

A REVIEW: BIOLOGICAL SIGNIFICANCES OF HETEROCYCLIC COMPOUNDS.

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Abstract

Heterocyclic chemistry offers an example for the lack of distinct demarcations; in fact, it pervades the plurality of the other chemical disciplines. Heterocycles are inextricably woven into the life processes. The vital interest of the pharmaceutical and agrochemical industries in heterocycles is often connected with their natural occurrence. Synthetic chemistry provides cornucopia of heterocyclic systems. More than 90% of new drugs contain heterocycles and the interface between chemistry and biology, at which so much new scientific insight, discovery and application is taking place is crossed by heterocyclic compounds. This review article covers the most active heterocycles that have shown considerable biological actions as antifungal, anti-inflammatory, antibacterial, anticonvulsant, antiallergic, herbicidal, anticancer activity

Key words: Heterocyclic, biological activities.

INTRODUCTION

Medicinal chemistry had its beginning when chemists, pharmacist and physicians isolated and purified active principles of plants and animals' tissues and taken from micro-organism and their fermentation products. Some of these chemicals has been associated with therapeutic properties: Medicinal chemistry which has leaned on the classical fields of chemistry, especially organic chemistry, biology and some area of physics. A limited number of natural and synthetic products and serve directly as therapeutic agents although lack of specificity frequently limits their application in human and veterinary medicines and in analogous pesticidal and other uses in agriculture. By dissecting the structure of these products chemically, one arrives at its therapeutically significant molecular sections, the pharmacophores, the portion that can be deleted are of no interest as components of drug action; they are regarded as the result of the biosynthetic efforts on the parent organism to construct materials for its own metabolic or defensive purposes.

Most of the drugs belong to the class of heterogenous compounds. Heterocyclic compounds played a vital role in the metabolism of all living cells; large number of them are five and six membered heterocyclic compounds having one to three heteroatoms in their nucleus. The compounds may be pyrimidine and purine basis of genetic material DNA, and these heterocyclic compounds may be isolated or fused heterocyclic systems.

Some of the common heterocyclic compounds used in the medicines are as amino acids like proline, histidine and tryptophan, the vitamins and coenzymes precursors such as thiamine, riboflavin, pyridoxine, folic acid, biotin, B₁₂ and E families of the vitamins. There is a vast number of pharmacologically active heterocyclic compounds, many of which are in regular clinical use. The pyrimidines and its derivatives have a vital role in biological properties. 2- Sulphanilamidopyrimidines viz. Sulphadiazine, Sulphamethoxydiazine and Sulphadiazine are well known antibacterial agents.

Pyrimidinetrinitrones commonly known as barbituric acids have important role in the biologically field. 5-alkylated pyrimidinetrinitrones have been reported to show antispasmodic, muscle relaxant and anticonvulsant activity.

Substituted 1,3,4-oxadiazoles have shown multifarious biological activities. 2-Acetamide-5-phenyl- 1, 3, 4-oxadiazole have antimetabolic, analgetic diuretic and antiemetic properties. Some of them also acts as hypnotics, sedative and antidiarrhoeal agents.

Literature survey shows that a number of heterocyclic compounds having condensed ring system possess various types of physiological activities. Condensed triazolo- pyrimidines and N-benzylidene derivatives exhibits antifungal [1-4], anti-inflammatory [5-12], antibacterial [13-20], anticonvulsant [21-24], antiallergic [25-33], herbicidal [34-41], anticancer activity [42-45].

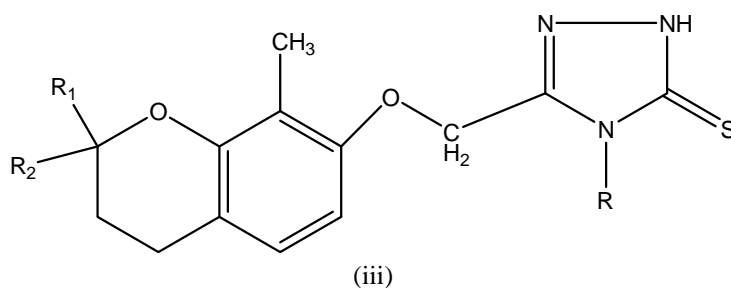
Biological activities**1-Antifungal activity**

Fungi are heterotrophic microorganisms that are distinguished from algae by lack of photosynthetic ability. Fungi includes both yeast and moulds. The former are spherical, oval and mucosid colonies in agar medium and the latter consists of elongated cells that usually reproduce by budding and forming branches of cells.

