A Platinum Open Access Journal for Organic Chemistry

Review

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2022**, part i, 221-261

Polyketopiperazines: triketopiperazines, tetraketopiperazines synthesis, reactions, bioactivities and applications

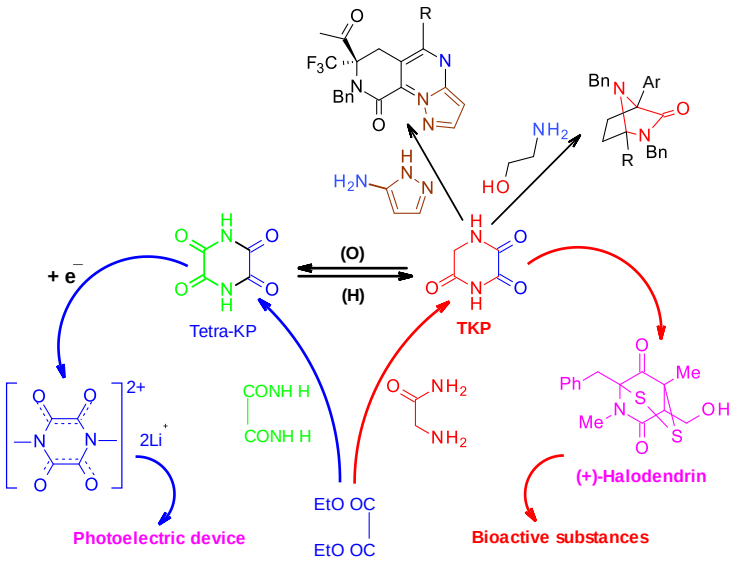
Nabaweya Abdelsalem Sharafeldin

Department of Pharmaceutical Chemistry, Tanta University, El Giesh street, 3111, Tanta, Egypt
Email: nabawia.eldeen@pharm.tanta.edu.eg

Received 02-02-2022 **Accepted** 03-23-2022 **Published on line** 05-12-2022

Abstract

Several polyketopiperazines represent the simplest heterocyclic compounds found in nature, acting as a vital base-structure for many bioactive compounds. They are widely distributed in microorganisms, food, and beverages with diverse bioactivities, such as antiviral, anticancer, antioxidant, and neuroprotective properties. Focusing on triketopiperazines and tetraketopiperazines; triketopiperazines possess important biological properties and used for production of the valuable molecular scaffolds in synthetic biology, whereas tetraketopiperazines are economically beneficial for chemical engineering. Noteworthy, they have extra-rigid conformations and are more resistant to degradation by enzymes. Therefore, they represent an interesting subclass of heterocycles with high potential to be used in the production of new effective therapeutic motif and sustainable energy storage structures.



Keywords: Polyketopiperazines; triketopiperazines; tetraketopiperazines; synthesis; reactions; bioactivities; applications

Table of Contents

1. Introduction

Nitrogen containing heterocycles have a vital role in life sciences, because they occur in many natural products, such as vitamins, hormones, antibiotics as well as in numerous approved and marketed medicines.[1-6] Further, the *N*-heterocycles are considerably used as a building blocks for a number of medications, owing to the ability of the nitrogen atom to form hydrogen bonding with biological receptors.[7-11] In addition, several nitrogen-containing heterocycles are well known to have a broad array of bioactivities.[12-18] Hence, these compounds have always been desirable objectives to synthetic organic chemists and researchers.

Most importantly, piperazine is an essential heterocyclic motif in many biologically active compounds with various pharmacological activities.[19-27] For example, clozapine **1** is strongly sedative and has muscle-relaxant

properties, amoxapine **2** has antidepressant activity, trimetazidine **3** is an antischemic agent and cyclizine **4** is used to treat nausea and vomiting[28,29] (Figure 1).

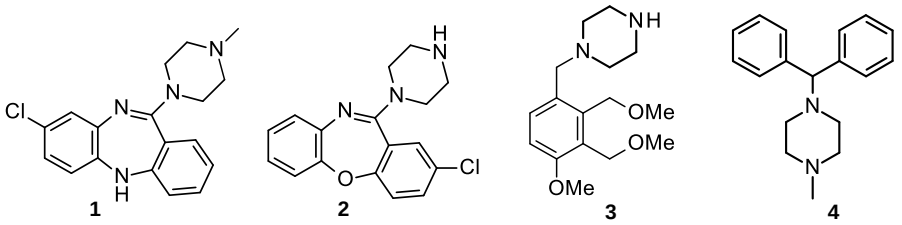


Figure 1. Structures of some piperazine-based drugs.

Structurally, piperazine has a six-membered saturated ring with two nitrogen atoms at 1- and 4-positions. This feature gives large polar surface area and relative rigidity with both hydrogen bond acceptor and donor leading to enhanced activities, water solubility, oral bioavailability, and ADME (absorption, distribution, metabolism, and excretion) properties.[30,31] Interestingly, the solubility of diosgenin was improved by the formation of cocrystals with piperazine in 2:1 stoichiometry (the solubility value was approximately 1.5 times more than the parent material in 0.2% SDS solution) due to the formation of hydrogen bonds.[32] Moreover, the salt of piperazine with chloroacetic acid has been created and structurally explored. The two hydrogen-bonding patterns (a small R [12] ring **5a** as well as a large R [18] ring **5b**) were formed. (Figure 2) The hydrogen-bonding structure **5b** is a quite stable supramolecular synthon which may be required further investigations in the fields of chemical engineering and pharmaceutical applications due to its rigidity and having a several synthons.[33] Finally, tetrameric hydrogen bonding structure was produced by linking two molecules of piperazines with two water molecules.[34]

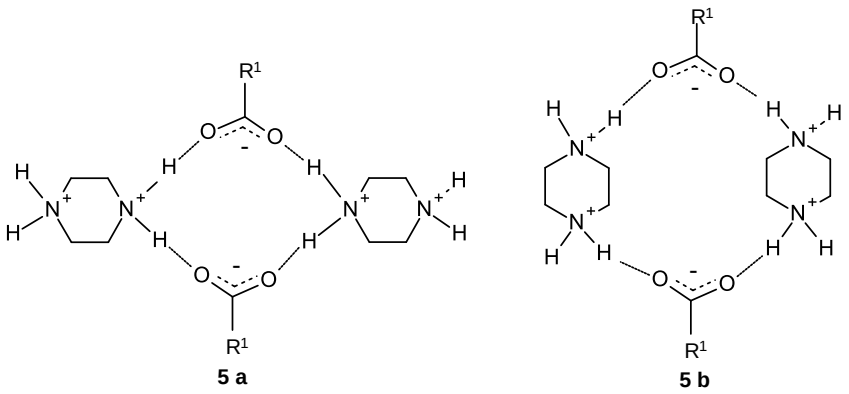


Figure 2. The hydrogen bond between piperazinediium and carboxylates.

Interestingly, the bioactivity of many hybrid molecules of bioactive natural products with piperazine moiety has been improved, for example, flavone derivative **6** displays potent antibacterial activity (2 to 2.5-fold more potency than ciprofloxacin).[35] Coumarin derivative **7** exhibits significant activity and good selectivity for acetylcholinesterase (AChE).[36] Similarly, the derivative **8** shows considerable antiarrhythmic activity with an ED_{50} value of 0.69 mg/kg in adrenaline-induced arrhythmia comparing to ED_{50} values of 1.05 mg/kg for propranolol.[37] The same was observed with myrrhanones B, the chemical modification of side chain of naturally occurring

myrrhanones B with piperazine moiety enhances the cytotoxicity and anti- inflammatory activities (N- methyl piperazine analogue **9** in Figure 2 exhibits about 12–13 folds higher activity against DU145 than myrrhanone B)[38] (Figure 3).

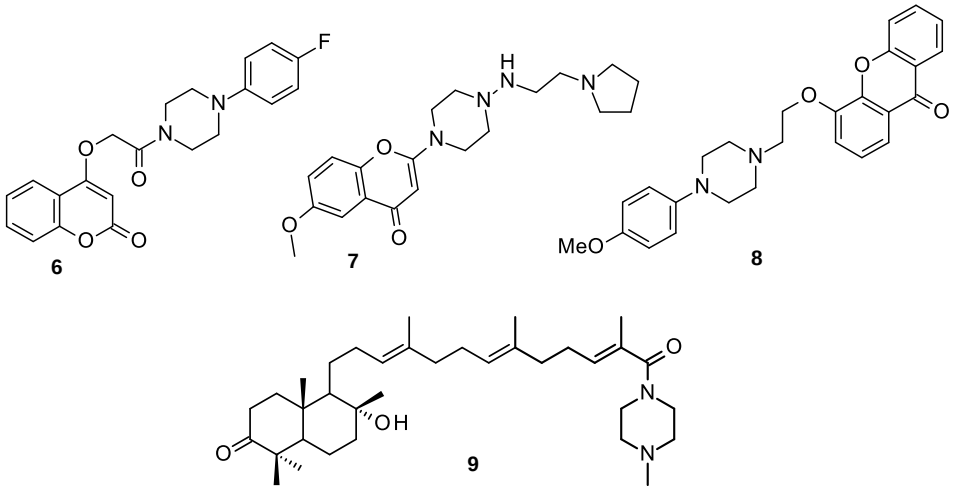


Figure 3. Some hybrid molecules of bioactive natural products with piperazine moiety.

Amongst piperazine derivatives, the oxo- or keto-forms (mono-keto- **A**, diketo- **B1**, **B2** and **B3**, triketo- **C** and tetraketopiperazines **D**) are shown in Figure 4.

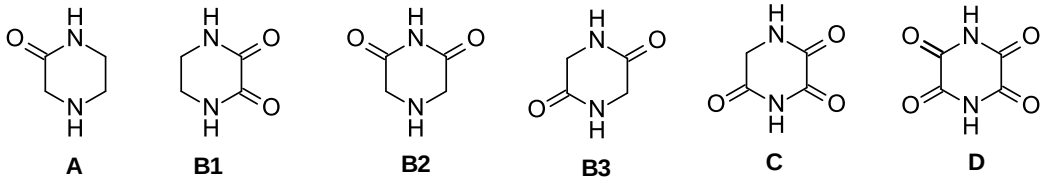


Figure 4. Polyketopiperazines.

The polyketopiperazines have received continuous attention because of their variety of pharmacological activities including antifungal,[39,40] antiviral,[41,42] antitumor[43,44] and antibacterial[45-47] activities. As an example, DKPs have been used as medicinal agents such as, retosiban **10** (tocolytic therapy) and tadalafil **11** (PDE5 inhibitor);[48] also, are used in tumor therapy e.g. plinabulin **12** (antitumor).[49] DKPs are not only present in food e.g. chicken extract, beef and coffee[50,51] but also, DKPs have been isolated from a variety of marine microorganisms (compounds **13** and **14**)[52] and several natural products (compounds **15** and **16**) as represented in Figure 5.

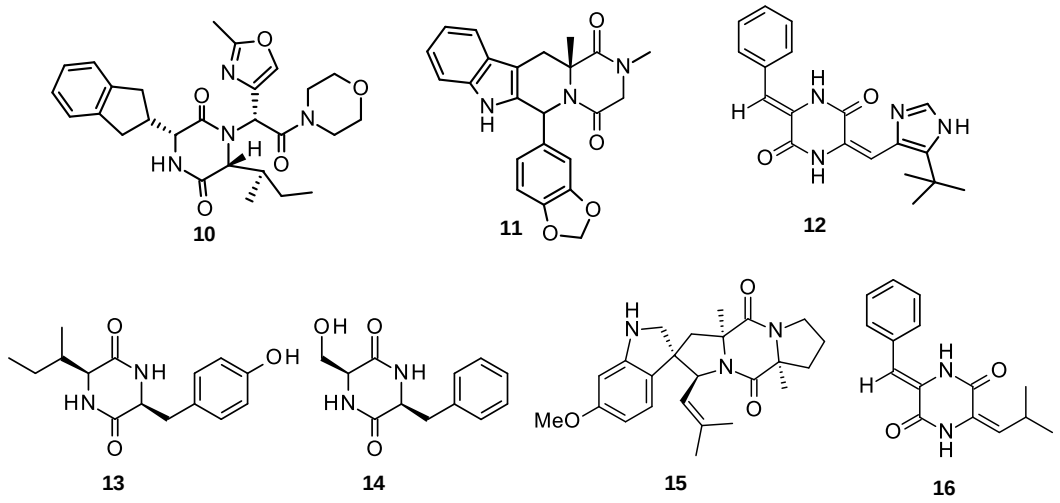


Figure 5. Some drug based DKPs and biologically active DKPs isolated from marine microorganisms and natural products.

Curiously, not only the diketopiperazine receptors consist of a rigid planar structure but also have functional groups that allow the formation of hydrogen bonds,[53] ionic and hydrophobic interactions with any predicted peptide in selective manner. On one side, a hydrogen-bonding ability is considered as a key drive of the self-assembly of the DKPs. As shown in Figure 6, the intramolecular hydrogen bond structures **c**, **d** and **e** were formed within the DKP derivative **17,** both structures **c** and **d** (10-membered H bond) were preferred in self-assembly interactions.[54] As well as, the DKP derived from 4-hydroxyproline **18** gives a rigid support and has a two-armed structure designed for insertion of the peptidic side chains[55] (Figure 6).

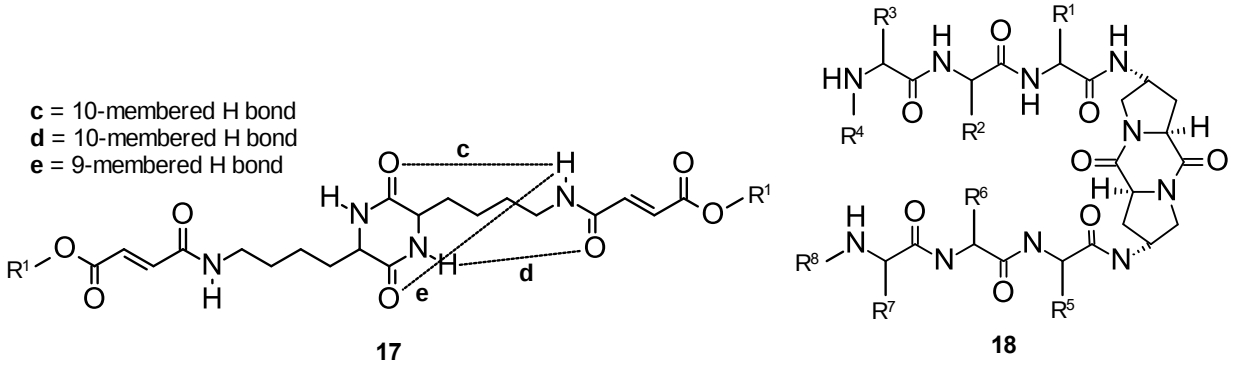


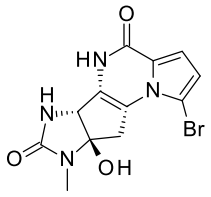
Figure 6. Some DKP receptors have H bond (**17**) and two-armed rigid planar structure (**18**).

To our knowledge, it was noticed that no comprehensive review concerning triketopiperazines and tetraketopiperazines have been published to date, probably because, they are less common in nature, hence, need more investigations to study their utility. Thus, the present review focuses on synthesis, reactions, bioactivities, and possible applications of both triketopiperazines and tetraketopiperazines and will briefly

discuss monoketopiperazines and diketoopiperazines which are commonly present in nature and are extremely well investigated.

2. Piperazinone (2-Oxypiperazine, 2-Ketopiperazine)

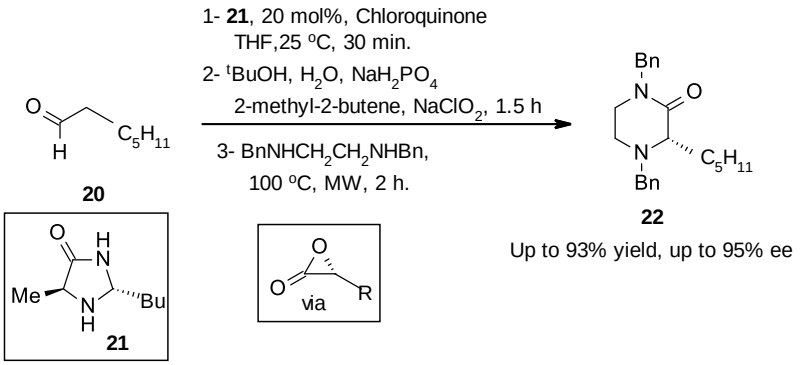
2-Oxopiperazines (piperazinones) are oxo-derivatives of piperazine through the oxidation of piperazine, and they represent essential basic moiety of various natural products such as agelastatin A **19** (Figure 7).[56]



19

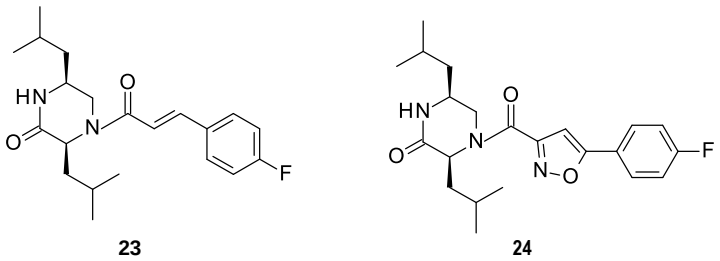
Figure 7. Agelastatin A.

