BIO ACTIVE CARVEDILOL DERIVATIVES: A REVIEW

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ABSTRACT:

Carvedilol is a third generation, non-selective, vasodilating β-blocker(β1,β2) mostly used in heart failure patients for the treatment of AMI(acute myocardial infarction), chronic heart failure,stable angina pectoris,Hypertension and also has selective α-blocking activity. It shows its therapeutic effect on cardio myocytes of heart by improving its contractile function.This drug also have anti-apoptotic, anti-bacterial (mostly gram positive), antiproliferative,and anti-inflammatory and antioxidant activities as the additional features.Methacrylic acid is the best molecular imprinted polymer for Carvedilol in the ratio 1:4.Innovations found that carvedilol is used in the treatment of arthritic joints by acting against collagen type- II and aggrecan in a dose dependent manner. Beyond all the above benefits of carvedilol our reviewliterature views on different procedures for the synthesis of effective carvedilol and it also enlists the impurities formed during its preparation.

KEY WORDS:- Carvedilol, Methacrylic acid, Anti-bacterial.

INTRODUCTION:

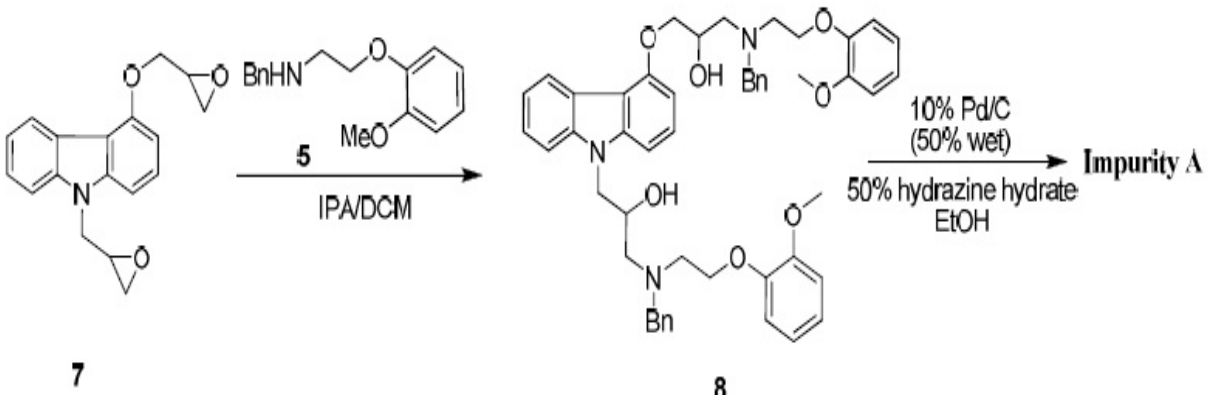
Carvedilol((2RS)-1-(9H-carbazol-4-yloxy)-3-[[2-(2-methoxyphenoxy) ethyl] amino] propan-2-ol) [1], a third generation non selective beta blocker and alpha blocker too which is widely used for the treatment of hypertension and several heart diseases [2]. In order to improve the poor water solubility of drug various techniques have been developed in the recent years like Co-grinding methods with the help of

polyvinylpyrrolidone (PVP) and sodium lauryl sulphate (SLS) [3], developing carvedilol (CAR) -eudragit RS 100 Nano fibres and Nano beads [4] and Solid micro emulsifying drug delivery systems- coated pellets with sufficient amount of carvedilol [5].

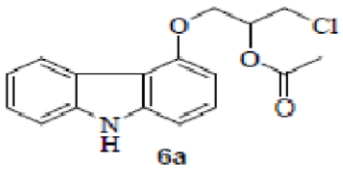
post- myocardial infarction heart failure is treated by Combination of carvedilol by suppressing more inflammation and oxidative stress, pulmonary congestion, LV end diastolic pressure and myocardial hypertrophy [6]. This findings regarding carvedilol revealed that it has a power to normalize cadmium incluptedcardiotoxicity [7]. The mechanism responsible for treatment of heart failure was AMP- activated protein kinase (AMPK), therefore carvedilol modifies AMPK signalling pathways leads to reductionof ischemia and reperfusion injuries [8].

