Biological deeds of Biphenyl derivatives - A short Review

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***Abstract*: Biphenyl is an organic compound that forms colorless crystals. Biphenyl derivative synthesis have been widely carried out and have yielded wide range of compounds with wide range of activities such as Anti -microbial, anti - diabetic, anti - proliferative, Anti - oxidant, analgesic, anti -inflammatory [1-13] and so on, A number of derivatives are obtained which are of therapeutic significance. This review is summarized to know about synthesis of biphenyl and its derivatives as well as various biphenyl analogs that has potential to act against number of affliction and disorders.**

***Keywords*: Biphenyl derivative, Anti -microbial, Anti-fungal, Anti - inflammatory**

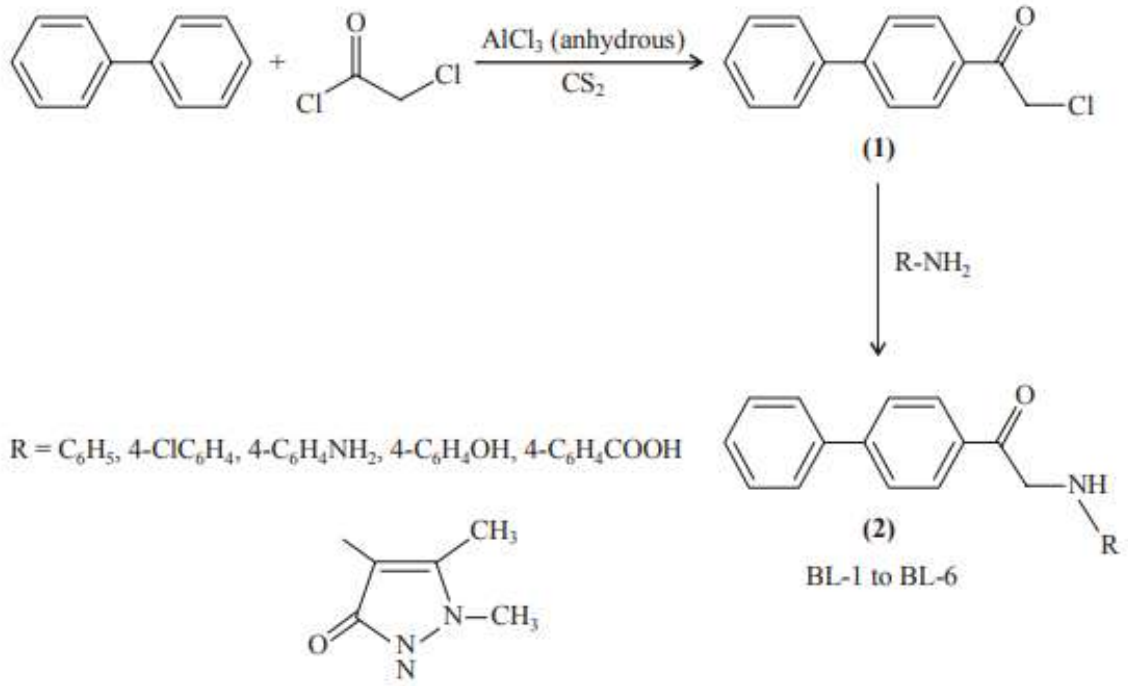
Introduction

Biphenyl is an aromatic hydrocarbon. It is notable as a starting material for the production of polychlorinated biphenyls, which were once widely used as dielectric fluids and heart transfer agents. Biphenyl is also an intermediate for the production of a host of other organic compounds such as emulsifiers, optical brighteners, crop protection products and plastics. The biphenyl molecule consists of two connected phenyl rings. Biphenyl prevents the growth of molds and fungus, and is therefore used as preservative, particularly in the preservation of citrus fruits during transportation. It's no longer approved as a food additive in the European Union. Its mildly toxic but can be degraded biologically by conversion into nontoxic compounds. Some bacteria are able to hydroxylate biphenyl and its polychlorinated biphenyl