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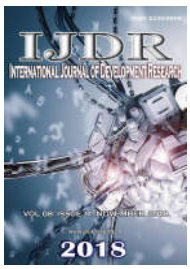

ORIGINAL RESEARCH ARTICLE OPEN ACCESS

THERAPEUTIC DIVERSIFICATION OF AZOLES AND THEIR DERIVATIVES

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ABSTRACT

About 30-40 years ago, relatively few agents of azoles were available for limited health problems. But in modern era, many classes of azoles have been introduced in market. Many azole compounds have been commercially developed and successfully proved beneficial in many human ailments including cancer. However, despite their widespread use, these agents became subject to a number of clinically important limitations related to their suboptimal spectrum of activity, the induction of hazardous drug-drug interactions, the development of resistance, their less than optimal pharmacokinetic profile and toxicity. In order to overcome these limitations, several analogues have been manufactured which have greater potency and possess increased activity against resistant and emerging pathogens. On the basis of authors' researches, literatures have been discussed in a comprehensive review to understand the latest developments in azole derivatives therapeutics.

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INTRODUCTION

History of Azoles: The most challenging situation in discovering new agents is the selection of new chemical from bulk of compounds present in nature (Lloyd, Golfis *et al.* 2006). In past, azole related compounds have been identified as a potential biological agents (Rozhkova, Lysko *et al.* 2000). First azole reported as antifungal was benzimidazole in 1944 discovered by Woolley (Woolley 1944). Jerchel *et al.* revived Woolley's discovery by substituting many compounds of benzimidazole (Fromtling 1988). Researchers become interested in azoles after reported activity of chlormidazole in 1958 (Maertens 2004). Chlormidazole was first azole which was sold as topical cream. Later in 1960s, within months, clotrimazole (by Bayer AG), miconazole and econazole (by Janssen Pharmaceutica) were also introduced (today are still in use for different fungal infections) (Fromtling 1988). Clotrimazole was tested *in-vitro* against many species of fungi that cause skin problems (Shadomy 1971). But this drug was banned later due to its severe side effects (Tettenborn 1974). Robinson *et al.* also reported thiabendazole as antifungal in 1961. It was effective against many species of Aspergillus and dermatophytes. Phenethylimidazole was also reported as antifungal against yeasts.

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Janssen Pharmaceutica also developed mebendazole as antifungal and antihelminthic agent in 1973 (Fromtling 1988). Another azole, terconazole, was also recommended as topical treatment in dermatomycoses and vaginal candidiasis (Maertens 2004). Later, ketoconazole emerged as a major antifungal drug but was replaced by fluconazole and itraconazole due to its side effects (Fromtling 1988).

Azole Compounds: An azole contain heterocyclic compounds with five-membered nitrogen and have electron-rich property. That's why, azoles can easily bind with receptors and target proteins with non-covalent bonding such as hydrophobic interactions, coordination bonds, hydrogen bonds, electrostatic and Vander Waals forces (Ahmad, Khan *et al.* 2018). Many drugs alter enzymatic and metabolic changes in the body when administered with another drug. This interaction may result in induction or inhibition of respective enzymes. Combined administration of drugs may harm body as reported in different cases. One such example is of terfenadine with ketoconazole, which can lead to heart ailments (Bibi 2008).

Azoles & Cytochrome P450 Enzymes: Enzymes including cytochrome P450, are present in extrahepatic tissues and liver. Cytochrome P450 (CYP) containsheme as hemoglobin and occur in lipid bilayer membranes of endoplasmic reticulum of liver cells in mammals, including humans. They regulates drug, steroid and cancer metabolism. Belonging to four

families, more than 30 enzymes have been discovered in humans. But only six enzymes are involved in 90% reactions. These enzymes are named as CYP1A2, 2C9, 2C19, 2D6, 2E1 and 3A4/5.CYP3A4 is found in liver and gut wall, where it helps in defensive property (Bibi 2008). Azoles can interact with these physiological enzymes in the body (Hofmeister, Bittler *et al.* 1995, Brodie and Njar 1999). CYP2C19 act as a potent inhibitor of omeprazole, pantoprazole and lansoprazole. Omeprazole is metabolized by CYP2C19 and CYP3A4. Former enzyme convert it into hydroxyomeprazole and latter enzyme into omeprazole sulphone. Omeprazole also induces CYP1A2 (Bibi 2008).

