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Review of synthetic strategies in the development of oxadiazine scaffolds

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Abstract: Heterocycles containing both oxygen and nitrogen are in a tremendous demand for their immense biological activities. Oxadiazines are the scaffolds shown pleasing activities like antibacterial, antifungal, anthelmintic, anti-inflammatory, locomotor, anticonvulsive, antiviral, antitumor, agricultural, insecticidal, nematocidal, miticidal, neurogenerative disorders like Alzheimer disease, blood disorders like anemia and plant regulation. Multiple syntheses of oxadiazine scaffolds like 1,2,4-oxadiazines, 1,2,5-oxadiazines, 1,3,4-oxadiazines, 1,3,5-oxadiazines have been summarized in the review. Several research chemists are making attempts to discover and introduce the new scaffolds for various diseases ailments in the present scenario. Here we made an attempt to introduce the scaffolds of substituted oxadiazines because a lesser amount of research was carried out on these nuclei.

Keywords: oxadiazines, heterocyclic scaffolds, 1,2,4-oxadiazines, 1,2,5-oxadiazines, 1,3,4-oxadiazines, 1,3,5-oxadiazines.

Introduction

Compounds contain nitrogen in their cyclic structure exists numerous biologically active moieties and exhibit numerous application's in chemistry, biology, and other sciences [1-6]. Oxadiazines are the molecules with oxygen and two nitrogen rest in different positions of the cyclic structure.

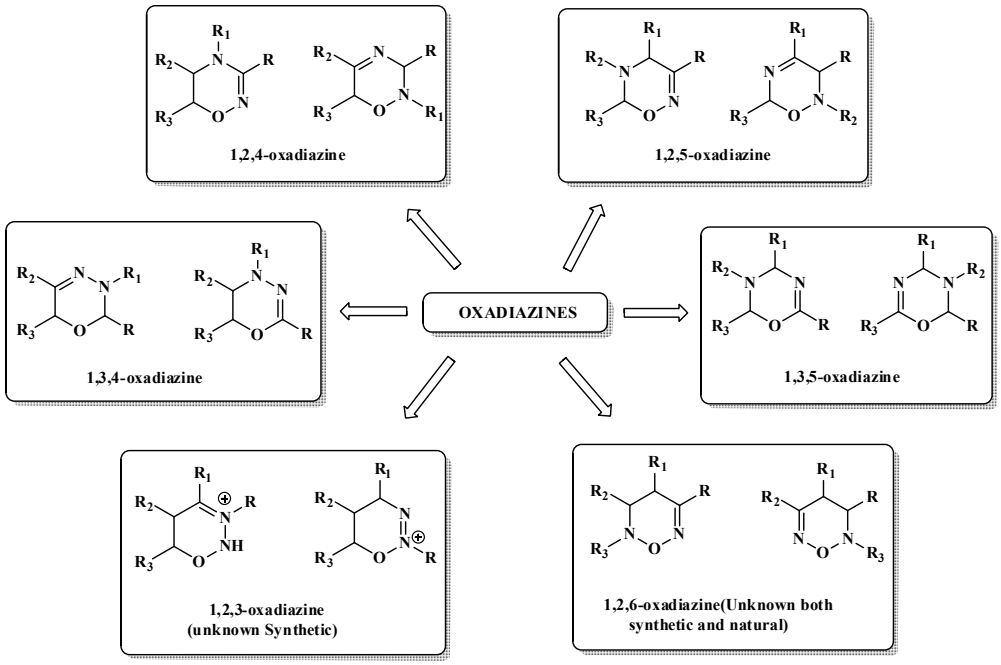

Figure 1. Substituted scaffolds of oxadiazine nucleus

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Oxadiazines have a reflective structure with certain peculiarities in which the molecules of the oxadiazine nucleus are non-planar in the arrangement, and the scaffolds are non-aromatic. The structures of different oxadiazines are 1,2,3-oxadiazine, 1,2,4-oxadiazine, 1,2,5-oxadiazine, 1,2,6-oxadiazine, 1,3,4-oxadiazine and 1,3,5-oxadiazine depicted in Fig.1. Medicinal chemists developed the various synthetic routes for different oxadiazines and its derivatives for their potential activity towards agriculture and medicin, but so far no synthetic route has been developed on 1,2,3-oxadiazines (except 1,2,3-oxadiazine of natural origin) and 1,2,6-oxadiazines [7-11].

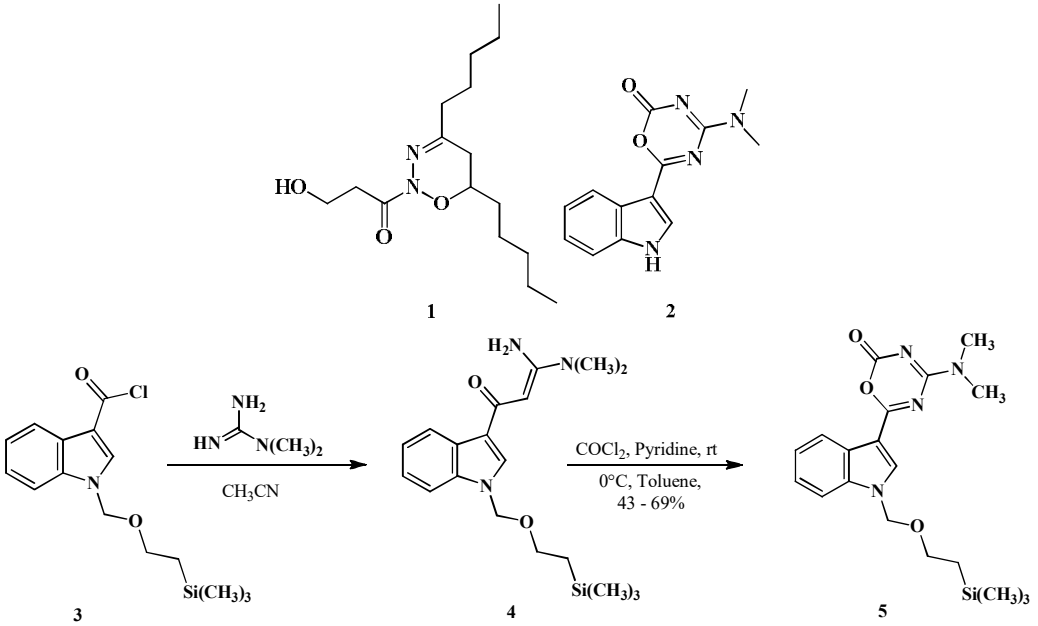
Materials and methods

Natural oxadiazine scaffold

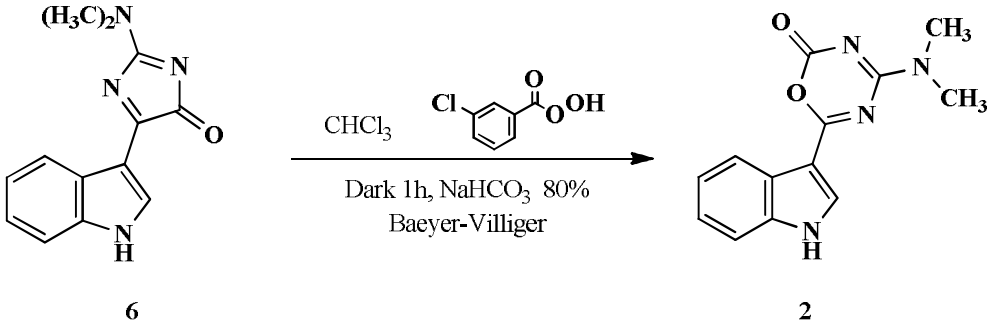
Nocuolin A(NoA) **1** which is the merely natural 1,2,3-oxadiazine scaffold obtained from three cyanobacterial strains of *Nostoc*, *Nodularia*, and *Anabaena*. A demonstration has been carried out that NoA has attributes of caspase-dependent apoptosis and moreover it exhibits potent antiproliferative activity against most cell lines, out of which the most effective was found in p53 mutated cell lines [12].

Synthetic oxadiazine scaffold

Another natural 1,3,5-oxadiazin-2-one alkaloid [13] Alboinon **2** isolated from Ascidian *Dendrodoa grossularia* and its synthetic routes has been developed from protected oxadiazinone **5** of acid chloride **3** reacted with *N, N*-dimethylguanidine to form **4** followed by phosgene to attain the desired scaffold **5** (Scheme 1) [14] and also from Baeyer-Villiger oxidation by rearrangement of imidazole **6** by reacting with *m*-chloroperbenzoic acid to get alboinin **2** (Scheme 2).

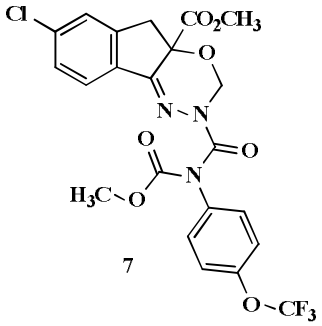


Scheme 1. Synthesis of Alboinon from acid chlorides



Scheme 2. Synthesis of Alboinon by Baeyer-Villiger Oxidation

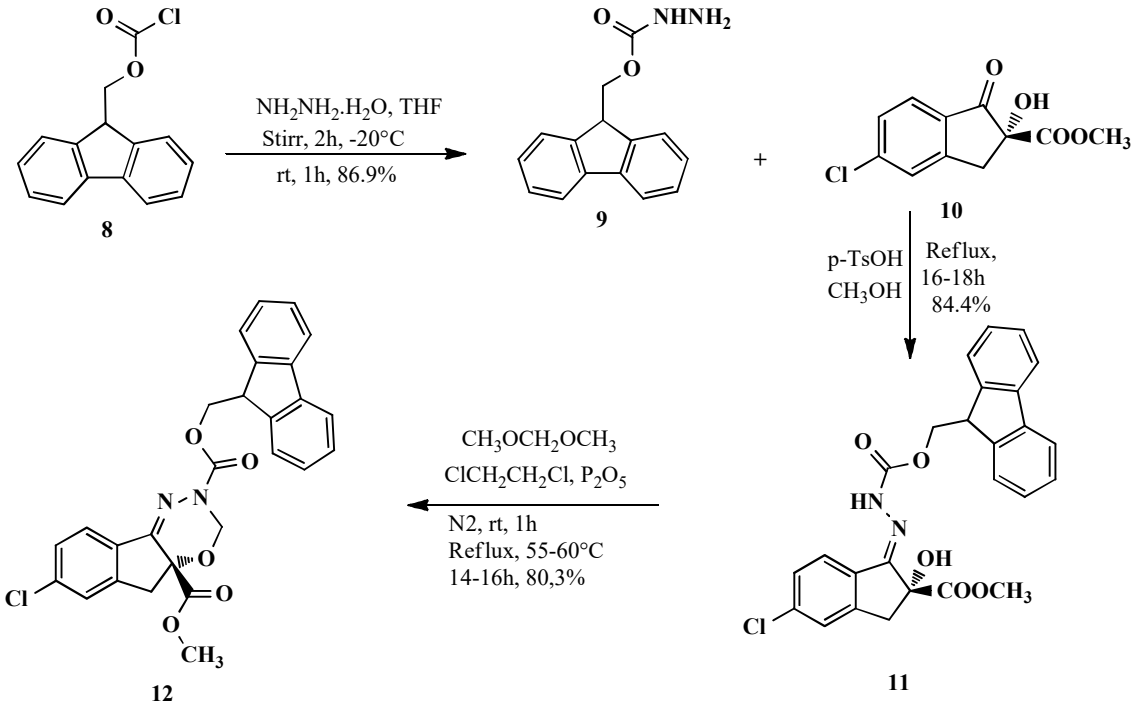
Indoxacarb **7** which is a 1,3,4-oxadiazine scaffold pesticide developed by E.I. du Pont de Nemours and company commonly referred to as "DuPont" which is an American company. It is active against lepidopteran larvae [15], and it blocks insect neuronal sodium channels [16].



7

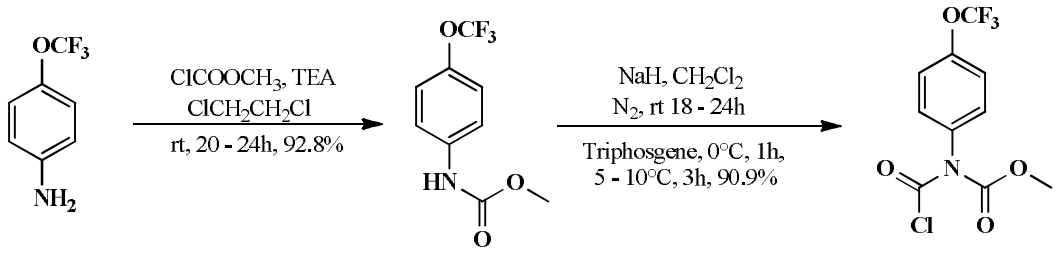
Indoxacarb

Synthesis of Indoxacarb takes place in two steps one from 9-fluorenylmethyl chloroformate **8** reacting with hydrazine hydrate to form the acid hydrazide derivative **9** further reacts with methyl 5-chloro-2-hydroxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate **10** in the presence of tosylic acid to form a Schiff base **11** undergoes cyclization at hydroxyl group with a nitrogen of an amide to form 1,3,4-oxadiazine dicarboxylate 12 (Scheme 3)and another from synthesis of halo carbonyl phenyl carbamates **15** (Scheme 4) from trifluoromethoxy aniline **13** via phenyl carbamates **14**. By combining **12** and **15,** we attain indoxacarb **7** (Scheme 5) [17].



