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Review Article

4-Thiadiazole: The Biological Activities

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ABSTRACT
4-Thiadiazole (1,3,4-thiadiazole) nucleus displayed noteworthy industrial efficiencies and has shown various biological activities, especially as a cancer chemo preventive agent. 4-Thiadiazole has been categorized as a member of family of azole that consist of thiadiazole ring. 4-Thiadiazole is chemical entity which has being synthesized in the past many forms of its derivatives; the entity provides the principal origin of motivating to numerous chemist to investigate its diverse medical efforts especially with regards to the antimicrobial, ant tubercular, anticancer, anti-inflammatory. Current survey supply a wide vision of the antibacterial activity possessed by molecules having a 4-thiadiazole moieties.

Key words: 4-thiadiazole, Anti-tubercular, Antimicrobial activity, Medical efforts, Anti-inflammatory.

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INTRODUCTION

Heterocyclic compounds may found in considerable number of organic molecules that exhibit antimicrobial efficiencies. The antimicrobial efficiencies of these molecules have is fundamentally contingent by structures of these molecules.[1] Thiadiazoles are quite motivating molecules because of the significant utilizations in considerable pharmaceuticals and medicinal domain.[2,3] Thiadiazole [4] have ring of unsaturated structures with moiety formula C2H3N3S having 2 atoms of carbon, Sulphur atom and 3 nitrogen atoms. Thiadiazoles have been utilized for medicinal activity like anti-viral, anti-microbial and anti-tubercular. Thiadiazoles were familiar also to displayed anti-inflammatory, antidepressant and analgesic activities, the latest existence generally investigated through the forced swim investigation.[5,6] Amid the medical profiles of thiadiazoles, their antibacterial and antifungal characteristics appear to be the superior notarized. The ring moiety of thiadiazole was the most significant nuclei, as a well-known whole characteristics of diversity of natural medicinal agents. As essence structural, thiadiazoles are show in configuration of drugs category.[7,8] Thiazoles show a wide range of pharmacological activities and were found in numerous effective pharmacologically active compounds such as anti-neoplastic drugs.[9] However, thiadiazoles especially recognized for their anti-cancer [10,11] activities. In continuation of previous studies on coumarins as heterocyclic compounds,[12-34] herein we are reporting a review for such recent derivatives of heterocyclic compound namely 4-thiadiazole with pharmacological activities.

Chemistry

Thiadiazoles were compounds with heterocyclic ring having nitrogen and sulfur atoms as part of the aromatic ring. Thiadiazoles with 2 nitrogens and 1 sulfur atoms were named 4-thiadiazole. Thiadiazoles exist in nature in 4 forms as 1,2,3-thiadiazole;1,2,5-thiadiazole; 1,2,4-thiadiazole and 1,3,4-thiadiazole (a, b, c and d) respectively. 1, 3, 4-thiadiazole were significant becdue to the biological actions.

(a) (b) (c) (d)

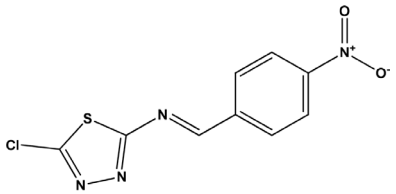
Biological applications

Thiadiazoles were known to displayed various of pharmacological activity. Thiadiazoles were utilized as antibacterial, antifungal and anti-cancer activities in addition to and anti-inflammatory activities.

Anti-Microbial Activity

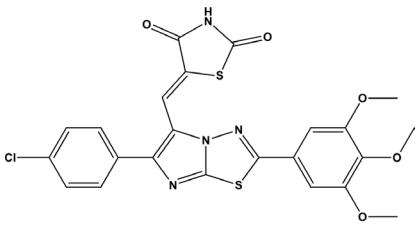
Nowadays research reviews have been shown that thiadiazoles have wide spectrum of biological activities exclusively effective anti-bacterial and anti-fungal activities that were displayed below in this review:

Mousa synthesis of thiadiazoles. The preparation compounds were evaluated for the antibacterial activities. The synthesized molecules have been studied for their antibacterial activity against the *S. aureus* and *B. Cereus as* gram positive and *E. coli* and *P. Aeroginosa* as gram negative bacteria. The prepared compound showed a noticeable antimicrobial activity as compared to standard drug. Compound [1] showed the best antimicrobial activity against the tested bacteria.[35]



