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REVIEW

An Overview on Biological Importance of Pyrrolone and Pyrrolidinone Derivatives as Promising Scaffolds

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Abstract—Pyrrolones and pyrrolidinones are five-membered heterocycles and are versatile lead compounds for designing powerful bioactive agents. Pyrrolone and pyrrolidinone moieties are among the most essential heterocyclic pharmacophores inducing prominent pharmaceutical effects. Therefore, researchers paid attention to synthesize various pyrrolone and pyrrolidinone derivatives. Numerous methods for the synthesis of pyrrolones and pyrrolidinones offer a great scope in the field of medicinal chemistry. This attractive group of compounds has diverse biological activities like antimicrobial, anti-inflammatory, anticancer, antidepressant, anticonvulsant, etc. The purpose of this review is to classify broad information on the chemistry and pharmaceutical effects of pyrrolones and pyrrolidinones to open a new perspective for future studies. It is clear that a wide spectrum of pyrrolones and pyrrolidinone derivatives have been synthesized and that most of them have various significant biological activities. Thus, these derivatives can be used for the future development of novel compounds active against different infections and diseases.

Keywords: pyrrolones, pyrrolidinone, biological activities, heterocycles, industrial applications

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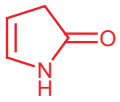
1. INTRODUCTION

Rising concern has been paid to the synthesis of N-heterocyclic compounds due to their useful biological activities and their role as intermediates in medicinal and organic chemistry [1]. Heterocyclic compounds are the most essential in the discovery of novel drugs. Various compounds such as alkaloids, amino acids, hemoglobin, vitamins, hormones, most synthetic drugs, and dyes contain heterocyclic ring systems. Nitrogen-containing heterocyclic compounds have been the topic of ample research due to their diverse and prominent biological, agrochemical, and synthetic applications. Pyrrolidin-2-one is a five-membered lactam present in both natural and synthetic compounds [2]. The presence of a pyrrol-2-one fragment in drugs and natural compounds has gained significant attention in the development of novel methods of their synthesis [3].

Pyrrolidin-2-ones have been used in the synthesis of various alkaloids [4] and unusual β-amino acids such as statin and its derivatives [5].

1,3-Dihydro-2*H*-pyrrol-2-one (pyrrolone) derivatives exhibit diverse biological activities such as anti-inflammatory, analgesic [6], antibacterial [7] cardiotonic [8], antimycobacterial [9], antidepressant [10], antiviral [11], antitumor [12], and other activities [13–18]. Pyrrolones can be synthesized by nucleophilic substitution from the corresponding furanones [6], as well as by different methods based on heterocyclization of various Schiff bases with maleic anhydride [19, 20] and the reaction of furanone derivatives with amines [21–23].



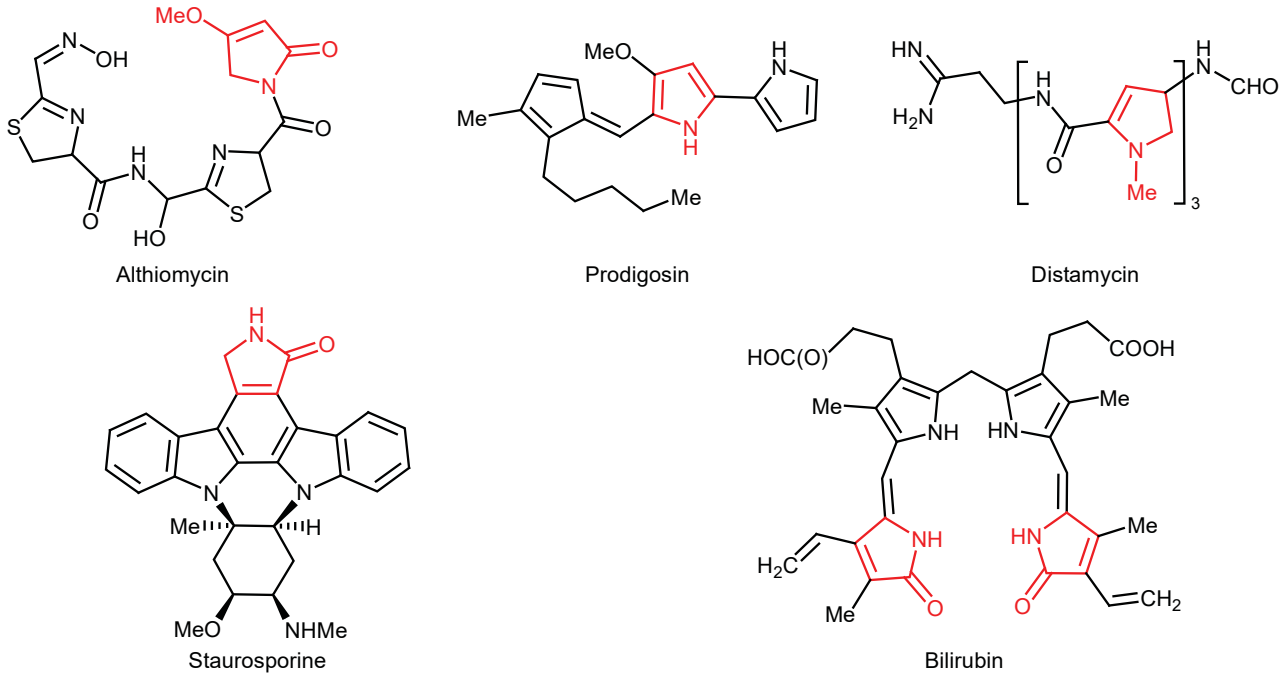
1,3-Dihydro-2*H*-pyrrol-2-one

2. PYRROLONE AND PYRROLIDINONE DERIVATIVES AND THEIR BIOLOGICAL USES

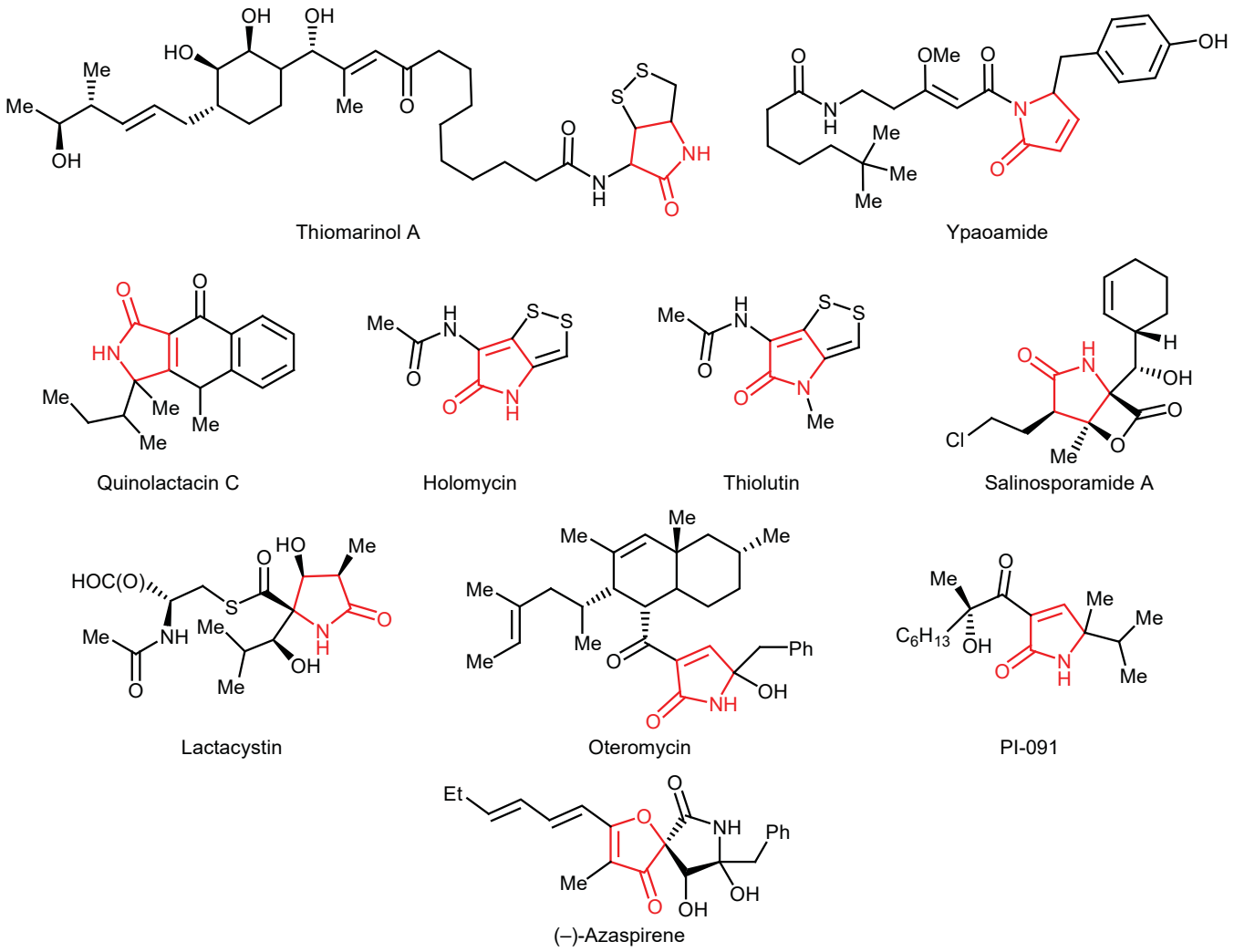
Compounds containing a pyrrolone moiety have wide clinical applications. For instance, althiomycin is a naturally occurring alkaloid produced by *Streptomyces althioticus* and is used as an antibiotic which inhibits protein synthesis [7]. The pyrrolinone system is also present in natural compounds such as vitamin B_{12}, prodigiosin, bile pigments, and some antibiotics like distamycin [24]. Various pyrrolone and pyrrolidinone derivatives are structural fragments of plentiful natural compounds such as holomycin, thiolutin [25], bilirubin [26], ypaoamide [27], lactacystin [28], indolocarbazole alkaloids (staurosporine) [29], oteromycin [30], pyrrocidines A and B [31], thiomarinol A4 [32], quinolactacin C [33], salinosporamide A [34], (–)-azaspirene (angiogenesis inhibitor isolated from the fungus *Neosartorya* sp.) [35]. Oteromycin is the ET_B receptor antagonist (IC_{50} = 2.5 pM) [30] (Scheme 1).

