International Journal of Research and Review
Volume 11; Issue: 8; August 2024
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

A Brief Review on Bioisosterism in Drug Design and Designing of Advanced Drugs

Seba M C

Associate Professor, The Dale View College of Pharmacy and Research Centre, Punalal

DOI: https://doi.org/10.52403/ijrr.20240836

ABSTRACT

This review predominantly focussed on the significance of bioisosterism in drug design and designing of novel advanced drugs. The broadest description of bioisosteres is, "molecules or groups those have chemical and physical similarities making broadly similar biological properties".[1] There are two types of bioisosteres namely Classical and Non classical bioisosteres. A chief tendency in this area is the growing prevalence of "nonclassical isosteres" moieties those do not have the equal number of atoms, but produce a resemblance in a key parameter.[2]

KEY WORDS: Bioisosteres, Lead molecule, Drug design, Docking.

INTRODUCTION

Drug design is a multifaceted pharmaceutical science with a long history. Lot of advancement have been made in the field of drug design since the end of 19th century, when Emil Fisher recommended that the drug–receptor interaction resembles the key and lock interplay. progressively, drug design has been changed into a rational and efficient science with a firm theoretical background and practical applications. currently, drug design is the superior approach for drug discovery. It combines the innovations in science and technology and includes them in its wide-ranging store of methods and tools in turn to accomplish the chief goal. It includes the discovery of efficient, specific, harmless, safe and well-tolerated drugs. Drug design is one of the rapidly developing modern sciences and its advancement is enhanced by the implication of artificial intelligence.[3]

Bioisosterism is a tactic of Medicinal Chemistry for the rational design of new drugs, by using a lead compound as a particular process of molecular modification. The lead compound should be of a utterly well known chemical entity and have a uniformly well known mechanism of action, if achievable at the level of topographic contact with the receptor, together with information of all of its pharmacophoric group. In addition to the pathways of metabolic inactivation, as well as the key determining structural factors of the physicochemical properties which control the bioavailability, and its side effects, whether directly or not, should be recognized so as to permit for defining the bioisosteric relation to be used. The achievement of this strategy in developing new moieties which are medicinally attractive has shown a considerable growth in diverse therapeutic classes, being sufficiently used by the pharmaceutical industry to find out new analogs of therapeutic findings commercially attractive otherwise known as me-too drugs, and as well as a tool useful in the molecular modification. There may be number of reasons for the use of bioisosterism to design new drugs, involves the requirement to get better pharmacological activity, make it highly selective for a receptor or enzymatic isoform subtype - with simultaneous reduction of some side-effects

or to exploit the pharmacokinetics of the lead molecule might present. This review paper, focussed on the significance of bioisosterism in drug design and designing of novel advanced drugs. This paper also showing the importance of bioisosterism in building a new series of compounds designed as candidate of new drugs, giving examples of successful cases in diverse therapeutic classes.[4]

BIOISOSTERISM BACKGROUND

In 1919, Langmuir studied the chemical properties and reactivity of determined substances holding atoms or groups with the similar number of valence electrons, i.e. isoelectronic, shaped the concept of isosterism to describe atoms or organic or inorganic molecules which have the similar number and/or arrangement of electrons.

O^{-2}, F^{-}, Ne, Na^{+}, Mg^{+2}

ClO_4^{-}, SO_4^{-2}, PO_4^{-3}

N=N, C=O

CO_2, NO2

N=N=N, $N=C=O^{-}$

In 1925, Grimm articulated the Hydride Displacement Law, an empiric rule which states that the addition of a hydrogen atom with a pair of electrons (i.e. hydride) to an atom, produces a pseudoatom presenting the same physical properties as those present in the column immediately behind on the Periodic Table of the Elements for the initial atom showing that any atom belonging to groups 4A, 5A, 6A, 7A on the Periodic Table change their properties by adding a hydride, becoming isoelectronic pseudoatoms.

