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## 1, 3, 4 THIADIAZOLE NUCLEUS BIOLOGICAL SCAFFOLD FOR PHARMACOLOGICAL SCREENING-COMPREHENSIVE REVIEW

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### Keywords:

1,3,4-Thiadiazole, Thiadiazole, Anticancer, Biological activities, Heterocyclic compounds

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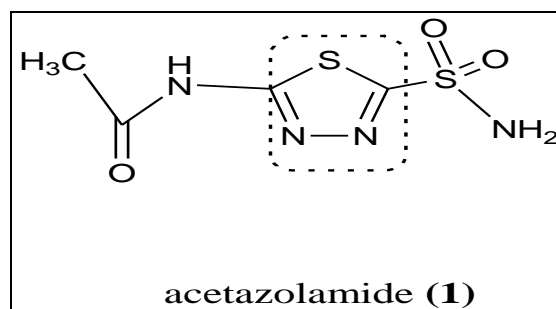
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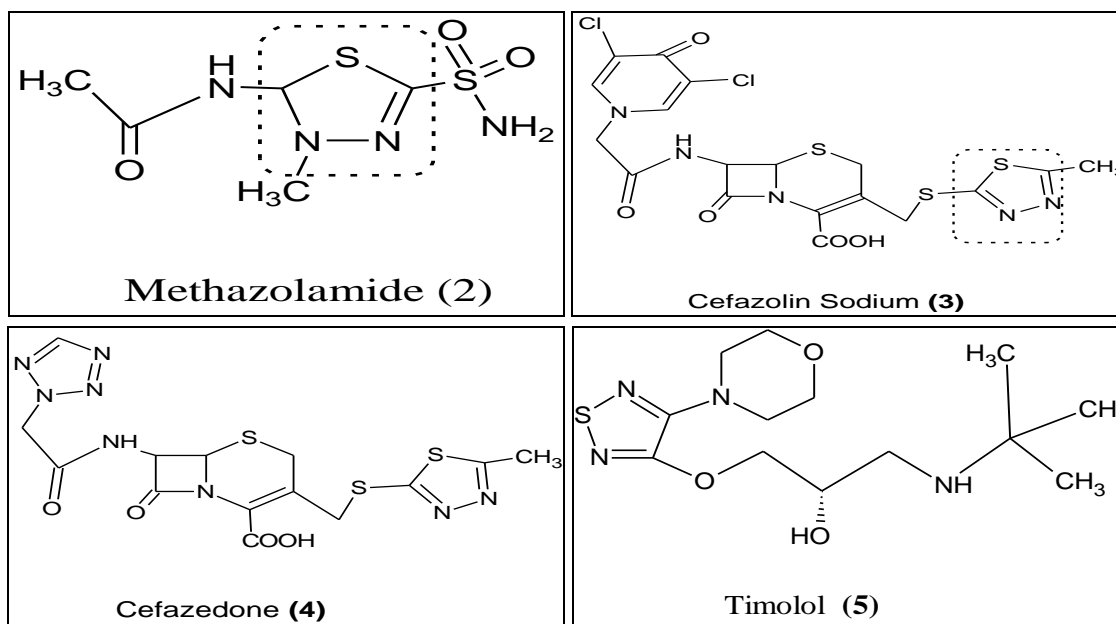
**ABSTRACT:** Despite different therapy, such as chemotherapy, for cancer, it has become the leading cause of death globally. This boosts the researcher for searching for a new lead molecule with a simple structure and maximum potency with little adverse effect. In recent years, 1,3,4-thiadiazole moiety attracted the attention of scientists for the development of novel compounds. The different articles reported that 1,3,4-thiazole derivatives have to exhibit various biological activities like antiviral, antitumor, antibacterial, antifungal, anti-inflammatory, antidepressant, and CNS depressant activities, *etc.* This review is tempted to highlight the detailed synthetic strategy and biological activities of 1,3,4-thiazole moiety and draw attention towards future development and drug discovery.

**INTRODUCTION:** The rising spread of cancer has triggered a global quest for novel chemicals that could be employed in developing anti-cancer medications. The development of substances that can recognise and bind to certain DNA base sequences has been a major focus in the search for more effective anticancer agents. Developing anticancer medications with very few or no side effects is crucial for tumor treatment. The hunt for such prospective anticancer medications has resulted in identifying small synthetic compounds with anti-proliferative activity and few adverse effects, especially in the immune system. This field of study is rising exponentially, and several interesting drug molecules have come up. Heterocyclic moieties are present in a huge variety of biologically active chemicals.

Compounds' biological action is largely determined by their molecular structures<sup>1</sup>. For the last few decades synthesis of sulfur and nitrogen-containing heterocycles was tremendously carried out. Thiadiazole containing drugs are currently in the market as such drugs function by the anticipating of carbonic anhydrases example acetazolamide (1) and metazolamide (2); derivatives of thiadiazole show different actions, such as anticonvulsants and cerebral vasodilation that is selective. Cefazolin sodium (3) and cefazedone (4) are first-generation cephalosporins that contain thiadiazoles; timolol (5) is a non-selective  $\beta$ -adrenergic receptor blocker used to treat hypertension, angina, tachycardia, and glaucoma.



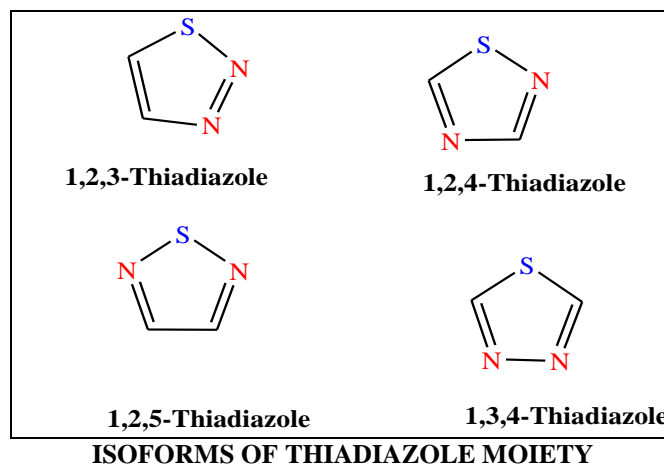
<p><b>QUICK RESPONSE CODE</b></p>	<p><b>DOI:</b> 10.13040/IJPSR.0975-8232.14(9).4251-65</p> <hr/> <p>This article can be accessed online on <a href="http://www.ijpsr.com">www.ijpsr.com</a></p> <hr/> <p>DOI link: <a href="http://doi.org/10.13040/IJPSR.0975-8232.14(9).4251-65">http://doi.org/10.13040/IJPSR.0975-8232.14(9).4251-65</a></p>
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**Chemistry:** The cyclization process of thiosemicarbazide derivatives yields substituted 1,2,4-triazole and 1,3,4-thiadiazole derivatives, which is dependent on two different conditions, the medium pH and on the substituent nature of thiosemicarbazide derivatives. In alkaline conditions, the cyclization reaction is frequently preferred, yielding 1,2,4-triazoles, but in acidic media, 1,3,4-thiadiazole derivatives were developed. Thiadiazole is a heteroatomic system with a five-membered heterocycle, and electron conjugation and defined regions of positive and negative charges, resulting in highly polarizable derivatives. Because of these unusual properties, mesoionic molecules can permeate cellular membranes and interact with biological components in novel ways. The sulphur atom in the heterocycle has a high liposolubility, would enable thiadiazole-containing drugs to have better biological activity and pharmacokinetic features.

