



Therapeutic potential of pyrrole and pyrrolidine analogs: an update

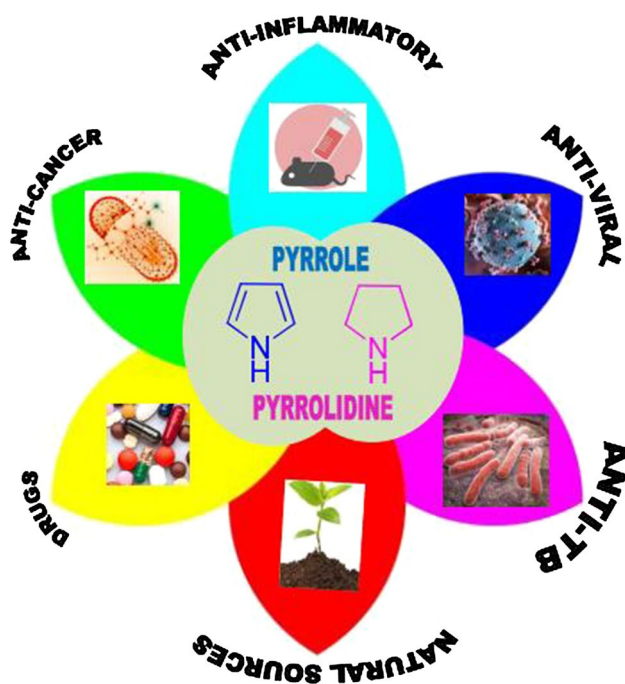
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Abstract

The chemistry of nitrogen-containing heterocyclic compound pyrrole and pyrrolidine has been a versatile field of study for a long time for its diverse biological and medicinal importance. Biomolecules such as chlorophyll, hemoglobin, myoglobin, and cytochrome are naturally occurring metal complexes of pyrrole. These metal complexes play a vital role in a living system like photosynthesis, oxygen carrier, as well storage, and redox cycling reactions. Apart from this, many medicinal drugs are derived from either pyrrole, pyrrolidine, or by its fused analogs. This review mainly focuses on the therapeutic potential of pyrrole, pyrrolidine, and its fused analogs, more specifically anticancer, anti-inflammatory, antiviral, and antituberculosis. Further, this review summarizes more recent reports on the pyrrole, pyrrolidine analogs, and their biological potential.

Graphical Abstract



Keywords Pyrrole · Pyrrolidine drugs · Anticancer · Anti-inflammatory · Anti-viral · Antitubercular activity

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Introduction

Heterocycles are cyclic compounds that have at least one different element than carbon, such as sulfur, oxygen, nitrogen [1]. These heterocycles have received considerable

Fig. 1 Naturally derived pyrrole analogs

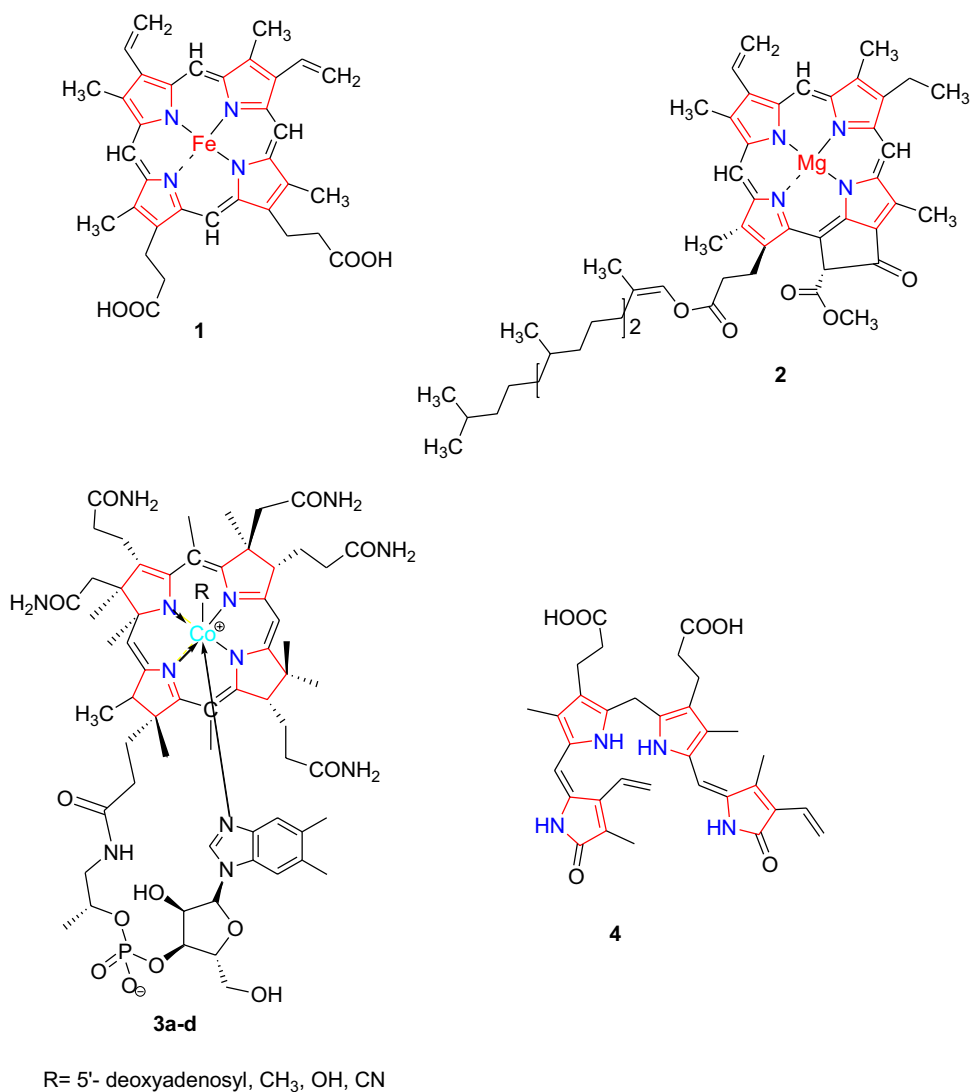
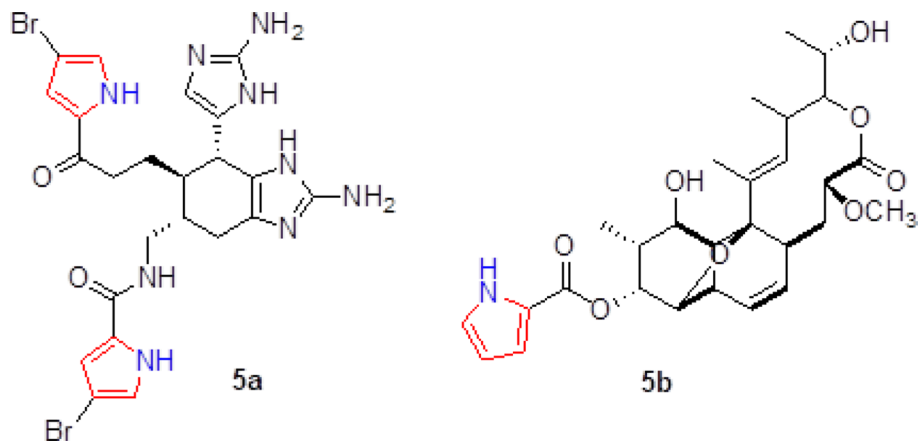


Fig. 2 Pyrrole analogs isolated from microorganism



attention because of their biological and pharmacological significance [2–5]. One of the heterocycles, pyrrole, is not naturally derived, but its analogs present in co-factors

and natural products such as vitamin B12, bile pigments: bilirubin and biliverdin [6, 7], and the porphyrins of heme, chlorophyll, chlorins, bacteriochlorins, and porphyrinogens

[8–11]. Pyrrole-containing secondary metabolites such as makaluvamine M, ryanodine, rhazinilam, lamellarin, prodigiosin, myrmicarin, and sceptrinare also exhibit potential biological activity [12–19]. Apart from this, pyrrole and pyrrolidine analogs have diverse therapeutic applications like fungicides, antibiotics, anti-inflammatory drugs, cholesterol-reducing drugs, anti-tubercular, and antitumor agents [20–25]. These are also known to inhibit reverse transcriptase in case of human immune deficiency virus type 1 (HIV-1) and cellular DNA polymerases protein kinases [26, 27]. The combination of different pharmacophore in a pyrrole and pyrrolidine ring system has led to more active compounds [28–32].

Naturally occurring pyrrole and pyrrolidine analogs

In naturally occurring metal complexes heme (1) and chlorophyll (2), four pyrrole rings are linked together to form porphyrin and then coordinate with iron and magnesium to form respective metal complexes (Fig. 1) [33]. These heme groups, surrounding a globin group, produce a tetrahedral structure known as hemoglobin, an oxygen carrier in animals [34]. Unlike hemoglobin, biomolecule myoglobin traps oxygen within muscle cells for energy production required for muscles to contract [35]. An essential biomolecule, vitamin B12, porphyrin, and cobalt metal complex, forms through the stable metal–carbon bond and plays a vital for proper growth (3 a–d) [36]. Further, the bile pigments (4) are obtained by the decomposition of the porphyrins ring. Formation of this yellowish pigment takes place in spleen, reticulo endothelial cells of the liver, and bone marrow [37]. Another pyrrole analog is ageliferin (5a), produced by sponges. First isolated from the caribbean and then okinawan marine sponges have potential antibacterial properties [38]. Similarly, nargenicin (5b) is isolated from

Nocardia argentinensis found to be more effective against gram-positive bacteria [39] (Fig. 2).

Similarly, pyrrolidine analogs including nicotine (6a), scalusamide (6b), bbugaine (6c), D-ribitol (6d), and aegyleptolidine (6e) showing diverse biological activities have been derived from natural sources and microorganisms [40, 41] (Fig. 3).

Pyrrole and pyrrolidine drug candidates

Nitrogen-containing heterocycles have been known for their therapeutic potential. Among medicinal drugs, many are containing pyrrole and pyrrolidine moiety [42, 43]. Some of the drugs have pyrrole, pyrrolidine moieties are already available in market, and some are under clinical trials. The following are the pyrrole, pyrrolidine (saturated pyrrole) drug candidates.

Telaprevir (7)

Pyrrolidine (saturated pyrrole) analog; telaprevir is an antiviral drug, peptidomimetic used in combination therapy to treat chronic Hepatitis C Virus (HCV) infection. This drug inhibits NS3/4A, a serine protease encoded by HCV genotype 1 and SARS-CoV-2 3CL proteases. Also, this drug is used with pegylated interferon and ribavirin for clinical trials [44–46] (Fig. 4).