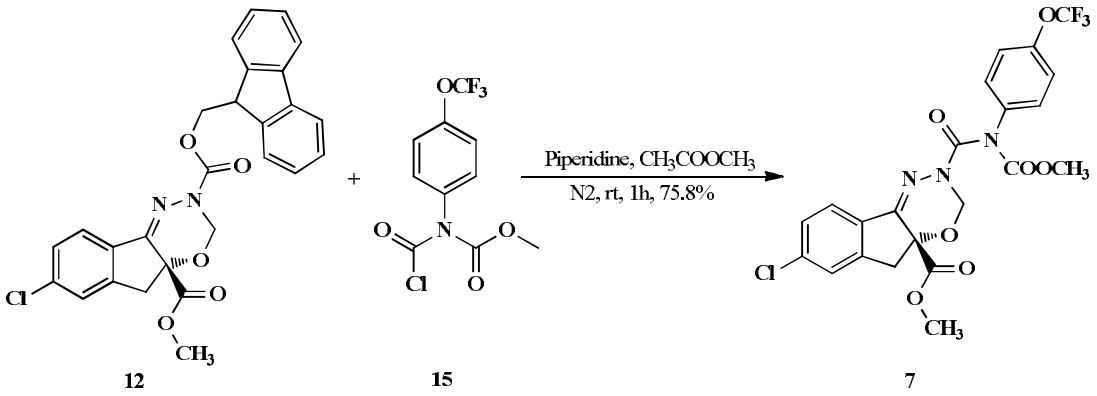
8 9 10 11 12

Scheme 3. Synthesis of 1,3,4-oxadiazine dicarboxylate from 9-fluorenylmethyl chloroformate



13 14 15

Scheme 4. Synthesis of halo carbonyl phenyl carbamates from trifluoromethoxy aniline

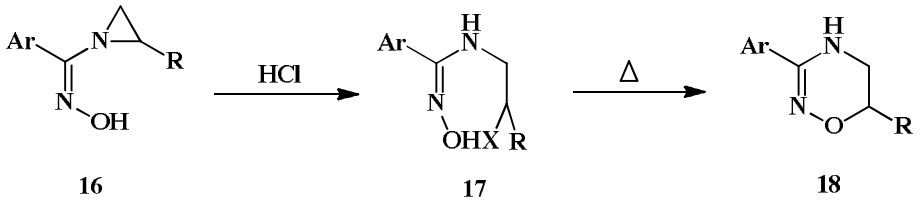


Scheme 5. Synthesis of Indoxacarb from 1,3,4-oxadiazine dicarboxylate with halo carbonyl phenyl carbamates.

Synthesis of oxadiazine scaffolds

1,2,4-oxadiazine scaffolds

Synthesis from 1-arylaziridine oximes **16** which is obtained from benzonitrile oxides with ethylene-imine or propylenimine in an ether, reacting with concentrated HCl by an acid catalyzed mechanism to get intermediate **17** then further basified with NaOH to get the desired scaffold of 1,2,4-oxadiazine **18** (Scheme 6) [18].



Scaffolds 16-18[a]:

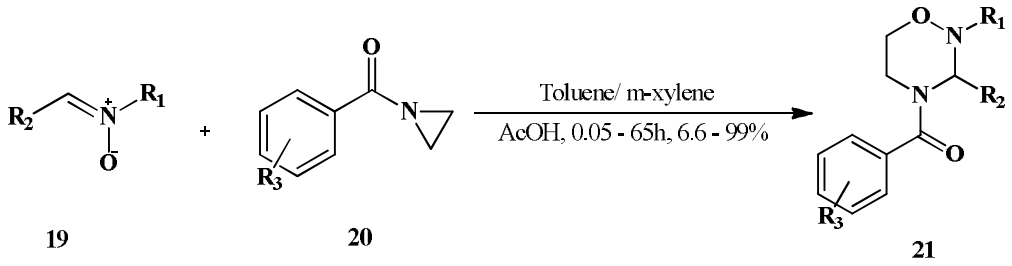
S.No	Substituents			
	R	Ar	X	
1	H	4-Cl-C_6H_4	Cl	→ Scaffold 17
2	H	4-Cl-C_6H_4	Br	
3	H	4-Cl-C_6H_4	-	→ Scaffold 16 and 18
4	H	C_6H_5	-	
5	H	3,4 $(Cl)_2C_6H_3$	-	
6	CH_3	C_6H_5	-	
7	H	$NO_2C_6H_4$	-	

[a] No data exists on yield and time

Scheme 6. Synthesis of 1,2,4-oxadiazines from 1-arylaziridine oximes

Heating the reaction mixture of nitrone **19** with 1-aroylaziridine **20** in toluene and acetic acid to form the corresponding 4-acyltetrahydro-2*H*-1,2,4-oxadiazines **21** with moderate to good yield (Scheme 7) [19].

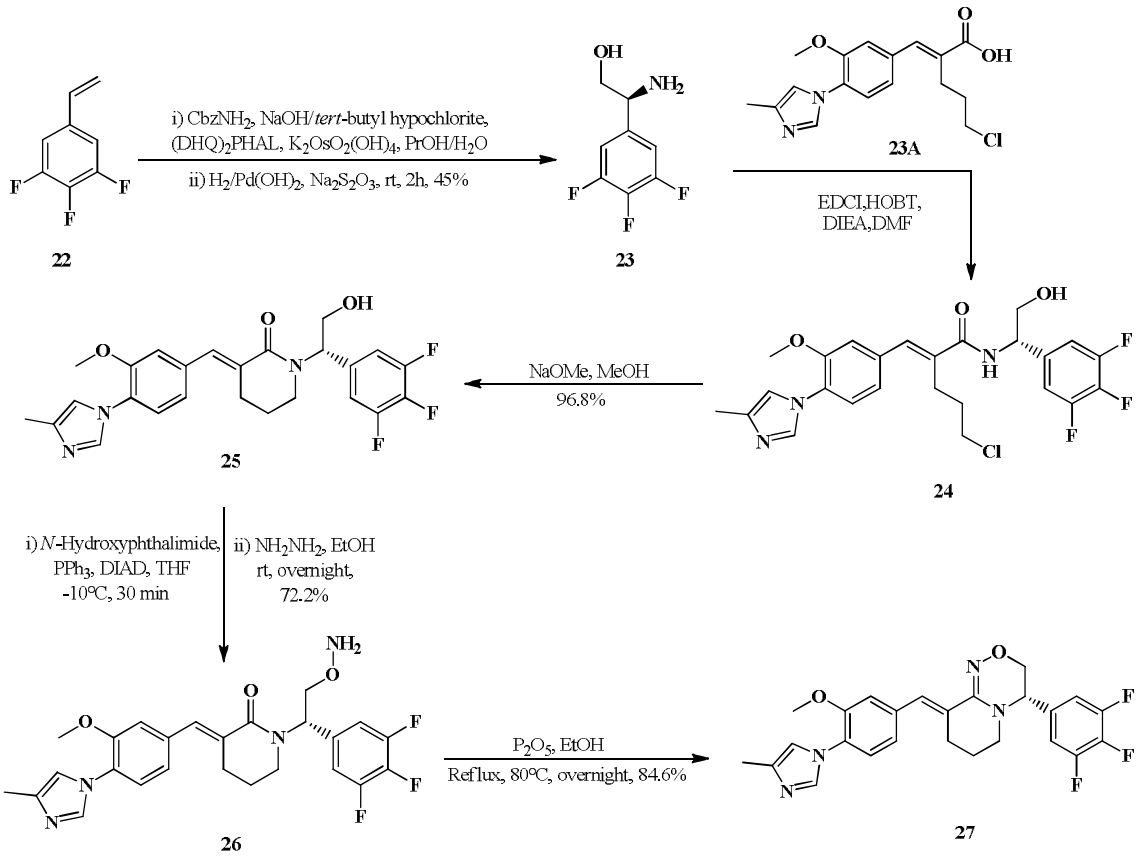
Enantiomeric form of amino alcohol **23** from 1,2,3-trifluoro-5-vinylbenzene **22** which on reacting with carboxylic acid derivative **23A** to form an amide **24**further undergoes cyclization to form lactam ring **25** then series of conversions to hydroxylamine **26** and cyclization leads to form 1,2,4-oxadiazine enantiomer **27** (Scheme 8) (Yield 90%). The obtained scaffold was subjected to γ-secretase modulators *in-vivo* in which the scaffold shows a potent activity for Alzheimer's disease. The compounds of monosubstituted 1,2,4-oxadiazines **28** at C-3 position with a trifluorophenyl group shows good activity along with good selectivity with 45% inhibition Aβ_{42} in rat cerebrospinal fluid, the compounds of monosubstituted 1,2,4-oxadiazines scaffolds **29** at C-4 Position with the same trifluorophenyl group and substituted chloro, fluoro derivatives to aryl groups shows potent along with good binding affinity [20-21].



19 20 21

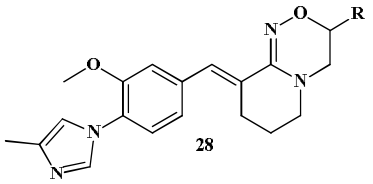
Scaffold 19-21 :

S.No	Substituents		
	R_1	R_2	R_3
1	C_6H_5	C_6H_5	4- NO_2-C_6H_4
2	4- CH_3-C_6H_4	C_6H_5	4- NO_2-C_6H_4
3	4- CH_3-C_6H_4	C_6H_5	3,5- $(NO_2)_2$-C_6H_3
4	CH_3	C_6H_5	3,5- $(NO_2)_2$-C_6H_3
5	C_6H_{11}	CH_3	3,5- $(NO_2)_2$-C_6H_3
6	$C(CH_3)_3$	C_6H_5	4- NO_2-C_6H_4
7	4- CH_3-C_6H_4	C_6H_5	3,4- $(Cl)_2$-C_6H_3
8	4- CH_3-C_6H_4	4-ClC_6H_5	3,5- $(NO_2)_2$-C_6H_3
9	4- C_2H_5-C_6H_4	C_6H_5	3,5- $(NO_2)_2$-C_6H_3
10	CH_3	C_6H_5	4- NO_2-C_6H_4



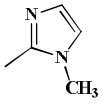
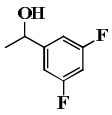
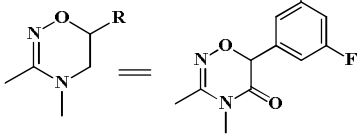
22 23 23A 24 25 26 27

Scheme 8. Synthesis of 1,2,4-oxadiazine scaffold from 3,4,5-trifluoro substituted styrene

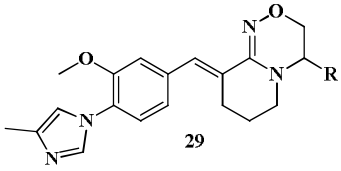


28

Scaffold 28

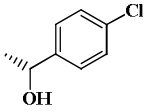
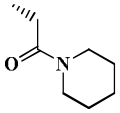
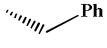
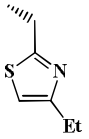
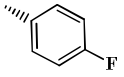
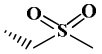
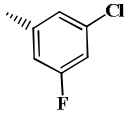
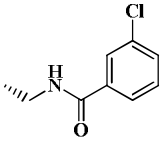
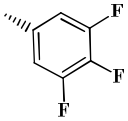
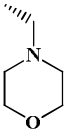
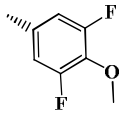
S.No	Substituents	S.No	Substituents	S.No	Substituents
	R		R		R
1		6		10	
2		7			
3		8		11	
4					
5		9		12	

SAR of monosubstituted 1,2,4-oxadiazines Scaffolds at the C-3 position



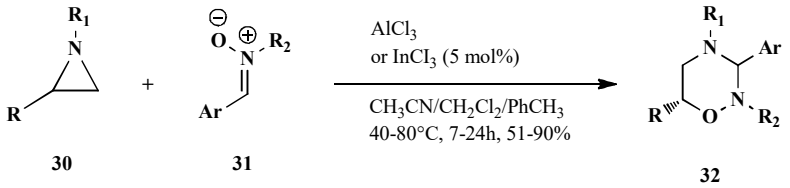
29

Scaffold 29

S.No	Substituents	S.No	Substituents	S.No	Substituents
	R		R		R
1	H	9		15	
2	=O				
3		10		`16	
4		11		17	
5		12		18	
6		13		19	
7					
8		14		20	

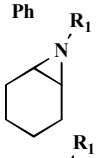
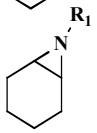
SAR of monosubstituted 1,2,4-oxadiazines Scaffolds at the C-4 position

Aziridines **30** with nitrones **31** by annulation in the presence of a Lewis acid catalyst $InCl_3$ to get the scaffolds of 1,2,4-oxadiazines **32** (Scheme 9)[22].