[1]

Alagawadi K. R. *et al*., have prepared series of novel thiazolidinones [2,3]. These molecules have been examined *the* anti-bacterial activities versus the Gram-positive *and* Gram-negative *bacteria named Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli*, *Pseudomonas aeruginosa bacteria in addition to fungi named* and *Candida albicans*, *Aspergillus flavus*, *Aspergillus niger*. They were found that some of the synthesized compounds *named p*-chlorophenyl and 6-*p*-bromophenyl displayed highest antimicrobial activities.[36]



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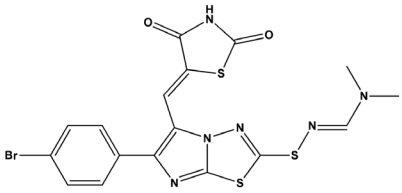
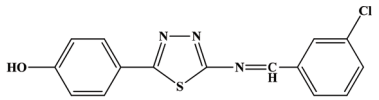
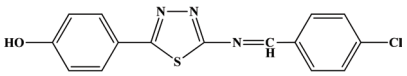


[3]

Baghel U. S. *et al* had been synthesized a new thiadiazoles and examined the anti-bacterial and antifungal activities for them. The novel prepared thiadiazoles were investigated against Gram positive and gram negative species named *Bacillus subtilis, Staphylococcus aureus* and Gram negative species *Pseudomonas aeruginosa, Escherichia coli* addition to fungi *Candida albicans and A. niger*. Compounds 4-(5-(3-chlorobenzylideneamino)-1,3,4-thiadiazol-2-yl)phenol [4] and 4-(5-(4-chlorobenzylideneamino)-1,3,4-thiadiazol-2-yl)phenol [5] shows potent activities comparing with the examined microbes.[37]

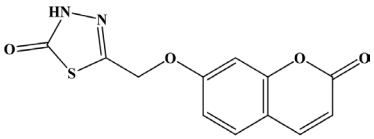


[4]



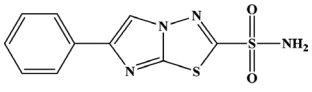
[5]

Al-Amiery *et al* had been synthesized new thiadiazoles that have coumarin moieties [6] and tested for their antimicrobial activity. *In vitro* anti-bacterial and anti-fungal investigations various microbes named (*Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus vulgaris*, *Pseudomonas aeruginosa* with *Aspergillus niger* and *Candida albicans*).[38]



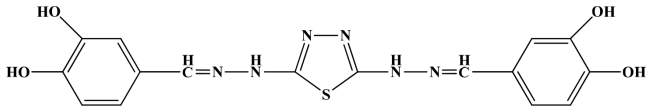
[6]

Fawzia *et al* synthesized 6-phenylimidazo[2,1-b][1,3,4]thiadiazole-2-sulfonamide [7] displayed the antimicrobial activities vs the *Escherichia coli* and *staphylococcus aureus* in addition to moderate activities vs *salmonella typhi*, *pseudomonas aeguginosa* and *pneumococci*.[39]



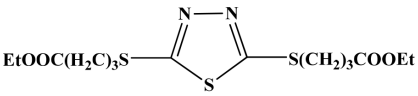
[7]

Al-Mosowy was synthesized compound named 4,4'-(2,2'-(4-thiadiazole-2,5-diyl)bi(hydrazin-2-yl-1-ylidene))bi(methan-1-yl-1-ylidene) di-benzene-1,2-diol [8] and investigated for the *in vitro* anti-microbial activities vs the Gram negative bacteria named *Escherichia coli* and Gram positive bacteria named *Staphylococcus aureus*. The synthesized compound showed highest efficiencies vs selected bacteria *Staphylococcus aureus and Escherichia coli.*[40]



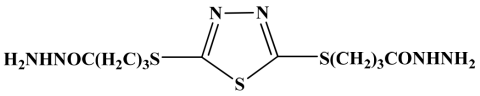
[8]

