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Review Article

A Review: Synthesis And Docking Study of Biologically Active Esters

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ABSTRACT

From many years chemists have been taking interests in synthesizing different kinds of ester derivatives due to their increasing medicinal importance. Lots of newer ester derivatives have different biological activities such as anticancer, antioxidant, anti-inflammatory, anti-tuberculosis, antimicrobial, antifungal etc. Chemists have prepared different bioactive ester drugs by using various methods and also carried out molecular modeling in silico of ester drug candidates with proteins (receptor) to predict bonding interactions of ester drugs with proteins responsible for that particular disease using computational methods. By finding all the results from docking one can predict the biological activities of the compounds under the study.

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Key-words: Ester derivatives, docking studies, biological activities, ligand, receptor.

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INTRODUCTION:

Esters have widespread applications as intermediates in the synthesis of fine chemicals, drugs, plasticizers, perfumes, food preservatives, cosmetics, pharmaceuticals, solvents etc. The esters particularly obtained from whale oil are used as lubricants, in pharmaceuticals, cosmetics and food industries [1, 2].Esters are important in the synthesis and manipulation of natural products [3]. Esters are functional derivatives of carboxylic acids. Cyclic esters are called lactones and are obtained by intramolecular condensation of alcoholic and carboxylic groups, called lactones like coumarins [4]. Esters are common in biological system and are frequently present in the food we eat and are generally pleasant smelling substances. Ester moiety has a wide applicability in peptide synthesis, medicinal chemistry, [5] as chiral auxiliaries [6] and polymer materials [7, 8]. Since esters have characteristics such as pleasant and fruity odor; they are extensively used in the fragrance and flavor industry. 2- phenylethyl alcohol is important ingredient of perfume industry[9]. It is a colourless volatile constituent of roses, which contributes to its aroma and of many other flowers [9, 10]. It has also been reported that they possess local anesthetic property [11]. In aromatherapy lavender and rosemary have been reported to lower the levels of stress hormone cortisol in the human saliva, [12] supporting the importance of aromatherapy in the depressed state.

The molecular docking has attracted considerable attention of bioorganic chemists. The study of molecular docking directs the synthetic chemists to design and synthesis of new drug candidates showing biological activities. By testing of thousands of compounds using softwares we can screen the compounds having biological activity rapidly in silico. Thus without going for preparing compounds in lab and checking the activity in vivo one should go for molecular docking in silico. Docking can be done by using softwares like hex [13], autodock, [14] Gold [15], Argus Dock [16] etc. The drug activity can be obtained through the molecular binding of one molecule (the ligand) to the pocket of another, usually larger, molecule (the receptor), which is commonly a protein and it is like a lock and key model. For the successful drug activity, the molecules should exhibit geometric and chemical compatibility of their binding conformations. Docking is the process which predicts the preferred orientation of one molecule with another bound to each other to form stable complex [17, 18]. The drug molecule which forms stable complex with receptor has minimum binding energy and strong hydrogen bonding.

Synthesis of bioactive Esters

Esterification is useful for the formation of carbon-carbon and carbon-oxygen bonds in many types of carbonyl compounds. Esterification is an important reaction in organic synthesis [19]. Esters can also be prepared by using primary amides, primary or secondary alcohols and scandium (III) triflate as a catalyst [20, 21]. It can also be prepared by oxidation, reduction and oxidative esterification.

Esters can be prepared by using different initial reactants.

1. By the reaction of carboxylic acid and alcohol [22].
2. By the reaction of acid chlorides and alcohol [23, 24].
3. By the reaction of an alkyl halides and carboxylic acid [25].
4. By using acid anhydride [26].
5. Trans – Esterification [27].

Many kinds of reagents for esterification reactions are known for preparation of aliphatic or simple esters, but for synthesis of aromatic, aryl or cyclic esters specific reagents are necessary. Esterification is a reversible reaction; it is difficult to carry out the reaction without specific reagents thus these days new reagents are emerging out.

Reagents used for synthesis of different ester derivatives

Boric Acid is used as a catalyst for chemoselective esterification of α hydroxycarboxylic acid [28]. For synthesis of alkyl esters; polymer supported carboxylate reagents such as crosslinked poly(N-methyl-4-vinylpyridinium) acetate and crosslinkedpoly (N-methyl-vinylpyridinium) Formate are used [29]. Dicyclohexyl carbodiimide with dimethyl amino pyridine (DCC/DMAP) as a coupling reagent is important for the synthesis of many ester derivatives like carabrol esters[30], niflumic acid esters[31], esters of salicylanide[32], fatty acid esters[33] gallic acid esters[34], 2-bromophenyl salicylate [35]. A new and very effective coupling reagent 1- ethyl 3, 3- dimethyl amino propyl carbodiimide hydrochloride (EDC) with DMAP is used for effective esterification as its urea is soluble easily in water [36]. 4,5-dichloro-2- [(4-nitrophenyl) sulfonyl] pyridazin -(2H)-one acts as a activator for direct, mild and convenient esterification of carboxylic acid and alcohols[37].

