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Review Article

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ANTICANCER POTENTIAL OF 1,3,4-THIADIAZOLE-AMIDE DERIVATIVES: A MEDICINAL CHEMISTRY PERSPECTIVE

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ABSTRACT

1,3,4 thiadiazole amide, heterocyclic ring system bearing nitrogen and sulfur heteroatoms along with an amide portion attached at C-3 position has attracted considerable interest in bioorganic and medicinal chemistry research due to its remarkable anticancer potential. This review unveils comprehensive exploration of their synthetic routes and anticancer efficacy, highlighting key structural modifications within the 1,3,4-thiadiazole amide core. Their efficacy against diverse anticancer targets—including kinases, tubulin, and specific cancer cell lines—is critically discussed. By focusing on the anticancer potential of 1,3,4-thiadiazole amides, this review aims to offer valuable insights for the design of novel and effective anticancer therapies, covering reports from the year 2005.

KEYWORD:- 1,3,4-Thiadiazole-Amide; Anticancer agents; Structure-activity relationship (SAR); Cytotoxicity; Tumor inhibition.

1. INTRODUCTION

Heterocyclic compounds are fundamentally important in organic and medicinal chemistry, forming the structural foundation of numerous commercially available drugs. Many five-membered heterocycles have been investigated for a diverse biological activities and efforts are been ongoing to identify novel heterocyclic compounds with potent bioactivities.[1] Among the five-membered heterocycles—such as imidazole, oxazole, thiazole, oxadiazole, and thiadiazole—are particularly significant due to their diverse bioactivities and prevalence in pharmaceuticals, agrochemicals, and natural products.[2]

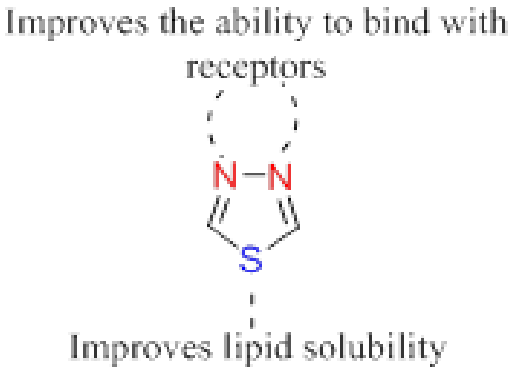


Figure 1: Thiadiazole scaffold with key pharmacophoric features.

Nitrogen- and sulfur-containing heterocycles have attracted extensive research interest, with 1,3,4-thiadiazole emerging as a privileged structure. Its unique electronic properties and ability to mimic peptide bonds make it a versatile pharmacophore, featured in antimicrobial, anti-inflammatory agents and notably, anticancer agents.[3] Furthermore, thiadiazole derivatives, especially 1,3,4-thiadiazole amides, exhibit enhanced bioavailability and target selectivity, driving efforts to design novel analogs with improved therapeutic potential.[4]

This five-membered ring, comprising one sulfur and two nitrogen atoms, exhibits strong aromaticity and serves as a bioisostere for thiazole, oxadiazole and pyrazole rings, enhancing its pharmacological relevance.[5,6]

Thiadiazoles demonstrate diverse biological properties, including anti-cancer,[7] anti-microbial,[8] anti-viral,[9] anti-phlogistic and analgesic,[10,11] anti-diabetic,[12] anti-convulsant,[13] anti-tuberculosis,[14] anti-depressants[15] and anti-hypertensive[16] making them a versatile pharmacophore.

1.1. Chemistry of 1,3,4 thiadiazole

Thiadiazoles are easy to synthesize and exhibit remarkable versatility due to their four isomeric ring variations (a-d), which have been extensively explored in medicinal chemistry for their exceptional aromaticity. Among these, 1,3,4-thiadiazole is particularly prominent owing to its straightforward synthesis, high aromatic stability, and significant medicinal properties making it the most studied isomer in pharmacological research.[5,17]

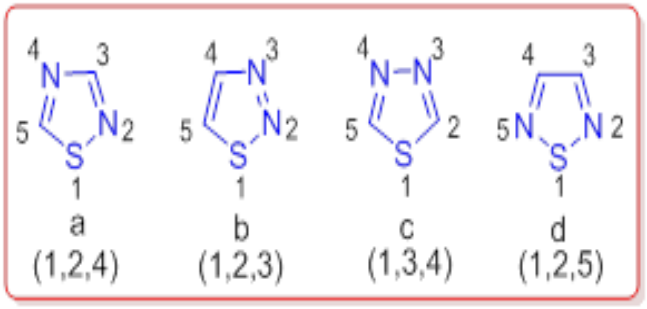


Figure 2: Isomers of thiadiazole.

The 1,3,4-thiadiazole nucleus is hypoelectronic, favoring nucleophilic substitutions at the 2nd and 5th positions, while remaining relatively inert to electrophilic attacks. Its high aromaticity ensures stability under acidic conditions but renders it susceptible to ring cleavage in basic environments. The –N=C–S– structural fragment plays a key role in reducing toxicity while ensuring remarkable *in vivo* stability.[18] Additionally, its mesoionic character (regions of positive and negative charge delocalization) enhances membrane permeability, improving oral bioavailability and interactions with biological targets (e.g., DNA, proteins).[6,19-20]

1.2. Medicinal importance

The 1,3,4-thiadiazole amide derivatives are notable considering their benefits like enhanced hydrogen-bonding capacity, which strengthens receptor interactions.[21]

