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## Pyrrole: a resourceful small molecule in key medicinal hetero-aromatics

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Pyrrole is widely known as a biologically active scaffold which possesses a diverse nature of activities. The combination of different pharmacophores in a pyrrole ring system has led to the formation of more active compounds. Pyrrole containing analogs are considered as a potential source of biologically active compounds that contains a significant set of advantageous properties and can be found in many natural products. The marketed drugs containing a pyrrole ring system are known to have many biological properties such as antipsychotic,  $\beta$ -adrenergic antagonist, anxiolytic, anticancer (leukemia, lymphoma and myelofibrosis etc.), antibacterial, antifungal, antiprotozoal, antimalarial and many more. Due to the diversity of these analogs in the therapeutic response profile, many researchers have been working to explore this skeleton to its maximum potential against several diseases or disorders. In this review, attempts have been made to disclose various tactical approaches to synthesize pyrrole and pyrrole containing analogs. The structure–activity relationship studies have been discussed along with their therapeutic applications which have been reported during last decade. Some molecules as the main components of the market and clinical trials have also been discussed.

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### 1. Introduction

Heterocyclic compounds are referred to those cyclic compounds that contain at least two different elements as ‘ring member’ atoms. Heterocyclic compounds may be organic or inorganic, containing one carbon atom, and one or more atoms of elements other than carbon, such as sulphur, oxygen, nitrogen *etc.* within the ring structure. Thus, the non-



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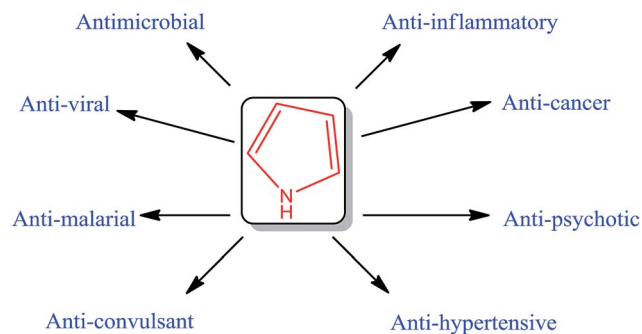
Dr S. Chauhan. In his short research career, he has contributed in two government funded projects. His research interest includes design and synthesis of bioactive heterocycles, physicochemical interactions, nano/microparticulates, topical formulations especially against microbial infections.



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carbon elements that replace the carbon atoms in a chemical structure are commonly termed as heteroatoms. Simple *N*-heterocycles have received considerable attention because of their important biological properties and their role as pharmacophores.<sup>1</sup> The synthesis, reactions, and biological activities of pyrrole derivatives stand as an area of research in heteroaromatic chemistry, and this fundamental construction unit appears in a large number of pharmaceutical agents and natural products.<sup>2</sup> In addition, biologically pyrroles could construct the structure of porphyrin rings, which act as a key moiety in chlorophyll, heme, vitamin B<sub>12</sub>, or bile pigments.<sup>3</sup> Pyrrole is a colorless volatile liquid that darkens readily upon exposure to air and polymerizes in light. Pyrroles have low basicity than amines and other aromatic compounds like pyridines. This decreased basicity is due to the delocalization of the lone pair of electrons of the nitrogen atom in the aromatic ring. Pyrrole is a very weak base with a  $pK_a$  of about  $-3.8$  and its protonation results in the loss of aromatic property. Both  $-NH-$  and  $-CH-$  protons of pyrrole are moderately acidic

and can be deprotonated with strong bases rendering the pyrrole nucleophilic. The resonance contributors of pyrrole provide insight to the reactivity of the compound. In simple terms, pyrrole is an aromatic five membered ring with the formula  $C_4H_5N$ , as shown below;



Pyrrole and its derivatives are ever present in nature. Pyrrole subunit has diverse applications in therapeutically active compounds including fungicides, antibiotics, anti-inflammatory drugs,<sup>4</sup> cholesterol reducing drugs,<sup>5</sup> antitumor agents<sup>6</sup> and many more. They are known to inhibit reverse transcriptase [human immunodeficiency virus type 1 (HIV-1)] and cellular DNA polymerases protein kinases. Moreover, they are also a component of polymers,<sup>7</sup> indigoid dyes<sup>8</sup> and of larger aromatic rings.<sup>8</sup> In catalytic reactions, pyrroles are well utilized as catalyst for polymerization process,<sup>9</sup> corrosion inhibitor,<sup>10</sup> preservative,<sup>11</sup> solvent for resin,<sup>12</sup> terpenes, in metallurgical process,<sup>13</sup> transition metal complex catalyst chemistry for uniform polymerization,<sup>14</sup> luminescence chemistry<sup>15</sup> and spectrochemical analysis.<sup>16</sup> Furthermore, some of these compounds are useful intermediates in the synthesis of biologically important naturally occurring alkaloids<sup>17</sup> and synthetic heterocyclic derivatives.<sup>18</sup> In this present review, attempt has been made to discuss various synthetic approaches that can be used to synthesize this resourceful moiety, in addition various biological active molecules containing pyrrole has been



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mercury(II) chloride gave the Boc-protected diguanidino analogues **7**. Deprotection of the Boc-protected guanidine analogues was carried out using ethanolic-HCl in dichloromethane at 0 °C to give the corresponding 2,5-bis(guanidino-aryl)-1-methyl-1*H*-pyrrole derivatives **8** in good yield as shown in Scheme 1. The SAR studies of the above synthesized compounds revealed that 4-guanidino compound having methyl substituent on the phenyl ring was the most active compound against *Candida albicans*, *Candida krusei*, *Candida parapsilosis*, *Candida glabrata*, *Candida tropicalis* and compound having a chloro substituent on the phenyl ring also showed moderate activity against *Candida* species.<sup>21</sup>

During the search of novel antitubercular drugs, Biava *et al.* designed and synthesized a new series of diarylpyrroles. Structure activity relationship (SAR) studies, along with a pharmacophoric model allowed them to find derivatives in which the following substituents and substitution pattern were responsible for the activity on the pyrrole ring; (i) a substituted phenyl

ring at both the positions 1 and 5 (F, Cl, and CH<sub>3</sub> were the best substituents) and (ii) an amino methyl group at position 3 (a thiomorpholinomethyl side chain was the optimal moiety). On this basis, the synthesis of a new derivative **13** bearing an ethyl group at position 2 of the pyrrole nucleus was carried out, while keeping the same substituents on both N1 and C5 phenyl rings, gave the best results in terms of activity. This approach includes the reaction of a suitable benzaldehyde **9** with ethyl vinyl ketone **10** that afforded 1,4-diketones **11**. In the presence of the appropriate amine, following the Paal-Knoor condensation conditions for 30 min, intermediates **11** were cyclized to yield the expected 1,5-diarylpyrroles **12**. Construction of the side chain at C3 was achieved in good yield by reaction with formaldehyde and *N*-methylpiperazine or thiomorpholine to give the expected derivatives **13** (Scheme 1).<sup>22</sup>

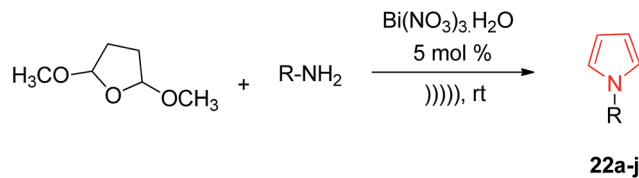
Based on the structure of HIV-1 gp41 binding site for small molecule inhibitors, He *et al.* synthesized a new series of 2,5-dimethyl-3-(5-(*N*-phenylrhodaninyl) methylene)-*N*-(3-(1*H*-tetrazol-



Scheme 2 Synthesis of rhodanine derivatives.

5-yl) phenyl) pyrrole compounds with improved anti-HIV-1 activity. The Paal-Knorr reaction was performed to synthesize 3-(2,5-dimethyl-1*H*-pyrrol-1-yl) benzonitrile **15** by the condensation of 3-aminobenzonitrile **14** with 2,5-hexanedione. An aldehyde group was then introduced at the 3-position on the pyrrole ring to obtain the 3-(3-formyl-2,5-dimethyl-1*H*-pyrrol-1-yl) benzonitrile **16**. The cyano group of **16** was further converted into tetrazolyl by treating with sodium azide and triethylamine hydrochloride in refluxed toluene to get the intermediate 2,5-dimethyl-*N*-(3-(1*H*-tetrazol-5-yl)phenyl)pyrrole-3-carbaldehyde **17**. To expand the structural scaffold of binding site in a more linear manner, a series of *N*-substituted rhodanine derivatives **19a-i** were prepared by treating substituted anilines **18a-i** with bis(carboxymethyl) trithiocarbonate. The intermediate **19j** was synthesized by the condensation of 4-trifluoromethylphenyl isothiocyanate with 2-mercaptoacetic acid and intermediates **19k** and **19l** were prepared by treating an amine with carbon disulfide and 2-bromoacetic acid successively. The rhodanine derivatives **19a-l** so prepared were refluxed with ammonium acetate in toluene and methanol (2 : 1, v/v) for 3–5 h to get the corresponding new compounds **20a-l** with a yield range of 55–95% (Scheme 2). Among the synthesized rhodanine derivatives, **20a** and **20i** showed good inhibitory activities against gp416-HB formation and HIV-1 replication.<sup>23</sup>

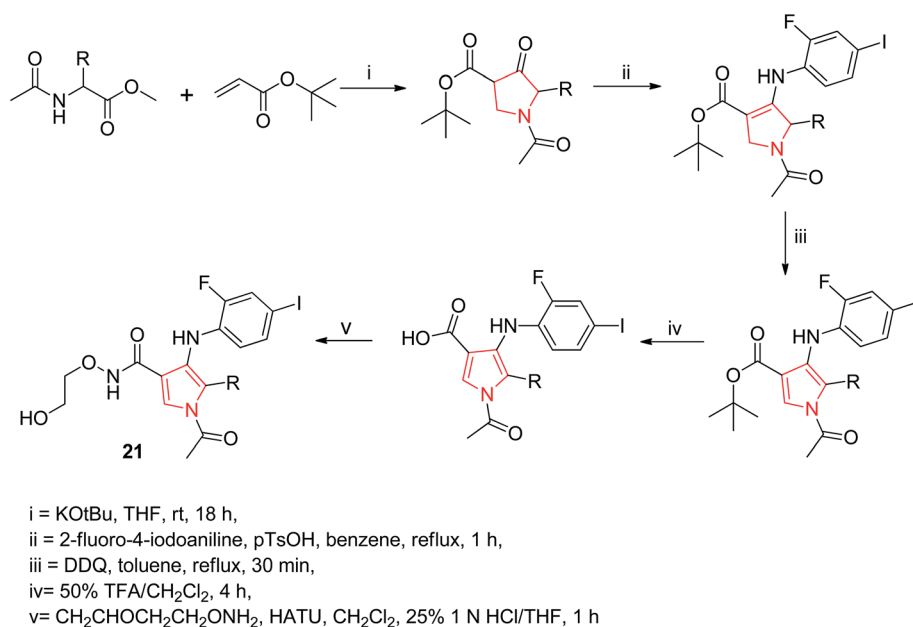
Wallace *et al.* designed various novel derivatives of 3-aminopyrrole compounds **21** that inhibited the MEK allosteric site. The *N*-acetyl pyrrole compounds **21** showed excellent enzymatic activity but weak micromolar activity in cellular assays due to the inherent chemical instability of pyrrole *N*-deacetylation during assay incubation. To solve this issue they modified the central core while retaining all of the key binding elements by changing the substitution from position 3 to position 2 *i.e.* 2-aminopyrrole scaffold<sup>24</sup> as presented in Scheme 3. Another



Scheme 4 Synthesis of *N*-substituted pyrrole derivatives by an eco-friendly route using ultrasound-assisted bismuth nitrate-catalyzed reaction.

series of novel *N*-substituted pyrrole derivatives were designed and synthesized by an eco-friendly route using ultrasound-assisted bismuth nitrate-catalyzed reaction. Ultrasonic exposure of different amines with 2,5-dimethoxytetrahydrofuran in the presence of catalytic amount (5 mol%) of bismuth nitrate pentahydrate produced the corresponding pyrroles **22** with excellent yield (Scheme 4). In addition, Table 1 represents different synthesized derivatives. The derivatives **22i** and **22j** exhibited good cytotoxic activity against some cancer cell lines.<sup>25</sup>

Yavari *et al.* reported a solvent-free synthesis of 1,2,3,5-tetrasubstituted pyrroles **23** from enamines and  $\alpha$ -halo-ketones by simple mixing the starting materials at room temperature for 3 h without the use of any solvent or catalyst. The different substitutions were made as per the required desired product. The preferred substitutions included; R = OEt, R' = *n*-Bu and R'' = 4-Br-C<sub>6</sub>H<sub>4</sub>, COOEt, 4-MeO-C<sub>6</sub>H<sub>4</sub>.<sup>26</sup> Another reaction of 1-aryl-1*H*-pyrrole-2,5-diones **24** with nonstabilized azomethineylides, which were generated *in situ* via decarboxylative condensation of isatins **25** and sarcosine **26**, afforded only one product *i.e.* 4'-aryl-5'a,6'-dihydro-1'-

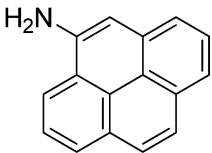
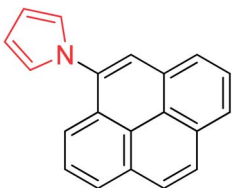
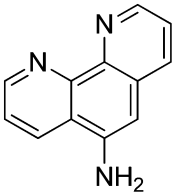
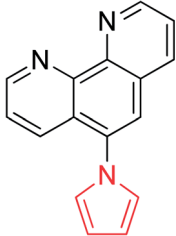
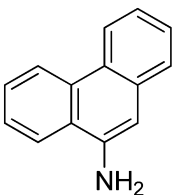
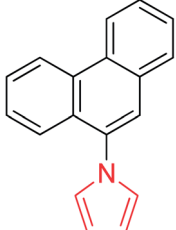


Scheme 3 Synthesis of 2-aminopyrrole scaffold.

