## Review

# Fluorine-containing bioactive benzimidazoles

Krishna C. Joshi*, Renuka Jain, Anshu Dandia
*Department of Chemistry, University of Rajasthan, Jaipur-302004 (India)*

and Kanti Sharma
*Department of Chemistry, Government College, Kaladera, Jaipur-303801 (India)*

## Introduction

Benzimidazole derivatives are important in the field of biochemistry and medicine. Although several reviews exist on benzimidazoles and some of the well-known fluorinated derivatives like astemizole, pimozide, benperidol and droperidol, there is nothing comprehensive on the fluorinated derivatives. In this article, we have tried to cover the synthesis and biological activity (where reported) of all types of fluorinated benzimidazoles.

The text has been classified on the basis of the position of fluorine or of fluorinated groups on the benzimidazole system, as follows:

I On a nitrogen atom
  (a) On one nitrogen
  (b) On both the nitrogens
II On imidazolyl carbon
III On the benzene ring
  (a) At one position
  (b) At more than one position
IV On more than one atom
  (a) On the benzene ring and on the nitrogen atom
  (b) On the benzene ring and on imidazolyl carbon
  (c) On the imidazolyl carbon and nitrogen atom
  (d) On the benzene ring, nitrogen atom and imidazolyl carbon
  (e) On two benzimidazole rings

## I On a nitrogen atom

*(a) On one nitrogen*

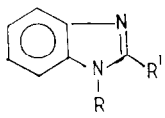
*Fluoroaliphatic/aromatic substituents*

N-Fluoroalkyl, alkenyl, alkynyl and aryl derivatives of benzimidazole (**I**) have been prepared by the reaction of fluorinated alkanes, alkenes,

0022-1139/92/$5.00 

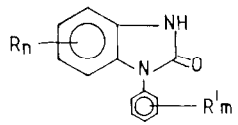
alkynes and arenes with benzimidazoles [1–6]. 1-Aryl-2-benzimidazolinones (**II**) were obtained using an organic solution of a carbanilide ($Rm^1C_6H_5mNHCONHC_6H_5–nR_n$) and an aqueous solution of hypohalite ion with a quaternary ammonium and/or phosphonium salt catalyst [7].

These compounds show insectoacaricidal [5] activity. Benzimidazoles containing $>NCOCF_3$ groups act as nucleating agents in the treatment of internal image emulsions after exposure [8] in photography.



(**I**)

R = $CHF_2$, $CF_2CHCF_2$, $CF_2CH_2CF_3$, $CF_3–C=CHCF_3$, $CF_2CHClF$, $CF=CClF$, *p*-$CF_3SO_2C_6H_4$, *p*-$CF_3C_6H_4$, $R^1$ = H, $CH_3$

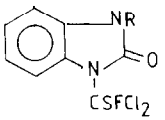


(**II**)

R, $R^1$ = $C_{1-4}$ alkyl, alkoxy, alkylthio, F, Cl, *m*, *n* = 0–2

*Sulfenic acid derivatives*

Benzimidazolyl sulfenic acid derivatives(**III**) were made [9] by treating the heterocycle with $ClSCOCl_2F$.



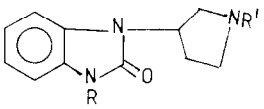
R = H, $CH_3$

(**III**)

These are used as fungicides [9, 10]: **III** (R = H) reduces phytopthora infection in tomato plants while **III** (R = $CH_3$) inhibits completely the germination of *Tusicladium dendriticum* spores [10].

*Pyrrolidinyl derivatives*

Benzimidazolyl pyrrolidines of type **IV** were obtained from benzimidazoles of type **I** ($R^1$ = H) [11, 12].

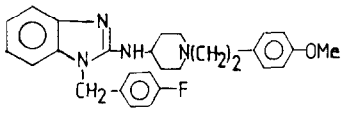


R = H, $CH_3$, $C_6H_5$, $CH_2C_6H_5$; $R^1$ = H, $(CH_2)_3CH(p\text{-}FC_6H_4)_2$, $(CH_2)_3CO(o\text{-}FC_6H_4)$

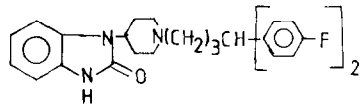
(**IV**)

*Piperidinyl derivatives*

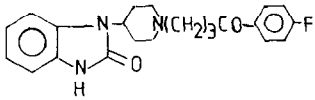
Various reviews have been published on the synthesis and biological activity of astemizole(**V**) [13–19], pimozide(**VI**) [20–23], benperidol(**VII**) [24–26] and droperidol(**VIII**) [27–31]. They are active as antihistaminic, anti-allergic, psychotropic and antimethamphetamine agents.



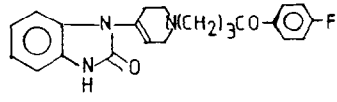
(V)



(VI)

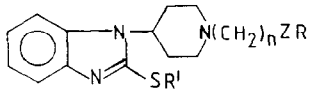


(VII)



(VIII)

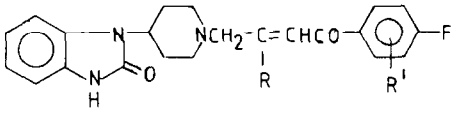
Benzimidazolyl piperidines(**IX**) [32–36] have been prepared from 2-amino-anilinopiperidines and compounds having a C=S bond ($CS_2$, potassium ethyl xanthate, etc.) and show psychotropic activity [32–36].



Z = CO, $CH_2$; R = $C_6H_5$, $FC_6H_5$; $R^1$ = H, $CH_3$, $C_2H_5$, $CH_3CHCH_3$; $n$ = 0–3.

(**IX**)

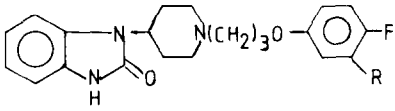
Benzimidazolyl piperidinobutyrophenones(**X**) [37–43] were made from halobutyrophenones and benzimidazolone. They act as analgesics [39, 41], tranquilizers [39, 41, 43–46], CNS depressants [40, 47], hypotensives [39], antiphlogistics [47] and fungicides [47].



R = H, OH, $R^1$ = OH, $NO_2$, $NH_2$, F

(**X**)

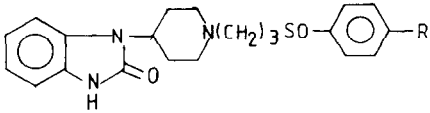
1-(3-*p*-Fluorophenoxy)-4-(2-oxo-1-benzimidazolinyl)piperidines(**XI**) [48, 49] were made from phenols and piperidinopropyl halides or on the reduction of propionyl piperidine derivatives. They have apomorphine antagonistic, sedative and CNS depressing activities [48, 49].



R = halo, alkyl, alkenyl, etc.

(**XI**)

Reaction of piperidinyl benzimidazolinone with *p*-$RC_6H_4SO(CH_2)_3X$ (X = halogen) gave **XII**, useful as tranquilizers and CNS depressants [50, 51].

