

HETEROCYCLES, Vol. 105, No. 1, 2022, pp. 244 - 286. © 2022 The Japan Institute of Heterocyclic Chemistry
Received, 25th February, 2022, Accepted, 28th March, 2022, Published online, 6th April, 2022
DOI: 10.3987/REV-22-SR(R)7

FIVE-MEMBERED NITROGEN HETEROCYCLES AS NEW LEAD COMPOUNDS IN DRUG DISCOVERY

Agustono Wibowo,^a Mohd Fazli Mohammat,^b Zurina Shaameri,^b Fatin Nur Ain Abdul Rashid,^b Noor Hidayah Pungot,^b and Ahmad Sazali Hamzah^{b*}

^a Faculty of Applied Sciences, Universiti Teknologi MARA (UiTM) Pahang Branch, Jengka Campus, 26400 Bandar Tun Abdul Razak Jengka, Pahang, Malaysia

^b Organic Synthesis Laboratory, Institute of Science, Universiti Teknologi MARA (UiTM), 42300 Bandar Puncak Alam, Selangor Darul Ehsan, Malaysia

Email address: asazali@uitm.edu.my

Abstract - Five-membered nitrogen heterocyclic compounds are a very important group with various pharmaceutical properties. The different substitutions and functionalization of these compounds contributed to various biological activities. Five-membered nitrogen heterocyclic scaffolds are used for synthesizing numerous natural and synthetic compounds with a significant biological application. They include antidiabetic, anticancer, antimalarial, antiviral, antimicrobial, anti-inflammatory, antibacterial, and anti-neurodegenerative agents. This mini-review provides an overview of the biological activities and the synthetic methods for preparing the five-membered nitrogen heterocyclic scaffolds and their functionalization. In the final part, this mini-review also listed some commercial drugs containing five-membered nitrogen heterocyclic motifs, highlighting the versatility of the five-membered nitrogen heterocyclic core in drug discovery.

CONTENTS

1. Introduction
2. Biological activities and synthetic methodology of five-membered nitrogen heterocyclic compounds
 - 2-1. Antidiabetic
 - 2-2. Anticancer
 - 2-3. Antibacterial
 - 2-4. Antiviral

- 2-5. Antifungal
 - 2-6. Antimalarial
 - 2-7. Antioxidant
 - 2-8. Anti-inflammatory
 - 2-9. Anti-neurodegenerative
3. Important drug containing five-membered nitrogen heterocyclic scaffold in the market
 4. Conclusion

1. INTRODUCTION

Five-membered nitrogen heterocyclic such as pyrrolidines are the prevalent group in natural products and pharmaceutical agents that constitute important synthetic targets for drug discovery.^{1,2} Numerous natural and synthetic compounds bearing five-membered nitrogen heterocyclic-types have received much attention because of their remarkable biological properties, such as antidiabetic, anticancer, and neuroprotection activities.³ Recently, the utilization of the five-membered nitrogen heterocyclic motif in the development of clinically active drugs has increased.⁴⁻⁸ This is due to the existence of a five-membered nitrogen heterocyclic scaffold in the drug that may increase aqueous solubility and improve other physicochemical properties in addition to being part of the pharmacophore.⁹ Structurally, five-membered nitrogen heterocyclic ring is a part of the amino acid proline, a building block in the enzymes, receptor, ion channels, and endogenous ligands; thus, it is not surprising that it plays a vital role in drug discovery. To date, the five-membered nitrogen heterocyclic structure occurs in more drugs than all other five-membered non-aromatic nitrogen heterocycles combined. According to the DrugBank's 2021 Highlights, more than hundreds of drugs containing five-membered nitrogen heterocyclic scaffold have been approved by the United States, Canada, and the European Food and Drug Administration (FDA) and are currently available in the market.

Recently, the development of novel drug candidates with better physicochemical properties, pharmacologic effectiveness, and less toxicity has been an essential subject. One of the effectively developed strategies in recent years is the combination of two different and independently acting structural subunits into one covalently linked hybrid compound. This molecular hybridization triggers diverse targets by a single molecule, thus increasing the drug's therapeutic effectiveness and bioavailability while reducing its side effect.¹⁰ This strategy has been used in the development of several pyrrolidine-based drug candidates, such as for antidiabetic (coumarin-proline-sulfonamide hybrids),¹¹ anticancer (pyrazoline-pyrrolidine-2,5-dione hybrids),¹² antiepileptics (dioxopyrrolidine-methoxypropanamides hybrids),¹³ and antimalarial (*N*-benzylpyrrolidine-carboxamides hybrids).¹⁴ The success of this strategy cannot be separated from the current development of the new synthetic methodology, which permits scientists to design compounds

through bypassing traditional synthetic procedures. Besides that, the application of molecular docking which allows to characterize of the behavior of molecules in the binding site of target proteins and their fundamental biochemical processes have expedited the drug design processes. This mini-review summarizes the biological activities and synthetic methodology of compounds with five-membered nitrogen heterocyclic framework published from 2016 to the present, featuring bioactive molecules reported as commercial drugs in the market.

2. BIOLOGICAL ACTIVITIES AND SYNTHETIC METHODOLOGY OF FIVE-MEMBERED NITROGEN HETEROCYCLIC COMPOUNDS

2-1. Antidiabetic

Five-membered nitrogen heterocyclic moiety occurs in several antidiabetic drugs, such as Glimepiride, Vildagliptin, and Sitagliptin, indicating that the five-membered *N*-heterocycle is an important part of their antidiabetic properties. Recently, dipeptidyl peptidase IV (DPP-IV) is a new important target for the treatment of type 2 diabetes mellitus. DPP-IV inhibitors shorten the inactivation of GLP-1, permitting the incretin to stimulate insulin release, thereby combating hyperglycemia.¹⁵ Durgapal and Soman¹¹ reported that coumarin-proline-sulfonamide hybrids can be a promising therapy for the treatment of diabetes, as three of the synthesized compounds **1-3** showed high potential in the DPP-IV assay (Figure 1). Another series of pyrrolidine-sulfonamide derivatives were reported by Sharma and Soman.¹⁶ From this series they found that compound **4** had good activity in inhibiting DPP-IV (IC_{50} 0.27 μ M). Also, among the series of camphor and cytosine-based cyanopyrrolidines derivatives, the reportedly most potential bornyl-based cyanopyrrolidines **5** and **6** were only moderately active to DPP-IV (1.27-15.78 μ M).¹⁷ However, the evaluation of *in vivo* hypoglycemic activities evaluation in mice showed that these compounds have good hypoglycemic activity.

Besides that, Karandikar *et al.*¹⁸ revealed that derivatives of benzisoxazole acetamide **7** containing pyrrolidin-2-amine group have also shown potential as DPP-IV inhibitor at 25–200 μ M concentrations. The amide group in the pyrrolidine ring seems essential in DPP-IV activity, as replacing the amide group at **7** with the ester or cyano group resulted in the loss of DPP-IV inhibitory activity. Similar results were reported by Deng *et al.*¹⁹ on the series of triazole-based uracil derivatives, in which the DPP-IV inhibitory activity of the uracil-triazole derivative **8** (IC_{50} 0.13 μ M) has reduced or lost when the amide group in the pyrrolidine ring was removed or replaced by a cyano group, respectively. This result has differed from that of the antidiabetic drug vildagliptin, where the cyano group is a part of an important active site in its antidiabetic properties.

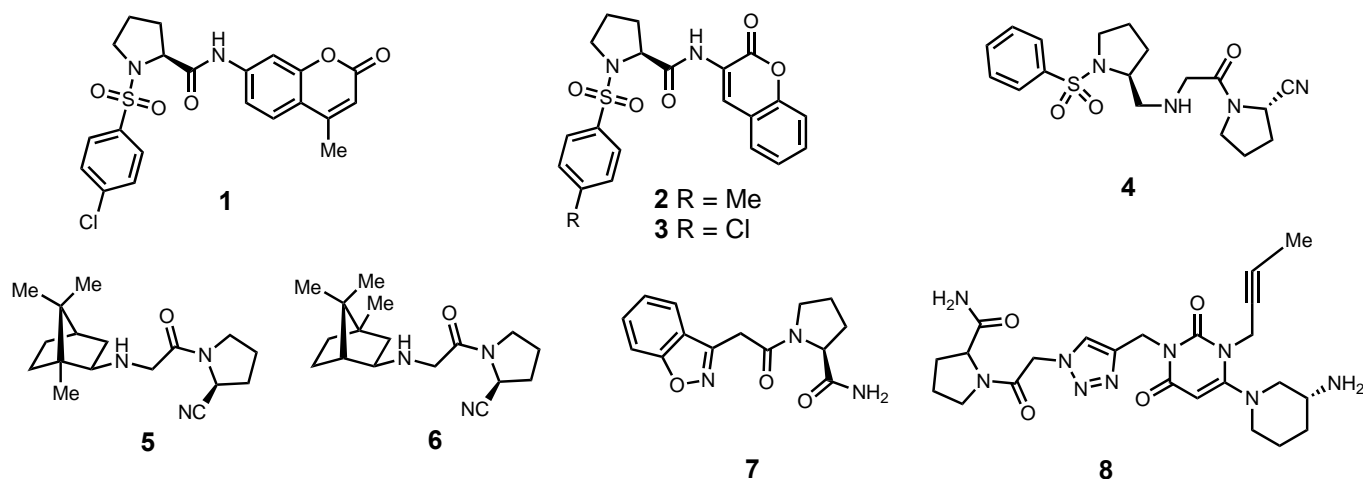


Figure 1. Structures of DPP-IV inhibitors bearing pyrrolidine scaffold **1-8**

In other antidiabetic assays, Luthra *et al.*²⁰ reported the synthesis of oxindole derivatives from a scaffold of four known α -glucosidase inhibitors, including oxindole,²¹ piperidine,²² cytidine,²³ and pyridofuranone.²⁴ The α -glucosidase evaluation of the synthesized compounds showed that oxindoles **9** and **10** containing pyrrolidine and piperidine rings had the most potent α -glucosidase inhibitor with IC_{50} 2.61 μ M and 0.6 μ M, respectively (Figure 2). Also, glucokinase activators **11** and **12** bearing pyrrolidine ring could reduce significantly the blood glucose levels in normal and diabetic mice.²⁵ However, compound **12** had issues with toxicity due to its high binding affinity to hERG potassium channels. Meanwhile, for pyrrolidine-containing GPR₄₀ agonists, by moving the position of its primary pharmacophore, carboxylic acid to C-2 and adding 4-*cis*-CF₃ **13** and **14** have improved the human GPR₄₀ binding K_i and agonist efficacy.²⁶ This finding revealed that a minor enantiomeric impurity with agonist activity led to the finding that enantiomers (*R,R*)-**13** and (*S,S*)-**14** have different effects on the radioligand used for the binding assay, with (*R,R*)-**13** potentiating the radioligand and (*S,S*)-**14** displacing the radioligand. The *in vitro* study showed that **13** activated both G_q-coupled intracellular Ca²⁺ flux and G_s-coupled cAMP accumulation, while *in vivo* study displayed that **13** significantly lowered plasma glucose levels in mice during an oral glucose challenge. Also, 3,4-disubstituted pyrrolidine acid analogues, i.e., compounds **15** (γIC_{50} 0.08 μ M/ αIC_{50} 0.18 μ M) and **16** (γIC_{50} 0.03 μ M/ αIC_{50} 0.96 μ M), were potent dual PPAR α/γ agonists, analogue **16** was effective in lowering fasting glucose and triglyceride levels in the diabetic *db/db* mice.²⁷

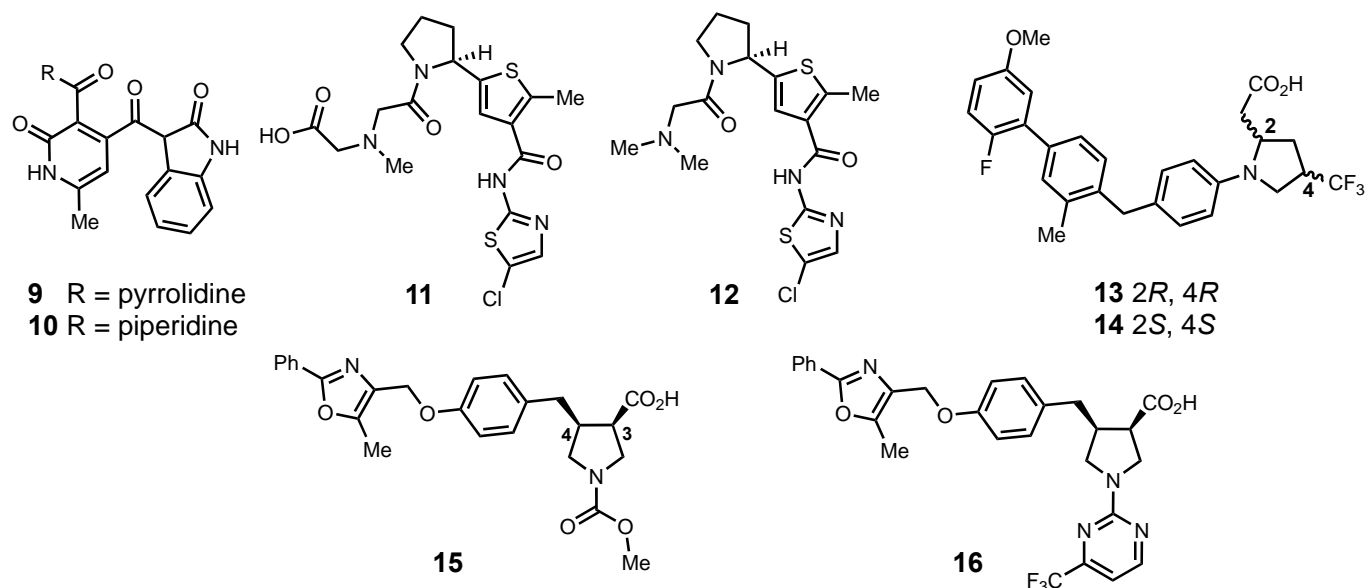


Figure 2. Structures of α -glucosidase inhibitors bearing pyrrolidine ring **9-16**

Besides being a part of the active site, five-membered nitrogen heterocyclic itself has also been reported to be an important framework in the antidiabetic drug candidates such as glucosidase inhibitors, iminohexitol and iminoarabinitol.²⁸ In this type of antidiabetic compounds, Hussain *et al.*²⁹ had reported the synthesis of a series of pyrrolidine-2,5-dione derivatives and evaluated for their ability to inhibit α -glucosidase. All synthesized compounds showed moderate to poor α -glucosidase inhibition. In particular, compound **17** with an IC_{50} value of 28.3 μ M emerged as an effective inhibitor of α -glucosidase, followed by compounds **18** and **19** (IC_{50} 31.9 and 33.4 μ M, respectively) (Figure 3). Likewise, Sansenya *et al.*³⁰ stated that the inhibitory activity of *N*-acetylpyrrolidine derivatives **20** and **21** on α -glucosidase and α -amylase to be only in a modest ranges. However, Guazzelli *et al.*³¹ revealed that polyhydroxylated pyrrolidine derivatives **22** significantly reduced the process of cell death and restored the physiological levels of oxidative stress when tested in the photoreceptor-like 661w cell line, thus proving to be effective in an *in vitro* model of diabetic retinopathy. Besides, a series of pyrrolidine-based iminosugars containing hydrazinyl, hydroxyamino, and hydroxypyrrolidine derivatives were evaluated for their α -glucosidase inhibitory activity by Wibowo *et al.*³² The most promising iminosugar derivatives were **23** and **24** (IC_{50} 1.12 mM and 1.17 mM, respectively), followed by compounds **25** and **26**. Based on the docking study, the hydrazine group at C-4 or methoxybenzene ring at C-2 seemed to play crucial roles in the antidiabetic activity of **23** and **24**.²⁸ The prospect of iminosugars as antidiabetic agents was also stated by Bacho *et al.*,³³ in which a series of iminosugar analogues studied, derivatives **27** and **28** were found to be the most potent α -glucosidase inhibitors at a low dosage (1.0 mM) compared to the standard drug (deoxynojirimycin).

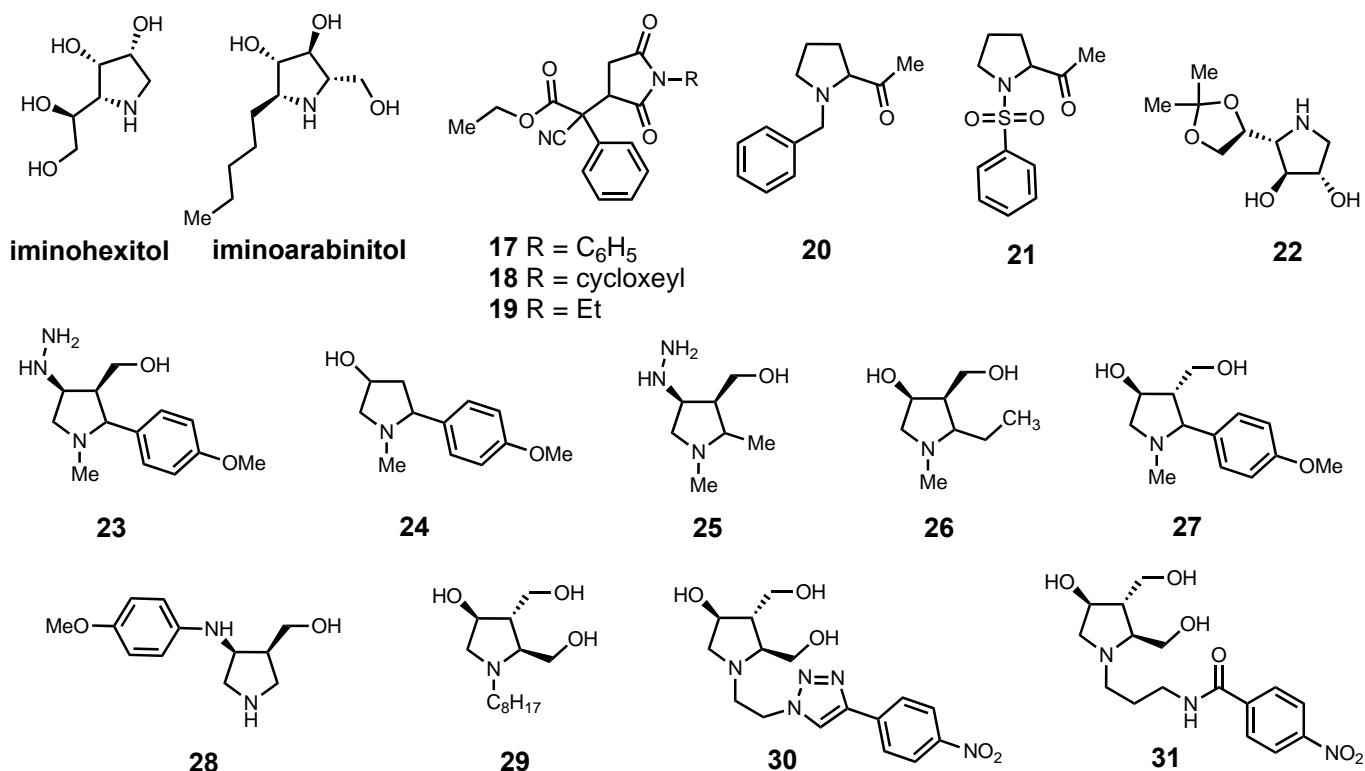
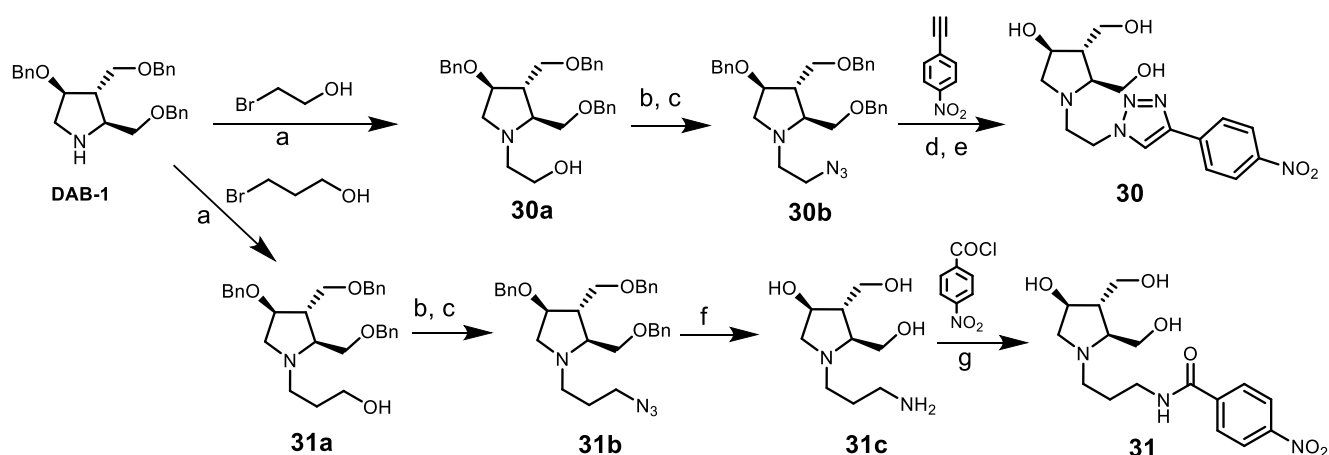