Ramipril (8)

Ramipril is a competitive inhibitor of ACE, angiotensin-converting enzyme (ACE), responsible for the conversion of angiotensin I (ATI) to angiotensin II (ATII) and regulates blood pressure. Ramipril is used to treat hypertension, congestive heart failure, and to control the death rate [47, 48] as shown in Fig. 5.

Fig. 3 Naturally derived Pyrrolidine analogs (6a–e)

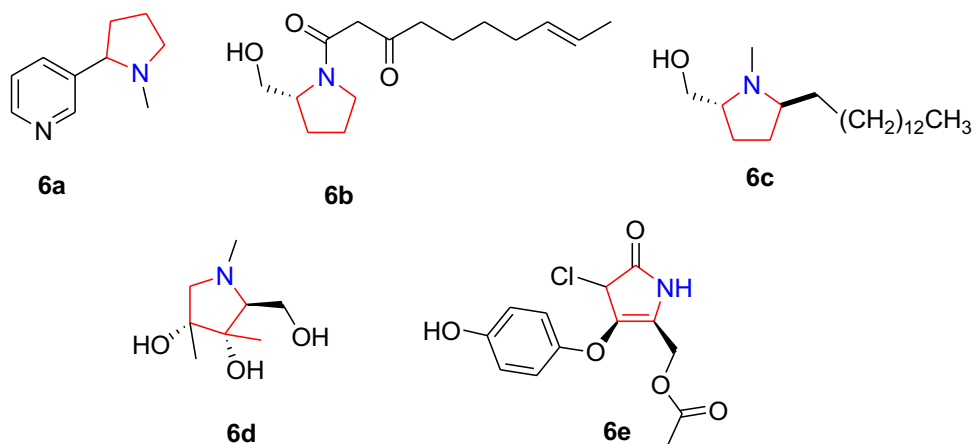


Fig. 4 Pyrrole, pyrrolidine analogs as drug candidates-I

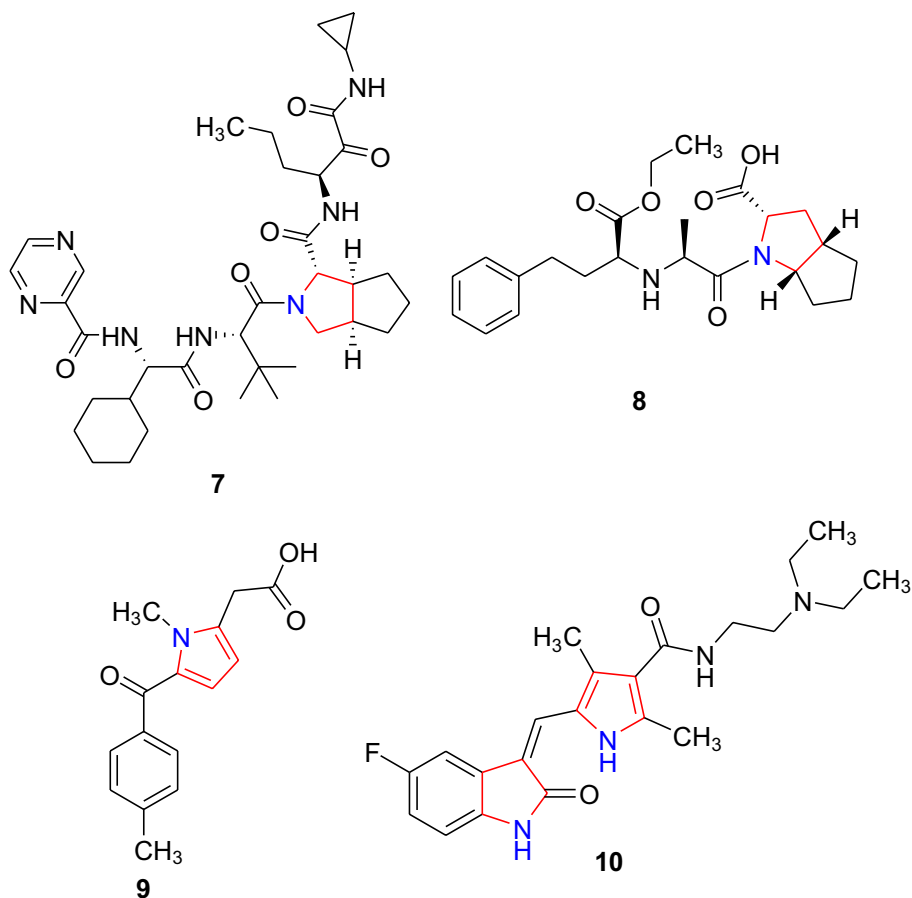
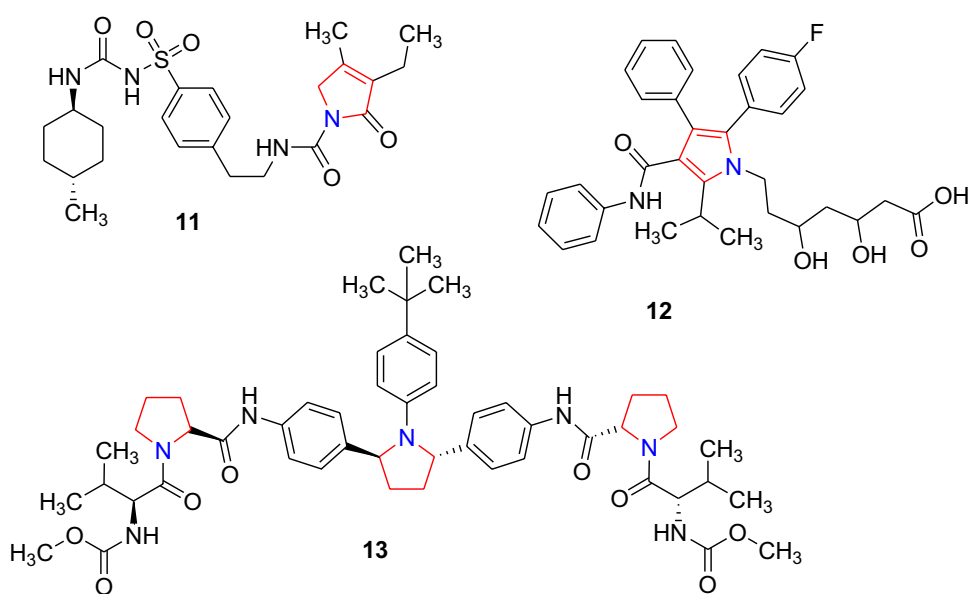


Fig. 5 Pyrrole, pyrrolidine analogs as drug candidates-II



Tolmetin (9)

Tolmetin is also known as 1-methyl-5-p-toluoylpyrrole-2-acetic acid or tolectin and belongs to class of non-steroidal

anti-inflammatory drug used for osteoarthritis, rheumatoid arthritis, and juvenile arthritis [49, 50].

Sunitinib (10)

FDA-approved anticancer drug sunitinib is a tyrosine kinase (RTK) inhibitor used for treating renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST). Because of this, sunitinib is an orally administered formulation that inhibits cellular signaling by targeting multiple RTKs such as rearranged during transfection (RET), colony-stimulating factor 1 receptor (CSF-1R), and fms-like tyrosine kinase 3 (flt3) [51, 52].

Glimepiride (11)

Organic compounds such as sulfonylureas are used as insulin secretagogues to control type 2 diabetes, thereby reducing blood glucose levels. Glimepiride, a pyrrole analog, second-generation sulfonylureas is used for type 2 diabetes mellitus (T2DM) [53, 54].

Atorvastatin (12)

Literature evidenced an enzyme hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase, known to catalyze the conversion of HMG-CoA to mevalonic acid. This conversion involves compounds that play different roles in lipid metabolism and transport, cholesterol, low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL) production. Like other statin medications, atorvastatin, a lipid-lowering drug, is also known to inhibit the HMG-CoA reductase, thereby control the endogenous production of cholesterol in the liver, and reduce the risk of cardiovascular disease. Further, combination of atorvastatin and aspirin is used for SARS-CoV-2 infection [55–57].

Ombitasvir (13)

Due to significant advances in antiviral drugs, many pyrrolidines ring containing analogs are also reported for their potential inhibitory activity toward different viruses. Like telaprevir, ombitasvir, another antiviral medication, is used as a combination therapy to treat chronic Hepatitis C. This molecule inhibits, more specifically, NS5A, a protein essential for viral replication and virion manifestation. This analog also acts as a potent inhibitor of SARS-CoV-2 [58–60].

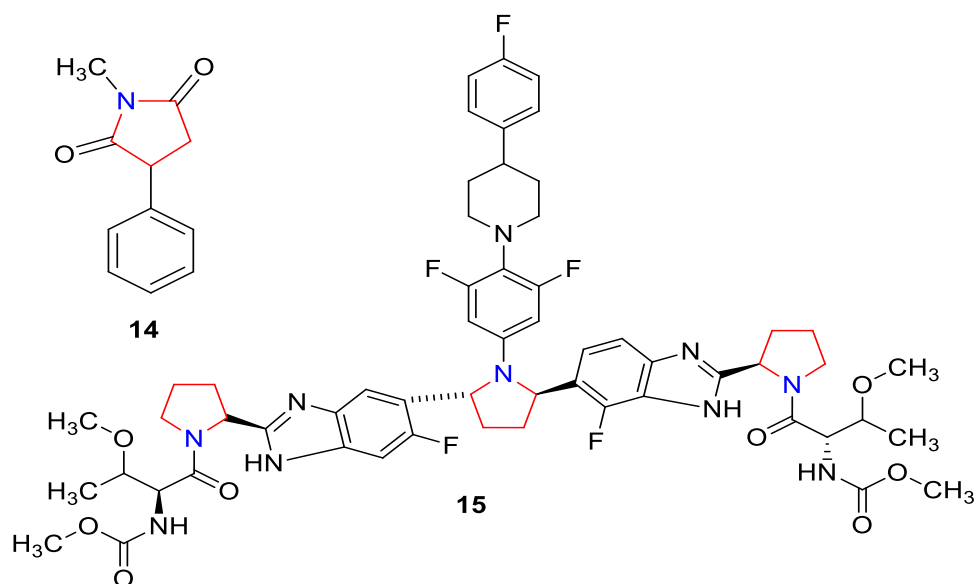
Phensuximide (14)

Phensuximide (Fig. 6), a succinimide analog, possesses antiepileptic and anticonvulsant properties. These orally active drugs produce depolarization-induced accumulation of cyclic adenosine monophosphate and cyclic guanosine monophosphate (*cGMP*) [61, 62].