The amide linkage further augments pharmacological properties by improving solubility, binding affinity, and metabolic stability. The versatile synthetic approaches for 1,3,4-thiadiazole amide derivatives have become a major focus for medicinal chemists owing to their extensive array of pharmacological applications. Marketed drugs such as acetazolamide, methazolamide, and sulfamethizole containing 1,3,4-thiadiazole amide exemplify the therapeutic potential of this scaffold.[18,22-23]

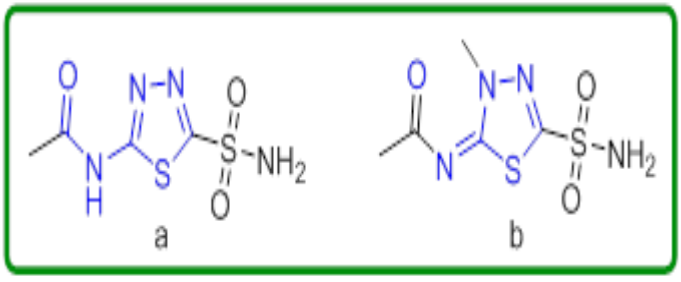


Figure 3: Marketed drugs acetazolamide (a) and methazolamide (b) containing1,3,4-thiadiazole amide scaffold.

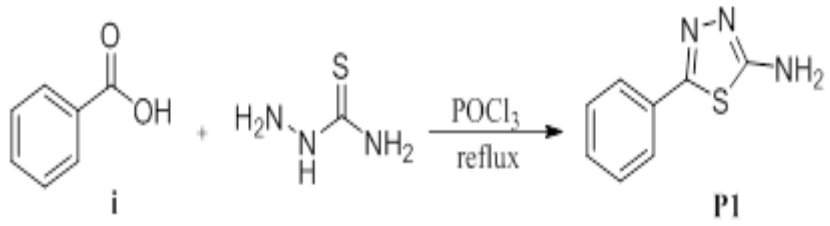
Given the emerging prominence of 1,3,4-thiadiazole amides as privileged scaffolds in anticancer drug discovery, this review critically evaluates recent advances in their synthetic strategies and structure-activity relationships (SAR). The findings presented here will provide valuable insights for researchers to refine and develop next-generation thiadiazole-based anticancer derivatives with improved target selectivity and therapeutic efficacy.

2. Synthetic methodologies for 1,3,4 thiadiazole amide scaffold

The synthesis of 1,3,4-thiadiazole amides typically proceeds through the initial formation of 1,3,4-thiadiazole amine intermediates. These key precursors are commonly prepared via multiple synthetic approaches involving the cyclocondensation of various substituted carbonyl compounds with thiosemicarbazide via multiple synthetic approaches. The following section

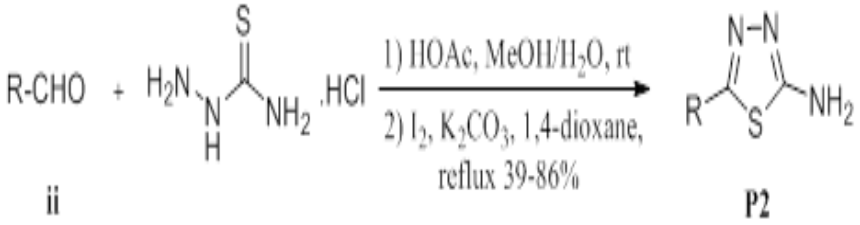
provides a detailed discussion of the most frequently employed synthetic approaches for obtaining amine-functionalized 1,3,4-thiadiazole compounds.

Brai *et al.*, accomplished the cyclization of benzoic acid (**i**) and thiosemicarbazide using phosphorus oxychloride under reflux, yielding compound **P1** (Scheme-1).[24]



Scheme 1

Niu *et al*., demonstrated a transition-metal-free approach to synthesize 1,3,4-thiadiazole-2-amines, via the reaction of substituted aldehyde (**ii**) and semicarbazide hydrochloride to yield desired product **P2** (Scheme-2).[25]

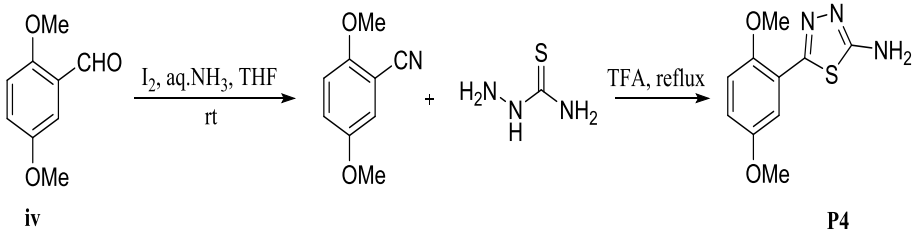


Scheme 2

Yang and co-workers performed regioselective cyclization of various thiosemicarbazides (**iii**) by refluxing in DMSO using EDC·HCl as catalyst to yield final compound **P3** (Scheme-3).[26]

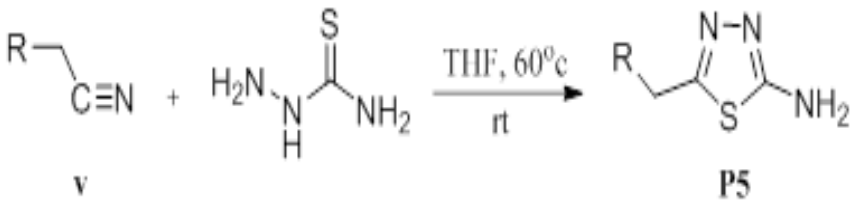
Scheme 3

Polkam *et al*., elucidated the cyclization reaction of 2,5-dimethoxybenzaldehyde (**iv**) with aqueous ammonia followed by reaction with thiosemicarbazide, yielding compound **P4** under reflux conditions (Scheme-4).[27]