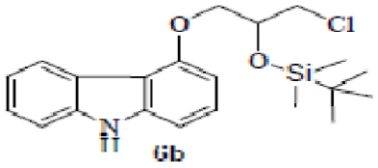
Carvedilol has anti-apoptotic, anti-inflammatory and antioxidant activities in heart. Onintake of carvedilol and thyroid hormones after acute myocardial infarctionleads to alleviated oxidative stress and can be used to modify cardiac function [9]. The fascinating element of carvedilol was to have antibacterial activity in which it is sensitive to the strains like Staphylococcus aureus and Staphylococcus epidermidis [10]. Carvedilol along with venlafaxine are used to treat testicular impairment in patients who has long standing Rheumatoid arthritis [11].

G. Madhusudan [12] et al., Carvedilol synthesis was done either by condensation of epichlorohydrin with 4-(oxiran-2-yl) methoxy) -9H- carbazole under base afforded 4, 9-Bis (oxirn-2-yl methyl) -9H- carbazole which is further reacted with 2-(2-methoxyphenoxy) ethanamine to obtain Impurity-A (or) synthesized by coupling reaction in which 2-(2-methoxyphenoxy)-N-benzyl ethanamine reacted with Di substitiuted carbazole to yield Dibenzylated Impurity-A.



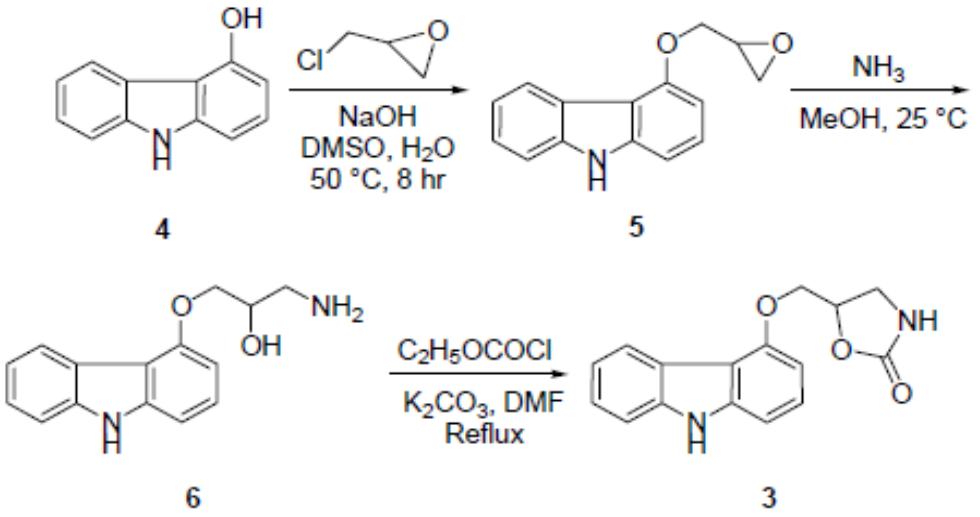
B.Anand kumar [13]et al., A novice approach to synthesize carvedilol has been reported in which main step is the synthesis of O– protected 1-(9H– Carbazole-4-yl oxy)-3- chloropropane -2-ol. Synthesis of carvedilol can be achieved by protecting alcohol group with acetyl and tertiary butyl dimethyl silyl chloride which is in 6a and 6b compounds.





G.Madhusudhan [14] et al ., facile synthesis of carvedilol have been reported in which 5- substituted -2-oxazolidinone is obtained as intermediate and there is no formation of bis side product (Impurity-B).