Pibrentasvir (15)

Like ombitasvir, pibrentasvir is an anti-hepatitis C virus (HCV) drug and specifically inhibits NS5A that targets the viral RNA replication and virion assembly. Also, in combination with glecaprevir, an NS3/4A protease inhibitor was used for patients with therapeutic failure from other NS5A inhibitors [63, 64].

Fig. 6 Pyrrole, pyrrolidine analogs as drug candidates-III



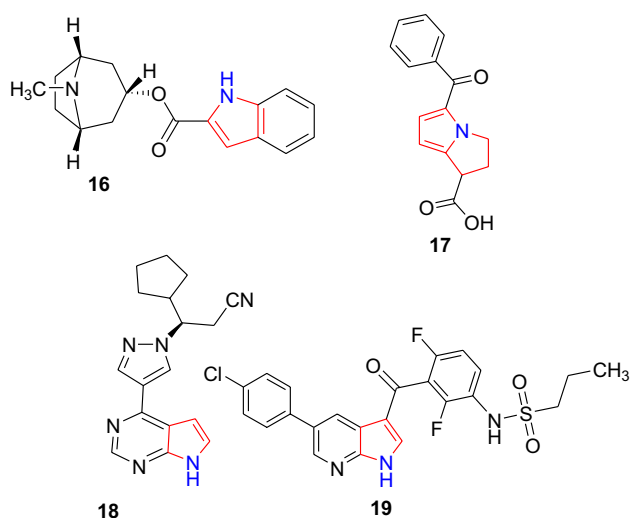


Fig. 7 Fused pyrrole analogs as drug candidates-I

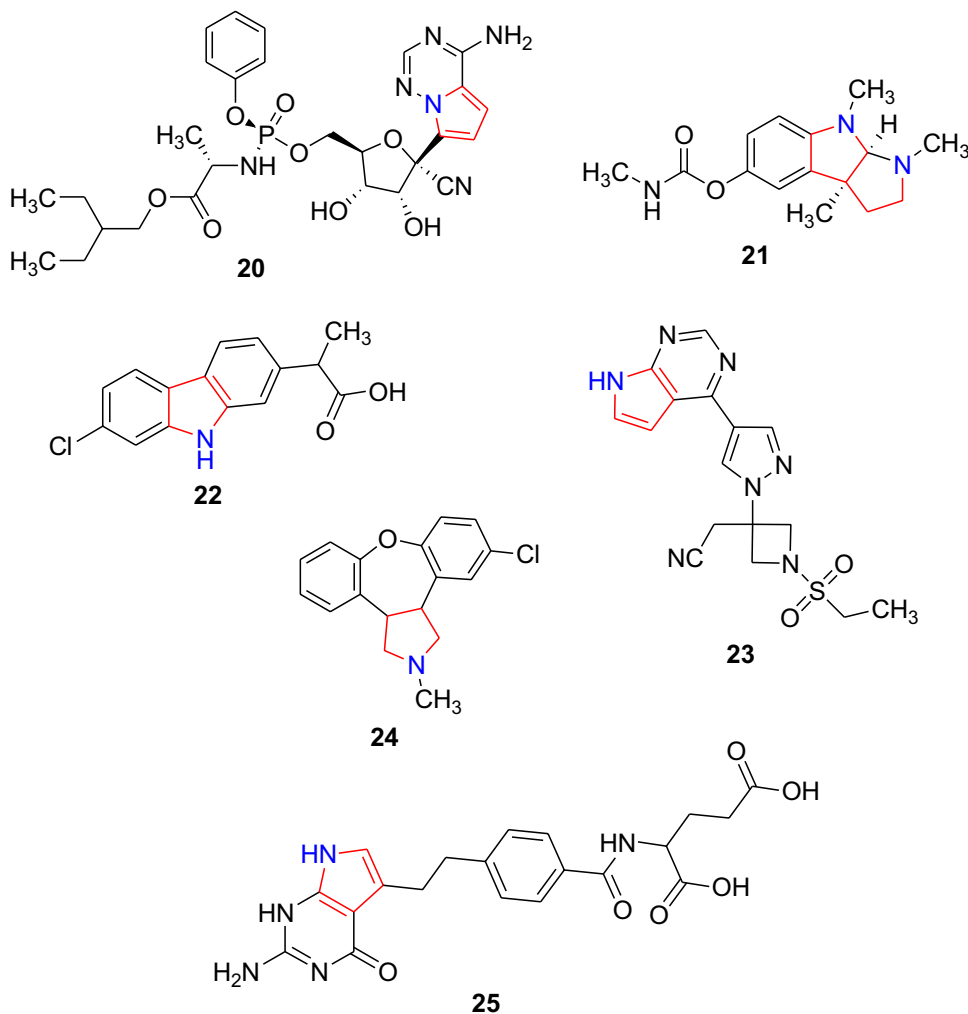
Fused pyrrole as drug candidate

As such pyrrole and pyrrolidine scaffold itself shows diverse pharmacological properties. However, to attain increased biological activities toward various diseases, many fused pyrrole and pyrrolidine analogs have been reported [65, 66]. Further, these medicinally potent fused analogs have been derived from synthetic routes and isolation [67–70]. Because of this, present review also focuses very potent fused pyrrole and pyrrolidine analogs.

Tropisetron (serotonin receptor antagonist) (16)

A serotonin receptor antagonist inhibits serotonin (5-HT) receptors that regulate many neurotransmitters such as gamma-aminobutyric acid (GABA), glutamate, dopamine, acetylcholine, and epinephrine or norepinephrine. These receptors modulate many hormones like oxytocin, prolactin, vasopressin, cortisol, and corticotropin. Serotonin receptors were also responsible for aggression, anxiety, memory, learning, nausea, mood, and sleep [71, 72]. Among such

Fig. 8 Fused pyrrole, pyrrolidine analogs as drug candidates-II



antagonists, tropisetron, a fused pyrrole, an indole analog blocks the action of serotonin at 5HT3 receptors, resulting in control of nausea and vomiting induced by chemotherapy and radiotherapy [73, 74].

Ketorolac (17)

Ketorolac (Fig. 7) is one more non-steroidal anti-inflammatory drug (NSAID) that belongs to this class. This drug is available as an oral tablet, injection, nasal spray, and eye solution. Due to its analgesic properties, this drug is used, for the treatment of rheumatoid arthritis, postoperative pain, osteoarthritis, menstrual disorders, and as well for spondylitis [75, 76].

Ruxolitinib (18)

FDA-approved kinase inhibitors like ruxolitinib are used for adult patients with bone marrow disorders. Reports suggest that ruxolitinib may use for patients suffering from an infection caused by covid-19. However, this drug is clinically not approved for the treatment of covid-19 disease [77, 78].

Vemurafenib (19)

Like ruxolitinib, vemurafenib also belongs to the class of competitive kinase inhibitor. Specifically, it is active against serine-threonine kinase (BRAF kinase) with mutant V600E. It binds to the ATP-binding domain of the mutant BRAF and thereby exerts its function. Further, this compound is more effective against severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) [79–81].

Remdesivir (20)

Remdesivir (GS-5734) is chemically named as *N*-[(*S*)-{[(2*R*,3*S*,4*R*,5*R*)-5-(4-aminopyrrolo[2,1-*f*][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxytetrahydrofuran-2-yl]methoxy} (phenoxy)phosphoryl]-L-alanine (Fig. 8). This adenosine triphosphate analog exhibits broad antiviral activity against viral families such as *Flaviviridae*, *Arenaviridae*, *Coronaviridae*, *Paramyxoviridae*, *Pneumoviridae*, and *Filoviridae*. Apart from this, remdesivir is in conditional use for COVID-19 infection as recommended by the World Health Organization [82–86].

Physostigmine (21)

Physostigmine, also known as eserine, a cholinesterase inhibitor, applied topically to the conjunctiva, can cross the blood–brain barrier and acts against anticholinergic toxicity [87].

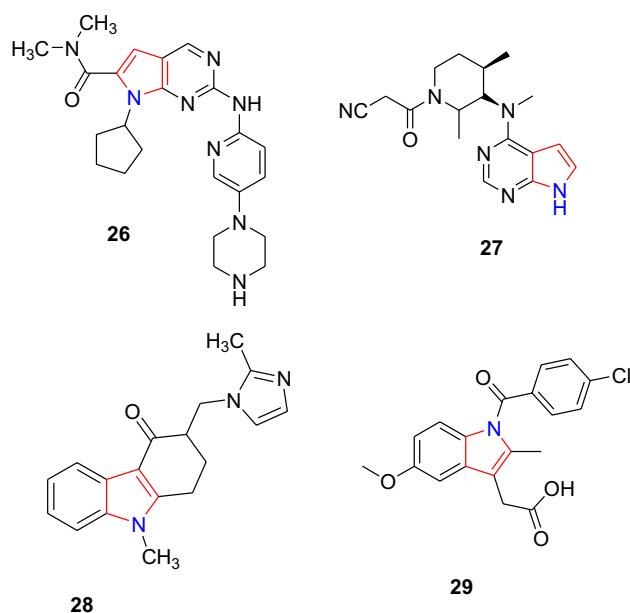


Fig. 9 Fused pyrrole analogs as drug candidates-III

Carprofen (22)

Carprofen is one more pyrrole analog, non-steroidal anti-inflammatory drug (NSAID) used for arthritic symptoms. Previously, carprofen was used for the treatment of gastrointestinal pain and nausea. Later, it is banned due to its toxicity [88, 89].

Baricitinib (23)

Literature evidences that Janus kinases belong to the tyrosine protein kinase family. These kinases play a role in the pro-inflammatory pathway signaling related to autoimmune disorders such as rheumatoid arthritis. Baricitinib, also known as olumiant, is used for rheumatoid arthritis. This analog is a selective and reversible *Janus kinase* 1 (JAK1) and 2 (JAK2) inhibitors, which disrupt the activation of downstream signaling molecules and proinflammatory mediators [90, 91].

Asenapine (24)

Asenapine is a sublingual tablet used as an antipsychotic to treat patients with bipolar I disorder and schizophrenia [92].

Pemetrexed (25)

Pemetrexed is a chemotherapy drug sold under the brand name alimta used in combination with cisplatin for patients with malignant pleural mesothelioma and non-squamous non-small cell lung cancer [93, 94].

Ribociclib (26)

Ribociclib is a selective anticancer drug and acts as a cyclin-dependent kinase inhibitor (Fig. 9). This drug inhibits specifically cyclin-dependent kinase 4 and 6 (CDK4/6), a protein that enables cancer cells to grow and divide vigorously [95, 96].