Nadjet R. *et al*., synthesized diethyl4,4′- [(1,3,4-thiadiazol- 2,5 diyl)bis (sulfa nediyl)]dibutanoate [9] and 4,4'- (1,3,4- thiadiazole-2, 5-diyl)bis (sulfa nediyl)dibutanehydrazide [10]. Compounds [9] and [10] showed a high degree of antibacterial activities vs bacterial species Gram-positive and Gram-negative in addition to fungi.[41]



diethyl 4,4'-((1,3,4-thiadiazole-2,5-diyl)bis(sulfanediyl))dibutanoate

[9]

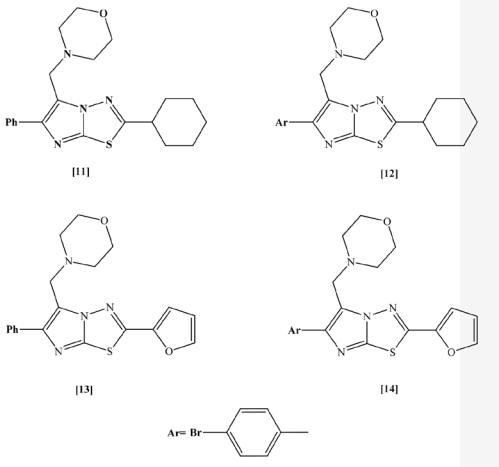


[10]

Anti-Tubercular Activity

Nowadays there were potent studies on thiadiazoles, some of them that were known to possess considerable medicinal characteristics such as anti-bacterial, anti-fungal, anti-tubercular, anti-inflammatory, anti-convulsing and anti-hypertension activities.

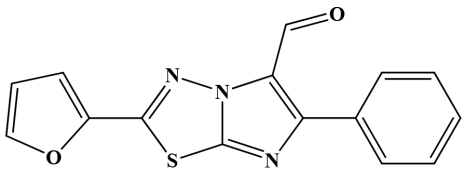
Onkol T *et al* synthesized of 4-((2-cyclohexyl-6-phenylimidazo[2,1-b][1,3,4] thiadiazol-5-yl)methyl)morpholine [11], 4-((6-(4-bromophenyl)-2-cyclohexylimidazo [2,1-b][1,3,4] thiadiazol-5yl) methyl)morpholine [12], 4-((2-(furan-2yl)-6-phenylimidazo[2,1-b][1,3,4]thiadiazol-5-yl) methyl)morpholine [13] and 4-((6-(4-bromophenyl)-2-(furan-2-yl) imidazo[2,1-b][1,3,4]thiadiazol-5-yl)methyl)morpholine [14]. The synthesis compounds show excellent activities vs Mycobacterium *tuberculosis.*[42]



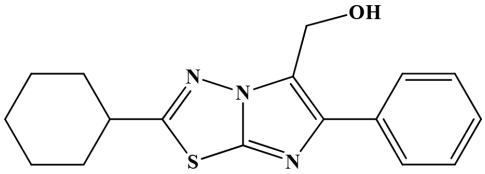
[11] [12] [13] [14]

Kolavi G. *et al*., were prepared substituted thiadiazoles that have imidazole moiety and were investigated for their anti-tubercular activities vs *Mycobacterium tuberculosis* H37Rv utilizing the BACTEC 460 radiometric system. Two of the investigated compounds [15 and 16] were exhibit the

highest inhibition efficiencies.[43]



[15]

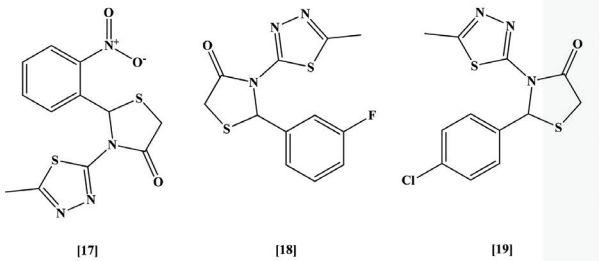


[16]

