Chemical Concepts

International Journal of Chemical Concepts
ISSN:2395-4256 www.chemconsai.com
Vol.02, No.02, pp 132-144, 2016

1,2,4-Triazole - a versatile azole, proves and popular as an antifungal agent

***[1]Ashwini H. Pagare, [2]Rani S. Kankate, [3]Anwar R. Shaikh**

[1*]Department of Pharmaceutical chemistry, KBHSS Trust's Institute of pharmacy, malegaon
[2,3]Department of Pharmaceutical chemistry, MET"S Institute of Pharmacy - Nashik, Maharashtra, India

Abstract : Several five membered ring systems, e.g., triazole, oxadiazole dithiazole and thiadiazole with three heteroatoms at symmetrical or asymmetrical positions have been studied because of their interesting pharmacological properties. In this review our emphasis is on synthetic development and pharmacological activity of the 1,2,4-triazole moiety which exhibit a broad spectrum of pharmacological activity such as antifungal, antibacterial, anti-inflammatory and anticancer etc. Triazoles have increased our ability to treat many fungal infections, for example, candidiasis, cryptococcal meningitis, aspergillosis etc. However, mortality due to these infections even with antifungal therapy is still unacceptably high. Therefore, the development of new antifungal agents targeting specific fungal structures or functions is being actively pursued. Rapid developments in molecular mycology have led to a concentrated search for more target antifungals. Although we are entering a new era of antifungal therapy in which we will continue to be challenged by systemic fungal diseases, the options for treatment will have greatly expanded.

Keywords: 1,2,4-triazole, 1,3,4-triazole, standard drugs containing 1,2,4-triazole, synthetic drugs containing 1,2,4-triazole, antifungal agents.

Introduction

The alarming rates of the growing emergence of antimicrobial resistance are major concerns to the public health and scientific communities worldwide, especially in the field of multidrug- resistant bacteria and fungi [1,2]. These trends have emphasized the urgent need for new, more effective, less toxic and safe antimicrobial agents and the development of structurally new classes of antimicrobials with novel mechanisms of action as well as structural modifications to improve both their binding affinity and their spectrum of activity. One such strategy that has been pursued in recent years with increasing significance employs a combination of two different active fragments in one molecule [3]. With this strategy, various drug moieties have been designed to bind independently to different biological targets to produce beneficial effects [4]. The chemistry of N-bridged heterocyclic compounds, such as triazole, has received considerable attention in recent years due to their biological activities. Triazole is one of a pair of isomeric chemical compounds with the molecular formula $C_2H_3N_3$. It is a basic aromatic heterocyclic ring [5]. Triazole derivatives are known to exhibit various pharmacological properties such as antimicrobial [6-10], antitubercular[11], anticancer [12,13], anticonvulsant [14], anti-inflammatory, analgesic [15] and antiviral [16]. Triazoles have also been incorporated in a wide variety of therapeutically interesting drugs including H_1/H_2 histamine receptor blockers, CNS stimulants, anti-anxiety agents and sedatives [17]. The most important use, however, is as antimycotics in drugs such as fluconazole, itraconazole and voriconazole[18,19].

The triazole moiety is stable to metabolic degradation and capable of hydrogen bonding, which could be favorable in binding biomolecular targets as well as in increasing solubility [20]. Moreover, triazoles can function as attractive linker units which could connect two pharmacophores to give an innovative bifunctional drug, and thus have become increasingly useful and important in constructing bioactive and functional molecules [21-23]. Notably, the bioisosteric replacement between triazole moiety and its bioisoster triazole has received special attention in medicinal chemistry, which represented an efficient concept for the discovery and development of novel triazole drugs, significantly extending the chemical space of triazole scaffolds possessing potent activities or enhancing biological activities [24]. Additionally, many investigations have shown that the addition of alkyl chains and/or various aromatic substituents, especially containing halogen atoms, has an important effect on the antimicrobial activities. The antifungal azoles are a class of synthetic compounds that possess one or more azole rings. Whilst both imidazole and triazole are five membered ring heterocycles, imidazole contains two ring nitrogen atoms, whereas triazoles have three. However, compared with imidazoles (clotrimazole, ketoconazole, miconazole), triazoles are less susceptible to metabolic degradation and have much greater target specificity, increased potency and an expanded spectrum of activity [25,26].

Chemistry of triazoles

Triazole refers to either one of a pair of isomeric chemical compounds with the molecular formula $C_2H_3N_3$, and has a five membered ring containing two carbon and three nitrogen atoms. Triazoles have two isomeric forms, i.e., 1,2,3-triazole (**1**) and 1,2,4-triazole (**2**) (Figure 1).

