

REVIEW

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Therapeutic potential of oxadiazole or furadiazole containing compounds

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Abstract

As we know that, Oxadiazole or furadi azole ring containing derivatives are an important class of heterocyclic compounds. A heterocyclic five-membered ring that possesses two carbons, one oxygen atom, two nitrogen atoms, and two double bonds is known as oxadiazole. They are derived from furan by the replacement of two methylene groups ($=CH$) with two nitrogen ($-N=$) atoms. The aromaticity was reduced with the replacement of these groups in the furan ring to such an extent that it shows conjugated diene character. Four different known isomers of oxadiazole were existed such as 1,2,4-oxadiazole, 1,2,3-oxadiazole, 1,2,5-oxadiazole & 1,3,4-oxadiazole. Among them, 1,3,4-oxadiazoles & 1,2,4-oxadiazoles are better known and more widely studied by the researchers due to their broad range of chemical and biological properties. 1,3,4-oxadiazoles have become important synthons in the development of new drugs. The derivatives of the oxadiazole nucleus (1,3,4-oxadiazoles) show various biological activities such as anti-bacterial, anti-mycobacterial, antitumor, anti-viral and antioxidant activity, etc. as reported in the literature. There are different examples of commercially available drugs which consist of 1,3,4-oxadiazole ring such as nitrofur derivative (Furamizole) which has strong antibacterial activity, Raltegravir as an antiviral drug and Nesapidil drug is used in anti-arrhythmic therapy. This present review summarized some pharmacological activities and various kinds of synthetic routes for 2, 5-disubstituted 1,3,4-oxadiazole, and their derived products.

Keywords: 1, 3, 4-oxadiazole, Heterocyclic compounds, Antiviral, Antitumor, Antitubercular

Background

Health problems were increasing day by day and become the most serious clinical problem. Recently, medicinal chemists have been looking for new drugs to be used safely to treat these serious clinical problems. There are a lot of heterocyclic compounds that are in clinical use to treat infectious disease [1].

The most common heterocyclic are those having five or six-member fused rings and possess nitrogen, oxygen, sulfur groups as heteroatoms. Some time boron, silicon, and phosphorus atoms can be used as hetero atoms [2].

Heterocyclic compounds containing nitrogen atom such as oxadiazole moieties are of interest to researchers

in the fields of medicinal and pharmaceutical chemistry [3].

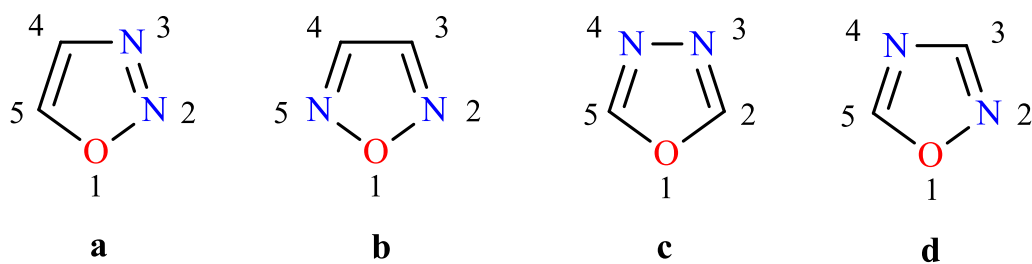
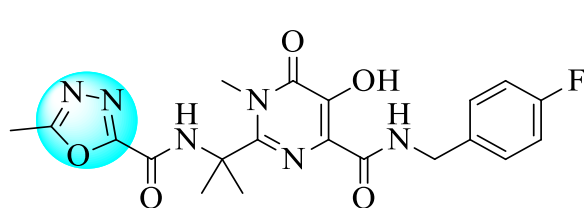
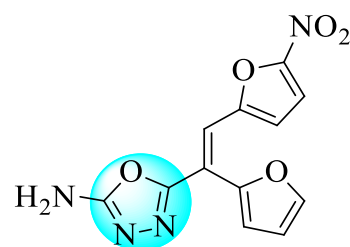
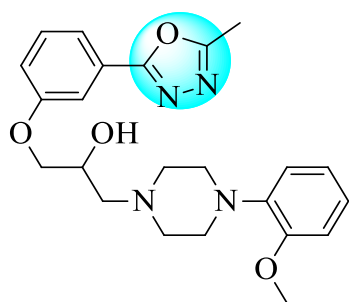
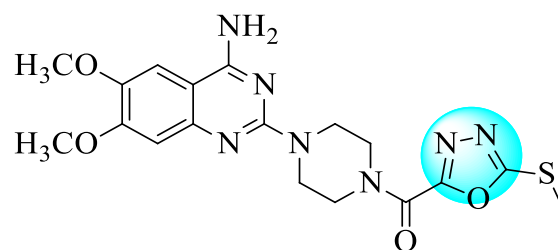
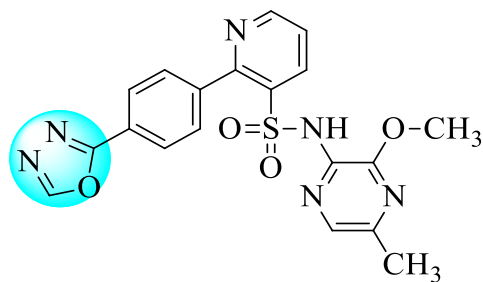
A heterocycles five-member ring that possesses one oxygen, two carbons, two nitrogen atoms, and two double bonds is known as oxadiazole [4]. This type of ring system is also known as azoximes, oxybiazole, biozole, diazoxole, furadiazole, and furoxans. Oxadiazole was first synthesized in 1965 by Ainsworth through the thermolysis of hydrazine. Its molecular formula is $C_2H_2ON_2$ and having a molecular mass of 70.05 g/mol which is soluble in water [2].

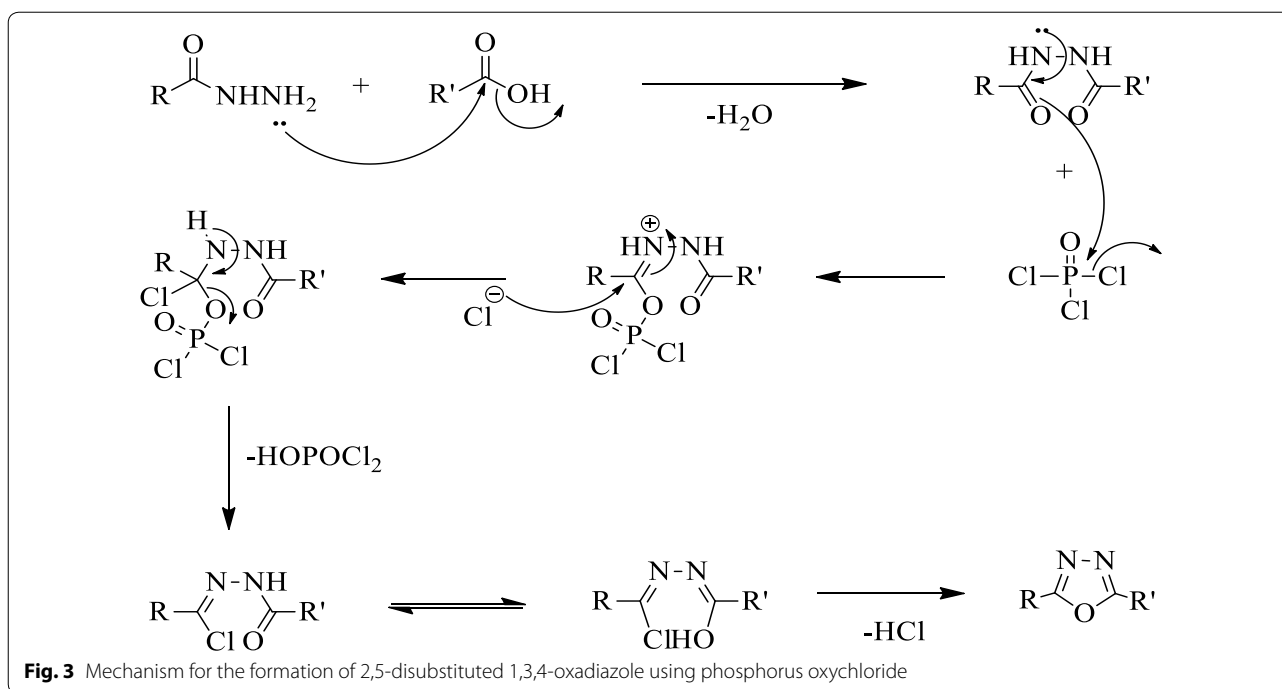
Oxadiazoles are thermally stable compounds and their calculated resonance energy is equal to 167.4 kJ/mol. The thermal stability of oxadiazoles is increased with the substitution at the second position [5].

1,3,4-oxadiazole heterocyclic ring is one of the most important heterocyclic moieties due to its versatile biological actions [6]. These are the derivatives of furan in

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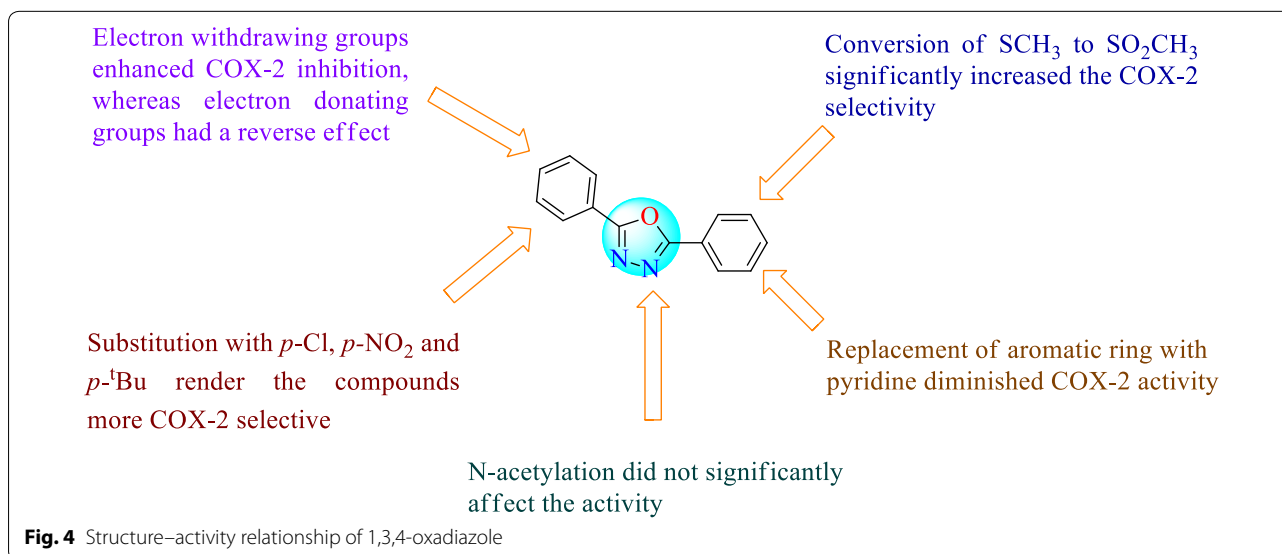
**Fig. 1** Oxadiazole**Raltegravir****Furamizole****Nesapidil****Tiodazosin****Zibotentan****Fig. 2** Commercially available drugs which contain 1,3,4-oxadiazole nucleus



which two methylene groups were replaced with two nitrogen atoms. Replacement of these two methylene groups by two nitrogen atoms reduces the aromaticity of the ring & the resulting oxadiazole ring exhibits conjugated diene character [7]. Another heteroatom makes a weak base to the oxadiazole due to the inductive effect [6]. Hydrogen atoms were replaced by nucleophiles which are seen in nucleophilic substitution reaction [8].

Nitrogen atoms are present in oxadiazole ring at different positions and based on the position there are four different possible isomers of oxadiazole such as 1,2,3-oxadiazole (a), 1,2,5-oxadiazole (b), 1,3,4-oxadiazole (c) and 1,2,4-Oxadiazole (d) were showed in Fig. 1 [6].

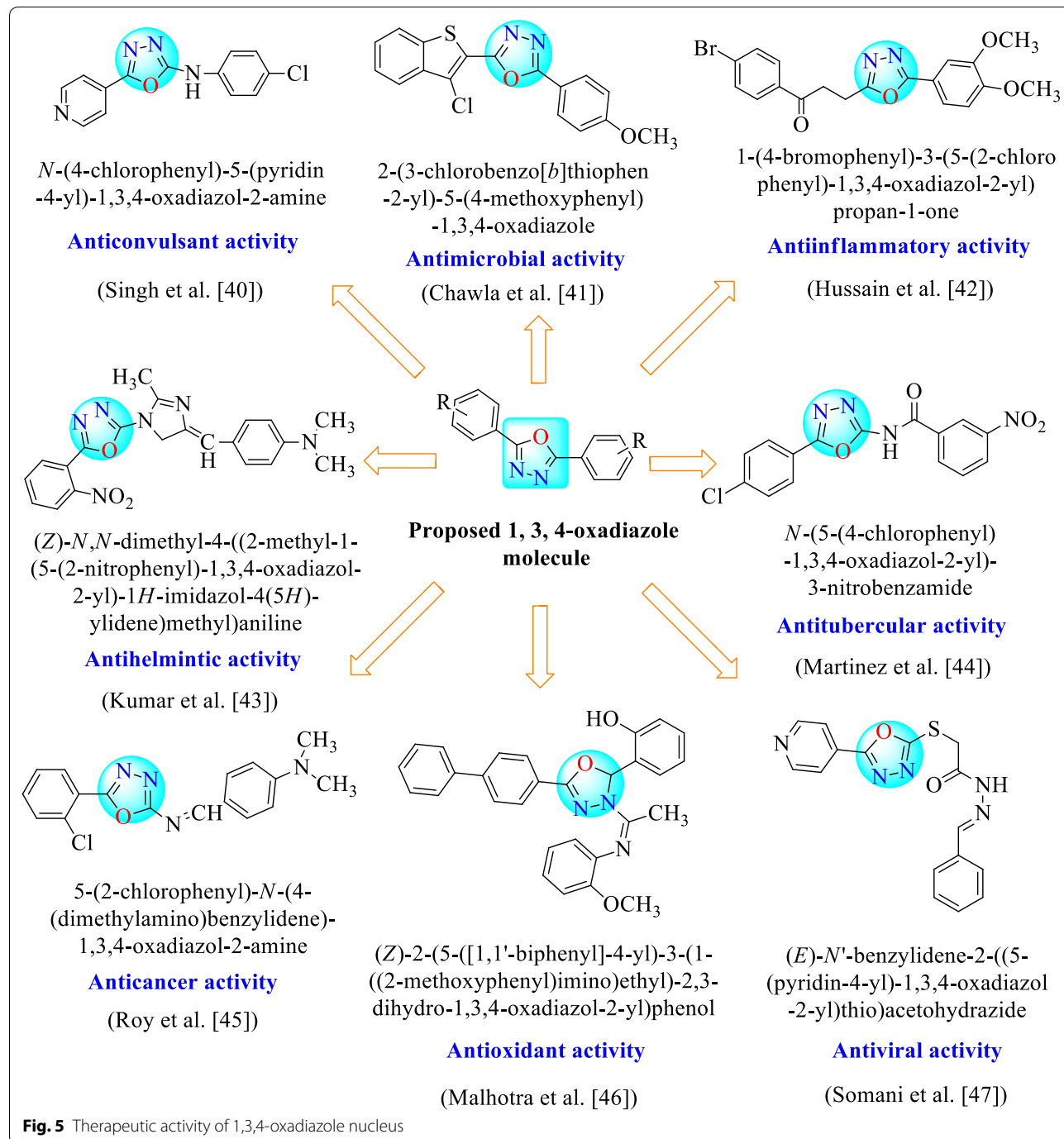
Among the different isomers, 1,3,4-oxadiazole isomer shows a lots of therapeutic activities like antibacterial [9, 10], anticonvulsant [11], antitumor [12–22],

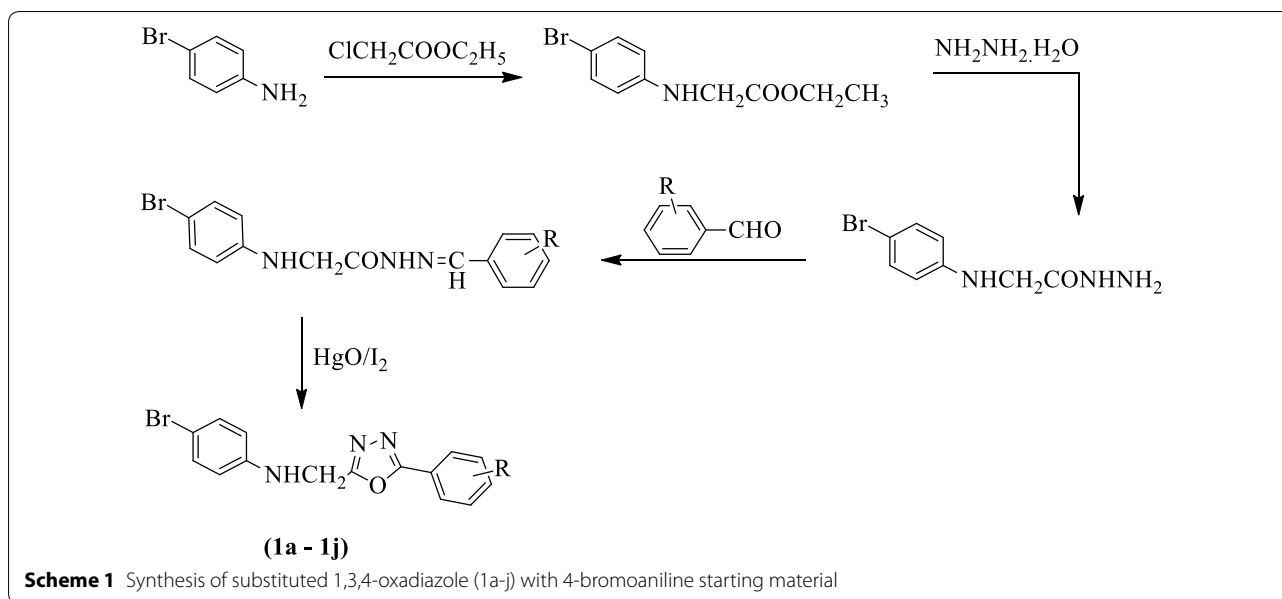


hypoglycemic, antipyretic [23], anti-tubercular [10, 24], anti-viral [25], immunosuppressive, spasmolytic, antioxidant [13, 26], anti-inflammatory [23, 27, 28], insecticidal [20], CNS stimulant, ant amoebic, antiemetic, antidepressant, anthelmintic activities, vasodilator activity, antimycotic activity [29], anti-allergic, anti-Alzheimer activity, ulcerogenic and antihypertensive activities etc.

as reported in the literature [30]. Keeping the view of this, we have discussed different oxadiazole derivatives carrying urea, amide, and sulphonamide groups to investigate their anticancer, antiviral, antimicrobial, antitubercular, and antioxidant activities [31].