Anti-Cancer Activity

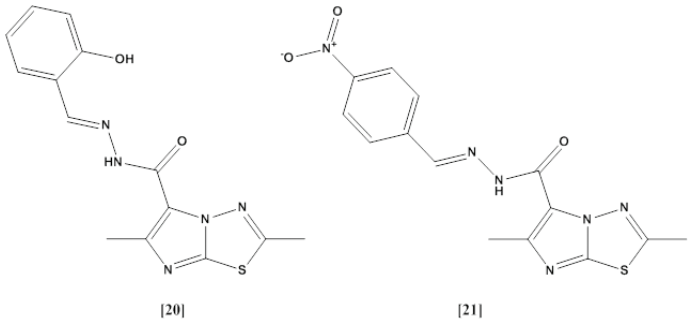
4-Thiadiazole that have Amino group were have inhibition activities against many trans-planted tumors.

Joseph A. *et al* were prepares new thiadiazoles having thiazolidin-4-ones moieties and *in vitro* anti-proliferative activity were examined on human breast adenocarcinoma cells (MCF-7) by MTT assay. Among the investigated compounds, 3-(5-methyl-1,3,4-thiadiazol-2-yl)-2-(2-nitrophenyl)-4-oxothiazolidin [17], 2-(3-fluorophenyl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)-4-oxothiazolidin [18], and 2-(4-chlorophenyl)-3-(5-methyl-1,3,4-thiadiazol-2-yl)-4-oxothiazolidin [19] were have the highest potent with IC_{50} values of (46.34, 66.84 and 60.71) µmol/L respectively.[44]



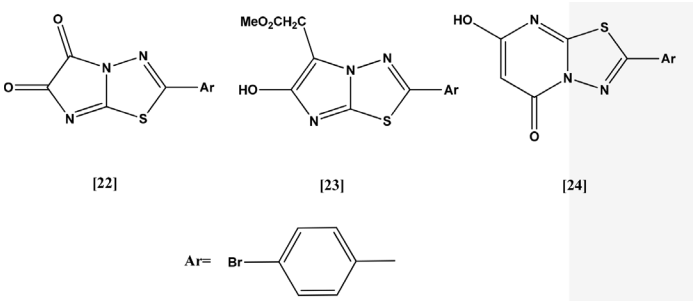
[17] [18] [19]

Terzioglu N. *et al.* were prepared new 4-thiadiazole substituted with carbohydrazides. (E)-N'-(2-hydroxybenzylidene)-2,6-dimethylimidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide [20] and (E)-2,6-dimethyl-N'-(4-nitrobenzylidene)imidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide [21] were passed the criteria for activities in the assay (20-29% growth percentages) and were automatically scheduled for investigation vs the full panel of 60 human tumor cell lines at minimum concentrations at 10-fold dilutions.[45]



[20] [21]

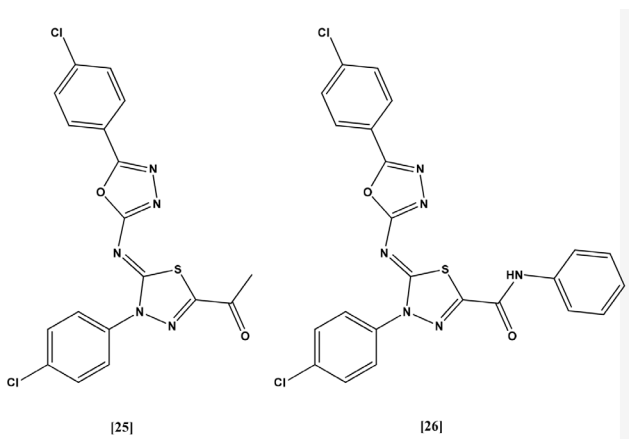
Doaa E. Abdel Rahman and Khaled O. Mohamed synthesized substituted imidazo-4-thiadiazoles. All the synthesized compounds have been investigated for their cytotoxic activities vs tumor cell line A549 (Non-Small Cell Lung Cancer Cell Line) utilizing Sulfo-Rodamine B (SRB) technique. The investigated molecules showed potent cytotoxicity especially compounds 2-(4-bromophenyl)imidazo[2,1-b][1,3,4]-5,6-dioxothiadiazole [22], Methyl 2-[2-(4-bromophenyl)-6-hydroxyimidazo[2,1-*b*]-1,3,4-thiadiazol-5-yl]acetate [23], 2-(4-bromophenyl)-5-hydroxy-7*H*-1,3,4 thiadiazolo[3,2-*a*]-7-oxopyrimidin [24] (IC_{50} 2.58-6.47 µM).[46]