The piperazinones were computed as prized intermediates for the formations of peptidomimetic compounds and natural products. So, many appropriate synthetic methodologies for the preparation of piperazinone derivatives have been collected.[57-61] For example, a catalytic enantioselective synthesis of piperazinone derivatives was explored.[62,63] The synthesis starts from aldehydes **20** using MacMillan's catalyst **21** and chloroquinone as the chlorinating reagent. [64,65] The α-chlorination of heptanal followed by oxidation producing α-chloroheptanoic acid which was cyclized with *N*,*N*′-dibenzylethylenediamine yielding 2-oxopiperazine **22** in good yield (Scheme 1).[47,66]



Scheme 1. Catalytic enantioselective synthesis of piperazones.

On the other hand, SAR studies of 2-piperazone derivatives were explored. This study shown that, the functionalization of amide group as well as C-3/C-6 cis configuration of the piperazinone moiety was essential for HCV activity. A 10-fold growth in GT-1 activity was detected when the chiral phenylcyclopropyl amide side chain in compound **23** was replaced with *p*-fluorophenylisoxazole-carbonyl moiety as in the compound **24**[67] (Figure 8).



23 **24**

Figure 8. Structures of compounds **23** and **24.**

3. Diketopiperazine (Cyclo-Peptides, *cyclo*[Gly-Gly)

2,5-Diketopiperazines (DKPs) are the simplest cyclo-dipeptides in nature and are naturally occurring in several microorganisms, food, and beverages. Although these compounds have been well recognized since the start of the 20th century, they have been lately raising the attention due to its diverse bioactivities, such as, anticancer, antiviral, antioxidant, and neuroprotective properties.[68-73]

Structurally, 2,5-diketopiperazines (DKPs) have six membered saturated rigid ring with two centrosymmetric s-cis-amide bonds leading to make several hydrogen bonding acceptor and donor positions which give its ability to create a planar molecular structure through the formation of intermolecular hydrogen bonding.[74-77] These features attract awareness of scientists in diverse fields, such as self-assembly synthesis of cyclic dipeptide derivatives and their applications[78,79] and bio-based mesoporous sponges of DKP derivatives.[80] Furthermore, supramolecule of DKP derived from hydroxyphenylglycine,[81] asymmetric catalytic promoted method for the synthesis of cyclo-peptides,[82] as well as, the synthesis and anti-cancer activity of naturally occurring 2,5-diketopiperazine derivatives were studied.[83] On the other hand, structural rigidity of DKP may be provide superior thermal stability and practical handling for the creation of DKPs polymers, such as, polyacetylenes carrying diketopiperazine moieties,[84] tubulin polymerization inhibitors[85] of proline-based 2,5-diketopiperazines by anionic ring-opening polymerization,[86] prebiotic thermal polymerization of crystals[87] and polymerization of amino-acid-based diene[88] which were synthesized and examined.

Observably, there are several reviews reported on DKPs, and will only collect some of them in this review, such as, Prasad reviewed the synthesis and biological activity in human of cycle(L-His-L-Pro),[89] the synthesis of bicyclomycin has been summarized on the basis of molecular structure and biological activities of DKPs.[90] Smythe et al[91] reviewed all structural advantages of the DKP moieties involving their rigidity, stability and diverse biological activity, another review discussed the methodologies for the formation of cyclic peptides,[92] Dismore and Beshore described the stereoselective methodology for the synthesis of DKP isomers,[93] and combinatorial chemistry and many advanced methods for DKPs synthesis were examined.[74]

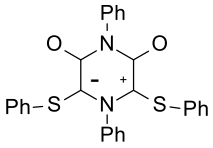
Recently, Borthwick summarized the synthesis, reactions, bioactivities of DKPs in addition to bioactive natural products.[94] Also, Cao et al. reported a chemical diversity and a biologically active indole diketopiperazine (DKP) alkaloids isolated from fungi,[95] the structures of DKP dimers from marines and their biological activity were discussed.[96,97] Additionally, Ma et al. reviewed cyclotetrapeptides and new diketopiperzine derivatives from the marine sponge-associated fungus.[98]

Interestingly, the reaction of DKP derivatives under different conditions and reagents were explored. Honzl and Šorm have been studied the reaction of 1,4-disubstituted 2,6-diketopiperazines with benzenesulfonyl and benzenesulfenyl chlorides in pyridine producing the mesoionic system with a six-membered ring structure **E**.[99]

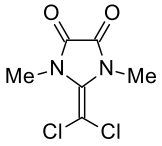
Also, the reaction of 1,4-disubstituted 2,6-dioxopiperazines with numerous oxidizing agents, such as selenium dioxide in dioxane afforded tetraketopiperazine.[100] While the α,α-disubstituted sarcosyl chloride has been isolated from the reaction of N-trifluoroacetyl sarcosine with first thionyl chloride followed by treatment with sulfuryl chloride.[101]

Furthermore, the reactions of glycine anhydride and its methyl derivatives (sarcosine anhydride) and alanine anhydride in deoxygenated aqueous solutions in the absence or presence of $K_3Fe(CN)_6$ as oxidant by pulse radiolysis producing 2,5-diketo-3-hydroxypiperazine were investigated.[102]

Moreover, the photoisomerization of 5, 6-dicholoro-1, 4-dihydro-1, 4-dimethylpyrazine-2, 3-dione was explored. It was treated with UV irradiation producing the compound **F** which then was converted into dimethylimidazolidinetrione by the effect of moisture. This photoisomerization is thermally reversible reaction, additional, the compound **F** was hydrolyzed to 1,4-dimethylpiperazine-2,3,5,6-tetrone.[103]

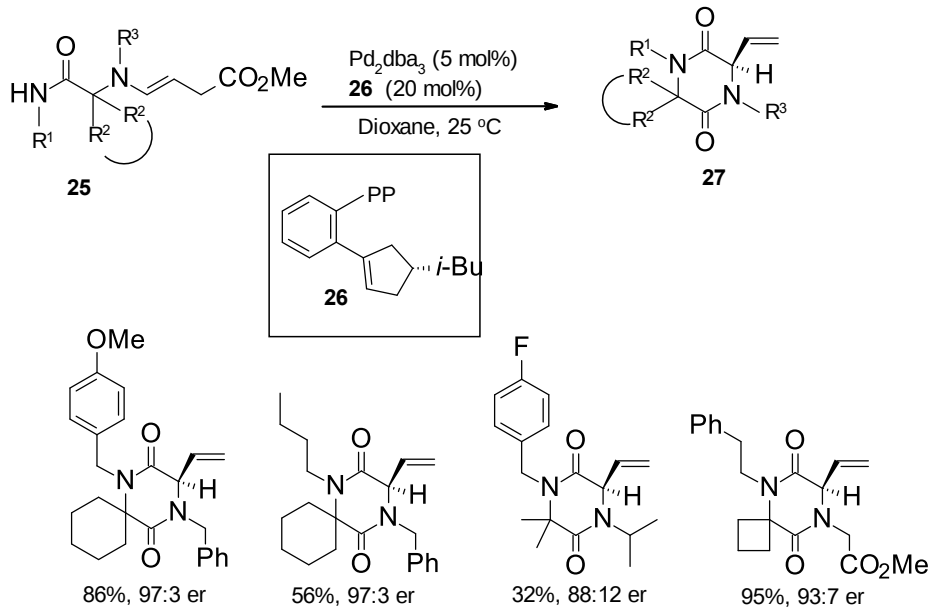


E



F

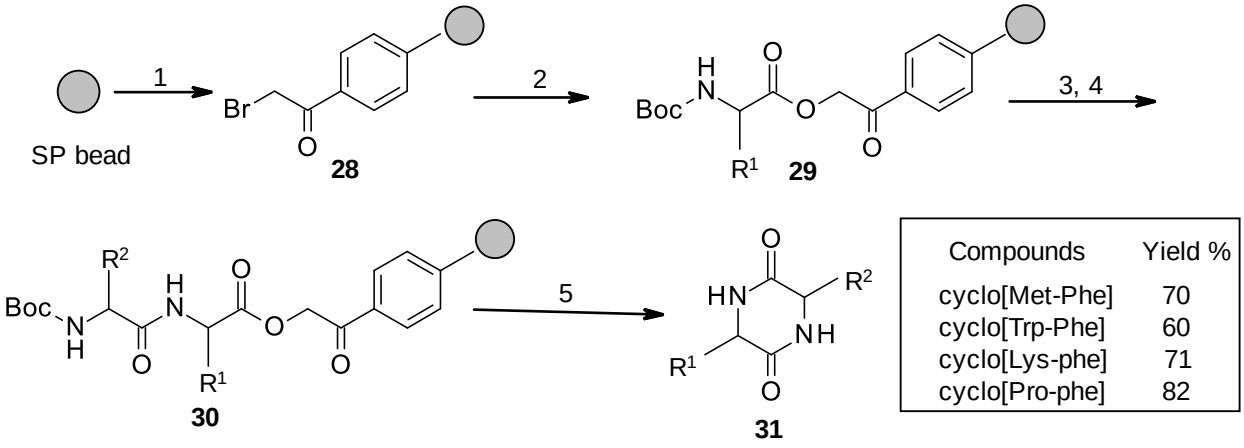
Moreover, several studies on the synthesis and biological activities of DKPs were explored. For example, the spiro-diketopiperazines **27** were synthesized in >90: 10 enantiomer ratios (er). These compounds have been shown numerous biological activities, including anti-inflammatory, neuroprotective and antiproliferative effects against drug-resistant human cancer cell lines[104,105] (Scheme 2).



Scheme 2. Synthesis of spiro-dioxopiperazines.

The cyclo(Phe-Cys) and cyclo(Tyr-Cys) were synthesized from protected amino acids using triethylamine and diethylphosphoryl cyanide as catalyst. The structure and conformation of these derivatives have been investigated with X-ray crystallographic and spectroscopic methods.[106,107]

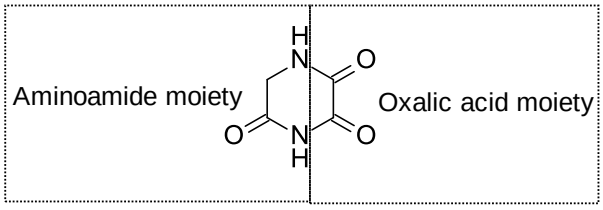
In addition, a number of DKP derivatives were synthesized in good yields using a solid-phase methodology as shown in Scheme 3,[108] as well as the total synthesis of biologically active and naturally occurring diketopiperazine type indole alkaloids (neoechinulin) was also explored.[109]



Scheme 3. Reagents and conditions: (1) $BrCH_2COBr$, $AlCl_3$, nitrobenzene DCM (1:1); (2) Boc-AA-OH, Et_3N, DMF; (3) 3.5N HCl/HOAc; (4) Boc-AA-OH, HOBt, DCC, NMM, DMF; (5) 5% Et_3N/ THF: H_2O (8:1).

4. Triketopiperazine

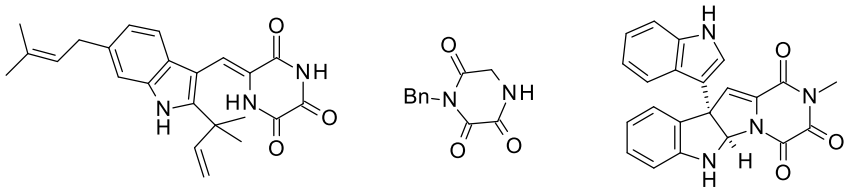
Logically, 2, 3, 5-triketopiperazine **C** (TKP) is produced by oxidation of one of the methylene groups of DKP.[110] The TKP can be produced from the reaction of any aminoamide with oxalic acid derivatives as in Figure 9. Hence, due to this alteration and modification in starting substances, the properties and reactivity of TKP are significantly different from DKP. TKPs are six-membered saturated rigid ring that possess only one methylene group which can be functionalized.[111]



C

Figure 9. The TKP produces from the reaction of any aminoamide with oxalic acid derivatives.

Also, the presence of TKP moiety in nature is considered rarely. Only a few examples have been separated from fungi and usually in combination with epidithiodioxopiperazine (ETP) and DKP derivatives (Figure 10).[112] For example, the metabolites neoechinulin C **32**, compound **33** and gliocladin **34**[113] were isolated from *Aspergillus amstelodami,*[112] and from *Emericella striata*[114] respectively. These metabolites showed antibacterial activity.[115] Additionally, the naturally occurring indole alkaloid gliocladin C **34** was isolated from a strain of *Gliocladium roseum* which was obtained from *sea hares, Aplysia kurodai.*[116]



Neoechinulin 32 **33** **Gliocladin C 34**

Figure 10. Some biologically active compounds contain TKP moiety.

Afterward, first total asymmetric synthesis of gliocladin C **34**,[117] and the enantioselective organocatalytic formation of the compound **34** with optimization of the reaction conditions were reported.[118] Further, a general methodology for making (+)-gliocladin A from triketopiperazine and the cytotoxic activity against persistent human prostrate (DU145) plus melanoma (A2058) cancer cell lines were described.[119] Finally, the total synthesis of the compound **34** using visible light-promoted coupling reaction was achieved. It was observed, by using microwave method, the overall yield was improved and the number of steps of TKP derivatives formation was reduced.[120]

4. 1. Historical background

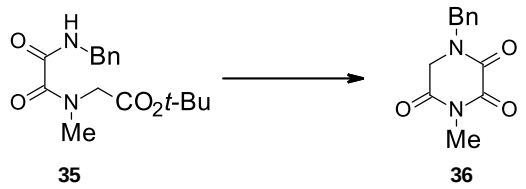
It is well known that the TKPs are less common than the DKP and are isolated from some natural products and microorganisms. In 1917, Bornwater is the first explorer that reported the preparation of *α*-benzyl-TKP through the reaction of phenylalanine amide with oxalyl chloride.[121] Bergmann and co-workers in 1927 reported another synthetic method of TKP but this technique required long sequence of reactions through amide couplings and ozonolysis.[122] Notice that both methods were difficult to reproduce.[123] Until 1953, Williams and co-workers described the first appropriate methodology for preparation of TKP *via* the reaction of ethyl oxalate with DL-β-phenylalanine amide.[123]

Later, in 1984, Mulliez and Royer reported a convenient method for synthesis of TKPs.[124] The functionalization of TKP (N- and O- alkylations with different halide derivatives) under mild reaction conditions was studied.[125] To this time, the biggest challenge would be to create effective methodology for the preparation of TKP on gram scale; only two methods have been reported to synthesis TKPs under mild conditions.[126, 127] Since, Overman has been described the total synthesis of gliocladin C **34**, the TKPs synthesis show increase in production and evaluation of these derivatives.[128-130] We will discuss some of these methods in the synthetic part.

4. 2. Synthesis of 2,3,5-triketopiperazines

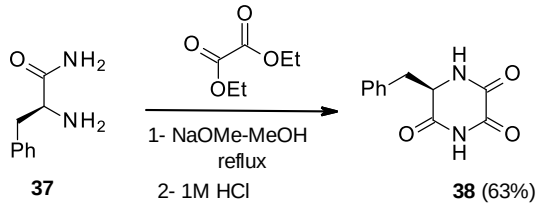
4. 2. 1. By the reaction of oxalic acid derivatives with amino acid amide. Williams and co-workers described the initial relevant synthetic method for TKP *via* the reaction of ethyl oxalate with DL-β-phenylalanine amide in ethanol in the presence of sodium methoxide yielding 60% product as TKP sodium salt.[123]

In 1984, Mulliez and Royer postulated intramolecular cyclization of amino-amide derivative **35** which was obtained *via* the reaction of oxalic acid derivatives with glycine, alanine or phenyl- alanine derivatives separately[124,131,132] (Scheme 4).



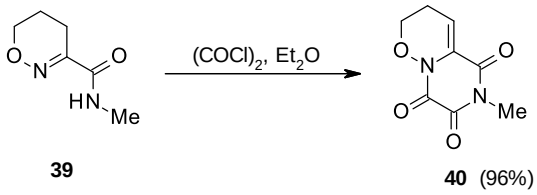
Scheme 4. The formation of TKP via intramolecular cyclization of amino-amide derivative.

While Bailey *et al.* utilized the same synthetic method using an enantiomerically pure amino amide **37**. As expected, racemization was observed with comparable yield under the given reaction conditions (Scheme 5). Also, N- and O- alkylation of TKP by different halides were investigated.[125,132]



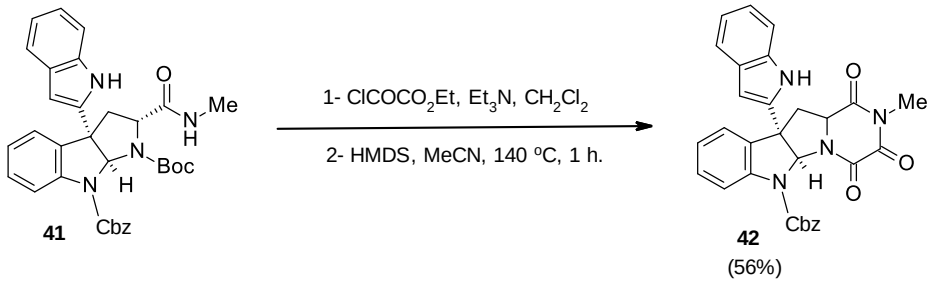
Scheme 5. The formation of TKP from oxalic acid derivatives and amino amide.

