Synthesis and Biological Properties of Dihydro-Oxadiazine-Based Heterocyclic Derivatives

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Abstract: Dihydro-oxadiazine and its derivatives have been demonstrated to be important heterocyclic scaffold platform with bioactive diversity, which present wide activities such as cardiovascular, antitumor, antibacterial, antimicrobial, acricidal, insecticidal, plant-growth regulating, chitin biosynthesis inhibitors and monoamine oxidase inhibition. Versatile features of dihydro-oxadiazine heterocycles have emerged, so the aim of the present paper was to review the recent advances of dihydro-oxadiazine-based heterocyclic derivatives mainly including synthesis and biological activities.

Keywords: Dihydro-oxadiazine, heterocycle, synthesis, biological activity.

INTRODUCTION

Azaheterocyclic compounds play an important role in medicinal chemistry and agrochemistry. The synthesis of azaheterocyclic compounds is of considerable interest owing to the wide-ranging biological activity of this series of compounds as medicinal and pesticidal agents. Moreover, most of them are extremely versatile building blocks for the manufacture of bioactive compounds in pharmaceutical drug design and agrochemical industry [1-6].

Among them, especially those that are six-membered heterocycles (Fig. **1**) bearing dihydro-oxadiazine skeleton arouse many researcher's interest, which have been demonstrated to be important heterocyclic scaffold platform with bioactive diversity such as cardiovascular, antitumor, antibacterial, antimicrobial, acricidal, insecticidal, plant-growth regulating, chitin biosynthesis inhibitors and monoamine oxidase inhibition. Otherwise, some 1,3,4-oxzdiazin-6-one, 1,3,4-oxzdiazin-2-one, 1,2,4-oxzdiazin-6-one and 1,2,5-oxzdiazin-6-one derivatives (Fig. **2**) can also be used as important synthons for further transformation to related heterocycles *via* various reaction conditions. Nowadays, numerous dihydro-oxadiazine derivatives are synthesized, and most of which are demonstrated to possess significant biological properties. However, a little document has been reported about the progress on the synthesis and biological activities of heterocyclic derivatives containing dihydro-oxadiazine nucleus up to the present.

It is clear that developing new nitrogen-containing heterocycles derivatives as pharmaceuticals is still an important area of interest in the life science and a major challenge for medicinal chemists presently. The promising biological potential of these classes of compounds urges us to review the recent advances of dihydro-oxadiazine-based heterocyclic derivatives with bioactive diversity.

STRUCTURAL FEATURES AND BIOLOGICAL PROPERTIES OF DIHYDRO-OXADIAZINE DERIVATIVES

Dihydro-oxadiazine and its derivatives, although known for several decades and constitute an important class of natural [7] and unnatural products for the manufacture of bioactive compounds, received little attention until the discovery of agrochemicals and medicinally useful products. Today, the dihydro-oxadiazine skeleton and its oxo derivatives (Fig. **2**), especially the 1,3,4-oxadiazinone and 1,2,4-oxadiazinone related compounds, have been recognized as versatile potential pharmacophores, and are highly useful in the fields of agriculture and medicine.

Recently, these key moieties are constituted in many biologically active substances with a broad range of biological and pharmaceutical activities. As a result in recent years, the construction of dihydro-oxadiazine heterocycles has attracted much attention, and many advances have taken place, including developing totally new synthetic approaches from new precursors or finding some novel biological properties. Firstly, we now investigate the recent report on novel biological activities associated with dihydro-oxadiazine and its oxo derivatives including highly potential medicinal and pesticidal activities.

Dihydro-Oxidiazine Derivatives with Medicinal Activities

1,3,4-Oxadiazine Ring System

Many dihydro-oxadiazine derivatives show a broad spectrum of biological activities such as antiviral, cardiovascular, antitumor, antibacterial, and monoamine oxidase inhibition etc. As for the research on medicinal activities of dihydro-

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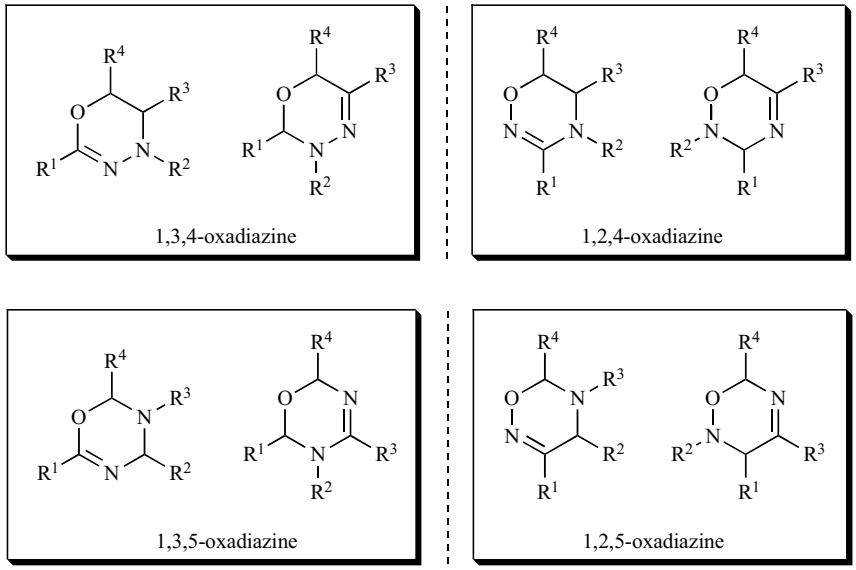


Fig. (1). Basic molecular scaffolds of dihydro-oxadiazine derivatives.

oxadiazines derivatives, as early as in 1965, Trepanier *et al*. [8] synthesized series of substituted-5,6-dihydro-4*H*-1,3,4-oxadiazines derivatives (**1** and **2**) and evaluated their activities. However, all 2-(4-pyridyl) oxadiazines in this series antagonized the effects of tremorine in mice.

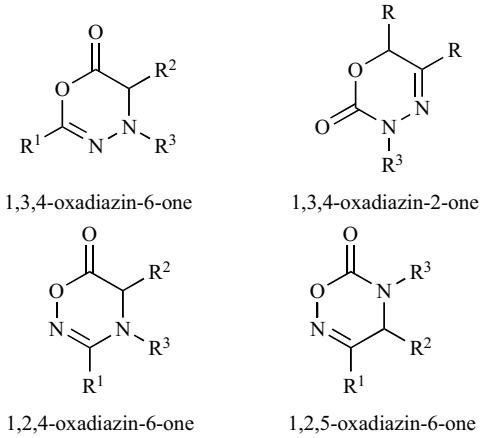


Fig. (2). Representative structures of oxadiazinones derived from oxadiazine scaffolds.

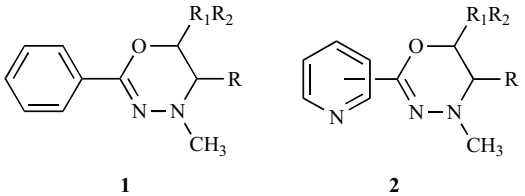


Fig. (3). Some substituted 1,3,4-oxadiazinones derivatives.

Milcent and co-workers [9, 10] from France have made systemic research on 1,3,4-oxadiazinone and 1,3,4-oxadiazinthione derivatives. In their study, some of the tested oxadiazinone **3** (Fig. **4**), were able to display obvious selective inhibition activity against monoamine oxidase (MAO), which can be used as lead compounds for further development of potential novel MAO inhibitors that are useful not only in the treatment of neurodegenerative diseases (MAOI-B), but also for effective disorders (MAOI-A). Meanwhile, Khan's research group [11] also reported some similar 1,3,4-oxadiazinone derivatives **4**, which exhibited certain antibacterial and MAO inhibition activities.