introduction of a carbonyl group in the biphenyl ring makes it electron withdrawing group. Biphenyl is a neutral molecule and fairly non-reactive due to lack of functional group. However, biphenyl participates in many of the reactions that are typical for benzene, for example, substitution reactions upon treatment with halogens in the presence of a Lewis acid. Also, it is required to convert biphenyls into the structural analogs containing the active groups in order for it to be able to use for synthetic intermediate for the production of a host of other organic compounds such as emulsifiers, optical brighteners, crop protection products, plastics and pharmaceuticals. etc. In recent years there has been a great deal of interest in exploiting multiple proximal functional groups in the design of novel structures capable of performing a variety of functions. Synthesis of molecules that are novel but still resemble known biologically active molecules by virtue of the presence of some critical structural features is an essential component of the search for new leads in drug design. Arulmani et al[14] have performed the synthesized compounds screened for anti - microbial studies carried out and the para nitro substituted compounds are found to be good inhibitor of Aspergillus Niger. Biphenyl derivative syntheses have been widely carried out. Biphenyl derivatives possess a wide range of biological activities like anti-microbial (anti -fungal and anti -bacterial), anti-inflammatory, anti -hypertensive, anti - viral, anti-cancer, and anti-diabetic activities were considered.

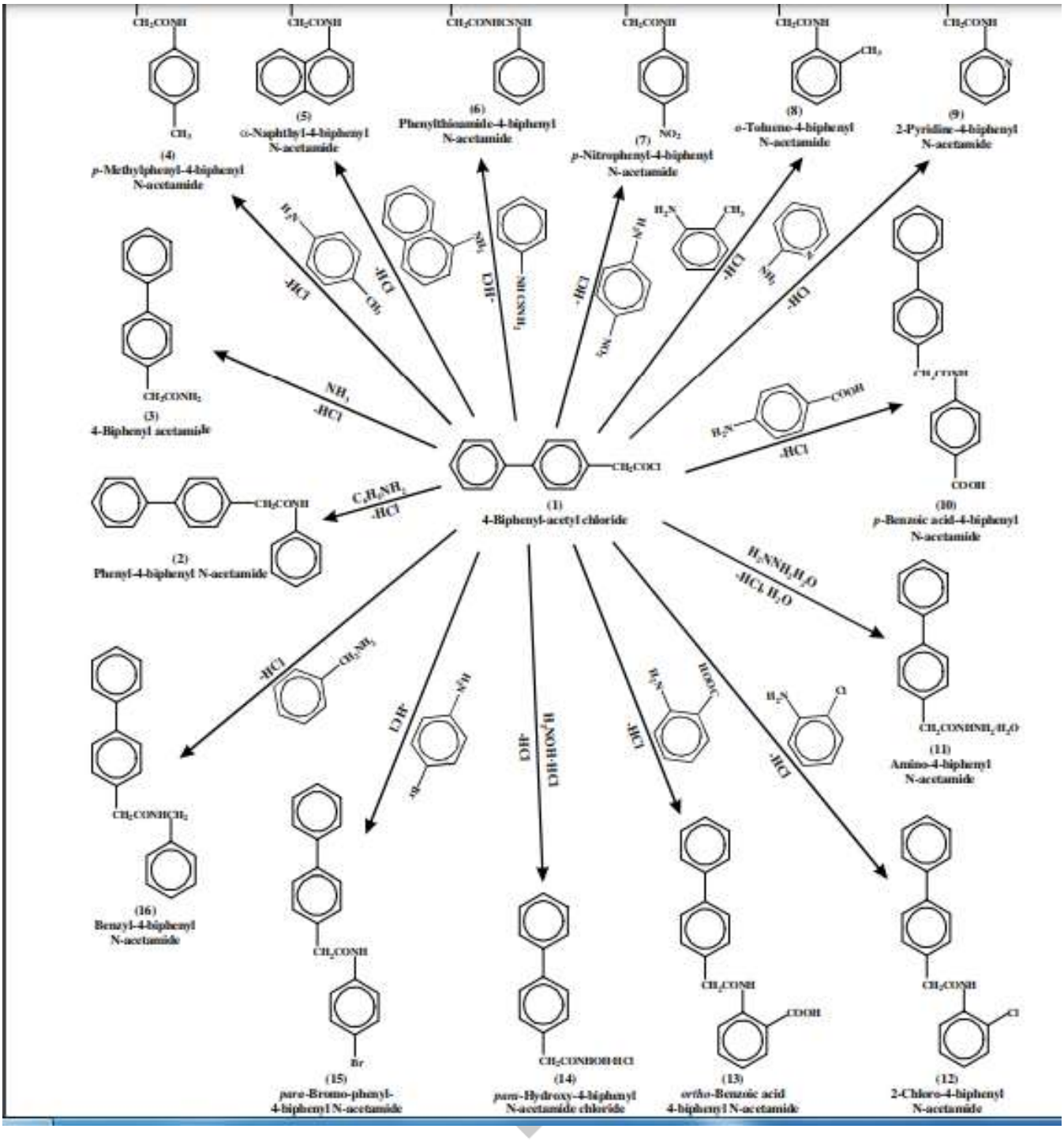
Biphenyl derivative as Anti -microbial activity