Scheme1: 9H-Carbazole-4-ol (4) reacts with epichlorohydrin to obtain glycidyl aryl ether (5). When treated with ammonia the oxirane ring of glycidyl aryl ether (5) gets open to give amino alcohol (6) which reacts with ethyl chloroformate and it is used as one of the carbon source in formation of the hydroxyl and amino functions of amino alcohol to furnish intermediate (3).

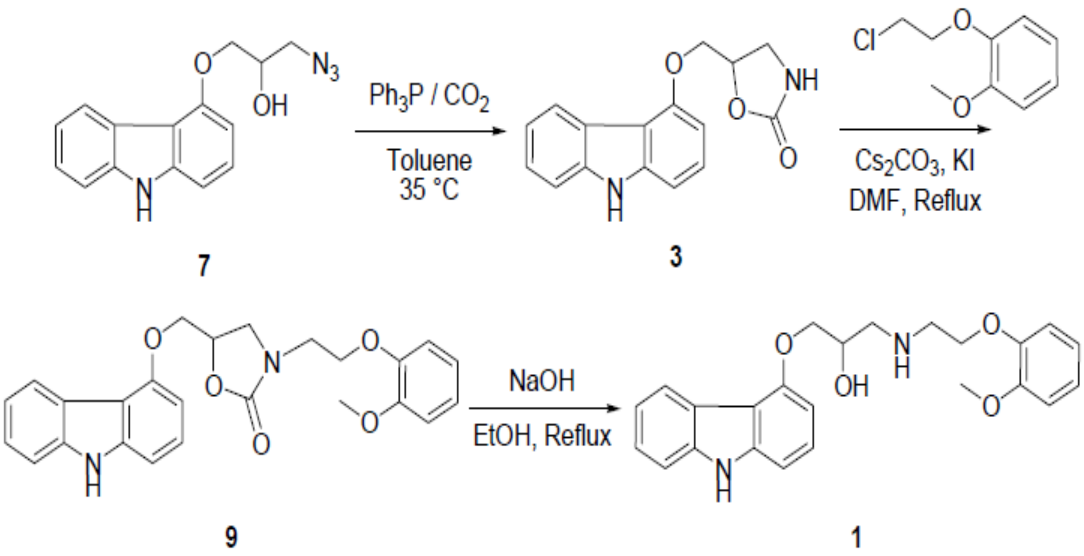


Scheme2:

Several impurities were detected during the formation of amino alcohol(6) from glycidyl eryl ether(5) inorder to avoid this, NaN_3/NH_4Cl were used instead of ammonia for opening of oxirane ring. Glycidyl eryl ether (5) reacted with sodium azide to give azido alcohol (7) which is further reacted with phenyl chloro formate in DMF under catalyst potassium carbonate at 140 ^{0}c to obtain O- protected azido alcohol(8) and is cyclized on reduction with Pd/ C to give 2- oxazolidinone (3).

Scheme3:

1,2 azido alcohol(7) reacts with Ph_3P to give 2-oxazolidinone(3).Condensation of 2-oxazolidinone with 1-(2-chloro ethoxy)-2- methoxy benzene in CS_2CO_3 / DMF at reflux to produce addition product 2-oxazolidinone (9) which on hydrolysis at basic condition gives carvedilol.



