A REVIEW ON SYNTHESIS AND ANTI-MICROBIAL ACTIVITY OF BIPHENYL DERIVATIVES

Shivali[1], Priyankul Palia[1], Amit Chaudhary[1], Pooja Devi[1]

[1]Department of Pharmaceutical Chemistry, School of Pharmacy, Abhilashi University, Mandi, HP, India, Pin-175028

Abstract

Biphenyls are the polynuclear aromatic hydrocarbons with a molecular formula ($C_{12}H_{10}$) having more than one aromatic nucleus. The two nuclei are attached to each other at one point. Biphenyls are also named as Diphenyl or 1, 1' Biphenyl or limonene. It is a solid compound that forms colourless to yellowish crystals. Biphenyl is insoluble in water but it is soluble in organic solvents. Biphenyl derivatives substituted with an aromatic or heteroaromatic radical have therapeutic use in pharmaceutical compositions intended for use in human or veterinary medicine or alternatively in cosmetic compositions. Literature findings have also been shown its various therapeutic uses as anti-inflammatory, analgesic, antipyretic, antimicrobial, anti-protozoal, antiviral and antifungal. The compounds have also pronounced activity in the fields of cell differentiation and proliferation. It has found more applications in topical and dermatological disorders. In view of the above findings biphenyl has been selected as pharmacophore and various biphenyl derivatives have been synthesized. The objective of present work involves synthesis of new derivatives having biphenyl as basic skeleton, since this ring system is present in some of the existing antibacterial and antifungals and the structural confirmation of the synthesized compounds by spectroscopic IR and NMR analysis and to carry out biological activities of newly synthesized compounds.

Keywords- Biphenyls, anti-inflammatory, anti-microbial, biphenyl derivatives, topical, synthesis.

1. Introduction

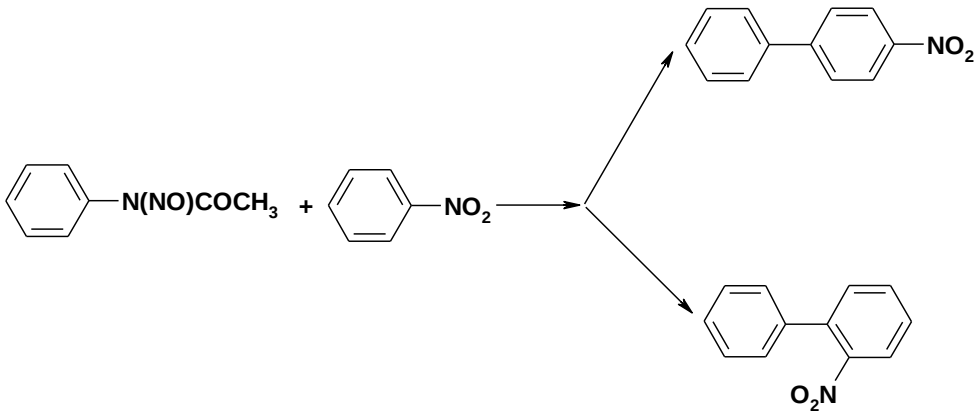
Biphenyls are the polynuclear aromatic hydrocarbons with a molecular formula ($C_{12}H_{10}$) having more than one aromatic hydrocarbons. The two nuclei are attached to each other at one point. Biphenyls are also named as Diphenyl or 1, 1' Biphenyl or limonene. It is a solid compound that forms colorless to yellowish crystals. Biphenyl is insoluble in water but it is soluble in organic solvents. Literature findings have also been shown its various therapeutic uses as anti-inflammatory[1], analgesic[2], anti-pyretic[3], anti-microbial[4], anti-protozal[5], anti-viral[6], anti-fungal[7].

Biphenyl derivatives substituted with an aromatic or heteroaromatic radical have therapeutic use in pharmaceutical compositions intended for use in human or veterinary medicine[8], or alternatively in cosmetic compositions. The compounds according to the invention have pronounced activity in the fields of cell differentiation and proliferation and find applications more particularly in the topical and systemic treatment of dermatological complaints associated with a keratinization disorder, dermatological (or other) complaints with an inflammatory and/or immunoallergic component, and dermal or epidermal proliferations, whether they are benign or malignant. These compounds can also be used in the treatment of connective tissue degenerative diseases, for controlling ageing of the skin, whether this is light-induced or chronological ageing, and for treating cicatrization disorders. They moreover find an application in the ophthalmological field, in particular in the treatment of corneopathy. The compounds can also be used in cosmetic compositions for body and hair hygiene. Honokiol (HNK), a naturally occurring biphenyl, possesses potent antineoplastic and antiangiogenic properties. HNK exhibited potent anti-proliferative activity against breast cancer cell lines and enhanced the activity of other drugs used for the treatment of breast cancer. Honokiol (HNK) is a naturally occurring biphenyl which can be extracted from either the root, stem bark or seed cone of several Magnolia species. HNK has long been known to have antithrombotic, antibacterial and anxiolytic effects.[9]