The presence of toxicophoric $-N=C-O-$ linkage in 1,3,4-oxadiazole ring might be responsible for their



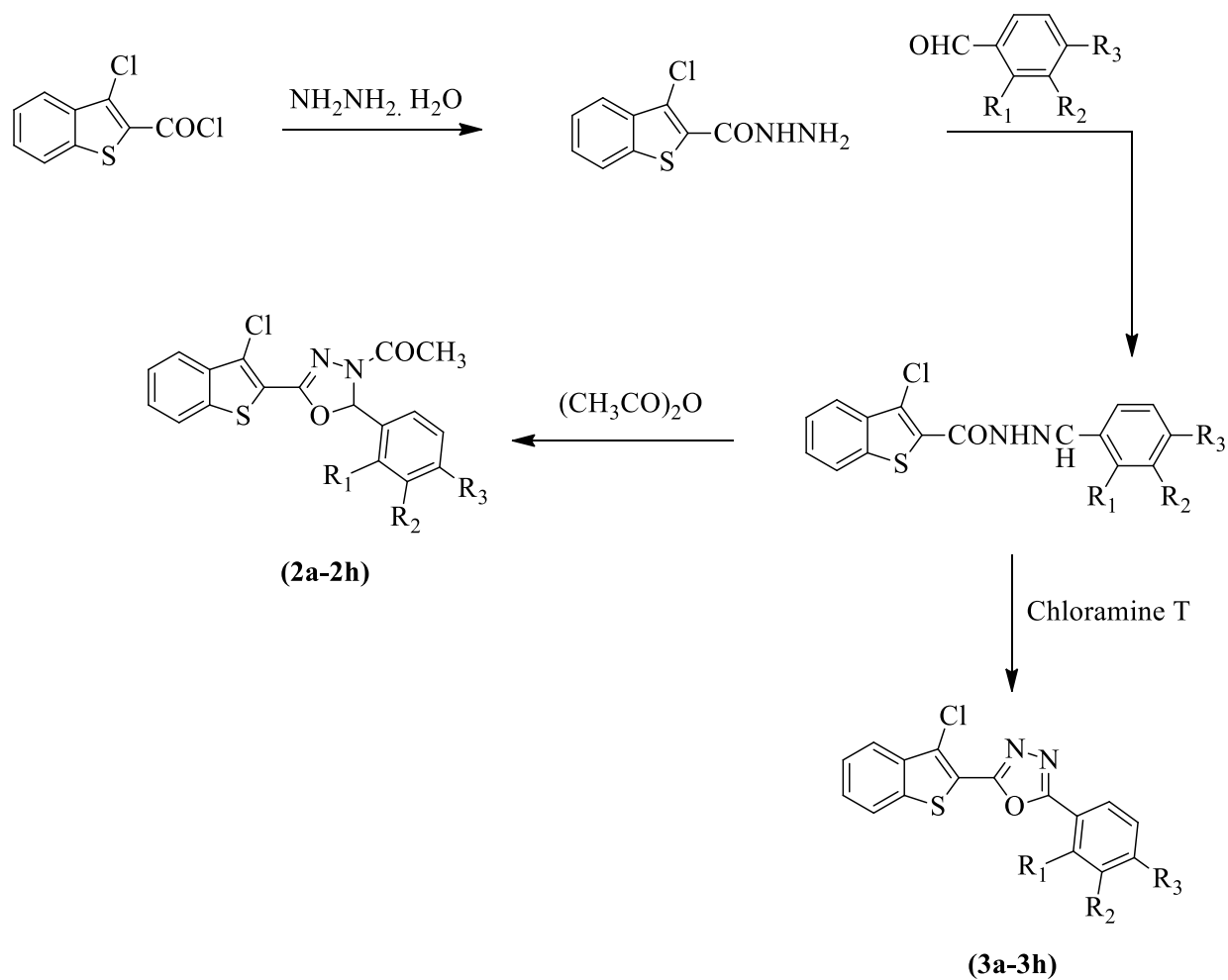
**Table 1** Antimicrobial activity of titled compounds (1a-j) [48]

Compound	Diameter of zone of inhibition (mm)				
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>
1a	13	15	14	13	08
1b	14	14	13	12	15
1c	14	15	14	15	14
1d	15	14	13	13	15
1e	18	19	18	15	08
1f	19	17	18	16	09
1g	14	12	15	10	15
1h	18	18	19	15	09
1i	16	15	14	13	10
1j	15	14	15	12	11
Amoxicillin	21	22	21	22	–
Ketoconazole	–	–	–	–	23

potent pharmacological activities. Among these, substituted 1,3,4-oxadiazoles are of considerable pharmaceutical interest. 2,5-disubstituted-1,3,4-oxadiazole derivatives are stable, especially 2,5-diaryl-1,3,4-oxadiazoles are more stable than the corresponding 2,5-dialkyl derivatives. Medicinal chemists have great perseverance in Research and development for the development of newer and safer antitumor agents. Tyrosine kinases (EGFR family) play a very important role in cancer proliferation.

So those compounds which inhibit the activity of tyrosine kinases play a substantial role in cancer treatment. Therefore Tyrosine kinases (EGFR family) were selected and explore the binding mode of the novel compounds to EGFR tyrosine kinase active site [32].

There is various kind of synthetic route from which we can synthesize 1,3,4-oxadiazole, and their derived products. In general, 1,3,4-oxadiazole can be synthesized by the reaction of acid hydrazide or hydrazine along with



Compound	R_1	R_2	R_3	Compound	R_1	R_2	R_3
2a	H	H	H	3a	H	H	H
2b	H	H	F	3b	H	H	F
2c	H	OCH_3	H	3c	H	OCH_3	H
2d	Cl	H	H	3d	Cl	H	H
2e	H	H	OCH_3	3e	H	H	OCH_3
2f	H	NO_2	H	3f	H	NO_2	H
2g	H	H	Cl	3g	H	H	Cl
2h	H	OCH_3	OH	3h	H	OCH_3	OH

Scheme 2 Synthesis of substituted 1,3,4-oxadiazole derivatives

Table 2 Antimicrobial activity of titled compounds (2a-h) and (3a-h) [41]

Compound	Diameter of zone of inhibition (mm)					
	Antibacterial activity				Antifungal activity	
	<i>S. aureus</i>	<i>B. subtilis</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>	<i>A. niger</i>
2a	14	21	10	17	09	10
2b	18	19	12	15	10	11
2c	30	27	14	18	09	11
2d	19	22	11	18	10	11
2e	28	28	14	14	10	09
2f	14	19	10	15	10	10
2g	21	23	13	19	11	09
2h	14	20	10	16	09	10
3a	11	12	10	09	11	11
3b	10	12	09	11	12	12
3c	20	21	12	13	11	11
3d	20	22	16	18	10	11
3e	18	19	11	13	11	10
3f	11	13	10	11	10	11
3g	12	14	09	12	10	10
3h	10	13	09	11	10	11
Ciprofloxacin	26	26	28	25	–	–
Fluconazole	–	–	–	–	26	25

carboxylic acids/acid chlorides and direct ring closure of diacyl hydrazines employing different kinds of the cyclizing agent such as phosphorus oxychloride, thionyl chloride, phosphorus pentoxide, triflic anhydride, polyphosphoric acid, acetic anhydride and the direct reaction of an acid with (N-isocyananimino-) triphenylphosphorane [33]. In some reaction, carbon disulfide is also used for ring closure [34].

There are different examples of commercially available drugs containing 1,3,4-oxadiazole ring (Fig. 2) such as a nitrofur derivative (Furamizole) which has strong antibacterial activity [35]. Raltegravir as an antiviral drug and Nesapidil drug is used in anti-arrhythmic therapy. The FDA approved anticancer agent Zibotentan is a 1,3,4-oxadiazole nucleus containing the most privileged derivatives available in the market [36]. Tiodazosin

is used as an antihypertensive agent [37]. This present review summarized some pharmacological activities and various kinds of synthetic routes for 2,5-disubstituted 1,3,4-Oxadiazole, and their derived products during the last decade (2005–2020).

The mechanism for the formation of 2,5-disubstituted 1,3,4-oxadiazole

The probable mechanism for the formation of the 1,3,4-oxadiazole is given in (Fig. 3). The presence of lone pair of electron on the nitrogen atom of acid hydrazide attacks the carbonyl carbon atom of carboxylic acid eliminates a water molecule to form a hydrazide derivative which further reacts with phosphorus oxychloride, undergoes ring closure with the elimination of hydrogen chloride, and form 1,3,4-oxadiazole ring [38].

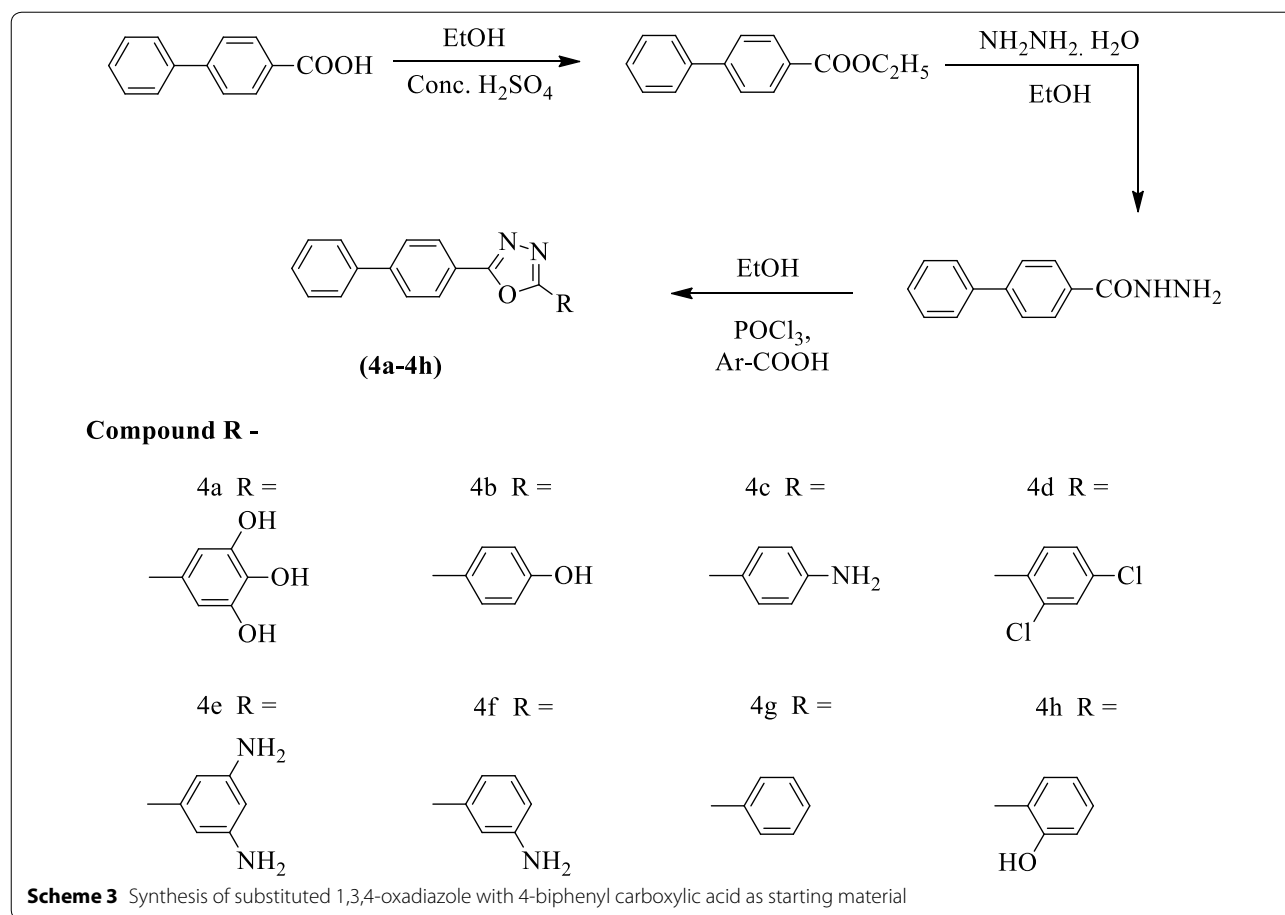
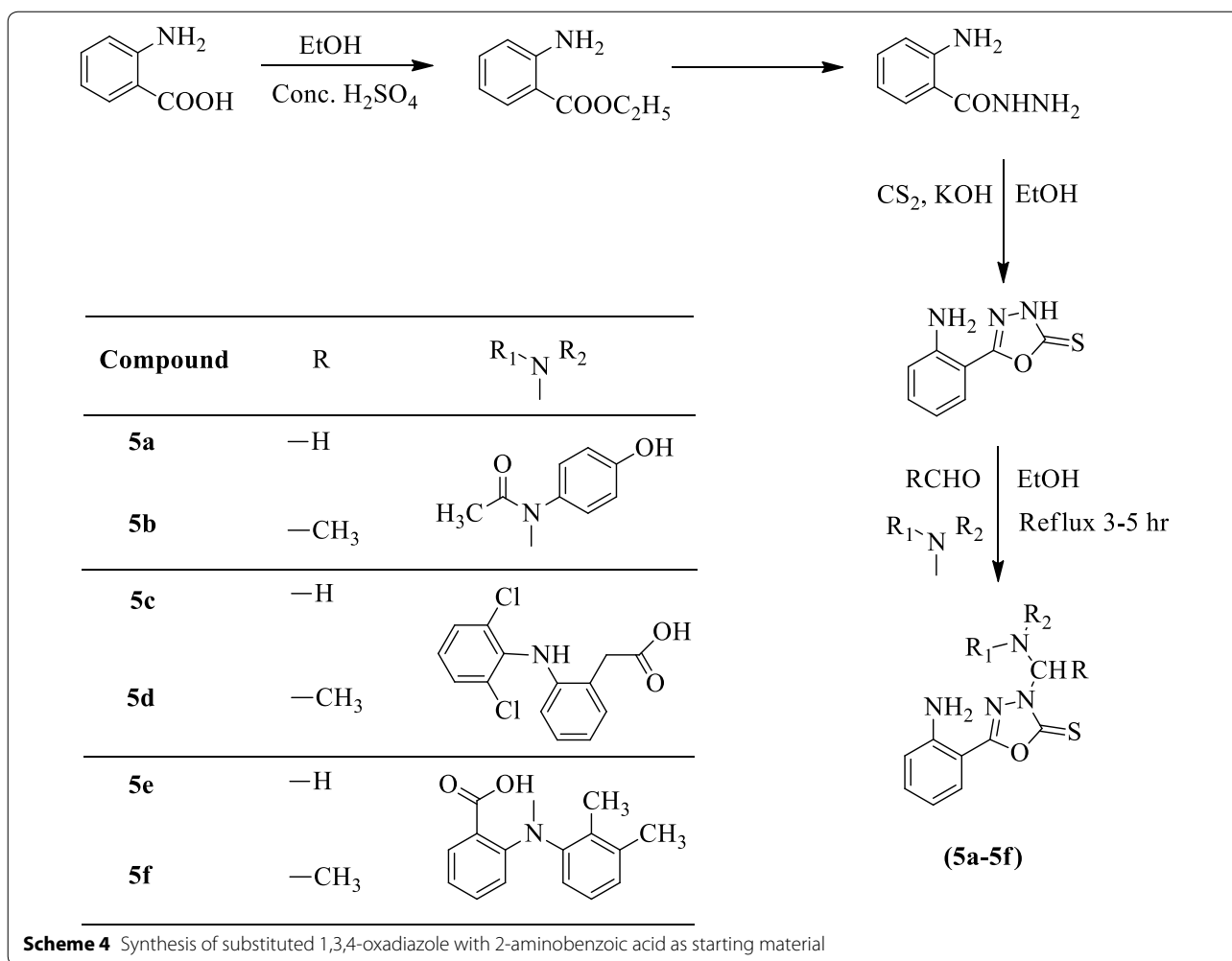


Table 3 In vitro antimicrobial activity of the titled compounds (4a-4 h) [43]

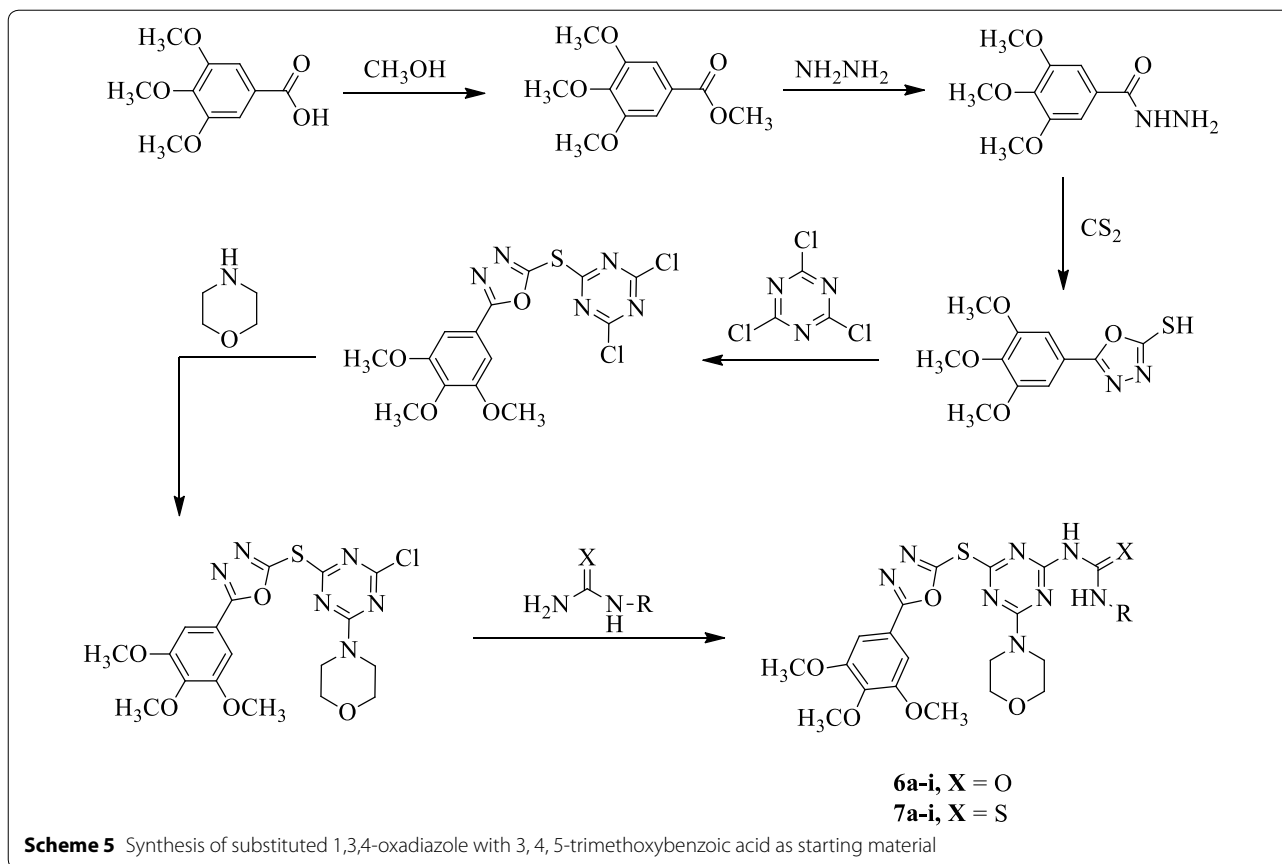
Compound	Diameter of zone of inhibition (mm)			
	Antibacterial activity			
	<i>S. aureus</i>	<i>P. aeruginosa</i>	<i>K. pneumonia</i>	<i>E. coli</i>
4a	19	17	18	19
4b	17	16	17	15
4c	14	13	16	17
4d	21	19	19	20
4e	12	11	13	12
4f	13	14	15	12
4g	12	13	11	11
4h	17	16	15	17
Ofloxacin	41	38	39	37

Structure–activity relationship of 1,3,4-oxadiazole derivatives

The structure–activity relationship of 1,3,4-oxadiazole is given in (Fig. 4). Substitution of phenyl ring with different substituents like *p*-Cl, *p*-NO₂ & *p*-^tBu further increases the activity. The conversion of the methylthio group into the methyl-sulfonyl group also increases the activity. The replacement of the phenyl ring along with the pyridine ring decreases the activity. If the acetyl group is present on the nitrogen atom of the oxadiazole ring did not significantly affect the activity [39]. Thus, based on the aforementioned results, we hypothesized that 2,5-disubstituted 1,3,4-oxadiazole scaffold may lead to novel potent agents with broad biological activity profile and improved pharmacokinetic properties.