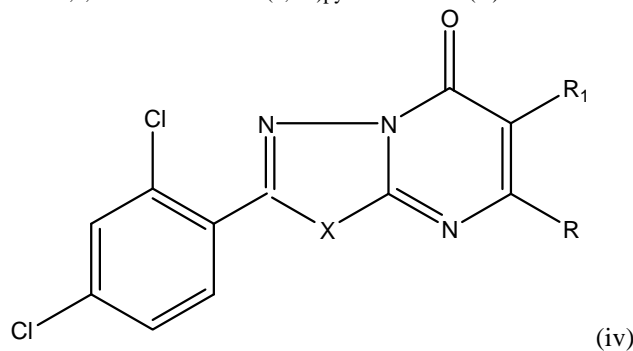
a). F. Russo et al have synthesized thiazolo pyrimidines (i) and their hydrazines (ii) $R = CF_3C_6H_4, 2-OEtC_6H_4$ and $4-NO_2C_6H_4$.



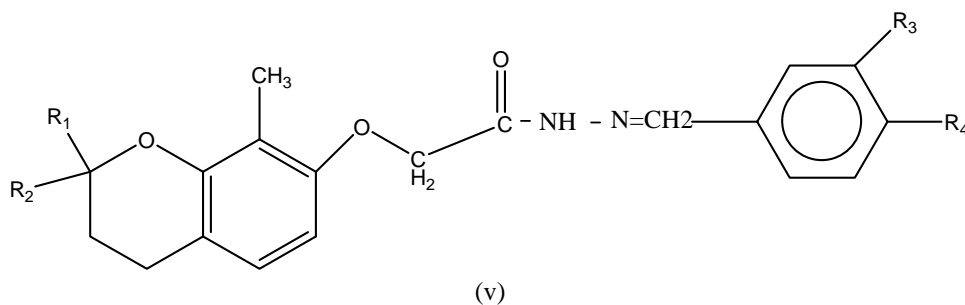
b). Ahluwalia et al have synthesized 5-(3',4'-dihydro-2',2',8'-trimethyl-2H-1'-benzopyran-7-ylloxymethyl)-4-phenyl-1,3,4-triazole-3(4H)-thiol (III) which shows significant antifungal activity. $R = C_6H_5, m\text{-}C_6H_4, p\text{-}C_6H_4, m\text{-}pCH_3, C_6H_4, pCH_3, O-C_6H_4, R_1 = CH_3, C_6H_5, R_2 = H, CH_3$.



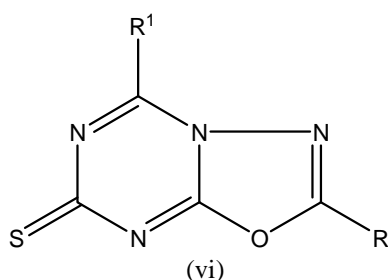
c). Gogia et al have synthesized 1,3,4-oxa / thiazolo -(3,2-a)pyrimidin-5-one (iv) which shows antifungal activity. $x = O, S$.



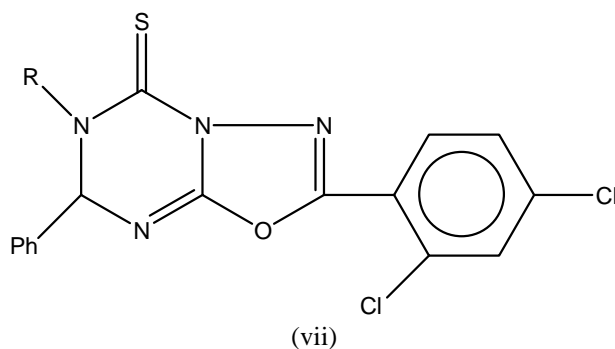
d). Ahluwalia et al have studied the N-benzylidene-3, 4-dihydro-2,2,8-trimethyl-2H-1-benzopyran-7-yl oxyacetic acid hydrazide (v) and found antifungal $R_1 = R_2 = CH_3, C_6H_5, R_3 = R_4 = H, CH_3$.



