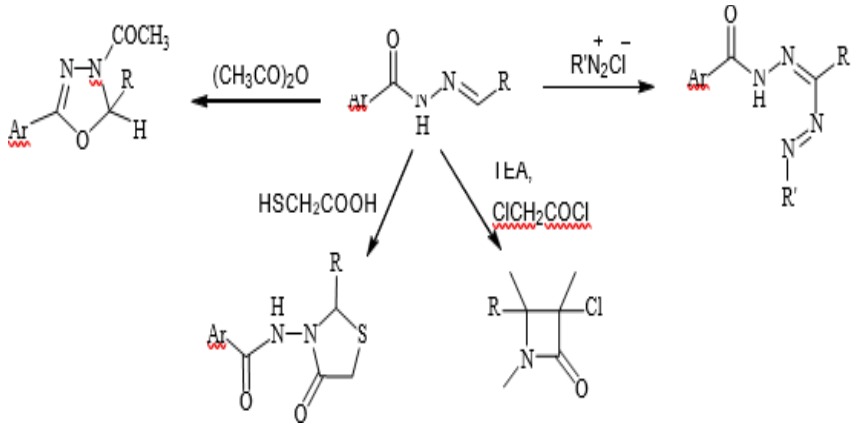
NALIDIXIC ACID BASED HYDRAZONE SYNTHESIS AND ANALYSIS FOR A RANGE OF BIOLOGICAL ACTIVITIES

Pankaj Kumar Maurya[1], Dr. Ranoji K.Shikkargol[2]
Department of Chemistry
[1,2]Sunrise University, Alwar, Rajasthan

Abstract
In the study synthesis of 1,3,4-thia(oxa)diazoles, as well as hydrazides & hydrazones done, based on nalidixic acid. On these chemicals, infrared, 1H, & 13C studies, as well as elemental analyses, was carried out. The combination of 5-(substituted aryl)-2-furfuraldehyde & NAH in ethanol was result in the formation of a new family of quinolone Schiff bases. Investigations using infrared radiation, nuclear magnetic resonance on hydrogen & carbon, mass spectrometry, & elemental spectroscopy (C, H, & N) was used to determine the structures of the chemicals that are created. IR spectra obtained with an FTIR spectrophotometer. "Tetramethylsilane" (TMS) was applied as an interior benchmark when utilising a DPX-300 NMR spectrophotometer operating at 300 MHz & 75 MHz. This allowed the instrument to collect 1H & 13C NMR spectra. The ESI Mass spectrophotometer was utilised in order to get the mass spectra.
Key words- *Nalidixic acid, Hydrazones, antimicrobial activity, 1,2,4 triazole*

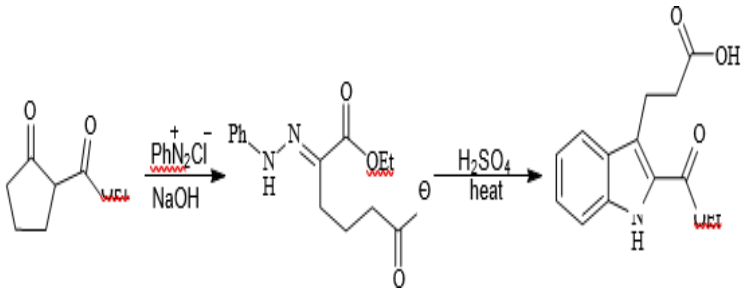
Introduction
Double-bonded carbon-nitrogen molecules are significant from both a chemical & biological standpoint. "R1R2C=NNH2" is the mathematical equation for the broad group of organic compounds that are referred to as hydrazones. These distinguish themselves from other compounds of the category (imines, oximes, etc.) [1-3] by consisting of two linked nitrogen atoms. Hydrazones containing an azomethine "-NHN=CH- "group may be produced by heating the suitably replaced "hydrazines/hydrazides" with "ketones and aldehydes". in solvents such as "ethanol, methanol, and tetrahydrofuran", what is "glacial acid, and gasoline-glacial acetic acid as solvents". Combining aryldiazonium salts with active hydrogen molecules is another method for making hydrazones. Three hydrazones have two linked nitrogen atoms of various types. The nitrogen atom's terminal electron pair is conjugated to the C=N bond. The physical & chemical characteristics of hydrazones are mostly caused by these structural pieces. Although the amino type of nitrogen is more reactive, both nitrogen atoms in the hydrazone group are nucleophilic [4,5]. The hydrazone group's carbon atom possesses both electrophilic & nucleophilic properties. The advantages of hydrazones over imines are their simplicity of synthesis & their hydrolytic stability. They are essential substances for the development of drugs as well as potential "ligands for metal complexes, organocatalysis, & the synthesis of heterocyclic compounds" [6-8]. In this study synthsis of 1,3,4-thia(oxa)diazoles, as well as hydrazides & hydrazones done, based on nalidixic acid was done and characterization done using various spectral techniques.