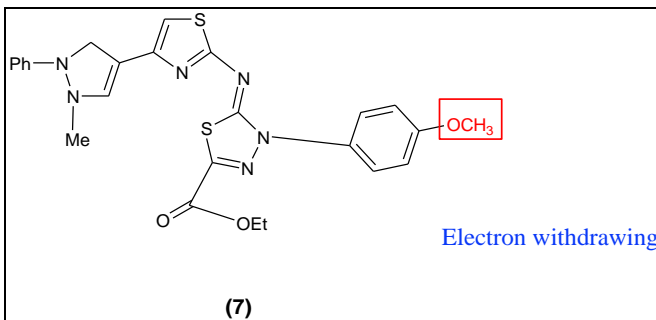
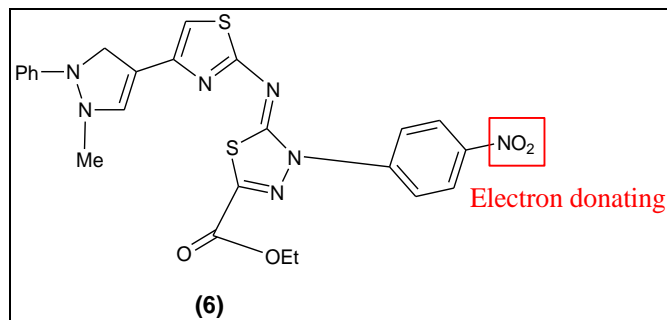
The thiadiazole ring is a bioisostere of its chemical characteristics identical to that of the pyrimidine ring. In consideration of the fact that the structure of pyrimidine present in nucleosides, nucleotides and elementary unit of Deoxyribonucleic acid and Ribonucleic acid, it shows plausible that thiadiazole might easily interact with DNA and RNA, which could explain its broad and often strong activity. Furthermore, the action of thiadiazole derivatives against DNA suggests that they could be employed for chemical intervention at the genomic level<sup>2</sup>. Because of its

intrinsic and complex biological reaction, the 1,3,4-thiadiazole skeleton, a renowned heterocyclic entity, has piqued researchers' curiosity<sup>3</sup>. Fischer primarily defined the molecule in 1882 and Busch and his colleagues worked to expand it<sup>4</sup>. Thiadiazole is a sulfur-containing 5-membered planar aromatic motif that enhances lipid solubility<sup>6</sup> and pharmacokinetics. The two-electron donor nitrogen system ( $-N=C-S$ ) and hydrogen-bonding orbit improve the molecule's pharmacodynamics for greater receptor interaction<sup>4,5</sup>. Thiadiazoles are bioisosteres of pyrimidines, oxadiazoles, oxazoles and benzene. It occurs in its four isomers, namely 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,2,5-thiadiazole and 1,3,4-thiadiazole, shown in below. They exhibit extensive biological and pharmacological features, namely antibacterial, antiviral, antifungal, antiparasitic, anti-inflammatory and anticancer activity.



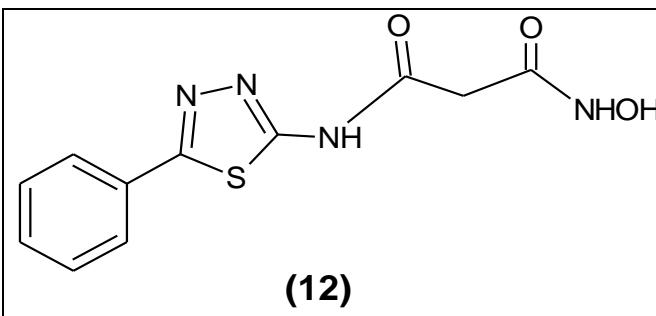
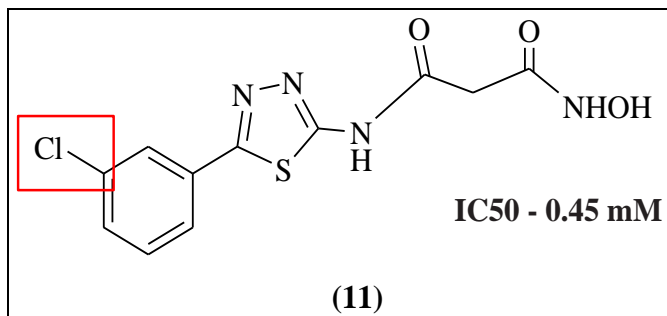
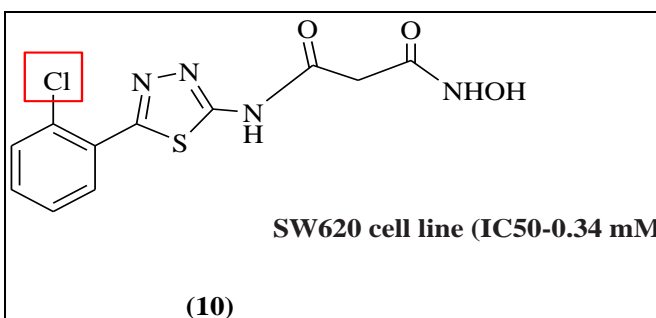
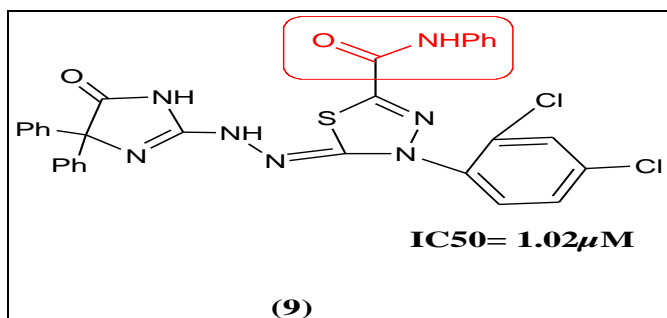
**Structure-Activity Relationship:** According to the anticancer HepG2 profile, test substances have a wide range of activity. Compounds 6 were the promising pyrazole derivatives in the study, with  $IC_{50}$  values of 8.107  $\mu$ M when compared to the reference standard. 6 ( $IC_{50}$  8.107 $\mu$ M) the molecule with the p-NO<sub>2</sub> phenyl moiety at N3 has the

strongest antitumor action. Both N3p-substituted electron donating 7 and drawing phenyl analogues 6 demonstrated significant anti MCF-7 activity ( $IC_{50}$  15.88 and 10.03 $\mu$ M, respectively), despite electron donating analogue 7 is somewhat less effective than the electron withdrawing analogue 6.



The 1,3,4-thiadiazole derivatives 8, 9 ( $IC_{50}$  = 0.86, 1.02  $\mu$ M, respectively) have promising antiproliferative activity in a cell line of liver malignancy. (HEPG2-1). The ester group (CO<sub>2</sub> Et) has stronger activity as compared to the amide group (CONHPh), the acetyl group (Ac), and the phenyl group (Ph) at position 2 of 1,3,4-thiadiazole<sup>8</sup>. Including the phenyl ring of one halogen atom at locations 2, 3, or 4, maintained or even significantly improved the cytotoxicity (compounds

10, 11. The replacement at the second position was shown to be the most favorable for cytotoxicity. In the SW620 cell line, compound 10 and 11 with a chlorine functional moiety at 2 and 3 positions were higher cytotoxic than compound 12. ( $IC_{50}$  values of 0.34 and 0.45mM versus 0.70mM). In the NCI-460 cell line, compound 10 was even 10-fold more active ( $IC_{50}$  value of 0.11mM versus 1.07 mM)<sup>9</sup>.

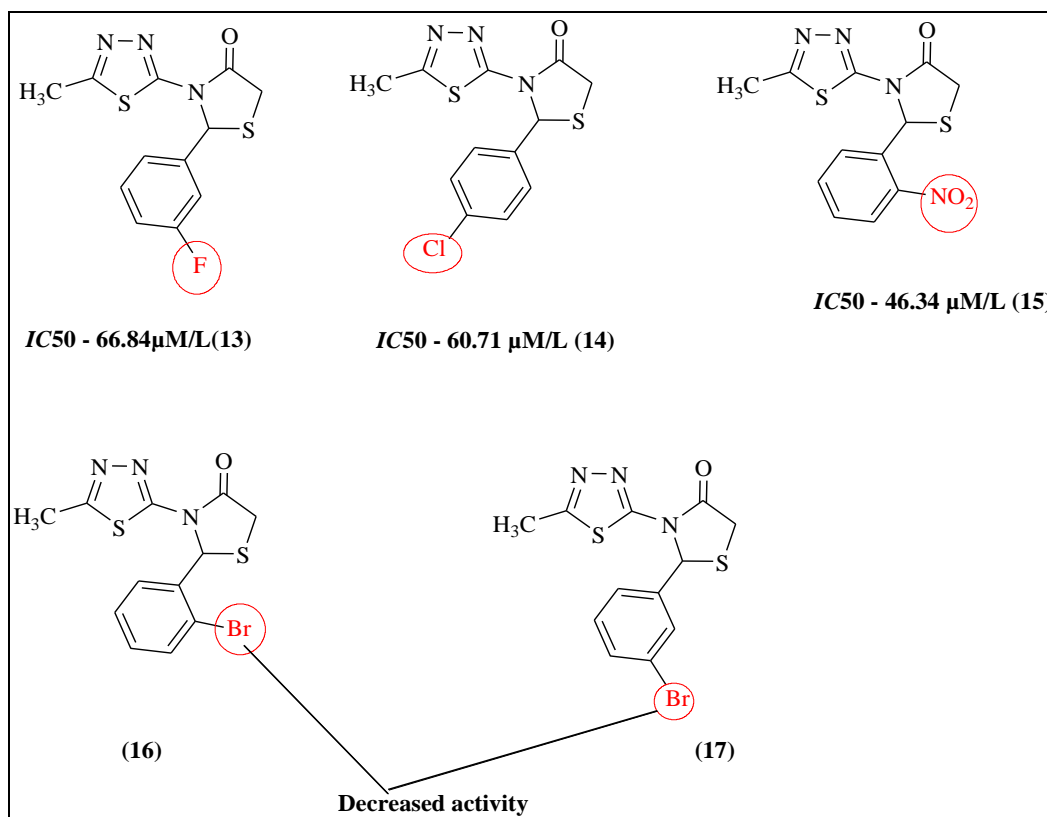


The findings of the anticancer as says revealed that compounds 2-(3-fluorophenyl)-3-(5-methyl-1,3,4-thiadiazol-2-yl) - thiazolidin - 4 - one(13), 2-(4-chlorophenyl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)-

thiazolidin-4-one(14) and 2-(2-nitrophenyl)-3-(5-methyl-1, 3, 4-thiadiazol - 2-yl)-thiazolidin-4-one (15) were the major significant cytotoxicagents with  $IC_{50}$  values of 66.84, 60.71 and 46.34 $\mu$ M/L,