Figure 3. Structures of simple pyrrolidine derivatives with α -glucosidase inhibitor properties **17-31**

Most recently, the development of multi-target antidiabetic drugs is a promising synthetic approach since they potentially exhibit lesser side effects than the combination of other drugs.³⁴ In this respect, a series of bifunctional iminosugar inhibitors was synthesized and tested for their activity on α -glucosidases and protein tyrosine phosphatase 1B (PTP1B).³⁵ Specifically, compounds **29**, **30**, and **31** were potentially effective for treating type 2 diabetes. In both *in vitro* and in a cell-based models, these bifunctional compounds maintained activity on both target enzymes. More importantly, they showed good insulin-mimetic activity, with an increased phosphorylation level of Akt in the absence of insulin stimulation. Besides, the presence of the iminosugar moiety was demonstrated to be essential in imparting inhibitory activity towards PTP1B; compounds lacking of the polyhydroxylated pyrrolidine moiety, did not show any inhibitory activity. Typically, the synthesis of bifunctional iminosugar derivatives **30** and **31** began with the condensation of 1,4-dideoxy-1,4-imino-D-arabinitol (**DAB-1**) with 2-bromoethanol or 3-bromopropanol in THF at room temperature to yield the corresponding alcohols **30a** and **31a**. Functionalization with an azide **30b** and **31b** or reduction to form an amino terminal **31c** was mandatory to further couple with the nitro aromatic moiety (Scheme 1).³⁵



Scheme 1. Synthesis of the target triazole **28** and amide **29**. Reagents and conditions: (a) NEt_3 , THF, rt, 3 days; (b) MsCl , NEt_3 , CH_2Cl_2 , rt, 2 h; (c) NaN_3 , 18-crown-6 ether, MeCN, reflux, 5 h; (d) CuI , DIPEA, THF, rt, 2 h; (e) 1. BCl_3 , CH_2Cl_2 , rt, 15–18 h, 2. Ambersep 900 OH, MeOH, rt, 30 min, quantitative; (f) H_2 , Pd/C, HCl, MeOH, rt, 2 days; (g) pyridine, rt, 22–40 h

2-2. Anti-cancer

Cancer is one of the primary causes of death worldwide.³⁶ To date, there is no effective treatment for many cancers. Therefore, the search for novel anticancer drugs is undoubtedly a rewarding endeavor. Bashandy and El-Gilil³⁷ investigated that the anticancer activity of pyrrolidine derivatives was investigated by synthesizing a series of compounds, each containing a benzenesulfonylpyrrolidine moiety that had a variably substituted 1,3-thiazole ring in the position C-4 of the phenyl ring. These compounds were tested for anti-proliferative efficacy against the MCF-7 human breast cancer cell line *in vitro*. From the assay showed that compounds **32–35** were highly potent against MCF-7 cell line with IC_{50} values of 49.11, 48.01, 49.78, and 49.27 M, respectively (Figure 4). The compounds yielded better activity than the positive control, i.e., doxorubicin (IC_{50} 68.6 M). Also, molecular docking showed that compounds **32–35** might bind to the active site of the dihydrofolate reductase (DHFR) that catalyzed the reduction of dihydrofolate, synthesis of DNA, and methylation in the cancer cells.³⁸

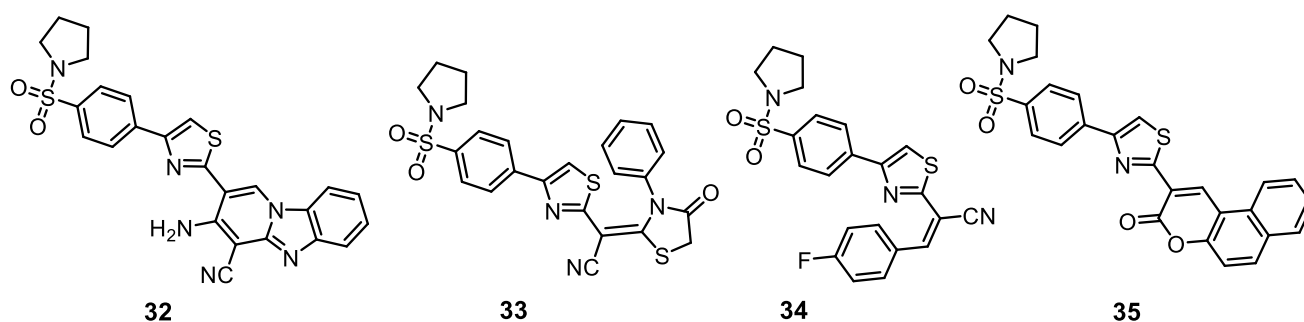


Figure 4. Structures of pyrrolidine containing benzenesulfonyl moiety **32–35**

Furthermore, Hassan *et al.*³⁹ synthesized a series of pyrrolidine-based 3-deoxysphingomyelin analogues with different acyl chains (α -linolenoyl, erucoyl, linoleoyl, oleoyl, palmitoyl, and palmitoleoyl) at the nitrogen atom of the pyrrolidine ring, and tested for their anticancer activity against several cancer cell lines, including A549 lung, Hep2 liver, A431 skin, and MCF-7 breast cancer cell lines. The assay showed that erucoyl-(**36-38**) or palmitoyl-(**39-41**) substituted 3-deoxysphingomyelins were the most promising analogs. Particularly, compounds **36-38** were the most potent analogues (Figure 5). They showed higher anti-proliferative efficacy against MCF-7 breast cancer cell lines (GI_{50} 15.7–24.8 μ M) than the positive control miltefosine (GI_{50} 28.4 μ M). Further investigation on Akt phosphorylation inhibition supported the potency of compounds **36-38**, and compound **37-39** were all equally active with cellular GI_{50} values of 21.1, 26.4, and 32.5 μ M, respectively. The results of this study revealed that, the type of fatty acid moiety in the structure among the 3-deoxysphingomyelin analogues, the structural fatty acid moiety yielded a higher impact on anticancer activity than the stereochemistry of substituent in the pyrrolidine ring.

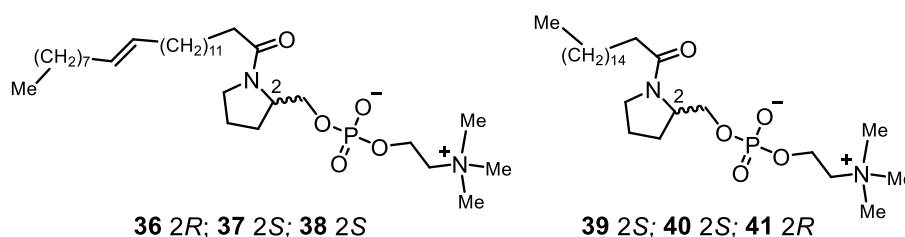


Figure 5. Structures of pyrrolidine-based 3-deoxysphingomyelin analogues **36-41**

Another study, Zhang *et al.*⁴⁰ had synthesized a hybrid benzofuroxan-based pyrrolidine hydroxamates with two distinct substituents on the pyrrolidine nitrogen atom, 3-phenoxybenzenesulfonyl or (3,4-dimethoxyphenyl)prop-2-enyl, and evaluated their anti-proliferative activity. All synthesized compounds showed anti-proliferative activity against numerous cancer cell lines, including A549, K562, MCF-7, ES-2, HeLa, and MDA-MB-231 with IC_{50} values 3.56–25.64 μ M, as well as NO-releasing capability (25.51–4.43 μ M). The anticancer effect was attributable to the inhibition of matrix metalloproteinases MMP-2 and MMP-9, as indicated by the decrease in the proteolytic activity following the separation of these enzymes from the treated cells. The 5-benzofuroxan **42** yielded higher MMP-2 and MMP-9 inhibitory activity (IC_{50} 8 and 162 nM, respectively) than 4-benzofuroxan **44** (IC_{50} 182 and 242 nM, respectively) (Figure 6). Meanwhile, 5-benzofuroxan **43** and 4-benzofuroxan **45** yielded a low inhibitory activity (IC_{50} values of 345–524 nM). Docking studies on the active site of MMP-2 (PDB ID: 1HOV) revealed that the hydroxamate group could chelate the catalytic zinc ion, as well as arylsulfonyl and benzofuroxan groups to form

hydrogen bonds with amino acid residues. These hybrid NO-MMPIs could be useful scaffolds for effective MMP inhibitors in developing new anticancer medications.

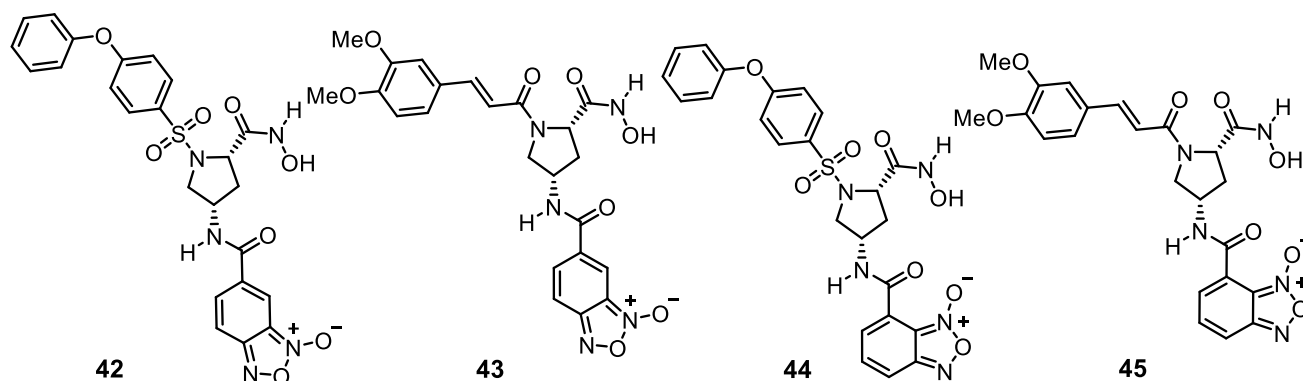


Figure 6. Structures of hybrid benzofuroxan-based pyrrolidine hydroxamates **42-45**

In 2018, Kumar *et al.*⁴¹ synthesized pyrrolidinone derivatives **46-49** by reacting substituted salicylaldehydes with the scaffold of pyrrolidin-2-one in antitumor agents, i.e., 2-(2-oxopyrrolidin-1-yl)acetamide (Figure 7). This synthesis yielded Schiff-base intermediates that were then reduced by sodium borohydride. Compounds **48** and **49** gave the highest inhibitory activity against CCRF-CEM leukaemia cell line with IG 73.2%, and NCI-H522 non-small cell lung cancer cell line with GI 41.1%. For the substituents on the aromatic ring, the methoxy group at the *meta*-position was unfavorable for anti-proliferative activity, based on the analysis of the structure-activity relationship (SAR). Compared to compounds **46** and **47**, inserting a hydroxy group at the *meta*-position **48** and **49** increased the anti-proliferative efficacy. Docking investigations suggested that interaction with the podophyllotoxin pocket of the protein gamma-tubulin (PDB ID: 1SA1) might be the possible mechanism of action underlying the anticancer effect. Besides that, the prospect of pyrrolidinone framework in the anticancer activity was reported by Mohammat *et al.*,³ in which the existence of hydrazones functionality at the C-3 position on 4-methoxyphenylpyrrolidin-2-one derivatives has high potential in inhibiting human histiocytic lymphoma (U937) and neuroblastoma (SH-SY5Y) cell lines.

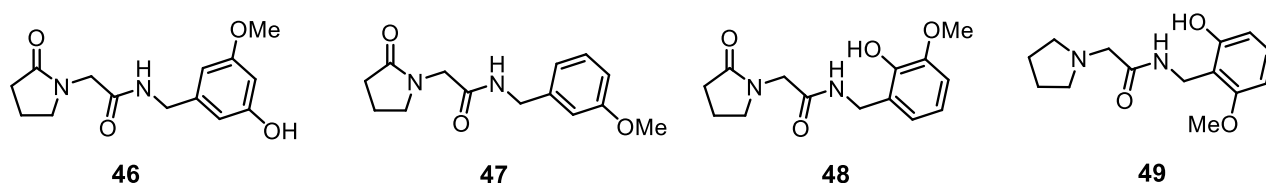


Figure 7. Structure of pyrrolidinone derivatives **46-49**

Recent studies showed that pyrazoline-substituted pyrrolidine-2,5-dione hybrids **50-54** were active against K562, HT29, and MCF7 cancer cell lines (Figure 8). Compounds **51-53** yielded nanomolar activity against MCF7 cancer cell lines with IC_{50} values of 0.78, 0.42, and 0.74 μM , respectively. Also, compounds **51** and **54** were effective against HT29 cancer cell lines in the sub-micromolar range (IC_{50} 0.92 μM and 0.39 μM , respectively). Compounds **50** and **53** with IC_{50} 24.74 and 31.56 μM , respectively, were more effective than the reference drug pioglitazone (IC_{50} 40.3 μM) in anticancer in a cytotoxicity experiment against K562.¹²

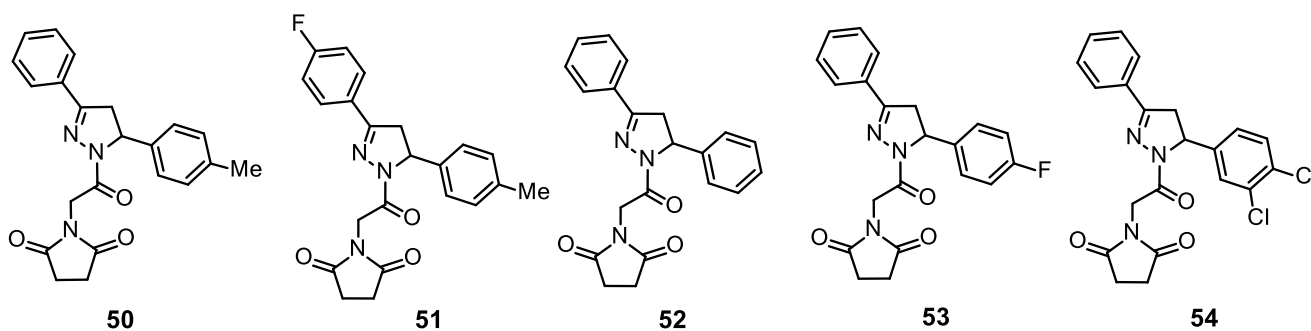
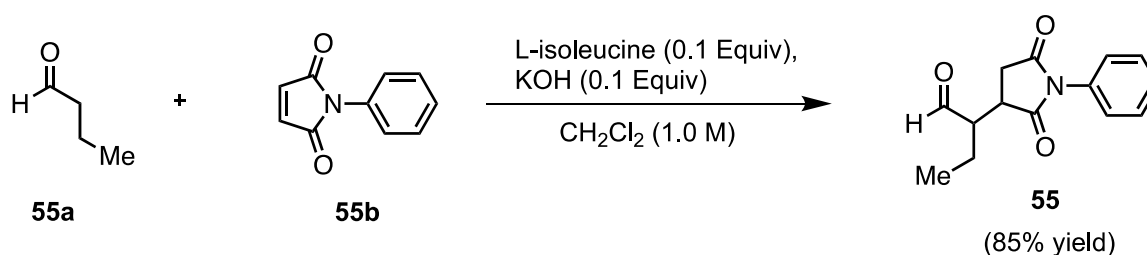


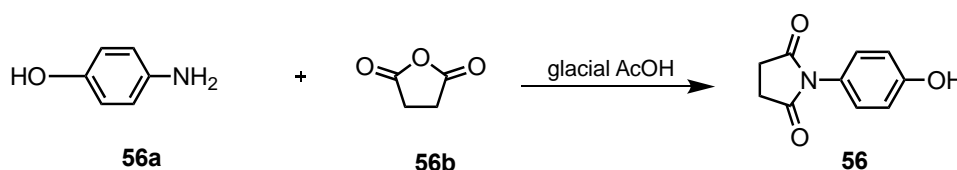
Figure 8. Structure of pyrazoline-substituted pyrrolidine-2,5-dione hybrids **50-54**

Based on the 2,5-dioxopyrrolidine analogue, Ahmad *et al.*⁴² discovered a bioactive succinimide aldehyde derivative, 2-(2,5-dioxo-1-phenylpyrrolidin-3-yl)butanal **55**, was synthesized, and tested for its biological potentials as an antioxidant, anti-cholinesterase, *in vitro* antidiabetic, and anthelmintic. Butyraldehyde **55a** and *N*-phenylmaleimide **55b** were used as the starting materials for preparing the succinimide aldehyde derivative. The C-C bond was formed between the Michael acceptor and donor using the Michael addition reaction.⁴³ L-Isoleucine (0.1 mol percent, 13.1 mg) and potassium hydroxide (0.1 mol, 5.6 mg) were added in dichloromethane to accelerate the process. Then, as indicated in Scheme 2, butyraldehyde (2.0 mmol, 0.359 L) and 1.0 mmol (173.17 mg) of *N*-phenylmaleimide were added at room temperature. Compound **55** was synthesized in a single-step synthesis at room temperature in 10 h to provide 85% yield. The cytotoxicity assay of **55** to several cell lines showed the lowest cytotoxic activity against MDAMB-231 cell lines. The cytotoxic activity is similar to the reference drug, doxorubicin, against practically all cell lines at the highest concentration of 1000 ppm.



Scheme 2. Synthesis of succinimide derivative **55**

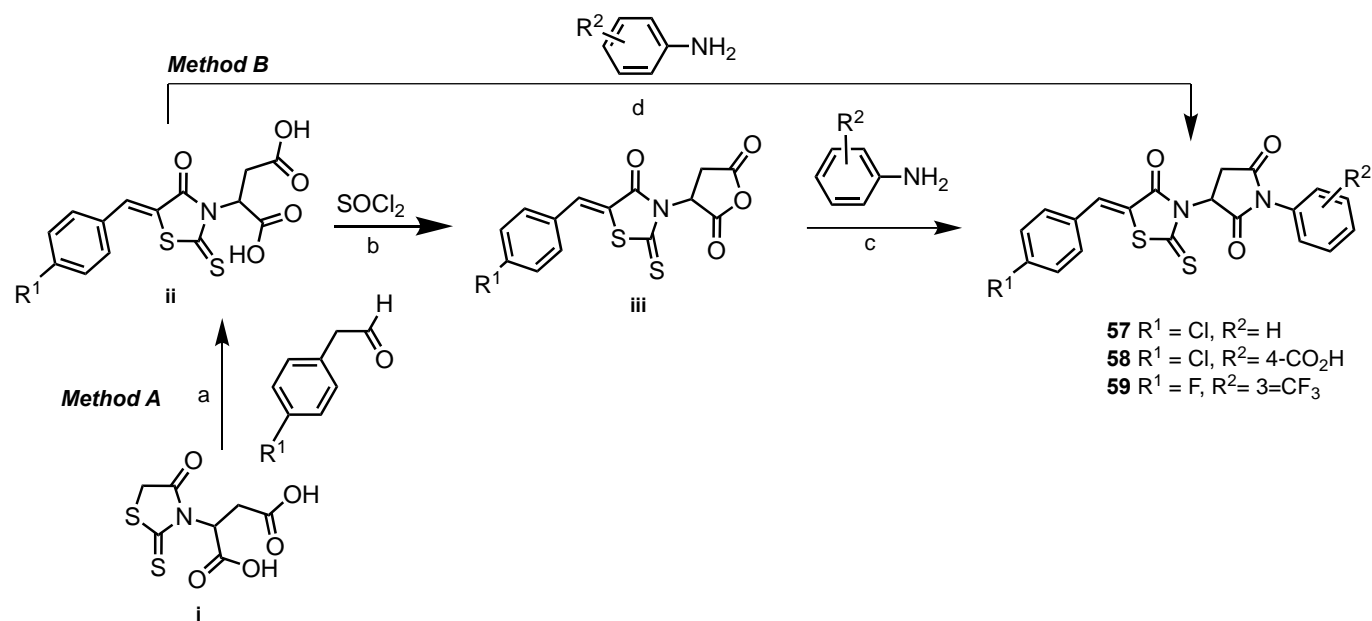
Furthermore, Zulfiqar *et al.*⁴⁴ investigated the synthesis of 4-(pyrrolidine-2,5-dion-1-yl)phenol **56** utilizing a process based on 4-aminophenol **56a** and succinic anhydride **56b** using glacial acetic acid as the solvent. 4-Aminophenol (1.6 g, 0.01 mol) and succinic anhydride (1.5 g, 0.01 mol) were dissolved in 15 mL of acetic acid. Then the reaction mixture was refluxed at 120–130 °C for 4 h. The compound was recrystallized after the reaction mixture was poured into ice cold water and the product **56** was obtained in 93% yield (Scheme 3). The MTT assay was used to assess the anti-proliferative activity of **56** against normal ADMSCs and human HCT-116 and HT-29 colorectal cancer cell lines. Colorectal cancer is the third most common cancer diagnosed, and it is linked to a high rate of morbidity and mortality. The tested compound **56** was less inhibitory against the HCT-116 cancer cell line than HT-29 cells and ADMSCs at different concentrations. The IC₅₀ value of **56** for HT-29 was 1.03 μM (196.7 μg/mL), which was substantially lower than that of ADMSCs (1.32 μM or 252.1 μg/mL) and HCT-116 (1.74 μM or 332.3 μg/mL). Together, compound **56** was a potential anticancer agent, and further investigations might help develop a novel anticancer medicine.