Tofacitinib (27)

Tofacitinib is a small molecule used for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis [97]. Also, it acts as a *Janus kinase* (JAK) inhibitor [98].

Ondasetron (28)

Ondansetron, one more serotonin 5-HT₃ receptor antagonist, is used for cancer patients to avoid nausea and vomiting due to chemotherapy, radiation therapy, or surgery [99]. Further, it prevents inflammation of the gastrointestinal tract [100].

Indomethacin (29)

Indomethacin, a benzopyrrole analog, is a nonsteroidal anti-inflammatory drug. The mechanism of action for this drug involves the inhibition of cyclooxygenase, an enzyme responsible for the production of prostaglandins [101].

Biologically potential of pyrrole and pyrrolidine analogs

Pyrrole and pyrrolidine, being an important ring structure, have 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. This review mainly covers recent reports on potential activities of pyrrole and pyrrolidine analogs such as anticancer, antituberculosis, antiviral, and anti-inflammatory activity in comparison with earlier reviews that focus on the importance of pyrrole and its analogs until the year 2015–2019 [102–104].

Anticancer agents

Epigenetic modification refers to changes that alter the physical structure of DNA. Epigenetic modification involves both DNA methylation and histone modification [105, 106]. These two phenomena play vital role in the regulation of pluripotency genes. Based on the evidence, it has been suggested that most epigenetic therapies for cancer focus modulation of chromatin structure [107, 108]. One such therapy is based on the development of HDAC inhibitors. In view of this, Chen et al. [109] recently reported HDAC/BRD4 dual inhibitors as epigenetic probes. On the basis of structural activity relationship studies, they synthesized three potent pyrrolo-pyridine analogs (30 a–c) as dual inhibitors of HDAC1/BRD4 (Fig. 10).

Based on three-dimensional quantitative structure–activity relationship (3D-QSAR), molecular docking, and molecular dynamics (MD) simulations, Zhang et al. [110] reported target-specific anticancer agents. This investigation suggests that set of thieno[3,2-*b*]pyrrole (31), as competitive inhibitors of lysine-specific demethylase 1 (LSD1), a histone-modifying enzyme, is overexpressed in various cancers. Further, pyrrole/fused pyrrole analogs have to be explored for target specific anticancer activity [111, 112]. Rasal et al. [113] reported synthesis and antiproliferative activity of series of pyrrole bearing benzimidazole analogs. Among these compounds, only

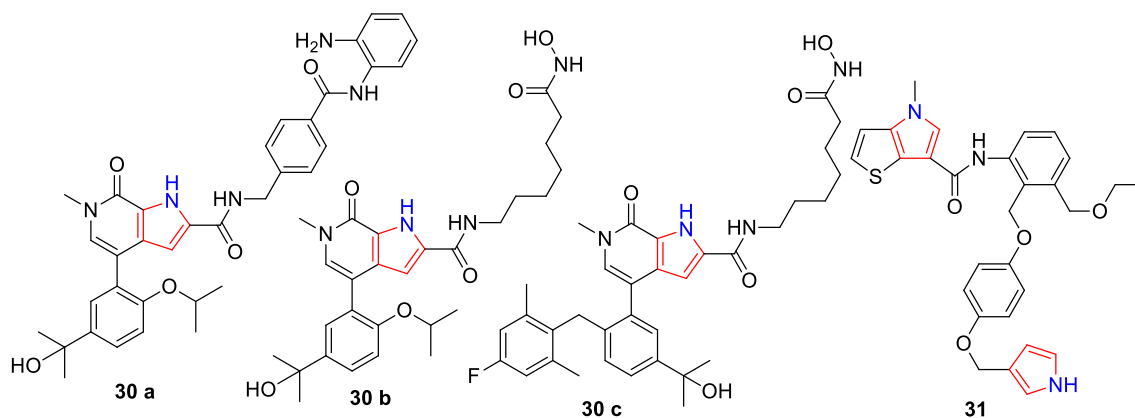


Fig. 10 Fused pyrrole analogs as potential anticancer agents I

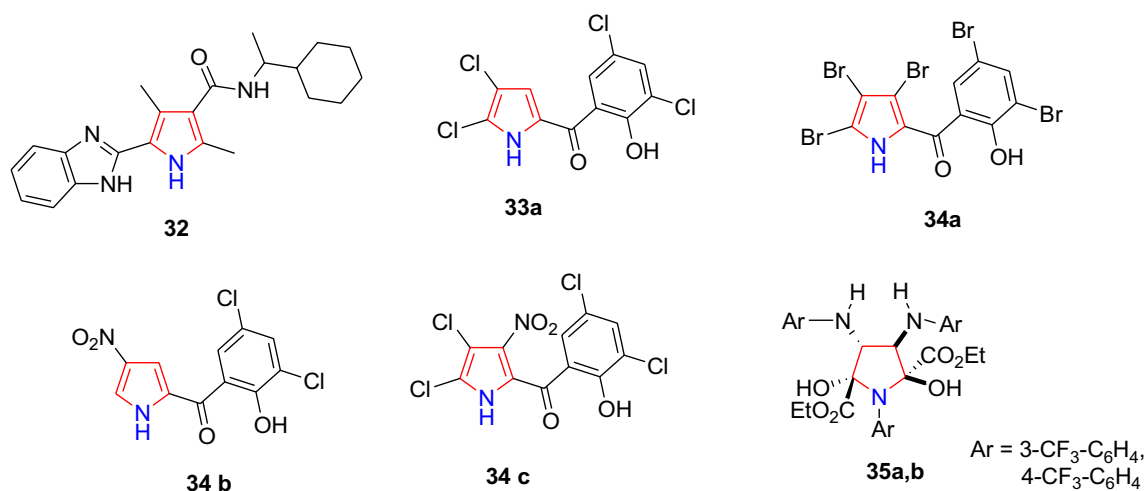


Fig. 11 Pyrrole, pyrrolidine analogs as potential anticancer agents-II

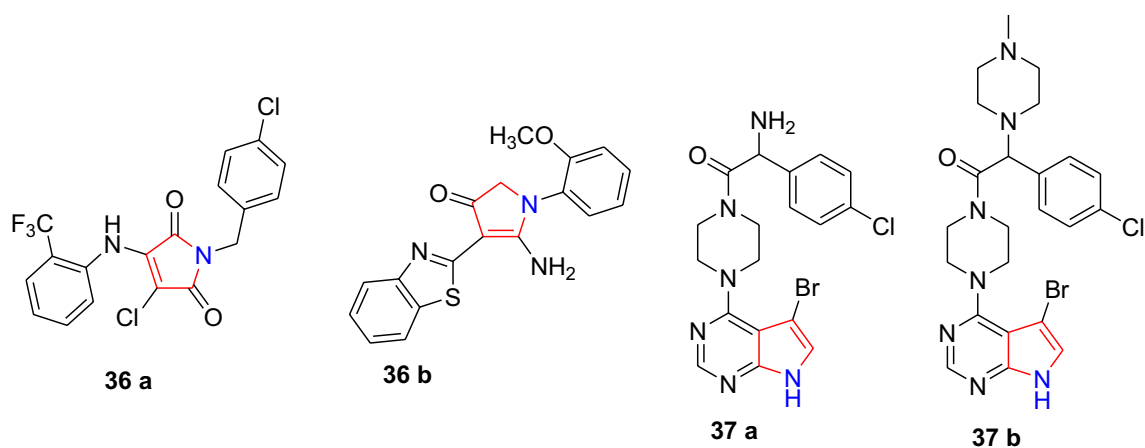


Fig. 12 Pyrrole (fused), pyrrolidine analogs as potential anticancer agents-III

compound (32) showed significant antiproliferative activity in MDA-MB human cancer cell lines. Many natural products are known to possess potential anticancer activity [114, 115]. One such natural product, pyrrolomycin, a polyhalogenated antibiotic (33 a), has potent anticancer activity. However, this molecule is associated with high cytotoxicity. To overcome this problem, Raimondi et al. [116] designed and synthesized new pyrrolomycins (34 a–c). Their report suggested that newly synthesized compounds with nitro substituent strongly inhibit the proliferation of colon (HCT116) and breast (MCF 7) cancer cell lines in comparison with (33 a). Also, these molecules exhibit good antibacterial activity. Ji et al. [117] reported ruthenium-catalyzed synthesis and antiproliferation activities of poly substituted pyrrolidines. Among these analogs, only compounds (35 a, b) have shown strong antiproliferation activity with IC₅₀—2.9 to 16 μM (Fig. 11).

Investigation reveals that epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) downstream signaling pathways contribute to the tumor growth and progression. So, VEGF and EGFR inhibitors constitute therapies that inhibit different signaling pathways to overcome tumor resistance caused by the inhibition of a single. Because of this, Kuznietsova et al. [118] reported the synthesis of novel pyrrole analogs as protein kinases inhibitors. Their investigation suggested that two compounds, namely chloro-1-(4-chlorobenzyl)-4-((3-(trifluoromethyl)phenyl)amino)-1H-pyrrole-2,5-dione (36 a) and 5-amino-4-(1,3-benzothiazol-2-yn)-1-(3-methoxyphenyl)-1,2-dihydro-3H-pyrrole-3-one (36 b), are the competitive inhibitors of EGFR and VEGFR (Fig. 12).