[22] [23] [24]

Ar= Br

Dawood and Gomha, Synthesized of (Z)-1-(4-(4-chlorophenyl)-5-((5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl)imino)-4,5-dihydro-1,3,4-thiadiazol-2-yl)acetaldehyde [25] and 4-(4-chlorophenyl)-5-(5-(4-chlorophenyl)-1,3,4-oxadiazol-2-ylimino)-N-phenyl-4,5-dihydro-1,3,4-thiadiazole-2-carboxamide [26]. The novel synthesized molecules have promising cancer potent against colon.[47]



[25] [26]

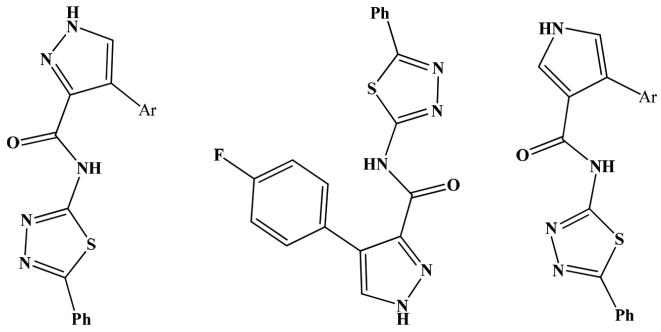
Anti-Inflammatory Activity

Maddila S. *et al.*, synthesized of 4-(4-Nitrophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-

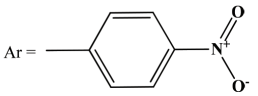
1H-pyrazole-3-carboxamide [27], 4-(4-Fluorophenyl)-N-(5-phenyl-1,3,4-thiadiazol-2-yl)-

1H-pyrazole-3-carboxamide [28] and 4-(4-Nitrophenyl)-N-(5-phenyl-

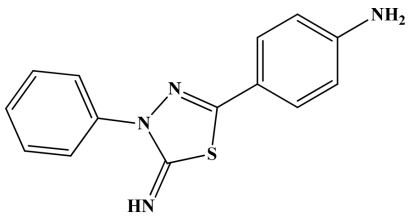
1,3,4-thiadiazol-2-yl)-1H-pyrrole-3-carboxamide [29]. The new compounds have been tested for their anti-inflammatory activities. Compounds were displayed important anti-inflammatory activities with high percentage inhibition in paw edema, compared with indomethacin as standard drug.[48]



[27] [28] [29]



Asif M. and Asthana C. were synthesized thiadiazoles with imino moiety. The synthesized compound named 4-(5-imino-4-phenyl-4,5-dihydro-1,3,4-thiadiazol-2-yl)aniline [30] have been examined for in vivo anti-inflammatory activities by using of carrageenan induced paw oedema technique and compared with Diclofenac as standard drug.[49]



[30]

CONCLUSION

Generally, thiadiazoles are extreme effective heterocyclic that have electron-deficient carbon atoms, with nitrogen and sulfur atoms in addition to an electron pair. these compounds have electron deficient nature and high stability, and due to these characteristics, they could react hardly. On the basis of new scientific research concerning a various medicinal activity of new thiadiazoles that have been provided in this review, it could be concluded that thiadiazoles have a considerable property for the lethal microbial infections therapy. Thus, the presented survey could give a another hope and considerable various technique to the chemists to try drug design and evolution of better and safer antimicrobial compounds for future.

ACKNOWLEDGEMENT

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATION USED

IC50: half maximal inhibitory concentration; **µ:** micro; **MTT assay:** 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide; **MCF-7:** Michigan Cancer Foundation-7.