A new series of chalcone derivatives have been synthesized and characterized by C. G. Darshan Raj et al[15]. The compounds were screened for DPPH scavenging activity and the tested compounds exhibited very good activity. Based on DPPH scavenging activity these molecules were selected to study modulatory effect on gamma radiation induced oxidative stress markers in E. *coli* K12. The compound (2E)-1-(biphenyl-4-yl)-3-(4-methoxyphenyl) prop-2-en-1-one exhibited significant demolition effect in the levels of lipid peroxidation product [TBARS]. The compounds (2E)-1-(biphenyl-4-yl)-3-(2,5-dimethoxyphenyl)prop-2-en-1-one and (2E)-1-(biphenyl-4-yl)-3-(3,4-dimethoxyphenyl)prop-2-en-1-one showed good activity towards demolition effect of TBARS level compared to irradiated sample but no statistically significant result was found compared to control. All the tested compounds were effective in bringing anti -oxidant enzyme levels [SOD and CAT] to near basal level in comparison with non-irradiated and irradiated controls. The count of Colony Forming Units (CFU) of E coli in the compound treated irradiated samples also supported the radio protective effect of the chalcone derivatives. In anti -fungal and anti -bacterial property evaluation studies the compounds exhibited promising activities. Among them compounds,(2E)-1-(biphenyl-4-yl)-3-(4-fluorophenyl) prop-2-en-1-one and(2E)-1-(biphenyl-4-yl)-3-(2-chlorophenyl) prop-2-en-1-one exhibited good activity.

K.Jenny et al[16]synthesized some of the biphenyl compounds and screened them for the anti -bacterial activity. The derivatives were synthesized using different substituted amines to the chloro biphenyl derivative. All the compounds were characterized using IR and NMR data. The anti -bacterial activity were screened against gram positive organism like Bacillus subtilis & Staphylococcus epidermidis and gram-negative organism against E. Coli & Pseudomonas aeruginosa. All the compounds show a moderate to good activity against the selected strains.