2. Chemistry of Biphenyls

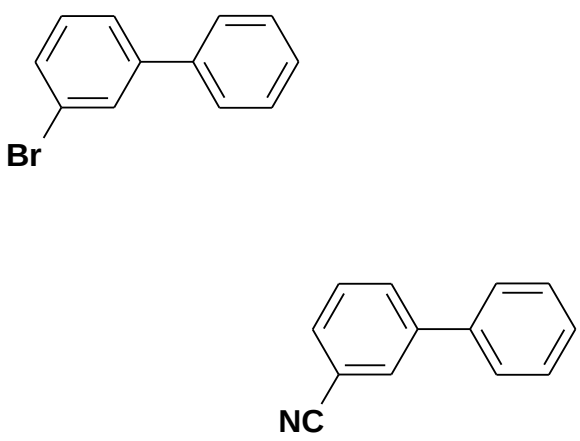
1. Synthesis of monosubstituted Biphenyls:

Substitution usually takes place para and ortho to the substitutent in the benzene ring, irrespecrive of the nature of the groups. Even with nitrobenzene, para and ortho derivatives are formed[10]. Thus, N-nitroso acetanilide and nitrobenzene give 2- and 4-nitrobiphenyl. Similarly ,in few reactions that have been carried out with benzaldehyde and benzonitrile , only the para isomer has been isolated from the reaction mixtures with ethyl benzoate all three isomers were obtained.



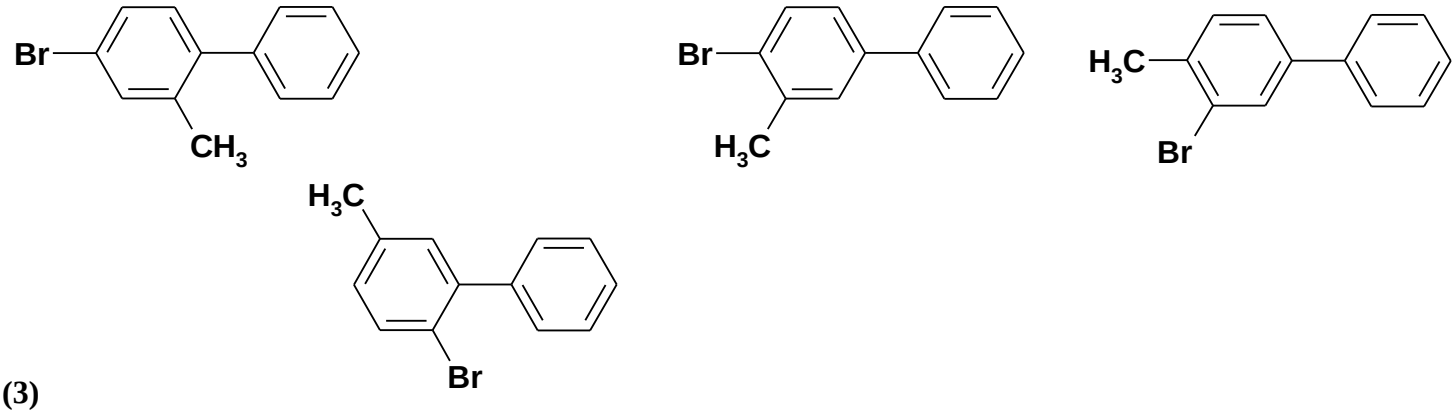
(1)

Large variety of biphenyl derivatives can be prepared in which only one of rings is substituted. In this manner monosubstituted biphenyls, $RCHC_6H_5$, have been prepared in which R=Br, Cl, CH_3, OCH_3, NO_2, CN etc. The meta derivatives such as 3-bromobiphenyl, 3-nitrobiphenyl and 3-cyanobiphenyl are of particular interest because they cannot be prepared readily from biphenyl.