Material and method
Utilising the azomethine group's active hydrogen atom (-CONHN=CH-), hydrazones produce coupling products. Hydrazones can be heated in the presence of acetic anhydride to produce 1,3,4-oxadiazolines. Hydrazone reactions with chloro acetyl chloride & triethylamine can produce 2-azetidinones, & reactions with thioglycolic acid & thiolactic acid can produce 4-thiazolidinones (Scheme 1).



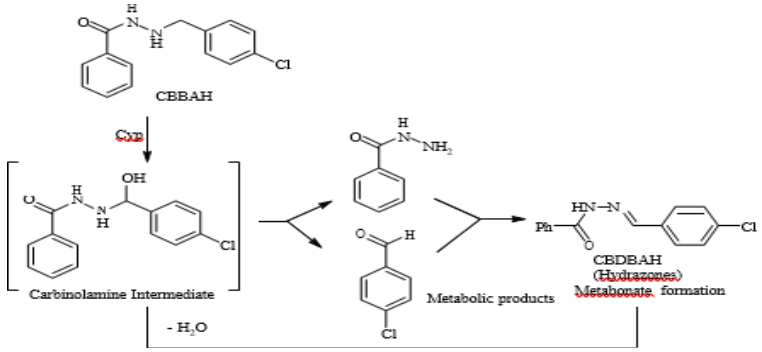
Scheme 1 Hydrazone reactions with chloro acetyl chloride & triethylamine

In the Japp-Klingemann reaction, hydrazones are created that can be used as intermediates in the synthesis of other organic molecules. For instance, the phenylhydrazone produced by the Japp-Klingemann reaction can be heated in the presence of strong acid to produce an indole via the Fischer indole synthesis (Scheme 2).



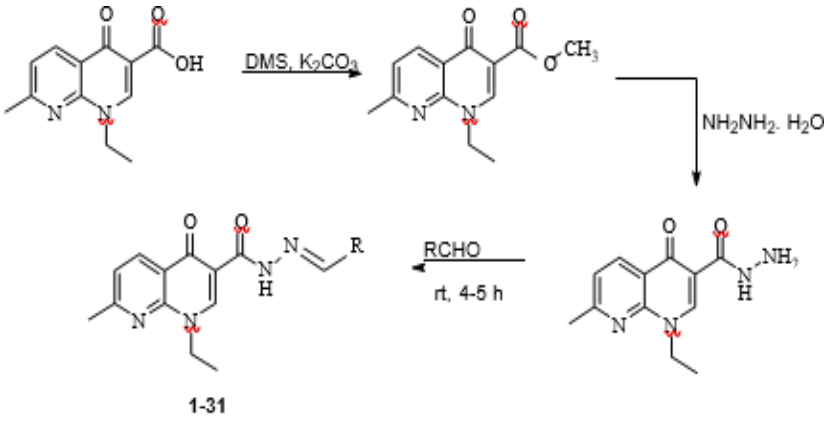
Scheme 2 The phenylhydrazone produced by the Japp-Klingemann reaction.

The metabolic process of hepatocytes microsomal cells in vitro "N-(4-chlorobenzyl)-N-benzoylhydrazine (CBBAH, Scheme 3)" was investigated by S.G. Kucukguzel et al. [217] In analytical chemistry, the detection, identification, & separation of molecules containing the carbonyl group are frequently accomplished by the creation of hydrazones. Low molecular weight aldehydes & ketones can be measured using photometric methods by forming the matching 2,4-dinitrophenyl hydrazones when they react with 2,4-dinitrophenyl hydrazine. One of the first hydrazones to be utilised for the spectrophotometric measurement of copper was biscyclohexanone oxalyldihydrazone. It produced a blue colour with traces of copper & was used to determine the presence of copper in steel, plants, non-ferrous metals, alloys, cadmium sulphide, human serum, paper pulp products.



