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REVIEW

A Review on the Biological Activity of Imidazo (4,5-b) Pyridines and Related Compounds

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A review on the various types of biological activities of imidazo (4,5-b) pyridines and related compounds is described.

Key Words: Biological activity, Imidazo (4,5-b) pyridines

o-Phenylenediamine is a valuable starting material for the synthesis of a large number of fused ring systems, most notably benzimidazoles, several derivatives of which have been reported to possess a variety of biological activities[1–4] However, its heterocyclic analogue, namely 2,3-pyridinediamine, has been screened much less, comparatively speaking, both for its reactivity and the biological activities of its derivatives.

2,3-Pyridinediamine is a derivative of pyridine with two amino groups *ortho* to each other and in the 2,3-positions. However, this diamine is different from a conventional *ortho*-diamine, such as *o*-phenylenediamine, in that, the reactivity of the two amino groups is different towards electrophilic reagents. In general, it has been found that the 3-amino group is more reactive and nucleophilic compared to the 2-amino group.

2,3-Pyridinediamines are generally prepared in the laboratory from the commercially available 2-aminopyridine using a known[5] procedure. 2,3-Pyridinediamine has m.f. $C_5H_7N_3$ and m.w. 109. It is a white, crystalline solid having the appearance of cottony needles when freshly prepared and can be stored as such for several months in the absence of air, acidic reagents etc. without any significant deterioration. However, when stored for a long time and kept exposed to air, it slowly undergoes oxidation as in the case of other aromatic amines and the colour changes from white to brown to brownish-black to black (m.p. 115–16°C).

It is highly soluble in water and hydoxylic solvents. It is also soluble reasonably in polar organic solvents. Once dissolved in water, its extraction is very difficult, with the help of organic solvents like benzene, ethyl acetate, chloroform etc.

2,3-Pyridinediamines are starting materials for the syntheses of differently substituted imidazo(4,5-b)pyridines which have been found to possess a variety

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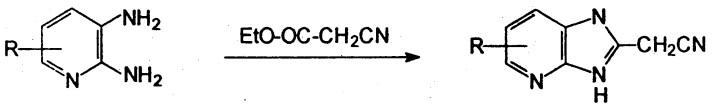
of biological activities. The imidazo(4,5-b)pyridines are obtained by condensation of 2,3-pyridinediamines with carbonyl compounds under different conditions. The biological activity of imidazo(4,5-b)pyridine derivatives has been classified and described below.

Antituberculostatic Activity

Bukowski *et al.*, in 1991, reported[6] 2-cyanomethylimidazo(4,5-b)pyridine **(I)** and its derivatives, obtained by condensing 2,3-pyridinediamines with ethyl cyanoacetate, to possess potential tuberculostatic activity with excellent coincidence between expected and observed bio-activity against *Micobacterium tuberculosis* stain.

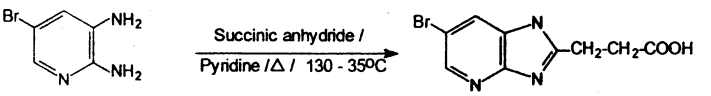


(I)

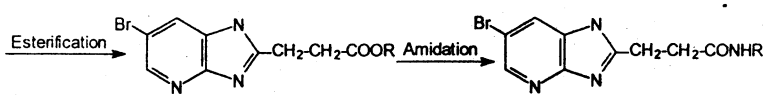
Several other 2-substituted imidazo(4,5-b)pyridines possessing different levels of tuberculostatic activity have also been reported by the same authors[7–9].

Antibacterial Activity

Youssef *et al.*, in 1985, reported[10] the anti-bacterial properties and structure-activity relationships (S.A.R.) of 3-[6-bromoimidazo(4,5-b)pyridinyl]propionic acid derivatives **(II–IV).** The latter were obtained by the treatment of 5-bromo-2,3-pyridinediamine with succinic anhydride in pyridine at 130–35°C followed by ester and amide formation. The majority of the compounds showed anti-bacterial activity with different selectivities.

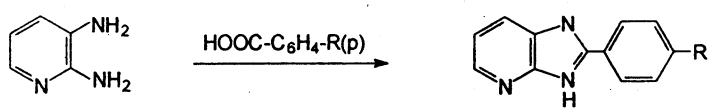


(II)



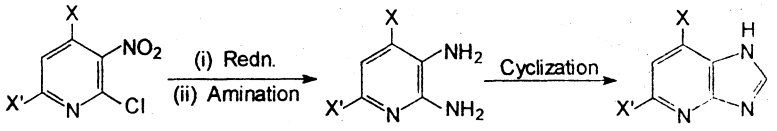
(III) **(IV)**

2-(*p*-Substituted phenyl)-3H-imidazo(4,5-b)pyridines **(V),** synthesised by Ozden *et al.*[11], in 1988, from 2,3-pyridinediamine and different *p*-substituted benzoic acids (R = H Me, CMe_3, F, Cl, Br, OMe, NO_2 etc.) were tested for *in-vitro* antibacterial activity. Out of several compounds obtained, V, R = Et, had minimum inhibitory concentrations against *Bacillus anthracis* and *B. subtilis* at 500 and 1000 μg/mL respectively.



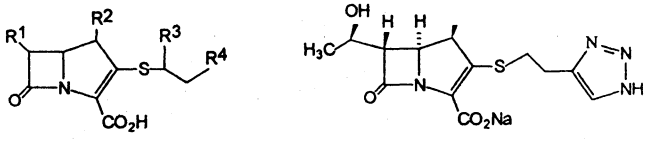
(V)

Kroon *et al.*[12] synthesised some mono and difluoroimidazo(4,5-b)pyridines, **VI** (X = H, X′ = F; X = X′ = F), as possible bactericides and tumor inhibitors by treating chloronitropyridines with KF, reducing the resulting fluoronitropyridines, aminating the aminofluoro derivatives and cyclizing the diaminofluoropyridines.



(VI)

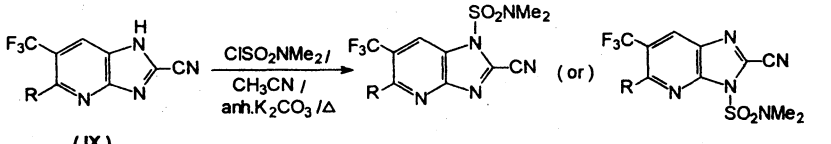
Similarly, Ishibashi *et al.*[13] synthesised carbapenems of the type structure **VII** (where R^1 = H, alkyl; R^2 = H, alkyl; R^3 = H, CN, alkoxy, alkylthio, carboxy; R^4 = N-containing heterocycle) for use as antibacterial agents with excellent antibacterial activities, oral absorbability and stability. Thus, **VIII** was prepared starting from 4-nitrobenzyl (4R, 5S, 6S)-3-[(diphenyl phosphono)oxy]-6-[(R) -1-hydroxyethyl]-4-methyl-7-oxo-1-azabicyclo [3.2.0] hept-2-ene-2-carboxylate and 2-(1-triphenylmethyl-1,2,3-trazol-4-yl)ethanol. **VIII** gave MIC values of 0.025 and 0.1 μg/mL when tested against *E. coli* NHIJ JC-2 & *H. influenzae* NN 400 respectively.



(VII) (VIII)

Antimicrobial Activity

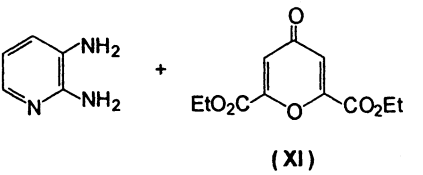
Nasu *et al.*[14] synthesised several 6-trifluoromethylimidazopyridines as microbicides. Thus, refluxing 2-cyano-5-(2,2,2-trifluoroethoxy)-6-trifluoromethyl-1H-imidazo(4,5-b)pyridine (**IX**, R = O-CH_2-CF_3), acetonitrile and anhydrous potassium carbonate for 1 h. followed by addition of dimethylsulfamoyl chloride and further refluxion for 1 h yielded 1H(3H)-2-cyano-1,(3)-dimethylsulfamoyl-5-(2,2,2-trifluoroethoxy)-6-trifluoromethylimidazo (4,5-b) pyridine (**XA** or **XB**, R = O-CH_2-CF_3), which was found to possess antimicrobial activity. The latter at 125 ppm totally controlled *Pseudoperonospora cubensis* on cucumbers, and at 500 ppm totally controlled *Tetranychus telarius* on beans. A formulation containing 5 parts of **X** (A or B) and 95 parts of talc was prepared.