Liu et al. [119] mentioned in their work synthesis and antiproliferative activity of 1-(4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)piperazin-1-yl)-2-phenylethan-1-one as Akt

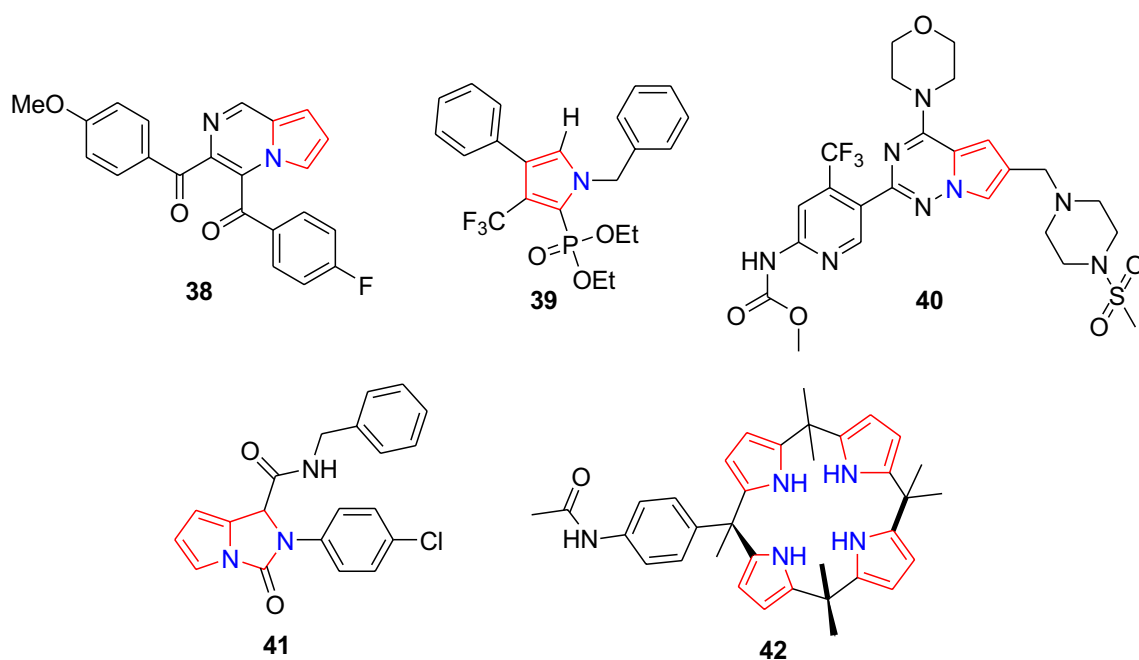


Fig. 13 Pyrrole (fused) analogs as potential anticancer agents-IV

inhibitors. Further, only compounds 37a and 37b showed high potency against all Akt isoforms. Dagar et al. [120] reported the one-pot synthesis of 3,4-diacetylpyrrolo[1,2-a]pyrazine by the reaction of an α -haloketone, azide, and N-substituted pyrrole-2-carboxaldehyde. This investigation reveals that only compound (38) showed potential *in vitro*

anticancer activity against oral adenosquamous carcinoma and triple-negative human breast cancer cells in comparison with standard capecitabine.

Olszewska et al. [121] reported the synthesis and anticancer activity of trifluoromethyl 2-phosphonopyrrole against denocarcinomic human alveolar basal epithelial

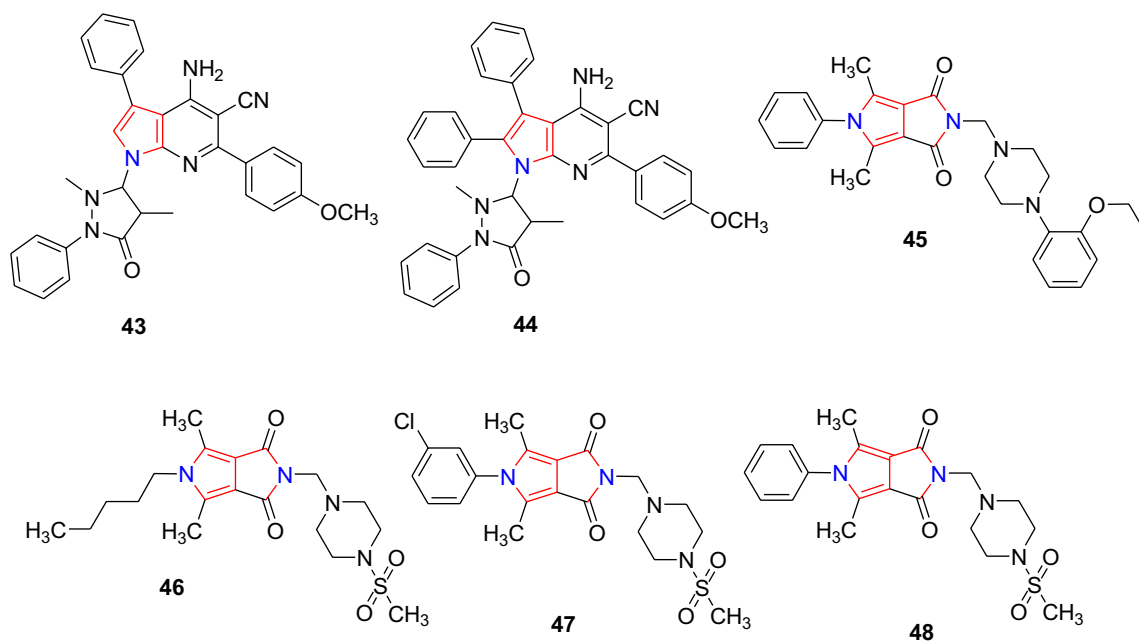


Fig. 14 Fused pyrrole analogs as potential anti-inflammatory agents-I

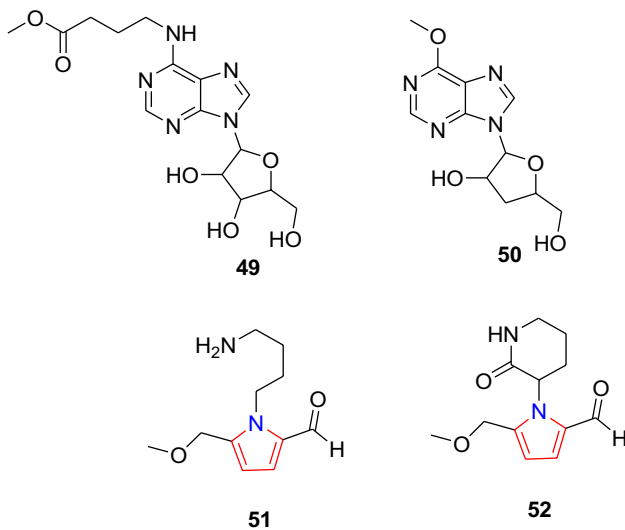


Fig. 15 Pyrrole and imidazole analogs as weak anti-inflammatory agents-II

cells (A549) and breast cancer cell line (MCF-7 cells). This study explains pyrrole analog (39) with trifluoro, phosphonyl, and phenyl group significantly inhibits cell cycle arrest at G1 and induces apoptosis in these cell line with IC_{50} $36.5 \mu\text{M} \pm 1.80$ and $27.9 \mu\text{M} \pm 1.68$. Recently,

Fig. 16 Pyrrole analogs as potential anti-inflammatory agents-III

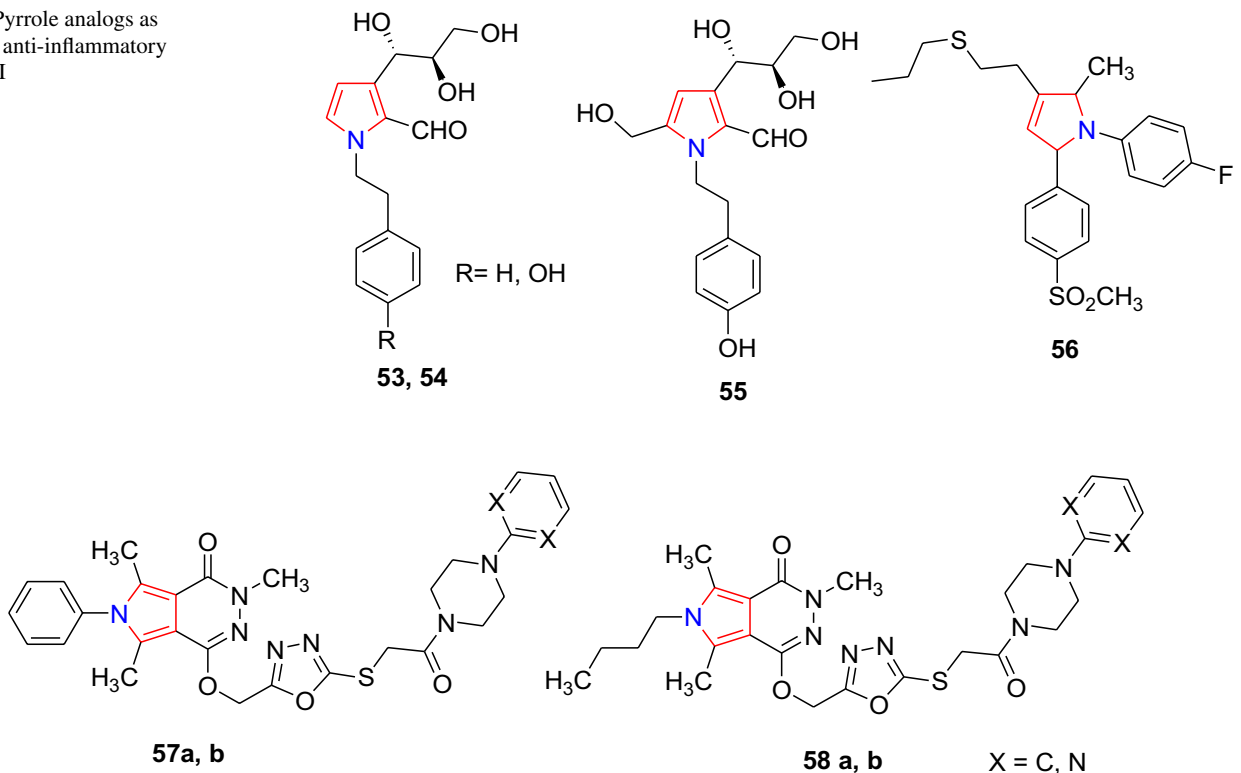


Fig. 17 Fused pyrrole analogs as potential anti-inflammatory agents-IV

Rathinaraj et al. [122] reported synthesis of nanoconjugates derived from folate gold bilirubin. Further, these nanoconjugates induce apoptosis in multidrug-resistant oral carcinoma cells. More recently, Xiang et al. [123] investigated the synthesis of bioavailable, potent pyrrolo[2,1-f][1,2,4]triazines as anticancer agent. The compound (40) showed PI3K alpha inhibition in human cancer cells with IC_{50} of 5.9 nM. Zhang et al. [124] reported one pot synthesis of pyrrole-imidazole analogs. Their work demonstrated that compound (41) has very potential inhibition for the two human pancreatic cancer cell lines such as PANC and ASPC-1. Furthermore, Geretto et al. [125] research on anticancer cancer activity of meso-(p-acetamidophenyl)-calix[4]pyrrole analog suggests that this compound (42) can cross the blood–brain barrier, forms DNA adduct and exhibits significant anticancer activity (Fig. 13).

Anti-inflammatory agents

Anti-inflammatory agents are the substances that reduce inflammation in the body caused due to the response of vascular tissues to damaged cells, pathogens, or irritants. These compounds prevent this response from the body that causes inflammation.