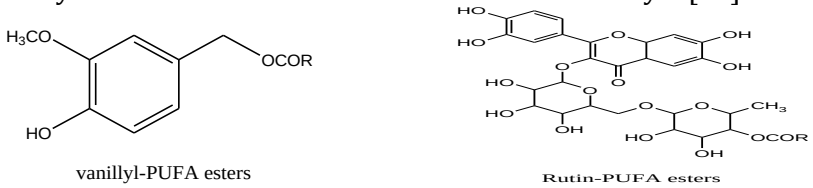
For esterification of acid chlorides and alcohols 1, 4 –diazabicyclo [2,2,2]octane (DABCO) is beneficial as a weak base [38]. Esterification reaction of aromatic diols with chloroacyl chloride carried out in presence of triethyl amine as a mild base under microwave. The magnesium curlings is used as a catalyst under conventional condition [39]. According to J.S. Yadav et al activated zinc dust acts as promoter for efficient esterification of acid chlorides and alcohols. Di-*p*-chlorobenzyl azodicarboxylate a new azodicarboxylate(DCAD) in presence of triphenyl phosphine is used for direct esterification of aromatic acids with benzylic alcohols[40]. Other heterogeneous azo reagent for esterification of phenols and benzylic alcohols is 5,5 -dimethyl-3,3-azoisoxazole[41]. For monoesterification of diols with carboxylic acid, $Al_2O_3/MeSO_3H$ (AMA) acts as dehydrating agent [42]. Samarium catalyst used for chemoselective esterification of homopthalic acid with alcohol [43], uranium based coupling agents [44] is also used for selective esterification. 5H-3-oxa-Octafluoropentanesulfonyl fluoride, moisture tolerant, non toxic condensing agent [45] is used in ester synthesis. Efficient methyl esterification was carried out using methoxyl silica gel as a novel dehydrating agent [46]. Kazunori Wakasugi, et al 2003 gave the efficient process for the preparation of esters from acid and alcohol using dimethyl sulfamoyl chloride and N, N -dimethylamines due to its simplicity, availability, and economy [47].

B. Vijaykumar, et al. 2009 used acid activated Indian bentonite as the catalyst for the effective esterification of long chain fatty acids with long chain alcohols. Takuji Hirose, et al 2003 developed effective method for preparation of esters by amidation agents like imdazole by using green approach [48]. Ying Qun Zhang, et al developed novel method for esterification of acid with alcohol using expandable graphite [49]. Solid Phosphorous pentoxide over silica acts as a good dehydrating agent for the synthesis of esters of aromatic and aliphatic acids with alcohols [50]. A.Khalafi-Nezhad, et al found an efficient method for the synthesis of esters of carboxylic acids and aryl alcohols using tosyl chloride as a catalyst and 1-methyl imidazole as a base under solvent free condition. Solvent free esterification is also carried out by using surfactant combined catalyst like dodecylbenzene sulfonic acid (DBSA) and copper dodecyl benzenesulfonate (CDBS) at room temperature [51]. Fe3+-K-10 montmorillonite clay is used as effective reagent for the preparation of esters of carboxylic acid with alcohols [52]. Polyaniline salts such as polyaniline hydrochloride, polyanilne sulphate, polyaniline nitrate, polyaniline phosphate and polyaniline p-toluene sulfonate are the efficient catalysts for esters synthesis [53]. Azopyridines are the potent and recyclable reagent used for effective esterification [54]. Ultrastable zeolite Y (H-USY), a naphtha cracking catalyst is used for salt free esterification of α amino acid [55].For selective esterification of non-conjugated carboxylic acid in the presence of aromatic carboxylic acid; active carbon supported methansulfonic acid is used as a specific catalyst [56]. Cylic esters like coumarins can also be prepared by using $ZrOCl_2.8H_2O$ catalyst [57].

Enzymatic Synthesis

Esterification by means of chemical reagents is nonspecific and requires special and selective electrophiles; also form low yield products. On the contrary enzymes are very specific, efficient in nonaqueous media and catalyse wide variety of processes [58]. *Candida rugosa* lipase in ionic liquid is an effective catalyst for enzymatic esterification because it easily removes the water produced in the esterification reaction by pervaporation coupled method [59]. *Candida rugosa* lipase is also used for esterification of dehydroepiandrosterone (steroid found in human blood) using acylating agents like ethyl carboxylate and acids results in good yield [60].

For specific esterification of rutin and vanillyl (obtained from fish byproducts) with carboylic acid in PUFA concentrate , Novozym435 in acetone also acts as a excellent catalyst [61].



vanillyl-PUFA esters Rutin-PUFA esters

fig 1: vanillyl and rutin pufa esters

Esters Showing biological activities:

Somepalli Venkateswarlu, et al 2006 made poly hydroxyl cinnamic acid ester derivatives having antioxidant and antimicrobial activity [62].