The inventing of the term bioisosterism goes back to the pioneer work of Friedman and Thornber during the early 50s. Friedman presented the term bioisosterism to define the phenomenon observed between substances structurally related which presented similar or antagonistic biological properties. Over the years, various bioisosteric relations have been identified in compounds both natural and synthetic.[5]

CLASSIFICATION OF BIOISOSTERISM: CLASSICAL AND NON-CLASSICAL BIOISOSTERISM

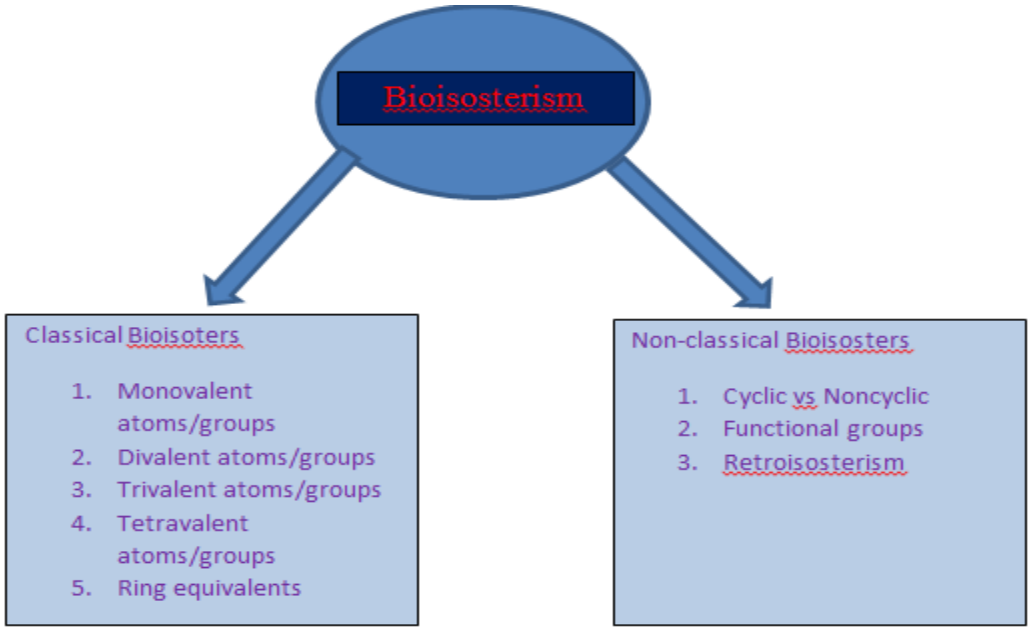

Fig 1: Classification of Bioisosterism[6]

Classic Bioisosteres:

They obey steric and electronic definition (Table 1)

Classic bioisostere atoms and groups

Monovalent	Divalent	Trivalent	Tetravalent
-OH, $-NH_2$, $-CH_3$, -OR	$-CH_2-$	=CH-	=C=
-F, -Cl, -Br, -I, -SH, $-PH_2$	-O-	=N-	=Si=
$-Si_3$, -SR	-S-	=P-	$=N^+=$
	-Se-	=As-	$=P^+=$
	-Te-	=Sb-	=As=
			$=Sb^+=$

Non classic bioisosteres

They do not obey the steric and electronic definition of classical isosteres. They do not have the same number of atoms as the substituent or moiety for which they are used as a replacement (Table 2)[7]

Non-Classic bioisosteres

-CO-	-COOH	$-SO_2NH_2$	-H	-CONH-	-COOR	$-CONH_2$
$-CO_2-$	$-SO_3H$	-$PO(OH)NH_2$	-F	-NHCO-	-ROCO-	$-CSNH_2$
$-SO_2-$	-tetrazole					
$-SO_2NR-$	$-SO_2NHR$		-OH $-CH_2OH$		-catechol	
-CON-	$-SO_2NH_2$				-benzimidazole	
-CH(CN)-	-3-hydroxy isoxazole		$-NHCONH_2$			C_4H_4S
R-S-R	-2-hydroxy chromones		$-NH-CS-NH_2$			$-C_5H_4N$
(R-O-R')						$-C_6H_5$
R-N(CN)-	=N-		$-NH-C(=CHNO_2)-NH_2-NH-C(=CHCN)-NH_2$			-C_4H_4NH
-halide	C(CN)=R' $-CF_3$ -CN $-N(CN)_2$ $-C(CN)_3$					

In 2021 Esma Eryılmaz Dogan et.al introduced a computational methodology and to design new, multi-targeted drug candidates aimed at treatment of bone cancer. Amongst them, Methotrexate was elected as a lead molecule because of its broader spectrum of bioactivity on the most significant drug targets described in literature. The lead molecule was exposed to basic bioisosteric modifications to attain a superior drug compound with enhanced bioactivity and a stronger drug-likeness profile using the known drug structure. Designed compounds produced by a number of bioisosteric replacements performed on the 2D structure of the lead compound were assessed in terms of both criteria; bioactivity and drug-likeness. Silicone modified compounds M4, M13, M14, and M15 showed a much broader spectrum of biological activity than that of the approved compound Methotrexate. The interesting effect of silicone incorporation makes their compounds promising drug candidates for further pharmaceutical investigation.[8]