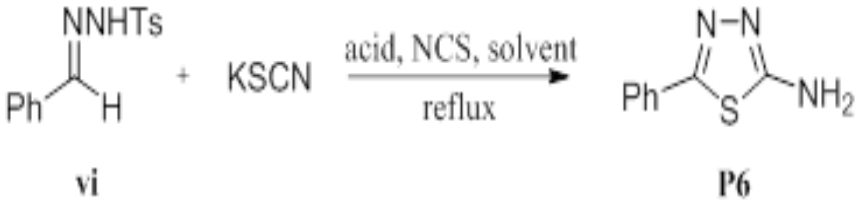
Scheme 4

Mustafa *et al*., obtained **P5** via treating substituted acetonitrile (**v**) with thiosemicarbazide in trifluoroacetic acid under reflux conditions (Scheme-5).[28]



Scheme 5

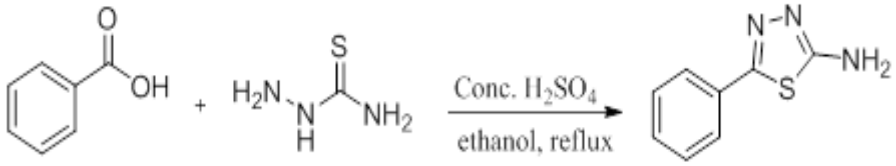
Wei and co-workers documented the cyclisation of *N*-tosylhydrazone (**vi**) with potassium thiocyanate, yielding **P6** under reflux conditions (Scheme-6).[29]



vi P6

Scheme 6

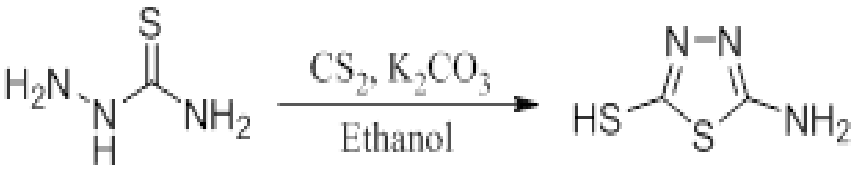
Bhinge *et al.*, conducted the cyclization of benzoic acid (**vii**) with thiosemicarbazide using concentrated sulfuric acid and ethanol, yielding compound **P7** (Scheme-7).[30]



vii P7

Scheme 7

Ruan *et al*., have reported cyclization reaction of thiosemicarbazide in the presence of carbon disulfide under reflux conditions in ethanol solvent yielding thiol substituted 2-amino-1,3,4-thiadiazole product **P8** (Scheme-8).[31]

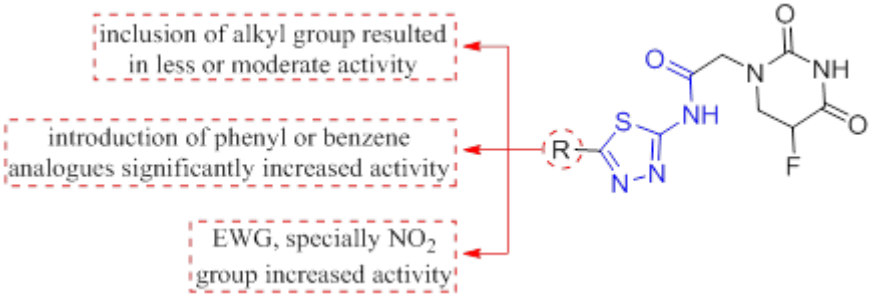


P8

Scheme 8

3. Anti-cancer activity of 1,3,4 thiadiazole amides

Zheng et al., have developed novel 5-Fluorouracil-thiadiazole conjugates and evaluated their cytotoxic effects on human cancer cell lines like A-549 (lung cancer) and Bcap-37 (breast cancer) using the MTT assay method, with 5-FU serving as the reference drug. Notably, compound **1**, featuring a dinitrophenyl group, exhibited the strongest growth inhibition against Bcap-37 cells. The SAR and anticancer efficacy of this derivative are summarized in Fig. 4.[32]

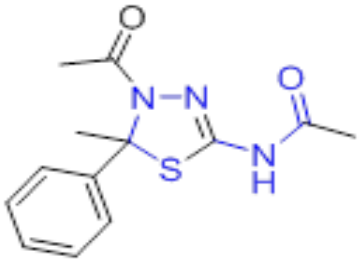


C. No.	R	IC_{50} (µg/mL)	
		A-549	Bacp-37
1	3,5-$(NO_2)_2C_6H_3$-	25.17	3.87
	5-FU	33.01	9.91

Figure 4: Anticancer properties of 5-Fluorouracil-thiadiazole derivative.