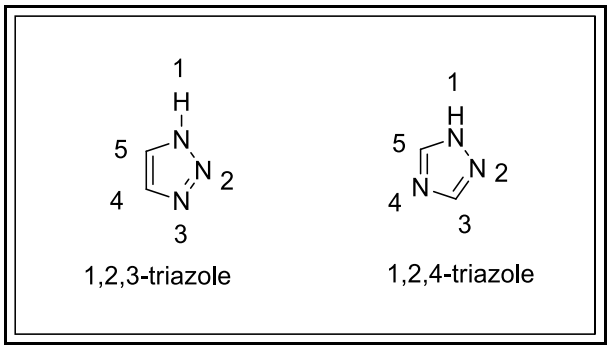
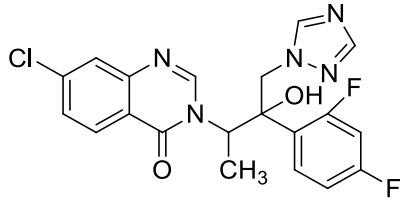


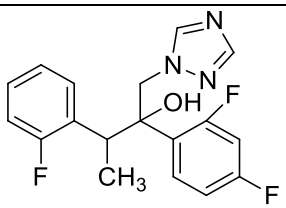
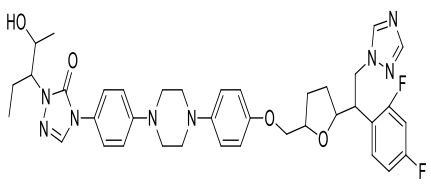
Figure 1: Isomeric forms of triazole.

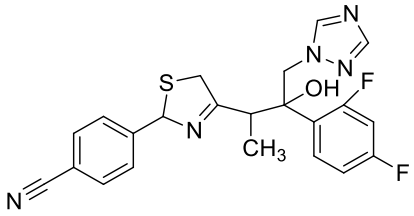
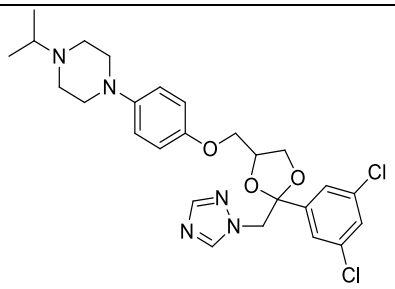
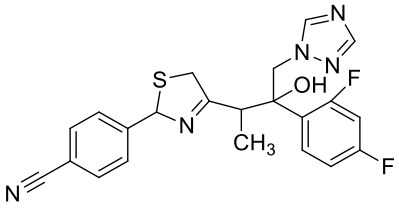
Triazoles are basic aromatic heterocyclic compounds. 1,2,3-Triazoles are surprisingly stable compared to other organic compounds with three adjacent nitrogen atoms. However, flash vacuum pyrolysis at 500 °C leads to loss of molecular nitrogen (N_2) to produce aziridine. Certain triazoles are relatively easy to cleave by ring–chain tautomerism.

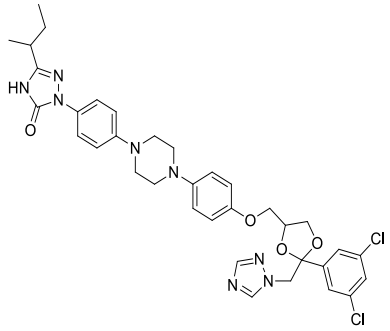
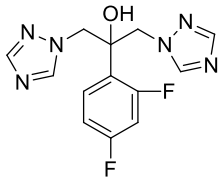
Literature survey reviewing marketed drugs containing 1,2,4-triazole moiety is depicted below with the help of table, in that salient features of 1,2,4-triazole containing marketed drugs has been explained along with their chemical structures. [Mds.mol files]

Table 1 Standard Marketed Drugs Containing 1,2,4-TRIAZOLE

Sr. no	Name of the drug	Chemical Structures	Salient features	References
1.	Albaconazole		1. It has potential broad-spectrum activity.	1.Wikipedia.org.in 2.Gadhave, P.P.; Dighe, N.S.; Pattan, S.R.; Deotarse, P.; Musmade, D.S.; Shete, R. Current biological and synthetic profile of triazoles: A review. *Annals Biol. Res.*