Azoles in Clinics: More than thousand azoles have been mentioned as therapeutically important (Ahmad, Khan *et al.* 2018). Azoles have been reported as having anti-tubercular (Adamec, Waisser *et al.* 2005), anti-inflammatory(Mohite, Pandhare *et al.* 2010), antioxidant, anthelmintic, antiviral, anti-parasitic, anti-HIV, antihypertensive (Ahmad, Khan *et al.* 2018), anti-arthritic, antidiabetic, anticholinergic, diuretic, anti-asthmatic, analgesic, antibacterial, antifungal, ulcerogenic (Farghaly and El-Kashef 2006) and anticonvulsant (Upadhayaya, Jain *et al.* 2004). Different other azoles can also be explored as anticancer agents (Ni, Man *et al.* 2012, Ma, Pang *et al.* 2014, Ma, Zheng *et al.* 2015). Azoles are important pharmaceutically, for example imidazole (Claiborne, Liverton *et al.* 1998), as they showed cytotoxicity against many human cancer cell lines at low concentrations (Cui, Zheng *et al.* 2003). Many azoles such as benzimidazole, oxazole, carbazole, thiazole and imidazole and many others, have been widely used at clinic level. Thiazoleshave shown analgesic, cardiotonic, anticonvulsant and antitumor properties. Pyrazole derivatives have been deeply investigated which showed bioactivities such as antibacterial, antipyretic, anti-inflammatory, analgesic, anti-tubercular and anti-hyperglycemic activities. Benzotriazoles showed antimalarial, antidiabetic and anti-inflammatory properties. Derivatives of benzotriazoles can treat Duchenne muscular dystrophy and epilepsy. Some tetrazoles derivatives displayed anticonvulsant, antimicrobial, anti-inflammatory and antinociceptive actions (Ren, Zhang *et al.* 2014). 2-amino-1,3,4-oxadiazoles reported by Katritzky *et al.*, was found to possess anti-inflammatory, anti-arthritic and antidiabetic activities. On the other hand, 1,2,4-triazoles are associated with diverse pharmacological activities such as anti-inflammatory, antibacterial, antifungal, anticholinergic, antihypertensive, diuretic, anti-asthmatic and analgasic. 1,2,4-triazoles, 1,3,4-thiadiazoles and 1,3,4-oxadiazoles have gained much attention due to their ulcerogenic, analgesic, anti-inflammatory and lipid peroxidation activities (Farghaly and El-Kashef 2006).

Gastric Ailments: Betazole can be used as a stimulant of gastric secretion without side effects because it is histamine analogue (Ahmad, Khan *et al.* 2018). Omeprazole is a proton pump inhibitorandwidely used for cure of peptic ulcers. Omeprazole is firstly reported by Gugler and Jensen. In *Helicobacter pylori* infected patients, omeprazole provided significantly better results as compared to normal group. Omeprazole is a member of heterocyclic aromatic organic compounds (benzimidiazoles) also known as proton pump inhibitor, which is commonly used as an effective treatment for all upper gastrointestinal ailments such as Gastroesophageal reflux disease (GERD) as well as in peptic ulcers. American College of Gastroenterology guidelines also suggested omeprazole as a therapy for the GERD. Acid suppression with omeprazole is very effective in reducing pain, heartburn and regurgitation. This drug acts by inhibiting the H^+/K^+ ATPase to prevent the acid production. As a result, omeprazole raised pH of the stomach lumen, a step thought to be important in the therapy for the treatment of gastritis (Bibi 2008).

Pulmonary Ailments: In some studies, it has been shown that GERD is common among patients with asthma. A double blind study was used to determine the suppression of GERD with omeprazole can improve the pulmonary function (Bibi 2008).