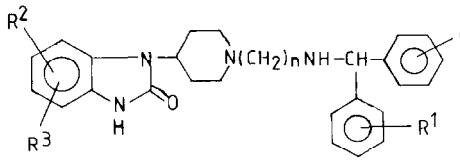


R = Cl, F, $NO_2$

(**XII**)

1-3-(Diarylaminoalkyl)piperidino derivatives of benzimidazole(**XIII**) [52, 53] have been prepared in two ways: (i) alkylation of Li salts of the appropriate diarylamine with chloroalkyl tosylate gave the heterohalide, which was reacted

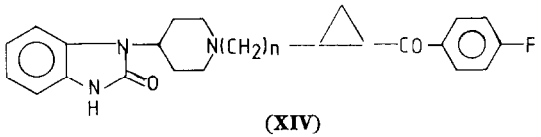
with piperidino benzimidazole; (ii) acylation of the diarylamine with the appropriate alkanoyl halide to the amide, reduction to the (diarylamino) halide which was treated with piperidino benzimidazole. These compounds show antipsychotic activity [52, 53].



R=H, F, Cl, $CH_3$, $NO_2$; $R^1$=H, F, $CF_3$; $R^2$, $R^3$=H, lower alkyl, lower alkoxy, $n$=2, 3

(XIII)

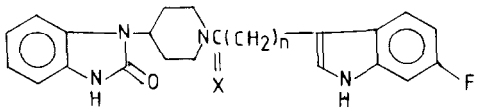
Benzimidazolyl piperidinocyclopropanes(**XIV**) [54–56] have been obtained by amination of the chloroalkylcyclopropane moiety with piperidino benzimidazole in the presence of KI. These exhibited analgesic, hypnotic, spasmolytic, catelptic and psychotric activities [54–57].



$n$=1, 2

(XIV)

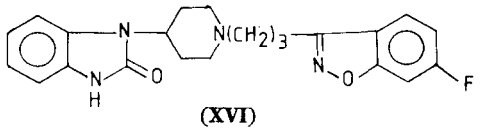
Some derivatives **XV** [58–60] were prepared from β-(2-methyl-6-fluoro-3-indolyl)alkanoic acid. Alkyl halocarbonate in THF was added to the mixture of acid, $NEt_3$ and THF, and then 4-(2-oxo-1-benzimidazolinyl)-piperidine was added to give **XV** (X=O), which on reduction with $LiAlH_4$ in THF gave **XV** ($X=H_2$). These show CNS depressant and analgesic activity [58–60].



X=O, $H_2$; $n$=2, 3

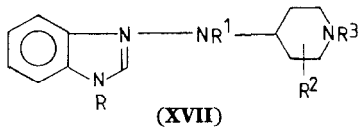
(XV)

The benzimidazolyl piperidinobenzisoxazole derivative(**XVI**) was effective in blocking amphetamine stereotypy and also showed neuroleptic activity [61, 62].



(XVI)

Various derivatives of type **XVII** [63–66] have been synthesized from piperidino benzimidazole and the corresponding heterohalide in DMF containing $Na_2CO_3$.

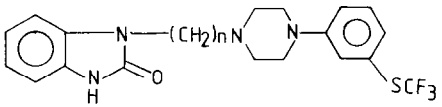


(XVII)

R=H, cycloalkyl, pyridinyl, pyrazinyl, alkyl, furanyl, thiazolyl, imidazolyl, F, $C_6H_5$, $R^1$=H, alkyl, cycloalkyl, alkanoyl, $R^2$=H, $CF_3$; $R^3$=$CF_3$, pyrrolidinyl, piperidinyl

*Piperizino derivatives*

Piperizino benzimidazoles(**XVIII**) [67, 68], obtained by reactions of piperazines with benzimidazolin-2-one in the presence of $K_2CO_3$ and KI in toluene, are useful as tranquilizers [67, 68].

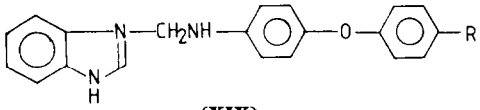


$n = 1–3$

(**XVIII**)

*Methylamino ethers*

(3-Benzimidazolyl methyl)amino diphenyl ethers(**XIX**), made by condensing 4-aminodiphenyl ethers with benzimidazoles in the presence of formalin under Mannich conditions, act as potential biologically active agents [69].

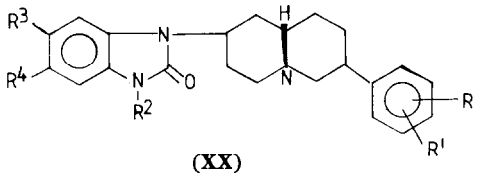


R = H, F, $CH_3$

(**XIX**)

*Quinolizino derivatives*

Benzimidazoloquinolizidines(**XX**), their racemates, enantiomers and addition salts, have been prepared and one of these compounds (**XX**, R = 2-F, $R^1 = R^2 = R^3 = H$, $R^4 = I$) shows neuroleptic anti-emetic and analgesic activities [70].

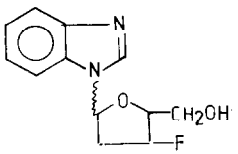


(**XX**)

R = 2-F, H, Cl, $CF_3$, $R^1$ = H, F, Cl, alkoxy, alkyl, $R^2$ = H, alkyl, $R^3$ = H, $R^4$ = Br, I, CN

*Nucleosides of fluoro sugars*

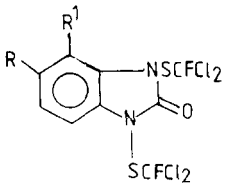
2,3′-Dideoxy-3′-fluoro-D-ribofuranosyl benzimidazole(**XXI**) [71] has been prepared by the benzimidazole displacement of thymine on fluoronucleoside. Deacetylation with $NH_3$ and $CH_3OH$ yielded the $\alpha$- and $\beta$-forms (**XXI**).



(**XXI**)

*(b) On both the nitrogens*

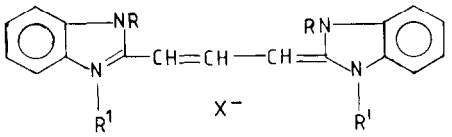
Benzimidazoles **XXII** arose by treating benzimidazolone and $ClSCFCl_2$ in $C_6H_6$ in the presence of $Et_3N$. They possess antimicrobial activity [72].



R, $R^1$ = H, $CH_3$

**(XXII)**

Imidacarbocyanines(**XXIII**) [73] were prepared by condensing salts of *N*-fluoroalkylated benzimidazoles with an orthoformate ester in nitrobenzene at 50–150 °C.