Table 1 The synthesized *N*-substituted pyrroles by  $\text{Bi}(\text{NO}_3)_3 \cdot 5\text{H}_2\text{O}$  catalyzed ultrasound-induced synthesis as obtained from Scheme 4

Compound code	Amine	Product	Time (min)	Yield (%)
22a			5	99
22b			5	95
22c			5	92
22d			5	95
22e			30	87
22f			35	79
22g			10	92

Table 1 (Contd.)

Compound code	Amine	Product	Time (min)	Yield (%)
22h			15	87
22i			60	76
22j			5	86

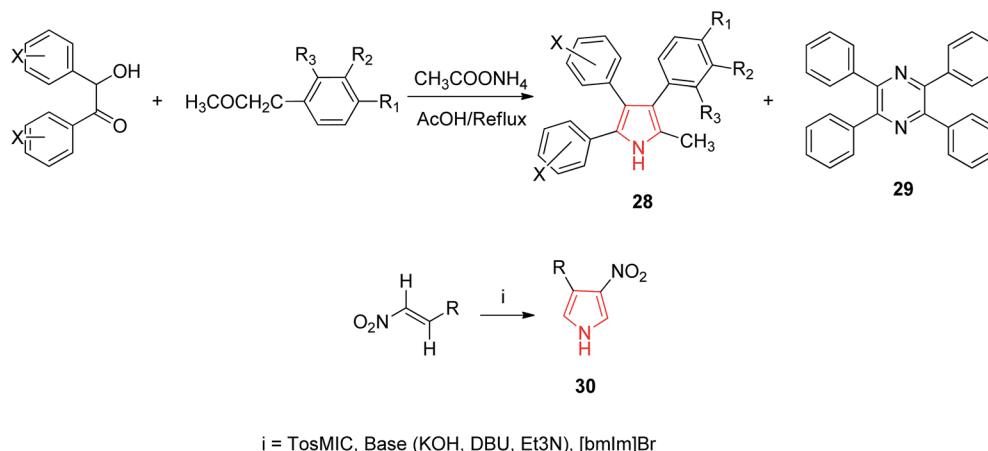
methyl-spiro [3*H*-indole-3,2'-(1*H*)-pyrrolo [3,4-*c*] pyrrole]-2,3',5'-(1*H*,2'*aH*,4'*H*)-triones **27** (Scheme 5). The synthesized compound **27** revealed moderate anti-tumor properties

against HCT116 (colon), MCF7 (breast) and HEPG2 (liver) human tumor cell lines, as compared to Doxorubicin.<sup>27</sup>

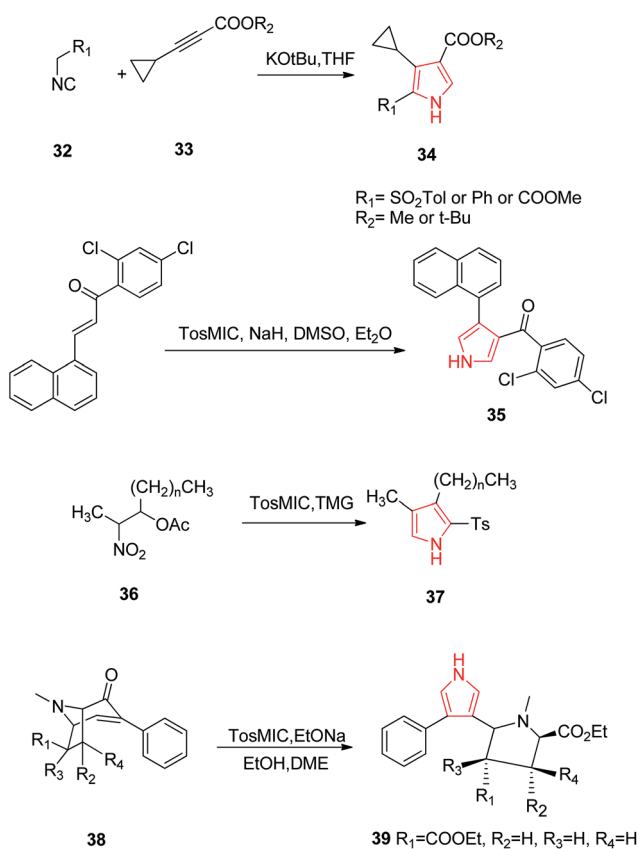
Goel *et al.* synthesized 2-methyl-3,4,5-triphenyl pyrrole derivatives **28** as antihyperglycemic agents by refluxing a mixture of benzoin, benzyl methyl ketone and ammonium acetate in acetic acid. It was also reported that this reaction also lead to a minor byproduct **29** which was possibly formed due to self-condensation of benzoin with ammonium acetate in presence of acetic acid and air as shown in Scheme 6. This byproduct was avoided by the synthesis of 3,4,5-triphenyl-1*H*-pyrroles under nitrogen atmosphere using anhydrous ammonium acetate. The synthesized compounds were evaluated for antihyperglycemic activity and the results suggested that unsubstituted-phenyl ring at positions 4 and 5 of the pyrrole reduces elevated blood sugar levels while substitution at positions 3 or 4 of phenyl ring resulted in either reduction or a complete loss of antihyperglycemic activity. A compound with trifluoromethyl group at position 3 of the aryl ring displayed good antidiabetic activity.<sup>28</sup> Qin *et al.* proposed a mild and convenient method for the synthesis of 4(3)-substituted 3-(4)-nitropyrrole **30** from nitro olefins and TosMIC in ionic liquid 1-butyl-3-methylimidazolium bromide ([bmIm] Br).<sup>29</sup> Borbas *et al.* found that bacteriochlorins gets absorbed strongly in the near infrared region and hence are suited for diverse photo medical application. A *de novo* route was exploited to prepare synthetic bacteriochlorins **31** using TosMIC chemistry (Scheme 6).<sup>30</sup>



Scheme 5 Synthesis of pyrrole containing analogs.



Scheme 6 Synthesis of methyl substituted pyrroles **28**, nitropyrrole **30** and synthetic bacteriochlorins **31**.



Scheme 7 Synthesis of tri-substituted pyrrole **34**, pyrrole containing imidazole **35**, cholephilic compound **37** and pyrrolidine analogues **39**.

Oligofunctional pyrroles play a pivotal role, being basic constituents of numerous natural products, potent pharmaceuticals, molecular sensors and devices. In this context,

Table 2 Synthesis of aryl pyrroles using TosMIC

Ar <sup>1</sup>	Ar <sup>2</sup>	Temperature (°C)	Reaction time (h)	Yield (%)
		25	4 h	91
		80	2 h	49
	CH <sub>3</sub>	60	3 h	53
	H	25	1 h	76
	H	50	18 h	47
		50	1 h	72

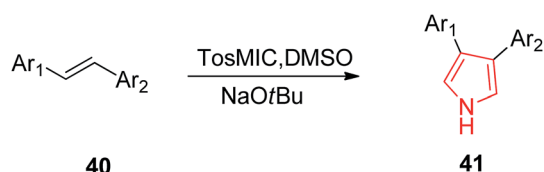
Larionov *et al.* developed a method for synthesizing tri-substituted pyrroles. They developed 2,3,4-trisubstituted pyrroles **34** by reacting toluene-4-sulfonylmethyl isocyanide (TosMIC) **32** and substituted acetylenes **33** by cycloaddition method. It involved a formal cycloaddition of an  $\alpha$ -methylated isocyanide across a C–C triple bond in an electron-substituted acetylene furnishing a transient 2*H*-pyrrole which led to a 1,5-hydrogen shift and protonation to give a 2,3,4-trisubstituted pyrrole **34**.<sup>31</sup> Santo *et al.* synthesized novel series of *N*-substituted derivatives of 1-[(aryl) (4-aryl-1*H*-pyrrolol-3-yl) methyl]-1*H*-imidazoles using TosMIC protocol and reported their QSAR studies. They developed the key intermediate (2,4-dichlorophenyl)-[4-(naphthalen-1-yl)-1*H*-pyrrol-3-yl] methanone **35** by using TosMIC chemistry. These compounds were found to be active against *Candida* species.<sup>32</sup> A new class of highly fluorescent low molecular weight water soluble cholephilic compounds were synthesized from dipyrinones in two steps. The reaction of acetylated  $\beta$ -hydroxynitro product **36** with TosMIC in presence of tetramethylguanidine (TMG) afforded tosyl pyrrole **37**, which was later converted to dipyrinones.<sup>33</sup> Airaksinen *et al.* prepared 3,4-disubstituted pyrroles **39** from 6/7-

carboxyethyl-3-phenyl-3-tropen-2-ones **38** regioselectively (Scheme 6). This synthetic procedure provided two distinct substituents of the pyrroles: a phenyl group and a pyrrolidine analogue (Scheme 7).<sup>34</sup>

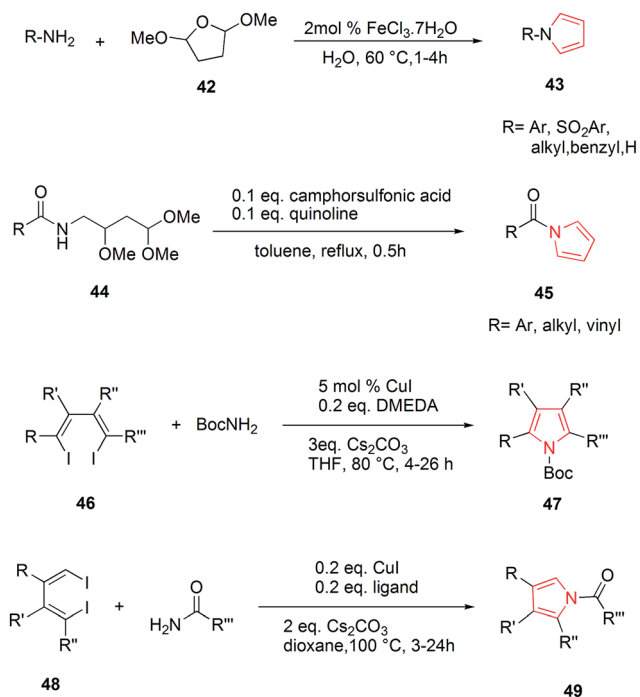
Smith *et al.* reported the synthesis of 3-aryl and 3,4-diaryl-(1*H*)-pyrroles **41** (Table 2) in one step from TosMIC and commercially available or easily synthesizable aryl alkenes **40**, as reported in Scheme 8. The methodology resulted in higher yields (>65%) when electron deficient aryl groups were attached to the alkenes.<sup>35</sup>

Various substitutions on the pyrrole ring were found to possess diversity of medicinal importance. Azizi *et al.* reported an operationally simple, practical and economical method for the synthesis of *N*-substituted pyrroles **43** under very mild reaction conditions in good to excellent yields as shown in Scheme 9. It included the condensation of 2,5-dimethoxy-tetrahydrofuran **42** with various amines and sulfonamides in the presence of water and a catalytic amount of iron(III) chloride.<sup>36</sup> The introduction of acyl group on nitrogen atom of pyrrole possessed medicinal importance. Maehara *et al.* reported the condensation of carboxylic acid moiety with substituted amine *i.e.* 2,4,4-trimethoxybutan-1-amine **44** under reflux conditions followed by acid-mediated cyclization, that resulted in the formation of *N*-acyl derivative of pyrrole **45** as shown in Scheme 9. This method was highly tolerant to various functional groups.<sup>37</sup> The highly substituted pyrrole ring was found to be highly stable and depending upon the various functional groups on each substituent, which can act on a variety of receptor sites. 1,2,5 or 3,4 substitutions on pyrrole ring and were found to possess biological importance. The copper catalyzed reaction of amine with 1,4-dihalo-1,3-dienes **46**, allowed the synthesis of pyrroles and heteroaryl pyrroles **47** with a wide variety of functional groups and substitution patterns.<sup>38</sup> Similarly, the Cu-catalyzed double alkenylation reaction of amide with 1,4-dihalo-1,3-dienes **48** afforded di- or trisubstituted *N*-acylpyrroles **49** (ref. 39) in good yields using CuI as the catalyst and Cs<sub>2</sub>CO<sub>3</sub> as the base (Scheme 9).