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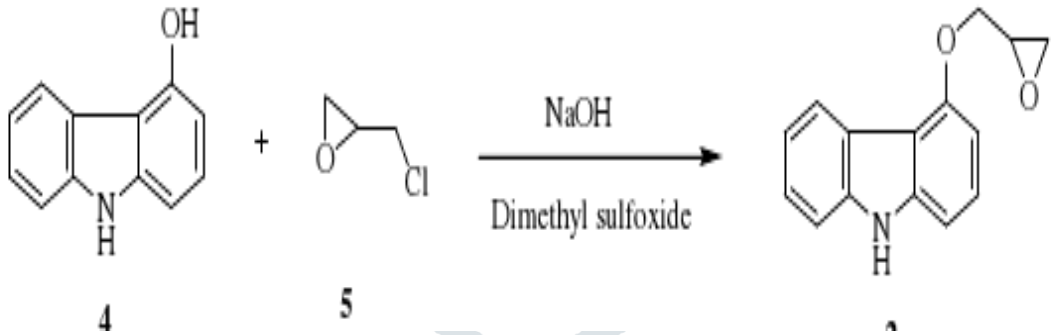
K.Suneel kumar[15] et al ., carvedilol synthesis can be afforded by reacting 4- hydroxy carbazole with epichlorohydrinin in presence of sodium hydroxide to give 4-(2,3-epoxypropoxy) carbazole which was condenced with 2-(2-methoxyphenoxy) ethyl amine in monoglyme. Impurity formation during the synthesis was detected and characterized by spectral analysis.



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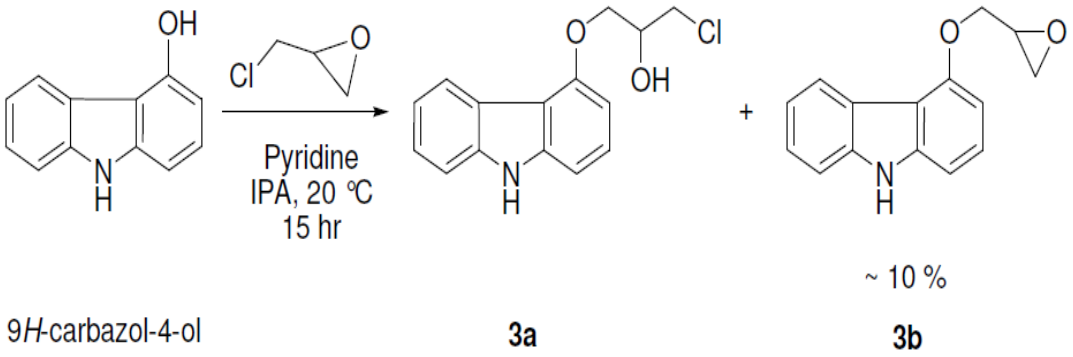
B.Anand kumar [16] et al.,By applying an intermediate 3-(9H – carbazole-4-yl oxy)-1-chloropropane-2-yl phenyl carbonate (8), the pharmaceutically important moiety Carvedilol was prepared. It involves the reaction of intermediate (8) with 2-(2-methoxyphenoxy) -ethanamine (5) by using N,N –Dimethyl -4-aminopyridine (DMAP) in N,N-di methyl formamide (DMF) which yield 3-(2-(2-methoxyphenoxy) ethyl) -5- (9H-carbazole-4-yloxy) methyl) oxazolidine-2-one (7) via 1-(9H-carbazole-4-yl oxy)-3- chloropropane-2-yl 2-(2-methoxyphenoxy) ethyl carbonate (6). The resulted compound (7) was further modified to give

carvedilol. However Impurity-B formation doesn't occur during this process and is useful for the preparation of many β-amino alcohols.



Jean hildesheim[17] et al.,A novel schematic way for synthesizing carvedilol invovles a step of reacting a compound 4-(oxirane-2-ylmethoxy)-9H –carbazole with 2-(2-methoxyphenoxy) ethylamine, where as 2-(2- methoxyphenoxy) ethylamine is at a molar excess over the compound 4-(oxirane-2-yl methoxy)-9H –carbazole. This approach gives different crystal forms like crystalline carvedilol, crystalline carvedilol hydrate, crystalline carvedilol solvate (methyl ethyl ketone) whose physical properties were determined by a variety of techniques such as X-ray diffraction spectroscopy, differential scanning calorimetry and Infra red spectroscopy.