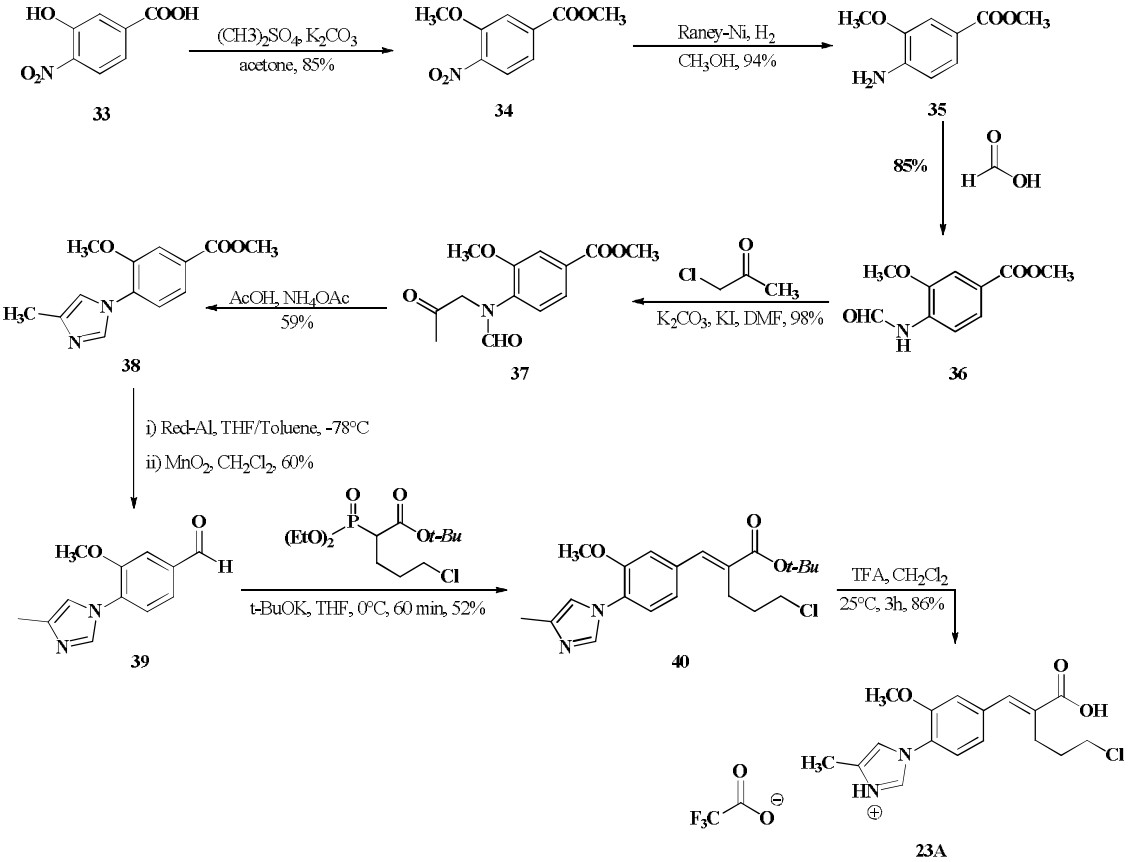


30 **31** **32**

Scaffold 30-32:

S. No	Substituents			
	R	R_1	R_2	Ar
1	Ph	Bn	$-CH_3$	Ph
2		Bn	$-CH_3$	Ph
3		Bn	Bn	4-OMe Ph
4	Ph	Et	$-CH_3$	Ph

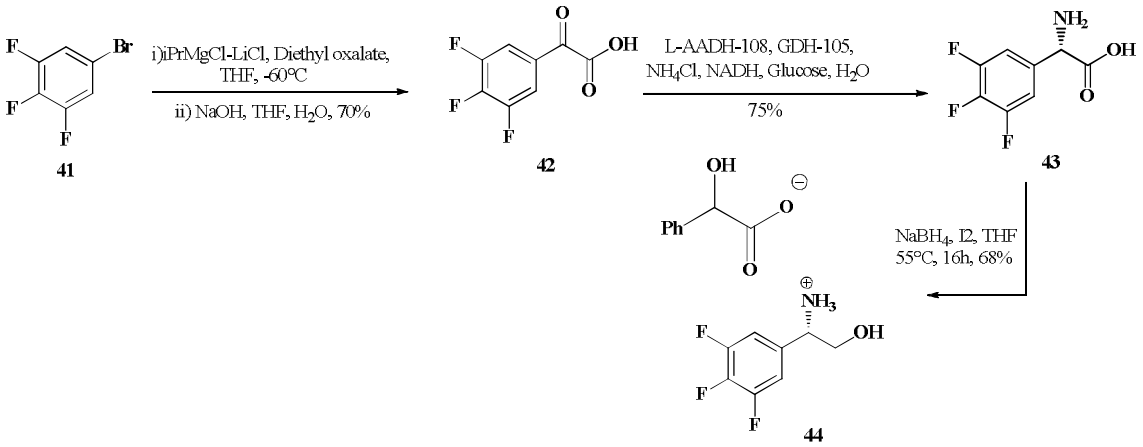
Scheme 9. Synthesis of 1,2,4-oxadiazines from aziridines and nitrones



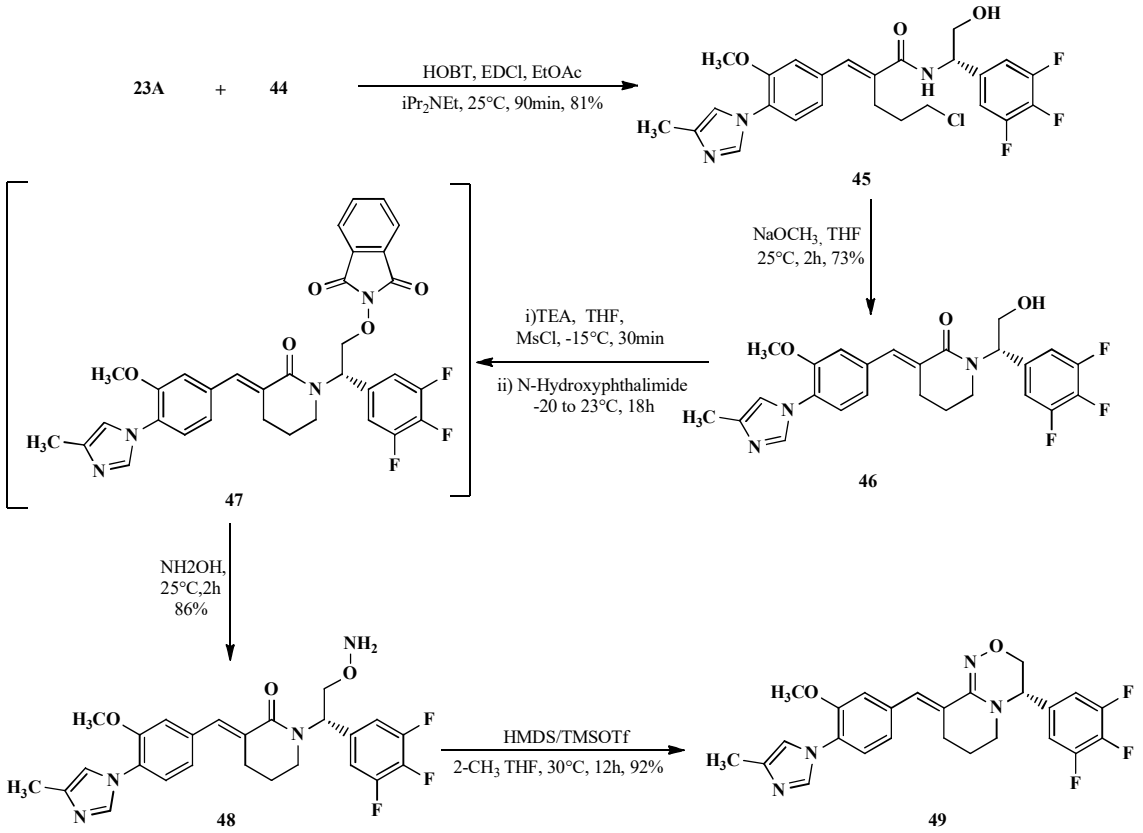
33 **34** **35** **36** **37** **38** **39** **40** **23A**

Scheme 10. Synthesis of α,β-Unsaturated carboxylic acid from 3-Hydroxy-4-nitrobenzoic acid

Application of retrosynthetic strategy in two steps to synthesize the 1,2,4-oxadiazines scaffold one from 3-Hydroxy-4-nitrobenzoic acid **33** undergoes methylation with dimethyl sulfate to get **34** further undergoes a series of reaction like reduction to form amino group **35** followed by formylation to get **36** dehalogenations by halo acetone to form **37** undergoes. The cyclization forms imidazole ring **38** reduced to aldehydes **39** with *tert*-Butyl ester to form **40** followed to form acid derivative **23A** (Scheme 10). Another from 5-bromo 1,2,3-trifluorobenzene **41** to form 2-oxo-2-(3,4,5-trifluorophenyl)acetic acid **42** which under reductive amination form amino acid **43,** which further reduced to amino alcohol **44** (Scheme 11).Combination of both **23A** and **44** forms an amide **45** cyclization takes place to form saturated pyridine **46. F**urther it reacts with *N*-hydroxypthalimide and hydroxylamine to form hydroxylamine **48** derivatives via **47** it rearranges to form 1,3,4-oxadiazine scaffold **49** (Scheme 12) [23].

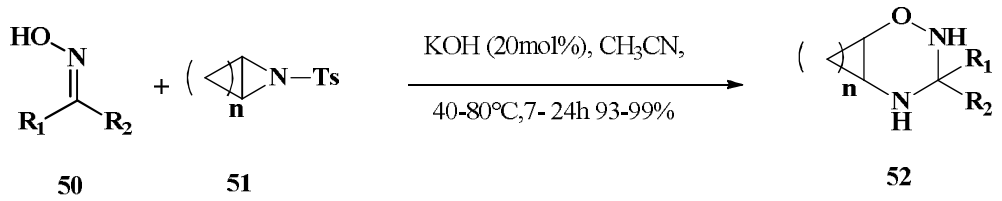


Scheme 11. Synthesis of amino alcohol from 5-bromo-1,2,3-trifluorobenzene



Scheme 12. Synthesis of 1,2,4-oxadiazines scaffold from both *α,β*-unsaturated carboxylic acid with amino alcohols

Development of 1,2,4-oxadiazines from [3+3] cycloaddition of Ketoximes **50** with *N*-tosylaziridines **51** in annelated carbocycles formed by extending the three-membered cycle into oxadiazines **52** (Scheme 13) [24].

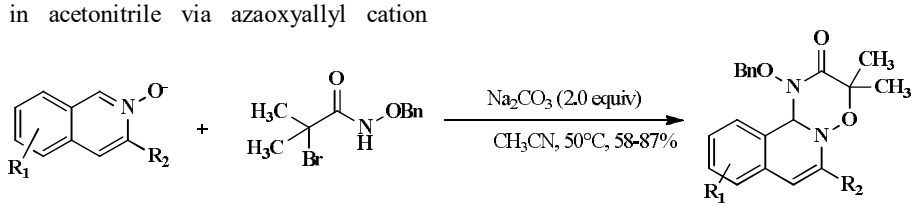


50 **51** **52**

n=1, 3, 4; R1=Ph, 2-thienyl, 2-naphthyl; R_2=Me, Et

Scheme 13. Synthesis of 1,2,4-oxadiazines scaffolds by [3+3] cycloaddition of Ketoximes with *N*-tosylaziridines

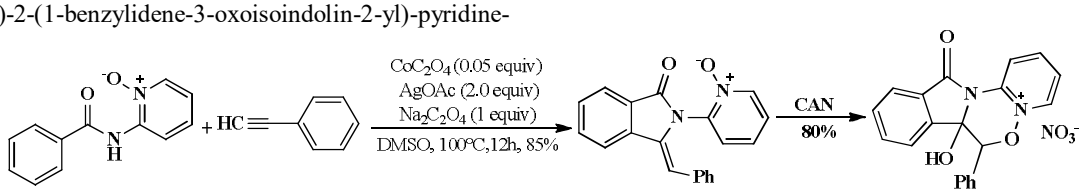
A base-controlled [3+3] cycloadditions of isoquinoline *N*-oxides **53** treated with α-halohydroxamates **54** in the presence of sodium carbonate in acetonitrile via azaoxyallyl cation to afford 1,11*b*-dihydro[1,2,4]oxadiazine[3,2-*a*]-isoquinolin-2(3*H*)-ones **55** with moderate to good yield (Scheme 14) [25].



53 **54** **55**

Scheme 14 Synthesis of 1,2,4-oxadiazines scaffolds by [3+3] cycloaddition of isoquinoline *N*-oxides with *α*-halohydroxamates

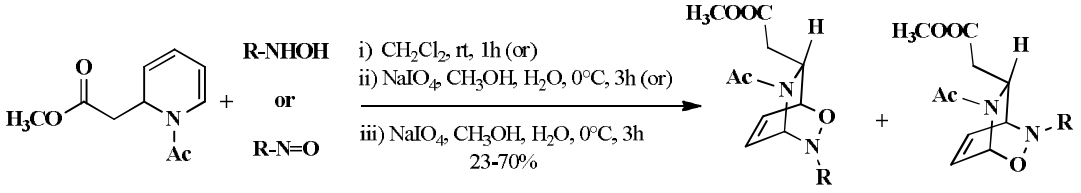
Cobalt (II) catalyzed oxidative coupling of 2-benzamidopyridine 1-oxide **56** with phenylacetylene **57** by alkynylation/Annulation to get the (*Z*)-2-(1-benzylidene-3-oxoisoindolin-2-yl)-pyridine-1-oxide **58** which undergoes annulation with Ceric (IV) ammonium nitrate to get the 1,2,4-oxadiazine **59** (Scheme 15) [26].