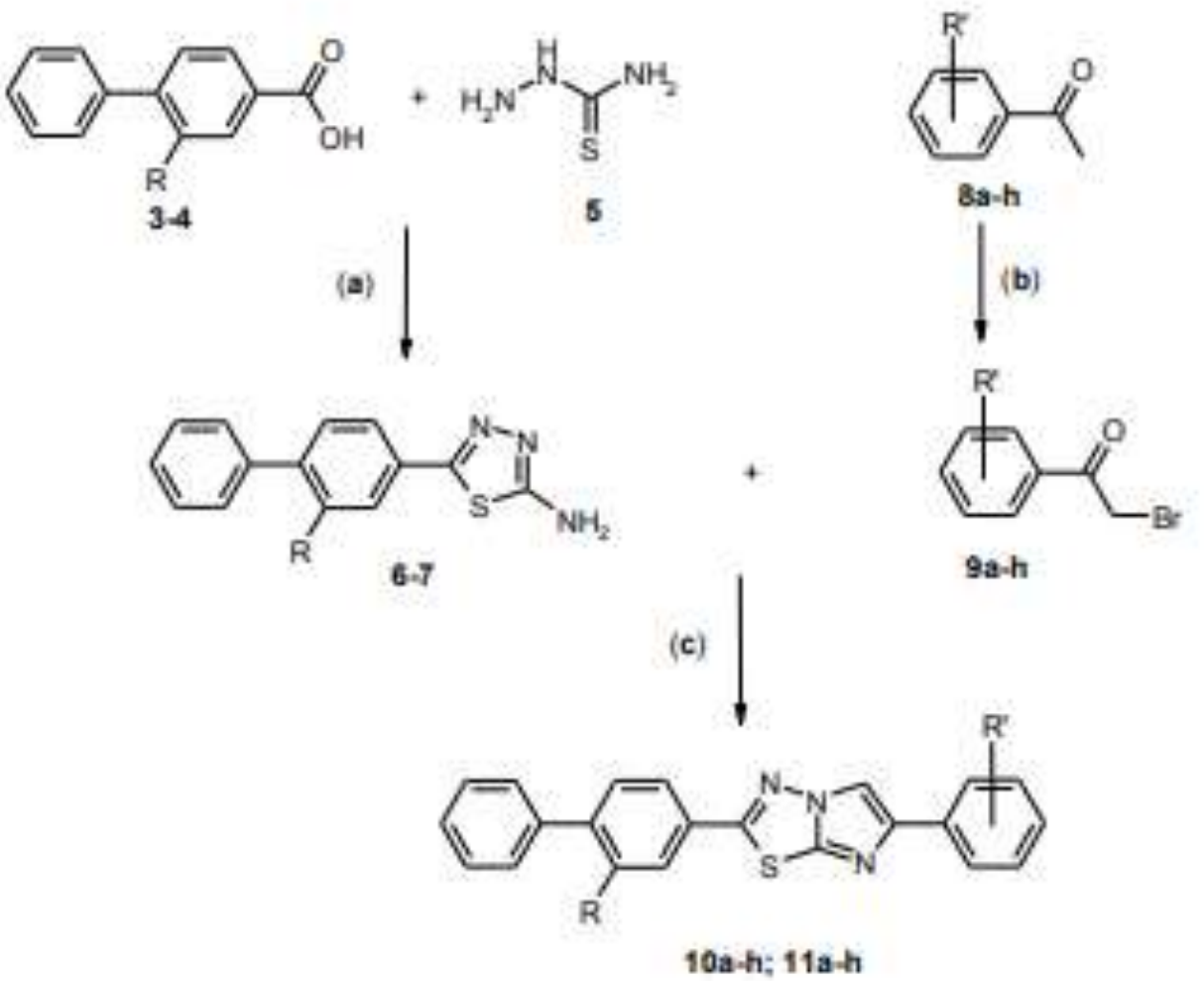


Anju Khullar[17] explained that a new series of substituted 4-biphenyl amides have been synthesized by condensation of 4-biphenyl acetic acid with different primary amines (aromatic and aliphatic). 4-Biphenyl acetic acid was first treated with thionyl chloride in dry benzene to prepare substituted 4-biphenyl acetyl chloride, which is then treated with different aliphatic or aromatic amines to synthesize various substituted 4-biphenyl acid-amide derivatives. The structure of newly synthesized compounds has been established by analytical and spectral methods. These synthesized compounds have shown anti -fungal properties against Fusarium udum and Curvularia lunata.



Seven biphenyl-4-carboxylic acid hydrazide-hydrazones have been synthesized by Aakash Deep et al[18] These hydrazone derivatives were characterized by CHN analysis, IR, and 1H NMR spectral data. All the compounds were evaluated for their in vitro anti - microbial activity against two Gram negative strains (Escherichia coli and Pseudomonas aeruginosa) and two Gram positive strains (Bacillus subtilis and Staphylococcus aureus) and fungal strain Candida albicans and Aspergillus niger All newly synthesized compounds exhibited promising results.