R = alkyl, $R^1$ = fluoro or fluorochloroalkyl, X = anion

**(XXIII)**

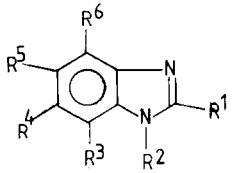
## II On imidazolyl carbon

*Perfluoroalkyl/chlorofluoroalkyl groups*

2-Perfluoroalkyl benzimidazoles(**XXIV**) have been prepared by various methods: (i) treating *o*-dinitrobenzene or *o*-nitroaniline with perfluoroalkanoic acids in the presence of HCl or $H_2SO_4$ and Fe, Sn, Zn or Al(**XXIV**, $R^1 = CF_3$, $C_2F_5$; $R^2$ = H; $R^3$ = H, Cl; $R^4$, $R^5$ = H, Cl, $CH_3SO_2$; $R^6$ = H) [74]; (ii) reactions of fluorinated $\beta$-diketones with *o*-phenylenediamines(**XXIV**, $R^1 = CF_3$, $C_2F_5$; $R^2$–$R^6$ = H) [75]; (iii) reactions of *o*-phenylenediamine with perfluoroalkanoic acids in the presence of HCl, $H_2SO_4$ or PPA* (**XXIV**, $R^1 = CF_3$, $C_2F_5$; $R^2$ = H, $CH_3$, $C_2H_5Ac$, CN, $CO_2Ph$; $R^3$ = H, Cl, $CMe_3$, $CHMe_2$, CHMeEt, cyclohexyl; $R^4$ = H, Cl, *o*-$BrC_6H_4$; $R^5$ = H, Cl, $NO_2$; $R^6$ = H, Cl) [76–88]; (iv) from orthobifunctional benzene compounds (**XXIV**, $R^1 = CHF_2$, $CF_3CHF$, $(CF_3)_2CH$; $R^2$, $R^3$, $R_6$ = H; $R^4/R^5$ = Cl, alkyl) [89–94]; (v) (a) reaction of *o*-phenylenediamine in an acid medium with $\alpha,\alpha$-difluoro-$\beta,\beta$-dichloroproprionimidazole and nitrating or chlorinating the product (or treating the Na salt of the product) with chloroformate ester or triethyl chlorides, (b) from 2-mercaptobenzimidazoles and polyhalogenated olefins, (c) reduction of substituted *o*-nitroanilines and alkylating, arylating or acylating the product formed (**XXIV**, $R^1$ = polyhaloalkyl, alkenyl or alkylthio; $R^3$ = H, alkoxy, aryloxy, alkyl or aryl, carbonate, $EtO_2CO$, $(CH_3)_2C{=}CHCO_2$, CN, $NO_2$; $R^3$–$R^6$ = H, Cl, $NO_2$, CN) [95]; (vi) reducing an amino nitrophenyl alkylsulphone with hydrazine and

*Polyphosphoric acid

Ni and treating the diaminophenyl alkylsulphone produced with perfluoroalkanoic acid (**XXIV**, $R^1 = CF_3$; $R^2$,$R^3$,$R^5$,$R^6 = H$; $R^4$ = alkylsulphonyl) [96, 97]; (vii) *o*-phenylenediamines and chlorofluoroalkanoic acids (**XXIV**, $R^1 = CClRF$; R = H, F; $R^2 = H$, $R^3$,$R^4 = H$, Cl, $NO_2$; $R^5 = H$, Cl; $R^6 = Cl$, Br) [98, 99].



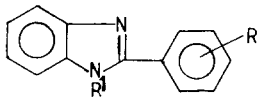
(**XXIV**)

Some workers [100, 101] have studied the structure activity relationship of 2-perfluoroalkyl benzimidazoles.

Various 2-fluoroalkyl benzimidazoles show insecticidal [83, 86, 102–107], herbicidal [85, 87, 108–113], antiviral [114], antihelmentic [83, 115–122], parasiticidal [123], pesticidal [124–134], fungicidal [135], acaricidal [136–144] and rodenticidal [145] activities; inhibit photosynthesis [146, 147], photophosphorylation [148] and ATP biosynthesis [149, 150]; are used as radiosensitizing agents [151]; and enhance the yield of grapes [152]. 2-Chlorofluoroalkyl derivatives showed fungicidal activity [98].

*Aryl/naphthyl groups*

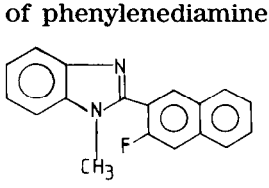
2-Aryl-substituted benzimidazoles(**XXV**) have been prepared by (i) reactions of *o*-phenylenediamines with benzaldehyde or benzoic acid derivatives [153–156]; (ii) reactions of benzimidazoles with metal hydride and an acyl halide [157]; (iii) heating *o*-phenylenediamines with substituted phenyl/$PhCCl_3$ at 150–185 °C [158]. These compounds show fungicidal, [153] anti-inflammatory, [153, 154], anti-obesity [159–161] and anthelmintic activities [157].



R = alkyl, alkoxy, $CO_2H$, F, $NH_2$, $R^1 = H$, Et, Ac

(**XXV**)

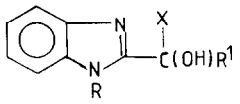
2-$\alpha$-Fluoronaphthyl benzimidazole(**XXVI**) arose from the condensation of phenylenediamine with 3-fluoro-2-naphthoic acid [162].



(**XXVI**)

*Alkanol groups*

Benzimidazolyl alkanols(**XXVII**) [163, 164] have been prepared by reducing the alkenoyl benzimidazoles [165].



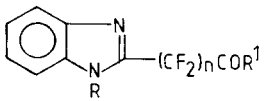
(**XXVII**)

X = H, F; R = H, $CH_2CH_2OH$, $R^1 = CF_3$, $CH_2CH_2R^2$, $R^2$ = phenyl, 4-$ClC_6H_4$, 4-$FC_6H_4$

They show respiratory, analeptic, analgesic, spasmolytic, anti-inflammatory, antihypertensive and antidiarrheal activities [163, 164].

*Perfluorocarboxylic acid groups*

Standard reactions gave **XXVIII** (R = H, $R^1$ = OH, $n$ = 1,2) [82]. Heating $o$-$NHRC_6H_4NHCO(CF_2)_nCONH_2$ (made by the action of $o$-$NHRC_6H_4NH_2$ on a perfluoroalkanamide [168] or cyclizing it by means of HCl [166, 167]) also gave **XXVIII**, which act as plant growth regulators [169], diuretics,



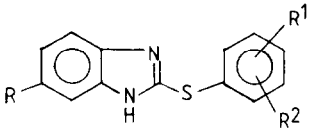
R = H, $CH_3$, $R^1 = NH_2$, OH, $CH_3$, $C_5H_4R^2$, $R^2$ = 4-F, 3-$CF_3$

(**XXVIII**)

sedatives, anti-ulcer agents, analgesics, anti-inflammatory agents and cardiac analeptics [170].

*Arylthio groups*

2-Arylthiobenzimidazoles(**XXIX**) [171] were made by the arylation of 2-mercaptobenzimidazoles with chloronitrobenzenes, and were hydrogenated over Raney nickel to give the corresponding amines. These were 100% effective against *Hymeno lepsisnana* in rodents.

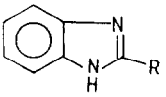


R = H, Cl, $NO_2$, $R^1$ = H, 2-Cl, 2-$CF_3$, $R^2$ = 4-$NO_2$, $NH_2$, NCS

(**XXIX**)

*Arylamino/arylaminomethyl groups*

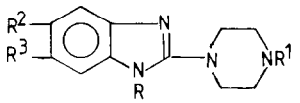
Cyclization of $o$-phenylenediamine with $R^1NHCS_2Me$ afforded 2-arylaminobenzimidazoles (**XXX**, R = $NHR^1$; $R^1 = C_6H_5$, $m$-$CF_3C_6H_4$) [172]. Substitution of 2-chloromethyl benzimidazole with the corresponding phenol and aniline derivatives [173] gave 2-arylaminomethyl benzimidazoles(**XXX**, R = $CH_2NHR^1$; $R^1 = C_6H_4F$, 2-thiadiazolyl fluorophenyl, 2-oxadiazolyl fluorophenyl) possessing fungicidal activity [174].