Ozdemir *et al.* synthesized new Pd–NHC complexes that were used for direct arylation of pyrrole derivatives. Electron-deficient aryl chlorides were used as coupling partners. The desired products **50a–e** were obtained in good yields by using 1 mol% of air-stable palladium complexes.<sup>40</sup> A three-component reaction of arylglyoxal hydrates was performed with  $\beta$ -dicarbonyl compounds in the presence of ammonium acetate and hydrazine hydrate for the preparation of 5-aryl-4-hydroxy-2-methyl-1*H*-pyrrole-3-carboxylic acid ester **51** (Scheme 10). Water was used as a solvent and the reaction proceeded under ultrasonic irradiations.<sup>41</sup> During samarium di-iodide mediated N–O cleavage of 3,6-dihydro-2*H*,1,2-oxazine **52**; an enantiopure 1,4-amino alcohol **53** and 3-methoxypyrrole derivative **54** were prepared in significant amounts<sup>42</sup> as shown in Scheme 10. A sequential multicomponent process was designed to prepare the polysubstituted functionalized pyrroles **55** that involved the high-speed vibration milling of ketones with *N*-iodosuccinimide and *p*-toluene sulphonic acid, followed by the addition of mixture of primary amines,  $\beta$ -dicarbonyl compounds, cerium(IV) ammonium nitrate and silver nitrate.<sup>43</sup> The dual role of



Scheme 8 One step synthesis of 3-aryl and 3,4-diaryl-(1*H*)-pyrroles using TosMIC.



Scheme 9 Synthesis of substituted pyrrole containing analogs.



Scheme 10 Systemic approach to synthesize substituted pyrroles.

nitriles was exploited during a novel multicomponent reaction that afforded 3*H*-pyrroles **56** from ketones.<sup>44</sup> The reaction revealed that nitriles can act both as nucleophiles and electrophiles. The reaction used two equivalents of malonitrile, the corresponding thiols and was catalyzed by triethylamine in water (Scheme 10).

Khulpe *et al.* synthesized the novel 2-methyl-7-(4-nitrophenyl)-5,6-diphenyl-3,7-dihydro-4-*H*-pyrrolo-[2,3-*d*]pyridine-4-one derivatives by the Paal-Knorr condensation reaction. Benzoin **57** was refluxed with primary aromatic amines in the presence of alcohol, which led to the formation of  $\alpha$ -amino-ketone intermediates **58**, which were condensed, without isolation, with malonitrile to yield various pyrrole derivatives **59** (Scheme 11).<sup>45</sup> 2,3-Fused pyrroles **61** were synthesized from cyclic ketones by rhodium-catalyzed reaction of 4-alkenyl-1-sulfonyl-1,2,3-triazoles **60**. The reaction involved an unusual 4*π* electrocyclicization.<sup>46</sup> A new method was developed for

the amino-acylation of pyrroles. The procedure involved a multicomponent one-pot cascade reaction between pyrroles, ynol ethers and sulfonyl azides leading to the formation of four different bonds regioselectively through *N*-sulfonyltriazole intermediates (Scheme 11). The desired oxo-pyrroloethanamines **62** were generated in moderate to high yields.<sup>47</sup>

Blackburn *et al.* synthesized substituted triarylpyrroles by reacting 1,2-dibenzoylthane **63** with 4-bromoaniline **64** that yielded 2,5-symmetrically substituted pyrroles **65**. Trifluoroethanol (TFE) was used as a solvent and trifluoroacetic acid (TFA) was used as a catalyst under microwave conditions. Vilsmeier-Haack conditions were applied for formylation of pyrroles **65** under microwave conditions to give 3-formylpyrroles **66**. Further condensation of **66** with barbituric acid or thiobarbituric acid in presence of ethanol at room temperature yielded pyrrole barbiturates **67** (Scheme 12).<sup>48</sup> The palladium(II)-catalyzed oxidative cyclization reaction of *N*-allylimines



Scheme 11 Synthesis of various catalyzed pyrrole containing products.

**68** was reported to form pyrrole. *N*-Allylimines were derived from methyl ketones, especially acetophenones, which afforded pyrrole derivatives **69** at room temperature in presence of oxygen. The reaction occurred through  $\alpha$ -palladation of imine followed by migratory insertion of olefin and  $\beta$ -hydride elimination. This reaction represented a new example of aerobic dehydrogenative Heck cyclization.<sup>49</sup> Various polysubstituted pyrroles **71** were synthesized in good yields (Scheme 12) by Ag(I)-mediated conjugated addition and cyclization reaction of terminal alkynes **70** with amines.<sup>50</sup> Natural products didebromohamacanthin A **74** and demethylaplysinopsine **73** were synthesized *via* oxidative nucleophilic addition of ethylenediamine and guanidine derivatives with pyrrole-amino acid diketopiperazines **72** (ref. 51) as shown in Scheme 12. Fesenko and Shutalev synthesized 2-phenyl-3-(phenylthio)-1*H*-pyrrole-1-

carboxamide **76** from 4-phenyl-5-(phenylthio)-1*H*-1,3-diazepin-2(3*H*)-one **75** under acidic conditions by refluxing in 95% ethanol and TsOH (0.23 equiv.) for three hours. On increasing the amount of TsOH to 1.01 equivalents, product **76** was obtained in 98% yield.<sup>52</sup> Some substituted pyrroles **78** were synthesized by metal-catalyzed heterocyclodehydration of 1-amino-3-yn-2-ol **77**. The heterocyclodehydration occurred by 5-exodig intramolecular nucleophilic attack of hydroxyl group to triple bond, coordinated to the metal center, which was followed by protonolysis and aromatization.<sup>53</sup> A new and efficient method was developed for the synthesis of uracil fused pyrrole derivative 5-(4-methoxyphenyl)-1,3-dimethyl-1*H*-pyrrolo[2,3-*d*]pyrimidine-2,4(3*H*,7*H*)-dione **80** as shown in Scheme 13. The process involved a three-component reaction comprising of 1,3-dimethyl-6-aminouracil **79**, *p*-methoxybenzaldehyde and



Scheme 12 Synthetic route for catalyzed pyrrole containing analogs.

nitromethane, while  $\text{CuFe}_2\text{O}_4$  was used as a catalyst. The reaction completed in 4 hours and product was obtained in good yield.<sup>54</sup> New three-component coupling process was designed to synthesize pyrroles **82** (Scheme 13). The reaction proceeded by reacting symmetrical vicinal diols **81** with enamines or imines, involving intramolecular ruthenium-catalyzed dehydration and N-H alkylation steps that resulted in substituted pyrroles.<sup>55</sup> Novel pyrrole derivatives were synthesized by click reaction using silver-catalyzed cycloaddition of terminal alkynes with isocyanides. Phenylacetylene was reacted with 2-isocynoacetate in presence of *N*-methyl-2-pyrrolidone and silver carbonate to give ethyl-3-phenyl-1*H*-pyrrole-2-carboxylate **83** in 89% yield<sup>56</sup> as shown in Scheme 13. A novel method was developed for the synthesis of substituted pyrroles *via* Paal-Knorr reaction (Scheme 13). The reaction was catalyzed by  $\alpha$ -amylase derived from hog pancreas. 4-Chloroaniline was

reacted with 2,5-hexanedione in presence of  $\alpha$ -amylase to obtain 1-(4-chlorophenyl)-2,5-dimethyl-1*H*-pyrrole **84** in 94% yield.<sup>57</sup>

Murugan *et al.* synthesized various substituted pyrroles *via* ruthenium-catalyzed oxidative cyclization of enamides with alkynes in water or dimethoxyethane. The product **86** was obtained in 95% yield by refluxing a mixture of ethyl-2-acetamidoacrylate **85**, dialkyl acetylene,  $[\text{Ru}(p\text{-cymene})\text{Cl}_2]$  (2 mol%),  $\text{KPF}_6$  and  $\text{Cu}(\text{OAc})_2$  in water.<sup>58</sup> A ruthenium carbene catalyzed ring-closing metathesis reaction and  $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$  or  $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$  catalyzed *in situ* oxidative dehydrogenation reaction was implied for synthesis of aryl-substituted pyrrole derivatives **88** and **89** (Scheme 14). Diallyl amines **87** was used as a starting material in the presence of oxygen and the reaction was mild, simple and convenient.<sup>59</sup> Polysubstituted pyrroles were synthesized from readily available isocyanides, primary or secondary amines and gem-diacivated olefins. The synthesis involved a multicomponent domino reaction to obtain the



Scheme 13 Different catalyzed synthetic route to synthesize substituted pyrroles.

chemoselective and structurally diverse pyrroles **90** and **91** without the use of any catalyst.<sup>60</sup> A novel four-component domino reaction of arylglyoxal monohydrate, aniline, dialkyl but-2-ynedioate and malonitrile was reported for the synthesis of polysubstituted pyrroles **92**. The reaction was highly efficient, ethanol was used as a solvent and proceeded without catalyst.<sup>61</sup> Novel 1,2,3-trisubstituted pyrroles were synthesized *via* iodocyclization from acetoacetate (Scheme 15). This one-pot two step reaction involved the treatment of ethyl-3-(propylamino) but-2-enoate **93** with acetaldehyde and iodine in basic conditions to give the desired product ethyl-2-methyl-1-propyl-1*H*-pyrrole-3-carboxylate **94** as shown in Scheme 15.<sup>62</sup>

Viradiya *et al.* developed an eco-friendly and highly efficient method for the one-pot synthesis of penta-

substituted pyrrole derivatives *via* a four-component reaction of pyrimidine-2,4,6-(1*H*,3*H*,5*H*)-trione **95**, 1-(4-fluorophenyl)-2,2-dihydroxyethanone **96**, dimethyl but-2-ynedioate and 4-methoxyaniline. This catalyst-free and environmental friendly reaction yielded dimethyl-5-(2,2-dimethyl-4,6-dioxohexahydropyrimidin-5-yl)-4-(4-fluorophenyl)-1-(4-methoxyphenyl)-1*H*-pyrrole-2,3-dicarboxylate **97** in excellent yield and short time duration<sup>63</sup> as shown in Scheme 16. Highly functionalized bicyclic pyrrole derivatives were synthesized through a three-component one pot reaction of 1-(4-fluorophenyl)-2-(tetrahydropyrimidin-2(1*H*)-ylidene)ethanone **98**, 1*H*-indole and 1-(4-fluorophenyl)-2,2-dihydroxyethanone **99**. The reaction proceeded in ethanol medium and was catalyzed by acetic acid to give the pyrrole containing product **100** (Scheme 16).<sup>64</sup> The reaction between



Scheme 14 Synthesis of metal catalyzed pyrroles.



Scheme 15 Synthesis of pyrroles using various solvent systems.

methyl-2,5-dioxopyrrolidine-1-carboxylate **101** and Petasis reagent led to the formation of dienamine product **102**, which was isomerized under mild conditions to give methyl-2,5-dimethyl-1*H*-pyrrole-1-carboxylate **103** in 96% yield.<sup>65</sup> Various trifluoromethyl substituted pyrrole derivatives were prepared. The phosphine-mediated reaction used commercially available trifluoroacetic anhydride as the only trifluoromethyl

source. Dimethyl-2-(phenyl(tosylimino)methyl)fumarate **104** was reacted with triphenyl phosphine and dichloromethane to give dimethyl-2-phenyl-1-tosyl-5-(trifluoromethyl)-1*H*-pyrrole-3,4-dicarboxylate **105** in 48–99% yield.<sup>66</sup> A green and rapid strategy was developed for the synthesis of novel pyrroles by using molybdate sulfuric acid (Scheme 16). Pechmann condensation of *meta*-aminophenol with ethylacetoacetate



Scheme 16 Various synthetic route to synthesize pyrroles incorporated analogs.

under solvent-free condition yielded 7-amino-4-methylcoumarin **106**, which was reacted with hexane-2,5-dione to give 7-(2,5-dimethylpyrrole-1-yl)-4-methylcoumarin **107** in overall 90% yield<sup>67</sup> as shown in Scheme 16.