(2)

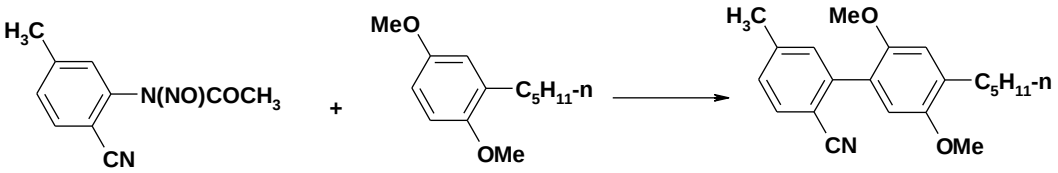
The following compounds have been prepared from the corresponding bromo-toludines and benzene:



(3)

2. Alkoxy derivatives of Biphenyl:

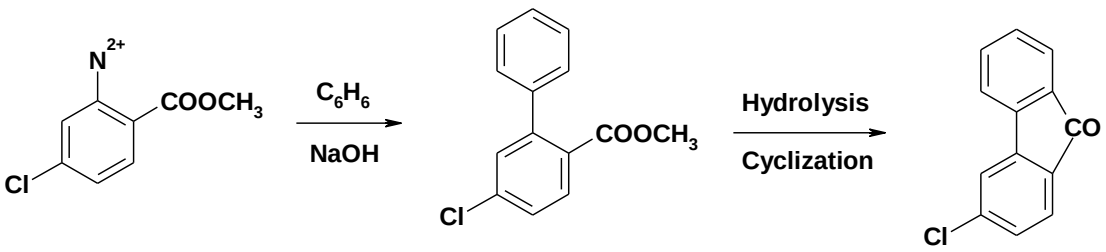
Alkoxy derivatives of biphenyls can be obtained either from alkoxy-anilines or by coupling with alkoxybenzenes. From diazotized p-bromoaniline and anisole a 20% yield of 4-bromo-2'-methoxybiphenyl and a 7% yield of 4-bromo-4'-methoxybiphenyl are obtained. Ghosh, Pascall and Todd prepared the highly substituted biphenyl compound,2-cyano-5-methyl-2',5'-dimethoxy-4'-n-amylbiphenyl,in 27% yield from the nitrosoacetyl derivative of 2-cyano-5-methylaniline and 2,5-dimethoxy-n-amylbenzene.



(4)

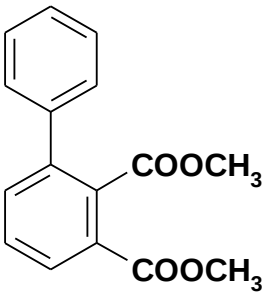
3. Synthesis of fluorenones:

Fluorenones can be prepared from the products obtained from esters of anthranilic acid and substituted anthranilic acids.From diazotized methyl anthranilate and benzene,2-carbomethoxybiphenyl is obtained in 245 yield. Hydrolysis affords 2-biphenylcarboxylic acid, which can be cyclized to fluorenone. By this procedure,a number of 2- and 3-substituted fluorenones have been prepared.Thus,3-chlorofluorenone was prepared from methyl 4-chloroanthranilate and benzene through the following steps:



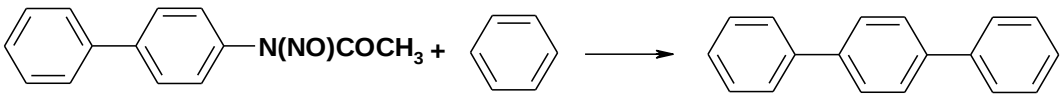
(5)

From diazotized methyl 3-aminophthlate and benzene, methyl 3-phenylphthalate is obtained in 35% yield.



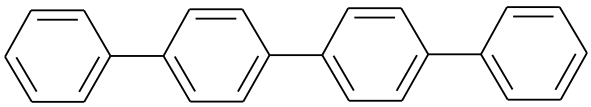
(6)

From the nitrosoacetyl derivative of p-aminobiphenyl, p-Terphenyl can be prepared in yield(50-60%).