The intermolecular cyclization of 5, 6-dihydro-N-methyl-4H-l,2-oxazine-3-carboxamide **39** with oxalyl chloride yielding bicyclic derivative of TKP **40** was reported (Scheme 6).[133]



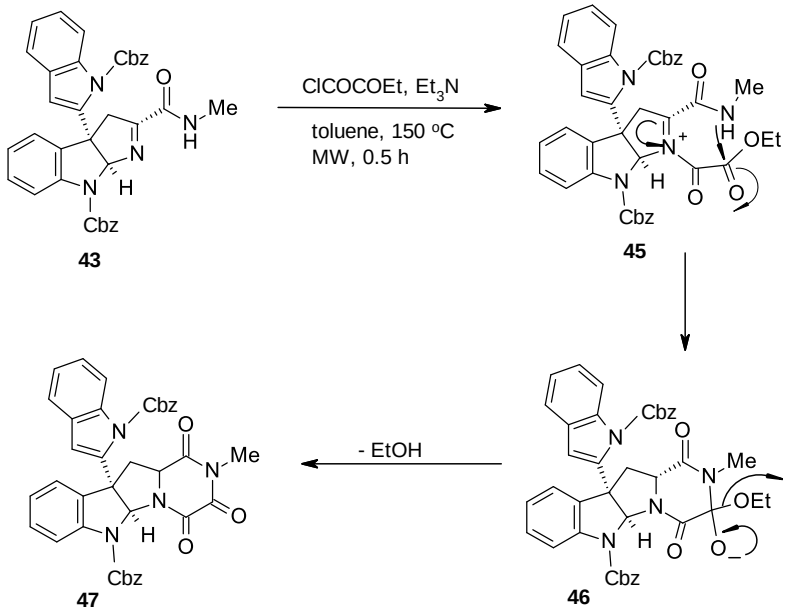
Scheme 6. Synthesis of bicyclic derivative of TKP.

Moreover, under microwave conditions the TKP **42** was produced from the reaction of amino amide **41** with chloro-oxalate using hexamethyl disilazine (HMDS) in the presence of Et_3N as catalyst at 140 ^oC as shown in Scheme 7.[120] The intermolecular C–H functionalization of many heteroaromatics with bromo-pyrroloindolines, e. g. compound **41**, was studied. This compound **41** was used for synthesis of gliocladin C **34** and several biologically active pyrroloindoline alkaloids employing lithium bis-catechol borate ($LiB(cat)_2$) as a reductive quencher in photo redox reaction.[134]



Scheme 7. Formation of indole derivative of TKP.

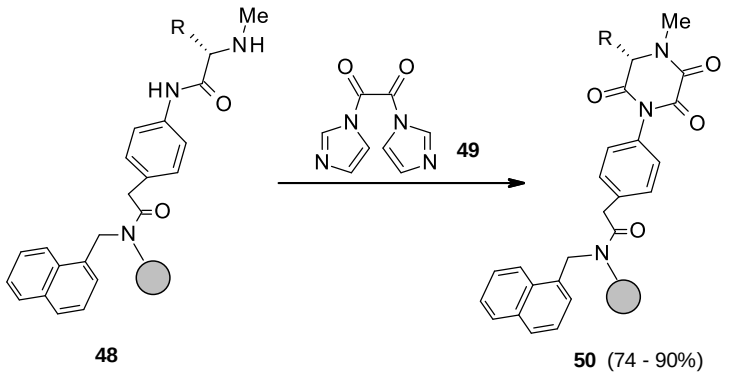
Under the same condition using toluene at 150 °C instead of CH_2Cl_2 the TKPs **47** was obtained in 76% yield as shown in Scheme 8.[135,136]



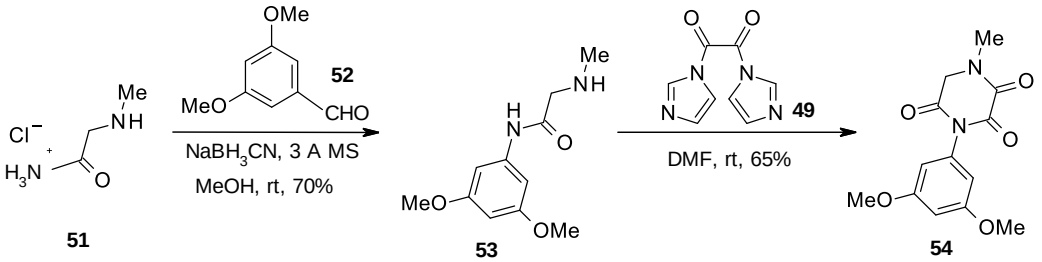
Scheme 8. Synthesis of TKP derivative using MW method.

4. 2. 2. *Via* the reaction of oxalyl diimidazole or oxalyl 1, 1'-dibenzotriazole with amino amide. It is noteworthy that, the oxalyl chloride used for cyclization step in the synthesis of TKPs is very reactive toward either reactants or products. Instead, oxalyl diimidazole **49** is preferred in both solid and in solution conditions. As example, Makino and co-workers were first pioneers that synthesized TKP **50** on solid support using oxalyl diimidazole **49** as a mild cyclizing agent[126] (Scheme 9).

Also, Overman *et al.*[117] synthesized TKP derivatives using amino amide intermolecular cyclization with oxalyl diimidazole. Afterward, the more applicable methods for total syntheses of TKP derivatives were performed by Overman, Stephenson, and Movassagui groups separately.[127,136,137] Noteworthy, Overman's group in 2011 synthesized the TKP derivatives under mild conditions in solution. While Stephenson and Movassagui cyclized the protected amino amide **53** under the same reaction conditions of Tsuji's group[127] to create the TKP derivatives **54** on the solid support (Scheme 10).



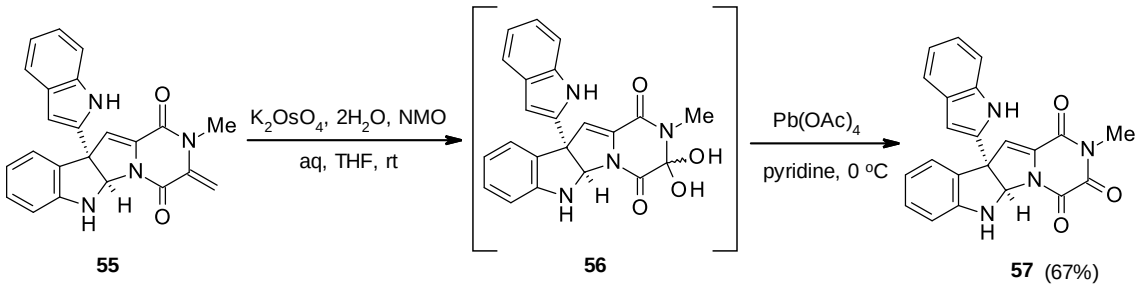
Scheme 9. Synthesis of TKPs using solid support method.



Scheme 10. Synthesis of TKP derivative using oxalyl diimidazole.

Additionally, the formation of the TKP system was achieved by the cyclization of protected amino amide with oxalyl diimidazole[138] under mild conditions producing TKP on gram scale. Noting that, oxalyl 1,1'-dibenzotriazole[139] was also employed in the preparation of TKPs.[140]

4. 2. 3. Conversion of DKP derivatives into TKP derivatives. Under Upjohn-like dihydroxylation conditions, the DKP derivative **55** was converted to dihydroxy derivative **56.** The product was treated with $Pb(OAc)_4$ in pyridine to produce TKP **57** in 67% yield.[141,142] (Scheme 11) Additionally, the $FeCl_3$-catalyzed photo-oxidation of N,N'-dimethyl-dioxopiperazine produced N,N'-dimethyl-2-benzylpiperazine-3,5,6-trione.[143]

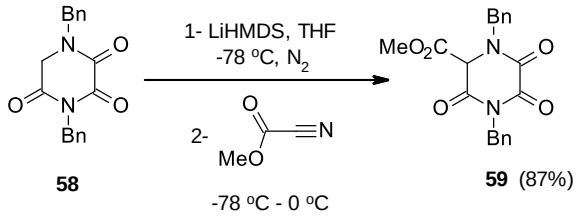


Scheme 11. Conversion of DKP to TKP.

4. 3. Reaction of TKPs

TKP has two imide groups incorporated within the ring structure of the molecule and only one methylene group accessible for further derivatization.

4. 3. 1. The formation of C–C bonds. 4. 3. 1. 1. Acylation of triketopiperazines. The acylation of protected DKPs **58** was achieved *via* reaction with Mander's reagent/ LiHMDS [144] at low temperatures producing 6-acyl triketopiperazine **59** in pure state with high yields (Scheme 12).[145]



Scheme 12. Acylation of TKPs.

4. 3. 1. 2. Michael-addition reactions. The Michael/conjugate-addition reaction is considered as one of the most common reactions for the creation of C–C bonds in a stereoselective way.[146,147] Also, it is utilized for the design of various series of highly functionalized bioactive compounds.

On the other hand, the acidity of the α-proton in cyclic peptides has a vital role in biochemical reactions with stereochemical control which is important for their biological activities. The acidity of TKPs is 10^6-times more acidic than their DKP analogues due to the formation of aromatic transition state **62** during the creation of the TKP enolate derivative[148,125] (Figure 11).

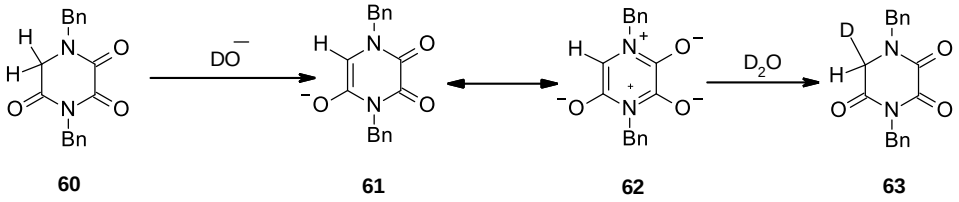
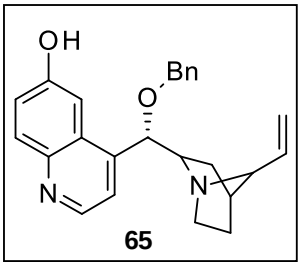
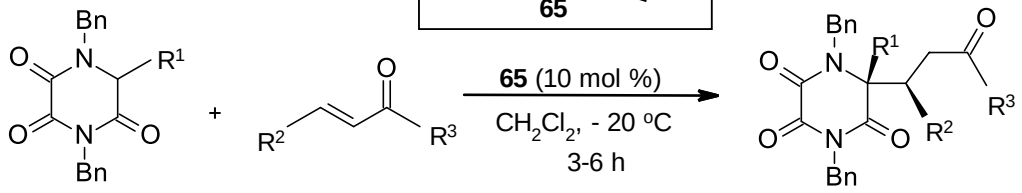


Figure 11. Hydrogen-deuterium exchange in the resonance structures of TKP enolate.

The triketopiperazine structure is considered as operational example of 1,4- addition reaction to enones or enals using chiral organo-catalysis (Scheme 13).[130]



65



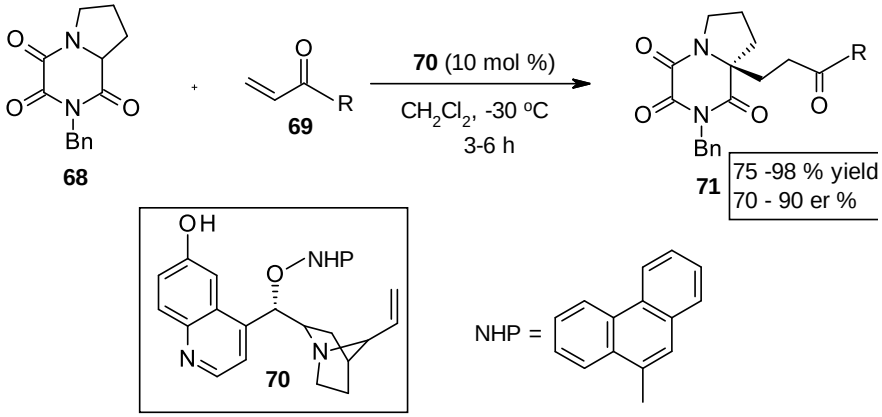
63 **64** **67**

R^1	R^2	R^3	Yield %	ee (%)
COOMe	H	Me	99	98
COOMe	H	aryl	87-98	98
H	H	Me	98	86
Ph	H	Ph	98	98(a)

(a) Isolated as a single diastereomer.

Scheme 13. Synthesis TKP using cinchona catalyst.

Kinetic resolutions with highly stereoselective reactions of TKPs with both aromatic and aliphatic enones, and acrolein using a chiral organo-catalyzed Michael addition were described.[149,150] For example, the 1,4-additions of alkyl vinyl ketone (MVK) **69** to TKP **68**, using chiral cinchona alkaloid derivative **70** as catalyst gave products with high levels of stereoselectivity and excellent yields; e.g. the products **71** were produced in up to 94:6 er.[150,151] (Scheme 14).



68 **69** **71**

75 -98 % yield
70 - 90 er %

70

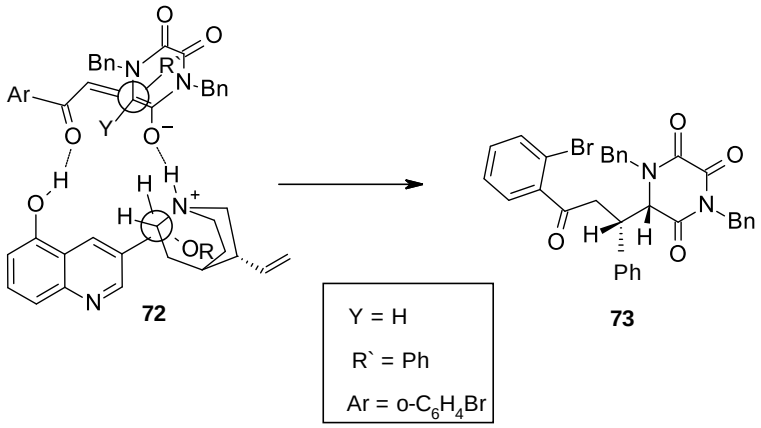
NHP =

Scheme 14. Michael addition reaction of TKP.

Also, a good to excellent yields with high degrees of enantioselectivity especially for derivatives having either phenyl, *p*-substituted phenyl or unsubstituted 5-membered heterocycles moieties separately, were produced.[152]

Interestingly, X-ray crystallography study for the reaction of TKP with ortho-bromo chalcone show that the formation of new asymmetric center at C-6 in the TKP ring has been happened, owing to enolate formation

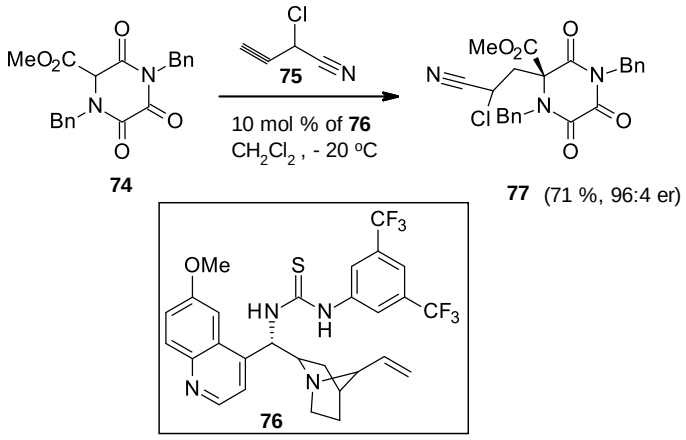
through the formation of 1-azabicyclo[2.2.2]octane amine moiety and the creation of hydrogen bond between the Michael acceptor with the quiuclidine phenol as shown in Scheme 15.[145,153,154]



72 **73**

Scheme 15. Hydrogen bond Michael acceptor and quiuclidine phenol.