Further, anti-inflammatory agents are used for the prevention and treatment of cancer [126, 127]. Based on this importance, Said Fatahala et al. reported synthesis of pyrrolopyridine and pyrrolopyridopyrimidine analogs as anti-inflammatory agents. Their findings reveals that only the fused pyrroles, pyrrolopyridines (43, 44) (Fig. 14) showed good anti-inflammatory activity. Also, molecular docking study shows binding of these analogs with COX-2 [128]. Redzicka et al. [129] research work is based on design, synthesis, molecular docking simulations, and anti-inflammatory activity of series of pyrrolo[3,4-c]pyrrole. According to the results, compounds (45–47) have shown strong activity toward COX-1 and COX-2. Furthermore, single-crystal X-ray diffraction was recorded for (48). Xue et al. [130] reported the isolation of two nucleosides (49, 50) and two pyrrole analogs (51, 52) (Fig. 15) from *Cordyceps militaris*

shown no significant activity against LPS-induced NO production in macrophage-like, Abelson leukemia virus-transformed cell line derived from BALB/c mice (RAW 264.7 cells).

Guan reported the isolation of pyrrol-2-aldehyde analogs such as jiangrine G (53), jiangrine A (54), and pyrrolezanthine (55) from the fermentation broth of *Jiangella alba* and *Maytenus austroyunnanensis*. Their results based on western blot analysis reveals that all three compounds modulate pro-inflammatory cytokines via MAPK p38 and NF- κ B signaling pathways. Also, compounds (53) and (54) inhibit the expression of iNOS in LPS-induced RAW 264.7 cells [131]. Reale et al. [132] reported synthesis and anti-inflammatory activity of novel series of 1,5-diarylpyrrol-3-sulfur analogs. Further, molecular modeling studies suggest compound (56) (Fig. 16)

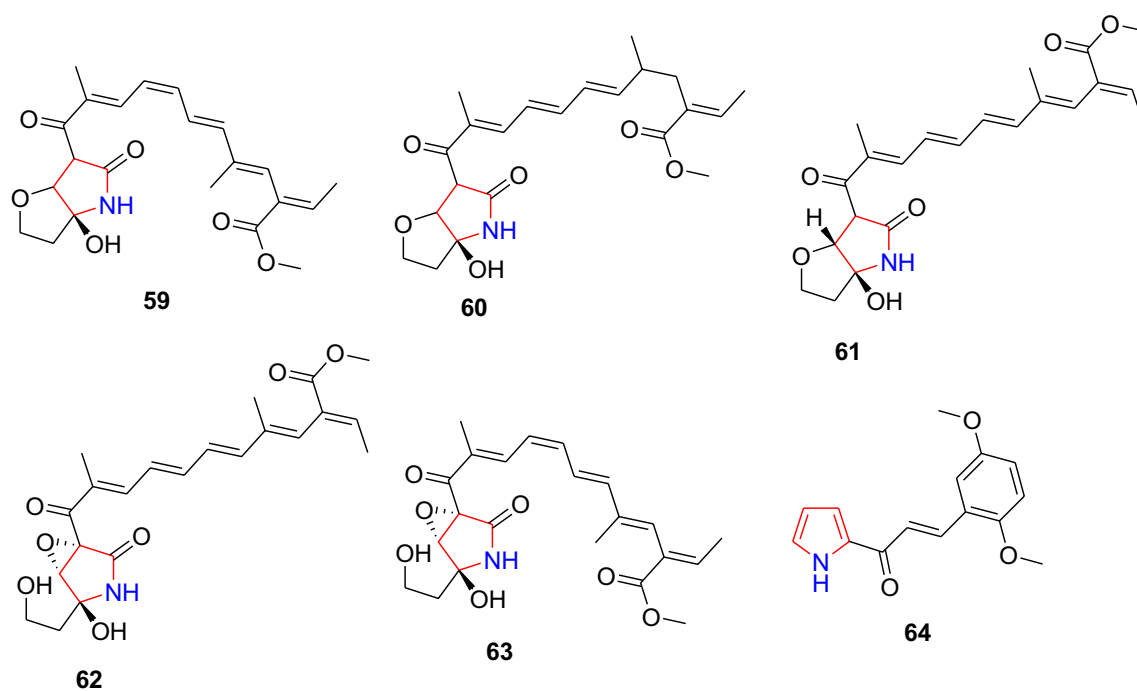
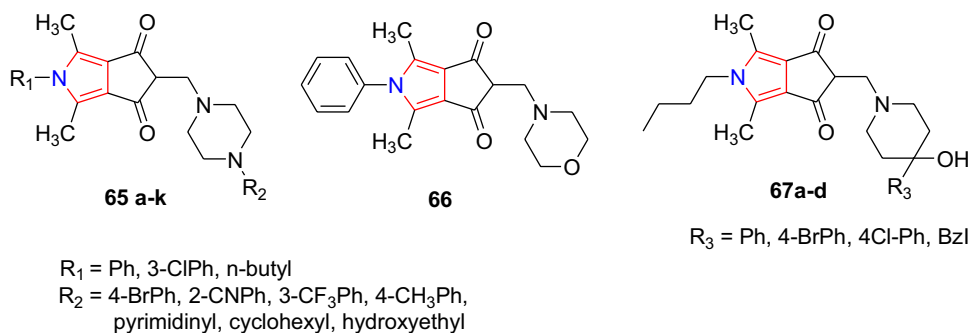


Fig. 18 Pyrrole, pyrrolidine analogs as potential anti-inflammatory agents-V

Fig. 19 Fused pyrrole analogs as potential anti-inflammatory agents-VI



has potential binding with COX-2 enzyme and showed a significant *in vivo* anti-inflammatory activity.

With the continuation of their work on pyrrolo[3,4-*d*]pyridazinone, Szczukowski et al. [133] recently reported synthesis and anti-inflammatory activity of novel pyrrolo[3,4-*d*]pyridazinone analogs bearing 4-aryl-1-(1-oxoethyl)piperazine. Among synthesized compounds, 57 (a, b) and 58 (a, b) inhibit cyclooxygenase, have better affinity to COX-2 isoenzyme, and thereby exert promising anti-inflammatory and anti-oxidant activity (Fig. 17).

Maharjan et al. [134] reported isolation of nine compounds including quinones, fusarubin, (+)-solaniol, javanicin, 9-desmethylherbarine, and pyrrole analogs; isomers of lucilactaene (59, 60, 61), (62), and (63) from roots of *Scutellariae baicalensis*. These isolated compounds showed potential anti-inflammatory activity by inhibiting NO production and pro-inflammatory cytokines in LPS-induced RAW 264.7 macrophage cells.

Mohd Faudzi et al. [135] reported synthesis of twenty-four chalcones of pyrroles as anti-inflammatory agents against nitric oxide (NO) and prostaglandin E₂ (PGE₂) controls IFN- γ /LPS-induced RAW 264.7 macrophage cells. Further, these results are supported by the crystal structure and molecular studies (64) (Fig. 18).

More recently, Redzicka et al. [136] reported design, synthesis, and anti-inflammatory activity of N-substituted 3,4-pyrroledicarboximides (65 a–k), (66) and (67 a–d) (Fig. 19). All the synthesized compounds have shown inhibitory activity against COX-1 and COX-2 cyclooxygenase isoform and thereby exhibit potential activity. Also, this work is supported by QSAR study and X-ray diffraction studies.

Fig. 20 Pyrrole (fused) analogs as potential antiviral agents-I

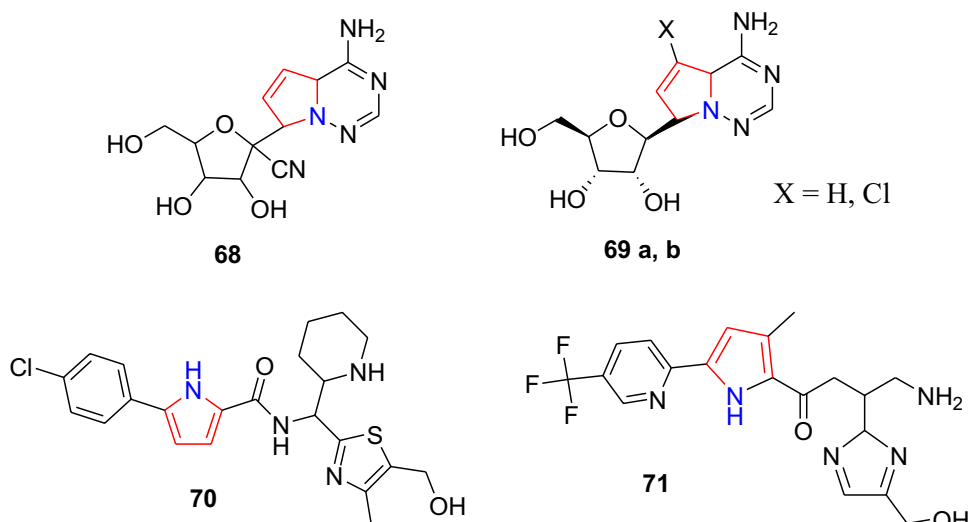
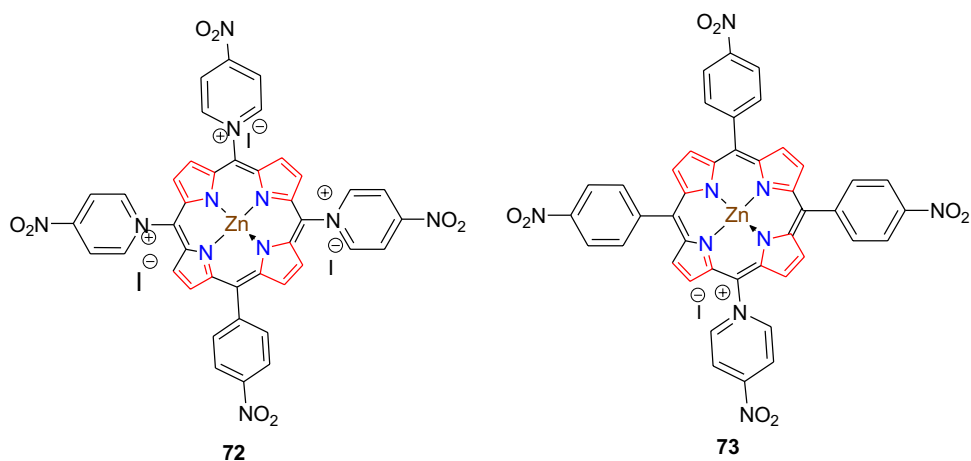