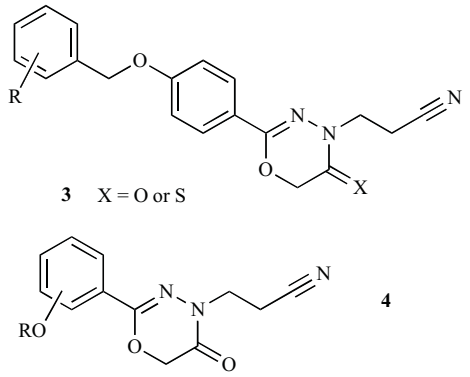


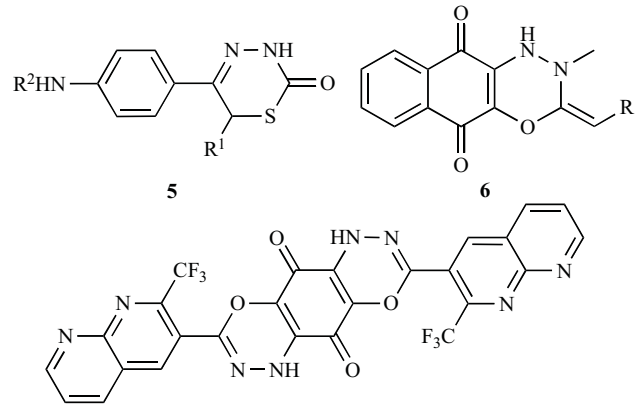
Fig. (4). Structures of dihydro-oxadiazine compounds as potential MAOI.

In 1995, series of 2*H*-1,3,4-oxadiazin-2-one analogs **5** (R^1 = H, Alk; R^2 = HetAr) containing aryl substitutents was reported by Furuya *et al*. [12], which exhibited certain cardiotonic activity. Meanwhile, series of 1*H*-naphtho[1,3,4] oxadiazine derivatives **6** [13] and **7** [14] also presented antibacterial activities.

In the meantime, another series of *N*-[4-(2-oxo(3*H*,6*H*-1,3,4-oxadiazin-5-yl))hetaryl]amides **8** has been discovered as potential agents for treatment of anemia [15]. On the other hand, some 1,3,4-oxadiazine derivatives containing uracil moiety **9** exhibit antiviral (herpes simplex virus, HSV) and antibacterial activities [16].

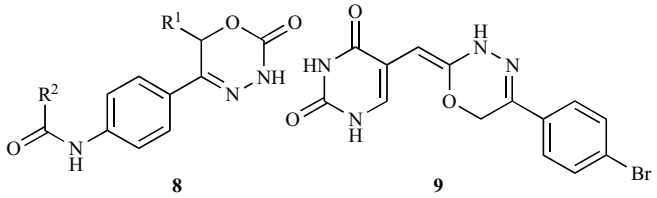
In 2006, Dittrich-Wengenroth *et al*. [17] reported novel 1,3,4-oxadiazine-5-one derivatives with general formula **10**,

which can be used as potential medicaments for treatment or prevention of diseases, preferably cardiovascular diseases, especially dyslipidemia and arteriosclerosis. Romine *et al*. [18] also reported series of 1,3,4-oxadiazine-5-one derivatives **11**, which can be used as a potential opener of large-conductance Ca^{2+}-activated potassium channels for further studies.



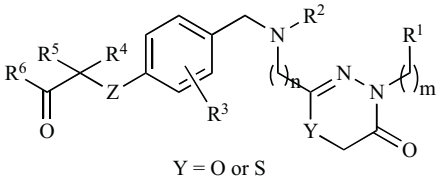
5 **6** **7**

Fig. (5). Some 1,3,4-oxadiazines derivatives.



8 **9**

Fig. (6). Structures of several 1,3,4-oxadiazine derivatives.



Y = O or S

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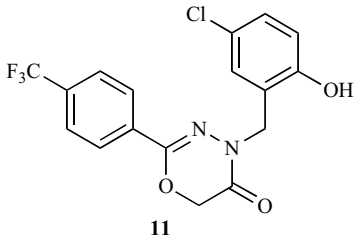

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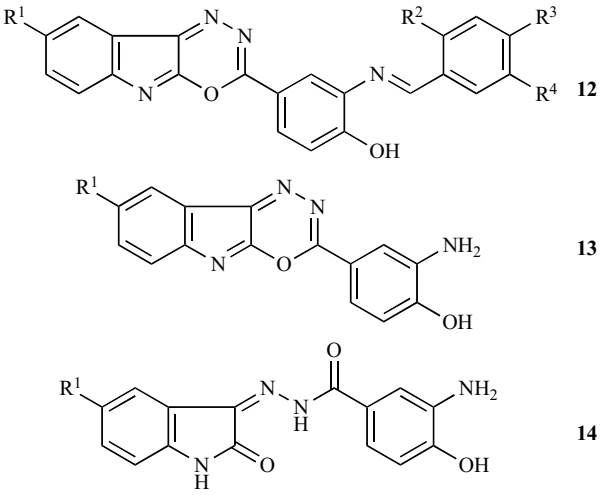
Fig. (7). Structures of several 1,3,4-oxadiazin-5-ones derivatives.

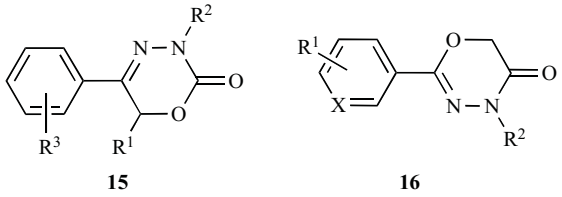
Very recently, some novel 1,3,4-oxadiazino[6,5-*b*]indoles derivatives have been synthesized by Nataraj *et al*. [19-24], and were widely screened for their antihelminthic, anti-inflammatory, antihistaminic, antimicrobial, and CNS activities. Some of target compounds (**12**, **13**) and precursors **14** exhibited obviously promising antihistaminic and anti-inflammatory activities, which might be used as lead molecules for further optimization for novel drugs.



12 **13** **14**

Fig. (8). Structures of novel 1,3,4-oxadiazino[6,5-*b*]indoles derivatives.

In 1993, the researchers [25] in Mitsui Toatsu Chem INC company also reported another series of 1,3,4-oxadiazin-2-one derivatives **15** (Fig. **9**), these compounds can stimulate platelet agglutination, and might be used as potential antithrombotic agents. Very recently, the promising bioactive diversity of dihydro-oxadiazine heterocycles compounds also urges us to synthesize and biologically evaluate a new series of 4*H*-1,3,4-oxadiazin-5(6*H*)-ones derivatives **16** with hydrophobic and long chains [26]. The preliminary assays indicated that some of the compounds displayed moderate to good inhibitory activities toward monoamine oxidase (MAO), and antitumor activities against human lung cancer A-549 and human prostate cancer PC-3 cell lines, which might provide new scaffold for anticancer agents. Furthermore, some compounds exhibited significant inhibitory activity on chitin biosynthesis, which might represent a novel class of highly potential inhibitors for chitin synthesis.



15 **16**

Fig. (9). Structures of 1,3,4-oxadiazinone derivatives.

Besides the aforementioned, some novel multi-heterocycles derived from 1,3,4-oxadiazine scaffolds **17** have been synthesized as potential anticancer agents [27]. Another series of 1,3,4-oxadiazine derivatives (**18**, **19**, **20**) starting from cyanoacetyl hydrazine also exhibited a high inhibitory effect towards the breast adenocarcinoma (MCF-7), non-small cell lung cancer (NCI-H460) and CNS cancer (SF-268) cell lines [28, 29].

In 2010, Leblanc *et al*. [30] reported the synthesis and antibacterial activities of series of novel 9-substituted-5-carboxy-oxadiazino-quinolone derivatives **21**. All com-

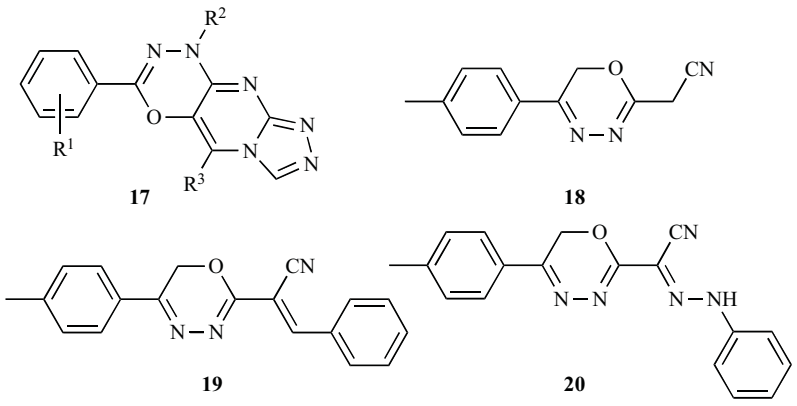


Fig. (10). Structures of some 1,3,4-oxadiazine derivatives.

