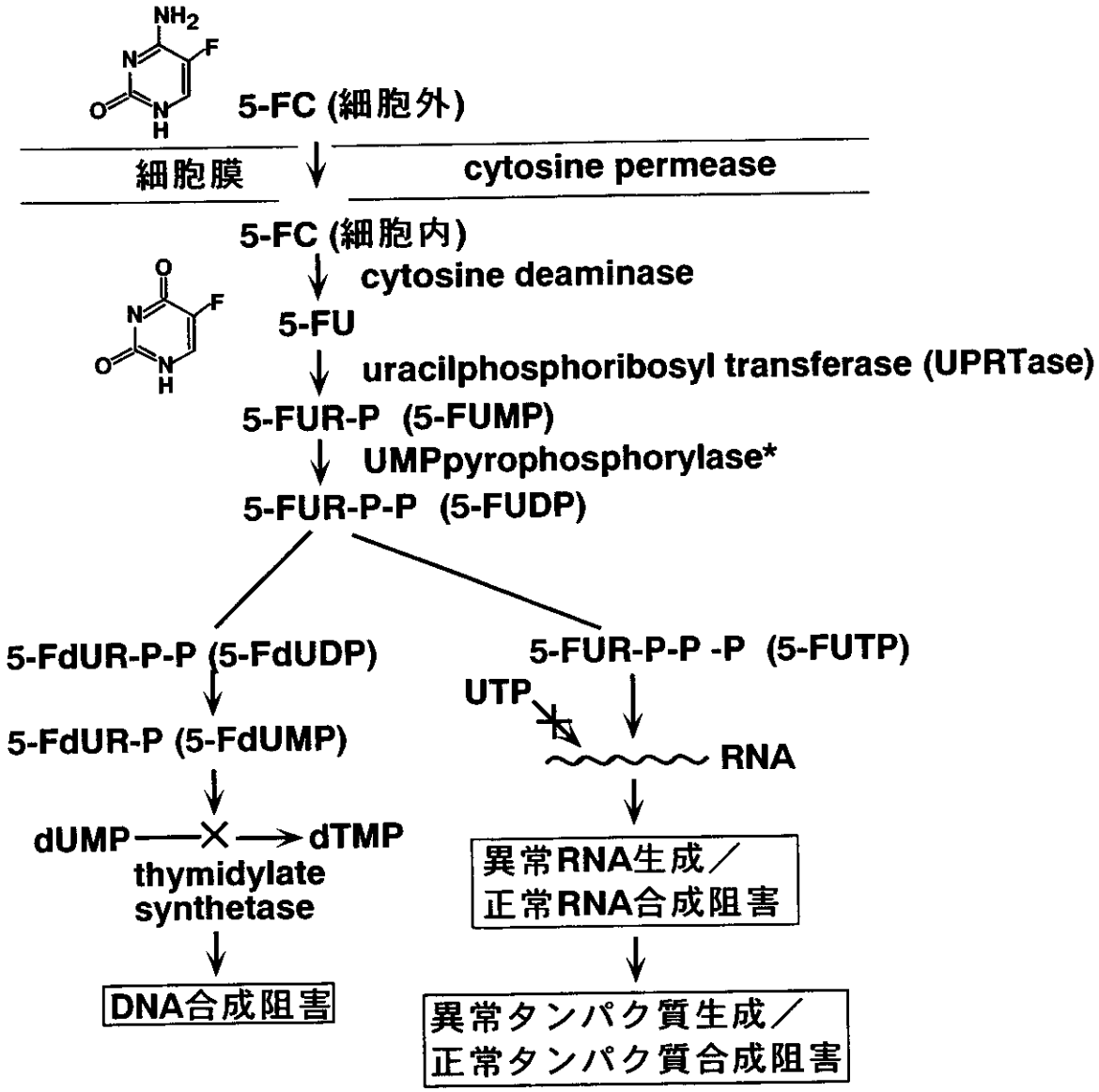


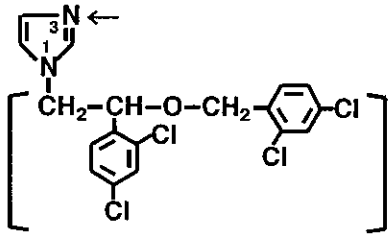
図1. Amphotericin Bの構造

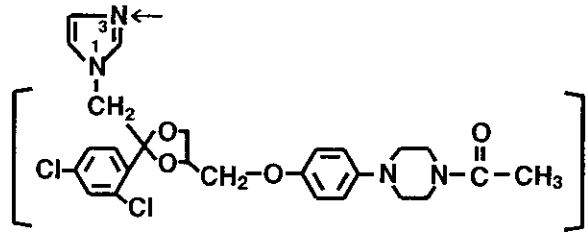


5-FU : 5-fluorouracil
5-FUMP : 5-fluorouridine-5'-monophosphate
5-FUDP : 5-fluorouridine-5'-diphosphate
5-FdUDP : 5-fluorodeoxyuridine-5'-diphosphate