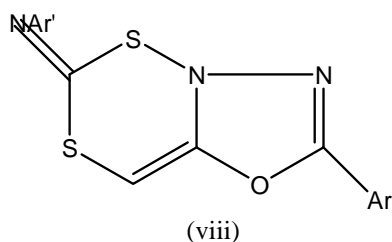
e).Singh et al have synthesized 1,3,4-oxadiazolo-(3,2-a)-s-triazin-7-thione(vi).and found antifungal.In compound(v), R= C₆H₅ CH₂-,C₆H₅,O-C₆H₄,m-MeC₆H₄,p-MeC₆H₄;R¹=C₆H₅,O- C₆H₄



f).Dutta et al have synthesized 2-substituted 1,3,4-oxadiazolo-[3,2-a]-1,3,5-triazin-5-(6H,7H)-thione derivatives(vii).and found antifungal.In compound (vii), R= C₆H₅ ,4-BrC₆H₄,4-ClC₆H₄,2-ClC₆H₄,3- ClC₆H₄,2-NO₂C₆H₄; 3-NO₂C₆H₄.

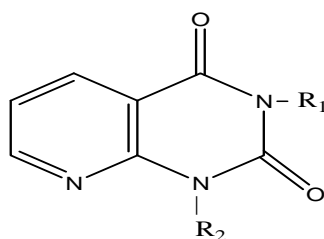


g).Dhar et al have synthesized 1,3,4-oxadiazolo-[3,2-a]- 1,3,4-dithiazines (viii). and found antifungal.In compound (viii) Ar=2- ClC₆H₄, Ar'=2- ClC₆H₄OCH₂.



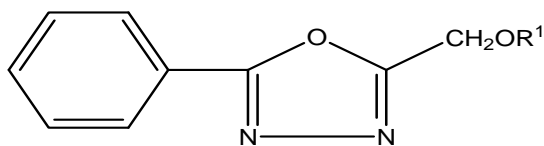
2. Anti-inflammatory : Anti-inflammatory refers to the property of a substance or treatment that reduces inflammation. Anti-inflammatory drugs make up about half of analgesics, remedying pain by reducing inflammation as opposed to opioids, which affect the central nervous system. Non-steroidal anti-inflammatory drugs (NSAIDs), Some common examples of NSAIDs are: aspirin, ibuprofen, and naproxen. The newer specific COX-inhibitors - although, it is presumed, sharing a similar mode of action - are not classified together with the traditional NSAIDs. Long-term use of NSAIDs can cause gastric erosions, which can become stomach ulcers and in extreme cases can cause severe haemorrhage, resulting in death. The risk of death as a result of use of NSAIDs is 1 in 12,000 for adults aged 16–45. The risk increases almost twentyfold for those over 75. Other dangers of NSAIDs are exacerbating asthma and causing kidney damage. Apart from aspirin, prescription and over-the-counter NSAIDs also increase the risk of myocardial infarction and stroke.

a).J.A. Beres and Coworkers have synthesized the compound associated with anti-inflammatory activity. Pyrido[2, 3,- d] pyrimidinone derivatives have been found to possess anti-inflammatory activities. In compound (I), R₁ =H, halo, alkyl, R₂ =Ph, Cyclohexyl, alkyl, OH.



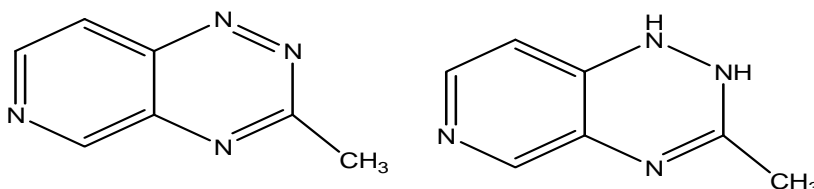
(ix)

b). Thomas et al have synthesised 2-(hydroxymethyl)-5-phenyl-1,3,4-oxadiazoles (x) and found that these show antiinflammatory activities in mice, rats and guineapigs. In compound (x), $R^1 = H, CONH_2$ OR $CONHMe$.



(x)

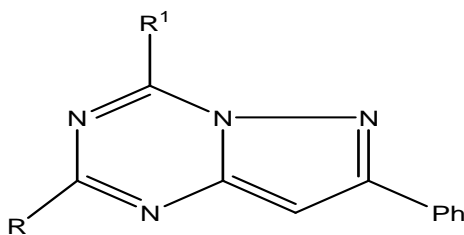
c). Lewis et al have synthesised 3-Substituted - Pyrido-[3,4-e]-as-triazines (xi), (xii). These compounds showed antiinflammatory activity.