REFERENCES

1. Elzahany EA, Hegab KH, Khalil SKH, Youssef NS. Synthesis, characterization and biological activity of some transition metal complexes with Schiff bases derived from 2- formylindole, salicylaldehyde, and N-amino rhodanine. Aust J Basic Appl Sci. 2008;2(2):210-20.
2. Hadizadeh F, Vosoogh R. Synthesis of a-[5-(5-Amino-1, 3, 4-thiadiazol-2-yl)-2 imidazolylthio]-acetic acids. J Heterocyclic Chem. 2008;45(5):1-3.
3. Kumar PT, Piyush G, Kumar JS. 3D QSAR Studies on Some 5-(1H-Indol-5-yl)-1, 3, 4-Thiadiazol-2 Amines as Potential PIM-1 Inhibitors. J Young Pharm. 2017;9(2):162-7.
4. Hiswa SA, Alkanabi TO. Study of Sum Physical and Biological Parameters of 5, 5¯-((Pentane-2,4-Diylidene bis (-1-yl-1Yalideneazan)) bis (1,3,4-Thiadazole-2-thiol) by Density Functional Theory. Journal of Chemical and Pharmaceutical Research. 2016;8(8):65-70.
5. Hu Y, Li CY, Wang XM, Yang YH, Zhu HL. 1,3,4-Thiadiazole: Synthesis, Reactions, and Applications in Medicinal, Agricultural, and Materials Chemistry. Chem Rev. 2014;114(10):5572-610.
6. Islam Md R, Zaman A, Jahan I, Chakravorty R, Chakraborty S. In silico QSAR analysis of quercetin reveals its potential as therapeutic drug for Alzheimer's disease. J Young Pharm. 2013;5(4):173-9.
7. Jain AK, Sharma S, Vaidya A, Ravichandran V, Agrawal RK. 1,3,4-Thiadiazole and its Derivatives: A Review on Recent Progress in Biological Activities. Chem Biol Drug Des. 2013;81(5):557-76.
8. Altıntop MD, Can ÖD, Özkay ÜD, Kaplancıkl ZA. Synthesis and Evaluation of New 1,3,4-Thiadiazole Derivatives as Antinociceptive Agents. Molecules. 2016;21(8):1004.
9. Siddiqui N, Arshad MF, AhsanW, Alam MS. Thiazoles: A valuable insight into the recent advances and biological activities. Int J Pharm Sci Drug Res. 2009;1(3):136-43.
10. Majumdar P, Pati A, Patra M, Behera RK, Behera AK. Acid Hydrazides, Potent Reagents for Synthesis of Oxygen-, Nitrogen-, and/or Sulfur-Containing Heterocyclic Rings. Chem Rev. 2014;114(5):2942-77.
11. Niu P, Kang J, Tian X, Song L, Liu H, Wu J. Synthesis of 2-Amino-1,3,4-oxadiazoles and 2-Amino-1,3,4-thiadiazoles via Sequential Condensation and I2-Mediated Oxidative C–O/C–S Bond Formation. J Org Chem. 2015;80(2):1018-24
12. Al-Amiery AA, Al-Majedy YK, Al-Duhaidahawi D, Kadhum AAH, Mohamad AB. Green Antioxidants: Synthesis and Scavenging Activity of Coumarin-Thiadiazoles as Potential Antioxidants Complemented by Molecular Modeling Studies. Free Radicals and Antioxidants. 2016;6(2):173-7.
13. Al-Amiery AA, Al-Bayati RI, Saour KY, Radi MF. Cytotoxicity, antioxidant and antimicrobial activities of novel 2-quinolone derivatives derived from coumarin. Research on Chemical Intermediates 2012.
14. Al-Amiery AA, Al-Bayati RIH, Saour KY, Radi MF. Cytotoxicity, antioxidant, and antimicrobial activities of novel 2-quinolone derivatives derived from coumarin. Res Chem Int Med. 2011.
15. Al-Bayati RI, Al-Amiery AAH, Al-Majedy YK. Design, synthesis and bioassay of novel coumarins. Afr J Pure Appl Chem. 2010;4:74-86.
16. Al-Bayati RI, Amier AA, Al-Amiery A, Al-Majedy YK. Synthesis and antimicrobial studies of novel metal complexes of testosterone thiosemicarbazone and methandrostenolone thiosemicarbazone. J Biotechnol Res Center (special edition). 2010;4:73-84.
17. Al-Majedy YK, Al-Amiery AA, Kadhum AAH, Mohamad AB. Antioxidant activities of 4-methylumbelliferone derivatives. PLoS ONE. 2016;11(5).
18. Al-Azawi KF, Al-Baghdadi SB, Mohamed AZ, Al-Amiery AA, Abed TK, Mohammed SA, *et al.* Synthesis, inhibition effects and quantum chemical studies of a novel coumarin derivative on the corrosion of mild steel in a hydrochloric acid solution. Chem Cent J. 2016;10(1).

