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A review analysis on the synthesis and biological activity analysis of Substituted Benzoxazines And 1,2-Disubstituted Benzimidazoles

Dr. Rahul Mishra
Associate Professor, Department of Chemistry
Hindu College, Moradabad.

Abstract:
For the development and designing of new compounds of biological significance there are several stages viz; preparation of new compounds by synthesis, its proper characterization and identifications by chemical and spectral methods, its acute toxicity test, its radiochemical and biochemical studies, its evaluations for a particular symptom on experimental animals and finally its chemical trial. To produce its characteristic effects a drug must be present in appropriate concentrations at its site of action. The concentration attained also depends upon the rate of its absorption, distribution, binding or localizations in tissues, biotransformation and excretion. It is of practical importance to know the manner in which the drugs are absorbed. Often there is a choice of the route by which therapeutic agent may be given and a knowledge of advantage and disadvantages of different route of administration is then of primary significance. Modern chemotherapy has markedly improved the drug delivery system. Attempts have been made to devise the methods in which the drug hits the target site by slow biodegradability and a major part is available for exerting biological response. Since a wide variety of new compounds can be synthesized involving amidoalkylation reaction, viz; aliphatic, aromatic, heterocyclic, semiaromatic etc it is thought that introduction of amidoalkyl groups in such class of compounds might confer better therapeutic results because of several reasons viz; increase in the polarity of compounds, increase in the hydrrophilic character of compounds etc. In addition, an investigation in this field underoubtedly provides an opportunity to prepare more powerful electrophilic reagents (amido alcohols), so that they may react with weaker nucleophilic reagents like cyclohexanone etc. under the identical reaction conditions.
Keywords: ***Quinoline Derivatives, biological activities, synthesis,***

I. Introduction

Substituted Benzoxazines

The chemical reactivity of biologically active benzoxazinoids towards various types of nucleophiles has been recently reviewed in relation to their biological activity. The influence and importance of o-functional substituents at position 2,4 and 7 of the 2H-1,4-benzoxazin-3(4H) one-skeleton have been investigated. The ability to form a multicentered electrophile under biological conditions has been found to be unique feature of the corresponding aglucones. Therefore, the bimolecule alkylating action of a benzoxazinoid derived cationic species is regarded as the chemical source of their biological activity42.

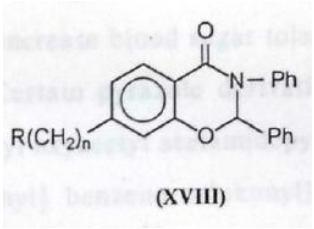
Recently, 2-[(4'-aryl-2'-thiazolyl)-4 oxo (4H), -3,1)]benzoxazines were found to show, marginal antibacterial activity against Staphylococcus aureus and Escherchia coli at 20 and 50 ug/ml concentrations. Antifungal activity of these compounds against Aspergillus niger and Aspergillus flavus was demonstrated to be less significant43. Some N3-aryl-N'-[4-(3,4-dihydro-3 oxo (2H)-1,4-benzoxazine-2-yl)-acetic acid hydrazido sulphonyl]phenyl ureas/thioureas were evaluated for their hypoglycemic activity. These compounds were also screened for their acute toxicity and gross behavioural effects using albino mice as experimental animals. The compounds were administered orally as their 0.5% CMC (carboxyl methyl cellulose)-Na-suspensions in graded doses. All of them were safe upto a dose of 1500 mg/kg, thus showing no toxic magnifestations. But, the test animals, however, could exhibit a marginal hyperactivity, probably due to central nervous system (CNS) stimulation. Moderate hypoglycemic activity was also demonstrated by these compounds".

These benzoxazines are the intermediates in the preparations of quinazolines which have been found biologically active in many areas. Thus, methaquolone, a quinazolone derivative has a very pronounced activity against metrazole induced convulsion. It has considerable electroshock and antipentylenetetrazole properties in mice*s. According to one report methaqualone in mice is about as active as phenobarbital against pentylenetetrazole and approximately one half as active as phenobarbital against electroshock 46. In rat brain homogenate it acts on the respiratory chain prior to the point of the transfer of an electron from NADH to cytochrome47. Boltze et.al. 48 synthesized a large number of structural variants of methaqualone and tested them in mice to determine the relationship between structure and hypnotic and anticonvulsant activities. Both

the hypnotic and anticonvulsant action of methaqualone are quite sensitive to structural alterations. Only a limited number of molecular modifications could be made with retention of activity. The replacement of 2-methyl with certain large moieties such as the styryl or B-pyridyl ethenyl groups was interesting because this led to a decrease in hypnotic activity with a concomitant increase in anticonvulsive activity. The compound, 2-(-pyridyl