Antithyroid Azole: Antithyroid activity of carbimazole, derivative of imidazole, was observed. Carbimazole does this by reducing the uptake capability of inorganic iodine by thyroid, due to which, formation of thyroid hormones are diminished. Methimazole (active form of carbimazole) reduces production of T3 and T4 by blocking the function of thyroid peroxidase. This will help in the treatment of thyrotoxicosis and hyperthyroidism (Ahmad, Khan *et al.* 2018).

Antibacterial Azoles: Azoles exhibited antibacterial activity against a number of bacteria such as *Mycobacterium tuberculosis*, *Staphylococcus aureus*, *Enterobacteriaceae*, *Proteus spp.*, *Bacillus subtilis(B. Subtilis)*,*Escherichia coli (E. Coli)*, *Streptococcus faecalis*, *Pseudomonas aeruginosa, Enterobacter cloacae*, *Salmonella typhi, Klebsiellapromioe*,*B. Pumilis*and *Entero. aerogens*(Ren, Zhang *et al.* 2014). Econazole, considered as a broad spectrum antifungal agent, also showed activity against Gram-positive bacteria (Ahmad, Khan *et al.* 2018).

Antifungal Azoles: Many azoles have been tested as a potent antifungal agents and are widely available commercially. Fluconazole and benzotriazoles could effectively inhibit the growth of many fungi including *Candida albicans*(*C. albicans*), *Cryptococcus neoformans*(*C. neoformans*), *Candida arachidicoa (C. arachidicoa)*, *Trichophytonrubrum*(*T. rubrum*), *Microsporumcanis*, *Dermatophytes*, *Physalosporapiricola*, *Gibberallazeae*, *Fusariumoxysporum*, *Cercosporaarachidicola*, *Alternariasolani*, *Aspergillusflavus* (*A. flavus*), *Aspergillusniger*(*A. niger*), *Penicilliumexpansum*, *Botrydepladiathio bromine*, *Nigrospora sp.*, *Trichothesium sp*., *Rhizopusnigricans* and *Saccharomyces cerevisiae (S. Cerevisiae)*. Benzotriazole derivatives showed antifungal activity against different fungal pathogens such as *Candida glabrata* (*C. glabrata*) and *A. niger* (Ren, Zhang *et al.* 2014). Econazole is also considered as a broad spectrum antifungal agent as it works by disturbing synthesis of membranes in fungi, results in death. Imidazole derivatives such as bifonazole, clotrimazole, miconazole and butoconazole displayed marvelous antifungal properties. Bifonazole kills fungi by penetrating into their cell membrane and make holes in it, which leads to cell lysis (Ahmad, Khan *et al.* 2018). It has a very effective role in the infection of Tineapedis, caused by *Trychophyton*sp. (Buchel 1986). Clotrimazole inhibits cell membrane biosynthesis and endogenous respiration in fungi. Miconazole was approved by FDA in 1974 as an antifungal drug. It affects the metabolic reactions in fungi resulting in death (Ahmad, Khan *et al.* 2018). Before 1969, all azoles were used topically, but in same year, miconazole was firstly used in injection form. At high concentrations, miconazole was very effective as it damages membranes of fungal cells resulting in death of cells. The drug was found very beneficial against

Pseudallescheriaboydii, dimorphic fungi, *Candida* species and dermatophytes and successfully treated many diseases like cryptococcal meningitis, pseudallescheriasis and systemic candida infection. But drug was more popular as a topical treatment and showed toxicity when used for parenteral administration. Later, it was withdrawn from market (Maertens 2004). Butoconazole is considered favorite for *Candida albicans* infections, especially in vulvovaginal candidiasis (Ahmad, Khan *et al.* 2018). Posaconazole, derivative of itraconazole, is also famous for its antifungal activity against many fungi such as dematiaceous molds, zygomycetes, *Aspergillus*spp and *Candida* spp. The drug is found more active in animal studies as compared to other drugs like itraconazole, fluconazole and amphotericin B. Ravuconazole, derivative of fluconazole, also has antifungal activity. The drug is very effective against *Candida neoformans* and *Candida krusei,* but no effect was found for *Fusarium*sp and *Pseudallescheriaboydii* (Chiou, Groll *et al.* 2000). Ketoconazole was approved by FDA in 1981. At that time, it was the only drug used orally as an antifungal.