Murthi *et al.* designed a faster and efficient method for the synthesis of polysubstituted pyrrole derivative **108** through a four-component reaction of  $\beta$ -ketoesters, benzylamines, aromatic aldehydes and nitromethane. The reaction was carried out under ultrasound and Amberlyst-15 was used as a catalyst<sup>68</sup> as shown in Scheme 17. Novel 3-arylamino substituted fused pyrrole derivatives were prepared through *p*-TsOH promoted *N*-arylation of 2,2-dihydroxy-1-(4-methoxyphenyl) ethanone **109**, (1-methyl-5-oxo-3-(phenylamino)cyclohex-3-en-1-yl)methylum

**110** and 4-nitroaniline. The reaction was carried out in ethanol under microwave heating and the product **111** was formed in 90% yield.<sup>69</sup> Polysubstituted pyrrole derivative 1-(1,4-bis(4-methoxyphenyl)-2-methyl-1*H*-pyrrole-3-yl)ethanone **112** was synthesized by one-pot four-component coupling of 4-methoxyaniline, 4-methoxybenzaldehyde, acetylacetone and nitromethane in gluconic acid aqueous solution (GAAS). Gluconic acid aqueous solution was recycled and reused several times without significant loss of its activity.<sup>70</sup> One more novel method was designed for the synthesis of pyrroles *via* palladium-catalyzed aerobic oxidative intramolecular alkenylation of Csp<sup>3</sup>-H bond. Ethyl-3-(allylamino)-3-phenylacrylate **113** was treated with palladium catalyst under mild conditions in



Scheme 17 Synthesis of various catalyzed pyrrole analogs.

presence of molecular oxygen as the terminal oxidant, to form ethyl-4-methyl-2-phenyl-1*H*-pyrrole-3-carboxylate **114**.<sup>71</sup> Various diversely functionalized pyrroles were synthesized under catalyst-free condition by using ionic liquid as a reaction media from an efficient four-component reaction of prop-2-yn-1-amine, 3-hydroxybenzaldehyde, nitromethane and pentane-2,4-dione (Scheme 17). The reaction completed by using an ionic liquid 1-*n*-butylimidazolium tetrafluoroborate [Hbim]BF<sub>4</sub>, that yielded 1-(4-(3-hydroxyphenyl)-2-methyl-1-vinyl-1*H*-pyrrol-3-yl)ethanone **115** without any additional catalyst or promoter.<sup>72</sup> Michlik and Kempe introduced a sustainable iridium-catalyzed synthesis of pyrroles by deoxygenating secondary alcohols and amino alcohols by linking them through the formation of C–N and C–C bonds. Oxidation of commercially available 1-phenylethanol from potassium tertiary butoxide led to the formation of acetophenone, which was fused with 2-aminobutan-1-ol to form 2-((1-phenylethylidene)amino)butan-1-ol **116**. Further treatment of this intermediate with potassium tertiary butoxide in presence of iridium catalyst

yielded 2-ethyl-5-phenyl-1*H*-pyrrole **117** (Scheme 18).<sup>73</sup> A novel and efficient method was developed for the synthesis of substituted pyrroles *via* palladium(II)-catalyzed alkenyl C–H activation oxidative annulations of enamides with alkynes. *N*-(1-Phenylvinyl)acetamide **118** was reacted with 1,2-diphenylethyne in presence of tertiary amyl alcohol and palladium catalyst to give 1-(2,3,5-triphenyl-1*H*-pyrrol-1-yl) ethanone **119** in good yield.<sup>74</sup> Highly functionalized pyrroles were synthesized by reaction of rhodium-stabilized imino-carbenes with furans. The reaction of dimethylfuran with *N*-sulfonyltriazole resulted in the formation of pyrrole **120** in 41% yield.<sup>75</sup> Novel 2,4,5-trisubstituted pyrrole derivatives **121** were synthesized through the coupling of  $\alpha$ -diazoketones with  $\beta$ -enaminoketones and esters using 10 mol% Cu(OTf)<sub>2</sub>.<sup>76</sup> Various pyrrole derivatives were synthesized from oxazolidines (Scheme 18). On boiling 2-butyl-2-methyl-3-(2-hydroxyethyl)oxazolidine **122** in presence of potassium hydroxide, equimolar amount of pyrrole derivatives **123** and **124** were formed in overall 61% yield (Scheme 18).<sup>77</sup>



Scheme 18 Synthesis of catalyzed pyrrole molecules.

Suresh *et al.* designed a facile and regioselective method for the synthesis of polysubstituted pyrroles from  $\alpha$ -azido chalcones and 1,3-dicarbonyl compounds. The reaction of 2-azido-1,3-diphenylprop-2-en-1-one **125** with pentane-2,4-dione, catalyzed by indium trichloride in water, resulted in formation of (1-(4-benzoyl)-2-methyl-5-phenyl-1*H*-pyrrol-3-yl) ethanone **126**.<sup>78</sup> A method was developed to synthesize novel pyrrole ring containing azepine skeleton **128**. The reaction was catalyzed by rhodium(II) azavinyl carbene intermediate, which initiated the intramolecular C–H functionalization with pyrrolyl ring of compound **127** (Scheme 19).<sup>79</sup> In 1910, Piloty discovered that 2,5-diethyl-3,4-dimethyl pyrrole **130** was formed upon heating diethyl ketone azine **129** at 230 °C. Later on, in 1918, Robinson and Robinson synthesized 2,3,4,5-tetraphenylpyrrole **132** by heating deoxybenzoin azine **131** in hydrogen chloride stream at 180 °C (Scheme 19). These reactions are known as Piloty–Robinson reaction.<sup>80</sup> The reaction of diaryl diazomethane with 1,4-dilithio-1,3-diene **133** yielded 2,3,4,5-tetrabutyl-*N*-(diphenylmethylene)-*H*-pyrrol-1-amine **134** in high yield. Diaryl diazomethane acted as an electrophile in this reaction.<sup>81</sup> A pyrrole-2,3,4,5-tetracarboxylate derivative **135** was obtained during a copper-catalyzed reaction of amine with but-2-ynedioate. The reaction required oxygen atmosphere and three bonds were formed during the process (Scheme 19).<sup>82</sup> Zhao *et al.* studied the palladium-catalyzed direct polyarylation of 1-methylpyrrole. In

presence of three equivalents of aryl bromide, 1-(4-(1-methyl-1*H*-pyrrol-2-yl) phenyl) ethanone **136** and 1,1'-((1-methyl-1*H*-pyrrole-2,5-diyl)bis(4,1-phenylene)) diethanone **137** were formed. These compounds were formed as the C<sub>2</sub> and C<sub>5</sub> positions of pyrroles are more reactive for C–H bond functionalization as compared to the C<sub>3</sub> and C<sub>4</sub> positions. 1 mol% PdCl(C<sub>3</sub>H<sub>5</sub>) (dppb) [dppb = 1,4-bis(diphenylphosphino)butane] was used as catalyst, while dimethylacetamide and potassium acetate were the solvents used.<sup>83</sup> A new approach was developed for the synthesis of tetrasubstituted pyrroles from the readily available amino acid esters (Scheme 19). Biosynthetic reaction of L-tryptophan **138** with RebO enzyme formed the imine intermediate, which was transformed into chromopyrrolic acid **139** with the action of RebD enzyme *via* oxidative deamination and cyclization (Scheme 20).<sup>84</sup>

### 3. Biological significance of pyrrole containing analogs

Pyrrole, being an important ring structure, has been found to possess a number of biological activities. This ring has a broad range of biologically active compounds, incorporated either as a substituent or with various substitutions on the ring itself. Some of the drugs containing pyrrole moiety are already available in market and some are under clinical trials as presented in Table 3.



Scheme 19 Substituted pyrrole molecules.

### 3.1. Anticoccidial activity

A series of various diarylpyrrole derivatives were analyzed for the anticoccidial activity by both *in vitro* and *in vivo* assays. The dimethyl amine substituted derivative **140** resulting was found to be the most potent inhibitor against *Eimeria tenella* (Et) PKG (cGMP-dependent protein kinase).<sup>85</sup> Further studies on diarylpyrrole derivatives suggested that the  $\omega$ -hydroxylated

derivatives **141** were more potent inhibitor as compared to their alkyl analogs.<sup>86</sup> *N*-Substituted derivatives of 2,3-diarylpyrrole were evaluated against commercially important strains of *Eimeria* in chickens. Among these, 5-(*N*-methyl, *N*-ethyl, and *N*-methylazetidyl methyl) piperidyl derivatives **142**, **143**, **144** were found to be most potent with a broad spectrum activity. The *N*-ethyl piperidine analog **143** had excellent activity when administered at 50–125 ppm levels in an *in vivo* spectrum model against eight of the most common *Eimeria* species *i.e.* *E. tenella*, *E. acervulina*, *E. necatrix*, *E. brunetti*, *E. maxima*, *E. mitis*, *E. mivati*, and *E. praecox*.<sup>87</sup> *N*-Alkyl-4-piperidyl-2,3-diarylpyrrole derivatives with heterocyclic substitutions were also evaluated and found to possess anticoccidial profile. Among the series of compounds evaluated, the azetidine derivative **145** and morpholine derivative **146** showed improvements in potency of Et-PKG inhibition.<sup>88</sup>

### 3.2. Anti-inflammatory activity

Tolmetin **147** and Zomepirac **148** are two pyrrole acetic acid derivatives that have now gained a degree of success in treatment of rheumatoid arthritis and pain. Wong and coworker reported that methylation of Zomepirac in the acetic acid chain **149** markedly increased the anti-inflammatory potency as measured by the rat paw kaolin edema assay. Benzoylpyrrolopyrrole carboxylic acid series of compounds also possess high anti-inflammatory and analgesic activity among which *p*-methoxy derivative of 5-benzoyl-1,2-dihydro-3*H*-pyrrolo-[1,2- $\alpha$ ]pyrrole-1-carboxylic acid and 4-vinylbenzoyl derivatives were most potent (**150** and **151**)<sup>89</sup> as shown in Fig. 1. Bimetopyrol **152**, a 2-substituted-4,5-diarylpyrrole derivative, was also reported to show anti-inflammatory and analgesic properties. A series of 2-substituted-4,5-diarylpyrroles as potent anti-inflammatory agents among which 2-[(trifluoromethyl) thio]-4-(4-fluorophenyl)-5-[4-(methylsulfonyl)phenyl] pyrrole **153** (Fig. 1) was reported as potent anti-inflammatory agent against paw edema produced in the adjuvant arthritis rat model.<sup>90</sup> A series of 1,2-diarylpyrroles were also found to be selective inhibitors of COX-2 and evaluated for anti-inflammatory activity by adjuvant induced arthritis rat model, among which 1-(4-fluorophenyl)-2-methyl-5-[4-(methylsulfonyl)phenyl]-1*H*-pyrrole-4-[1-(4-fluorophenyl)-5-methyl-1*H*-2-pyrrolyl] phenylmethylsulfone **154** and



Scheme 20 Catalysis assisted formation of pyrrole containing compound.

Table 3 Marketed pyrrole containing drugs and molecules under clinical trial

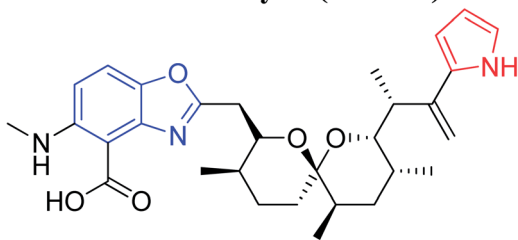
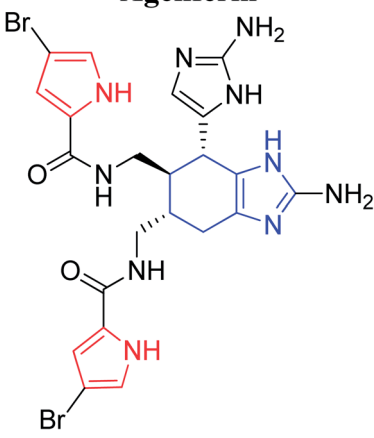
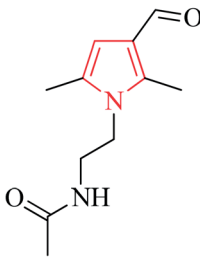
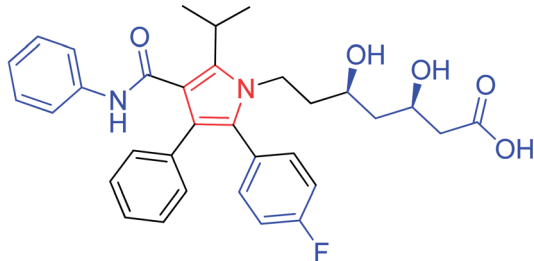
S. no.	Compounds	Description
1	<p style="text-align: center;"><b>Calcimycin(A23187)</b></p>  <p>5-(Methylamino)-2-((2<i>R</i>,3<i>R</i>,6<i>S</i>,8<i>S</i>,9<i>R</i>,11<i>R</i>)-3,9,11-trimethyl-8-[[1<i>S</i>]-1-methyl-2-oxo-2-(1<i>H</i>-pyrrol-2-yl)ethyl]-1,7-dioxaspiro[5.5]undec-2-yl)methyl)-1,3-benzoxazole-4-carboxylic acid</p>	<ul style="list-style-type: none"> <li>• It is produced by fermentation of <i>Streptomyces chartreusensis</i></li> <li>• It possesses antibiotic properties against Gram positive bacteria and fungi</li> <li>• It acts as divalent cation ionophore and its order of selectivity is: <math>Mn^{2+} &gt; Ca^{2+} &gt; Mg^{2+} &gt; Sr^{2+} &gt; Ba^{2+}</math></li> <li>• It inhibits mitochondrial ATPase activity</li> <li>• It uncouples oxidative phosphorylation</li> <li>• It induces apoptosis in some cells and prevents it in others</li> </ul>
2	<p style="text-align: center;"><b>Ageliferin</b></p>  <p><i>N</i>-[[[(5<i>S</i>,6<i>R</i>,7<i>R</i>)-2-Amino-7-(2-amino-1<i>H</i>-imidazol-5-yl)-5-[[[(4-bromo-1<i>H</i>-pyrrol-2-yl)carbonyl]amino]methyl]-4,5,6,7-tetrahydro-1<i>H</i>-benzimidazol-6-yl]methyl]-4-bromo-1<i>H</i>-pyrrole-2-carboxamide</p>	<ul style="list-style-type: none"> <li>• It is a chemical compound produced by some sponges</li> <li>• It was first isolated from Caribbean and then Okinawan marine sponges in the genus <i>Agelas</i></li> <li>• It has antibacterial properties</li> <li>• It can cause biofilms to dissolve</li> </ul>
3	<p style="text-align: center;"><b>Aloracetam</b></p>  <p><i>N</i>-[2-(3-Formyl-2,5-dimethylpyrrol-1-yl)ethyl]acetamide</p>	<ul style="list-style-type: none"> <li>• It is a neotropic drug of the racetam family</li> <li>• It is useful for the treatment of Alzheimer's disease</li> </ul>
4	<p style="text-align: center;"><b>Atorvastatin</b></p>  <p>(3<i>R</i>,5<i>R</i>)-7-[2-(4-Fluorophenyl)-3-phenyl-4-(phenylcarbamoyl)-5-propan-2-ylpyrrol-1-yl]-3,5-dihydroxyheptanoic acid</p>	<ul style="list-style-type: none"> <li>• It is used for the treatment of dyslipidemia</li> <li>• It is useful in preventing cardiovascular diseases</li> <li>• It is recommended to be used only after other measures, such as, if diet, exercise and weight reduction have not improved cholesterol levels</li> </ul>