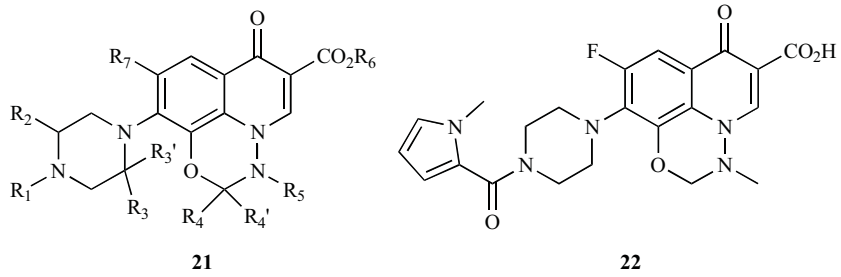


Fig. (11). Novel oxadiazino-quinolone derivatives.

pounds were tested against various bacteria (MIC values were given), and which will be useful as anti-bacterial drugs in both human and veterinary medicine.

1,2,4-Oxadiazine Ring System

Besides the aforementioned 1,3,4-oxadiazine ring system, many 1,2,4-oxadiazine derivatives also presented broad bioactivities. Berkowitz *et al*. [31] reported series of 1,2,4-oxadiazin-3-one derivatives (**23** and **24**) and evaluated their antimicrobial and antiviral activities in 1977. The preliminary test results indicated that most compounds exhibited broad-spectrum antibacterial and antifungal activities.

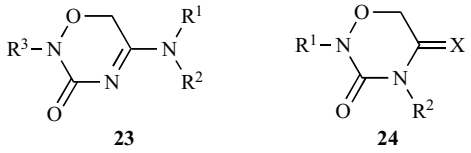


Fig. (12). Structures of 1,2,4-oxadiazine compounds.

In 1993, Weller *et al*. [32, 33] investigated another series of novel 1,2,4-oxadiazin-5-one derivatives attached with biphenyl unit **25** and indole or benzimidazole core **26**, many of which exhibited inhibition activities against angiotensin II, and might be used as lead compounds for further development of new potential therapeutic agents to treat hypertension, congestive heart failure, and cardiac hypertrophy disease.

In 2008, Arikan *et al*. [34] also investigated series of 1,2,4-oxadiazin-5-(thi)ones **27** and 1,2,4-oxadiazin-6-ones **28** containing pyridinyl moiety. The bioassay results indicated that all tested compounds presented good antimicrobial activities against both gram-positive and gram-negative bacteria and were moderately active against yeasts, which may help in the discovery of new chemical classes of antibiotics that could serve as selective agents against infectious diseases.

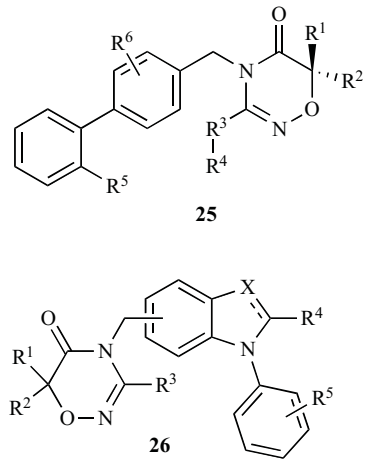
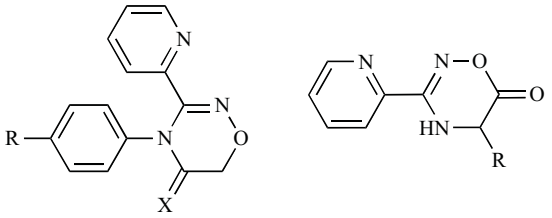


Fig. (13). Dihydro-oxadiazine derivatives with inhibition activity against angiotensin II.

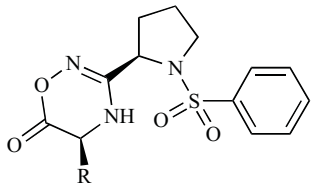
In 2010, Tka *et al*. [35] synthesized novel series of chiral 1,2,4-oxadiazin-6-one derivatives **29** bearing benzenesulfonylpyrrolidine moiety and evaluated their antibacterial and antifungal activities against some strains of bacteria and fungi. The bioassay proved that all compounds showed excellent antibacterial activities, much better than levofloxacin.

As for compound **29e** (R = Bn) against *C. glabrata*, it showed a high antifungal activity at a minimum concentration (0.03 mg / mL).



27 **28**

Fig. (14). Structures of some dihydro-oxadiazine derivatives.

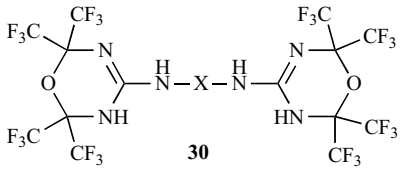


29 (2'S, 5R)

Fig. (15). Structures of chiral dihydro-oxadiazine derivatives.

1,3,5-Oxadiazine Ring System

Compared with 1,3,4-oxadiazine and 1,2,4-oxadiazine ring systems, relatively less research has been carried out on 1,3,5-oxadiazine compounds as pharmaceutical agents. In 2007, Posypanova *et al*. synthesized series of novel polyfluorinated 1,3,5-oxadiazine derivatives **30** [X = $(CH_2)_n$, CH_2CHMe; n = 2, 3, 4, 6, 10] by bis(heterocyclization) of hexafluoroacetone with the corresponding bis(guanidine) dihydrochlorides. The preliminary cytotoxic activity of compounds against various human tumor cell lines has been studied *in vitro*. Compounds **30a** [X = $(CH_2)_6$] showed significant activity against human ovarian tumor cell line SKOV3 [36]. Further evaluation indicated that **30a** was shown to have a high activity against melanoma [37]. Meanwhile, 1,3,5-oxadiazin-4-thiones derivatives **31** bearing 1,2,4-triazole core [38] have also been reported as highly potential antibacterial agents.



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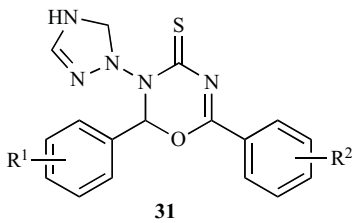

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Fig. (16). Structures of 1,3,5-oxadiazine derivatives.

1,2,5-Oxadiazine Ring System

In 2001, some novel fused heterocycles pyrazolo[4,3-c][1,2,5]oxadiazin-3(5*H*)-one ring system **32** have also been evaluated as serine protease inhibitors by Vicentini *et al*. [39]. Various substitutions on the pyrazole ring with both aliphatic or aromatic groups and the replacement of the carbonyl oxygen on the reactive oxadiazinone ring with sulfur were all explored.

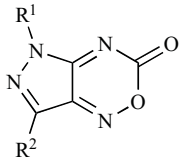

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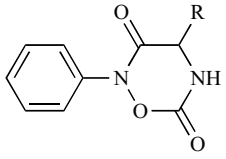
Fig. (17). Structures of pyrazolo[4,3-c][1,2,5]oxadiazin-3(5*H*)-one ring derivatives.

In 2003, Barnarić *et al*. [40] developed a new synthetic approach to the 1,2,5-oxadiazine-3,6-diones derivatives **16** (Table **1**), and the cytotoxic and cytostatic activities against HeLa and GMK cell lines were all evaluated. Selected biological studies indicated that oxadiazines **33a** and **33c** had no cytotoxic effect on HeLa and GMK cells at tested concentrations, but they had a pronounced cytostatic effect, *i.e.,* they inhibited cell growth in the 25-75% range. These preliminary findings indicate that these 1,2,5-oxadiazine derivatives might be used as potential leads for optimization of novel antiviral drugs.

Table 1. IC_{50} for compounds 33.



a R = H
b R = Me
c R = Bzl

33

Cell Line	IC_{50} (mol L^{-1})	
	33a	**33c**
GMK	1.125×10^{-4}	5.800×10^{-5}
HeLa	0.897×10^{-5}	0.824×10^{-4}

Dihydro-Oxidiazine Derivatives with Pesticidal Activities

It is well known, dihydro-oxadiazines belong to a group of heterocyclic compounds that present a wide range of pharmacological activities. However, up to now, many dihydro-oxadiazine heterocyclic derivatives have also been discovered as agrochemical agents including fungicidal, antimicrobial, acaricidal, insecticidal, herbicidal and chitin synthesis inhibition activities etc.