56 **57** **58** **59**

Scheme 15 Synthesis of 1,2,4-oxadiazines scaffolds by oxidative coupling of 2-benzamidopyridine 1-oxide with phenylacetylene

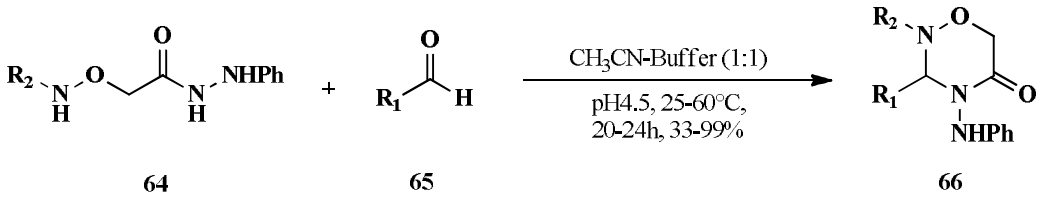
Methyl 2-(1-acetyl-1, 2-dihydropyridin-2-yl) acetate **60** with either nitroso/hydroxyl amino group **61** by [4+2] cycloaddition reaction to attain a high degree of regioselectivity to prepare 1,2,4-oxadiazine **62** and its isomer of 1,2,5-oxadiazine **63** (Scheme 16) [27].



60 **61** R= Phi, BnCOii, Bociii **62** **63**

Scheme 16. Synthesis of 1,2,4-oxadiazines scaffolds by [4+2] cycloaddition of either nitroso/hydroxylamino group with dihydropyridinyl acetate

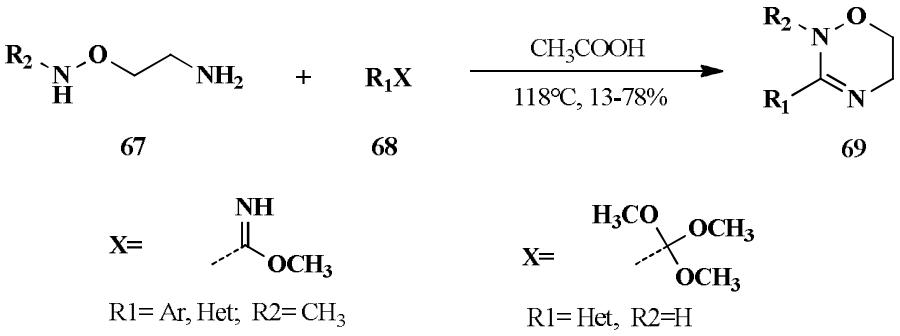
Irreversible condensation reacting aliphatic, aromatic, unsaturated aldehydes and isatins **65** with α-aminooxyacetohydrazides **64** in acetonitrile and acetate buffer to attain 1,2,4-oxadiazinan-5-one heterocycles **66** moderate to good yields (Scheme 17) [28].



R1=Het, Ar, Alkyl, Alkenyl; R2= Bn, i-Pr, Ph(CH2)3, Allyl, Cy

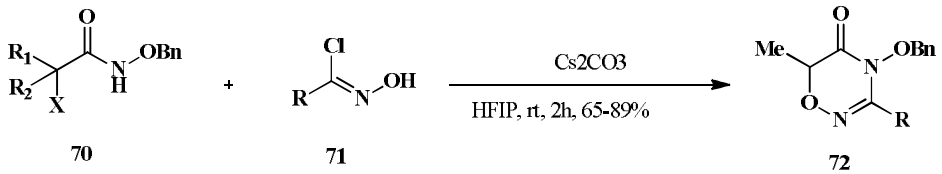
Scheme 17. Synthesis of 1,2,4-oxadiazinan-5-one from α-aminooxyacetohydrazides

Cyclocondensation reaction with a substituted 2-(aminooxy) ethanamine **67** with an orthoesters imino ethers **68** in the presence of acetic acid to affords 1,2,4-oxadiazines **69** with a low to moderate yield (Scheme 18) [29].



Scheme 18. Synthesis of 1,2,4-oxadiazines from 2-(aminooxy) ethanamine

[3+3] cycloaddition reaction of α-halohydroxamate **70** with hydroximoyl chloride **71** in the presence of base accessed the novel 1,2,4-oxadiazinan-5-ones **72** (Scheme 19) [30].

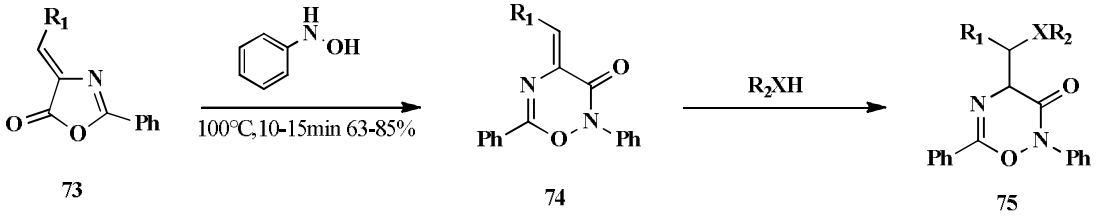


R = -C6H5, 2ClC6H4,2OCH3C6H4, 3ClC6H4,4-ClC6H4, 4-CH3C6H4, 4-NO2C6H4, 4-FC6H4, 2Cl,4ClC6H3, 2-Furyl, 2-Napthyl, n-Propyl
R1= -CH3, -C2H5, -C6H5, R2= -H, -CH3, -C2H5 X = Br, Cl

Scheme 19. Synthesis of 1,2,4-oxadiazinan-5-ones by [3+3] cycloaddition reaction α-halohydroxamate with hydroximoyl chloride

1,2,5-oxadiazine scaffolds

Aza lactone **73** when reacting with *N*-Phenylhydroxylamine by removal of the water molecule to form the 4-arylmethylene-2,6-diphenyl-2*H*-1,2,5-oxadiazin-3(4*H*)-ones **74** which on reacting with different amines or benzene thiols further obtained 2*H*-1,2,5-oxadiazin-3(4*H*)-ones **75** (Scheme 20) [31].



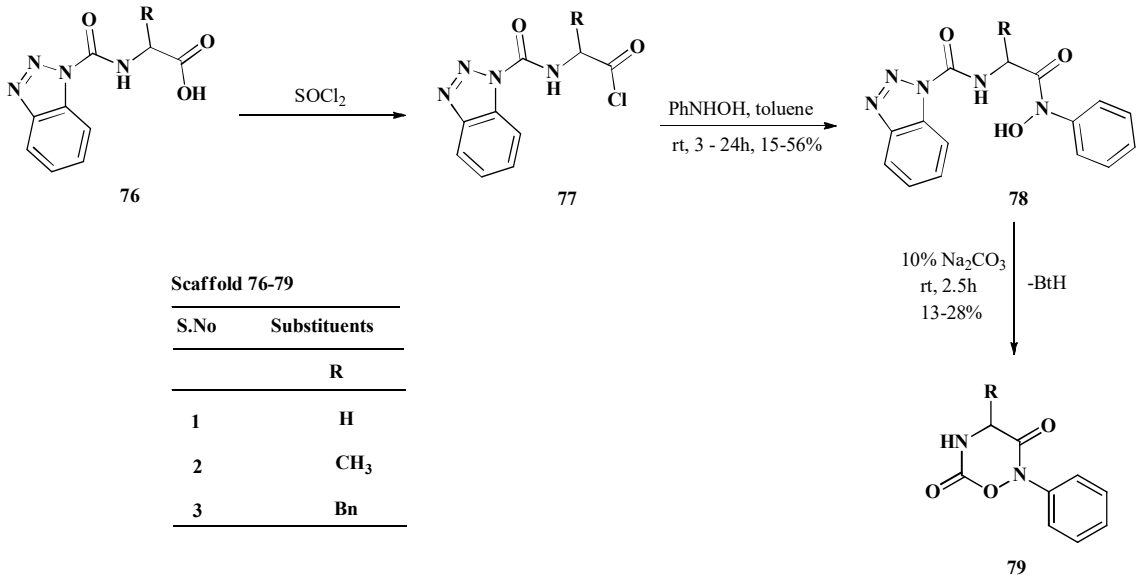
73 74 75

Scaffold 73-75:

S.No	Substituents		S.No	Substituents	
	R_1	XR_2		R_1	XR_2
1	Ph	NHBn	6	Ph	S-3-Tol
2	4-To;	NHBn	7	4-$MeOC_6H_4$	SPh
3	4-$MeOC_6H_4$	NHBn	8	4-$MeOC_6H_4$	S-2-Tol
4	Ph	SPh	9	4-$MeOC_6H_4$	S-3-Tol
5	Ph	S-2-Tol			

Scheme 20. Synthesis of 1,2,5-oxadiazines from azalactones reacting with *N*-Phenylhydroxylamine

Substituted 1,2,5-oxadiazin-3,6-dione **79** (Scheme 21) from *N*-Phenyl hydroxyl amine reacting on 2-(1*H*-benzo[*d*][1,2,3]triazole-1-carboxamido) carboxylic acid chloride **77** which was obtained from 2-(1*H*-benzo[*d*][1,2,3]triazole-1-carboxamido) carboxylic acid **76** to get*N*-(1-(hydroxyl-(phenyl)-amino)-1-oxo-2-yl)-1*H*-benzo[*d*][1,2,3]-triazole-1-carboxamide **78** with low to moderate yields [32].



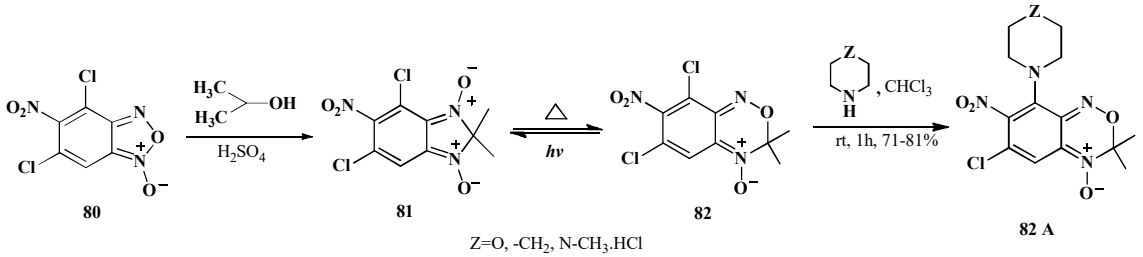
76 77 78 79

Scaffold 76-79

S.No	Substituents
	R
1	H
2	CH_3
3	Bn

Scheme 21. Synthesis of 1,2,5-oxadiazines from benzotriazole-1-carboxamido carboxylic acid

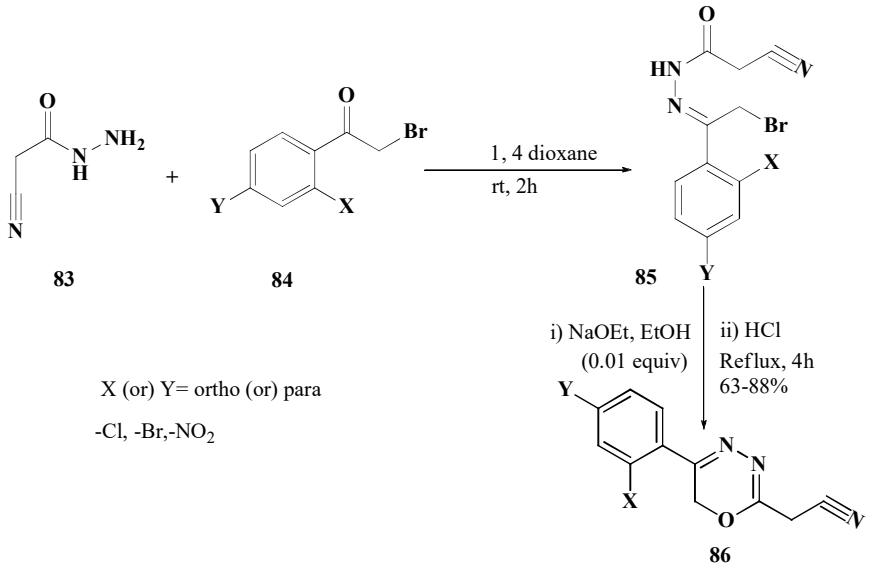
4,6-dichloro-5-nitrobenzo[*c*][1,2,5]oxadiazole-1-oxide **80** with propan-2-ol in presence of sulphuric acid to obtain 4,6-dichloro-2,2-dimethyl-5-nitro-2*H*-benzo[*d*]imidazole 1,3-dioxide **81** which on heating in presence of light affords to give 6,8-dichloro-3,3-dimethyl-7-nitro-3*H*-benzo[*c*][1,2,5]oxadiazine 4-oxide **82** which on further reaction with amine to undergo dehydrohalogenation reaction to obtain the scaffold of **82A** (Scheme 22) which is reacted with secondary cyclic amines to get 8-substituted scaffolds with an good yield [33].