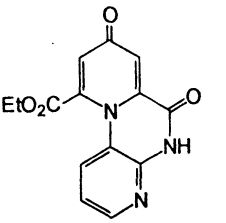
(IX) (XA) (XB)

Another compound, **XII,** was prepared by El-Kerdawy *et al.*[15] by condensing diethyl chelidonate **(XI)** with 2,3-pyridinediamine under unstated conditions. **XII**

was tested against a number of pathogenic micro-organisms and found to show promising effect against microbes.



(XI)

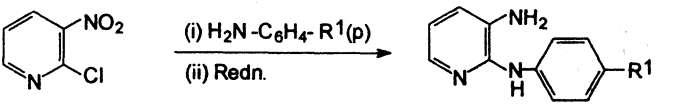


(XII)

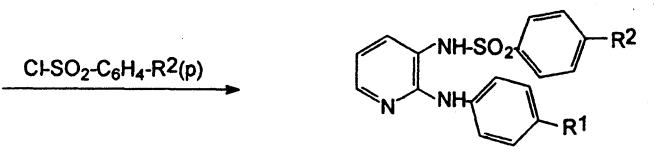
Antitumour Activity

The synthesis of N-[(2-arylamino)aryl]benzenesulphonamides **(XIV)**, as compounds containing antitumour activity, was reported by Yoshino *et al.*[16] in 1992. Thus, condensation of 2-chloro-3-nitropyridine with a substituted aniline and subsequent reduction gave **XIII** which with arylsulphonyl chloride gave **XIV.**

One of these compounds, **XIV** ($R^1 = R^2 = OMe$), showed 99% inhibition of colon 38 tumors in mice at 100 mg/kg/day orally for 21 days.

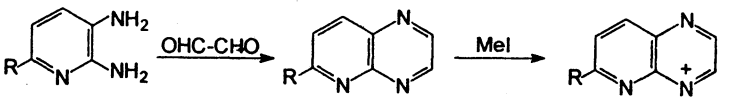


(XIII)



(XIV)

PyridinO [2,3-b]pyrazines were synthesised by Postovski *et al.*[17] by cyclocondensation of 6-substituted-2-3-pyridinediamine ($R = Me_2N$, morpholino, piperidino) with glyoxal to give XV and the product was quaternised with methyl iodide to yield **XVI.** Both **XV** and **XVI** ($R = Me_2N$) inhibited Sarcoma 37 in mice to the extent of 50–55% at 50–100 μg/kg dosage.

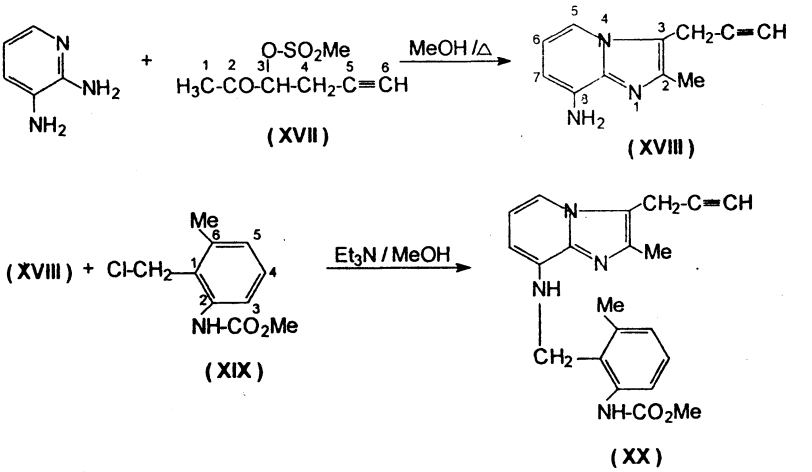


(XV) (XVI)

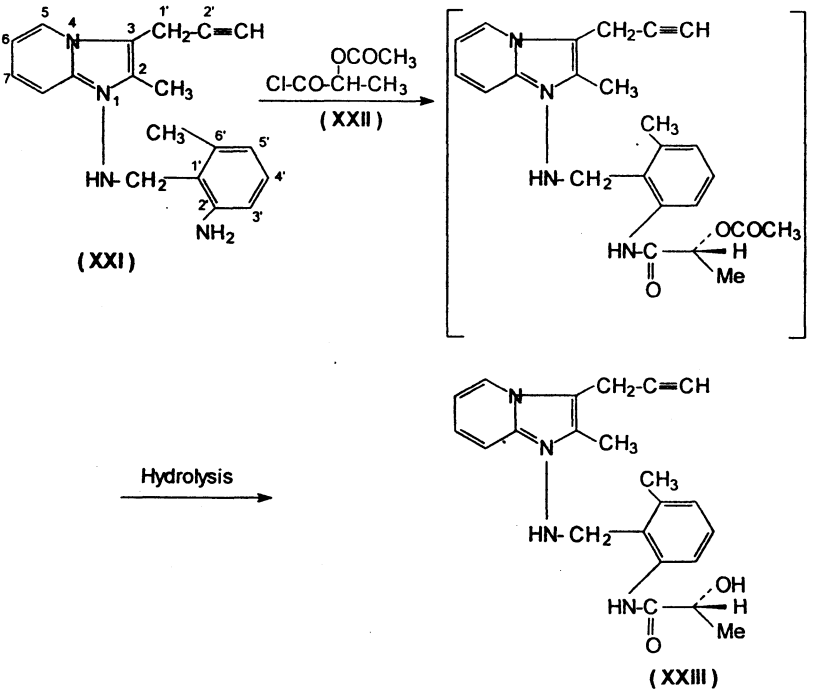
Antiulcer Activity

Shiokawa *et al.*[18], in 1989, reported the synthesis of imidazopyridine derivatives for the treatment of ulcers. Thus, cyclocondensation of 2,3-pyridinediamine with 3-mesyloxy-5-hexyn-2-one **(XVII)** in refluxing methanol gave 8-amino-3(2′-propynyl)2-methylimidazo[1,2-a]pyridine **(XVIII).** The latter was alkylated

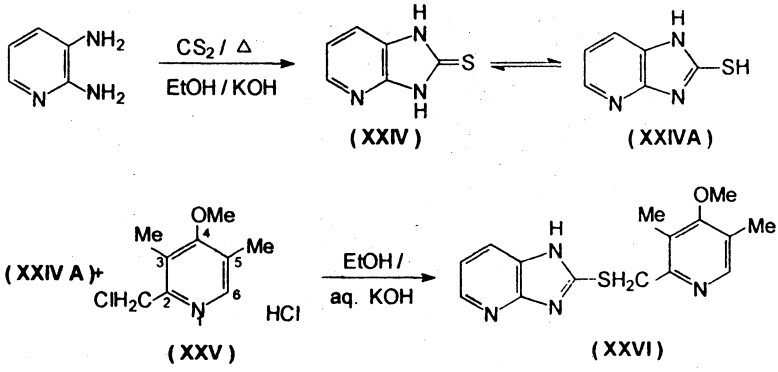
with 2-carbamato-6-methylbenzyl chloride **(XIX)** and triethylamine in methanol to give **XX.** The compound **XX** at 3.2 mg/kg orally in dogs with Heidenhain Pouches, completely inhibited gastric acid secretion induced by i.v. gastrin (10 μg/kg/h).



A similar report[19] was published about the syntheses of acetylenic derivatives of imidazopyridines as antiulcer agents. Thus, reaction of 8-(2′-aminobenzyl-amino-6′-methyl)-3-(2′-propynyl)-2-methylimidazo[1,2-a]pyridine **(XXI)** with (S)-2-acetoxypropionyl chloride **(XXII)** followed by hydrolysis gave **XXIII. XXIII** at 3.2 mg/kg orally gave 100% inhibition of gastric acid secretion in dogs.