2-Oxodihydropyrrole ring is present in some alkaloids possessing diverse pharmaceutical activities. Pyrrolone derivatives are used as optoelectronic materials [36], PI-091 is a platelet aggregation inhibitor [37], and thiomarinol A4 is a potent antibiotic. Inhibitors of HIV integrase [38], cardiac cyclic AMP phosphodiesterase (PDE) [39], and vascular endothelial growth factor receptor [40], neuritogenic [41], pesticidal [42], antibacterial, antifungal, and nootropic agents [43], peptidomimetics [44], synthetic intermediates [45], DNA polymerase inhibitors [46], caspase-3 inhibitors [47], anticancer and cytotoxic agents [48], human cytomegalovirus (HCMV) protease inhibitors [49], human cytosolic carbonic anhydrase isozyme inhibitors [50], antibiotics [51], and annexin A2–S100A10 protein interaction inhibitors [52] were found among pyrrolone derivatives. Cotinine is an alkaloid present in tobacco and the main metabolite of nicotine [53]. Ethosuximide

Scheme 1.



Scheme 1. (Contd.).



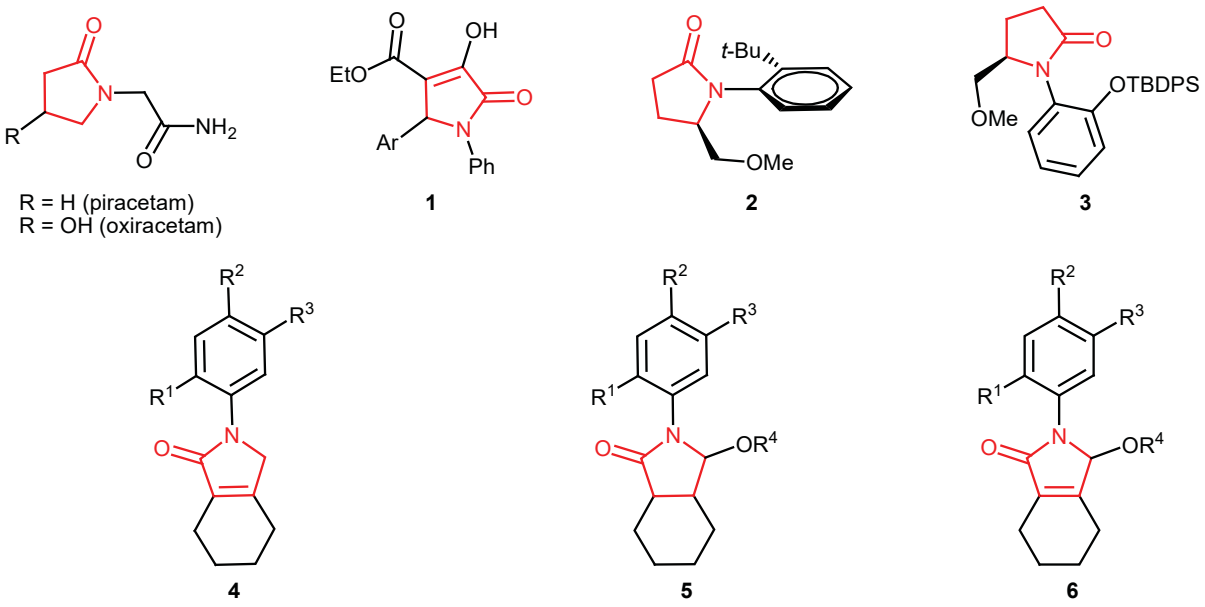
is a succinimide anticonvulsant used mainly in the treatment of the absence of seizures [54].

Despite their diverse usages, existing ways for their synthesis are limited mainly to multicomponent reactions (MCRs) [55]. *N*-Alkyl-5-methylpyrrolidin-2-ones can be synthesized by reductive amination of levulinic acid or its esters. They are widely used as surfactants, solvents, intermediates for pharmaceuticals and agrochemicals [56]. *N*-Vinylpyrrolidone (NVP) has been studied for its usages in various fields [57] due to its good biocompatibility, hydrophilic character, and low cytotoxicity [58].

Pyrrolidinone cognition enhancers like piracetam and oxiracetam (Scheme 2) constitute a separate group due to their unique selectivity for brain areas involved in the procedures of acquiring knowledge and memory processes and safe profile [59]. These features make them suitable for chronic therapy in aged patients. Poly(vinylpyrrolidone) (PVP) is an important water-soluble polymer having diverse applications ranging from pharmacology (as a binder in tablets) to nanoparticles and membranes for water purification [60]. Blending with PVP improves the anti-fouling properties of biomedical membrane materials used in plasma separation and hemodialysis [61]. The *R* enantiomer of the marine natural product (*S*)-ypaoamide (Scheme 1) was obtained by asymmetric synthesis. The 3-pyrrolin-2-one moiety is the most important fragment responsible for the immunosuppressive effect [62]. One-pot multicomponent synthesis of substituted 3-pyrrolin-2-ones **1** using citric acid as a green catalyst in a green solvent under ultrasound irradiation has been reported [63].

Optically pure forms (98%) of 1-(2-*tert*-butylphenyl)-5-(methoxymethyl)pyrrolidin-2-one (**2**) and 1-{2-[*tert*-butyl(diphenyl)siloxy]phenyl}-5-(methoxy-

Scheme 2.

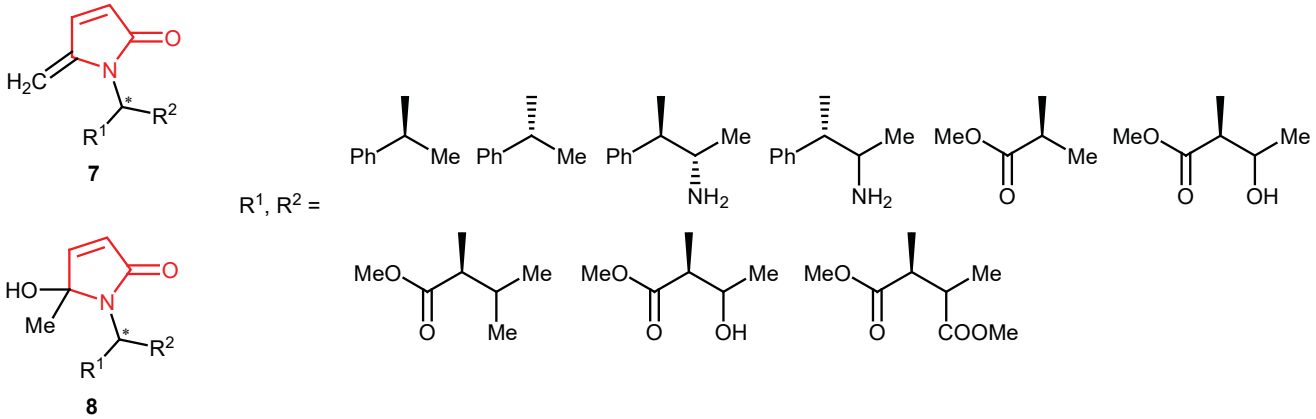


methyl)pyrrolidin-2-one (**3**) (including atropisomerism) were prepared from (*S*)-5-(methoxymethyl)butyrolactone in a stereoselective fashion [64]. Monocarbonyl analogs of cyclic imides, *N*-phenylpyrrolidin-2-ones and *N*-phenyldihydro-1*H*-pyrrol-2-ones **4**–**6**, acted as potential protoporphyrinogen oxidase (PPO) inhibitors. The in vitro assay showed that most of the synthesized compounds have good to excellent PPO inhibition activity and significant herbicidal activity [65] (Scheme 2).