(xi)

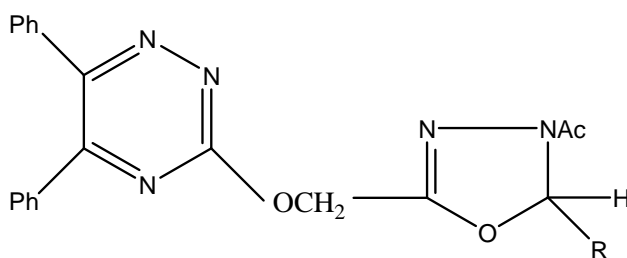
(xii)

d). Kim et al have reported 7-phenyl pyrazolo-[1,5-a]-1,3,5-triazine derivatives as anti-inflammatory agents (xiii) where R= Thia alkyl, $R^1 =$ Substituted amino, N-heterocycloalkyl.

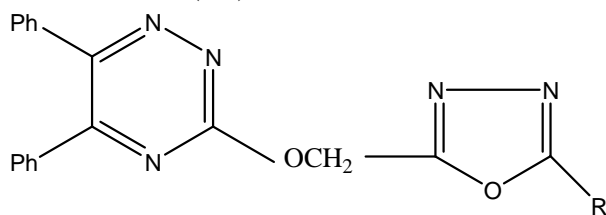


(xiii)

e). Abdle et al have synthesised some novel 1,3,4-oxadiazole derivatives (xiv), (xv). In compound xv $R = 4-ClC_6H_4, 4-MeOC_6H_4, 3,4-(MeO)_2C_6H_3, 4-(Me_2N)C_6H_4$

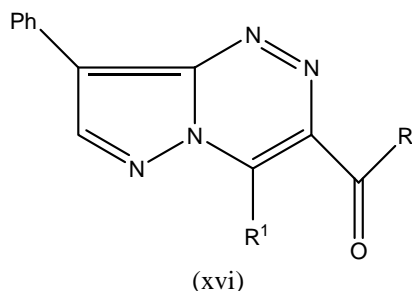


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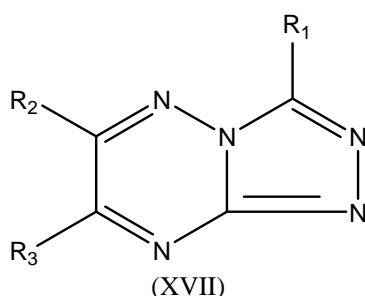


(xv)

f).Joshi et al have synthesised somefluorine containing pyrazolo[5, 1,-C]- 1, 2, 4-triazine (xvi) whereR=3,4-CIFC₆H₃

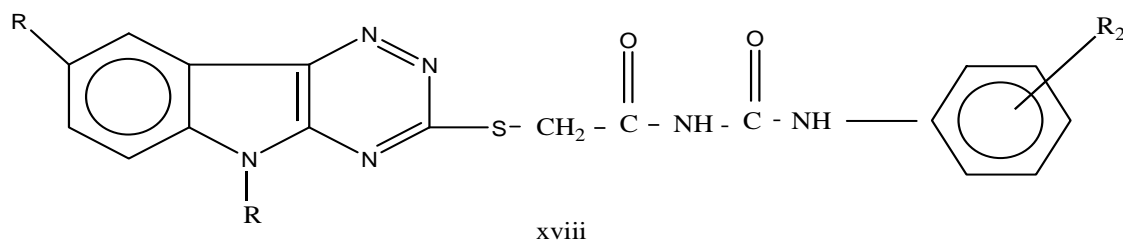


g).Heilman et al have synthesized 1,2,4-triazolo [4, 3-b]-1, 2, 4-triazines (xvii) where R¹=H,alkyl,alkoxyalkyl,haloalkyl,R²= H, alkyl, pyridyl, R³= alkyl, pyridyl,haloalkyl



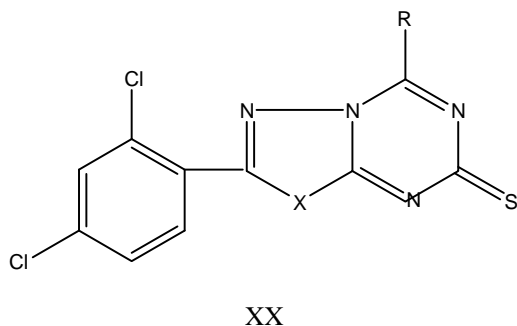
3.Antibacterial: Bacteria are the simplest and smallest unicellular organisms found individually or in clusters. The multitude of highly effective and relatively non-toxic drugs available for the treatment of bacterial infections have provided tough competition for the medicinal chemist,attempting synthesis of new antibacterial agents.

a).Sen Gupta et al have synthesized (xviii),some triazine derivatives and found antibacterial agents.