(**XXX**)

*Piperazino groups*

These compounds, **XXXI**, made from 2-chlorobenzimidazole and piperazines, show hypotensive [175] and antihistaminic activity [176].

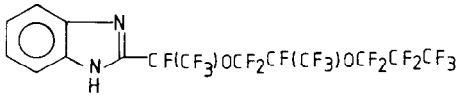


R = H, $CH_3$, $R^1 = C_{1-6}$alkyl, $(CH_3)_2CHCH_2CO$, $C_6H_5$, $CF_3C_6H_4$, $R^2$ = H, $OCH_3$, etc.

**(XXXI)**

*Perfluoropolyether groups*

Lithiation of *o*-$(NH_2)_2C_6H_4$ and reaction with $EtO_2CF(CF_3)OCF_2CF(CF_3)OCF_2CF_2CF_3$ followed by cyclization gave **XXXII** [177], which is used as a corrosion inhibitor and lubricating grease [177, 178].



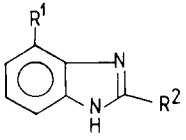
**(XXXII)**

## III On the benzene ring

*(a) At one position*

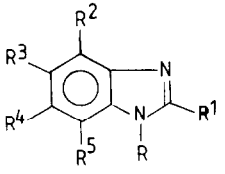
*At position 4*

Benzimidazoles **XXXIII** have been prepared by the reactions of (i) α,α,α-trifluoro-2,3-toluenediamine with HCOOH and HCl (**XXXIII**; $R^1 = CF_3$ $R^2$ = H) [179]; (ii) 2-$FC_6H_4NHCOCH$: NOH with $H_2SO_4$ (**XXXIII**; $R^1$ = F; $R^2 = CO_2H$) [180]; (iii) 2-fluoroaniline with 4-cyanothiazole(**XXXIII**; $R^1$ = F; $R^2$ = thiazole) [181]; and (iv) benzimidazole with $CF_3I$ [product as (I)] [182]. These possess high reactivity towards peptide nucleophiles [183].



**(XXXIII)**

*At position 5/6*



**(XXXIV)**

5-/6-Fluoro-substituted benzimidazoles **XXXIV** have been prepared by the following reactions:

(i) *o*-Phenylenediamine with $CS_2$ ($R^1 = SH$; $R^3 = CF_3$; $R,R^2,R^4,R^5 = H$) [184, 185] and showed anthelmintic [186, 187] and insecticidal activity [188] besides acting as sensitizers [189].

(ii) *o*-Phenylenediamine with fluorinated acids gave **XXXIV** ($R^3/R^4 = CF_3$; $R^1 = CHMe_2$; $R^3 = Me$, Cl; $R,R^2,R^5 = H$) [190, 191], which are useful as herbicides [191].

(iii) *o*-Phenylenediamines with MeC(:NH)OEt · HCl and $Ac_2O$ gave **XXXIV** ($R = H$, Et; $R^1 = H$, Me; $R^3 = F_2CHSO_2$; $R^2,R^4,R^5 = H$) with herbicidal activity [192].

(iv) Rearrangement of aromatic aldehyde arylhydrazones [193] with $AlCl_3$ afforded **XXXIV** ($R,R^2,R^4,R^5 = H$; $R^1 = Ph$, 4-$MeC_6H_4$, 2-naphthyl, 4-$OEtC_6H_4$, 4-$MeOC_6H_4$, 4-$ClC_6H_4$, pyridyl; $R^3 = F$, $CF_3$). These compounds exhibit antipsychotic activity [194, 195].

(v) Reaction of $RNH_2$ and 2,4,5-$Cl_2(NO_2)C_6H_2CF_3$ followed by hydrogenation and treatment with $R^1C(:NH)OEt \cdot HCl$ gave **XXXIV** ($R = Pr$, $Me_2CN$, cyclopropyl, Et, H, Me; $R^1 = H$, Me, Pr, Et; $R^2,R^3 = H$, $CF_3$; $R^4 = Cl$, MeO; $R^5 = NO_2$) [196–198]. These act as post-emergent herbicides [199–202] on a broad class of crops and are useful intermediates for cyanine dyes [203].

(vi) *o*-$NH_2CF_3C_6H_3NHOH_2CH_2OH$ and ethyl-5-nitrofurimidate · HCl or 3,4-$(NH_2)_2C_6H_3CF_3$ and 5-nitro-2-furoic acid with ethylpolyphosphate as a cyclizing agent gave **XXXIV** ($R = H$, Me, Et, Ph; $R^1 =$ nitrofuryl; $R^3 = Cl$, F, $CH_3$, $CF_3$; $R^2,R^5 = H$; $R^4 = H$, $CH_3$) [204, 205] useful as antimicrobial agents [204, 205], anthelmintics [204] and germicides [206].

(vii) Benzimidazoles, where $R^1$ is an N-, O- or S-heterocycle with 1,3-heteroatoms (**XXXIV**; $R = H$, lower alkyl, aralkyl, acyl; $R^1 =$ N-, O- or S-heterocycle; $R^2,R^4,R^5 = H$, $R^3 = H$, halogen, alkyl, alkylamine, amino) exhibit anthelmintic properties [207–210].

(viii) Schiff bases of a substituted *o*-phenylenediamine and 5-nitro-2-thiophene carboxaldehyde gave **XXXIV** ($R = H$, alkyl; $R^1 =$ nitrothienyl; $R^2,R^5 = H$; $R^3 = H$, alkyl, alkoxy, halogen, $CF_3$; $R^4 = H$, alkyl, alkoxy) which act as germicidal and anthelmintic agents [211, 212].

(ix) Cyclization of *o*-acyl hydrazido-anilines with BrCN gave **XXXIV** ($R = NH_2$; $R^1 = NH_2$; $R^2,R^4,R^5 = H$; $R^3 = CF_3$, Cl, $CH_3$) [213, 214] which inhibited the PNMT activity in the adrenal glands and brain stream of rats [215].

(x) Condensation of diamines and $Cl_3CCl(:NH)$ afforded compounds **XXXIV** ($R = H$; $R^2 = CN$; $R^3 = CF_3$-  -O–; $R^2,R^4,R^5 = H$, alkyl, alkoxy, amino, etc.). One with $R = Me_2NSO_2$ exhibited pesticidal activity [216].

(xi) From the cyclization of *N*-(*o*-nitroanilino)amines in mineral acid, **XXXIV** had $R = NHCH_3$, $NHCH_2NO_2$; $R^1 = H$, $NO_2$; $R^3 = H$, Cl; $R^4 = CF_3$, $NO_2$, H, $CO_2Et$; $R^2,R^5 = H$ [217].

(xii) 1,2-Diaminobenzene derivatives with imino esters formed **XXXIV** ($R = (CH_2)_2NEt$, $(CH_2)_3NEt$, etc.; $R^1 =$ substituted $CH_2Ph$; $R^3 = CF_3$; $R^2,R^4,R^5 = H$) which showed analgesic, spasmolytic, hypocholesteremic and anaesthetic activities [218].

(xiii) 2-Aminobenzimidazoles with MeONa and $K_2CO_3$ gave **XXXIV** ($R^1$ = (alkoxycarbonyl)amino; $R^2$ = H; $R^3$ = fluoro-substituted phenoxy/phenylthio/phenylcarbonyl; $R^4$ = H, Cl; $R^5$ = H) used as anthelmintics [219–221].

