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Review Article

OXIME ESTERS AS POTENTIAL PHARMACOLOGICAL AGENTS – A REVIEW

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ABSTRACT

Numerous oxime derivatives have been synthesized and their biological activities were evaluated over the last several decades. Of all the oxime derivatives, oxime esters have been reported to hold more promise as potential therapeutic agents. Oxime esters are the group of organic compounds synthesized by condensation of aldoximes or ketoximes with carboxylic acids and include a large number of heterogenous compounds. Biological activities such as anti-oxidant, anti-microbial, anti-inflammatory, anti-cancer and tranquilizer action have been reported for oxime esters of diverse chemistry. This review is intended to study the synthetic routes, chemistry and biological activities of the various oxime esters.

Keywords: Oxime esters, anti-oxidant, anti-microbial, anti-inflammatory.

1. INTRODUCTION

Oximes are the chemical compounds under the category of imines and having the general formula $R^1R^2C{=}N\ O\ H$, in which if R^1 is an organic side chain and R^2 Hydrogen it is called Aldoxime or if R^2 is another organic group, it is called as ketoxime.[1-3]

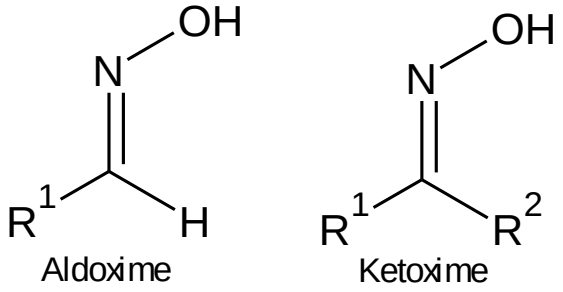


Fig. 1: General structure for aldoxime and ketoxime

Oximes and their derivatives are important class of organic compounds that are used in pharmaceutical as well as synthetic chemistry applications. Previous studies reported that oximes possess antioxidant property[4-5], anti-inflammatory[6] and anti-microbial[4-5] activities. Recent reports show that oxime derivatives also possess anti-cancer[7] activities. Another report states that oxime derivatives possess wide range of activities such as miticidal, nematocidal and antidote activities towards organophosphorous poisons[4]. Some of the oximes are used as building blocks for the synthesis of agrochemicals[8]. Studies have revealed that oxime derivatives possess insecticidal action.[4] Oxime derivatives include oxime ethers, oxime esters, dioximeoxalates, oxime glyoxalates, oxime oxalate amides, oxime carbonates, oxime carbamates. [9]

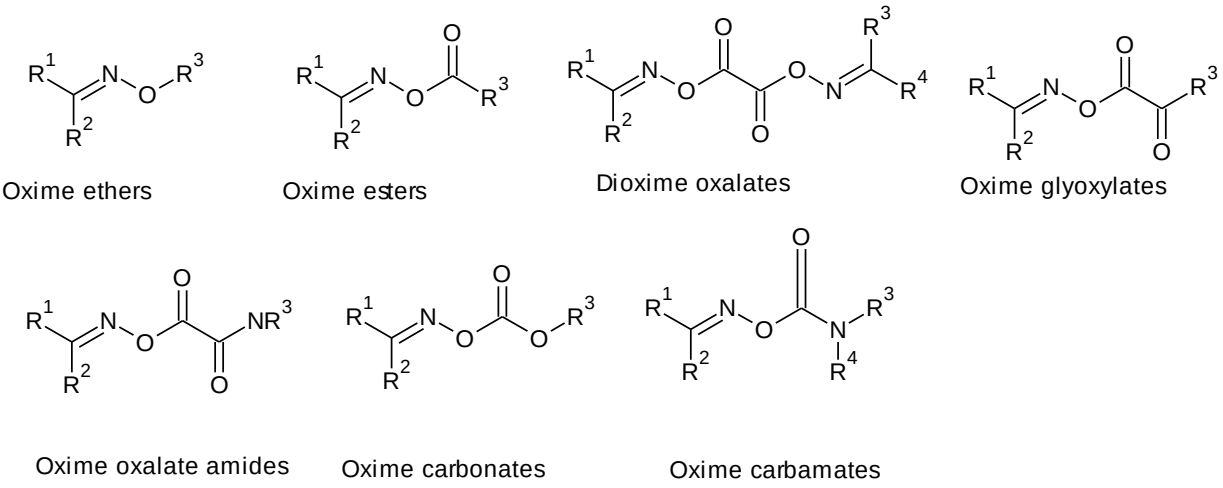


Fig. 2: Oxime derivatives

Among the oxime derivatives, oxime esters have been reported to possess wide range of activities such as anti-microbial,[4-5]anti-inflammatory[6], fungicidal[4-5], antidepressant, antiulcer, analgesic,[10-11], anti-HIV[12] activity and in the field of agrochemicals also.[13-15]