19. Al-Amiery AA, Al-Majedy YK, Kadhum AAH, Mohamad AB. Synthesis of new coumarins complemented by quantum chemical studies. Res Chem Intermed. 2016;42(4):3905-18.
20. Al-Majedy YK, Al-Duhaidahawi DL, Al-Azawi KF, Al-Amiery AA, Kadhum AAH, Mohamad AB. Coumarins as potential antioxidant agents complemented with suggested mechanisms and approved by molecular modeling studies. Molecules. 2016;21(2).
21. Al-Majedy YK, Kadhum AAH, Al-Amiery AA, Mohamad AB. Coumarins: The antimicrobial agents. Syst Rev Pharm. 2016;8(1):62-70.
22. Al-Majedy Y, Al-Amiery A, Kadhum AA, BakarMohamad A. Antioxidant activity of coumarins. Syst Rev Pharm. 2016;8(1):24-30.
23. Issa AY, Rida KS, Salam AQ, Al-Amiery AA. Acetamidocoumarin as a based eco-friendly corrosion inhibitor. Int J ChemTech Res. 2016;9(11):39-47.
24. Al-Amiery AA, Al-Majedy YK, Kadhum AAH, Mohamad AB. Hydrogen peroxide scavenging activity of novel coumarins synthesized using different approaches. PLoS ONE. 2015;10(7).
25. Al-Amiery AA, Al-Majedy YK, Kadhum AAH, Mohamad AB. Novel macromolecules derived from coumarin: Synthesis and antioxidant activity. Sci Rep. 2015;5.
26. Al-Amiery AA, -Majedy YKA, Kadhum AAH, Mohamad AB. New coumarin derivative as an eco-friendly inhibitor of corrosion of mild steel in acid medium. Molecules. 2015;20(1):366-83.
27. Al-Majedy YK, Kadhum AAH, Al-Amiery AA, Mohamad AB. Synthesis and characterization of some new 4-hydroxycoumarin derivatives. Molecules. 2014;19(8):11791-11799.
28. Mohamad AB, Kadhum AAH, Al-Amiery AA, Ying LC, Musa AY. Synergistic of a coumarin derivative with potassium iodide on the corrosion inhibition of aluminum alloy in 1.0 M H2SO4. Met Mater Int. 2014;20(3):459-67.
29. Kadhum AAH, Mohamad AB, Hammed LA, Al-Amiery AA, San NH, Musa AY. Inhibition of mild steel corrosion in hydrochloric acid solution by new coumarin. Mater. 2014;7(6):4335-48.
30. Al-Amiery AA, Kadhum AAH, Al-Majedy YK, Ibraheem HH, Al-Temimi AA, Al-Bayati RI, *et al*. The legend of 4-aminocoumarin: Use of the Delépine reaction for synthesis of 4-iminocoumarin. Res Chem Intermed. 2013;39(3):1385-91.
31. Al-Amiery AA, Jaffar HD, Obayes HR, Musa AY, Kadhum AAH, Mohamad AB. Thermodynamic studies on 4-aminocoumarin tautomers. Int J Electrochem Sci. 2012;7(9):8468-72.
32. Al-Amiery AA, Kadhum AAH, Mohamad AB. Antifungal activities of new coumarins. Molecules. 2012;17(5):5713-23.
33. Al-Amiery AA, Al-Bayati RIH, Saour KY, Radi MF. Cytotoxicity, antioxidant, and antimicrobial activities of novel 2-quinolone derivatives derived from coumarin. Res Chem Intermed. 2012;38(2):559-69.
34. Kadhum AAH, Al-Amiery AA, Musa AY, Mohamad AB. The antioxidant activity of new coumarin derivatives. Int J Mol Sci. 2011;12(9):5747-61.
35. Mousa M. Synthesis, Characterization and Evaluation of Antibacterial Activity Of 1,3,4- Thiadiazole Derivatives Containing Schiff Bases. IJPCBS. 2017;7(1):71-6.