(7)

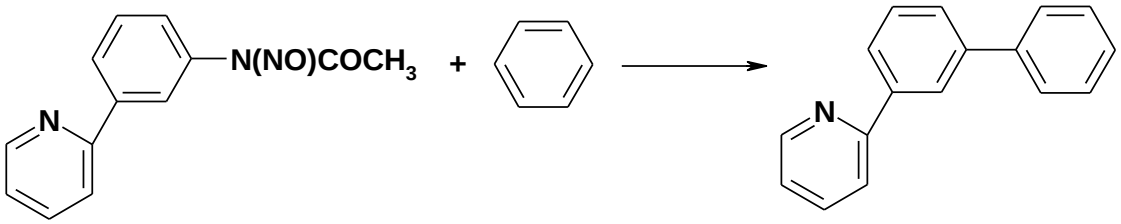
m-Terphenyl can be prepared by analogous reactions from 3-aminobiphenyl.Derivatives of m-terphenyl and p-terphenyl can be prepared from the substituted aminobiphenyls. By coupling the bis-nitrosoacetyl derivatives of benzidine with benzene, quaterphenyl is obtained in 17% yield.



(8)

4. Pyridine derivatives of biphenyl:

Pyridine derivatives can be prepared from amines containing the pyridyl group. Thus, the nitrosoacetyl derivative of m-α-pyridyl-aniline can be couples with benzene to yield 3-α-pyridylbiphenyl.

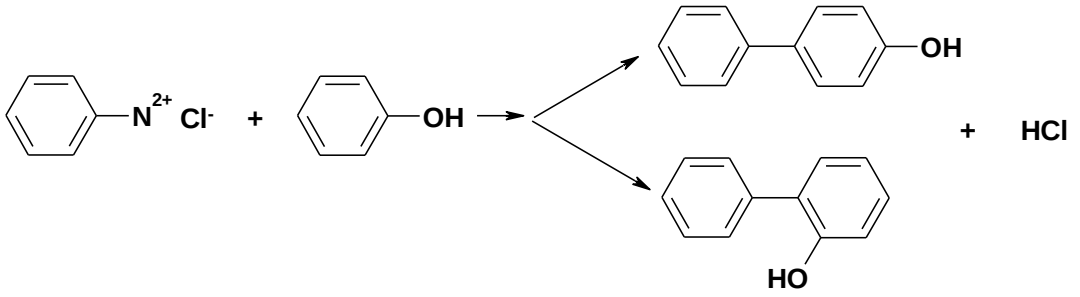


(9)

Similarly, the β- and γ-pyridyl derivatives of biphenyl can be prepared.

5. Hydroxy derivatives of biphenyl:

Hydroxy derivatives of biphenyl can be prepared from diazonium salts such as the chloride or sulphate and phenols if no alkali is added. From a solution of of diazotized aniline in a large excess of phenol, a good yield of a mixture of 2- and 4-hydroxybiphenyl is obtained in addition to diphenyl ether.

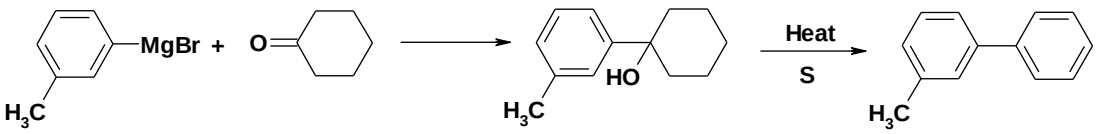


(10)

From diazotized aniline and p-nitrosophenol,2-hydroxy-5-nitrosobiphenyl is obtained in 8% yield.With 2-methyl-4-nitrosophenol,2-hydroxy-3-methyl-5-nitrosobiphenyl is obtained[11].

6. Grignard reaction:

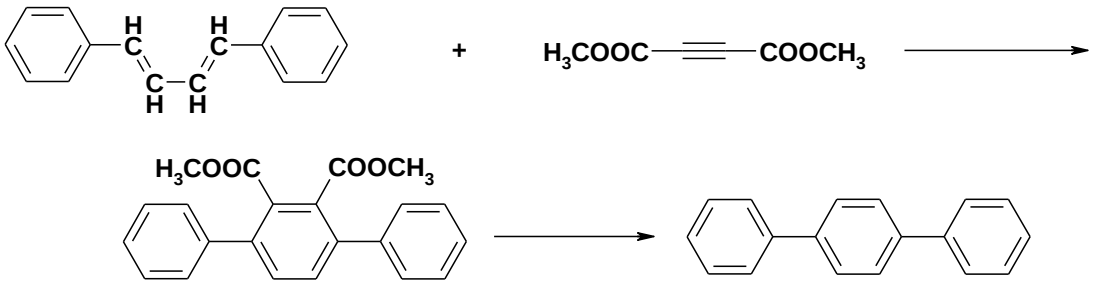
By addition of an arylmagnesium halide to a cyclic ketone,a carbinol is formed which can be dehydrated and dehydrogenated to a biaryl compound.m-tolyl-magnesium bromide and cyclohexinol yield 1-m-tolylcyclohexanol,which on dehydration and dehydrogenation gives 3-methylbiphenyl[12].