1,3,4-Oxadiazine Ring System

As early as in 1986, Dekeyser and co-workers [41] in Canada reported series of diphenyl substituted 1,3,4-oxadiazin-5-one derivatives **34**, many of which exhibited

good miticidal and nematocidal activities. In addition, Dekeyser *et al*. have developed systemic structure-activity relationship on series of 1,3,4-oxadiazine and 1,3,4-oxadiazinone derivatives [42-46] based on molecular modeling techniques during the year of 1991-1993, and many of these compounds (**35**, **36**) exhibited obvious insecticidal and acaricidal activities and represented conformationally restricted analogs of octopamine.

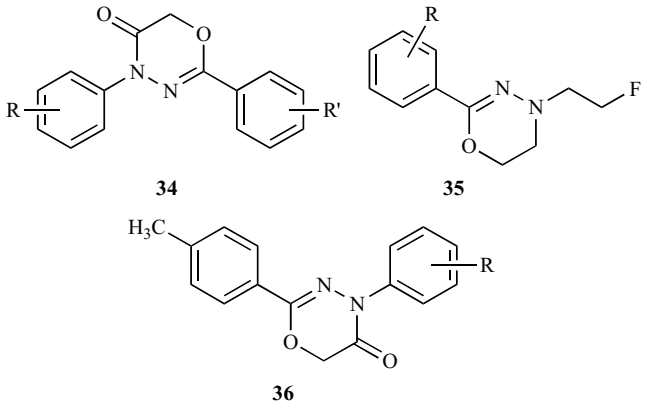


Fig. (18). Structures of 1,3,4-oxadiazine derivatives with pesticidal activities.

Whereafter, some 4-substituted-2-aryl-5,6-dihydro-1,3,4-oxadiazines **37** [47] and 2-aryl-5,6- dihydro-1,3,4-oxadiazin-4-yl-carboxamides **38**, **39** [48, 49] have been reported that exhibited obvious pesticidal activity. Meanwhile, benzo [4,2,1]oxadiazines derivatives **40** were also discovered to be used as potential herbicides [50].

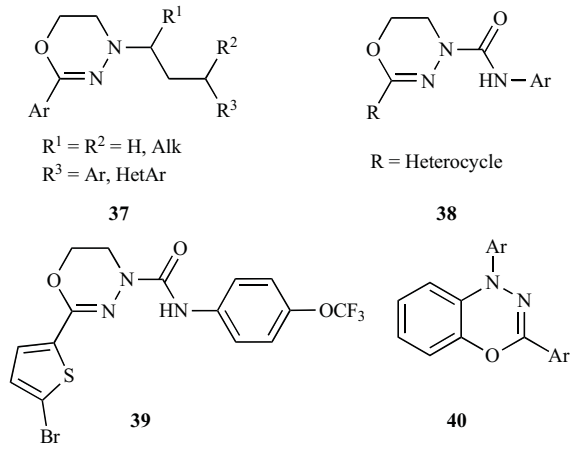


Fig. (19). Structures of 1,3,4-oxadiazine derivatives.

Ito *et al*. [51] reported some novel 1,3,4-oxadiazinone derivatives containing pyridine ring **41** as AMPA receptor antagonists. In the meantime, Dyker *et al*. in Bayer Crop Protection Company discovered series of novel 1,3,4-oxadiazinone derivatives **42** [52], which exhibited wide biological activities as insecticide, acaricide and nematicide agents. Compound **43** bearing thiophene ring is the typical highly potential compound.

At the end period of last century, the novel insecticide Indoxacarb (**44**) targeting voltage-dependent block of sodium channels was developed by DuPont Company [53-56], which is a newly dihydro-oxadiazine type of insecticide that has been developed as Steward^{TM} and Avaunt^{TM} for controlling a broad spectrum of pest insects on various crops and exhibiting low toxicity to non-target organisms. This compound **44** is the representative of 1,3,4-oxadiazine ring system that has been successfully developed and is currently on the market.

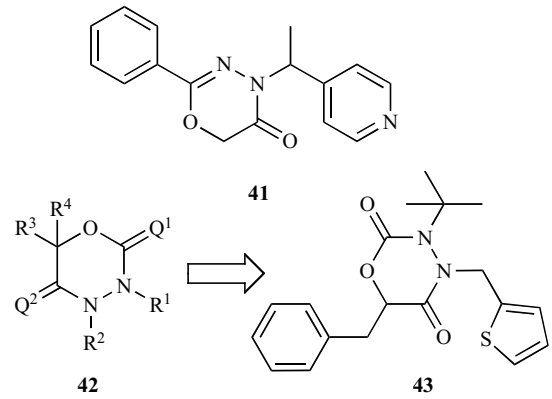
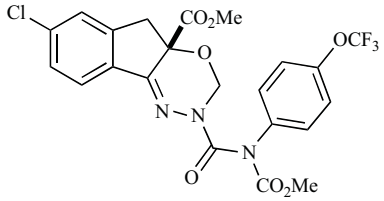


Fig. (20). Structures of some 1,3,4-oxadiazine derivatives.



Indoxacarb 44

Fig. (21). Commercial dihydro-oxadiazine insecticides.

In 2000, fluorinated 1,3,4-oxadiazines derivatives attached with various heterocycles **45** [57] and some 1,3,4-oxadiazines **46** incorporated trifluoromethyl unit [58] have been reported as novel potential insecticide and acaricides.

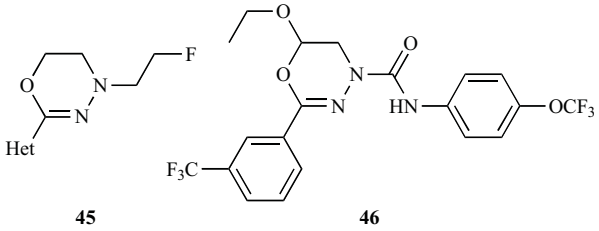
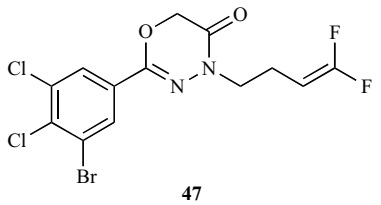


Fig. (22). Structures of fluorinated 1,3,4-oxadiazine derivatives.

Manabe *et al*. [59] also reported series of aryl-substituted 1,3,4-oxadiazin-5-one derivatives attached with difluorobutenyl moiety in 2003. The representative compounds **47** exhibited excellent insecticidal and acaricidal activities. Whereafter, Meazza *et al*. [60] also discovered series of *N*-substituted 1,3,4-oxadiazin-5-one derivatives bearing uracil unit **48** that presents obvious herbicidal activity.

Recently, some novel 1,3,4-oxadiazine derivatives based on pyrimidine heterocycles [61] have been reported as poten-

tial broad spectrum heribicides (**49** and **50**). Nevertheless, another series of 1,3,4-oxadiazine derivatives **51** derived from substituted cinnamic acid [62] exhibited a significant insecticidal activity, and the mortality of *Culex pipiens pallens* of **51a**, **51b**, **51c** and **51d** at the concentration of 50 mg/L reached 91.7%, 86.1%, 85.5% and 93.9%, respectively.



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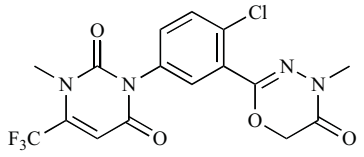
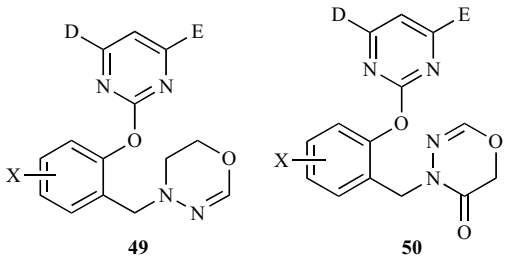
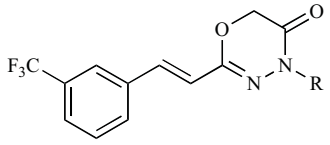


48

Fig. (23). Structures of some 1,3,4-oxadiazine derivatives.