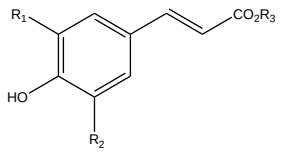


fig 2: polyhydroxyl cinnamic acid derivatives

Sonal Dubey, et al 2009 prepared novel aliphatic and aromatic esters of metronidazole using prodrug approach. These esters possess good antiprotozoal and antimicrobial activity than the parent metronidazole drug to improve the lipophilicity and to increase the activity of the parent drug [63].

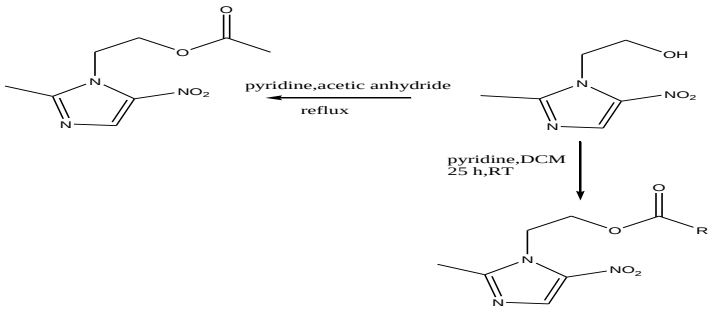


Fig 3: Esterification of metradinazole

Jian-yong Li, et al. 2012 prepared aspirin eugenol ester derivatives by using prodrug concept. Aspirin and eugenol themselves have many biological activities but the carboxyl group of aspirin and hydroxyl group of eugenol have major side effects. Because of this there is a need for combination and modification of these functional groups to reduce the side effects; this resulted in increasing their therapeutic effects and stabilization [64].

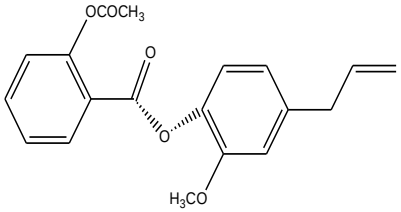


Fig 4: Aspirin eugenol ester

Chen Hong et al, 2006 synthesized nitro or trifluoromethyl substituted benzimidazolyl-phenoxyacetic acid acetylglucosyl saccharide esters by the reaction of acetylglucosyl bromide with substituted benzimidazolyl - phenoxyacetic acid at room temperature. The synthesized compound showed good anti-plantviral activity [65].

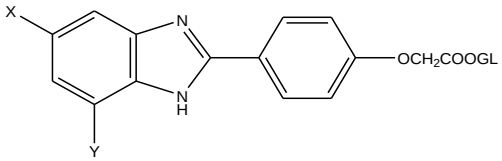


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Fig 5: benzimidazolyl- phenoxyacetic acid acetylglucosyl saccharide esters

Giorgio Tarzia, et al. 2003 designed the Alkylcarbamic Acid Aryl Esters, a New Class of Fatty Acid Amide hydrolase Inhibitors [66]. Jern B. Christensen gave simple method for the synthesis of active esters of isonicotinic and picolinic acids [67].

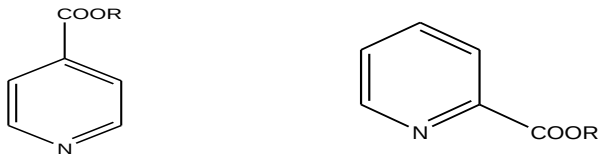


Fig 6: Isonicotinic acid ester Piconlinic acid ester

Jintao Han and et al prepared the different ester derivatives of 5-(4-Hydroxybenzyl)-2-Thioxoimidazolidin-4-one and evaluated the herbicidal activity in vivo. These ester derivatives have shown to possess excellent herbicidal activity [68].

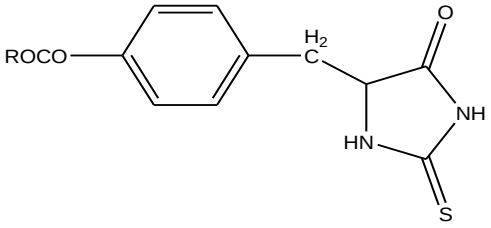


Fig 7: ester derivatives of 5-(4-Hydroxybenzyl)-2- Thioxoimidazolidin-4-one

Abdul Majeed Khan et al. synthesized and evaluated the antimicrobial, antifungal activity of esters of Succinylanthranilic Acid. Along with this they also checked inhibitory action of chymotrypsin (serine protease enzyme involved in many biological processess). It is reported that these ester derivatives possessed good antimicrobial, antifungal and protein inhibitory activity [69].

Ethyl acetate extract from Acacia catechu have shown to possess antipyretic, anti-diarrhoeal, hypoglycaemic and hepatoprotective activities [70].