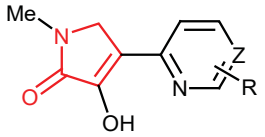
Homochiral 5-methylidene-1,5-dihydro-2*H*-pyrrol-2-one derivatives **7** and **8** were synthesized from amino acid esters, amino alcohols, and chiral amines via photooxygenation [51] (Scheme 3). These compounds are useful precursors to various bioactive compounds like alkaloids and unusual amino acids. The multifunctional character of these derivatives can contribute to multiple stereoselective reactions like conjugate additions, allylic substitutions, and cycloadditions [66].

Kawasuji et al. [38] reported the synthesis of a series of HIV inhibitors **9** containing a 3-hydroxy-1,5-dihydro-pyrrol-2-one moiety as a developmental derivative of 2-hydroxy-3-heteroaryl acrylic acid inhibitors (HHAAs). The cyclic modification of the chelating entity of HHAA provided a favorable configuration for the coordination of two metal ions in HIV, which improved not only enzymatic evaluation but also antiviral cell-based assays in many cases [38].

Scheme 3.

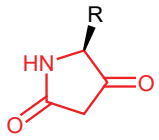


Scheme 4.



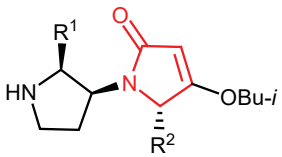
9

R = $OCH_2C_6H_4F$-4, $CH_2C_6H_4F$-4, OC_6H_4F-4, $CH_2CH_2C_6H_4F$-4
Z = CH, N



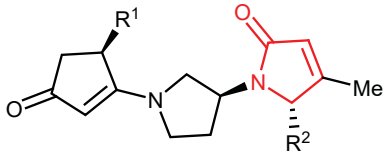
10

R = Me, Bn, *i*-Bu



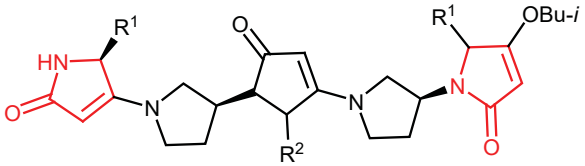
11

R^1 = Me, Bn, *i*-Bu
R^2 = Me, Bn



12

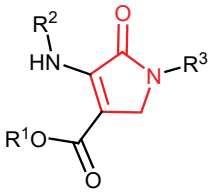
R^1 = Me, Bn, *i*-Bu
R^2 = Me, Bn, *s*-Bu, *i*-Bu



13

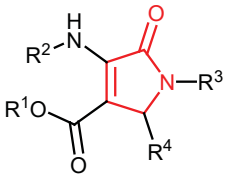
R^1 = Me, Bn, *i*-Bu
R^2 = Me, Bn, *s*-Bu, *i*-Bu

Scheme 5.



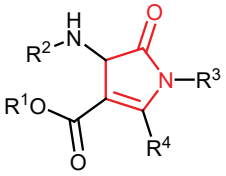
14

R^1 = Me, Et
R^2 = Ph, 4-MeC_6H_4, 4-FC_6H_4, 4-BrC_6H_4, Bn
R^3 = PhNH



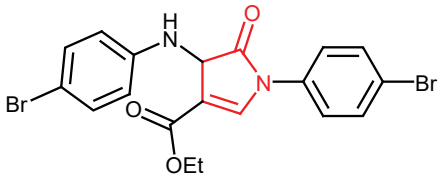
15

R^1 = Me, Et
R^2, R^3 = Ar, Alk
R^4 = Ph

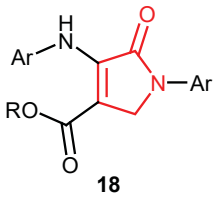


16

R^1 = Me, Et
R^2, R^3 = Ar, Alk
R^4 = H, Alk, Ar

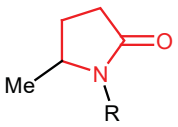


17



18

Ar = Ph, 4-MeC_6H_4, 4-EtC_6H_4, 4-BrC_6H_4
4-$MeOC_6H_4$, 4-ClC_6H_4



19

R = 4-CNC_6H_4, 4-$OCHC_6H_4$, 4-$MeOC_6H_4$
4-ClC_6H_4, 3-ClC_6H_4, 2-ClC_6H_4

Peptidomimetic analogs **10** were prepared from amino acid-derived tetramic acids as the key starting materials [44] (Scheme 4).

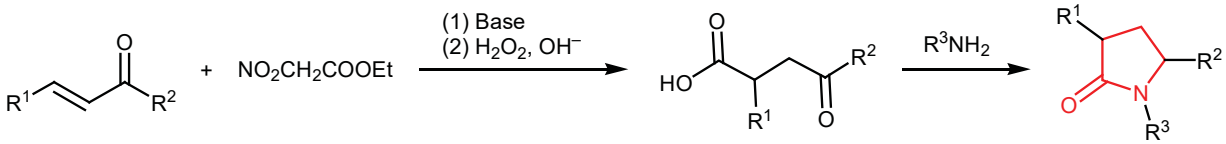
Tetra- and pentasubstituted polyfunctional dihydropyrrole derivatives **14** and **15** were synthesized by the reaction of but-2-ynedioates, aldehydes, and amines at room temperature or 70°C. Their in vitro pharmacological evaluation against HIV-1 showed a considerable effect with IC_{50} values in the micromolar range (38–58 μM) [67]. Dihydropyrrole derivatives **16** and **17** exhibited inhibitory activity against caspase-3 with IC_{50} values ranging from 5 to 20 μM; one compound (IC_{50} = 5.27 μM) can be regarded as a superior caspase-3 inhibitor [47]. The synthesis of polyfunctional 2-oxodihydropyrrole derivatives **18** by one-pot four-component domino reaction of dialkyl acetylene-

dicarboxylate, amine, and formaldehyde at room temperature was reported [68]. N-Substituted 5-methylpyrrolidin-2-one derivatives **19** were synthesized by one-pot reaction of ethyl levulinate and nitro compounds in presence of nanosized Pt catalyst [69] (Scheme 5).

1*H*-Pyrrol-2(5*H*)-ones **20** were synthesized from α,β-unsaturated ketones and ethyl nitroacetate under Paal–Knorr conditions [70] (Scheme 6).

N-Acyl-5-oxopyrrolidine-2-carbonitriles **21** were prepared by reacting 5-oxopyrrolidine-5-carboxamide (pyroglutamide) with trimethylchlorosilane in presence of zinc chloride as a catalyst [71]. Compounds **22** and **23** were claimed as potentially useful in the treatment of a wide range of diseases like schizophrenia, Alzheimer's disease, Parkinson's disease, anxiety, depression, stroke, down syndrome, traumatic brain injury, and normal aging. The neurogenic features of the compounds were tested on the proliferation of human embryonic stem cells. The compound efficacy was measured by the increase in cells based on ATP levels. Among the compounds tested, **22** showed the strongest neurogenic features [72]. Six derivatives of 3,3-diphenylpyrrolid-2-one were synthesized and tested for anticonvulsant activity. Among them, 2-imino-1,5-dimethyl-3,3-diphenylpyrrolidine hydrochloride **24** was effective in mice against maximal electroshock-induced seizures [73]. The anticonvulsant effects of these derivatives depended on the substituent at the 3-position, and the presence of an asymmetric center generally increased the anticonvulsant activity [74]. *N*-Aryl-3-amino-2-oxo-1,5-dihydropyrrole-4-carboxylates **25** were synthesized by vitamin B_{12}-catalyzed condensation between formaldehyde, dialkyl acetylenedicarboxylates, and amines at ambient temperature in ethanol [75]. Pyrrolidinone derivatives **26** were regioselectively synthesized by a one-pot intermolecular reductive coupling of acrylamides and

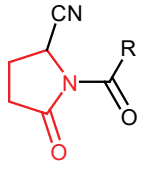
Scheme 6.