2. SYNTHESIS OF OXIME ESTERS

General Scheme of Synthesis

Oximinoesters were prepared by condensation of oximes and acid anhydrides in the presence of strong acids or by acid chlorides in basic condition. Acid chlorides used in this step is highly unstable and can be used only under anhydrous conditions.[16-19]

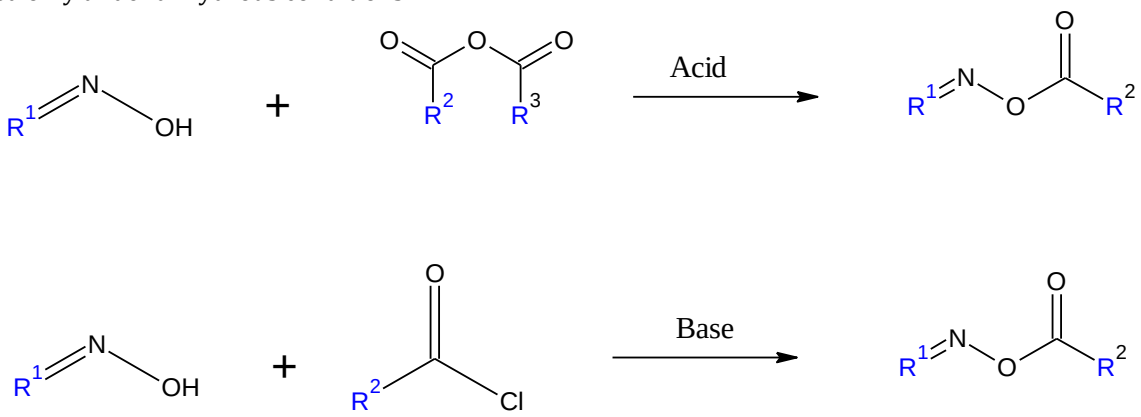
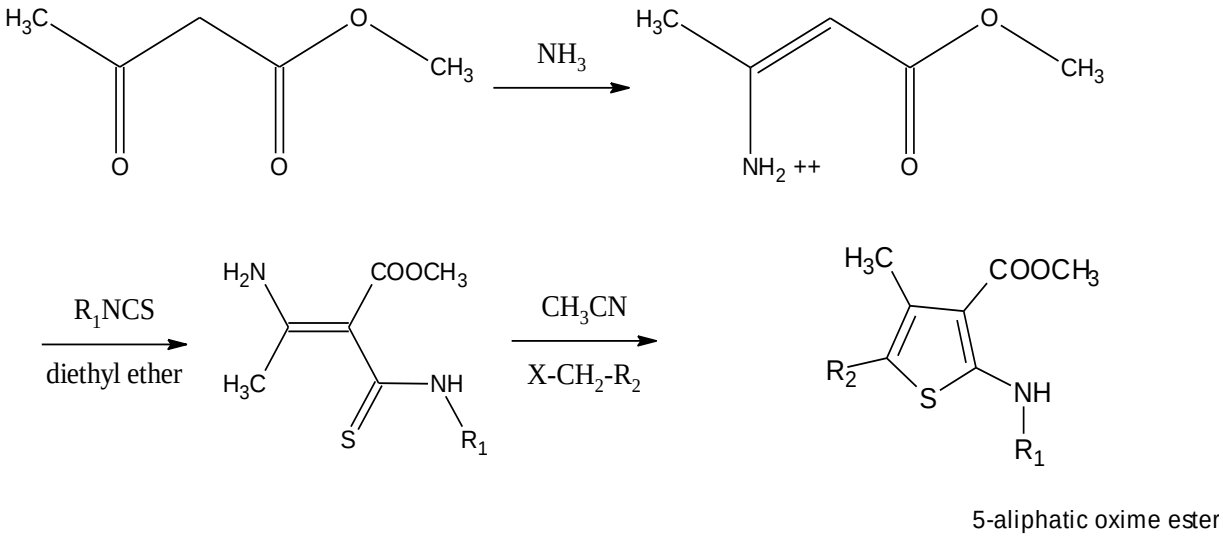