Scheme 3 "The in vitro hepatic microsomal metabolism of N-(4-chlorobenzyl)-N-benzoylhydrazine"

From the aforementioned research, it can be concluded that while hydrazones have enormous potential in analytical, medicinal, & synthetic organic chemistry, their potential in agricultural applications has not yet been fully explored. Additionally, quinoline der.(s) in particular are crucial & are frequently discovered in favoured structures (pharmacophore), in a variety of physiologically active chemicals. The first synthetic quinolone AB, nalidixic acid (1,8-naphthyridine der.), was introduced in the 1960s.61 A sizable collection of synthetic bioactive molecules have been produced as a result of the NA-based SAR of comp.(s). It was believed beneficial to combine two putative pharmacophores in the current study & assess them for their diverse pesticidal properties. Therefore, a study was conducted to create hydrazones based on nalidixic acid as potential pesticidal compounds.



1. R= 2-FC_6H_4
2. R= 4-FC_6H_4
3. R= 3-BrC_6H_4
4. R= 2-ClC_6H_4
5. R= 3-ClC_6H_4
6. R= 4-ClC_6H_4
7. R= 2-$O_2NC_6H_4$
8. R= 3-$O_2NC_6H_4$
9. R= 4-$O_2NC_6H_4$
10. R= 4-HOC_6H_4
11. R= 3-$CH_3OC_6H_4$
12. R= 4-$CH_3OC_6H_4$
13. R= 2-$CH_3C_6H_4$
14. R= 3-$CH_3C_6H_4$
15. R= 4-$CH_3C_6H_4$
16. R= 4-$(CH_3)_2HCC_6H_4$
17. R= 2,4-$Cl_2C_6H_3$
18. R= 2,6-$Cl_2C_6H_3$
19. R= 2,4-$(HO)_2C_6H_3$
20. R= 2,4-$(CH_3O)_2C_6H_3$
21. R= 3,4-$(CH_3O)_2C_6H_3$
22. R= 3-(CH_3O)-4-$(HO)C_6H_3$
23. R= 3-(C_2H_5O)-4-$(HO)C_6H_3$
24. R= 3,4,5-$(CH_3O)_3C_6H_2$
25. R= 2-Pyridyl
26. R= 1-Naphthyl
27. R= 2-Naphthyl
28. R= 9-Anthryl
29. R= Cyclohexyl
30. R= Admantyl
31. R= Crotonyl

Scheme 4: Presesnt work to create hydrazones based on nalidixic acid.

3.0 Result and discussion

The current study focuses on the synthesis of 1-ethyl-N'-(2-fluorobenzylidene)-"7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (1)", 1-ethyl-N'-(4-fluorobenzylidene)-7-methyl-4-oxo-1,4-dihydro-1,8-nap1-ethyl-7-methyl-N'-(3-nitrobenzylidene), & 4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide1-ethyl-7-methyl-N'-(4-nitrobenzylidene), (4)-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (8)1-ethyl-7-methyl-N'-(2-hydroxybenzylidene), -4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (9).- 1-ethyl-7-methyl-N'- (3-methoxybenzylidene), 4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (10).-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (11), 1-ethyl-7-methyl-N'-(4-methoxybenzylidene)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (12), 1-ethyl-7-methyl-N'-(2-methylbenzylidene)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (13), 1-ethyl-7-methyl-N'-(3-methylbenzylidene)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (14), 1-ethyl-7-methyl-N'-(4- methylbenzylidene)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (15), 1-ethyl-7-methyl-N'-(4-isopropylbenzylidene)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (16), N'-(2,4-dichlorobenzylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (17), N'-(2,6-dichlorobenzylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3 carbohydrazide (18), N'- (2,4-dihydroxybenzylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine- 3-carbohydrazide (19), N'-(2,4-dimethoxybenzylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (20), N'-(3,4-dimethoxybenzylidene)1-ethyl-N'-(4-hydroxy-3-methoxybenzylidene) & 1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (21),N'-(3-ethoxy-4-hydroxybenzylidene), -7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3- carbohydrazide (22),-1-ethyl-7-methyl-4-oxo-1,4- dihydro-1,8-naphthyridine-3-carbohydrazide (23), 1-ethyl-7-methyl-4-oxo-N'-(3,4,5-trimethoxybenzylidene)-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (24), 1-ethyl-7-methyl-4-oxo-N'-(pyridin-4-ylmethylene)-1,4-dihydro-1,8-naphthyridine-3- carbohydrazide (25), 1-ethyl-7-methyl-N'-(naphthalen-1-ylmethylene)-4-oxo-1,4- dihydro-1,8-naphthyridine-3-carbohydrazide (26), 1-ethyl-7-methyl-N'-(naphthalen-2- ylmethylene)-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (27), 1-ethyl-7-methyl-N'-(anthracen-9-ylmethylene)-4-oxo-1,4-dihydro-1,8-naphthyridine-3- carbohydrazide (28), N'-cyclohexylidene-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8- naphthyridine-3-carbohydrazide (29), N'-adamantan-2-ylidene-1-ethyl-7-methyl-4- oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazide (30) & N'-(but-2-enylidene)-1- methyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carbohydrazides (31)" & their screening for fungicidal, insecticidal & nitrification inhibitory activities.