Scheme 3. The synthesis of 4-(pyrrolidine-2,5-dion-1-yl)phenol **56**

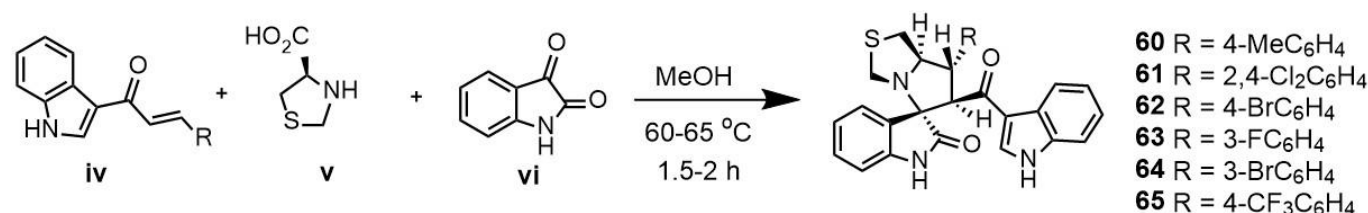
Recently, a series of anti-leukemic from rhodanine pyrrolidinedione hybrids, 2,5-dioxopyrrolidine analog were synthesized by Kryshchyshyn *et al.*⁴⁵ The synthesis of rhodanine-pyrrolidinedione derivatives was based on the modification of rhodanine-3-succinic acid **i** and involved multiple phases, including the synthesis of 5-arylidenerhodanine-3-succinic acids **ii**, which were then transformed into target imides *via* the cyclic anhydride **iii** production stage. To omit this step, an alternative one-step technique for the synthesis of target 5-arylidene-3-(1-arylpyrrolidine-2,5-dione)rhodanine derivatives **57-59** was devised: long-term heating of **ii** with aromatic amine (1:1) in an acetic acid medium was devised (method B) (Scheme 4). The activity of 15 target compounds was tested against four leukemia cell lines (Dami, HL-60, Jurkat, and K562), and rhodanine derivatives **57-59** inhibited the growth of all tested cell lines by more than 50% at the dose of 10 μM. In this assay, rhodanine derivative **57** was most effective in inhibiting Dami and HL-60 cell lines. Despite a lack of modification in the arylidene moiety of the pyrrolidine ring, compound **57** still showed good and specific anti-proliferative activity against Dami and HL-60 cell lines with low toxicity (acute toxicity evaluated *in vivo* in mice). Although this lipophilic group was most

effective in inhibiting the growth of leukemia cell lines, the carboxylic group at the *para*-position and the trifluoromethyl group at the *meta*-position of the phenyl ring were preferred.



Scheme 4. The synthesis of target 5-arylidene-3-(1-arylpyrrolidine-2,5-dione)rhodanines hybrids (**57-59**). Reagents and conditions: (a) aldehyde (1 eq), AcONa (1 eq), AcOH, reflux 3 h; (b) SOCl₂ (3 eq), dioxane, reflux, 1 h; (c) amine (1 eq), dioxane, reflux, 3 h; (d) amine (1 eq), AcOH, reflux, 12 h

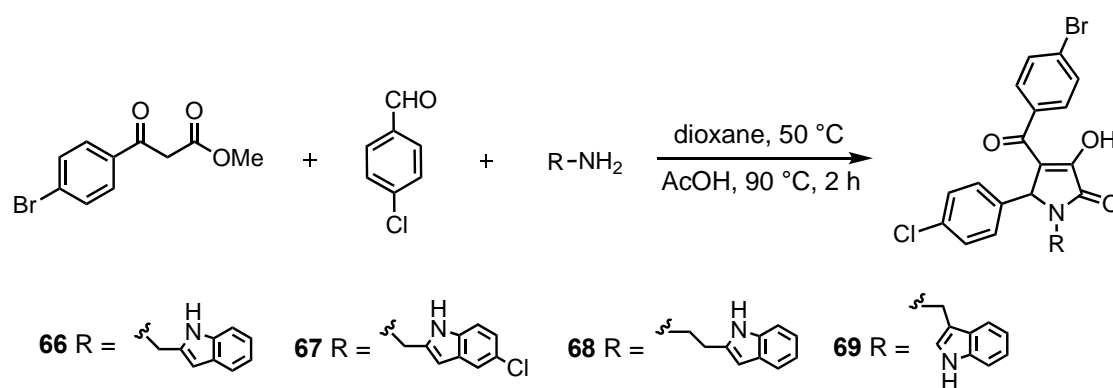
Besides that analogs, several potential anticancer agents from a series of functionalized spirooxindole derivatives linked with 3-acylindole scaffold were also reported by Islam *et al.*⁴⁶ These derivatives were prepared from a one-pot reaction of three components; 3-acetylindole, isatin, and 1-4-thiazolidinecarboxylic acid. The reactions were regioselective and stereoselective, with high yields (71–89%) and no side products (Scheme 5). These new spirooxindole hybrids were tested *in vitro* for anti-proliferative properties against colon cancer (HCT-116), prostate cancer (PC-3), and hepatocellular carcinoma (HepG2). In the assay, compound **65** showed excellent cytotoxic activity and selectivity against colon cancer cells HCT-116 (IC₅₀ 7 μM, SI: 3.7) and HepG2 (IC₅₀ 5.5 μM, SI: 4.7). Compared with cisplatin (IC₅₀ 5 μM, SI: 1.0), compound **65** was less active (IC₅₀ 6 ± 0.3 μM, SI: 4.3) but at a higher selectivity on PC-3 prostate cancer cell lines. Meanwhile, compounds **60**, **61**, **63**, and **65** were more active and selective than the reference drug cisplatin in battling against HCT-116 colon cancer cell lines.



Scheme 5. The synthesis of spirooxindole derivatives **60-65**

2-3. Antibacterial

A series of pyrrolidine-2,3-diones was synthesized as new non- β -lactam inhibitors against penicillin-binding proteins (PBP3) of the bacterium *Pseudomonas aeruginosa* via a multicomponent reaction of *p*-bromophenylpyruvate, 4-chlorobenzaldehyde, and different amines in dioxane (Scheme 6).⁴⁷ Compounds **66-69** satisfactorily inhibited two *P. aeruginosa* strains, the wild-type PAO1 (MIC 3.13, 3.13, 6.25, and 6.25 μ M) and the efflux mutant K2896 (MIC 12.5, 12.5, 12.5, and 25.0 μ M), respectively, in the presence of polymyxin B nonapeptide (PMBN). No inhibitory activity was detected for these compounds in the absence of PMBN, probably because these highly hydrophobic compounds could not cross the *P. aeruginosa* cell membrane without a permeabilizer. Also, the presence of a hydroxyl group at the C-3 position and a heteroaryl group at the nitrogen of the pyrrolidine ring, were responsible for the inhibition.



Scheme 6. One-pot three-component reaction of pyrrolidine-2,3-diones **66-69**

Besides, a thiazole-based pyrrolidine **70** showed good antibacterial activity against *Bacillus cereus* and *Staphylococcus aureus* with minimum toxicity values (Figure 9).⁴⁷ At 400 μ g concentration, the compound inhibited both *B. cereus* and *S. aureus* with the values of 21.7 and 30.5 mm, respectively. Meanwhile, at 160 μ g concentration, the compound only showed an inhibition activity against *B. cereus* with the value of 9.0 mm.⁴⁸ Also, another study discovered three active thiazole-based pyrrolidine derivatives **71-73** against *Acinetobacter baumannii* and *Mycobacterium tuberculosis* H37Rv strain with MIC values of 31.3 mg/mL (MIC of ampicillin 125 mg/mL) and 0.98-1.96 mg/mL (MIC of isoniazid 0.98 mg/mL, MIC of ethambutol 1.96 mg/mL), respectively. The presence of phenylsulfonyl group as R² substituent and a halogen atom as R³ substituent seemed to have satisfactorily affected the activity as they showed more inhibition than other compounds.⁴⁹

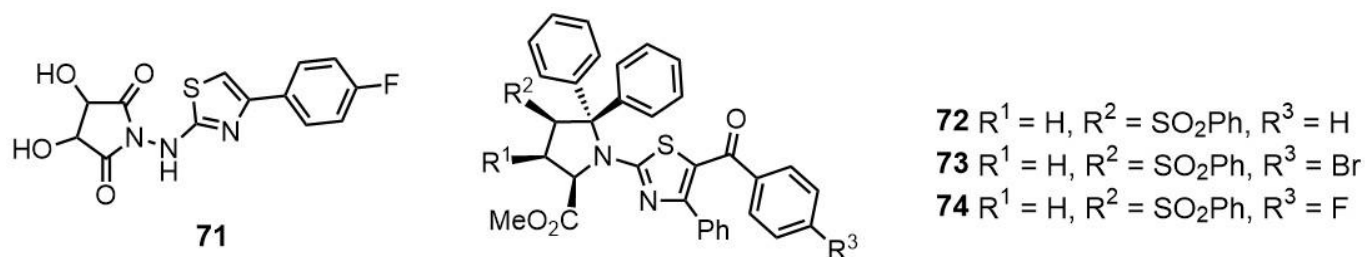


Figure 9. Structures of thiazole-based pyrrolidine derivatives **71-74**

A library of chiral 3,4-disubstituted pyrrolidines **74-79** was synthesized and evaluated for inhibitory activities against methicillin-resistant strains of *S. aureus* (MRSA) and *Escherichia coli* (Figure 10). These compounds inhibited the growth of *S. aureus* and *E. coli*. The most efficient derivative, compound **75**, showed excellent inhibition with MIC₅₀ and MIC₁₀₀ values of 17 and 37 $\mu\text{mol/L}$, respectively, for both bacteria.⁵⁰ Besides, another study⁵¹ evaluated 28 substituted pyrrolidine derivatives as analogues of codonopsinine **80** for their anti-MRSA activity against a panel of *S. aureus* isolates. Among the derivatives, compounds **81** and **82** exhibited good inhibitory activity against four *S. aureus* isolates (N441, U949, ATCC25923, and ATCC33591) with MIC values of 125 to 250 $\mu\text{g/mL}$.

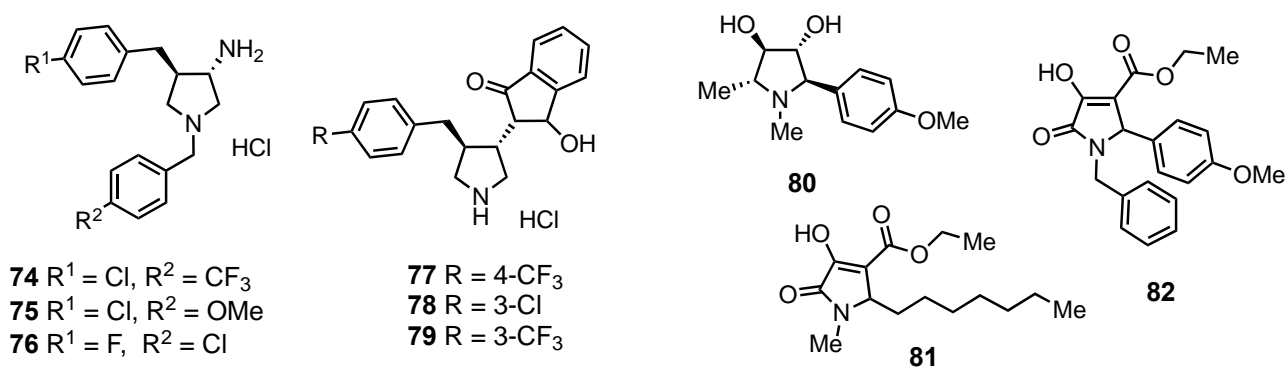
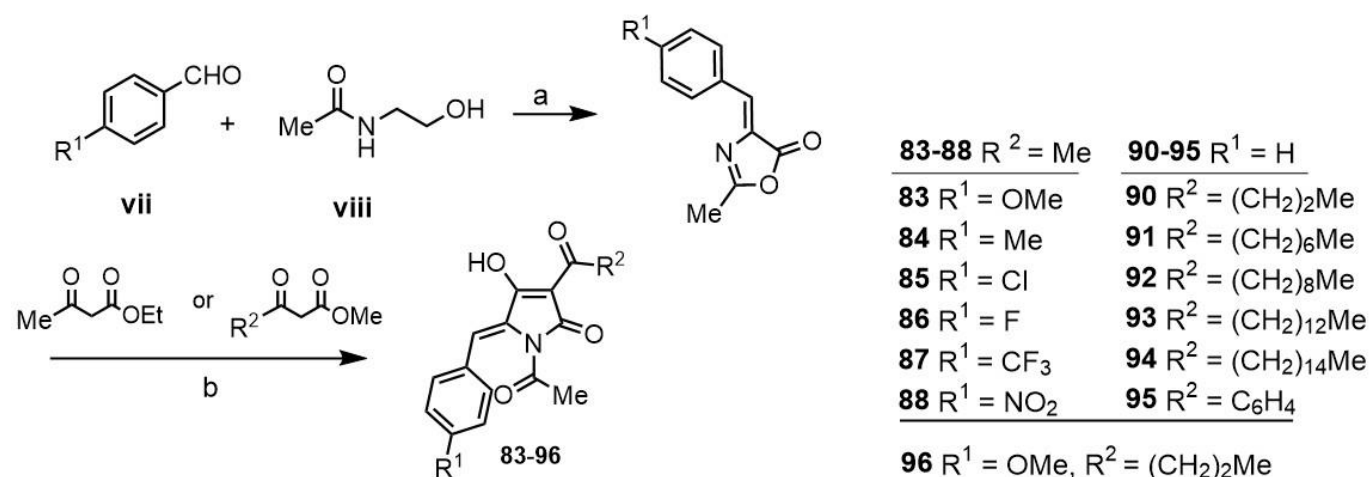


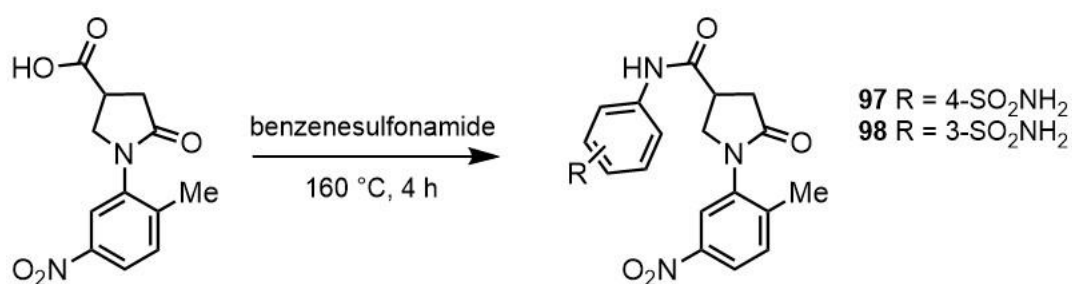
Figure 10. Structures of 3,4-disubstituted pyrrolidine analogues **74-82**

In another study,⁵² the synthesis and antibacterial activity of tetramic acids against MRSA was reported. The tetramic acid was synthesized *via* the condensation of aromatic aldehyde **vii** and *N*-acetylglycine **viii**, followed by a one-pot two-component reaction (Scheme 7). The tetramic acid **83-96** with a lipophilic acyl group at C-3 position, displayed a moderate to high activity against MRSA with MIC values of 4-32 $\mu\text{g/mL}$. Compounds **90-93** showed excellent anti-MRSA activity with a MIC value of 4 $\mu\text{g/mL}$. SAR studies revealed that compounds with 8 to 16 carbon-chained acyl groups at the C-3 position of the ring demonstrated good activities compared to those containing fewer lipophilic groups. The *para*-position substituent of the benzyl ring at the C-5 position of tetramic acid showed little or no effect on the activity.⁵²



Scheme 7. Synthesis of tetramic acids **83-96**. Reagents and conditions: (a) acetic anhydride, MeCO_2Na , 1 h, reflux; (b) NaH , dry THF, 0 °C to rt, 10% HCl

1,3-Disubstituted pyrrolidinone derivatives **97** and **98** with sulfanilamides moiety also showed potent antibacterial activity against *P. aeruginosa*, *Listeria monocytogenes*, *E. coli*, and *S. aureus* with MIC and MBC values of 7.8-31.25 $\mu\text{g/mL}$ (Scheme 8). Compound **98** with the sulfamoyl group at the C-3 position of a phenyl ring showed higher activity than compound **97** with the sulfamoyl group at the C-4 position. Compound **98** displayed an exceptional antibacterial activity against *P. aeruginosa* with MIC and MBC values of 7.8 $\mu\text{g/mL}$ eight times higher than the positive control, oxytetracycline (62.5 $\mu\text{g/mL}$). Also, compound **98** showed excellent activity against *E. coli* and *L. monocytogenes* with MIC and MBC values of 15.6 $\mu\text{g/mL}$.⁵³



Scheme 8. Synthesis of 1,3-disubstituted pyrrolidinone derivatives **97** and **98**

2-4. Antiviral

A recent publication reported the discovery of camphene-containing *N*-heterocycle derivatives with *in vitro* antiviral activity against a panel of enveloped pathogenic viruses, i.e., Ebola virus (EboV), influenza virus A/PR/8/34 (H1N1), and Hantavirus.⁵⁴ Among the derivatives, the camphene-based pyrrolidine **99** displayed potent antiviral activity against EboV (IC_{50} 18.3 μM), Ebola pseudo-type virus (EboV-GP; IC_{50} 0.12 μM), H1N1 (IC_{50} 45.3 μM), and pseudoviruses with Gn-Gc glycoprotein of Hantavirus (IC_{50} 9.1 μM) (Figure

11). Based on a molecular modelling study,⁵⁴ the surface proteins of the viruses were essential for the fusion between viral and cellular membranes, and these proteins were deemed the potential target of derivatives. The nitrogen atom and bicyclic natural framework were the key species responsible for the effective binding to the hydrophobic part of the binding site of the surface proteins.⁵⁴

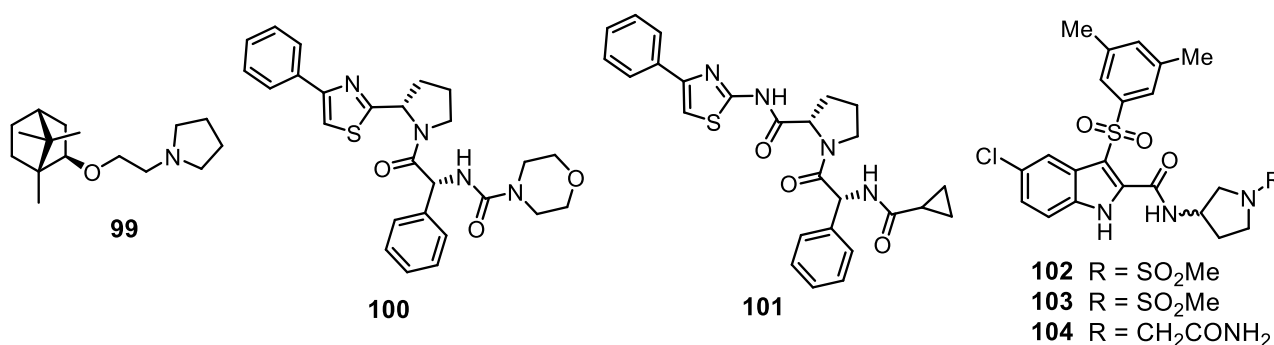


Figure 11. Structures of *N*-substituted pyrrolidine derivatives **99-104**

Based on the scaffold of 4-phenylthiazole **100**, i.e., a modest hepatitis C virus (HCV) inhibitor (EC₅₀ 9440 nM), a highly potent and selective HCV NS5A inhibitor was discovered.⁵⁵ Introducing an amide group between pyrrolidine and thiazole ring led to the discovery of compound **101** with excellent inhibition against HCV NS5A (EC₅₀ 4.6 nM) and greater therapeutic index (CC₅₀/EC₅₀ > 10000). Besides, compound **101** showed good pharmacokinetic properties and superior oral bioavailability of 45% based on the oral administration in rats.