				2010, *1*, 82–89. 3.Pasqualotto AC, Thiele KO, Goldani LZ (2010). "Novel triazole antifungal drugs: focus on isavuconazole, ravuconazole and albaconazole". *CurrOpinInvestig Drugs***11** (2): 165–74. PMID 20112166.
2.	Voriconazole		1.Voriconazole has become the new standard of care in the treatment of invasive aspergillosis, which may occur in immunocompromised patients, including allogeneic BMT, hematologic cancers, and solid organ transplants. 2.Voriconazole cleared *Candida* from the bloodstream as quickly as amphotericin B (median 2 days) and showed a trend toward better survival.	1.wikipedia.org.in 2.Herbrecht R, Denning D, Patterson T, Bennett J, Greene R, Oestmann J, Kern W, Marr K, Ribaud P, Lortholary O, Sylvester R, Rubin R, Wingard J, Stark P, Durand C, Caillot D, Thiel E, Chandrasekar P, Hodges M, Schlamm H, TrokeP, de Pauw B; Invasive Fungal Infections Group of the European Organisation for Research and Treatment of Cancer and the Global Aspergillus Study Group (Aug 8, 2002). "*Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis". N Engl J Med**347** (6): 408–15*.doi:10.1056/NEJMoa020191. PMID 12167683.
3.	Posaconazole		1.It is used to treat invasive infections by *Candida* species, Mucor, and *Aspergillus* species in severely immunocompromisedpatients. 2.posaconazole may be the most effective	1.wikipedia.org.in 2. Schiller DS, Fung HB (September 2007). "Posaconazole: an extended-spectrum triazole antifungal agent". *ClinTher***29** (9): 1862–86.

			treatment for both chronic and acute Chagas disease, showing much better efficacy than benznidazole	doi:10.1016/j.clinthera.2007.09.015. PMID 18035188.
4.	Ravuconazole		1.Ravuconazole (BMS-207147 and ER-30346) is a potent triazole antifungal, being developed by Bristol-Myers Squibb, that is currently in phase I/II clinical trials. 2.The drug has a shown to have a similar spectrum of activity to voriconazole, with an increased half-life. However, ravuconazole has limited activity against species of *Fusarium*, *Scedosporium*, and *Zygomycetes*.	1.wikipedia.org.in 2.Pasqualotto AC, Thiele KO, Goldani LZ (2010). "Novel triazole antifungal drugs: focus on isavuconazole, ravuconazole and albaconazole". *CurrOpinInvestig Drugs***11** (2): 165–74. PMID 20112166.
5.	Terconazole		1. Terconazole is an anti-fungal medication, primarily used to treat vaginal fungal infections.	1.wikipedia.org.in 2.Heeres, J.; Hendrickx, R.; Van Cutsem, J. (1983). "Antimycotic azoles. 6. Synthesis and antifungal properties of terconazole, a novel triazole ketal". *Journal of Medicinal Chemistry***26** (4): 611. doi:10.1021/jm00358a032.
6.	Isavuconazole		1.Isavuconazole (BAL4815) is an experimental triazole antifungal	1.wikipedia.org.in 2. 2.Pasqualotto AC, Thiele KO, Goldani LZ (2010). "Novel triazole antifungal drugs: focus on isavuconazole, ravuconazole and albaconazole". *CurrOpinInvestig Drugs***11** (2): 165–74. PMID 20112166.

7.	itraconazole		1.Itraconazole has a broader spectrum of activity than fluconazole 2.It is also licensed for use in blastomycosis, sporotrichosis, histoplasmosis, and onychomycosis. 3.Itraconazole is over 99% protein-bound and has virtually no penetration into cerebrospinal fluid. Therefore, it should never be used to treat meningitis or other central nervous system infections. 4.Itraconazole has also recently been explored as an anticancer agent for patients with basal cell carcinoma, non-small cell lung cancer, and prostate cancer	1.wikipedia.org.in 2. Yoshida Y, Aoyama Y. In Vitro and In Vivo Evaluation of Antifungal Agents; Iwata, K.; VandenBossche H. Eds.; Elsevier Science, Amsterdam, **1986**; pp. 123-134.
8.	Fluconazole		1.Fluconazole is an antifungal medication that is administered by mouth or intervenously. 2.It is used to treat a variety of fungal infections, especially *Candida* infections of the vagina ("yeast infections'), mouth, throat, and bloodstream. 3.It is also used to prevent infections in people with weak immune systems, including those with neutropenia due to cancer chemotherapy, transplant patients, and premature babies. 4.Its mechanism of action involves interfering with synthesis of the fungal cell membrane.	1.Xu, Yi; Wang, Yan; Yan, Lan; Liang, Rong-Mei; Dai, Bao-Di; Tang, Ren-Jie; Gao, Ping-Hui; Jiang, Yuan-Ying (2009). "Proteomic Analysis Reveals a Synergistic Mechanism of Fluconazole and Berberine against Fluconazole-ResistantCandida albicans: Endogenous ROS Augmentation". *Journal of Proteome Research***8** (11): 5296–5304. doi:10.1021/pr900507 4. ISSN 1535-3893. PMID 19754040. Free Full Text 2.http://online.lexi.com.proxy1.lib.tju.edu/lco/action/doc/retrieve/docid/patch_f/6918