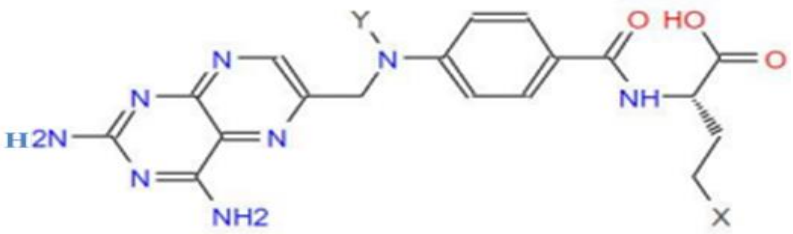

Fig 2: Methotrexate

Compound	X	Y	GPCR	ICM	KI	NRL	PI	EI
Methotrexate	COOH	CH_3	0.51	0.23	0.38	-0.38	0.27	0.72
M1	$B(OH)_2$	CH_3	0.46	0.22	0.42	-0.29	0.65	1.20
M2	NH_2	CH_3	0.62	0.35	0.53	-0.44	0.39	0.80
M3	SiH_3	CH_3	0.55	0.29	0.44	-0.43	0.29	0.78
M4	$Si(CH_3)_3$	CH_3	0.76	0.49	0.60	-0.40	0.53	1.07
M5	COOH	SiH_3	0.47	0.16	0.34	-0.47	0.27	0.63
M6	COOH	$Si(CH_3)_3$	0.54	0.22	0.39	-0.43	0.38	0.73
M7	COOH	OH	0.30	0.04	0.16	-0.66	0.29	0.64
M8	COOH	F	0.47	0.16	0.35	-0.46	0.27	0.63
M9	COOH	Cl	0.47	0.16	0.34	-0.47	0.26	0.63
M10	BH_2	OH	0.26	-0.06	0.17	-0.73	0.30	0.75
M11	$B(OH)_2$	OH	0.25	-0.05	0.20	-0.57	0.67	1.12
M12	$Si(CH_3)_3$	OH	0.55	0.23	0.39	-0.67	0.55	0.99
M13	$Si(CH_3)_3$	$B(OH)_2$	0.67	0.37	0.57	-0.35	0.67	1.08
M14	$Si(CH_3)_3$	F	0.71	0.42	0.57	-0.48	0.52	0.98
M15	$Si(CH_3)_3$	Cl	0.71	0.42	0.57	-0.49	0.52	0.98

Khanna et.al proved that, Luliconazole, or NND-502 (Figure 3), is a novel vinyl-imidazole antifungal agent of topical use and a follow-up candidate of lanoconazole (Figure 3), which is a bioisosterically modified derivative, an imidazole compound with a ketene dithioacetal moiety which has shown antifungal activity against a variety of fungal strains as the *R*-enantiomer (with stronger potency than the racemate). Similarly, the structurally related *R*-enantiomer of luliconazole (1) displayed higher antifungal potency than the racemic compound, and stronger activity than lanoconazole (2).[9]

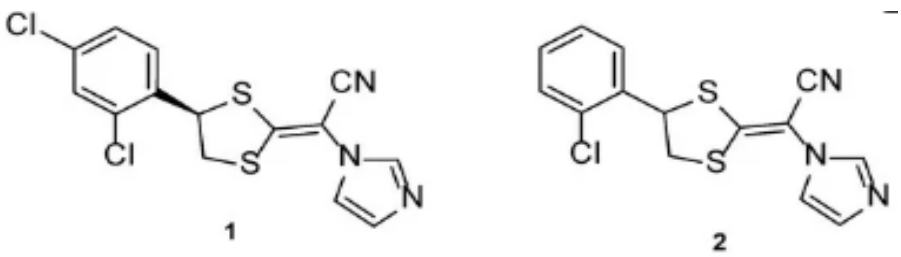

Fig 3: Chemical structures of luliconazole (1) and lanoconazole (2)