Fig. 3: General scheme for synthesis of oximes

2.1 Synthesis of 5-aliphatic oxime esters of Thiophene

Methyl aceto acetate when reacted with ammonia produced corresponding enamine which on further reaction with various isothiocyanates yielded addition products. These addition products react with oximes with halogroup to give novel thiophene analogues[6] as in
Fig: 4.



5-aliphatic oxime ester

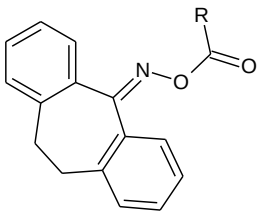
Fig. 4: Scheme for synthesis of 5-aliphatic oxime esters of Thiophene

Table 1: Derivatives of 5-aliphatic oxime esters of Thiophene

5-ALIPHATIC OXIME ESTERS	R1	R2
A1	-C6H5	Z-CO-C(=N-OCH3)-COOCH2CH3
A2	-C6H5	Z-CO-C(=N-OH)-COOCH2CH3
A3	-C6H5	-C(=N-OH)-COOCH2CH3
A4	-C6H5	-CO-C(=N-OH)-CH3
A5	4-(Cl)-C6H4	Z-CO-C(=N-OH)-COOCH2CH3
A6	4-(Cl)-C6H4	Z-CO-C(=N-OCH3)-COOCH2CH3
A7	4-(Cl)-C6H4	-C(=N-OH)-COOCH2CH3
A8	4-(Cl)-C6H4	-CO-C(=N-OH)-CH3
A9	-CO-C6H5	Z-CO-C(=N-OH)-COOCH2CH3
A10	-CO-C6H5	Z-CO-C(=N-OCH3)-COOCH2CH3
A11	-CO-C6H5	-C(=N-OH)-COOCH2CH3

2.1 SYNTHESIS OF KETOXIMINO ESTERS

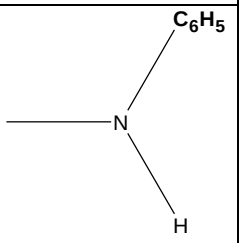
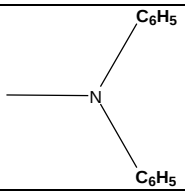
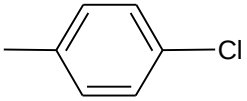
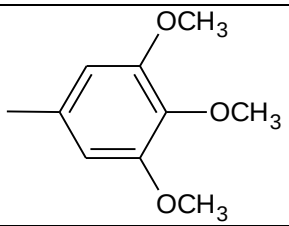
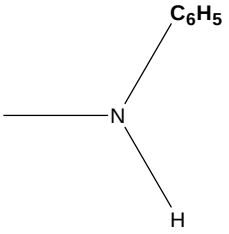
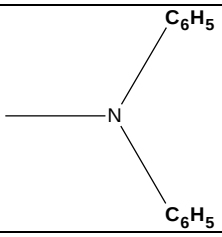
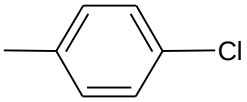
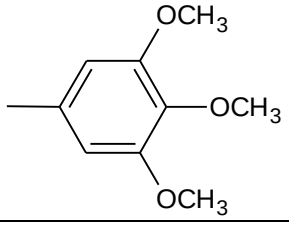
Ketoximino esters were prepared from 10,11- Dihydrodibenzo[a,d]cyclohepten-5-one, 9-Fluorenone, Benzophenone and 3-Benzoylindole which on reaction with hydroxylaminehydrochloride gave respective oximes. Each of these oximes were treated with phenylisocyanate, diphenylcarbamylchloride, p-chlorobenoylchloride, 3,4,5-trimethoxybenzoylchloride to get 16 oximino esters.[20]