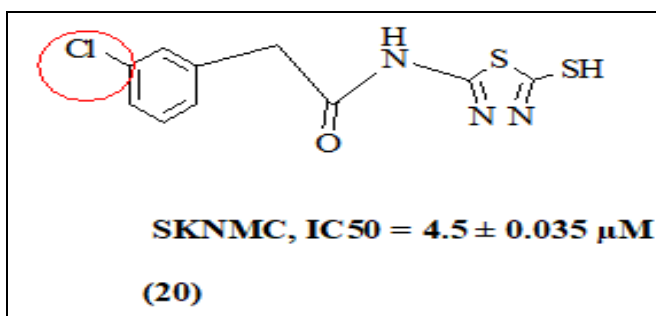
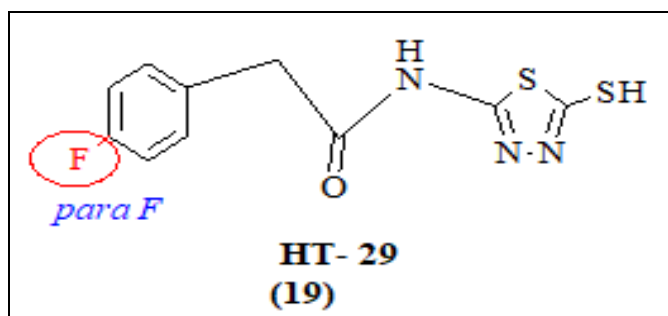
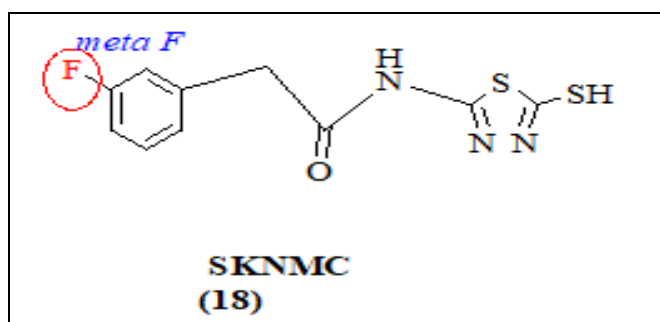
respectively. The presence of 3-fluoro (13), 4-chloro (14), and 2-nitrogroups (15) at the phenyl ring of the thiazolidin-4-one moiety resulted in the

highest activity, where as bromo replacements on the phenyl ring (16, 17) resulted in the lowest activity<sup>10</sup>.

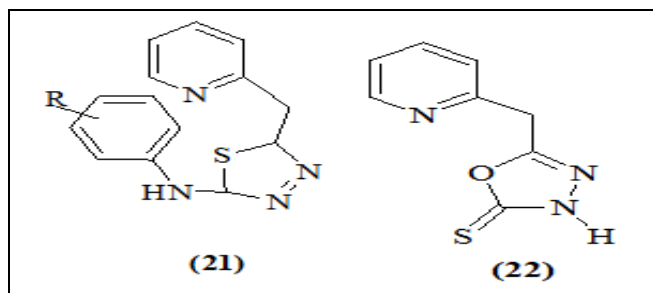


In relative to SKNMC, all compound had better activity against PC3 and HT-29 cell lines. Against the SKNMC and PC3 cell lines, the fluorine substituent at met site (compound 18) had the potent anticancer effect. However, par substitution

(compound 19) of fluorine seems to have a greater action against HT-29 cell line. Against the SKNMC C cell line the chlorine entity at position 2 of the phenyl ring (20)  $IC_{50} = 4.50.035 Mm$ , imparts high anticancer efficacy<sup>11</sup>.

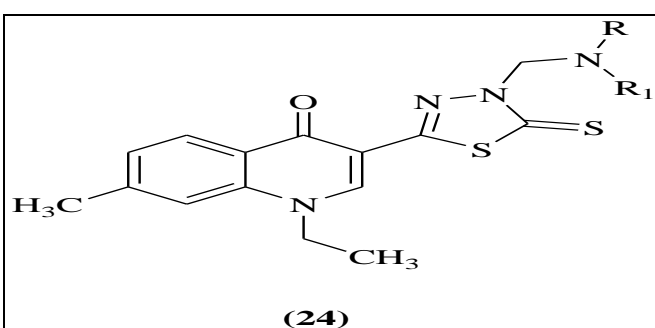
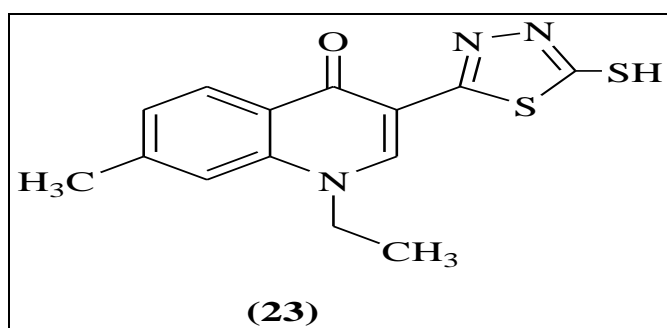


**Synthetic Strategies:** Daniel Szulczyk *et al.*; Compounds (21) and (22) heterocyclic derivatives of ethyl 2-(2-pyridylacetate) were efficiently synthesized, including Thiourea, 1,2,4-triazole, Thiadiazole and Oxadiazole moieties<sup>12</sup>.



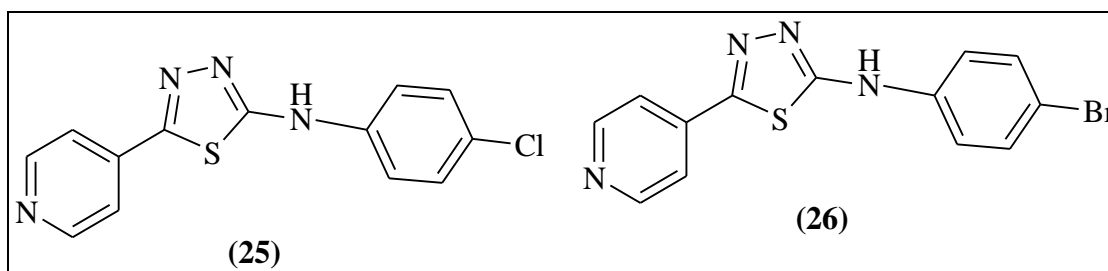
Synthesis of Novel Nalidixic Acid-Based 1,3,4-Thiadiazole and 1,3,4-Oxadiazole Derivatives by Nisha Aggarwal *et al.*

The reaction of nalidixic acid hydrazide with carbon disulfide and potassium hydroxide to form potassium dithiocarbazinate was followed by cyclization in acidic medium to yield 1-Ethyl-3-(5-mercapto-1,3,4-thiadiazol-2-yl)-7-methyl-1H-1,8-naphthyridin-4-one. All of the synthesized compounds (23, 24) exhibited potent effect against the investigated bacterial strains *P. aeruginosa* and *E. coli* and *K. pneumonia*<sup>13</sup>.