N Sun et.al stated that Iodiconazole (Figure 4) is a innovative triazole antifungal agent in investigation, which possesses broad spectrum antifungal activity and particular interest against Aspergillus species. In 2013, Sun et al. tested iodiconazole for in vitro activity against different fungi using the broth microdilution method, and further in vivo studies were executed to assess the pharmacokinetics and correlate with pharmacodynamics data. In terms of pharmacodynamics data, minimum inhibitory concentration values were calculated in vitro using several azole agents as standards such as fluconazole, itraconazole, ketoconazole, and miconazole. By analyzing the attained results, iodiconazole demonstrated promising results against C. albicans, Candida parapsilosis, Nannizzia gypsea, Microsporum canis, Trichophyton violaceum, Trichophyton mentagrophytes, and Epidermophyton floccosum, with MIC values ranging from <0.129 to 0.258 µM, lower than those presented for the standard drugs, meaning stronger antifungal potency against these fungal strains.[10]

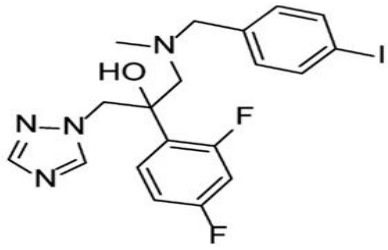

Fig 4: Iodoconazole

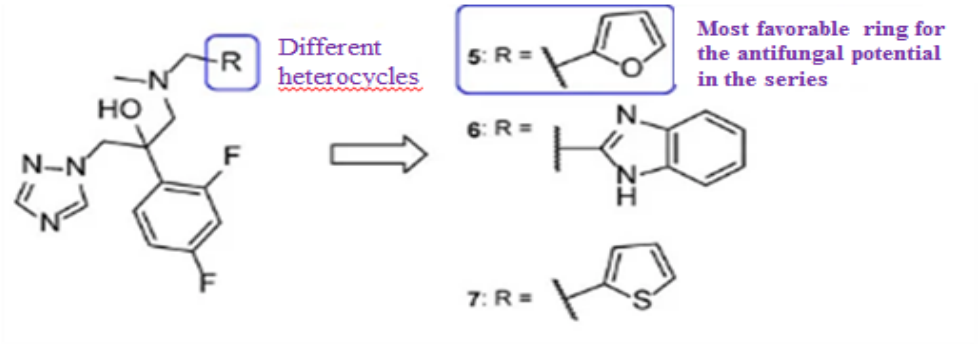

Fig 5: Isosterically modified structures of Iodoconazole.

In 2020, novel triazole compounds were designed based on albaconazole and verified using the broth microdilution method against C. albicans, C. neoformans, A. fumigatus, and N. gypsea. All tested compounds showed good activity against the tested strains, with particular interest regarding the activity of some compounds against A. fumigatus. The novel Compound (Figure 6) showed promising results against all fungal species assessed, with MIC values ranging from 0.036 to 0.58 µM , comparable to albaconazole , with MIC ranging from 0.036 to 2.3 µM.[11].