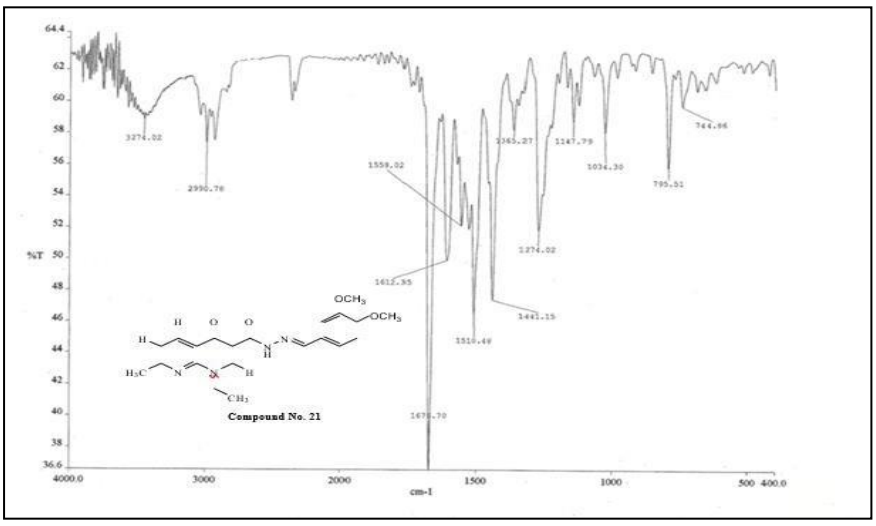


Figure 1: IR spectra N'-(3,4-dimethoxybenzylidene)—ethyl-7 methyl-1,8-naphthyridine-carbohydarzide