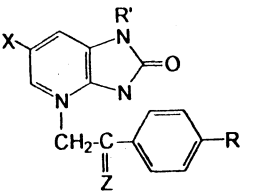


Mitsuaki *et al.*[20] reported the synthesis of 2-pyridylthio or 2-pyridylsulphinyl-imidazopyridines, as antiulcer agents. Thus, cyclocondensation of 2,3-pyridine-diamine with carbon disulphide in ethanol containing KOH under reflux gave imidazo(4,5-b)pyridine-2-thione **(XXIV)** which was alkylated by 2-(chloro-methyl)-3,5-dimethyl-4-methoxypyridine **(XXV)** in ethanol in the presence of aq. KOH under ice-cooling to yield **XXVI.**



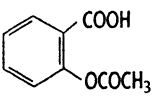
Analgesic Activity

The synthesis of certain imidazo(4,5-b)pyridines of the type structure **XXVII** (where R = H, Br, Cl, Me, MeO, NO_2; R′ = H, —CO—C_6H_4-alkyl(*p*), Z = O, NOH; X = H, Br) by the known methods and their biological activity evaluations were reported by El-Gendy *et al.*[21]

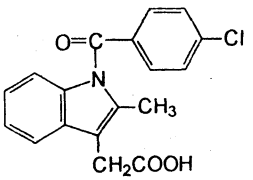


Some compounds, in the series of the type **XXVII**, showed reasonable analgesic activity in comparison to aspirin **(XXVIII)** and indomethacin **(XXIX).**

It may be mentioned here that aspirin **(XXVIII)** is synthesised by the acetylation of salicylic acid with acetic anhydride[22]. It is used as analgesic, antipyretic and antiinflammatory agent in a variety of conditions ranging from discomfort to headache to fever, associated with the common cold, muscular pains and body aches. Aspirin is used as a drug of choice in the reduction of fever because of its high degree of effectiveness and wide safety margin, As aspirin inhibits platelet function, it has been employed prophylactically to minimise the incidence of myocardial infarction and transient ischemic attacks.



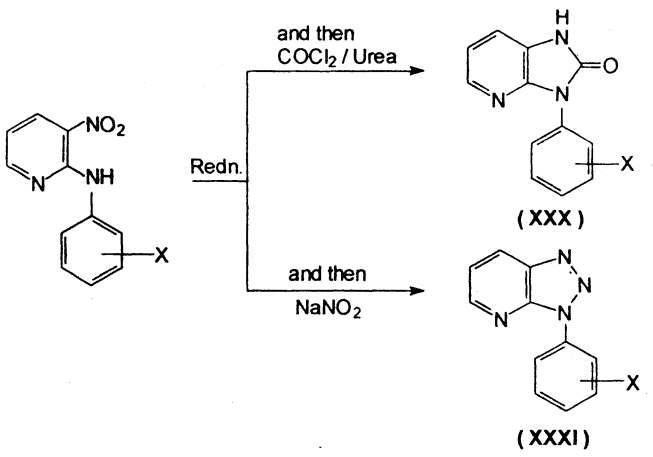
(XXVIII)



(XXIX)

Since aspirin is a drug almost without side effects, it can be used as an OTC drug. On the other hand, indomethacin is a non-steroidal drug possessing anti-inflammatory, antipyretic and analgesic properties. It is usually employed for the treatment of rheumatoid arthritis, ankylosing (rheumatoid) spondylitis, gouty arthiritis and osteoarthritis. It is not an ordinary, simple analgesic and owing to its reasonably serious untoward effect, it should be used with great caution. It is normally taken only on the prescription by a clinician and comes under the category of schedule "H" drug.

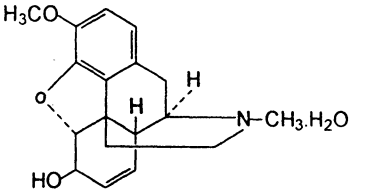
Robert *et al.*, in 1979, reported[23] the synthesis and analgesic activity of 1,3-dihydro-3(substituted phenyl)-imidazo(4,5-b)pyridine-2-ones (**XXX,** where R = H or alkyl, X = H, halo, alkyl, NH_2 etc.) and 3-(substituted phenyl)1,2,3-triazolo(4,5-b)pyridines (**XXXI,** where X = H, halo, alkyl, alkoxy, NO_2 etc). Thus, the former and latter compounds were prepared by cyclising 3-nitro-2-anilinopyridines with phosgene/urea and sodium nitrite respecively after reduction of the nitro group to the amino group.

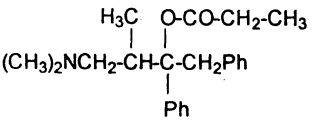


(XXX)

(XXXI)

The two sets of compounds, **XXX, XXXI,** increased the pain threshold of both the inflamed and the normal foot in a modified Randall-Sclitto test. **XXX** (where, R = H, alkyl, and —$CHMe_2$; X = 3,4-OCH_2O) and **XXXI** (where X = H or F) were the most active compounds. The analgesic activity of **XXX** was found[23] to be superior to that of codeine **(XXXII)** or D-propoxyphene **(XXXIII)** while showing no narcotic characteristics. Some **XXX** and **XXXI** were effective in the carragenin edema test.

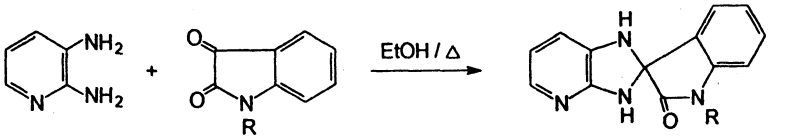




It may be mentioned here that codeine **(XXXII)** is a narcotic analgesic exhibiting[22] mild sedative effects. However, its activity is much less compared to that of naturally occurring morphine or semi synthetic heroin.

Antineoplastic Activity:

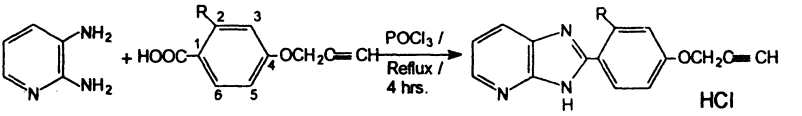
Popp[24], in 1973, reported the synthesis of spiroindoles **(XXXV)** as potential antineoplastic agents by heating isatin and N-acetylisatin **(XXXIV,** R = H or Ac) with 2,3-pyridinediamine in ethanol.



(XXXIV) **(XXXV)**

Inotropic activity

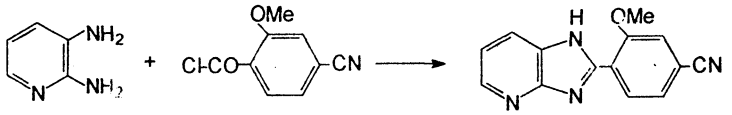
In 1983, Jonas *et al.*[25] reported the preparation of 2-arylimidazo(4,5-b)pyridines which were found to be inotropic agents for cardiac insufficiency. Thus, a mixture of 2,3-pyridinediamine and 4-propargyloxy-2-substituted benzoic acid **(XXXVI)** was added in portions to phosphoryl chloride and the mixture refluxed to give compound **(XXXVII)** as its hydrochloride.



(XXXVI) **(XXXVII)**

Subsequently, Barraclough *et al.*[26] reported the synthesis of a series of 2-substituted-1H-imidazo(4,5-b)pyridines by condensing 2,3-pyridinediamine with benzoyl chlorides which were evaluated as inotropic agents. In a typical experiment, 2,3-pyridinediamine was condensed with 2-methoxy-4-cyanobenzoylchloride to yield 2-(2′-methoxy-4′-cyanophenyl)imidazo(4,5-b)pyridine **(XXXVIII).**

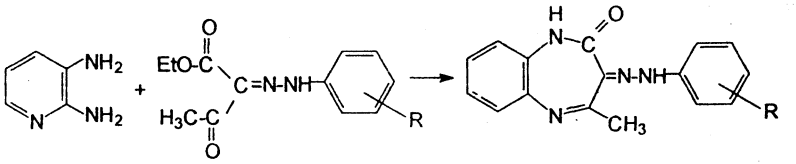
The 1H-imidazo(4,5-b)pyridine derivatives were consistently more potent than their isomers in the (4,5-c) series in isolated guinea pig papillary muscle preparations. Further, they also discussed[26] the structure-activity relationships and species dependence of inotropic potencies.



