1, 2, 4 – TRIAZOLES:A REVIEW OF SYNTHESIS AND THEIR BIOLOGICAL ACTIVITY

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Abstract

Triazole, which contains three nitrogen atoms and two carbon atoms, is divided into two isomers 1,2,3-triazole and 1,2,4-triazole. In the five-membered aromatic azole series, triazole compounds containing two carbon and three nitrogen atoms are easily able to bind with a variety of enzymes and receptors in biological systems and thus show versatile biological activities.

1,2,4-Triazoles are widely used in the pharmaceutical and medicinal chemistry field due to their unique biological activities. They play a significant role in the synthesis of various heterocyclic compounds. This review aims to provide a comprehensive overview of the literature on the various forms of triazoles and their synthetic processes.

Keywords: 1,2,4-Traizole,antibacterial, anti-tubercular, anti-inflammatory.

Introduction:

Azoles are normally used in medicinal chemistry and are included in the class of antimicrobials due to their health importance and good therapeutic index. Humankind has been affected by death-causing infectious diseases caused by a wide range of Gram-positive and Gram-negative bacteria, which have now proven to be multidrug-resistant. Therefore, there is aneed to develop new classes of antibacterial agents to fight multidrug-resistant pathogens.

The chemistry of 1,2,4-triazoles and their associated heterocyclic derivatives has attracted significant attention due to their synthetic and effective biological importance. The 1,2,4-triazole moieties have been incorporated into a wide variety of therapeutically interesting drug candidates, including antifungal, antibacterial, analgesic and anti-inflammatory, antineoplastic, antiviral, sedative, anxiolytic, anti-convulsant, antimigraine, antihistaminics, CNS stimulants and other activities are included. .[1-14]

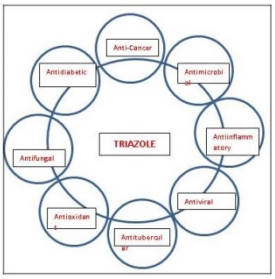

Fig.01: Biological activities of Triazole scaffold

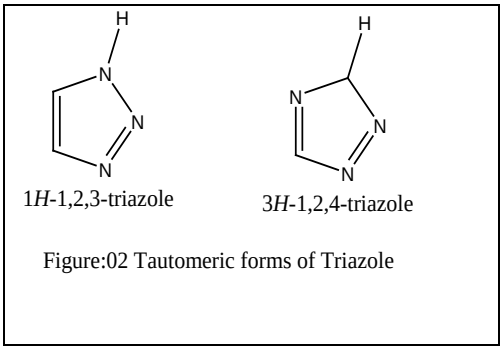

Figure:02 Tautomeric forms of Triazole

Some new drugs containing a triazole nucleus are Fluconazole, Itraconazole, Terconazole, Posaconazole, Voriconazole (antifungal agents),Ribavirin (antiviral agent), non-nucleoside reverse transcriptase inhibitors, Anastrozole, Letrozole, Virazole (antineoplastics, nonsteroidal competitive aromatase inhibitors), Alprazolam, Triazolam,

Estazolam (anxiolytic, hypnotic, sedative, tranquilizer), Rizatriptan (antimigrane agent), Trazodone (antidepressant, anxiolytic), Nefazodone (antidepressant, 5-HT 2A-antagonist), Trapidil (hypotensive).