5-FdUMP : 5-fluorodeoxyuridine-5'monophosphate
5-FUTP : 5-fluorouridine-5'-triphosphate

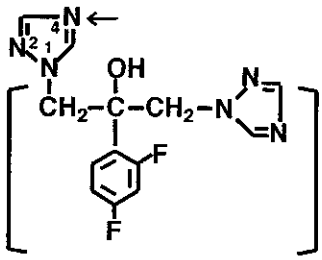
図2. 真菌のピリミジン再利用経路におけるflucytosine (5-FC)の代謝産物の生成と高分子合成に及ぼす影響

イミダゾール系：





トリアゾール系：



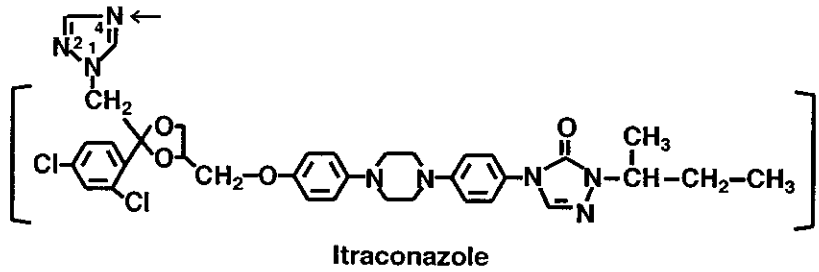
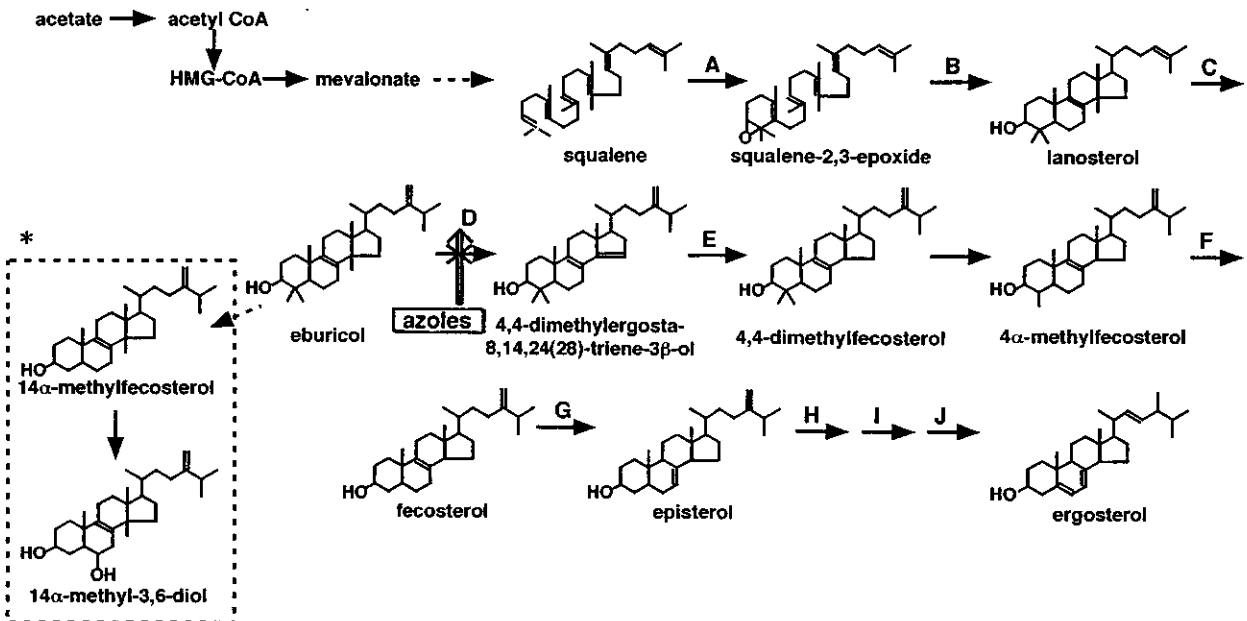