**Table 4** Antimicrobial activity of the titled compounds (5a-5f) [5]

Compound	Diameter of zone of inhibition (mm)				
	Antibacterial activity				Antifungal activity
	<i>S. aureus</i>	<i>S. pyrogenes</i>	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>C. albicans</i>
5a	10	13	12	08	14
5b	13	11	14	09	12
5c	12	13	15	09	14
5d	12	11	13	10	13
5e	09	09	10	07	11
5f	08	09	09	06	10
Amikacin	16	15	17	18	-
Ketoconazole	-	-	-	-	18



Pharmacological profile of some oxadiazole derivatives

Compound N-(4 chlorophenyl) amino-5-(4-pyridyl)-1,3,4-oxadiazole having electron-withdrawing group shows better anticonvulsant activity [40]. Compounds with p-methoxy group increase the antimicrobial potential [41] and 3, 4-dimethoxy containing compound increase anti-inflammatory activity as compared to reference drug [42]. 1,3,4-Oxadiazole nucleus containing compounds along with different substituents shows various kinds of activities (Fig. 5).

Antimicrobial activity

Bhat et al. [48] developed 4-bromo-N-[(5-(substituted phenyl)-1,3,4-oxadiazol-2-yl)methyl]aniline (Scheme 1) and these derivatives were screened for antimicrobial

activity against *S. aureus*, *E. coli*, *B. Subtilis*, and *P. aeruginosa* using amoxicillin as a positive control. The antimycotic activity was evaluated for these compounds against *A. niger* and *C. albicans* using ketoconazole as a reference standard. Derivatives with different groups like -OH, -NO₂ [1b, 1c, 1d, 1g] shows good antimicrobial activity against fungal strains. Derivatives with groups like p-methoxy, p-chloro, p-methyl [1e, 1f, 1h] show better antimicrobial potential as compared to amoxicillin. The results of the antimicrobial activity of synthesized 1,3,4-oxadiazole derivatives were presented in (Table 1, Bhat et al. [48]).

Chawla et al. [41] developed 1-(5-(3-chlorobenzo[b]thiophen-2-yl)-2-(2,3,4-trisubstituted phenyl)-1,3,4-oxadiazol-3(2H)-yl)ethanone and 2-(3-chlorobenzo[b]

Table 5 Minimum inhibitory concentration (MIC) of titled compounds [49]

Compound			<i>S. aureus</i>	<i>B. subtilis</i>	<i>P. aeruginosa</i>	<i>E. coli</i>	<i>C. albicans</i>
	R	X	ATCC 25923	ATCC 6633	ATCC 27853	ATCC 27853	ATCC 10231
6a	C ₆ H ₅	O	0.3	0.15	0.15	1.25	2.5
6b	2-CH ₃ C ₆ H ₅	O	0.31	0.07	1.25	0.625	5.0
6c	3-CH ₃ C ₆ H ₅	O	0.625	0.15	5.0	2.5	10
6d	4-CH ₃ C ₆ H ₅	O	2.5	2.5	0.03	5.0	1.25
6e	2-Cl C ₆ H ₅	O	0.15	1.25	0.019	0.019	5.0
6f	3-Cl C ₆ H ₅	O	0.15	0.625	1.25	1.25	2.5
6g	4-Cl C ₆ H ₅	O	0.15	0.3	0.019	0.07	0.15
6h	3-NO ₂ C ₆ H ₅	O	-	10	1.25	-	-
6i	4-NO ₂ C ₆ H ₅	O	2.5	-	0.625	5.0	10
7a	2-CH ₃ C ₆ H ₅	S	1.25	-	2.5	10	-
7b	4-CH ₃ C ₆ H ₅	S	1.25	5.0	2.5	1.25	5.0
7c	3-OH C ₆ H ₅	S	2.5	1.25	0.019	2.5	10
7d	4-OH C ₆ H ₅	S	0.15	0.625	2.5	0.625	1.25
7e	4-Cl C ₆ H ₅	S	0.625	0.07	5.0	0.03	0.31
7f	3-NO ₂ C ₆ H ₅	S	2.5	2.5	10	1.25	2.5
7g	4-NO ₂ C ₆ H ₅	S	2.5	5.0	5.0	0.1	0.15
Ampicillin			0.019	0.005	0.005	0.01	-
Fluconazole			-	-	-	-	0.01

thiophen-2-yl)-5-(2,3,4-trisubstituted phenyl)-1,3,4-oxadiazole by using Scheme 2. The antibacterial activity of synthesized derivatives was evaluated against different bacterial strains such as (*S. aureus*, *B. Subtilis*, *E. coli*, and *P. aeruginosa*) using ciprofloxacin as standard drug. The antimycotic activity of these derivatives was evaluated against *A. niger* and *C. albicans* using fluconazole as a reference standard and the results were summarized in (Table 2, Chawla et al. [41]).

Kumar et al. [43] developed 2-((1, 1'-biphenyl)-4-yl)-5-(substituted phenyl)-1,3,4-oxadiazole by using Scheme 3. The antibacterial activity of these derivatives

was evaluated against different Gram +ve (*S. aureus*) and Gram -ve (*K. pneumonia*, *E. coli*, and *P. aeruginosa*) strains using ofloxacin as a reference standard. The cup plate agar diffusion method was used for the determination of the zone of inhibition. The results of antibacterial activity were summarized in (Table 3, Kumar et al. [43]).

Kanthiah et al. [5] developed 5-(2-aminophenyl)-3-(substituted (disubstituted amino) methyl)-1,3,4-oxadiazole-2(3H)-thione by using Scheme 4. The antimicrobial activity of synthesized derivatives was evaluated against different two Gram +ve (*S. aureus* and *S. pyogenes*) and Gram -ve (*E. coli* and *K. aerogenes*) strains using amikacin

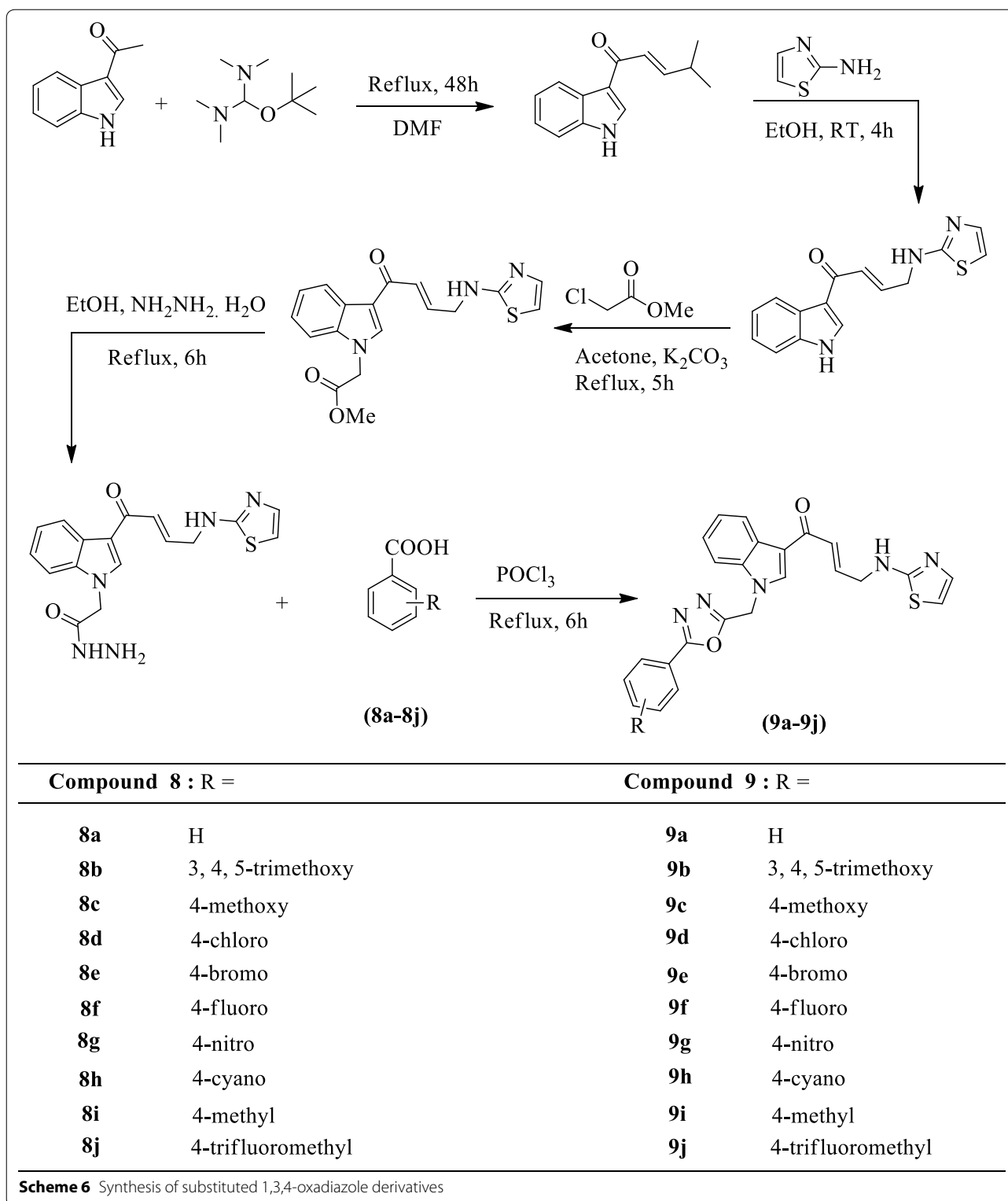


Table 6 In vitro cytotoxicity (IC₅₀M)^a data of compounds (9a-j) [30]

Compound	A549 ^{bc}	MCF-7 ^d	A375 ^e	HT-29 ^f
9a	1.20 ± 0.16	0.098 ± 0.004	2.56 ± 0.36	0.012 ± 0.001
9b	0.023 ± 0.006	0.011 ± 0.001	–	1.90 ± 0.71
9c	2.30 ± 0.21	2.19 ± 0.28	–	8.30 ± 1.60
9d	3.56 ± 0.19	2.11 ± 0.23	6.13 ± 1.12	7.14 ± 0.86
9e	5.02 ± 1.02	12.4 ± 0.96	–	–
9f	0.27 ± 0.02	1.07 ± 0.59	2.81 ± 0.25	1.55 ± 0.65
9g	0.013 ± 0.001	0.80 ± 0.15	1.05 ± 0.53	1.24 ± 0.17
9h	1.02 ± 0.50	0.010 ± 0.004	1.99 ± 0.29	3.78 ± 0.16
9i	13.9 ± 0.54	18.50 ± 0.86	8.23 ± 1.35	–
9j	0.90 ± 0.09	0.12 ± 0.01	0.39 ± 0.012	1.10 ± 0.54
Combretastatin-A4	0.11 ± 0.01	0.18 ± 0.01	0.21 ± 0.02	0.93 ± 0.03

^a Each data represented as mean ± S.D values. From three different experiments performed in triplicates, ^{bc}A549: Human lung cancer cell line, ^dMCF-7: Human breast cancer cell line, ^eA375: Human melanoma cancer cell line, ^fHT-29: Human colon cancer cell line. –: Not active

as a reference standard. The antimycotic activity was also evaluated for these derivatives against *C. albicans* using ketoconazole as positive control and the results were summarized in (Table 4, Kanthiah et al. [5]).

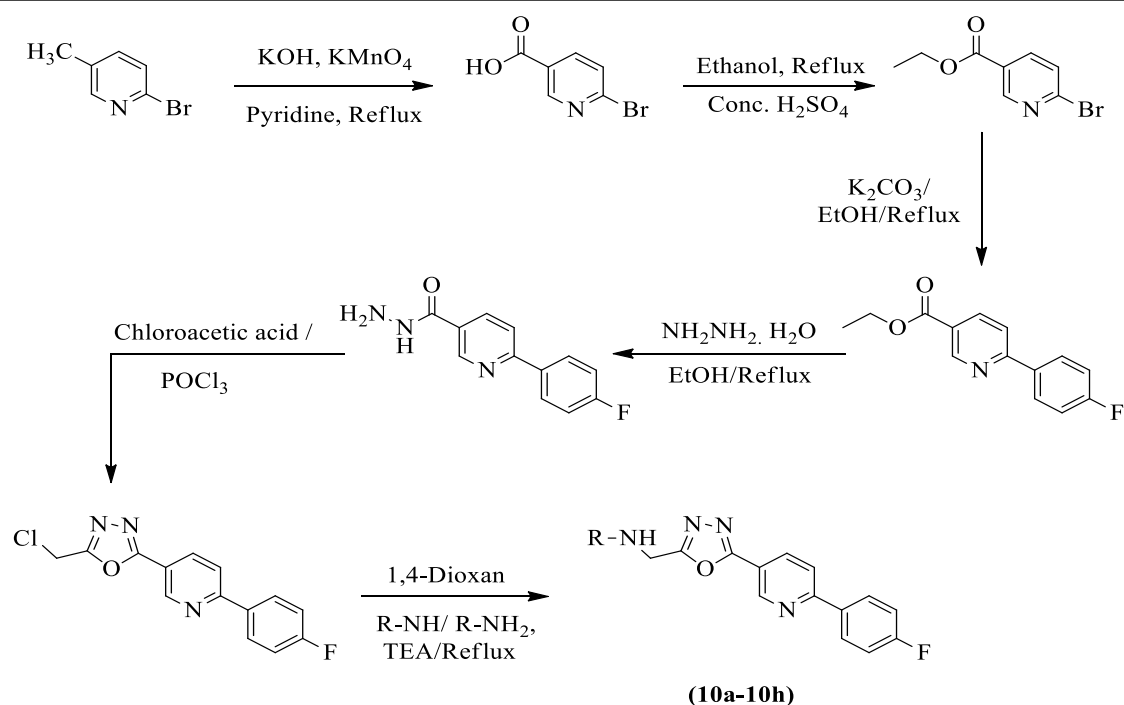
Chikhalia et al. [49] developed *1-substituted-3-(4-morpholino-6-((5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl)thio)-1,3,5-triazin-2-yl)substituted urea* (Scheme 5) and evaluated for antimicrobial activity against different strains such as (*Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, and *Pseudomonas aeruginosa*) using ampicillin as a reference standard. The antifungal activity was also evaluated for these derivatives against *C. albicans* using fluconazole as a reference standard. Compound **6e** shows better activity against *E. coli* and *P. aeruginosa* as compared to a positive control (ampicillin). Compound **6g** also shows better activity towards *P. aeruginosa* but lower than that of ampicillin. Compound **7c** and **7g** showed good activity against *C. albicans* but slightly lower than that of fluconazole. The results of

antimicrobial activity were shown in (Table 5, Chikhalia et al. [49]).

Antitumor activity

Srinivas et al. [30] developed *(E)-1-(1-((5-substituted-1,3,4-oxadiazol-2-yl)methyl)-1H-indol-3-yl)-4-(thiazol-2-ylamino)but-2-en-1-one* (Scheme 6) and evaluated for antitumor activity by MTT assay against four different cancer cell lines such as HT-29 (colon), A375 (melanoma), MCF-7 (breast) and A549 (lung) using combretastatin-A4 as reference standard. All derivatives of 1,3,4-oxadiazole fused indole ring was showed a variable degree of anticancer activity along with IC₅₀ values ranging from 0.010 ± 0.004 and 18.50 ± 0.86 μM. Among the different derivatives **9a**, **9b**, **9f**, **9g**, **9h**, and **9j** were exhibited more potent than the positive control. The results of antitumor activity were presented in (Table 6, Srinivas et al. [30]).

Vinayak et al. [50] developed *N-[(5-(6-(4-fluorophenyl)pyridine-3-yl)1,3,4-oxadiazol-2-yl)*



Compound	R =	Compound	R =
10a		10e	
10b		10f	
10c		10g	
10d		10h	

Scheme 7 Synthesis of substituted 1,3,4-oxadiazole derivatives

methyl]-substituted-1-amine by using Scheme 7 and evaluated for antiproliferative activity against different cell lines such as HeLa, HepG2, and Caco by MTT assay using 5-Fluorouracil as a reference standard. The derivative **10a** and **10d** showed excellent activity against HepG2 cell lines. The compound **10f** gives better results

against the Caco-2 cancer cell line. The results of the anti-proliferative activity of synthesized derivatives were showed in (Table 7a, b, and c, Vinayak et al. [50]).

Kapoor et al. [51] developed 2-(substituted phenyl)-5-(2-(2-(substituted phenyl)-1H-benzo[d]imidazol-1-yl)

Table 7 (a) IC₅₀ values of the synthesized novel amine derivatives. (b) CC₅₀ values of the synthesized novel amine derivatives. (c) Selectivity index (SI) of the synthesized novel amine derivatives [50]

Panel (a)			
Compound	IC ₅₀ [#] values of 10(a-h) in (μM)		
	HeLa	Caco-2	HepG2
10a	212.4 ± 1.2	203.6 ± 2.3	2.6 ± 0.5
10b	85.6 ± 0.8	112.5 ± 1.2	45.6 ± 1.1
10c	34.8 ± 1.3	123.8 ± 1.4	128.9 ± 3.5
10d	112.9 ± 0.4	145.6 ± 0.4	5.8 ± 1.6
10e	118.4 ± 0.5	212.3 ± 0.4	32.2 ± 0.3
10f	78.3 ± 5.4	2.3 ± 0.5	23.5 ± 4.6
10 g	56.4 ± 3.4	56.8 ± 1.2	156.7 ± 2.3
10 h	88.6 ± 1.2	34.6 ± 0.9	176.4 ± 1.6
5-FU	7.6 ± 0.3	8.8 ± 0.6	7.6 ± 0.2
Panel (b)			
Compound	CC ₅₀ [*] of the compound 10(a-h) in (μM)		
	HeLa	Caco-2	HepG2
10a	120 ± 1.2	112 ± 1.3	34 ± 0.5
10b	7.6 ± 0.6	145 ± 1.1	129 ± 0.3
10c	200	178 ± 2.3	102 ± 1.1
10d	450	100 ± 2.6	112 ± 1.4
10e	56 ± 2.4	62 ± 1.2	76 ± 3.4
10f	127 ± 3.4	87 ± 2.6	77 ± 0.4
10 g	200	23 ± 1.5	91 ± 4.3
10 h	123 ± 2.3	156 ± 0.4	73 ± 1.4
5-FU	57 ± 0.3	69 ± 2.3	52 ± 1.8
Panel (c)			
Compound	SI of the compound 10(a-h)		
	HeLa	Caco-2	HepG2
10a	0.566	0.551	13.06
10b	0.887	1.288	2.828
10c	5.747	1.437	0.791
10d	3.985	0.686	19.31
10e	0.472	0.292	0.236
10f	1.621	37.8	3.276
10g	3.546	0.404	0.580
10h	1.388	4.508	0.413
5-FU	7.5	7.84	6.84