It was proved very effective against coccidioidomycosis, paracoccidioidomycosis, histoplasmosis, blastomycosis and chronic mucocutaneous candidiasis. It was found ineffective against mucormycosis and aspergillosis(Maertens 2004). But with the passage of time, many side effects of this drug were reported such as unpredictable drug interactions, inhibition of production of cortisol from adrenal gland and testosterone from testes when given in dose more than 400 mg daily, caused drug-induced hepatitis, gastrointestinal disorders and activity influenced by gastric pH, not recommended for fungal meningitis due to its poor penetration through blood-brain barrier and gynecomastia with pain(Trachtenberg, Halpern *et al.* 1983, WILLIAMS, Kerle *et al.* 1986, Trump, Havlin *et al.* 1989, Gerber and Chodak 1990, Small, Halabi *et al.* 2004). Fluconazole is preferable over ketoconazole due to many reasons such as it is favorite in many ailments like cryptococcal meningitis, disseminated candidiasis, coccidioidomycosis, chronic mucocutaneous candidiasis, genito-urinary, peritoneal, vaginal, oesophageal andoropharyngeal candida infections (Maertens 2004). Voriconazole is structurally related to fluconazole (Sabo and Abdel-Rahman 2000). It is effective against a number of moulds and fungi such as *Trichosporon*, *Acremonium*, *Scedosporium*, *Penicillium*, *Fusarium*spp., dermatophytes, scedosporiosis, fusariosis, dimorphic fungi, *Candida neoformans*, *Aspergillus*spp. and *Candida* spp. Due to resistance in zygomycetes, it was found ineffective. It can easily cross blood-brain barrier. Voriconazole especially proved useful in treating oropharyngeal candidiasis in patients suffering from cerebral aspergillosis, oesophageal candidiasis and AIDS. But it has side effects too especially it affects the liver (Potoski and Brown 2002).

It has also affected physiology of eyes in 10% patients (Maertens 2004). Itraconazole was approved in 1992. It showed efficacy against many species of fungi such as some phaeohyphomycetes, *Sporothrixschenckii*, *Paracoccidioides Brasiliensis*, *Blastomyces Dermatitidis*, *Histoplasma Capsulatum*, *Coccidioides Immitis*, *Cryptococcus neoformans*, *Aspergillus*spp. and *Candida* spp(Espinel-Ingroff, Shadomy *et al.*1984). Itraconazole replaced amphotericin B & ketoconazole in many ailments. It was also more effective than fluconazole in sporotrichosis and aspergillosis(Terrell 1999). This drug has also shown results in trials conducted in patients of HIV & neutropenia (Boogaerts and Maertens 2001). High concentrations of plasma can be achieved in emergency patients with itraconazole. At high concentrations, itraconazole reduces cholesterol levels in humans (Schneider, Gerdsen *et al.* 2007) and inhibits fungal growth (Lamb, Maspahy *et al.* 1999, Trösken, Adamska *et al.* 2006).Both conditions are relevant to same enzyme inhibition by itraconazole (Georgopapadakou and Walsh 1996).

Antiviral Azoles: Azoles have also been found as an antiviral agents and prevents from many viral diseases. Benzotriazole derivatives could inhibit Hepatitis B Virus, Hepatitis C Virus, Respiratory Syncytial Virus (RSV), HIV, HSV-I, HSV-II, Para influenza-3, Coxsackie virus B4 and Punta Toro virus(Ren, Zhang *et al.* 2014). Many triazole compounds have also been found as containing antiviral activities(Farghaly and El-Kashef 2006).