(11)

7. Diels-Alder Reaction:

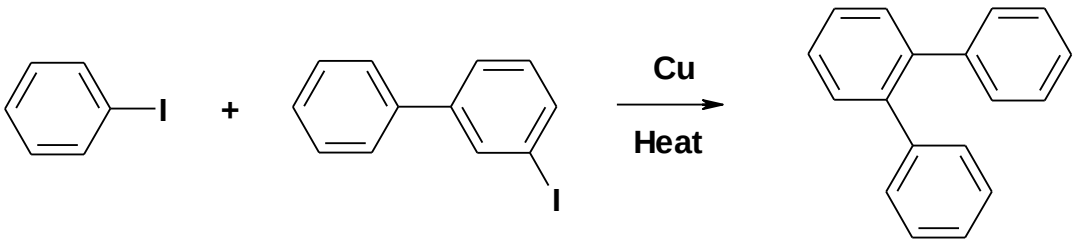
By means of Diels-Alder reaction a considerable number of hydrobiphenyls have been prepared. Only a few of the adducts have been converted to the completely aromatic compounds. O-Terphenyl has been prepared from the adduct of maleic anhydride and 3, 4-diphenylcyclopentadienone and p-terphenyl has been obtained in practical quantitative yield from the adduct of the methyl ester of acetylenedicarboxylic acid and 1, 4-diphenylbutadiene[13, 14].



(12)

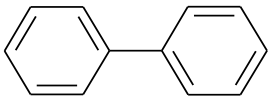
8. Ullmann Reaction:

Although the ullmann reaction is considered usually in connection with the preparation of symmetrical biaryls, it has been employed also to prepare unsymmetrical biaryls.Thus,o-terphenyl has been synthesized by treating a mixture of iodobenzene and 2-iodobiphenyl with copper,biphenyl and 2,2'-diphenylbiphenyl were by-products of the reaction[15-19].



(13)

3. Drug Profile



Biphenyl:	
Molecular Formula:	$C_{12}H_{10}$
Description:	Colourless, shiny plates
Molecular Mass:	154.21 g/mol
Melting Point:	68 - 70 °C
Properties:	Insoluble in water,
	Soluble in organic solvent

4. Pharmacological Activity

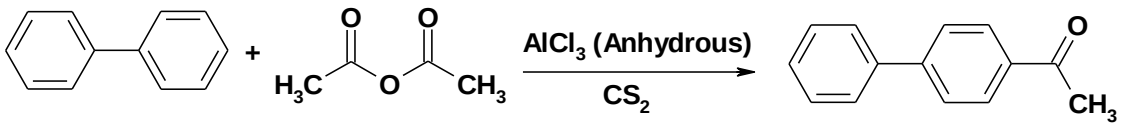
Biphenyl has been selected in our scheme as a pharmacophore and various biphenyl derivatives have been synthesized. Literature survey shows that biphenyl has found to have anti- inflammatory activity. Biphenyl moiety also possesses antimicrobial, anti-inflammatory, antihyperglycemic[20, 21] antihypertensive[22], and anti-proliferative activity.

5. Synthesis of Biphenyl Derivatives:

The general scheme of synthesis is outlined as under:

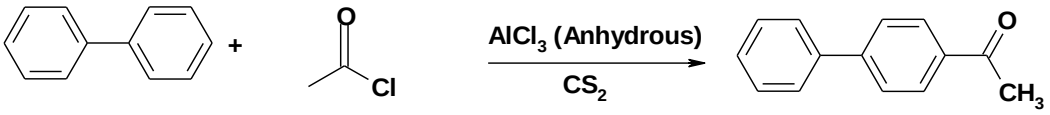
This scheme involves Friedel Crafts acylation of biphenyl with acetic anhydride in the presence of aluminium chloride as lewis acid catalyst to give p-phenyl acetophenone(A). Bromination of p-phenyl acetophenone was carried out to give desired product 1-Biphenyl-4-yl-2-bromoethanone (B) This 1-Biphenyl-4-yl-2-bromoethanone was substituted with different aryl or heteroaryl amines(R) to give different analogues (C) in presence of pyridine.