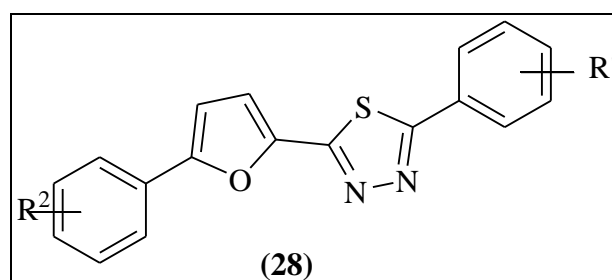
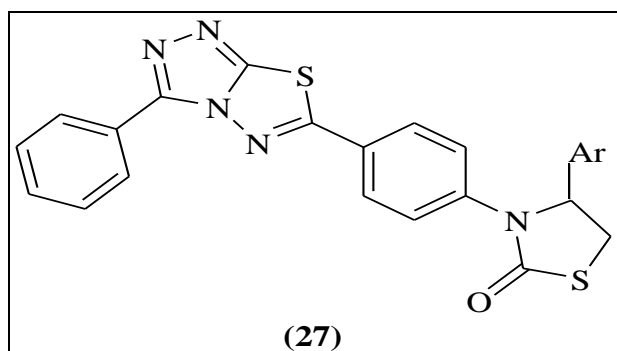
Nadia Youssef Megally, Synthesis series of 1,3,4-Oxadiazoles, 1,3,4-Thiadiazoles, 1,2,4-Triazoles and Mannich Bases by the cyclization of hydrazine carbothioamide derivatives 2a-d derived from is

nicotinic acid hydrazide. He discovered that the 4-chlorophenyl (25) and 4-bromophenyl (26) substituents were required for activity<sup>14</sup>.



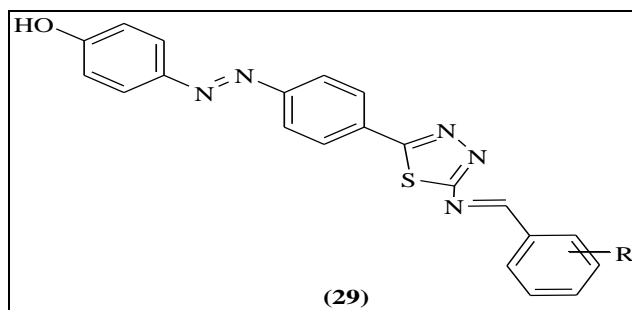
Parmar Kokil *et al.*; Synthesize 1,3,4-thiadiazole-2-aryl-thiazolidine-4-one Derivatives (27) by reacting of Schiff bases with mercaptoacetic acid in presence of THF and adding anhydrous  $ZnCl_2$ <sup>15</sup>.

Synthesis of new 2,5-disubstituted-1,3,4-thiadiazole compounds using 5-phenyl-2-furan by Zi-Ning Cui *et al.* Under microwave irradiation, a series of 2,5-disubstituted-1,3,4-thiadiazoles (28) were prepared using Lawesson's reagent with excellent yields<sup>16</sup>.

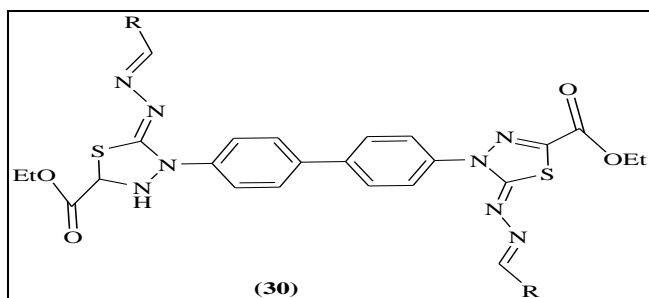


Synthesis heterocyclic compounds such as (1,3,4-thiadiazole derivatives, imidazolidine derivatives, tetrazole derivatives, oxazepine derivatives and  $\beta$ -Lactam derivatives) were prepared by reacting 4-

aminobenzoic acid with phenol in Acidic medium and sodium nitrate to yield azo derivative which react with thiosemicarbazide to get 1, 3, 4-thiadiazole derivative (29)<sup>17</sup>.

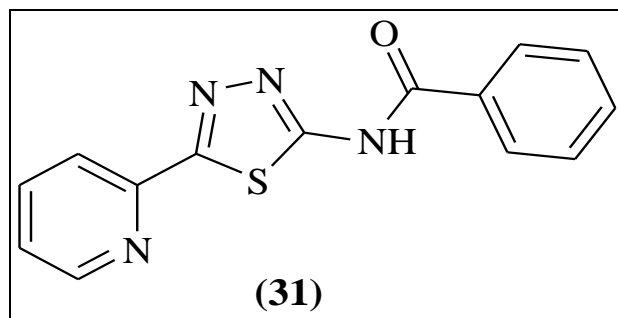


Sobhi M. Gomha *et al*, synthesize novel Bis (1,3,4-thiadiazole) derivatives (30) as potential cytotoxic agents. The novel one-pot-synthesis of bis(1,3,4-thiadiazole) derivatives were carried out through condensation reaction between bis-hydrazonoyl chloride and various reagents<sup>18</sup>.



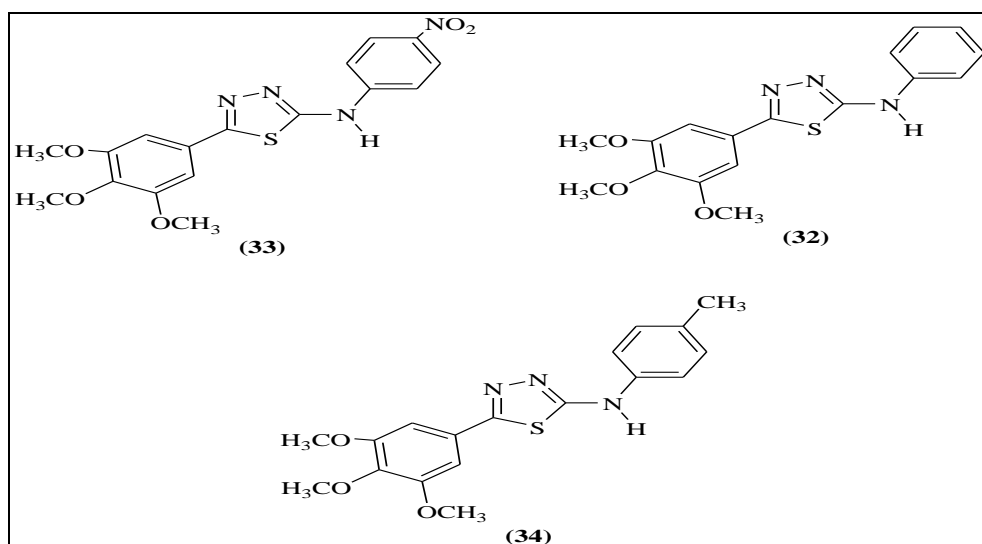
A novel series of 1,3,4-thiadiazole derivatives containing 2-pyridyl moiety (31) was prepared and the cytotoxicity of the each members of this series was screened by using MTT assay. The synthesized compounds' enzyme einhibitory activity was further tested against 15-lipoxygenase-1, a novel

target for the identification of anticancer medicines<sup>19</sup>.



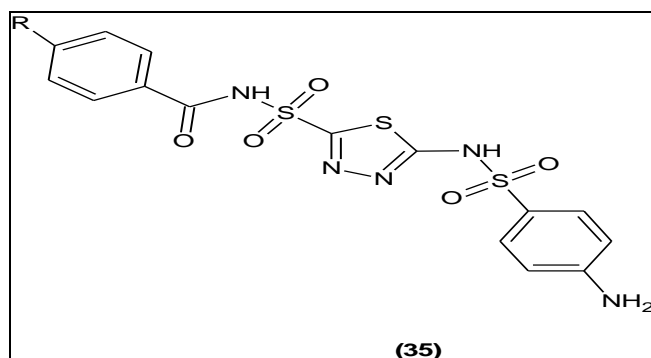
The 1, 3, 4-thiadiazoles were synthesized in one pot by refluxing aryl aldehydes, hydrazinehydrate, and aryl isothiocyanates in methanol and then oxidative cyclization with ferric ammonium sulphate.

The compounds (32), (33), (34) with trimethoxyphenyl at the C-5 position displayed extremely potent anticancer activity with at least two fold selectivity (IC<sub>50</sub>:4.3–9.21M)<sup>20</sup>.

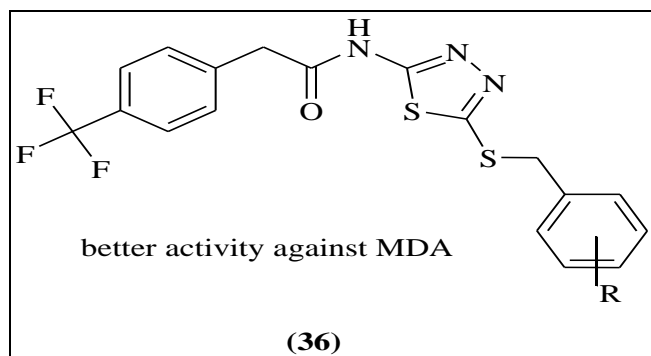


**Pharmacological Activity:**

**Anticancer Activity:** Mahavir Chhajed *et al.*; Synthesis 1, 3, 4-thiadiazol sulphonamides (35) and determined cytotoxic activity against various human cancer cell lines HEK293, BT474 and NCI-H226 cells by MTT assay. He comes to the conclusion that the electron-releasing group on the phenyl ring is to blame for the lower activity<sup>21</sup>.