36. Alagawadi KR, Alegaon SG. Synthesis, characterization and antimicrobial activity evaluation of new 2,4-Thiazolidinediones bearing imidazo[2,1-b][1,3,4]thiadiazole moiety. Arabian Journal of Chemistry. 2011;4:465-72
37. Baghel US, Kaur H, Chawla A, Dhawan RK. Synthesis and antimicrobial evaluation of thiadiazole derivatives. Der Pharma Chemica. 2014;6(2):66-9.
38. Al-Amiery AA, Al-Temimi AA, Sulaiman GM, Aday HA, Kadhum AAH, Mohamad AB. Synthesis, Antimicrobial And Antioxidant Activities of 5-((2-Oxo-2h-Chromen-7-Yloxy)Methyl)-1,3,4-Thiadiazol-2(3h)-One Derived From Umbelliferone. Chemistry of Natural Compounds. 2013;48:950-4.
39. Fawzia AA, Habib NS, Nargues S, Taibbi Mel, Dine S , Dine ASE I. Synthesis of imidazo(2, 1-b)-1, 3, 4-thiadiazole derivatives as antibacterial agents against Escheria coli & Candida albicans. Chem Abst. 1991.
40. Al-Mosowy HH. Synthesis of hetrocyclic compound derived from 2,5-dimercapto-1,3,4-thiadiazole and their using as photostabilization for PVC films,A thesis of the college of Sience Al-Nahrain University,M.Sc.2006.
41. Nadjet R., Amjad M. Al-Yahyawi , Sanaa K. Bardaweel, Fawzia F. Al-Blewi and Mohamed R. Aouad, Synthesis of Novel 2,5-Disubstituted-1,3,4-thiadiazoles Clubbed 1,2,4-Triazole, 1,3,4-Thiadiazole, 1,3,4-Oxadiazole and/or Schiff Base as Potential Antimicrobial and Antiproliferative Agents. Molecules. 2015;20:16048-67.
42. Onkol TD, Uzun DS, Adak L, Ozkan S, Ahin S. Synthesis and antimicrobial activity of new 1,2,4-triazole and 1,3,4-thiadiazole derivatives. J Enzyme Inhib Med Chem. 2008;23(2):277-84.
43. Kolavi GD, Hegde VS, Khazi IM, Gadad P. Synthesis and evaluation of antitubercular activity of imidazo[2,1-b][1,3,4]thiadiazole derivatives. Bioorg Med Chem. 2006;14:3069-80.
44. Joseph A, Shah S, Kumar S, Alex A, Maliyakkal N, Moorkoth S, Mathew J. Synthesis, *in vitro* anticancer and antioxidant activity of thiadiazole substituted thiazolidin-4-ones. Acta Pharm. 2013;63:397-408.
45. Terzioglu N, Gursoy A. Synthesis and anticancer evaluation of some new hydrazone derivatives of 2,6-dimethylimidazo[2,1-b][1,3,4]thiadiazole-5-carbohydrazide. Eur J Med Chem. 2003;38:781-6.
46. Abdel Rahman DE, Mohamed KO. Synthesis of novel 1,3,4-thiadiazole analogues with expected anticancer activity. Der Pharma Chemica. 2014;6(1):323-35.
47. Dawood KM, Gomha SM. Synthesis and Anti-cancer Activity of 1,3,4-Thiadiazole and 1,3-Thiazole. J Heterocyclic Chem. 2015;52(5):1400.
48. Maddila S, Gorle S, Sampath C, Lavanya P. Synthesis and anti-inflammatory activity of some new 1,3,4-thiadiazoles containing pyrazole and pyrrole nucleus. Journal of Saudi Chemical Society. 2016;20(30):S306–S312.
49. Asif M, Asthana C. 2, 4- Di substituted-5-Imino-1, 3, 4- Thiadiazole derivatives: Synthesis and Biological Evaluation of Antiinflammatory Activities. Int J Chem Tech Res. 2009;1(4):1200-5.