図3. アゾール系抗真菌薬の化学構造
薬剤分子のイミダゾール環またはトリアゾール環のリガンドを矢印（←）で、N_1-置換基（非リガンド部分）を[　　]内に示す。前者は$P450_{14DM}$のヘム鉄イオン（Fe^{+++}）と、後者はそのアポタンパク質（ポリペプチド鎖）と各々結合する。



A, squalene epoxidase [ERG1] ; B, lanosterol synthase [ERG7] ; C, S-adenosyl-methyltransferase;
D, $P450_{14DM}$ (sterol-demethylase) [ERG11] ;E, Δ^{14}-reductase [ERG24] ; F, Δ^{24}-methyltransferase [ERG6] ;
G, $\Delta^{8,7}$-Isomerase [ERG2] ; H, $\Delta^{5,6}$-desaturase [ERG3] ; I, Δ^{22}-desaturase [ERG5] ; J, Δ^{24}-desaturase [ERG4]
＊$P450_{14DM}$ 活性が喪失または低下した場合の副次的代謝経路

図4. 真菌におけるエルゴステロール合成主要経路とアゾール系抗真菌薬（azoles）の作用点

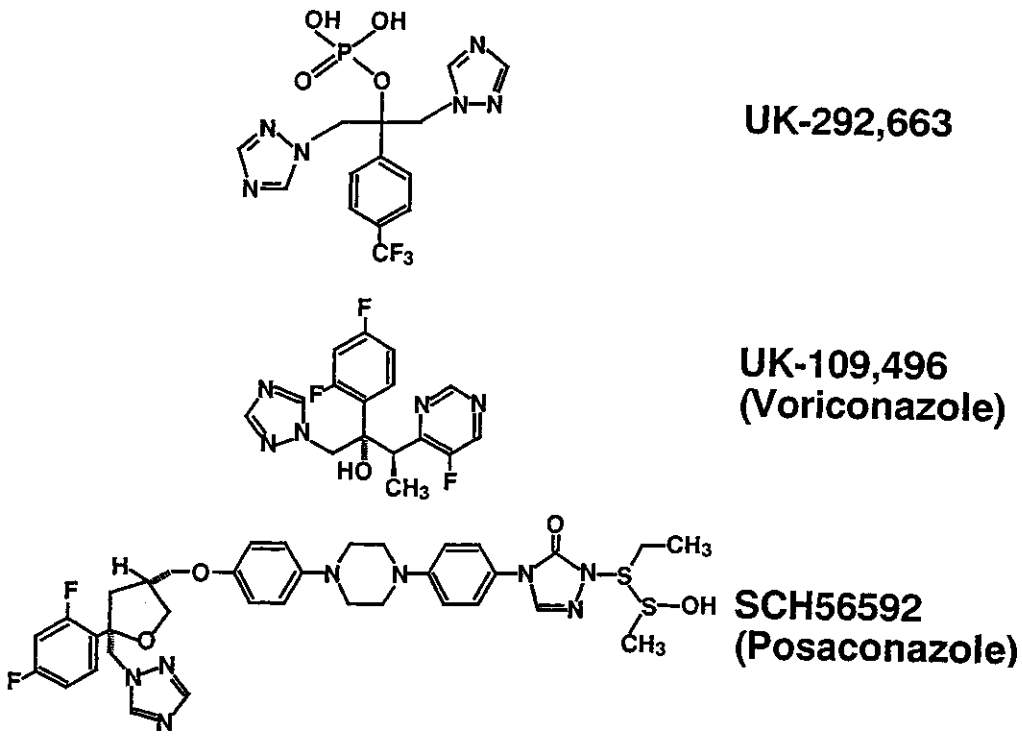


図5.　臨床開発中のアゾール系抗真菌薬

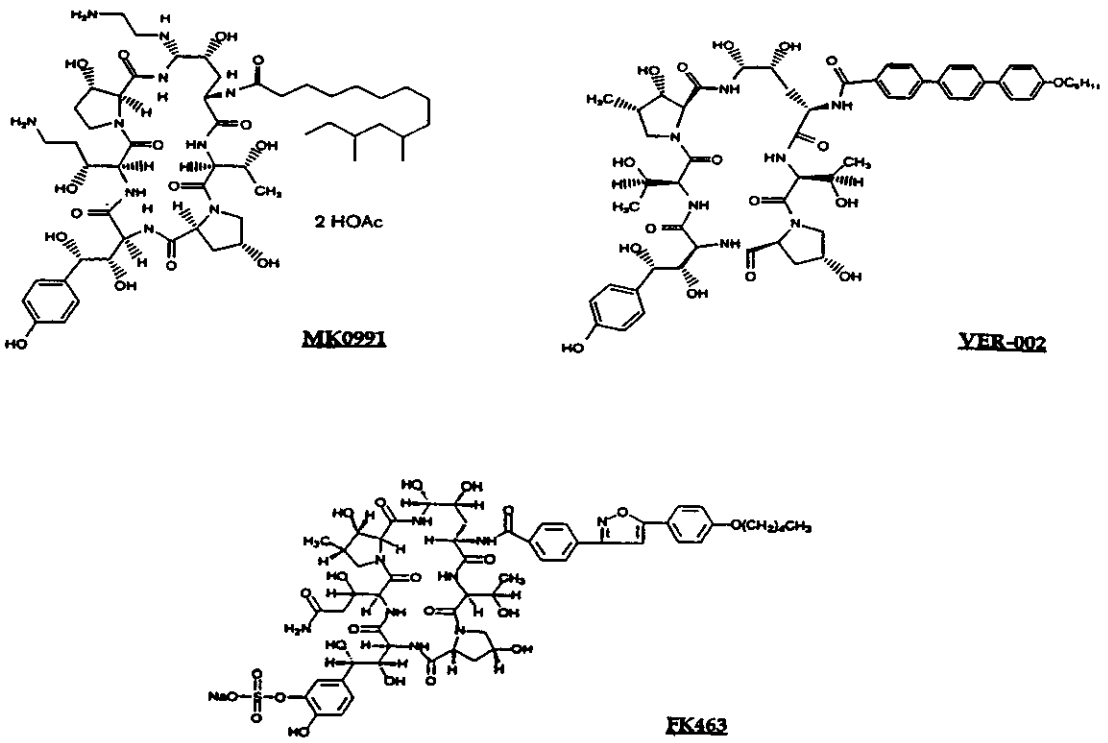


図6.　臨床開発中のリポペプチド系抗真菌薬