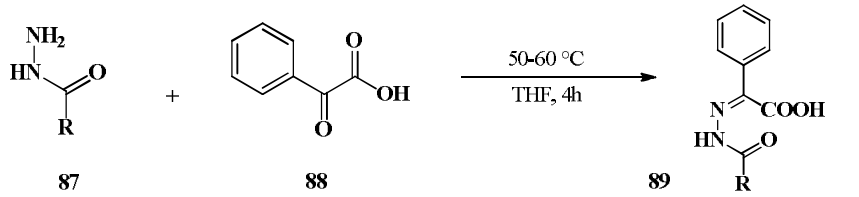
Scheme 22. Synthesis of 1,2,5-oxadiazines from substituted benzooxadiazole-1-oxide

1,3,4-oxadiazine scaffolds

1,3,4-oxadiazines from 2-Cyanoaceto hydrazide **83** with 2-bromoketones **84** to form 2-bromohydrazone moieties **85** which undergoes cyclization with sodium ethoxide in ethanol to get the desired moiety **86** (Scheme 23) which was evaluated for antimicrobial, antifungal activities. It has shown good activity against *Bacillus cereus*, less active against *Bacillus Subtilis, C.albicans*, no active towards *E.coli*., and al antitumor activity on different human cell lines like MCF-7(adenocarcinoma), NCI-H460(non-small cell lung cancer) and SF-268(CNS cancer) out of which nitro compound in ortho position showed the highest inhibitory effect [34-35].



Scheme 23. Synthesis of 1, 3, 4-oxadiazines scaffolds from hydrazide-hydrazones



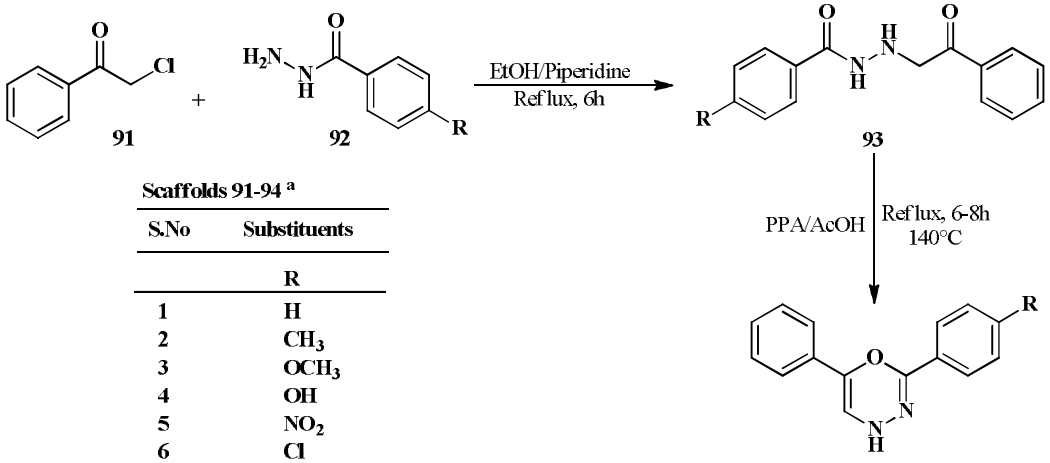
Scaffolds 87, 89 & 90

S.No	Substituents	S.No	Substituents
	R		R
1	3-Br C_6H_4	7	4-Br C_6H_4
2	3-Cl C_6H_4	8	4-Cl C_6H_4
3	3-OMe C_6H_4	9	4-OMe C_6H_4
4	4-*t*Bu C_6H_4	10	4-NO_2
5	4-OH C_6H_4	11	4-OMe C_6H_4
6	3-Pyridyl	12	C_6H_5

Scheme 24. Synthesis of 1,3,4-oxadiazines from *N*-acyl hydrazones

Synthesis and characterization of different 2,5-disubstituted 1,3,4-oxadiazin-6-ones **90** (Scheme 24) from variously substituted aroyl hydrazones **87** and phenylglyoxylic acid **88** by intermediate formation of *N*-acyl hydrazones **89** with a high yield [36].

A chemical reaction involving a mixture of phenacyl chloride **91** with substituted benzhydrazides **92** in ethanol and piperidine to get hydrazides **93** which on cyclization with polyphosphoric acid in acetic acid to get the desired scaffolds of 2,6-diaryl-1,3,4-oxadiazines **94** (Scheme 25) which have found that it is effective against gram-positive bacteria rather than gram-negative bacteria [37].



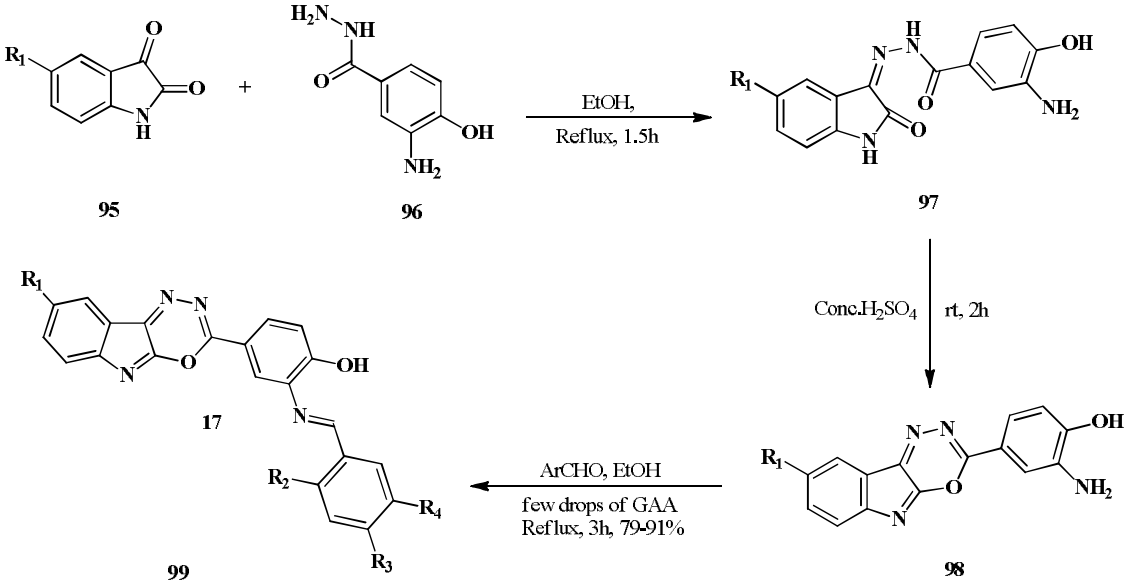
Scaffolds 91-94 [a]

S.No	Substituents
	R
1	H
2	CH_3
3	OCH_3
4	OH
5	NO_2
6	Cl

[a] No data exists on yield.

Scheme 25. Synthesis of 2,6 diaryl 1,3,4-oxadiazines from phenacyl chloride and substituted benzhydrazides.

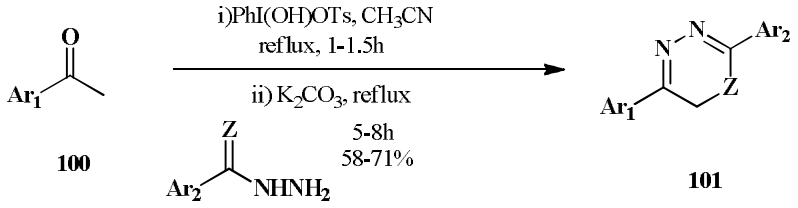
Isatin derivatives **95** were reacted with 3,4-disubstituted acid hydrazide **96** in ethanol to form hydrazones **97** which is an intermediate molecule treated with a strong acid(conc.H_2SO_4) undergoes cyclization to form 1,3,4-oxadiazines **98** further reacted with aldehydes gives imines or Schiff's base **99** (Scheme 26). The final scaffolds have screened for antimicrobial and antifungal activities in which the chloro derivatives have shown the minimal zone of inhibition when compared to that of standards [38].



R1 = F, Cl, CH_3 R2 = H, OH
R3 = H, OH, OCH_3 $N(CH_3)_2$ R4 = H OCH_3

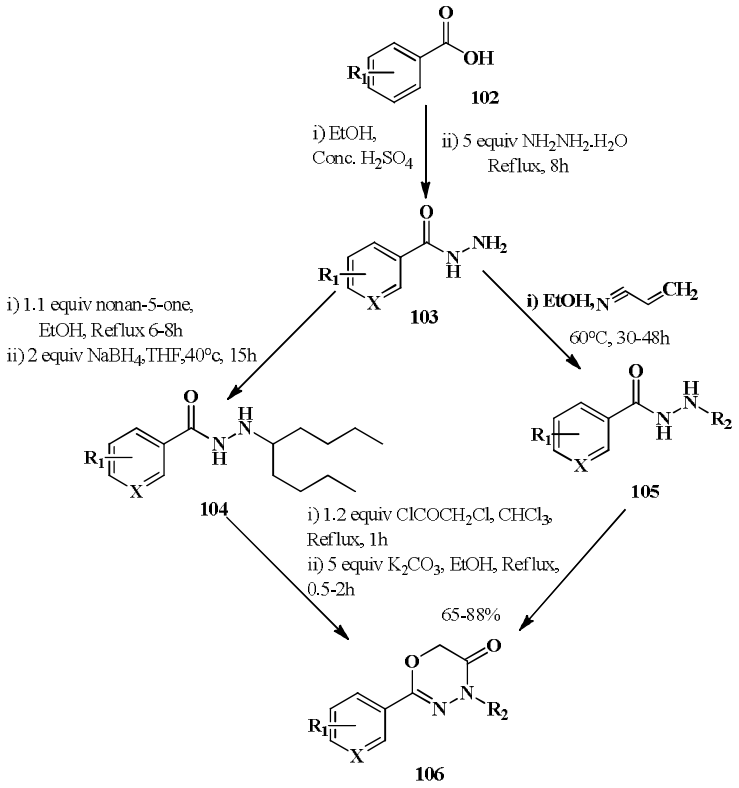
Scheme 26. Reaction of isatin derivatives with acid hydrazides to form 1,3,4-oxadiazino[5,6-*b*] indole derivatives

One pot synthesis by reacting substituted acetophenones **100** and acid hydrazides using [Hydroxy(tosyloxy)iodo]benzene (HTIB) which is a hypervalent iodine (III) reagent to form 2,5-disubstituted 1,3,4-oxadiazine **101** (Scheme 27) [39].



Scheme 27. Synthesis of 2,5 disubstituted 1,3,4-oxadiazines from substituted acetophenones using HTIB.

Synthesis of hydrophobic long alkyl chains from a basic skeleton of carboxylic derivative **102** which is converted to hydrazides **103** by hydrazine hydrate, further condensed with nonan-5-one with a specific reducing agent $NABH_4$ and on the other hand, it is condensed with acrylonitrile or *n*-butyl acrylate to get the desired moieties **104** and **105**. The obtained compounds undergo cyclization with chloroacetyl chloride get the 1,3,4-oxadiazine scaffolds **106** (Scheme 28). The obtained scaffolds are evaluated for inhibition of monoamine oxidase, chitin synthesis and on tumor cell lines (Human lung cancer cell A-549 and Prostate cancer cell PC-3). Trimethoxy scaffolds shown to be most potential growth inhibition in monoamine oxidase and antitumor activities but for chitin synthesis inhibition, the moieties with ethoxy and *n*-butyl acrylate are potential [40].

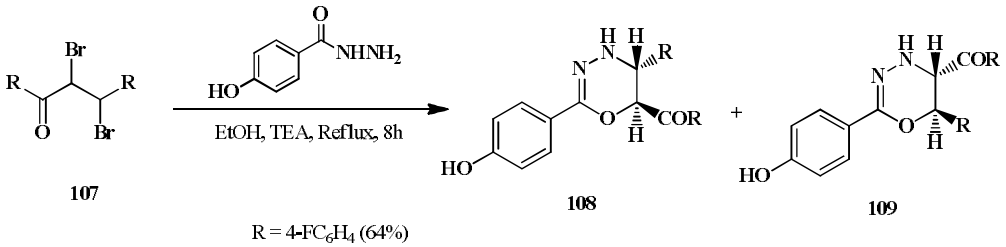


Scaffolds 102-106

S.No	Substituents		
	R_1	R_2	X
1	3,5 Me_2	$(^nBu)_2CH$-	C
2	3,4,5-$(OMe)_3$	$(^nBu)_2CH$-	C
3	3,4-OCH_2O	$(^nBu)_2CH$-	C
4	3,4-$(CH)_4$	$(^nBu)_2CH$-	C
5	4-Et	$(^nBu)_2CH$-	C
6	2-Cl	$(^nBu)_2CH$-	C
7	4-Cl	$(^nBu)_2CH$-	C
8	2,4 Cl_2	$(^nBu)_2CH$-	C
9	2-OEt	$(^nBu)_2CH$-	N
10	4-Et	$CNCH_2CH_2$-	C
11	H	$CNCH_2CH_2$-	C
12	4-F	$CNCH_2CH_2$-	C
13	3-Me	$^nBuOCOCH_2CH_2$-	C

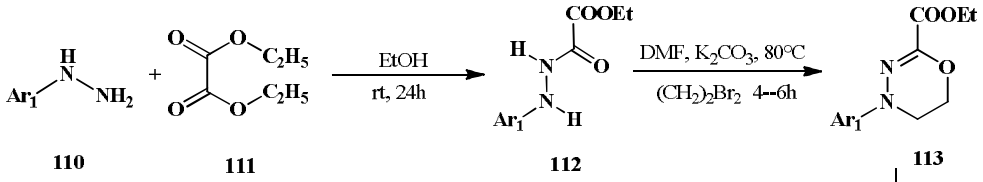
Scheme 28. Synthesis of some new *4H 1*,3,4-oxadiazin-5(6*H*)-ones with hydrophobic and long alkyl chains

Design of heterocycles from a common precursor (2*RS*,3*SR*)-2,3-dibromo-1,3-bis (4-fluorophenyl)-propan-1-one **107** with 4-Hydroxybenzo-hydrazide to give the 1,3,4-oxadiazine scaffolds **108** and **109** (Scheme 29) with two stereogenic centers [41].