Antiparasitic Azoles: Azoles have an important role in combating parasitic problems in humans. Benzotrizoles can treat amebiosis very well. Chagas disease is also included in this cue. Derivative of benzotriazole showed good antiparasitic activity against epimastigotes. Combination of azole with other compounds such as chalcones, exhibited inhibitory action against *Setariacervi* and *Plasmodium falciparum*(Ren, Zhang *et al.* 2014).

Antioxidative Azoles: Azoles also showed antioxidative property. As free radicals pose harmful effects on body such as aging. Hence, azoles can reduce free radicals so promoting antiaging effects in body. Azoles also reduce lipids level in blood and displayed good lipid peroxidation inhibition(Ren, Zhang *et al.* 2014).

Azoles in Cancer: Recently, many azole derivatives have been highlighted as an anticancer compounds(Ahmad, Khan *et al.* 2018). Current researches of benzotriazole derivatives in medicinal chemistry have obtained great progress to treat different kinds of clinical diseases including fungal infections and cancers. 4,5,6,7-tetrabromobenzotriazole (TBB) (compound 1a) is commercially available that have been found to possess potent anticancer activity. The *in-vitro* evaluation of benzotriazole derivatives showed inhibitory activity against murine lymphocytic leukemia cell line (P388), human leukemia cell line (HL60), oral epidermoid carcinoma (KB) cells, non-smallcell lung carcinoma (H460) cells, stomach carcinoma (MKN45) cells, humanhepatocarcinoma(BEL-7402) cells, breast cancer cells (4T-1), myelogenouserythroleukemia K562, breast adenocarcinoma (MCF7), human breast cancer (MDA-MB231), endometrial cancer, esophageal cancer and human ovarian cancer (OVCAR-8). More importantly, these compounds possessed very low toxicity toward normal human breast and ovarian cell lines(Ren, Zhang *et al.* 2014). Clotrimazole also proved successful in cancer treatment in recent years. Bifonazolewas found effective in skin cancer treatment when it was proved in an experiment conducted by Penso *et al.* The use of miconazole in breast cancer and econazole in prostate cancer has also been reported earlier. Other compounds include 2,4,5-triaryl imidazole derivatives has also anticancer potential, reported by Elahian *et al.* and Arif *et al.*, 2011 (Ahmad, Khan *et al.* 2018). Itraconazolehas reduced medulloblastoma in a study (Kim, Lee *et al.* 2010).

Future Perspectives of Azolesin Diseases Prevention and Treatment: In the modern era, many disciplines work together to adopt specific preventive way for treatment of cancer and other lethal diseases by targeting various cellular pathways. Azole compounds can interact at molecular level to reveal cure of various pathological modalities and serve humanity in future.

Conclusion

Azole derivatives are hydrophilic as well as lipophilic, having polar functionalities in different positions and thereby modulation of a diverse group of molecular targets of various metabolic pathways involved in the biotransformation of different compounds. The present review reveals about the therapeutic diversification of azoles and their derivatives for various pharmacological accomplishments. This information might be useful for current and future researchers in designing novel and potent multifunctional azole analogues for the treatment of cancer and other multifactorial diseases.

REFERENCES

Adamec, J., K. Waisser, J. Kuneš and J. Kaustová, 2005. "A Note on the Antitubercular Activities of 1-Aryl-5-benzylsulfanyltetrazoles." Archiv der Pharmazie: An *International Journal Pharmaceutical and Medicinal Chemistry* 338(8): 385-389.

Ahmad, K., M. K. A. Khan, M. H. Baig, M. Imran and G. K. Gupta, 2018. "Role of Azoles in Cancer Prevention and Treatment: Present and Future Perspectives." *Anticancer Agents Med Chem* 18(1): 46-56.

Bibi, Z. 2008. "Role of cytochrome P450 in drug interactions." Nutr Metab (Lond) 5: 27.

Boogaerts, M. and J. Maertens, 2001. "Clinical experience with itraconazole in systemic fungal infections." Drugs 61(1): 39-47.