Esters having anti-inflammatory activity

Satish K. Lakde, et al. in 2010 synthesized esters of niflumic acid to improve the physicochemical properties of parent drug. The esters of niflumic acid have more solubility and anti inflammatory activity than niflumic acid [31].

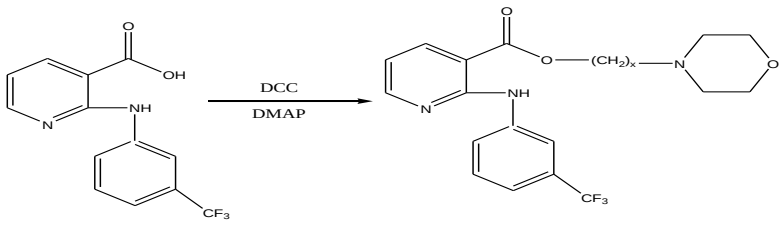


Fig 8: Esterification of niflumic acid

The α hederin methyl esters extract from bark of *kalopanas pictus* showed significant antinflammatory activity [71].

Prodrug of aceclofenac with salicylamide is reported to have good anti-inflammatory activity [72].

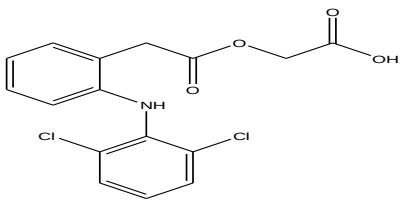


Fig 9: aceclofenac

Esters having antimicrobial activity

Lindstedt, et al. in 1990 introduced a new series of quaternary ammonium compounds that are esters of betaine and fatty alcohols with hydrocarbon chain lengths of 10 to 18 carbon atoms possessing good antimicrobial activities and rates of hydrolysis [73]

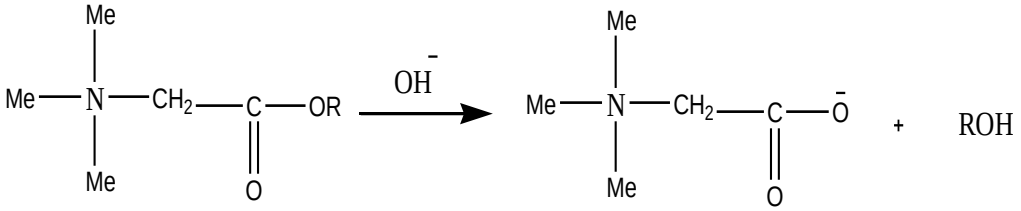


Fig10: Betaine esters

Meltem Ceylan ¨Unl¨Usoy et al. in 2005 have designed new series of flavonyl pro-drug esters of ampicillin. It was prepared by condensing the appropriate bromomethyl flavone with ampicillin trihydrate potassium salt. Both flavone derivatives and ampicillin possess good antibacterial activity. [74]

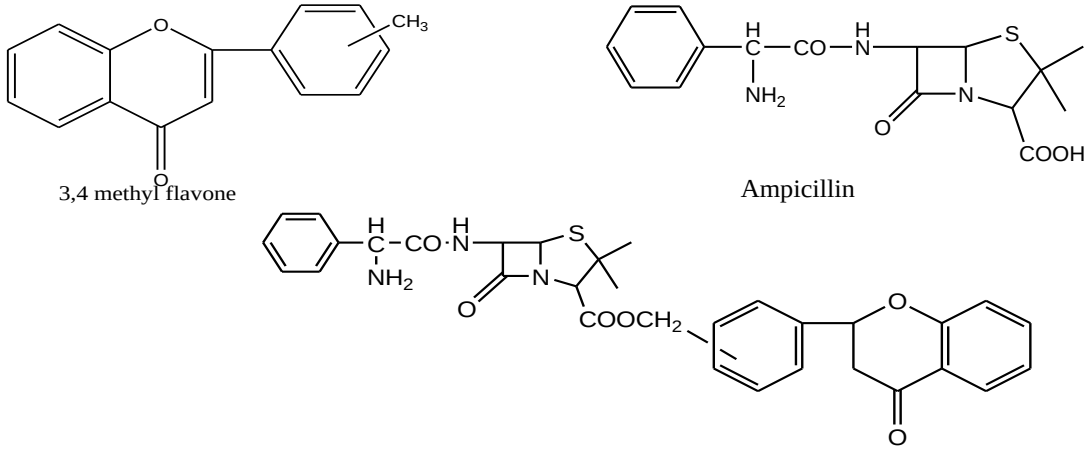


Fig11: flavonyl prodrug ester of ampicillin

Salicylanilide acetate esters possessed significant antimicrobial and antifungal activity [75].