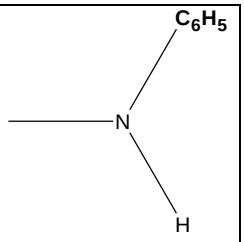
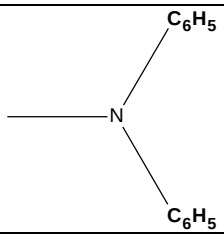
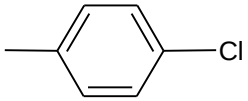
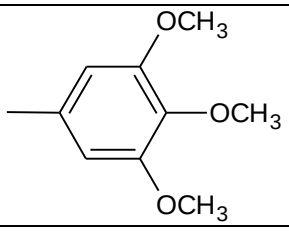
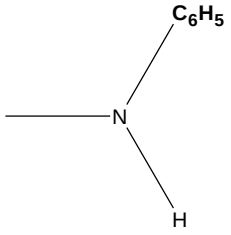
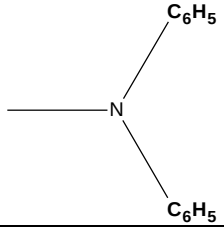
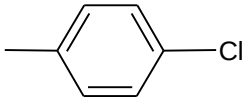
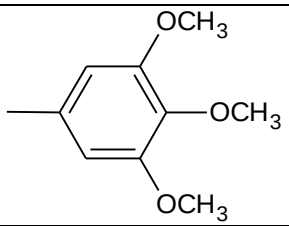


Ketoximino esters

Fig: General structure for 5-Ketoximino esters

Table 2: Substituents of some biologically active compounds of 5-Ketoximino esters

Ketoximino esters	Reactant(Oxime)	R
I.	Dihydrodibenzo[a,d]cyclohepten-5-one oxime	
II.	Dihydrodibenzo[a,d]cyclohepten-5-one oxime	
III.	Dihydrodibenzo[a,d]cyclohepten-5-one oxime	
IV.	Dihydrodibenzo[a,d]cyclohepten-5-one oxime	
V.	9-Fluorenone oxime	
VI.	9-Fluorenone oxime	
VII.	9-Fluorenone oxime	
VIII.	9-Fluorenone oxime	

IX.	Benzophenone oxime	
X.	Benzophenone oxime	
XI.	Benzophenone oxime	
XII.	Benzophenone oxime	
XIII.	3-Benzoylindole oxime	
XIV.	3-Benzoylindole oxime	
XV.	3-Benzoylindole oxime	
XVI.	3-Benzoylindole oxime	

2.2 SYNTHESIS OF UNDECANOIC ACID BASED OXIME ESTERS

Phenolic aldehydes react with hydroxylamine hydrochloride to yield various hydroxyl benzaldoximes which on further acylation with undecenoic acid chloride in the presence of triethyl amine to form corresponding Oximes-N-O-undecenoates.[4]

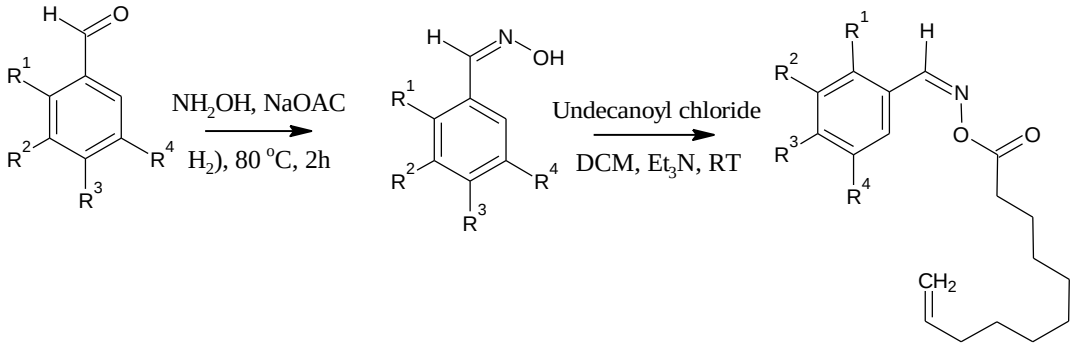


Fig. 6: Scheme for synthesis of undecanoic acid based oxime esters

Table 3: Substituents of some biologically active compounds of undecanoic acid based oxime esters