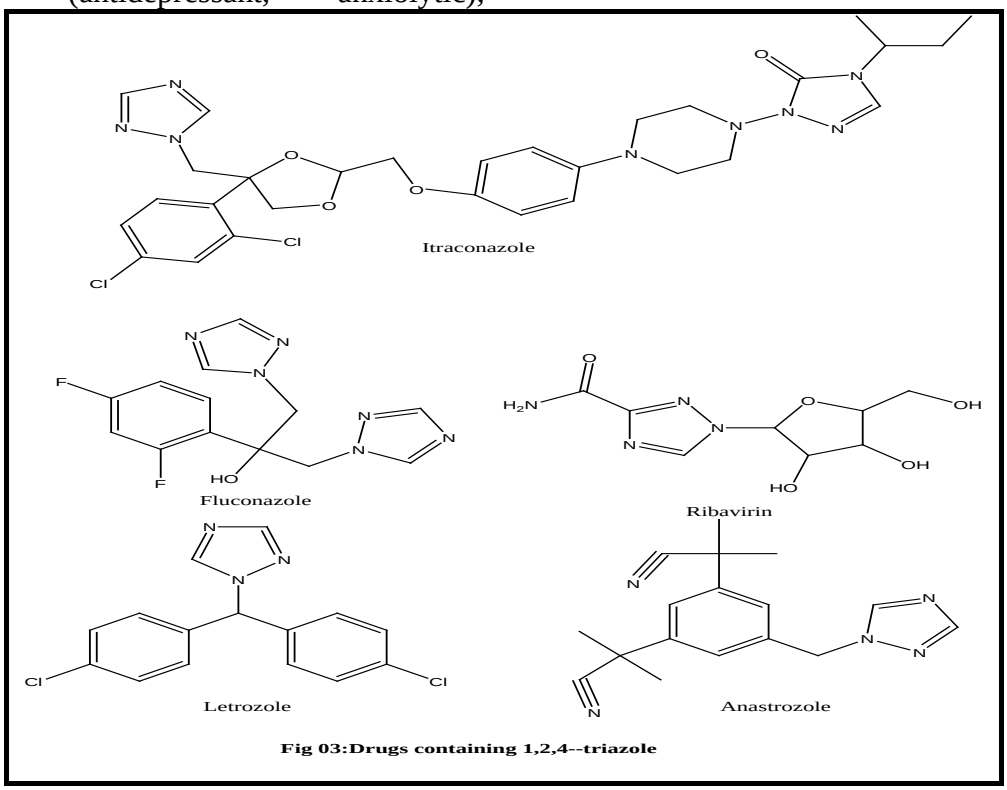

Fig 03:Drugs containing 1,2,4--triazole

Again several1,2,4-triazole derivatives are reported as insecticides [15], antiasthmatics [16], anticonvulsants[17], antidepressants [18], anti-inflammatory [19], insecticidal [20], and plant growth regulators [21]. In addition to these compounds having triazole moieties, such as vorozole, letrozole, and anastrozole are found to be very effective aromatase inhibitors, which can prevent breast cancer [22-24]. 1,2,4-triazole moiety is reported to interact strongly with heme iron, and aromatic substituents on the triazole are very effective in interacting with the active site of aromatase [25, 26].

Synthesis of 1,2,4-triazoles

.1,2,4-Triazole is an important heterocyclic compound broadly present in molecular structures with sequences of bioactivity, including anticancer, antibacterial, anti-HIV, etc. The main synthesis methods include amidines, imidates, amidrazones, aryl diazonium, and hydrazones as raw materials to provide nitrogen atoms to prepare 1,2,4-triazole derivatives.

Amidines as a nitrogen source

Amidines were widely used as organic catalysts and ligands for nitrogen–carbon bond formation due to the reactivity of nucleophilic nitrogen atoms. In 2011, a general method for the production of 1,3,5-trisubstituted-1,2,4-triazole with excellent yield (up to 90%) was developed via a one-pot, two-step process [27].This sequence began with the in-situ formation of amide from carboxylic acid and amidine. The aniline further reacted with monosubstituted hydrazine and cyclized to trisubstituted triazole. This method had the advantages of high regioselectivity and good tolerance of functional groups (Scheme 13a).

In 2015, Huang described an efficient CuCl2-promoted synthesis of 2,4,6-trisubstituted and 1,3-disubstitued-1,2,4-triazoles [28]. Triazole was prepared with a high yield (85%) [28] using K3PO4 as alkali, O2 as oxidant, amide as raw material, and DMF in the presence of CuCl2 and DMF.Nitrogen atoms and methyl groups from DMF were incorporated into the triazole. For amides substituted by various functional aromatic moieties (fluorine, bromine, methyl, ethoxy, and trifluoromethyl), the reaction sequence appears to be highly effective (Scheme 13b).