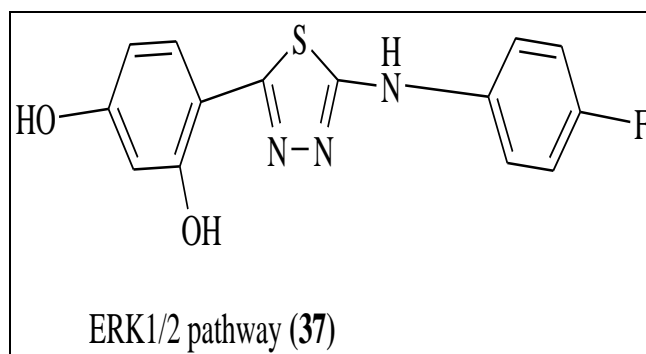


Alireza Aliabadia *et al.*; Synthesis Benzylthio-1, 3, 4-thiadiazolphenyl acetamide. The MTT experiment revealed that compound (36) has superior anticancer effect against MDA (breast cancer) than PC3 (prostate cancer) and U87 (prostate cancer) (Glioblastoma)<sup>22</sup>.



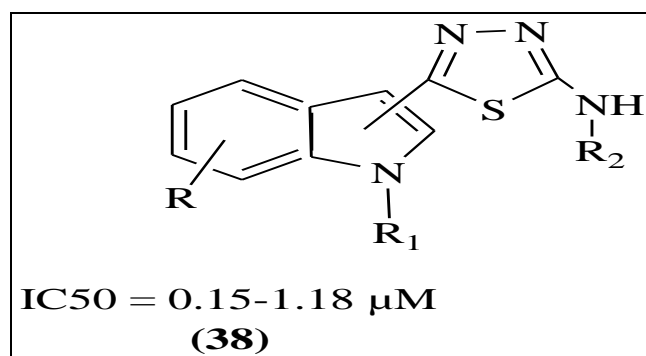
The activity of the (ERK1/2) pathway is inhibited by a series of 1, 3, 4-thiadiazole derivatives (FABT). The activity of the extracellular-signal-regulated kinase (ERK1/2) pathway in non-small cell lung cancer cells after treatment with a 2-amino-1, 3, 4-thiadiazole derivative was investigated in this study (37).

The ERK1/2 kinase pathway is a member of the mitogen-activated protein kinase (MAPK) family that controls cell proliferation, survival and differentiation. Compound FABT had good antiproliferative activity against A549 lung cancer cells, according to the results of anti-proliferative and Western-blot assays<sup>23</sup>.



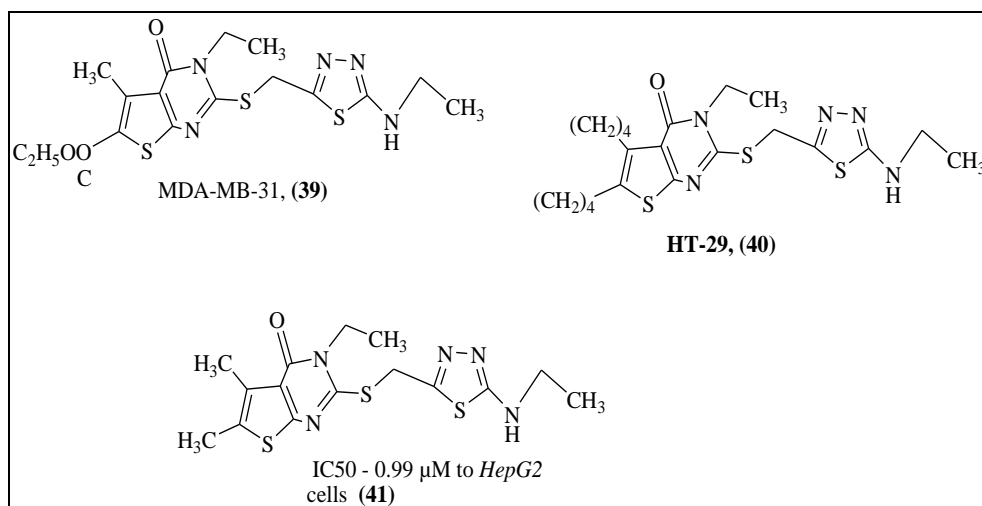
Chemical structure of 2-(4-fluorophenyl amino)-5-(2, 4 - dihydroxyphenyl)-1, 3,4-thiadiazole (FABT).

Treatment of indolyl hydrazides. With various aryl isothiocyanates produced thiosemicarbazides, which were then treated with acetylchloride to yield 2-arylamino-5-(indolyl)-1,3,4-thiadiazoles in good yields. They were tested for anticancer efficacy against MCF-7, LnCap, MDA-MB-231, DU145, HeLa and Ovar-3 human cell lines. 2-arylamino-5-(indolyl)-1,3,4-thiadiazole (38) was shown to have potent activity against all of the cancer cell lines examined ( $IC_{50}=0.15-1.18M$ )<sup>24</sup>.



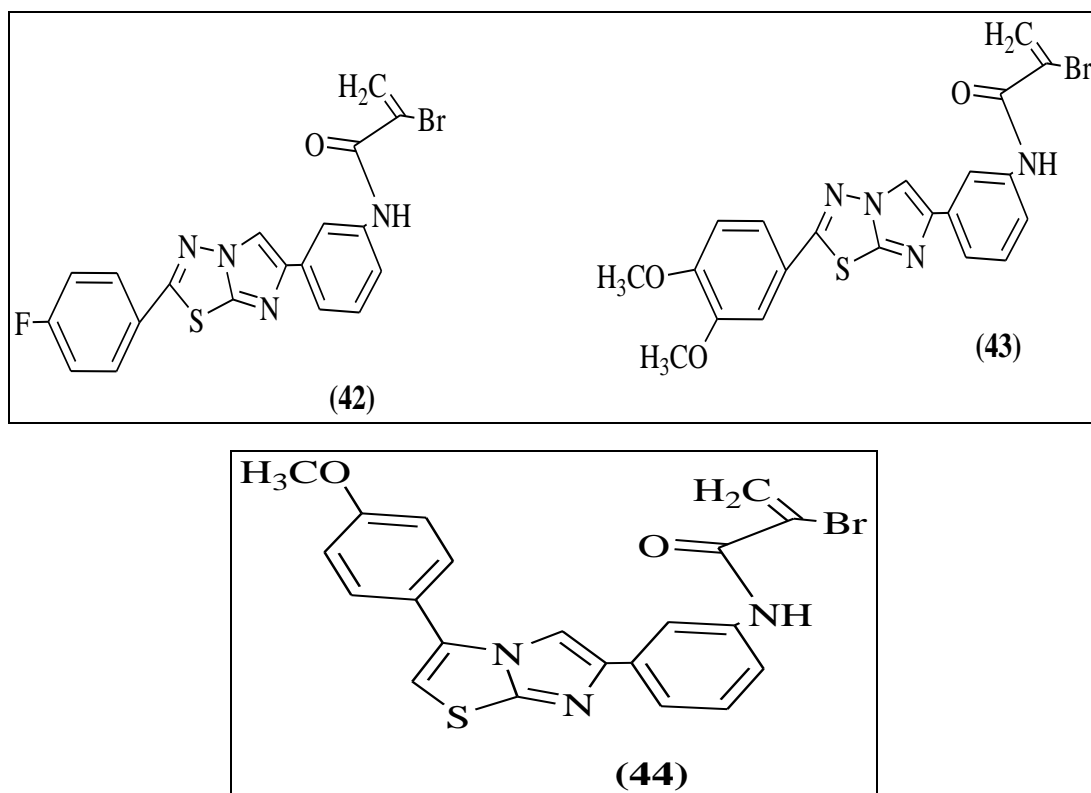
Cytotoxic effects of thienopyrimidin ones containing thiosemicarbazide and 1, 3, 4-thiadiazole moieties on four cancer cell lines were investigated: HT-29, MDA-MB-231 breast cancer cells, HeLa, HepG2 and a human diploid cell line Lep-3.

Compounds (39), (40) and (41) were found to be cytotoxic to the four cancer cell lines tested. The thiosemicarbazide (39), but not the thienopyrimidine (40), showed the highest cytotoxicity against MDA-MB-31 cell lines, with an  $IC_{50}$  of 0.001M. Compound (41) had the best inhibitory effect against human liver cancer HepG2 cells, with an  $IC_{50}$  of 0.99M<sup>25</sup>.