Compound	R1	R2	R3	R4
B1	OCH3	H	H	H
B2	H	OCH3	H	H
B3	H	H	OCH3	H
B4	OCH3	OCH3	H	H
B5	H	OCH3	OCH3	H
B6	H	OCF3	H	H
B7	H	H	OCH3	H
B8	H	OCH3	OCH3	OCH3
B9	OH	H	H	H
B10	H	OH	H	H
B11	OH	OH	H	H

2.3 SYNTHESIS 5-ARYL PYRAZOLE OXIME ESTERS[21]

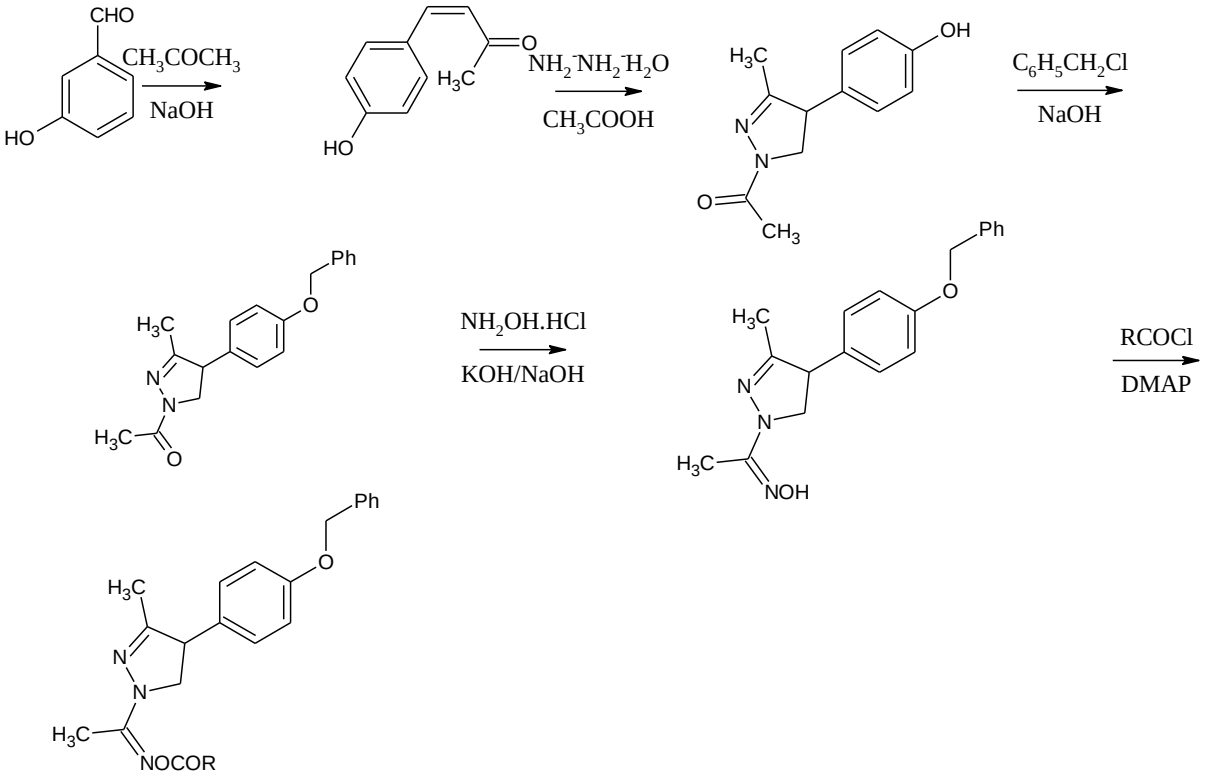
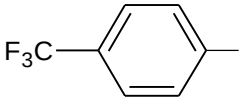
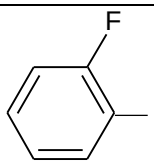
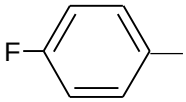


Fig. 7: Scheme for synthesis of 5-aryl pyrazole oxime esters

Table 4: Substituents of some biologically active compounds of oxime esters of 5-aryl pyrazole