In 2019, Xia developed a facile copper-catalyzed one-pot method to synthesize 3,5-di substituted 1,2,4-triazole from amide and nitrile

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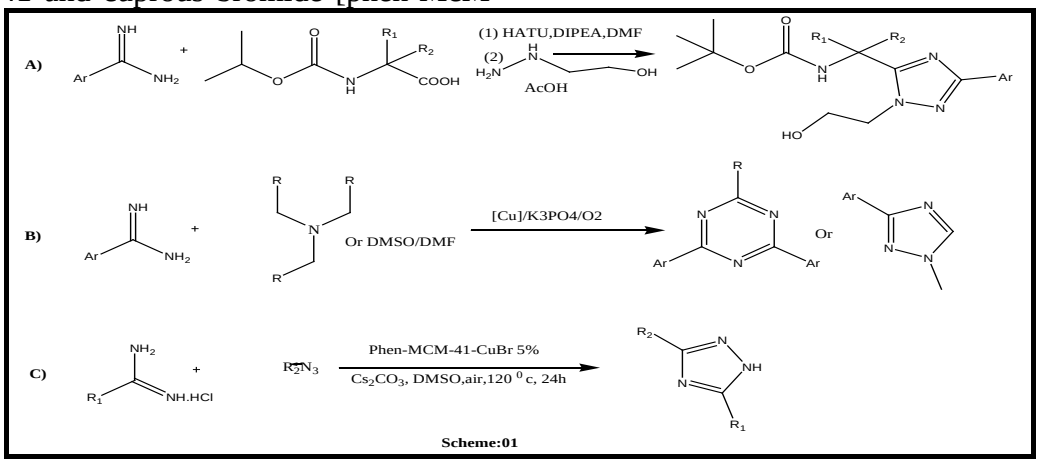
by cascade addition oxidation cyclization [29]. In this reaction, O2 was used as the oxidant, and functionalization was catalyzed by the complex of McM-41 and cuprous bromide [phen-McM-41-CuBr] with a high yield (91%)[28]. The route was used to prepare a variety of 1,2,4-triazole derivatives (Scheme 01C).



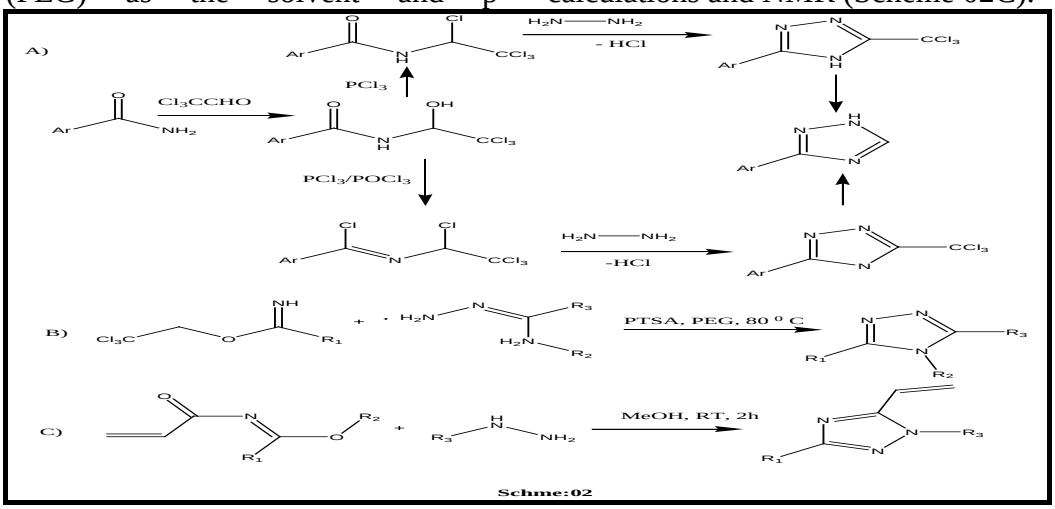
Scheme:01

Imidates as nitrogen source

Imidates are good precursors of triazoles, which have been extensively usedin this field. In 2016, Guirado gave a simplifiedmethod for the preparation of 3-aryl-1,2,4-triazole chloroformamide, which was obtained by the reaction of benzamide with chloral hydrate in high yield [30]. When imidates reacted with the mixture of phosphorus pentachloride/phosphorus oxychloride, maximum quantitatively converted to bis(1-tetrachloroethyl) benzimine chloride, which was then handled with hydrazine hydrate to prepare 3-aryl-1,2,4-triazoles with of yield (86%) [28]. The method had the advantages ofgood versatility, high yield, easy access to starting materials, and mild and simple experimental steps. (Scheme 02A).