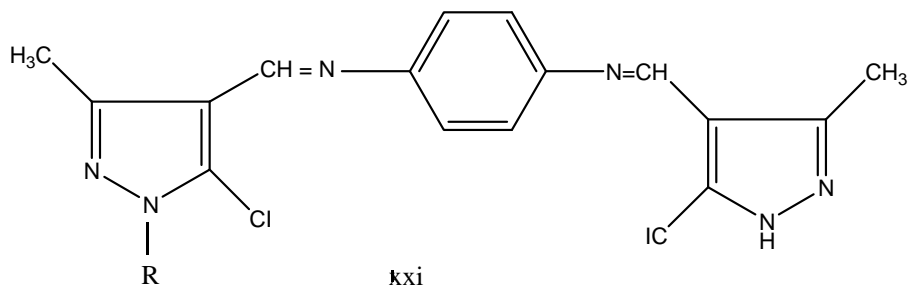


b).Desai et al have synthesized(xix),2,4-bis(4-methoxy-anilino)-6-(N-aryl-thiourido-N-amino-acyl)-1,3,5-triazine derivatives and found antibacterial agents.

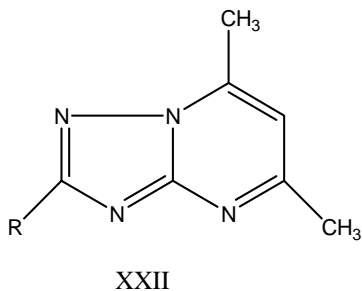
c).Dutta et al have synthesized 2,5-disubstituted-1,3,4-oxadiazolo/ thiadiazolo -[3,2-a]-S-triazine-5-7-thiones (xx).and found antibacterial agents.In compound (xx),



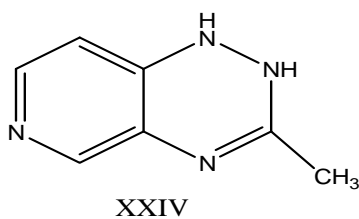
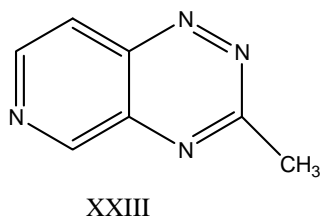
d).Pawar et al have synthesized 6-hydroxy-3-methyl-1-phenylpyrazolo [5,4-d] pyrimidine. (xxi), found antibacterial agents.



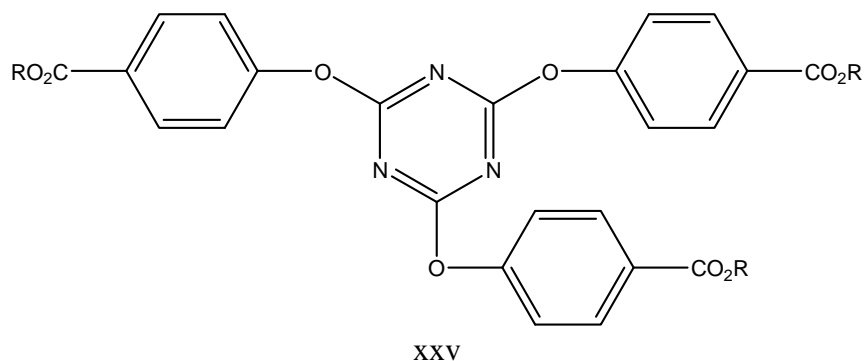
e).Novinson et al have synthesized substituted triazolo-pyrimidine derivatives and found antibacterial activity.In compound (xxii), R= pyridyl



f).Lewis et al have synthesized 3-substituted pyrido [3,4-e]-as-triazine(xxiii)&(xxiv) and found antibacterial useful agents.

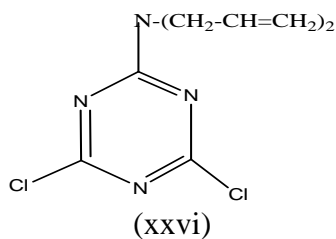


g).Saeki et al have synthesized triazine derivatives (xxv), where R=alkyl,Ph. and found antibacterial useful agents.