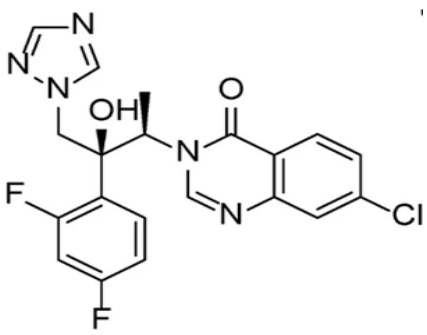

Fig 6: Albaconazole

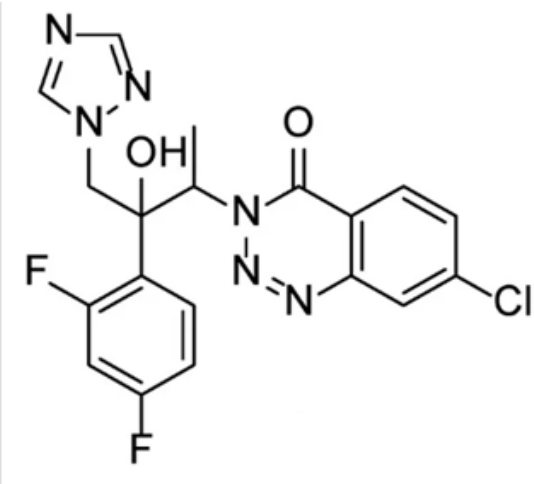

Fig 7: Novel albaconazole derivative

Jacobs et.al demonstrated that, Compound PC945 (Figure 8) is a novel antifungal agent, with a triazole scaffold and characteristics that allow nasal administration. This new triazole molecule has potent antifungal potential. PC945 presented a broad spectrum of activity against azole-susceptible and resistant strains of *A. fumigatus*, with MIC values from 0.047 to 11.72 µM, lower/comparable to voriconazole (MIC from 0.183 to 11.45 µM) and comparable to posaconazole (MIC from 0.023 to 2.85 µM). Against *C. albicans*, *Candida glabrata*, and *C. krusei*, this compound showed strong inhibition of fungal growth, with MIC values ranging from 0.119 to 12.08 µM (stronger than voriconazole, with MIC values from 0.4 to 28.6 µM, and comparable to posaconazole, with MIC values from 0.116 to 11.6 µM). When tested against *C. neoformans*, PC945 presented equal antifungal potential that voriconazole and posaconazole (MIC = 0.023 µM vs. MIC = 0.023 µM to the standards), and against *Cryptococcus gattii* the antifungal activity was similar to voriconazole and posaconazole (MIC = 0.37 µM vs. MIC = 0.359.[12]

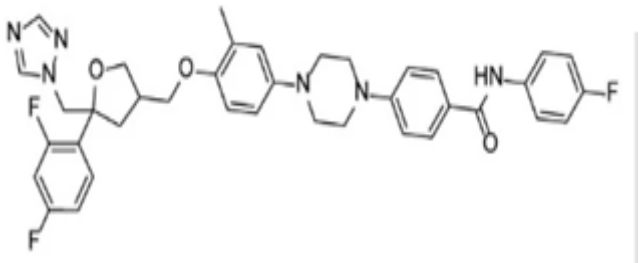

Fig 8: Chemical structure of PC945, A novel triazole molecule

Compound VT-1598 (Figure 9) is a new generation tetrazole hybrid, with a broad spectrum activity against yeasts, endemic fungi, and molds, including Candida auris and Aspergillus species. It has received QIDP (Qualified Infectious Disease Product), fast track and orphan drug designation by the FDA for the treatment of coccidioidomycosis. Furthermore, in vivo studies by means of the murine model have confirmed the antifungal activity of VT-1598 against invasive aspergillosis and are an chief base for future studies.[13]

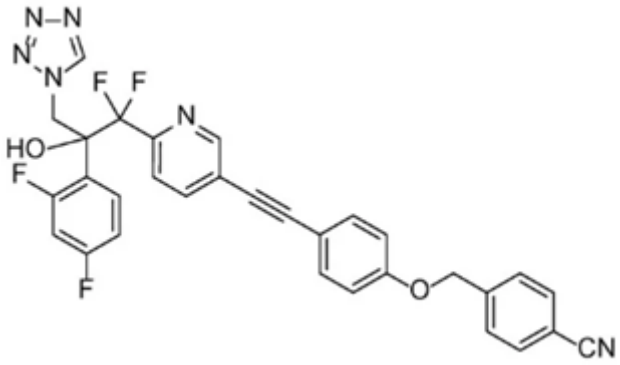

Fig 9: Chemical structure of VT-1598, A new generation tetrazole hybrid.

In 2023, panel Vinícius Augusto Campos Peret et.al described the design, synthesis and antifungal activity study of new imidazoles and 1,2,4-triazoles derived from eugenol and dihydroeugenol. These new compounds were fully characterized by spectroscopy/spectrometric analyses and certain imidazoles derivatives showed relevant antifungal activity against *Candida* sp. and *Cryptococcus gattii* in the range of 4.6–75.3 μM. Although no compound has shown a broad spectrum of antifungal activity against all evaluated strains, some azoles were more active than either reference drugs employed against specific strains. Docking studies with CYP51 revealed an interaction between the imidazole ring of the active substances with the heme group, as well as insertion of the chlorinated ring into a hydrophobic cavity at the binding site, consistent with the behavior observed with control drugs miconazole and fluconazole. The increase of azoles-resistant isolates of *Candida* species and the impact that *C. auris* has had on hospitals around the world reinforces the importance of discovery of novel azole derivatives as new bioactive compounds for further chemical optimization to afford new clinically antifungal agents.[14]