It was also revealed that, indolylarylsulfones (IASs) with chiral *N*-substituted pyrrolidine at indole-2-carboxamide exhibited potent activity against the wild-type HIV-1 with an EC₅₀ value of 4.7 nM for compound **102** and 4.3 nM for compound **103** which were more active than the control drugs efavirenz, lamivudine, and nevirapine, and were as potent as etravirine. Besides, compound **104** showed prominent activity against various single-HIV-1 mutants, such as L100I, E138K, and K103 N, as well as one double-mutant F227L/V106A with EC₅₀ values of 11.0, 14.0, 25.0, and 95.0 nM, respectively. Interestingly, compound **104** showed no acute toxicity at a dose of 1000 mg/kg and also no subacute toxicity at a dose of 50 mg/kg in healthy mice.⁵⁶

2-5. Antifungal

Pyrrolidine scaffold is a crucial fragment in antifungal drugs. Examples of synthesized antifungal drugs bearing pyrrolidine rings in their skeleton include micafungin, anidulafungin, and caspofungin. These drugs belong to the antifungal class of compounds known as echinocandins, and they inhibit the synthesis of 1,3-β-D-glucan synthase, an essential enzyme of the fungal wall synthesis.^{57,58} Micafungin, anidulafungin, and

casposfungin were similar in their cyclic hexapeptide antibiotics linked to long modified *N*-linked acyl fatty acid chains. The chains act as anchors on the fungal cell membrane to facilitate antifungal activity.⁵⁹ In the search of antifungal drug candidate, Shi *et al.*⁶⁰ reported on the isolation of 63 amide alkaloids from the aerial parts of *Piper flaviflorum* and *Piper sarmentosum* and they found that three amides **105-107** bearing pyrrolidine ring have potential in the antifungal assay against *Cryptococcus neoformans* with IC₅₀ values of 7.1, 10.4 and 15.9 μg/mL, respectively (Figure 12). With regard to the structure of **106**, α,β-unsaturated amide moiety and unsaturated aliphatic chain seem to be essential, while 3,4-methylenedioxyphenyl and phenyl groups are not the key factors for the antifungal activity. Meanwhile, Badampudi *et al.*⁶¹ studied the antifungal activity of 3,4-disubstituted pyrrolidine-sulfonamides against *Aspergillus flavus* and *Candida albicans* and found that compounds **108-110** exhibit privileged activity among the tested compounds. The moderate activity of 1,3,4-oxadiazole possessing pyrrolidine-3,4-diylsulfonamide derivative **111** bearing thiazolidin-4-one moiety showed that 1,3,4-oxadiazole does not have a significant effect on the activity. A different result was observed from a series of polysubstituted methyl 5,5-diphenyl-1-(thiazol-2-yl)pyrrolidine-2-carboxylate derivatives, where compounds **112** and **72** exhibited the best antifungal activity, but did not perform better than the reference drug fluconazole.⁴⁹

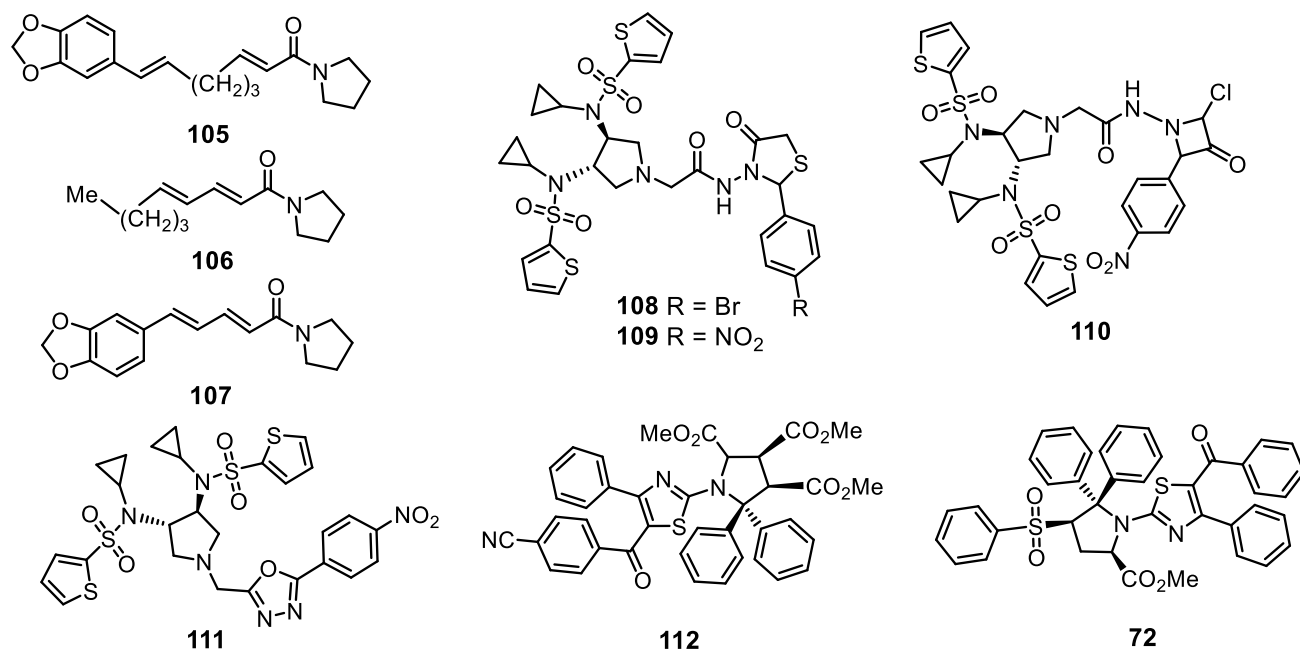


Figure 12. Structures of pyrrolidine derivatives isolated from nature **105-112**

On the basis of antifungal potential tetrazole derivatives, Łukowska-Chojnacka *et al.*⁶² synthesized a series of tetrazole derivatives bearing pyrrolidine moiety and tested their antifungal activity against *C. albicans*. The result showed that compound **115** exhibited the highest biofilm inhibitory activity with an IC₅₀ value

of 10.37 μM , followed by **113** (IC_{50} 23.90 μM), **114** (IC_{50} 46.05 μM), and **116** (IC_{50} 79.54 μM). The result also discovered that incorporation of 1-(3-chloropropyl)-5-aryl-2*H*-tetrazoles into methylated **114** or fluorinated **115** 2-arylpyrrolidines enhanced the anti-*Candida* biofilm effect *in vitro* and *in vivo*. A similar approach have been used by Sheikhi-Mohammareh *et al.*⁶³ on designing a series of antifungal selenium-containing heterocycles, 7-imino[1,3]selenazolo[4,5-*d*]pyrimidine-5(4*H*)-thiones containing pyrrolidine scaffold. From that series, *para*-bromo (**118**, MFC 0.32 mM) and fluoro (**117**, MFC 1.12 mM) substituted *N*-phenylselenazolo[4,5-*d*]pyrimidines bearing pyrrolidine ring displayed higher potency for death and blocking of *C. albicans* fungus than ketoconazole drug (MFC 1.92 mM), respectively. Another study reported that quinoline-naphthyl-based chalcones bearing pyrrolidine scaffold **119-122** displayed strong activity against two fungal strains *A. flavus* and *C. metapsilosis* at concentrations 25-100 $\mu\text{g/mL}$.⁶⁴ The result also revealed that the hydroxyl group at naphthyl moiety **119** and **121** is important in the antifungal activity besides the naphthyl scaffold itself. The importance of naphthyl in combination with the pyrrolidine ring has also been stated by Alsarahni *et al.*,⁶⁵ in which the derivatives of 7-methoxy-2-naphthol **123** bearing pyrrolidine moiety showed the highest antifungal activity with MIC of 62.5 $\mu\text{g/mL}$. Furthermore, Tret'yakova *et al.*⁶⁶ reported on the antifungal activity of abietic acid derivatives bearing pyrrolidine scaffold against *C. albicans*, *C. neoformans var. grubii*, and found that 7-formylabietic derivatives **124** and **125** were the most potent compounds with MIC of 8.0 and 4.0 $\mu\text{g/mL}$ against *C. albicans* and *C. neoformans*, respectively. While Mohini *et al.*⁶⁷ discovered that ricinoleic acid-based lipoamino acid derivative **126** exhibited excellent antifungal activity against studied fungal strains.

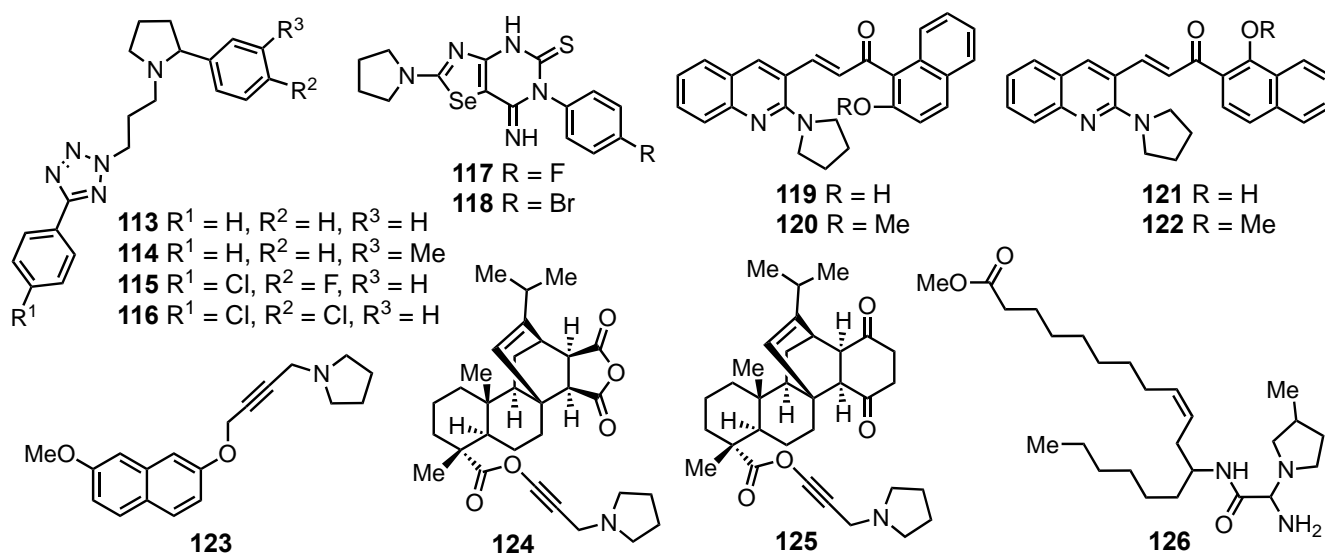


Figure 13. Structures of tetrazoles **113-116**, selenium-containing heterocycles **117-118**, quinoline-naphthyl-based chalcones **119-122**, 7-methoxy-2-naphthol **123**, 7-formylabietic derivatives **124-125**, and ricinoleic acid-based lipoamino acid **126** derivatives bearing pyrrolidine scaffold

Considering the importance of L-pyrroglutamic acid structure (pyrrolidin-2-one), and hydrazine or acylhydrazone functionalities in the antimicrobial activity, a series of 5-pyrrolidin-2-ones functionalized by hydrazine or acyl hydrazone groups and evaluated their antifungal activity.⁶⁸ From the study, compounds **127** and **128** which functionalized by hydrazine displayed a broad-spectrum antifungal activity (Figure 14). Replacing the hydrazine group **128** and **129** with an acylhydrazone group narrowed the spectrum of activity, but these derivatives exhibited good activity, adequate “fungicide-like” properties and were devoided of cytotoxicity. Furthermore, Zhang *et al.*⁶⁹ studied the antifungal activity of tetramic acid (2,4-pyrrolidinedione), a class of compound that exhibited various biological activities such as antibacterial, antiviral, antifungal, and anticancer.⁷⁰ In their study, a series of 2,4-pyrrolidinedione derivatives have been synthesized, and found that compounds **132** and **133** showed stronger activity against *Rhizoctonia cerealis* (EC₅₀ 1.63 and 2.04 µg/mL, respectively), followed by compounds **133-138** which showed the EC₅₀ values in the range of 2.6-5.8 µg/mL. Besides that, Hu *et al.*⁷¹ also reported that pyrrolidine-2,4-dione derivatives **139-148** containing the pharmacophores of both hydrazine and diphenyl ether showed strong antifungal activity against *R. solani*, *Botrytis cinerea*, and *Fusarium graminearum*. Strikingly, compound **139** obviously inhibited the growth of *R. solani in vitro* with an EC₅₀ value of 0.39 µg/mL, which was better than the commercialized fungicide boscalid (2.21 µg/mL). Based on the 3D-QSAR analysis, Hu *et al.*⁷¹ explained that introducing hydrophobic 4-fluorobenzene, 4-chlorobenzene, or 4-bromobenzene fragments at the diphenyl ether position could considerably increase the antifungal activity. However, the strong antifungal activity was not shown on the isolated pyrrolidine-2,4-dione derivatives **149** and **150** from *Aspergillus restrictus*, where both compounds showed only weak antifungal activity.⁷²

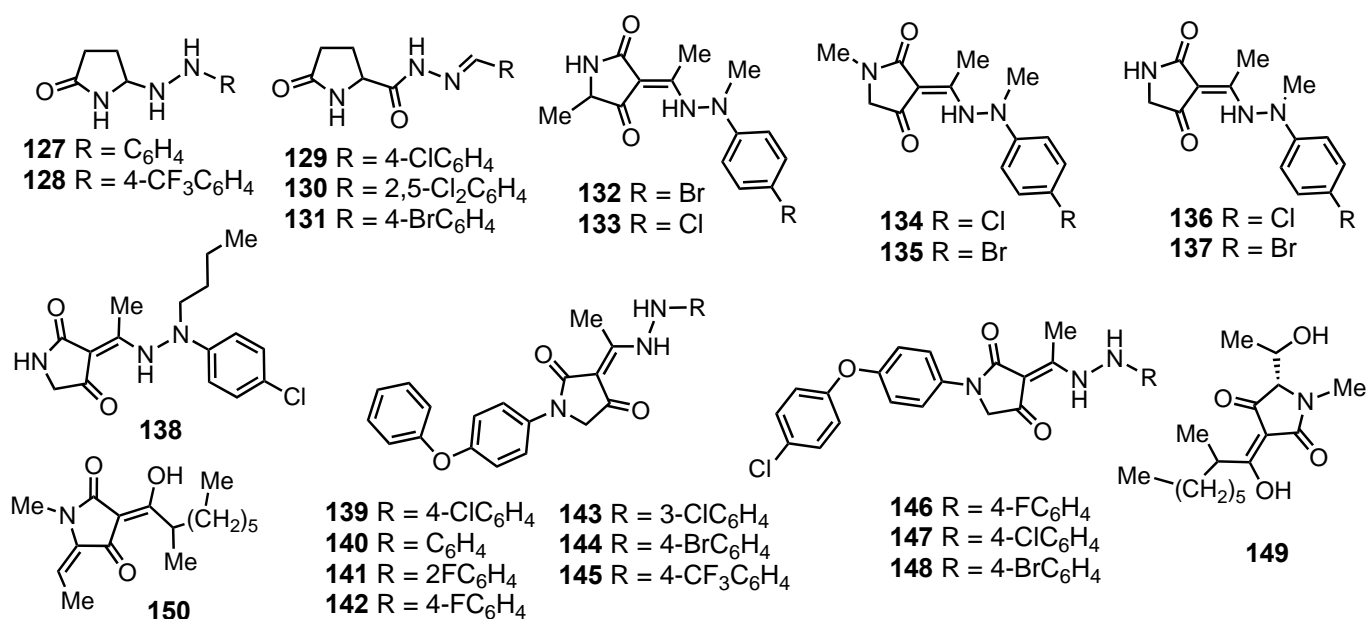


Figure 14. Structures of 2-pyrrolidinone derivatives and 2,4-pyrrolidinedione derivatives

In other reports, Dhavan *et al.*⁷³ had focused on the antifungal activity of 2,3-pyrrolidinedione derivatives as these structure of feature in this study has been considerably less investigated. Dhavan *et al.*⁷³ successfully established synthesis routes to the substituted 2,3-pyrrolidinedione core that allowed the introduction of a wide range of skeleton diversity. In their work, they found that almost all synthesized compounds showed fungicidal activity and, specifically derivatives **151-153** exhibited a concentration-dependent activity on *C. albicans* biofilm (Figure 15). On the other hand, Obydenov *et al.*⁷⁴ had designed fungicidal compounds to fight potato diseases based on the structural framework of 2,4,5-pyrrolidinetrione. Obydenov *et al.*⁷⁴ synthesized a series of 2-(2,4,5-trioxopyrrolidin-3-ylidene)-4-oxo-1,3-thiazolidin-5-ylideneacetate derivatives **154-159** with 1,3-thiazolidin-4-one and pyrrolidine-2,3,5-trione moieties linked by an exocyclic double bond. The *in vitro* antifungal assay demonstrated that all synthesized compounds were found to be active against five potato pathogens; *Phytophthora infestans*, *Fusarium solani*, *Alternaria solani*, *Rhizoctonia solani*, and *Colletotrichum coccodes*. The result also showed that compound **156** with a benzyl group attached to 2,4,5-trioxopyrrolidine ring (EC₅₀ values in the range of 0.052–0.445 mg/mL) was better in comparison with the positive control, consento. Therefore, it can be suggested that the structure of the *N*-substituent at 2,4,5-pyrrolidinetrione core was essential for antifungal activity.

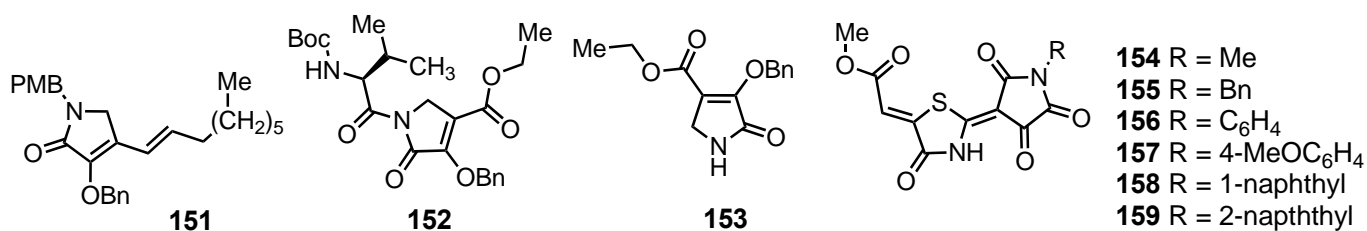
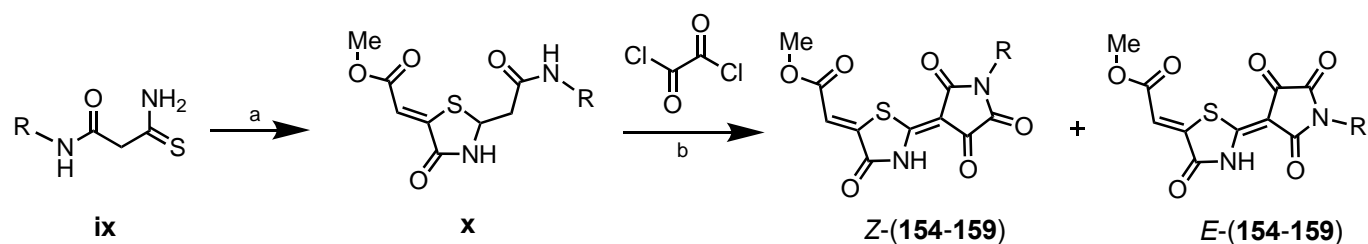


Figure 15. Structures of 2,3-pyrrolidinedione derivatives **151-159**

In the preparation of 2,4,5-pyrrolidinetrione core structures **154-159**, Obydenov *et al.*⁷⁴ followed a straightforward synthetic protocol using enamides and oxalyl chloride as starting materials. In their route, Obydenov *et al.*⁷⁴ used the 2-methylidene-1,3-thiazolidin-4-one derivatives **x** as the intermediates to the targeting compounds **154-159**. The synthesis began with the reaction of thioamides **ix** with acetylenedicarboxylate to give intermediates **x** in 45-80% yield as a mixture of *E* and *Z* **154-159**. The reaction continues with the condensation of intermediates **x** and oxalyl chloride to effort targeting products **154-159** in 57–87% yield (Scheme 9).