49 **50**



a R = C_2H_5, b R = n-Pr
c R = i-Pr, d R = $PhCH_2$

51

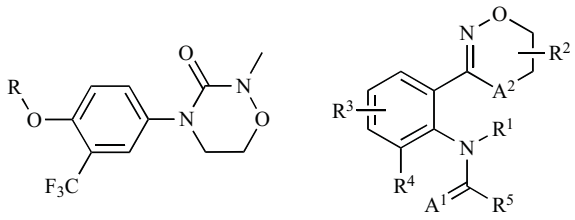
Fig. (24). Structures of some 1,3,4-oxadiazine derivatives.

1,2,4-Oxadiazine Ring System

Compared with 1,3,4-oxadiazine derivatives, some aryl substituted 1,2,4-oxadiazin-3-one derivatives **52** [63] were also discovered to present herbicidal activity especially for cereal crops. On the other hand, some other arylamide-substituted oxadiazine derivatives **53** have also been discovered by researchers in Bayer Crop Protection Company [64], which can be widely used as pesticides to treat transgenic plants, combat animal parasites, and as plant protecting agents, herbicides, safeners, growth modulators or fungicides.

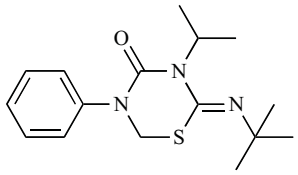
1,3,5-Oxadiazine Ring System

Another typical compound is successfully developed and currently on the market as novel insect growth regulator (IGR) *i.e.* Buprofezin **54** [65], which is the bioisosterism product of 1,3,5-oxadiazinone developed by Nihon Nohyaku Co., Ltd. Buprofezin is a novel IGR without any structural similarity to benzoylurea, but has the same mode of action as chitin synthesis inhibitors. Buprofezin is highly effective against several species of insect pests, such as planthoppers, leafhoppers, whiteflies and scales, and is quite harmless for beneficial insects, natural enemies, fishes and mammals.



52 **53**

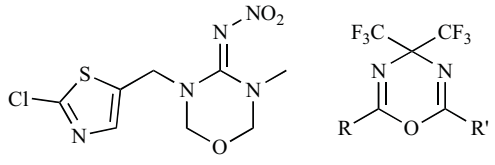
Fig. (25). Structures of 1,2,4-oxadiazine derivatives.



Buprofezin **54**

Fig. (26). Structures of dihydro-oxa(thia)diazine insecticides.

Meanwhile, the researchers [66] in Novartis Crop Protection Company synthesized some heterocycle derivatives bearing 1,3,5-oxadiazine unit (Namely Thiamethoxam **55**), which present excellent insecticidal activity against Lepidoptera insect. In 2003, Chee *et al.* designed and synthesized series of novel 1,3,5-oxadiazines containing ditrifluoromethyl group **56** [67], which can be used as potential agents for pest integrated control. Some 1,3,5-oxadiazines **57** derived from substituted cinnamic acid also presented good pesticidal activity [68].



55 **56**

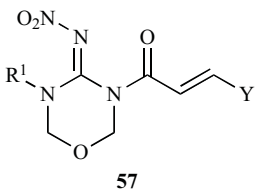


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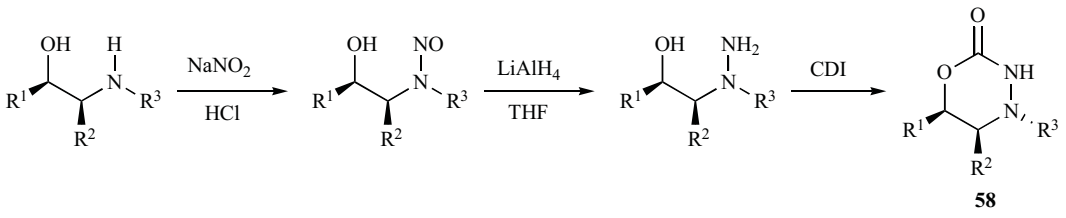
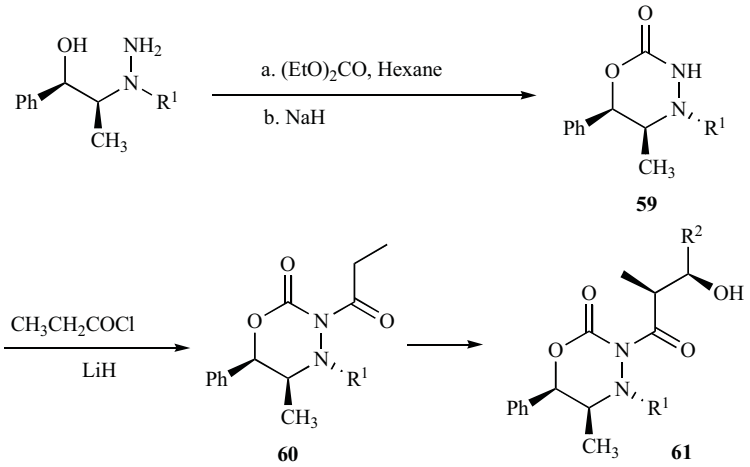
Fig. (27). Structures of dihydro-oxadiazine insecticides.

General Synthetic Method for Dihydro-Oxadiazine Derivatives

Many novel heterocyclic compounds derived from dihydro-oxadiazine scaffold present a diversity of biological ef-



Scheme 1.



Scheme 2.

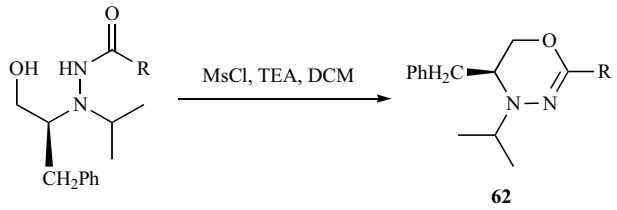
fects and have also been shown to be important building blocks for further organic transformation. Nowadays, many advances have taken place, including developing novel synthetic approaches from new precursors or utilizing modern synthetic methodologies. We now survey recent reported synthetic approaches to dihydro-oxadiazines and highlight new methodologies.

1,3,4-Oxadiazine Ring System

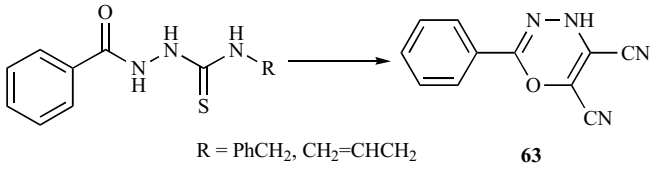
Noteworthy in relation to discussion is the synthesis for 1,3,4-oxadiazin-2-one [69-72], which have recently been introduced as versatile chiral auxiliaries for the asymmetric synthesis. The most prevalent methodology for the synthesis of these heterocycles is based on cyclization reaction of *β*-hydrazino alcohols as shown in Scheme **1**.

Recently, Hitchcock *et al*. [73], developed different cyclizing agents for the construction of 1,3,4-oxadiazin-2-one derivatives (Scheme **2**). In the process of their discovery, they demonstrated that the use of diethyl carbonate in conjunction with a metal hydride (sodium or lithium) proved to be just as effective as 1,1'-carbonyldiimidazole. The formed 1,3,4-oxadiazin-2-one **60** can be employed as versatile building blocks for further asymmetric Aldol reaction [74]. Subsequently, Hitchcock *et al*. [75] extended their research and prepared series of chiral 5,6-dihydro-4*H*-1,3,4-oxadiazines **62** (Scheme **3**).

It is well-known that 1,4-disubstituted thiosemicarbazides can be used as key units to further transform into versatile heterocycles under different conditions. Recently, Hassan *et al*. [76] presented the rationales for the role of the solvent and the conversions observed on cyclization of 1,4-disubstituted thiosemicarbazides (Scheme **4**). From their research, some 1,3,4-oxadiazines **63** can be obtained from 1,4-disubstituted thiosemicarbazides.



Scheme 3.

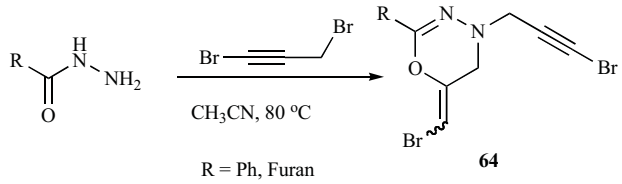


Scheme 4.