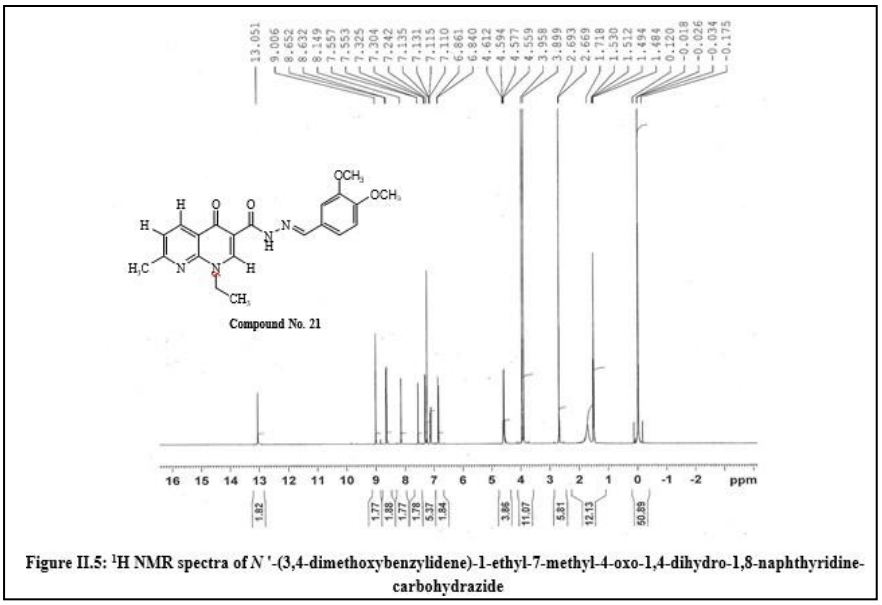


Figure II.5: ^{1}H NMR spectra of *N* '-(3,4-dimethoxybenzylidene)-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-carbohydrazide

Figure 2: 1H NMR spectra N'-(3,4-dimethoxybenzylidene)—"ethyl-7 methyl-1,4-oxo-1,4, dihydro-1,8 naphthyridine-carbohydarzide"

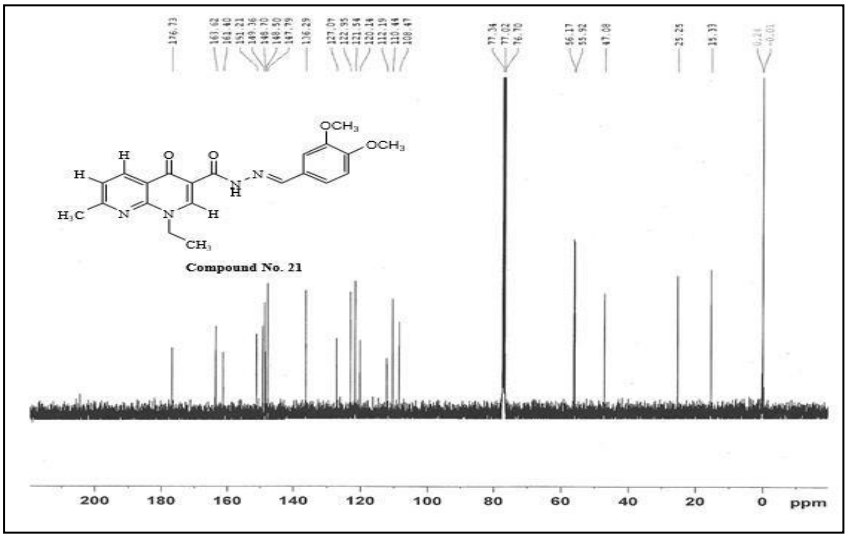


Figure 3: 13C NMR spectra N'-(3,4-dimethoxybenzylidene)—"ethyl-7 methyl-1,4-oxo-1,4, dihydro-1,8 naphthyridine-carbohydarzide"

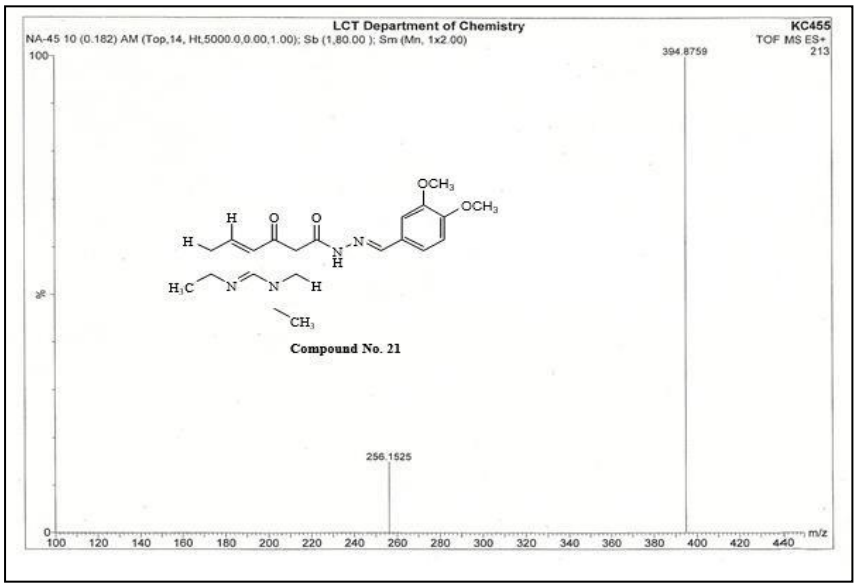


Figure 4: MASS spectra N'-(3,4-dimethoxybenzylidene)—"ethyl-7 methyl-1,4-oxo-1,4, dihydro-1,8 naphthyridine-carbohydarzide"