Although a good result was observed as shown in Scheme 15, but the use of substituted enones may lead to decrease in reaction reactivity. However, the Michael additions with enones having electron withdrawing groups in β-position provide better yields.[155] On the other hand, by using another organo-catalyst (thiourea catalyst) **76,** the TKP **74** was reacted with *α*-chloroacrylonitrile **75** producing the product **77** in an excellent yield (Scheme 16).[145]

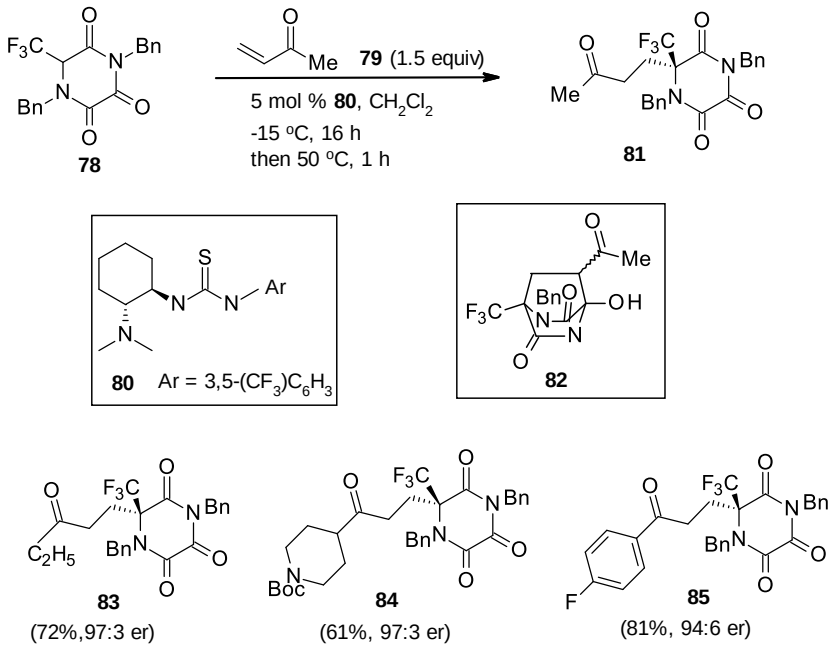


74 **75** **77** (71 %, 96:4 er)

76

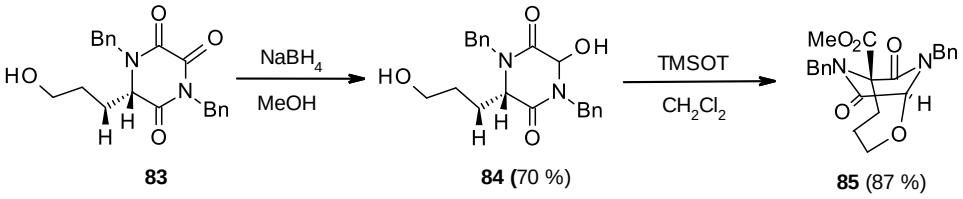
Scheme 16. Reaction of TKP with chloroacrylonitrile using thiourea catalyst.

The 1,4-addition of methyl vinyl ketone (MVK) **79** to (±)-triketopiperazine **78** using thiourea catalyst **80** in CH_2Cl_2 at −158 °C, the derivative **81** was produced in 61-81% yield and 97:3 er, on a 2.5 g scale *via* compound **82**[156,157] (Scheme 17).



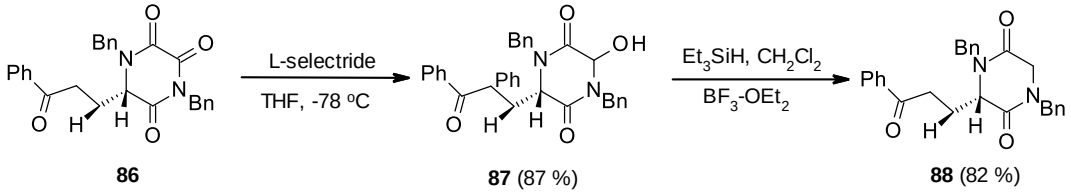
Scheme 17. Catalytic asymmetric Michael addition of CF_3-triketopiperazine.

4. 3. 2. Reduction of the C-3 position. Remarkably, the carbonyl group at position C-3 showed the specific electrophilic properties compared to carbonyl groups at positions C-2 and C-5 due to carbonyl group at C-3 connected to both the imide and the oxalyl moieties. The complete reduction of carbonyl C-3 into methylene group by $NaBH_4$ yielding the chiral DKP was studied. As example, the transformation of derivative **83** into the ether bridged compound **85**, through the diol derivative **84** by using AgOTf[158] or TMSOTf[159] was explored. In Scheme 18, the chiral compound **85** (>96 : 4 er) exhibits 4-atom ether-bridged DKP similar to that present in the antibiotic bicyclomycin which was isolated from *Streptomyces sapporonensis*[160] (Scheme 18).



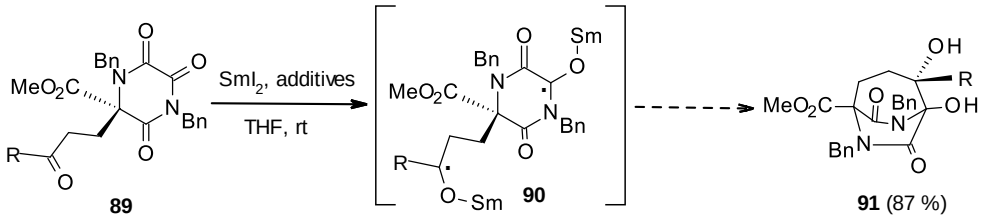
Scheme 18. Reduction of TKP with $NaBH_4$.

Likewise, the reduction of TKPs to the corresponding DKPs, with the retention of configuration, could be achieved in high yield by reducing agent L-selectride, then treatment with Et_3SiH and BF_3–OEt_2[145] (Scheme 19).



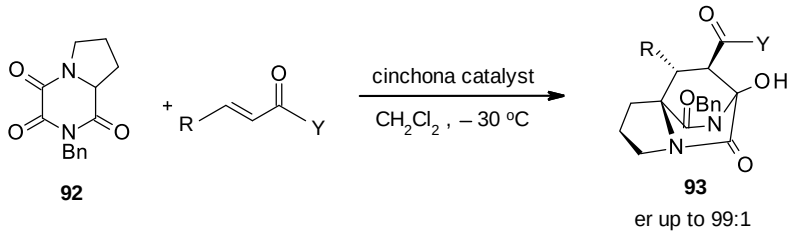
Scheme 19. Reduction of TKP with L-selectride.

Further, the TKPs were reduced using SmI_2 in THF/water. The diradical reaction intermediate **90** would then form a new carbon-carbon bond producing bicyclo[2.2.3]diazanonane derivative **91** (Scheme 20).[145]



Scheme 20. Reduction of TKP with SmI_2.

4. 3. 3. Rearrangement of TKP to bicyclo[2.2.2]diazaoctane. Remarkably, triketopiperazine (TKP) **92** reacts with β-substituted enones using cinchona alkaloid catalyst creating bicyclo[2.2.2]diazaoctane **93** with 99 : 1 enantiomeric ratio (er)[151] (Scheme 21).



Scheme 21. Formation bicyclo[2.2.2]diazaoctane.

Also, some of bicyclo[2.2.2]diazaoctane derivatives obtained from rearrangement of TKPs can be collected in the following Figure 12 using different catalysts.[140]

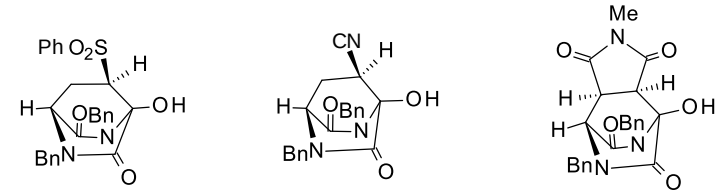
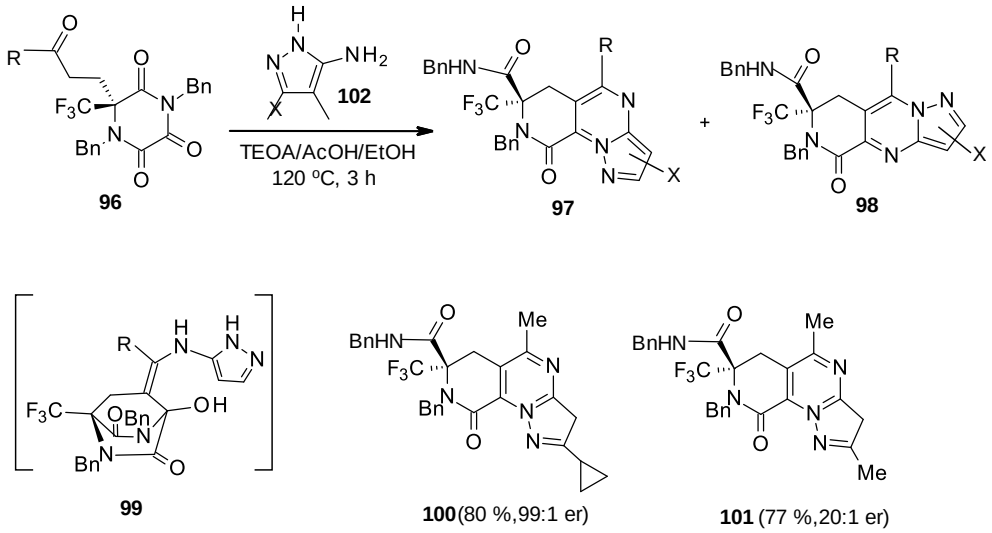


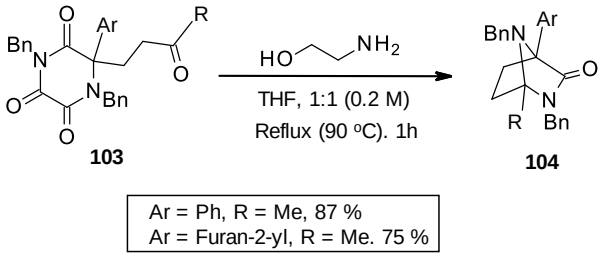
Figure 12. Some of bicyclo[2.2.2]diazaoctane derivatives obtained from rearrangement of TKPs.

Moreover, tricyclic pyrazolopyrimidines **97** and **98** can be produced from the reaction of the triketopiperazine derivative **96** with 3-aminopyrazole **102** *via* enamine mediated rearrangement of intermediate **99** (bicyclo[2.2.2]diazaoctane derivatives). (Scheme 22) It was found that, both acetic acid and triethyl orthoacetate (TEOA) were preferred to use attributing to minimize the formation of regioisomer **98**. Hypothesized that this method may be used to get numerous derivatives of bioactive tricyclic pyrazolopyrimidines in both stereo- and regiocontrol manner.[156]



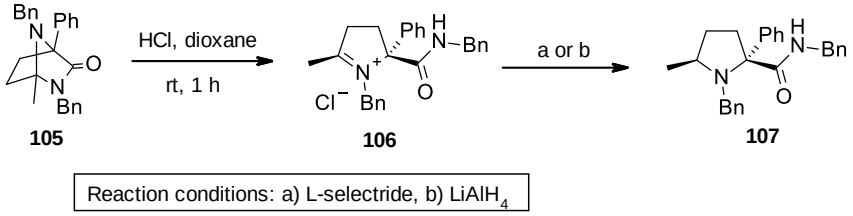
Scheme 22. Formation of tricyclic pyrazolopyrimidines from TKP derivatives.

4. 3. 4. Rearrangement of TKP to diazabicyclo- [2.2.1] heptane. Excitingly, the treatment of compound **103** with ethanolamine forms an unusual bridged N-acyl derived structures **104** in good to high yields by removing the oxalyl moiety[152] (Scheme 23).



Scheme 23. Rearrangement of TKP to diazabicyclo- [2.2.1] heptane.

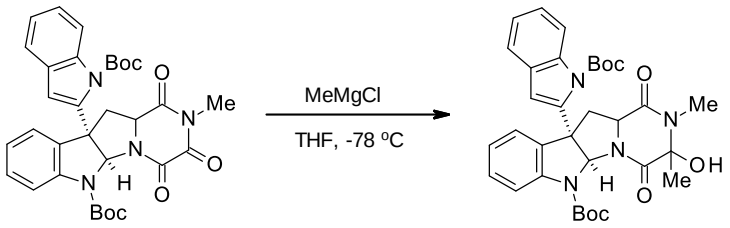
Interestingly, the diazabicyclo- [2.2.1] heptane **105** can be reacted with HCl in dioxane to form derivative **106** which can be converted to prolinamides **107** through the reductive ring opening of **106** (Scheme 24).[152]



Scheme 24. Reaction pathway to prolinamides.

4. 3. 5. Reaction with Grignard reagent. Another example indicating that the carbonyl group of C-3 position shows specific electrophilic properties comparing to carbonyl groups at C-2 and C-5[151] is represented by the

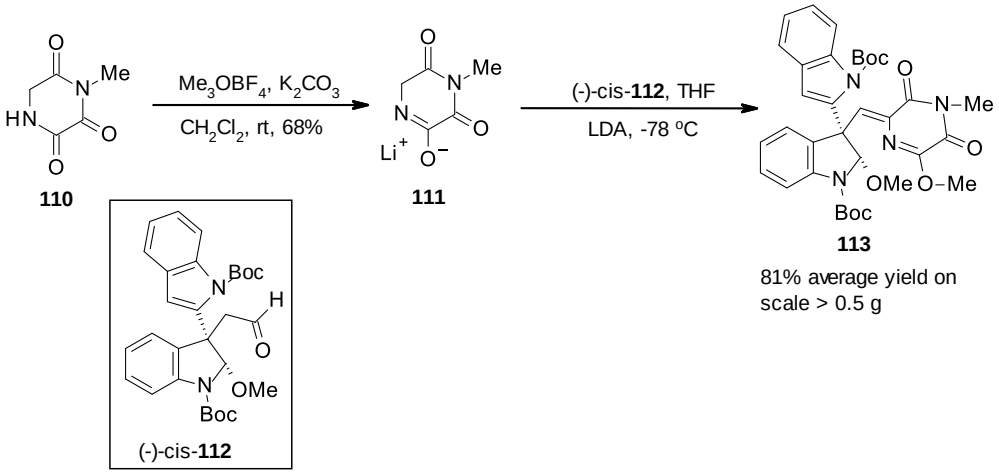
addition of MeMgCl to the TKP derivative **108** in THF at -78 °C yielding compound **109** (Scheme 25).[119,151]



108 **109** (86 %, 9:1 dr)

Scheme 25. Reaction of THP derivative with Grignard reagent.

4. 3. 6. Aldol condensation. The aldol condensation of aldehyde **112** with lithium enolate derivatives **111** using lithium diisopropylamide (LDA) achieved a pure *Z* isomer of compound **113**[127] (Scheme 26).



110 **111** **113**

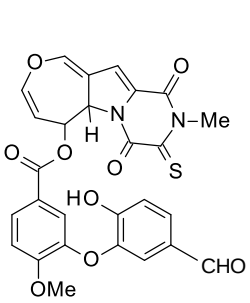
81% average yield on scale > 0.5 g

(-)-cis-**112**

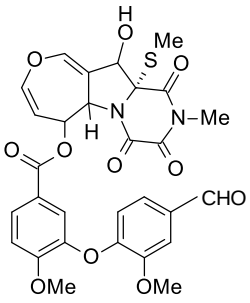
Scheme 26. Aldol reaction of TKP derivatives.