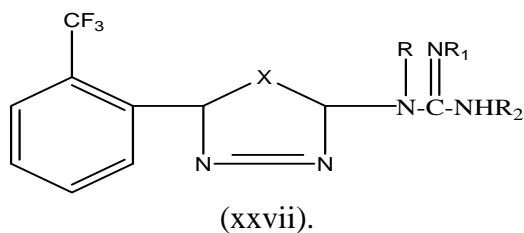


4. Anticonvulsant : These are defined as the agents that prevents the severity of convulsive seizures.

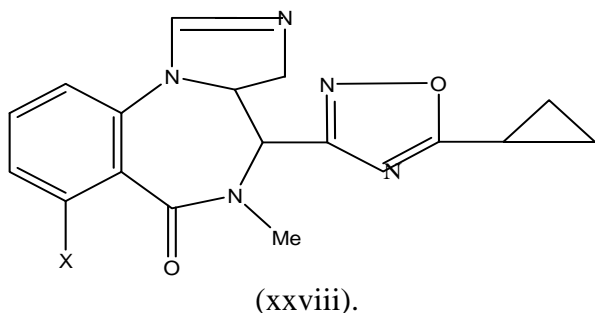
a). Kreutzberger et al have synthesized 2,4-dichloro-6-dialkylamino-1,3,5- triazine derivatives(xxvi) and found anticonvulsant useful agent



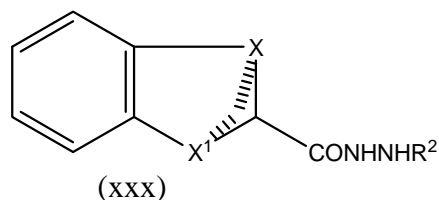
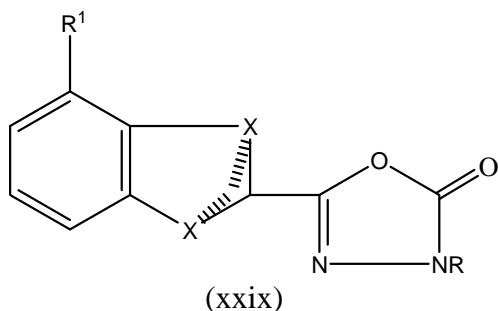
b). Chapleo et al have synthesized some substituted-1,3,4- thia/ oxadiazoles (xxvii.) and found anticonvulsant useful agent. X=O,S,R=H,Me,R₁=R₂=H,alkyl,Ph-CH₂



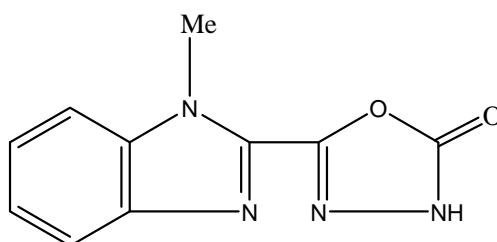
c). Waetzen et al have synthesized oxadiazolyl imidazobenzodiazepines (xxviii) which has useful anticonvulsant activity in mice. In compound (xxviii) X=Br, Cl ,F, Me, CF₃,CN.

**5. Antiallergic:** A number of heterocyclic compounds have shown the antiallergic activity.

a). Musser et al have synthesized 2-(2, 3-dihydro-2-oxo-1, 3 ,4-oxadiazol-5-yl) benzoheterocycles (xxix), (xxx). In compound xxix X=O, NMe, CCl, CH, CMe; X'=N, S, CH₂, NH; R=H, Ac, CO₂Et, Me etc. R¹=H, 5-Cl', 5-(CO₂Me), 5-CO₂Et and in compound xxx R²=H, CO₂ET



b).Khandwala et al have synthesized 1-methyl-2-[1,3,4-oxadiazol-2(3H)-one-5-yl] benzimidazole(xxxi)and related compounds as antiallergic agents.

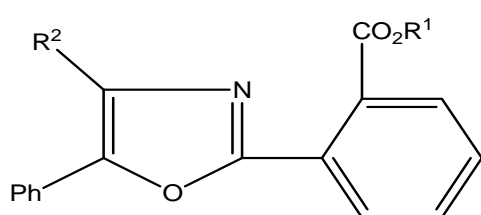


(xxx1)

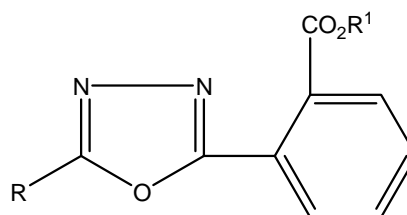
6. HERBICIDAL ACTIVITY

These are the drugs which destroy the unwanted plants alongwith some grasses without affecting the food crops. Some substituted Oxadiazoles , triazines and condensed heterocyclic systems posses this activity.

a). Brouwer, et al have synthesized oxazole and Oxadiazole benzoic acid derivatives (xxxii & xxxiii) as herbicides. In compound xxxiii $R^1=H$, $R^2=H$, Me; $R^3=Et$, Bu; $R^4=H$ and in compound XXIV $r=Ph$, substituted phenyl, (3-pyridyl),Me, $R^5=H$, Me, Et, Propyl, Butyl, Octyl, Dodecyl.