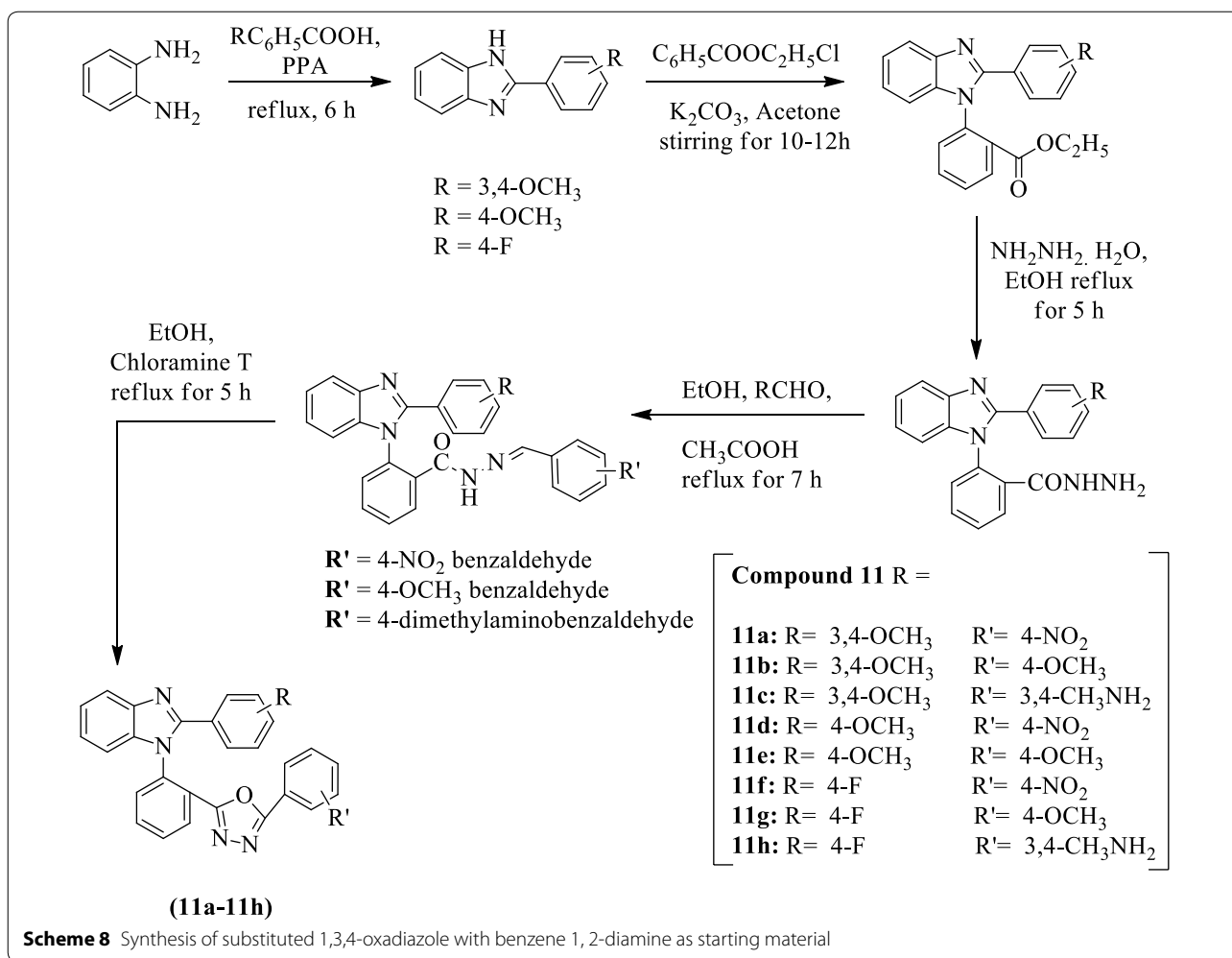
*Concentration of compound at 50% of the remaining viable cells

Inhibitory concentration at 50% of the viable cells

± Average value of the two independent experiments

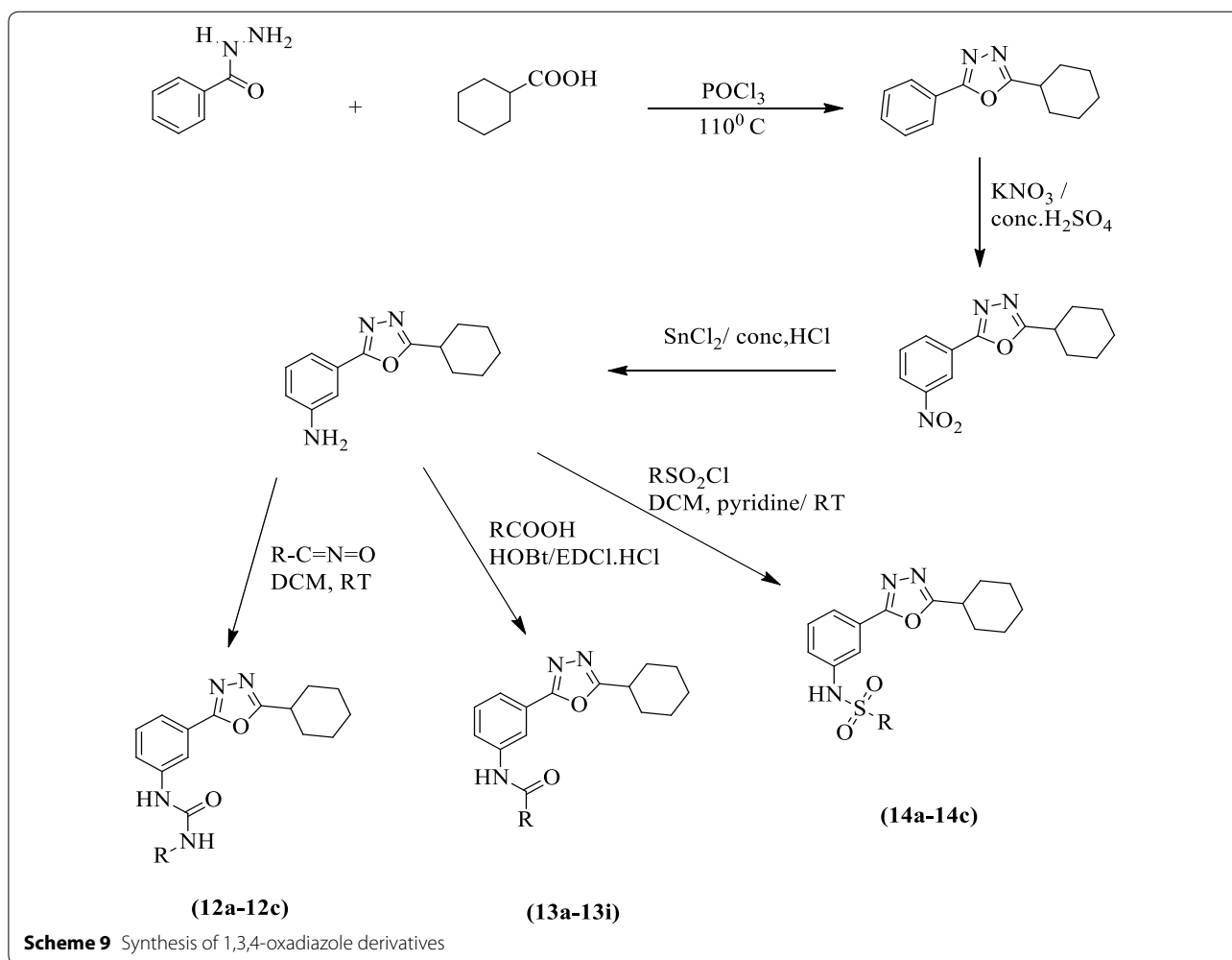
phenyl)-1,3,4-oxadiazole by using Scheme 8 and evaluated for antitumor activity against MCF-7 (breast) cancer cell line by MTT assay. Compound **11e** shows better cytotoxic activity as compare to **11a**, **11b**, and **11c**. Compounds **11f**, **11g**, **11h** also show the excellent cytotoxic

activity as compared to the rest of the derivatives. Compounds **11e** and **11h** flourished potent cytotoxic activity with minimum percentage viability. Each compound was tested to calculate the percentage viability of cell line

**Table 8** In-vitro cytotoxicity of synthesized compounds against Breast cancer cell line (MCF-7) [51]

Compound	% Viability				
	6.25 µg/ml	12.5 µg/ml	25 µg/ml	50 µg/ml	100 µg/ml
11a	38.04	37.15	39.68	35.11	40.31
11b	38.26	42.70	37.90	38.84	43.24
11c	44.35	41.6	41.81	39.64	37.24
11d	42.70	39.46	40.48	37.61	37.37
11e	30.60	32.20	34.48	33.86	37.54
11f	32.57	33.09	30.88	30.75	24.87
11g	34.39	33.58	28.80	32.40	30.96
11h	32.03	35.40	31.25	33.69	34.45

Control % viability = 100



against the different concentrations which is presented in (Table 8, Kapoor et al. [51]).

Kavitha et al. [31] developed *N*-substituted-(3-(5-cyclohexyl-1,3,4-oxadiazol-2-yl)phenyl)benzamide, urea, and substituted benzenesulfonamide derivatives by using Scheme 9. The anticancer activity of synthesized derivatives was evaluated against different cancer cell lines like HeLa and MCF-7 using cisplatin as a reference standard. Among the different derivatives, compounds **12a**, **12b**, **12c**, **13c**, **13d**, and **14b** showed significant activity after 48 h exposures. Further derivatives **12a**, **13c**, **13d**, and

14b also showed excellent antitumor activity as compared to the positive control. Compound **12b** showed excellent antitumor activity as compared to the rest of other compounds. The results of the antitumor activity of these derivatives were presented in (Table 9, Kavitha et al. [31]).

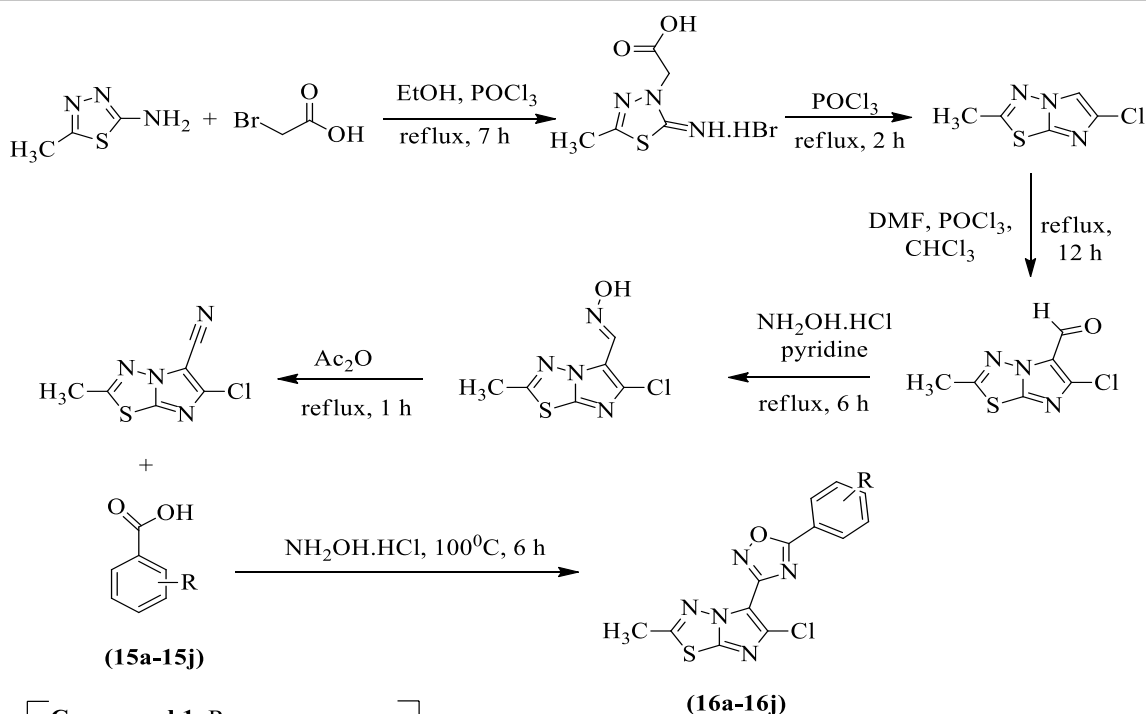
Chakrapani et al. [52] developed 3-(6-chloro-2-methylimidazo[2,1-b][1,3,4]thiadiazol-5-yl)-5-(substituted phenyl)-1,2,4-oxadiazole by using Scheme 10. The antitumor activity of the synthesized derivatives was evaluated by MTT assay against ACHN (renal), MCF-7 (breast), and

Table 9 Preliminary cytotoxicity screening of synthesized 1,3,4-oxadiazole derivatives [31]

Compound	IC ₅₀ μM	
	HeLa	MCF-7
12a	79.7	81.6
12b	30.4	23.5
12c	45.6	28.6
13a	≥ 100	≥ 100
13b	≥ 100	≥ 100
13c	80.1	78.3
13d	58.8	62.4
13e	≥ 100	≥ 100
13f	100.3	≥ 100
13g	≥ 100	≥ 100
13h	≥ 100	≥ 100
13i	≥ 100	≥ 100
14a	≥ 100	≥ 100
14b	62.9	60.9
14c	≥ 100	≥ 100
Standard	3.5	3.5

A375 (melanoma) tumor cell line using doxorubicin as a reference standard. The compound **16b** shows good cytotoxic activity in comparison to the reference drug. The compound **16j** exhibits excellent activity towards melanoma cancer cell line (A375) and potent activities towards MCF-7 and ACHN cancer cell lines. The results of the antitumor activity of synthesized derivatives were presented in (Table 10, Chakrapani et al. [52]).

Gudipati et al. [53] developed (*Z*)-3-[(4-(5-mercapto-1,3,4-oxadiazol-2-yl)phenyl) imino]-5 or 7-substituted indolin-2-one (Scheme 11) and evaluated for antitumor activity by MTT assay against MCF-7, IMR-32, and HeLa tumor cell lines using cisplatin as a reference standard. The compounds **17b-17d** showed the most potent antitumor activity than the rest of other



Compound 1 R =
15a, 16a: R = H
15b, 16b: R = 3,4,5-trimethoxy
15c, 16c: R = 4-methoxy
15d, 16d: R = 4-chloro
15e, 16e: R = 4-bromo
15f, 16f: R = 4-fluoro
15g, 16g: R = 4-nitro
15h, 16h: R = 3-nitro
15i, 16i: R = 4-methyl
15j, 16j: R = 4-trifluoromethyl

Scheme 10 Synthesis of 1,2,4-oxadiazole derivatives

Table 10 Cytotoxicity data for compound 16a-j [52]

Compound	IC ₅₀ values, μ M		
	A375	MCF-7	ACHN
16a	11.4	10.2	18.5
16b	1.22	0.23	0.11
16c	2.98	0.70	1.89
16d	14.6	19.1	6.47
16e	8.20	11.2	7.7
16f	2.70	8.41	17.6
16g	17.7	9.7	12.2
16h	2.20	5.98	10.6
16i	9.56	13.7	2.44
16j	0.37	1.47	0.33
Doxorubicin	5.51	2.02	0.79

derivatives. The results of antitumor activity were summarized in (Table 11, Gudipati et al. [53]).

Polothi et al. [54] developed 5-(substituted phenyl)-3-(4-(5-(3,4,5-trimethoxyphenyl)-1,3,4-oxadiazol-2-yl)phenyl)-1,2,4-oxadiazole by using Scheme 12 and evaluated for antitumor activity by MTT assay against MDA MB-231, MCF-7 (breast cell line), A549 (lung cell line) cancer cell lines using doxorubicin as a reference standard. Among the different derivatives, compounds **19b**, **19g**, **19h**, and **19i** showed good cytotoxic activity as compared to the reference standard. The compound **19b** with 3, 4, 5-trimethoxy group on phenyl ring shows excellent antitumor activity against human cancer cell lines such as A549 and MCF-7. The results of the antitumor activity of

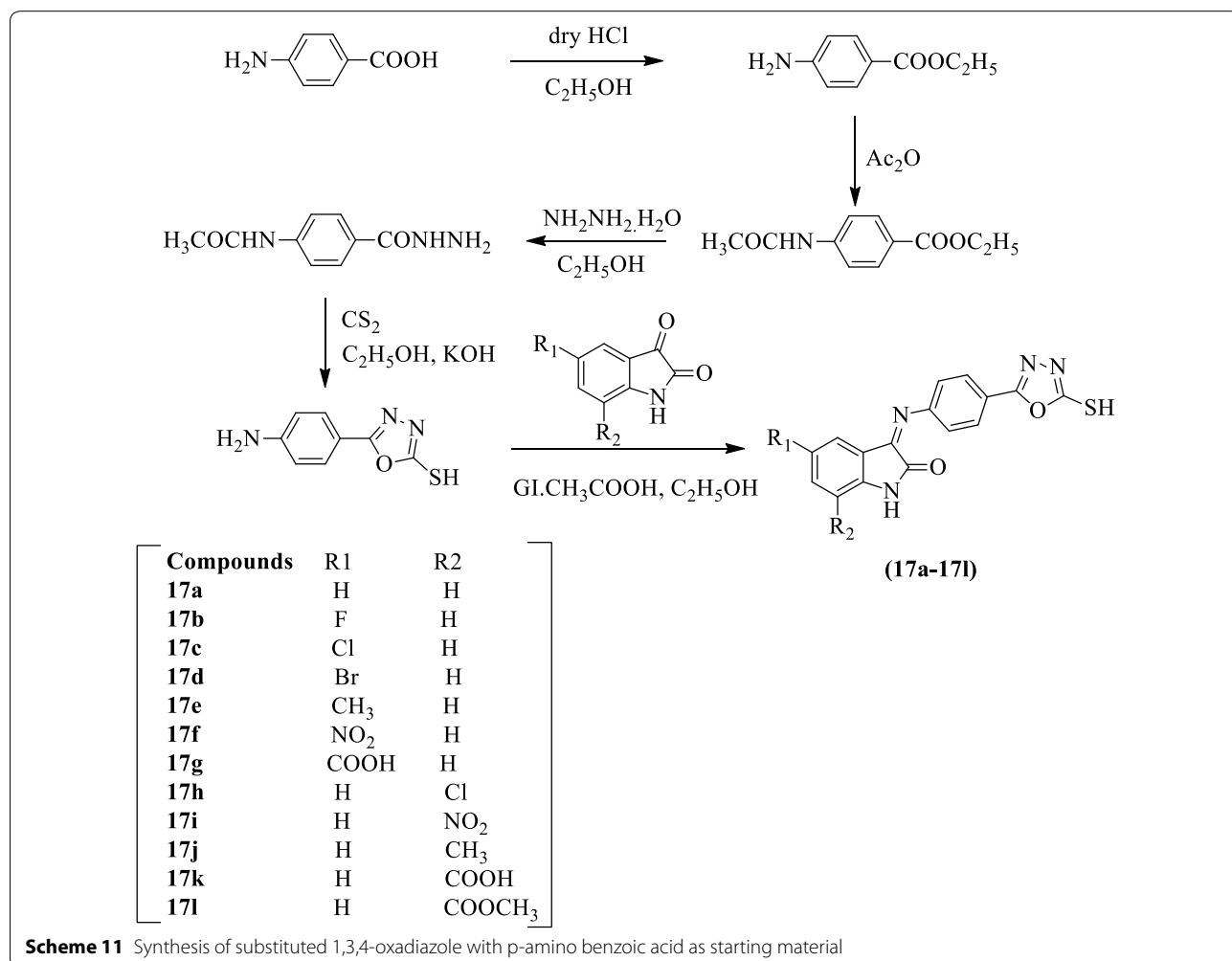


Table 11 Anticancer activity of synthesized compounds against HeLa, IMR-32 & MCF-7 cancer cells using MTT assay [53]

Compound	R ₁	R ₂	IC ₅₀ (μM) ^a (HeLa)	IC ₅₀ (μM) ^a (IMR-32)	IC ₅₀ (μM) ^a (MCF-7)
Isatin			521.9	352.74	410.95
17	Intermediate		309.59	176.85	206.95
17a	H	H	25.47	30.65	33.62
17b	F	H	11.99	13.48	15.57
17c	Cl	H	12.84	15.84	16.68
17d	Br	H	10.64	12.68	16.06
17e	CH ₃	H	22.59	27.25	29.38
17f	NO ₂	H	18.60	22.51	24.48
17g	COOH	H	17.25	20.85	22.95
17h	H	Cl	18.69	22.51	24.92
17i	H	NO ₂	16.20	19.35	20.38
17j	H	CH ₃	15.12	18.32	20.95
17k	H	COOH	20.36	24.28	25.98
17l	H	COOCH ₃	19.32	23.85	25.18
Cisplatin			14.08	13.64	13.54

Values are expressed as means (n = 4)