Fig. 21 Pyrrole analogs as potential antiviral agents-II



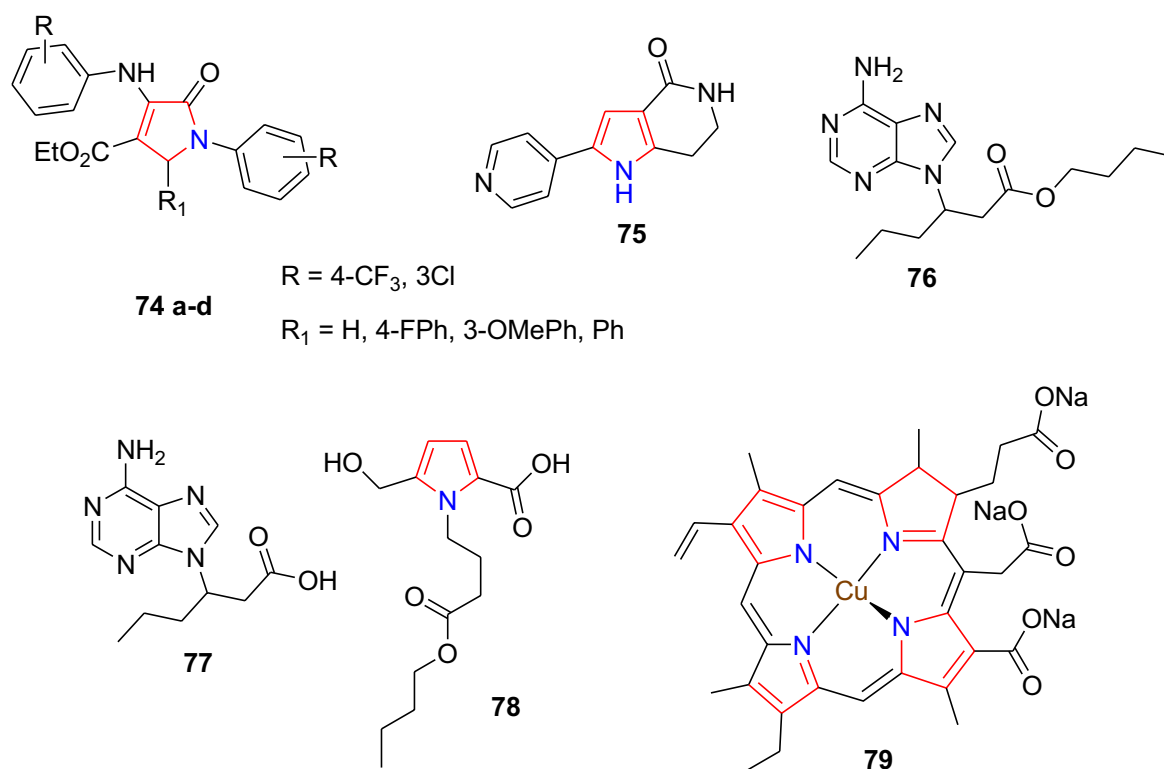


Fig. 22 Pyrrole, purine analogs as potential antiviral agents-II

Antiviral agents

Antiviral agents are known for their use in viral infections caused by HIV, herpes viruses, hepatitis B and C viruses, influenza A, B viruses, and SARS-CoV-2. A lot of research has been carried out for the development of antivirals and to study their mechanism toward pathogens. However, many antiviral agents have been restricted for their use. The main drawback of the antiviral drug is viruses use the host's cells to replicate. Today, the main difficulty associated with vaccines and antiviral drugs is viral variation and resistance. There will be a real challenge for the medicinal chemist to synthesize safe, specific, and effective antiviral drugs without harming the host [137–140]. In view of these findings, to find more potent antiviral agents, Tao et al. [141] recently studied effect of GS-441524 (68) (Fig. 20) and hydrolyzed product of remdesivir in Vero E6, Vero CCL-81, Calu-3, Caco-2 cells for anti-SARS-CoV-2 activity and anti-HCoV-OC43 activity in Huh-7 cells. Their investigation reveals that both remdesivir and GS-441524 have similar anti-SARS-CoV-2 potency in Vero cells, but higher in Calu-3 and Caco-2 cells, whereas in case of Huh-7 cells, remdesivir exhibits higher anti-HCoV-OC43 activity than GS-441524.

Li et al. [142] more recently reported synthesis and antiviral activity of novel nucleoside analogues of pyrrolo-triazines. Their investigation reveals that

7-chloro-4-amino-pyrrolo[2,1-f][1,2,4]triazine (69 b) specifically inhibits human norovirus RNA-dependent RNA polymerase (RdRp), whereas compound 4-amino-pyrrolo[2,1-f][1,2,4]triazine (69 a) inhibits both murine and human norovirus RNA-dependent RNA polymerase (RdRp) in different cell lines. With the continuation of their work on pyrrole analog (70), a potent HIV inhibitor, Curreli reported a new and novel analog, NBD-14189 (71), with optimized antiviral activity against HIV-1, with IC₅₀ of 89 nM. In addition, the in vitro ADME data suggest improvements in aqueous solubility and other properties of this compound compared to (70) [143]. Hawerkamp et al. [144] reported antiviral activity of tofacitinib, a kind of novel Janus kinase (JAK) inhibitor in keratinocytes. This study reveals that tofacitinib reduces T cell activation and down regulates gene regulation.

Based on the importance of porphyrin and its metal complexes, Sengupta et al. [145] synthesized novel Zn (II) complexes of nitro porphyrin derivatives (72, 73) (Fig. 21) and carried out anticancer and antiviral activities. This metal complexes showed very good anticancer activity against human lung cancer cell-line A549 and improved antiviral activity against a HIV-1 and SIVmac.

In the year 2020, Liu et al. [146] reported the synthesis of dihydropyrrolidines. These analogs were screened for anti-influenza activity. Among these analogs, (74 a–d) (Fig. 22) has shown potential activity against IAVs with IC₅₀ ranges

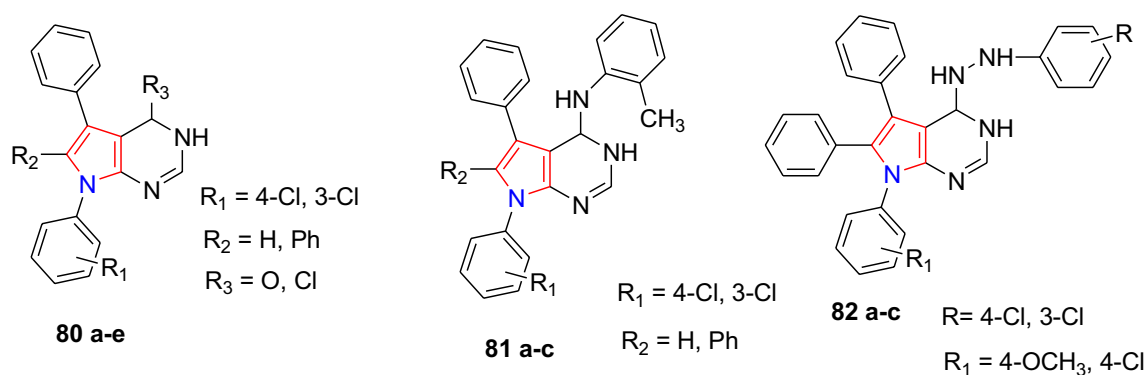


Fig. 23 Fused pyrrole analogs as potential antiviral agents-III

from 3.11 to 9.23 μM . This investigation further illustrates that these compounds suppress NDAPH oxidase, NOX1 in MDCK cells.

Like human alphaherpesvirus 2 (HHV-2), Caprine alpha herpesvirus 1 (CpHV-1) causes the genital disorder. Because of this, Lanave et al. [147] studied the antiviral efficacy of compound PHA767491, fused pyrrole (75) toward HSV-1 and HSV-2 in vitro and as well in the mouse model. Yao et al. [148] reported isolation and anti-hepatitis B virus activity of natural products delicatulines A (76) and B (77), an adenine analogs and pyrrole analog (78). Their study is based on *n*-BuOH extract of *Selaginella delicatula*. Further, none of these compounds and few known compounds have exhibited better anti-HBV activity. Based on colorimetric viral infection and qRT-PCR assays, Liu et al. [149] studied sodium copper chlorophyllin (79) as potential antiviral agent against infection caused by divergent EV-A71 and coxsackievirus-A16 (CV-A16). In addition, viral gastroenteritis has become serious concern for children caused by rotavirus, coxsackievirus, and adenovirus which are the most common viruses that cause gastroenteritis. Taking this into consideration, Mohamed et al. reported synthesis and antiviral activity of pyrrolo[2,3-d] pyrimidine and pyrrolo[3,2-e][1,2,4] triazolo[4,3-c]pyrimidine analogs against gastroenteric viral infections. Screening of the new compounds for anti-viral activities against Rotavirus Wa strain and coxsackievirus B4 suggests that compounds (80 a–e), (81 a–c) and (82 a–c) (Fig. 23) exhibited significant antiviral activity [150].

Another virus, the novel SARS-CoV-2 that causes coronavirus disease 2019 (COVID-19) results in an inevitable pandemic. Development of antiviral drug against SARS-CoV-2 is considered to be real challenge. Comprehensive literature of this virus reveals that the main protease (Mpro), a SARS-CoV-2 enzyme, is an attractive drug target that prevents viral replication and transcription. Because of this, Ianevski et al. reported screening of 136 antivirals against the SARS-CoV-2 infection in Vero-E6 cells. Their investigation suggests that among these antivirals, only compounds

nelfinavir, salinomycin, amodiaquine, obatoclox (83) (pyrrole analog), a small molecule and a pan-inhibitor of Bcl-2 family proteins, emetine, and homoharringtonine (fused pyrrole) (84) exhibited anti-SARS-CoV-2 activity [151] as shown in Fig. 23.

To find a probe that targets the main protease, Rao et al. work based on molecular docking, dynamics simulation, and screening of small molecules investigated pyranonigrin A (85), a secondary fungal metabolite as potential inhibitor against the main protease (Mpro) expressed in SARS-CoV-2 virus [152]. Lu et al. [153] more recently reported synthesis of protoporphyrins (86 a–e) as antiviral agent against series of viruses such as Lassa virus (LASV), Machupo virus (MACV), and SARS-CoV-2 and subtypes of influenza A viral strains. Their results show that these compounds are very significant antiviral with IC_{50} values ranged from 0.91 to 1.88 μM .

Fakhar et al. [154] report based on the structure-based pharmacophore modeling, virtual screening workflow, ADMET, and molecular dynamics simulations revealed that compound ABBV-744 (87) has a strong affinity ($\Delta G_{\text{bind}} - 45.43 \text{ kcal/mol}$) to the main protease. Further, this study also considered the other two compounds (88, 89) as potential inhibitors of SARS-CoV-2. In the year 2021, by the experimental evidence, Varghese et al. [155] have proposed a combination of obatoclox and berberine as possible antiviral drugs for SARS-CoV-2 infection (Fig. 24).