Scheme 29. Synthesis of 1,3,4-oxadiazines from 2,3-dibromo propan-1-one with stereogenic centers

Synthesis of a new series of scaffolds from substituted hydrazines **110** with diethyl oxalate **111** in ethanol to get an intermediate **112**, which reacts with a solvent DMF in a basic condition to deprotonate the moderately acidic proton to form the cyclic scaffold by dihaloethane **113** to get the *N*-aryl-1,3,4-oxadiazine-2-carboxylic acid **114** (Scheme 30). This scaffold further reacted with amine moieties of thiazoles to get carboxamides compounds which were screened towards antioxidant activity and DNA damage inhibition. All the synthesized scaffolds exhibited good antioxidant activities compared to standard and the compounds with electron donating groups on para position exhibited good DNA damage inhibition [42].

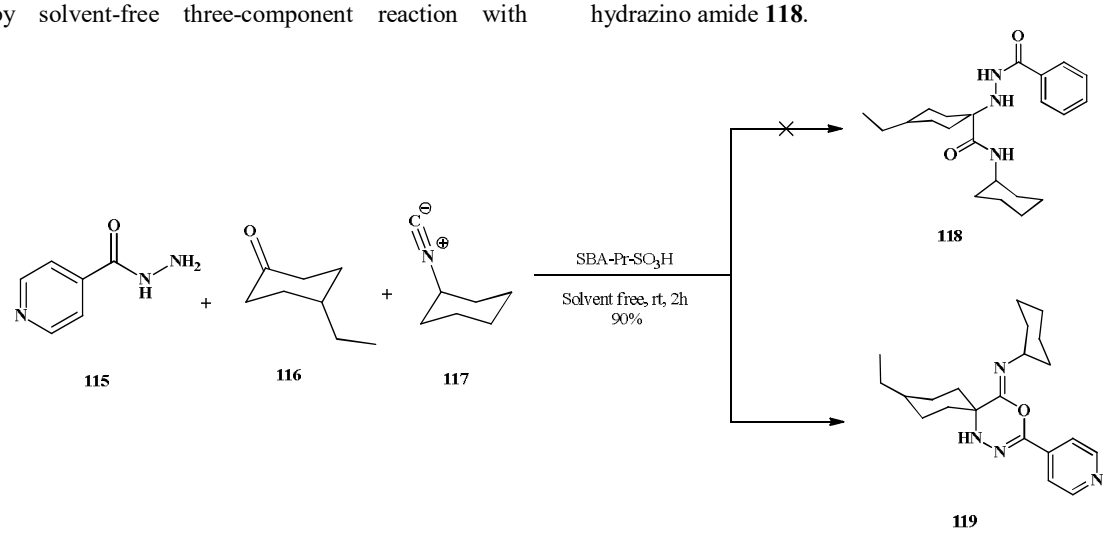


Scaffolds 107, 109-111

S.No	Substituents
	Ar_1
1	C_6H_5
2	4-ClC_6H_5
3	4-$OCH_3C_6H_5$
4	4-$NO_2C_6H_5$,

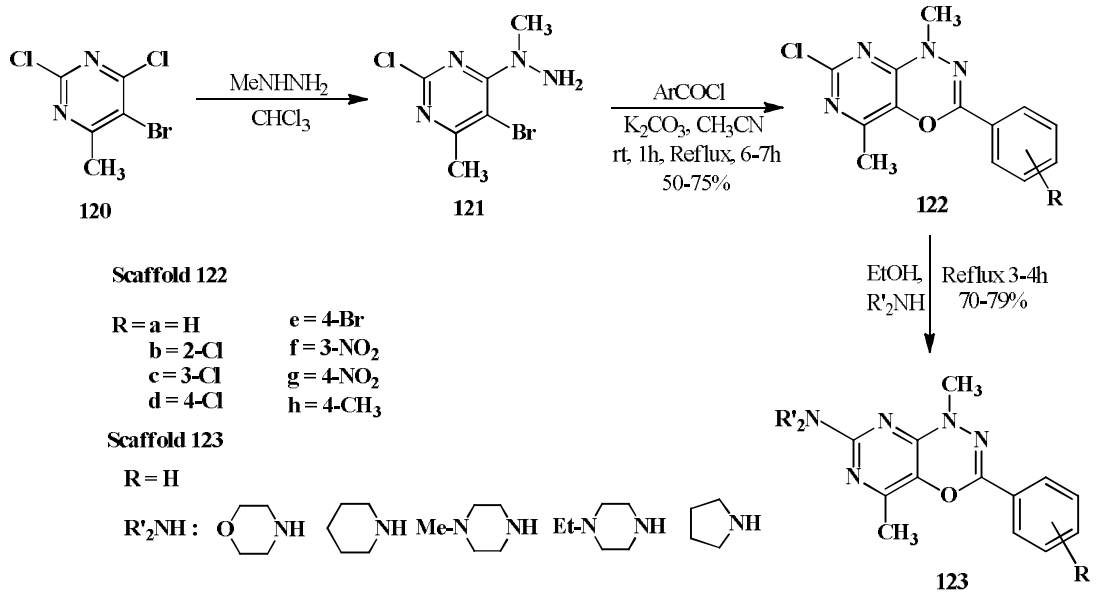
Scheme 30. Synthesis of substituted1,3,4-oxadiazines from substituted hydrazines and diethyl oxalate

Development of a spiro compound with functionalized propyl sulfonic acid SBA-15 mesoporous silica (SBA-Pr-SO_3H) as an acid catalyst by solvent-free three-component reaction with hydrazide **115** cyclic ketones **116** cyclohexyl isocyanide **117** to obtain an unexpected scaffold [43] of spirooxadiazine **119** (Scheme 31) rather than hydrazino amide **118**.

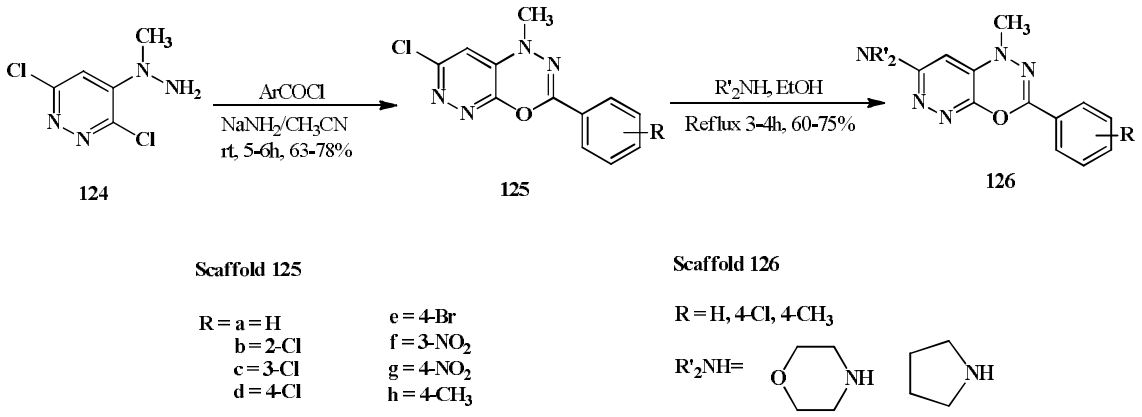


Scheme 31. Spirooxadiazines from three component reaction scaffold by acid catalyzed SBA-Pr-SO_3H

In 2011, developed a series of scaffolds with the help of two substituted diazine moieties 5-bromo-2,4-dichloro-6-methylpyrimidine **120** with *N*-methylhydrazine in chloroform are converted into 5-bromo-2-chloro-4-methyl-6-(1-methyl-hydrazinyl)-pyrimidine **121** and 3,6-dichloro-4-(1-methyl-hydrazinyl) pyridazine **124** which on reacting with acyl halides in dry acetonitrile and bases (K_2CO_3 and $NaNH_2$) undergoes heterocyclization to obtain fused pyrimidine **125** and pyridazine **122** of 1,3,4-oxadiazines. The obtained scaffolds further undergo condensation with secondary amines to form substituted products **123** (Scheme 32) and **126** (Scheme 33). Both the scaffolds show highest antimicrobial sensitivity when the electron donating groups or withdrawing groups are present in the para-position [44-45].

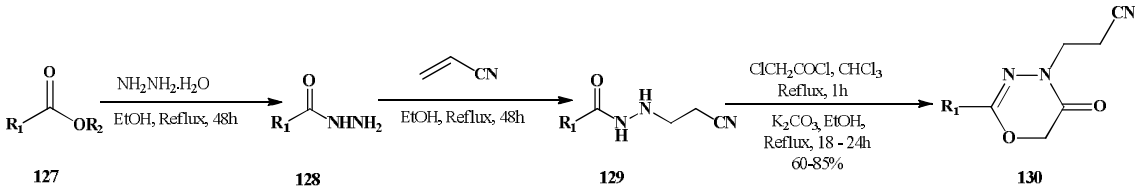


Scheme 32. Synthesis of fused 1,3,4-oxadiazines from substituted pyrimidine

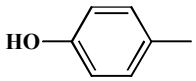
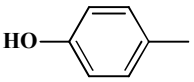
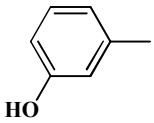
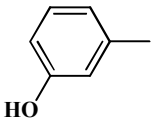
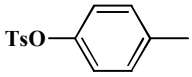
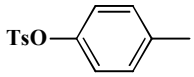
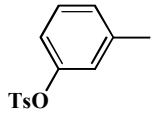
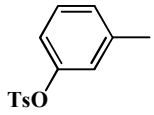
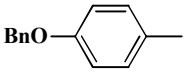
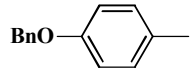
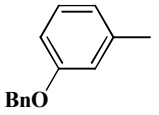
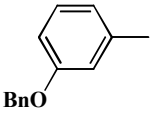
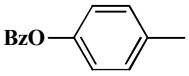
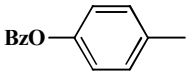
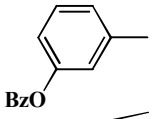
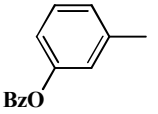
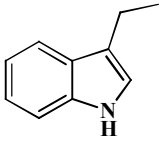


Scheme 33. Synthesis of fused 1,3,4-oxadiazines from substituted pyridazine.

Substituted groups like phenolic, *p*-toluenesulfonyl, indole acetate, benzyl, benzoyl of **127** which was treated with hydrazine hydrate in ethanol to afford hydrazides **128** with acrylonitrile to form 2-(2-cyanoethyl) hydrazides **129** which undergoes cyclization with chloroacetyl chloride in presence of potassium carbonate to attain a target of 5,6-dihydro-5-oxo-4*H*-1,3,4-oxadiazine6-4-propane-nitriles **130** (Scheme 34) with good yields [46].

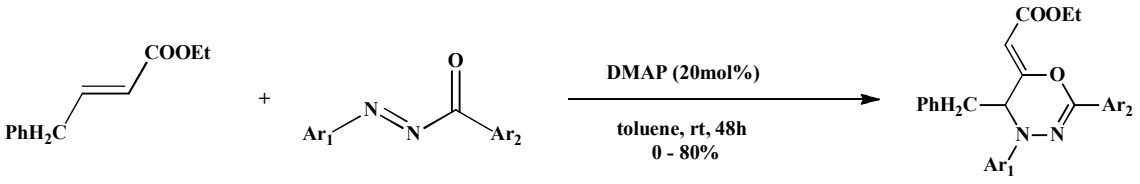


Scaffold 127 **Scaffold 128-130**

S.No	Substituents		S.No	Substituents
	R_1	R_2		R_1
1		CH_3	1	
2		C_2H_5	2	
3		CH_3	3	
4		C_2H_5	4	
5		CH_3	5	
6		C_2H_5	6	
7		CH_3	7	
8		C_2H_5	8	
9		C_2H_5		

Scheme 34. Synthesis of substituted 1,3,4-oxadiazines 4-propanenitriles and their intermediates from an ester

A series of scaffolds from DMAP (4-dimethylaminopyridine)-catalyzed [2+4] cyclo-additions of (*E*)-ethyl 4-phenylbut-2-enoate **131** with *N*-acyldiazines **132A & 132B** undergoes cyclization to form a heterocyclic scaffold 1,3,4-oxadiazine **133A & 133B** (Scheme 35) with a low to high yields [47].