20

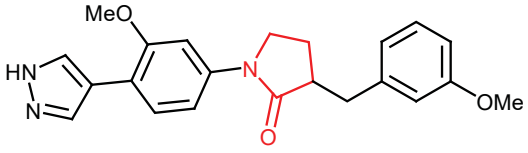
R^1 = Ph, 4-$MeOC_6H_4$, 4-ClC_6H_4, 4-HOC_6H_4, thiophen-3-yl
R^2 = Ph, 4-FC_6H_4, Et, Me; R^3 = H, Bn, 3,5-$(MeO)_2C_6H_3$

Scheme 7.

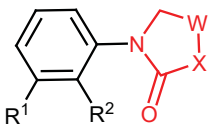


21

R = H, CH_2Cl, Bn

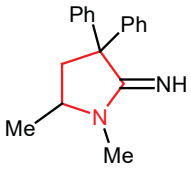


22



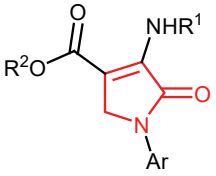
23

W = CH_2, CH_2CH_2; X = CR^3R^4, NR^5
R^1 = H, MeO, Cl; R^2 = H, Cl, F



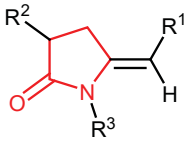
24

1,5-Dimethyl-3,3-diphenylpyrrolidin-2-imine



25

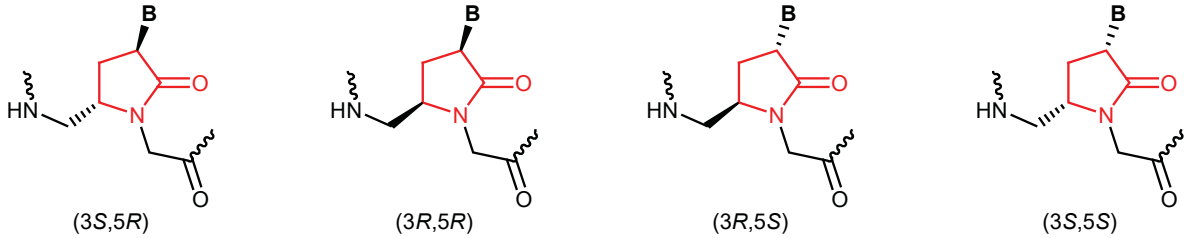
R^1, Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4, 4-BrC_6H_4, Bn, Bu
R^2 = Me, Et



26

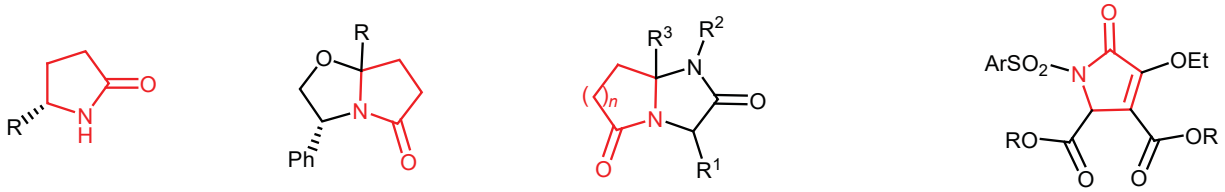
R^1 = Et, Me, thiophen-3-yl, thiophen-2-yl, naphthalen-1-yl, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-ClC_6H_4
R^2 = H, Me, Pr
R^3 = Bn, 3-$MeOC_6H_4(CH_2)_2$, thiophen^{-2}-ylmethyl, Ph, Pr, *i*-Pr, Cy

Scheme 8.



B is adenin-9-yl

Scheme 9.



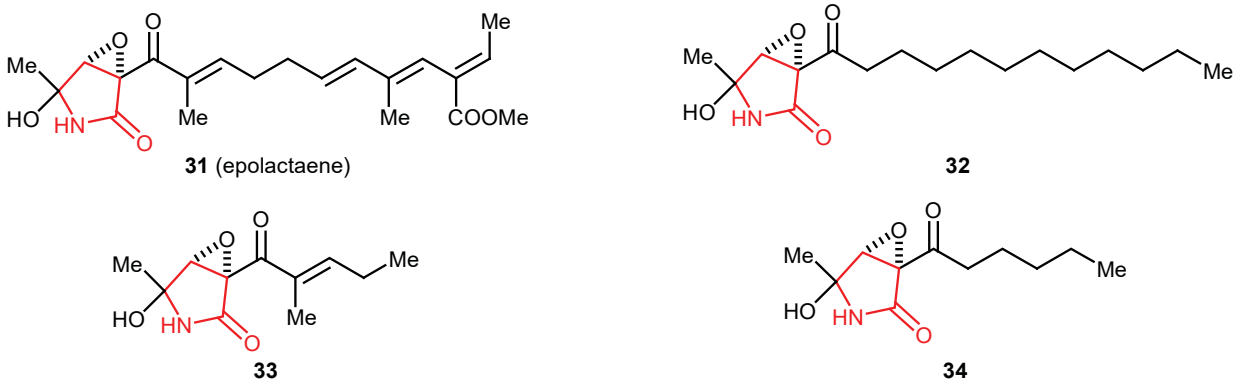
27
R = *n*-C_7H_{15}, cyclopentyl, *i*-Bu, *i*-Pr, chiral bicyclic lactam residue

28

29
R^1 = H, Et, CH_2COOEt, CH_2CONH_2, Ac
R^2 = H, Me, CH_2OH, $PhCH_2$
R^3 = H, Me, COOH, COOEt, $CONH_2$

30
R = Me, Et, *t*-Bu
Ar = Ph, 4-MeC_6H_4

Scheme 10.



31 (epolactaene)

32

33

34

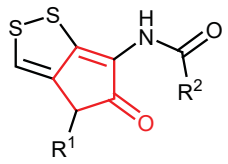
nitriles in the presence of a cobalt catalyst [76] (Scheme 7).

The synthesis and hybridization activities of four stereoisomeric adenine pyrrolidinone PNA analogs toward DNA, RNA, and PNA (peptide nucleic acid) were reported [77] (Scheme 8). A special asymmetric synthesis of pyrrolidinone derivatives **27** starting from 3-acylpropionic acids and N-substituted pyrrolidinone was accomplished by reduction of chiral bicyclic lactams **28** which were prepared from (*R*)-phenylglycinol using triethylsilane and titanium tetrachloride [78]. A series of dihydro-1*H*-pyrrolo[1,2-*a*]imidazole-2,5(3*H*,6*H*)-diones **29** were prepared and were found to exhibit anti-amnesic activity. The unsubstituted compound (**29**, $R^1 = R^2 = R^3 = H$, $n = 1$, dimiracetam) is 10–30 times stronger than oxiracetam [59] (Scheme 9). *N*-Arenesulfonyl-5-oxopyrrole-2,3-dicarboxylates **30** were synthesized by the reaction of dialkyl acetylenedicarboxylates, ethyl chlorooxoacetate, and arenesulfonamides in the presence of Et_3N and Ph_3P under mild conditions [79] (Scheme 9).

The synthesis of thiolutin (Scheme 1) and its derivatives was achieved by reacting methoxycarbonylacetyl chloride and *N*-methyl-1-ethoxycarbonyl-2-diethoxyethylamine [80]. Holomycin (Scheme 1) and its derivatives were synthesized using *S*-benzyl-L-cysteine ethyl ester as a starting material [81]. Epolactaene (**31**), a neurogenic substance in human neuroblastoma cells, and its derivatives **32**–**34** (Scheme 10) showed DNA polymerase activities on mammalian and human DNA topoisomerase II with IC_{50} values of 25, 94, and 10 μM, respectively [46].

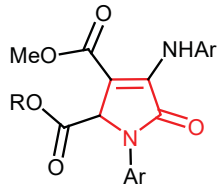
A series of substituted 6-amino-4*H*-[1,2]dithiolo-[4,3-*b*]pyrrol-5-ones **35** exhibited cytotoxicity effect

Scheme 11.



35

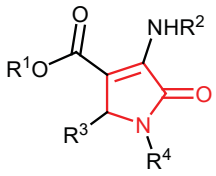
R^1 = H, 4-$MeOC_6H_4$, 2,4-$(MeO)_2C_6H_3$, 4-*i*-PrC_6H_4, $PhCH_2$
R^2 = hexan-2-yl, Me, CF_3, 2,4-$(MeO)_2C_6H_3$, 4-$CF_3C_6H_4$, 3,5-$F_2C_6H_3$, 3,5-$(CF_3)_2C_6H_3$, furan-2-yl, thiophen-2-yl, 3,5-$(OH)_2$-4-*i*-PrC_6H_2



36

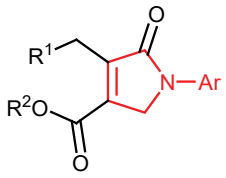
R = Et, Me; Ar = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 3-MeC_6H_4, 4-ClC_6H_4, 3-ClC_6H_4

Scheme 12.