(XXXVIII)

CNS Depressant Activity

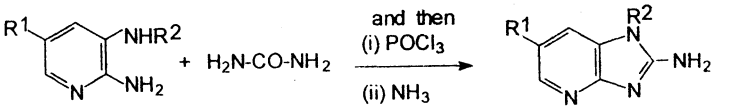
8-Arylhydrazonopyrido[2,3-b][1,5]diazepin-2-ones **(XXXX)** (where, R = 2-F, 2,4-F_2, 3-F_3C, 3,5$(F_3C)_2$, 2-MeS and 3-MeS) were synthesised[27] as potential CNS depressants by cyclocondensation of 2,3-pyridinediamines with arylhydrazones of ethyl 2,3-dioxobutyrate **(XXXIX).**



(XXXIX) (XXXX)

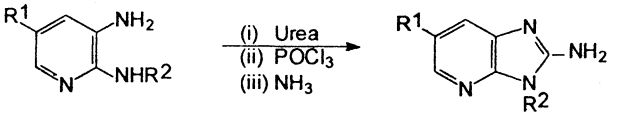
Mutagenic Activity

The preparation of 2-aminoimidazo(4,5-b)pyridine derivatives of the type **XXXXII** useful as mutagens was reported by Tanasca *et al.*[28], in 1989. Thus, in a typical example, cyclocondensation of 2-amino-3-methylamino-5-phenylpyridine (**XXXXI,** R^1 = Ph, R^2 = Me) with urea followed by reaction with $POCl_3$ and amination with ammonia gave the compound **XXXXII** (R_1 = Ph, R_2 = Me).



(XXXXI) (XXXXII)

Compounds having the general structure **XXXXIII** (where R^1 = hydrocarbyl, R^2 = H, alkyl) were also prepared[28] by the same method and tested for their biological activity. The compounds were found to be useful as mutagens.

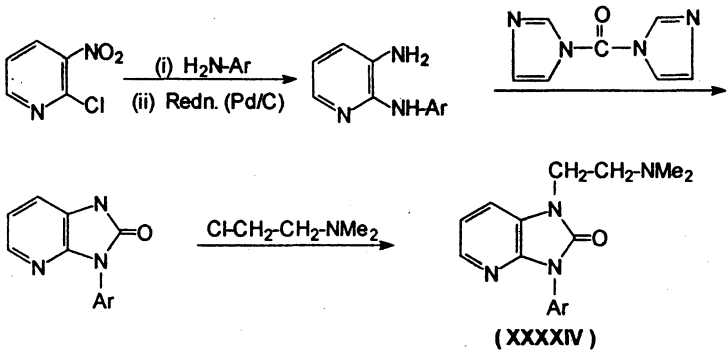


(XXXXIII)

Antidepressant Activity

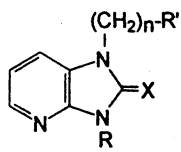
Robinson *et al.*[29] synthesised 1-(aminoalkyl)-2,3-dihydroimidazo (4,5b)pyridines **(XXXXIV)** as compounds containing anti-depressant activity. Thus, in a typical procedure, 2-chloro-3-nitropyridine was treated with a substituted aniline, the product hydrogenated over Pd/C and then reacted with 1,1′-car-

bonyldiimidazole, followed by treatment with α-dimethylaminoethyl chloride to obtain **XXXXIV.** The latter were isolated as dicyclohexyl sulfamate salts.



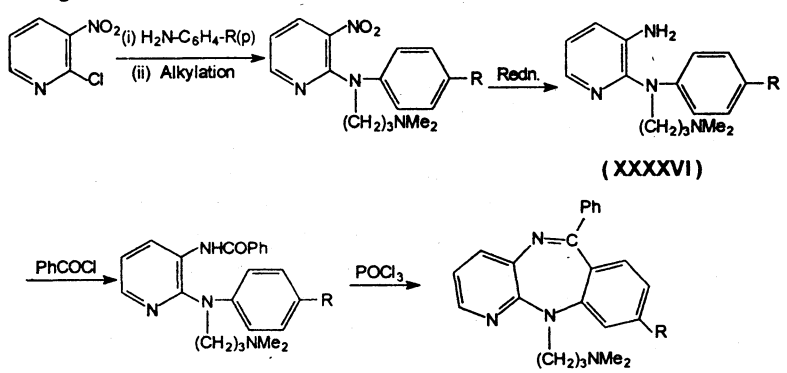
(XXXXIV)

The same researchers prepared[29] compounds of the type **XXXXV** (where R = cyclohexyl, $PhCH_2$, Ph, *p*-F-C_6H_4 etc. R′ = Me_2N, 4-Me-1-piperazinyl; X = O, S; n = 2, 3) which were found to possess antidepressant activity. The compounds **XXXXV** were found to be antidepressants at 2.5–100 mg/kgl/day in higher animals.



(XXXXV)

The preparation of pyrido[1,4]benzodiazepines **(XXXXVII)** as antidepressants was reported by Taylor *et. al.*[30] These researchers cyclocondensed 2-chloro-3-nitropyridine with a substituted aniline, the product alkylated and reduced to give **XXXXVI.** The latter on benzoylation and then cyclisation with phosphoryl chloride gave **XXXXVII.**

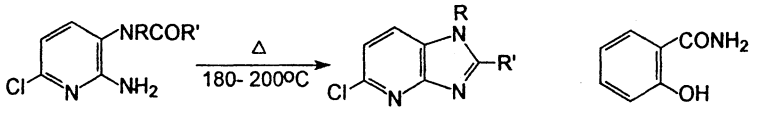


(XXXXVI)

(XXXXVII)

Antiphlogistic Activity

Von Bebenburg and Walter[31], in 1973, synthesised 6-chloro-imidazo(4,5-b)pyridines **(XXXXIX)** which were found to have antiphlogistic activity comparable to that of salicylamide **(L). XXXXIX** were obtained by heating 2-amino-3-(N-substituted)acylamino-6-chloropyridines **(XXXXVIII)** at 180– 200°C.

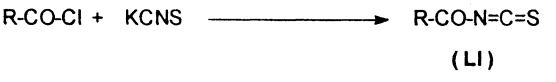


(XXXXVIII) **(XXXXIX)** **(L)**

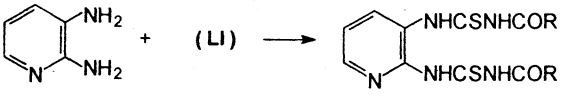
It may be mentioned here that salicylamide has antipyretic and analgesic activity comparable[22] to that of aspirin. It is used in place of salicylates where apparent sensitivity problems arise.

Antihelmintic Activity

2 3-Bis(3-acyl-2-thioureido)pyridines **(LII),** useful as antihelmintics in sheep at 3–50 mg/kg in feed, were prepared[32] by reacting 2,3-pyridinediamine with acylisothiocyanates **(LI).** The latter reagents were prepared[32] by treating acyl chlorides with potassium thiocyanate.

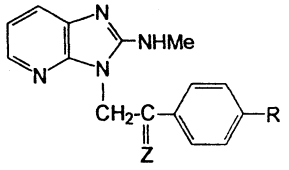


(LI)

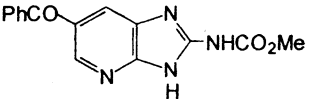


(LII)

Several imidazo(4,5-b)pyridines of the type structure **LIII** (where, R = H, Br, Cl, Me, MeO, NO_2; Z = O, NOH; X = H, Br) were prepared and tested[18] for antihelmintic activity against the cattle parasite *Ascaris vitulorum* and compared with the activity of mebendazole **(LIV).**



(LIII)



(LIV)

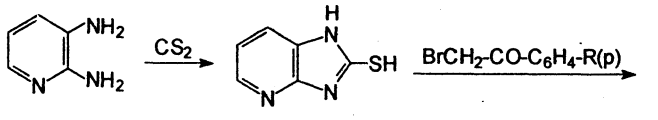
It may be mentioned here that mebendazole **(LIV)** is an antihelmintic[22] with an LD_{50} orally; > 80 mg/kg in sheep; 40 mg/kg in mice, rats and chicken.