Compound	R
1	CH2CH3
2	-(CH2)2CH3
3	
4	
5	

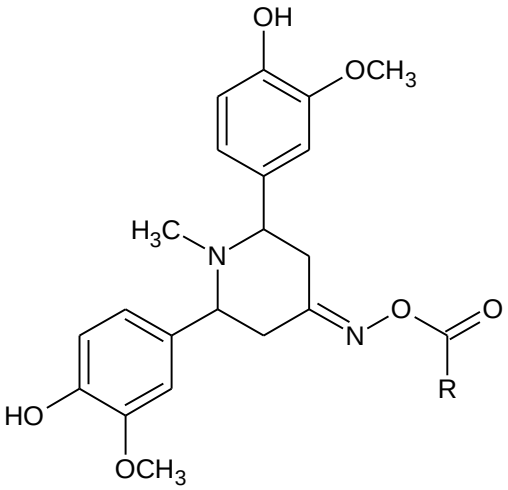
3 APPLICATION OF OXIME ESTERS

3.1 Application in Pharmaceutical Chemistry

3.1.1 Anti-microbial activity

Studies revealed that oxime esters of Undecanoic acid (B1-B11) showed activity against gram positive bacteria. B3 which is derived from meta-methoxy benzaldehyde showed activity against Gram positive organism, Micrococcus luteus MTCC 2470 with Minimum inhibitory concentration of 31.2 µg/ml where the standard drug Ciprofloxacin showed activity at 0.9 µg/ml. B10 showed anti-fungal activity against Candida albicans MTCC 3017 with MIC of 31.2µg/ml and where Miconazole used as standard showed MIC 7.8 µg/ml.[4] LIU Xin-hai, ZHI Li-ping v et.al, reported that mechanism of antibacterial activity of oximinoesters was due to inhibition of DNA gyrase and suppresses bacterial cell growth.

Vanillin derived Piperidin-4-one oxime esters at different concentrations shows anti-bacterial as well as antifungal activity.[5]



R = Phenyl Derivatives

Fig. 8: General structure for vanillin derived piperidin-4-one oxime esters

3.1.2 Anti-Oxidant activity

It has been reported that oxime esters of Undecanoic acid showed anti-oxidant activity by three in-vitro methods such as DPPH radical scavenging activity, superoxide radical scavenging activity and inhibition of lipid peroxidation assay. B7 and B11 showed activity against all three methods. Where B11 was the most potent anti-oxidant.[4]

Vanillin derived Piperidin-4-one oxime esters at different concentrations exhibited anti-oxidant activity by ABTS radical scavenging assay.

3.1.3 Anti-Inflammatory activity

5-aliphatic Oximes esters of Thiophene showed anti-inflammatory activity. Oxime ester A1, A2, A5, A9, A10 showed anti-inflammatory action which contain oxime ester functionality attached through a ketone to the fifth position of the thiophene nucleus.[6]

3.1.4 Anti-cancer activity

A series of 2,3,4-trimethoxyacetophenoxime esters containing benzothiazole moiety exhibited antitumor activity which was assayed by the MTT method. It was found that these oxime esters showed some activities against two cancer cell line in vitro. [7]

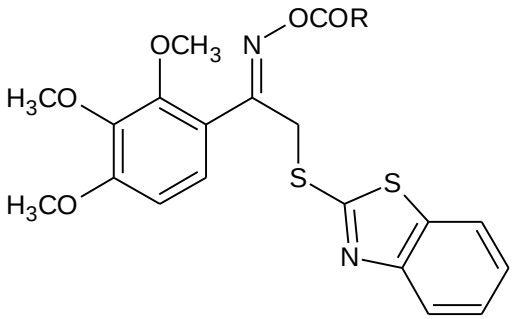
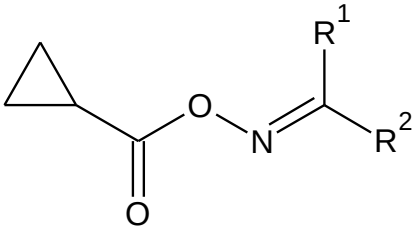


Fig. 9: General structure for 2,3,4-trimethoxyacetophenoxime esters

3.2 Application in Agrochemicals

Oxime esters with cyclopropane moiety was reported to have herbicidal activity. Compound C3 showed inhibitory activity to the rice KARI enzyme, inhibitory rates against dicotyledonous rape and monocotyledon. Compound C1 and C2 also showed herbicidal activity.[8]



C(1-3)