(xiv) *o*-Phenylenediamines with acid anhydrides gave **XXXIV** (R = H; $R^1 = (CH_2)_2CO_2H$; $R^2,R^5$ = H; $R^3 + R^4$ = halo, Me, MeO, $NO_2$) which acted as neoplasm inhibitors and antitumour agents [222].

(xv) Made from 2-benzimidazolinone and $Cl(CH_2)_nCO_2R^1$, **XXXIV** (R = H, alkyl; $R^1$ = H, alkyl, alkali metal ion; $R^2,R^5$ = H; $R^3/R^4$ = H, halo, Me, $CF_3$, MeO, $NO_2$, $NH_2$) showed anti-allergic, anti-asthamatic and antithrombotic activities [223].

(xvi) 2-Amino-4-fluoro-1-propylamine and mandelic acid gave **XXXIV** (R = Ph; $R^1$ = CHOHPh; $R^2,R^4,R^5$ = H; $R^3$ = F) [224] exhibiting antiviral activity [224, 225].

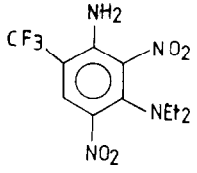
(xvii) 2-Hydroxy or 2-sulfonyl benzimidazoles with $POCl_3/POBr_3/PCl_5$ gave **XXXIV** (R = H; $R^1$ = Cl; $R^2,R^4,R^5$ = H, Cl; $R^3$ = (4,3-$(CF_3)ClC_6H_3SO_2NH$), (4,3-$Cl(CF_3)C_6H_3NHCO$)), potential insecticides and nematocides [226].

(xviii) 2-Aminobenzimidazoles with isocyanates afforded **XXXIV** (R = NH, NPh, NMe; $R^1$ = NHCONH-⬡, N(Me)CONH-⬡, NHCONH-⬡⬡; $R^2,R^4,R^5$ = H; $R^3/R^4$ = H, Cl, $CO_2Et$, $CF_3$, $NO_2$, OMe). These are immune regulants [227].

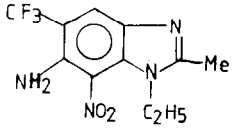
(xix) Diamines with benzotriazolylacetic acid gave **XXXIV** ($R = (CH_2)_nNMe_2$, $(CH_2)_nNEt_2$, $n = 2,3$; $R^1$ = benzotriazolylmethyl; $R^2,R^4,R^5$ = H; $R^3$ = Cl, $CF_3$, Ac, $NO_2$) [228].

5-/6-Trifluoromethylbenzimidazoles and their hydrochlorides killed a variety of weeds and crop plants [229], whilst 5-/6-$CF_3$-2-isopropyl benzimidazoles are anti-androgens [230] and *l*-lupinyl-2-(*p*-methoxybenzyne)-5-trifluoromethylbenzimidazole an anti-inflammatory agent [231]. Benzimidazolyl anilines are anti-inflammatory, antipyretic, analgesic and blood-pressure-depressing drugs [232]. Various piperidyl benzimidazoles possess psychotropic [233, 234], anti-emetic [235], antihistaminic [236], anti-ulcer and antisecretary activity [237] and are used as beta adrenergic receptor blockers [238].

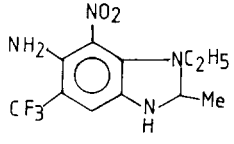
Photolysis [239–241] of the herbicide dinitramine (**XXXV**) in methanol and water yielded various benzimidazoles (**XXXVI–XXXIX**).



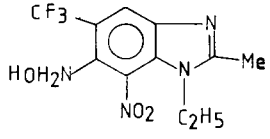

**(XXXV)**



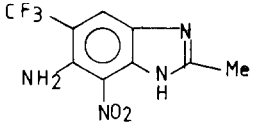

**(XXXVI)**




**(XXXVII)**

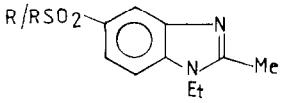



**(XXXVIII)**

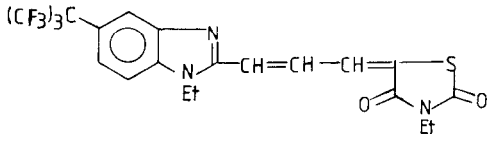



**(XXXIX)**

$\omega$-Imidacyanine dyes (**XL**) [242, 243] prepared from 2-methyl-5-perfluoroalkyl/perfluoroalkylsulfonyl benzimidazole, were quaternized and converted to symmetric and non-symmetric carbocyanines and other dyes (**XLI**).



(**XL**)



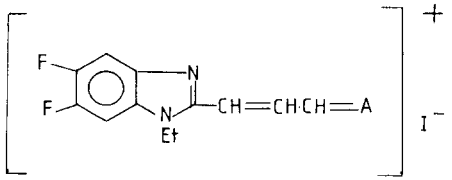
R = $CF_2CF_2CF_3$, $(CF_2)_5CF_3$, $CF(CF_3)_3$, $(CF_3)_3C$, etc.

(**XLI**)

*(b) At more than one position*

4,5-Bis-(trifluoromethyl) benzimidazole has been prepared from 3,4-bistrifluoromethyl-*o*-phenylenediamine and formic acid; it possesses bacteriostatic activity [244, 245].

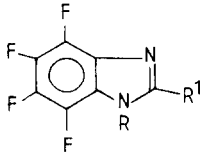
5,6-Difluorobenzimidazole methine iodides of the general formula **XLII**, where A is a fused or non-fused 5-membered heterocyclic group, have been used as photographic and electrophotographic sensitizers [246].



(**XLII**)

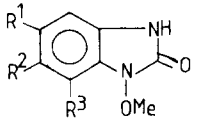
The first tetrafluoro derivatives (**XLIII**; R,$R^1$ = H; R = Me; $R^1$ = H) were made from tetrafluoro-*o*-phenylenediamine and formic acid [247]. Fluorobenzimidazolinones (**XLIV**) were made [248, 249] by reacting fluorobenzenes with ambident nucleophiles generated *in situ* from ureas and their derivatives in the presence of NaH.

Cyclization of MeONHCONHAr under basic conditions [250] also afforded benzimidazolinones(**XLIV**).



(**XLIII**)

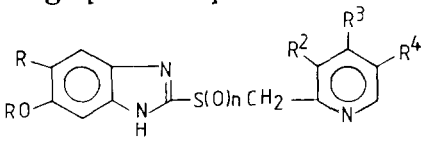
R, $R^1$ = H, $CH_3$, $C_6H_5$



(**XLIV**)

$R^1$ = H, Cl, $CF_3$; $R^2$ = H, $NO_2$, CN, $SO_2Me$; $R^3$ = H, Cl, $CF_3$

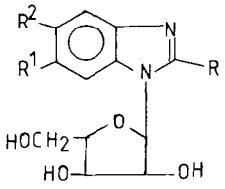
HCl salts of 2-(chloromethyl)pyridine and benzimidazole-2-thiols (made from *o*-phenylenediamines and $CS_2$/$EtOCS_2K$) gave **XLV** which are anti-ulcer drugs [251–253].