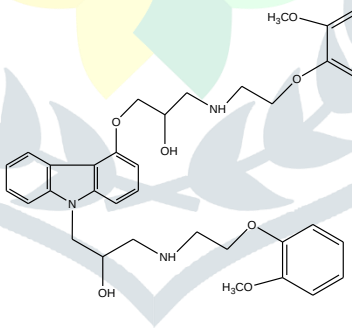
Stojanovic jelena[18] et al., In order to know about the stability and degradation products of carvedilol, a new HPLC method was developed. Chromatographic separation was achieved on a chromolit RP8, 100×4.6mm, analytical column. The mobile phase consists of mixture of acetonitrile and water (45:55v/v), where the p^H was adjusted with formic acid. With the help of UV detector at 40°C the absorbance was measured at 280nm.

Haggag[19] et al., For evaluation of carvedilol and hydrochlorothiazide, RP- HPLC methods with UV detection were introduced .The chromatographic separation was achieved by using RP-C8 (Octylsilyl) analytical column in which mobile phase consists of acetonitrile 0.05M disodium hydrogen phosphate (50 + 50, v/v), pH 4.0, and was detected at 220 nm. on the basis of measurement of the peak areas,quantification of

analytes were done. The mixture was resolved in less than 6 min. The reliability and analytical performance of the proposed HPLC procedures were statistically validated with respect to linearity, range, precision, accuracy, selectivity, robustness, LOD, and LOQ. The validated HPLC methods were successfully applied to the analysis of their commercial tablet dosage forms, for which no interfering peaks were encountered from common pharmaceutical adjuvants.

M. Srinivasa Ra [20]et al., designed LC-MS multiple reaction monitoring (MRM) method had been evaluated for the determination of the very low level of 4-Oxiranylmethoxy-9H-Carbazole(potential genotoxic impurity) in drug substances such as Carvedilol (U.S. Pharmacopoeia (USP), 32NF-27,British pharmacopoeia (BP), 2009, Martindale 35th edition). LC-MS was found to be more promising and the limit of quantification was 15µg/gm.

Madhusudhan[21] et al., Almost all the synthetic approaches of carvedilol involves the production of major impurities A, B, C, D and E are listed in European pharmacopoeia and the control of these impurities in pharmaceutical industry is currently a critical issue. In this publication, a description of these impurities and their origins in carvedilol process are presented along with the preparation of Impurity-A.

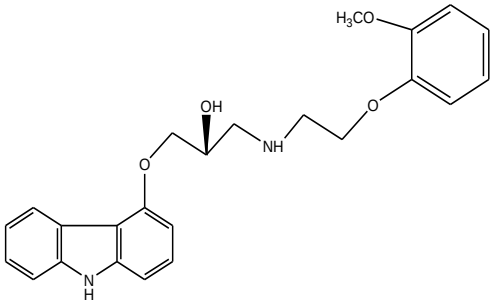


Impurity-A

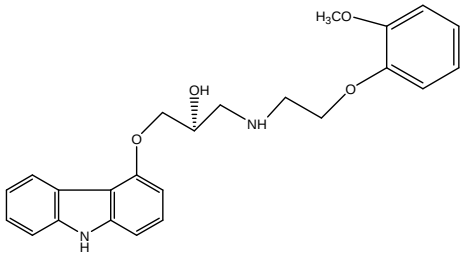
1-[[9-[2-Hydroxy-3[[2-(2-methoxyphenoxy) ethyl amine] propyl]-9H-carbazole-4-yl] oxy]-3-[[2-(2-methoxy phenoxy) ethyl] amine] propane-2-ol

Anand kumar[22]et al.,2-(chloromethyl) oxirane ((±)-2) is used as starting material for the synthesis of a racemic mixture of carvedilol ((±)-1) in a four step sequence. 5-(Chloromethyl) oxazolidin-2-one ((±)-3) and 5-((9*H*-carbazol-4-yloxy) methyl) oxazolidin-2-one ((±)-4) are intermediates. A similar sequence starting from (*R*) - or (*S*) -2-(chloromethyl) oxirane 2 give corresponding chiral 5-((9*H*-carbazol-4-yloxy)

methyl) oxazolidin-2-one 4 followed by chiral Carvedilol 1. Impurity-B (Bis impurity) is not formed during this process and it is useful for the preparation of pharmaceutically important moieties containing β-amino alcohols.