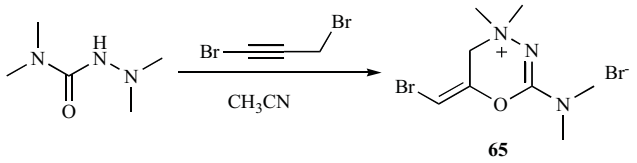
On the other hand, Volkova *et al*. [77] also conveniently constructed multi-substituted 1,3,4-oxadiazines **64** starting from various acylhydrazines (Scheme **5**). Subsequently, the researchers in this group extended their synthetic method for the synthesis of 6-(bromomethylidene)-2-(dimethylamino)-4,4-dimethyl-5,6-dihydro-4*H*-1,3,4-oxadiazin-4-ium bromide (Scheme **6**) by reaction of 1,1,4,4-tetramethylsemicarbazide with 1,3-dibromoprop-1-yne in acetonitrile [78].

In 2006, Kudelko *et al*. [79] reported series of 1,3,4-oxadiazin-5-one derivatives as shown in Scheme **7**, which

were conveniently transformed from α-hydroxy acid hydrazides and triethyl orthoesters (orthoformate, orthoacetate, orthopropionate, orthobenzoate) in the presence of glacial AcOH.



Scheme 5.



Scheme 6.

In 2007, Takamura *et al*. [80] presented a novel synthetic route to 1,3,4-oxadiazine derivatives from *α*-amino acid esters. The various hydrazones obtained *via* diazotization and reduction reactions are acylated to give electrophiles *N*-acylhydrazones, which are subjected to further reactions to give 1,3,4-oxadiazin-6-one **67** that serve as useful synthetic intermediates for the Diels–Alder reaction.

Furthermore, some aromatic and heteroaromatic acid hydrazides can also react directly with oxalyl chloride in benzene or chloroform to give previously unknown 2-aryl(hetaryl)-4*H*-1,3,4-oxadiazine-5,6-diones derivatives **68** [81].

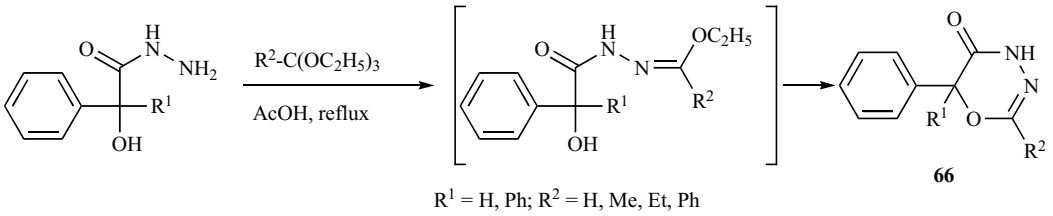
Recently, Mohareb *et al*. [29, 82] obtained series of 1,3,4-oxadiazine derivatives (**69**, **70**, **71**) using easily available cyanoacetylhydrazine as substrates (Scheme **10**), which can be used for synthesis of versatile heterocyclic derivatives with potential antitumor activity.

Karade *et al*. [83] reported a novel and general method for the efficient construction of 2,5-diaryl- 1,3,4-oxadiazines **72** from the reactions of [hydroxy(tosyloxy)iodo]benzene with easily available substituted acetophenones, followed by the treatment with acid hydrazide. In their process, a versatile hypervalent iodine(III) reagent was employed as the key oxidant.

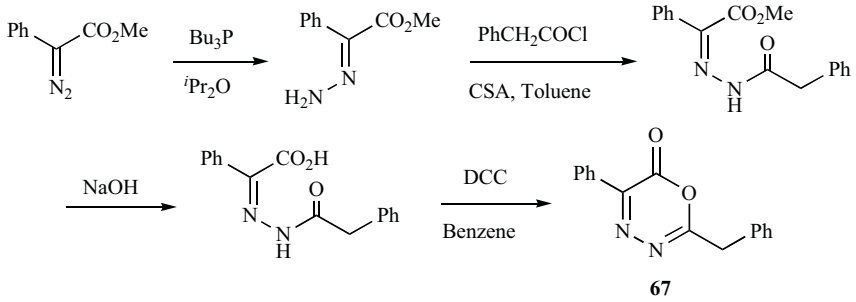
Very recently, Shet *et al*. [84] also investigated series of chiral and nonchiral pyrido[3,2-*e*] [1,3,4]oxadiazines derivatives **73** *via* different synthetic methods by exploring 3,5,6-trichloropyrine-2-ol as starting materials.

1,2,4-Oxadiazine Ring System

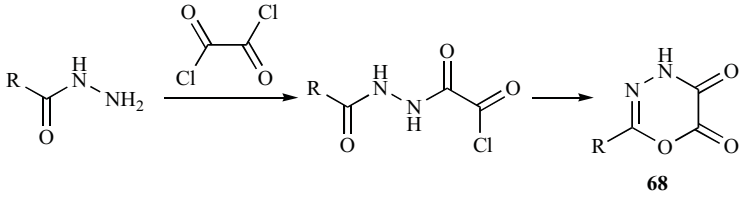
Besides the method to access 1,3,4-oxadiazine ring system, Cho *et al*. [85] developed a convenient and facile one-pot procedure to construct 1,2,4-oxadiazine ring system (Scheme **13**). In their process, various aziridin-1-yloximes



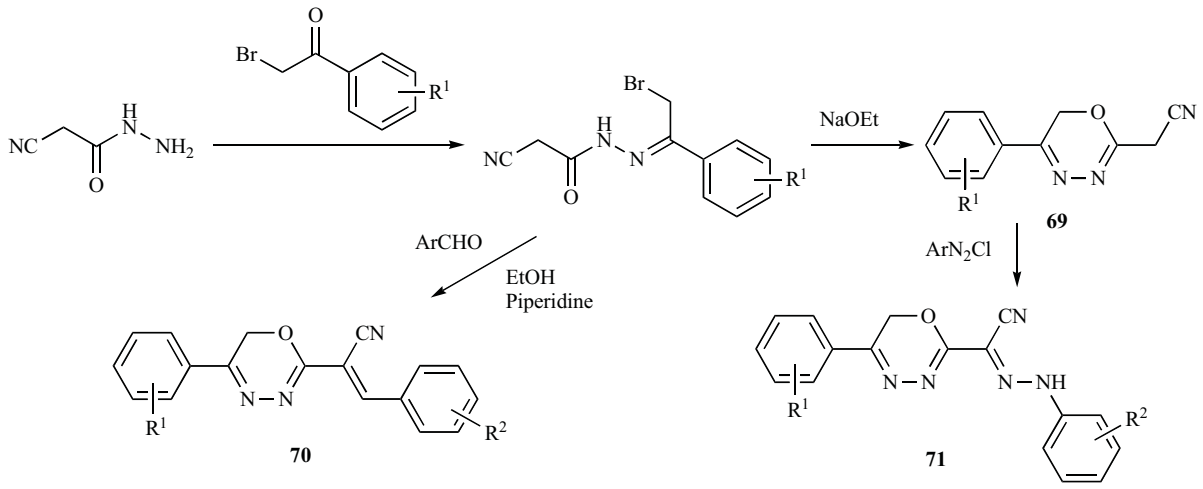
Scheme 7.



Scheme 8.

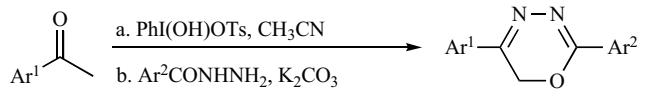


Scheme 9.



Scheme 10.

were treated with Scandium(III) triflate in the presence of chlorotrimethylsilane to afford 5,6-dihydro-4*H*-1,2,4-oxadiazine **74**.



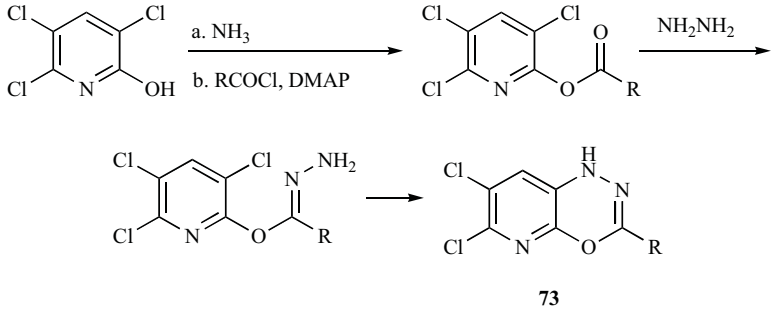
Scheme 11.