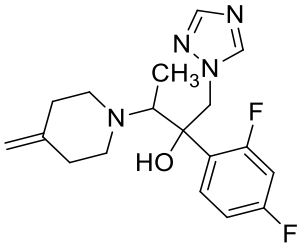
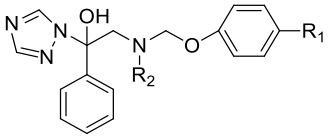
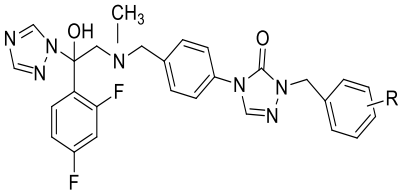
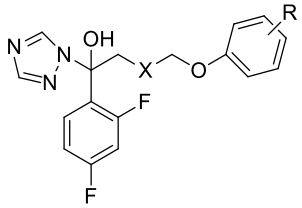
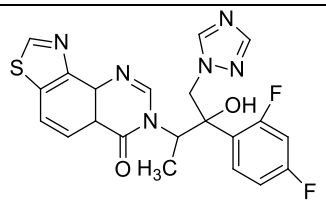
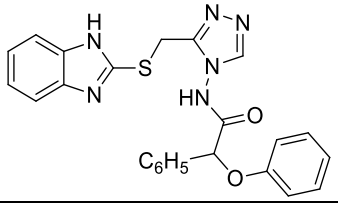
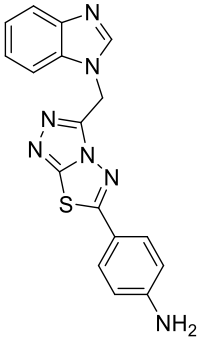
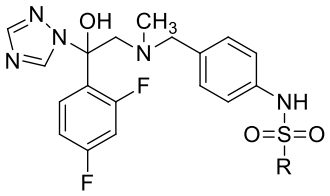
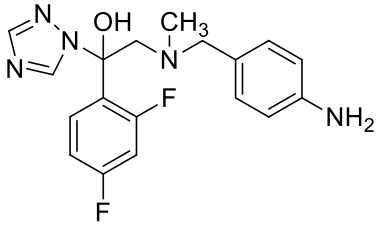
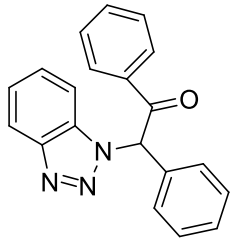
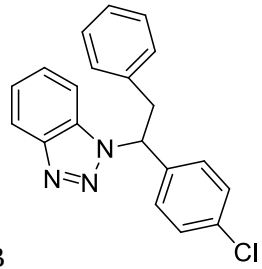
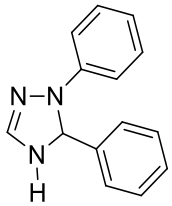
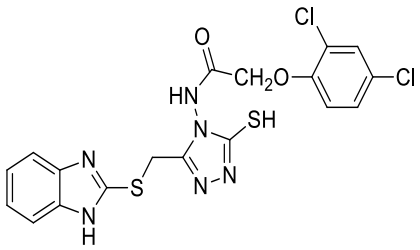
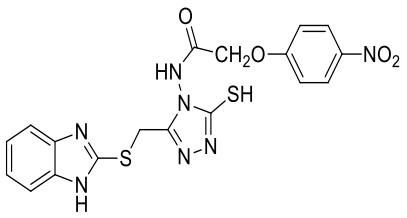
9.	Efinaconazole		1.It is approved for use in Canada and the USA as a 10% topical solution for the treatment of onychomycosis (fungal infection of the nail). 2.Efinaconazole acts as a 14α-demethylaseinhibitor.	1.wikipedia.org.in 2.Patel T, Dhillon S (Nov 2013). "Efinaconazole: first global approval". *Drugs***73** (17): 1977–1983. doi:10.1007/s40265-013-0152-x. PMID 24249649.