Brodie, A. and V. C. Njar, 1999. 17-azolyl steroids useful as androgen synthesis inhibitors, Google Patents.

Buchel, K. 1986. The history of azole chemistry. ACS Symposium series-American Chemical Society (USA).

Chiou, C. C., A. H. Groll and T. J. Walsh, 2000. "New drugs and novel targets for treatment of invasive fungal infections in patients with cancer." *The Oncologist* 5(2): 120-135.

Claiborne, C. F., N. J. Liverton and K. T. Nguyen, 1998. "An efficient synthesis of tetrasubstituted imidazoles from N-(2-Oxo)-amides." Tetrahedron letters 39(49): 8939-8942.

Cui, B., B. L. Zheng, K. He and Q. Y. Zheng, 2003. "Imidazole alkaloids from Lepidium meyenii." *J Nat Prod* 66(8): 1101-1103.

Espinel-Ingroff, A., S. Shadomy and R. J. Gebhart, 1984. "In vitro studies with R 51,211 (itraconazole)." *Antimicrobial Agents and Chemotherapy* 26(1): 5-9.

Farghaly, A.-R. and H. El-Kashef, 2006. "Synthesis of some new azoles with antiviral potential." Arkivoc 11: 76-90.

Fromtling, R. A. 1988. "Overview of medically important antifungal azole derivatives." *Clinical Microbiology Reviews* 1(2): 187-217.

Georgopapadakou, N. H. and T. J. Walsh, 1996. "Antifungal agents: chemotherapeutic targets and immunologic strategies." *Antimicrobial agents and chemotherapy* 40(2): 279.

Gerber, G. S. and G. W. Chodak, 1990. "Prostate specific antigen for assessing response to ketoconazole and prednisone in patients with hormone refractory metastatic prostate cancer." *The Journal of urology* 144(5): 1177-1179.

Hofmeister, H., D. Bittler, H. Michna, U. Habenicht, K.-H. Fritzemeier and Y. Nishino, 1995. Antiandrogenic [3, 2-c] pyrazole and [3, 2-d] triazole steroids, Google Patents.

Kim, Y. J., J. S. Lee, K. S. Hong, J. W. Chung, J. H. Kim and K. B. Hahm, 2010. "Novel application of proton pump inhibitor for the prevention of colitis-induced colorectal carcinogenesis beyond acid suppression." *Cancer Prevention Research*: 1940-6207. CAPR-1910-0033.

Lamb, D. C., S. Maspahy, D. E. Kelly, N. J. Manning, A. Geber, J. E. Bennett and S. L. Kelly, 1999. "Purification, reconstitution, and inhibition of cytochrome P-450 sterol Δ22-desaturase from the pathogenic fungus Candida glabrata." *Antimicrobial agents and chemotherapy* 43(7): 1725-1728.

Lloyd, D. G., G. Golfis, A. J. Knox, D. Fayne, M. J. Meegan and T. I. Oprea, 2006. "Oncology exploration: charting cancer medicinal chemistry space." *Drug Discov Today* 11(3-4): 149-159.

Ma, L.-Y., L.-P. Pang, B. Wang, M. Zhang, B. Hu, D.-Q. Xue, K.-P. Shao, B.-L. Zhang, Y. Liu and E. Zhang, 2014. "Design and synthesis of novel 1, 2, 3-triazole-pyrimidine hybrids as potential anticancer agents." *European journal of medicinal chemistry* 86: 368-380.

Ma, L.-Y., Y.-C. Zheng, S.-Q. Wang, B. Wang, Z.-R. Wang, L.-P. Pang, M. Zhang, J.-W. Wang, L. Ding and J. Li 2015. "Design, synthesis, and structure–activity relationship of novel LSD1 inhibitors based on pyrimidine–thiourea hybrids as potent, orally active antitumor agents." *Journal of medicinal chemistry* 58(4): 1705-1716.

Maertens, J. 2004. "History of the development of azole derivatives." *Clinical Microbiology and Infection* 10: 1-10.