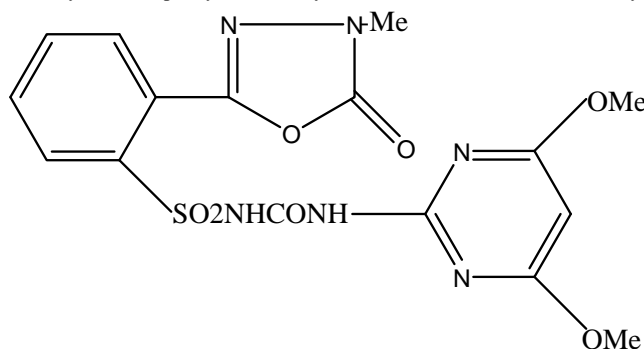


xxxii



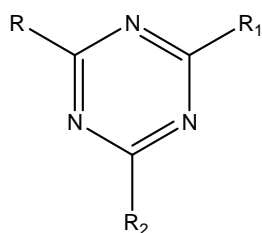
xxxiii

b). Rorer and coworkers have synthesised phenyl-2-[3-methyl-1,3,4-oxadiazol-2-(3H)-one] sulfonyl pyrimidyl urea (xxxiv).



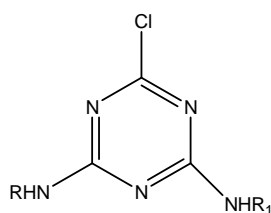
xxxiv

c). Bandarenko et al have synthesised -s-triazines (xxxv), a new series of biologically active compounds. In these compounds R, R1,R2= Cl, MeO,-NH2, NMe2,NHCHMe2, SH, Sme, SE_v. Some of these shows herbicidal activity.



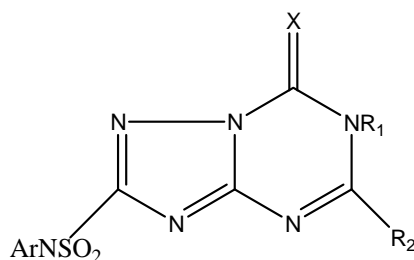
xxxv

d). Two well known herbicides such as simazine (xxxvi) $R=R_1$ = ethyl and atrazine R =ethyl; R_1 =isopropyl are persistent soil acting herbicides which can be applied n large concentration (5-10/ha) as total weed killer.



xxxvi

e). Westerman et al have prepared 6,7-dihydro-1,3,4-triazolo[1,5-a]-1,3,5-triazin-2-Sulfonamides (xxxvii) and found them as agents with herbicidal and plant growth regulating activity. In compound xxxvii Ar =(un) / substituted Ph, naphthyl, pyridyl; R =H, acyl, alkyl, phenyl-alkyl, (un) substituted carbonyl etc. R_1, R_2 = phenyl; X =O, S.

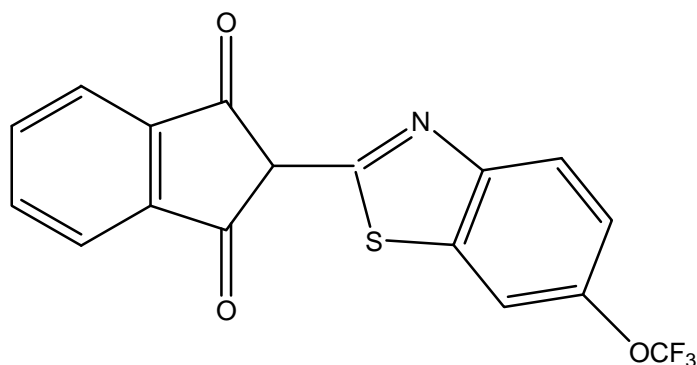


xxxvii

Anticancer activity

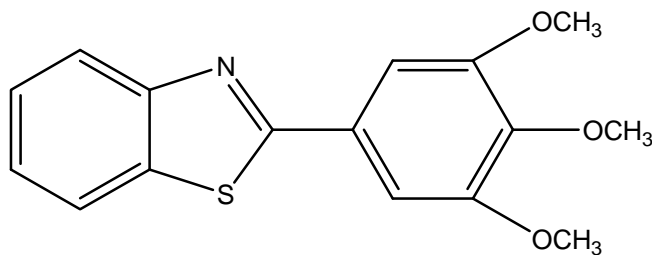
Anticancer refers to a group of disease caused by several agents like as chemical compound, radiant energy. Cancer is characterized by an abnormal & uncontrolled division of cell exhibiting varying degree of malignancy which produce tumor & invade adjacent normal tissue. These agents are used for treatment of cancer or either kill cancer cells or modify their growth.