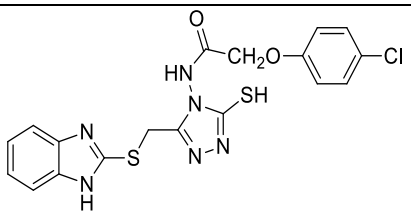
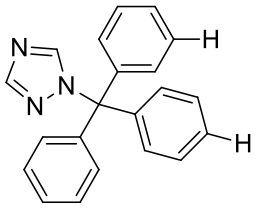
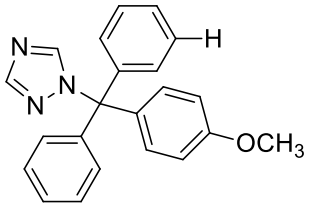
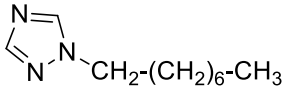
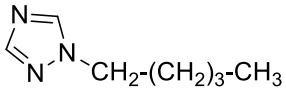
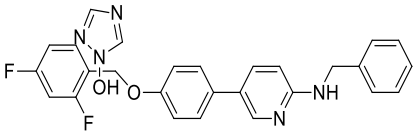
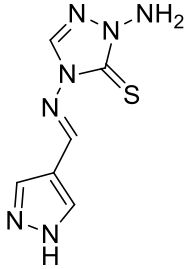
Table 2 Synthetic Drugs / Derivatives / Analogues Containing 1,2,4-TRIAZOLE

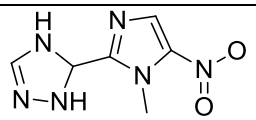
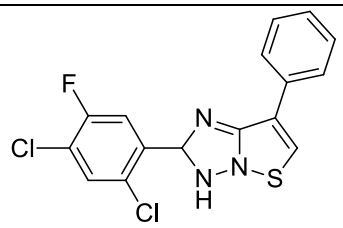
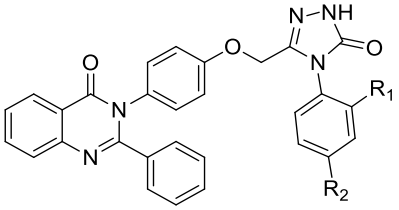
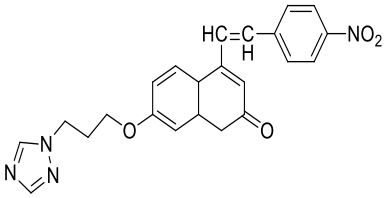
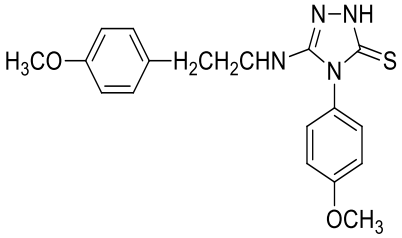
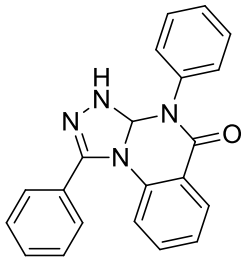
Sr.no	Chemical Structures	Salient features and SAR	References
1.		1.N-methyl group could form hydrophobic interaction with the surrounding residues and maintain the suitable conformation of the side chain in the CYP51 active site . 2.hydrogen atom, showed better antifungal activity than FLC with broad antifungal spectrum. However, they are less potent against the C. albicans strain, indicating the introduction of the methyl group could enhance the antifungal activity.	1.W. Wang, C. Sheng, X. Che, H. Ji, Y. Cao, Z. Miao, J. Yao, W. Zhang, Discovery of highly potent novel antifungal azoles by structure-based rational design, Bioorg. Med. Chem. Lett. 19 (2009) 5965e5969. (1)
2		1.They showed excellent activity against most of the tested pathogenic fungi. For *C. albicans* and *C. neoformans,* 2.They are more potent than fluconazole, itraconazole and ketoconazole	1.Giraud, F.; Loge, C.; Pagniez, F.; Crepin, D.; Le Pape, P.; Le Borgne, M. Design, synthesis, and evaluation of 1-(N-benzylamino)-2-phenyl-3-(1H-1,2,4-triazol-1-yl) propan-2-ols as antifungal agents. *Bioorg. Med. Chem. Lett.*, **2008**, *18*, 1820-1824. 2.Chai, X.; Zhang, J.; Hu, H.; Yu, S.; Sun, Q.; Dan, Z.; Jiang, Y.; Wu, Q. Design, synthesis, and biological