Nakai and co-workers performed a phenotype-based screening and discovered **K858** (**2**) as a new Eg5-targeting compound. The antimitotic effects of compound **2** were further evaluated across multiple human cancer cell lines, including HCT-116 (colorectal cancer), A2780 (ovarian Cancer), and ARPE-19 (retinal

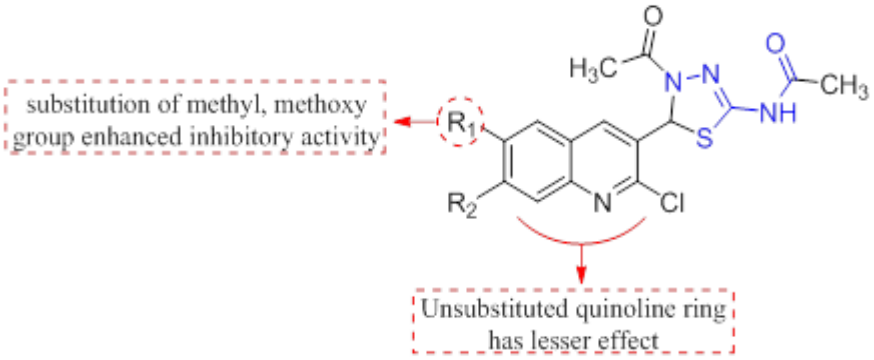
epithelium), using Paclitaxel and Carboplatin as reference standards. Among these, the HCT-116 cell line exhibited the highest sensitivity to Compound **2**. The structural details and activity data are illustrated in Fig. 5.[33]



C. No.	Eg5 IC_{50} (µmol/L)
2	1.3

Figure 5: Antitumor activity of K858.

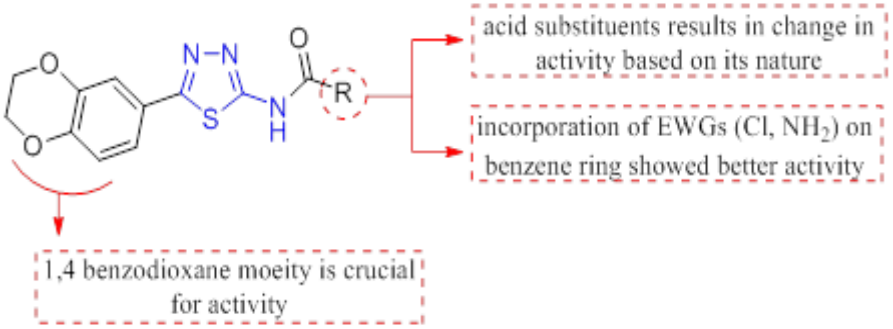
Marganakop and colleagues achieved an innovative synthesis of substituted 2-chloroquinolinyl thiadiazole acetamides and assessed their antitumoral properties against cervical cancer cell line (Hela). Within this series, compounds **3**, **4**, and **5** exhibited significant efficacy against HeLa cells, inducing cell disruption at a concentration of 10 µg/mL. Structure-activity relationship (SAR) investigations elucidated that introducing methyl or methoxy substituents at the C-6, C-7, or C-8 positions of the quinoline ring significantly enhanced bioactivity, as illustrated in Fig. 6.[34]



C. No.	R_1	R_2	HELA IC_{50} (µg/mL)
3	CH_3	H	10.0
4	OCH_3	H	10.0
5	OCH_3	OCH_3	10.0

Figure 6: Antitumor activity of 2-chloroquinolinyl thiadiazole acetamides on HELA cancer cell line.

Sun *et al*., synthesized 2,3-Dihydrobenzo[b][1,4]dioxin-linked thiadiazole acetamide derivatives as FAK inhibitors and determined their antitumor effects on multiple human cancer cell lines (HEPG2, HELA, SW1116, BGC823), using Staurosporine as the reference drug. Of the screened compounds, 6 emerged as the most effective, demonstrating significant inhibitory activity (Fig. 7). Compound **6** was further investigated through molecular docking, apoptosis assays, and Western blot analysis, with results confirming that compound **6** binds effectively to FAK and exhibits strong antitumor potential through the induction of apoptosis.[35]



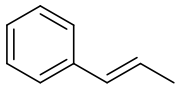
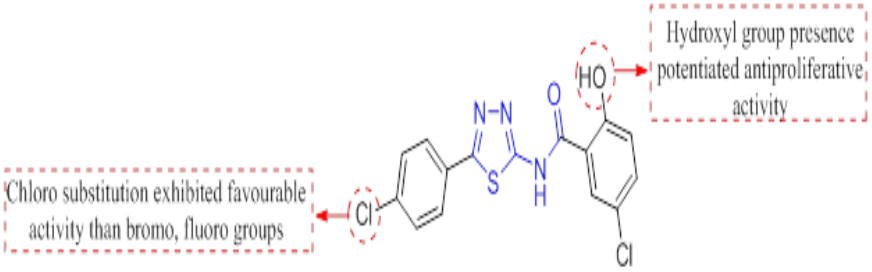
C. No.	R	IC_{50} (µg/mL)				FAK inhibitory activity (µM)
		HEPG2	HELA	SW1116	BGC823	
6		10.28	>100	60.17	45.36	10.79
	5-Fluorouracil	23.31	31.02	28.52	17.37	-
	Staurosporine	21.74	29.12	24.92	26.83	11.32

Figure 7: FAK Inhibitory and Anti-cancer activity of dihydrobenzo linked thiadiazole acetamide derivatives on various cancer cell lines.