Table 3 (Contd.)

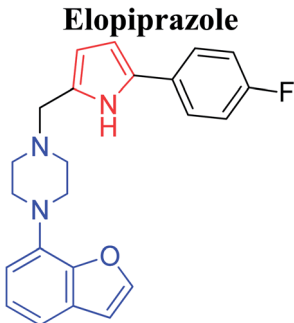
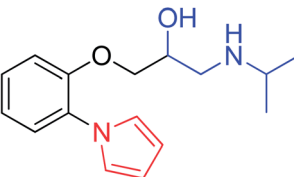
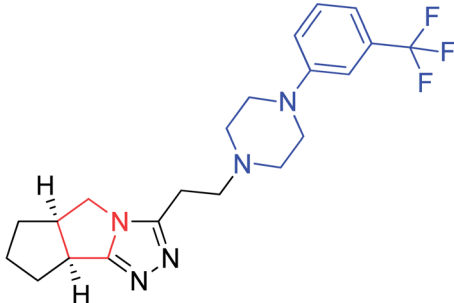
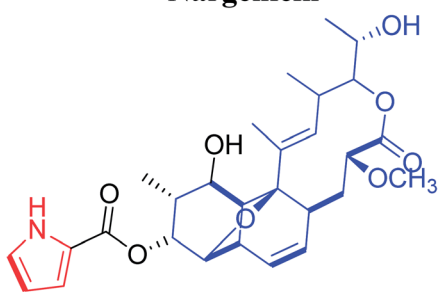
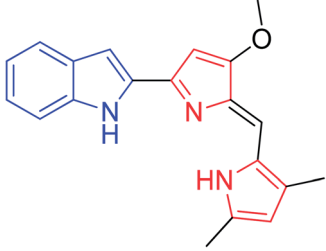
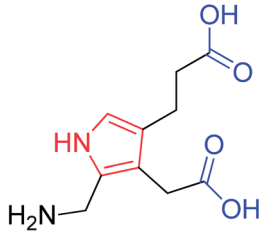
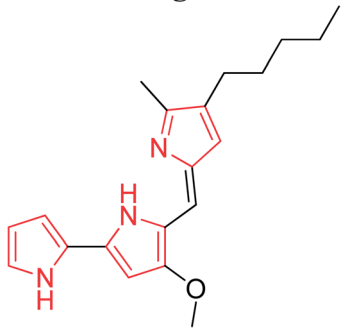
S. no.	Compounds	Description
5	<p><b>Elopirozole</b></p>  <p>1-(1-Benzofuran-7-yl)-4-[[5-(4-fluorophenyl)-1H-pyrrol-2-yl]-methyl]piperazine</p>	<ul style="list-style-type: none"> <li>• It is an antipsychotic drug of the phenylpiperazine class</li> </ul>
6	<p><b>Isamoltane</b></p>  <p>1-(Propan-2-ylamino)-3-(2-pyrrol-1-ylphenoxy)propan-2-ol</p>	<ul style="list-style-type: none"> <li>• Isamoltane (CGP-361A) is a drug of scientific research</li> <li>• It acts as antagonist at <math>\beta</math>-adrenergic, 5-HT<sub>1A</sub> and 5-HT<sub>1B</sub> receptors</li> <li>• It has anxiolytic effect in rodents</li> </ul>
7	<p><b>Lorpirozole</b></p>  <p>(5<i>aR</i>,8<i>aS</i>)-3-(2-{4-[3-(Trifluoromethyl)phenyl]piperazin-1-yl}ethyl)-5,5<i>a</i>,6,7,8,8<i>a</i>-hexahydrocyclopenta[3,4]pyrrolo[2,1-<i>c</i>][1,2,4]triazole</p>	<ul style="list-style-type: none"> <li>• It is also known as Normarex</li> <li>• It is an anxiolytic drug of phenylpiperazine class</li> </ul>
8	<p><b>Nargenicin</b></p>  <p>14-Hydroxy-4-((<i>S</i>)-1-hydroxyethyl)-7-methoxy-1,3,13-trimethyl-6-oxo-3,4,6,7,8,8<i>a</i>,11,12,13,14,14<i>a</i>-dodecahydro-11,14<i>b</i>-epoxynaphthol [2,1-<i>e</i>]oxecin-12-yl 1<i>H</i>-pyrrole-2-carboxylate</p>	<ul style="list-style-type: none"> <li>• It is a 28 carbon macrolide with a tricyclic lactone ring and unique ether bridge</li> <li>• It is isolated from <i>Nocardia argentinensis</i></li> <li>• It is effective against Gram positive bacteria</li> <li>• It induces cell differentiation, thus used for neoplastic diseases</li> </ul>

Table 3 (Contd.)

S. no.	Compounds	Description
9	<p style="text-align: center;"><b>Obatoclax</b></p>  <p style="text-align: center;">2-((3,5-Dimethyl-1H-pyrrol-2-yl)methylene)-3-methoxy-2H-pyrrol-5-yl)-1H-indole</p>	<ul style="list-style-type: none"> <li>• It is an experimental drug for the treatment of various types of cancer</li> <li>• It is in phase II clinical trials for the treatment of leukemia, lymphoma, myelofibrosis and mastocytosis</li> </ul>
10	<p style="text-align: center;"><b>Porphobilinogen (PBG)</b></p>  <p style="text-align: center;">3-[5-(Aminomethyl)-4-(carboxymethyl)-1H-pyrrol-3-yl]-propanoic acid</p>	<ul style="list-style-type: none"> <li>• PBG is a drug that involves pyrrole in porphyrin metabolism</li> <li>• An acute intermittent porphyria causes an increase in urinary porphobilinogen</li> </ul>
11	<p style="text-align: center;"><b>Prodigiosin</b></p>  <p style="text-align: center;">4-Methoxy-5-[[Z]-(5-methyl-4-pentyl-2H-pyrrol-2-ylidene)-methyl]-1H,1'H-2,2'-bipyrrole</p>	<ul style="list-style-type: none"> <li>• It possesses antibacterial, antifungal, antiprotozoal, antimalarial, immune suppressive and anticancer properties</li> </ul>

2-(4-fluorophenyl)-5-methyl-1-[4-(methylsulfonyl)phenyl]-1H-pyrrole-4-[2-(4-fluorophenyl)-5-methyl-1H-pyrrolyl] phenyl methyl sulfone **155** (Fig. 1) showed excellent potency for *in vivo* testing in the carrageenan induced paw edema model in the rat.<sup>91</sup>

On the other side, 1,3,4-thiadiazoles when reacted with pyrrole-3-carboxamide moiety were found to hold anti-inflammatory activity. The synthesized compounds were evaluated for their anti-inflammatory activity against carrageenan-induced acute paw edema in Wistar albino rats among which nitro **156** and fluoro **157** substituted derivatives (Fig. 2) were found to be potent showing high activity profile.<sup>92</sup> The new class of pyrrole derivatives was synthesized containing a small appendage fragment (carbaldehyde, oxime, nitrile) on the central core. The compound **158** was most effective *in vivo* and

showed a significant profile when compared to the already marketed reference compound. When compared to celecoxib, this compound was more efficient and potent inducing a percentage of writhes reduction.<sup>93</sup> The novel pyrrolo [2,3-*d*] pyrimidine and pyrrolo [1,2,4] triazolo[1,5-*c*] pyrimidine derivatives were synthesized as anti-inflammatory agents. When compared to the standard drug, ibuprofen, it was observed that compounds **159**, **160** and **161** showed increased activity (Fig. 2) due to the introduction of hydrazine group, thione group and phenyl group respectively.<sup>19</sup>

### 3.3. EP<sub>1</sub> receptor antagonist

Synthesized 1,5-biarylpyrroles were found to exhibit potential EP<sub>1</sub> receptor antagonist activity. The compound **162** was found

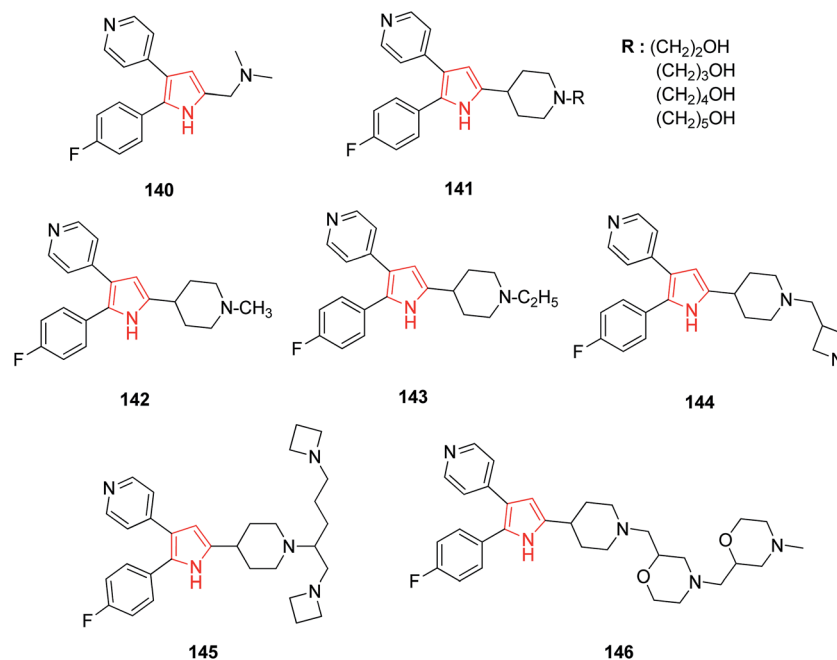


Fig. 1 Pyrrole containing compounds with anticocidal activity.

to be the most potent among a synthesized series of 1,5-biarylpyrrole derivatives containing two fluorine atoms.<sup>94</sup> It was reported that the substitution of benzoic acid moiety at the 5-position by electron donating group such as NH<sub>2</sub> **163** increased the affinity towards EP<sub>1</sub> receptors.<sup>95</sup> The substitution of benzoic acid moiety at 6-position and the 5,6-disubstitution also influenced the *in vitro* affinity profile. The substitution of -F-(**164**), -OMe-(**165**), -OCHF<sub>2</sub>-(**166**) and -NHAc-(**167**) at 6-position showed exceptionally high affinities.<sup>96</sup> The replacement of carboxylic acid in the side chain of 1,5-biarylpyrroles **72** led to the discovery of novel non-acidic antagonists such as sulfonamide **77**, amide **168** and benzimidazole **169** derivatives.<sup>97</sup> The respective compounds have been presented in Fig. 3.