Hetero-bivalent ligands, which are made up of two separate pharmacophores that bind to two different sites on the same molecular target or to two different molecular targets, could be used to treat cancer. Because imidazo [1,2-b] [1,3] thiazole and imidazo [1,2-b] [1,3,4] thiazole are favoured structures for the development of new

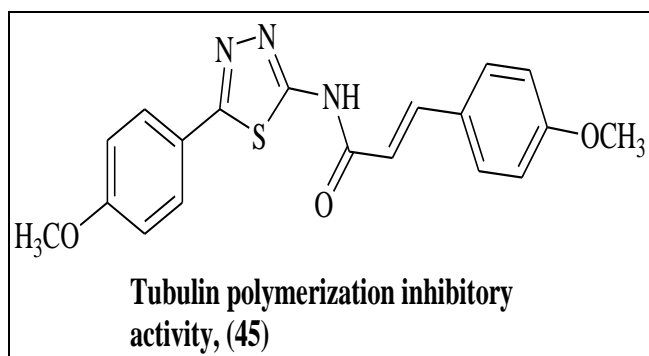
anticancer drugs. Romeo Romagnoli and colleagues set out to investigate the synthesis and biological evaluation of molecular conjugates made up of these fused bicyclic systems. Apoptosis was produced by compounds 42, 43 and 8c, which was linked to the release of cytochrome c<sup>26</sup>.



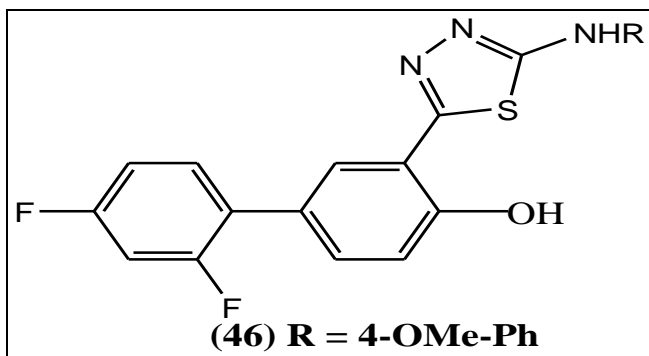
Yang *et al.* created a variety of cinnamicacyl 1, 3, 4-thiadiazole derivatives and tested their ability to inhibit Tubulin polymerization. The compound 45 was shown to be the most powerful among the produced compounds, inhibiting the growth of MCF-7 and A549 cell lines with IC<sub>50</sub>

values of 0.28 and 0.52g/mL, respectively. The Tubulin polymerization inhibitory action of compound (45) was also significant (IC<sub>50</sub> = 1.16g/mL). To find the most likely binding model, a docking simulation was run<sup>27</sup>.

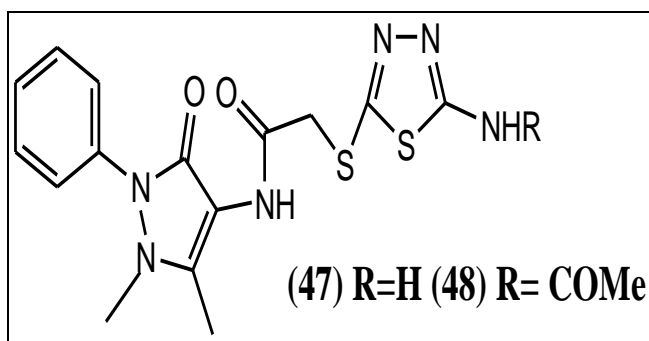




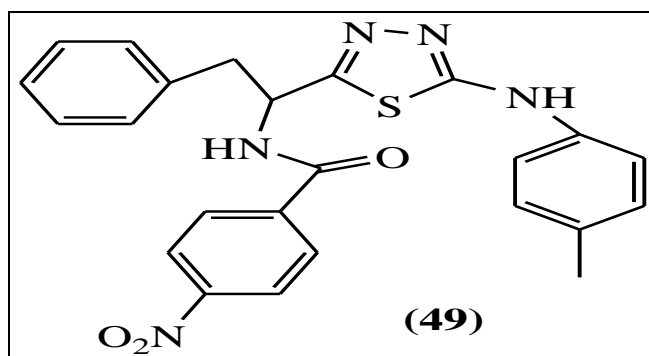
**Analgesic and Anti-inflammatory Activity:** In the carrageenan-induced rat paw edema test, compound 46, obtained by replacing the carboxyl in diflunisal with N-(p-tolyl)-1,3,4-thiadiazol-2-amine, showed better anti-inflammatory activity than the parent compound diflunisal, a marketed NSAID in clinical use, with percent inhibition values of 55 percent and 24 percent for compound 46 and diflunisal, respectively. Compound 46 had a value of  $19.2 \pm 0.91$  *in-vivo* for analgesic activity (paw with drawal latency in seconds SEM), where as diflunisal had a value of  $19.1 \pm 1.1$  <sup>28</sup>.



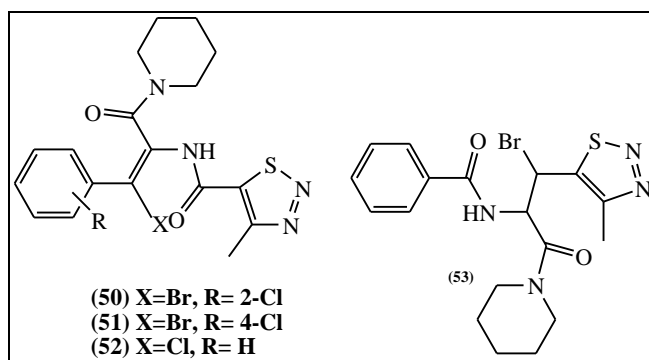
Rostom *et al.* reported the anti-inflammatory effects, as well as the antimicrobial activities, of a series of compounds including 47 and 48 <sup>29</sup>.



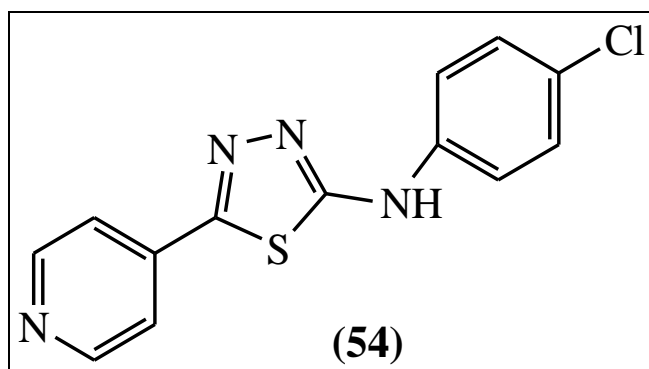
According to Moise *et al.*, all anti-inflammatory compounds prepared had lower toxicity than the similar compounds without the thiazolopyridine, with compound 49 having the lowest toxicity <sup>30</sup>.



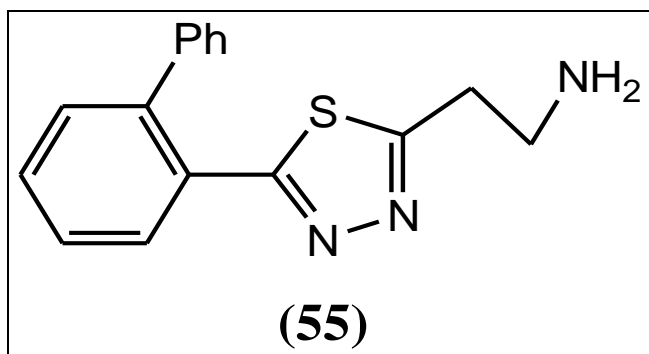
**Antiviral Activity:** Compounds 50–52, developed by Dong *et al.*, showed strong suppression of hepatitis B virus (HBV) DNA replication, with  $IC_{50}$  values lower than the recognized HBV medicine lamivudine ( $IC_{50}$  (mg/ml) = 10.4 for 84; 3.59 for 85; 9.00 for 86; 14.8 for lamivudine). Furthermore compound 53 considerably reduced HBV extracellular antigen HBeAg production ( $IC_{50}=12.26$ mg/ml) <sup>31</sup>.