37

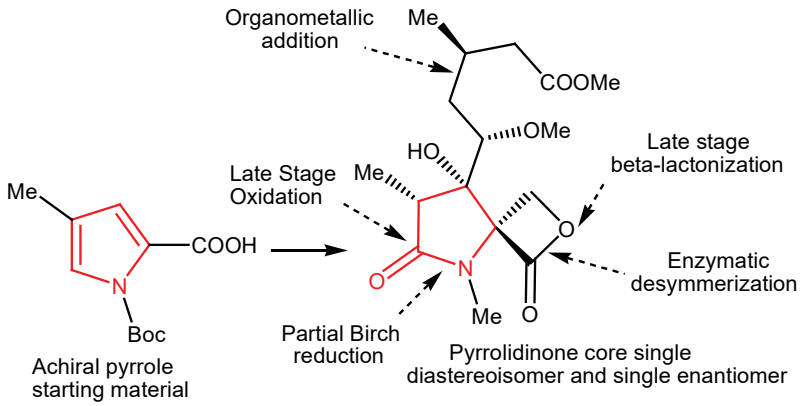
R^1 = Et, Me
R^2 = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-ClC_6H_4, 3-MeC_6H_4, 3-$MeOC_6H_4$, 3-BrC_6H_4, 3,4-$Me_2C_6H_3$
R^3 = Ph, 4-BrC_6H_4, 3-$NO_2C_6H_4$, 4-ClC_6H_4, 4-MeC_6H_4, 4-$NO_2C_6H_4$, 3,4-$(MeO)_2C_6H_3$
R^4 = Pr, Et, pyridin-2-yl



38

R^1 = Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4, 4-FC_6H_4 4-ClC_6H_4, 4-BrC_6H_4, $PhCH_2$
R^2 = Et, Me

Scheme 13.



[48]. An effective synthetic route to functionalized dihydropyrrol-2-one derivatives **36** via domino reaction of ethyl glyoxylate with acetylenedicarboxylate and 2 equiv of aromatic amines in the presence of benzoic acid was described [82] (Scheme 11).

2-Oxo-2,5-dihydro-1*H*-pyrrole-4-carboxylic acid alkyl esters **37** were prepared by a novel, facile, and general approach involving multicomponent reaction of aldehyde, amine, and dialkyl acetylenedicarboxylate in the presence of reusable TiO_2 nanopowder [83]. Lactic acid was used as a more valuable and greener additive for the one-pot synthesis of pyrrole derivatives **38** in ethanol at ambient temperature [84] (Scheme 12).

Donohoe et al. [85] reported the asymmetric synthesis of the fully elaborated pyrrolidinone core of the β-lactone/γ-lactam antibiotic oxazolomycin A. The procedure included the Birch reduction of an aromatic pyrrole nucleus, RuO_4-catalyzed pyrrolidine oxidation, and diastereoselective organocerium addition to an aldehyde (Scheme 13).

3. BIOLOGICAL PROPERTIES

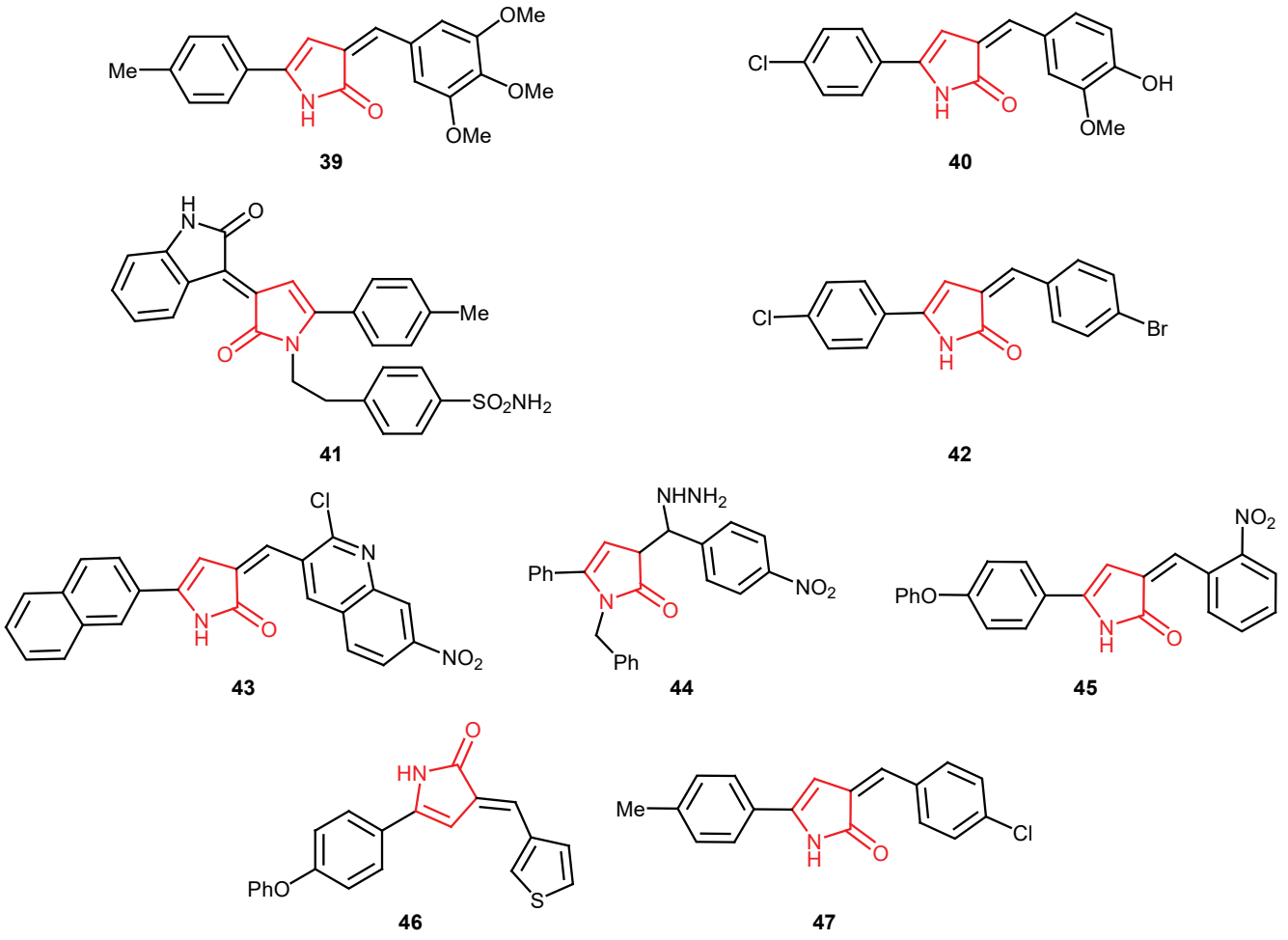
Various pyrrol-2-one derivatives exhibited diverse types of pharmacological activities against different types of diseases or disorders.

3.1. Antimicrobial Activity

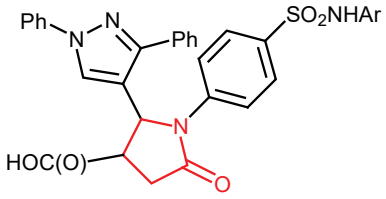
Pyrrole-2-one derivative **39** exhibited significant activity against *S. aureus* with a minimum inhibitory concentration (MIC) of 6.5 μg/mL and good activity against *E. coli* (MIC 15 μg/mL) [86]. 2(3*H*)-Pyrrolone derivatives were evaluated as antibacterial agents. Compound **40** showed significant antibacterial activity against *S. aureus*, *E. coli*, and *P. aeruginosa* at a level comparable to ciprofloxacin (MIC 6.25 μg/mL) [87]. A series of indolylpyrrolones displayed antibacterial activity. For instance, compound **41** was equipotent to chloramphenicol against *E. coli* with a MIC value of 2.5 μg/mL [88]. A series of pyrrolone and *N*-benzylpyrrolone derivatives were evaluated for antibacterial activity, and compound **42** exhibited the strongest antibacterial effect against *E.coli* and *P. aeruginosa* (MIC 6.25 μg/mL) and *S. aureus* (MIC 12.5 μg/mL) compared to ciprofloxacin (MIC 6.5 μg/mL) [89]. Among the quinolinyl pyrrolone series, compound **43** showed the highest antibacterial activity against *E. coli* and *P. aeruginosa* (MIC 12.5 μg/mL) and *S. aureus* (6.25 μg/mL) [90]. *N*-Benzylpyrrolone derivative **44** displayed remarkable antibacterial activity against *S. aureus* and *E. coli* with inhibition zone diameters of 5 and 7 mm, respectively, compared to penicillin (32 and 15 mm, respectively) [91]. 5-Phenoxyphenylpyrrol-2-one derivatives **45** and **46** showed antimicrobial activity against *S. aureus* (MIC 20 and 15 μg/mL, respectively) and *C. albicans* (MIC 10 μg/mL) [92]. Compound **47** showed the most promising antimycobacterial activity with IC_{50} of 11.34 μg/mL [93] (Scheme 14).