### 3.4. Antipsychotic and anticonvulsant activity

2,5-Disubstituted-1*H*-pyrrole derivatives were synthesized and the modification of basic side chain was carried out by introducing piperidine **170** and 2-phenylazacycloheptane **171** (Fig. 4). The new compounds formed by this reaction showed D<sub>3</sub> antagonist activity with 30 fold selectivity for the D<sub>3</sub> receptor over the D<sub>2</sub> receptor.<sup>98</sup> Further modifications of the ethyl sulfone substituent to either phenyl sulfonate **172** or sulfonamides **173**, **174** and **175** (Fig. 4) showed high affinities and selectivity for the dopamine D<sub>3</sub> receptor over the D<sub>2</sub> receptor. These compounds therefore represent valuable pharmacological tools for the characterization of the role of the dopamine D<sub>3</sub> receptor in central nervous system.<sup>99</sup> Boyfield *et al.* modified 2,5-disubstituted pyrroles by introducing different substituent in the side chain of phenyl group. The introduction of  $\alpha$ -methylbenzyl **176** and aminoindane **177** side chains retained high affinity for the dopamine D<sub>3</sub> receptor.<sup>100</sup> Similarly, synthesized 2-aryl-4-( $\omega$ -aminoacyl)-1-(1-piperidinyl-acetyl) - 1,3,5-trimethylpyrrole derivatives represent a

new, structurally novel class of anticonvulsant agents among which 2-(4-chlorobenzoyl) derivative *i.e.* RWJ-37868 **178**, showed better potency and therapeutic index in comparison to those of phenytoin and carbamezpine moreover greater than sodium valproate. This compound blocked bicuculline induced seizures, and did not elevate seizure threshold following i.v. infusion of metrazole and blocked influx of Ca<sup>2+</sup> ions into cerebellar granule cells induced by K<sup>+</sup> or veratridine.<sup>101</sup> Pyrrole ring has also been found to possess biological activity when incorporated as a substituent. A number of novel pyrrole [1,2-*a*] pyrazine compounds displayed promising seizure protection in the maximal electroshock seizure (MES), subcutaneous metrazol seizure (scMET) and pilocarpine induced status prevention (PISP) tests in epileptic models comparable to the reference anticonvulsant drugs. Among the synthesized pyrrole [1,2-*a*] pyrazine derivatives, the 4*S*,8*aS* diastereomer **179**, its ethoxycarbonylmethyl **180** and 2-phenylethyl **181** derivatives (Fig. 4) were found to be highly potent anticonvulsant agents.<sup>102</sup>

### 3.5. Antifungal and antibacterial activity

Pyrrrolomycins are natural antibiotics and contain nitropyrrole nucleus which is stable and chemically reactive for antifungal activity. *N*-Alkylation of pyrrrolomycin **A 182** caused reduction of antimicrobial activity against *Candida albicans* and *Trichophyton mentagophytes* strains, but *N*-iodoalkylation caused an enhancement of the biological potency. *N*-(iodopropargyl) pyrrrolomycin **A 183** and *N*-(triiodoallyl) pyrrrolomycin **A 184** derivative exhibited more antifungal activity than pyrrrolomycin **A** and a known antifungal agent *i.e.* clotrimazole.<sup>103</sup> The compounds with antifungal and antibacterial activity have been presented in Fig. 5.

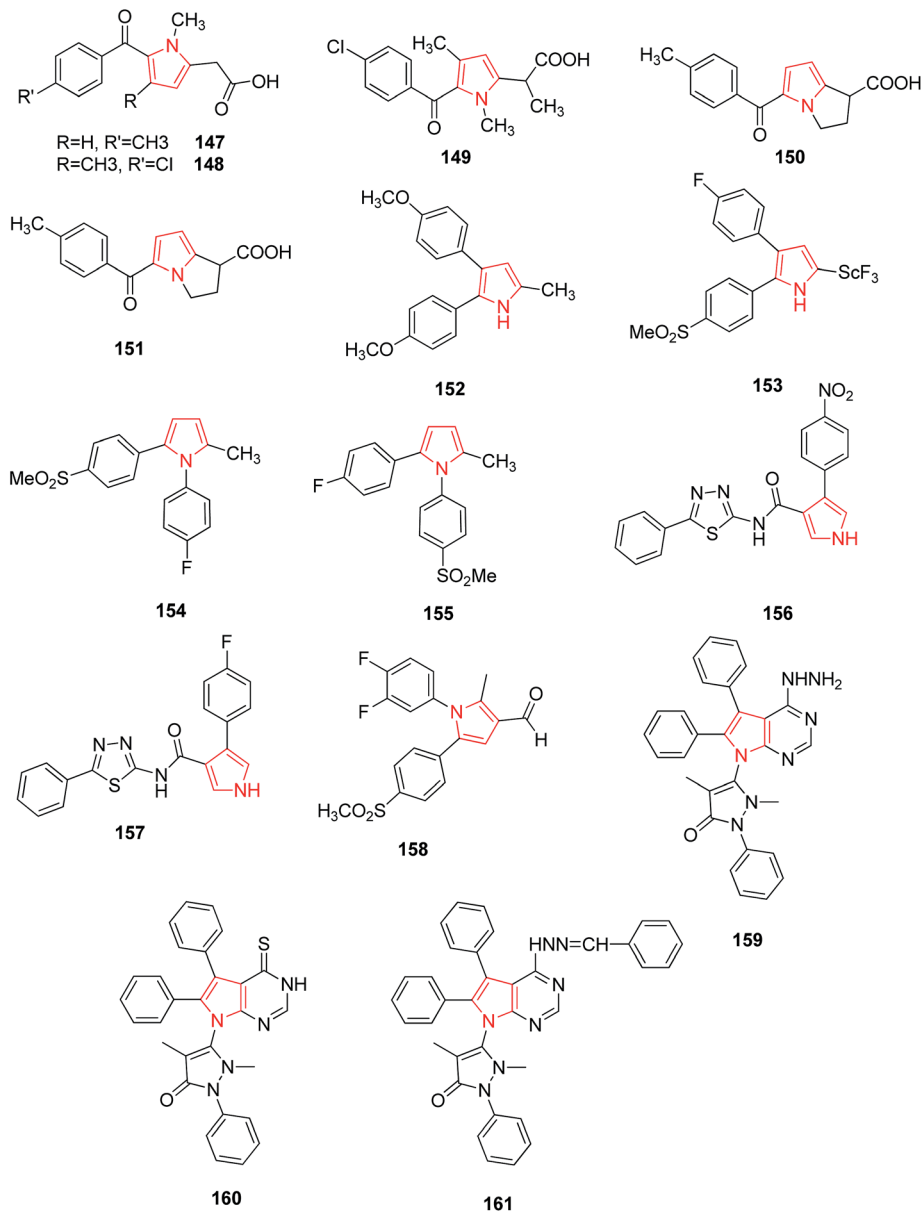


Fig. 2 Pyrrole containing compounds with anti-inflammatory activity.

Pyrrolnitrin **185** and Pyrrolomycin B **186** are synthetic pyrroles that possess antifungal activity, indicating that the bulky substituents on the pyrrole ring weakens the activity whereas nitro group has a potential enhancing affect. It was further concluded that the antifungal activity of nitropyrrole was due to electro-negativity offered by nitro group transmitted through the pyrrole ring. The compounds 3-aryl-4-[ $\alpha$ -(1*H*-imidazol-1-yl) arylmethyl]pyrroles, when related to bifonazole and pyrrolnitrin were discovered as a new class of potential antifungal agents. Among the 3-aryl pyrrole derivatives that contains an (arylmethyl) imidazole moiety, two derivatives **187** and **188** (Fig. 5) were found to be highly active *in vitro* against *C. albicans*.<sup>104</sup> Sulfonamide is well known to possess a variety of biological activities. The introduction of a heterocyclic sulfonamide in the pyrrole ring increases antifungal activity. On the

other hand, lack of any substituent of sulfonamide caused partial or complete reduction in antifungal activity. Among a series of sulfonamide containing pyrroles, compounds **189**, **190**, **191** and **192** (Fig. 5) exhibited a remarkable antifungal activity compared with the standard fungicide mycostatine.<sup>105</sup> Encyclopedia of organic reagents reported that pyrrole containing Verrucarine E **193** and Fenpiclonil **194** are therapeutically useful antibacterial compounds and presence of nitro group at position 3 in 3-nitro-4-phenyl-1*H*-pyrrole **195** increases the antibacterial activity of the compound. A naturally occurring halogenated pyrrole derivative *i.e.* pyoluteorin **196** was found to possess antibacterial activity. Synthesized 4,5-dihalopyrrole derivatives were also reported as potential antibacterial agents derived from the modification of naturally occurring antibiotic pyoluteorin. Substitution of trichloroacetylated pyrrole with



Fig. 3 Pyrrole containing compounds as EP<sub>1</sub> receptor antagonist.

chloro **197**, bromo **198** and iodo **199** group led to the improvement in antibacterial activity.<sup>106</sup> (*R*)-Reutericyclin, (2*R*)-4-acetyl-1,2-dihydro-5-hydroxy-2-(2-methyl-propyl)-1-[(2*E*)-1-oxodec-2-enyl]-3*H*-pyrrol-3-one **200** is a bactericidal natural compound with a trisubstituted tetramic acid moiety which acts against a broad spectrum of Gram-positive bacteria.<sup>107</sup> Hilmy *et al.* synthesized a series of new pyrrole derivatives and pyrrolo[2,3-*d*] pyrimidine derivatives. Compounds **201**, **202** and **203** (Fig. 5) displayed best antifungal activity against *Staphylococcus aureus* with MIC 0.31  $\mu\text{g mL}^{-1}$  when compared with the standard drug ampicillin, with MIC 0.62  $\mu\text{g mL}^{-1}$ . These compounds also showed antibacterial activity against Gram negative *Escherichia coli* similar to the standard drug.<sup>108</sup> A facile method was used for the design and synthesis of a series of novel pyrrole alkaloid analogs. Compounds **204** and **205** exhibited good antifungal activity against *Psylla piricola* at low dosage.<sup>109</sup>

### 3.6. Antiviral activity

Migawa *et al.* synthesized several heterocyclic analogs of antibiotic toyocamycin and tricyclic nucleoside triciribine. They reported that 4-amino-1-( $\beta$ -D-ribofuranosyl) pyrrole [2,3-*d*] [1,2,3] triazine-5-carboxamidrazone **206** and 4-amino-1-( $\beta$ -D-ribofuranosyl) pyrrole [2,3-*d*] [1,2,3] triazine-5-carboxamidoxime **207** (Fig. 6) were active against Human Cytomegalo Virus

(HCMV) and Herpes Simplex Virus type I (HSV-1) but their activity was poorly separated from cytotoxicity.<sup>110</sup> In another study, 1-arylsulfonyl-1*H*-pyrroles were identified as a novel class of non-nucleoside HIV-1 reverse transcriptase inhibitors because of the presence of a specific chemical feature *i.e.* diarylcarbinol moiety which correlated with anti HIV-1 activity. Among the synthesized derivatives, pyrrolyl aryl sulfones (PAS) **208** and 1-benzenesulfonyl-3-( $\alpha$ -hydroxy-2,4-dichlorobenzyl) pyrrole **209** showed the highest activity when tested in MT-4 cells infected with HIV-1.<sup>111</sup> SAR studies conducted on PAS derivatives revealed that the presence of a *p*-chloroaniline moiety and an ethoxycarbonyl group at position 2 of the pyrrole nucleus led to enhanced activity.<sup>112</sup> The new substituent on the amino group at position 2 of the aryl moiety led to the formation of acylamino pyrrolyl aryl sulfones (APASS) **210** which resulted as active as PAS. Further substitutions were done to synthesize PAS derivatives among which the highest antiviral activity within the series was found to be 2-methylpropyl (*sec*-butyl) ester of 1-[(2-amino-5-chlorophenyl)sulfonyl]-1*H*-pyrrole-2-carboxylic acid **211** (Fig. 6).<sup>113</sup> The SAR performed in the central core of NS5B polymerase inhibitors led to the discovery of a novel series of thieno[3,2-*b*]pyrroles that are potential allosteric inhibitors of the Hepatitis C virus (HCV) NS5B RNA-dependent polymerase. Introduction of a polar substituent led to compound **212** which efficiently blocked subgenomic HCV RNA replication in HUH-7

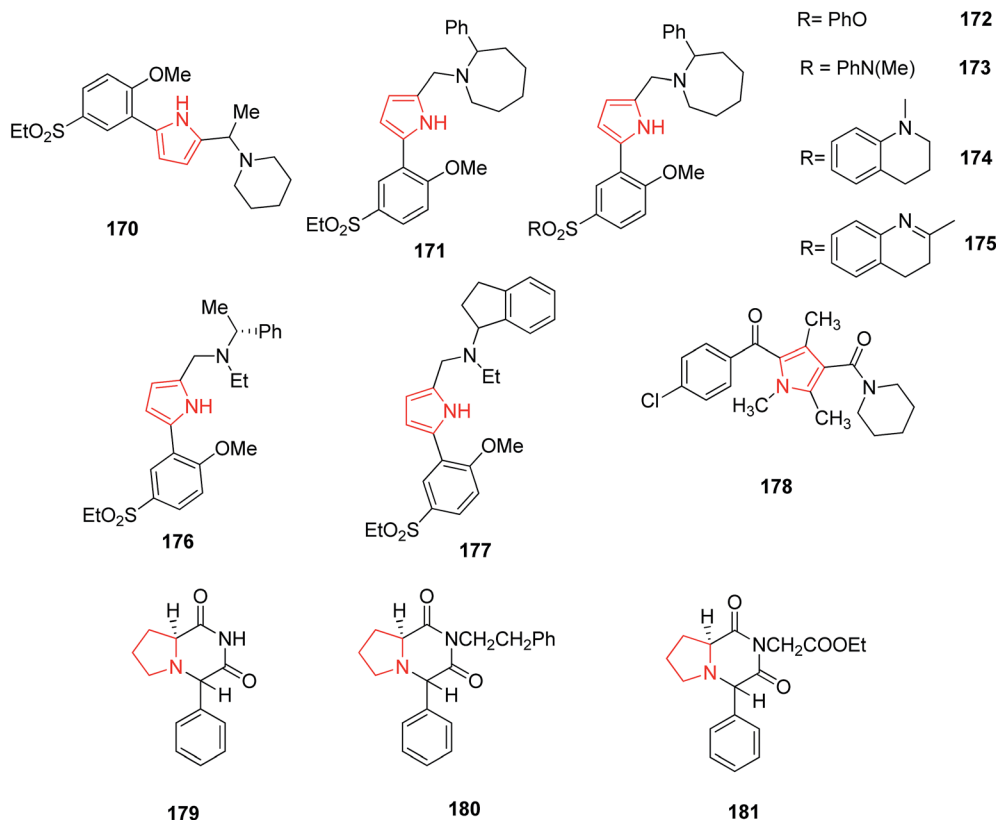


Fig. 4 Pyrrole containing compounds with antipsychotic and anticonvulsant activity.

cells at low micromolar concentration.<sup>114</sup> The chemical structures of compounds with antiviral activity have been shown in Fig. 6.