			evaluation of novel triazole derivatives as inhibitors of cytochrome P450 14alphademethylase. *Eur. J. Med. Chem.*, **2009**, *44*, 1913-1920.
3.		1.Molecular docking studies revealed that the hydrophobic and *van der Waals* interactions between the alkyl group and CACYP51 could compensate for the loss of TT–TT stacking interactions of the aromatic group. 2.SAR results indicated that linkers (X) played important roles in their antifungal activities., 3.*N*-methyl group and piperazinyl group are much better than hexahydropyrimidinyl and piperidin-4-imino group. The length of alkyl group is suitable for 3 or 4 carbon atoms. Various substitutions attached to the terminal phenyl group, such as halogens and nitro group, are favorable for the antifungal activity.	1.Xu, Y.; Sheng, C.; Wang, W.; Che, X.; Cao, Y.; Dong, G.; Wang, S.; Ji, H.; Miao, Z.; Yao, J.; Zhang, W. Structure-based rational design, synthesis and antifungal activity of oxime-containing azole derivatives. *Bioorg. Med. Chem. Lett.*, **2010**, *20*, 2942-2945.
4		1.This compound target the biosynthesis of ergosterol by inhibiting the cytochrome P450-dependent lanosterol 14α-demethylase (Erg11p, CYP51), encoded by the ERG11 gene, resulting in accumulation of toxic methylsterols in membranes that may culminate in fungistatic effect or fungal death.	Kelly, S. L.; Arnoldi, A.; Kelly, D. E. Molecular genetic analysis of azole antifungal mode of action. Biochem. Soc. Trans. 1993, 21, 1034−1038.

		.	
5.		1.Exhibits broad spectrum antifungal activity against candida species 2.shows appreciable antifungal activity with mycostalin	Laura, G.; Marinella, R.; Annalisa, P.; Emanuela, L. *Bioorg. Med Chem.Lett.* 2001, *11*, 3147-3149.
6.		1.Incorporation of triazole nucleus,a biologically important and accepted pharmacophore , into benzimidazole ring system makes it versatile heterocyclepossesing wide spectrum of antifungal activity against candida albicans and aspergillusniger.	Hassan m.eisa.alla-eldin M.B.,sahAm.b.,A,A, Farahat,synthesis and antimicrobial activity of certain benzimidazole and fused benzimidazole derivatives.,Ind.J.Chem. 2010:49,1515-25
7	 	1.Exhibit the capacity to overcome CDR and ERG11 gene upregulation and to maintain antifungal activity despite a recognized critical CYP51 substitution in C. albicans isolates. 2.Decreased intracellular accumulation of azoles due to the overexpression of genes encoding efflux transporters belonging to the ATP-binding cassette (ABC) superfamily (CDR1 and CDR2) or major facilitator superfamily (MDR1) 3. Genetic alterations in the ERG11 gene leading to amino acid substitutions in the target enzyme CYP51 that decrease drug binding; alterations in the sterol biosynthesis pathway that bypass the accumulation of toxic sterols and overexpression of the ERG11 gene. Therefore, the antifungal	1.G. Del Sorbo, H. Schoonbeek, M. A. De Waard, Fungal Genet. Biol. 2000, 30, 1 –15. 2. J. Morschh_user, Fungal Genet. Biol. 2010, 47, 94– 106. 3.S. L. Kelly, D. C. Lamb, D. E. Kelly, FEMS Microbiol. Lett. 1999, 180, 171 – 175. 4.S. L. Kelly, D. C. Lamb, J. Loeffler, H. Einsele, D. E. Kelly, Biochem. Biophys. Res. Commun. 1999, 262, 174 –179. 5.D. C. Lamb, D. E. Kelly, T. C. White, S. L. Kelly, Antimicrob. Agents Chemother. 2000, 44, 63–67. 6.A. S. Chau, M. Gurnani, R. Hawkinson, M. Laverdiere, A. Cacciapuoti, P. M. McNicholas, Antimicrob. Agents Chemother. 2005, 49,

		agent is overwhelmed, and routine therapeutic concentrations can no longer effectively inhibit ergosterol synthesis.	3646 –3651. 7.D. Sanglard, A. Coste, S. Ferrari, FEMS Yeast Res. 2009, 9, 1029–1050.
8	 A.  B  C.	1.The best MFC was 0.5 mg/mL that was observed for compounds A. against clinical Candida albicans and B.against standard Candida albicans and Candida kruzei. 2.Compounds A and B were also effective against all the tested fungi. 3.These compounds have imidazole ring and smaller size than the other compounds. 4.These compounds are very close to clotrimazole. 5.May be attributed to the better penetration into fungi cell.	1.S. Emami, M. Falahati, A. Banifatemi, K. Moshiri, A. Shafiee, Arch. Pharm. Pharm. Med. Chem. 2002, 7, 318–324. 2. S. Emami, M. Falahati, A. Banifatemi, K. Moshiri, A. Shafiee, Arch. Pharm. Pharm. Med. Chem. 2002, 7, 318–324.
9.	A.  B.  C.	1.Presence of chlorine and nitro substituent at the ortho and para position of the phenyl ring in A & B led to increase in activity. 2. Chlorine at ortho position of the phenyl ring provided activity to compound C. 3. Thetriazolyl ring clubbed with benzimidazole moiety in same molecule frame led to response in anthelmintic activity.	1.Valdez J., Cedillo R., Hernandez-Compos A., Yepez L., Hernandez-Luis F., Navarrte-Vazquez G., Tapia A., Cortes R., Hernandez M and Castillo R. *Bioorg. Med. Chem. Lett*. **12(16)**: 2221-4 (2002). 2.p. sudhirkumar and j. sahoo,ojcheg 2014, Vol. 30, No. (1): Pg. 211-217