Meanwhile, some novel thiophene-substituted 1,2,4-oxadiazines derivatives **75** were also conveniently obtained by the reaction of thiophene-ring substituted amidoximes with chloroacetylchloride [86].

In 2009, Attanasi *et al*. [87] also reported a novel method exploring aryl amidoximes as substrates for the construction of 1,2,4-oxadiazine scaffolds **76** (Scheme **15**). Reports in the literature indicate that 1,2-diaza-1,3-dienes can easily react as Michael acceptors with aryl amidoximes in a one-pot, high-yield heterocyclization process.

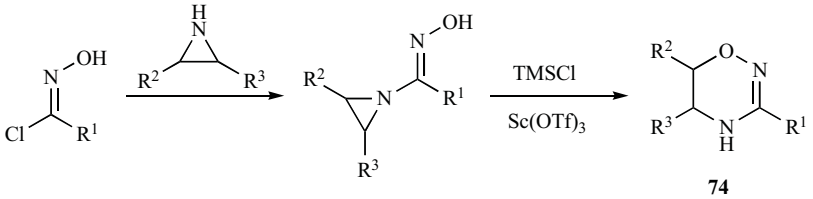
Very recently, Tka *et al*. [35] also employed substituted amidoximes as substrates to construct chiral 1,2,4-oxadiazin-6-one derivatives **77** bearing benzenesulfonylpyrrolidine moiety *via* intramolecular cyclization (Scheme **16**).

Except the aforementioned, some 1,2,4-oxadiazole derivatives can also be used for further transformation into 1,2,4-oxadiazine heterocycles. In 2009, Piccionello *et al*. [88] investigated the reaction of 3-ethoxycarbonyl-5-perfluoroalkyl-1,2,4-oxadiazoles with hydroxylamines, and



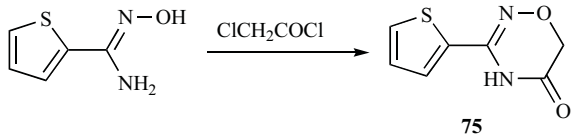
R = Phenyl, Naphthyl, Substituted Phenyl or Alkyl

Scheme 12.



Scheme 13.

evidencing the possibility of competitive reaction paths. From their method, fluorinated 1,2,4-oxadiazin-6-one derivatives **78** can be easily accessed through serial rearrangement of 1,2,4-oxadiazoles.

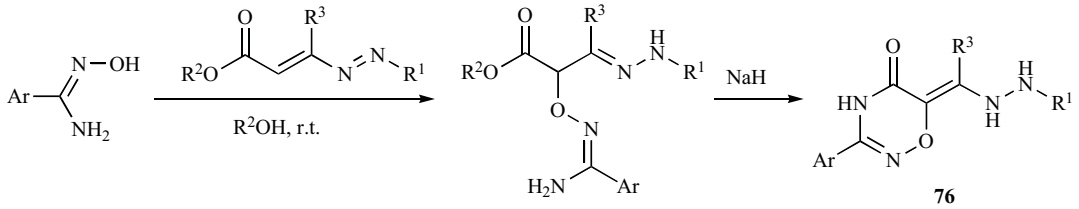


Scheme 14.

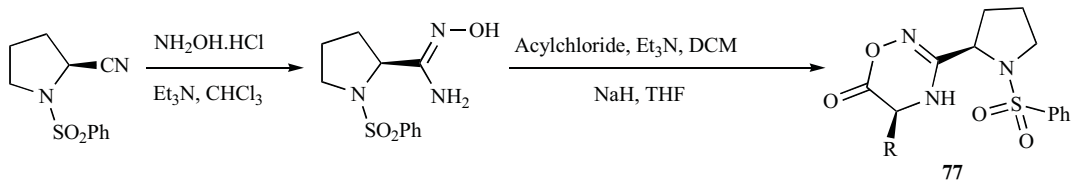
Some Transformation of Dihydro-Oxadiazine Ring

Except the aforementioned methods to construct dihydro-oxadiazine ring system, some dihydro-oxadiazine derivatives can also be used as important building blocks for further transformation to versatile heterocycles or important intermediates.

It is well known, many methods have been developed to construct oxadiazine-based heterocycles, and however, few have been explored using the so-called cycloaddition. Recently, Huang *et al*. [91] reported an unprecedented enantioselective [4+2] cycloaddition reaction of ketenes with *N*-benzoyldiazenes catalyzed by chiral NHCs to give 1,3,4-oxadiazin-6-ones **84**. These heterocycles are highly function-



Scheme 15.



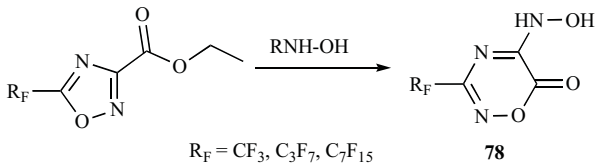
Scheme 16.

1,2,5-Oxadiazine Ring System

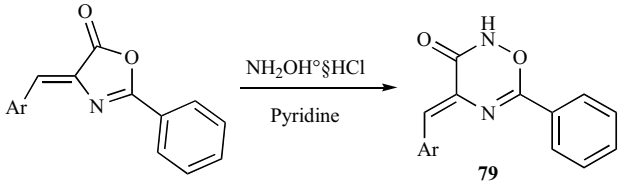
In 2002, Madkour [89], exploring the synthetic usefulness of a series of 1,3(4*H*)-oxazol-5-one intermediates, synthesized series of substituted 1,2,5-oxadiazin-3-ones **79**. The key 1,3(4*H*)-oxazol-5-one was allowed to react with hydroxylammonium chloride in the presence of pyridine, then the ring-expansion occurred to give the oxadiazinone derivatives (Scheme **18**). The 1,3(4*H*)-oxazol-5-one were also useful intermediates for further transformation to other heterocycle analogs, such as triazinone, tetrazole and imidazolinone derivatives.

Subsequently, Barnarić *et al*. [40] developed a new general approach to the 1,2,5-oxadiazine-3,6-diones derivatives **80** (Scheme **19**), which were conveniently accessed by cyclization of appropriate hydroxamic acids derived from *N*-(1-benzotriazolylcarbonyl)-amino acids. Since various methods for the preparation of a wide range of *N*-monosubstituted hydroxylamines are available, this procedure constitutes a convenient access to construction of the 1,2,5-oxadiazine ring system.

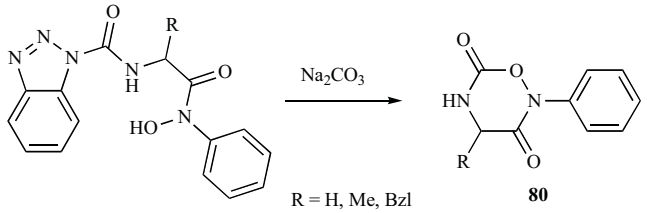
Recently, some novel 3-alkoxy-5,6-dihydro-4*H*- 1,2,5-oxadiazines derivatives were conveniently obtained by Kurz *et al*. [90]. Their method explored alkyl *α*-aminohydroximates as valuable building blocks to construct versatile molecules bearing 4*H*-1,2,5-oxadiazines scaffolds (Scheme **20**).



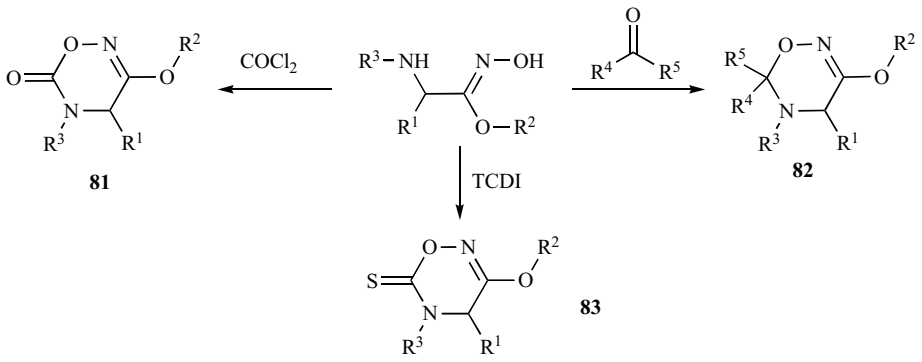
Scheme 17.