### 3.7. Antimycobacterial activity

A pyrrole derivative BM212 **213** (Fig. 7) as the most active and potential antimycobacterial agent, was also found active against drug resistant mycobacteria of clinical origin including strains resistant to Etambutol, Isoniazid and also against *Candida albicans* but also found to possess cytotoxicity. To improve the antimycobacterial activity and to reduce cytotoxicity, various derivatives of BM212 were prepared. Among them, 4-substituted pyrrole with *N*-methyl piperaginyll **214** was found more active against *Candida* species as compared to thiomorpholinyl containing derivative **215**.<sup>115</sup> A program was further followed to systematically modify BM212 which led to individuate the importance of the substitutions at C5, N1 and C3. The microbiological results showed the importance of the presence of the thiomorpholine at C3 of the pyrrole and the *p*-chlorophenyl substituent in N1 and C5. The introduction of *p*-fluorophenyl at N1, phenyl at C5 and thiomorpholone at C3 **216** was found to be more active than the corresponding derivatives.<sup>116</sup> To establish the role of the pyrrole ring as a pharmacophoric group and hence, its influence on the antimycobacterial activity, 3-D-QSAR studies were undertaken on a set of pyrrole derivatives. As no information regarding their putative receptor was available, classical quantitative structure–activity relationships

(QSAR) and comparative molecular field analysis (CoMFA) were used to correlate the anti-mycobacterial activity of compounds against *M. tuberculosis*. Among the synthesized compounds using QSAR studies, compound **217** (Fig. 7) showed the highest potency.<sup>117</sup>

Pyrolnitrin, **218** a natural antibiotic used in topical anti-fungal diseases, was found to possess antimycobacterial activity also. Keeping in view its structure, derivatives of 4-aryl-3-nitropyrrole were prepared and evaluated for antimycobacterial activity. Three among other synthesized derivatives, **219**, **220** and **221** (Fig. 7) showed appreciable activity against *M. tuberculosis*.<sup>118</sup> The new diarylpyrroles were designed and synthesized *via* structure–activity relationship analysis of the already designed pyrroles. Compound **222** was found to be most active antitubercular agent having better MIC and PI value than the reference compound, moreover it displayed very low cytotoxicity. This compound was found active against both MTB H37 Rv and MTB rifampicin-resistant strains, with MIC value of 0.25  $\mu\text{g mL}^{-1}$  in both cases.<sup>21</sup> Joshi *et al.* synthesized a new series of pyrrolyl-Schiff base derivatives. The *in vitro* synthesis revealed that compounds **223** and **224** exhibited promising antitubercular activity with less toxicity. On assessment of these compounds against mammalian vero cell lines and A<sub>549</sub> (lung adeno carcinoma) cell lines, it was found that these compounds were active at non-cytotoxic concentrations. By molecular modeling and docking studies, it was revealed that **224** interacted with InhA enzyme more efficiently.<sup>119</sup> While exploring the

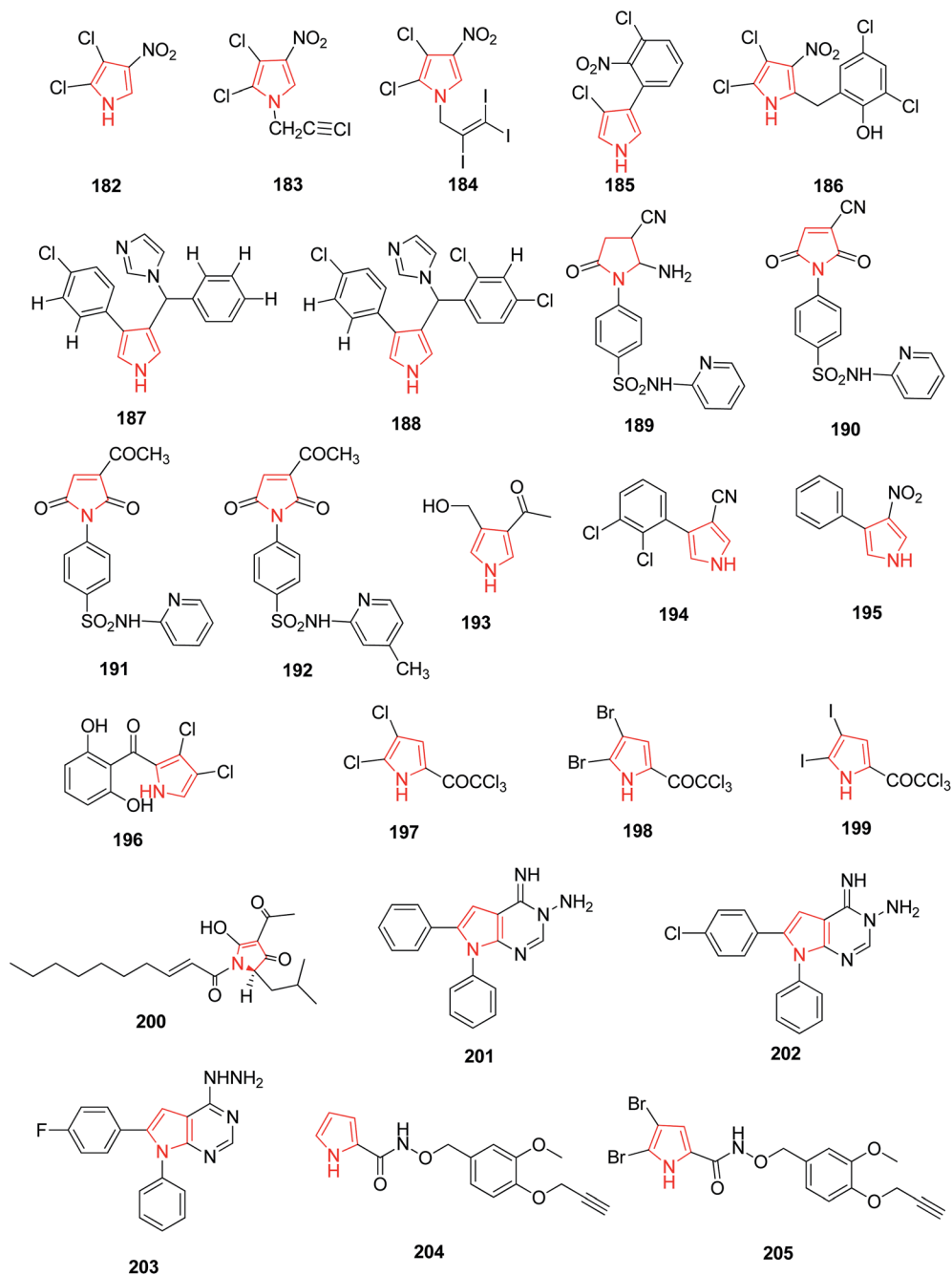


Fig. 5 Pyrrole containing compounds with antifungal and antibacterial activity.

benzochromenone based pyrrole derivatives, Refat *et al.* identified a novel compound **225** with significant antimicrobial activity. This compound was highly active against all the tested bacteria, due to the presence of electron withdrawing group attached to the benzochromenone ring.<sup>120</sup>

### 3.8. Antitumor activity

Roseophilin **226** and Prodigiosins **227** are the natural products of pyrrolo-alkaloids that exhibit a broad range of activity. Furstner reported that roseophilin exhibits higher cytotoxicity against several cancer cells. *In vivo* studies suggests that

prodigiosins acts synergistically with cyclosporine A which is a reference immunosuppressive agent.<sup>121</sup> A series of synthesized aryl pyrroles were evaluated *in vivo* and *in vitro* for antitumor activity among which [1-[[1-(1,3-benzodioxol-5-ylmethyl)-1H-imidazole-5-yl]-methyl]-4-(1-naphthyl)-1H-pyrrol-3-yl][(4-methyl-1-pipazyryl) methanone (LB42908) **228** was found as a highly active antitumor agent, and currently undergoing in preclinical studies as inhibitor of RAS farnesyl transferase (FTase).<sup>6</sup> Cdc7 serine/threonine kinase is a key regulator of DNA synthesis in eukaryotic organisms. Cdc7 inhibition through siRNA or prototype small molecules causes p53 independent apoptosis in

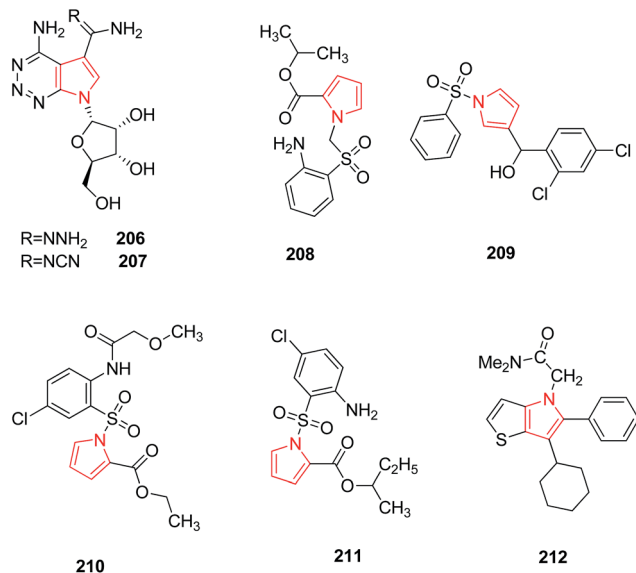


Fig. 6 Pyrrole containing compounds with antiviral activity.

tumor cells while reversibly arresting cell cycle progression in primary fibroblasts. This implies that Cdc7 kinase could be considered a potential target for anticancer therapy. A new chemical class of 5-heteroaryl-3-carboxamido-2-substituted pyrrole derivative **229** was synthesized by introducing a variety

of substituents at position 2 of pyrrole ring. The compound **230** with phenyl substituent at 2 position of pyrrole and 2-amino-4-pyrimidin-4-yl chain at position 5 represented a novel prototype Cdc7 kinase inhibitor.<sup>122</sup> Similarly, Siddiqui *et al.* synthesized compound **231** that showed promising anticancer activity against human leukemia cell line (HL-60) by MTT assay. The presence of [3',5'-dimethylpyrazole-1-yl] carbonylmethoxy moiety attached at 3 $\beta$  position was responsible for this enhanced activity.<sup>123</sup> Compounds with antitumor activity have been presented in Fig. 8.

The ultrasound assisted and bismuth nitrate catalyzed eco-friendly route was developed to synthesize a series of novel *N*-substituted pyrrole derivatives. Compounds **232** and **233** were highly cytotoxic against some cancer cell lines. When compared with normal hepatocytes *in vitro*, these compounds were selectively cytotoxic against hepatic cancer cell lines. The study suggested that *N*-substituted pyrrole exhibits different mechanism of cytotoxicity as compared to other polyaromatic derivatives.<sup>25</sup> The dual inhibitors of Bcl-2 and Mcl-1, 3-thiomorpholine-8-oxo-8*H*-acenaphtho [1,2-*b*] pyrrole-9-carbonitrile were developed. The novel dual inhibitor **234** was obtained by various SAR studies to exploit the difference in the p2 binding pocket of Bcl-2 and Mcl-1. This compound was more effective, having 10 fold lower IC<sub>50</sub> as compared to other synthesized compounds that enhanced the affinity to Mcl-1 as well as maintained the affinity to Bcl-2.<sup>124</sup> The novel 1*H*-pyrrolo



Fig. 7 Pyrrole containing compounds with antimycobacterial activity.



Fig. 8 Pyrrole containing compounds with anti tumor activity.