In 2014, Mangarao et al. prepared a series of 3,4,5-trisubstitued-1,2,4-triazoles from 2,2,2-trichloroethyl imidate, using polyethylene glycol (PEG) as the solvent and p-toluenesulfonic acid as the solvent. Acid (PTSA) was used. catalysis during mild conditions (Manga Rao et al., 2014).In conclusion, it was a convenient, effective, and environment-friendly simple method for the synthesis of 1,2,4-triazole from 2,2,2-trichloroethyl imidate in PEG and the corresponding 1,2-triazole by employing PTSA as a catalyst have been taken. 4-triazoles under mild conditions with excellent yield (92%) [31] (Scheme 02b).

In 2018, Azzouni et al. The focus was on the production of vinylimidates as precursors for the synthesis of functionalized 1,2,4-triazoles. [32]. The method allowed to establish a large number of substitutions at the (N1, C3, and C5) positions of 1,2,4-triazole with good yield (98%) [32]. The experiment showed that the formation of 5-vinyl-1,2,4-triazoles can selectively inhibit potential five-membered and seven-membered byproducts through theoretical calculations and NMR (Scheme 02C).



Schme:02

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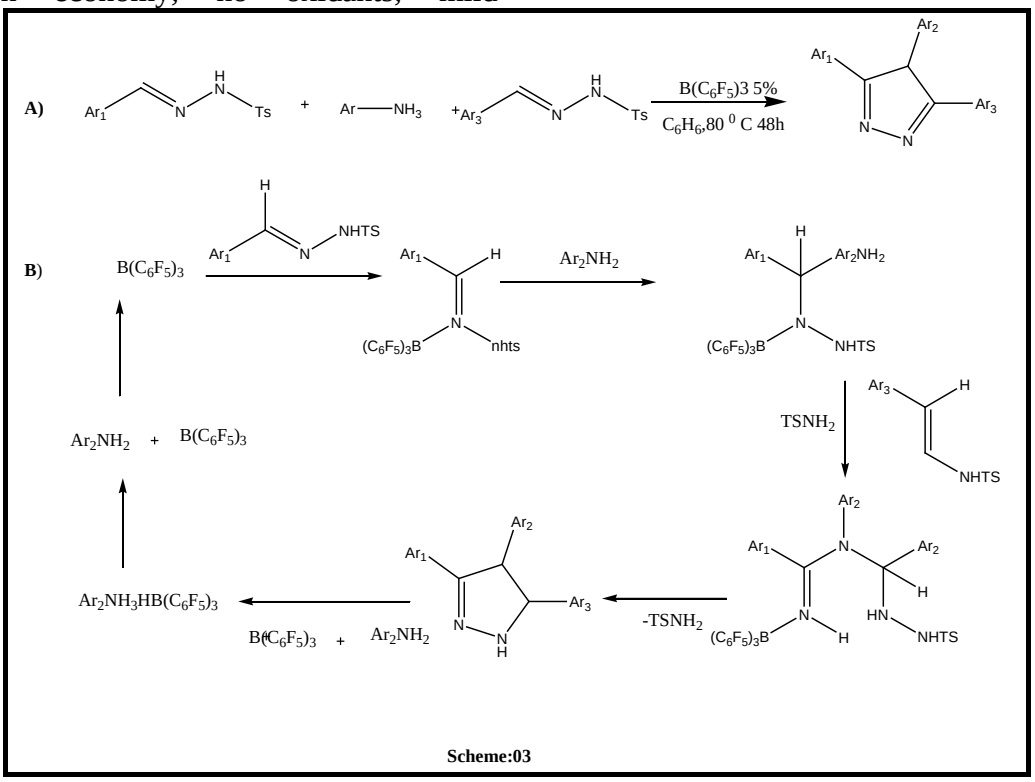
Hydrazones as nitrogen source

Hydrazones were popular precursors to nitrogen heterocycles in most methods of producing fused 1,2,4-triazoles. In 2019, Guru et al. A metal-free catalytic method for dehydrogenation cyclization based on B(C6F5)3 (Guru et al., 2019) is described. B(C6F5)3 followed modification, intramolecular cyclization, and dehydrogenation steps in the appropriate order to prepare 3,4,5-T-substituted-1,2,4-triazole with 85% yield, with the hydrazine portion being nucleophilic. Activated the attack. [33].This reaction pathway was characterized by green economy, no oxidants, mild conditions, and selectivity, which provided a potential platform for catalytic chemical conversion without the use of transition metals (Scheme 03a). (Scheme 03B) A predicted mechanism was described in [34].