Pharmaceuticals, agrochemicals, additives, & modifiers used in cosmetics, reproduction, information storage, & polymers are just some of the many uses for heterocyclic molecules, which make up the biggest & most diverse family of organic compounds. Chemical reactions involving the participation of various heterocyclic chemicals, such as vitamins, enzymes, coenzymes, ATP, DNA, RNA, & serotonin, underpin many biological activities, including the transmission of nerve impulses, vision, metabolism, & the transfer of genetic information. In the heterocyclic series, tautomerism is universal due to the occurrence of various heteroatoms. The electronic dispersion in heterocyclic compounds is associated with their broad reactivity. Biologically active nitrogen heterocycles with a ring size between 3 & 6 are of particular interest. These compounds are found both in nature & in synthesized forms [221-230].

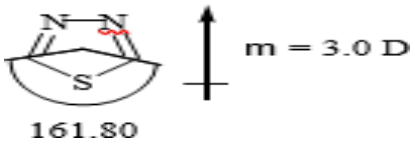
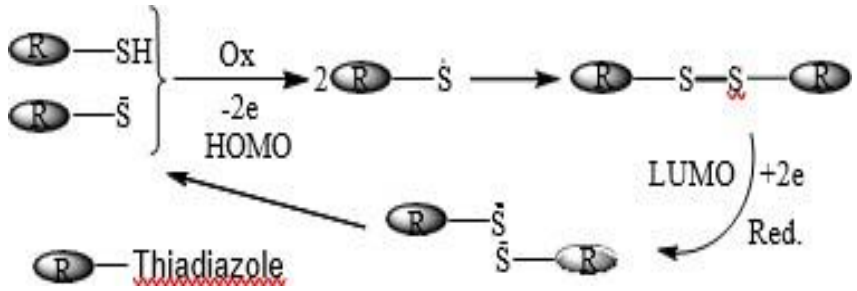


Figure 5: Dipolar description with bond angel in 1,3,4-thiadiazole core

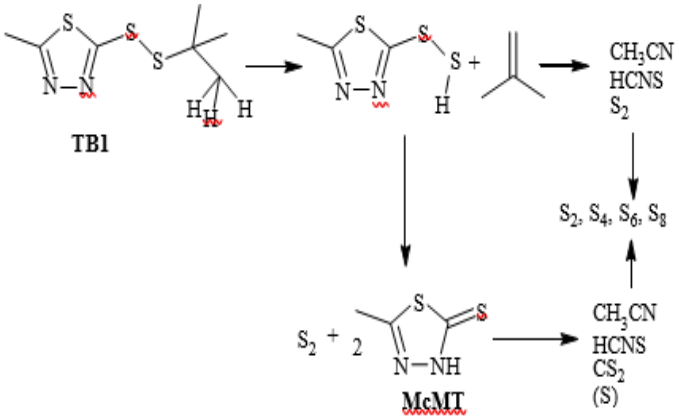
There is a wide range of pharmacological activity among compounds that have a five-membered heterocyclic ring in their structures. Medical chemists have long investigated the biological properties of 1,3,4-thiadiazoles & 1,3,4-oxadiazoles. The discovery of phenylhydrazines contributed to the advancement of 1,3,4-thiadiazole chemistry. Fischer described the first 1,3,4-thiadiazole in 1882, the ring system for what it really was. Both the "hydrogen binding domain" & the "two-electron donor system" are provided by the thiadiazole moiety. A restricted pharmacophore effect is also present. Many pharmaceuticals, including acetazolamide, methazolamide, sulfamethazole, etc., have a thiadiazole nucleus. Bio-isosterically, thiadiazole can stand in for the thiazole molecule. Therefore, it can be utilized in AB preparations because it functions similarly to third- & fourth generation cephalosporins. The nitrogen & sulphur atoms in 1,3,4-thiadiazole make it a 5-membered ring. Thiadiazole comes in a few different isomers, including 1,2,3,1,2,5, & 1,3,4-thiadiazole. The synthesis of 1,3,4-oxadiazole & 1,3,4-thiadiazole der.(s) has received a lot of focus in recent decades. Significant lateral

dipole moments (Figure 3.8) in the 1,3,4-thiadiazole core unit lead to physical factors such elevated dielectric anisotropy & dielectric biaxiality