Antiparasitic Activity

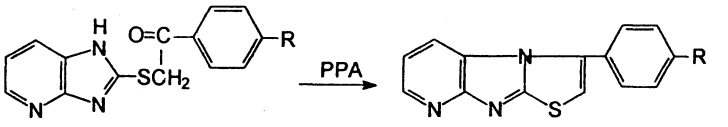
3-Arylpyridoimidazothiazolines **(LVII)** (where, R = H, Me, Br, Cl, NO_2) of

potential antiparasitic activity were prepared[33] by cyclisation of the corresponding unreported 2-(substituted phenacylthio)imidazo(4,5-b)pyridines **(LVI)** with polyphosphoric acid. **LVI** were prepared in turn from the 2-mercaptoimidazo(4,5-b)pyridine **(LV).**

The same compound **(LVII)** could also be prepared by a single step condensation of **LV** with arylacylamides in polyphosphoric acid as one-pot reaction.



(LV)

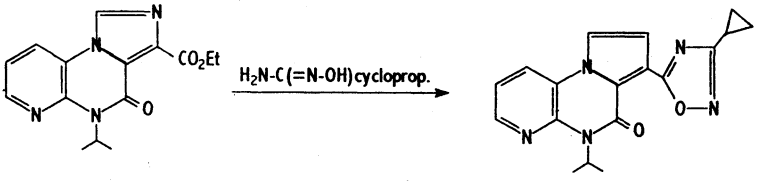


(LVI) **(LVII)**

Anticonvulsants

The preparation of imidazoquinoxaline **(LIX)** and its analogues were reported by Hansen and Watjen[34], which were useful as anticonvulsants in improving cognitive functions of the brain. Thus, in a typical procedure, **LVIII** was treated with cyclopropylcarboxamidoxine in the presence of sodium ethoxide in ethanol and crushed molecular sieves of the type 4A to give **LIX.** The latter showed an ED_{50} of 0.33 mg/kg for displacing 3H-flunitrazepam from benzodiazepine receptors.

A tablet was also formulated containing 10 parts of **LIX,** lactose 67.8, avicel 31.4, amberlite IRP 881.0 and Mg stearate 0.25 mg.



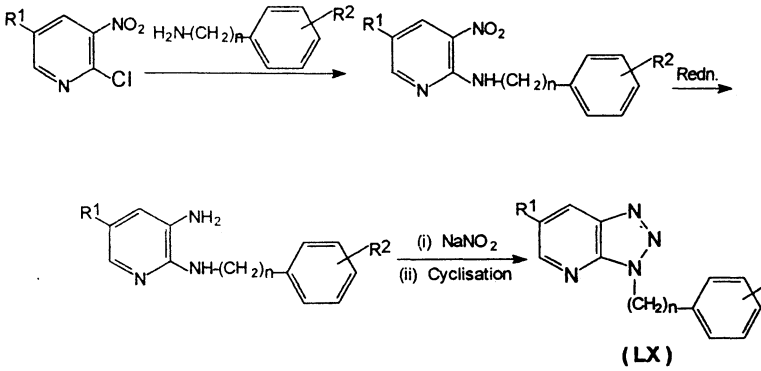
(LVIII) **(LIX)**

Antiinflammatory, Antipyretic and Analgesic Activities

Clark *et al.*, in 1977, repored[35] the synthesis of 3H-1,2,3-triazolo(4,5-b)pyridines **(LX)** (where, R^1 = H, Me; R^2 = H, 2F, 2-Me, 2,4-F_2, 2,4-Me_2, 3-CN, 3-F_3C, 3-MeO, 4-Et etc.; n = 0,1,2) useful as antiinflammatory, antipyretic and analgesics.

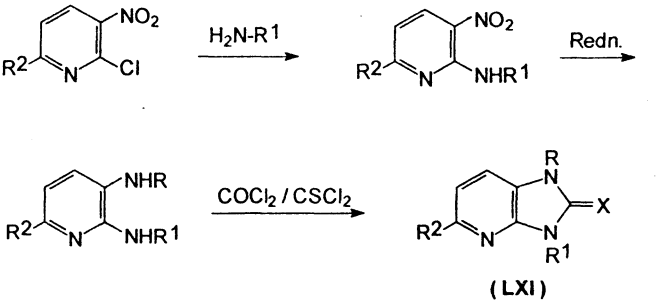
The title compounds were prepared by the reaction of 2-chloro-3-nitropyridine with aniline, benzylamine or phenethylamine derivatives, reduction of the nitro group to the amino group in the anilino, benzylamino or phenethylamino

nitropyridine and diazotisation (with sodium nitrite) of the amino group followed by cyclisation.



(LX)

Clark *et al.*[36] also reported the synthesis of 1,3-dihydroimidazo(4,5-b)pyridin-2-ones and thiones **(LXI)** (where, R = H, Pr, $H_2C=CHCH_2$, Me, $PhCH_2$; R^1 = Ph, 2,4-$(MeO)_2$-C_6H_3, 2,4$(Me)_2$-C_6H_3, 3,4-$(OCH_2O)_2$-C_6H_3, 2-Br-C_6H_4, 3-F-C_6H_4, 2-methyl-6-pyridinyl, 1,3-dihydro-5-isobenzofuranyl: R^2 = H, Me, NO_2, NH_2; X = O, S), useful as inflammation inhibitors, antipyretics and analgesics, by reaction of a 2-chloro-3-nitro-6-substituted pyridine with a substituted aniline, reduction of the resulting 2-anilino-3-nitropyridine followed by cyclocondensation with $COCl_2$ or $CSCl_2$.

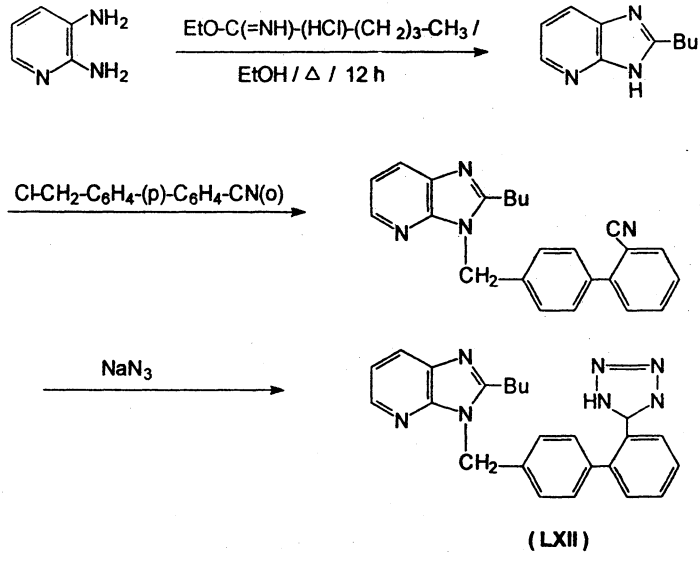


(LXI)

Cardiovascular Agents, Cardiotonics and Agents for Heart Insufficiencies

Refluxing 2,3-pyridinediamine, ethyl valeramidate hydrochloride and triethylamine in ethanol for 12 h, followed by benzylation using 4-(2-cyanophenyl) benzylchloride and then cyclocondensation with sodium azide gave[37] **LXII.** The biphenylalkylimidazopyridine was found to be a cardiovascular agent. The latter compound at 30 mg/kg, orally, gave > 70% inhibition of angiotensin-II induced pressor action in rats.

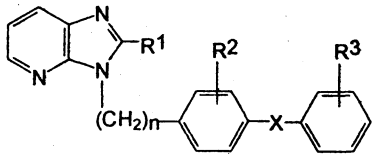
Similarly, compounds of the type structure **LXIII** (where R^1 = H, substituted alkyl, aralkyl, aryl: R^2 = H, halo, NO_2; R^3 = CO_2H, C_{1-4} alkoxycarbonyl, cyano, tetrazolyl etc., n = 1,2; X = bond, spacer containing 2 atoms or less) were also



(LXII)

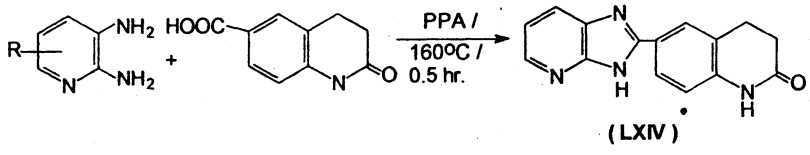
synthesised[37], which were angiotensin-II antagonists, useful as cardiovascular agents.

Several drug formulations containing **LXIII** were also prepared.