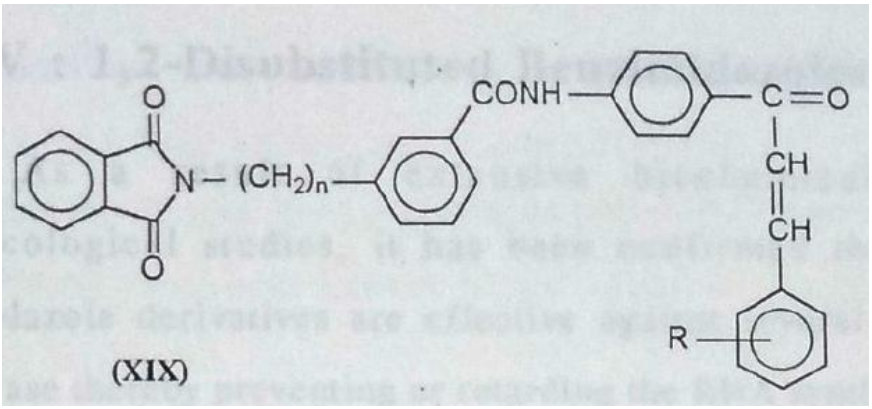
2-ethenyl)-3H-(0-tolyl)-4-quinazolone possessed marked anticonvulsant activity, had a low order of toxicity and was almost without hypnotic depressant action on animal tests. Some derivatives with amino groups in the 5-, 6-, 7- and 8- positions have been reported in the patent literature to have muscle relaxant activity S0,SI. 2-Styryl-3-aryl-thiouryl-3,4-dihydro-oxoquinazolines have been demonstrated to possess pronounced central nervous systems (CNS) depressant activity as these compounds significantly increased the pentobarbitone sleeping time:2.

Very recently, 7-arylamido/imido-alkyl-2,3-dihydro-2,3diphenyl-1,3-benzoxazine-4-ones (XVIII) have been demonstrated to possess moderate degree of antiviral activity against two animal viruses viz; Influenza virus and Herpes simplex viruss3.



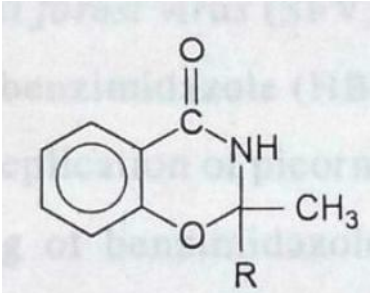
(XVIII)

In addition, various amides and imides have rencently been demonstrated to exhibit varying degree of hypoglycemic activity. Thus, the administration of nicotinamide (50 mg/100 g c.p.) is followed by pronounced hypoglycemic effect with a simultaneous decrease of glucose content in lens, sciatic nerve and aorta in streptozotocin induced diabetes and also by a complete normalization of parameters of intraperitoneal glucose tolerance test in rats with diabetic type glucose tolerance. A fourteen days nicotinamide treatment of patients with diabetes mellitus results in the improvement of glycemic profile, a decrease of glucosuria and protein-bound hexoses as well as possible shifts in the conditions of cardiovascular and nervous systems54. Further, some substituted benzamides have been recently demonstrated to give 13% decrease in blood glucose levels in mice orally at a dose of 30 mg/kg. At 200 mg/kg./day for 3 days orally in rats, one compound of this category gave 82% decrease in serum cholesterol level and 85% decrease in triglyceridess. The antidiabetic activity of certain carboxylic imides has been reported recently. N-[2-Cyclohexyl-carbonyloxy-3 {4-(2-pyridyl)} peperazine-1-yl)-propyl succinimide maleate showed antidiabetic activity at 10 mg/kg. orally in ratssó. Other compounds of the series were found to increase blood sugar tolerance in rats with induced diabetes57. Certain pyrazole derivatives with suitable substituents viz; N-aryl oxyacetyl acetamidopyrazoles and N-[4{2-(acetyl-amino) ethyl} benzene sulphonyl]-2-pyrizolin-1-ylcarboxamidesso have been reported for lowering the blood sugar in experimental animals. A few m-(phthalimidoalkyl)-(4substituted-cinnamoyl)-benzanilides (XIX) were synthesized and evaluated for their hypoglycemic activity in experimental animals



(XIX)

Encouraged by these results, the author synthesized a few substituted benzoxazines of the type (XX) with a view to study their antimicrobial and antidiabetic activities62.