Antimycobacterial agents

Today, treatment for multidrug-resistant (MDR) tuberculosis (TB) has become a real challenge [156]. Tuberculosis is an infection caused by gram-positive bacteria mycobacterium tuberculosis. This disease is treated with first-line drugs like isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin [157]. Second-line drugs that have been reported are

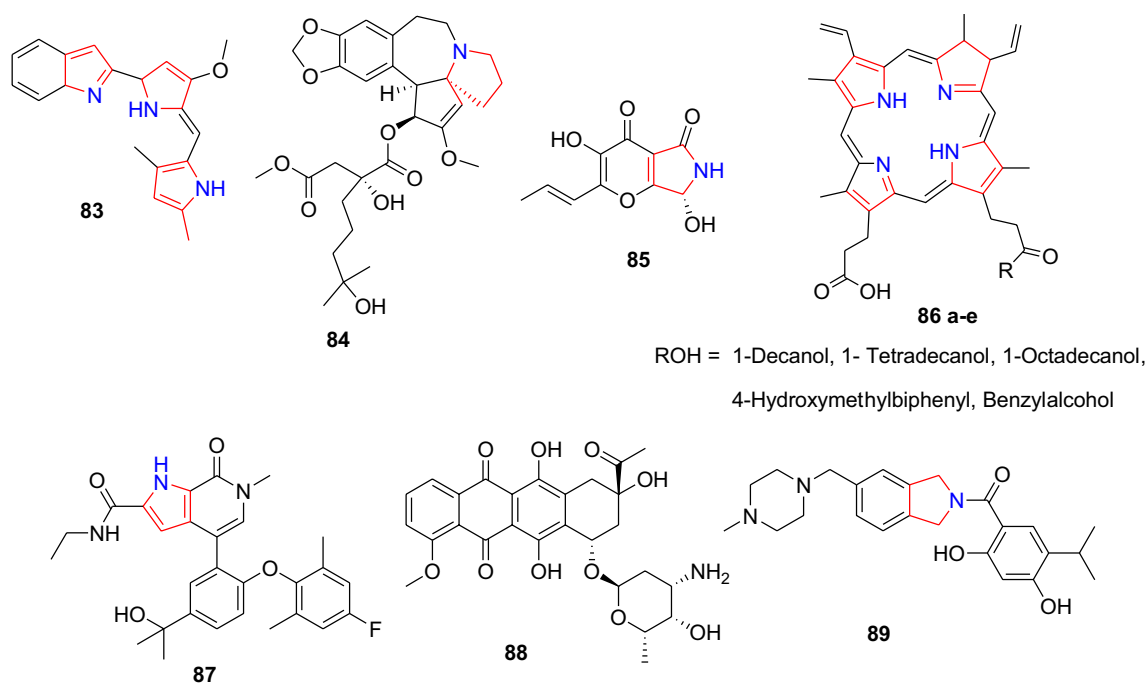


Fig. 24 Pyrrole (fused), pyrrolidine, quinone analogs as potential antiviral agents-IV

capreomycin, kanamycin, and amikacin [158]. Due to the multidrug-resistant developed by the mycobacterium, there is a need for a potent drug candidate that can suppress the growth of this pathogen [159, 160]. To develop antitubercular agent, Volynets et al. reported synthesis and antitubercular activity of novel isoniazid bearing pyrrole analogs. Compound 1-methyl-1H-pyrrol-2-ylmethylene)-hydrazide (90)

(Fig. 25) has shown inhibitory activity toward isoniazid-resistant strain with IC_{50} of 0.14 μ M [161]. Shiva Raju et al. [162] also reported 1*H*-pyrrolo[2,3-*d*]pyrimidine-1,2,3-triazole analogs as novel anti-tubercular agents. In the series of compounds, (91 a, b) has shown very good anti-tubercular activity against mycobacterium tuberculosis H37Rv strain with minimum inhibitory concentration of 0.78 μ g/mL.

Fig. 25 Pyrrole (fused) analogs as potential antimycobacterial agents-I

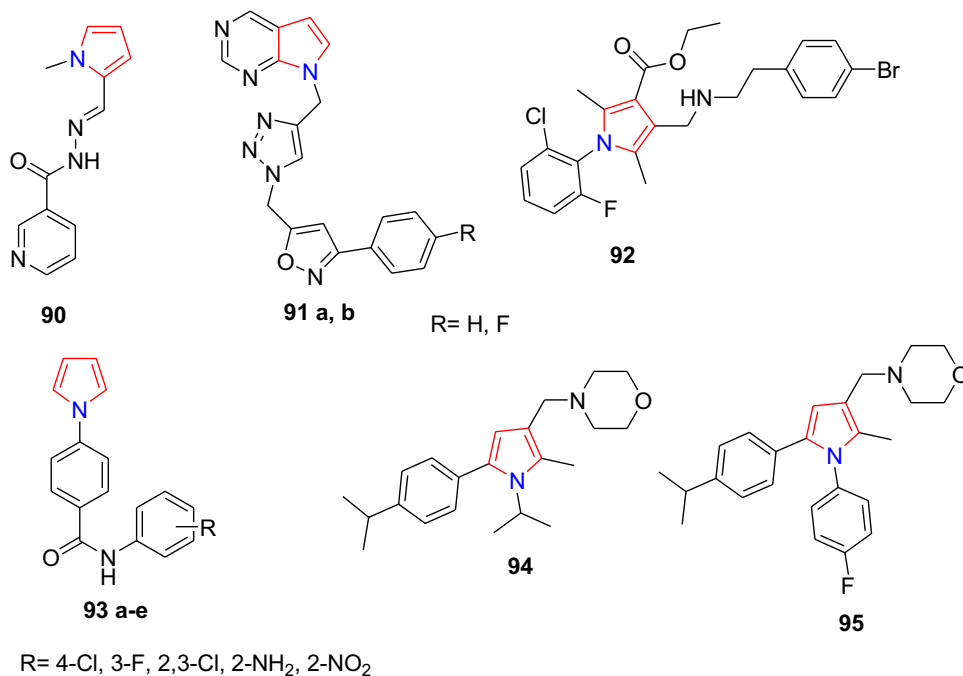
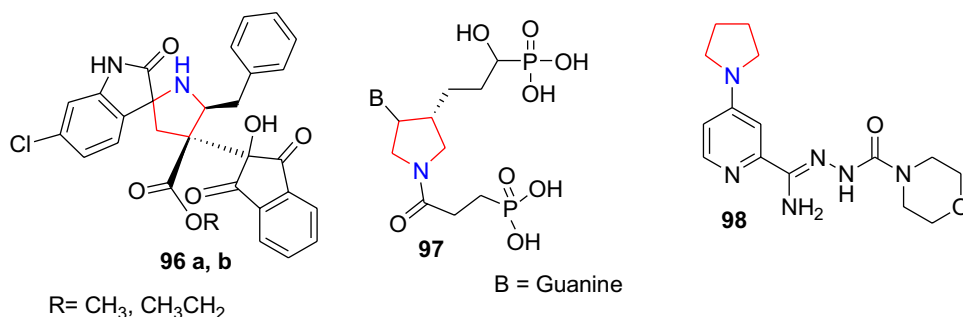


Fig. 26 Pyrrole (fused) analogs as potential antimycobacterial agents-II



Liu et al. [163] used virtual high-throughput screening, in vitro assay, and synthesized 1-(2-chloro-6-fluorobenzyl)-2,5-dimethyl-4-((phenethylamino)methyl)-1H-pyrrole-3-carboxylate (92) as anti-tubercular agents that inhibit ClpPIP2 peptidase in *M. tuberculosis*. Many nitrogen-containing heterocyclic compounds were designed, synthesized, and screened for their biological activities [164, 165]. However, pyrrole and pyrrolidine analogs have been attracted more for their diverse pharmacological activities [166].

By finding these significances in the literature, Joshi et al. [167] reported the synthesis and antimycobacterial activity of novel pyrrolyl benzamide derivatives against *M. tuberculosis* H37Rv and enoyl-ACP reductase enzyme. Compounds (93a–e) have shown significant InhA inhibitory activity. Furthermore, Poce et al. [168] reported pyrrole analog (94) as potential inhibitor of mycobacteria. Their study is based on synthesis of pyrrole analog by the variations in hit compound (95).

More recently, Arumugam et al. [169] synthesized new spirooxindolopyrrolidine-embedded indandione for in vitro anti-tubercular activity against *Mycobacterium tuberculosis* H37Rv. Their results suggest that chlorine-substituted indandione (96 a, b) displayed potential activity with MIC 0.78 µg/mL compared to ethambutol having MIC of 1.56 µg/mL as shown in Fig. 26.

Eng et al. [170] reported as synthesis of [3R,4R]-4-Hypoxanthin-9-yl-3-((S)-2-hydroxy-2-phosphonoethyl)oxy-1-N-(phosphonopropionyl)pyrrolidine and [3R,4R]-4-guanin-9-yl-3-((S)-2-hydroxy-2-phosphonoethyl)oxy-1-N-(phosphonopropionyl)pyrrolidine as potent inhibitors of hypoxanthine–guanine phosphoribosyltransferase (HGPR) with K_i values of 60 nM. Krause et al. [171] reported synthesis and antimycobacterial activity of series of new 4-substituted picolinohydrazonamides. Among these compounds, (98) acts as antimycobacterial agent with MIC 0.4 µg/mL.

Based on the literature survey, it has been suggested that compared to pyrrole analogs, pyrrolidine scaffold will be having more preference to the drug design because of unrestricted conformation of the ring [172]. Further, pyrrolidine analog has privileged N – 1 position for substitutions which were present in US FDA-approved drugs

[173]. We restricted this review on pyrrole, pyrrolidine, and its therapeutic potential for the aspects such as anti-cancer, anti-inflammatory, antiviral, and antimycobacterial activity. Other biological activities of this scaffold deserve special attention.

Conclusion

The literature evidenced five-membered nitrogen-containing pyrrole and pyrrolidine have been known for their extensive biological and pharmacological activities. Many biomolecules have possessed either pyrrole, pyrrolidine, or fused pyrrole. Using structure–activity relationship and molecular docking studies, pyrrole and pyrrolidine analogs have been designed, synthesized, and screened for diverse therapeutic activities. Based on the comprehensive literature on the importance of these molecules, this review mainly highlights recent reports on these versatile molecules for anti-cancer, anti-inflammatory, antiviral, and antitubercular activity. Also, this review focuses on the pyrrole, pyrrolidine, and fused pyrrole-containing drug candidates. This review will be a useful platform for innovative researchers to work on pyrrole analogs to overcome drug resistance and toxicity.

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