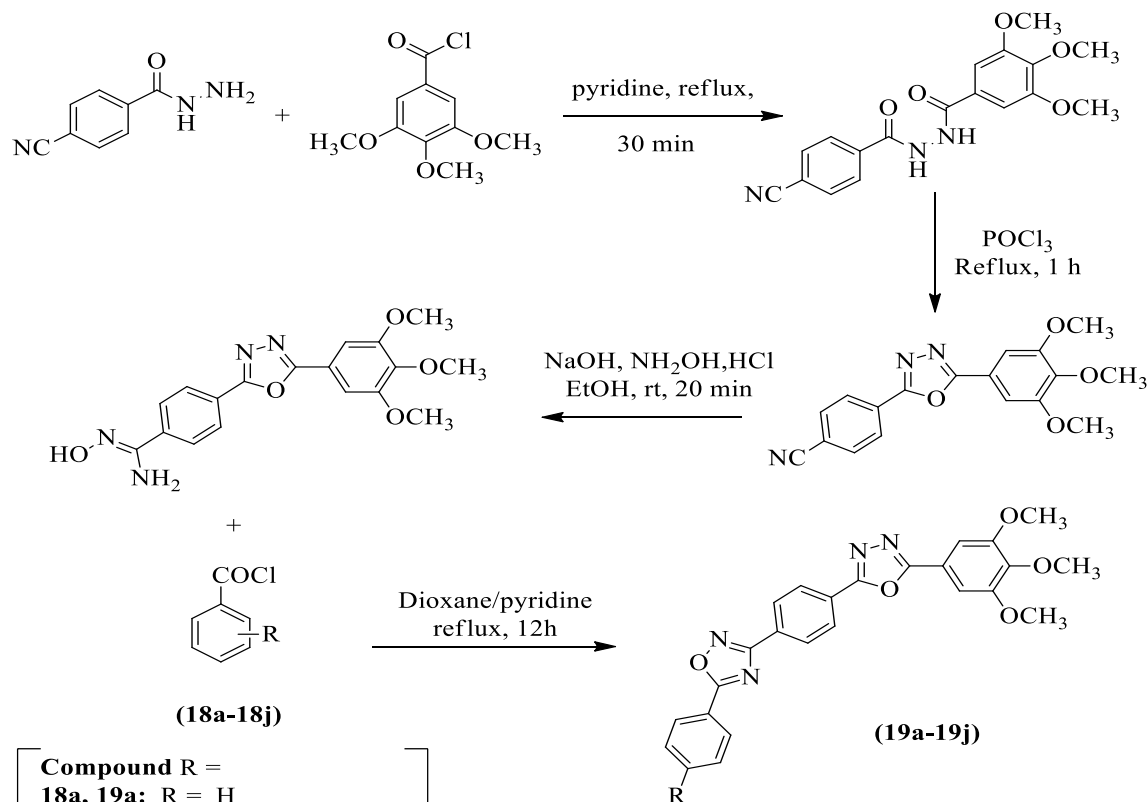
**Scheme 12** Synthesis of substituted 1,3,4-oxadiazole linked 1,2,4-oxadiazole

Table 12 In vitro cytotoxic activity [IC_{50} (μM)^a] of compounds (19a-j) [54]

Compound	Lung cancer A549 ^c	Breast cancer	
		MCF-7 ^b	MDA MB-231 ^d
19a	9.78 ± 0.27	34.55 ± 2.34	–
19b	0.45 ± 0.03	1.76 ± 0.34	2.11 ± 0.21
19c	3.67 ± 0.18	2.89 ± 0.67	12.76 ± 0.81
19d	4.56 ± 0.19	2.33 ± 0.56	7.34 ± 0.26
19e	13.78 ± 1.78	12.4 ± 0.79	19.5 ± 2.11
19f	34.9 ± 2.30	15.3 ± 1.72	–
19g	1.03 ± 0.17	1.23 ± 0.30	1.89 ± 0.35
19h	2.45 ± 0.23	0.34 ± 0.025	1.11 ± 0.18
19i	1.89 ± 0.38	1.90 ± 0.41	3.78 ± 0.29
19j	87.5 ± 4.67	6.30 ± 0.35	22.5 ± 1.28
Doxorubicin	2.10 ± 0.14	3.12 ± 0.17	3.41 ± 0.23

(–) not active, ^aEach data represents as mean ± S.D values. From three different experiments performed in triplicates. MCF-7: Human breast cancer cell line.

^cA549: Human lung cancer cell line. MDA MB-231^d: Human breast cancer cell line

synthesized derivatives were showed in (Table 12, Polothi et al. [54]).

Antitubercular activity

Pattan et al. [55] developed 2-(5-(substituted thio)-1,3,4-oxadiazol-2-yl) phenol and 4-(substituted-1-ylmethyl)-1-(2-hydroxy benzoyl)-3-methyl-1H-pyrazol-5(4H)-one by using Scheme 13. The antimycobacterial activity of the synthesized derivatives was evaluated against *Mycobacterium tuberculosis* ($H_{37}Rv$) by MB 7H9 agar medium. Streptomycin was used as a reference standard. Compounds 20a, 21b, 22a, 22b, 22c, and 22e showed promising antitubercular activity. Compounds 20b, 20c, and 22d showed moderate activity and the results of activity were presented in (Table 13, Pattan et al. [55]).

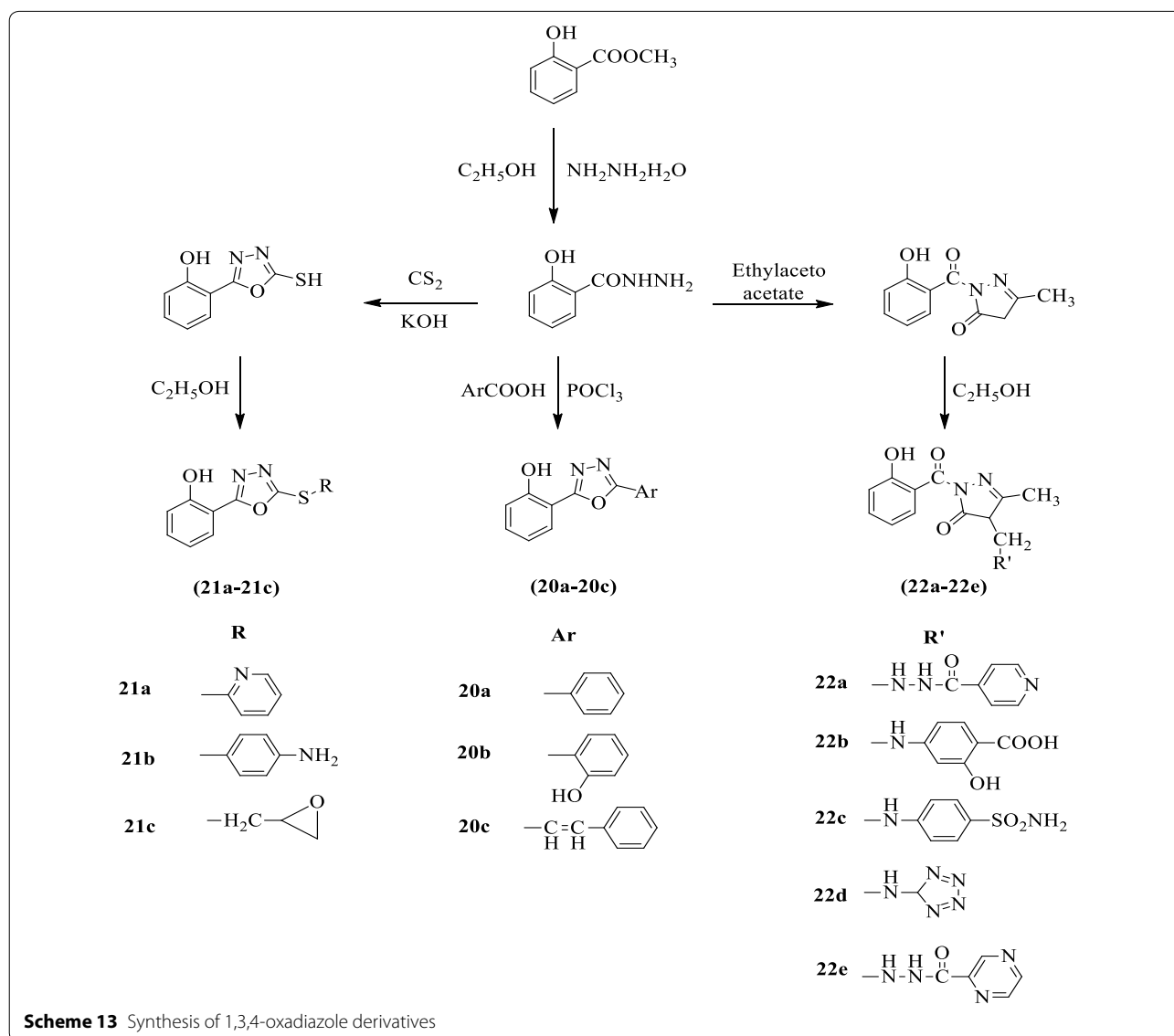


Table 13 Antitubercular activity data of the synthesized compounds [55]

Compound	Antitubercular activity	
	50 µg/mL	100 µg/mL
20a	S	S
20b	R	R
20c	R	R
21a	R	R
21b	S	S
21c	R	R
22a	S	S
22b	S	S
22c	S	S
22d	R	R
22e	S	S
Streptomycin	S	S

R Resistant; S Sensitive

Martinez et al. [44] developed *N*-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl) substituted amide by using Scheme 14. The antimycobacterial activity of synthesized derivatives was evaluated against different *Mycobacterium tuberculosis* strains such as 209, H37Ra, and H₃₇Rv using rifampin as a reference standard. Compound **23a** shows more potent activity in comparison to the rest of other compounds. The results of the antitubercular activity of the synthesized derivatives were presented in (Table 14, Martinez et al. [44]).

Das et al. [56] synthesized 6-(pyrazin-2-yl)-[1,3,4]oxadiazolo[3,2-*d*]tetrazole and 6-(pyrazin-2-yl)-[1,2,4]triazolo[3,4-*b*][1,3,4]oxadiazole (Scheme 15) and antimycobacterial activity of these derivatives were evaluated by (L) agar method against *Mycobacterium tuberculosis* H₃₇Rv (MTCC200) using isoniazid and rifampicin as a reference standard. The compound **25** shows more potent antitubercular activity but still, it is lesser active

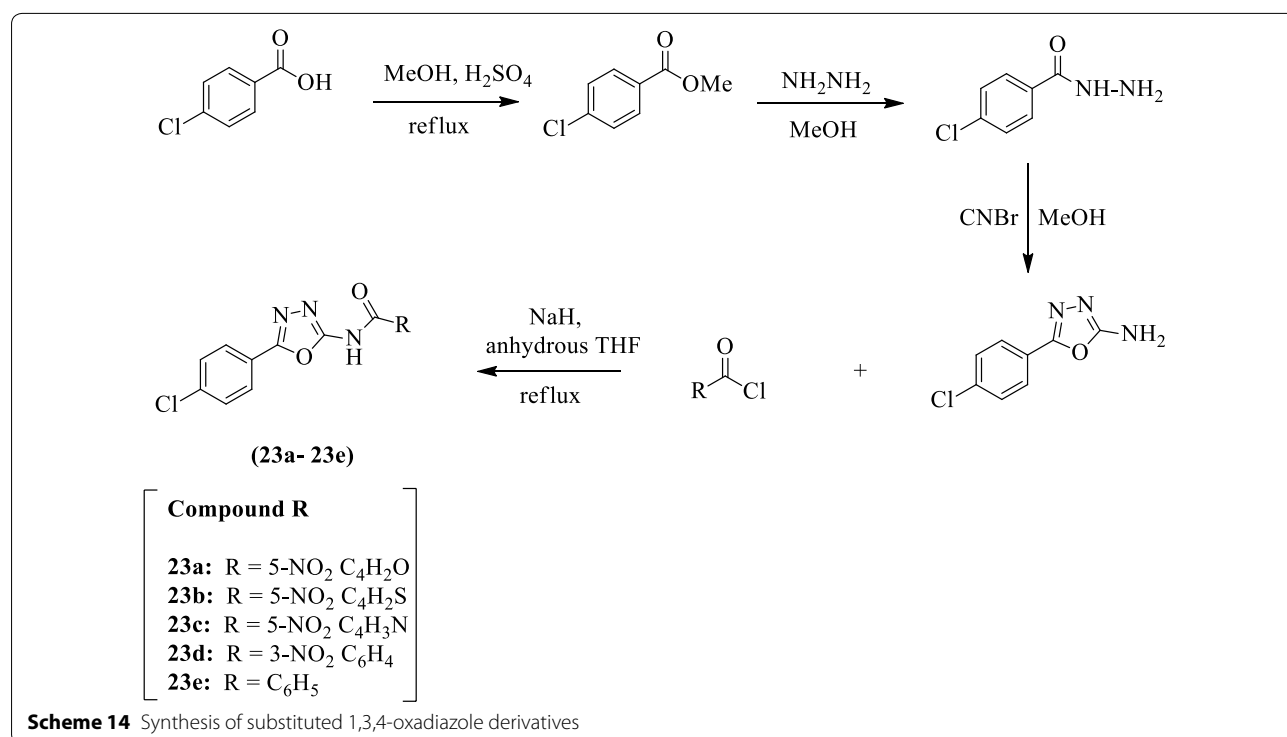
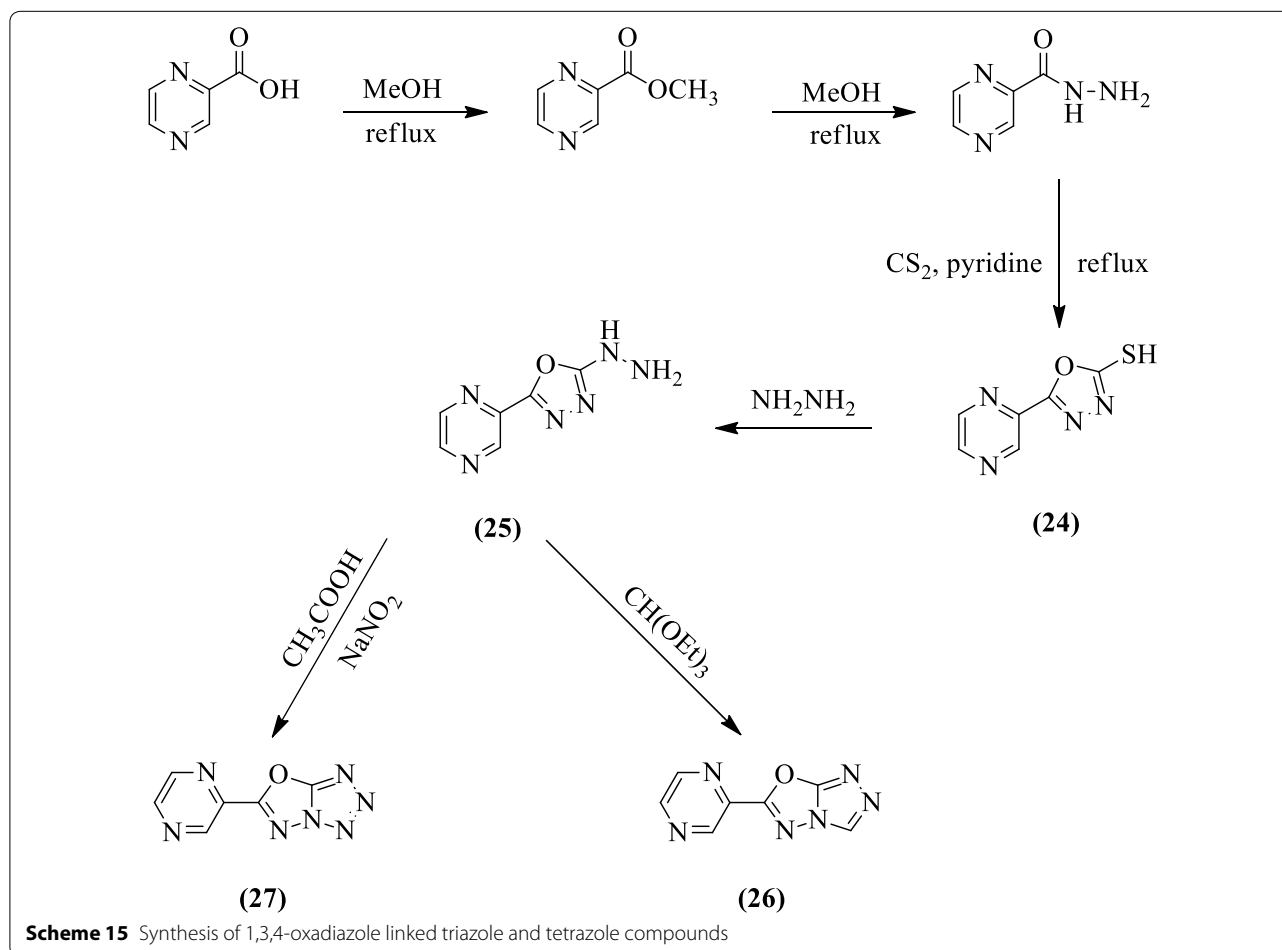


Table 14 MIC₁₀₀ values of 23a-e against virulent, non-virulent and RIF-resistant *M. tuberculosis* bacteria [44]

Compound	R	MIC ₁₀₀ (µg/ml) in H ₃₇ Rv ATCC 27294	MIC ₁₀₀ (µg/ml) in H ₃₇ Ra	MIC ₁₀₀ (µg/ml) in Mtb-209 (resistant)
23a	5-NO ₂ C ₄ H ₂ O	7.80	1–2.00	7.8
23b	5-NO ₂ C ₄ H ₂ S	15.60	15.60	15.60
23c	5-NO ₂ C ₄ H ₃ O	31.25	7.8	7.8
23d	5-NO ₂ C ₆ H ₄	15.60	31.30	15.60
23e	5-C ₆ H ₅	15.60	62.50	31.25
Rifampin	-	0.06	0.008	> 64

M. tuberculosis H₃₇Rv ATCC 27294 reference strain; Mtb. *M. tuberculosis* H₃₇Ra non-virulent strain; Mtb-209 RIF-resistant clinical isolate of *M. tuberculosis*

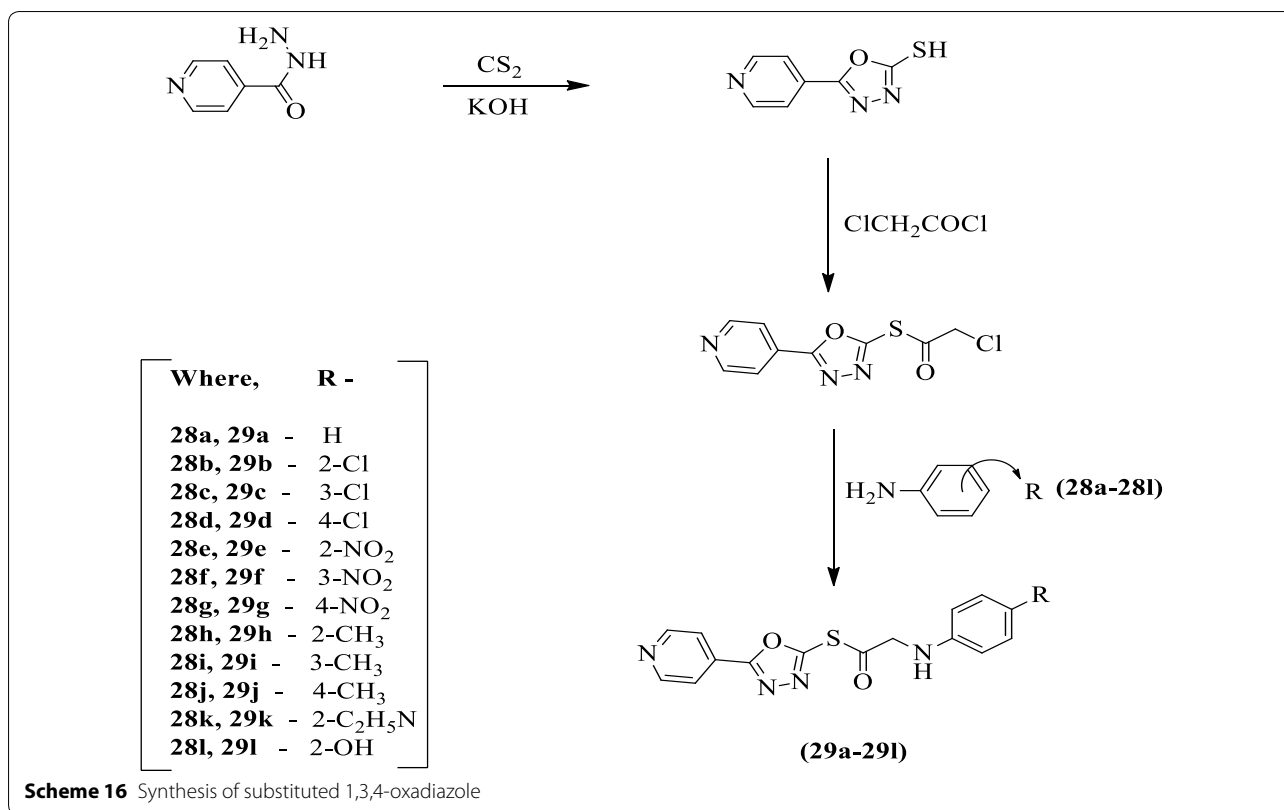
**Table 15** Anti Tuberculosis activity against *Mycobacterium tuberculosis* H₃₇Rv (MTCC200) [56]

Compound	MIC (µg/ml)
24	> 100
25	6.25
26	50
27	50
Rifampicin	0.25
Isoniazid	0.20

MIC Minimum inhibitory concentration

than the reference standard. The results of antimycobacterial activity were showed in (Table 15, Das et al. [56]).