**(XLV)**

R=fluoroalkyl, $ClF_2C$; $R^1$=H, fluoroalkyl, fluoroalkoxy, halo; $R^2$,$R^4$=H, alkyl, $R^3$=H, alkyl, alkoxy; $n$=0, 1

Fusion of halobenzimidazoles and 1,2,3,5-tetra-*o*-acetyl-β-D-ribofuranose by a fusion method followed by deacetylation [254] afforded nucleosides **XLVI**.

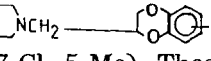


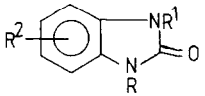
**(XLVI)**

R=H, $CH_3$, $(CH_3)_2CH$; $R^1$=H, F, I; $R^2$=H, F, I

## IV On more than one atom

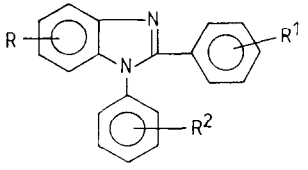
*(a) On the benzene ring and on the nitrogen atom*

Benzimidazolones **XLVII** have been prepared (i) by the $PdCl_2$-catalyzed reactions of nitrobenzenes and the thermal reactions of phenyl azides with CO (**XLVII**); R=$CONHC_6H_4F$; $R^1$=$C_6H_4F$; $R^2$=5-/6-F) [255]; (ii) by reaction of benzodioxanes with benzimidazolyl piperidines in the presence of base (**XLVII**; R=H; $R^1$=  ; $R^2$=5-Br, 5-OMe, 5-$CF_3$, 5-F, 6-Cl; $R^3$=H, 6-F, 7-F, 7-Cl, 5-Me). These show neuroleptic activity [256].



**(XLVII)**

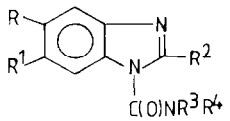
Benzimidazoles **XLVIII**, obtained by the reaction of diamines with aldehydes in MeOH, followed by the cyclization of the Schiff bases so obtained in nitrobenzene, exhibited anti-inflammatory activity [257].



**(XLVIII)**

R=H, 4-$CF_3$; $R^1$=4-$CH_3O$, $R^2$=4-$CH_3O$, $CF_3$

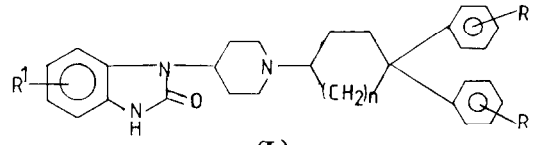
Reaction of benzimidazoles with MgO and $ClCOONR^3R^4$ in $CHCl_3$ gave the pesticidal compounds **XLIX** [258].



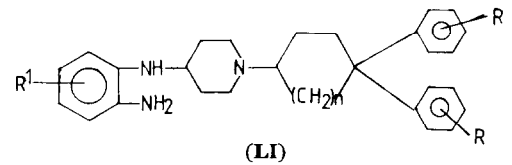
$R = H, CF_3$; $R^1 = H$; $R^2 = H, CH_3$; $R^3 = H$; $R^4 = m\text{-}CF_3C_6H_4$

**(XLIX)**

Oxobenzimidazolinyldiphenyl piperidino cycloalkanes (**L**) and cycloalkenes and their HCl salts were prepared by the cyclization of **LVI** with urea. These are analgesics, anticonvulsants, antihypertensives coronary vasodilators and CNS depressants [259, 260].



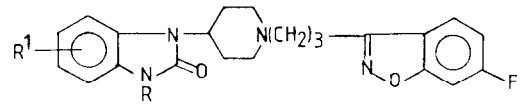
**(L)**



**(LI)**

$R = H$, 4-F, 4-Cl, 3,4-$F_2$, 2,4-$F_2$, 4-$CH_3$; $R^1 = H$, 5-Cl, 5-Br, 5-F, 5,6-$Cl_2$; $n = 1, 2$

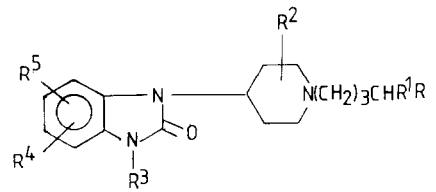
Piperidines of type **LII** were prepared by condensing 1-(4-piperidinyl)-2-benzimidazolinone with 3-(3-chloropropyl)-6-fluoro-1,2-benzisoxazole; their HCl salts had analgesic and antipsychotic activity [261, 262].



**(LII)**

$R = H$, alkyl; $R^1 = H$, alkyl, alkoxy, halo, $CF_3$

Benzimidazolinone derivatives **LIII** were prepared from piperizino benzimidazoles and $RR^1CH(CH_2)_3Cl$. These are tranquilizers [263] and show antihistaminic [264] and anti-emetic activity [265–267].



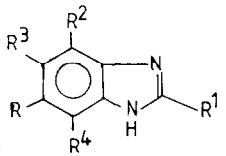
**(LIII)**

$R = R^1 = 4\text{-}FC_6H_4$, 4-$ClC_6H_4$, 3-$CF_3C_6H_4$, $C_6H_5$; $R^2 = H$, 2-$CH_3$, 3-$CH_3$;
$R^3 = H$, $CH_2CH_2CO_2CH_3$, $CH_2COCH_3$, $CH_2C_6H_5$, $CH_3$; $R^4 = H$, 5-Cl, 5-$CF_3$, 5-F, 5-Br;
$R^5 = H$, 6-Cl, 7-Cl, 7-$CH_3$

Some other biologically active fluorine-containing benzimidazoles are: benzimidazolyl alkanols [268, 269], alkyl phenyl ketones [270], amino ethers [271], butenylamines [272] and amino alkyls [273, 274].

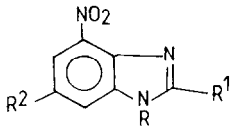
*(b) On the benzene ring and on imidazolyl carbon*

Benzimidazoles having fluorinated groups in both rings were synthesized from *o*-phenylenediamines and fluorinated acids in the presence of HCl (**LIV**; $R^1,R^2,R^3 = CF_3$; $R,R^4 = H$ [82, 275]: $R^1 = CF_3$; $R,R^2,R^3,R^4 = F$ [276]); others ($R = CF_3$, $CF_2HSO_2$, $CF_3CHClSO_2$, $CHF_2CF_2SO_2$; $R^1 = CF_3$, $HCF_2$, $CF_2CF_3$; $R^2,R^3,R^4 = H$) show fungicidal [277] and herbicidal [278] activity.



(**LIV**)

4-Nitro-2,6-bis(fluoroalkyl) benzimidazoles (**LV**) were prepared by the following methods:



(**LV**)

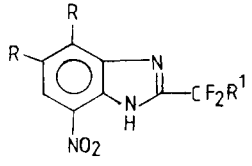
(i) Reaction of $4,2,6\text{-}CF_3(NO_2)_2C_6H_2Cl$ with $NH_4Cl$ followed by ammonium polysulphide and S gave **LV** ($R = H$; $R^1 = ClCF_2$, $CF_2$; $R^2 = CHF_2$, $CF_3$) [279, 280]. These gave complete control of root knot nematoda in tomatoes [280].

(ii) Alkylation of **LV** ($R = OH$) gave **LV** ($R = OR^3$; $R^3 = CH_2C_6H_5$, $C_2H_5$, $CH_3$; $R^1 = CF_3$, $C_2F_5$, $CHF_2$; $CF_3$). These show herbicidal action [281].