154 R = Me; **155** R = Bn; **156** R = C₆H₄; **157** R = 4-MeOC₆H₄; **158** R = 1-naphthyl; **159** R = 2-naphthyl

Scheme 9. Synthesis of targeted 2,3,5-pyrrolidinetrione **154-159**. Reagents and conditions: (a) dimethyl acetylenedicarboxylate, EtOH, 2 h, rt; (b) MeCN, 4 h, 70 °C

2-6. Antimalaria

Malaria has killed hundreds of thousands people every year.⁷⁵ The emergence of new *Plasmodium* drug-resistant strains necessitates the development of new medicines with novel chemotypes and modes of action. Recently, Frydrych *et al.*⁷⁶ employed commercially available D- and L-prolinol were used as the starting materials to synthesize nucleotide analogues with a pyrrolidine ring and incorporated with a linker connecting the purine base to a phosphonate group. All synthesized compounds were evaluated for their inhibitory activity against plasmodial hypoxanthine-guanine-(xanthine)-phosphoribosyltransferase from *Plasmodium vivax* (HGPR), *P. falciparum* (HGXPRT), and human (HGPR). However, the inhibitory assays did not improve the activity of compounds **168** and **169**, even though increasing flexibility was achieved by implementing a CH₂ group between the nucleobase and the pyrrolidine ring for a free rotation (Figure 16). However, the phosphoramidates **161**, **163**, **164**, and **165** showed strong antimalarial efficacy in an experiment of *P. falciparum*-infected human erythrocytes. At the dose of 100 μM, the bisphosphoramidate **164** was effective (IC₅₀ 2.5 μM) against the chloroquine-resistant *P. falciparum* (W2

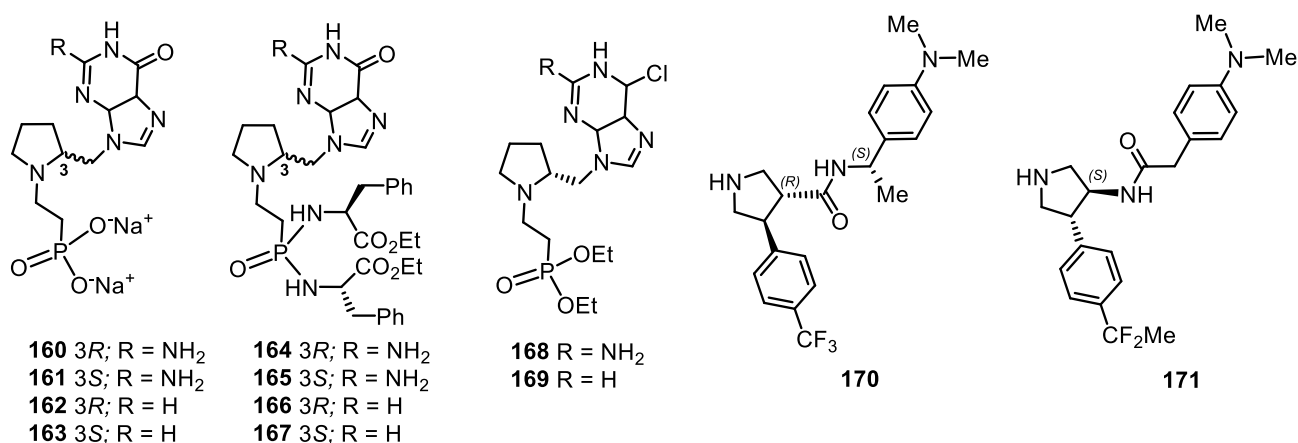


Figure 16. Structures of pyrrolidine nucleotide analogues **160-169**, and pyrrolidine carboxamides derivatives **170** and **172**

strain), with minimal cytotoxicity on human hepatocellular liver cancer (HepG2) and normal human dermal fibroblasts (NHDF) cell lines.

In 2019, Meyers *et al.*¹⁴ used a hybrid target-phenotype antimalarial (GNF-Pf-4691) as the target to identify and evaluate the antimalarial activity of 4-aryl-*N*-benzylpyrrolidine-3-carboxamides (Figure 16). From the series of compounds tested, compound **170** showed the most potent with EC₅₀ values of 46 and 21 nM against drug-sensitive *P. falciparum* 3D7 and drug-resistant Dd2 strains, respectively. The SAR study showed that dimethylaniline on the carboxamide aryl ring was the best functional group. On the pyrrolidine aryl ring, *p*-CF₃ would be replaced with small lipophilic moieties, such as *t*-butyl, CHF₂, and CF₂Me, while the substitution of phenyl at pyrrolidine ring itself with heterocycles, such as pyridine, pyrimidine, benzofuran, and thiophene, were also tolerated. Addition of a halogen at the *meta*-position was beneficial, while the (3*R*,4*S*)-configuration of pyrrolidine ring and (*S*)-Me orientation in the benzyl-carboxamide was preferred. In a further SAR study to prove the influence of the (3*R*,4*S*) and (*S*)-Me configurations on the activity, Meyers *et al.*⁷⁷ used a series of reverse amide homologue 2-aryl-*N*-(4-arylpyrrolidin-3-yl)acetamides which do not require a third chiral center at benzyl-acetamide position and the (3*S*,4*R*)-configuration is opposite to 4-aryl-*N*-benzylpyrrolidine-3-carboxamides series. In this series, compound **171** has an *in vitro* IC₅₀ of 51 nM in the *P. falciparum* 3D7 assay and an *in vivo* ED₉₀ < 10 mg/kg/day and an ED₉₉ < 30 mg/kg/day in a murine *P. chabaudi* model. SAR study revealed that antimalarial activity of **171** is remarkable since the preferred (3*S*,4*R*)-configuration of acetamide **171** is opposite from the (+)-(3*R*,4*S*)-configuration of carboxamides **170**. However, optimization for 4-aryl-*N*-benzylpyrrolidine-3-carboxamides and 2-aryl-*N*-(4-arylpyrrolidin-3-yl)acetamides series are needed because these series have modest affinities for the hERG channel and inhibit CYP 3A4.

2-7. Antioxidant

Antioxidants are molecules that inhibit or delay oxidation reactions from producing free radicals and the chain reactions that may damage the cells. Numerous studies on the antioxidant activity of pyrrolidine alkaloids have been published. One of the alkaloids is pyrrolidine dithiocarbamate (PDTC), which is a potent antioxidant and inhibitor of nuclear factor kappa-B (NF-κB). Also, PDTC showed an antioxidant effect in rat models of isoniazid/rifampicin-induced liver injury,⁷⁸ immunological liver injury,⁷⁹ liver failure,⁸⁰ liver cirrhosis,⁸¹ and hypoxia–ischemia (HI) brain injury.⁸² In another study, PDTC created a contraction-relaxation response in rat bladder smooth muscle *via* α-adrenergic receptors and non-adrenergic non-cholinergic (NANK) system.⁸³

A recently published study indicated that 4-(pyrrolidine-2,5-dion-1-yl)phenol **56**, exhibited high 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical scavenging activity (IC₅₀ 36.9 μM) compared to the standard ascorbic acid (IC₅₀ 60.5 μM) (Scheme 3).⁴⁴ Also, a series of pyrrolidin-2-one derivatives **172–184**

showed potent to moderate DPPH free radical scavenging activity with IC_{50} values of 22–98 $\mu\text{g/mL}$ compared to the standard gallic acid (IC_{50} 18 $\mu\text{g/mL}$) (Figure 17). Different substituents of a compound might vary the scavenging ability. Antioxidants scavenge DPPH radicals by hydrogen donation, resulting in a reduction of DPPH absorbance. Moreover, the compounds with hydroxyl or amino substituents show high radical scavenging activity. Among the tested compounds, compounds **172**, **175**, **178**, **179**, **180**, **183**, and **184** showed significant antioxidant activity with the lowest IC_{50} values of 43, 43, 23, 22, 28, and 24 $\mu\text{g/mL}$, respectively. Compounds **173**, **174**, **175**, **177**, **181**, and **182** showed moderate antioxidant activity with IC_{50} values of 82, 78, 78, 69, 93, and 98 $\mu\text{g/mL}$, respectively.⁸⁴

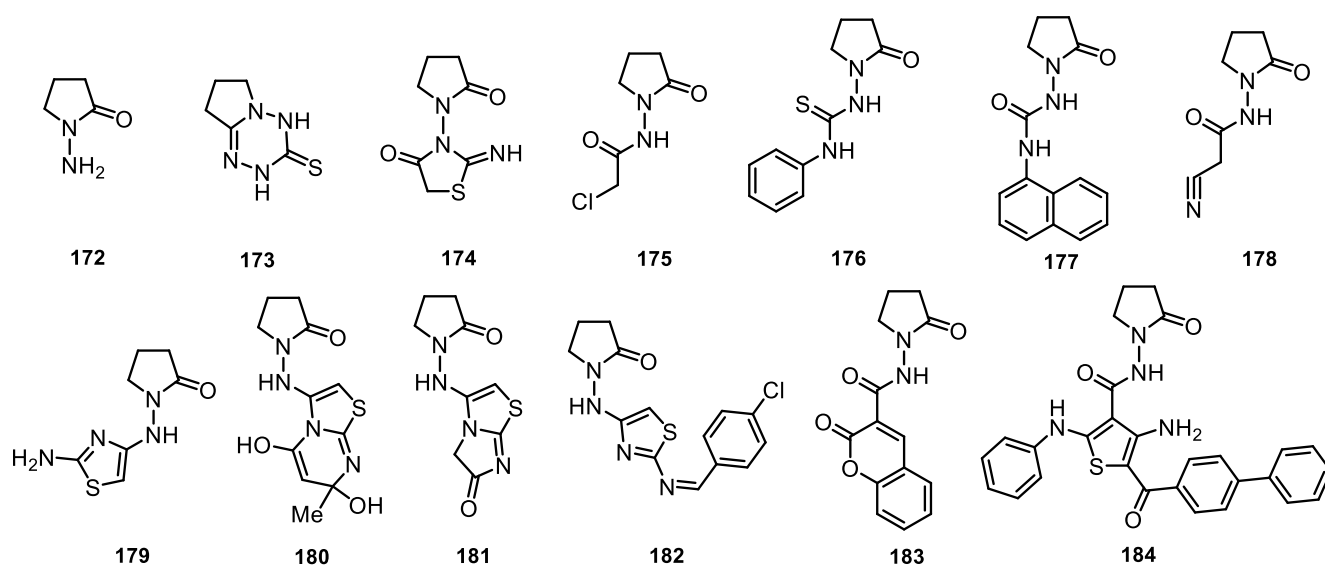
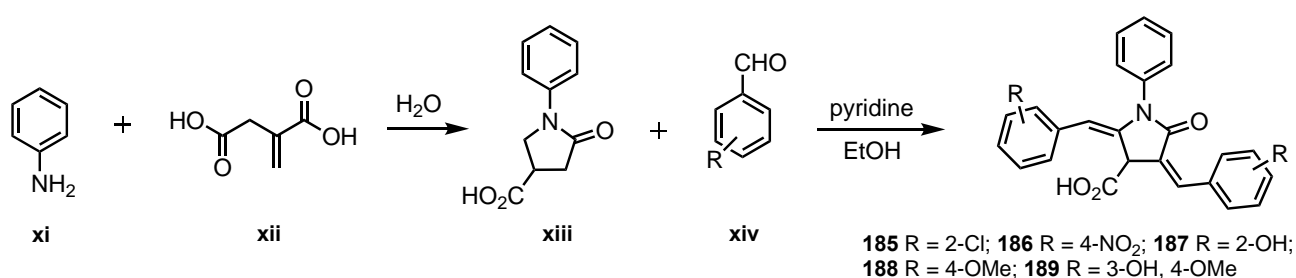


Figure 17. Structures of pyrrolidin-2-one derivatives **172–184**

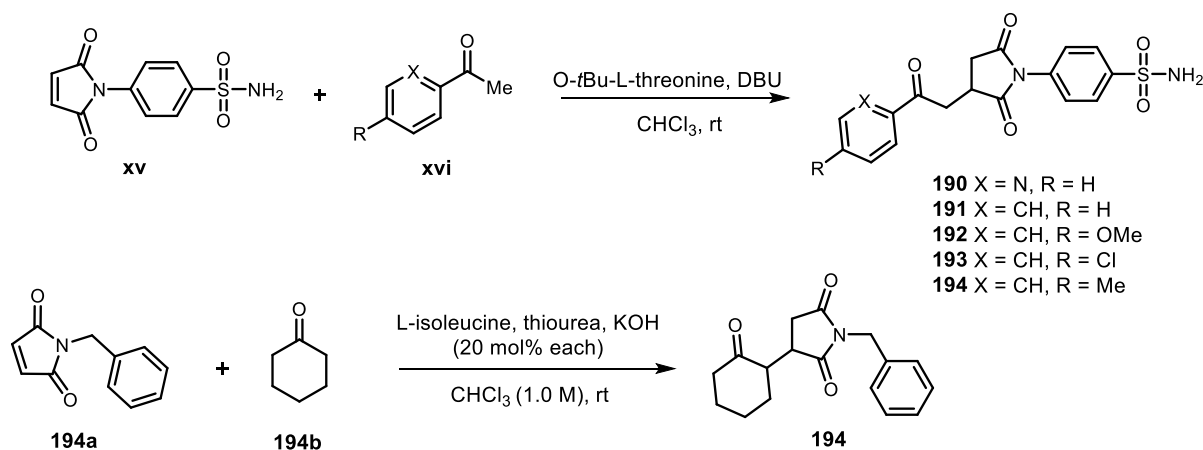
Besides, antioxidant activity was also observed for 5-oxo-1-phenylpyrrolidine-3-carboxylic acid derivatives **185–189** by using potassium ferri-cyanide reducing power assay (PFRAP) method. New pyrrolidine derivatives **185–189** were prepared by reacting 1-phenylpyrrolidine-3-carboxylic acid **xiii** with different aromatic aldehydes **xiv** in the presence of pyridine as a base. Compounds with 2-chloro **185**, 4-nitro **186**, 2-hydroxy **187**, 4-methoxy **188**, and 3-hydroxy and 4-methoxy **189** on the phenyl rings showed positive antioxidant activity (Scheme 10).⁸⁵



Scheme 10. Synthesis of 5-oxo-1-phenylpyrrolidine-3-carboxylic acid derivatives **185–189**

2-8. Anti-inflammatory

Inflammation is a body's natural defense to injury, infection, and disease.⁸⁶ This process involves the release of various substances, known as inflammatory mediators such as hormones bradykinin and histamine.⁸⁷ However, inflammations do not always help the body. In some diseases, the immune system fights against the body's cells, causing harmful inflammations, such as rheumatoid arthritis, atherosclerosis, periodontitis, and hay fever.⁸⁸ Therefore, anti-inflammatory substances are needed to relieve pain, reduce inflammation, and bring down a high temperature which are caused by inflammation mechanism. Numerous studies investigating the anti-inflammatory activity of pyrrolidine scaffolds are published. Jan *et al.*⁸⁹ described that pyrrolidine-2,5-dione derivatives **190-194** with cycloalkyl, alkyl, and aryl substituents at C-3 position exert anti-inflammatory activity by using different *in-vitro* assays, such as cyclooxygenase-1 (COX-1), cyclooxygenase-2 (COX-2), and 5-lipoxygenase (5-LOX), albumin denaturation and anti-protease assays. Compounds **190-194** were synthesized *via* Michael addition reaction of *N*-substituted maleimide and ketones at room temperature in chloroform as outlined in Scheme 11. Among the synthesized compounds, *N*-benzenesulfonamide derivatives **190-194** with aryl ketone at C-3 position exhibited good inhibition in low micromolar to sub micromolar ranges.⁸⁹ These compounds also demonstrated selectivity towards COX-2, particularly derivative **193** where the compound demonstrated IC₅₀ value of 0.98 μ M and selectivity index (SI) of 31.5. *N*-benzyl derivative **194** with cyclic ketone at C-3 position also showed COX-2 selectivity with IC₅₀ value of 19.98 μ M and SI of 3.13. Compounds **193** and **191** were further testing for in-vivo anti-inflammatory activity by carrageenan induced paw edema method, which is COX-2 dependent method of inflammation. In preliminary screening, compound **193** showed excellent activity (55.17-68.22%) at highest dose 100 mg/kg as compared to standard drug aspirin (47.54-57.64%). Compound **191** displayed comparable activity than that of positive control with 44.68-55.07%



Scheme 11. The synthesis of pyrrolidine-2,5-dione derivatives **190-194**

inhibition of inflammation. The finding described that substitution of cyclic and alkyl ketone at C-3 position of pyrrolidine-2,5-dione gave poor to moderate inhibition as compared to aryl ketone substitution. Besides, the substitution of bulkier cycloalkyl ketone at C-3 position of pyrrolidine-2,5-dione improve the COX-2 selectivity.

In another study, Gerokonstantis *et al.*,⁹⁰ synthesized derivatives of pyroglutamic acid that possess interesting *in-vitro* inhibitory activity against autotaxin (ATX). ATX is a glycoprotein that hydrolyze lysophosphatidylcholine (LPC) to the bioactive lipid lysophosphatidic acid (LPA), which is unregulated in different pathological inflammatory situations such as cancer, fibrosis, thrombosis, and liver toxicity. Compounds **195-197** with acidic 4,4,5,5-tetramethyl-1,2,3-dioxaborolane moiety and boronic acid **198** exhibited excellent ATX inhibition at nanomolar level with IC_{50} values of 50, 120, 180, and 35 nM, respectively (Figure 18). Based on Lipinski's rules, compound **198** had favorable physicochemical properties with ClogP 3.48 (<5) and molecular weight 458.32 (<500) as compared to other compounds. Interestingly, molecular docking studies showed that compound **198** had similar binding energy as the known ATX-inhibitor, HA155.

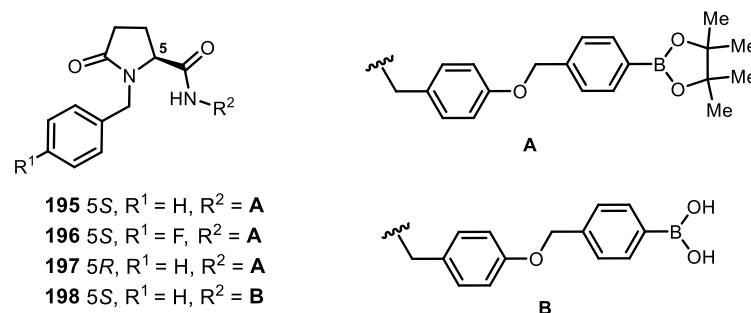


Figure 18. Structures of pyrrolidine pyroglutamic acid derivatives **195-198**

In the study conducted by Zhou *et al.*⁹¹ a new series of pyrrolidine amide derivatives was developed as NAAA inhibitors. These compounds were synthesized based on modification of **199** and **200** which are the effective NAAA inhibitors with IC_{50} values of 12.8 and 2.1 μ M, respectively (Figure 19). Replacing the phenyl group at **199** and **200** with the cyclohexyl group led to a progressive increase in NAAA inhibition, as shown in **201** (IC_{50} 0.5 μ M) and **202** (IC_{50} 0.7 μ M). Besides, the replacement of conformationally restricted linker at **197** with more flexible linkers may significantly affect their inhibitor potency to NAAA. Compound **203** (IC_{50} 0.48 μ M) was 4-fold more potent inhibition compared to **200**. Compound **204** (IC_{50} 1.5 μ M), with a 4-phenylcinnamoyl group, was comparable to **200** in inhibition.

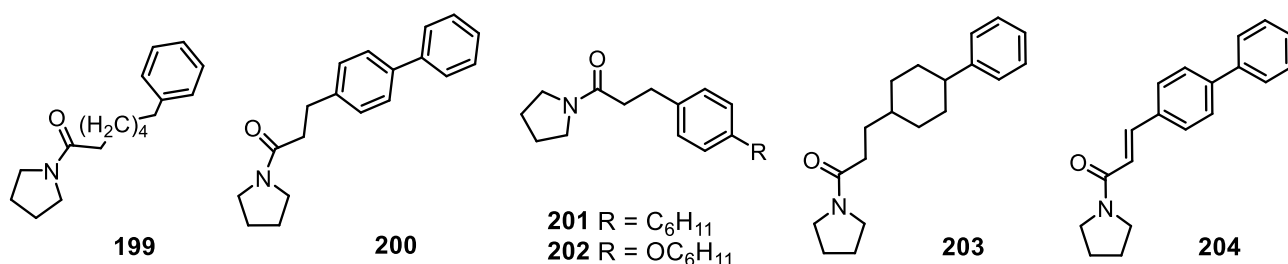


Figure 19. Structures of pyrrolidine amide derivatives **199-204**

Recently, Abdel-Aziz *et al.*⁹² successfully identified cyclic imides derivatives bearing 3-benzenesulfonamide **205-208** and oxime **209-212** as the remarkable anti-inflammatory agents with 71.2-82.9% oedema inhibition as compared to the standard drugs, diclofenac, and celecoxib (83.4 and 85.6% oedema inhibition) (Figure 20). Also, the compounds **205-212** also showed comparable COX-2 inhibition (IC₅₀ 0.26, 0.20, 0.18, 0.15, 0.22, 0.16, 0.16, and 0.15 μ M, respectively) as standard drug celecoxib (IC₅₀ 0.129 μ M).