Raval et al. [57] developed *S*-(5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)-2-((substituted phenyl)amino)ethanethioate using Scheme 16. The antitubercular activity of synthesized derivatives was evaluated against *Mycobacterium tuberculosis* H₃₇Rv (ATCC27294). Rifampin was used as a reference standard. Compounds **29e**, **29g**, and **29k** show better activity and exhibited >90% inhibition. The conclusion of antimycobacterial activity was presented in (Table 16, Raval et al. [57]).

**Table 16** Antitubercular activity of the synthesized compounds (29a-l) against *M. tuberculosis* H₃₇Rv [57]

Compound	Primary screen (6.25 µg/ml)	% inhibition	Concentration (µM)	Actual MIC (µg/ml)	Clog P
29a	>6.25	64	0.0354	–	0.4996
29b	>6.25	12	0.1640	–	1.5150
29c	>6.25	32	0.1706	–	1.5150
29d	>6.25	28	0.1735	–	1.5150
29e	>6.25	92	0.0077	6.05	0.8964
29f	>6.25	86	0.00132	5.92	0.8964
29g	>6.25	96	0.0052	6.00	0.8964
29h	>6.25	63	0.1130	–	0.9986
29i	6.25	62	0.1138	–	0.9986
29j	>6.25	64	0.1133	–	0.9986
29k	>6.25	96	0.0089	5.77	– 0.8943
29l	6.25	69	0.1184	–	– 9.1673
Isoniazid	>6.25	98	0.025	0.05	– 0.6680

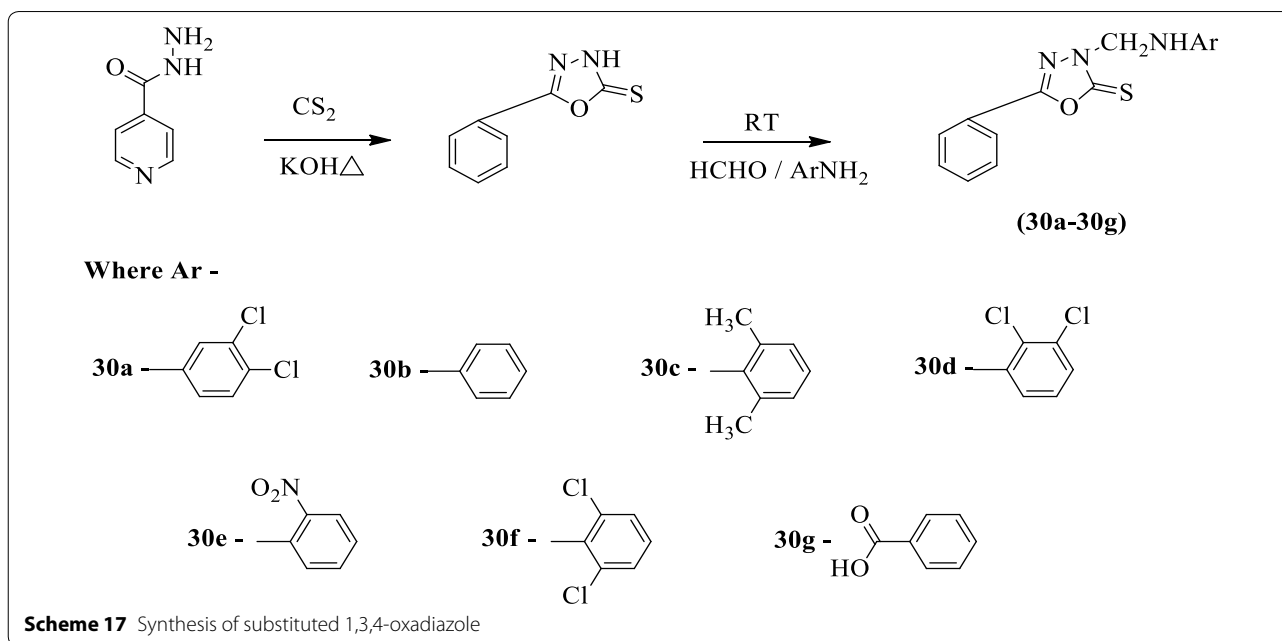
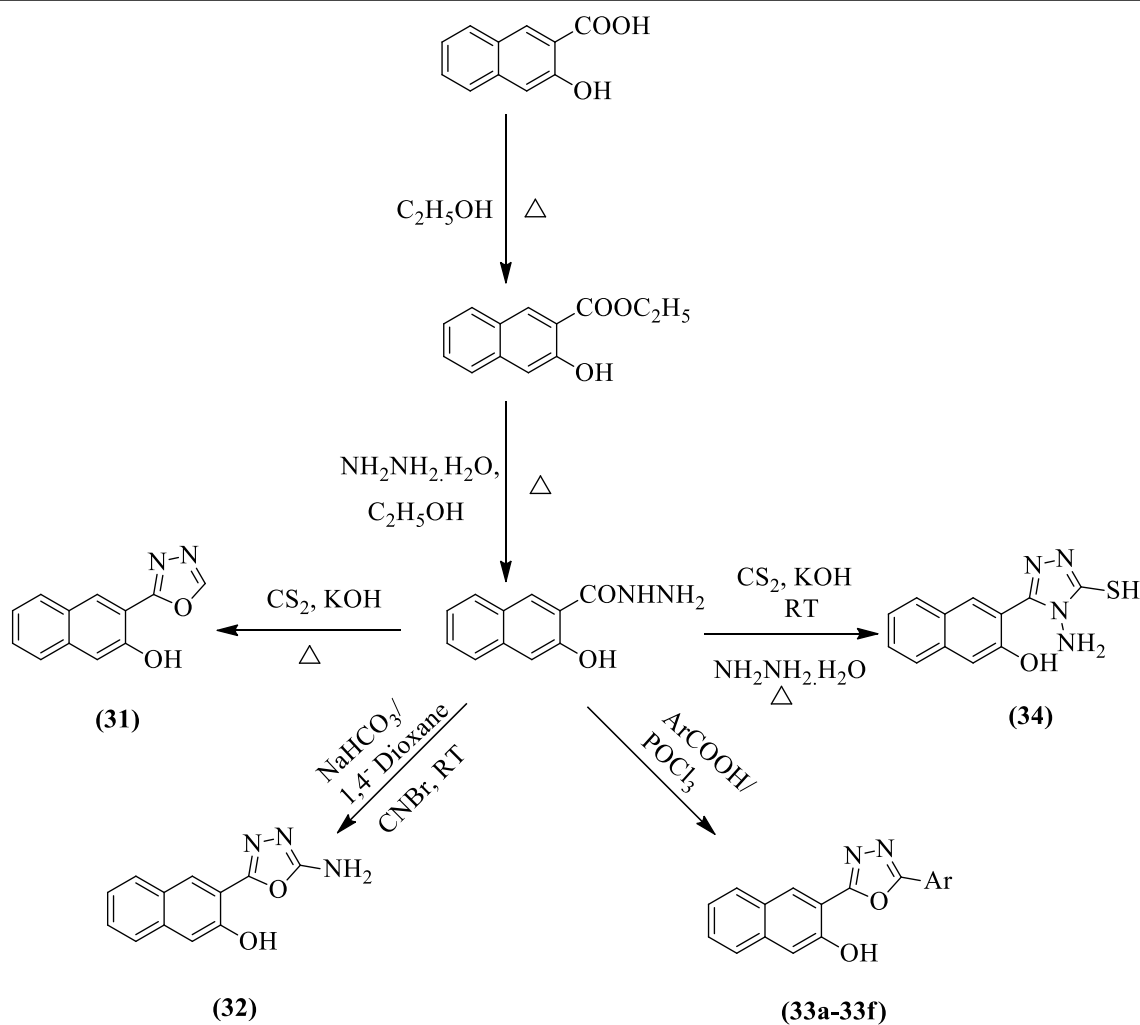


Table 17 Antitubercular activity of the synthesized compounds (30a-3g) against *M. tuberculosis* H₃₇Rv [58]

Compound	Antitubercular activity		
	25 (µg/ml)	50 (µg/ml)	100 (µg/ml)
30a	R	R	S
30b	R	S	S
30c	S	S	S
30d	S	S	S
30e	S	S	S
30f	R	R	S
30g	R	R	S
Rifampicin	S	S	S

Somani et al. [58] developed 3-((substituted amino) methyl)-5-phenyl-1,3,4-oxadiazole-2(3H)-thione by using Scheme 17. The antimycobacterial activity of synthesized derivatives was evaluated against *Mycobacterium tuberculosis* H₃₇Rv strain in MB 7H-9 agar medium using rifampicin as a reference standard. The conclusion of the antimycobacterial activity of synthesized derivatives was presented in (Table 17, Somani et al. [58]).

Gavarkar et al. [59] developed 3-(5-substituted-1,3,4-oxadiazol-2-yl) naphthalen-2-ol using Scheme 18. These derivatives were evaluated for antimycobacterial activity by tube dilution method against *Mycobacterium tuberculosis* H₃₇Rv strain using MB 7H-9 agar broth.



Compound Ar-

- 33a - Phenyl
- 33b - 4-aminophenyl
- 33c - 2-hydroxyphenyl
- 33d - 4-pyridyl
- 33e - 4-nitrophenyl
- 33f - 4-methylphenyl

Scheme 18 - Synthesis of substituted 1, 3, 4-oxadiazole

Scheme 18 Synthesis of substituted 1,3,4-oxadiazole

Table 18 Antitubercular activity of the titled compounds against *M. tuberculosis* H₃₇Rv [59]

Compound	Antitubercular activity		
	5 (µg/mL)	10 (µg/mL)	25 (µg/mL)
31	R	S	S
32	R	R	R
33a	R	R	R
33b	R	R	R
33c	R	S	S
33d	S	S	S
33e	R	R	R
33f	R	R	R
34	R	S	R
Streptomycin	R	S	S
Pyrazinamide	R	S	S

Streptomycin and Pyrazinamide were used as a reference standard. Compounds **31**, **33c**, and **33d** exhibited good antitubercular activity as compare to reference standards and the results were summarized in (Table 18, Gavarkar et al. [59]).

Antiviral activity

Somani et al. [47] developed *N*-substituted-2-((5-(pyridin-4-yl)-1,3,4-oxadiazol-2-yl)thio)acetohydrazide (Scheme 19) and evaluated for antiviral activity against a different type of strains such as HIV-2 ROD and HIV-1 IIIB using MTT assay in MT-4 cells. Nevirapine was used as a reference standard. These derivatives were also evaluated for cytotoxic activity using MTT assay in

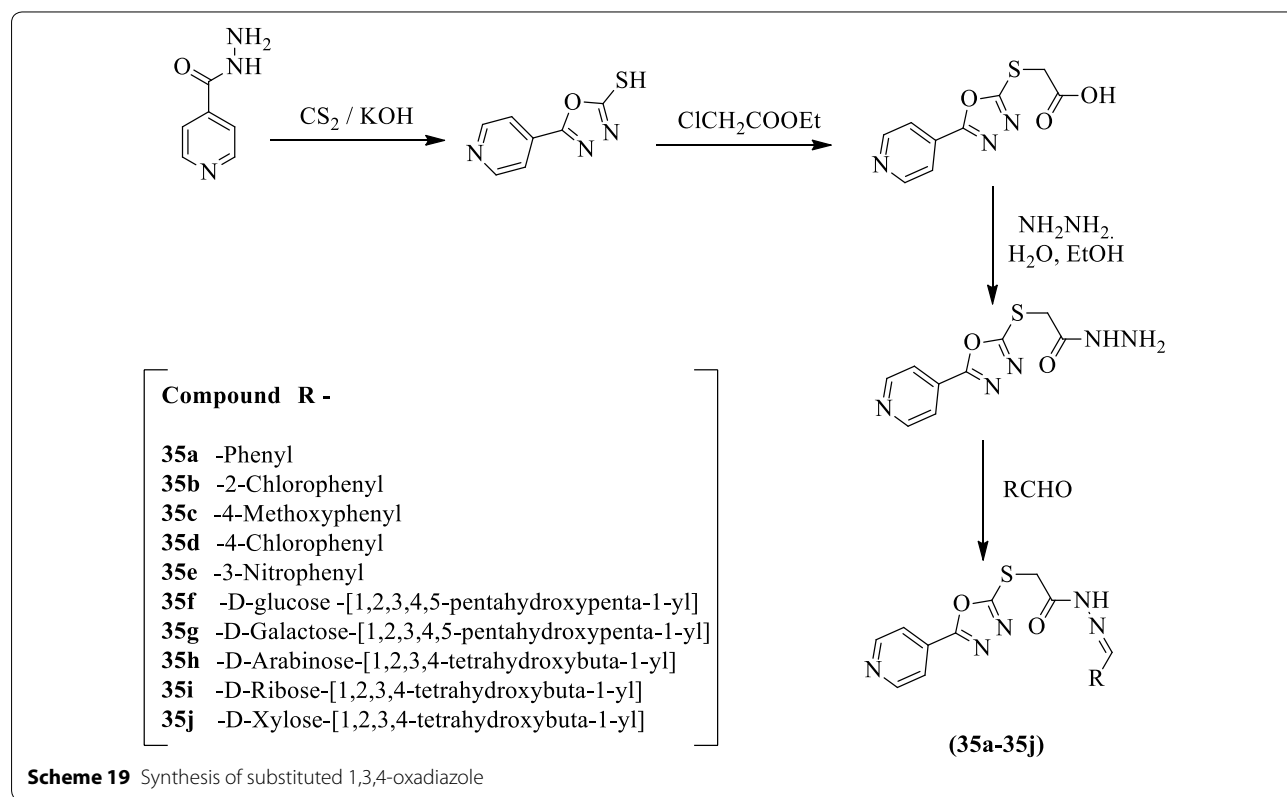


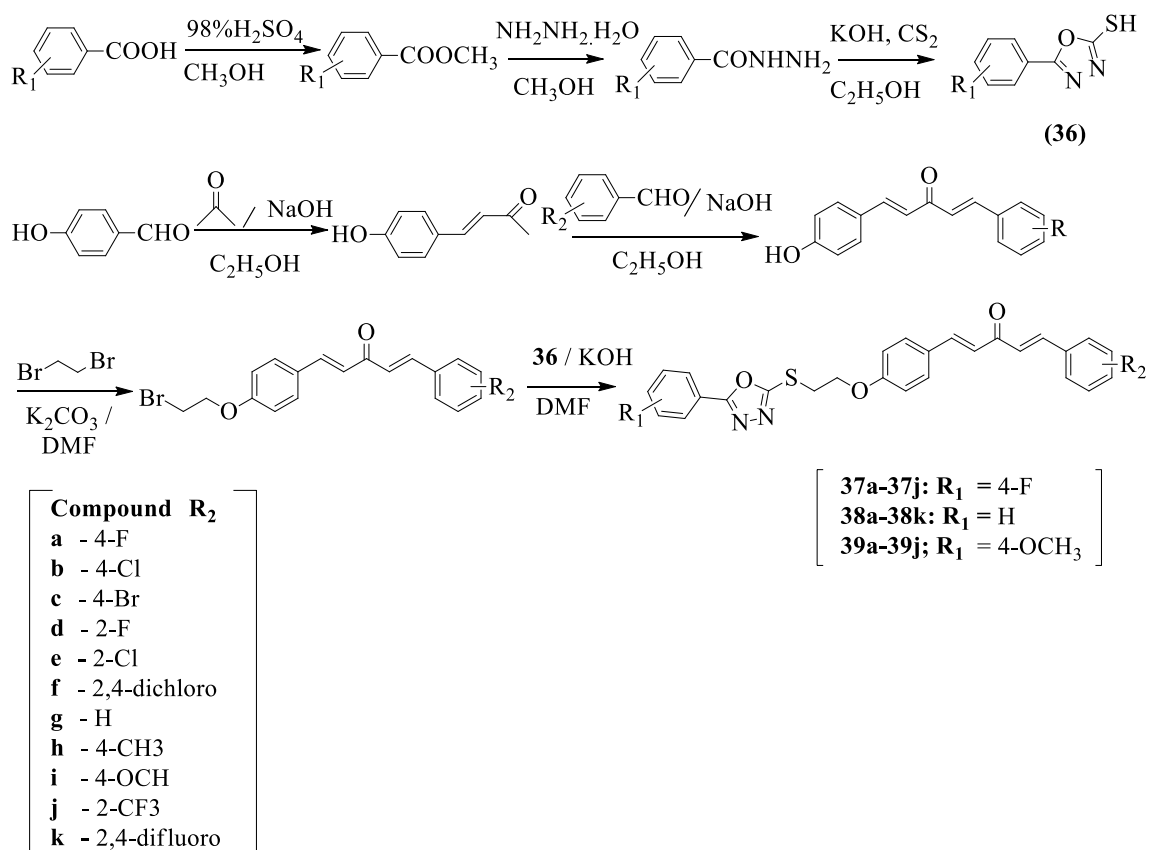
Table 19 (a) Anti HIV activity of synthesized compounds. (b) Cytotoxicity and antiviral activity of titled compounds in Vero cell cultures. (c) Cytotoxicity and antiviral activity of titled compounds in HEL cell cultures [47]

Panel (a)						
Compound	HIV I ($\mu\text{g/ml}$)		SI	HIV II ($\mu\text{g/ml}$)		SI
	IC50	CC50		IC50	CC50	
35a	> 50	= 50	< 1	> 57	= 57	< 1
35b	> 65	= 65	< 1	> 60	= 60	< 1
35c	> 125	> 125	X1	> 125	> 125	X1
35f	> 125	> 125	X1	> 38	> 125	> 3
35g	> 125	> 125	X1	> 125	> 125	X1
35h	> 125	> 125	X1	> 125	> 125	X1
35i	> 125	> 125	X1	> 125	> 125	X1
35j	> 125	> 125	X1	> 125	> 125	X1
Nevirapine(μM)	> 0.25	> 200	> 800	-	-	-
DDI (μM)	> 5.37	> 529	> 98	2.71	> 529	> 195
Panel (b)						
Compound	Minimum cytotoxic concentration ^a ($\mu\text{g/ml}$)		EC ₅₀ ^b ($\mu\text{g/mL}$)			
	Para-influenza-3 virus	Retrovirus	Sindbis virus	Coxsackie B4 virus	Punta Toro virus	
35a	20	> 20	> 20	> 20	> 20	
35b	100	> 20	> 20	> 20	> 20	
35c	100	> 20	> 20	> 20	> 20	
35f	> 100	> 100	> 100	> 100	> 100	
35g	> 100	> 100	> 100	> 100	> 100	
35h	> 100	> 100	> 100	> 100	> 100	
35i	> 100	> 100	> 100	> 100	> 100	
35j	> 100	> 100	> 100	> 100	> 100	
Ribavirin (μM)	> 250	146	250	> 250	146	
Panel (c)						
Compound	Minimum cytotoxic concentration ^a ($\mu\text{g/mL}$)		EC ₅₀ ^b ($\mu\text{g/mL}$)			
	Herpes simplex virus-1	Herpes simplex virus-2	Vaccinia virus	Coxsackie B4 virus	Vesicular stomatitis virus	
35a	> 100	100	45	> 20	> 100	
35b	100	> 20	> 20	> 20	> 20	
35c	> 100	> 100	> 100	> 100	> 100	

Table 19 (continued)

Panel (c)	Compound	Minimum cytotoxic concentration ^a (µg/mL)	EC ₅₀ ^b (µg/mL)	Herpes simplex virus-1	Herpes simplex virus-2	Vaccinia virus	Vesicular stomatitis virus
	35f	> 100	> 100	> 100	> 100	> 100	> 100
	35g	> 100	> 100	> 100	> 100	> 100	> 100
	35h	> 100	> 100	> 100	> 100	> 100	> 100
	35i	> 100	> 100	> 100	> 100	> 100	> 100
	35j	> 100	> 100	> 100	> 100	> 100	> 100
	Brivudin (µM)	> 250	0.04	50	2	2	250
	Cidofovir (µM)	> 250	1	1	2	2	> 250
	Ganciclovir (µM)	> 100	0.02	0.07	> 100	> 100	> 100

^a Concentration required to cause a microscopically detectable alteration of normal cell morphology, ^b Concentration required to reduce virus-induced cytopathogenicity by 50%



Scheme 20 Synthesis of substituted 1,3,4-oxadiazole with benzoic acid as starting material

uninfected MT-4 cells. The results of synthesized derivatives were expressed as CC_{50} , IC_{50} , and SI values which were summarized in Table 19a. The results of the antiviral activity of synthesized derivatives against other viruses in (HEL) and (Vero) culture were reported in (Table 19b, c, Somani et al. [47]).