(iii) Benzimidazoles **LV** ($R = OH$), with $R^3OH$, $R^3X$ ($X = Cl$, I, Br) or MeNCO, afforded **LV** ($R = OR^3$; $R^3 = CH_2C_6H_5$, $C_2H_5$ $CH_3$, $CONHCH_3$, $SO_2C_6H_5$, $COCH_3$, etc.; $R^1 = CF_3$, $C_2F_5$; $R^2 = CF_3$). These show herbicidal [282], insecticidal [283], parasiticidal [284, 285] and acaricidal activities [286].

(iv) Sodium 2,6-bis(trifluoromethyl)-4-nitrobenzimidazole and $Ph_2SO_2Cl$ in MeCN gave **LV** ($R = CO_2R^3$ and $SO_2R^3$; $R^3 = Ph$, benzyl, *p*-nitrophenyl, Me, n-hexyl, Et, $Pr^i$, piperidine, $Pr_2N$, $Et_2N$, $Me_2N$; $R^1 = CF_3$; $R^2 = CF_3$), possessing insecticidal and acaricidal activity [287].

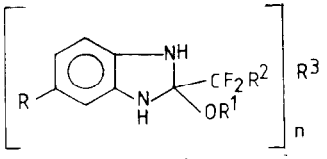
4-Substituted-5-cyano-7-nitro-2-($\alpha,\alpha$-difluoroalkyl) benzimidazoles (**LVI**) [288] prepared from chloro compounds ($R^2 = Cl$) and amines in EtOH, show herbicidal and fungicidal activity [288].



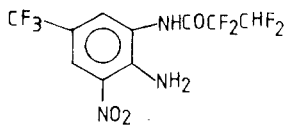
$R = CN$, $CF_3$; $R^1 = F$, $CF_3$;
$R^2 = CH_3O$, $C_2H_5S$, $CH_2CH_2CH_2NH$, $C_2H_5O$,  , etc.

(**LVI**)

Hydroxybenzimidazolines **LVII** (R = Br, Cl, $CF_3$; $R^1$ = H, $C_{1-4}$alkyl; $R^2$ = H, F, $CHF_2$, $CF_3$; $R^3$ = Na, K, Li, Ag, Ca, $NH_4$; $n$ = valency of $R^3$), which are useful as herbicides [289], insecticides [289, 290] and ectoparasiticides [289, 291], were prepared by keeping **LVIII** in $R_3OH$ for 24 h at room temperature.

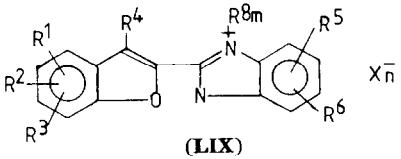


**(LVII)**



**(LVIII)**

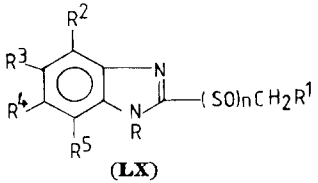
Benzofuranyl benzimidazoles **LIX** [292], made by cyclo-condensation of $R^5R^6C_6H_2(NH_2)NHR^1$-*o* with 2-benzofuran carboxylic acids, are used as fluorescent whiteners (for cellulosic and synthetic fabrics, paper and PVC).



**(LIX)**

$R^1$ = H, alkenyloxy, etc.; $R^2$,$R^3$ = H, alkyl, halo, etc.; $R^4$ = H, alkyl, Ph; $R^5$ = $CF_3$, CN, sulpho or carboxy or their derivatives; $R^6$ = H, halo, alkyl; $R^7$,$R^8$ = cyclo-alkyl, alkenyl, etc.; $X^-$ = anion; $m$,$n$ = 0,1

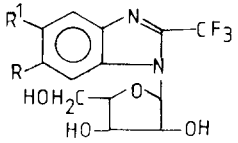
Benzimidazoles **LX**, obtained by alkylating the benzimidazolethione followed by oxidation, show anthelmintic [293, 294] and anti-inflammatory [295, 296] activities, and are used as anti-ulcer agents [297–301].



**(LX)**

R = H, alkanoyl, benzyl; $R^1$ = fluorophenyl, fluoroalkyl, substituted piperidyl; $R^2$–$R^5$ = H, alkyl, alkoxy, alkanoyl, carbonyl, halo, $CF_3$, $CF_3O$, SMe, SOMe, $NO_2$, OPh, SPh; $n$ = 0–2

2-Trifluoromethyl-substituted benzimidazole ribofuranosides (**LXI**) [302] were made from halobenzimidazoles and 1,2,3,5-tetraacetyl-β-D-ribofuranose (fusion followed by deacetylation).

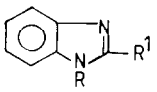


**(LXI)**

R = $R^1$ = H, $CH_3$, Cl, F; R = Cl; $R^1$ = H

*(c) On the imidazolyl carbon and nitrogen atom*

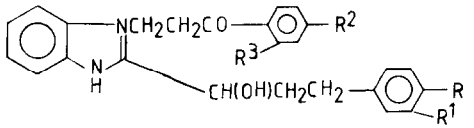
Fluoroalkyl and alkenyl derivatives of benzimidazole **LXII** [303] are used to prepare cyanine dyes [303] and possess herbicidal [304], fungicidal [305], insecticidal and acaricidal activities [306].



R = $CF{=}CF_2$, $CF{=}CFCl$, $CF{=}CFCF_3$; $R^1 = CH_3$, $CF_3$

(LXII)

1-Benzoylethyl-2-(3-phenyl-1-hydroxypropyl) benzimidazoles (**LIX**) were prepared by reducing 2-cinnamoyl benzimidazoles and treating the 2-hydroxypropyl derivatives with the piperazinopropiophenones. Various **LXIII** compounds demonstrated anti-ulcer, vasodilator, respiratory, analeptic, analgesic, hypotensive, diuretic, CNS stimulant and sedative properties [307].

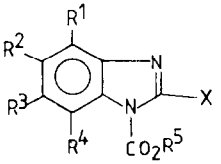


(LXIII)

R = $OCH_3$, H, $CH_3$, F; $R^1$ = H, $OCH_3$; $R^2$ = H, $OCH_3$,F, $CH_3$; $R^3$ = H, $OCH_3$

*(d) On the benzene ring, nitrogen atom and imidazolyl carbon*

1-(Alkoxycarbonyl)-2-fluoroalkyl) benzimidazoles(**LXIV**) made from alkali metal salts of 2-(fluoroalkyl) benzimidazoles and alkyl chloroformates showed acaricidal activity [308].

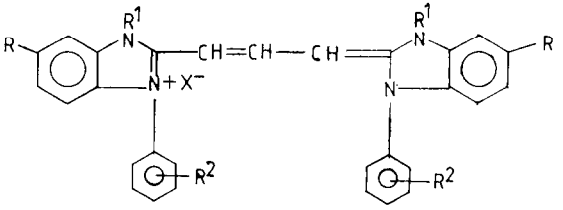


(LXIV)

X = $CF_3$, $C_2F_5$; $R^1$ = Cl, Br, $CF_3$, etc.;
$R^2$ = H, Cl; $R^3$ = H, Br, Cl; $R^4$ = H, Br, $C_2H_5$, $CH_3$, $CF_3$, etc.;
$R^5$ = H, $CF_3$, $(CH_3)_2CH$, etc.