131 132 (A & B) 133 (A & B)

Scaffold 132 A & 133 A

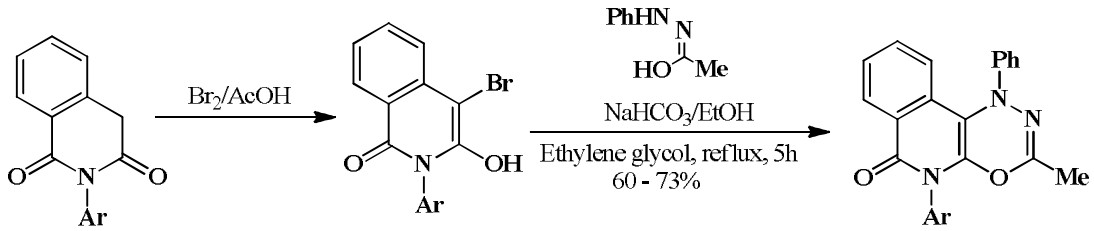
S.No	Substituents	
	Ar_1	Ar_2
1	Ph	Ph
2	4-MePh	Ph
3.	4-ClPh	Ph
4	4-BrPh	Ph
5	4-NO_2Ph	Ph
6	2-ClPh	Ph
7	3-ClPh	Ph
8	2,4 $(Cl)_2$Ph	Ph
9	3,4 $(Cl)_2$Ph	Ph
10	3,5 $(Cl)_2$Ph	Ph

Scaffold 132 B & 133 B

S.No	Substituents	
	Ar_1	Ar_2
1	Ph	4-MeOPh
2	Ph	4-MePh
3	Ph	4-FPh
4	Ph	4-ClPh
5	Ph	4-BrClPh
6	Ph	4-NO_2Ph
7	Ph	2-MePh
8	Ph	3,4-$(MeO)_2$Ph
9	Ph	3,5-$(MeO)_2$Ph
10	Ph	3,4,5-$(MeO)_3$Ph
11	Ph	2-furanyl
12	Ph	1-naphthyl

Scheme 35. Synthesis of 1,3,4-oxadiazines from DMAP- catalyzed [2+4] cycloadditions of (*E*)-ethyl 4-phenylbut-2-enoate with *N*-acyldiazines.

Synthesis by *N*-arylhomophthalimides **134** which undergoes bromination at highly reactive methylene in cold acetic acid to get the monobromo derivatives **135** which is reacted with *N*-phenylaceto-hydrazonic acid in basic condition to yield the scaffold of 1,3,4-oxadiazine **136** with an yield of 60-73% which is reacted with iodide (methyl/1-methylpyridinium/ methylquinolinium iodide) salts to yield monomethine cyanine dyes which on further reaction with picolinium or quinaldinium iodide salts to synthesize the trimethyl cyanine dyes. The compounds exhibit some moderate to high antibacterial activities (Scheme 36) [48].

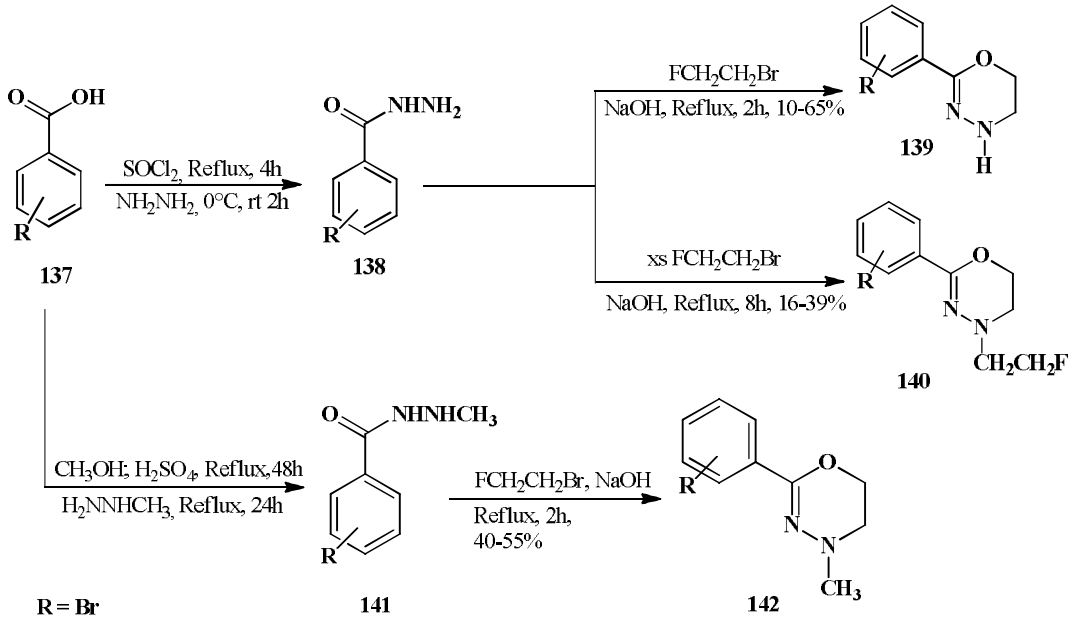


134 135 136

Ar = a = Ph; b = 4-MeOPh

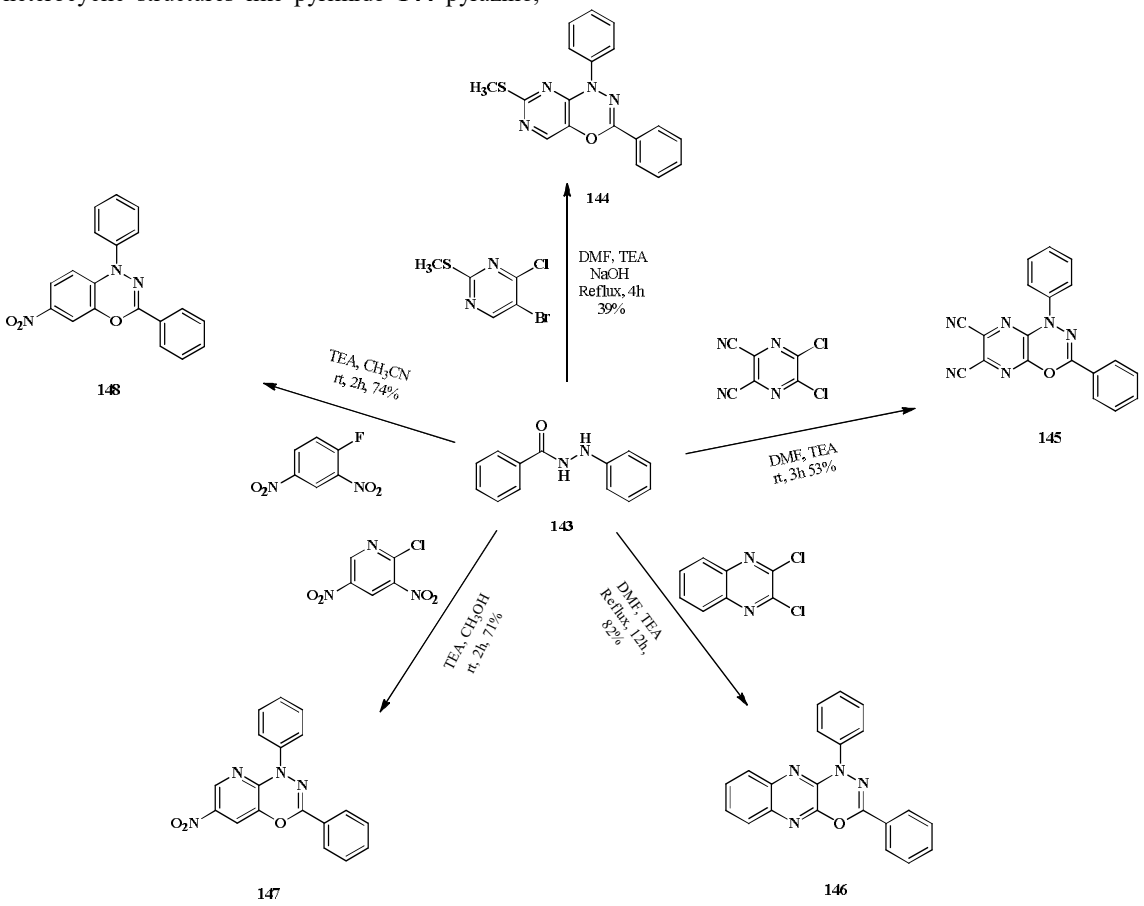
Scheme 36. Synthesis of 1,3,4-oxadiazines from *N*-arylhomopthalimides

Three types of 1,3,4-oxadiazines from a substituted benzoic acid **137** which undergoes condensation with hydrazine and *N*-methylhydrazine to obtain substituted benzoic acid hydrazide **138** and *N*-methylatedbenzoic acid hydrazide **141** which further reacted with 1-bromo-2-fluoroethane in a basic condition to get the one with unsubstituted **139** and two with substituted1,3,4-oxadiazines **140** and **142** (Scheme 37) [49-50].



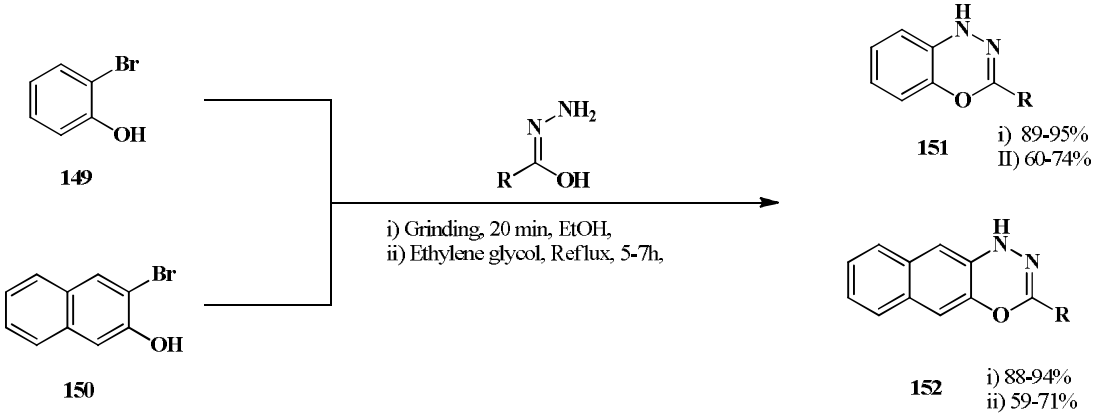
Scheme 37. Synthesis of 1,3,4-oxadiazines scaffolds from hydrazides and substituted hydrazides.

Bidentate nucleophile with *N*-Phenylbenzohydrazides **143** which lead to derivatives of different heterocyclic structures like pyrimido **144** pyrazino, **145** quinoxalino **146** and pyridino **147** 4*H*-1,3,4-benzooxadiazine **148** (Scheme 38) [51].



Scheme 38. Synthesis of different scaffolds of fused heterocyclic of 1,3,4-oxadiazines from *N*-phenylbenzohydrazides

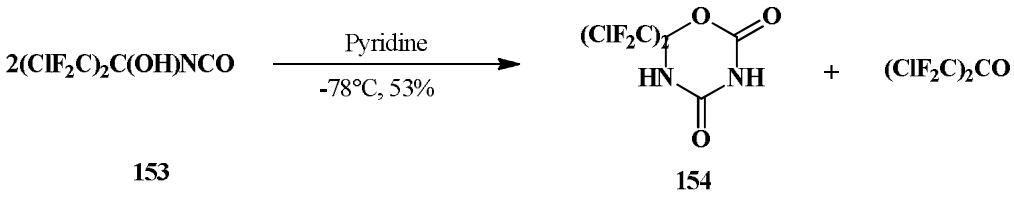
2-bromo-phenol **149** and 3-bromo-2-naphthol **150** of equimolar ratios and acid hydrazides derivatives were reacted by a conventional method with ethylene glycol containing 20% $NaHCO_3$ and green method with 20% $NaHCO_3$ under the solvent-free condition at room temperature with good yield rather than the conventional method (Scheme 39) [52].



Scheme 39. Green synthesis of 1,3,4-oxadiazines from acid hydrazides

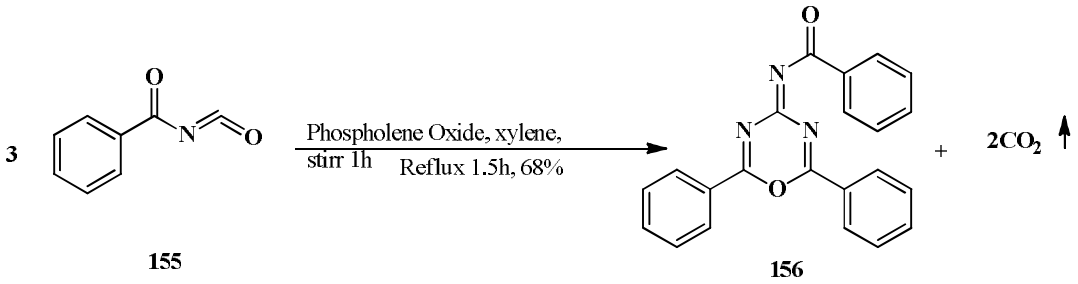
1, 3, 5-oxadiazine scaffolds

A new class of 1,3,5-oxadiazine scaffolds **154** (Scheme 40) from α-hydroxy isocyanates **153** in the presence of base pyridine which is obtained from isocyanic and carbonyl compounds [53].