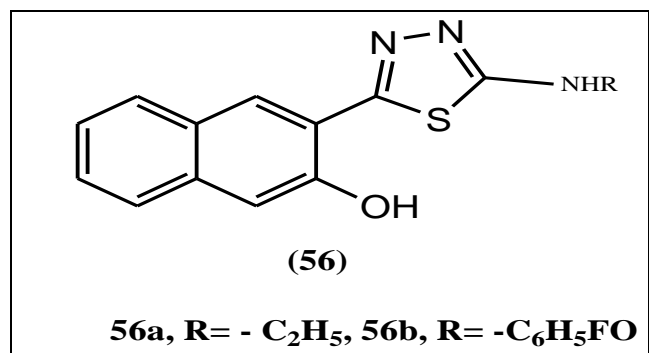
**Activity in the CNS:** Using a maximal electroshock seizure (MES) test, Yar *et al.* synthesised and analysed a series of thiazolopyridines, including 54, for their anticonvulsant properties. In comparison to the standard antiepileptic medication phenytoin sodium, compound 54 provided 100 percent protection against shock-induced seizures at a dose of 25mg/kg <sup>32</sup>.



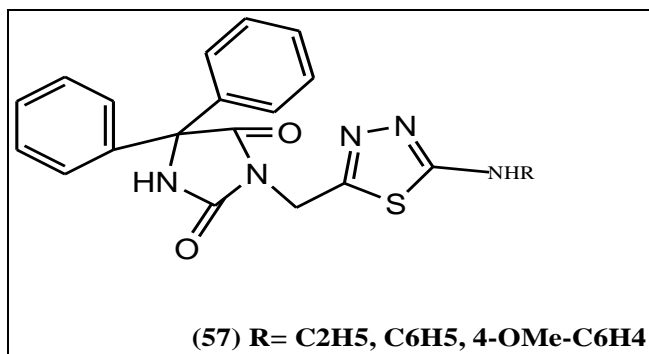
Anticonvulsant effects of a number of substituted 2-hydrazino-1,3,4-thiadiazoles were described by Stillings *et al.* In addition, they discovered that 2-(aminomethyl)-5-(2-biphenyl)-1, 3, 4-thiadiazole (55) has potent anticonvulsant characteristics in rats and mice, and that it compares favorably to the traditional anticonvulsants drugs phenytoin, phenobarbital, and carbamazepine in a variety of tests<sup>33</sup>.



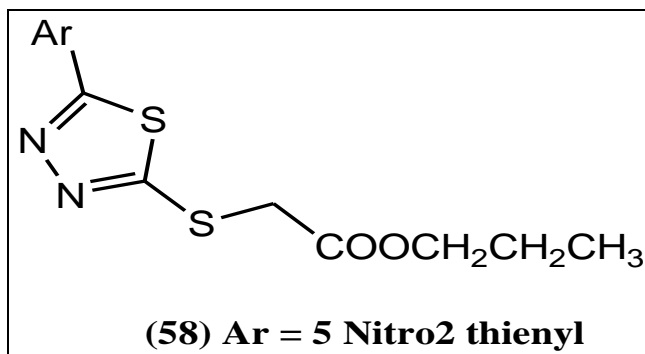
Dogan *et al.* produced several compound sand discovered that compound 56a and 56b have anticonvulsant properties. They also discovered these two chemicals could be useful in the creation of novel anticonvulsants<sup>34</sup>.



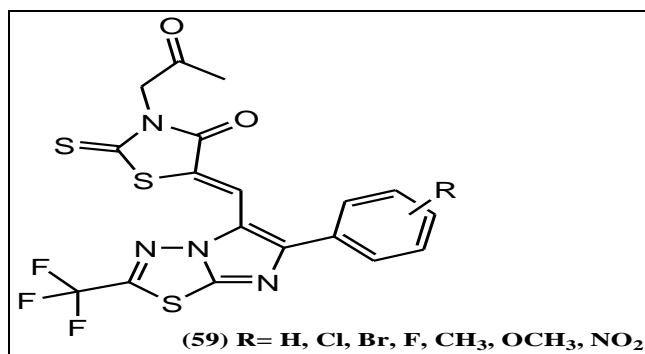
Only the phenyl substituted (22) molecule exhibited promising anticonvulsant efficacy among the produced compounds<sup>35</sup>.



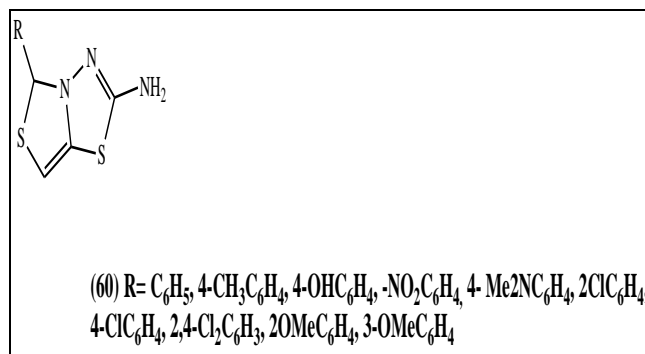
**Antitubercular Activity:** Foroumadi *et al.*, produced two series of 2-and3-[5-(nitroaryl)-1,3,4-thiadiazol-2-yl-thio, sulfinyl and sulfonyl] propionic acid alkylesters and screened for antituberculosis efficacy against Mycobacterium TB, finding that compound 58, propyl 3-[5-(5-nitrothiophen-2-yl)-1,3,4-thiadiazol-2-ylthio] propionate was the most active one<sup>36</sup>.



A new class of Imidazo [2,1-b] [1,3,4]-thiadiazoles with rhodanine-3-acetic acid as antitubercular agents (59). Some of the synthesized compounds had extremely excellent antitubercular efficacy against *M. tuberculosis in-vitro*<sup>37</sup>.

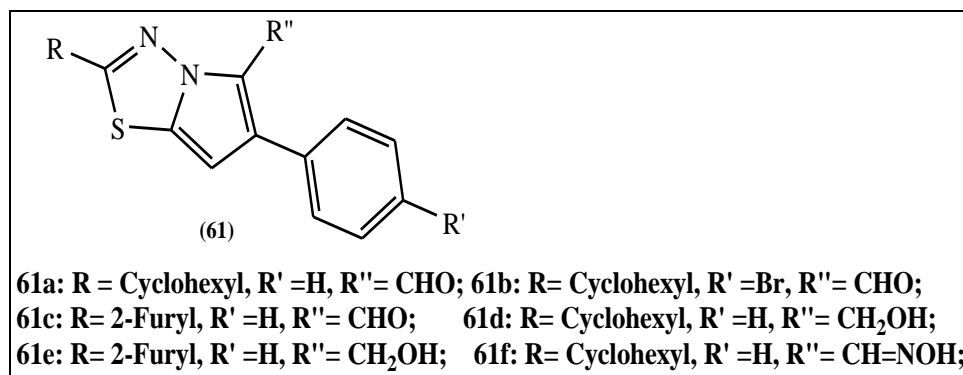


2-Amino-5-aryl-thiazolo [1, 3, 4]-Thiadiazole derivatives (60) were synthesised. Antitubercular action was demonstrated in some of the produced drugs<sup>38</sup>.

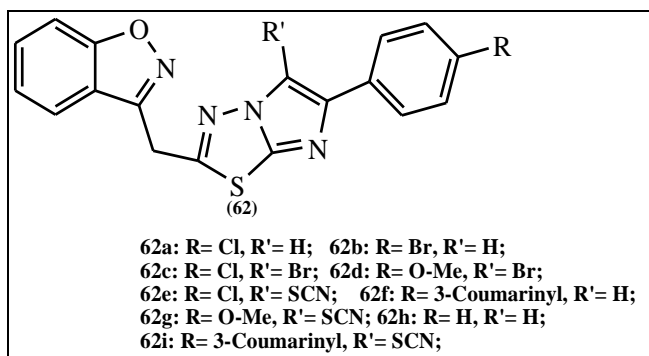


G.Kolavi *et al.* described the synthesis of a series of 2,6-disubstituted and 2,5,6-trisubstituted imidazo [2,1-b] [1,3,4] thiadiazoles. The BACTEC 460 radiometric system and broth dilution tests were used to determine the structure of the compounds and to screen them for antitubercular activity against *Mycobacterium TBH37 Rv.* The

compounds (61c) and (61d) demonstrated the strongest inhibitory activity (100 percent). Compounds (61a), (61b), (61e), and (61f) demonstrated mode rate anti-tubercular activity *in-vitro* against *M. tuberculosis* strain H37Rv with a MIC of 6.25g/ml<sup>39</sup>.