[2,3-*b*]pyridine derivatives were synthesized for the treatment of DMPM. Compounds 235, 236 and 237 (Fig. 8) consistently reduced DMPM cell proliferation by inducing a caspase-dependent apoptotic response with a concomitant reduction of the expression of active Thr<sup>34</sup>-phosphorylated form of the anti-apoptotic protein surviving.<sup>125</sup> The SAR investigation studies were done on the C2-position of PBD monomer

antitumor agents. Compound 238 delayed tumor growth in HCT-116 (bowel) human tumor xenograft model. The study demonstrated that the cytotoxicity and DNA binding affinity of PBD conjugates can be enhanced by introducing C2-quinolinyl substituent. Moreover, this compound delayed tumor growth in HCT-116 colon cancer xenograft model without causing weight loss or other adverse effects, which suggested that C2-

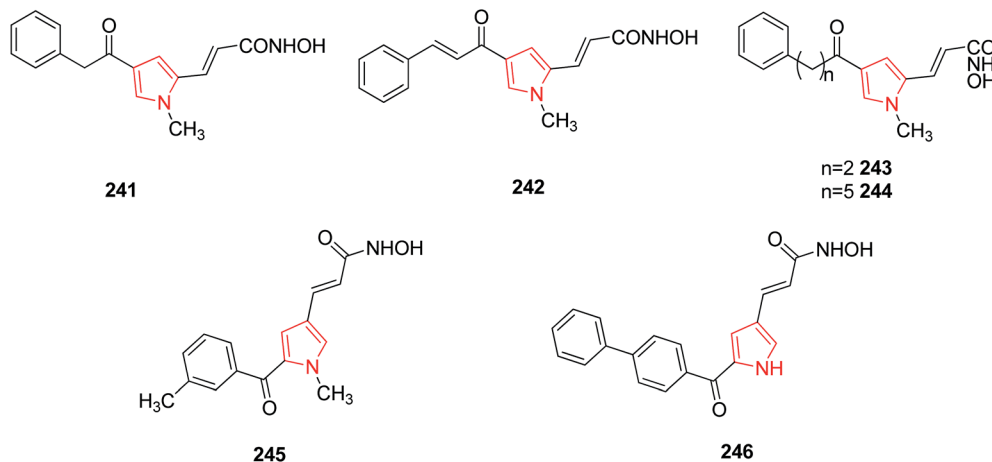


Fig. 9 Pyrrole containing compounds as Histone deacetylase inhibitors.

aryl PBD monomers be used as potential agents in the treatment of human disease.<sup>126</sup>

A hit compound identified in a fungus was used to design a class of polyenyl pyrroles and their analogues. Two compounds **239** and **240** exhibited potential cytotoxicity against human non-small cell lung carcinoma cell lines A549 with  $IC_{50}$  of 0.6 and 0.01  $\mu$ M, respectively. Anticancer activity of compounds could be attributed to the induction of caspases activation dependent apoptosis through loss of mitochondrial membrane potential, followed by release of cytochrome-c and increase in B-cell lymphoma-2-associated X protein ( $B_{ax}$ ) level, and decrease in B-cell lymphoma-2 ( $Bcl-2$ ) level.<sup>127</sup>

### 3.9. Histone deacetylase inhibitors

SAR studies performed on some portions (pyrrole-C4, pyrrole-N1, and hydroxamate group) of 3-(4-benzoyl-1-methyl-1H-pyrrol-2-yl)-N-hydroxy-2-propenamide highlighted its 4-phenylacetyl **241** and 4-cinnamoyl **242** analogues as more active compounds as HD2 active inhibitors *in vitro*. Other homologues

of **241** were prepared by varying hydrocarbon spacer length ranging from two to five methylenes between benzene and carbonyl groups at the pyrrole C4 position. Compounds with two methylenes **243** and five methylenes **244** were most potent while the introduction of higher number of methylene units decreased the inhibitory activities of derivatives.<sup>128</sup> Aroyl-pyrrolyl-hydroxy-amides (APHAs) are a class of synthetic HDAC inhibitors. Their derivatives were prepared by applying chemical modifications on the benzoyl moiety among which **245** and **246** were found to inhibit class IIb and class I histone deacetylase inhibitors.<sup>129</sup> The chemical structures have been provided in Fig. 9.

### 3.10. CDK inhibitors (CDKs)

Wang *et al.* reported that various substitutions on 2-anilino-4-(1H-pyrrol-3-yl) pyrimidine showed inhibition of cyclic dependent kinase enzyme which is key regulators of cell cycle progression. The introduction of a nitrile group at position 5 of the pyrrole ring **247** found to possess 10-fold higher cellular

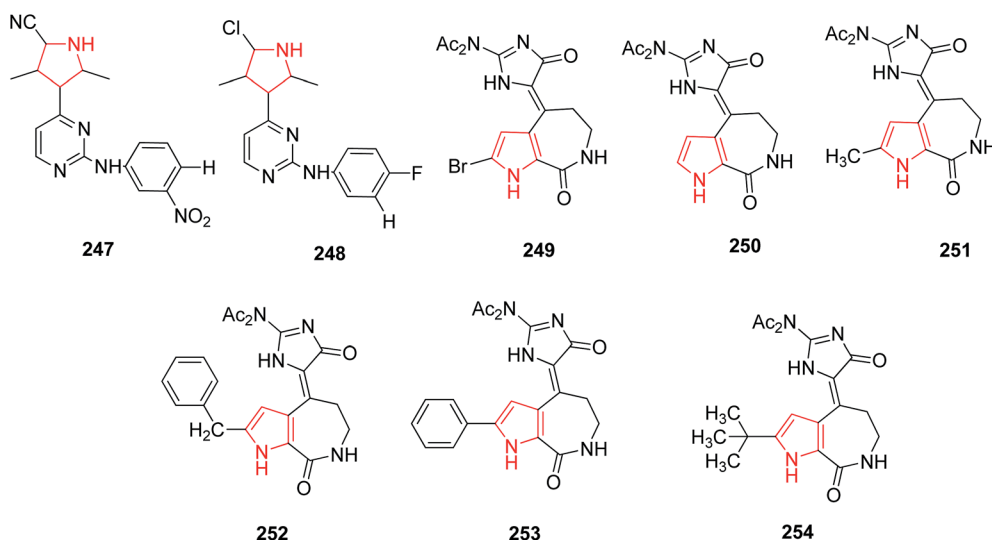


Fig. 10 Pyrrole containing compounds as CDK inhibitors.

activity as compared to halogenated derivative **248** against tumor cells.<sup>130</sup> Hymenialdisine, a marine natural product, was originally isolated from the sponges *Axinella verrucosa* and *Acantella aurantiaca* and found to possess inhibitory activity against members of CDK family. The inhibition activity of diacetyl hymenialdisine **249** is 2-fold higher against CDK5 than that of debromodiacyl hymenialdisine **250** (Fig. 10).

X-ray structure of hymenialdisine-CDK2 complex reveals some hydrophobic interaction between the bromine atom and the hydrophobic backbone of CDK thus showing the key role of bulky and lipophilic effects of the bromo atom of hymenialdisine against CDK inhibition. To further understand its role, various 2-substituted *endo*-hymenialdisine derivatives were synthesized by substituting the bromo atom with methyl **251**, benzyl **252**, phenyl **253** and *tert*-butyl groups **254** (Fig. 10). Thus, a variety of derivatives with substitutions at the  $\alpha$ -position of the pyrrolyl ring were obtained with promising kinase inhibitory activity.<sup>131</sup>

### 3.11. Monoamine oxidase inhibitors

A series of substituted pyrrolylethanoneamine derivatives were evaluated for monoamine oxidase enzyme inhibition activity and SAR studies revealed that aminoketone derivative **255** (Fig. 11) was potentially active and selective inhibitor of MAO-A enzyme where as methylation of this compound results in *N,N*-dimethylamino derivative **256** which was less potent.<sup>132</sup> Bruyne *et al.* demonstrated the study of radio labelling of [<sup>11</sup>C]-labelled pyrrole-2-carboxamide derivative **257** and its *in vivo* properties were categorized. Specific binding was observed in MAO-A when blocking and imaging study was performed. It was observed by *in vivo* studies that this compound penetrated rapidly in the brain, followed by an efficient washout.<sup>133</sup> A novel series of 5-substituted 3-(1-alkyl-1*H*-pyrrol-3-yl)-2-oxazolidinones were synthesized as reversible, highly active and selective MAO-A inhibitors. Compound **258** showed 380 times higher MAO-A inhibitory activity with respect to toloxatone. When compared to bexloxtone, this compound showed similar MAO-A activity but there was an increase in A-selectivity ratio.<sup>134</sup>

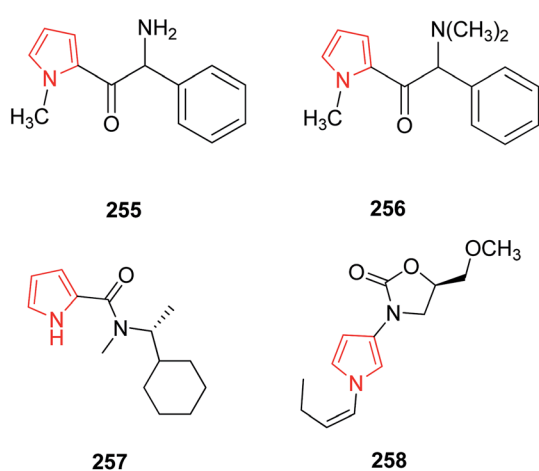


Fig. 11 Pyrrole containing compounds as monoamine oxidase inhibitors.

### 3.12. EGFR tyrosine kinases inhibitors

Over expression of the epidermal growth factor-R tyrosine kinase has been implicated in many disease indications such as tumor and psoriasis. A series of 4,5-disubstitued-5,7-dihydropyrrole [2,3-*d*] pyrimidine-6-ones were found as potentially active and selective inhibitors of the EGFR tyrosine kinase family. The core molecule (5,7-diazaindolone) without substitution at the C-3 position **259** was inactive against any kinases where as condensation of core with substituted pyrrole-2-carboxaldehyde **260** was observed to be active against the EGFR kinase.<sup>135</sup> The novel series of chiral and non-chiral 4-*N*-substituted 6-aryl-pyrrolo pyrimidines were synthesized and tested for their *in vitro* EGFR-TK inhibitor properties. Compound **261** (Fig. 12) was found to be most active EGFR-TK inhibitor with IC<sub>50</sub> of 2.0.<sup>136</sup>

### 3.13. As diagnostic and therapeutic agents

Bacteriochlorins bear a germinal dimethyl group in each pyrroline ring and a symmetrically branched 1,5-dimethoxypentyl group is also attached to each pyrrole ring. Both these groups are well required for the stability and solubility in lipophilic media. Bacteriochlorins absorb strongly in near infra red spectral region and thus, are best suited for photo-medical purposes including optical imaging and photodynamic therapy (PDT). As they possess diverse applications in photo-medicine, they were synthesized synthetically from swallowtail dihydropyrrin which in turn were obtained from swallowtail pyrrole. The swallowtail groups include all hydrocarbon units that afford increased solubility in organic media and polar terminated analogues (*e.g.* 1,5-diphosphonopent-3-yl) that afford solubility in aqueous media. The synthesized swallowtail bacteriochlorins **262** and **263** (Fig. 13) display strong absorption bands in UV.<sup>30</sup> The natural pigment bilirubin, is a bichromophoric structure comprising two *Z*-dipyrinones bearing intramolecularly hydrogen-bonded propionic acid. Bilirubin and its analogues are useful probes for hepatobiliary dysfunction. Based on their structure, fluorinated



Fig. 12 Pyrrole containing compounds as EGFR inhibitors.



Fig. 13 Pyrrole containing compounds as diagnostic and therapeutic agents.

fluorescent dipyrinones were synthesized. The fluorinated and sulphonated *N,N'*-carbonyl-bridged dipyrinones **264** and **265** as their sodium salts possess strong fluorescence and thus used as  $^{19}\text{F}$  MRI imaging agents for use in probing liver and biliary metabolism.<sup>137</sup>

A new class of highly fluorescent and low molecular weight water soluble sulphonated *N,N'*-carbonyldipyrinone (*3H,5H*-dipyrrolo[1,2-*c:2',1'-f'*]pyrimidine-3,5-dione) derivatives **266–270** were synthesized and isolated as their sodium salts. The alkyl substituent of the lactam ring was lengthened from ethyl to decyl showing an increase in lipophilicity thus excreted more selectively in bile. They are thus useful in clinical diagnosis as they will appear in urine when hepatic elimination is impaired by cholestatic liver disease.<sup>33</sup>

## 4. Conclusion

Conclusively, the synthesis of pyrrole analogs is still an active field in medicinal research and development industries.

Various new methods are being employed for its preparation and it will continue to be an important area for research in future. By presenting this review, we hope that the scientific community will be beneficial in developing new synthetic routes for the preparation of this resourceful heterocyclic system with better biological outcomes.

## Conflict of interest

The authors declare no conflict of interest.

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