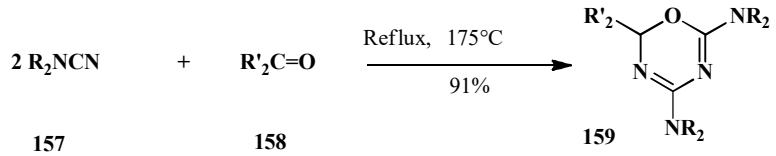
Scheme 40. Synthesis of 1,3,5-oxadiazines from α-hydroxy isocyanates

Cyclization reaction with three moles of Benzoyl isocyanate **155** by taking 1-ethyl-3-methyl-3-phospholene-1-oxide as a catalyst to form a substituted 1,3,5-oxadiazine scaffold **156** (Scheme 41) by the liberation of carbon dioxide with a yield [54] of 68%.



Scheme 41. Synthesis of 1,3,5-oxadiazines from benzoyl isocyanate

Substituted cyanamides **157** with perhaloacetones **158** gave corresponding 1,3,5-oxadiazine scaffolds **159** (Scheme 42) with good yield [55].



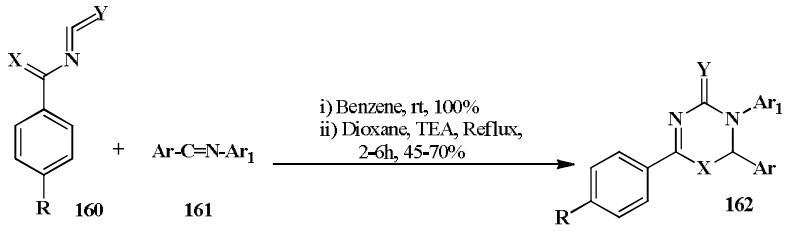
157 158 159

Scaffolds 157-159

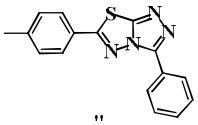
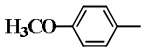
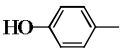
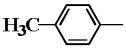
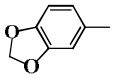
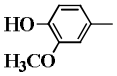
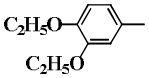
S.No	Substituents	
	R	R'
1	H	CF_3
2	H	CF_2Cl
3	CH_3	CF_3
4	CH_3	
5	CH_2=CH-CH_2-	CF_3

Scheme 42. Synthesis of 1,3,5-oxadiazines from substituted cyanamides with perhaloacetones.

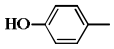
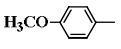
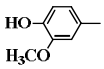
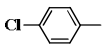
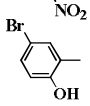
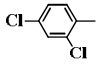
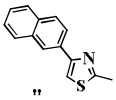
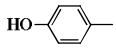
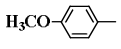
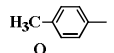
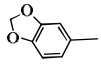
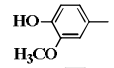
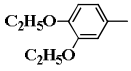
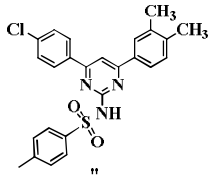
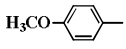
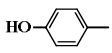
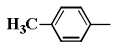
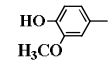
Design of 1,3,5-oxadiazine scaffold **162** (Scheme 43) from benzoyl isothiocyanate or thioiso-cyanate **160** with an imine**161**with good yields [56-60].



Scaffolds 160-162

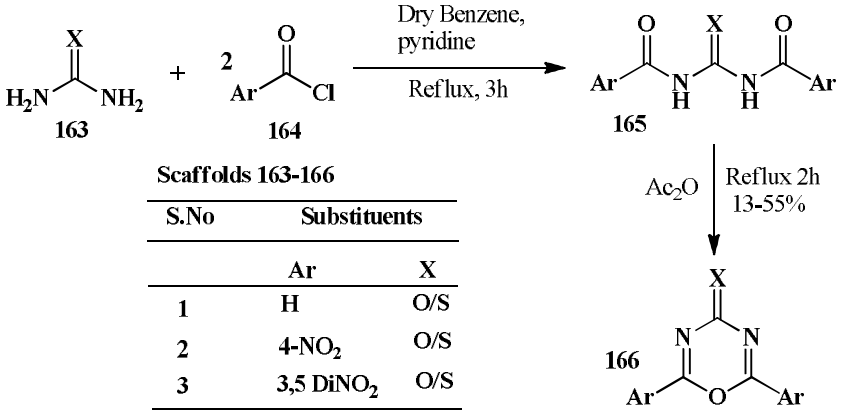
S.No	Substituents				
	R	Ar	Ar_1	X	Y
1	H	C_6H_5	$CH_2C_6H_5$	O/S	O
2	OCH_3	C_6H_5	$CH_2C_6H_5$	O/S	O
3	Cl	C_6H_5	$CH_2C_6H_5$	O/S	O
4	NO_2	C_6H_5	$CH_2C_6H_5$	O	O
5	H	H		O	S
6	H		"	O	S
7	H		"	O	S
8	H		"	O	S
9	H		"	O	S
10	H		"	O	S
11	H		"	O	S
12	H		"	O	S

Scaffolds 160-162 Contd....

S.No	Substituents				
	R	Ar	Ar_1	X	Y
13	H			O	S
14	H		"	O	S
15	H		"	O	S
16	H		"	O	S
17	H		"	O	S
18	H		"	O	S
19	H		"	O	S
20	H		"	O	S
21	H		"	O	S
22	H			O	S
23	H		"	O	S
24	H		"	O	S
25	H		'	O	S
26	H		"	O	S
27	H		"	O	S
28	H		"	O	S
29	H		"	O	S
30	H			O	S
31	H		"	O	S
32	H		"	O	S
33	H		"	O	S
34	H		"	O	S
35	H		"	O	S
36	H		"	O	S

Scheme 43. Synthesis of 1,3,5-oxadiazines from benzoylisothiocyanate

The reaction of urea or thiourea **163** with Acyl Chlorides **164** to form *N,N'*-diaroyl urea/thiourea **165** which undergoes cyclization reaction with acetic anhydride to form Scaffolds of 1,3,5-oxadiazines **166** (Scheme 44) with a yield [61] of 13-55%.

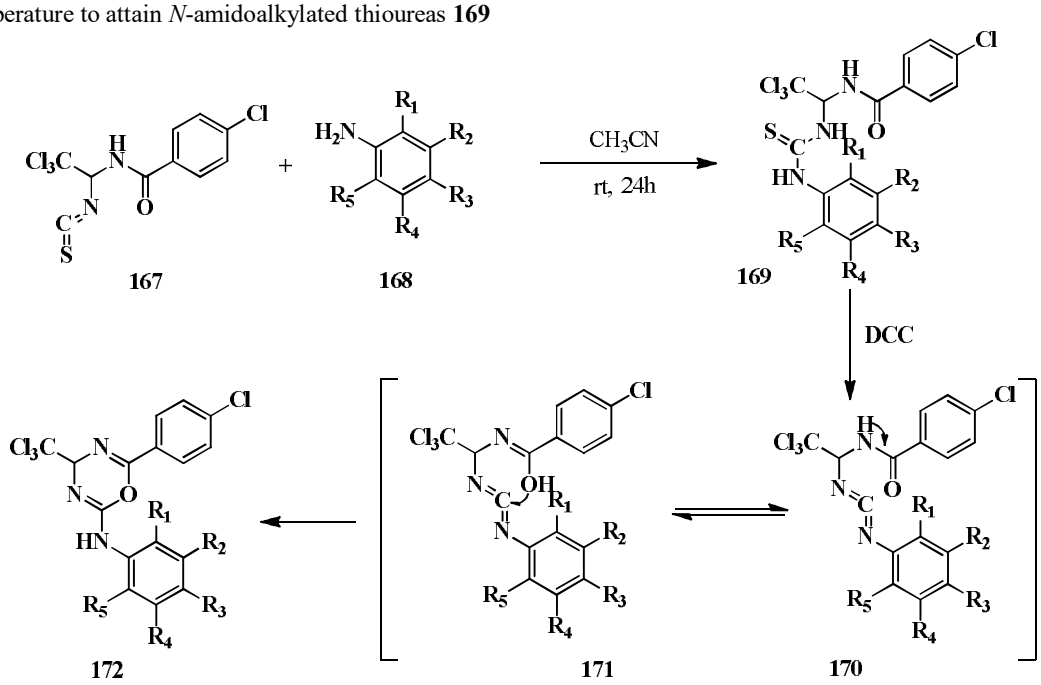


Scaffolds 163-166

S.No	Substituents	
	Ar	X
1	H	O/S
2	4-NO_2	O/S
3	3,5 $DiNO_2$	O/S

Scheme 44. Synthesis of 1,3,5-oxadiazines from urea/thiourea with acyl derivatives

4-Chloro-*N*-(2,2,2-trichloro-1-isothiocyanato-ethyl)benzamide **167** with substituted aromatic amines **168** in polar solvent acetonitrile at room temperature to attain *N*-amidoalkylated thioureas **169** which undergoes reaction with DCC to form carbodiimide **170** and **171** which rearranges to form 1,3,5 scaffold **172** (Scheme 45) [62].



Scaffolds 167-172

S. No	Substituents				
	R_1	R_2	R_3	R_4	R_5
1	H	H	H	H	H
2	CH_3	H	CH_3	H	H
3	OCH_3	H	H	H	H
4	OCH_3	H	H	OCH_3	H
5	NO_2	H	CH_3	H	H
6	H	Br	H	H	H
7	Cl	H	H	Cl	H
8	H	H	*nBu*OC(O)	H	H

Scheme 45. Synthesis of 1,3,5-oxadiazines from haloisothiocyanoalkyl benzamide

Conclusion

Researchers made curiosity in developing the new scaffolds with six-membered heterocyclic rings with oxygen and two nitrogen atoms which have limited access. Oxadiazines made mounting interest in the development of scaffolds for targeting the diseased conditions. This review highlights the various synthetic protocols for the development of surplus and enormous scaffolds upon the different oxadiazines. There is a gigantic possibility of these scaffolds because of its different molecular targets. So far different pharmacological activities on some of the oxadiazines like antibacterial, antifungal, anthelmintic, anti-inflammatory, locomotor, anticonvulsive, antiviral, agricultural, antitumor insecticidal, nematocidal, miticidal, neurogenerative disorders like Alzheimer disease, blood disorder like anemia and plant regulation which have been discussed in synthetic part. Future investigations of this scaffold will give some promising results in the field of medicine. Advances of this field can be done to outcome the structure-activity relationship and mechanism of action of the particular compounds. This review gives great research ideas for the medicinal chemists to concentrate on these particular moieties for pharmacological activities in developing new scaffolds for their prominent effect on the real world.

Conflicts of interest

The authors declare no conflicts of interest.

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Abbreviations

HFIP	hexafluoro-2-propanol
DCC	*N, N'*-Dicyclohexylcarbodiimide
rt	Room Temperature
THF	Tetrahydrofuran
NaOMe	Sodium methoxide
Cbz NH_2	Benzyl Carbamate
NaOH	Sodium Hydroxide
tert	Tertiary
*i*PrOH	Isopropyl Alcohol
$(DHQ)_2PHAL$	Hydroquinine 1,4-phthalazinediyl diether
$K_2OsO_2(OH)_4$	Potassium Osmate
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
HOBT	Hydroxybenzotriazole
DIEA	N, N-Diisopropylethylamine
DMF	Dimethylformamide
PPh_3	Triphenylphosphine
DIAD	Diisopropyl azodicarboxylate
NH_2NH_2	Hydrazine
P_2O_5	Phosphorus Pentoxide
$AlCl_3$	Aluminium trichloride
$InCl_3$	Indium chloride
CH_3CN	Acetonitrile
CH_2Cl_2	Dichloromethane
Ph	Phenyl
Bn	Benzyl
h	Hour
K_2CO_3	Potassium Carbonate
$(CH_3)_2SO_4$	Dimethylsulphate
NH4OAc	Ammonium Acetate
MnO_2	Manganese dioxide
Red-Al	Sodium bis(2-methoxyethoxy)aluminium dihydride
TFA	Trifluoroacetic acid
*t-Bu*OK	Potassium tert-butoxide
NADH	Nicotinamide adenine dinucleotide
GDH	Glucose dehydrogenase
L-AADH	Aromatic amine dehydrogenase
$NABH_4$	Sodium Borohydride
iPrMgCl-LiCl	Isopropyl magnesium chloride-lithium chloride
iPr_2NEt	*N,N*-Diisopropyl Ethylamine
MsCl	Methane Sulfonyl chloride
HMDS	Hexamethyldisilazane
TMSOTf	Trimethylsilyltrifluoromethanesulfonate
BtH	Benzotriazole
SAR	Structure Activity Relationship