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Type-V: 1,2-Disubstituted Benzimidazoles

As a result of extensive biochemical and pharmacological studies, it has been confirmed that the benzimidazole derivatives are effective against several RNApolymerase thereby preventing or retarding the RNA synthesis62. Benzimidazole derivatives are found to be the potent inhibitors of the influenza virus growth 63-66. Further, benzimidazolyl thiosemicarbazones are shown to exhibit pronounced antiviral activity against Semliki forest virus (SFV) in experimental mice67. 2-a-Hydroxy benzyl benzimidazole (HBB)] is found to be a truly selective inhibitor of replication of picorna virus68. Other potential useful drug consisting of benzimidazoles nucleus is enviroxime which is used against the common cold. It has antiviral effects against rhino, coxsackie, echo and polio viruses. It prevents viral uncoating and inhibits viral RNA polymerase from acting on late phase replication. It is beleived that benzimidazoles readily take part in the intermolecular H-bonding HBB and its alkyl derivatives form H-bonded structure linked by either --N---H-O or H-O---H-O bonds thus forming copper chelates as well?o. This suggests that highly specific H-bonding or possible metal chelation involving HBB and a macromolecule (either viral DNA itself or a specific enzyme required in its production) might result in the inhibition of RNA synthesis?!. Benzimidazole are remarkably effective compounds both with respect to its degree of virus inhibiting activity and its favourable selectivity ratio. Reports

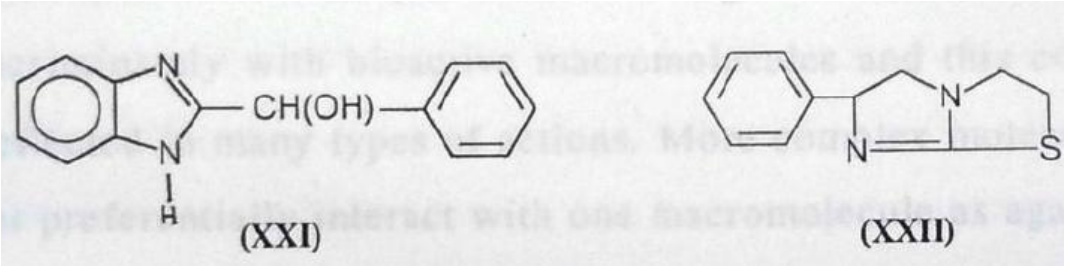
have appeared that benzemidazole compounds like LY 122771-72 and LY 127123 have shown very significant antiviral activity against picorna viruses. It was also shown that PVP mixture of LY 127771-72 is a well known blood expender as well as antivirally active in vitro and in vivo?2. Schlacher et. al.73 established antipicorna virus activity of compound A 37536 which is also a benzimidazole. Recently, 2-substituted benzimidazoles containing nicotinamide moiety have shown both increased inhibitory activity and selectivity. These compounds were found to show toxicity upto 62.5 ug/ml and 75% cytopathic effect (CPE) inhibition at 15.6 ug/ml?4.

An interesting compound related to HBB is 2-(0-hydroxy benzyl)-benzimidazole which was prepared to see whether intramolecular hydrogen bonding has an effect on antiviral activity. This was found like the case with o-hydroxybenzyl derivatives which has considerable activity against polio virus2. The corresponding 2-(p-hydroxybenzyl)-benzimidazole which is unable to form H-bond did not have much activity O'Sullivan found that 2-a-hydroxybenzyl)-benzimidazolium salts, 2-amethoxybenzyl)-benzimidazoles and its 1-alkyl derivatives all possess high protective activity against the type-2 virus and thus it seems likely that H-bonding is concerned is polio virus inhibiting activity of HBB75. It was possible that HBB and its effective derivatives may inactivate the viral RNA of susceptible in other way for example, by ionic interactions resulting from

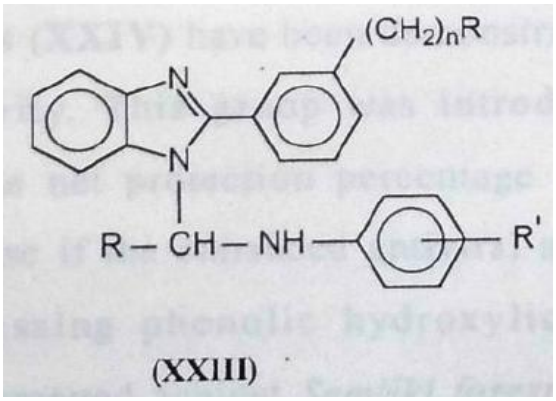
salt formation with RNA phosphoric acid groups or by the formation of face to face adducts (the heterocyclic ring of the HBB derivatives and of basic group in RNA lying in parallel planes). Alternatively, the active compound might specifically inactivate an enzyme which is itself specifically required for synthesis of the viral RNA of susceptible viruses.