Gan et al. [25] developed (1*E*, 4*E*)-1-(substituted)-5-(4-(2-((5-substituted)-1,3,4-oxadiazol-2-yl)thio)ethoxy)phenyl)Penta-1,4-dien-3-one by using Scheme 20. The antiviral activity of synthesized compounds was evaluated against (TMV) using ribavirin as a reference standard. Among the synthesized derivatives, compounds 37a, 37c, 37f, 38a, 38b, 38c, 38d, 38e, 38f, 38g, 38h, 38i, 39e, and 39f exhibited potent curative activities as

Table 20 Antiviral activity of the titled compounds [25]

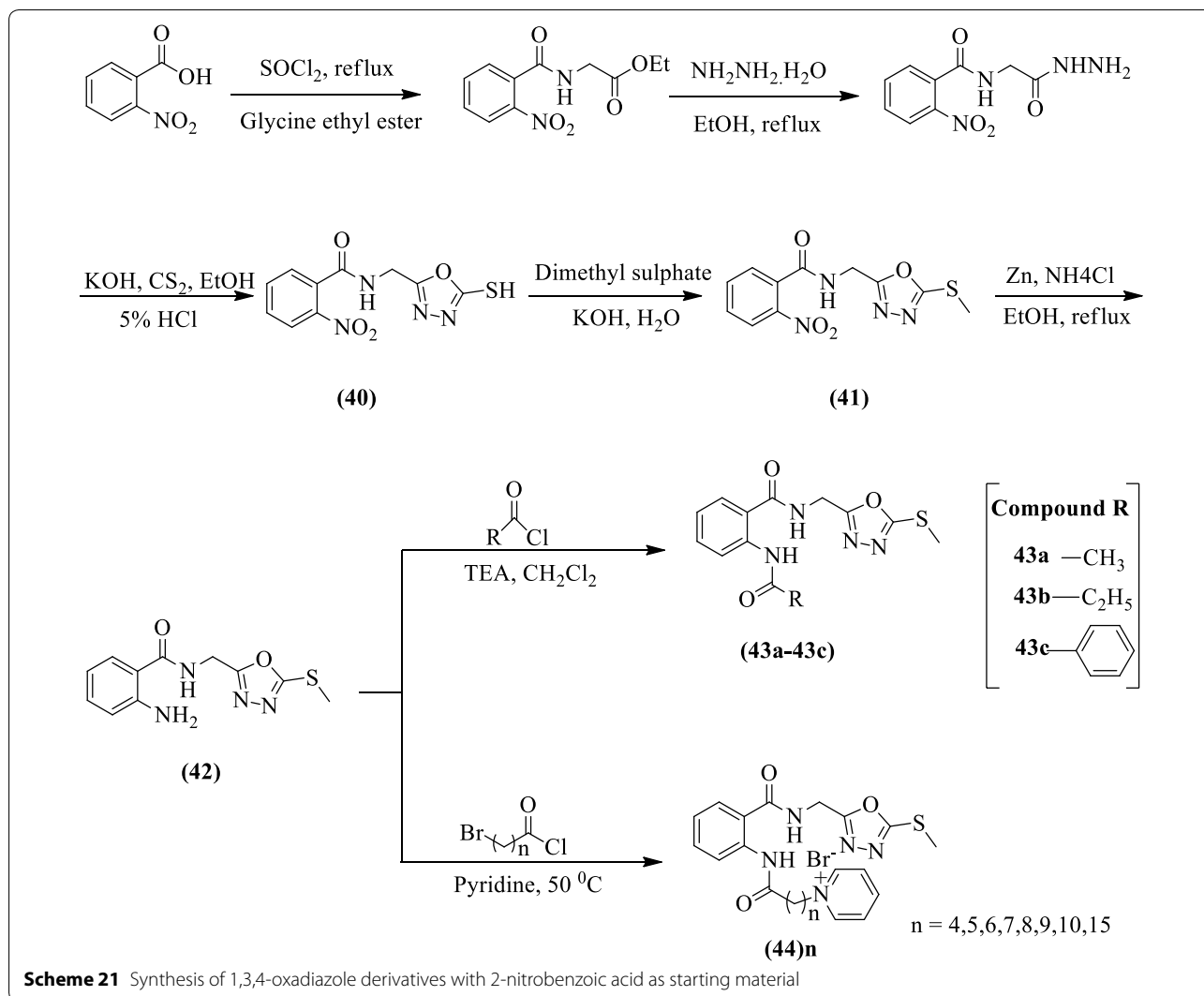
Compound	R ₁	R ₂	Curative activity(%)	Protective activity(%)	Inactivation activity(%)
37a	4-F	4-F	43.2±2.1	55.9±1.7	84.4±1.2
37b	4-F	4-Cl	25.9±1.8	52.5±1.5	88.4±0.8
37c	4-F	4-Br	45.6±1.9	67.9±3.9	74.8±1.3
37d	4-F	2-F	31.1±2.3	68.4±3.2	83.4±1.6
37e	4-F	2-Cl	23.7±3.1	56.8±2.6	56.2±1.9
37f	4-F	2,4-Di-Cl	52.9±4.5	65.1±3.2	83.5±2.7
37g	4-F	H	28.2±1.1	52.9±0.7	74.5±0.9
37h	4-F	4-CH ₃	19.2±0.9	60.5±1.1	61.3±0.8
37i	4-F	4-OCH ₃	27.5±2.1	50.0±1.5	61.4±1.0
37j	4-F	2-CF ₃	28.3±2.3	47.5±2.4	60.2±1.7
38a	H	4-F	45.8±1.8	61.5±2.9	69.1±1.2
38b	H	4-Cl	44.1±2.5	55.7±1.6	59.4±2.5
38c	H	4-Br	47.2±3.6	53.8±3.9	83.1±2.4
38d	H	2-F	38.1±2.6	66.3±1.9	70.1±2.0
38e	H	2-Cl	41.1±4.2	61.5±3.1	75.6±2.1
38f	H	2,4-Di-Cl	49.8±3.9	69.2±2.1	90.4±2.8
38g	H	H	20.9±2.1	66.7±2.8	78.0±2.5
38h	H	4-CH ₃	48.1±3.6	57.5±2.7	72.7±3.3
38i	H	4-OCH ₃	40.6±3.2	58.4±3.8	79.3±4.1
38j	H	2-CF ₃	35.5±1.7	50.5±1.9	56.8±2.1
39a	4-OCH ₃	4-F	20.8±1.2	44.0±0.9	83.0±1.1
39b	4-OCH ₃	4-Cl	18.4±0.9	34.4±1.1	87.1±1.8
39c	4-OCH ₃	4-Br	34.8±2.1	41.1±3.6	82.3±5.1
39d	4-OCH ₃	2-F	25.4±1.7	35.8±1.4	81.3±2.1
39e	4-OCH ₃	2-Cl	43.5±2.2	46.1±2.6	77.7±2.0
39f	4-OCH ₃	2,4-Di-Cl	43.9±2.4	49.6±1.8	85.6±1.9
39g	4-OCH ₃	H	37.8±1.6	42.5±2.0	78.8±2.1
39h	4-OCH ₃	4-CH ₃	26.5±1.2	42.1±2.1	86.3±5.4
39i	4-OCH ₃	4-OCH ₃	35.1±1.5	41.5±1.8	81.5±2.6
39j	4-OCH ₃	2-CF ₃	30.5±2.1	49.3±2.3	77.9±4.5
38k	H	2,4-Di-F	55.4±2.8	71.3±1.9	85.2±4.0
Ribavirin			37.9±1.9	51.8±2.3	72.9±2.4

compared to a reference standard. Compounds **37a-37h** and **38a-38g** showed good protective activity against TMV as compared to the reference standard. Moreover, compounds **37a-37g**, **38c**, **38e**, **38f**, **38g**, **38i**, and **39a-39j** showed better activities as compared to the positive control. Among them, compound **38f** shows the best curative, inactivation, and protective activity as compare to the reference standard. The results of the antiviral activity of different derivatives were showed in (Table 20, Gan et al. [25]).

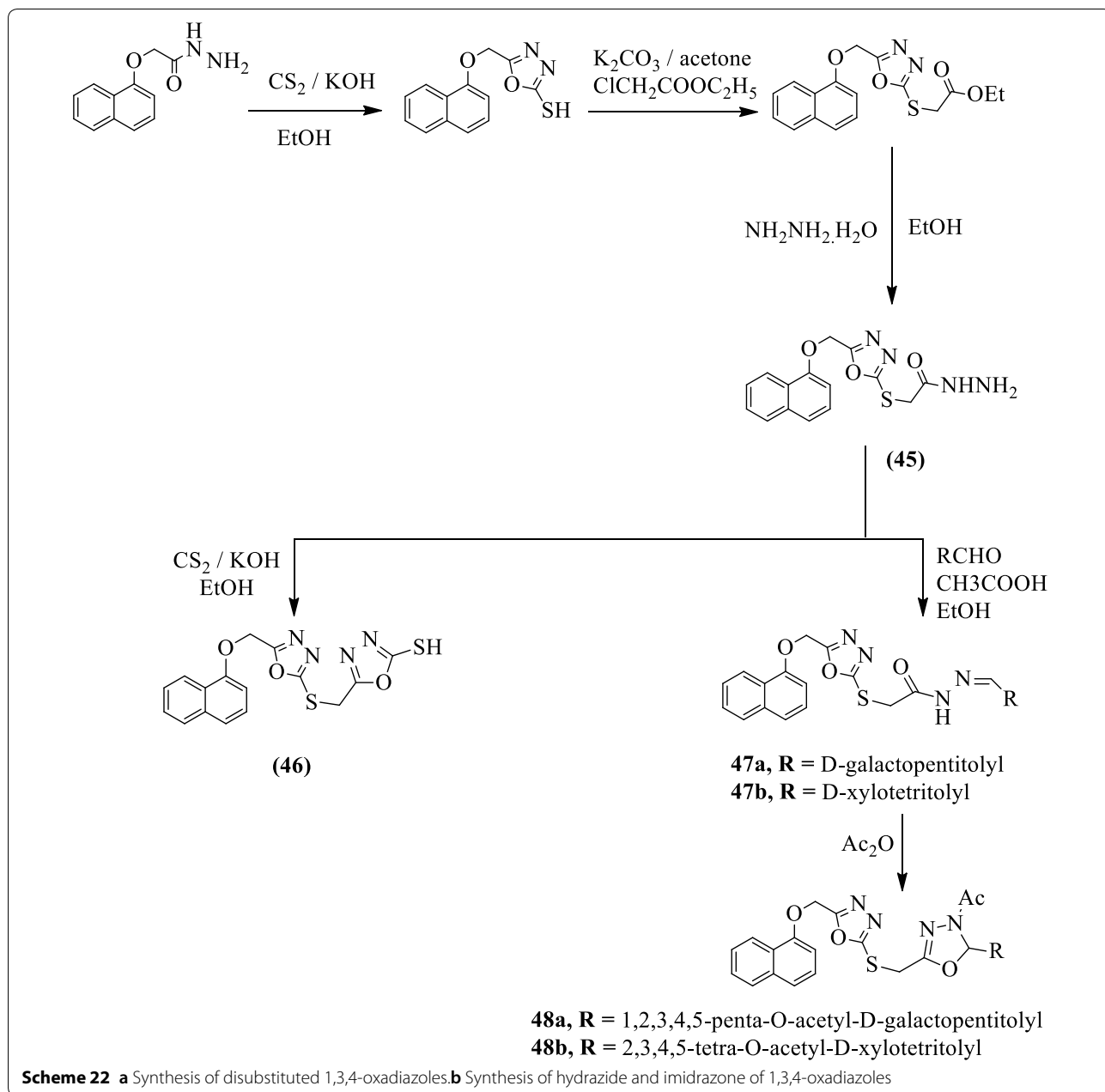
Wang et al. [1] developed *N*-((5-mercapto-1,3,4-oxadiazol-2-yl)methyl)-2-nitro benzamide, *N*-((5-(methylthio)-1,3,4-oxadiazol-2-yl)methyl)-2-nitro benzamide, 2-amino-*N*-((5-(methylthio)-1,3,4-oxadiazol-2-yl)methyl)benzamide and

2-(substituted)-*N*-((5-(methylthio)-1,3,4-oxadiazol-2-yl)methyl)benzamide (Scheme 21) and evaluated for antiviral activity. NNM was used as a reference standard. Among the synthesized derivatives, compounds **44₆**, **44₈**, and **44₁₅** showed a more potent activity than the reference standard. The position of the substituent's also affected the antiviral activity and the results of antiviral activity were represented in (Table 21, Wang et al. [1]).

EI-Sayed et al. [60] developed 1,2,3,4,5-Penta-*O*-acetyl-*D*-galactopentitolyl and 2,3,4,5-tetra-*O*-acetyl-*D*-xylofrititolyl, hydrazide, and imidrazone of 1,3,4-oxadiazole by using Scheme 22a, b respectively. The antiviral activity of synthesized derivatives was evaluated as reverse transcriptase inhibitors with fresh human peripheral blood mononuclear cells. Compound **47b** shows good antiviral

**Table 21** Anti-TMV activities of titled compounds at 500 µg/mL in vivo [1]

Compounds	Rate (%)		Compounds	Rate (%)	
	Curative activity	Protective activity		Curative activity	Protective activity
40	38.5 ± 1.2	35.2 ± 3.1	44 ₈	60.0 ± 5.6	36.4 ± 1.0
41	36.9 ± 5.1	14.4 ± 2.9	44 ₉	26.9 ± 2.9	43.3 ± 3.0
42	26.8 ± 5.2	54.5 ± 2.9	44 ₁₀	48.7 ± 5.1	25.2 ± 2.9
43a	22.3 ± 6.4	54.6 ± 5.2	44 ₁₅	51.9 ± 3.0	45.6 ± 4.2
43b	47.2 ± 2.8	38.8 ± 4.5	40'	41.8 ± 1.0	41.7 ± 1.7
43c	44.8 ± 9.5	36.8 ± 0.8	41'	17.5 ± 1.2	32.2 ± 1.6
44 ₄	7.1 ± 1.7	51.2 ± 7.6	42'	17.7 ± 1.2	42.6 ± 2.2
44 ₅	37.4 ± 3.5	27.8 ± 5.5	43 ₂ '	49.3 ± 2.0	19.6 ± 2.4
44 ₆	50.6 ± 4.7	42.9 ± 2.5	44 ₁₀ '	33.9 ± 1.3	20.2 ± 1.0
44 ₇	37.1 ± 3.3	23.5 ± 1.1	44 ₁₅ '	35.3 ± 2.3	19.3 ± 0.8
NNM	54.2 ± 2.9	65.7 ± 2.2			



activity followed by compounds **45** and **49a**. Compounds **48b** and **52** showed moderate activity while **47a** and **48a** showed the weakest activity among the series of tested compounds. The results of the antiviral activity of

synthesized derivatives were presented in (Table 22, El-Sayed et al. [60]).