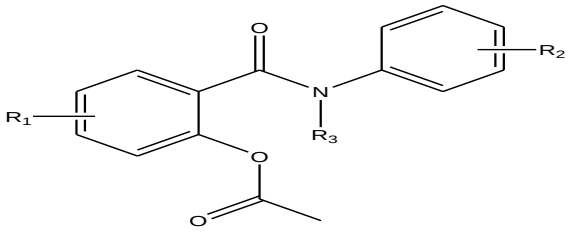


Fig 12: salicylanide acetate

Uma Ravi Sankar, et al. in 2007 have synthesized new heterocycles in which amino acid esters are linked to a phosphorus atom, studied their antimicrobial activity and phosphate degradation potential in several bacterial species. According to them the presence of an exocyclic P-N bond in an amino acid ester attached to benzoxazaphosphorin system is expected to increase cellular uptake of their chemotherapeutic properties. [76]

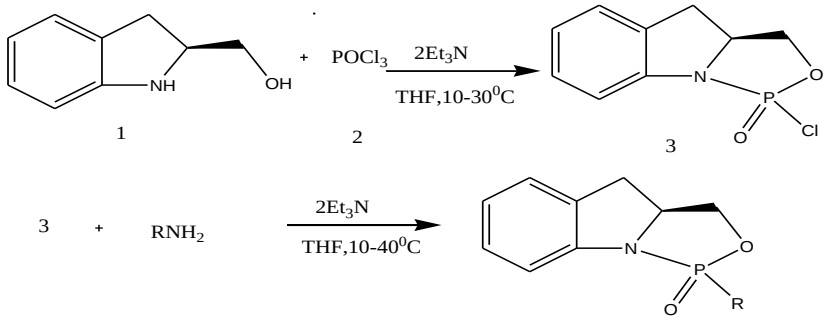


Fig 13: Amino acid ester attached with benzoxazaphosphorin system

Phenolic acid alkyl esters proposed by Roman Merkl, et al. have antimicrobial activity [77]. Ronald N. Jones et al studied and checked the antimicrobial activity of novel ester linked codrug of fleroxacin and desacetylcefotaxamine in vitro. It is found that this co-drug has significant antimicrobial activity and highly effective against organism resistant to fluroquinolones or ceftadizime [78].

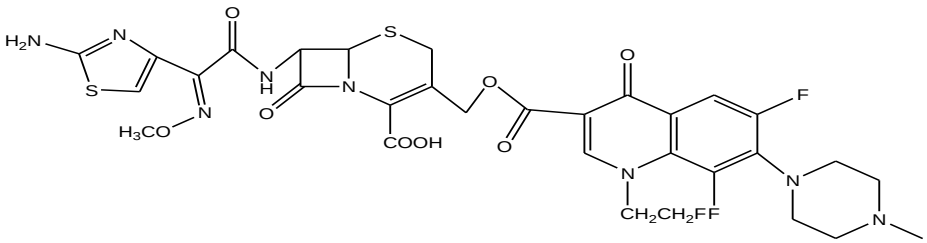


Fig14: co-drug of fleroxacin and desacetyl cefotaxamine

P. L. Tardrew et al investigated the antimicrobial activity of erythromycin and the ester of erythromycin substituted at 2-postion. They have reported the ester group substituted at 2-postion of erythromycin has less antimicrobial activity than parent erythromycin [79].

Esters having antifungal activity

Martin Krátký and Jarmila Vinšová have synthesized salicylanilide esters with 4-(trifluoromethyl) benzoic acid and assayed as potential antimycotic agents against eight fungal strains in vitro, along with their parent salicylanilides. The most active salicylanilide have shown to possess significant antifungal activity [32].

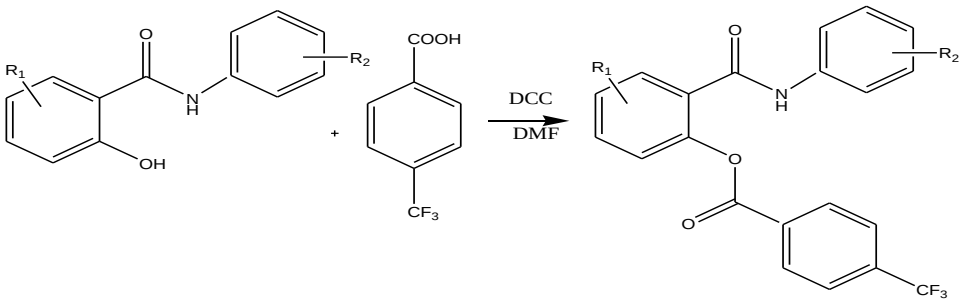
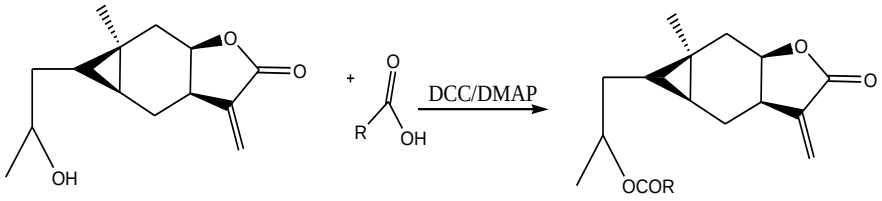


Fig15: Reaction of 4-(trifluoromethyl) benzoic acid with salicylanides

Jun-Tao Feng, et al. in 2012 have prepared a novel class of carabrol esters and checked their antifungal activity against the fungal pathogen. *Colletotrichum lagenarium* were evaluated using a spore germination assay. C-4 position of carabrol was a key position involving its antifungal activity. The ester derivatives substituted by phenyl ring with electron-attracting groups showed higher activity than those with electron-donating ones [30].