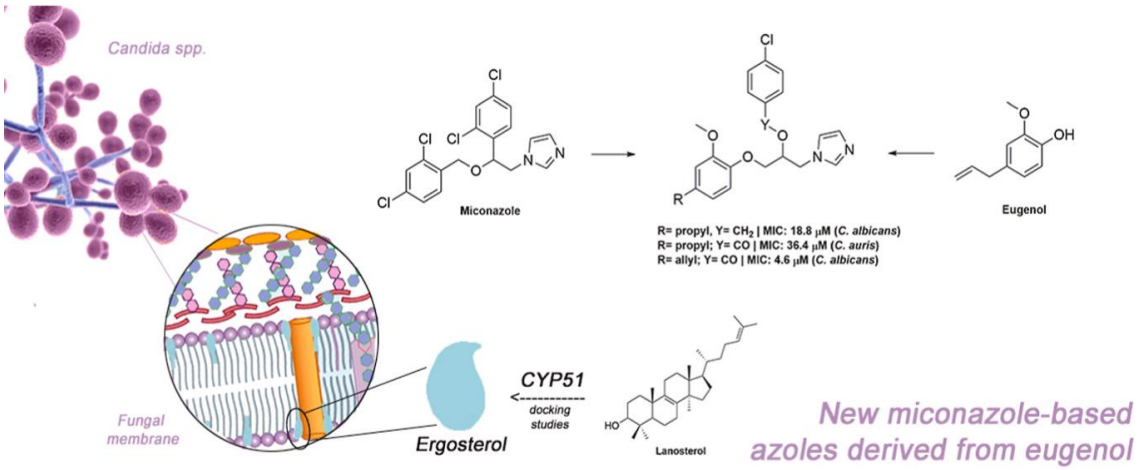

Fig 10: New miconazole based azoles derived from eugenol

CONCLUSION

In the current review major role and significance of bioisosterism in drug design and designing of novel advanced drugs has been investigated with clear illustration of chemical structures of drugs of therapeutic importance. Bioisosterism possess a major role in all these properties of ligands and biological response of the ligands. In summary, bioisosterism is a superior process of rational molecular modification in drug design and is one of the key tactics, commonly exploited in

pharmaceutical organic chemistry to optimize lead compounds.

Declaration by Authors

Ethical Approval: Not Required
Acknowledgement: None
Source of Funding: None
Conflict of Interest: The authors declare no conflict of interest.

REFERENCE

1. Christopher A. Lipinski, Bioisosterism in Drug Design , Annual Reports in Medicinal Chemistry,1986;21,283-291
2. George A. Patani et.l, Bioisosterism: A Rational Approach in Drug Design,Chem. Rev. 1996; 96, 3147−3176
3. Nicholas A. Meanwell,The Influence of Bioisosteres in Drug Design: Tactical Applications to Address Developability Problems, National Library of Medicine, 2015; 9: 283–381.
4. IriniDoytchinova et.al, Drug Design—Past, Present, Future, Molecules,2022; 27(5): 1496.
5. Lídia Moreira Lima et.al, Bioisosterism: A Useful Strategy for Molecular Modification and Drug Design, Current Medicinal Chemistry, 2005, 12, 23-49
6. Gowhar Ali et. Al, Input of Isosteric and Bioisosteric Approach in Drug Design, Journal of the chemical society of Pakistan, 2014,36(5),1-20
7. Priyanka L. Gaikwad, The Use of Bioisosterism in Drug Design and Molecular Modification, Am. J. PharmTech Res. 2012; 2(4), 1-23
8. New Design Compounds for Bone Cancer Treatment: Broader Bioactivity of Silicon Modified Methotrexate Esma Eryılmaz Doğan, European Journal of Science and Technology Special Issue 28, pp. 1521-1527, November 2021
9. Khanna et.al, Luliconazole for the treatment of fungal infections: An evidence-based review. Core Evid. 2014, 9, 113–124
10. Sun, N, In vivo pharmacokinetics and in vitro antifungal activity of iodiconazole, a new triazole, determined by microdialysis sampling. *Int. J. Antimicrob. Agents* 2013, *41*, 229–235.
11. Ding et.al, Design, synthesis, and structure-activity relationship studies of novel triazole agents with strong antifungal activity against *Aspergillus fumigatus*. *Bioorg. Med. Chem. Lett.* 2020, *30*, 126951
12. Jacobs S et.al, Novel antifungal agents in clinical trials version 2; peer review: 2 approved. F1000Research 2022, 10, 507.
13. Garvey et.al. The novel fungal CYP51 inhibitor VT-1598 displays classic dose-dependent antifungal activity in murine models of invasive aspergillosis. *Med. Mycol.* 2020, *58*, 505–513.
14. Vinícius Augusto Campos et.al, New miconazole-based azoles derived from eugenol show activity against *Candida* spp. and *Cryptococcus gattii* by inhibiting the fungal ergosterol biosynthesis, European Journal of Medicinal Chemistry, 2023, 256,5,115436

How to cite this article: Seba M C. A brief review on bioisosterism in drug design and designing of advanced drugs. *International Journal of Research and Review*. 2024; 11(8): 341-348. DOI: *10.52403/ijrr.20240836*

******