Tribological qualities, such as wear resistance of steel surfaces & corrosion inhibition, can be enhanced with the help of thiadiazole der.(s) used as additives. Tribochemically active species, including "2-methylpropene, HNCS, 2-mercapto-5-methyl-1,3,4-thiadiazole (McMT), CS2, CH3CN, & sulphur species Sx (x = 2, 4, 6, 8)", were formed from "2-(tert-Butyldithio)- 5-methyl-1,3,4-thiadiazole (TB1) (Scheme IV.2)".



Scheme 3.5 proton transfer reaction of thiadiazole



Scheme- IV.2

Scheme 5 Synthesis of "2-methylpropene, HNCS, 2-mercapto-5-methyl-1,3,4-thiadiazole (McMT), CS2, CH3CN, & sulphur species Sx (x = 2, 4, 6, 8)"

Conclusion

The information presented up to this point indicates that 1,3,4-thiadiazoles and oxadiazoles can be utilized in a diverse selection of settings. They provide critical functionality and nuclei in a wide variety of bioactive compounds, which enables them to play an important part as pharmacophores in many different types of bioactive molecules. The chemotherapeutic effects that quinolone nuclei have were described at the beginning of this article, thus it should come as no surprise that they are also of significant interest. As a consequence of this, the primary objective of this research was to design and fabricate some novel compounds that combine the characteristics of nalidixic acid with those of either "1,3,4-thiadiazole or 1,3,4-oxadiazole".

References

1. Deeba, F., Abbas, N., Butt, M.T., Khan, R.A. and Muneeb, M., 2018. Synthesis, characterization and biological activities of 1, 3, 4-oxadiazole derivatives of nalidixic acid and their copper complexes. *Chemistry International*, *4*(4), pp.206-215.

2. Aggarwal, N., Kumar, R., Srivastva, C., Dureja, P. and Khurana, J.M., 2010. Synthesis of nalidixic acid-based hydrazones as novel pesticides. *Journal of agricultural and food chemistry*, *58*(5), pp.3056-3061.

3. Popiołek, Ł., Biernasiuk, A. and Malm, A., 2016. Synthesis and in vitro antimicrobial activity of nalidixic acid hydrazones. *Journal of Heterocyclic Chemistry*, *53*(5), pp.1589-1594.

4. Narsimha, N., Ranjithreddy, P., Mohmed, J., Sujitha, P. and Devi, C.S., 2019. Synthesis, Characterization, DNA Cleavage, Docking and Cytotoxic Studies of Novel Nalidixic acid Hydrazone and its Cu (II), Ni (II) and Co (II) Complexes. *JOURNAL OF THE INDIAN CHEMICAL SOCIETY*, *96*(3), pp.335-348.

5. Ali, K.F., AL-qaissi, M.H. and Saleem, D., Synthesis, Characterization and Antimicrobial Activity Study of new Metal Complexes with Nalidixic acid Hydrazones.

6. Aggarwal, N., Kumar, R., Srivastava, C., Dureja, P. and Khurana, J.M., 2014. Synthesis, biological activities and SAR studies of novel 1-Ethyl-7-methyl-4-oxo-1, 4-dihydro- [1, 8] naphthyridine-3-carboxylic acid based diacyl and sulfonyl acyl hydrazines. *Pest management science*, *70*(7), pp.1071-1082.

7. Popiołek, Ł. and Gawrońska-Grzywacz, M., 2015. The impact of modifying the chemical structure of Nalidixic Acid on the antimicrobial activity of its derivatives: a review. *International Research Journal of Pure and Applied Chemistry*, *7*(4), pp.191-202.

8. Liu, R., Cui, J., Ding, T., Liu, Y. and Liang, H., 2022. Research Progress on the Biological Activities of Metal Complexes Bearing Polycyclic Aromatic Hydrazones. *Molecules*, *27*(23), p.8393.