STEP 1:

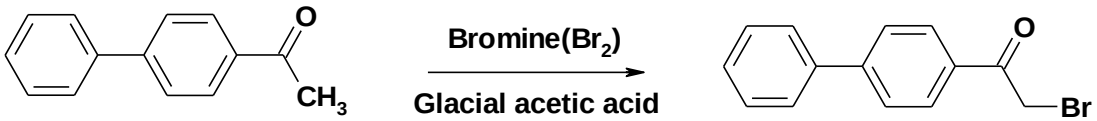


(A)

ALTERNATIVE ROUTE OF SYNTHESIS:

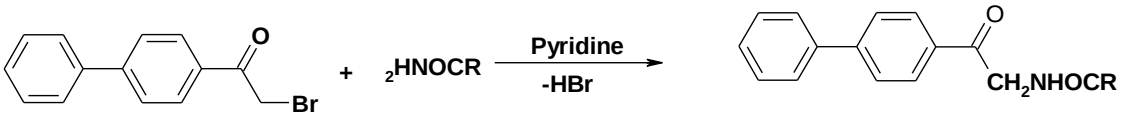


STEP 2:



(B)

STEP 3:



(C)

Where R is different aryl or heteroaryl amines ($ClC_6H_4NH_2$, $N_2OC_6H_4NH_2$)

6. Objective of Study

Biphenyls are well known as anti-bacterial and antifungal drugs. In the earlier years, they have also been shown its various therapeutic uses as anti-inflammatory, analgesic, antipyretic, antimicrobial and antiprotozoal. In view of the above literature findings, biphenyl has been selected as pharmacophore and different biphenyl derivatives have been synthesized as antimicrobial agent.

The objective of present work involves synthesis of new derivatives having biphenyl as basic skeleton and the structural confirmation of the synthesized compounds by spectroscopic IR and NMR analysis and to carry out biological activities of newly synthesized compounds.

7. CONCLUSION

We conclude in this review the biphenyls are very important basic moiety to synthesize various derivatives and other compounds. They have various pharmacological activities i.e. anti-inflammatory, analgesic, antipyretic, antimicrobial anti-protozoal, anti-viral, anti-fungal, anti-hyperglycemic and anti-proliferative activity. From the literature survey, we found that many antifungal and antimicrobial contains biphenyl as basic moiety. This synthesis selected for the development of anti-microbial and anti-fungal agents. The series of biphenyl derivatives may be potent alternative to some other anti-bacterial and anti-fungal agents.