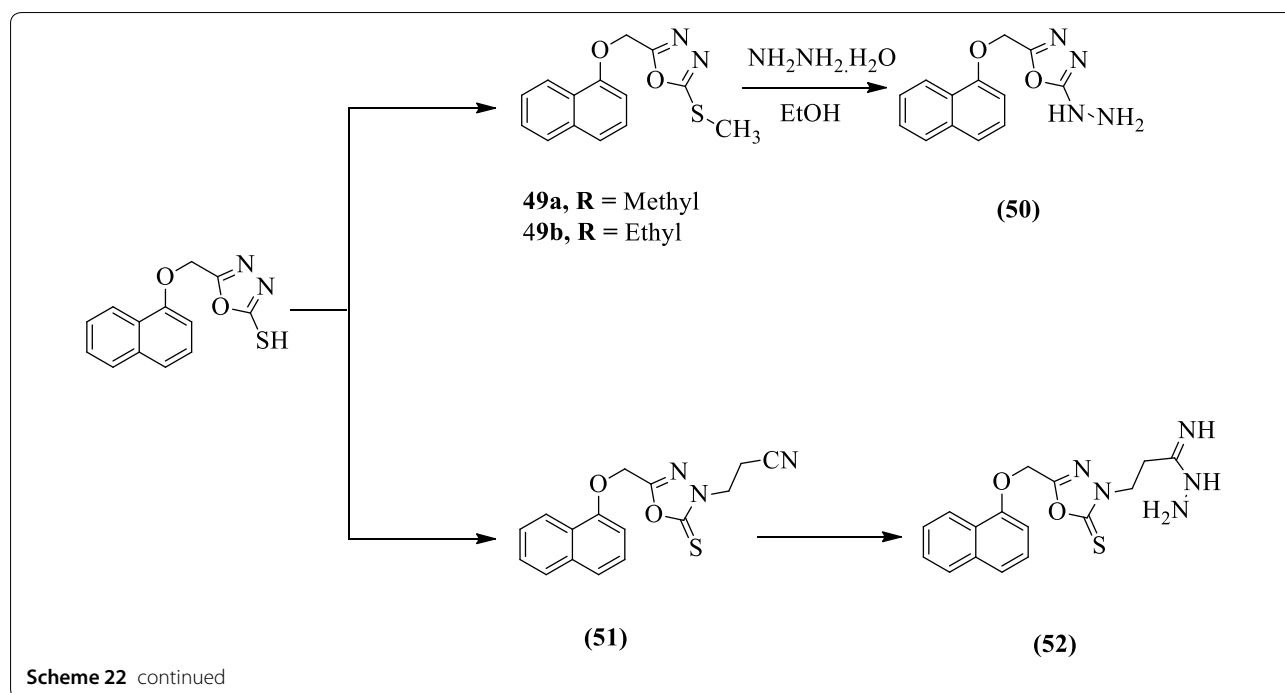
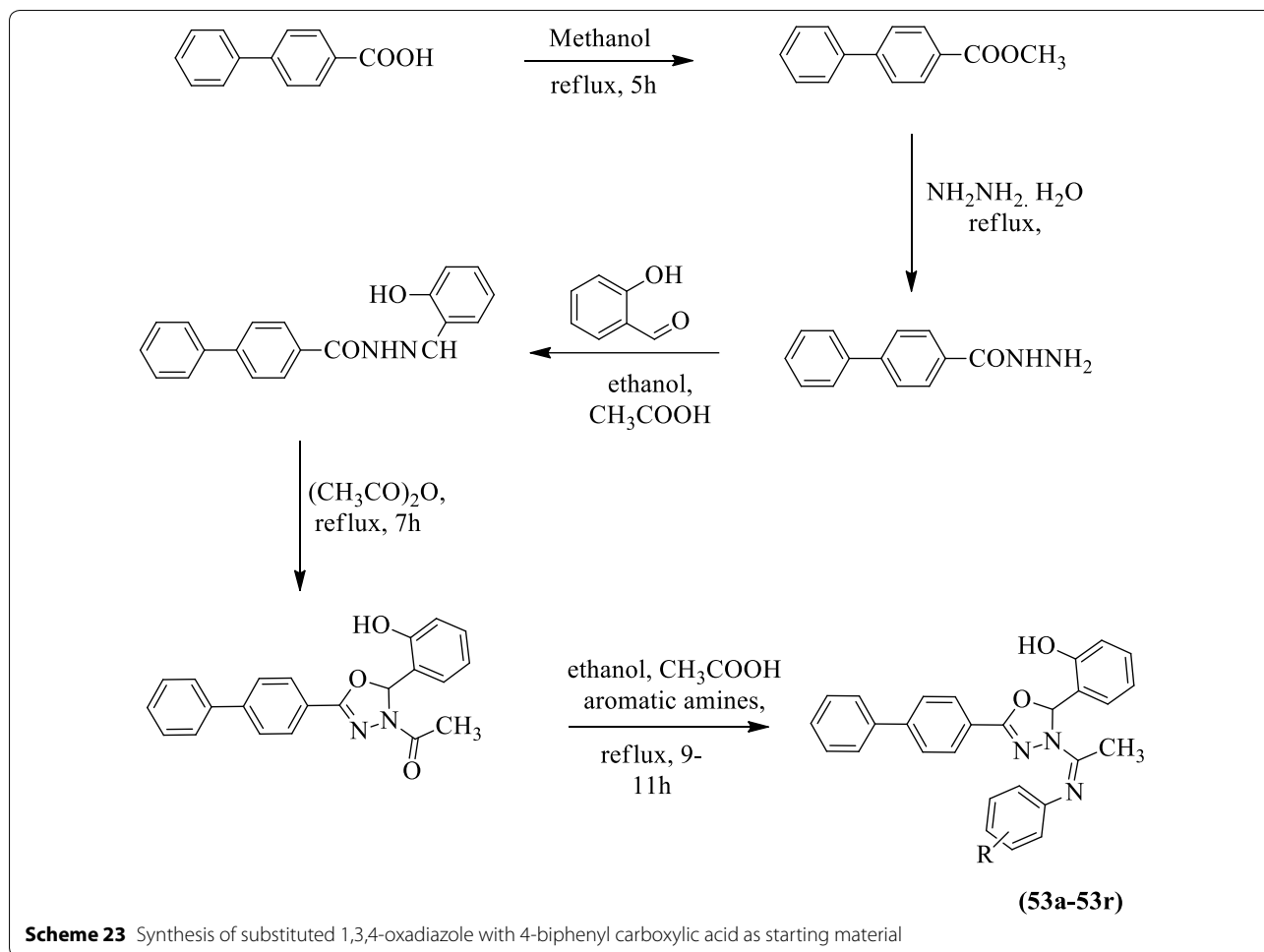


Table 22 HIV inhibition activities (reverse transcriptase inhibitor) with therapeutic index [60]

Compound	EC50 (μM)	IC50 (μM)	Therapeutic index
45	$3.24 \cdot 10^{-3}$	1.88	$2.88 \cdot 10^{-7}$
47a	$1.1 \cdot 10^{-5}$	12.89	$66.24 \cdot 10^{-8}$
47b	$5.26 \cdot 10^{-4}$	1.44	$3.15 \cdot 10^{-7}$
48a	$5.23 \cdot 10^{-4}$	12.44	$5.78 \cdot 10^{-6}$
48b	$1.56 \cdot 10^{-3}$	3.11	$3.45 \cdot 10^{-6}$
49a	$3.81 \cdot 10^{-3}$	2.12	$8.14 \cdot 10^{-6}$
52	$2.72 \cdot 10^{-3}$	2.9	$5.12 \cdot 10^{-6}$

Antioxidant activity

Malhotra et al. [46] developed (*Z*)-2-(5-[(1, 1-biphenyl)-4-yl]-3-(1-((substituted)imino) ethyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)phenol (Scheme 23) and evaluated for antioxidant activity in terms of hydrogen peroxide scavenging activity. The results of the antioxidant activity of the synthesized derivatives were presented in (Table 23, Malhotra et al. [46]).



Rahul R. et al. [8] synthesized 5-(4-(4-chlorophenyl)thiazol-2-yl)-3-(substituted benzyl)-1,3,4-oxadiazole-2(3H)-thione by using Scheme 24 and evaluated for antioxidant activity by different methods such as Hydrogen peroxide scavenging, Nitric oxide scavenging, and DPPH assay. In

DPPH assay compound **54c** shows more significant activity in comparison to ascorbic acid. In other methods such as hydrogen peroxide and nitric oxide scavenging assay, compound **54c** gives more potent activity than the rest of

Table 23 Hydrogen peroxide scavenging activity of synthesized compounds [46]

Compound	Scavenging of hydrogen peroxide at different concentration (%)		
	100 (µg/ml)	300 (µg/ml)	500 (µg/ml)
53a	41.55	39.84	41.22
53b	46.34	44.55	45.77
53c	51.11	48.12	44.59
53d	41.92	42.33	41.72
53e	45.65	46.19	45.91
53f	51.21	43.12	39.57
53g	39.58	42.61	43.18
53h	43.45	41.37	45.27
53i	41.88	45.19	48.11
53j	47.52	54.15	53.18
53k	45.35	50.27	52.15
53l	51.15	52.27	58.18
53m	45.87	41.37	41.93
53n	42.98	39.72	39.57
53o	41.03	43.06	44.14
53p	51.62	52.18	52.91
53q	54.18	53.76	57.36
53r	49.87	51.35	48.74
BHA	63.27	66.19	68.25
Ascorbic acid	51.47	53.45	55.38

the other compounds but was not significant as compared to the results obtained in the DPPH assay. This shows that compound **54c** gives more potent antioxidant activity as compared to the rest of the synthesized compounds. The results of the antioxidant activity of synthesized derivatives were presented in (Table 24, Rahul R. et al. [8]).

Dureja [61] developed 3-(4-acetyl-5-(substituted phenyl)-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-one (Scheme 25) and evaluated for antioxidant activity by using DPPH assay. Ascorbic acid was used as a reference standard and the results were summarized in (Table 25, Dureja [61]).

Conclusion

In this present review article, we have summarized different pharmacological activities of 1,3,4-oxadiazole containing compounds. From this study, we have found that 1,3,4-oxadiazole containing compounds can be

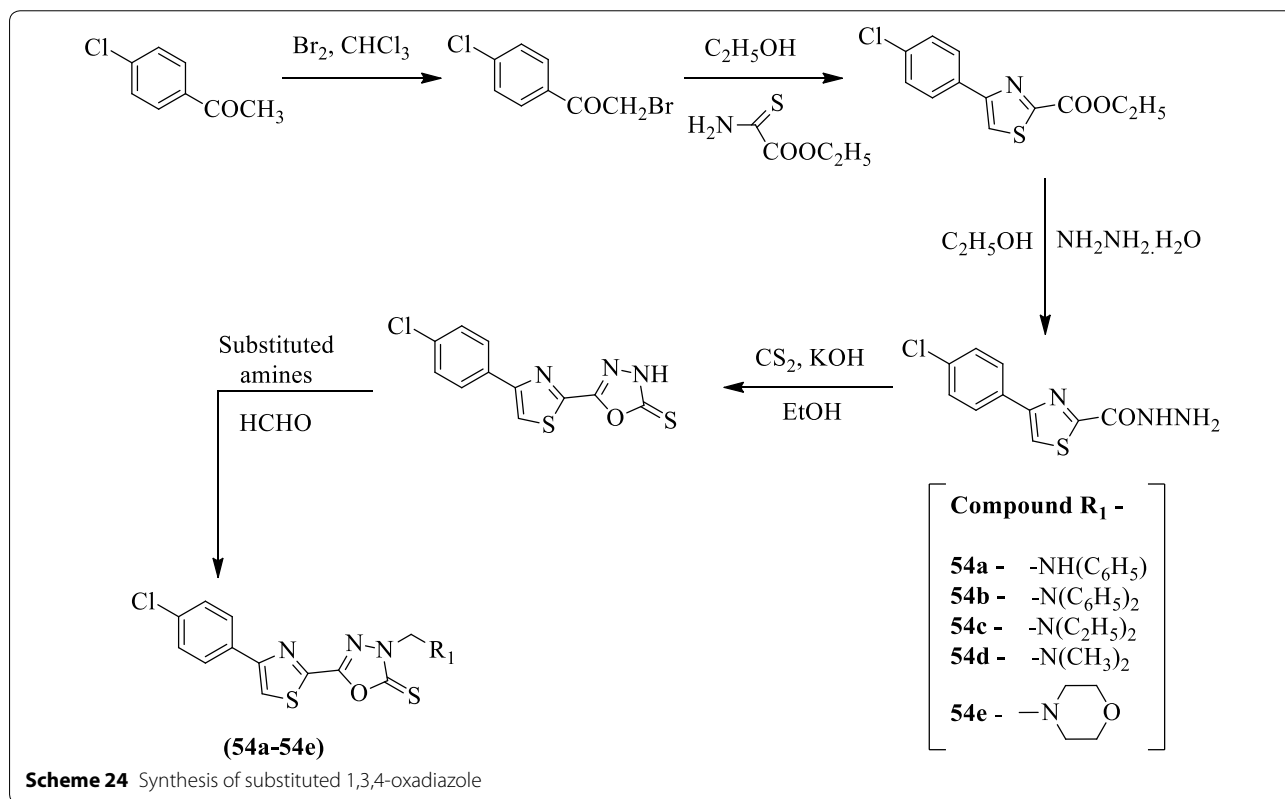


Table 24 (a) DPPH assay of synthesized compounds. (b) Nitric oxide scavenging of synthesized compounds. (c) Hydrogen peroxide scavenging of synthesized compounds

Compound	% Scavenging activity at different concentrations					IC ₅₀
	20 (µg/ml)	40 (µg/ml)	60 (µg/ml)	80 (µg/ml)	100 (µg/ml)	
Panel (a)						
54a	39.94 ± 0.521	59.14 ± 0.652	61.38 ± 0.631	63.59 ± 0.245	65.34 ± 0.534	29.7
54b	46.63 ± 0.342	49.7 ± 0.352	57.51 ± 0.421	60.51 ± 0.634	62.65 ± 0.453	43.3
54c	44.86 ± 0.245	62.22 ± 0.214	64.66 ± 0.341	65.82 ± 0.372	67.76 ± 0.215	26.7
54d	44.64 ± 0.234	53.89 ± 0.123	62.73 ± 0.223	64.02 ± 0.321	66.92 ± 0.431	27.1
54e	47.34 ± 0.235	48.16 ± 0.516	49.54 ± 0.461	52.98 ± 0.371	55.75 ± 0.297	61.3
Ascorbic acid	49.38 ± 0.515	67.03 ± 0.541	75.78 ± 0.223	91.92 ± 0.561	95.34 ± 0.111	21.3
Panel (b)						
54a	34.83 ± 0.527	40.63 ± 0.654	43.87 ± 0.691	52.15 ± 0.215	53.11 ± 0.514	72.1
54b	27.34 ± 0.372	29.81 ± 0.352	38.25 ± 0.421	42.55 ± 0.639	50.54 ± 0.450	98.3
54c	33.57 ± 0.243	44.97 ± 0.211	48.69 ± 0.348	52.35 ± 0.442	53.15 ± 0.218	66.2
54d	33.28 ± 0.232	44.40 ± 0.128	45.70 ± 0.224	52.01 ± 0.331	54.29 ± 0.481	69.8
54e	26.67 ± 0.295	29.30 ± 0.506	44.95 ± 0.411	51.98 ± 0.381	52.07 ± 0.297	70.6
Ascorbic acid	47.53 ± 0.624	63.44 ± 0.521	84.28 ± 0.623	90.53 ± 0.411	93.56 ± 0.221	25.2
Panel (c)						
54a	35.75 ± 0.612	44.97 ± 0.237	55.19 ± 0.226	65.93 ± 0.662	67.14 ± 0.653	47.1
54b	34.01 ± 0.563	43.51 ± 0.464	58.83 ± 0.152	60.48 ± 0.353	62.50 ± 0.452	49.1
54c	34.24 ± 0.263	46.06 ± 0.533	58.82 ± 0.623	62.12 ± 0.621	63.63 ± 0.236	43.3
54d	33.93 ± 0.235	46.81 ± 0.516	56.52 ± 0.532	59.89 ± 0.623	61.39 ± 0.425	45.6
54e	34.48 ± 0.342	44.88 ± 0.345	55.57 ± 0.173	56.61 ± 0.535	58.63 ± 0.654	50.6
Ascorbic acid	44.53 ± 0.526	64.65 ± 0.653	71.74 ± 0.36	89.22 ± 0.621	96.19 ± 0.456	26.9

IC₅₀ values in µg/ml for samples were determined using ED50 plus V 1.0 software. Data are the mean of three or more experiments and reported as mean ± standard error of the mean (SEM)

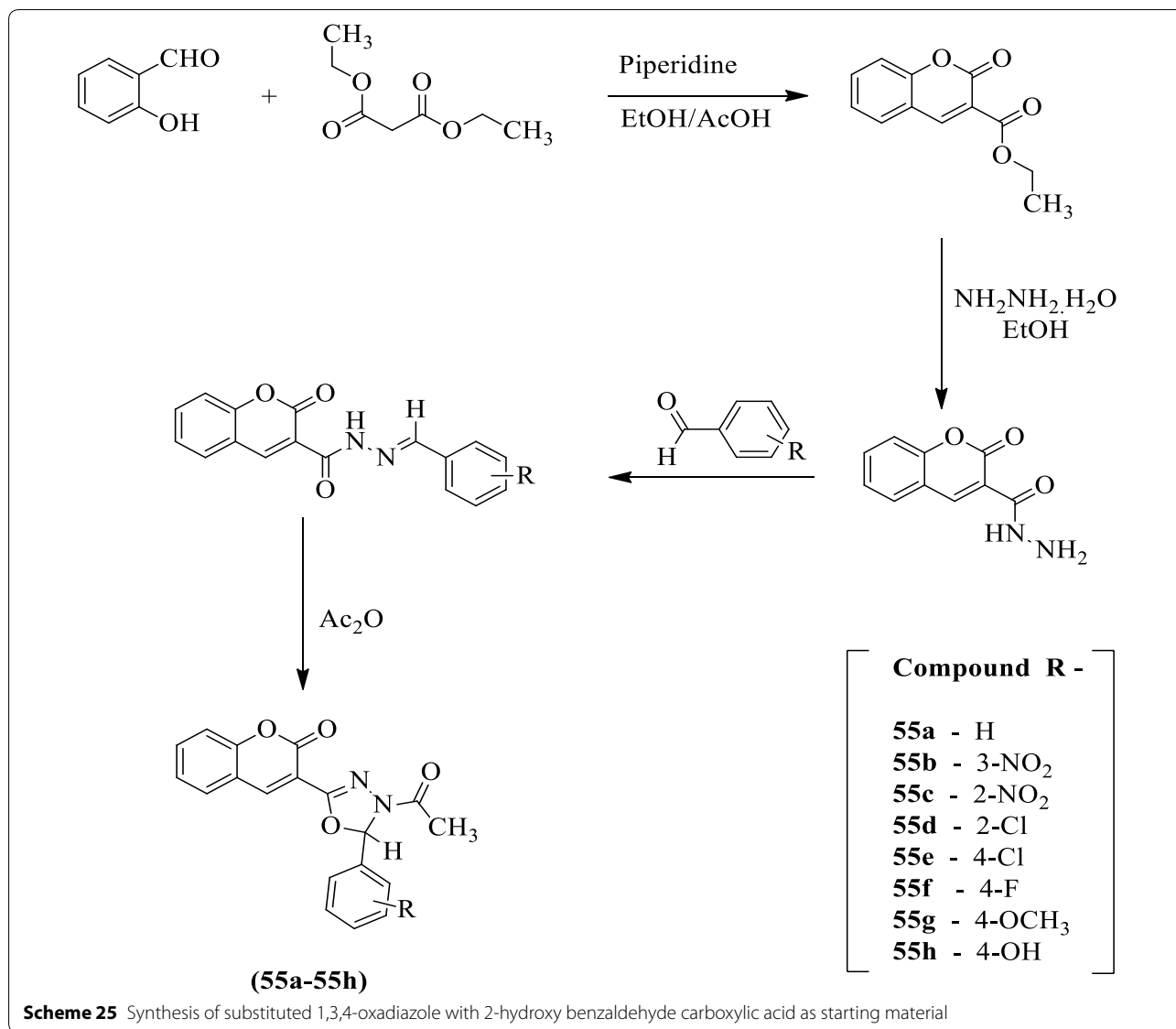


Table 25 Antioxidant activity of synthesized compounds by DPPH method [61]

Compound	% Scavenging activity	IC ₅₀
55a	19.97–85.95	47.47 ± 2.473
55b	3.07–64.92	197.96 ± 2.454
55c	7.4–48.75	> 500
55d	13.87–77.45	60.93 ± 1.560
55e	12.60–85.95	> 500
55f	14.70–69.70	130.8 ± 3.602
55g	4.9–74.77	90.26 ± 2.442
55h	6.85–69.42	91.70 ± 2.778
Ascorbic acid	44.95–95.5	12.7 ± 0.68

synthesized by various kinds of synthetic routes, and these derivatives having a wide range of biological activities such as antitumor, antitubercular, antimicrobial, antiviral and antioxidant, etc. This review article established the fact that 1,3,4-oxadiazole as useful templates for further modification or derivatization to design more potent biologically active compounds.

Abbreviations

CNS: Central Nervous System; FDA: Food and Drug Administration; MTT: 3-(4, 5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; IC₅₀: Half maximal inhibitory concentration; L.J: Lowenstein-Jensen; MB: Middle brook; HeLa: Henrietta Lacks; MIC: Minimum inhibitory concentration; HIV: Human immunodeficiency virus; CC₅₀: Half maximal cytotoxic concentration; SI: Selectivity index; HEL: Human embryonic lung fibroblast; VERO: Verda reno (means green kidney); TMV: Tobacco mosaic virus; DPPH: 2, 2-Diphenyl-1-picrylhydrazyl; MTCC: Microbial type cell cultures.

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Authors' contributions

PKV- endeavored and accomplished the scheme; AS-completed review work and wrote the manuscript. Both authors read and approved the final manuscript.

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Availability of data and materials

All data are provided in the manuscript or cited in the references.

Ethics approval and consent to participate

Not applicable.

Competing interests

The author(s) have no conflicts of interest.

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