Several imidathiazoles have been reported to exert favourable influence on the immune system. The laevorotatory antipode of tetramisole commonly referred as levamisole (XXII) and used as an anthelmintic drug against a wide range of nematodal infections in human as well as animalso has shown great promise as an agent capable of restoring an impaired immune response. This synthetic compound restored the delayed type of hypersenstivity in patients with damaged immune mechanism and its utility in clinical practice has been proved of use in cancer chemotherapy??. Although levamisole does not exhibit any direct antitumour activity in experimental animal including immunologically healthy animals78,79, it does increase the number of survivors when combined with a cancerostatic drug such as cytoxan (cyclophosphamide) for the treatment of mouth sarcomaso. Positive adjuvant effects of levamisole have also been observed in the case of many other diseases including aphtous stomatitis herpes and certain other infections81-83. Itsuse in rheumatic disease is well documented84.

The molecular mechanism of the adjuvant activity of levamisole has not been fully elucidated as yet. In the light of observed effects and results obtained from various experiments, this compound is thought to influence the fundamental functions of all the cells of the immune systems. However, some investigators feel that it can not be classed among immunostimulants because it never raises the immunity above a normal level86. Several derivatives of this compound were prepared for elucidation of their immunostimulant activity in various test systems87 but none of the derivatives were found to elicit an immunoadjuvant effect more than the parent compound8%.

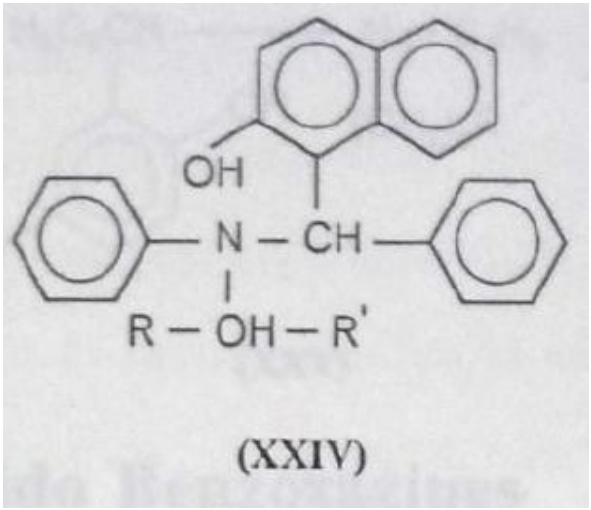


These valid observations led the author to undertake the synthesis of some new benzimidazole derivatives of the type (XXII) for evaluating their antimicrobial activity89.



Type-VI: 2-Substituted-1,4-Dihydroxy Benzenes

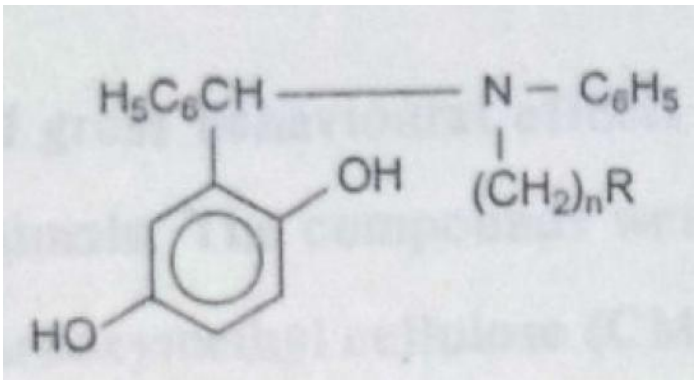
Substituted benzyl amines were mainly synthesized with a view to evaluate their anticonvulsant activity. Most of the compounds commonly in practice contain amido/imido group or other polar group together with a lipophilic moiety. It is tempting to associate these features with convulsant activity. It might be speculated that these features operate together to alter the structure of macromolecules associated with miantenance of CNS activity or hyperactivity. These features are typical of some CNS depressants including anticonvulsants, alcohols, carbamates and barbiturates90,91. The simple molecules might interact relatively indiscriminately with bioactive macromolecules and this could be reflected in many types of actions. More complex molecules might preferentially interact with one macromolecule as against another resulting in differences in qualitative action. It has been established that qualitative differences in action are a function of the agent's ability to interact with different macromolecules differently92. In addition, presence of a B-naphthyl group in some molecular structures (XXIV) have been demonstrated to increase the antiviral activity. This group was introduced with the expectation that the net protection percentage would increase considerably because if the enhanced antiviral activity of some compounds possessing phenolic hydroxylic group. Such compounds were screened against Semliki forest virus (SFV) in mice and were found antivirally active93.