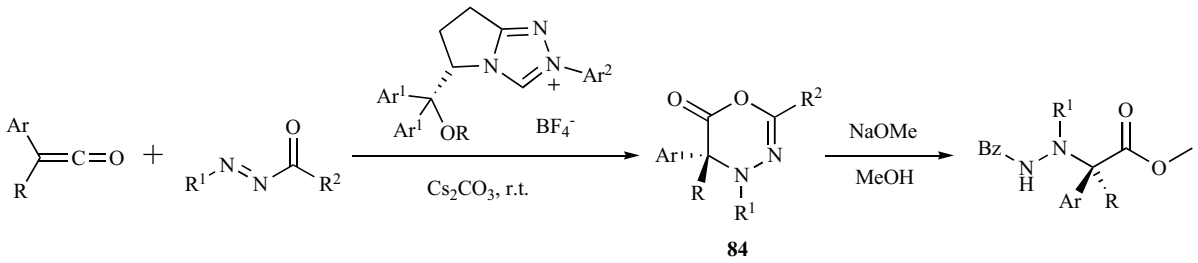
Scheme 18.



Scheme 19.



Scheme 20.



Scheme 21.

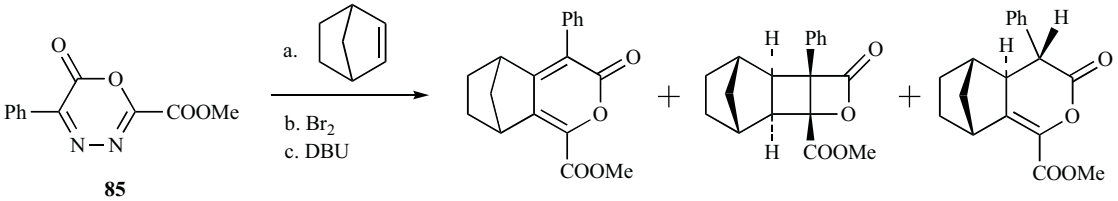
alized and are a useful intermediate in organic synthesis, which can be further transformed into α,α-disubstituted α-amino acid derivatives (Scheme **21**).

As early as in 1998, Tidwell *et al*. [92] also reported a serial transformation of 1,3,4-oxadiazines **85**. This reaction sequence may prove useful for the synthesis of α-pyrones and β-lactone derivatives.

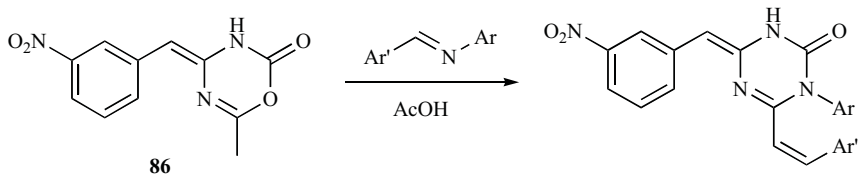
Meanwhile, some 1,3,5-oxadiazin-2-ones **86** can be easily transformed to 1,3,5-triazinones heterocycles. Kumar *et al*. [93] prepared series of substituted 1,3,5-triazinones derivatives *via* condensation of Schiff base with 1,3,5-oxadiazin-2-ones **86**. The formation of target compounds is assumed to proceed *via* Michael type addition, followed by aminolysis of the dihydro-oxadiazine to form the open chain intermediate.

OTHER APPLICATION ASPECTS OF DIHYDRO-OXADIAZINE DERIVATIVES

Except the aforementioned diversity of biological activities with dihydro-oxdiazine derivatives, some novel compounds bearing dihydro-oxadiazine moiety have been applied in other fields such as materials, dyes etc. Noteworthy in relation to further discussion is the work of Shindy and Eissa [94, 95] who reported the formation of novel cyanine dyes bearing dihydro-oxadiazine heterocycles as depicted in Fig. **28**. In this point of view, Shindy *et al*. synthesized series of novel heterocyclic compounds **87** having 1,3,4-oxadiazine nuclei with the hope that a combination of the favorable properties of both dihydro-oxadiazine and cyanine dyes may be achieved. The photosensitization properties have been investigated and antimicrobial activities of selected compounds against some bacterial strains were tested. Subse-

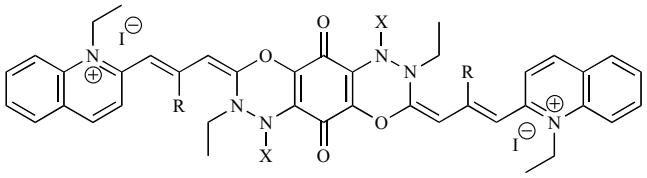


Scheme 22.

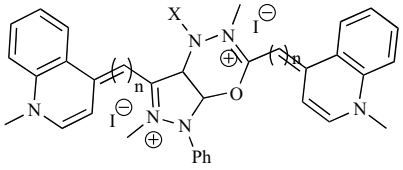


Scheme 23.

quently, Eissa reported another series of pyrazolo [4,3-*e*]-1,3,4-oxadiazine cyanine dyes **88**, and the antibacterial activity and adsorption spectra were all investigated.



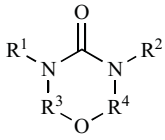
87



88

Fig. (28). Cyanine dyes containing dihydro-oxadiazine heterocycles.

On the other hand, some dihydro-oxadiazine heterocyclic derivatives have also been used as ink compositions. The researchers in Toyo Ink Mfg. Company [96] reported the following compounds represented by the formula **89** as normal ink compositions, and which has low smell, printing stability and drying properties, causes no corrosion to a printer, and is excellent in adhesion to non-absorbable printing media.



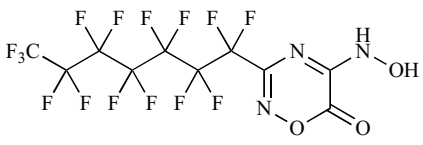
R^1, R^2 = H or C_1-C_5-alkyl

R^3, R^4 = C_1-C_4-alkylene,
C_2-C_4-alkenylene

89

Fig. (29). Dihydro-oxadiazine derivatives as ink compositions.

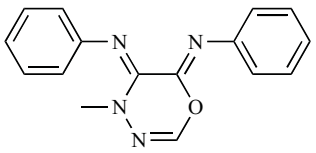
In 2009, dihydro-oxadiazine heterocycle has also been used as a key structural unit to construct novel surfactants by Buscemi *et al*. [88]. The physicochemical behavior of the newly synthesized fluorinated 5-hydroxyamino-3-perfluoroheptyl-1,2,4-oxadiazin-6-one (PFHO, **90**) surfactant was investigated [97]. It exhibits an enhanced self-assembling behavior than those of a similar surfactant having the same phobicity, such as sodium perfluorooctanoate.



90

Fig. (30). 1,2,4-Oxadiazinone derivatives as surfactant.

Besides the aforementioned applications, some dihydro-oxadiazine derivatives such as *N*,*N*′-(4-methyl-4*H*-1,3,4-oxadiazine-5,6-diylidene)-bis-aniline derivatives **91** can also be used as novel ligand in catalytic fields [98].



91

Fig. (31). Substituted 1,3,4-oxadiazine as catalytic ligands.

CONCLUSION

In conclusion, we have demonstrated that a large number of structurally novel dihydro-oxadiazine-based heterocyclic derivatives possess a broad range of biological activities including potential pharmacological and pesticidal applications. The increased interest of these novel dihydro-oxadiazine heterocycle scaffolds in the field of drug research may be linked to its unique molecular structure, which serves as versatile building blocks, scaffolds or pharmacophores. Meanwhile, some of the dihydro-oxadiazine ring can be further transformed into different heterocyclic compounds with interesting biological properties, thereby generating new opportunities for novel drug development.

Undoubtedly, the wide application and development of heterocycles bearing dihydro-oxadiazine scaffold foreshow the appearance of the promising useful application in life science and agrochemical industry. The systemic research on the design, synthesis and biological evaluation of series of dihydro-oxadiazine heterocycles derivatives will definitely lead to further discovery of novel functional molecules.

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