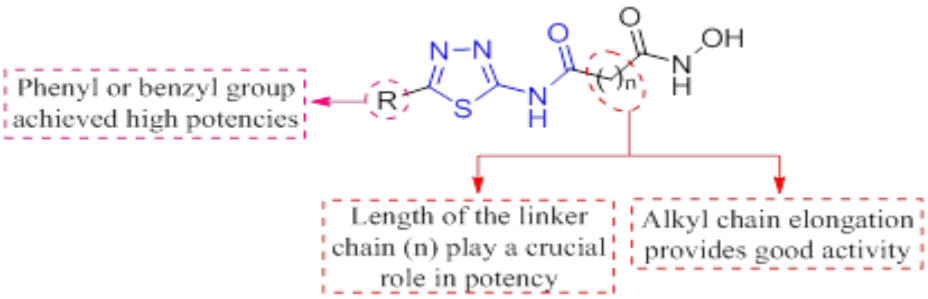
Yang *et al*. developed and synthesized a diverse range of 1,3,4-thiadiazol amide derivatives from substituted benzoic acids. These compounds were screened for FAK inhibitory ability thus suppress cancer growth using MCF-7 (human breast cancer) and B16-F10 (mouse melanoma) tumor cell lines. From the series, compound **7** featuring a 5-Cl substituent on the salicylic acid moiety exhibited the most potent inhibitory effects, comparable to the positive control, staurosporine. Additionally, Western blot analysis confirmed the significant antiproliferative effectiveness of **7**. Fig. 8 summarizes the SAR and anti-cancer activity profile of compound **7**.[36]



C. No.	IC_{50} (µg/mL)		FAK inhibitory activity (µM)
	MCF-7	B16-F10	
7	0.45±0.03	0.31±0.04	5.32±0.69
Staurosporine	3.07±0.13	2.82±0.22	11.32±0.85

Figure 8: Anti-cancer FAK Inhibitory properties and of 1,3,4-thiadiazol amide derivative.

Guan and co-workers synthesized and developed a new class of hydroxamic acids derived from 1,3,4-thiadiazole scaffold as potent inhibitors of histone deacetylases (HDACs). They then assessed their pharmacological potential using MDA-MB-231(breast cancer) and K562 (chronic myeloid leukemia) human cancer cell lines, and their HDAC inhibitory activity (Color de Lys assay) was assessed as well. Of the series, several derivatives exhibited promising anti-cancer activity, with one standout molecule compound **8** showing superior HDAC inhibition outperforming the reference drug. SAR investigations revealed that judicious modifications at the 'R' position influenced the effectiveness, as delineated in Fig. 9.[37]



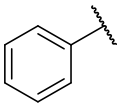
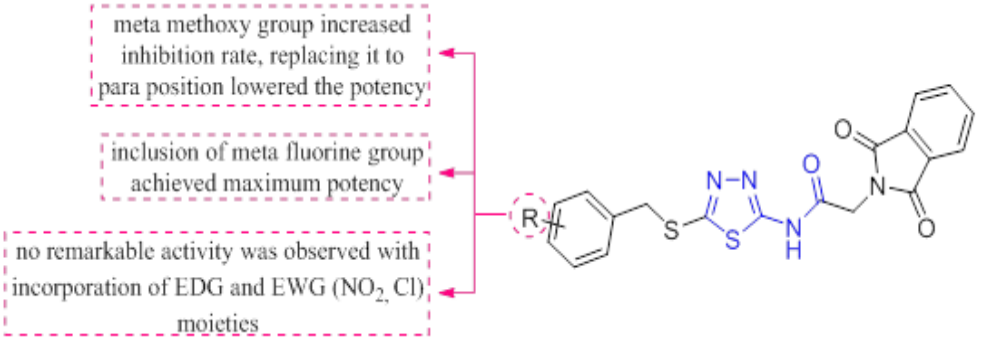
C. No.	R	IC_{50} (µM)		IC_{50} of HDAC (µM)
		MDA-MB-231	K562	
8		5.52 ± 2.62	12.9 ± 3.18	0.089 ± 0.005
	SAHA	1.32 ± 0.46	1.69 ± 0.04	0.15 ± 0.02

Figure 9: HDAC inhibitory and anticancer activity of compound 8.

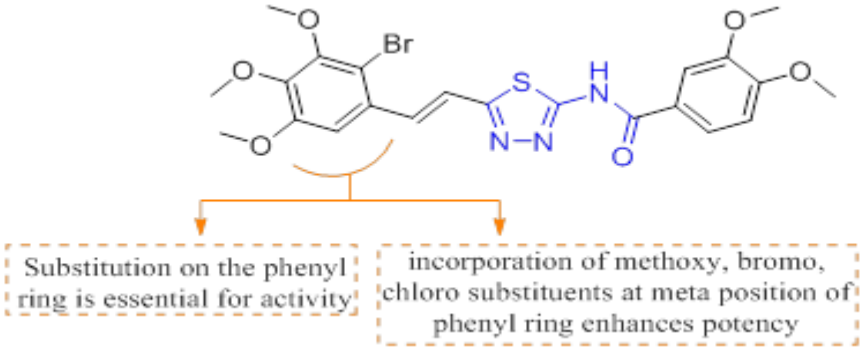
Aliabadi and colleagues investigated the antineoplastic potential of newly synthesized N-Phthalimidoacetyl thiadiazole amides bearing substituted benzylthio moiety derivatives by employing in vitro MTT protocol. The authors tested these compounds against three human cancer cell lines (PC3, HT29, SKNMC) while also investigating their inhibitory efficacy against 15-lipoxygenase-1. From the experimental data, only compounds **9** and **10** demonstrated appreciable cytotoxicity towards the HT29 cell line (Fig. 10). Thus, authors concluded that further structural alterations were necessary to yield derivatives with superior efficacy.[38]



C. No.	R	IC_{50} ± SD (µM)			15-Lipoxygenase-1 (%of inhibition)
		PC3	HT29	SKNMC	
9	*o*-F	100<	10.91 ±4.1	100<	31
10	p-Cl	>100	24.06 ±3.1	69.7 ±3.6	No activity
	Doxorubicin	3.8 ±0.75	2.1 ±0.26	1.3 ±0.4	-
	Quercetin	-	-	-	100

Figure 10: Anticancer and Lipoxygenase inhibitory data of Phthalimidoacetyl thiadiazole amide derivatives.