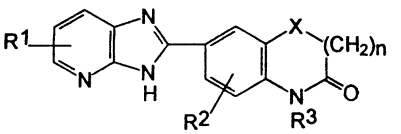
(LXIII)

Nakao *et al.*, in 1988, synthesised[38] quinolinylimidazopyridine derivatives, useful as cardiovascular agents. Thus, by reacting 2,3-pyridinediamines with 2-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylic acid in polyphosphoric acid at 160°C for 0.5 h gave 2-(2′-oxo-1,2,3,4-tetrahydroquinolin-6-yl)imidazopyridines **(LXIV).** The hydrochloride of **LXIV** *in vitro* exhibited an IC_{50} of 10 μg/mL against blood platelet aggregation.



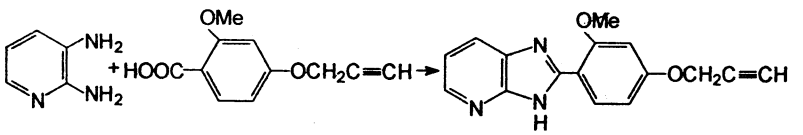
(LXIV)

Similarly, compounds of the general structure **LXV** (where R^1 = H, halo, lower alkyl, alkoxy, NO_2, alkylaminoalkyl; X = O, S, CR^4CR^5; R^4,R^5 = H, lower alkyl; n = 0–2) were also prepared[38]. The latter were useful as cardiovascular agents.



(LXV)

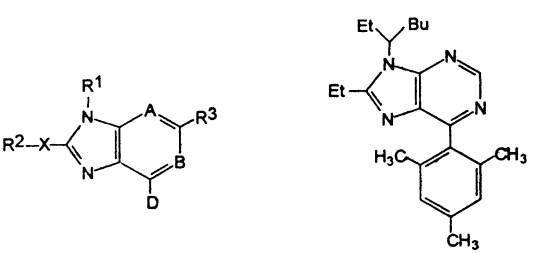
2-Arylimidazopyridines, useful in the treatment of heart insufficiency, were synthesised by Jonas *et al.*[39] Thus, in a typical procedure, they cyclocondensed 2,3-pyridinediamine with a substituted benzoic acid such as **LXVI** to give **LXVII.** The compound **LXVI** was itself obtained by treating 2,4-dihydroxymethylbenzoate with propargyl chloride and methyl iodide followed by saponification.



(LXVI) (LXVII)

Wilde *et al.*[40] reported the synthesised and formulated purine derivatives of the type structure **LXVIII** (where A = N, CR^7; B = N; CR^8; at least one of A and B = N; D = aryl or heteroaryl attached through an unsaturated carbon atom; X = CHR^9, NR^{10}, O, S, (O)n; a bond; n = 0–2; R^1 = C_{1-10} alkyl, C_{2-10} alkynyl etc; R^2 = C_{1-4} alkyl, C_{3-8} cycloalkyl, C_{2-4} alkenyl etc., R^3, R^7 and R^8 = H, halo, cyano etc. R^9 , R^{10} = H, C_{1-4} alkyl, C_{3-6} cycloalkyl etc.) Corticotropin releasing factor (CRF) antagonists (no data) useful in treating psychiatric disorders and neurological disorders as well as treatment of immunological cardivascular or heart related diseases and colonic hypersensitivity associated with psychopathological disturbance and stress in mammals.

Thus, a six step synthesis of purine **LXIX** starting from 5-amino-4,5-dichloropyrimidine and benzylamine is given. Compounds **LXVIII** are effective at 0.01–10 mg/kg/day.



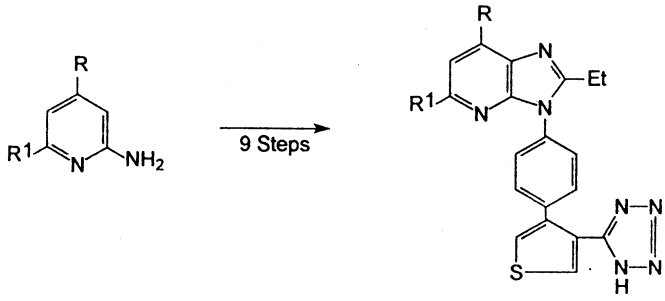
(LXVIII) (LXIX)

Angiotensin-II Antagonistic Activity

The synthesis of [[(tetrazolyl)thienyl]benzyl]imidazopyridines and related compounds, under unstated conditions, was reported by Allen *et al.*[41] in 1994.

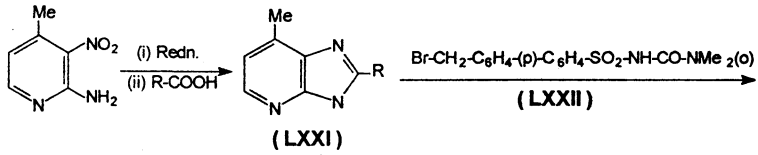
The latter compounds were useful as angiotensin-II antagonists for the treatment of hypertension, elevated intraocular pressure and conjunctive heart failures.

The title compounds **LXX** were synthesised starting from 4,6-dialkyl-2-aminopyridines in 9 steps.

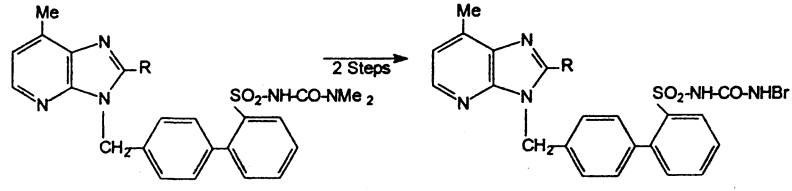


(LXX)

Heitcsch *et al.*[42], in 1993, reported the synthesis of 3-[2′(ureidosulphonyl)biphenyl-4-yl]-methylimidazo(4,5-b)pyridines and analogues as angiotensin-II antagonists. Thus, 2-amino-4-methyl-3-nitropyridine was reduced and the product condensed with propanoic acid to give imidazopyridine **LXXI** (R = Et).The latter was condensed with $BrCH_2$-C_6H_4-(*p*)-C_6H_4-(*o*)-SO_2-NHCO-NMe_2 **(LXXII)** and the product converted, in two steps, to **LXXIII.** This compound (*i.e.*, **LXXIII,** R = Et) had IC_{50} of 0.48 nM against angiotensin-II binding *in vitro.*



(LXXI) **(LXXII)**

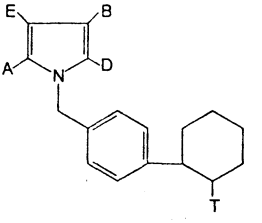


(LXXIII)

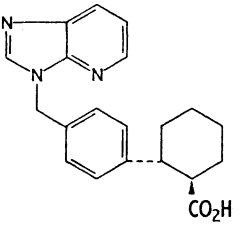
The synthesis of imidazo(4,5-b)pyridinylmethylphenyl cyclohexane carboxylates as angiotensin antagonists were reported by Mueller *et al.*[43] Thus imidazolylmethylphenyl cyclohexane carboxylate derivatives and pyrrolylmethylphenylcyclohexane carboxylate derivatives of the type structure **LXXIV** (A = H, aryl etc, B, D = substituted; BD = fused ring fragment; E = nitrogen, methine, L = H, halo, nitro etc. T = carboxy or amide function) were disclosed as agents for the treatment of arterial hypertomia and atherosclerosis.

LXXIV are antihypertensives (angiotensin = II antagonists). An example

compound *i.e.*, imidazo(4,5-b)pyridinylmethyl phenyl cyclohexane carboxylate **LXXV** was prepared.



(LXXIV)

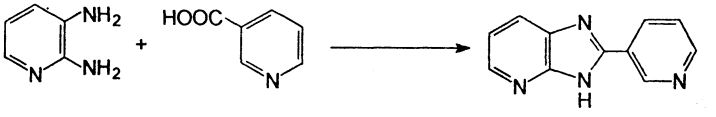


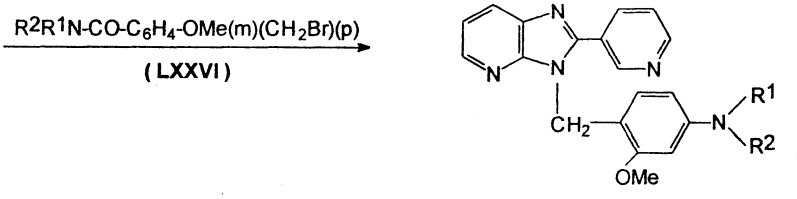
(LXXV)

Platelet Activating Factor Antagonistic Activity

N,N-cycloalkyl/alkyl carboxamides of 4H-imidazo(4,5-b)pyridines as PAF antagonists was reported by Weier *et al.*[44] in 1994. Thus, 2,3-pyridinediamine was cyclised with nicotinic acid and the product condensed with **LXXVI** (R^1 = cyclohexyl, R^2 = i-propyl) to give **LXXVII** (R^1 = cyclohexyl, R^2 = i-propyl).