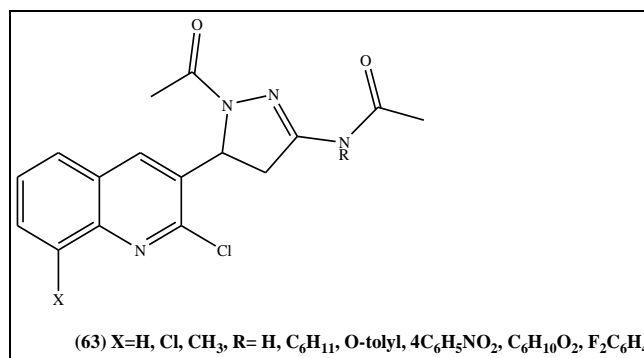
**Antimicrobial Activity:** The synthesis of novel methylene bridged benz isoxazolyl imidazo [2,1-b][1,3,4] thiadiazoles was reported by Lamani RS *et al.* Using the Agar Diffusion technique, the newly synthesized compounds were tested for antibacterial and antifungal activities. *S. aureus*, *B. subtilis*, *P. aeruginosa* and *E. coli* were used to test the antibacterial activity. *C. albicans* and *A. fumigates* were used to test the antifungal activity. The chemicals (62a), (62b), (62c), (62d), and (62e) inhibited bacteria moderately to well, where as the compounds (62b), (62f), (62g), (62h), and (62i) displayed strong antifungal action<sup>40</sup>.



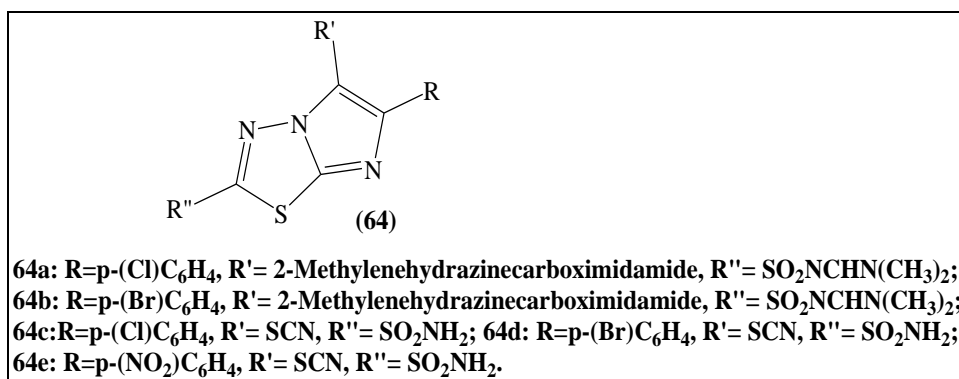
A series of 3-(1,3,4-Thiadiazole-2-yl) quinoline derivatives (63) derived from chloroquinone with the goal of studying their effect on the *in-vitro* growth of microbial infection-causing bacteria. In their most basic structural form, synthesized molecules have two physiologically active components: quinoline and thidiazoles.

The intermediate chemicals were evaluated for their effect on microorganism development and managed to be stable.

Some leads were discovered by screening the intermediate" thiosemicarbazones" and final" thiadiazoles" for gram-negative and positive bacteria<sup>41</sup>.



Gadad AK *et al.* synthesized 5-guanyl hydrazone/thiocyanato-6-arylimidazo [2, 1-b] [1, 3, 4] thiadiazole – 2 - sulfonamide derivatives. The antibacterial activity of synthesized compounds against *E. coli*, *S. aureus*, *P. aeruginosa*, *S. typhi*, and *S. pneumococci* was investigated using the Cup Plate technique and Mueller Hinton agar medium. The antibacterial activity of compounds (64a), (64b), (64c), (64d) and (64e) has been demonstrated. The presence of 5-guanyl hydrazone and 5-thiocyanato groups on the compounds led to good antibacterial action<sup>42</sup>.



Zayeri *et al.* produced and tested antibacterial activity of gatifloxacin derivatives containing 5-(5-nitroheteroaryl)-1, 3, 4-thiadiazol-2-yl groups at C-7. The presence of nitro furan (65) at the C-2 position of the thiadiazole ring completely inhibited DNA gyrase or DNA topoisomerase IV, and it had a stronger inhibitory effect against Gram-positive bacteria like *S. epidermidis* (MIC=0.0078g/mL), *B. subtilis* (MIC=0.0039g/mL), *E. faecalis* (MIC=0.125g/mL)<sup>43</sup>. Furthermore, numerous thiadiazole-containing compounds have entered clinical trials as single agents or in combination

with currently available anticancer medicines (summarized in **Table 1**).

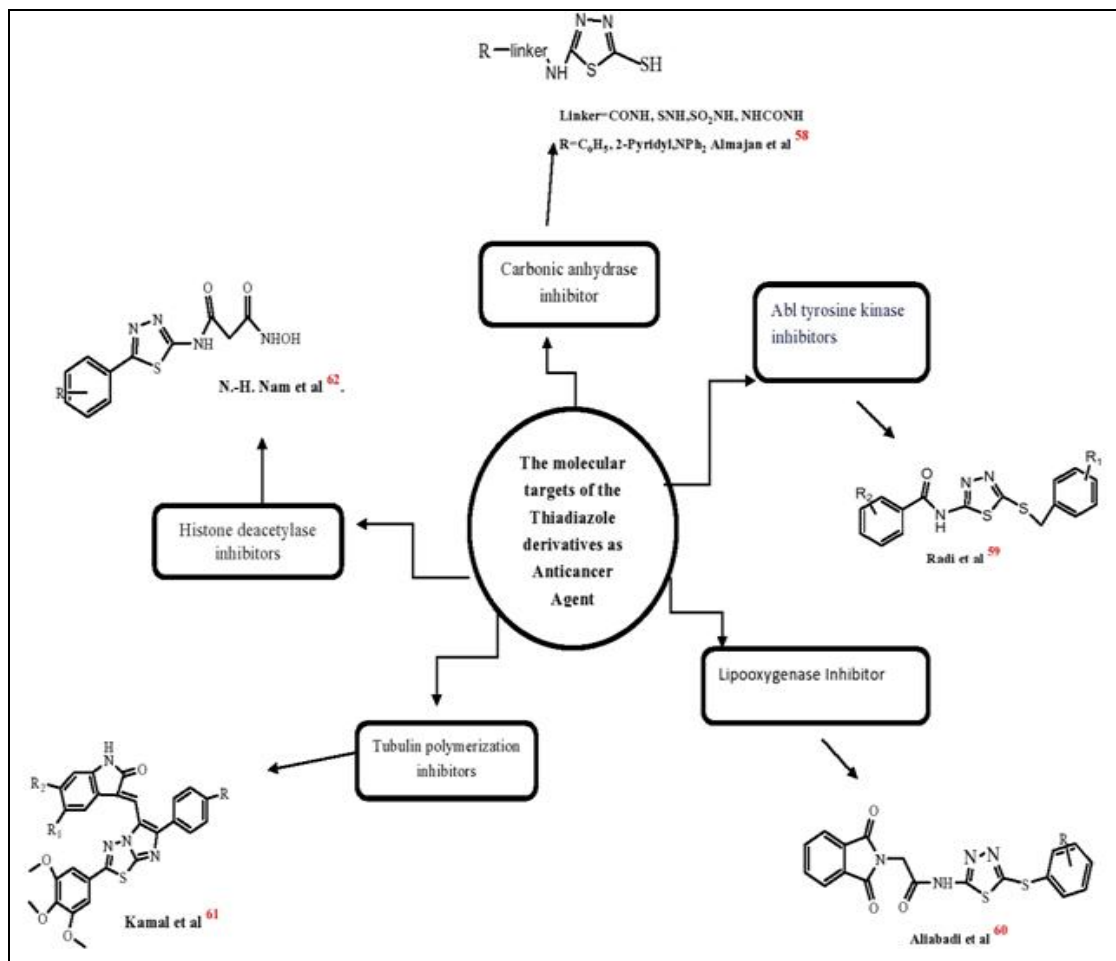
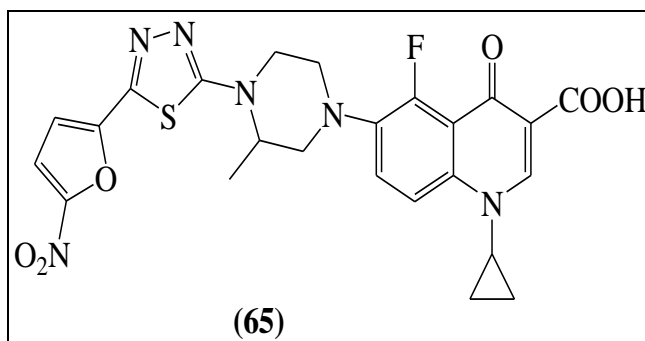


FIG. 1: THE MOLECULAR TARGETS FOR THIADIAZOLE MOIETYAS ANTICANCER AGENT

**CONCLUSION:** It may be concluded that 1,3,4-thiadiazole moiety exert a spectrum of pharmacological activity which may be used to design new scaffold.

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