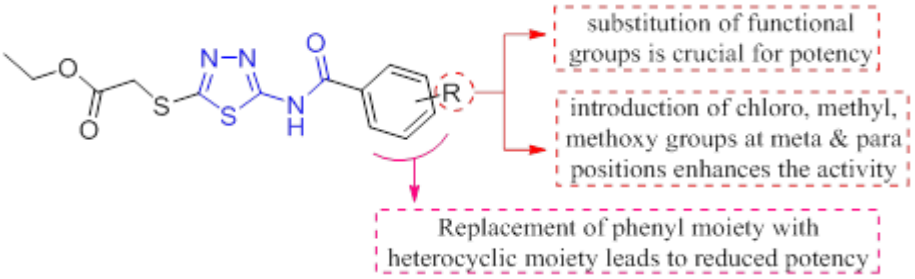
Jing Li and co-workers synthesized benzamide derivatives of a styryl-1,3,4-thiadiazole scaffold and assessed their effects on tubulin polymerization along with in vitro anticancer potential. Among these, derivatives featuring methoxy or halogen substitutions at the phenyl ring's C-3 position demonstrated notable biological activity. From the series, compound **11** emerged as a standout candidate, displaying strong tubulin polymerization inhibition and remarkable cellular toxicity on A549 (lung), MCF-7 (breast), and HepG2 (liver) cancer cell lines. SAR and pharmacological activity of 11 are represented in Fig. 11.[39]



C. No.	IC_{50} ± SD (µM)			
	A549	MCF-7	HepG2	Tubulin
11	0.03 ±0.01	0.06 ±0.03	0.05 ±0.01	1.73 ±0.28
Combretastatin A-4	0.10 ±0.02	0.31 ±0.06	0.16 ±0.02	2.1 ±0.12

Figure 11: In vitro cytostatic properties of benzamide linked styryl-1,3,4-thiadiazole amides on human tumor cell lines.

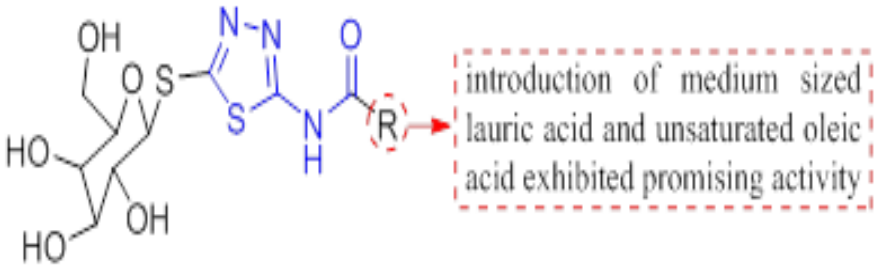
Almasirad *et al*., developed a series of novel 1,3,4-thiadiazol-thioacetates and subsequently evaluating anticancer effects on multiple tumor cell lines, including HL-60 (promyelocytic leukemia), SKOV-3 (ovarian cancer) and MOLT-4 (T-cell lymphoblastic leukemia). From this series, compound 12, which featured a 4-methoxyphenol group, exhibited marked potency across all investigated neoplastic cell lines. Additionally, compounds **13** and **14** demonstrated significant growth inhibition against the SKOV-3 line. A concise SAR investigation elucidated that judicious aromatic substitution at the 'R' position modulated the observed potency, as illustrated in Fig. 12.[40]



C. No.	R	IC_{50} (µM)		
		HL-60	SKOV-3	MOLT-4
12	3-MeC_6H_4	30.8 ± 6.4	26.3 ± 5.0	>100
13	4-$OMeC_6H_4$	30.1 ± 2.7	19.5 ± 2.1	>100
14	2-ClC_6H_4	33.8 ± 4.4	22.2 ± 0.7	>100
	Doxorubicin	0.013 ± 0.002	0.018 ± 0.016	0.047 ± 0.015
	Cisplatin	2.1 ± 0.3	8.5 ± 4.8	3.1 ± 0.1

Figure 12: Anticancer activity of 1,3,4-thiadiazol-thioacetate derivatives.

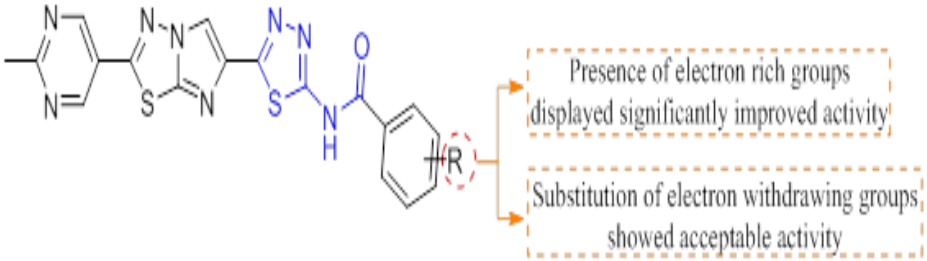
Vudhgiri *et al*., reported the synthesis of glycoside linked 5-fatty acyl amido-1,3,4-thiadiazole-2-thiol derivatives, and assessed their cytotoxic potential. SAR analysis indicated that derivatives with specific short-chain (acetate-protected) and long-chain (free hydroxyl) fatty acids at 'R' enhanced cytotoxicity. The synthesized series was further evaluated against multiple human cancer cell lines (SKOV3, HeLa, MDA-MB-231, DU145, CHO-K1), while Doxorubicin and Mitomycin C served as reference drugs. From the synthesized series, the lauric acid derivative with a free hydroxyl group (**15**) and the oleic acid-based compound (**16**) displayed significant efficacy against the HeLa cell line as shown in Fig. 13.[41]