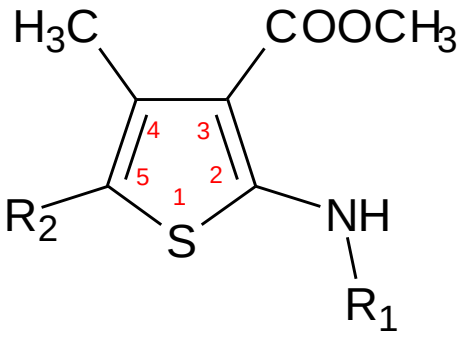
C1 - R1 = 2,4- Cl2, R2 = H
C2 - R1 = 3,4 –(OMe)2, R2 = H
C3 – R1 = p-Cl ph, R2 = H

Fig. 10: General structure for oxime esters with cyclopropane moiety

4 STRUCTURE ACTIVITY RELATIONSHIP (SAR) OF OXIME ESTERS

4.1 SAR of 5-aliphatic oxime esters of Thiophene

Presence of oxime function enhance the anti-inflammatory activity. It has been reported that compounds with oxime ester group attached via ketone to the fifth position of the thiophene has greater anti-inflammatory activity. It has also been found that ketone bridge connecting oxime ester to the thiophene nucleus at fifth position enhance anti-inflammatory action of the compound. Further study reported that aliphatic oxime esters of thiophene are more potent than aromatic oxime esters. Enhanced anti-inflammatory activity of the ester functional group may be due to the better absorption of the ester analogues after getting hydrolysed to acids.[6]



5-aliphatic oxime esters

Fig. 11: General structure for 5-aliphatic oxime esters

4.2 SAR of Ketoximino esters of 10,11- Dihydrodibenzo[a,d]cyclohepten-5-one, 9-Fluorenone, Benzophenone and 3-Benzoylindole

Studies reported that phenyl carbamyloximino derivatives (I&V) showed ataractic activity. These observations proved that conjugation of benzene rings as well as dimethyl aminopropyl group of most phenothiazine derivatives may not be needed for tranquilizing activity. As Diphenyl carbamyloximino ester analogues(II&XIV) exhibited considerable a psychotropic activity, the R/Ar group on the –N- of the sidechain may be necessary in blocking the receptor site. The p-chlorobenzoyloximino ester analoges (III&XV) showed activity against antiserotonin. It has also been revealed that compounds (IV, VII, IX, XII & XVI) showed activity against serotonin or amphetamine due to electron density around the carbonyl carbon affected by the presence of p-chloro and 3-methoxy group. [20]

Correlation between Structure And Activity

Table 5: Correlation between structure and activities of various oxime esters

Oxime Esters (OXE)	Biological activity	Functional group responsible for biological activity
OXE of Undecanoic acid	anti-microbial & anti-oxidant activity	oxime ester group attached via ketone bridge to the fifth position of the thiophene
Vanillin derived Piperidin-4-one OXE	anti-microbial & anti-oxidant activity	Not identified
5-aliphatic oxime esters of Thiophene	anti-inflammatory activity	Not identified
2,3,4-trimethoxyacetophenoxime esters	antitumor activity	Not identified
p-chlorobenzoyl OXE	activity against antiserotonin	Not identified
Phenyl carbamyl & Diphenyl carbamyl OXE	psychotropic activity	R/Ar group on the –N- of the sidechain and electron density around the carbonyl carbon affected by the presence of p-chlorophenyl and 3-methoxyphenyl group
Cyclopropane OXE	Herbicidal activity	Not identified

5. CONCLUSION

Oxime esters were shown to possess different types of biological activities. Oxime esters of Undecanoic acid and Vanillin derived Piperidin-4-one oxime esters showed anti-microbial as well as anti-oxidant activity. 5-aliphatic oxime esters of Thiophene showed anti-inflammatory activity whereas 2,3,4-trimethoxyacetophenoxime esters containing benzothiazole moiety exhibited antitumor activity. The p-chlorobenzoyloximino ester analoges showed activity against antiserotonin. Phenyl carbamyloximino derivatives and Diphenyl carbamyloximino ester analogues exhibited considerable ataractic activity. Oxime esters with cyclopropane moiety were reported to have herbicidal activity. As numerous activities of oximinoesters have been reported, this moiety seems to have enormous potential to be explored further in design of novel molecules.

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