S (-) carvedilol



R (+) Carvedilol

Narendra[23] et al., Carvedilol (coreg) is a non selective β-blocker which is used for the treatment of congestive heart failure and hypertension due to its vasodilating property.

Senthil kumar[24] et al A simple efficient synthetic route for active metabolites of carvedilol is reported. Commercially by using vanillin and isovanillin the active metabolites like 4'-hydroxycarvedilol and 5'-hydroxycarvedilol respectively were synthesized which have high β blockade activity.

Fibele Analine[25]et al., According to ICH guidelines Q1A (R2), accelerated degradation studies of carvedilol were carried. The drug was submitted to a wide variety of pH like acid (1.0 N HCl), alkaline (1.0 N NaOH), and neutral hydrolytic conditions by relaxing at 90°C, as well as to oxidative (7.5% H_2O_2) decomposition, protected from light, at room temperature. Photolysis was carried out in solid state of the drug and in methanolic solution. The stress degradation samples were evaluated by LC and LC–MS.

Rajendra[26] et al., 2,3-epoxypropoxy carbazole of formula (II) (II) or the R or S enantiomer reacted with N-[2-(2-methoxyphenoxy)ethyl]-benzyl amine of formula (V) (V) to obtain benzyl carvedilol of formula (VI) (VI) which is de benzylated to afford carvedilol of formula (I) by catalytic hydrogenation, either in enantiomeric substantially pure form, or as an enantiomeric mixture, and if desired reacting the thus

formed carvedilol of formula (I) with an inorganic or organic acid to yield a pharmaceutically acceptable salt thereof, and/or, if desired, separating the enantiomers.

Dhiraj R.Shah[27] et al., 4-(oxiran-2-ylmethoxy)-9H-carbazole (II) is reacted with 2-(2-methoxyphenoxy) ethylamine (III) in a molar ratio of 1:1.4 and the reaction is carried out at 70° C to 80° C in a suitable solvent such as primary, secondary or tertiary lower alcohol containing 1-6 carbon atoms, The preferred solvent is methanol, ethanol, 2-propanol, isobutanol, tertiary butanol, acetonitrile, and ethyl acetate. The Most preferred solvent is 2-propanol. The reaction is carried out for 40 to 90 minutes. After completion of reaction, the reaction mass is then added to a solution of carboxylic acid having general formula R′(COOH)n whereas, n=1 and R′=(un) substituted aryl group i.e. benzoic acid, salicylic acid, et. Most preferred carboxylic acid is salicylic acid.

Bar-shavit[28] et al., The invention provides a process for reducing Bis impurities ((1, 1′-[2-(2-methoxyphenoxy) ethyl] imino bis-[3-(9H-carbazol-4-yloxy)]-propan-2-ol)) in carvedilol preparations. In particular, for reducing the amounts of Bis 1 and Bis 2 in carvedilol preparations. In certain embodiments, this process comprises of (a) Combining carvedilol base with phosphoric acid in ethanol to obtain a reaction mixture and (b) Precipitating carvedilol phosphate from the reaction mixture, where the carvedilol phosphate comprises low levels of Bis 1 and Bis 2.

Herbert leinert[29]et al., A process for the preparation of S- or R-carbazole derivatives in which R may be unsubstituted or substituted amino radical and pharmacologically acceptable salt, by either reacting R-(-)-epichlorohydrin (for the S-carbozole derivative) or reacting an S-epoxide derivative in which R1 is the residue of a substituted sulphonic acid derivative (for the R-carbazole derivative) with 4-hydroxycarbazole and then with ammonia or a substituted amine of the and recovering the compound or converting it to a pharmacologically acceptable salt.