C. No.	R	IC_{50} (µM)				
		SKOV3	HeLa	MDA-MB-231	DU145	CHO-K1
15	-$(CH_2)_{10}$-CH_3	–	8.7 ±0.59	32.0 ±0.58	–	–
16	-$(CH_2)_7$-CH=CH-$(CH_2)_7$-CH_3	–	8.8 ±0.61	43.6 ±0.61	–	–
	Doxorubicin	0.7 ±0.23	0.7 ±0.22	0.7 ±0.20	0.8 ±0.19	–
	Mitomycin c	–	–	–	–	13.4 ±0.21

Figure 13: Cytotoxicity evaluation data of glycoside linked 5-fatty acyl amido-1,3,4-thiadiazole derivatives.

Sridhar and colleagues prepared a series of novel Imidazo linked 1,3,4-thiadiazole amide derivatives and assessed their anticancer potential. Among these, derivatives containing electron-donating groups and halogens (particularly chlorine) at the benzene ring's C-4 position exhibited strong biological activity. Notably, compounds **17** and **18** exhibited potent cytotoxicity, with activity observed against several human cancer cell lines, including MCF-7, A549, DU-145, and MDA-MB-231 (see Fig. 14). Further SAR analysis indicated that modifications at the C-3, C-4, and C-5 positions were critical for anticancer efficacy.[42]

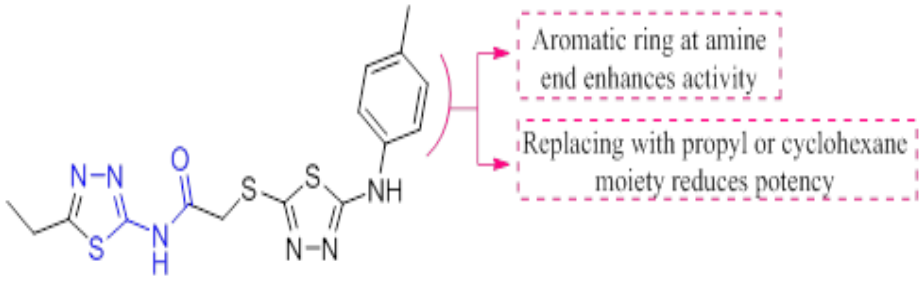


C. No.	R	IC_{50} (μM)			
		MCF-7	A549	DU-145	MDAMB-231
17	3,4,5-trimethoxy	0.071 ±0.009	0.045 ±0.0034	0.67 ±0.051	1.33 ±0.76
18	4-chloro	13.8±6.33	ND	ND	12.91±6.10
	Etoposide	2.11 ±0.024	3.08 ±0.135	1.97 ±0.45	1.91 ±0.84

ND: not determined

Figure 14: Anticancer activity profile of Imidazo linked 1,3,4-thiadiazole amide derivatives.

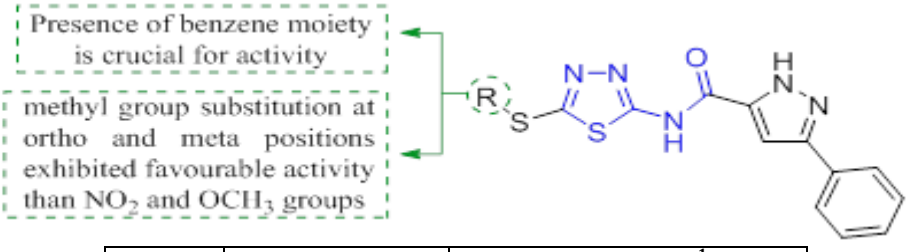
Çevik *et al*., developed a new set of bis-thiadiazole thioacetamide compounds and assessed their anticancer effects on A549 (lung cancer) and MCF-7 (breast cancer) cell lines. Many derivatives exhibited significant activity against A549 cell line, with compound **19** (containing a 4-methylphenyl group) being the most active and outperforming cisplatin. The SAR study revealed that incorporation of an aromatic ring onto the thiadiazole's amine moiety boosted anticancer performance as shown in Fig. 15. Furthermore, these highly efficacious derivatives were screened against non-malignant NIH3T3 cells to ascertain cancer-selective toxicity.[43]



C. No.	R	IC_{50} (mmol L^{-1})		
		MCF-7	A549	NIH3T3
19	4-Methylphenyl	0.084 ± 0.020	0.034 ± 0.008	1.791 ± 0.087
	Cisplatin	0.019 ± 0.009	0.013 ± 0.003	111.26 ± 3.745

Figure 15: Anticancer activity of bis-thiadiazole thioacetamide derivatives.