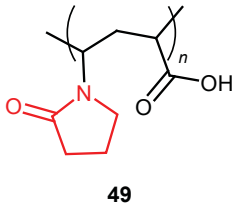
Pyrrolidin-2-ones possess both antibacterial and antifungal activity. Aqueous Lutrol® F127 system comprising *N*-methylpyrrolidin-2-one (NMP) showed antimicrobial effect against *S. aureus*, *E. coli*, and *C. albicans* in a dose-dependent manner with respect to NMP [94]. 2-[1,3-Diphenyl-1*H*-pyrazol-4-yl]-5-oxopyrrolidine-3-carboxylic acids **48** containing a benzenesulfonamide moiety exhibited similar or better

Scheme 14.

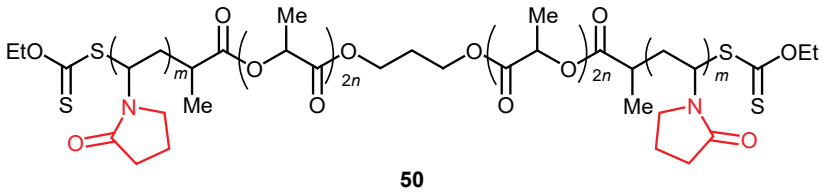


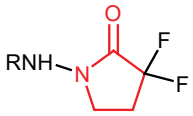
Scheme 15.



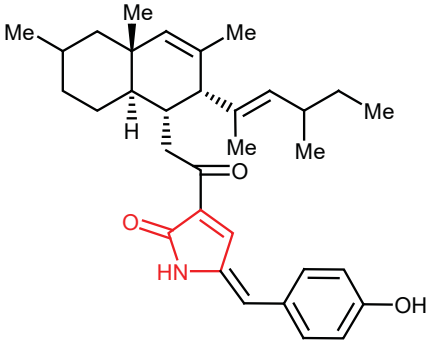


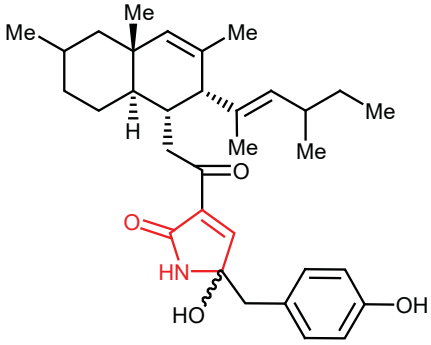
Scheme 16.





Scheme 17.



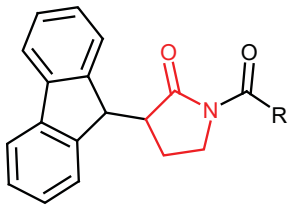


antibacterial activity than those of ampicillin, tetracycline, gentamycin, and chloramphenicol against *B. subtillis*, *S. aureus*, *E. coli*, and *P. aeruginosa* [95]. *N*-Vinylpyrrolidone (NVP)–acrylic acid (AA) copolymer **49** was synthesized and grafted with *N*,*N*-diethylaminoethanol through the carboxylic acid group to form an ester. The resulting copolymer showed antibacterial activity against gram-negative *Klebsiella aerogenes* NCIM-2098, *Pseudomonas desmolyticum* NCIM-2028, and *E. coli* NCIM-5051, as well as gram-positive *S. aureus* NCIM-5022. A significant antibacterial effect was observed at a copolymer dose of 150 μg in all bacterial pathogens tested [96] (Scheme 15).

A series of amphiphilic poly(*N*-vinylpyrrolidone) (PNVP)-*b*-poly(D,L-lactide)-*b*-PNVP triblock copolymers **50** have been synthesized, and doxorubicin (DOX) was loaded into the block copolymer micelles with a loading efficiency of 37.5%. The antibacterial properties of DOX-loaded micelles were found to be significantly more effective with respect to free DOX [97]. Poly(vinyl alcohol)/poly(vinyl pyrrolidone) (PVA/PVP) hydrogel was obtained by using γ-irradiation method. The antimicrobial effect of PVA/PVP hydrogels was tested against *S. aureus*, *P. aeruginosa*, *B. subtilis*, and *E. coli*, as well as against the fungi *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, and *C. albicans* [98]. 3,3-Difluoropyrrolidin-2-one derivatives **51** were synthesized by the reaction of ethyl 2,2-difluoro-4-iodo-4-(trimethylsilyl)butanoate with amines and were found to be biologically significant [99] (Scheme 16).

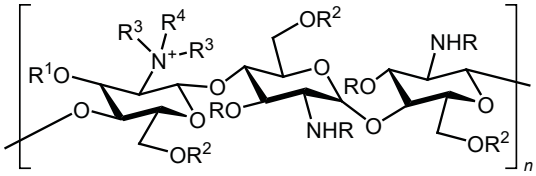
Pyrrocidines A and B, the two antibiotics including 13-membered macrocycles, were isolated from the fermentation broth of a fungus, LL-Cyan426; pyrrocidine A showed a stronger effect against gram-positive bacteria than that of pyrrocidine B. It was also effective against *C. albicans* [31]. The pyrrolidinone moiety was found in other antifungal agents such as talaroconvolutin A and the novel platelet-activating factor acetyltransferase inhibitor ZG-1494 (Scheme 17), but the 13-membered macrocycle including phenyl, ether, pyrrolidinone, and ketone moieties as in talaroconvolutin A is the prime instance discovered in natural products [100, 101].

Scheme 18.



52

R = Ph, C_8H_{17}



53

R = H, Ac; R^1 = H, Me, R^2 = H, Me; R^3 = Me; R^4 = Bu

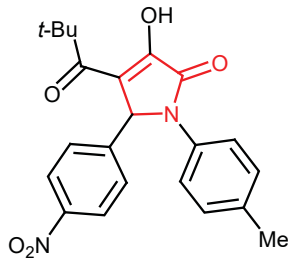
A series of GEQ (Genz-10850) analogs were synthesized in a few steps to afford pyrrolidinone and pyrrolidine derivatives **52**. These compounds were tested against InhA, an essential target for *Mycobacterium tuberculosis* (*M.tb*) survival. Compounds **52** were found to be quite active with MIC values of 1.4 and 2.8 μM respectively [102]. Photo-cross-linked quaternized chitosan analogs **53** (Scheme 18) prepared by electrospinning exhibited a strong antibacterial effect against gram-positive *S. aureus* and gram-negative *E. coli*. These materials can be used for wound dressing. Poly(vinyl pyrrolidone) (PVP) has numerous applications in the biomedical field due to its useful features such as non-toxicity, high hydrophilicity, biocompatibility, excellent complexation features, and film-forming ability [103].

3.2. Anticancer Activity

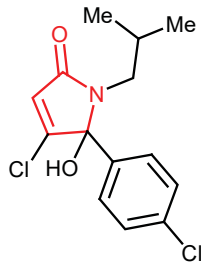
3-Hydroxy-1-(4-methylphenyl)-5-(4-nitrophenyl)-4-pivaloyl-2,5-dihydro-1*H*-pyrrol-2-one (**54**) exhibited antitumor activity against lung cancer with growth inhibition of 55% and CNS cancer with growth inhibition of 67% [104]. A series of 5-aryl-5-hydroxypyrrol-2-ones like **55** inhibited the growth of colon and pancreatic cancer models and acted as cholecystokinin-1 receptor antagonists with IC_{50} of 0.008 and 0.4 μM against CCK-A and CCK-B, respectively; this compound was more effective than lorglumide (IC_{50} 0.17 and >10 μM, respectively) [105]. A series of pyrrolone derivatives showed anticancer activity against HePG2, HCT116, and PC3 cancer cell lines. Compound **56** exhibited comparable activity to doxorubicin against Hep-G2 cancer cell line. Compounds **57** and **58** showed good cytotoxic activity against Hep-G2 cancer cell line with IC_{50} of 11.47 and 7.11 μM, respectively, compared to paclitaxel (IC_{50} 0.73 μM). These two compounds displayed promising inhibition for tubulin polymerase [106]. A series of indolylpyrrolone derivatives were tested as PIM1 kinase inhibitors, and compound **59** showed the highest activity with ID_{50} of 4.5 μM [107] (Scheme 19).