4. 4. Bioactivity of TKP derivatives and applications

Although the triketopiperazine is far less common in nature, but its derivatives have significant biological activity, such as the TKP (neoechinulin C **32**), thione-derivative of TKP (aurantioemestrin) **114** and MPC1001F **115** which have been confirmed as a potent antimicrobial and antifungal activities.[114,161-163]

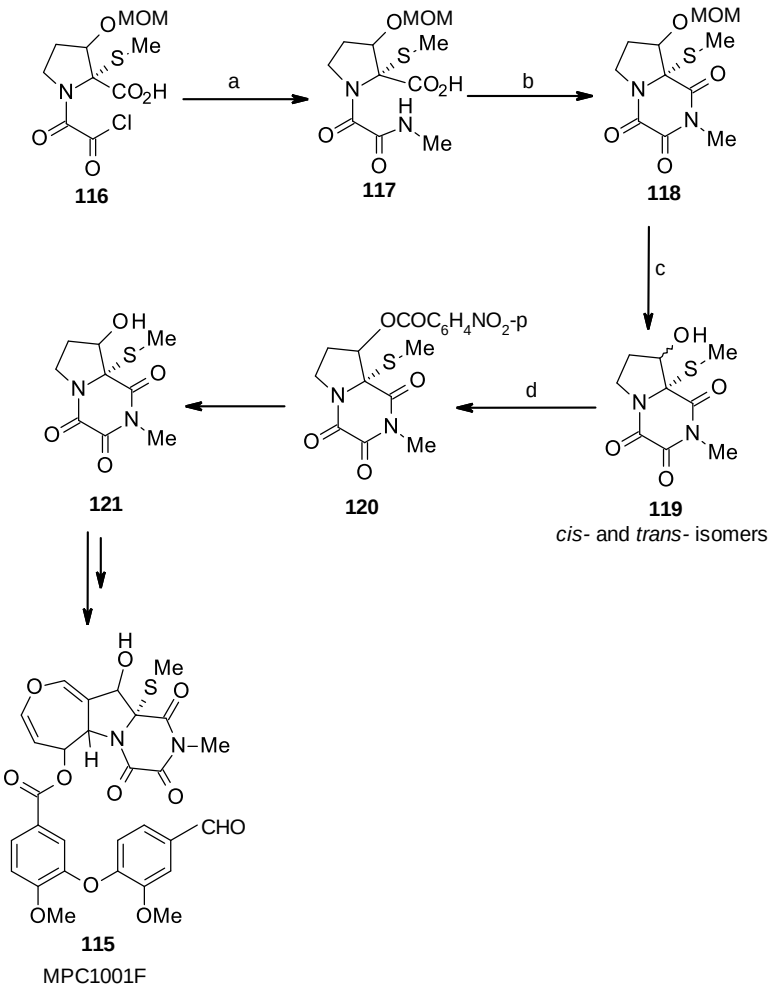


114
Aurantioemestrin



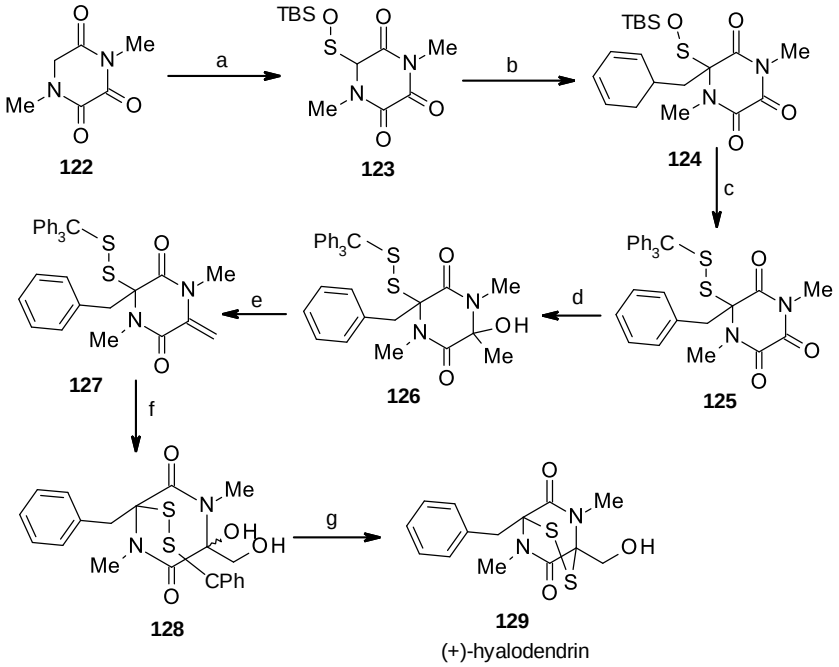
115
MPC1001F

Moreover, natural product, MPC1001F, **115** was first isolated from the fungus *Cladorrhinum sp. KY4922* in 2004.[164] It exhibits high antimicrobial activity against Gram positive bacteria but moderate effects towards Gram negative bacteria.[165] Also, it is about 40 times more active against the human prostate cancer cell line DU145 comparing with etoposide.[165] The synthesis of MPC1001F was carried out by the cyclization of an α-ketoamide **116** as indicated in Scheme 27.[166]

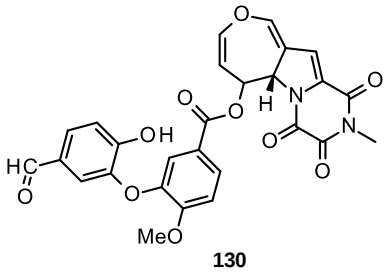


Scheme 27. Reagents and conditions: (a) $MeNH_2$, THF, −78 °C, 73%. (b) Et_3N, MeOH, 45 °C, 1 h, 91% for **118** (c) Conc. HCl, MeOH, 60 °C, 1 h, 94% for **119** (d) Ph_3P, *p*-$O_2NC_6H_4CO_2H$, THF, −78 °C.

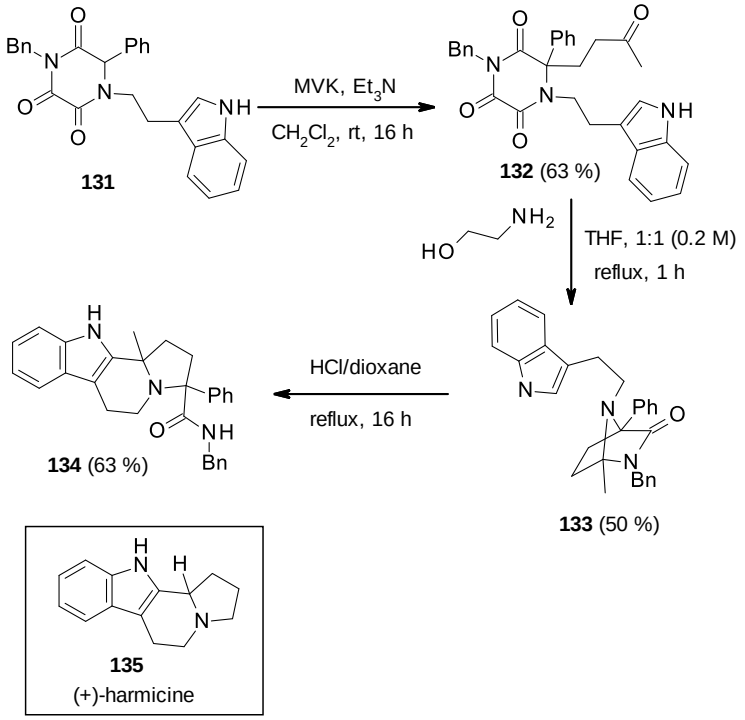
The utility of triketopiperazine moiety in the synthesis of bioactive compounds is described in Scheme 28. As example, the treatment of the compound **122** first with LiHMDS followed by trapping of the resulting enolate with Clive's silyl ether protected reagent achieved the *S*-substituted TKP **123** in excellent yield on 5 g scale. A second enolization with LiHMDS followed by the reaction with benzyl bromide afforded the fully substituted TKP **127** which was cyclized producing hyalodendrin **129** (well known as fungitoxic and anticancer agent).[111] In addition, natural product (dethiosecoemestrin **130**) is found in secondary metabolites of fungal species and exhibits various antimicrobial activities as well as cytotoxic activity.[164,167-170]



Scheme 28. Conditions: (a) LiHMDS, THF, −78 °C, *S*-[[(*tert*-butyldimethylsilyl)oxy]methyl] 4-methylbenzene-sulfonothioate, 85%; (b) LiHMDS, THF, DMPU, 0 °C, BnBr, 84%; (c) TBAF, TrSCl, THF, 85%; (d) MeMgBr, THF, −78 °C; (e) PTSA, DCM, 58%; (f) OsO_4, NMO, acetone/H_2O, 89%; (g) $BF_3{\cdot}OEt_2$, DCM, −78 °C to rt, 70%.



As reported, numerous natural product classes were obtained from rearrangement of TKP, for example the bicyclo[2.2.2]diazaoctane moieties which were isolated as the fungal metabolite from *stephacidin A*, and show a potent and selective antitumor activity.[171-173] Moreover, diazabicyclo- [2.2.1] heptane **133** was produced from TKP **131** as illustrated in Scheme 29, the treatment of **133** with HCl achieved the derivative **134** as a single isomer, which has similar structure as the natural product harmicine **135**.[152] This natural product **135** has antispasmodic, antipyretic, and anticancer properties[174,175] as well as antileishmanial and antinociceptive activities.[176]



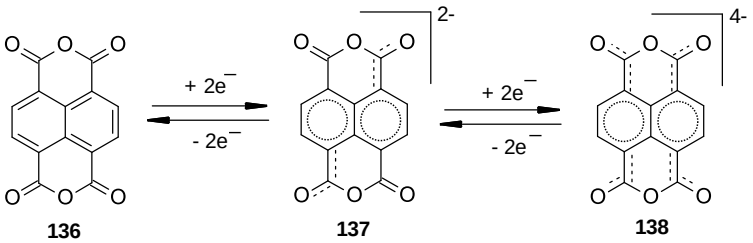
Scheme 29. Synthesis of (+)-harmicine.

5. Tetraketopiperazines

Logically, an oxidation of the methylene group in TKP leads to the formation of a tetraketopiperazine. It is a six membered saturated heterocyclic ring with two nitrogen atoms in opposite positions and four carbonyl groups. Tetraketopiperazine is slightly soluble in water, soluble in boiling acetic acid and freely soluble in dilute aqueous sodium hydroxide or carbonate but not reprecipitated by acids. It has two pK_as; pK_{a1} = 4.8 and the second pK_{a2} = 8.2.[177]

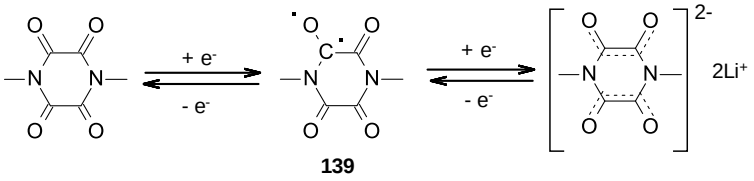
Tetraketopiperazine is one of polyketopiperazines and it has not been found in nature to date. Although it is a fully synthetic compound from oxalic acid derivatives, but it has a utility for creation of sustainable energy storage systems [178, 179] which is the one of the major challenges of the 21st century.

The carbonyl group displays a reversible reductive/oxidative ability. In general, carbonyl containing compounds require functional moieties to stabilize the negative charge resulting from the resonance structures of carbon-oxygen groups for electrical energy storage applications (Scheme 30). Such as the compound **136** has carbonyl groups and two benzene rings needed to stabilize the enolates structures resulting from reduction.[180, 181]



Scheme 30. Illustration of the dianion stabilization by the resonance.

The resonance over the heterocycle ring can lead to further stabilization depending on the nature of substituents on nitrogen atom. Therefore, the influence of the nature and type of *N*-substituted tetraketopiperazine motifs and their working as the active material in organic batteries were studied[178] (Scheme 31).

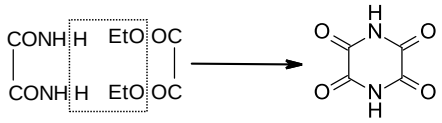


139

Scheme 31. Dianion stability of tetraketopiperazine.

5. 1. Synthesis of tetraketopiperazine

de Mouilpied and Ruke discovered the first method for the synthesis of tetraketopiperazine with high yield from the reaction of oxamide with ethyl oxalate in the presence of sodium ethoxide[182] (Scheme 32).



D

Scheme 32. Formation of tetraketopiperazine.

Additionally, many methodologies can be used for preparation of mono- or di-tetraketopiperazine derivatives (**G** or **H** respectively), such as, the reaction of oxalyl halide **140** with an oxamide **141** or with silylamine **142**, then water or an aqueous alkali solution was added to the reaction mixture producing monotetraketopiperazine **G**. Also, the monotetraketopiperazine **G** was obtained *via* reaction of compound **140** with mixture of oximidyl halide **143** and amine **144**. On the other hand, the di-tetraketopiperazine derivatives **H** were produced from the reaction of compound **140** with diamine **145** or with the mixture of oximidyl halide **143** and diamine **146** as represented in Figure 13.[183] Additionally, tetraketopiperazines were produced from the reaction of appropriate oxanilyl chloride in the presence of triethylamine in benzene.[184]

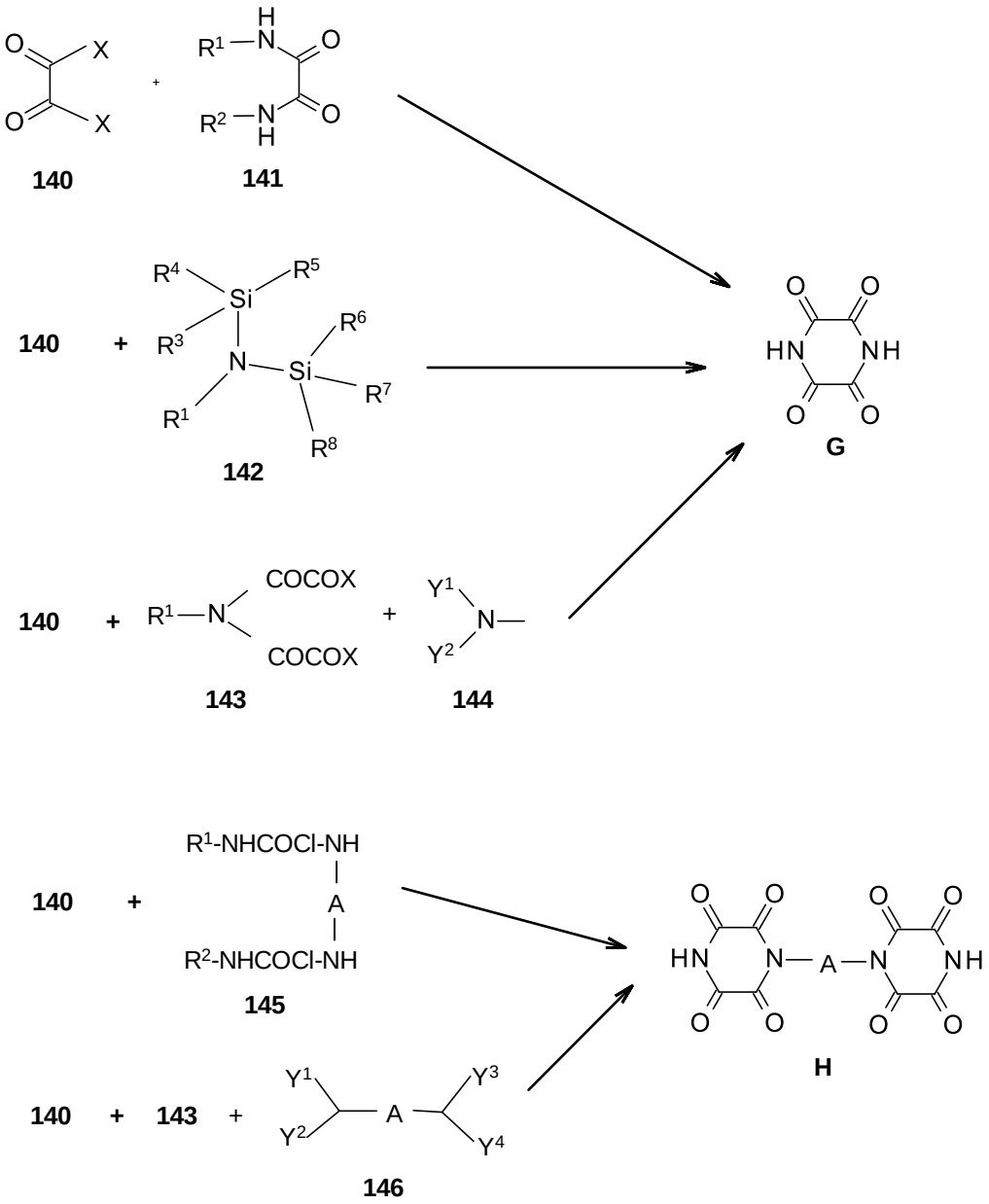
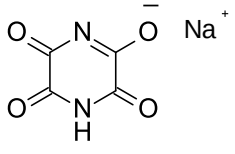


Figure 13. Methodologies for preparation of tetraketopiperazines.

5. 2. Reactions of tetraketopiperazines

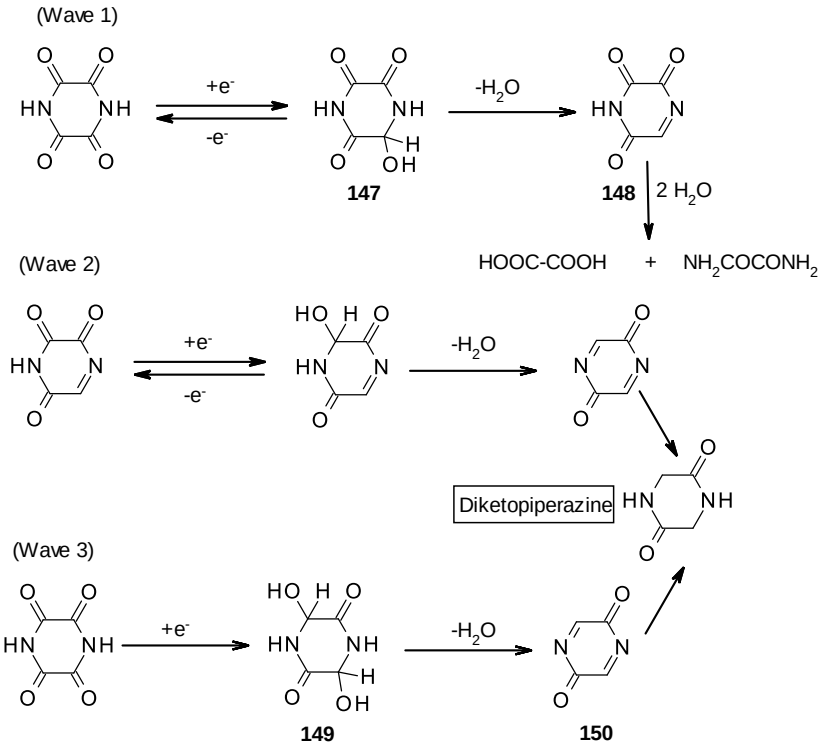
5. 2. 1. Salt formation. The tetraketopiperazine contains two slightly acidic N-H bonds. So, tetraketopiperazine yields a monosodium **J** with sodium bicarbonate or sodium hydroxide or sodium alkoxide.[185]



J

5. 2. 2. Hydrazone formation. The mono-hydrazone derivative was obtained from the reaction of tetraketopiperazine with hydrazine.[185]

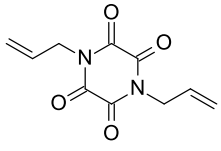
5. 2. 3. Reduction of tetraketopiperazine. Reduction of tetraketopiperazine yields triketopiperazine then diketopiperazine with oxamide and glyocalic acid as byproducts.[177] Furthermore, the polarographic reduction of tetraketopiperazine at pH 0 and 2 shows three polarographic reduction waves. The first wave represents a reversible reduction of tetraketopiperazine to 2-hydroxytriketopiperazine **147** which by dehydration gives triketopiperazine derivative **148** and then under kinetic control decomposes into oxamide and glyoxylic acid. Second wave shows further electrochemical reduction of triketopyrazine **148** to 2,5-diketopiperazine. While the last wave indicates reduction of tetraketopiperazine to 2,5-dihydroxydiketopiperazine **149** and by removal two molecules of water giving 2,5-dioxopyrazine **150**[177] (Scheme 33).