The compound **LXXVII** demonstrated 68% inhibition of the binding of tritiated platelet activating factor to platelet activating factor receptors from human neutrophil membranes at 10 nM.

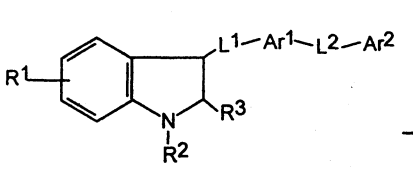




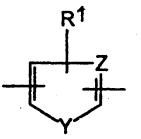
(LXXVII)

Summers *et al.*[45] synthesised imidazopyridineindoles of the type structure (**LXXVIII,** where R = one or more of the groups independently selected from *e.g.*, H, halo, hydroxy, cyano; R^2 is selected from the group consisting of H, alkyl of 1–6 C atoms); R^3 is selected from the group consisting of H, alkyl of 1–6 C atoms; L′ = CO, $COCH_2NR^4$, R^4 = H, alkyl of 1–6 C atoms; Ar′ = radical **LXXIX** where Y = O, S or CH:CH, Z = N or CH; R″ = H, alkyl of 1–6 C atoms; L^2 = a valance band, (un) substituted straight chain alkylene of 1–6 C atoms; Ar^2 = substituted benzimidazol-1-yl, imidazopyridine group **LXXX** where R^{13} = alkyl of 1–6 C atoms, alkenyl of 2–6 C atoms ; R^{14} & R^{15} = H, alkyl of 1–6 C atoms, alkenyl of 2–6 C atoms and the pharmaceutically acceptable salts thereof which are potent antagonists of platelet activating factor and are useful in the treatment of PAF related disorders including asthma, shock, respiratory distress syndrome,

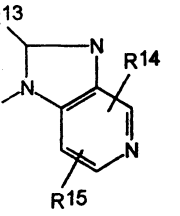
acute inflammation, transplanted organ rejection, gastrointestinal ulceration, allergic skin diseases, delayed cellular immunity, parturition, fetal lung maturation and cellular differentiation, useful as platelet activating factor antagonists.



(LXXVIII)



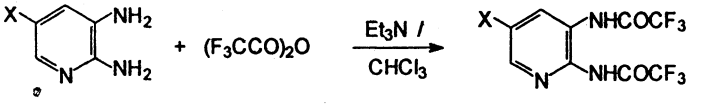
(LXXIX)



(LXXX)

Herbicidal Activity

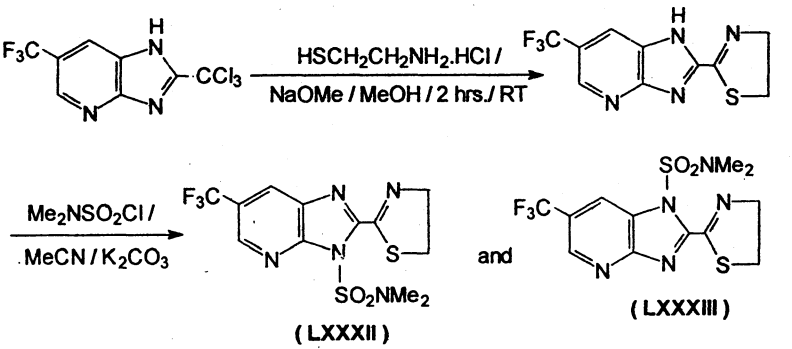
Doherty *et al.*[46, 47], in 1973, synthesised the N-(2,2-difluoroalkanoyl)2,3-pyridinediamines as herbicides. Thus, by reacting 5-chloro-2,3-pyridinediamines with trifluoroacetic anhydride in presence of chloroform and triethylamine at 25°C gave **LXXXI.** The latter compound at 2 lb/acre was 100% effective against crabgrass, pigweed, foxtail and velvet leaf in post-emergent test, but had no effect on corn even at 8 lb/acre.



(LXXXI)

Fungicidal Activity

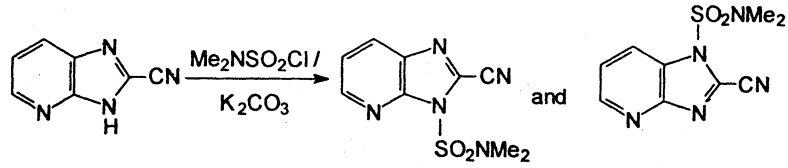
2-(Thiazole-2-yl)imidazo(4,5-b)pyridine and its analogues were prepared[48] by reacting 2-(trichloromethyl)-6-(trifluoromethyl)imidazo(4,5-b)pyridine with 2-mercaptoethylamine hydrochloride in the presence of sodium methoxide in methanol for 2 h at room temperature. The product, thus obtained, on treatment with N,N-dimethylsulfamoyl chloride in acetonitrile containing potassium carbonate gave a 1 : 1 mixture of **LXXXII** and its isomer **LXXIII.** The compounds **LXXXII** and **LXXIII** at 500 ppm inhibited by 100% the growth of *Pseudoperonospora cubensis* in cucumbers.



(LXXXII)

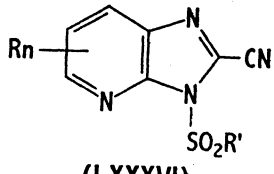
(LXXXIII)

Giraudon *et al.*[49], in 1985, reported the synthesis of 2-cyanoimidazo(4,5-b)pyridine derivatives useful as fungicides. Thus, imidazopyridine-2-carbonitrile was treated with dimethylsulfamoyl chloride and potassium carbonate to give the compounds **LXXXIV** and **LXXXV.**



(LXXXIV) (LXXXV)

Other imidazopyridine carbonitriles of the general structure **LXXXVI** (where, n = 0–3, R = halo, alkyl, haloalkyl, NO_2, cyano; R′ = alkyl, haloalkyl, cycloalkyl, halocycloalkyl, amino, alkylamino, dialkylamino) were also prepared[49]. The latter exhibited fungicidal activity.

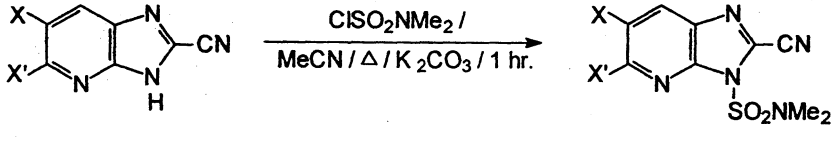


(LXXXVI)

Pesticidal Activity

In 1988, Nash *et al.*[50] reported a method for the preparation of imidazo (4,5-b)pyridines as pesticides and medicinal microbicides. Thus, by refluxing **LXXXVII** (X = Cl, X = CF_3) with dimethylsulfamoyl chloride in the presence of acetonitrile and potassium carbonate for 1 h gave **LXXXVIII.** The latter showed 100% control of pseudoperonospora cubensis at 125 ppm and 500 ppm when infected after and before the treatment respectively.

A wettable powder containing **LXXXVIII** (50 parts), zhigulite (40 parts), sodium ligninsulphonate (7 parts) and dialkyl succinate (3 parts) was prepared.