REFERENCES

1. Han, M. S. Y., Akhter, Mymoona. and Hussain, A.,(2004), "Synthesis , biological evaluation and kinetic studies of glyceride prodrugs of biphenyl acetic acid," Indian journal of chemistry, Vol 45B, pp.1014-1019.
2. Husain, Asif., Ahmed, Ausaf., Alam, M. M., Ajmal, Mohd., Ahuja, Priyanka., (2009), "Fenbufen based 3-[5-(substituted aryl) – 1,3,4-oxadiazol-2-yl]-1-(biphenyl-4-yl)propan-1-ones as safer anti inflammatory and analgesic agents," European journal of medicinal chemistry, Vol 44,pp. 3798-3804.
3. Ito Y., Miyasaka T., Fukuda H.,Akahane K. and Kimura K., (1996), "Inhibition of GABA receptor chloride channel by quinolones and norfloxacin-biphenylacetic acid hybrid compounds," Neuropharmacology, Vol 35,pp.1263-1269.
4. Marino, Artico., Antonello, Mai., Gianluca, Sbardella., Silvio, Massa., Giorgio, Lampis., and Raffaello, Pompei., (1998), "N-[4-(1,1'-biphenyl)methyl]-4-(4-thiomorpholinmethyl) benzamines as non-oxazolidinone analogues of antimycobacterial,." Bio-organic and medicinal chemistry, Vol 8**,** pp.1493-1498.
5. Mohamed, A. Ismail., Adalgisa, Batista. Parra., Yi, Miao., W, David. Wilson., Tanza, Wenzler., Reto, Brun., and David, W. Boykin., (2005), "Dicationic near-linear biphenyl benzimidazole derivatives as DNA-targeted antiprotozoal agents," Bio-organic and medicinal chemistry, Vol 13**.** pp. 6718-6726.
6. Pandey, V.K., Singh, V.K., Tandon, M., Joshi, M.N., and Bajpai, S.K., (2003), "Synthesis and antiviral activity of furanobenzopyrones," Indian journal of chemistry, Vol 43B**,** pp.1770-1773.
7. Setzu , Maria. G., Stefancich G., Colla, P. La., and Castellano S. (2002) " Synthesis and antifungal properties of *N*-[(1,1′-biphenyl)-4-ylmethyl]-1*H*-imidazol-1-amine derivatives" II Farmaco, Vol 57(12), pp. 1015-1018.
8. Bernardon, (2006) **"**Biphenyl derivatives substituted with an aromatic or heteroaromatic radical, and pharmaceutical and cosmetic compositions containing them**."** U.S Patent 7148245.
9. Wolf I., Kelly O' J., Wakimoto N.1, Nguyen A.,(2007) "Honokiol, a natural biphenyl, inhibits in vitro and in vivo growth of breast cancer through induction of apoptosis and cell cycle arrest, International journal of oncology. Vol 30 ,pp. 1529-1537.
10. Werner, E. Bachmann, Org Chem by Fieser, "The preparation of unsymmetrical biaryls by diazo reactions and the nitrosoacetylamine reactions. pp 224-261.
11. Huntrress, H. Ernest., Seikel, K. Margret., (1939), " Flavorenones and diphenic acids: ring cleavage of 1,8- 1,6 and 3,6 – Di chlorofluorenones with potassium hydroxide in Diphenyl ether" Journal of American chemical society, Vol- 11, pp. 1066-1071.
12. Francis, H. Case.,(1936), " The preparation of 3,4- Dibromodiphenyl," Journal of American chemical society, Vol-58, No. 58, pp. 1249-1251.
13. Richard, T. Arnold., Collins, Clair., Zenk, W. M., (1940), "Low temperature Dehydrogenations," Journal of American chemical society, Vol-62, No. 4, pp.983-984.
14. Allen, C.F.H., Pingert, F.P., (1942), "The chemistry of O- Terphenyl (O- Diphenyl benzene) , The general reactivity , basal structure and re arrangements of the hydrocarbon," Journal of American chemical society, Vol- 64, No. 6, pp- 1365-1371.
15. Bachmann, W. E., Clarke, H. T., (1927), "The mechanism of Wurtz Fittig reaction," Journal of American chemical society, Vol- 49, No. 8, pp.2089-2098.
16. Adams, Roger., Teeter, H. M., (1940), "Stereochemistry of biphenyls. L. comparison of the interference of a methoxyl and a Hydroxyl group," Journal of American chemical society, Vol- 62, No. 8, pp. 2188-2190.
17. Gomberg, M., Pernert, C. J., (1926), " Methylbiphenyls," Journal of American chemical society, Vol-48, No. 5, pp. 1372-1384.
18. Gomberg, M., Bachmann, W.E., (1924), "The synthesis of biaryl compounds by means of the diazo reactions," Journal of American chemical society, Vol- 46, No. 10, pp. 2339-2343.
19. Marvel, C.S., Emanuel., Ginsberg, Mueller, Max, B.,(1939) " Effect of substitution on the dissociation of hexa aryl ethanes," Hexa- m- biphenylethane," Journal of American chemical society, Vol-61, No. 1, pp. 77-78.
20. Kulkarni, M. Vithal., Agarwal, Ritesh., Sachan, Narsingh., Thareja, Suresh.,(2009), " substituted biphenyl ethanones as antidiabetic agents: synthesis and in vivo screening ," International journal of pharma tech research, Vol 1 , No. 4, pp. 1625- 1631.
21. Zhang, Zun. Ting., Xu, Fei. Fei.,(2009), "One pot synthesis of 4,5- Biphenyl- 2- pyrimidinyl guanidine derivatives," Journal of comb chemistry, Vol 11, No 3, pp. 880-885.
22. Jat, Rakesh. Kumar., Jat, Jawahar.L., Pathak ,D.P.,(2006) , " Synthesis of Benzimidazoles derivatives as antihypertensive agents," E-Journal of Chemistry , Vol.3, No. 3, pp. 278-285.