Scheme 33. Polarographic reduction of tetraketopiperazine at pH 0 and 2.

5. 3. Utility of tetraketopiperazine

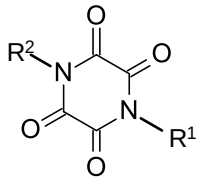
In recent years, the growth of photoelectric materials is promoted by replacing inorganics by organic materials. Tetraketopiperazine derivative (AP) **151** is already used in photoelectric devices and in organic light emitting diodes (OLEDs).[178,186]



151

Figure 14. Structure of AP.

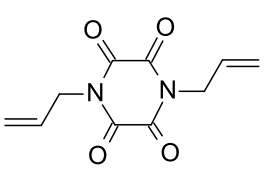
Moreover, a little information has been found in the literature about the tetraketopiperazine.[187,188] However, the four carbons of tetraketopiperazine structure can be produced from oxalic acid derivatives (renewable resources) which are very common compounds, widely distributed in nature[189] and can be readily produced by fungi like *Aspergilus niger.*[190]



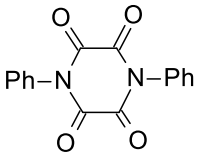
152

Figure 15. Tetraketopiperazine derivatives.

In 2008, several tetraketopiperazine derivatives **152** (R = aromatic groups, unsaturated and alkyl functions) were synthesized. Figure 16 shows some molecular structures of tetraketopiperazine which showed stability in electroactivity.[187]

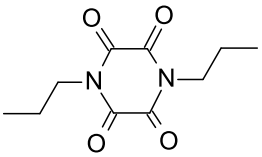


N,N-diallyltetraketopiperazine (AP)



153

N,N-diphenyltetraketopiperazine (PHP)



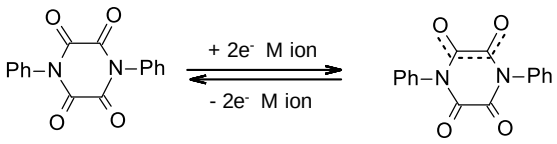
154

N,N-di-n-propyltetraketopiperazine (PRP)

Figure 16. Some of tetraketopiperazines with electroactivities.

Today, the research on growths of organic electrode materials especially on the conjugated carbonyl compounds, their monomers and polymers continues,[191-194] due to the organic-based electrode (OBE) materials have advantages over inorganic electrodes, such as high specialized capacity, low-cost, environmental safety, flexibility, and highly adjustable redox reaction without structural changes.[195-198] These develop the potential hopefuls as electrode materials for green lithium ion batteries (LIBs). However, some of them are very toxic, have low thermal tolerance, poor conductivity, and low mechanical stability.[199-201] Nonetheless the use of organic substance instead of inorganic electrodes is an essential due to the lower carbon dioxide emissions and renewable sustainability and also for reducing the price of rechargeable metal-ion batteries.[186,202-204]

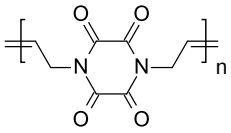
Therefore, many different synthetic methods for producing monomeric and polymeric derivatives of these carbonyl containing compounds have been explored.[205-208] Especially, the carbonyl-based electrodes that can hold the charge carrying dynamic deviation comparing to inorganic ones by kinetics of the enolization reaction[178,209-211] (Scheme 34).



155

Scheme 34. Enolization of tetraketopiperazine.

Noteworthy, some polycarbonyl motifs are difficult for derivatization *via* the enolization reactions because of the electronic repulsion and steric hindrance causing a wide difference between the calculated and practical values in the redox processes.[187,205,212] Therefore, intensive studies have been performed for the design of chemical structures containing the carbonyl groups that can be incorporated in the redox processes. Organic polymers may be decreased these difficulties because of their lower solubility, lower self-discharge rates, high mechanical strength, flexibility, thermal stability, and versatility.[213-215] Such polymeric structure can be illustrated by N,N`-diallyl-2,3,5,6-tetraoxopiperazine **156** which is stabilized by resonance[216,217] (Figure 147).



156

Figure 17. N,N`-diallyl-2,3,5,6-tetraketopiperazine polymer.

6. Conclusions

Taking all the above into consideration, we can conclude that polyketopiperazines especially triketopiperazines and tetraketopiperazines are simplest compounds obtained either from natural or synthetic sources. These heterocyclic skeletons have rigid structural conformation, which can control their stereochemistry. Triketopiperazines have interesting properties for production of valuable molecular skeletons in synthetic bioactive derivatives while tetraketopiperazines are economically useful for chemical engineering. In addition, both are less common in nature and require more research to investigate their utility. Further, these compounds need additional study and examination in the fields of drug discovery and in sustainable energy storage systems.

Abbreviations

DKP	– diketopiperazines
TKP	– triketopiperazine
ADME	– absorption, distribution, metabolism, and excretion
SDS	– Sodium dodecyl sulfate
PDE5	– phosphodiesterase type 5
THF	– tetrahydrofuran
MW	– microwave

HCV	– hepatitis C virus
GT	– gastro tract
er	– enantiomer ratios
PD_2DBa_3	– Tris(dibenzylideneacetone)dipalladium
Boc	– tert-butyloxycarbonyl,
DMF	– dimethylformaamide
Et_3N	– triethylamine
rt	– room temperature,
$Pb(OAc)_4$	– lead tetraacetate
NMO	– N-methymorpholine-N-oxide
K_2OsO_4	– dipotasium osmate
LiHMDS	– lithium bis(trimethylsilyl)amide
TMSOTf	– trimethylsilyl trifluoromethanesulfonate
TEOA	– triethanolamine
LDA	– lithium diisopropylamide
ETP	– epidithiodioxopiperazine
AP	– N, N- diallyltetraketopiperazine derivative
PHP	– N, N- diphenyltetraketopiperazine derivative
PRP	– N, N- di-n-propyltetraketopiperazine derivative
OLEDs	– organic light emitting diodes
OBE	– organic-based electrode

References

1. Kalaria, P. N.; Karad, S. C.; Raval, D. K. *Eur. J. Med. Chem*. **2018**, *158*, 917. https://doi.org/10.1016/j.ejmech.2018.08.040
2. Eftekhari-Sis, B.; Zirak, M.; Akbari, A. *Chem. Rev*. **2013**, *113*, 2958. https://doi.org/10.1021/cr300176g
3. Vitaku, E.; Smith, D. T.; Njardarson, J. T. *J. Med. Chem*. **2014**, *57*, 10257. https://doi.org/10.1021/jm501100b
4. Smith, B. R.; Eastman, C. M.; Njardarson, J. T. *J. Med. Chem*. **2014**, *57*, 9764. https://doi.org/10.1021/jm501105n
5. Kerru, N.; Gummidi, L.; Maddila, S.; Gangu, K. K.; Jonnalagadda, S. B. *Molecules* **2020**, *25*, 1909. https://doi.org/10.3390/molecules25081909
6. Heravi, M. M.; Zadsirjan, V. *RSC Adv*. **2020**, *10*, 44247. https://doi.org/10.1039/D0RA09198G
7. Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem*. **1994**, *37*, 1385. https://doi.org/10.1021/jm00036a001
8. Walsh, C. T. *Tetrahedron Lett*. **2015**, *56*, 3075. https://doi.org/10.1016/j.tetlet.2014.11.046
9. Zhang, B.; Studer, A. *Chem. Soc. Rev*. **2015**, *44*, 3505.

https://doi.org/10.1039/C5CS00083A
10. Green, M. T.; Peczkowski, G. R.; Al-Ani, A. J.; Benjamin, S. L.; Simpkins, N. S.; Jones, A. M. *RSC Adv*. **2017**, *7*, 48754. https://doi.org/10.1039/C7RA10483A
11. He, P.; Zhang, J. G.; Wang, K.; Yin, X.; Zhang, T. L. *J. Org. Chem*. **2015**, *80*, 5643. https://doi.org/10.1021/acs.joc.5b00545
12. Chaudhari, K.; Surana, S.; Jain, P.; Patel, H. M. *Eur. J. Med. Chem*. **2016**, *124*, 160. https://doi.org/10.1016/j.ejmech.2016.08.034
13. Sameem, B.; Saeedi, M.; Mahdavi, M.; Shafiee, A. *Eur. J. Med. Chem*. **2017**, *128*, 332. https://doi.org/10.1016/j.ejmech.2016.10.060
14. Akhtar, J.; Khan, A. A.; Ali, Z.; Haider, R.; Shahar Yar, M. *Eur. J. Med. Chem*. **2017**, *125*, 143. https://doi.org/10.1016/j.ejmech.2016.09.023
15. Ma, X.; Lv, X.; Zhang, J. *Eur. J. Med. Chem*. **2018**, *143*, 449. https://doi.org/10.1016/j.ejmech.2017.11.049
16. Kaur, R.; Dahiya, L.; Kumar, M. *Eur. J. Med. Chem*. **2017**, *141*, 473. https://doi.org/10.1016/j.ejmech.2017.09.029
17. Martins, P.; Jesus, J.; Santos, S.; Raposo, L.; Roma-Rodrigues, C.; Baptista, P.; Fernandes, A. *Molecules* **2015**, *20*, 16852. https://doi.org/10.3390/molecules200916852
18. Houston, D. R.; Synstad, B.; Eijsink, V. G. H.; Stark, M. J. R.; Eggleston, I. M.; van Aalten, D. M. F. *J. Med. Chem*. **2004**, *47*, 5713. https://doi.org/10.1021/jm049940a
19. Mao, Z. W.; Zheng, X.; Lin, Y. P.; Hu, C. Y.; Wang, X. L.; Wan, C. P.; Rao, G. X. Bioorg. *Med. Chem. Lett*. **2016**, *26*, 3421. https://doi.org/10.1016/j.bmcl.2016.06.055
20. Henary, M.; Kananda, C.; Rotolo, L.; Savino, B.; Owens, E. A.; Cravotto, G. *RSC Advances* **2020**, *10*, 14170. https://doi.org/10.1039/D0RA01378A
21. Upadhayaya, R. S.; Sinha, N.; Jain, S.; Kishore, N.; Chandra, R.; Arora, S. K. *Bioorg. Med. Chem*. **2004**, *12*, 2225. https://doi.org/10.1016/j.ejmech.2004.03.004
22. Chaudhary, P.; Kumar, R.; Verma, A. K.; Singh, D.; Yadav, V.; Chhillar, A. K.; Sharma, G. L.; Chandra, R. *Bioorg. Med. Chem*. **2006**, *14*, 1819. https://doi.org/10.1016/j.bmc.2005.10.032
23. Bhati, S.; Kaushik, V.; Singh, J. *Int. J. Pept. Res. Ther*. **2019**, *25*, 845. https://doi.org/10.1007/s10989-018-9734-5
24. Hosseinzadeh, Z.; Ramazani, A.; Razzaghi-Asl, N. *Curr. Org. Chem*. **2018**, *22*, 2256. https://doi.org/10.2174/1385272822666181008142138
25. Jain, A.; Chaudhary, J.; Khaira, H.; Chopra, B.; Dhingra, A. *Drug Res*. **2021**, *71*, 62. https://doi.org/10.1055/a-1323-2813
26. Reilly, S. W.; Mach, R. H. *Org. Lett*. **2016**, *18*, 5272.

https://doi.org/10.1021/acs.orglett.6b02591
27. Suresh, G.; Nadh, R. V.; Srinivasu, N.; Yennity, D. *Lett. Org. Chem*. **2018**, *15*, 1070. https://doi.org/10.2174/1570178615666180430122641
28. Bradley, P. B. In Introduction to Neuropharmacology, *Elsevier* **1989**, 201. https://doi.org/10.1016/B978-0-7236-1271-1.50017-1
29. Ban, T. A.; Fujimori, M.; Petrie, W. M.; Ragheb, M.; Wilson, W. H. *Int. Pharmacopsychiatry* **1982**, *17*, 18. https://doi.org/10.1159/000468553
30. Walker, M. A. *Expert Opin. Drug Discov*. **2014**, *9*, 1421. https://doi.org/10.1517/17460441.2014.960839
31. Ye, Z.; Adhikari, S.; Xia, Y.; Dai, M. *Nat. Commun*. **2018**, *9*, 721. https://doi.org/10.1038/s41467-018-03085-3
32. Gong, N.; Yu, H.; Wang, Y.; Xing, C.; Hu, K.; Du, G.; Lu, Y. *Nat. Products Bioprospect*. **2020**, *10*, 261. https://doi.org/10.1007/s13659-020-00256-y
33. Hawes, C.; Chen, C.; Tran, A.; Turner, D. *Crystals* **2014**, *4*, 53. https://doi.org/10.3390/cryst4010053
34. Zhou, X.; Wang, X. B.; Kong, L. Y. *Acta Crystallogr. Sect. C Cryst. Struct. Commun*. **2006**, *62*, o58. https://doi.org/10.1107/S1600536805039322
35. Hatnapure, G. D.; Keche, A. P.; Rodge, A. H.; Birajdar, S. S.; Tale, R. H., Kamble, V. M. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 6385. https://doi.org/10.1016/j.bmcl.2012.08.071
36. Modh, R. P.; Kumar, S. P.; Jasrai, Y. T.; Chikhalia, K. H. *Arch. Pharm. (Weinheim)* **2013**, *346*, 793. https://doi.org/10.1002/ardp.201300242
37. Szkaradek, N.; Rapacz, A.; Pytka, K.; Filipek, B.; Siwek, A.; Cegła, M.; Marona, H. *Bioorg. Med. Chem*. **2013**, *21*, 514. https://doi.org/10.1016/j.bmc.2012.11.014
38. Mallavadhani, U. V.; Chandrashekhar, M.; Shailaja, K.; Ramakrishna, S. *Bioorg. Chem*. **2019**, *82*, 306. https://doi.org/10.1016/j.bioorg.2018.10.039
39. Musetti, R.; Polizzotto, R.; Vecchione, A.; Borselli, S.; Zulini, L.; D'Ambrosio, M.; Toppi, L. S. di; Pertot, I. *Micron* **2007**, *38*, 643. https://doi.org/10.1016/j.micron.2006.09.001
40. Zhang, Q.; Zhao, M.; Xu, M.; Gu, F.; Liu, Q.; Chen, Y.; Zhang, H.; Kijlstra, A. *Infect. Drug Resist*. **2019**, *12*, 2487. https://doi.org/10.2147/IDR.S204025
41. Mas, V.; Falco, A.; Brocal, I.; Perez, L.; Coll, J. M.; Estepa, A. *Antiviral Res*. **2006**, *72*, 107. https://doi.org/10.1016/j.antiviral.2006.04.005
42. Hawas, U. W.; Abou El-Kassem, L. T. *Lett. Org. Chem*. **2019**, *16*, 409. https://doi.org/10.2174/1570178615666181009120422
43. Bojarska, J.; Wolf, W. M. *Proceedings* **2020**, *79*, 10. https://doi.org/10.3390/IECBM2020-08804
44. Perez-Mellor, A.; Zehnacker, A. *Chirality* **2017**, *29*, 89.
45. Yang, Y. H.; Yang, D. S.; Li, G. H.; Pu, X. J.; Mo, M. H.; Zhao, P. J. *J. Antibiot. (Tokyo)*. **2019**, *72*, 752.