Rakesh Yadav[19] have reported the synthesis of some novel heterocyclic derivatives comprising imidazole and 1,3,4-thiadiazole containing moiety. Imidazothiadiazoles are of interest because of their diverse biological activities and clinical applications. Reactions of biphenyl carboxylic acid with thiosemicarbazide in the presence of phosphorous oxychloride resulted in biphenyl containing 2-amino-1,3,4-thiadiazole which is then further subjected to condensation with α-bromoarylketone



R = H (3, 6, 10a-h) or F (4, 7, 11a-h)

R' = **a**: H; **b**: 4'Cl; **c**: 4'F; **d**: 2',4'diCl; **e**: 4'NH_2; **f**: 2',4'diOH; **g**: 4'Br; **h**: 2'OH

Biphenyl derivative as anti - diabetic activity

Zenish J. Jain et al[20] have summarized that biphenyl can be easily synthesized as well as functionalized by the use of adequate catalysts such as palladium derivatives, suitable reagents and reactants such as haloarenes. Also, the substituted biphenyls can be synthesized by Suzuki cross coupling reactions. The substituted biphenyls in turn can be used as an intermediate in the synthesis of pharmacologically active molecules. Compounds containing biphenyl moiety possess a wide range of anti - diabetic activity. Thus, there is a wide scope for the synthetic scientists and chemists to synthesize more and more compounds with different substitutions using substituted biphenyl along with an adequate heterocycle as a basic moiety. The investigation on this ring can still be continued and a number of such therapeutic importance of the biphenyl moiety can be explored.

Lakshminarayanan B. et al[21]. Eleven has taken the newly synthesized compounds (E1-E11) to evaluate their in vitro anti -oxidant activity by DPPH and hydrogen peroxide assay method and six compounds which contain electron donating groups were selected for screening of in vivo anti -diabetic potential by high fat diet, streptozotocin induced diabetes in Albino Wistar rats. The compounds containing electron donating groups were found to be good anti -oxidants when compared to standard ascorbic acid. All the selected compounds were found to be effective for anti -diabetic activity. Amongst them compound E4 shows more prominent anti -diabetic activity when compared to standard metformin.

Anti -viral activity and anti - cancer activity

Ahmed I. Khodair et al[22] has carried out a detailed study on biphenyl system from poly functionalized pyridine tethered with benzotriazole moiety which was synthesized in very simple method. This system linked to glycoside formation with glucose and galactose epimers. The glycoside side chain was either S-glycosides or N- glycosides. S-Glycosides are more reactive than N-glycosides analogues. In case of anti -viral activity, the deacetylated sugars are more active which indicate to importance of lipophilicity. Finally, we recommend further *in vivo* cancer models for this compound so that it can be developed as chemotherapeutic anti -cancer agent.

Daniel Tarade et al[23] have reported the *cis*-stilbene, combretastatin A4 (CA4), is a potent microtubule targeting and vascular damaging agent. Despite promising results at the pre-clinical level and extensive clinical evaluation, CA4 has yet to be approved for therapeutic use. One impediment to the development of CA4 is an inherent conformational instability about the ethylene linker, which joins two aromatic rings. We have previously published preliminary data regarding structurally simplified biphenyl derivatives of CA4, lacking an ethylene linker, which retain anti -proliferative and pro-apoptotic activity, albeit at higher doses. Our current study provides a more comprehensive evaluation regarding the anti -proliferative and pro-apoptotic properties of biphenyl CA4 derivatives in both 2D and 3D cancerous and non-cancerous cell models. Computational analysis has revealed that cytotoxicity of CA4 and biphenyl analogues correlates with predicted tubulin affinity. Additional mechanistic evaluation of the biphenyl derivatives found that their anti -cancer activity is dependent on prolonged mitotic arrest, in a similar manner to CA4. Lastly, we have shown that cancer cells deficient in the extrinsic pathway of apoptosis experience delayed cell death following treatment with CA4 or analogues. Biphenyl derivatives of CA4 represent structurally simplified analogues of CA4, which retain a similar mechanism of action. The biphenyl analogues warrant *in vivo* examination to evaluate their potential as vascular damaging agents.