A series of helicid–pyrrolidone derivatives **60** (Scheme 20) were tested for their anticancer effect

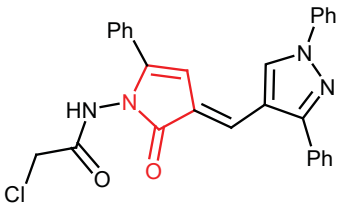
Scheme 19.



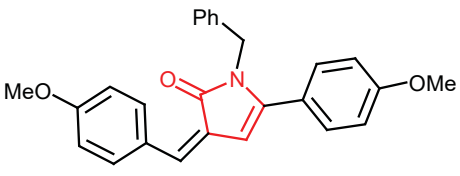
54



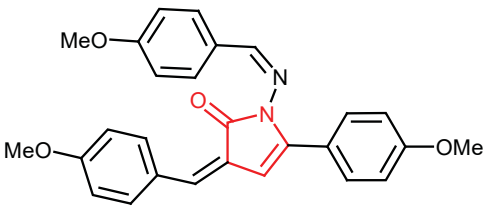
55



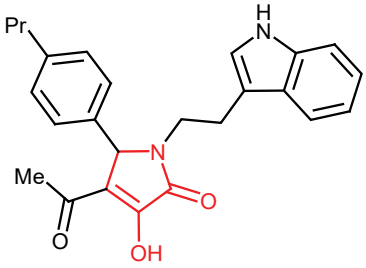
56



57

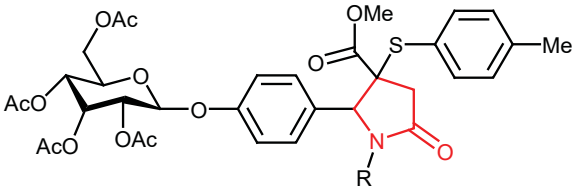


58



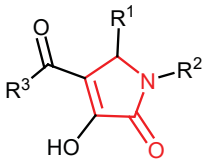
59

Scheme 20.



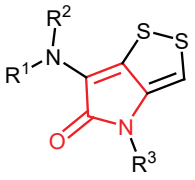
60

R = Pr, *i*-Bu, cyclohexyl, Bn



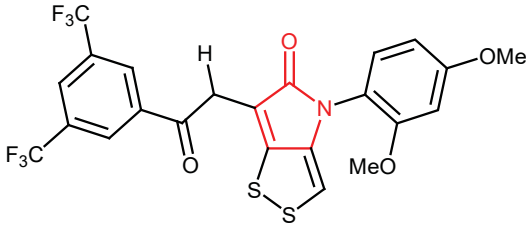
61

R^1 = *i*-Pr, Ph, substituted phenyl, naphthalen-2-yl
R^2 = $CH_2CH(Me)OH$, *i*-Bu, CH_2CH_2OH, CH_2CH_2OMe, $CH_2(CH_2)_2OMe$, $CH_2CH{=}CH_2$
R^3 = substituted phenyl, pyridin-4-yl, 4-methylpyridin-3-yl



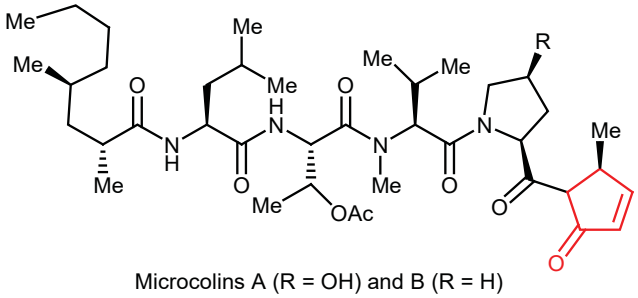
62

R^1 = acyl, R^2 = H, R^3 = Me
R^1 = acyl, R^2 = R^3 = H
R^1 = marinolic acid residue, R^2 = R^3 =H

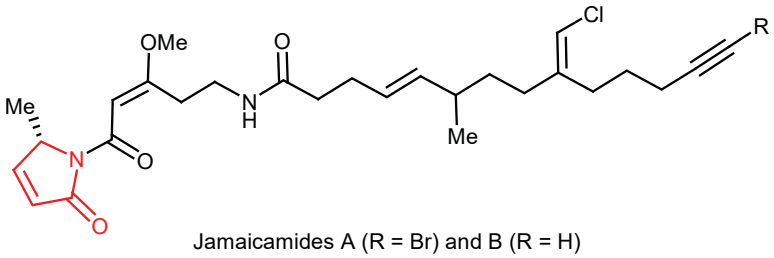


63

Scheme 21.



Microcolins A (R = OH) and B (R = H)



Jamaicamides A (R = Br) and B (R = H)

against human SKOV3 cells. Two derivatives showed a high anticancer effect against this cell line with an IC_{50} range of 0.22 to 6.5 μM, respectively, and were more potent than 17AAG, the heat shock protein 90 (Hsp90) inhibitor [62]. 1-Substituted 4-aroyl-3-hydroxy-5-phenyl-1*H*-pyrrol-2(5*H*)-one derivatives **61** (Scheme 20) were synthesized as Annexin A2-S100A10 protein inhibitors. Selected analogs interrupted the complex structure of Annexin A2 and S100A10 both in broken cell preparation and inside MDA-MB-231 breast cancer cells [52]. The toxic effect of NEP (*N*-ethylpyrrolidone) was exhibited when used by gavage to Sprague-Dawley rats at doses of 5, 50, and 250 mg/kg/day for four weeks. Finally, 28 days of repeated oral exposure to NEP at doses of up to 250 mg/kg/day resulted in mild renal and hepatic effects in rats. The adverse effects consisted of a reversible reduction in body heaviness gain and a growth in urine volume [108]. Dithiolopyrrolone derivatives **62** constitute a class of strong natural antibiotics effective against both gram-negative and gram-positive bacteria. They include a 4*H*-[1,2]dithiolo[4,3-*b*]pyrrol-5-one chromophore, and have recently attracted growing attention in synthetic and biological studies as

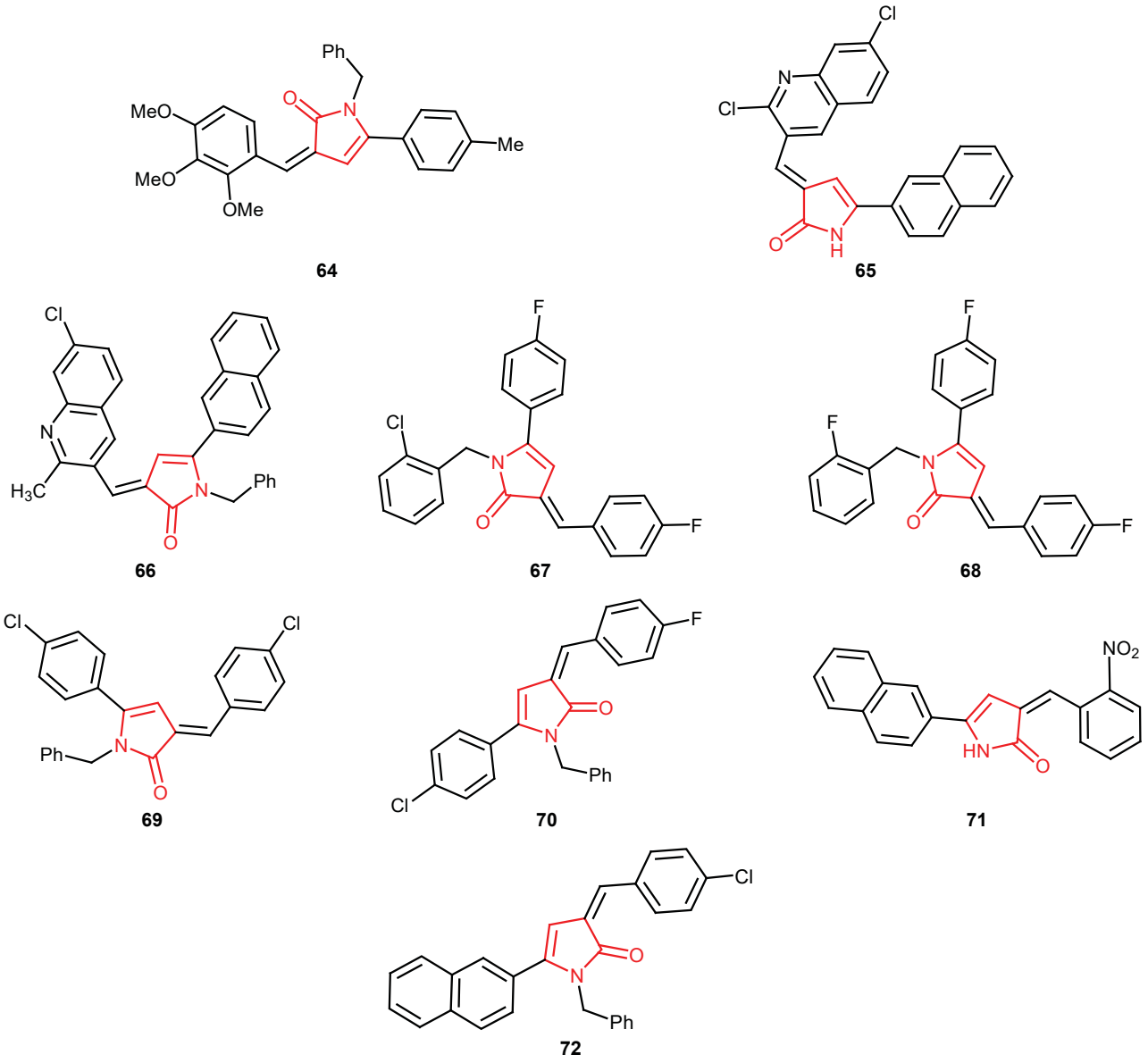
antiproliferative factors [109]. Compound **63** was selected for its anticancer effect tested on human SKMEL-28 V+ xenografts both in monotherapy and in combination with Taxol or Cisplatin, where potent effectiveness was found [48] (Scheme 20).