Conclusion: Beyond all the above benefits of carvedilol our review iterature views on different procedures for the synthesis of effective carvedilol and it also paved a way for future research in the field of pharmacy.

References:

1. LevinBeattieGeetaPhadkeJasminaNovakovic.Chapterfour-Carvedilol. Profiles of Drug substances, Excipients and Related Methodology.2013; 38:113-157.

2. Ailoye SA[1], Jafferany M, Osuagwu V, PlathDL.The man who saw things on carvedilol.Tokai J ExpClin Med.2019; 44(2):29-30.

3. BolourchianN[1], Talamkhani Z[1], Nokhodchi A[2].Preparation and physicochemical characterization of binary and ternary ground mixtures of carvedilol with PVP and SLS aimed to improve the drug dissolution. Pharm Dev Technol.2019:1-32.

4. Selselehjonban S[1,2],Garjani A[3]*et al*.Physicochemical and pharmacological evaluation of carvedilol-eudragit RS100 electrosprayednanostructures.Iran J Basic Med Sci.2019;22(5):547-556.

5.Mandic J[1], Lustrik M[2],Vrecer F[1],Gasperlin M[3], Zvonarpobirk A[4].Solidification of carvedilol loaded SMEDDS by swirling fluidized bed pellet coating.Int J pharm.2019;566:89-100.

6.Grandinetti V[1],Carlos FP[1],Antonio EL[2]*et al*.Photobiomodulation therapy combined with carvedilol attenuates post-infarction heart failure by suppressing excessive inflammation and oxidative stress in rats.Sci Reo.2019;9(1):9425.

7.Refaie MMM[1], El-Hussieny M[2],Bayoumi AMA[3],Shehata S[4].Mechanisms mediating the cardioprotective effect of carvedilol in cadmium induced cardiotoxicity. Role pf eNOS and HO1/Nrf2 pathway.Environ ToxicolPharmacol.2019;70:103198.

8.Hu H[1], Li X[2], Ren D[2], Tan Y[3] *et al*.The cardioprotective effects of carvedilol on ischemia and reperfusion injury by AMPK signalling pathway.Biomed Pharmacother.2019;117:109106.

9.Vanessa DuarteOrtiz[a]PatrickTurck[a] *et al*.Carvedilol and thyroid hormones co-administration mitigates oxidative stress and improves cardiac function after acute myocardial infarction.European Journal of Pharmacology.2019;854:159-166.

10.KatarzynaZawadzkaPrzemyslawBernatAlesandraFelczakSylwiaRozalskakatarzynaLispwska.Antibacterial activity of high concentrations of carvedilol against Gram-positive and Gram-negative bacteria.International journal of Antimicrobial Agents.2018;51(3):458-467.

11.Ahmed H.Eid[a]AmanyM.Gad[a]EbtehalMohammadFikry[a]HanyH.Arab[b].Venalafaxine and carvedilol ameliorate impairment and disrupted spermatogenesis in rheumatoid arthritis by targenting AMPK/ERK and PI3K/AKT/mTOR pathways. Toxicology and Applied Pharmacology.2019;364:83-96.

12.G. Madhusudan, K. Chinnam Naidu, B. Anand kumar, R. Satyanarayana and V. Balraju, A facile synthesis of carvedilol impurity-A, Indian j. chem, May 2009, vol.46B, Page: 680-694.

13.B.Anandkumar, R.Buchireddy, I. Gangaiah, G.Madhusudhan, K.Mukanti, A new alternative synthesis of carvedilol, scholar research library, 2011, vol. 3(6), page: 620-626.

14.G.Madhusudhan,B.Anand kumar, US. Chintamani,M.Narasimha rao, D.Udya kiran, T.suresh,V.kiran kumar, K.Mukkanti a facile synthesis of carvedilol via a key intermediate -2- oxazolidinone intermediate. Indian j.chem. 2010, vol.49B ,page: 606-610.