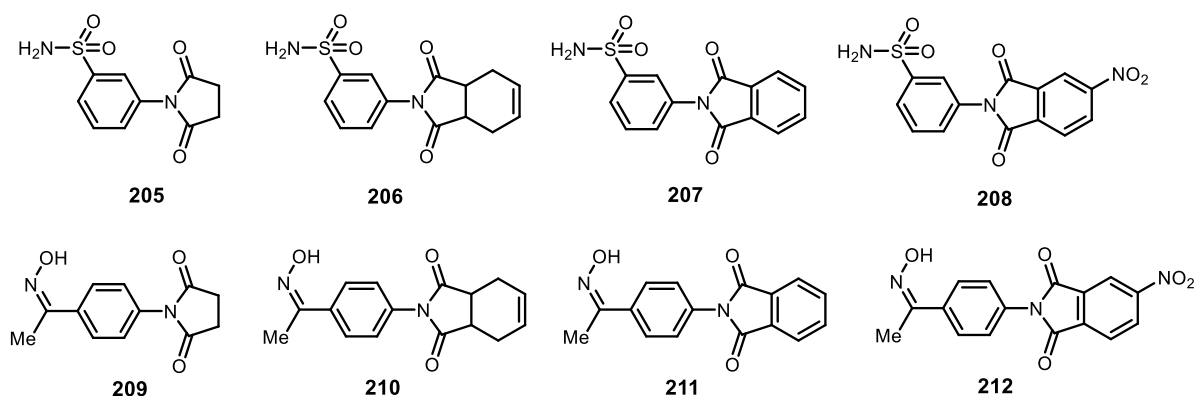


Figure 20. Structures of pyrrolidine imide derivatives **205-212**

2-9. Anti-neurodegenerative

The etiology of neurodegeneration is complex and involves a plethora of factors. These factors include a reduced level of acetylcholine (AChE), the formation of extracellular aggregates of amyloid- β , accumulation of α -synuclein, mutations in the glucocerebrosidase gene (GBA1), and an overproduction of free radicals and reactive oxygen species resulting from oxidative stress.⁹³ All these neurological pathologies will lead to Alzheimer's, Parkinson's, Gaucher, Huntington, ataxia, motor neuron diseases, dementia, and many more.⁹⁴ Only a few naturally derived pyrrolidine alkaloids exhibit anti-neurodegenerative properties by inhibiting AChE, oxidative stress enzymes, excitotoxicity, apoptosis, A β

accumulation, and tau phosphorylation.⁹⁵ Consequently, synthetic pyrrolidines are crucial in the new development pathologies in treating neurodegenerative diseases.

Within that context, Leiva *et al.*⁹⁶ successfully reported the synthesis of novel pyrrolidine-based 11 β -HSD1 inhibitors as a non-cholinergic mechanism to deal with neurodegenerative cognitive disorders, particularly Alzheimer's diseases. In general, mammals with cognitive deficits show increased expression of 11 β -HSD1 in the hippocampus and forebrain, and overexpression of 11 β -HSD1 leads to premature memory decline. Using potent inhibitor 11 β -HSD1 of PF-877413 (adamantly pyrrolidine amide) (IC₅₀ 4 nM) as the base compound,⁹⁷ this study⁹⁶ constructed different arrays of polycyclic pyrrolidines **213-223** with excellent IC₅₀ ranging from 0.02-0.03 μ M (Figure 21). It was observed, pyrrolidine-based polycyclic amides **213-219** with smaller polycyclic rings were more potent than other derivatives **220-223** in inhibiting the neurodegenerative symptoms. It was reasoned that smaller hexacyclic substituent might reach the upper-limit size to fill the hydrophobic pocket of the binding site of the Ser170 enzymes during the inhibition. Nonetheless, the trend in terms of the bioactivity between the alkene and alkane pairs **214-223** containing the same polycyclic ring system remained unknown.

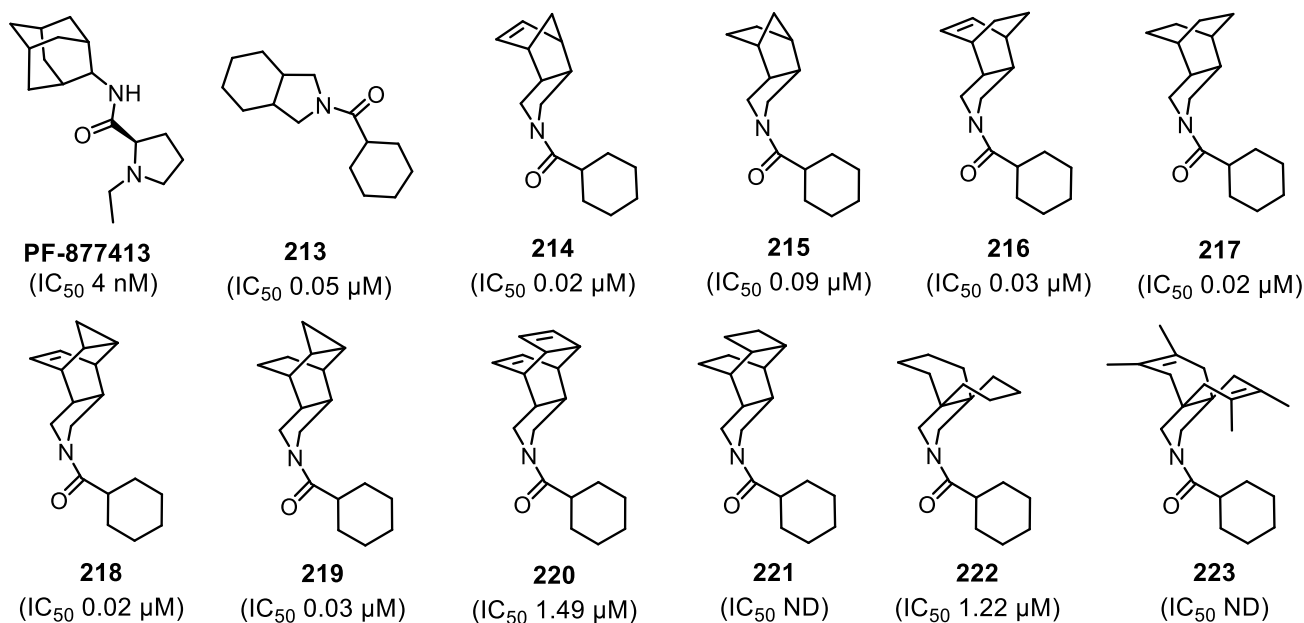


Figure 21. Structures of polycyclic pyrrolidine derivatives **213-223**

In a different strategy of multifunctional hybrid compounds derived from 2-(2,5-dioxopyrrolidin-1-yl)-3-methoxypropanamides, Abram *et al.*¹³ successfully integrated the active-pyrrolidine scaffold with well-known commercial antiepileptic drugs, such as ethosuximide, levetiracetam, and lacosamide. The hybrids **224-233** were effective on two of the most widely used animal seizure models, namely, the maximal

electroshock (MES) test and the psychomotor 6 Hz (32 mA) seizure models, indicating their versatility as broad-spectrum anticonvulsant and antinociceptive agents (Figure 22). Interestingly, compound **231** with tri-fluorinated moiety showed the highest protection (ED_{50} MES 79.5 mg/kg; ED_{50} 6 Hz 22.4 mg/kg at the time point of 0.25 h). To note, racemic of **231** was also capable in decreasing the pain responses in formalin-induced pain, capsaicin-induced pain, and OXPT-induced neuropathic pain in mice.

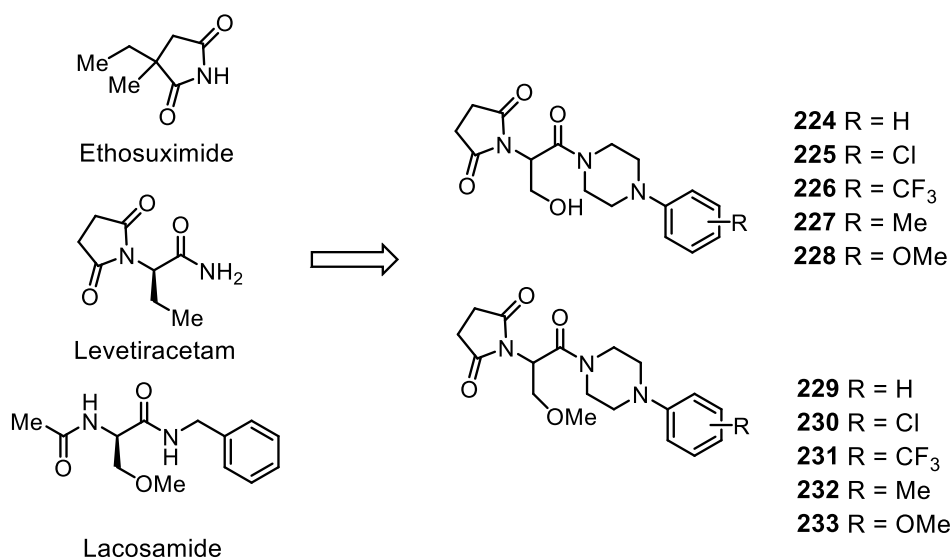
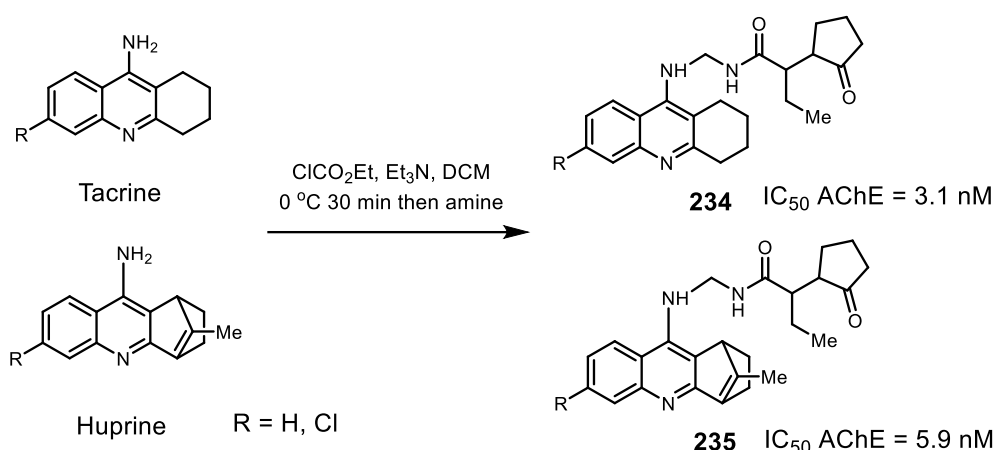


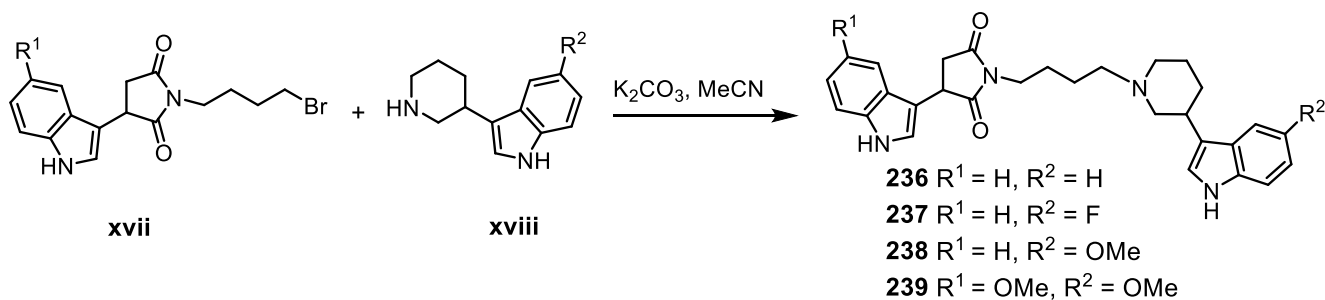
Figure 22. Hybrid compounds of 2-(2,5-dioxopyrrolidin-1-yl)-3-methoxypropanamides **224-233**

Repeating similar strategy by fusing a neurological active compound of tacrine with antiepileptic drugs of levetiracetam was also successfully demonstrated by Sola *et al.*⁹⁸ (Scheme 12). This strategy furnished them with a library of heptamethylene-linked levetiracetam-huprine **234** and levetiracetam-6-chlorotacrine **235** hybrids. These libraries of compounds showed potent inhibition against human recombinant AChE in a nanomolar range. Both series were prepared by reacting the corresponding starting materials with triethylamine at 0 °C before adding ethyl chloroformate and amine in a two-step reaction. Subsequent experiments further supported that both series of compounds have potential towards reducing neuroinflammation around the A β plaques and displaying putative effect on epileptiform activity via the direct effect on amyloid and tau pathologies.



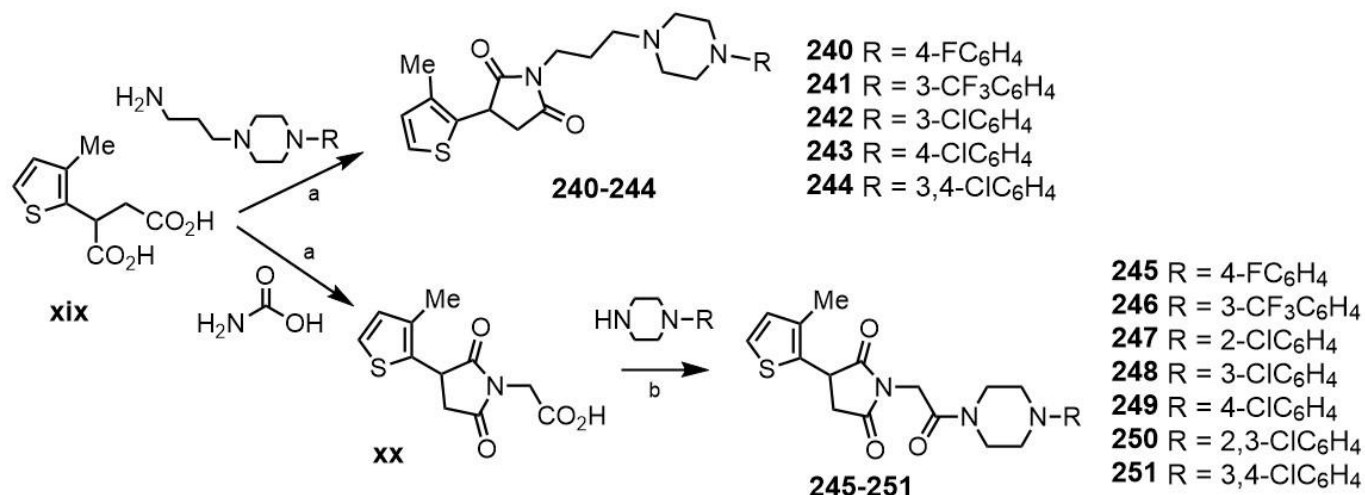
Scheme 12. Synthesis towards heptamethylene-linked levetiracetam-huprine **234** and levetiracetam-6-chlorotacrine **235** hybrids

In anti-neurodegenerative activity, Wróbel *et al.*⁹⁹ successfully reported on the development of drugs aiming at potential multi-receptor therapies using the earlier-mentioned molecular hybridization strategy (Scheme 13). These series of 3-(1*H*-indol-3-yl)pyrrolidine-2,5-diones **236-239** showed high affinities for 5-HT_{1A} receptors in *in vivo* antidepressant-like activity using the forced swim test. Amongst these analogues, compound **237** showed the highest polypharmacological profiles, potentially benefiting the treatment of depression (K_i [nM]: 5-HT_{1A} 7.5, SERT 505, D2 14, 5-HT_{2A} 71, 5-HT₆ 63, 5-HT₇ 196). Presumptively, the fluoro **237** or methoxy **238** (R^1) moieties in the carbon scaffold increased the affinity of the compounds for the 5-HT₇ receptor. Synthetically, the *N*-alkylation of compounds **236-239** was achieved easily by reacting the reactants of 3-piperidin-3-yl-1*H*-indoles **xviii** with pyrrolidinone-base compound **xvii** and potassium carbonate as a base in an excellent yield. However, the latest finding showed that the depression that presents comorbid neurodegenerative diseases (e.g., Alzheimer's and Parkinson's diseases) was partially or entirely unresponsive to the traditional antidepressant treatment.¹⁰⁰



Scheme 13. The synthesis series of 3-piperidin-3-yl-1*H*-indole derivatives **236-239**

Góra *et al.*¹⁰¹ successfully generated a library of 3-(2-chlorophenyl) and 3-[(3-chlorophenyl)-2,5-dioxopyrrolidin-1-yl]acetamides **240-251** with an excellent anticonvulsant and antinociceptive properties.¹⁰¹ These derivatives were generated by reacting corresponding succinic acid **xix** with 2-aminoacetic acid, producing intermediates of (2,5-dioxopyrrolidin-1-yl)acetic acid **xx** which then underwent subsequent reaction with a series of 4-arylpiperazine to yield the hybrid compound series **245-251**. Meanwhile, compounds **240-244** were synthesized by the one-step reaction of succinic acid **xix** with arylpiperazine (Scheme 14). *In vivo* experiment revealed that several compounds exhibited excellent anticonvulsant activity, especially in the psychomotor seizure (6 Hz) test [(ED₅₀ (MES) = 68.3 mg/kg and ED₅₀ (6 Hz) = 28.2 mg/kg)]. None of the hybrid series showed acute neurological toxicity. In particular, compound **240** and its dichloro-analogue **250** showed significant antinociceptive activity in the formalin test, i.e., a model of tonic pain, which might be applicable for analgesic neuropathic treatment.



Scheme 14. Synthetic route of the target compounds **240-251**. Reagents and conditions: (a) H₂O, rt-180 °C 1.5 h; (b) DCC, DMF, 0.5 h at rt

Nowadays, natural product compounds play an important role in the development of drugs lead compounds particularly for the treatment of neurodegenerative diseases.¹⁰² Upon screening six natural compounds based on their chemical functionalities (tenuazonic acid (TA), visoltricin/fungerin, 6-methoxymellein, mycophenolic acid, radicinin, epi-radicinol), Poliseno *et al.*¹⁰³ concluded that TA was the most promising pyrrolidine-carbon scaffold for the development of new neurodegenerative pathologies, particularly Alzheimer drugs. Interestingly, in similar works, further chemical functionalization, TA with neuro-active donepezil-mimetic-moiety successfully generated novel tenuazonic congeners and tenuazonic-donepezil hybrids but in racemic mixtures.

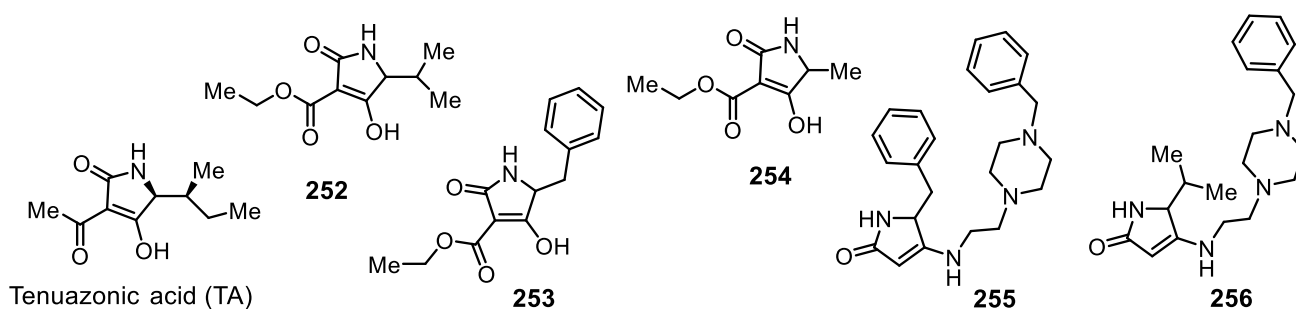


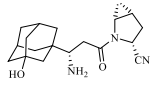
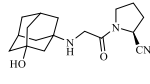
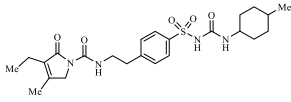
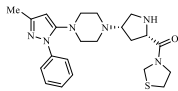
Figure 23. Structures of tenuazonic congeners and tenuazonic-donepezil hybrids **252–256**

Detail results obtained for the AChE inhibition study from synthesized tenuazonic congeners and tenuazonic-donepezil hybrids **252-254** revealed their promising biological properties in the range of micromolar and quite similar to tenuazonic acid (Figure 23). In addition, these analogues **252-256** also displayed significant improvement for inhibition A β aggregation, potential oral absorbance, metal chelation capacity and also non-cytotoxic towards SH-SY5Y human neuroblastoma cell line. The fact that compound **252** showed good selective metal chelating properties towards either zinc, copper, and iron confirming compound **252** to be a potential candidate for the development of novel multi-target anti-neurodegenerative molecules. In addition, both hybrids **255** and **256** of donepezil-mimetic hybrid moiety also portrayed significantly higher inhibition toward A β aggregation (72.0-78.4% at 40 μ M) and AChE assay (IC₅₀ 16-24 μ M) and to be highlighted potential of both congeners and hybrids for future applications as anti-neurodegenerative drugs.