https://doi.org/10.1038/s41429-019-0209-5
46. P. de Carvalho, M.; Abraham, W. R. *Curr. Med. Chem*. **2012**, *19*, 3564. https://doi.org/10.2174/092986712801323243
47. Magriotis, P. A. *RSC Med. Chem*. **2020**, *11*, 745. https://doi.org/10.1039/D0MD00053A
48. Wang, Y.; Gloer, J. B.; Scott, J. A.; Malloch, D. *J. Nat. Prod*. **1995**, *58*, 93. https://doi.org/10.1021/np50115a011
49. Chai, C. L. L.; Hockless, D. C. R.; Vinindra Weerasuria, K. D. *Polyhedron* **1997**, *16*, 1577. https://doi.org/10.1016/S0277-5387(96)00440-8
50. Borthwick, A. D.; Da Costa, N. C. *Crit. Rev. Food Sci. Nutr.* **2017**, *57*, 718. https://doi.org/10.1080/10408398.2014.911142
51. Minelli, A.; Bellezza, I.; Grottelli, S.; Galli, F. *Amino Acids* **2008**, *35*, 283. https://doi.org/10.1007/s00726-007-0629-6
52. Harizani, M.; Katsini, E.; Georgantea, P.; Roussis, V.; Ioannou, E. *Molecules* **2020**, *25*, 1509. https://doi.org/10.3390/molecules25071509
53. Palacin, S.; Chin, D. N.; Simanek, E. E.; MacDonald, J. C.; Whitesides, G. M.; McBride, M. T.; Palmore, G. T. R. *J. Am. Chem. Soc*. **1997**, *119*, 11807. https://doi.org/10.1021/ja962905b
54. Kaur, N.; Zhou, B.; Breitbeil, F.; Hardy, K.; Kraft, K. S.; Trantcheva, I.; Phanstiel IV, O. *Mol. Pharm*. **2008**, *5*, 294. https://doi.org/10.1021/mp700096e
55. Wennemers, H.; Conza, M.; Nold, M.; Krattiger, P. *Chem. - A Eur. J.* **2001**, *7*, 3342. https://doi.org/10.1002/1521-3765(20010803)7:15<3342::AID-CHEM3342>3.0.CO;2-7
56. Mordini, A.; Reginato, G.; Calamante, M.; Zani, L. *Curr. Top. Med. Chem*. **2014**, *14*, 1308. https://doi.org/10.2174/1568026614666140423114013
57. Dinsmore, C. J.; Beshore, D. C. *Org. Prep. Proced. Int*. **2002**, *34*, 367. https://doi.org/10.1080/00304940209458075
58. Lencina, C. L.; Dassonville-Klimpt, A.; Sonnet, P. *Tetrahedron: Asymmetry* **2008**, *19*, 1689. https://doi.org/10.1016/j.tetasy.2008.06.030
59. Jana, A. K.; Das, S. K.; Panda, G. *Tetrahedron* **2012**, *68*, 10114. https://doi.org/10.1016/j.tet.2012.09.109
60. Khan, N. M.; Cano, M.; Balasubramanian, S. *Tetrahedron Lett.* **2002**, *43*, 2439. https://doi.org/10.1016/S0040-4039(02)00268-X
61. Limbach, M.; Lygin, A. V.; Korotkov, V. S.; Es-Sayed, M.; de Meijere, A. *Org. Biomol. Chem*. **2009**, *7*, 3338. https://doi.org/10.1039/b908548c
62. De Risi, C.; Pela, M.; Pollini, G. P.; Trapella, C.; Zanirato, V. *Tetrahedron: Asymmetry* **2010**, *21*, 255. https://doi.org/10.1016/j.tetasy.2010.02.008
63. Feng, G. S.; Zhao, Z. B.; Shi, L.; Zhou, Y. G. *Org. Chem. Front.* **2021**, *8*, 6273. https://doi.org/10.1039/D1QO01144H
64. Brochu, M. P.; Brown, S. P.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2004**, *126*, 4108.

https://doi.org/10.1021/ja049562z
65. Moyano, A.; Rios, R. *Chem. Rev*. **2011**, *111*, 4703. https://doi.org/10.1021/cr100348t
66. Kaplaneris, N.; Spyropoulos, C.; Kokotou, M. G.; Kokotos, C. G. *Org. Lett*. **2016**, *18*, 5800. https://doi.org/10.1021/acs.orglett.6b02699
67. Kakarla, R.; Liu, J.; Naduthambi, D.; Chang, W.; Mosley, R. T.; Bao, D.; Steuer, H. M. M.; Keilman, M.; Bansal, S.; Lam, A. M.; Seibel, W.; Neilson, S.; Furman, P. A.; Sofia, M. J. *J. Med. Chem*. **2014**, *57*, 2136. https://doi.org/10.1021/jm4012643
68. Song, Z.; Hou, Y.; Yang, Q.; Li, X.; Wu, S. *Mar. Drugs* **2021**, *19*, 403. https://doi.org/10.3390/md19080403
69. Ortiz, A.; Sansinenea, E. *Curr. Med. Chem*. **2017**, *24*, 2773. https://doi.org/10.2174/0929867324666170623092818
70. Abd El-Hady, F. K.; Fayad, W.; Iodice, C.; El-Shahid, Z. A.; Abdel-Aziz, M. S.; Crudele, E.; Tommonaro, G. *Curr. Microbiol*. **2017**, *74*, 6. https://doi.org/10.1007/s00284-016-1144-3
71. Wang, X.; Li, Y.; Zhang, X.; Lai, D.; Zhou, L. *Molecules* **2017**, *22*, 2026. https://doi.org/10.3390/molecules22122026
72. Ma, Y. M.; Liang, X. A.; Kong, Y.; Jia, B. J. *Agric. Food Chem*. **2016**, *64*, 6659. https://doi.org/10.1021/acs.jafc.6b01772
73. Farhadian, S.; Shareghi, B.; Tirgir, F.; Reiisi, S.; Dehkordi, N. G.; Momeni, L.; Heidari, E. *J. Mol. Liq.* **2019**, *294*, 111585. https://doi.org/10.1016/j.molliq.2019.111585
74. Fischer, P. M. *J. Pept. Sci.* **2003**, *9*, 9. https://doi.org/10.1002/psc.446
75. Luo, T.-J. M.; Palmore, G. T. R. *J. Phys. Org. Chem*. **2000**, *13*, 870. https://doi.org/10.1002/1099-1395(200012)13:12<870::AID-POC324>3.0.CO;2-O
76. Jiang, J.; Ma, Z.; Castle, S. L. *Tetrahedron* **2015**, *71*, 5431. https://doi.org/10.1016/j.tet.2015.06.001
77. Zhao, Q.; Schafmeister, C. E. *Peptidomimetics II* **2015**, 51. https://doi.org/10.1007/7081_2015_165
78. Manchineella, S.; Govindaraju, T. *Chempluschem* **2017**, *82*, 88. https://doi.org/10.1002/cplu.201600450
79. Yin, H.; Takada, K.; Kumar, A.; Hirayama, T.; Kaneko, T. *RSC Adv.* **2021**, *11*, 5938. https://doi.org/10.1039/D0RA10086B
80. Takada, K.; Yin, H.; Matsui, T.; Ali, M.A.; Kaneko, T. *Journal of Polymer Research*. **2017**, *24*,1. https://doi.org/10.1007/s10965-017-1372-7
81. Ohta, Y., Terada, K. and Masuda, T. *Heterocycles* **2009**, *78*, 1477. https://doi.org/10.3987/COM-08-11635
82. Davie, E. A. C.; Mennen, S. M.; Xu, Y.; Miller, S. J. *Chem. Rev.* **2007**, *107*, 5759. https://doi.org/10.1021/cr068377w

83. Mollica, A.; Costante, R.; Fiorito, S.; Genovese, S.; Stefanucci, A.; Mathieu, V.; Kiss, R.; Epifano, F. *Fitoterapia* **2014**, *98*, 91. https://doi.org/10.1016/j.fitote.2014.07.010
84. Terada, K.; Masuda, T.; Sanda, F. *Macromolecules* **2009**, *42*, 913. https://doi.org/10.1021/ma8023552
85. Tian, Z.; Chu, Y.; Wang, H.; Zhong, L.; Deng, M.; Li, W. *RSC Adv*. **2018**, *8*, 1055. https://doi.org/10.1039/C7RA12173C
86. Tezgel, O.; Puchelle, V.; Du, H.; Illy, N.; Guegan, P. *J. Polym. Sci. Part A Polym. Chem*. **2019**, *57*, 1008. https://doi.org/10.1002/pola.29356
87. Mosqueira, F. G.; Ramos-Bernal, S.; Negron-Mendoza, A. *Biosystems* **2008**, *91*, 195. https://doi.org/10.1016/j.biosystems.2007.09.001
88. Fuhrer, F. N.; Schlaad, H. *Macromol. Chem. Phys*. **2014**, *215*, 2268. https://doi.org/10.1002/macp.201400166
89. Prasad, C. *Peptides* **1995**, *16*, 151. https://doi.org/10.1016/0196-9781(94)00017-Z
90. Kohn, H. and Widger, W. *Curr. Drug Targets-Infectious Disord*. **2005**, *5*, 273. https://doi.org/10.2174/1568005054880136
91. Horton, D.A., Bourne, G.T.; Smythe, M.L. *J. Comput. Aided. Mol. Des.* **2002**, *16*, 415. https://doi.org/10.1023/A:1020863921840
92. Lambert, J. N.; Mitchell, J. P.; Roberts, K. D. *J. Chem. Soc. Perkin Trans. 1* **2001**, *5*, 471. https://doi.org/10.1039/b001942i
93. Dinsmore, C.J.; Beshore, D., *Tetrahedron* **2002**, *58*, 3297. https://doi.org/10.1016/S0040-4020(02)00239-9
94. Borthwick, A. D. *Chem. Rev*. **2012**, *112*, 3641. https://doi.org/10.1021/cr200398y
95. Cao, J.; Wang, B. G. *Mar. Life Sci. Technol*. **2020**, *2*, 31. https://doi.org/10.1007/s42995-019-00023-0
96. Huang, R. M.; Yi, X. X.; Zhou, Y.; Su, X.; Peng, Y.; Gao, C. H. *Mar. Drugs* **2014**, *12*, 6213. https://doi.org/10.3390/md12126213
97. Gomes, N. G. M.; Pereira, R. B.; Andrade, P. B.; Valentão, P. *Mar. Drugs* **2019**, *17*, 551. https://doi.org/10.3390/md17100551
98. May Zin, W.; Buttachon, S.; Dethoup, T.; Fernandes, C.; Cravo, S.; Pinto, M.; Gales, L.; Pereira, J.; Silva, A.; Sekeroglu, N.; Kijjoa, A. *Mar. Drugs* **2016**, *14*, 136. https://doi.org/10.3390/md14070136
99. Honzl, J.; Sorm, M. *Tetrahedron Lett*. **1969**, *10*, 3339. https://doi.org/10.1016/S0040-4039(00)99757-0
100. Tanaka, T.; Yamazaki, H.; Ohta, M. *Bull. Chem. Soc. Jpn*. **1977**, *50*, 1821. https://doi.org/10.1246/bcsj.50.1821
101. Ottenheym, H. C. J.; Spande, T. F.; Witkop, B. *J. Org. Chem.* **1972**, *37*, 3358. https://doi.org/10.1021/jo00986a040
102. Mieden, O. J.; Sonntag, C. *von. Zeitschrift für Naturforsch*. *B* **1989**, *44*, 959.

https://doi.org/10.1515/znb-1989-0818
103. Wamhoff, H.; Kleimann, W. J. *Chem. Soc. Chem. Commun*. **1981**, *15*, 743. https://doi.org/10.1039/c39810000743
104. Kuster, G. J. T.; van Berkom, L. W. A.; Kalmoua, M.; van Loevezijn, A.; Sliedregt, L. A. J. M.; van Steen, B. J.; Kruse, C. G.; Rutjes, F. P. J. T.; Scheeren, H. W. *J. Comb. Chem*. **2006**, *8*, 85. https://doi.org/10.1021/cc050072s
105. Faltracco, M.; Cotogno, S.; Vande Velde, C. M. L.; Ruijter, E. *J. Org. Chem*. **2019**, *84*, 12058. https://doi.org/10.1021/acs.joc.9b01994
106. Grant, G., Hunt, A., Milne, P. et al. *J. Chem. Crystallogr*. **1999**, *29*, 435. https://doi.org/10.1023/A:1009567127868
107. van der Merwe, E.; Huang, D.; Peterson, D.; Kilian, G.; Milne, P. J.; Van de Venter, M.; Frost, C. *Peptides* **2008**, *29*, 1305. https://doi.org/10.1016/j.peptides.2008.03.010
108. Wang, D. X.; Liang, M. T.; Tian, G. J.; Lin, H.; Liu, H. Q. *Tetrahedron Lett.* **2002**, *43*, 865. https://doi.org/10.1016/S0040-4039(01)02005-6
109. Inoue, S.; Takamatu, N.; Kishi, Y. *J. Pharm. Soc. Jap*. **1977**, *97*, 564. https://doi.org/10.1248/yakushi1947.97.5_564
110. Marcuccio, S.; Elix, J. *Aust. J. Chem*. **1985**, *38*, 343. https://doi.org/10.1071/CH9851785
111. Snaddon, T. N.; Scaggs, T. D.; Pearson, C. M.; Fyfe, J. W. B. *Org. Lett.* **2019**, *21*, 4873. https://doi.org/10.1021/acs.orglett.9b01770
112. Dossena, A.; Marchelli, R.; Pochini, A. *J. Chem. Soc. Chem. Commun*. **1974**, *19,* 771. https://doi.org/10.1039/c39740000771
113. Tayu, M.; Hui, Y.; Takeda, S.; Higuchi, K.; Saito, N.; Kawasaki, T. *Org. Lett.* **2017**, *19*, 6582. https://doi.org/10.1021/acs.orglett.7b03293
114. Seya, H.; Nozawa, K.; Udagawa, S. I.; Nakajima; S.; Kawai, K. I. *Chem. Pharm. Bull*. **1986**, *34*, 2411. https://doi.org/10.1248/cpb.34.2411
115. Cardillo, R.; Fuganti, C.; Gatti, G.; Ghiringhelli, D.; Grasselli, P. *Tetrahedron Lett.* **1974**, *15*, 3163. https://doi.org/10.1016/S0040-4039(01)91850-7
116. Usami, Y., Yamaguchi, J. and Numata, A. *Heterocycles* **2004**, *63*, 1123. https://doi.org/10.3987/COM-04-10037
117. Overman, L. E.; Shin, Y. *Org. Lett*. **2007**, *9*, 339. https://doi.org/10.1021/ol062801y
118. Song, J.; Guo, C.; Adele, A.; Yin, H.; Gong, L. *Chem. – A Eur. J.* **2013**, *19*, 3319. https://doi.org/10.1002/chem.201204522
119. DeLorbe, J. E.; Horne, D.; Jove, R.; Mennen, S. M.; Nam, S.; Zhang, F.-L.; Overman, L. E. *J. Am. Chem. Soc.* **2013**, *135*, 4117. https://doi.org/10.1021/ja400315y
120. Furst, L.; Stephenson, C. R. J. *Strategies and Tactics in Org. Chem*. **2014**, *1*, 207. https://doi.org/10.1016/B978-0-12-417185-5.00009-0
121. Bornwater, J. T. *Recl. des Trav. Chim. des Pays-Bas la Belgique* **2010**, *36*, 250.

https://doi.org/10.1002/recl.19170360702
122. Bergmann, M.; Miekeley, A. *Justus Liebigs Ann. der Chemie* **1927**, *458*, 40. https://doi.org/10.1002/jlac.19274580104
123. Safir, S. R.; Hlavka, J. J.; Williams, J. H. *J. Org. Chem.* **1953**, *18*, 106. https://doi.org/10.1021/jo01129a017
124. Mulliez, M.; Royer, J. *Tetrahedron* **1984**, *40,* 5143. https://doi.org/10.1016/S0040-4020(01)91263-3
125. Bailey, P. D.; Boa, A. N.; Baker, S. R.; Clayson, J.; Murray, E. J.; Rosair, G. M. *Tetrahedron Lett*. **1999**, *40,* 7557. https://doi.org/10.1016/S0040-4039(99)01602-0
126. Makino, S.; Nakanishi, E.; Tsuji, T. *Synlett* **2003**, *6*, 0817. https://doi.org/10.1055/s-2003-38757
127. DeLorbe, J. E.; Jabri, S. Y.; Mennen, S. M.; Overman, L. E.; Zhang, F.-L. *J. Am. Chem. Soc.* **2011**, *133*, 6549. https://doi.org/10.1021/ja201789v
128. Boyer, N.; Movassaghi, M., *Chem. sci.* **2012**,*3*, 1798. https://doi.org/10.1039/c2sc20270k
129. Coste, A.; Kim, J.; Adams, T.C.; Movassaghi, M., *Chem. sci*. **2013**, *4*, 3191. https://doi.org/10.1039/c3sc51150b
130. Jabri, S. Y.; Overman, L. E. *J. Am. Chem. Soc*. **2013**, *135*, 4231. https://doi.org/10.1021/ja401423j
131. Ranganathan, D.; Vaish, N. K.; Shah, K. *J. Am. Chem. Soc.* **1994**, *116*, 6545. https://doi.org/10.1021/ja00094a008
132. Bailey, P.D.; Bannister, N.; Bernad, M.; Blanchard, S.; Boa, A.N., *J. Chem. Soc. Perkin Trans. 1* **2001**, *24*, 3245. https://doi.org/10.1039/B108872F
133. Lee, V. J.; Woodward, R. B. *J. Org. Chem.* **1979**, *44*, 2487. https://doi.org/10.1021/ja00094a008
134. Sevrin, M. J.; Furst, L.; Nguyen, J. D.; Collins, J. L.; Stephenson, C. R. J. *Tetrahedron* **2018**, *74*, 3246. https://doi.org/10.1016/j.tet.2018.04.053
135. Xi, Y.; Yi, H.; Lei, A., *Org. biomol. chem.*, **2013**, *11*, 2387. https://doi.org/10.1039/c3ob40137e
136. Furst, L.; Narayanam, J. M. R.; Stephenson, C. R. J. *Angew. Chemie Int. Ed.* **2011**, *50*, 9655. https://doi.org/10.1002/anie.201103145
137. Boyer, N.; Movassaghi, M. *Chem. Sci.* **2012**, *3*, 1798. https://doi.org/10.1039/c2sc20270k
138. Murata, S. *Chem. Lett.* **1983**, *12*, 1819. https://doi.org/10.1246/cl.1983.1819
139. Katritzky, A.R.; Levell, J.R.; Pleynet, D.P. *Synthesis* **1998**, *1998*, 153. https://doi.org/10.1002/(SICI)1099-0690(199811)1998:11<2623::AID-EJOC2623>3.0.CO;2-M
140. Cabanillas Navarro, A. Enantioselective synthesis of diketopiperazines and triketopiperazines, **2015**.