(XXIV)

Some of the compounds of the general structure (XXIV) were evaluated for their antiviral activity against Encephalomyo carditis virus (EMCV), Japanese encephalites virus (IEV) and Tobacco mosaic virus. EMCV pools were made by intracerebral inoculation of 7-8 g swiss albino mice and JEV was propagated in the brains of suckling mice infected by cerebral injection. Lg29 cells were used for anti EMCV activity in vitro and chick embryo fibroblast cells were used for anti JEV in vitro studies. For in vivo studies, swiss albino mice (14-16g body weight) were injected with test compound intraperitoneally after every 24 h for three consecutive days followed by virus challenge. In general, these compounds exhibited anti EMCV activity upto 75 percent but no significant activity was demonstrated by these compounds against JEV. All the compounds were antivirally active against Tobacco mosaic virus (TMV) in vitro and in vivo, both but more significantly against TMV in vitro94.

In order to explore the possibility of finding antiviral activity, compounds of the general structure (XXV) were synthesized



(XXV)

Type VII : Pyrido Benzoxazines

The chemical reactivity of biologically active benzoxazinoids towards various types of nucleophiles has been recently reviewed in relation to their biological activity%. The influence and significance of o-functional substituents at positions 2,4 and 6 of the 2H-1,4-benzoxazin-3 (4H) one skelton have been investigated. The ability to form a multicentered electrophile under biological conditions has been found to be unique feature of the corresponding aglucones. Therefore, the bimolecule alkylating action of a benzoxazinoid derived cationic species is regarded as the chemical source of their biological activityo?

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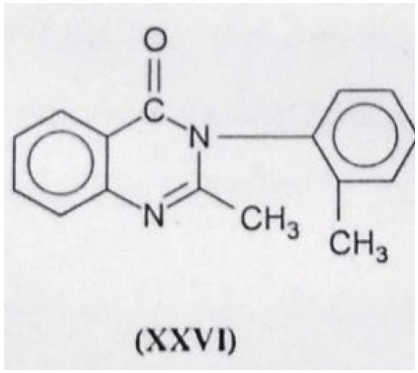
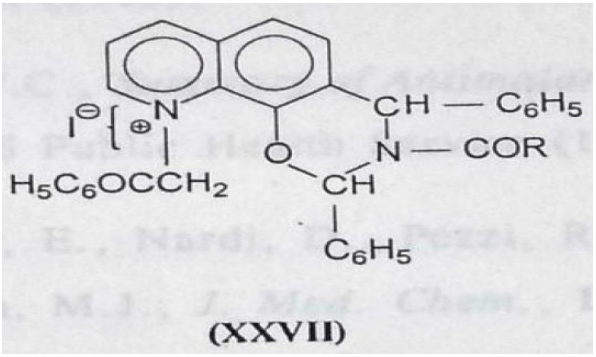
manfestations. However, the test animals could exhibit a marginal hyperactivity probably due to central nervous system stimulation. Moderate order of hypoglycemic activity was demonstrated by these compounds".

In addition, these benzoxazines are intermediates in the preparation of quinazolone derivatives which have well established anticonvulsant and central nervous system depressant activities. Thus, methaqualone (XXVI) has been demonstrated to be active against pentylene tetrazole induced seizures in experimental animals



(XXVI)

Several authors have recently reported the usefulness of quinazolone derivatives against viral diseases particularly against Encephalomyo carditis virus (EMCV), Japanes encephalites virus (IEV), Herpes simplex virus (HSV-1) and Ranikhet disease virus (RDV) 100-103. It is speculated that quinazole derivatives inhibit the multiplication of virus by inhibiting the RNA-induced polymerase thus retarding the synthesis of DNA 104.
This gave an impetus to the author to undertake the synthesis of 3-acyl-2,4-diphenyl-(3, 2h) (1, 3) benzoxazinyl-2'acetophenone pyridinium iodides (XXVII) for their antiviral activity 105



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