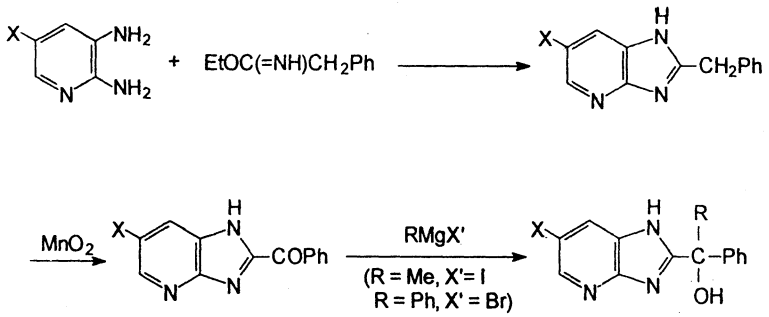


(LXXXVII) (LXXXVIII)

Virucidal Activity

Synthesis of phenyl(2-imidazo[4,5-b]pyridyl)carbinols was reported[51] by Berner and Reinshagen in 1975. Thus, 2,3-pyridinediamines were cyclised with iminoether derivatives of benzylcyanide yielding 2-benzylimidazo(4,5-b)pyridines. The latter on oxidation with MnO_2 followed by reaction with MeMgI and

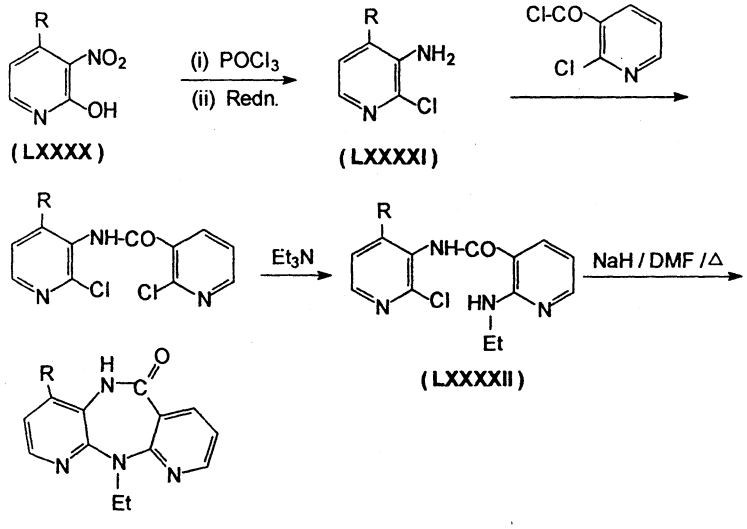
PhMgBr respectively gave title compound **LXXXIX.** The latter were effective virucides.



(LXXXIX)

Human Immuno Virucidal Activity

Hargrave *et al.*[52], in 1991, reported the preparation of 5,11-dihydro-6H-dipyrido[3,2-b:2′,3′-e]-(1,4)diazepines **(LXXXXIII)** and their use in the prevention or treatment of HIV-infection. For example, 2-hydroxy-4-methyl-3-nitropyridine (**LXXXX,** R = Me) was converted by chlorination (with phosphoryl chloride) and reduction to 3-amino-2-chloro-4-methylpyridine (**LXXXXI,** R = Me). The latter underwent amidation with 2-chloronicotinoyl chloride and condensation with ethylamine to give (chloromethylpyridinyl)ethylaminopyridine carboxamide (**LXXXXII,** R = Me), which on dehydrochlorinative cyclisation with sodium hydride in DMF at reflux temperature gave the title compound **LXXXXIII.** The compound **LXXXXIII** (R = Me) at 3 μg/ml, gave 100%

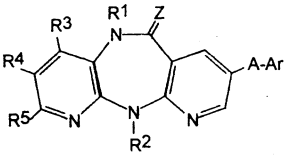


(LXXXX) **(LXXXXI)** **(LXXXXII)**

inhibition of **HIV-I** replication in human T-cell culture assay. **LXXXXIII** also gave 100% inhibition of HIV-I reverse transcriptase at 10 mg/mL *in vitro*.

Three formulations, 77 synthetic examples and additional test results including cytotoxicity were reported.

The preparation of 8-aralkyl-5,11-dihydro-6H-dipyrido[3,2-b:2′,3′-e]-[1]diazepines for treatment of HIV-1 infection was reported by Cywin *et al.*[53] in 1998. The title compounds (**LXXXXIV,** A = Chain of 1-3 atoms, cyclopropylene, oxyranylene Ar = (substituted)5,6-membered(hetero)aryl; R′ = H, alkyl, fluoroalkyl, alkenylmethyl, alkynylmethyl, (substituted)aryl , arylmethyl alkanoyl, thioalkanoyl, alkylsulfonyl etc.; Z = O,S, NCN, alkoximino; R^2 = H, alkyl, fluoroalkyl, cycloalkyl, oxetanyl, thietanyl, tetrahydrofuryl, alkenylmethyl, alkynylmethyl, alkoxdyalkyl, alkylthioalkyl,alkanoyl, cyano, cyanoalkyl, hydroxyalkyl, acyloxyalkyl etc.; R^3 = H, alkyl, alkenyl, alkynyl, trihalomethyl, hydroxyalkyl, alkoxyalkyl, alkylthio alkyl, halo; R^4 = H, methyl, halo; R^5 = H; R^3 R^4 or R^4 R^5 = cycloalkyl; with provisos] were prepared.

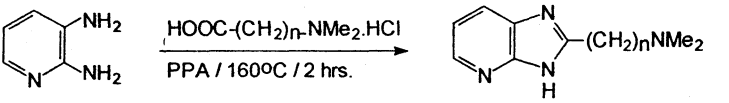


(**LXXXX**IV)

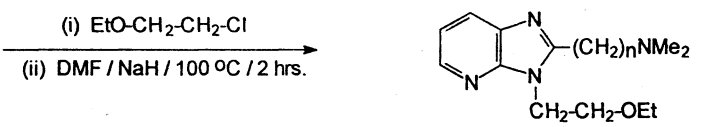
Thus, 2-chloro,5,11-dihydro-11-ethyl-5-methyl-8-[2-(pyrid-4-yloxy)ethyl]-6H-dipyrido[3,2-b:2′,3′-e][1,4]-diazepin-6-one showed an IC_{50} = 0.03μM in the syncytia assay using HIV-I in CD4 + T-cells.

Antiallergic Activity:

Preparation of 2-substituted -3-(2-ethoxyethyl)imidazo[4,5-b]pyridines as antiallergic and antihistaminic agents was reported by Giani *et al.*[54] in 1991. Thus, in a typical example, 2,3-pyridinediamine was cyclocondensed with 4-dimethylaminobutyric acid hydrochloride in polyphosphoric acid at 160°C for 2 h to yield 2-(3-dimethylaminopropyl)-3H-imidazo [4,5b]pyridine (**LXXXXV,** n = 3) which was alkylated with ethoxyethyl chloride in DMF containing sodium



(**LXXXXV**)



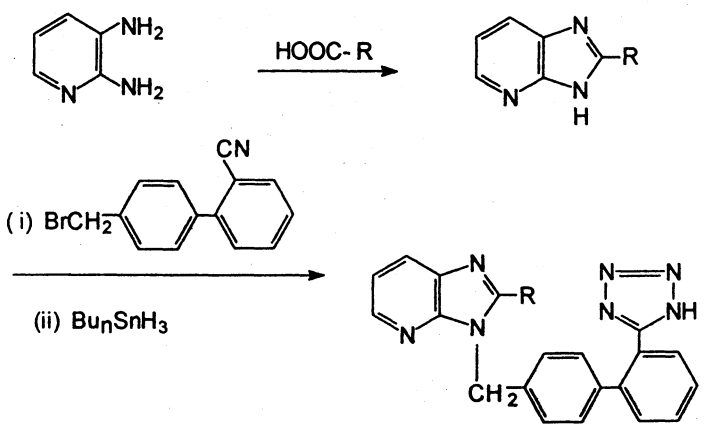
(**LXXXXVI**)

hydride at 100°C for 2 h to give **LXXXXVI** (n = 3). **LXXXXVI** (where n = 2) in guinea pigs, exhibited histamine-induced mortality with ED_{50} of 25 mg/kg p.o.

Antihypertensive Activity:

The synthesis of biphenylylalkylazabenzimidazoles (*i.e.*, biphenylylalkylimidazopyridines) possessing antihypertensive activity was reported[55] by Herold *et al.*, in 1991. Thus, 2,3-pyridinediamine was treated with pentanoic acid followed by 4-CH_2-C_6H_4-C_6H_4-CN-2 and Bu_2SnH_3 to give pyridoimidazole **LXXXXVII** (R = n-Bu).

Tablet formulations containing title compounds were reported.



(LXXXXVII)

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