Because of the suggested mechanism of the reduced dehydrogenative cyclization of B(C6F5)3-catalyzed receptors of N-tosyl-hydrazone with aniline, investigators set out to research sophisticated reaction mechanisms and gain a deeper understanding of the driving forces for the production of DFT calculations were done for. of the 1,2,4-triazoles.



Scheme:03

Pharmacological Activities

1-substituted-1, 2, 4-triazole

Cristali et al [35] reported the synthesis of a series of erythro-1-(2-hydroxy-3-nonyl)azole derivatives (1), which were evaluated for adenosine deaminase (ADA) inhibitory activity, to Simplification can be introduced. ADA inhibitors. Compound (1) was the most potent ADA inhibitor in the series with Ki=0.3μM

Pouts et al [36] prepared a series of 4-acyl/aryl-substituted-1-[benzofuran-2-yl-phenylmethyl]-1triazoles(2) and their activity against CYP26A1 (IC504.5 and 7 μM), respectively. Inhibitory activity was evaluated. Using MCF-7 cell-based assay

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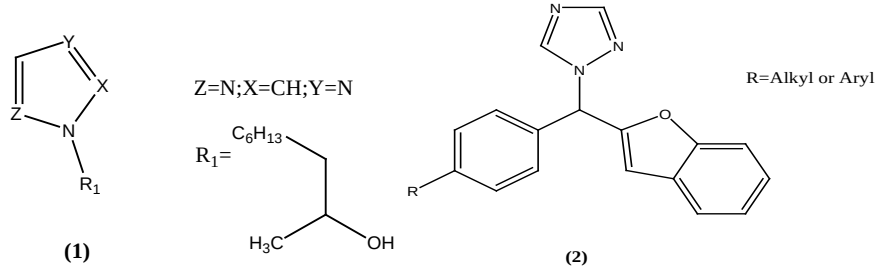
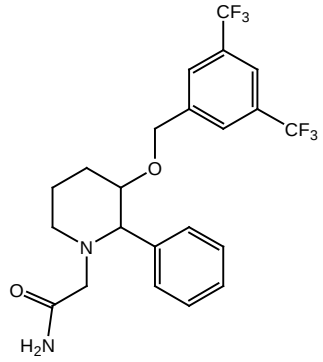


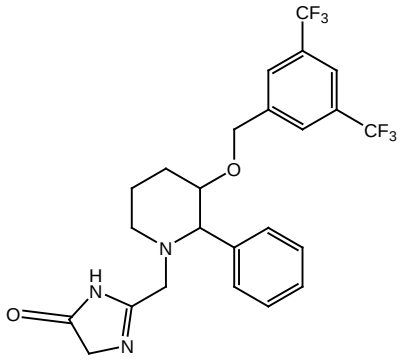
(1) **(2)**

3-Substituted-1, 2, 4-Triazole

Ladduwahetti et al [37] reported the preparation of a series of N-heteroaryl piperidine ether-based human NK1 antagonists. Two compounds (3-[{(2S,3S)-3-(((3,5-bis(trifluoromethyl)phenyl)methyl)oxy)-2-phenylpiperidino}methyl]-1,2,4-triazole (4) In particular, are orally bioavailable and have demonstrated significant improvements in potency both in vitro and in vivo compared to lead carboxyamidomethyl)-piperidine ether (3).



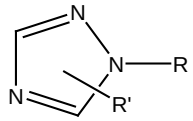
(3)



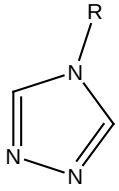
(4)

4-Substituted-1, 2, 4-Triazole

A series of 1- and 4- substituted 1,2,4-triazoles have been studied by Ainsworth et al [38] for convulsant and anticonvulsant activity by both the maximal electroshock seizure and subcutaneous pentylinetetrazole seizure tests in ratsof the p-substituted phenyl compounds (05a-d), 1-pichlorophenyl-1,2,4-triazole is the most active against electroshock seizures, but so ispentylenetetrazole against o-tolyl (06a) and o-chlorophenyl (06b). There is weak activity. anticonvulsant and o-Methoxyphenyl (06C) was an anticonvulsant even at high dose levels. The triazole analog (07) is the most potent and selective, orally bioavailable.[39-42]