Jiaoli *et al.* designed and synthesized a new class of pyrazole substituted 1,3,4-thiadiazole amides, assessing their anticancer properties. Among the synthesized compounds, **20** exhibited the highest efficacy against both HepG2 (liver cancer) and MGC803 (stomach cancer) cell lines, while derivatives **21** and **22** also showed significant inhibition of HepG2 cells, with activity levels similar to the control drug 5-fluorouracil. SAR analyses revealed that the introduction of a methyl substituent at the ortho and meta positions of the benzene ring at the 'R' locus potentiated antitumor activities, as delineated in Fig. 16.[44]

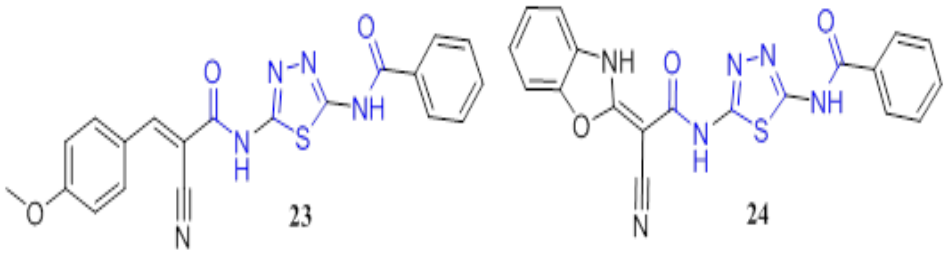


C. No.	R	IC_{50} (mmol L^{-1})	
		HepG2	MGC803
20	$C_6H_5CH_2$	0.0695	0.0420
21	2-$CH_3C_6H_4CH_2$	0.0682	—
22	3-$CH_3C_6H_4CH_2$	0.0753	—
	5-Fluorouracil	0.0787	0.0820

- indicates that there is basically no anti-cancer cell inhibitory activity.

Figure 16: Anticancer properties pyrazole substituted 1,3,4-thiadiazole amide derivatives.

Hekal *et al.*, documented the creation of 24 novel annulated 1,3,4-thiadiazole benzamide homologues and subsequently evaluated their antiproliferative efficacy against multiple human cancer cell lines (MCF-7, HCT-116, PC-3, HepG2, WI-38). Notably, two specific congeners **23** and **24** were observed to exhibit marked inhibitory activity against CDK1. The antiproliferative and CDK inhibitory effects of these two compounds are summarized in Fig. 17.[45]



C. No.	IC_{50} (µM)				
	MCF-7	HCT-116	PC-3	HepG2	WI-38
23	9.48 ± 0.8	8.15 ± 0.7	7.41 ± 0.6	15.88 ± 1.3	50.39 ± 0.9
24	7.70 ± 0.5	5.98 ± 0.3	6.35 ± 0.5	19.40 ± 1.5	60.28 ± 3.7
Doxorubicin	4.17 ± 0.2	5.23 ± 0.3	8.87 ± 0.6	4.50 ± 0.2b	6.72 ± 0.5

Figure 17: Antiproliferative activity results of 1,3,4-thiadiazole benzamide homologues.

The therapeutic potential of these compounds is further supported by clinically studied and patented examples have been summarized in Tables 1 and 2.

Table 1: 1,3,4 thiadiazole amide nucleus containing patents having numerous biological activities.

Research group	Patent number	Target activity	Year
Joel L. Kirkpatrick	US4097263A	Herbcide [46]	1978
William C. Doyle	CA1151179A	Herbicide [47]	1972
Steven R. Turner	WO1999047507A2	Herpesvirus Infection [48]	1999
Tony Cebalo	US4092148A	Herbicide [49]	1970
Pottayil Govindan Nair	WO2015033301A1	Immunomodulators [50]	2015
Natalya Alekseevna Pulina	RU2549572C2	Analgesic [51]	2015
Liu Xinghai Weng	CN103030606A	Fungicide [52]	2014
Li Wan	CN111747946A	Plant Bactericide [53]	2020
Wang Meiyi	CN114507194A	Bactericide [54]	2022
Xue Wei	CN104086508B	Antibacterial agent [55]	2017
Xue Wei	CN104086508A	Antimicrobial agent [56]	2014
Liu Weiwei	CN112480031B	Antimicrobial agent [57]	2022
Liu Aiqin	CN103864776A	Anticancer agent [58]	2015

Table 2: Marketed and Investigational Drugs Containing a 1,3,4-Thiadiazole amide Moiety.

Name	Current status	Use	1,3,4-thiadiazole amide nucleus containing
Acetazolamide	Marketed drug	Carbonic anhydrase inhibitor [59,60]	Sulfonamide
Methazolamide	Marketed drug	Carbonic anhydrase inhibitor [61]	Sulfonamide
Sulfamethizole	Marketed drug	Antibiotic [62]	Sulfonamide
Megazole	Discontinued (due to toxicity)	Antitrypanosomal [63]	Amino group
CB-839	Phase II clinical stage	Glutaminase inhibitor [64]	Heterocyclic system
K858	Preclinical stage	Eg5 inhibitor [33]	Heterocyclic system

4. CONCLUSION

Heterocyclic compounds incorporating nitrogen and sulfur atoms represent a highly adaptable group of molecules with diverse biological activities. Among these, the 1,3,4-thiadiazole core, a versatile heterocyclic system incorporating nitrogen and sulfur atoms, has demonstrated significant potential in the development of anticancer agents. This review first explores the synthetic methodologies—including conventional, multi-component, and alternative approaches—used to prepare substituted 1,3,4-thiadiazole amines highlighting their synthetic adaptability.

By consolidating synthetic strategies, structure-activity relationships, and promising therapeutic applications in the anticancer field, this review aims to guide researchers in developing target-selective, optimized 1,3,4-thiadiazole amide derivatives with enhanced potential for treating cancer.

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