Carabrol carabrol esters

Fig16: Esterification of carabrol

Esters having antiulcer activity

K.J. Kore, et al.have studied antiulcer activity of Protocatechuic acid ethyl ester using different models of gastric ulceration in rats. Antiulcer activity of Protocatechuic acid ethyl ester was studied in rats in which gastric ulcers were induced by oral administration of ethanol or aspirin or by pyloric ligation. They found this antiulcer property of Protocatechuic acid ethyl ester was more effective in animals in which ulcers were induced by ethanol and aspirin [80]. Larissa L. G. Costa, et al. extracted phorbol esters from the bark of *Synadenium grantii*; identified as 12-deoxyphorbol-13-(2-metilpropionate) and phorbol 12, 13, 20-triacetate. Due to the presence of ester moiety they are reported to have significant antiulcer activity [81].

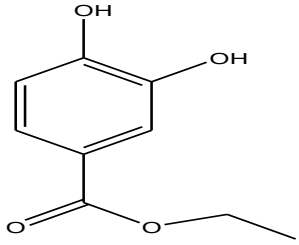
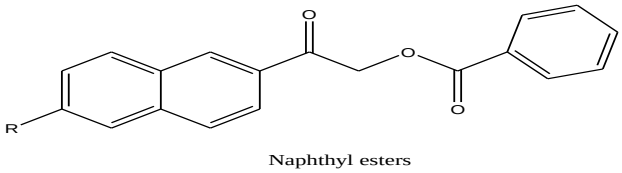


Fig17: protocatechuic acid ethyl ester

Esters having antioxidant activity

G. Thirunarayanan, et al. in 2011have developed solvent free method for the synthesis of naphthyl esters having significant antioxidant activities [19].



Naphthyl esters

Fig18: Naphthyl esters

Hiroshi Matsufuji, et al. have reported the antioxidant activity of capsanthin and fatty acid esters in *paprika*. The esterified capsanthins are found good radical scavengers than non-esterified. It was reported that capsanthin was the more effective antioxidant than β carotene [82].

Esters having anticancer activity

Fatemeh Kalalinia, et al.have indicated a link between levels of cyclooxygenase-2 (COX-2) and development of the multidrug resistance (MDR) phenotype. The ATP-binding cassette (ABCG2) is a major MDR-related transporter protein that is over expressed in cancer patients. This study is aimed at evaluating positive correlation between COX-2

and ABCG2 gene expression using the COX-2 inducer 12-O-tetradecanoylphorbol-13-acetate (TPA) in human breast cancer cell lines [83].

G. Berkovitcha, et al. investigated the mutual anti-cancer activity of ALA prodrugs which on hydrolysis by unspecific esterases release ALA, formaldehyde or acetaldehye and the histone deacetylase inhibitor (HDACI) butyric acid. The most potent prodrug in this study was butyryloxyethyl 5-amino-4-oxopentanoate (AN-233) that stimulated a rapid biosynthesis of protoporphyrin IX (PpIX) in human glioblastoma U-251 cells and generated an efficient photodynamic destruction [84].

Cinnamic acid and its esters are known to display interesting antioxidant and anti-tumour properties. Actually numerous reports on the antioxidant and anticancer activities of structurally modified cinnamic acids and its alkyl chain esters are found to display significant anti-proliferative effects towards human cancer [85].

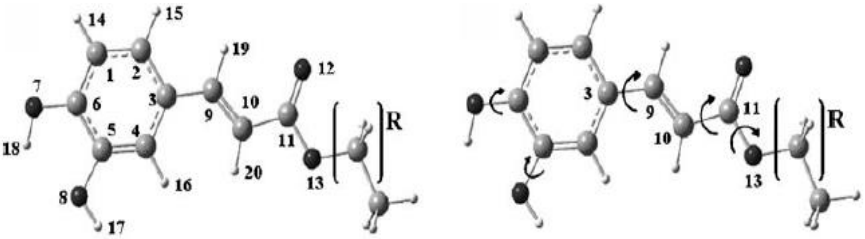


Fig19: Schematic representation of the dihydroxycinnamic esters studied in this work and of the main internal rotations affecting the overall stability of the molecules.

Ester derivatives of brefeldin A (BFA) were synthesized to determine which of its two hydroxyl groups could be modified while still maintaining biological activity [9]. The compounds were tested for anti-proliferative activity in the National Cancer Institute's 60 cancer cell line screen. Monoderivatization at the C4 and C7 alcohols indicated improvement in the biological activity whereas the analogues derivatized at both positions were found to be the least active in the series. The BFA ester conjugates synthesized in this study were cytotoxic to cancer cells. The brefeldin A ester derivatives are reported to be potential anticancer agents [86].

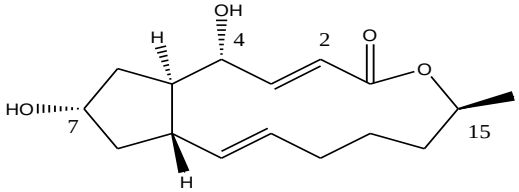


Fig20: Brefeldin A

Esters having anti-trypanosomal activity

On treatment of sleeping sickness caused by *tsetse fly* (generally found in Africa) Jean Fotie et al. synthesized and evaluated the anti-trypanosomal activity of ester derivatives of 1,2 -dihydroquinolin 6-ols [87].

Docking of ester drugs

The docking study of highly active compound 1-Formyl-beta-carboline-3-carboxylic acid methyl ester against the receptors HIV reverse transcriptase (RT), integrase (IN) and protease (PR) has been reported. This compound has anti-HIV activity docked into the active sites of all these receptors (enzymes). The compound was shown to have good binding energy score and binding interactions with RT as compared to PR and IN [88].

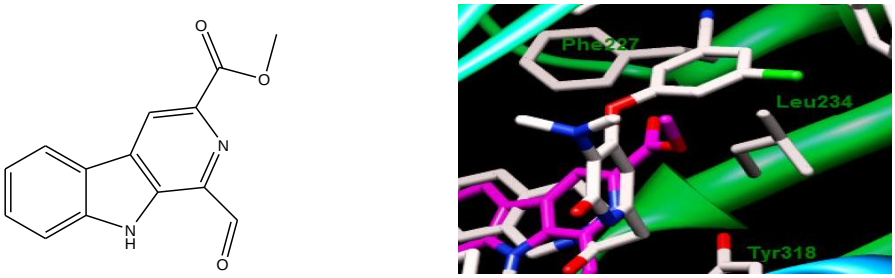


Fig21: - Binding interactions of 1-Formyl-beta-carboline-3-carboxylic acid methyl ester into the active site of RT (3FFI) as obtained by docking studies. Magenta color sticks for docked conformation of compound; white color sticks for co-crystallized ligand.

N-substituted pyrrole derivatives block HIV fusion. Docking studies were carried out on different pyrrole derivatives for better anti-HIV-1 activity. Here selected different receptors which show anti-HIV-1 activity. The receptors were docked with different pyrrole derivatives like 2-Amino-1-(4-Iodophenyl)- oxo-4, 5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester(1), 2-Amino-1-(4-Fluoro-phenyl)-oxo-4, 5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester(2) and 2-amino-1-(4-methoxy-phenyl)-oxo-4, 5-dihydro-1H-pyrrole-3-carboxylic acid ethyl ester(3).Among these three derivatives ,(1) showed high energy value and more compatible with receptor compared to other anologues [89].

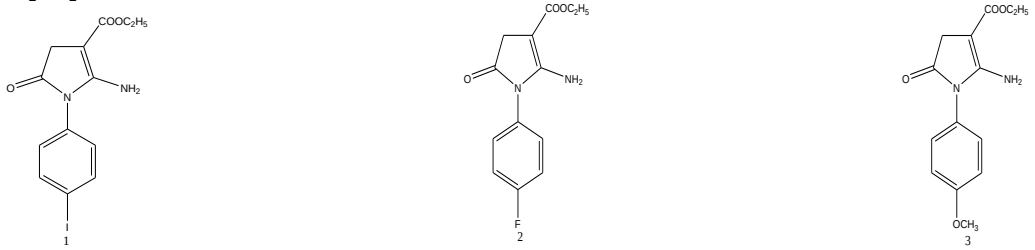


Fig 22: Pyrole derivatives

Shaomeng Wang, et al. presented the results of molecular modeling and site-directed mutagenesis on the determination of the phorbol ester-binding site in the domain of PKC. These results facilitated a detailed analysis of the interactions between the receptor (Protein Kinese C.) and various ligands (phorbol esters) [90].

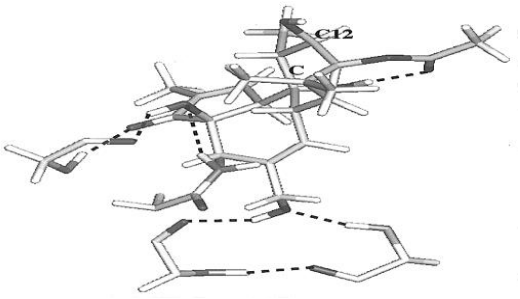


Fig23: Hydrogen bonds between PKC*ä*/phorbol 13-acetate in the X-ray-determined structure.