			
10.	A.  B.  C.  D. 	1. A possessing smaller size than the other compounds and may be attributed to the better Penetration into fungi cell. 2. The activity was decreased by the presence of methoxy group on the triazoles and benzotriazoles Moiety in B. 3. Compounds C and D also possessed great inhibitory effect on tested fungus.	Zahra Rezaei , SoghraKhabnadideh , KeyvanPakshir , Zahra Hossaini , FatemehAmiri , ElhamAssadpour doi:10.1016/j.ejmech.2008.07.012
11.		1.Structure–activity relationship clearly suggested that introduction of a biaryloxy side chain greatly enhanced the antifungal activity of triazole	Liu, P., Zhu, S., Xie, W., Synthesis and SAR studies of biaryloxysubstituted triazoles as antifungal agents. Bioorg Med ChemLet,t 2008, 18, 3261–3265.
12		Thiones group exhibiting significant antifungal activity agains candida species.	Isloor, A.M., Kalluraya, B., Shetty, P., Regioselective reaction: synthesis, characterization and pharmacological studies of some new Mannich bases derived from 1,2,4-triazoles. Eur J Med Chem, 2009, 44, 3784–3787.

13		Shows moderate effect against fungi.	Shafiee, A., Sayadi, A., Roozbahani, M.H., Foroumadi, A., Kamal, F., Synthesis and *in vitro* antimicrobial evaluation of 5-(1-methyl-5-nitro-2-imidazolyl)-4*H*-1,2,4-triazoles. Arch Pharm, 2002, 335, 495-499.
14		Presence of electron withdrawing groups on phenyl ring with thiazolotriazole demonstrates significant antifungal activity.	Karthikeyan, M.S., Synthesis, analgesic, anti-inflammatory and antimicrobial studies of 2,4-dichloro-5-fluorophenyl containing thiazolotriazoles. Eur J Med Chem, 2009, 44, 827-833.
15		Exhibit good activity against *Aspergillusniger*.	Havaldar, F.H., Patil, A.R., Syntheses of 1, 2, 4 Triazole Derivatives and their Biological Activity. Eur J Med Chem, 2008, 5, 347-354.
16		1.Shows moderate antifungal activity against candida albicans. 2.Nitro substitution at para position show antifungal activity as compared to ketoconazole.	Kokil, R.G., Synthesis and In Vitro Evaluation of Novel 1, 2, 4-Triazole Derivatives as Antifungal Agents. Letters in drug Design & Discovery, 2010, 7, 46-49.
17		1.Methoxy substituted triazole derivatives shows antifungal activity against candida albicans and aspergillusniger. 2.Thiol group is also responsible to show antifungal activity.	Siddiqui, A. A., Arora, Amit., Synthesis of some 1,2,4-triazoles as potential antifungal agents. Indian journal of chemistry, 2005, 44 B, 838.
18		1. Exhibits antifungal activity against fungal strains such as Candida albicans, Aspergillusfumigatus, Aspergillusflavus, and Aspergillusniger. 2.Some compounds showed potent antifungal activity.	Pandey, S.K., Singh, A., Nizamuddin, A., Antimicrobial studies of some novel quinazolinones fused with[1,2,4]-triazole,[1,2,4]-triazine and[1,2,4,5]- tetrazine rings. Eur J Med Chem, 2009, 44, 1188-1197.

Conclusion

The azole antifungal drugs have introduced a new era in antifungal chemotherapy. Although they all act through a similar mechanism, they vary widely in fungal spectrum, pharmacokinetics and toxicities. Other potent agents in earlier stages of development may further expand the options available in this remarkable group of compounds. Recent advances in antifungal chemotherapy and the addition of newer broad spectrum triazoles, offer clinicians more effective and less toxic alternatives to conventional amphotericin B. Even with the introduction of azole antifungal drugs and despite recent advances, mortality rates from invasive fungal infections remain high and there is a necessity for new treatment options. Earlier diagnosis, rapid restoration of the host immune system, the combination of antifungals and development of other compounds may improve the outcome of IFIs.