More than 300 nitrogen-containing natural products have been isolated and identified from marine cyanobacteria [110]. Among these, microcolins A and B isolated from a Venezuelan sample of the blue-green algae *Lyngbya majuscule* [111] showed very effective immunosuppressive and antiproliferative effects [112]. Jamaicamides A–C belong to a class of strong neurotoxins isolated from the Jamaican strain of *L. majuscule* [48, 113] (Scheme 21).

3.3. Anti-inflammatory Activity

A series of pyrrol-2-one exhibited anti-inflammatory activity, and compound **64** has comparable activity to diclofenac [86]. Quinolinylpyrrolone derivatives were tested as anti-inflammatory agents using carrageenan-induced paw edema. Compounds **65** and **66** produced 53% and 63% inhibition, respectively. The results indicated that the conversion of secondary NH group into tertiary moiety by introducing a benzyl substituent increased the anti-inflammatory activity [90]. Compounds **67** and **68** showed an edema inhibition percentage comparable to that of diclofenac (71.47, 76.22, and 80.98%), respectively. These compounds suppressed

Scheme 22.

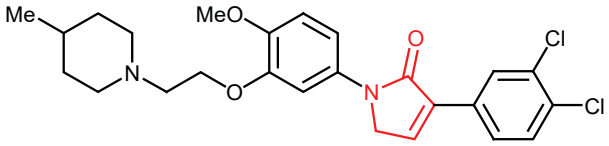


the TNF-a level by 60.90 and 65.03%, respectively, compared to indomethacin (68.40%) [114]. A series of furan-2(3*H*)-ones and their 1-benzylpyrrol-2(3*H*)-one analogs, in particular compounds **69** and **70** displayed comparable anti-inflammatory activity to ibuprofen with inhibition % of 88.88, 89.50, and 89.50, respectively. These two compounds also showed superior gastric safety with protection % of 57.83 and 59.03 compared to ibuprofen (65.06%) and reduced lipid peroxidation to a greater extent than did the reference drug [9, 115]. Pyrrolone derivatives **71** and **72** exhibited significant anti-inflammatory activity which was comparable to that of diclofenac and a twice as high safety profile as that of diclofenac (1.3, 1.3, and 2.6, respectively) [116] (Scheme 22).

3.4. Antidepressant Activity

Pyrrolone **73** exhibited significant antidepressant potency, selectivity, and pharmacokinetic profile and showed nanomolar affinity to 5-HT2C receptor [117] (Scheme 23).

Scheme 23.

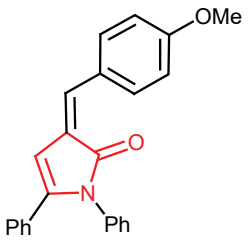


73

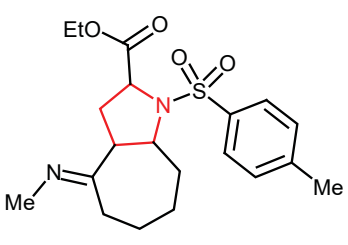
3.5. Anti-HCV Activity

A series of pyrrolone derivatives were tested for their antiviral activity against the hepatitis C virus (HCV). Compound **74** showed moderate interference with the helicase unwinding activity with IC_{50} of 438 μM and proved to be less potent than primuline (IC_{50} 10 μM) [11]. A series of bicyclic octahydrocyclohepta[*b*]pyrrol-4(1*H*) one derivatives exhibited antiviral activity against HCV. For example, *N*-tosyl derivative **75** was characterized by EC_{50} values of 1.8 and 4.5 μM in genotypes 1b and 2a, respectively. This compound did not affect HCV NS5B, IRES, and NS3 helicase [118] (Scheme 24).

Scheme 24.



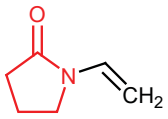
74



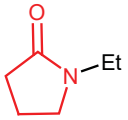
75

4. INDUSTRIAL APPLICATIONS

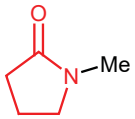
The main features of 1-vinylpyrrolidin-2-one (**76**) are its polarity characteristics and polymerizability to form soluble poly(vinylpyrrolidone) (PVP) or insoluble polyvinylpolypyrrolidone (PVPP, a highly cross-linked modification of PVP). PVP-based products are used in various fields are produced on large scale. PVP is used as an excipient in pharmacological formulations like tablets, food additive, and UV-durable inks. 1-Vinylpyrrolidin-2-one is capable of permeating skin [57, 58]. An analytical procedure has been developed for the determination of 1-vinyl-2-pyrrolidone–mercapturic acid (VPMA) in urine using electrospray liquid chromatography–tandem mass spectrometry (ESI-LC/MS) column switching approach [119].



76



77



78

N-Ethyl-2-pyrrolidone (NEP, **77**) is an industrial chemical used as a solvent, catalyst, and surfactant. It was proposed as a substitute for its analog, *N*-methyl-2-pyrrolidone (NMP, **78**), in many areas of usage, including coatings industry and cleaning of metals, glass, and plastics [108]. *N*-Methyl-2-pyrrolidone (NMP) is the 4-methylaminobutyric acid lactam. It is a colorless thermally stable liquid with low viscosity, low toxicity, and good biocompatibility. The dissolving power of NMP is similar to those of ethanol and dimethyl sulfoxide (DMSO). NMP increases transdermal sorption of some drugs like ibuprofen, flurbiprofen, phenolsulfonphthalein, and estradiol. It is isolated from a marine sponge for biosynthesis [120]. NMP can be used in the parenteral preparation of drugs since its increased solubilizing potency and low viscosity are the main factors for fine-gauge needles or microcatheters [121]. It is an important solvent used in extraction, purification, and crystallization of drugs [122]. NMP is used in nanoemulsions for the transdermal delivery of granisetron hydrochloride [123]. Many drugs contain NMP in their topical formulations as an absorption improver, in particular fluoxetine hydrochloride [124], lidocaine, granisetron hydrochloride [122], griseofulvin, [125] insulin [126], estradiol [125–127], bupranolol [128], spantide II

[129], levonorgestrel [127], luteinizing hormone-releasing hormone [130], ibuprofen, flurbiprofen [131], and morphine hydrochloride. An additional syringe wash with NMP can improve the stability of injections using gas chromatography syringes by getting better peak symmetry and reproducibility [132].

5. CONCLUSIONS

Pyrrolidinone derivatives are regularly investigated, and this review mainly focused on different significant biological activities of pyrrolidinone derivatives such as anti-inflammatory, antibacterial, antimicrobial, anticoagulant, antihypertensive, antimycobacterial, and most importantly their anticancer activities [133, 134]. Medicinal chemists from all over the world have synthesized different substituted pyrrolone derivatives to explore their biological activity and their drug target. Despite the known biological activities of these scaffolds, there is a direction in the future toward the use of this nucleus in the design of novel molecules with effective biological activities.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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