*(e) On two benzimidazole rings*

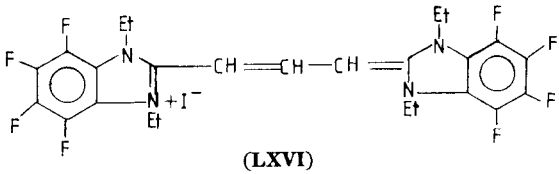
*N-m*-(Trifluoromethyl)phenyl and *N-p*-trifluoromethylsulfonyl)phenyl imidacyanine dyes (**LXV**) and other cyanine dyes are known [309–312].



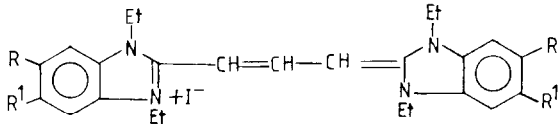
(LXV)

R = H, $CF_3$; $R^1 = C_2H_5$, $CH_2CH_2CF_3$;
$R^2 = m$-$CF_3$, $p$-$SO_2CF_3$; X = $ClO_4$, I

Cyanine dyes **LXVI** and **LXVII** have been obtained from 2-methyl4,5,6,7-tetrafluorobenzimidazole, 5,6-bis(trifluoromethyl)benzimidazole and 5-(trifluoromethylsulfonyl)benzimidazole derivatives [313–315]. These are useful as optical sensitizers for photographic silver halide emulsions [316].



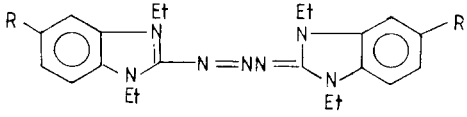
(LXVI)



$R = CF_3$, $CF_2SO_2$; $R^1 = H$, $CF_3$

(LXVII)

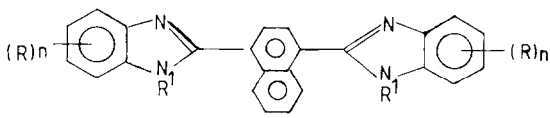
Triazatrimethine cyanine dyes **LXVIII** [317] were prepared by treating 2-chloro-1-ethyl-5-R-benzimidazole with $Et_3OBF_4$.



$R = H$, $CH_3$, $CH_3O$, $CF_3$, Cl, $CO_2C_2H_5$, $NO_2$

(LXVIII)

Derivatives of type **LXIX** are useful as fluorescent whiteners and were prepared by the reaction of $1,4\text{-}C_{10}H_6(COCl)_2$ with *o*-nitroanilines [318].



$R = F$, $CF_3$; $R^1 = alkyl$

(LXIX)


## Acknowledgement

One of the authors (K.S.) is thankful to the U.G.C., New Delhi for the award of a minor research project.


## References


1 V. G. Poludnenko, O. B. Didinskaya, A. F. Pozharskii and M. M. Gilburd, *Khim. Geterotsikl. Soedin., 12* (1982) 1696.

2 V. G. Poludnenko, O. B. Didinskaya and A. F. Pozharskii, *Khim. Geterotsikl. Soedin., 4* (1984) 520.

3 V. G. Poludnenko, O. B. Didinskaya and A. F. Pozharskii, *Khim. Geterotsikl. Soedin., 4* (1984) 524.

4 J. L. Davidson, I. E. P. Murray and P. N. Preston, *J. Chem. Res. Synop., 5* (1981) 126.

5 A. D. Dzyuban, L. I. Reidalova, N. S. Lagoshina, V. I. Rudyn and V. I. Troitskaya, *Fiziol. Akt. Veschestva, 7* (1975) 29.

6 V. I. Rudyk, V. I. Troitskaya and L. M. Yagupolskii, *Zh. Org. Khim., 16* (1980) 2624.
7 R. R. Ison, *Br. Pat. 1 575 386*(1980) [*Chem. Abstr., 95* (1981) 43 103q].
8 G. Willis Roland and W. R. Schleigh, *US Pat. 3 850 638*(1974) [*Chem. Abstr., 82* (1975) 105 476h].
9 E. Kuehle, E. Klauke, F. Grewe and H. Kaspers, *Ger. Pat. 1 302 649*(1972) [*Chem. Abstr., 77* (1972) 126 643v].
10 C. Hennart, *Fr. Pat. 1 488 287*(1976) [*Chem. Abstr., 69* (1968) 59 244k].
11 G. Hasegawa, M. Shiroki and A. Kotani, *Jpn. Kokai 78 09 770*(1978) [*Chem. Abstr., 88* (1978) 190 835p].
12 M. Shiroki and A. Kotani, *Jpn. Kokai 76 149 274*(1976) [*Chem. abstr., 87* (1977) 68 357y].
13 M. B. Emanuel, *Med. Actual, 22* (1986) 39.
14 H. Koch, *Pharm. Int., 6* (1985) 130.
15 D. M. Richards, R. N. Brogden, R. C. Heel, T. M. Speight and G. S. Avery, *Drugs, 21* (1984) 38.
16 F. H. F. Awouters, C. J. E. Niemegeers and P. A. J. Janssen, *Arzneim. Forsch., 33* (1983) 381.
17 F. E. Montserrat, *Span. E. S. Pat. 516 089*(1983) [*Chem. Abstr., 100* (1984) 139 109u].
18 J. Abad, A. I. Cossent, F. M. J. Antonio, S. A. Alonso and T. C. Tomas, *Span. E.S. Pat. 544 320*(1986) [*Chem. Abstr., 106* (1987) 84 601q].
19 M. I. Fernandez, S. M. Izquierdo, S. A. Martiney, M. C. Fuertes and P. M. L. Lucerode, *Span. E.S. Pat. 534 276*(1984) [*Chem. Abstr., 106* (1987) 18 548b].
20 P. Lundbory and J. Engel, *Neuro-Psychopharmacol. Proc. Congr. Coll. Int. Neuro-Psychopharmacol., 10th (1976), 2* (1978) 1351.
21 R. M. Pinder, R. N. Brogden, P. R. Wawyer, T. M. Speight, R. Spencer and G. S. Avery, *Drugs, 12* (1976) 1.
22 M. A. C. Janssen, *Jpn. Kokai 77 19 672*(1977) [*Chem. Abstr., 87* (1977) 201 532v].
23 P. A. J. Janssen, C. J. E. Niemegeers, K. H. L. Schellekenes, F. M. Leneerts and A. Wauquier, *Arzneim. Forsch., 25* (1975) 1287.
24 G. P. Takla, K. C. James and A. E. H. Gassin, *Anal. Profiles Drug Subst., 14* (1985) 245.
25 S. Germane and S. V. Veselova, *Eksp. Klin. Farmakoter., 11* (1982) 6.
26 T. J. Van de Merwe, *Geneeskunde, 19* (1977) 112.
27 R. Krebs, *Neuroleptanalg. NLA Workshop,* (1974) (Publ. 1975) 11.
28 W. Soudijn, *Boerhaave Ser Postgrad Med. Educ., 12* (1976) 139.
29 E. Etchenberg, *Books, 23* (1973) 289pp.
30 E. Etschenberg, *Book Suppl.,* (1973) 289pp.
31 W. Soudijn, V. W. Ineke and P. A. J. Janssen, *Int. Anesthesiol Clin., 12* (1974) 145.
32 K. Ueno, M. Sato, H. