Research article Available online www.ijsrr.org ISSN: 2279–0543

International Journal of Scientific Research and Reviews

Role of Microwave Technology in Synthesis of Medicinally Potent Indole Derivatives

Rajendra[1], Sharma Swapnil[2], Tiwari S. P.[3] and Dwivedi Jaya[1]*

[1]Department of Chemistry, Banasthali University, Banasthali, Rajasthaan-304022
[2]Department of Pharmacy, Banasthali University, Banasthali, Rajasthaan-304022
[3]Department of Chemistry, The IIS University, Jaipur, Rajasthaan-302 020

ABSTRACT

This review explores importance of synthesis of various indole derivatives using microwave assisted techniques. Additionally, this review enlightens the biological applications of indole and its derivatives. Preparation of differently substituted indoles through microwave-assisted technique found to be efficient and resulted in intermediate to high yields. These reactions did not involve any added catalyst like acid, or base, and conventional heating. This approach has been used for catalytic hydrogenation reactions and furnishes the indole derivatives in good yields. Eventually, in this review microwave-assisted engineered indole derivatives are discussed to develop new drugs for instance thieno[3,2-b]indoles for M. tuberculosis H37Rv (MTB) and multi-drug resistant M. tuberculosis (MDR-TB).

KEYWORDS: Role of Microwave Technology in Synthesis of Medicinally Potent Indole Derivatives

***Corresponding author**

Jaya Dwivedi

Department of Chemistry, Banasthali University, Banasthali, Rajasthaan-304022
Department of Chemistry, The IIS University, Jaipur, Rajasthaan-302 0

E-mail: jayadwivedi@yahoo.co.in

INTRODUCTION

In recent years, the use of microwave technology in organic synthesis has received considerable attention[1,2]. Microwave heating has emerged as a powerful technique to promote a variety of chemical reactions. Although first reported by the group of Gottlieb[3,4] and Gigure Majetich[5] in 1986, the use of microwave in organic synthesis was initially hampered by lack of understanding of the basic principle of microwave dielectric heating and the inability to obtain reproducible result with domestic microwave ovens. The application of microwave irradiation has led to support for the development of many reaction procedures, which are environment friendly, falling in the domain of green chemistry. Indole is an aromatic heterocyclic organic compound. It has a bicyclic structure, consisting of a six-membered benzene ring fused to a five-membered nitrogen-containing pyrrole ring. Indole is a popular component of fragrances and the precursor to many pharmaceuticals. Indole has been validated as a privileged structure, a scaffold, capable of providing useful ligands for diverse receptors[6].

Indole nucleus is associated[7]with a large number of pharmaceutical properties like antibacterial[8], anticancer[8,9], antibiotic[10], central nervous system modulating[11] etc. Indole derivatives and in particular indole-2 carboxamide, showed excellent inhibitory activity against both HIV-112 and HIV-AB1, in lymphocytes and against HIV WT in macrophages. In the same way aromatic ketone those form the central core for a variety of important biological compounds, which are known collectively as chalcones. They show antibacterial, antifungal, antitumor, anti-inflammatory, and anti-HIV properties[12,13]. Isatin (Indole 2,3-dione), and its 5-chloro and 5-bromo derivatives were added to 3-amino-2-methylmercapto quinazolin-4(3H)-one to form Schiff bases and N-Mannich bases of these compounds show anti-HIV activity against replication of HIV-1 (III B) in MT-4 cells. Chalcones demonstrated the ability to block voltage-dependent potassium channels[14].

The syntheses of a variety of new compounds containing indole moiety mainly aim at providing new drugs for management of bacterial infections which have not been cured by existing drugs on account of high resistance against immune disorder. The development of new heterocycles with a broad spectrum of immune modulating properties reveals high relevance of the present project in medical sciences. Substituted indole nucleus and their derivatives represent an important class of compounds. Thus, in this order, we have reviewed concise literature to explore an importance of indole derivatives

ROLE OF MICROWAVE TECHNOLOGY

Carpita A et al.[15] have reported an extraordinary green methodology to describe the preparation of differently substituted indoles of 2-alkynylaniline derivatives in water. Moderate to good yields in the cyclization havr been achieved for a variety of 2-aminoaryl alkynes. Carpita A et al.[16] also described and exploited for the preparation of differently substituted indoles and azaindoles via microwave-assisted cycloisomerization in water of 2-alkynylanilines and alkynylpyridinamines. This has been promoted by catalytic amounts of neutral or basic salts or by stoichiometric weak organic bases. Development of enhanced conditions for Lewis acid catalyzed Leimgruber–Batcho indole synthesis using microwave acceleration has been reported by Siu J et al.[17] This approach has been permitted the preparation of a variety of heteroaromatic enamine intermediates in good yield and high purities. Subsequent catalytic hydrogenation reactions, under various conditions including the use of a solid-phase encapsulated catalyst, furnish the corresponding indole derivatives in good yields. Barluenga J et al.[18] stimulated the design and development of new synthetic strategies to construct these heterocycles. One of the most effective ways of achieving efficiency is to implement reaction cascades, enabling multiple bond-forming and bond-cleaving events to occur in a single synthetic operation, thus circumventing the waste associated with traditional stepwise synthesis. In general, cascade reactions offer the opportunity to access highly functionalized final products from simple starting materials. For all these reasons, it is not a surprise that most of the recently reported methods for the synthesis of indoles and quinolines are based on the use of cascade reactions. Ohta Y et al.[19] synthesized benzo-1,4-diazepines by copper-catalyzed domino three-component coupling−indole formation−N-arylation under microwave irradiation from a simple N-mesyl-2-ethynylaniline. This method has also been applicable to the formation of heterocycle-fused 1,4-diazepines. Zhu SL et al.[20] synthesized a series of polysubstituted (3′-indolyl)pyrazolo[3,4-b]pyridine and (3′-indolyl)benzo[h]quinoline derivatives via one-pot multi component reactions of aldehydes, 3-cyanoacetyl indoles with 5-aminopyrazol or naphthylamine. Particularly valuable features of this method include high yields of products, broad substrate scope, short reaction time and straightforward procedure. Additionally, Algul O and co-workers[21] have synthesized 2-substituted benzimidazole, benzothiazole and indole derivatives using on both microwave irradiation and conventional heating methods. The microwave method was observed to be more beneficial as it provided an increase of yield from 3% to 113% and a 95 to 98% reduction in time. These compounds were tested by a stains-all assay at pH 7 and by a Morgan-Elson assay at pH 3.5 for hyaluronidase inhibitory activity at a concentration of 100 μM. The most potent compound was 2-(4-hydroxyphenyl)-3-phenylindole with an IC_{50} value of 107 μM at both pH 7 and 3.5. Patil AS et al.[22] also used this methods for the preparation of indole analogs to speed up the synthesis, therefore,

microwave assisted organic synthesis (MAOS) in controlled conditions is an invaluable technique for medicinal chemistry. They have used indole forming classical reactions such as Fischer, Madelung, Bischler-Mohlau, Batcho-Leimgruber, Hemetsberger-Knittel, Graebe-Ullmann, Diels-Alder, and Wittig type reactions using microwave radiations.

Walker MS and co-workers[23] have reported an excited-state solute—solvent complex (exciplex) which was responsible for a large red shift and loss of vibrational structure in the fluorescence spectra of indole and indole derivatives in polar solvents. Solute—solvent stoichiometry of 1:2 and 1:1 has been observed with associating and non-associating solvents, respectively. Hydrogen bonding between the indole >N–H group and solvent was shown not to be responsible for the interaction. It has been suggested that the exciplex state was a charge-transfer state and is an intermediate in the process of electron transfer from the solute to the solvent.

Xu DQ et al.[24] developed a novel one-pot Fischer indole synthesis approaches by using Bronsted acidic ionic liquids as dual solvent-catalysts. Yields of 83–97 % were obtained after reaction in [BMIM] HSO_4 at 70–110 ℃ in 0.5–6 h, and exclusive formation of 2,3-disubstituted indoles was observed in the reaction of alkyl methyl unsymmetrical ketones. The indoles produced have been be conveniently separated from the reaction mixture without any volatile organic solvents, and the [BMIM] HSO_4 could be readily reused without efficiency loss after simple treatment involving only 1 equiv. of HCl for neutralization followed by filtration.

Dandia A et al.[25]synthesized a spiro[3*H*-indole-3, 2′-[4*H*] pyrido[3, 2-e]-1, 3-thiazine]-2, 4′ (1H)diones, a class of previously unknown compound which does not form under conventional conditions, can be prepared by treatment of '*in situ*' generated 3-indolylimine derivatives with 2-mercaptonicotinic acid under microwave irradiation in absence of any solvent or solid support in 85–92% yields in 3–8 min. The facile one pot reaction has been generalized for a variety of ketones and amines to give pure pyrido[3,2-e] thiazine derivatives, which do not require further purification processes. Olyaei A et al. one-pot, three-component coupling reactions of indole, aromatic aldehydes, and heteroaryl amines under solvent-free conditions lead to the formation of the corresponding novel 3-[(N-heteroaryl)(aryl)methyl]indoles in moderate to high yields[26]. The key features of this multi-component reaction were the simple reaction procedure, no organic solvent or acid catalyst, and easy product separation without further purification. Indole-2-carboxylic acid on condensation with benzene sulfonyl hydrazide and p-toluene sulfonyl hydrazide gives condensation products[27]. 1*H*-tetrazole-5-acetic acid, hydantoin-5-acetic acid, orotic acid, 5-bromo nicotinic acid, and indole 2-carboxylic acid have been condensed with furfuryl amine to give corresponding condensation products whereas condensation of succinic acid and adipic acid with furfuryl amine

gives corresponding products. Additionally, 3, 5-Pyrazole dicarboxlic acid, 4,5-imidazole dicarboxylic acid and 3-carboxy-1,4-dimethyl pyrole-2-acetic acid on condensation with furfuryl amine give their respective compounds. All these compounds have been characterized by spectroscopic means and screened for anti-inflammatory and analgesic activity. These compounds exhibit good anti-inflammatory and good analgesic activities. Gengan RM et al.[28] an efficient synthesis of a methyl derivative of the indoloquinoline alkaloid cryptosanguinolentine based on microwave-assisted reactions. The microwave-assisted synthesis of an intermediate 4-hydroxy-2-methylquinoline yielded 86% of the desired product and other intermediates prepared yielded high % of products in shorter reaction times, under optimum conditions, as compared to traditional methods. Gu L et al.[29] improved procedure for the synthesis of indole-2-carboxylic acid esters in excellent yields has been achieved by the condensation of 2-halo aryl aldehydes or ketones and ethyl isocyanoacetate using ionic liquid under controlled microwave irradiation (100 W) at 50 ℃. This method offers a number of advantages in terms of methodology, high-product yield, and short period of conversion, mild reaction conditions and easy workup. Khan MA et al.[30] have synthesized a series of Ti (III), V (III), Cr (III), Mn (III), Fe (III), Co (III) and Ru (III) complexes from the Schiff base ligand. The Schiff base ligand is N'-Tosyl-1H-indole-2-carbohydrazide has been synthesized by the condensation of Indole-2-carboxyllic acid with p-tolune sulfonyl hydrazide. The resulting complexes were characterized by elemental analyses, magnetic moment measurement, conductivity measurement, IR, 1HNMR and EPR spectral studies. All the complexes were tested for their anti-Inflammatory and analgesic activities. From the data, an octahedral geometry around the central metal ion has been suggested for all the metal complexes. The biological activity data show that the ligand and its complexes possess good analgesic activity. Majumder A and co-workers[31] have used microwave (MW) radiation as a source of heating in organic synthesis. Since the discovery of the MW heating approach, MW-assisted reaction has emerged as a new green-method in organic synthesis as it provides spectacular accelerations, higher yields under milder reaction conditions, and higher product purities, and it reduces pollution of the environment through the use of solvent-free reaction protocols. N-containing heterocyclic hold a special place among pharmaceutically significant natural products and synthetic compounds needed for any developed human society. Therefore, organic chemists have been engaged in extensive efforts to produce these compounds following various greener techniques, primarily to circumvent growing environmental concerns. In this review, we discuss only the MW-assisted synthesis of N-containing heterocyclic compounds and medicinal importance of indole and its derivatives.

Medicinal Importance

Das AA et al.[32] have explored on Oxidative stress results from an imbalance in the production of reactive oxygen species (ROS) and cell's own antioxidant defenses that in part lead to numerous carcinogenesis. Several phytochemicals, derived from vegetables, fruits, herbs and spices, have demonstrated excellent chemopreventive properties against carcinogenesis by regulating the redox status of the cells during oxidative stress. Indole-3-carbinol and diindolylmethane are the phytochemicals that are found in all types of cruciferous vegetables and demonstrated exceptional anti-cancer effects against hormone responsive cancers like breast, prostate and ovarian cancers. Novel analogs of its designed to enhance the overall efficacy, particularly with respect to the therapeutic activity and oral bioavailability and that result in several patent applications on symptoms associated with endometriosis, vaginal neoplasia, cervical dysplasia and mastalgia. Likewise, diindolylmethane and its derivatives have been patented for treatment and prevention of leiomyomas, HPV infection, respiratory syncytial virus, angiogenesis, atherosclerosis and anti-proliferative actions. On the other hand, phytochemicals in cardamom have not been explored in great details but limonene and cineole demonstrated promising effects against carcinogenesis. Thus studies with selected phytochemicals of cardamom and bioavailability research might lead to many patent applications. They focused on the patents generated on the effects of indole-3-carbinol, diindolylmethane and selected phytochemicals of cardamom on carcinogenesis. Ziedan NI et al.[33] have designed a series of new indole based 3, 5-disubstituted 1, 2, 4-oxadiazoles as potential pro-apoptotic antitumour agents, via the base-catalysed condensation reaction between substituted amidoximes and indole esters. Antiproliferative activity against the human cancer cell lines COLO 320 (colorectal) and MIA PACA-2 (pancreatic) has been observed that revealed IC_{50} values in the low micromolar range. Selected compounds were able to trigger apoptosis in sensitive cell lines, for example via activation of caspase-3/7, demonstrating that indole-based oxadiazoles possess in vitro antitumour and pro-apoptotic activity.

Tan DX et al.[34] have found melatonin as a potent free radical scavenger in 1993. Since, then over 800 publications have directly or indirectly confirmed this observation. Melatonin scavenges a variety of reactive oxygen and nitrogen species including hydroxyl radical, hydrogen peroxide, singlet oxygen, nitric oxide and peroxynitrite anion. Based on the analyses of structure-activity relationships, the indole moiety of the melatonin molecule is the reactive center of interaction with oxidants due to its high resonance stability and very low activation energy barrier towards the free radical reactions. However, the methoxy and amide side chains also contribute significantly to melatonin's antioxidant capacity. The carbonyl group is key for melatonin to scavenge the second reactive species and the nitrogen in the N-C=O structure is necessary for melatonin to form the new five membered ring after melatonin's interaction with a reactive species.

The methoxy group in C5 appears to keep melatonin from exhibiting prooxidative activity. If the methoxy group is replaced by a hydroxyl group, under some in vitro conditions, the antioxidant capacity of this molecule may be enhanced. However, the cost of this change is decreased lipophility and increased prooxidative potential. Therefore, in vivo studies the antioxidant efficacy of melatonin appears to be superior to its hydroxylated counterpart. The mechanisms of melatonin's interaction with reactive species probably involves donation of an electron to form the melatoninyl cation radical or through a radical addition at the site C3. Other possibilities include hydrogen donation from the nitrogen atom or substitution at position C2, C4 and C7 and nitrosation. Melatonin has also the ability to repair damaged biomolecules as shown by the fact that it converts the guanosine radical to guanosine by electron transfer. Unlike the classical antioxidants, melatonin is devoid of prooxidative activity and all known intermediates generated by the interaction of melatonin with reactive species are also free radical scavengers. This phenomenon is defined as the free radical scavenging cascade reaction of the melatonin family. Srivastava B et al.[35] studied the antitumour promoting potential of indole-3-carbinol, a major indole metabolite present in the cruciferous vegetables. There has been growing interest in recent years in the potential of brassica vegetables (cabbage, cauliflower, brussels sprouts, etc.) as vectors for the introduction of anticarcinogenic compounds in the diet. Indole-3-carbinol, has also been found to inhibit various rodent tumours when administered prior to or during carcinogen exposure. In this study, the antitumour promoting potential of indole-3-carbinol was studied in a two-stage mouse skin model of carcinogenesis. After one week, 250 µg of indole-3-carbinol was applied topically to each animal prior to promotion with 5 µg Tissue plasminogen activator twice per week. Tumour development was significantly inhibited in indole-3-carbinol-supplemented animals in terms of cumulative numbers of tumours and average tumours per mouse. About 44% of male and 29% of female mice remained tumour-free in this group at the end of the experiment. A significant delay in the tumour induction time was also observed in indole-3-carbinol-supplemented animals. This evidence suggests that indole-3-carbinol, in the manner and dose given, inhibits the development of tumours in the two-stage mouse skin model of carcinogenesis Gazit A et al.[36] prepared a series of 3-indoleacrylonitrile tyrphostins, 2-chloro-3-phenylquinolines, and 3-arylquinoxalines and tested for inhibition of platelet-derived growth factor receptor tyrosine kinase (PDGF-RTK) activity. The potency of the inhibitors was found to be quinoxalines > quinolines > indoles. Lipophilic groups (methyl, methoxy) in the 6 and 7 positions and phenyl at the 3 position of quinoxalines and quinolines were essential for potency, in contrast to the hydrophilic catechol group in tyrphostins active against Epidermal Growth Factor Receptor (EGFR) kinase inhibition at different sites. The inhibitors showed selectivity for PDGF and were not active against EGF receptor and HER-2/c-ErbB-2 receptor. Xiong WN et al.[37] were synthesized

Mono(indolyl)-4-trifluoromethylpyridines and bis(indolyl)-4-trifluoromethylpyridines by using Suzuki cross-coupling reaction between 2-chloro-4-trifluoromethylpyridine , 2,6-dichloro-4-trifluoromethylpyridine or 2,6-dichloro-3-cyano-4-trifluoromethylpyridine and N-tosyl-3-indolylboronic acid . They were evaluated for cytotoxic activity against P388 and A-549 cells with IC_{50} values. 4-trifluoromethyl-2,6-bis[3′-(N-tosyl-6′-methoxylindolyl)]pyridine was identified as the most potent in this series. Angenot L et al.[38] described the chemical separation and identification of ten alkaloids extracted from the roots of Strychnosusambarensis. One of the tertiary amine alkaloids (usambarensine) presents atopine-like and spasmolytic activities while the bisquaternary ammonium compounds (dihydrotoxiferine, calebassine, C-curarine and afrocurarine) are competitive neuromuscular blocking agents. Ölgen S et al.[39] reported a series of N-substituted indole-2-carboxamide and indole-3-acetamide derivatives and their *in vitro* effects on rat liver lipid peroxidation levels and superoxide anion formation were determined. The results clearly demonstrated that indole derivatives were very efficient antioxidants compared to α-tocopherol. Delorenzi JC et al.[40] showed in their study the leishmanicidal effects of a chloroform fraction (CLF) and a purified indole alkaloid obtained from crude stem extract of Peschiera australisagainstLeishmania amazonensis, a causative agent of cutaneous leishmaniasis in the New World. In a bioassay-guided chemical fractionation, the leishmanicidal activity in CLF completely and irreversibly inhibited promastigote growth. This fraction was also active against amastigotes in infected murine macrophages. Chemical analysis of CLF identified an iboga-type indole alkaloid coronaridine as one of its major compounds. Coronaridine showed potent antileishmanial activity, inhibiting promastigote and amastigote growth. Promastigotes and amastigotes treated with CLF or coronaridine showed pronounced alterations in their mitochondria as assessed by transmission electron microscopy.

Kuş C et al.[41] synthesized some 6-fluoro-5-substituted-benzimidazole derivatives in which indole and 1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene groups were attached to the 2-position of the benzimidazole ring and tested for antioxidant properties in vitro. Almost all the synthesized compounds at the 10^{-3} M concentrations showed superoxide anion scavenging activity. Some of these copmpouds have strong inhibitory effects on superoxide anion formation at 10^{-3} M concentration and these results are better than 30 IU of superoxide dismutase (SOD) (76%).

Matsumoto K and co-workers[42] have investigated the opioid effects of 7-hydroxymitragynine, which is isolated as its novel constituent, on contraction of isolated ileum, binding of the specific ligands to opioid receptors and nociceptive stimuli in mice. In guinea-pig ileum, 7-hydroxymitragynine inhibited electrically induced contraction through the opioid receptors. Receptor-binding assays revealed that 7-hydroxymitragynine has a higher affinity for μ-opioid receptors relative to the other

opioid receptors. It has been administrated that the 7-hydroxymitragynine (2.5–10 mg/kg) induced dose-dependent antinociceptive effects in tail-flick and hot-plate tests in mice. Its effect was more potent than that of morphine in both tests. When orally administered, 7-hydroxymitragynine (5–10 mg/kg) showed potent antinociceptive activities in tail-flick and hot-plate tests. In contrast, only weak antinociception was observed in the case of oral administration of morphine at a dose of 20 mg/kg. It was found that 7-hydroxymitragynine is a novel opioid agonist that is structurally different from the other opioid agonists, and has potent analgesic activity when orally administered. Sinha D et al.[43] derived eight novel heterocyclic Schiff bases from the condensation reactions of indole 3-carboxaldehyde with different L-amino acids (histidine, glutamic acid, aspartic acid, leucine, valine) as well as with some aminophenols, have been synthesized and characterized by various spectroscopic methods (IR, MS, ^{1}H NMR). Schiff base derivatives of indole 3-carboxaldehyde were labeled with ^{99m}Tc and radiochemical purity was above 97% which is ascertained by instant thin layer chromatography using different solvent conditions. Stability studies of all the derivatives of indole 3-carboxaldehyde was determined under physiological conditions and were stable for more than 24 h. Blood clearance showed a quick wash out from the circulation and biological half-life was found to be $t_{½}$(F) = 1 h 15 min; $t_{½}$(S) = 10 h 05 min. Excellent quality radioimages of tumor bearing mice were recorded showing rapid clearance of background activity, visualization of tumor at 3 h and clearance from kidneys of histidine analogue which was further evidenced in biodistribution studies. Antimicrobial activity of these Schiff base compounds was evaluated against Bacillus subtilis, Pseudomonas fluorescence, Staphylococcus aureus, Aspergillus niger, Candida albicans and Trichophyton rubrum. Brancale A and co-workers[44] have reported that microtubules are the basic components of cell structure, which take part in a wide number of pivotal cellular functions. Drugs that are able to modulate the microtubule assembly either by inhibition of tubulin polymerization or by blocking microtubule disassembly are of great interest in anti-cancer therapy. Several tubulin polymerization inhibitors characterized by the presence of an indole nucleus have been obtained from natural sources or have been prepared by semi-synthesis. In the last decade the numbers of synthetic indoles have been reported. They have reviewed anti-tubulin agents obtained by synthesis having an indole as core nucleus. The synthesis, biological activity, and the structure–activity relationship aspects of 3-formyl-2-phenylindoles, heterocombretastatins, diarylindoles, 2-aroylindoles, D-24851, 2-aryl-3-aroylindoles, 3-aroyl- and 1-aroylindoles, and arylthioindoles have been discussed. Stansfield I et al.[45] reported the evolutionary path from an open-chain series to conformationally constrained tetracyclic indole inhibitors of HCV NS5B-polymerase, where the C2 aromatic is tethered to the indole nitrogen. SAR studies led to the discovery of zwitterionic compounds endowed with good intrinsic enzyme affinity and cell-based potency, as well as superior

DMPK profiles to their acyclic counterparts, and ultimately to the identification of a pre-clinical candidate with an excellent predicted human pharmacokinetic profile.

Vliegen I et al.[46] identified substituted imidazopyridines as potent and selective inhibitors of in vitro HCV replication has optimize by them. The particular characteristics of one of the most potent compounds in this series (5-[[3-(4-chlorophenyl)-5-isoxazolyl]methyl]-2-(2,3-difluorophenyl)-5H-imidazo[4,5-c]pyridine or GS-327073), were studied. Harper S et al.[47]observed that the infections caused by hepatitis C virus (HCV) are a significant world health problem for which novel therapies are in urgent demand. Compounds that block replication of subgenomic HCV RNA in liver cells are of interest because of their demonstrated antiviral effect in the clinic. In follow up to our recent report that indole-N-acetamides are potent allosteric inhibitors of the HCV NS5B polymerase enzyme, they describe here their optimization as cell-based inhibitors. The crystal structure of 3-cyclohexyl-1-(2-(2-((dimethylamino) methyl) morpholino)-2-(4-methoxyphenyle)-1H indole-6-corboxylic acid bound to NS5B was a guide in the design of a two-dimensional compound array that highlighted that formally zwitterionic inhibitors have strong intracellular potency and that pregnane X receptor (PXR) activation (an undesired off-target activity) is linked to a structural feature of the inhibitor. Optimized analogues devoid of PXR activation (e.g., 55, EC50 = 127 nM) retain strong cell-based efficacy under high serum conditions and show acceptable pharmacokinetics parameters in rat and dog.

Lan R et al.[48] designed a series of pyrazole derivatives was to aid in the characterization of the cannabinoid receptor binding sites and also to serve as potentially useful pharmacological probes. As a potent, specific antagonist for the brain cannabinoid receptor (CB1), the biarylpyrazole *N*-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1*H*-pyrazole-3-carboxamide (SR141716A; 1) was the lead compound for initiating studies designed to examine the structure−activity relationships of related compounds and to search for more selective and potent cannabimimetic ligands. Therapeutically, such compounds may have the ability to antagonize harmful side effects of cannabinoids and cannabimimetic agents. Structural requirements for potent and selective brain cannabinoid CB1 receptor antagonistic activity included (a) a para-substituted phenyl ring at the 5-position, (b) a carboxamido group at the 3-position, and (c) a 2,4-dichlorophenyl substituent at the 1-position of the pyrazole ring. The most potent compound of this series contained a p-iodophenyl group at the 5-position, a piperidinyl carboxamide at the 3-position, and a 2,4-dichlorophenyl group at the 1-position of the pyrazole ring. The iodinated nature of this compound offers additional utility as a γ-enriching single photon emission computed tomography (SPECT) ligand that may be useful in characterizing brain CB1 receptor binding *in vivo*.

Lange JH et al.[49] designed a series of thiazoles, triazoles, and imidazoles as bioisosteres, based on the 1,5-diarylpyrazole motif that is present in the potent CB1 receptor antagonist rimonabant (SR141716A, 1). A number of target compounds has been synthesized and evaluated in cannabinoid (hCB1 and hCB2) receptor assays. The thiazoles, triazoles, and imidazoles elicited in vitro CB1antagonistic activities and in general exhibited considerable CB1 vs CB2 receptor subtype selectivities, thereby demonstrating to be cannabinoid bioisosteres of the original diarylpyrazole class. Some key representatives in the imidazole series showed potent pharmacological in vivo activities after oral administration in both a CB agonist-induced hypotension model and a CB agonist-induced hypothermia model. Molecular modeling studies showed a close three-dimensional structural overlap between the key compound and rimonabant. A structure−activity relationship (SAR) study revealed a close correlation between the biological results in the imidazole and pyrazole series.

Sauzem PD et al.[50] reported the synthesis and evaluation of the analgesic and anti-inflammatory properties of novel 3- or 4-substituted 5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-1-carboxyamidepyrazoles (where 3-/4-substituent = H/H, Me/H, Et/H, Pr/H, i-Pr/H, Bu/H, t-Bu/H, Ph/H, 4-Br-Ph/H and H/Me) designed in the exploration of the bioisosteric replacement of benzene present in salicylamide with a 5-trifluoromethyl-4,5-dihydro-1H-pyrazole scaffold. Target compounds were synthesized from the cyclocondensation of 4-alkoxy-1,1,1-trifluoromethyl-3-alken-2-ones with semicarbazide hydrochloride through a rapid one-pot reaction via microwave irradiation. In addition to spectroscopic data, the structure of the compounds was supported by X-ray diffraction. Subcutaneous administration of the 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles decreased pain-related behavior during neurogenic and inflammatory phases of the formalin test in mice. Moreover, the more active analgesic compounds (3-/4- = Et/H and H/Me) significantly decreased carrageenan-induced paw edema in mice. The data obtained in this work suggest that the synthesized compounds could be promising candidates for the future development of novel analgesic and anti-inflammatory agents. Diana P et al.[51] developed a series of 10 bis-indolylpyrazoles by cyclization of diketones using hydrazine monohydrate or methylhydrazine in refluxing acetic acid/THF. Derivatives were selected, by the National Cancer Institute (NCI, Bethesda, USA), to be evaluated against the full panel of about 60 human tumor cell lines derived from nine human cancer cell types and showed antiproliferative activity in the micromolar range.

Singh K et al.[52] have synthesized and characterized by two new Schiff bases of 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde and 4-amino-5-mercapto-3-methyl/H-1,2,4-triazole [HL1–2] and their cobalt, nickel, copper and zinc complexes. A square planar geometry for Cu(II) and octahedral geometry for Co(II), Ni(II) and Zn(II) complexes have been proposed. In order to evaluate

the biological activity of Schiff bases and to assess the role of metal ion on biological activity, the pyrazole Schiff bases and their metal complexes have been studied in vitro antibacterial against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa and antifungal against Aspergillus niger, and Aspergillus flavus. In most of the cases higher activity was exhibited upon coordination with metal ions.

Tanitame A et al.[53] synthesized new pyrazole derivatives and found that 5-[(E)-2-(5-chloroindol-3-yl)vinyl]pyrazole possesses potent antibacterial activity and selective inhibitory activity against bacterial topoisomerases. Previously found that a pyrazole derivative possesses antibacterial activity and inhibitory activity against DNA gyrase and topoisomerase IV. Many of the synthesized pyrazole derivatives were potent against clinically isolated quinolone- or coumarin-resistant Gram-positive strains and had minimal inhibitory concentration values against these strains equivalent to those against susceptible strains.

Sivaram H et al.[54] synthesized a series of Au(I) and Au(III) mono-, homobis-, and heterobis(carbene) complexes. Complexes have been fully characterized using multinuclei NMR spectroscopy, ESI mass spectrometry, X-ray diffraction analyses and elemental analysis. Together with the previously reported [AuCl(iPr2-bimy)], the cytotoxic activities of all complexes have been studied in vitro with the NCI-H1666 non-small cell lung cancer cell line. Some of cationic bis(carbene) complexes show better cytotoxicity in comparison to cisplatin. In particular, the heterobis(carbene) complexes [Au(FPyr)(iPr2-bimy)]PF6 and [AuCl2(FPyr)(iPr2-bimy)]PF6 have superior activity, with IC50 values of around 0.2 μM.

McClure K et al.[55] screened anagonised activity for compound 3-(1-(4-methoxyphenyl)-5-p-toly-1*H*-pyrazol-3-yl)-2-(naphalen-1-yl) propanoic acid as a potent antagonist of the CCK1 receptor. Evaluation of the CCK1 SAR in a series of these diarylpyrazole antagonists was conducted in a matrix synthesis format revealing additive (Free–Wilson) and non-additive SAR. This use of additive QSAR modeling in conjunction with combinatorial libraries represents a unique approach to the evaluation of SAR interactions between the variables of any combinatorial matrix.

Bekhit AA et al.[56] described the synthesis of novel series of structurally related 1H-pyrazolyl derivatives. All the newly synthesized compounds were tested for their in vivo anti-inflammatory activity by two different bioassays namely; cotton pellet-induced granuloma and sponge implantation model of inflammation in rats. In addition, COX-1 and COX-2 inhibitory activities, ulcerogenic effects and acute toxicity were determined. The same compounds were evaluated for their *in vitro* antimicrobial activity against Escherichia coli, as an example of Gram negative bacteria, Staphylococcus aureus as an example of Gram positive bacteria, and Candida albicans as a representative of fungi. The combined anti-inflammatory data from local and systemic in vivo animal

models showed that most of the compounds exhibited anti-inflammatory activity comparable to that of indomethacin with no or minimal ulcerogenic effects and high safety margin (LD50>500 mg/Kg). In addition, some of compounds displayed appreciable antibacterial activities when compared with ampicillin, especially against S. aureus. Therefore, such compound would represent a fruitful matrix for the development of anti-inflammatory-antimicrobial candidates.

Pitucha M et al.[57] have prepared N-substituted 3-amino-5-hydroxy-4-phenyl-1*H*-pyrazole-1-carboxamide derivatives by heterocyclization of 1-cyanophenyl acetic acid hydrazide with isocyanates. Representative compounds were evaluated as potential antimicrobial agents. The most promising compound in this series, the N-(1-naphthyl)-3-amino-5-hydroxy-4- phenyl-1H-pyrazole-1-carboxamide, was the most effective against the reference strains of pathogenic S. aureus ATCC 25923 and S. aureus ATCC 6538 or opportunistic S. epidermidis ATCC 12228 with MIC value of 7.81 µg/ml and against the other Gram-positive species with MIC values 15.63-31.25 µg/ml. This compound also showed high activity against clinical isolates of MSSA (methicillin-sensitive Staphylococcus aureus) with MIC of 0.98 - 31.25 µg/ml and MRSA (methicillin- resistant Staphylococcus aureus) with MIC of 1.96 - 7.81 µg/ml. A Mohd et al.[58] designed a new class of 4-arylhydrazono-1-benzothiazolyl-3-methylpyrazolin-5-ones and 4-arylazo-1-benzothiazolyl-3,5-dimethylpyrazoles as pharmacophore hybrids between pyrazolinone/pyrazole and benzothiazole moiety. The target molecules were efficiently synthesized by the cyclization of various oxobutyrates/pentane-2,4-dione derivatives with 6-chloro-2-hydrazinobenzothiazole in the presence of glacial acetic acid. The compounds were evaluated for their *in vitro* antimicrobial activity. Preliminary study of the structure–activity relationship revealed that electron-withdrawing groups in phenyl ring had a promising effect on the antimicrobial activity. Also, correlation study has been used to establish the relationships between the antibac terial activity and physicochemical parameter clog P. Dhanya S al.[59] synthesized a series of 5-substituted-4-amino-3-mercapto-1,2,4-triazoles and were treated with various 3-substituted pyrazole aldehydes to obtain a series of new Schiff bases. Few of the selected Schiff bases were converted into Mannich bases by reaction with diphenylamine/morpholine in presence of formaldehyde in ethanol media. These newly synthesized compounds were characterized by elemental analysis, IR, NMR and mass spectrometry studies. A comparative study on the cytotoxic activities of few selected Schiff and Mannich bases was done in HepG2 cells using MTT assay. The screened Schiff bases showed dose dependent cytotoxic activity, being the most potent with an IC_{50} value of 0.018 g/l comparable to the standard drug doxorubicin. The Schiff bases were found to be more active, when compared to Mannich bases derived from them. The morpholine derived Mannich bases were more potent than those obtained from diphenyl amine.

Vijesh AM et al.[60] described about the synthesis of three series of new 1,2,4-triazole and benzoxazole derivatives containing substituted pyrazole moiety. The newly synthesized compounds were characterized by spectral studies and C, H, N analyses. All the synthesized compounds were screened for their analgesic activity by the tail flick method. The antimicrobial activity of the new derivatives was also performed by MIC by the serial dilution method. The results revealed that the compound 11c having 2, 5-dichlorothiophene substituent on pyrazole moiety and a triazole ring showed significant analgesic and antimicrobial activity. Fancelli D et al.[61] optimized a series of 5-phenylacetyl 1,4,5,6-tetrahydropyrrolo[3,4-c]pyrazole derivatives the inhibition of Aurora kinases led to the identification of compound, a potent inhibitor of Aurora kinases that also shows low nanomolar potency against additional anticancer kinase targets. Its high antiproliferative activity on different cancer cell lines, favorable chemico-physical and pharmacokinetic properties, and high efficacy in vivo tumor models. Milano J et al.[62] evaluated the antinociceptive effect of the novel pyrazoline methyl ester: 4-methyl-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole methyl ester (MPF4). The effect of MPF4 was assessed in two models of pain: arthritic pain caused by Complete Freund's Adjuvant (CFA) and postoperative pain caused by surgical incision in mice. MPF4 given intraperitoneally (1.0 mmol/kg, i.p.) produced marked antinociception in inflammatory allodynia caused by CFA. The antinociceptive effect produced by MPF4 was reversed with the pre-treatment of animals with naloxone or naltrindole. Oral administration of MPF4 (1.0 mmol/kg, p.o), dipyrone (1.0 mmol/kg, p.o.) and morphine (0.026 mmol/kg, p.o.) also produced an anti-allodynic effect. However, none of the compounds evaluated reversed the paw edema produced by Complete Freund's Adjuvant (CFA). Moreover, MPF4, dipyrone and morphine also produced an anti-allodynic effect in the surgical incisional pain model. The maximal inhibitions obtained with preemptive drug treatment were 66 ± 7%, 73 ± 9% and 88 ± 8% for MPF4 (1.0 mmol/kg, p.o.), dipyrone (1.0 mmol/kg, p.o.) and morphine (0.026 mmol/kg, p.o.), respectively. The maximal inhibitions obtained with curative drug treatment were 53 ± 9%, 83 ± 7% and 84 ± 7%, for MPF4, dipyrone and morphine, respectively. Unlike indomethacin, MPF4 did not induce gastric lesions at the dose that caused the highest antinociception (1.0 mmol/kg). The anti-allodynic action of MPF4, dipyrone and morphine was not associated with impairment of motor activity.

Ishioka T et al.[63] designed and prepared 3-Substituted (Z)-4-(4-N,N-dialkylaminophenylmethylene)-5(4*H*)-isoxazolones and its related compounds as candidates for structurally novel androgen antagonists. Several compounds showed potent anti-androgenic activity as assessed by nuclear androgen receptor binding assay and growth inhibition assay using androgen-dependent Shionogi carcinoma cells SC-3. They were approximately 10–220 times more potent than flutamide in these assay systems. They also showed anti-androgenic activity toward prostate tumor

cell line LNCaP, which has an aberrant nuclear androgen receptor. Deng BL[64] reported alkenyldiarylmethanes (ADAMs) as a unique class of non-nucleoside reverse transcriptase inhibitors that have potential value in the treatment of HIV/AIDS. However, the potential usefulness of the ADAMs is limited by the presence of metabolically labile methyl ester moieties. They were synthesized a series of novel ADAMs in order to replace the metabolically labile methyl ester moieties of the existing ADAM lead compounds with hydrolytically stable, fused isoxazolone, isoxazole, oxazolone, or cyano substituents on the aromatic rings. The methyl ester and methoxy substituents on both of the aromatic rings in the parent compound were successfully replaced with metabolically stable moieties with retention of anti-HIV activity and a general decrease in cytotoxicity. Tong Y et al.[65] synthesized a series of isoxazolo[3,4-b]quinoline-3,4(1*H*,9*H*)-diones as potent inhibitors against Pim-1 and Pim-2 kinases. The structure–activity-relationship studies started from a high-throughput screening hit and were guided by molecular modeling of inhibitors in the active site of Pim-1 kinase. Installing a hydroxyl group on the benzene ring of the core has the potential to form a key hydrogen bond interaction to the hinge region of the binding pocket and thus resulted in the most potent inhibitor like 6-chloro-4-ethyl-7-hydroxyfuro[3,4-*b*]quinolone-1,9(3*H*,4*H*)-dione, with K_i values at 2.5 and 43.5 nM against Pim-1 and Pim-2, respectively. Compound 19 also exhibited an activity profile with a high degree of kinase selectivity. Spiro derivatives of oxindole and isoxazole-5-one by Chande MS et al.[66] synthesized by using Michael addition reaction, highlighting the regioselective approach towards the synthesis of Michael diadduct followed by condensation of Michael diadduct. The spiro compound showed antitubercular activity against Mycobacterium tuberculosis H37Rv. Pandeya SN et al.[67]synthesized by Isatin (Indole 2,3-dione) and its 5-chloro and 5-bromo derivatives to 3-amino-2-methylmercapto quinazolin-4(3*H*)-one to form Schiff bases and the N-Mannich bases of these compounds by reacting with formaldehyde and several secondary amines. Their chemical structures have been confirmed by means of their IR, 1H NMR data and by elemental analysis. Investigation of antimicrobial activity of compounds was done by an agar dilution method against 26 pathogenic bacteria, 8 pathogenic fungi and anti-HIV activity against replication of HIV-1 (III B) in MT-4 cells. Among the compounds tested 5-chloro-3-(3′,4′-dihydro-2′-methylmercapto-4′-oxoquinazolin-3′-yl)-1-morpholino methyl imino isatin was the most active antimicrobial agent.

Tanushree RB et al.[68] synthesized and evaluate a series of isatin β-thiosemicarbazone derivatives for their anti-HIV activity in HTLV-III_B strain in the CEM cell line on the basis of pharmacophoric modelling studies of existing NNRTIs. Most of the compounds showed significant anti-HIV activity, whereupon one compound was found to be the most active compound with an EC_{50} value of 2.62 μM and a selectivity index of 17.41, while not being cytotoxic to the cell line at a

CC_{50} value of 44.90 µM. Other tested compounds exhibited marked activity below their toxicity threshold. Wang J et al.[69] isolated a diprenylated indole, (E)-3-(3-hydroxymethyl-2-butenyl)-7-(3-methyl-2-butenyl)-1*H*-indole and six known carbazole alkaloids were from the twigs and leaves of Glycosmis montana Pierre (Rutaceae). Their structures were determined on the basis of analysis of spectral evidence including 1D and 2D NMR and MS. The alkaloids exhibited weak to moderate take in vitro inhibitory activity against HIV replication in C8166 cells, and they (as well as carbalexine A and B) had cytotoxic activity against the human leukaemia cell line CCRF-CEM.

Pandeya SN et al.[70] reported the reaction between Isatin (indole 2,3-dione) and its 5-chloro and 5-bromo derivatives with 3-(4'-pyridyl)-4-amino-5-mercapto-4-(*H*)-1,2,4-triazole to form Schiff bases and the N-Mannich bases of these compounds were synthesized by reacting them with formaldehyde and several secondary amines. Their chemical structures have been confirmed by means of their IR, 1H NMR data and by elemental analysis. Investigation of antimicrobial activity of compounds was done by agar dilution method against 27 pathogenic bacteria, 8 pathogenic fungi and anti-HIV activity against replication of HIV-1 (III B) in MT-4 cells. Among the compounds tested 1-(piperidinomethyl) 5-bromo 3-[3'-(4"-pyridyl)-5'-mercapto-4'-(*H*)-1',2',4'-triazol 4'-yl]imino isatin showed the most favourable antimicrobial activity. Traxler P et al. in the course of the random screening of a pool of CIBA chemicals, the two pyrazolopyrimidines have dentified[71] as fairly potent inhibitors of the EGF-R tyrosine kinase. Using a pharmacophore model for ATP-competitive inhibitors interacting with the active site of the EGF-R protein tyrosine kinase (PTK), the class of the pyrazolo[3,4-d]pyrimidines was then optimized in an interactive process leading to a series of 4-(phenylamino)-1*H*-pyrazolo[3,4-d]pyrimidines as highly potent inhibitors of the EGF-R tyrosine kinase. The most potent compounds of this series inhibited the EGF-R PTK with IC_{50} values below 10 nM. High selectivity toward a panel of nonreceptor tyrosine kinases (c-Src, v-Abl and serine/threonine kinases (PKC α, CDK1) was observed. In cells, EGF-stimulated cellular tyrosine phosphorylation was inhibited by compounds at IC_{50} values below 50 nM, whereas PDGF-induced tyrosine phosphorylation was not affected by concentrations up to 10 µM, thus indicating high selectivity for the inhibition of the ligand-activated EGF-R signal transduction pathway, at the ATP-binding site of the EGF-R tyrosine kinase is proposed. 4-(Phenylamino)-1*H*-pyrazolo[3,4-d]pyrimidines represent a new class of highly potent tyrosine kinase inhibitors which preferentially inhibit the EGF-mediated signal transduction pathway and have the potential for further evaluation as anticancer agents. The beginning of pyrimidine chemistry may be traced back to the isolation of alloxan, a pyrimidine derivative. The synthesis of barbituric acid from urea and malonic acid perhaps marked the next major event in the development. Since then pyrimidines have occupied a unique and important place in the fields of biological and medicinal chemistry[72]. It is well known that uracil,

thymine, and cytosine are essential constituents in nucleic acids; thiamine that possesses antiberiberi activity was the first vitamin discovered in the B series; barbiturates are widely used as sedatives; pyrimethamine is highly potent against erythrocytic parasites in antimalarial study; aminometradine (Mictine) is an orally effective diuretic; and the 5-halogen-substituted uracils and derivatives have recently been reported as antitumour or antiviral agents, or both. Other pyrimidine derivatives have been found to possess fungicidal, antibacterial, antimitotic, antithyroid and surface-anaesthesia activities. With the exception of pyrimidine antibiotics, in this chapter, pyrimidines are classified based on special structural features and functional groups. The chapter discusses the following areas: 2,4- diaminopyrimidines, halogenated pyrimidines, sulphur-substituted pyrimidines, 2-substituted 4-amino-5-hydroxymethylpyrimidines, pyrimidine sulphonamides and pyrimidine antibiotics.

This research group[73] lists some pyrimidines of biological and medicinal interest, including 5-hydroxypy rimidines, barbituric acid and its derivatives, aminohydroxypyrimidines, pyrimidine amino acids, and nitro and nitrosopyrimidines. This chapter discussed pyrimidines containing biological alkylating functions. A large number of derivatives of the original nitrogen mustard and other biological akylating agents, such as ethylenimines and epoxides have been prepared as potential anticancer agents. This chapter further explains that the alkylating agents consist of a carrier and the alkylating group, and those differences in selectivity of action upon the tumour, or ability to reach the site of desired action, with minimum damage to the host, is dependent upon the carrier. In their chapter they also reviewed some pyrimidines containing two ethylenimine functions and found to possess anticancer activity. 2, 4-Bis (aziridinyl)-6-chloropyrimidine (CV, ethymidine, etimidin) significantly inhibits growth of many transplantable mouse and rat tumours.

A putative binding mode of the isoflavone genistein was proposed[74] by using a pharmacophore model for ATP-competitive inhibitors interacting with the active site of the Epidermal growth factor receptor (EFGR) protein tyrosine kinase together with published X-ray crystal data of quercetin in complex with the Hck tyrosine kinase and of deschloroflavopiridol in complex with CDK2. Then, based on literature data suggesting that a salicylic acid function, which is represented by the 5-hydroxy-4-keto motif, could serve as a pharmacophore replacement of a pyrimidine ring, superposition of 1 onto the potent Epidermal growth factor receptor (EFGR) tyrosine kinase inhibitor 4-(3‘-chlorophenylamino)-6,7-dimethoxyquinazoline led to 3‘-chloro-5,7-dihydroxyisoflavone as a target structure which in fact was 10 times more potent than isoflavone genistein . The putative binding mode of 3‘-chloro-5,7-dihydroxyisoflavone suggests a sulfur−aromatic interaction of the m-chlorophenyl moiety with Cys 773 in the “sugar pocket” of the Epidermal growth factor receptor (EFGR) kinase model. Replacement of the oxygen in the

chromenone ring of 3‘-chloro-5,7-dihydroxyisoflavone by a nitrogen atom further improved the inhibitory activity against the EGFR kinase.

Ostrowski T et al.[75]described a new series of anhydrohexitol nucleosides, having a pyrimidine base moiety substituted in the 5-position with a chloro, trifluoromethyl, vinyl, 2-thienyl, ethynyl or propynyl substituent. The vinyl, propynyl and in particular, the 5-trifluoromethyl analogue showed potent activity against herpes simplex virus (HSV), with a selectivity index of >16000 against HSV-1 and >1000 against HSV-2. Conformational analysis of anhydrohexitol nucleosides using computational methods indicates that these nucleosides occur in equilibrium between the C1 and 1C form with a ΔE of 5.9 kJ/mol. When the anhydrohexitol nucleoside is co-crystallized with the HSV-1 thymidine kinase it adopts a 1C conformation, which is opposite to the conformation found for the small molecule alone. The enzyme, apparently, induces a conformational change, and conformational flexibility of an anhydrohexitol nucleoside may be advantageous for recognition by viral enzymes.

Extensive research on developing non-peptide human luteinizing hormone-releasing hormone (LHRH) antagonists has been carried[76] out by employing a strategy of replacing the thienopyridin-4-one nucleus with other heterocyclic surrogates. They described the design and synthesis of a series of thieno[2,3-d]pyrimidine-2,4-dione derivatives containing a biaryl moiety, which led to the discovery of a highly potent and orally active non-peptide LHRH antagonist, 5-(N-benzyl-N-methylaminomethyl)-1-(2,6-difluorobenzyl)-6-[4-(3-methoxyureido)phenyl]-3-phenylthieno[2,3-d]pyrimidine-2,4(1*H*,3*H*)-dione. This compound showed high binding affinity and potent in vitro antagonistic activity for the human receptor with half-maximal inhibition concentration (IC_{50}) values of 0.1 and 0.06 nM, respectively. Oral administration of this caused almost complete suppression of the plasma LH levels in castrated male cynomolgus monkeys at a 30 mg/kg dose with sufficient duration of action (more than 24 h). The results demonstrated that the thienopyrimidine-2,4-dione core is an excellent surrogate for the thienopyridin-4-one and that thienopyrimidine-2,4-diones and thienopyridin-4-ones constitute a new class of potent and orally bioavailable LHRH receptor antagonists. Furthermore, molecular modeling studies indicate that the unique methoxyurea side chain of this compound preferentially forms an intramolecular hydrogen bond between the aniline NH and the methoxy oxygen atom. On the basis of its profile, this has been selected as a candidate for clinical trials and it is expected that it will provide a new class of potential therapeutic agents for the clinical treatment of a variety of sex-hormone-dependent diseases.

Kumar R et al.[77]synthesized a series of pyrimidine nucleosides possessing a variety of substituents at the C-5 position, and a 1-[(2-hydroxy-1-(hydroxymethyl)ethoxy)methyl] flexible acyclic glycosyl moiety at the N-1 position, that have the ability to mimic the natural 2‘-deoxyribosyl

moiety. Hepatitis B virus (HBV) is the most common cause of chronic liver disease worldwide. Development of drug resistance against clinical anti-HBV drug lamivudine due to long-term use and rebound of viral DNA after cessation of treatment has been a major setback of the current therapy. Other variations of the uracil derivatives were the 6-aza congeners. 4-amino and 4-methoxy pyrimidine derivatives have also been made. Compounds in which the base moiety was substituted by 5-chloro, 5-(2-bromovinyl), or 5-bromo-6-methyl groups possess significant activity against duck-HBV, wild-type human HBV (2.2.15 cells), and lamivudine-resistant HBV containing single and double mutations. No cytotoxicity was seen in host HepG2 and Vero cells, up to the highest concentration tested. The anti-HBV activity exhibited by compounds which are substituted with5-chloro, 5-(2-bromovinyl), and 5-bromo-6-methyl was superior for human HBV and comparable for DHBV to that of the corresponding purine nucleoside, ganciclovir. Further, they were only 10−15-fold less inhibitory against human HBV in 2.2.15 cells than the reference drug, lamivudine. Other compounds in the series were moderately inhibitory against DHBV and wild-type human HBV. The size of the halogen and the electronegativity of the substituents at the 5- and 6-positions are important for antiviral activity toward HBV. These compounds were also evaluated for their antiviral activity for West Nile virus, respiratory syncytial virus, SARS-coronavirus, and hepatitis C virus. They were generally inactive in these antiviral assay systems (at concentrations upto 100 µg/mL). 1-[(2-Hydroxy-1-(hydroxymethyl) ethoxy)methyl]-5-fluorocytosine showed some inhibitory activity against hepatitis C virus. Taken together, these data support our previous observations that the 5-substituted pyrimidine nucleosides containing acyclic glycosyl moieties have potential to serve as a new generation of potent, selective, and nontoxic anti-HBV agents for wild-type and lamivudine-resistant mutant HBV.

Trivedi AR et al.[78] synthesized a series of phenothiazine clubbed pyrazolo[3,4-d]pyrimidines by using the Biginelli multi-component cyclocondensation reaction and their ability to inhibit growth of Mycobacterium tuberculosis in vitro have been determined. The results showed that compounds exhibited excellent anti-tubercular activity at of <6.25 µg/ml. Oral B [79] et al**.** synthesized novel derivatives of substituted hydrazone, 2-pyrazoline-5-one and 2-isoxazoline-5-one derivatives possessing 1,3,4-thiadiazole moiety were and evaluated for their antitubercular activity. The highest inhibitions were observed with the synthesized compounds are 87% for 3-methyl-4-[4-(5-cyclohexylamino- 1,3,4-thiadiazole-2-yl)phenylhydrazono]-2-isoxazoline-5-one and 86% for ethyl 2-[4-(5-cyclohexylamino-1,3,4-thiadiazole-2-yl)phenylhydrazono]-3-oxobutirate. Mantu D et al.[80] have design, synthesis, structure and the antimycobacterial activities of a new class of nitrogen heterocycles, namely N1-substituted-diphenyl ether-bis-pyridazine (BP). An efficient, facile and straight applicable method for preparation of BP derivatives has been described. The primary cycle

high throughput screening reveals that two BP compounds are potent inhibitors against Mycobacterium tuberculosis (Mtb), with their antitubercular activity being superior to the second-line antitubercular drug Pyrimethamine and being equal to Cycloserine. The data from cycle-2 screening confirm the results from cycle-1. The MIC, MBC, LORA, intracellular (macrophage) drug screening, and MTT cell proliferation, indicate the intracellular drug effectiveness against Mtb of these compounds, the lack of toxicity, a significant activity against both replicating and non-replicating Mtb and, a bactericidal mechanism of action. SAR correlations have also been done. Overall, the BP derivatives, appeared as a new leading antitubercular structure, which makes it a promising lead for further drug development.

A series of 6,7,8-substituted thiosemicarbazones of 2-chloro-3-formyl-quinoline derivatives were cyclized[81] to 1,3,4-thiadiazole using acetic anhydride. The structures of the final compounds 1,3,4-thiadiazole were confirmed by elemental and spectral (IR, ^{1}H NMR and MS) analysis. Some of the title compounds have shown promising anticancer and antitubercular activities. Mannich base sydnone derivatives were prepared[82] via a four-step procedure using starting material 4-methoxyaniline. The structure of all synthesized compounds was confirmed by FT-IR,^{1}H NMR, ^{13}C NMR, and CHN analysis. The synthesized compounds were tested for their antibacterial and antifungal activity (MIC) in vitro against organisms viz. B. subtilis, S. aureus, E. coli,P. aeruginosa, and C. albicans taking ciprofloxacin, ampicillin, streptomycin, penicillin-G, fluconazole, and nystatin as the standard drugs. Kenchappa R et al.[83] synthesized a novel series of benzofuran derivatives, containing barbitone moiety, 5-[(2/4-substitutedphenyl)(5-substituted-1-benzofuran-2-yl)methylidene]pyrimidin-2,4,6(1*H*,3*H*,5*H*)-trione and thiobarbitone moiety, 5-[(2/4-substitutedphenyl)(5-substituted-1-benzofuran-2-yl)methylidene]-2-thioxodihydropyrimidin-4,6(1H, 5H)-dione. The target compounds were synthesized by the Knoevenagel condensation of (5-substituted-1-benzofuran-2-yl)(2/4-substitutedphenyl) methanone with barbituric acid and thiobarbituric acid, respectively, in acid medium. These compounds were screened for the antimicrobial and antioxidant activities. From antimicrobial activity results it was found that these compounds displayed good antibacterial and antifungal activity against all tested strains. Further, the synthesized compounds were studied for docking on the enzyme, Glucosamine-6-phosphate synthase and the compounds have emerged has an active antimicrobial agent with least binding energy (−5.27 and −4.85 kJ mol^{-1}). Mugnaini C et al.[84] fluoroquinolones have approved by the WHO as second-line drugs to treat tuberculosis (TB), and their use in multidrug-resistant (MDR)-TB is increasing due to the fact that they have a broad and potent spectrum of activity and can be administered orally. In the last years, quinolones endowed with “nonclassical” biological activities, such as antitumor, anti-HIV-1 integrase, cannabinoid receptor 2 agonist/antagonist activities have been reported by their

research group as well as by other researchers. Their review focuses on the 4-quinolone-3-carboxylic acid motif as a privileged structure in medicinal chemistry for obtaining new compounds possessing antibacterial, antitumor, anti-HIV, and cannabinoid receptors modulating activities. Synthetic approaches, structure-activity relationships, mechanisms of action, and therapeutic potentials of these novel classes of pharmacologically active compounds have been presented.

The emergence and rapid spread of Multi Drug Resistant (MDR) infectious microbial flora embracing a variety of bacterial, fungal as well as mycobacterium strains are causing a threat to public health worldwide[85]. To cure this dilemma, a library of two series of coumarin based Schiff bases and thiourea derivatives was rationalized, synthesized and accessed for their in vitro antibacterial activity (against Staphylococcus aureus MTCC 96, Bacillus subtilis MTCC 441, Escherichia coli MTCC 739, Pseudomonas aeruginosa MTCC 741 and Klebsiella pneumoniae MTCC 109) and antifungal activity (against Aspergillus niger MTCC 282, Aspergillus fumigates MTCC 343, Aspergillus clavatus MTCC 1323, Candida albicans MTCC 183) using broth dilution technique. Furthermore all the newly synthesized congeners have also been examined for *in vitro* antituberculosis activity (against Mycobacterium tuberculosis H37Rv) using BACTEC MGIT method as well as MIC method on Lowenstein–Jensen medium. Patel NB et al.[86] prepared a series of 6-amino-substituted pyridine-2-(1H)-ones by coupling of substituted 6-(pyrrolidin-1-yl)-2(1H)-pyridinones with aryl diazonium chlorides. The overall sequence provides a simple and efficient route to prepare 6-amino-substituted pyridine-2-(1H)-ones in the form of two isomers, which were separated using column chromatography. The structure of all the compounds has been assigned unambiguously on the basis of elemental analysis, IR and NMR spectral data and has been evaluated for antibacterial and antifungal activities. The active compounds were evaluated for antitubercular activity and compared with standard drug rifampicin. Pandit U synthesized a series of 2-(substituted-phenyl)-3-(((3-(pyridin-4-yl)-1-(p-tolyl)-1H-pyrazol-4-yl)methylene) amino)-quinazolin-4(3*H*)-ones. The structures of the synthesized compounds were assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR, and mass spectral data, while their abilities to inhibit growth of Mycobacterium tuberculosis in vitro have been determined. The results showed that compounds exhibited excellent antitubercular activity MIC of <6.25 µg/mL, Parmar NJ et al.[88] synthesized some new compounds, belonging to three families; dipyrazolo[3,4-b:4′,3′-e]pyranylquinolones and its precursors (pyrazolonylidene)methylquinolones and 4,4′-[(quinolinyl)methylene]bispyrazols , 8 from each, has been achieved in the presence of catalyst tetrabutylammonium hydrogen sulfate (TBA–HS) in solvent-free conditions. In addition to assuring chromatography-free product isolation, this method had also allowed the reaction to proceed in a regio-selective manner provided the temperature and amount of pyrazolone are varied. At 100 ℃, while 1:1 mixture of aldehyde and

pyrazolone underwent Knoevenagel condensation, same reactants taken in ratio of 1:2 mainly domino/Knoevenagel–Michael reaction. At 120 ℃, however, the domino/Knoevenagel–Michael-adducts converted into cyclized product, highlighting a new domino/Knoevenagel–Michael-cyclization synthetic sequence. The structure of all heterocycles has been confirmed by mass, IR and NMR spectral data. Based on 2D NMR NOESY experiment, it was also confirmed that the formation of only 'Z' configuration of Knoevenagel alkene took place in the transformation. All were good antitubercular agents as they were found to be active against M. tuberculosis H37RV, in addition to being found active against three Gram-positive (Streptococcus pneumoniae, Clostridium tetani, Bacillus subtilis) and three Gram-negative (Salmonella typhi, Vibrio cholerae, Escherichia coli) bacteria, respectively.

Al-Soud YA et al.[89] synthesized a series of 1,4-bis-(1,5-dialkyl-1H-1,2,4-triazol-ylmethyl)piperazines and N-methyl-piperazine analogs spontaneously from the cycloaddition of various reactive cumulenes with the piperazino-1,4-(bis-ethanenitrile) and 1-cyanomethyl-4-methyl-piperazine, respectively. The new compounds were evaluated for their DNA affinity and antitumor activity. Anthramycin, sibiromycin and tomaymycin are structurally related antibiotics produced by various actinomycetes[90]. Anthramycin was originally isolated from the fermentation broth of a thermophilic actinomycete, Streptomyces refruineus var. thermotolerans found in a compost heap in the 1950's. The active compound, originally called "refuin" (from the Hebrew "refuah" meaning a medicine), was isolated as a pure crystalline antibiotic in 1965. This antibiotic was subsequently shown to have antibiotic, antitumor, antiprotozoal and chemosterilant activity against houseflies. Tomaymycin, a Japanese antibiotic, produced by Streptomyces achromogenes var. tomaymyceticus, was isolated from a soil sample collected in Musashikoganei-city. The isolation and properties of this antibiotic were first reported in 1972. The structure of tomaymycin and the structurally related but biologically inactive compound, oxotomaymycin, were reported in 1971. Tomaymycin has been shown to have antitumor, antiviral and antibiotic activities. Sibiromycin, the most recent of the three antibiotics to be fully characterized, is produced by the actinomycete, Streptosporangium sibiricum and was first reported at the Moscow Institute for New Antibiotics. Sibiromycin has been shown to have antitumor as well as antibiotic activity. In addition to anthramycin, sibiromycin and tomaymycin, three further structurally related antibiotics have appeared in the literature. The first of these compounds, dextrochrysin which is produced by Streptomyces calms var. dextrochrysus, has been demonstrated to have antiviral as well as antibiotic activity. In recent two isomeric anthramycin-related compounds, neothramycins A and B produced by Streptomyces No. MC916-C4 has been reported. These compounds have been shown to have weak antibiotic and antifungal activity as well as antitumor activity. Rajanarendar E et al.[91] synthesized a series of novel methylene

bis-isoxazolo[4,5-b]azepines by reaction of 3,5-dimethyl-4-nitroisoxazole with an appropriate Methylene bis-chalcones to obtain various Michael adducts , which on treatment with $SnCl_2$–MeOH underwent reductive cyclization to afford the title compounds (Methylene-bis-isoxazolo[4,5-b]azepines) . Structure of these compounds were established on the basis of IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. The title compounds Methylene-bis-isoxazolo[4,5-b]azepines were evaluated for their in vitro antimicrobial and anticancer activities. Compounds exhibited potent antimicrobial and anticancer activities as that of standard drugs.

Gangjee A et al.[92] synthesized a series of 2,4-diamino-6-(arylaminomethyl)pyrido[2,3-d]pyrimidines and evaluated as inhibitors of Pneumocystis carinii (pc), Toxoplasma gondii (tg), and rat liver (rl) dihydrofolate reductase (DHFR) and as inhibitors of the growth of tumor cell lines in culture.some compounds were designed as part of a continuing effort to examine the effects of substitutions at the 5-position, in the two-atom bridge, and in the side chain phenyl ring on structure−activity/selectivity relationships of 2,4-diaminopyrido[2,3-d]pyrimidines against a variety of DHFRs. Reductive amination of the common intermediate 2,4-diaminopyrido[2,3-d]pyrimidine-6-carbonitrile with the appropriate anilines afforded the target compounds . Nucleophilic substitution or reductive methylation afforded the N10-methylwere targeted compounds**.** As predicted, compounds were, in general, less potent against all three DHFRs compared to the corresponding 2,4-diamino-5-methyl analogues previously reported; however, the greater decrease in potency against rlDHFR compared to pcDHFR and tgDHFR resulted in appreciable selectivity toward pathogenic DHFRs from different pathogens. The 2‘,5‘-dichloro analogue showed selectivity ratios (IC_{50} against rlDHFR/IC_{50} against pcDHFR or tgDHFR) of 15.7 and 23 for pcDHFR and tgDHFR, respectively. Thus, the selectivity of this for pcDHFR is higher than the first line clinical agent trimethoprim (TMP). In a P. carinii cell culture study, analogue of this exhibited 88% cell growth inhibition at a concentration of 10 μM and afforded marginal effects in an in vivo study in the T. gondii mouse model. Selected compounds were evaluated in the National Cancer Institute (NCI) in vitro preclinical antitumor screening program and inhibited the growth of tumor cells in culture at micromolar to submicromolar concentrations and were selected for evaluation in a NCI in vivo hollow fiber assay.

Rajanarendar E et al.[93] synthesized a series of novel phenylmethylene bis-isoxazolo[4,5-b]azepine derivatives from 3-methyl-4-nitro-5-styrylisoxazoles . The reaction of 3-methyl-4-nitro-5-styrylisoxazoles with 3,5-dimethyl-4-nitroisoxazole in piperidine afforded the Michael type adducts , which on treatment with different substituted chalcones in the presence of piperidine gave the Michael adducts. Michael adducts underwent reductive cyclization on treatment with $SnCl_2$–MeOH to afford the phenylmethylene bis-isoxazolo[4,5-b]azepine. Structure of these compounds was established on the basis of IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data. The title

compounds derivatives were evaluated for in vitro and in vivo anticancer activity. Phutdhawong WS et al.[94] reported a rapid route to a series of naphthoquinone-fused indole derivatives via irradiation in a modified commercial domestic microwave. The desired products were produced in high yields and short reaction times. The naphthoquinone-fused indole derivatives were evaluated for their pro-inflammatory cytokines responses using lipopolysaccharide (LPS)-stimulated RAW264.7 murine macrophages. The results showed that most of the tested compounds inhibit the production of nitric oxide (NO), prostaglandin (PG)E_2, tumour necrosis factor (TNF)-α, interleukin (IL)-6 and IL-1β in RAW264.7 cells treated with LPS. The polyamine transport system (PTS) whose activity is up-regulated in cancer cells is an attractive target for drug design. Two heterocyclic (azepine and benzazepine) systems were conjugated[95] to various polyamine moieties through an amidine bound to afford some compounds which were evaluated for their affinity for the PTS and their ability to use the PTS for cell delivery. Structure−activity relationship studies and lead optimization afforded two attractive PTS targeting compounds. The azepine−spermidine conjugate is a very selective substrate of the PTS that may serve as a vector for radioelements used for diagnoses or therapeutics in nuclear medicine. The nitrobenzazepine−spermine conjugate is a very powerful PTS inhibitor with very low intrinsic cytotoxicity, able to prevent the growth of polyamine depleted cells in presence of exogenous polyamines.

CONCLUSIONS

From the review of various articles we are able to describe an efficient methodology which is exploited for the preparation of differently substituted indoles through microwave-assisted with good to high yields. The application of microwave irradiation has led to support for the development of many reaction procedures, which are environment friendly, falling in the domain of green chemistry. In this review we also stressed on biological applications of indole and its derivatives in details. There are many derivatives of indoles that are associated with anti-cancer, patented for treatment and prevention of leiomyomas, potent against HPV infection, respiratory syncytial virus, angiogenesis, atherosclerosis, anti-proliferative actions, breast, prostate and ovarian cancers. Several compounds showed potent anti-androgenic activity as assessed by nuclear androgen receptor binding assay and growth inhibition.

ACKNOWLEDGEMENT

We gratefully acknowledge support from the Ministry of Human Resource Development Department of Higher Education, Government of India under the scheme of Establishment of Centre of Excellence for Training and Research in Frontier Areas of Science and

Technology (FAST), for providing the necessary financial support to carry out this study vide letter No, F. No. 5-5/201 4-TS.Vll.

REFERENCES

[1] S. Masamune, Y. Hanzawa, S. Murakami, T. Bally, J. F. Blount, J. Am. HIGHLIGHTS

[2] Angew. Chem. Int. Ed. 2002, 41, No. 11 ¹ WILEY-VCH Verlag GmbH, 69451 Weinheim, Germany, 2002 1433-7851/02/4111-1863 $ 20.00+.50/0 1863

[1] Laurent R, Laporterie A, Dubac J, Berlan J, Lefeuvre S, Audhuy M. Specific activation by microwaves: myth or reality? J. Org. Chem. 1992; 57(26): 7099-7102.

[2] Caddick S. Microwave assisted organic reactions. Tetrahedron Lett. 1995; 5: 10403-10432.

[3] Anastas P, Eghbali N. Green Chemistry: Principles and practice. Chem. Soc. Rev. 2010; 39: 301-312.

[4] Gottlieb MS, Schroff R, Schanker HM, Weisman JD, Fan PT, Wolf RA, and Saxon A. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. N. Eng. J. Med. 1981; 305: 1425-1431.

[5] Giguere RJ, Bray TL, Duncan SM, Majetich G. Application of commercial microwave ovens to organic synthesis. Tetrahedron Lett. 1991; 23: 4945-4958.

[6] Wang X, Lane BS, Sames D. Direct C-Arylation of Free (NH)-Indoles and Pyrroles Catalyzed by Ar−Rh(III) Complexes Assembled In Situ. J. Am. Chem. Soc. 2005; 127(14): 4996–4997.

[7] Haibach MC, Deb I, De CK, Seidel D. Redox-Neutral Indole annulation cascades. J. Am. Chem. Soc. 2011; 133(7): 2100-2103.

[8] Lefemine DV, Damn M, Baratschi F, Hausmann WK, Zbinovsky V, Monikendam P, Adam J, Bochonos N. Isolation and characterization of Mitiromycin and other Antiboitics produced by *streptomyces virticilltaus.* J. Am. Chem. Soc. 1962; 84: 3184-3185.

[9] Collinus JF. Antibiotics, proteins and nucleic acids. Br. Med. Bull. 1965; 21: 223-228.

[10] Sundar L, Chang FN. Antimicrobial activity and biosynthesis of indole antibiotics produced by Xenorhabdus nematophilus. J. Gen. Microbiol. 1993; 139(12): 3139-3148.

[11] Rake AV. Involvement of biogenic amines in memory formation: The central nervous system indole amine involvement. Psychopharmacologia. 1973; 29(2): 91-100.

[12] Wu JH, Wang XH, Yi YH, Lee KH. Anti-AIDS agents 54. A potent anti-HIV chalcone and flavonoids from genus *Desmos.* Bioorg. Med. Chem. Lett. 2003; 13(10): 1813-1815.

[13] López SN, Castelli MV, Zacchino SA et al. In vitro antifungal evaluation and structure-activity relationships of a new series of chalcone derivatives and synthetic analogues, with inhibitory properties against polymers of the fungal cell wall. Bio org. Med. Chem. Lett. 2001; 9(8): 1999-2013.

[14] Yarishkin VO, Park JY, Yang MS, Hong SG, Park KH. Sulfonate chalcone as new class voltage-dependent K^+ channel blocker. Bioorg. Med. Chem. Lett. 2008; 18(1): 137-140.

[15] Carpita A, Ribecai A, Stabile P. Microwave-assisted synthesis of indole- and azaindole-derivatives in water via cycloisomerization of 2-alkynylanilines and alkynylpyridinamines promoted by amines or catalytic amounts of neutral or basic salts. Tetrahedron 2010; 66(35): 7169-7178.

[16] Carpita A, Ribecai A. Microwave-assisted synthesis of indole-derivatives via cycloisomerization of 2-alkynylanilines in water without added catalysts, acids, or bases. Tetrahedron Lett. 2009; 50(9): 6877-6881.

[17] Siu J, Baxendale I R, Ley. Microwave assisted Leimgruber–Batcho reaction for the preparation of indoles, azaindoles and pyrroylquinolines. Org. Biomol. Chem. 2004; 2: 160-167.

[18] Barluenga J, Rodríguez F, Fañanás FJ. Recent advances in the synthesis of indole and quinoline derivatives through cascade reactions. Chemistry: An Asian Journal 2009; 4(7): 1036-1048.

[19] Ohta Y, Chiba H , Oishi S, Fujii N, Ohno H. Concise synthesis of indole-fused 1,4-diazepines through copper(I)-catalyzed domino three-component coupling−cyclization−*N*-arylation under microwave irradiation. Org. Lett. 2008; 10(16): 3535-3538.

[20] Zhu SL, Ji SJ, Zhao K, Liu Y. 6-(1*H*-Indol-3-yl)-4-phenyl-2,2'-bipyridine-5-carbonitrile.Tetrahedron Lett. 2008; 49(6): 2578-2582.

[21] Algul O, Kaessler A, Apcin Y, Yilmaz A. J. Jose. Comparative studies on conventional and microwave synthesis of some benzimidazole, benzothiazole and indole derivatives and testing on inhibition of Hyaluronidase. Molecules. 2008; 13(4): 736-648.

[22] Patil AS, Patil R, Miller DD. Microwave-assisted synthesis of medicinally relevant indoles. Current Med. Chem. 2011; 18(4): 615-637.

[23] Walker MS, Bednar TW, Lumry R. Exciplex studies. II. Indole and indole derivatives. J. Chem. Phys. 1967; 47(3): 1020-1028.

[24] Xu DQ, Yang WL, Luo SP, Wang BT, Wu J, Xu ZY. Fischer Indole synthesis in Brønsted acidic ionic liquids: A green, mild, and regiospecific reaction system. Eur. J. Org. Chem. 2007; 2007(6); 1007-1012.

[25] Dandia A, Arya K, Sati M, Gautam S. Microwave assisted green chemical synthesis of novel spiro [indole-pyrido thiazines]: A system reluctant to be formed under thermal conditions. Tetrahedron. 2004; 60(24): 5253-5258.

[26] Olyaei A, Shams B, Sadeghpour M, Gesmati F, Razaziane Z. A simple, solvent and catalyst-free green synthesis of novel *n*-[(1*H*-indol-3-yl)arylmethyl]heteroarylamines. Tetrahedron Lett. 2010; 51(47): 6086-6089.

[27] Sondhi SM, Jain S, Rani R, Kumar A, Microwave assisted synthesis of indole and furan derivatives possessing good anti-inflammatory and analgesic activity. Ind. J. Chem. Sect. B. 2007; 46 B (11): 1848-1854.

[28] Gengan RM, Pandian P, Kumarsamy C, Mohan PS. Convenient and efficient microwave-assisted synthesis of a Methyl derivative of the fused indoloquinoline alkaloid cryptosanguinolentine molecules. 2010; 15(5): 3171-3178.

[29] Gu L, Li X. Microwave-assisted synthesis of Indole-2-carboxylic acid esters in ionic liquid. J. Braz. Chem. Soc. 2011; 22(11): 2036-2039.

[30] Khan MA, Ahmad S. Microwave assisted synthesis of indole derivatives and their complexation behaviour possessing good biological activities. J. Chem. Pharm. Res. 2013; 5(7), 194-198.

[31] Majumder A, Gupta R, Jain A. Microwave-assisted synthesis of Nitrogen-containing Heterocycles. Green Chem. Lett. Rev. 2013; 6(2): 151-182.

[32] Das AA, Singh I, Tapas SS, Chemopreventive Properties of Indole-3-Carbinol, Diindolylmethane and other constituents of cardamom against carcinogenesis. Recent Patents on Food, Nutrition & Agriculture. 2010; 2(2): 166-177.

[33] Ziedan NI, Stefanelli F, Fogli S, Westwell AD. Design, synthesis and pro-apoptotic antitumour properties of Indole-based 3,5-disubstituted oxadiazoles. Eur. J. Med. Chem. 2010; 45: 4523-4530.

[34] Tan DX, Reiter RJ, Manchester LC, Yan MT, M El-Sawi, et al. Chemical and physical properties and potential mechanisms: melatonin as a broad spectrum antioxidant and free radical scavenger. Current Topics in Med. Chem. 2002; 2(2): 181-197.

[35] B Srivastava, Y Shukla. Antitumour promoting activity of indole-3-carbinol in mouse skin carcinogenesis. Cancer Lett. 1998; 134(1): 91-95.

[36] Gazit A, App H, Mahon GM, Chen J, Levitzki A, Bohmer FD. Tyrphostins. Potent inhibitors of platelet-derived growth factor receptor tyrosine kinase: structure activity relationships in quinoxalines, quinolines, and indole tyrphostins. J. Med. Chem. 1996; 39(11): 2170-2177.

[37] Xiong WN, Yang CG, Jiang B. Synthesis of Novel analogues of marine Indole alkaloids: Mono(indolyl)-4-trifluoromethylpyridines and Bis(indolyl)-4-trifluoromethylpyridines as potential anticancer agents. Bio org. Med. Chem. 2001; 9(7): 1773-1780.

[38] Angenot L, Dubois M, Ginion C, Dorsser W V, Dresse A. Chemical structure and pharmacological (curarizing) properties of various indole alkaloids extracted from an african strychnos. Archives Internationales De Pharmacodynamie et de Therapie. 1975; 215(2): 246-258.

[39] Ölgen S, Çoban T. Synthesis and Antioxidant Properties of Novel *N*-Substituted indole-2-carboxamide and indole-3-acetamide Derivatives. Archiv der Pharmazie. 2002; 335(7): 331-338.

[40] Delorenzi JC, Attias M , Gattass CR, Andrade M, Rezende C , Pinto Â da Cunha , Henriques AT, Bou-Habib DC, Saraiva EMB. Antileishmanial activity of an indole alkaloid from *Peschiera australis.* Antimicrob. Agents Chemother. 2001; 45(5): 1349-1354.

[41] Z Ateş-Alagöz, Kuş C, T Çoban. Synthesis and antioxidant properties of novel benzimidazoles containing substituted indole or 1,1,4,4-tetramethyl-1,2,3,4-tetrahydro-naphthalene fragments. J. Enzyme Inhib. Med. Chem. 2005; 20(4): 325-331.

[42] Matsumoto K, Horie S, Ishikawa H et al. Antinociceptive effect of 7-hydroxymitragynine in mice: Discovery of an orally active opioid analgesic from the Thai medicinal herb Mitragyna speciosa. Life Sciences. 2004; 74(17): 2143-2155.

[43] Sinha D, Tiwari AK, Singh S, Shukla G et al. Synthesis, characterization and biological activity of Schiff base analogues of Indole-3-carboxaldehyde. Eur. J. Med. Chem. 2008; 43(1): 160-165.

[44] Brancale A, Silvestri R. Indole, a core nucleus for potent inhibitors of Tubulin polymerization. Med. Res. Rev. 2007; 27(2): 209-238.

[45] Stansfield I, Ercolani C, Mackay A et al, F Narjes. Bio org. Med. Chem. Lett. 2009; 19: 627-632.

[46] Vliegen I, Paeshuyse J, De Burghgraeve T et al. Substituted imidazopyridines as potent inhibitors of HCV replication. J. Hepatol. 2009; 50(5): 999-1009.

[47] Harper S, Avolio S, Pacini B et al. Potent inhibitors of subgenomic hepatitis C virus RNA replication through optimization of Indole-N-acetamide allosteric inhibitors of the viral NS5B polymerase. J. Med. Chem. 2005; 48(14): 4547-4557.

[48] Lan R, Liu Q, Fan P, Lin Set al. Structure-activity relationships of Pyrazole derivatives as cannabinoid receptor antagonists. J. Med. Chem. 1999; 42(4): 769-776.

[49] Lange JH, HH Stuivenberg van, Coolen HK et al. Bioisosteric replacements of the Pyrazole moiety of rimonabant: synthesis, biological properties, and molecular modeling investigations of thiazoles, triazoles, and imidazoles as potent and selective CB1 cannabinoid receptor antagonists. J. Med. Chem. 2005; 48(6): 1823-1838.

[50] Sauzem PD, Machado P, Rubin MA et al. Design and microwave-assisted synthesis of 5-trifluoromethyl-4,5-dihydro-1*H*-pyrazoles: Novel agents with analgesic and anti-inflammatory properties. Eur. J. Med. Chem. 2008; 43(6): 1237-1247.

[51] Diana P, Carbone A, Barraja Pet al. 3,5-Bis(3′-indolyl)pyrazoles, analogues of marine alkaloid Nortopsentin: Synthesis and antitumor properties. Bioorg. Med. Chem. Lett. 2007; 17(22): 6134-6137.

[52] Singh K, Kumar Y, Puri P, Kumar M, Sharma C. Cobalt, nickel, copper and zinc complexes with 1,3-diphenyl-1*H*-pyrazole-4-carboxaldehyde Schiff bases: Antimicrobial, spectroscopic, thermal and fluorescence studies. Eur. J. Med. Chem. 2012; 52: 313-321.

[53] Tanitame A, Oyamada Y, Ofuji K et al. Synthesis and antibacterial activity of a novel series of potent DNA gyrase inhibitors. Pyrazole derivatives. J. Med. Chem. 2004; 47(14): 3693-3696.

[54] Sivaram H, Tan J, Huynh HV. Syntheses, Characterizations, and a preliminary comparative cytotoxicity Study of Gold (I) and Gold (III) Complexes bearing benzimidazole- and pyrazole-derived N-Heterocyclic carbenes. Organometallics. 2012; 31(16): 5875-5883.

[55] McClure K, Hack M, Huang L et al. Pyrazole CCK_1 receptor antagonists. Part 1: Solution-phase library synthesis and determination of Free–Wilson additivity. Bioorg. Med. Chem. Lett. 2006; 16(1): 72-76.

[56] Bekhit AA, Abdel-Aziem T. Design, Synthesis and biological evaluation of some Pyrazole derivatives as anti-inflammatory-antimicrobial agents. Bioorg. Med. Chem. 2004; 12(8): 1935-1945.

[57] Pitucha M, Kosikowska U, Urszula L, Malm A. Synthesis, Structure and Antibacterial Evaluation of Some N-substituted 3-amino-5-hydroxy-4-phenyl-1H-pyrazole-1-carboxamides. Medicinal Chemistry. 2011; 7(6): 697-703.

[58] A Mohd, Sadique AJ, ZH Mohd. Synthesis and antimicrobial activity of Pyrazolinones and Pyrazoles having Benzothiazole moiety. Med. Chem. Res. 2012; 21(7): 1261-1270.

[59] Dhanya S, Isloor AM, Shetty P, Chandrakantha B, Satyamoorthy K. Synthesis, characterization and in vitro cytotoxic properties of some new Schiff and mannich bases in Hep G2 cells. Med. Chem. Res. 2011; 20(7): 1024-1032.

[60] Vijesh AM, Isloor AM, Shetty P, Sundershan S, Kun Fun H. New Pyrazole derivatives containing 1,2,4-triazoles and benzoxazoles as potent antimicrobial and analgesic agents. Eur. J. Med. Chem. 2013; 62: 410-415.

[61] Fancelli D, Moll J, Varasi M et al. 1,4,5,6-Tetrahydropyrrolo[3,4-*c*]pyrazoles: Identification of a Potent Aurora Kinase Inhibitor with a favorable Antitumor Kinase Inhibition Profile. J. Med. Chem. 2006; 49(24): 7247-7251.

[62] Milano J, Rossato MF, Oliveira SM et al. Antinociceptive action of 4-methyl-5-trifluoromethyl-5-hydroxy-4, 5-dihydro-1*H*-pyrazole methyl ester in models of inflammatory pain in mice. Life Sciences. 2008; 83(21-22): 739-740.

[63] Ishioka T, Kubo A, Koiso Y et al. Novel Non-Steroidal/Non-Anilide type Androgen antagonists with an isoxazolone moiety. Bioorg. Med. Chem. 2002; 10(5): 1555-1566.

[64] Deng B-L, Hartman TL, Buckheit RW et al. Replacement of the metabolically labile methyl esters in the alkenyldiarylmethane series of non-nucleoside reverse transcriptase inhibitors with isoxazolone, isoxazole, oxazolone, or cyano substituents. J. Med. Chem. 2006; 49(17): 5316-5323.

[65] Tong Y, Stewart KD, Thomas S et al. Isoxazolo[3,4-*b*]quinoline-3,4(1H,9H)-diones as unique, potent and selective inhibitors for Pim-1 and Pim-2 kinases: Chemistry, biological activities, and molecular modeling. Bioorg. Med. Chem. Lett. 2008; 18: 5206-5208.

[66] Chande MS, Verma RS, Barve PA, Khanwelkar RR, Vaidya RB, kumar KBA. Facile synthesis of active antitubercular, cytotoxic and antibacterial agents: a Michael addition approach Eur. J. Med. Chem. 2005; 40(11): 1143-1148.

[67] Pandeya SN, Sriram D, Nath G, DeClercq E. Synthesis, antibacterial, antifungal and anti-HIV evaluation of schiff and mannich bases of isatin derivatives with 3-amino-2-methylmercapto quinazolin-4(3*H*)-one. Pharmaceutica Acta Helvetiae. 1999; 74(11): 11-17.

[68] Tanushree RB, Balasubramani A, Perumal Y, Dharmarajan S. Synthesis and evaluation of anti-HIV activity of isatin β-thiosemicarbazone derivatives. Bioorg. Med. Chem. Lett. 2005; 15(20): 4451-4455.

[69] Wang J, Zheng Y, Efferth T, Wang R, Shen Y. Indole and carbazole alkaloids from *Glycosmis montana* with weak anti-HIV and cytotoxic activities. Xiaojiang Hao, Phytochemistry. 2005; 66(6): 697-701.

[70] Pandeya SN, Sriram D, Nath G, DeClercq E. Synthesis, antibacterial, antifungal and anti-HIV evaluation of schiff and mannich bases of isatin and its derivatives with triazole. Arzneimittel-Forschung 2000; 50(1): 55-59.

[71] Traxler P, Bold G, Frei J et al. Use of a Pharmacophore model for the design of EGF-R tyrosine kinase inhibitors: 4-(Phenylamino)pyrazolo[3,4-*d*]pyrimidines**.** J. Med. Chem. 1997; 40(22): 3601-3016.

[72] Cheng GC. 3 Some Pyrimidines of Biological and Medicinal Interest—I. Prog. Med. Chem. 1969; 6: 67-134.

[73] Cheng CC. 3 Some Pyrimidines of Biological and Medicinal Interest—Part III. Prog. Med. Chem. 1971; 8: 61-117.

[74] Traxler P, Green J, Mett H, Séquin U, Furet P. Use of a Pharmacophore Model for the Design of EGFR Tyrosine Kinase Inhibitors: Isoflavones and 3-Phenyl-4(1*H*)-quinolones. J. Med. Chem 1999; 42(6): 1018-1026.

[75] Ostrowski T, Wroblowski B, Busson R et al. 5-Substituted Pyrimidines with a 1,5-Anhydro-2,3-dideoxy-D-*arabino*-hexitol Moiety at N-1: Synthesis, antiviral activity, conformational analysis, and interaction with viral thymidine kinase. J. Med. Chem. 1998; 41(22): 4343-4353.

[76] Sasaki S, Cho N, Nara Y et al. Discovery of a Thieno[2,3-*d*]pyrimidine-2,4-dione bearing a *p*-methoxyureidophenyl moiety at the 6-Position: A Highly potent and orally bioavailable non-peptide antagonist for the Human Luteinizing Hormone-Releasing Hormone Receptor. J. Med. Chem. 2003; 46(1): 113-126.

[77] Kumar R, Semaine W, Johar M et al. Effect of Various Pyrimidines Possessing the 1-[(2-Hydroxy-1-(hydroxymethyl)ethoxy)methyl] Moiety, able to Mimic Natural 2‘-deoxyribose, on wild-type and mutant hepatitis B virus replication. J. Med. Chem. 2006; 49(12): 3693-3700.

[78] Trivedi AR, Dholariya BH, Vakhariya CP et al. Synthesis and anti-tubercular evaluation of some novel pyrazolo[3,4-*d*]pyrimidine derivatives. Med. Chem. Res. 2012; 21(8): 1887-1891.

[79] Oral B, Rollas S. The synthesis and antitubercular activity of substituted hydrazone,2-pyrazoline-5-one and 2-isoxazoline-5-one derivatives possessing 1,3,4-thiadiazole moiety. Marmara Pharm. J. 2012; 16: 222-228.

[80] Mantu D, Antoci V, Ionel I M. Design, synthesis and antimycobacterial activity of some new pyridazine derivatives: bis-pyridazine. part IV &12-14. Mangalagiu, Ionel, Infectious

Disorders - Drug Targets (Formerly Current Drug Targets - Infectious Disorders). 2013; 13(8): 344-351.

[81] Marganakop SB, Kamble RR, Taj T, Kariduraganvar MY. An efficient one-pot cyclization of quinoline thiosemicarbazones to quinolines derivatized with 1,3,4-thiadiazole as anticancer and anti-tubercular agents. Med. Chem. Res. 2012; 21(2): 185-191.

[82] Savaliya PP, Akbari VK, Modi JA, Patel KC, Synthesis, characterization, and antimicrobial screening of some mannich base sydnone derivatives. Med. Chem. Res. 2013; 22(12): 5789-5797.

[83] Kenchappa R, Bodke YD, Asha B, Telkar S, Sindhe MA. Synthesis, antimicrobial, and antioxidant activity of benzofuran barbitone and benzofuran thiobarbitone derivatives. Med. Chem. Res. 2014; 23(6): 3065-3081.

[84] Mugnaini C, Pasquini S, Corelli F. The 4-quinolone-3-carboxylic acid motif as a multivalent scaffold in medicinal chemistry. Current Med. Chem. 2009; 16(22): 1746-1767.

[85] Lakum HP, Shah DR, Chikhalia KH. The novel derivatives of 3-(iminomethyl)-2h-chromen-2-one with thiourea and piperazine structural motive: rationale, synthesis, antimicrobial and anti-TB evaluation. Lett. Drug Des. Discov. 2015; 12(18): 324-341.

[86] Patel NB, Sharma RD, Rajani SD. In vitro antimicrobial and antitubercular studies of novel 6-substituted (pyrrolidin-1-yl)-2(1*H*)-pyridinones. Med. Chem. Res. 2012; 21(12): 4108-4119.

[87] Pandit U, Dodiya A. Synthesis and antitubercular activity of novel pyrazole–quinazolinone hybrid analogs. Med. Chem. Res. 2013; 22(7): 3364-3371.

[88] Parmar NJ, Pansuriya BR, Parmar BD, Barad HA. Solvent-free, one-pot synthesis and biological evaluation of some new dipyrazolo [3,4-*b*:4′,3′-*e*]pyranylquinolones and their precursors. Med. Chem. Res. 2014; 23(1): 42-56.

[89] Al-Soud YA, Al-Masoudi NA. DNA-directed alkylating agents: synthesis, antitumor activity and DNA affinity of bis-*N,N*′-trisubstituted 1,2,4-triazolo-piperazines. Farmaco. 2004; 59(1): 41-46.

[90] Hurley LH. Pyrrolo(1,4)benzodiazepine antitumor antibiotics comparative aspects of anthramycin. tomaymycin and sibiromycin. The Journal of antibiotics 1977; 30(5): 349-370.

[91] Rajanarendar E, Reddy MN, Krishna SR et al. Design, synthesis, *in vitro* antimicrobial and anticancer activity of novel methylenebis-isoxazolo[4,5-*b*]azepines derivatives. Eur. J. Med. Chem. 2012; 50: 344-349.

[92] Gangjee A, Adair OO, Queener SF. Synthesis and biological evaluation of 2,4-diamino-6-(arylaminomethyl)pyrido[2,3-*d*]pyrimidines as inhibitors of *pneumocystis carinii* and *toxoplasma gondii* dihydrofolate reductase and as antiopportunistic infection and antitumor agents. J. Med. Chem. 2003; 46(23): 5074-5082.

[93] Rajanarendar E, Reddy MN, Murthy KR et al. Synthesis and *in vitro* and *in vivo* anticancer activity of novel phenylmethylene bis-isoxazolo[4,5-*b*]azepines. Bioorg. Med. Chem. Lett. 2012; 22(1): 149-153.

[94] Phutdhawong WS, Ruensamran W, Phutdhawong W, Taechowisan T. Synthesis of 1,6,7,8-tetrahydro-naphtho[2,3-*d*]-azepino[4,5-*b*]indole-9,14-diones and their inhibitory effects on pro-inflammatory cytokines. Bioorg. Med. Chem. Lett. 2009; 19(19): 5753-5756.

[95] Tomasi S, J Renault, B Martin et al. Targeting the Polyamine Transport System with Benzazepine- and Azepine-Polyamine Conjugates. J. Med. Chem. 2010; 53(21): 7647-7663.