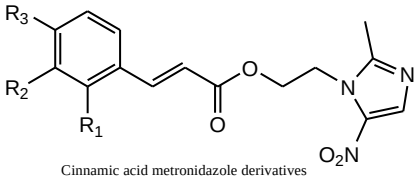
Samira Yousefi, et al. designed new glucose and xylitol esters of 5-amino salicylic acid and screened for their anticancer activity in silico against cyclooxygenase and lipoxygenase proteins. Both the esters showed good binding interactions (binding energy) and strong hydrogen bonding with receptors (proteins) cyclooxygenase and lipoxyoxygenase than parent acid [91].

For the treatment of Parkinsons and Alzeimers diseases monoamine oxidases inhibitors (MAO-A and MAO-B) and acetyl-cholinesterase inhibitors such as carbamates and esters with coumarin scaffold like multi-targets are used. In this docking study the stability of carbamates with coumarin substituted at different positions with target proteins

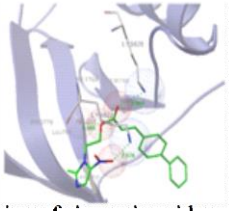
done by using two different softwares like Glide and Autodock. Here coumarin substituted at 6 positions forms most stable complex with MAO-A; while coumarin substituted at 3 and 7 positions forms stable complex with MAO-B [92]. Tuberculosis is a disease which kills millions of people every year. It requires novel drug target for treatment. Qsay Al-Bales, et al. docked the 2-aminothiazole-4-carboxylate derivatives against the target proteins such as M. tuberculosis $H_{37}R_v$ and β ketoacyl synthase enzyme mtFabH using Gold software [93].

Peruze Ayhan, et al. synthesized esters of aryl butanoic acid and carried out molecular docking study of these derivatives with histone deacetylase (HDAC) which affects the chromatin structure and gene activities at particular chromosomal region. Among all derivatives, (E)-4-(4-methoxyphenyl)-1-(2,6-dimethylmorpholino) but-3-ene-1,2-dione acts as a good capping agent to inhibit the activity of histone deacetylase (HDAC) and have significant binding capacity[94].

Cinnamic acid metranidazole ester derivatives are potent inhibitors of EGFR kinase (protein) as a novel anticancer agent. In this binding model, these derivatives nicely bound to the protein and show good hydrogen bonding [95].



Cinnamic acid metronidazole derivatives
A



docking of cinnamic acid metronidazole ester with EGFR kinase protein
B

Fig24: cinnamic acid metronidazole derivatives (A) and complex of cinnamic acid metronidazole ester with EGFR kinase

Ahmed Z. Abdel-Azeem and et al. synthesized Chlorzoxazone esters of some non-steroidal anti-inflammatory (NSAI) carboxylic acids as a mutual pro-drug because these non-steroidal anti-inflammatory (NSAI) carboxylic acids have undesirable side effects. For improving therapeutic potency and to reduce the adverse effects of gastrointestinal origin, Chlorzoxazone is combined with different carboxylic acids like ibuprofen, naproxen mefenamic acid etc. The docking study of these mutual pro-drugs are carried out against cyclooxygenase (COX-2) responsible at the site of inflammation. Docking simulations revealed that pro-drug of ibuprofen and naproxen are effective inhibitors of COX-2 [96].

Hydroxymethyl chlorzoxazone

R= ibuprofen, naproxen, mefanamic acid

Fig25: reaction of hydroxyl methyl chlorzoxazone with different acids.

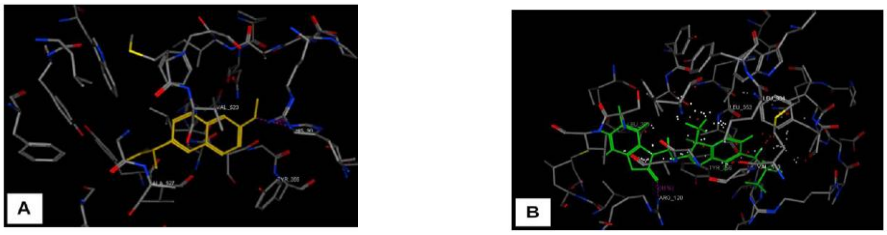


Fig26: Complex of ibuprofen with COX-2(A) and complex of naproxen with COX-2(B

Conclusion

The present review highlights that esters are the important class of functional groups. Esters and their derivatives can be prepared by using various methods and reagents. They show broad spectrum of biological activities such as antimicrobial, antifungal, anticancer, antioxidant, anti-tubercular, anti-inflammatory, anti-HIV etc. They are also useful for many organic transformations. It reveals that some ester drugs are the inhibitors of receptors (proteins) such as reverse transcriptase (RT), integrase (IN), protease (PR), Protein Kinese C., cyclooxygenase, lipoxygenase, M. tuberculosis $H_{37}R_v$, β ketoacyl synthase enzyme mtFabH and histone deacetylase etc.

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