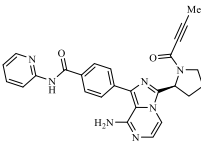
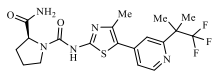
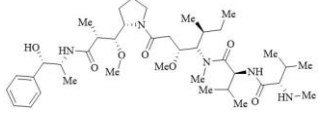
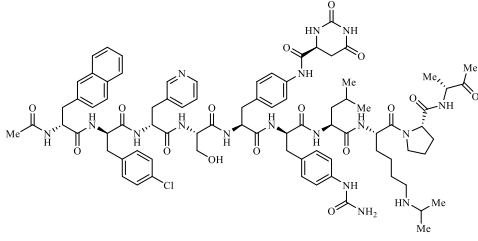
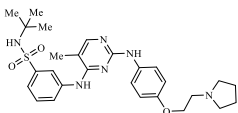
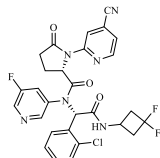
3. IMPORTANT DRUG CONTAINING FIVE-MEMBERED NITROGEN HETEROCYCLIC SCAFFOLD IN THE MARKET

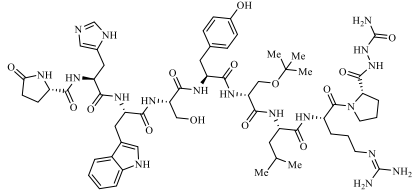
In the drug discovery, five-membered nitrogen heterocyclic scaffold such as pyrrolidine has been employed to improve a drug's potency, selectivity, and pharmacokinetic profile. This is due to the similarity of the pyrrolidine skeleton with a natural amino acid, proline which is commonly found as a building block in enzyme, receptor, ion channel, and endogenous ligands. Five-membered nitrogen heterocyclic framework on drug offers enhanced aqueous solubility and improves other physiochemical properties in addition to being part of the pharmacophore.¹⁰⁴ Up to recently, more than dozens of five-membered nitrogen heterocyclic-containing drugs are in the market, such as high-ceiling diuretic Piretanide, ACE inhibitor Fosinopril, and cephalosporin antibiotic Cefepime.¹⁰⁵ In this part, we listed 41 drugs bearing five-membered nitrogen heterocyclic scaffold which are already available in the market and have been approved by Food and Drug Administration (FDA) from 2000 to 2021.

3-1. Antidiabetic

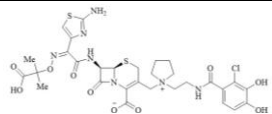
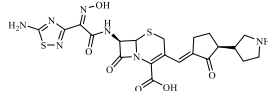
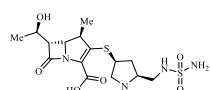
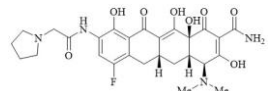
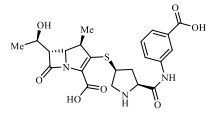
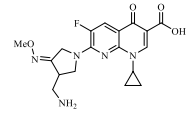
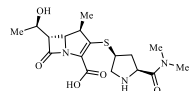
Generic Name	Approved	Summary	Structure
Saxagliptin	2009	A DPP-4 inhibitor which is used for the management of type-2 diabetes mellitus.	
Vildagliptin	2008	A once-daily dipeptidyl peptidase 4 (DPP-4) inhibitor which is used in the management of type-2 diabetes mellitus.	
Anagliptin	2012 (Japan)	Under investigated for the treatment of diabetes mellitus and dipeptidyl-peptidase 4 Inhibitors.	
Teneligliptin	2012 (Japan)	Under investigated for the treatment of type-2 diabetes mellitus.	

3-2. Anticancer

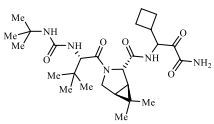
Generic Name	Approved	Summary	Structure
Acalabrutinib	2017	A Bruton tyrosine kinase inhibitor which is used to treat mantle cell lymphoma, chronic lymphocytic leukemia, and small lymphocytic lymphoma.	
Alpelisib	2019	A phosphatidylinositol 3-kinase (PI3K) inhibitor with potent antitumor activity	
Brentuximab vedotin	2011	A CD30-directed antibody-drug conjugate which is used to treat various types of lymphoma.	
Degarelix	2008	A GnRH receptor antagonist which is used in the management of advanced prostate cancer.	
Fedratinib	2019	A tyrosine kinase inhibitor which is used to treat intermediate-2 and high-risk primary and secondary myelofibrosis.2,7 It is an anilinopyrimidine derivative.	
Ivosidenib	2018	An isocitrate dehydrogenase-1 inhibitor which is used to treat acute myeloid leukemia with a susceptible mutation.	

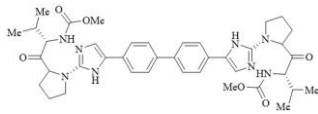
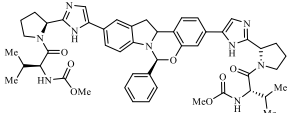
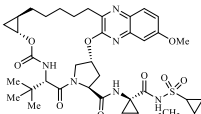
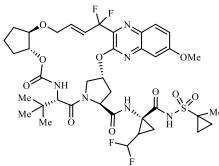
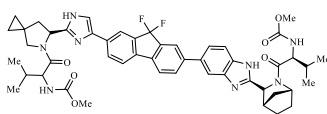
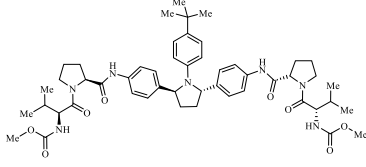
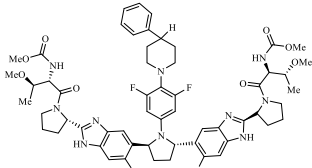
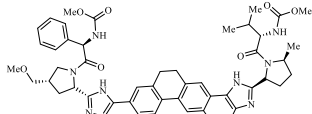
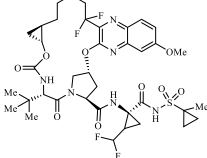
Triptorelin	2000	A GnRH agonist which indicated for the palliative treatment of advanced prostate cancer.	
-------------	------	--	---

3-3. Antibacterial

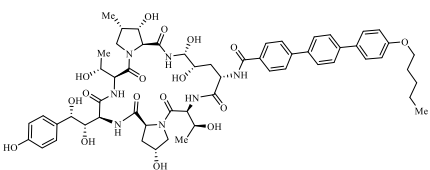
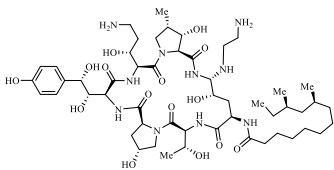
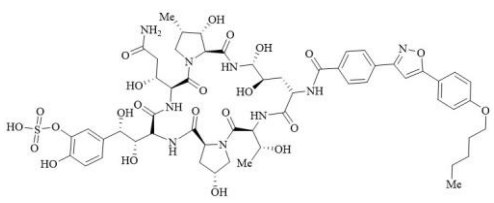
Generic Name	Approved	Summary	Structure
Cefiderocol	2019	A cephalosporin antibiotic which is used in complicated urinary tract infections.	
Ceftobiprole	2009	A cephalosporin antibiotic which is used to treat both community and hospital-acquired pneumonia caused by susceptible bacteria.	
Doripenem	2014	An antibiotic of the penem class which is used to treat complicated intra-abdominal and urinary tract infections.	
Eravacycline	2018	A tetracycline antibiotic which is used to treat complicated intra-abdominal infections.	
Ertapenem	2021	A carbapenem antibiotic which is used for the treatment of moderate to severe bacterial infections caused by specific sensitive organisms.	
Gemifloxacin	2013	A quinolone antibacterial agent which is used for the treatment of acute bacterial exacerbation of chronic bronchitis and mild to moderate community-acquired pneumonia caused by susceptible bacteria.	
Meropenem	2017	A carbapenem antibiotic which is used to treat a wide variety of infections in the body.	

3-4. Antiviral

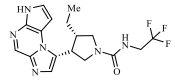
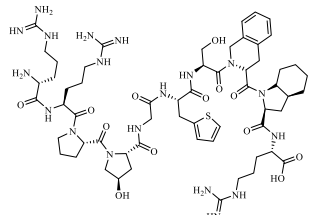
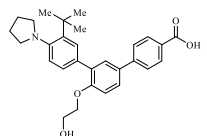
Generic Name	Approved	Summary	Structure
Boceprevir	2011	A hepatitis C virus NS3/4A protease inhibitor which is used in combination with other medications to treat chronic hepatitis C genotype 1 infection. Boceprevir is not indicated as monotherapy.	

Daclatasvir	2015	A direct-acting antiviral agent which is used to treat specific hepatitis C virus (HCV) infections in combination with other antiviral agents.	
Elbasvir	2016	An antiviral and NS5A inhibitor which is used to treat hepatitis C infections.	
Glecaprevir	2017	A Hepatitis C NS3/4A protease inhibitor which is used to treat Hepatitis C.	
Grazoprevir	2016	An antiviral and NS3/4A protease inhibitor which is used to treat hepatitis C infections.	
Ledipasvir	2014	A direct-acting antiviral agent which is used to treat specific hepatitis C virus (HCV) infections in combination with other antiviral agents.	
Ombitasvir	2015	A direct acting antiviral agent which is used in combination with other antiviral agents for the treatment of Hepatitis C Virus (HCV) infections.	
Pibrentasvir	2007	A Hepatitis C NS5A inhibitor which is used to treat Hepatitis C.	
Velpatasvir	2016	A NS5A inhibitor which is used to treat chronic hepatitis C infections in patients without cirrhosis or with compensated cirrhosis.	
Voxilaprevir	2017	A nonstructural protein 3 and 4a protease inhibitor which is used to treat Hepatitis C infections.	

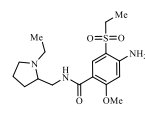
3-5. Antifungal

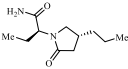
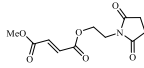
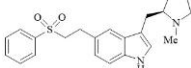

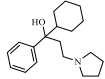
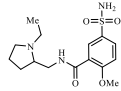
Generic Name	Approved	Summary	Structure
Anidulafungin	2006	An antifungal which is used in the treatment of several types of candida infections.	
Caspofungin	2001	An echinocandin which is used to treat a variety of fungal infections.	
Micafungin	2005	An antifungal agent which is used for the treatment of candidemia, acute disseminated candidiasis, and certain other invasive Candida infections, and for the prophylaxis of Candida infections during stem cell transplantation.	

3-6. Anti-inflammatory

Generic Name	Approved	Summary	Structure
Upadacitinib	2019	An oral Janus kinase (JAK)1-selective inhibitor which is used in the treatment of moderate to severe rheumatoid arthritis in adult patients who did not respond well to methotrexate.	
Icatibant	2011	A bradykinin B2 receptor antagonist which is used to treat acute episodes of swelling and inflammation associated with hereditary angioedema (HAE).	
Trifarotene	2019	A topical retinoid which indicated for the treatment of acne vulgaris.	

3-7. Anti-neurodegenerative

Generic Name	Approved	Summary	Structure
Amisulpride	2020	A dopamine D2 receptor antagonist which is used in the treatment of acute and chronic schizophrenia, and in the prevention and treatment of postoperative nausea and vomiting in adults.	

Brivaracetam	2016	An anticonvulsant which is used for the treatment of partial-onset seizures that functions by binding to synaptic vesicle glycoprotein 2A (SV2A) in the brain.	
Diroximel fumarate	2019	A drug which is used for the treatment of relapsing forms of Multiple Sclerosis (MS).	
Eletriptan	2016	A triptan which is used for the treatment of migraines.	
Ethosuximide	2000	An anticonvulsant which is used to treat petit mal seizures.	
Procyclidine	2009	An antispasmodic drug which is used to treat parkinsonism of various types and in the treatment of extrapyramidal symptoms.	
Sulpiride	2007	A selective D2 dopamine receptor antagonist which used to treat chronic and acute schizophrenia.	

4. CONCLUSION

This mini-review gave an overview of the biologically active compounds bearing five-membered nitrogen heterocyclic scaffolds. These compounds were isolated from natural products or synthetically derived. Different strategies for preparing the five-membered nitrogen heterocyclic scaffolds and their functionalization were also discussed. Finally, matching chemical functionalities with reported bioactivities might help synthetic and medicinal chemists to understand the pyrrolidine SAR properties better. This mini-review also listed some commercially available drugs with five-membered nitrogen heterocyclic nuclei and their reported activity, which might verify the importance of the five-membered nitrogen heterocyclic core in drugs discovery. In general, these versatile compounds, containing five-membered nitrogen heterocyclic moiety as active scaffolds, served as the pharmacological application in anticancer, antibacterial, antiviral, antifungal, antimalarial, antidiabetic, antioxidant, anti-inflammatory, and anti-neurodegenerative treatments. Their structural diversity has high a potential for developing new bioactive compounds.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Universiti Teknologi MARA and Malaysian Government (MOHE) for financial support (600-IRMI/FRGS 5/3 (109/2019)).

REFERENCES

1. P. Garner, P. B. Cox, U. Rathnayake, N. Holloran, and P. Erdman, *ACS Med. Chem. Lett.*, 2019, **10**, 811.

2. S. Lee, H. Lei, and T. Rovis, *J. Am. Chem. Soc.*, 2019, **141**, 12536.
3. M. F. Mohammat, N. Najim, N. S. Mansor, S. Sarman, Z. Shaameri, M. M. Zain, and A. S. Hamzah, *ARKIVOC*, 2011, **ix**, 429.
4. M. V. Raimondi, A. Presentato, G. Li Petri, M. Buttacavoli, A. Ribaudo, V. De Caro, R. Alduina, and P. Cancemi, *Antibiotics*, 2020, **9**, 292.
5. M. V. Raimondi, R. Listro, M. G. Cusimano, M. La Franca, T. Faddetta, G. Gallo, D. Schillaci, S. Collina, A. Leonchiks, and G. Barone, *Bioorg. Med. Chem.*, 2019, **27**, 721.
6. V. Spanò, R. Rocca, M. Barreca, D. Giallombardo, A. Montalbano, A. Carbone, M. V. Raimondi, E. Gaudio, R. Bortolozzi, R. Bai, P. Tassone, S. Alcaro, E. Hamel, G. Viola, F. Bertoni, and P. Barraja, *J. Med. Chem.*, 2020, **63**, 12023.
7. S. Cascioferro, B. Maggio, D. Raffa, M. V. Raimondi, M. G. Cusimano, D. Schillaci, B. Manachini, A. Leonchiks, and G. Daidone, *Med. Chem. Res.*, 2016, **25**, 870.
8. J. L. Whatmore, E. Swann, P. Barraja, J. J. Newsome, M. Bunderson, H. D. Beall, J. E. Tooke, and C. J. Moody, *Angiogenesis*, 2002, **5**, 45.
9. J. Fischer, C. R. Ganellin, and D. P. Rotella In *Pioneer and Analogue Drugs*, p 1.
10. R. S. Kumar, D. M. Al-thamili, A. I. Almansour, N. Arumugam, and F. Mohammad, *Molecules*, 2020, **25**, 5581.
11. S. D. Durgapal and S. S. Soman, *Synth. Commun.*, 2019, **49**, 2869.
12. K. Tilekar, N. Upadhyay, F.-J. Meyer-Almes, F. Liodice, A. Yu, S. Tatiana, D. Sokolova, G. Smirnova, J.-y. Choe, V. Pokrovsky, A. Lavecchia, and C. S. Ramaa, *ChemMedChem.*, 2020, **15**, 1813.
13. M. Abram, M. Zagaja, S. Mogilski, M. Andres-Mach, G. Latacz, S. Baś, J. J. Łuszczki, K. Kieć-Kononowicz, and K. Kamiński, *J. Med. Chem.*, 2017, **60**, 8565.
14. M. J. Meyers, J. Liu, J. Xu, F. Leng, J. Guan, Z. Liu, S. A. McNitt, L. Qin, L. Dai, H. Ma, D. Adah, S. Zhao, X. Li, A. J. Polino, A. S. Nasamu, D. E. Goldberg, X. Liu, Y. Lu, Z. Tu, X. Chen, and M. D. Tortorella, *J. Med. Chem.*, 2019, **62**, 3503.
15. B.-R. Kim, H. Y. Kim, I. Choi, J.-B. Kim, C. H. Jin, and A.-R. Han, *Molecules*, 2018, **23**, 1998.
16. R. Sharma and S. S. Soman, *Eur. J. Med. Chem.*, 2015, **90**, 342.
17. S. O. Kuranov, I. P. Tsypysheva, M. V. Khvostov, L. F. Zainullina, S. S. Borisevich, Y. V. Vakhitova, O. A. Luzina, and N. F. Salakhutdinov, *Bioorg. Med. Chem.*, 2018, **26**, 4402.
18. S. Karandikar, R. Soni, S. S. Soman, S. Umar, and B. Suresh, *Synth. Commun.*, 2018, **48**, 2877.
19. X. Deng, L. Han, J. Zhou, H. Zhang, and Q. Li, *Bioorg. Chem.*, 2017, **75**, 357.
20. T. Luthra, K. Naga Lalitha, R. Agarwal, A. Uma, and S. Sen, *Bioorg. Med. Chem.*, 2018, **26**, 4996.
21. M. Khan, M. Yousaf, A. Wadood, M. Junaid, M. Ashraf, U. Alam, M. Ali, M. Arshad, Z. Hussain, and K. M. Khan, *Bioorg. Med. Chem.*, 2014, **22**, 3441.