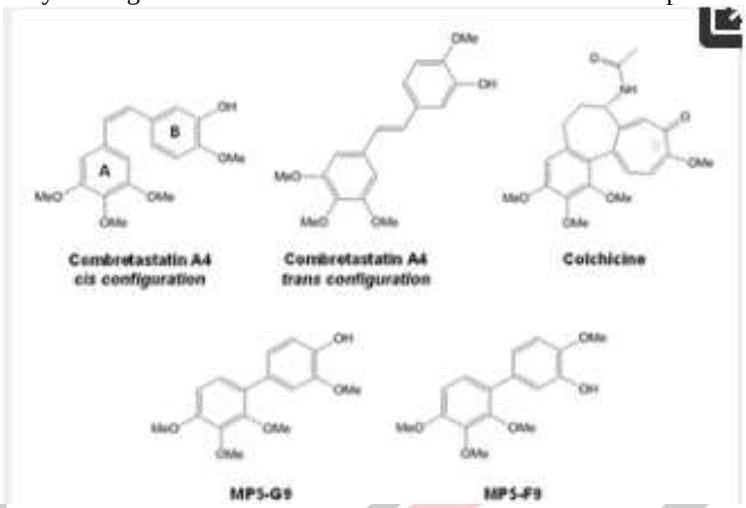


Fig 1. Structure of CA4 and related anti cancer coumpounds

Analgesics activity

Analgesics are agents which selectively relieve pain by acting in the CNS and peripheral pain mediators without changing consciousness. Analgesics may be narcotic or non-narcotic. The study of pain in animals raises ethical, philosophical, and technical problems.

HG Akkammaet al[24] have explained Nimesulide (Biphenyl Ether) derivatives were synthesized by four steps, Step-1- Ulmaan ether synthesis, Step-2- Reduction of NO2, Step-3- Condensation reaction, Step-4- Nitration and evaluated for their anti -inflammatory and analgesic activities. The compounds have been characterized on the basis of preliminary methods, spectral data and tested for anti - inflammatory activity and compared with standard drug as per the standard drug rat hind paw edema method by using Plethesimograph and analgesic activity by Eddies-hotplate method. Among the derivatives prepared, few showed the moderate activity and few showed decreased activity.

Anti - inflammatory activity

A. L. V. Kumar Reddy et al[25]have made detailed studyonthe intense research work in the field of medicinal chemistry that has enhanced the significance of Biphenyl moiety as pharmacologically important compound.The present article describes the synthesis of novel benzohydrazides and 2-phenylbenzohydrazides bearing Biphenyl moiety and vanillin hybrid. The synthesized compounds (31-40) were characterized by ^{1}H NMR, Mass and IR spectroscopic techniques and were evaluated for anti -inflammatory activity by carrageenan paw edema method. The results of the study revealed that compounds 39 and 40 (bearing 2-phenylacetohydrazides) showed maximum anti -inflammatory activity while the compounds 31, 32, 33, 34 and 38 bearing benzohydrazides displayed moderate anti -inflammatory activity.

Thongchai Taechowisan et al[26]has demonstrated in this that biphenyl compounds, isolated from endophytic Streptomyces sp. BO07, showed significantly suppression in the releases of TNF-", IL-1$, IL-6 and IL-10 and the production of NO and expression of COX-2 and iNOS enzyme in LPS-stimulated macrophages in a dose-dependent manner. These results suggest that biphenyl compounds can inhibit inflammatory response and may be a potential therapeutic candidate for the treatment of chronic inflammatory diseases.

Anti - hypertensive activity

Jie Liu et al[27] have performed a series of novel in which 1,2,4-triazole bearing 5-substituted biphenyl-2-sulfonamide derivatives were designed and synthesized to develop new angiotensin II subtype 2 (AT2) receptor agonists as novel anti -hypertensive candidates. It was found that 14f (IC50=0.4 nM) and 15e (IC50=5.0 nM) displayed potent AT2 receptor affinity and selectivity in binding assays. Biological evaluation in vivo suggested that 14f is obviously superior to that of reference drug losartan in RHRs, and meanwhile, 14f has no significant impact on heart rate. The interesting activities of these compounds may make them promising candidates as anti -hypertensive agents.