15.K.Suneel Kumar, K.Tatendra reddy, G.Omprakash, P.K.Dubey ,synthesis and charecterization of potential impurities in key intermediates of carvedilol. j.chem.pharma.res,2011,vol 3(6), page:33-45.

16.B.Anand kumar, Md. Ashrafuddin, V.Rajesh, Sadika praveen, G.Madhusudhan, convenient synthesis of carvedilol utilizing 3-(9H-carbazole-4yloxy)-1-chloropropane-2-yl phenyl carbonate as key intermediate. Indian j.chem. may2012, vol.51B, page: 780- 784.

17.Jean Hildesheim, Sergey Finogueev, Judith Aronhime,Ben-Zion Dolitzkey,Shoshana Benvalid, United states patent on synthesis of carvedilol, Patent No:US 7, 126008 B2

18.Stojanovic jelena, Vladimirovsote, MarinkovicValantina, monitoring the photo chemical stability of carvedilol and its degradation product by RP-HPLC method journal of the serbian chemical society 2007, vol.72, pages: 37-44.

19.Haggag, Rim S, Shaalan, Rasha A, Belal, Tarek, Validated HPLC Determination of the Fixed Dose Combination Carvedilol and Hydrochlorothiazide in their Tablets.J AOAC Inter, July 2010, Vol.4, Page: 1192-1200.

20.M. Srinivasa Rao, Sumathi V, U.K.Ray, G.Sri Siva Kumar, Hemanth Kumar, Sharma and K.Mukkanti, Quantification of 4-Oxiranyl Methoxy-9h-Carbazole a Genotoxic Impurity in Carvedilol Drug Substances by LC-MS, J of Bioanalysis and Bio medicine 2010, vol. 2(4), page: 91-95.

21.Madhusudhan G, Naidu K, Chinnam, B Anand, Satyanarayana, R Balraju, Synthesis of impurity- A in carvedilol, Indian j chem, vol.48 B (05), page: 741-745.

22. B Anand Kumar, K Veera babu, Rama Rao, Koteshwar, Srenivas, Kumbam, MadhusudhanG ,Mukkanti, Synthesis of recemic and chiral carvedilol starting from corresponding 5-(chloromethyl) oxazolidin-2-one. Indian J Chem, SEP2012, vol.51B (09), Page: 1430-1435.

23.Somisetti Narendra, SitaramaiahDevarasetty, Srimannarayana, ChellaNageswarraoPeddi Srinivas Babu, K. Sudhakar, Synthesis and characterization of potential impurities of carvedilol,ananti hypertensive drug, Synthetic communications, January 2011, vol. 41, page: 85-93.

24.N Senthikkumar, Y.S Somannavar, Shankarb Reddy, B RajeshKumarSinha, G.K.S.A.S.S Narayan, Ramesh Dandala, Synthesis of active metabolites of carvedillol, an anti hypertensive drug. An international journal for rapid communication of synthetic organic chemistry 2010, vol.41 (2), Page: 268-276.

25.Fibele AnalineLanzanova, Debora Argenta, Marcela ZartArend, LC and LC-MS evaluation of stress degradation behavior of carvedilol Journal of liquid chromatography and related technologies 2009, vol.32 (4), Page: 526-543.

26.Rajendra, Narayan Rao Kankan, Dharmaraj, Ramachandra Rao "Process for the preparation of carvedilol", Patent No: 20080234492.

27.Dhiraj R.Shah, Ashish P, Naik, Parva, Y.Purohit, "Process for the preparation of carvedilol" patent no: 20080214833.

28.Bar-Shavit, Santiago, Isaeu, Marina, Process for the purification of carvedilol or its salts, Patent No: 20080207726.

29.Herbert leinert, Heppenheim, Process for the preparation of optically active carbazole derivatives, new R and S carbazole derivatives and pharmaceutical compositions containing these compounds, Patent 5071868.