http://etheses.bham.ac.uk/id/eprint/6370
141. Partch, R. E. *J. Org. Chem*. **1965**, *30*, 2498. https://doi.org/10.1021/jo01019a002
142. Hodges, T. R.; Benjamin, N. M.; Martin, S. F. *Tetrahedron* **2018**, *74*, 3329. https://doi.org/10.1016/j.tet.2018.04.001
143. Barbier, M. *Helv. Chim. Acta* **1986**, *69*, 152. https://doi.org/10.1002/hlca.19860690118
144. Crabtree, S. R.; Chu, W. L. A.; Mander, L. N. *Synlett* **1990**, *1990*, 169. https://doi.org/10.1055/s-1990-21025
145. Cabanillas, A.; Davies, C. D.; Male, L.; Simpkins, N. S. *Chem. sci*. **2015**, *6*, 1350. https://doi.org/10.1039/C4SC03218G
146. Csaky, A. G.; de la Herran, G.; Carmen, M. M. *Chem. Soc. Rev*. **2010**, *39*, 4080. ? https://doi.org/10.1039/B924486G
147. Zhang, Y.; Wang, W. *Catal. Sci. Technol.* **2012**, *2*, 42. https://doi.org/10.1039/C1CY00334H
148. Maguire, O. R.; Taylor, B.; Higgins, E. M.; Rees, M.; Cobb, S. L.; Simpkins, N. S.; Hayes, C. J.; O'Donoghue, A. C. *Chem. Sci*. **2020**, *11*, 7722. https://doi.org/10.1039/D0SC02508A
149. Pellissier, H. *Tetrahedron* **2016**, *72*, 3133. https://doi.org/10.1016/j.tet.2016.04.053
150. Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. https://doi.org/10.1021/ja047281l
151. Rees, M.; Simpkins, N. S.; Male, L. *Org. Lett*. **2017**, *19*, 1338. https://doi.org/10.1021/acs.orglett.7b00193
152. Peczkowski, G. R.; Craven, P. G. E.; Stead, D.; Simpkins, N. S. *Chem. Comm*. **2019**, *55*, 4214. https://doi.org/10.1039/C8CC10263E
153. Wang, B.; Wu, F.; Wang, Y.; Liu, X.; Deng, L. *J. Am. Chem. Soc*. **2007**, *129*, 768. https://doi.org/10.1021/ja0670409
154. Singh, G.; Yeboah, E. *Reports Org. Chem*. **2016**, *6*, 47. https://doi.org/10.2147/ROC.S73908
155. Liu, X.; Li, H.; Deng, L. *Org. Lett*. **2005**, *7*, 167. https://doi.org/10.1021/ol048190w
156. Foster R.W.; Lenz E.N.; Simpkins N.S.; Stead D., *Chem.–A Eur. J*. **2017**, *23*, 8810. https://doi.org/10.1002/chem.201701548
157. Zhang, X.; Gao, Y.; Hu, X.; Ji, C.; Liu, Y.; Yu, J. *Adv. Synth. Catal*. **2020**, *362*, 4763. https://doi.org/10.1002/adsc.202000966
158. Frebault, F. C.; Simpkins, N. S. *Tetrahedron* **2010**, *66*, 6585. https://doi.org/10.1016/j.tet.2010.04.093
159. Frebault, F.; Simpkins, N. S.; Fenwick, A. *J. Am. Chem. Soc.* **2009**, *131*, 4214. https://doi.org/10.1021/ja900688y
160. Williams, R. M.; Durham, C. A. *Chem. Rev.* **1988**, *88*, 511.

https://doi.org/10.1021/cr00085a004
161. Kawai, K.; Nozawa, K.; Seya, H.; Kawahara, N.; Udagawa, S.; Nakajima, S. *Heterocycles* **1987**, *26*, 475. https://doi.org/10.3987/R-1987-02-0475
162. Kawahara, N.; Nozawa, K.; Nakajima, S.; Kawai, K. *J. Chem. Soc. Chem. Commun*. **1986**, *19*, 1495. https://doi.org/10.1039/c39860001495
163. Nozawa, K.; Udagawa, S. I.; Nakajima, S.; Kawai, K. I. *Chem. Pharm. Bull*. **1987**, *35,* 3460. https://doi.org/10.1248/cpb.35.3460
164. Onodera, H.; Hasegawa, A.; Tsumagari, N.; Nakai, R.; Ogawa, T.; Kanda, Y. *Org. Lett*. **2004**, *6*, 4101. https://doi.org/10.1021/ol048202d
165. Tsumagari, N.; Nakai, R.; Onodera, H.; Hasegawa, A.; Rahayu, E. S.; Ando, K.; Yamashita, Y. J. *Antibiot*. (Tokyo) **2004**, *57*, 532. https://doi.org/10.7164/antibiotics.57.532
166. Dong, S.; Indukuri, K.; Clive, D. L. J.; Gao, J. M. *Chem. Commun*. **2016**, *52*, 8271. https://doi.org/10.1039/C6CC04169H
167. Wang, L.; Clive, D. L. J. *Tetrahedron Lett.* **2012**, *53*, 1504. https://doi.org/10.1016/j.tetlet.2012.01.055
168. Welch, T. R.; Williams, R. M. *Nat. Prod. Rep*. **2014**, *31*, 1376. https://doi.org/10.1039/C3NP70097F
169. Boyer, N.; Morrison, K. C.; Kim, J.; Hergenrother, P. J.; Movassaghi, M. *Chem. Sci*. **2013**, *4*, 1646. https://doi.org/10.1039/c3sc50174d
170. Choi, E. J.; Park, J. S.; Kim, Y. J.; Jung, J. H.; Lee, J. K.; Kwon, H. C.; Yang, H. O. *J. Appl. Microbiol*. **2011**, *110*, 304. https://doi.org/10.1111/j.1365-2672.2010.04885.x
171. Qian-Cutrone, J.; Huang, S.; Shu, Y. Z.; Vyas, D.; Fairchild, C.; Menendez, A.; Krampitz, K.; Dalterio, R.; Klohr, S. E.; Gao, Q. *J. Am. Chem. Soc.* **2002**, *124*, 14556. https://doi.org/10.1021/ja028538n
172. Nising, C. F. *Chem. Soc. Rev*. **2010**, *39*, 591. https://doi.org/10.1039/B900407F
173. Miller, K. A.; Williams, R. M. *Chem. Soc. Rev*. **2009**, *38*, 3160. https://doi.org/10.1039/b816705m
174. Spindola, H. M.; Vendramini-Costa, D. B.; Rodrigues, M. T.; Foglio, M. A.; Pilli, R. A.; Carvalho, J. E. *Pharmacol. Biochem. Behav.,* **2012**, *102*, 133. https://doi.org/10.1016/j.pbb.2012.03.030
175. Marinovic, M.; Perkovic, I.; Fontinha, D.; Prudencio, M.; Held, J.; Pessanha de Carvalho, L.; Tandaric, T.; Vianello, R.; Zorc, B.; Rajic, Z. *Molecules* **2020**, *25*, 4376. https://doi.org/10.3390/molecules25194376
176. Chakraborty, I.; Jana, S. *Synthesis* **2013**, *45*, 3325. https://doi.org/10.1055/s-0033-1338562
177. Owens, J. L.; Dryhurst, G. *Anal. Chim. Acta*, **1976**, *87*, 37. https://doi.org/10.1016/S0003-2670(01)83118-4
178. Geng, J.; Bonnet, J.-P.; Renault, S.; Dolhem, F.; Poizot, P. *Energy Environ. Sci*. **2010**, *3*, 1929.

https://doi.org/10.1039/c0ee00126k
179. Aoyama, H.; Ohnota, M.; Sakamoto, M.; Omote, Y. *J. Org. Chem*. **1986**, *51*, 247. https://doi.org/10.1021/jo00352a024
180. Haupler, B.; Wild, A.; Schubert, U. S. *Adv. Energy Mater*., **2015**, *5*, 1402034. https://doi.org/10.1002/aenm.201402034
181. Song, Z. Carbonyl-containing Polymers for Organic Batteries.; **2020**. https://doi.org/10.1039/9781788019743-00198
182. de Mouilpied, A. T.; Rule, A. *J. Chem. Soc., Trans*. **1907**, *91*, 176. https://doi.org/10.1039/CT9079100176
183. Umemoto, T., Tetraketopiperazine unit-containing compound as an active material in batteries, US Patent 6,737,193, **2004**. https://patents.google.com/patent/US6737193B2/en
184. Tetenbaum, M. T. *J. Chem. Eng. Data* **1973**, *18*, 345. https://doi.org/10.1021/je60058a024
185. de Mouilpied, A. T.; Rule, A. *J. Chem. Soc., Trans.* **1909**, *91*, 549. https://doi.org/10.1039/CT9099500549
186. Song, Z.; Zhou, H. *Energy Environ. Sci.,* **2013**, *6*, 2280. https://doi.org/10.1039/c3ee40709h
187. Liang, Y.; Zhang, P.; Chen, J. *Chem. Sci.* **2013**, *4*, 1330. https://doi.org/10.1039/c3sc22093a
188. Karlsson, C.; Huang, H.; Stromme, M.; Gogoll, A.; Sjodin, M. *RSC Adv*. **2015**, *5*, 11309. https://doi.org/10.1039/C4RA15708G
189. Baran, E.J. and Monje, P.V. *Oxalate biominerals*; **2008**, *4*, 219. https://doi.org/10.1002/9780470986325.ch7
190. Mandal, S. K.; Banerjee, P. C. *Process Biochem*. **2005**, *40*, 1605. https://doi.org/10.1016/j.procbio.2004.06.013
191. Walker, W.; Grugeon, S.; Mentre, O.; Laruelle, S.; Tarascon, J.-M.; Wudl, F. *J. Am. Chem. Soc*. **2010**, *132*, 6517. https://doi.org/10.1021/ja1012849
192. Novák, P.; Müller, K.; Santhanam, K. S. V.; Haas, O. *Chem. Rev*. **1997**, *97*, 207. https://doi.org/10.1021/cr941181o
193. Zeng, R.; Li, X.; Qiu, Y.; Li, W.; Yi, J.; Lu, D.; Tan, C.; Xu, M. *Electrochem. commun*. **2010**, *12*, 1253. https://doi.org/10.1016/j.elecom.2010.06.033
194. Han, X.; Chang, C.; Yuan, L.; Sun, T.; Sun, J. *Adv. Mater*. **2007**, *19*, 1616. https://doi.org/10.1002/adma.200602584
195. Nishide, H.; Oyaizu, K., *Science*, **2008**, *319*, 737. https://doi.org/10.1126/science.1151831
196. Lee, S.; Kwon, G.; Ku, K.; Yoon, K.; Jung, S.-K.; Lim, H.-D.; Kang, K. *Adv. Mater*. **2018**, *30*, 1704682. https://doi.org/10.1002/adma.201704682
197. Lu, Y.; Zhang, Q.; Li, L.; Niu, Z.; Chen, J. *Chem* **2018**, *4*, 2786. https://doi.org/10.1016/j.chempr.2018.09.005

198. Wu, Y.; Zeng, R.; Nan, J.; Shu, D.; Qiu, Y.; Chou, S. L. *Adv. Energy Mater*. **2017**, *7*, 1700278. https://doi.org/10.1002/aenm.201700278
199. Genorio, B.; Pirnat, K.; Cerc-Korosec, R.; Dominko, R.; Gaberscek, M. *Angew. Chemie Int. Ed*. **2010**, *49*, 7222. https://doi.org/10.1002/anie.201001539
200. Chen, Y.; Luo, W.; Carter, M.; Zhou, L.; Dai, J.; Fu, K.; Lacey, S.; Li, T.; Wan, J.; Han, X.; Bao, Y.; Hu, L. *Nano Energy* **2015**, *18*, 205. https://doi.org/10.1016/j.nanoen.2015.10.015
201. Wu, H.; Wang, K.; Meng, Y.; Lu, K.; Wei, Z. *J. Mater. Chem. A* **2013**, *1*, 6366. https://doi.org/10.1039/c3ta10473g
202. Armand, M.; Tarascon, J. M. *Nature* **2008**, *451*, 652. https://doi.org/10.1038/451652a
203. Chen, H.; Armand, M.; Demailly, G.; Dolhem, F.; Poizot, P.; Tarascon, J. M. *Chem. Sus. Chem*. **2008**, *1*, 348. https://doi.org/10.1002/cssc.200700161
204. Chen, H.; Armand, M.; Courty, M.; Jiang, M.; Grey, C. P.; Dolhem, F.; Tarascon, J.-M.; Poizot, P. *J. Am. Chem. Soc*. **2009**, *131*, 8984. https://doi.org/10.1021/ja9024897
205. Zhu, L.; Ding, G.; Xie, L.; Cao, X.; Liu, J.; Lei, X.; Ma, J. *Chem. Mater*. **2019**, *31*, 8582. https://doi.org/10.1021/acs.chemmater.9b03109
206. Yang, H.; Lee, J.; Cheong, J. Y.; Wang, Y.; Duan, G.; Hou, H.; Jiang, S.; Kim, I. D. *Energy Environ. Sci*. **2021**, *14*, 4228. https://doi.org/10.1039/D0TA03321A
207. Wang, H.; Yao, C. J.; Nie, H. J.; Wang, K. Z.; Zhong, Y.-W.; Chen, P.; Mei, S.; Zhang, Q. J. *Mater. Chem. A* **2020**, *8*, 11906. https://doi.org/10.1039/D0TA03321A
208. Xiang, J.; Chang, C.; Li, M.; Wu, S.; Yuan, L.; Sun, J. *Cryst. Growth Des*. **2008**, *8*, 280. https://doi.org/10.1021/cg070386q
209. Deng, W.; Shen, Y.; Qian, J.; Cao, Y.; Yang, H. *ACS Appl. Mater. Interfaces* **2015**, *7*, 21095. https://doi.org/10.1021/acsami.5b04325
210. Chen, D.; Avestro, A.; Chen, Z.; Sun, J.; Wang, S.; Xiao, M.; Erno, Z.; Algaradah, M. M.; Nassar, M. S.; Amine, K.; Meng, Y.; Stoddart, J. F. *Adv. Mater*. **2015**, *27*, 2907. https://doi.org/10.1002/adma.201405416
211. Luo, W.; Allen, M.; Raju, V.; Ji, X. *Adv. Energy Mater*. **2014**, *4,* 1400554. https://doi.org/10.1002/aenm.201400554
212. Lu, Y.; Hou, X.; Miao, L.; Li, L.; Shi, R.; Liu, L.; Chen, J. *Angew. Chem.* **2019**, *131*, 7094. https://doi.org/10.1002/ange.201902185
213. Le Gall, T.; Reiman, K.H.; Grossel, M.C.; Owen, J.R. *J. Power Sources* **2003**, *119*, 316. https://doi.org/10.1016/S0378-7753(03)00167-8
214. Suga, T.; Pu, Y.-J.; Kasatori, S.; Nishide, H. *Macromolecules* **2007**, *40*, 3167. https://doi.org/10.1021/ma0628578

215. Song, Z.; Zhan, H.; Zhou, Y. *Angew. Chem. Int. Ed.* **2010**, *49*, 8444. https://doi.org/10.1002/anie.201002439
216. Renault, S.; Geng, J.; Dolhem, F.; Poizot, P. *Chem. Comm*. **2011**, *47*, 2414. https://doi.org/10.1039/C0CC04440G
217. Sabir, A.; Zia, T.; Usman, M.; Shafiq, M.; Khan, R.U.; Jacob, K.I., Organic Electrode Material for Sodium-Ion Batteries; Springer, Cham. **2020**, p 353. https://doi.org/10.1007/978-3-030-29522-6_12

Authors' Biographies

Nabaweya Sharafeldin works at Faculty of Pharmacy, Tanta University, Egypt and received her B.Sc. at faculty of Pharmacy, Cairo University and both M.Sc. in Chemistry and PhD in Organic Chemistry (1984), at Belgrade University (Yugoslavia). She was appointed as a Lecturer at Faculty of Pharmacy, University of Tanta in 1984, associate professor in 1989 and Emeritus Professor since 2001. Her research interest focuses on synthesis of heterocyclic compounds, computational chemistry, chromatography, as well as medicinal chemistry.