Mohite, P., R. Pandhare, S. Khanage and V. Bhaskar, 2010. "Synthesis and anti-inflammatory activity of some 5-phenyl-1-(acyl)-1, 2, 3, 4-tetrazole." *Journal of Pharmacy Research* 3(1): 43-46.

Ni, W.-X., W.-L. Man, S.-M. Yiu, M. Ho, M. T.-W. Cheung, C.-C. Ko, C.-M. Che, Y.-W. Lam and T.-C. Lau, 2012. "Osmium (VI) nitrido complexes bearing azole heterocycles: a new class of antitumor agents." *Chemical Science* 3(5): 1582-1588.

Potoski, B. A. and J. Brown, 2002. "The safety of voriconazole." *Clinical infectious diseases* 35(10): 1273-1275.

Ren, Y., L. Zhang, C.-H. Zhou and R. Geng, 2014. "Recent development of benzotriazole-based medicinal drugs." Med chem 4: 640-662.

Rozhkova, E. A., A. I. Lysko, K. V. Kuleshov and R. P. Evstigneeva, 2000. "[Synthesis and antioxidant activity of azole derivatives of hemin]." Bioorg Khim 26(6): 466-470.

Sabo, J. A. and S. M. Abdel-Rahman, 2000. "Voriconazole: a new triazole antifungal." *Annals of Pharmacotherapy* 34(9): 1032-1043.

Schneider, B., R. Gerdsen, J. Plat, S. Dullens, I. Björkhem, U. Diczfalusy, P. Neuvonen, T. Bieber and D. Lütjohann 2007. "Effects of high-dose itraconazole treatment on lipoproteins in men." *International journal of clinical pharmacology and therapeutic*s 45(7): 377-384.

Shadomy, S. 1971. "In vitro antifungal activity of clotrimazole (Bay b 5097)." Infection and immunity 4(2): 143-148.

Small, E. J., S. Halabi, N. A. Dawson, W. M. Stadler, B. I. Rini, J. Picus, P. Gable, F. M. Torti, E. Kaplan and N. J. Vogelzang, 2004. "Antiandrogen withdrawal alone or in

combination with ketoconazole in androgen-independent prostate cancer patients: a phase III trial (CALGB 9583)." *Journal of clinical oncology* 22(6): 1025-1033.

Terrell, C. L. 1999. Antifungal agents. Part II. The azoles. Mayo Clinic Proceedings, Elsevier.

Tettenborn, D. 1974. "Toxicity of clotrimazole." *Postgraduate medical journal* 50: 17.

Trachtenberg, J., N. Halpern and A. Pont, 1983. "Ketoconazole: a novel and rapid treatment for advanced prostatic cancer." *The Journal of urology* 130(1): 152-153.

Trösken, E. R., M. Adamska, M. Arand, J. A. Zarn, C. Patten, W. Völkel and W. K. Lutz, 2006. "Comparison of lanosterol-14α-demethylase (CYP51) of human and Candida albicans for inhibition by different antifungal azoles." Toxicology 228(1): 24-32.

Trump, D. L., K. H. Havlin, E. M. Messing, K. B. Cummings, P. H. Lange and V. C. Jordan, 1989. "High-dose ketoconazole in advanced hormone-refractory prostate cancer: endocrinologic and clinical effects." *Journal of Clinical Oncology* 7(8): 1093-1098.

Upadhayaya, R. S., S. Jain, N. Sinha, N. Kishore, R. Chandra and S. K. Arora, 2004. "Synthesis of novel substituted tetrazoles having antifungal activity." *European journal of medicinal chemistry* 39(7): 579-592.

WILLIAMS, G., D. Kerle, H. Ware, A. Doble, H. DUNLOP, C. Smith, J. ALLEN, T. Yeo and S. Bloom, 1986. "Objective responses to ketoconazole therapy in patients with relapsed progressive prostatic cancer." *British journal of urology* 58(1): 45-51.

Woolley, D. 1944. "Some biological effects produced by benzimidazole and their reversal by purines." *J Biol Chem* 152: 225-232.

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