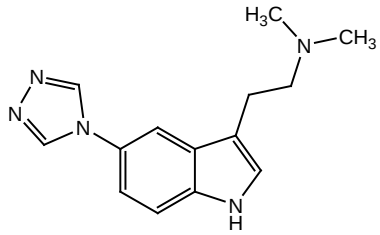


R
a. p-$NO_2C_6H_4$
b.p-$NH_2C_6H_4$
c. p-$CH_2CONHC_6H_4$
d-P-ClC_6H_4

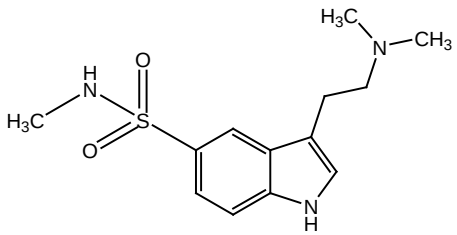


R
a.o-$CH_2C_6H_4$
b.m-$CH_3C_6H_4$
c.o$^-$ ClC_6H_4

(05) **(06)**



(07)



(08)

CONCLUSION

Triazoles have expressed biological and medicinal importance, and hold a unique place in organic chemistry and our lives. With a vast literature continuously accumulating over the years, the chemistry of triazoles remains a promising field in the coming years. The multifunctional synthetic applicability and biological activity of these heterocycles will facilitate medicinal chemists to plan, design, and implement new approaches for novel drug discovery.

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CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest in the content of this article.

References:

1. Miyauchi H., Kozuki K., Tanio T., Ohashi N. Bioorg. Med. Chem. Lett. 1995; 5(14):1479–1482.
2. Nair H.K., Peterson A.C., Yazdi P.T. Bioorg. Med. Chem. Lett.1997; 7(18):2379–2382.
3. Wood P.M., Woo L.W.L., Labrosse J., Trusselle M.N., Abbate S. J. Med Chem.2008; 51:4226–4238.
4. Mavrova A.T., Wesselinova D., Tsenov Y.A., Pavletta D. Eur. J. Med. Chem.2009;44:63–69.
5 Klimesova V., Zahajska L., Waisser K., Kaustova J.,Mollmann U. IL.Farmaco.2004; 59:279-288.
6. Pickering M.V., Witkowski J.T., Robins R.K. J. Med. Chem.1976; 19(6):841-842.
7. Xia Y., Fan Z., Peng L. Bioorg. Med.Chem.2006; 16:2693-2698.
8. Zhang Q., Peng Y., Xin I.W., Keenan S.M., Arora S., Welsh W. J. J. Med. Chem.2007; 50:749-754.
9. Kane J.M., Staeger M.A., Dalton C.R., Miller F.P., Dudley M. W., Chmielewski P.A., Miller J.A. J. Med. Chem.1994; 37:125-132.
10. Sternfeld F.et al. Bioorg.Med. Chem. Lett.1996; 6(15):1825–1830.
11. Lipinski C.A.. J. Med. Chem.1983; 26(1):1–6.
12. Zhu Y., Olson S.H., Vosatka A.H., Wright S., BalkovecJ.M..Bioorg. Med. Chem. Lett. 2008; 18:3405-3411.
13. KucukguzelI., Rollas S., Kiraz M. Bioorg. Med. Chem. Lett.2001; 11:1703–1707.
14. Rosa M.D., Kim H.W., Zhang W., Lang S.ABioorg. Med. Chem. Lett.2006; 16:4444-4449.
15. Chaia, B.; Qian, X.; Cao, S.; Liu, H.; Song, G. Arkivoc. 2003, (ii),141-145.
16. Naito, Y.; Akahoshi, F.; Takeda, S.; Okada, T.; Kajii, M.; Nishimura,H.; Sugiura, M.; Fukaya, C.; Kagitani, Y. J. Med. Chem., 1996, 39(15), 3019-3029.
17. Kucukguzel, I.; Kucukquzel, S.G.; Rollas, S.; Otuk-Sanis, G.; Ozdemir, O.; Bayrak, I.; Altug, T.; Stables, J.P. Farmaco. 2004, 59(11), 893-901.
18 Oruc, E.E.; Rollas, S.; Kabasakal, L.; Uysal, M.K..Metabol. Drug Interact., 1999, 15(2-3), 127-140.
19. Maddila, S.; Gorle, S.; Singh, M.; Lavanya, P.; Jonnalagadda, S.B. Lett. Drug Design. Dis. (In Press – 2013).
20. Maddila, S.; Pagadala, R.; Jonnalagadda, S.B. J. Heterocycl. Chem.2013 (MS ID: JHET-13-0053.R1-In Press).
21. Oh, K.; Yamada, K.; Asami, T.; Yoshizawa, Y. Bioorg. Med. Chem. Lett., 2012, 22(4), 1625-1628.
22. Santen, J.R. Inhibition of aromatase: insights from recent studies.Steroids. 2003, 68, 559-567.
23. Clemons, M.; Coleman, R.E.; Verma, S. Cancer Treatment Rev., 2004, 30(4), 325 332.
24. Delea, E.; El-Ouagari, K.; Karnon, J.;Sofrygin, O. Canadian perspective. Breast Cancer Res Treatment. 2008, 108, 375-387.
25. Christova, K.; Shilkaitis, A.; Green, A.; Mehta, R.G.; Grubbs, C.; Kelloff, G.; Lubet, R. Breast Cancer Res Treatment. 2000, 60, 117-128.
26. Roman, G.; Rahman, M.N.; Vukomanovic, D.; Jia, Z.; Nakatsu, K.; Szarek, W.A. Chem. Biol. Drug. Des., 2010, 75(1), 68-90.
27. Castanedo, G. M., Seng, P. S., Blaquiere, N., Trapp, S., and Staben, S. T. 2011. J. Org. Chem. 76, 1177–1179. doi:10.1021/jo1023393
28. Huang, H., Guo, W., Wu, W., Li, C. J., and Jiang, H. 2015. Org. Lett. 17, 2894–2897. doi:10.1021/acs.orglett.5b00995
29. Xia, J., Huang, X., and Cai, M. 2019. 51, 2014–2022. doi:10.1055/s-0037-1611712
30. Guirado, A., López-Caracena, L., LóPEZ-SáNCHEZ, J. I., Sandoval, J., Vera, M.,Bautista, D., et al. 2016. 72, 8055–8060. doi:10.1016/j.tet.2016.10.045
31. Mangarao, N.,MahaboobBasha, G., Ramu, T., Srinuvasarao, R., Prasanthi, S., and Siddaiah, V. 2014..Tetrahedron