References:

1. Dismukes, W. E. Clin. Infect. Dis. 2006, 42, 1289–1296. doi:10.1086/503043
2. Goossens, H. Chemotherapy 2005, 51, 177–181. doi:10.1159/000086919
3. Bremner, J. B.;Ambrus, J. I.;Samosorn, S.Curr. Med. Chem.2007,14,1459–1477. doi:10.2174/092986707780831168
4. Hubschwerlen, C.;Specklin, J.-L.;Sigwalt, C.;Schroeder, S.;Locher, H. H. Bioorg. Med. Chem. 2003, 11, 2313–2319. doi:10.1016/S0968-0896(03)00083-X
5. Gilchrist, T. L. Heterocyclic chemistry, 2nd ed.; Wiley: New York, 1992.
6. Holla, B. S.; Gonsalves, R.; Shenoy, S. Farmaco 1998, 53, 574–578. doi:10.1016/S0014-827X(98)00068-8
7. Holla, B. S.; Veerendra, B.; Shivananda, M. K.; Kumari, N. S. Indian J. Chem. 2003, 42, 2010–2014.
8. Ashok, M.;Holla, B. S.J. Pharmacol. Toxicol.2007,2,256–263. doi:10.3923/jpt.2007.256.263
9. Prasad, D. J.; Ashok, M.; Karegoudar, P.; Poojary, B.; Holla, B. S.; Kumari, N. S. Eur. J. Med. Chem. 2009, 44, 551–557. doi:10.1016/j.ejmech.2008.03.025
10. Turan-Zitouni, G.; Kaplancikli, Z. A.; Yildiz, M. T.; Chevallet, P.; Kaya, D. Eur. J. Med. Chem. 2005, 40, 607–613. doi:10.1016/j.ejmech.2005.01.007
11. Walczak, K.; Gondela, A.; Suwiński, J. Eur. J. Med. Chem. 2004, 39, 849–853. doi:10.1016/j.ejmech.2004.06.014
12. Holla, B. S.; Poojary, K. N.; Rao, B. S.; Shivananda, M. K. Eur. J. Med. Chem. 2002, 37, 511–517. doi:10.1016/S0223-5234(02)01358-2
13. Holla, B. S.; Veerendra, B.; Shivananda, M. K.; Poojary, B. Eur. J. Med. Chem. 2003, 38, 759–767. doi:10.1016/S0223-5234(03)00128-4
14. Amir, M.; Shikha, K. Eur. J. Med. Chem. 2004, 39, 535–545. doi:10.1016/j.ejmech.2004.02.008
15. Almasirad, A.; Tabatabai, S. A.; Faizi, M.; Kebriaeezadeh, A.; Mehrabi, N.; Dalvandi, A.; Shafiee, A. Bioorg. Med. Chem. Lett. 2004, 14, 6057–6059. doi:10.1016/j.bmcl.2004.09.072
16. Masuda, K.; Toga, T.; Hayashi, N. J. Labelled Compd. 1975, 11, 301–304. doi:10.1002/jlcr.2590110219
17. Schreier, E. Helv. Chim. Acta 1976, 59, 585–606. doi:10.1002/hlca.19760590223
18. Budavari, S., Ed. The Merck Index, 12th ed.; Merck Co. Inc: White House Station, NJ, 1996.
19. Haber, J. Cas. Lek. Cesk. 2001, 140, 596–604.
20. Vatmurge, N. S.; Hazra, B. G.; Pore, V. S.; Shirazi, F.; Chavan, P. S.; Deshpande, M. V. ,Bioorg. Med. Chem. Lett. 2008, 18, 2043–2047. doi:10.1016/j.bmcl.2008.01.102
21. Zhang, J.; Zhang, H.; Cai, W.; Yu, L.; Zhen, X.; Zhang, A. Bioorg. Med. Chem. 2009, 17, 4873–4880. doi:10.1016/j.bmc.2009.06.019
22. Jagasia, R.; Holub, J. M.; Bollinger, M.; Kirshenbaum, K.; Finn, M. G. J. Org. Chem. 2009,74,2964–2974.doi:10.1021/jo802097m
23. Huber, D.; Hübner, H.; Gmeiner, P. J. Med. Chem. 2009, 52, 6860–6870. doi:10.1021/jm901120h
24. Chrysina, E. D.; Bokor, É.; Alexacou, K.-M.; Charavgi, M.-D.; Oikonomakos, G. N.; Zographos, S. E.;Leonidas, D. D.;Oikonomakos, N. G.;Somsák, L. Tetrahedron: Asymmetry 2009, 20, 733–740. doi:10.1016/j.tetasy.2009.03.021.

25. Akri, K. E.; Bougrin, K.; Balzarini, J.; Faraj, A.; Benhida, R. Bioorg. Med. Chem. Lett. 2007, 17, 6656–6659. doi:10.1016/j.bmcl.2007.08.077.
26. Karthikeyan, M. S.; Holla, B. S.; Kumari, N. S. Eur. J. Med. Chem. 2008, 43, 309–314. doi:10.1016/j.ejmech.2007.03.024.

*****