22. K. Ikeda, M. Takahashi, M. Nishida, M. Miyauchi, H. Kizu, Y. Kameda, M. Arisawa, A. A. Watson, R. J. Nash, G. W. J. Fleet, and N. Asano, [*Carbohydr. Res.*, 1999, **323**, 73.](#)
23. Z. Yin, W. Zhang, F. Feng, Y. Zhang, and W. Kang, [*Food Sci. Hum. Wellness*, 2014, **3**, 136.](#)
24. G. M. Morris, R. Huey, W. Lindstrom, M. F. Sanner, R. K. Belew, D. S. Goodsell, and A. J. Olson, [*J. Comput. Chem.*, 2009, **30**, 2785.](#)
25. H. Fujieda, M. Kogami, M. Sakairi, N. Kato, M. Makino, N. Takahashi, T. Miyazawa, S. Harada, and T. Yamashita, [*Eur. J. Med. Chem.*, 2018, **156**, 269.](#)
26. E. A. Jurica, X. Wu, K. N. Williams, A. S. Hernandez, D. S. Nirschl, R. A. Rampulla, A. Mathur, M. Zhou, G. Cao, C. Xie, B. Jacob, H. Cai, T. Wang, B. J. Murphy, H. Liu, C. Xu, L. K. Kunselman, M. B. Hicks, Q. Sun, D. M. Schnur, D. F. Sitkoff, E. A. Dierks, A. Apedo, D. B. Moore, K. A. Foster, M. E. Cvijic, R. Panemangalore, N. A. Flynn, B. D. Maxwell, Y. Hong, Y. Tian, J. J. Wilkes, B. A. Zinker, J. M. Whaley, J. C. Barrish, J. A. Robl, W. R. Ewing, and B. A. Ellsworth, [*J. Med. Chem.*, 2017, **60**, 1417.](#)
27. H. Zhang, C. Z. Ding, Z. Lai, S. S. Chen, P. Devasthale, T. Herpin, G. Morton, F. Qu, D. Ryono, R. Smirk, W. Wang, S. Wu, X.-X. Ye, Y.-X. Li, A. Apedo, D. Farrelly, T. Wang, L. Gu, N. Morgan, N. Flynn, C. Chu, L. Kunselman, J. Lippy, K. Locke, K. O'Malley, T. Harrity, M. Cap, L. Zhang, V. Hosagrahara, P. Kadiyala, C. Xu, A. M. Doweyko, R. Zahler, N. Hariharan, and P. T. W. Cheng, [*Bioorg. Med. Chem. Lett.*, 2015, **25**, 1196.](#)
28. A. Wibowo, Z. Shaameri, A. Hamzah, and M. Mohammat, *Malaysian J. Chem.*, 2020, **22**, 76.
29. F. Hussain, Z. Khan, M. S. Jan, S. Ahmad, A. Ahmad, U. Rashid, F. Ullah, M. Ayaz, and A. Sadiq, [*Bioorg. Chem.*, 2019, **91**, 103128.](#)
30. S. Sansenya, C. Winyakul, K. Nanok, and W. Phutdhawong, [*Res. Pharm. Sci.*, 2020, **15**, 14.](#)
31. L. Guazzelli, F. D'Andrea, S. Sartini, F. Giorgelli, G. Confini, L. Quattrini, I. Piano, S. Nencetti, E. Orlandini, C. Gargini, and C. La Motta, [*Bioorg. Chem.*, 2019, **92**, 103298.](#)
32. A. Wibowo, Z. Shaameri, A. Hamzah, and M. Mohammat, [*Org. Commun.*, 2020, **13**, 79.](#)
33. M. Bacho, M. Mohammat, Z. Shaameri, A. Wibowo, F. Kamarulzaman, and A. Hamzah, [*Oriental J. Chem.*, 2020, **36**, 309.](#)
34. F. F. Lillich, J. D. Imig, and E. Proschak, [*Front. Pharmacol.*, 2021, **11**, 554961.](#)
35. X. Ferhati, C. Matassini, M. G. Fabbrini, A. Goti, A. Morrone, F. Cardona, A. J. Moreno-Vargas, and P. Paoli, [*Bioorg. Chem.*, 2019, **87**, 534.](#)
36. H. Sung, J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, and F. Bray, [*CA: A Cancer J. Clin.*, 2021, **71**, 209.](#)
37. M. Bashandy and S. El-Gilil, [*Heterocycles*, 2016, **92**, 431.](#)
38. B. S. Askari and M. Krajcinovic, [*Curr. Genomics*, 2010, **11**, 578.](#)

39. A. Hassan, H. Park, Y. Yoon, H. Kim, S. Yoo, K. Lee, and Y. Lee, [Bioorg. Chem., 2018, 84, 444.](#)
40. H. Zhang, W. Xuejian, J. Mao, Y. Huang, W. Xu, Y. Duan, and J. Zhang, [Bioorg. Med. Chem., 2018, 26, 4363.](#)
41. A. Kumar, U. Singh, F. Muzaffar, P. Pathak, and P. Tomar, [Der Pharma Chem., 2018, 10, 124.](#)
42. A. Ahmad, F. Ullah, A. Sadiq, M. Ayaz, H. Rahim, U. Rashid, S. Ahmad, M. Jan, R. Ullah, A. Shahat, and H. Mahmood, [Drug Des. Dev. Ther., 2019, 13, 4185.](#)
43. T. C. Nugent, A. Bibi, A. Sadiq, M. Shoaib, M. N. Umar, and F. N. Tehrani, [Org. Biomol. Chem., 2012, 10, 9287.](#)
44. S. Zulfiqar, M. Haroon, M. W. Baig, M. Tariq, Z. Ahmad, M. N. Tahir, and T. Akhtar, [J. Mol. Struct., 2021, 1224, 129267.](#)
45. A. Kryshchysyn, D. Kaminsky, O. Roman, R. Kralovics, O. Karpenko, and R. Lesyk, [Ukr. Biochem. J., 2020, 92, 108.](#)
46. M. S. Islam, H. M. Ghawas, F. F. El-Senduny, A. M. Al-Majid, Y. A. M. M. Elshaier, F. A. Badria, and A. Barakat, [Bioorg. Chem., 2019, 82, 423.](#)
47. A. López-Pérez, S. Freischem, I. Grimm, O. Weiergräber, A. J. Dingley, M. P. López-Alberca, H. Waldmann, W. Vollmer, K. Kumar, and C. Vuong, [Antibiotics, 2021, 10, 529.](#)
48. E. Kocabaş, A. B. Sarigüney, F. Erci, R. Çakir-Koç, H. Ö. Kocabaş, E. Torlak, and A. Coşkun, [Biointerface Res. Appl. Chem., 2021, 11, 12178.](#)
49. Y. Nural, M. Gemili, M. Ulger, H. Sari, L. M. De Coen, and E. Sahin, [Bioorg. Med. Chem. Lett., 2018, 28, 942.](#)
50. L. Rodriguez, R. Fišera, B. Gaálová, K. Koči, H. Bujdáková, M. Mečiarová, R. Górová, H. Jurdáková, and R. Šebesta, [Eur. J. Org. Chem., 2020, 2565.](#)
51. S. A. Johari, M. Mohtar, S. A. Syed Mohammad, R. Sahdan, Z. Shaameri, A. S. Hamzah, and M. F. Mohammat, [Biomed. Res. Int., 2015, ID823829.](#)
52. D. Matiadis, D. Tsironis, V. Stefanou, S. Boussias, A. Panagiotopoulou, V. McKee, O. Igglessi-Markopoulou, and J. Markopoulos, [Bioorg. Med. Chem. Lett., 2020, 30, 127107.](#)
53. B. Balandis, K. Anusevičius, J. Šiugždaitė, K. Kantminienė, and V. Mickevičius, [Res. Chem. Intermed., 2019, 45, 5499.](#)
54. A. S. Sokolova, V. P. Putilova, O. I. Yarovaya, A. V. Zybkina, E. D. Mordvinova, A. V. Zaykovskaya, D. N. Shcherbakov, I. R. Orshanskaya, E. O. Sinegubova, I. L. Esaulkova, S. S. Borisevich, N. I. Bormotov, L. N. Shishkina, V. V. Zarubaev, O. V. Pyankov, R. A. Maksyutov, and N. F. Salakhutdinov, [Molecules, 2021, 26, 2235.](#)
55. I. J. Kang, S. J. Hsu, H. Y. Yang, T. K. Yeh, C. C. Lee, Y. C. Lee, Y. W. Tian, J. S. Song, T. A. Hsu, Y. S. Chao, A. Yueh, and J. H. Chern, [J. Med. Chem., 2017, 60, 228.](#)

56. T. Zhao, Q. Meng, D. W. Kang, J. B. Ji, E. De Clercq, C. Pannecouque, X. Y. Liu, and P. Zhan, [*Eur. J. Med. Chem.*, 2019, **182**, 111619.](#)
57. M. I. Morris and M. Villmann, [*Am. J. Health Syst. Pharm.*, 2006, **63**, 1813.](#)
58. M. I. Morris and M. Villmann, [*Am. J. Health Syst. Pharm.*, 2006, **63**, 1693.](#)
59. D. W. Denning, [*Lancet*, 2003, **362**, 1142.](#)
60. Y.-N. Shi, F.-F. Liu, M. R. Jacob, X.-C. Li, H.-T. Zhu, D. Wang, R.-R. Cheng, C.-R. Yang, M. Xu, and Y.-J. Zhang, [*Planta Med.*, 2017, **83**, 143.](#)
61. S. Badampudi, G. Madhu, and L. Ravindranath, *KazNU. Chem. Bull.*, 2019, 28.
62. E. Łukowska-Chojnacka, A. Kowalkowska, M. Gizińska, M. Koronkiewicz, and M. Staniszevska, [*Eur. J. Med. Chem.*, 2018, **164**, 106.](#)
63. S. Sheikhi-Mohammareh, A. Shiri, H. Beyzaei, and E. Yarmohammadi, [*Monatsh. Chem.*, 2020, **151**, 963.](#)
64. D. Ashok, M. Elsanosi, B. F. H. Alanab, M. Sarasija, and S. Ravi, [*Russ. J. Gen. Chem.*, 2016, **86**, 1120.](#)
65. A. Alsarhni, Z. Muhi-Eldeen, E. Al-Kaissi, and R. abu-safiah, *Int. J. Pharm. Clin. Res.*, 2017, **9**, 622.
66. E. V. Tret'yakova, G. s. F. Zakirova, E. V. Salimova, O. S. Kukovinets, V. N. Odinokov, and L. V. Parfenova, [*Med. Chem. Res.*, 2018, **27**, 2199.](#)
67. Y. Mohini, R. B. N. Prasad, M. S. L. Karuna, Y. Poornachandra, and C. Ganesh Kumar, [*Bioorg. Med. Chem. Lett.*, 2016, **26**, 5198.](#)
68. A.-E. Dascalu, A. Ghinet, E. Lipka, C. Furman, B. Rigo, A. Fayeulle, and M. Billamboz, [*Bioorg. Med. Chem. Lett.*, 2020, **30**, 127220.](#)
69. L. Zhang, Z. Ren, A. Lu, Z. Zhao, W. Xu, Q. Bao, W. Ding, and C. Yang, [*Chem. Res. Chin. Univ.*, 2015, **31**, 228.](#)
70. Z.-J. Lin, Z.-Y. Lu, T.-J. Zhu, Y.-C. Fang, Q.-Q. Gu, and W.-M. Zhu, [*Chem. Pharm. Bull.*, 2008, **56**, 217.](#)
71. H.-R. Hu, A. Wang, L.-L. Qiu, X.-B. Wang, M. Chen, A.-M. Lu, and C.-L. Yang, [*New J. Chem.*, 2020, **44**, 20071.](#)
72. J. Wang, Q.-F. Yao, M. Amin, X.-H. Nong, X.-Y. Zhang, and S.-H. Qi, [*J. Antibiot. Res.*, 2017, **70**, 763.](#)
73. A. A. Dhavan, A. C. Ionescu, R. D. Kaduskar, E. Brambilla, S. Dallavalle, E. M. Varoni, and M. Iriti, [*Bioorg. Med. Chem. Lett.*, 2016, **26**, 1376.](#)
74. K. L. Obydenov, L. A. Khamidullina, A. N. Galushchinskiy, S. A. Shatunova, M. F. Kosterina, T. A. Kalinina, Z. Fan, T. V. Glukhareva, and Y. Y. Morzherin, [*J. Agric. Food Chem.*, 2018, **66**, 6239.](#)
75. WHO, [*Bull. World Health Organ.*, 2021, **99**, 756.](#)

76. J. Frydrych, D. Keough, M. Chavchich, J. Travis, M. Dračinský, M. Edstein, L. Guddat, D. Hockova, and Z. Janeba, [Eur. J. Med. Chem., 2021, 219, 113416](#).
77. M. Meyers, J. Liu, Z. Liu, H. Ma, L. Dai, D. Adah, S. Zhao, X. Li, X. Liu, Y. Lu, Y. Huang, Z.-C. Tu, X. Chen, and M. Tortorella, [ACS Med. Chem. Lett., 2019, 10, 966](#).
78. X. He, Y. Song, L. Wang, and J. Xu, [Mol. Med. Rep., 2020, 21, 463](#).
79. J. D. Qin, Z. H. Cao, X. F. Li, X. L. Kang, Y. Xue, Y. L. Li, D. Zhang, X. Y. Liu, and Y. Z. Xue, [Pharm. Biol., 2014, 52, 1460](#).
80. F. Yang, X. Li, L.-k. Wang, L.-w. Wang, X.-q. Han, H. Zhang, and Z.-j. Gong, [Inflammation, 2014, 37, 848](#).
81. R. Bruck, R. Schey, H. Aeed, A. Hochman, O. Genina, and M. Pines, [Liver Int., 2004, 24, 169](#).
82. A. Nurmi, G. Goldsteins, J. Närväinen, R. Pihaja, T. Ahtoniemi, O. Gröhn, and J. Koistinaho, [Free Radic. Biol. Med., 2006, 40, 1776](#).
83. H. Dayioğlu, A. Yilmaz, A. Erdoğan, F. Alan, and S. Darcan, [J. Sci. Rep.-A, 2020, 45, 28](#).
84. N. A. Betti, S. A. Khadim, and R. A. Hussain, [J. Res. Lepid., 2020, 51, 362](#).
85. P. Devi, A. Bishnoi, and V. Singh, [ChemistrySelect, 2019, 4, 629](#).
86. M. H. Md Idris, S. N. Mohd Amin, S. N. Mohd Amin, A. Wibowo, Z. A. Zakaria, Z. Shaameri, A. S. Hamzah, M. Selvaraj, L. K. Teh, and M. Z. Salleh, [J. Recept. Signal Transduct. Res., 2021, 1](#).
87. L. Chen, H. Deng, H. Cui, J. Fang, Z. Zuo, J. Deng, Y. Li, X. Wang, and L. Zhao, [Oncotarget, 2017, 9, 7204](#).
88. D.-H. Tsai, M. Riediker, A. Berchet, F. Paccaud, G. Waeber, P. Vollenweider, and M. Bochud, [Environ. Sci. Pollut. Res. Int., 2019, 26, 19697](#).
89. M. S. Jan, S. Ahmad, F. Hussain, A. Ahmad, F. Mahmood, U. Rashid, O. U. Abid, F. Ullah, M. Ayaz, and A. Sadiq, [Eur. J. Med. Chem., 2020, 186, 111863](#).
90. D. Gerokonstantis, A. Nikolaou, C. Magkrioti, A. Afantitis, V. Aidinis, G. Kokotos, and P. Moutevelis-Minakakis, [Bioorg. Med. Chem., 2019, 28, 115216](#).
91. P. Zhou, L. Xiang, D. Zhao, J. Ren, Y. li, and Q. Yan, [MedChemComm., 2018, 10, 252](#).
92. A. A. M. Abdel-Aziz, A. S. El-Azab, N. A. AlSaif, M. M. Alanazi, M. A. El-Gendy, A. J. Obaidullah, H. M. Alkahtani, A. A. Almehizia, and I. A. Al-Suwaidan, [J. Enzyme Inhib. Med. Chem., 2020, 35, 610](#).
93. M. Tanaka, J. Toldi, and L. Vécsei, [Int. J. Mol. Sci., 2020, 21, 2431](#).
94. D. Krewski, C. Barakat-Haddad, J. Donnan, R. Martino, T. Pringsheim, H. Tremlett, P. van Lieshout, S. J. Walsh, N. J. Birkett, J. Gomes, J. Little, S. Bowen, H. Candundo, T.-K. Chao, K. Collins, J. A. G. Crispo, T. Duggan, R. El Sherif, N. Farhat, Y. Fortin, J. Gaskin, P. Gupta, M. Hersi, J. Hu, B. Irvine, S. Jahanfar, D. MacDonald, K. McKay, A. Morrissey, P. Quach, R. Rashid, S. Shin, L. Sikora, S.

- Tkachuk, M. K. Taher, M.-D. Wang, S. Darshan, and N. R. Cashman, [NeuroToxicology](#), 2017, **61**, 266.
95. Y. R. Kong, K. C. Tay, Y. X. Su, C. K. Wong, W. N. Tan, and K. Y. Khaw, [Molecules](#), 2021, **26**, 728.
96. R. Leiva, C. Griñan-Ferré, C. Seira, E. Valverde, A. McBride, M. Binnie, B. Pérez, F. J. Luque, M. Pallàs, A. Bidon-Chanal, S. P. Webster, and S. Vázquez, [Eur. J. Med. Chem.](#), 2017, **139**, 412.
97. E. Valverde, C. Seira, A. McBride, M. Binnie, F. J. Luque, S. P. Webster, A. Bidon-Chanal, and S. Vázquez, [Bioorg. Med. Chem.](#), 2015, **23**, 7607.
98. I. Sola, E. Aso, D. Frattini, I. López-González, A. Espargaró, R. Sabaté, O. Di Pietro, F. J. Luque, M. V. Clos, I. Ferrer, and D. Muñoz-Torrero, [J. Med. Chem.](#), 2015, **58**, 6018.
99. M. Z. Wróbel, A. Chodkowski, F. Herold, M. Marciniak, M. Dawidowski, A. Siwek, G. Starowicz, K. Stachowicz, B. Szewczyk, G. Nowak, M. Belka, T. Bączek, G. Satała, A. J. Bojarski, and J. Turło, [Eur. J. Med. Chem.](#), 2019, **183**, 111736.
100. M. Baquero and N. Martín, [World J. Clin. Cases](#), 2015, **3**, 682.
101. M. Góra, A. Czopek, A. Rapacz, A. Gębska, K. Wójcik-Pszczola, E. Pękala, and K. Kamiński, [Molecules](#), 2021, **26**, 1564.
102. R. Dash, I. Jahan, M. C. Ali, S. Mitra, Y. A. Munni, B. Timalina, M. A. Hannan, and I. S. Moon, [Neurochem. Int.](#), 2021, **145**, 105011.
103. V. Poliseño, S. Chaves, L. Brunetti, F. Liodice, A. Carrieri, A. Laghezza, P. Tortorella, J. D. Magalhães, S. M. Cardoso, M. A. Santos, and L. Piemontese, [Biomolecules](#), 2021, **11**, 111.
104. G. Li Petri, M. V. Raimondi, V. Spanò, R. Holl, P. Barraja, and A. Montalbano, [Top. Curr. Chem.](#), 2021, **379**, 34.
105. D. S. Wishart, Y. D. Feunang, A. C. Guo, E. J. Lo, A. Marcu, J. R. Grant, T. Sajed, D. Johnson, C. Li, Z. Sayeeda, N. Assempour, I. Iynkkaran, Y. Liu, A. Maciejewski, N. Gale, A. Wilson, L. Chin, R. Cummings, D. Le, A. Pon, C. Knox, and M. Wilson, [Nucleic Acids Res.](#), 2018, **46**, D1074.



Dr. Agustono Wibowo received Ph.D. degree in 2014 from Universiti Teknologi MARA, Malaysia, and he joined the Centre for Chemical Synthesis and Polymer Technology, Institute of Science, Universiti Teknologi MARA from Universiti Teknologi MARA as a postdoctoral fellow (2015-2018). Currently, he works as a senior lecturer at the Department of Chemistry, Faculty of Applied Sciences, Universiti Teknologi MARA Pahang Branch, Jengka Campus, Pahang, Malaysia. His research interests are organic synthesis, drug discovery, and natural product chemistry. Their current project is synthesis, biological evaluation, and molecular docking study of pyrrolidine-based iminosugars as potential antidiabetic and anticancer agents.



Dr. Mohd Fazli Mohammat received B.Sc. in 1995 from University of Malaya, Malaysia before further continued in MPhil from University of Liverpool UK. He Received Ph.D. in Chemistry from Universiti Teknologi MARA (UiTM), Malaysia in 2010. His research interest are natural product synthesis, green chemistry, and medicinal chemistry. He is currently acting as head of Centre for Chemical Synthesis & Polymer Technology (CCSPT), Institute of Science, UiTM Shah Alam, Malaysia.



Professor Dr. Zurina Shaameri received her Ph.D. in Organic Chemistry from the Universiti Teknologi MARA (UiTM), Malaysia in 2007. Prior to furthering her doctoral study, she earned her master's degree (MPhil) from the University of Cambridge, United Kingdom in 1997. She was the Director of the Institute of Science, UiTM in 2018-2022 and became a full professor in 2019. Her research works concentrate on the syntheses of nitrogen heterocycles with a pyrrolidine ring system and bicyclic lactone-lactam/lactam-lactam rings, synthetic/chemical exploration, and natural products synthesis.



Dr. Fatin Nur Ain Abdul Rashid is a researcher at the Centre for Chemical Synthesis & Polymer Technology (CCSPT), Institute of Science, Universiti Teknologi MARA (UiTM), Malaysia. She received her B.Sc. degree in Chemistry (2010) from UiTM and M.Sc. degree in Organic Chemistry (2014) from Universiti Malaysia Terengganu. In 2016, she joined Professor Dr Ahmad Sazali's group at UiTM as a Ph.D. student and obtained her Ph.D. degree in 2020. Her research interest is in synthetic methodology and chemical exploration of pyrrolidinone type compounds. Currently, she has been working on the development of new synthetic chelators for upstream oil and gas industry.



Dr. Noor Hidayah Pungot is a senior lecturer at the Department of Chemistry, Faculty of Applied Sciences, Universiti Teknologi MARA (UiTM), Malaysia. She is also a research fellow at the Centre for Chemical Synthesis & Polymer Technology (CCSPT), Institute of Science, UiTM. She obtained her Ph.D. in 2019 in Organic Chemistry from UiTM and M.Sc. degree in Analytical Chemistry and Instrumentation from University of Malaya. She also holds a Bachelor of Science (Honours) in Applied Chemistry from UiTM. She has been working in chemistry for more than 10 years. Her research interests are in the area of organic synthesis (synthetic methodology/chemical exploration) for nitrogen heterocycles with a pyrrolidine ring system, natural products synthesis, and analytical chemistry & instrumentations.



Professor Dr. Ahmad Sazali Hamzah is a senior professor at the Universiti Teknologi MARA (UiTM), Malaysia. He received his B.Sc. (Hons) Chemistry in 1985 from the University of Liverpool, United Kingdom. He studied natural product chemistry at the Graduate School of Universiti Putra Malaysia (UPM) in 1994. In 2000, he received his Ph.D. in Organic Chemistry from the University of Loughborough, United Kingdom. He was appointed as the Director of the Institute of Science, UiTM for ten years, and currently, he is the Rector of UiTM Selangor Campus since 2021. His research focuses on the research areas of organic chemistry and organocatalyst.