Lett. 55, 177–179. doi:10.1016/j.tetlet.2013.10.147

32. Azzouni, S., Abdelli, A., Gaucher, A., Arfaoui, Y., Efrit, M. L., and Prim, D. 2018 Tetrahedron 74, 6972–6978. doi:10.1016/j.tet.2018.10.050
33. Guru, M.M., De, S., Dutta, S., Koley, D., and Maji, B. 2019. Chem. Sci. 10, 7964–7974. doi:10.1039/c9sc02492a
34. Cai, Z. J., Lu, X. M., Zi, Y., Yang, C., Shen, L. J., Li, J., et al. 2014Org. Lett. 16, 5108–5111. doi:10.1021/ol502431b
35. Cristalli G., Eleuteri A., Volpini R., Vittori S., Camaioni E., Lupidit G. J. Med.Chem.1994; 37:201-206.
36. Pautus S., Jayne M., Coogan M.P., Simons C. Bioorg.Med. Chem.2006; 14: 3643-3653.
37. Ladduwahetty T.et al, J. Med. Chem.1996; 39:2907-2914.
38. Ainsworth C., Nelson R., Livezey E.M., Morrison D.E.,Gibson W.R. 1962; 5:383-389.
39. Dai J, Tian S, Yang X and Liu Z 2022, A review. Front. Chem. 10:891484.doi: 10.3389/fchem.2022.891484

40 ParminderKaur&AnshulChawla 2017. Int. Res. J. Pharm. 2017, 8 (7)DOI: 10.7897/2230-8407.087112

41. Subhasis Banerjee, etal.Journal of Advanced Pharmacy Education & Research Jul-Sept 2013 Vol 3 Issue 3 102
42. Maddila et al.Letters in Organic Chemistry, 2013, Vol. 10, No. 10693-714