a). Stanton HLK, *et al* have synthesized (xxxviii) benzothiazole containing phthalimide and studied their anti-cancer activity on human carcinoma cell lines



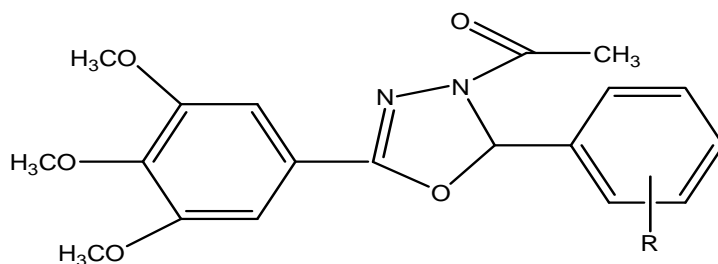
(xxxviii)

b). Wang M *et al* have (xxxix) synthesized carbon 11 labeled fluorinated 2-aryl benzothiazoles used for protein emission tomography (PET) to image tyrosine kinase in cancer



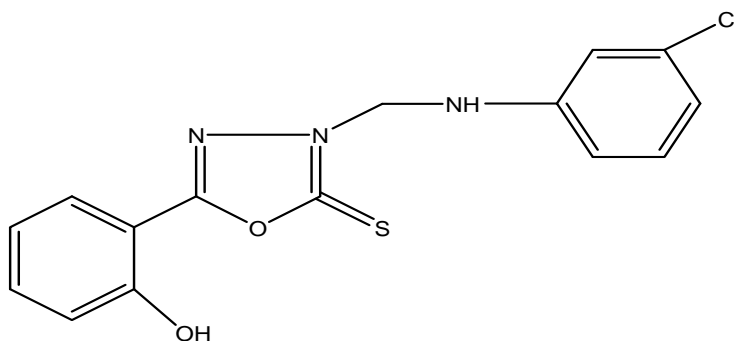
(xxxix)

c) Aboraia S. Ahmed et al have synthesized 3-acetyl-2-substituted phenyl -5-(3,4,5-trimethoxyphenyl)-2,3-dihydro-1,3,4-oxadiazole derivatives and these compound were screened for their in vitro antitumor activities against PC3, BGC823, & Bcap-37 by MTT method



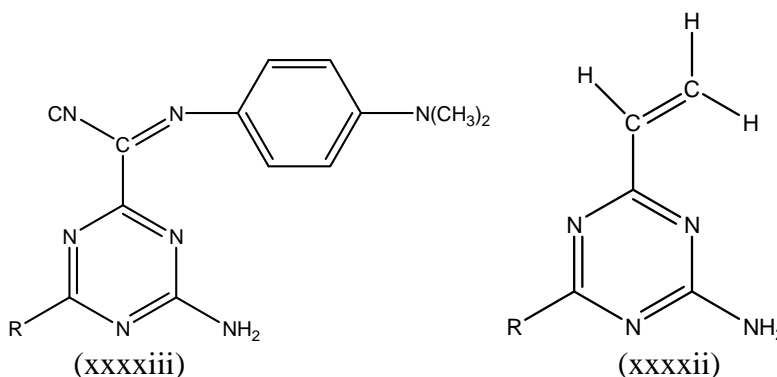
(XXXX)

d). Jin Jiang Chen et al have synthesized a new series of 5-(2-hydroxyphenyl)-2-substituted -2,3-dihydro-1,3,4-oxadiazole-2-thione derivatives. The promising anticancer activities were reported.



(xxxxi)

e). Sączewski F *et al* have synthesized (xxxxii) and (xxxxiii) and reported anticancer activity of novel 2,4-diamino-1,3,5-triazine derivatives and of novel alkenyl-1,3,5-triazine derivatives, it showed growth inhibitory activity in low micromolar concentrations against renal cancer A498 cell line and colon cancer cell line COLO 205.



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