Mukesh C. Sharma et al[28] have explained two- and three-dimensional quantitative structure activity and relationship studies of 5-(biphenyl-4-ylmethyl) pyrazoles derivatives which were performed for their AT_1 selective angiotensin II receptor antagonists' activity using VlifeMDS 3.5™ software. The best 2D QSAR model for the prediction of AT_1 selective angiotensin II receptor antagonists' activity was obtained by applying stepwise variable selection with partial least square analysis giving $r^2 = 0.8962$ and $q^2 = 0.7831$, r^2_se = 0.3986, q^2_se = 0.2004, with external predictive ability of pred_$r^2 = 0.8293$, pred_r^2se = 0.5852. By using kNN-MFA with stepwise variable selection method approach, 3D QSAR models were generated to study the effect of steric, electrostatic, and hydrophobic descriptors on anti -hypertensive activity. The model with good external and internal predictivity for the training and test set has shown cross validation (q^2) and external validation (pred_r^2) values of 0.74 and 0.68, respectively. The SW-kNNMFA contour maps suggest some important structural features-like steric, electropositive, electronegative, hydrophobic substituent's requirements of anti -hypertensive activity. Thus, this validated model brings important structural insight to aid in the design of novel anti -hypertensive agents.

Anti - oxidant activity

S. Maddila, G. L et al[29]have described simple and efficient protocol for the synthesis of novel biphenyl-3,5-dihydro-2H-thiazolopyrimidines derivatives (8a-j) with good yields. All the synthesized compounds have been investigated for their anti -oxidant activity. With our newly synthesized compounds, it is evident that 8j and 8i have highest anti -oxidant activity. Accordingly, these novel class of biphenyl-3,5-dihydro-2H-thiazolopyrimidines derivatives reported from our laboratory emerge as a valuable lead series with great potential to be used as anti -oxidant activity agent, and as promising for further efficacy evaluation.

Excessive accumulation of free radicals results in cellular oxidative damage which has been reported to initiate the progression of several diseases such as cancer, Alzheimer's disease and Parkinson's disease. Anti -oxidants are free radical scavengers that play an important role in preventing oxidative cell damage and repairing the damage caused by free radicals. Biphenyls have been reported as a promising free radical scavenging scaffold. The objective of the present study was to evaluate the anti -oxidant activity of biphenyl-2,6- diethanone derivatives. A series of biphenyl derivatives were synthesized by the reported procedures. The anti -oxidant activity of these derivatives was evaluated using DPPH and lipid peroxidation assay. The in vitro anti -oxidant studies indicated that substituted biphenyl-2,6- diethanones, 1(a-i) exhibited significant free radical scavenging activity. Compounds 1e exhibited maximum anti -oxidant potential with an IC50 value of 54.96µg/ml. The present investigation indicated that derivatives containing hydroxyl, amine and methoxy groups on the biphenyl-2,6-diethanone scaffold exhibited significant anti -oxidant activity by Megha Rikhi et al.

Tan Nhut Doan et al[30] have described that a new series of chalcones (4a-c) and allylicchalcones (11a-b) have been prepared by the Claisen-Schmidt condensation. A novel series of pyrazolicchalcones (5a-c) have been synthesized by the reaction of respective chalcones (4a-c) and hydrazine hydrate. The structures of the compounds were confirmed by spectral data (infrared spectroscopy and ^{1}H nuclear magnetic resonance). All of the compounds (4/5a-c and 11a-b) have been tested for their anti -microbial activities (agar disc-diffusion method) and anti -oxidant activities (1,1-biphenyl-2-picrylhydrazyl free radical scavenging method). The test compounds failed to show anti -bacterial properties (4a-c, 5b, and 11a-b) or exhibited such properties poorly (5a and 5c). None of the test compounds displayed anti -fungal properties. Of the compounds tested, compounds 5a-c and 11a-b exhibited promising anti -oxidant activities.

Conclusion

This paper analyses all the experiments carried out by various researchers on biphenyl derivatives in the past decade through which we understand that the biphenyls derivatives can be used as an intermediate in the synthesis of pharmacologically active molecules. Also, compounds containing biphenyl moiety possess a wide range of activity such as, anti -microbial, diuretic, anti - diabetic, anti - oxidant, anti -viral and anti -cancer activity. More investigation on this ring, a number of such therapeutic importance of the biphenyl moiety can be explored.

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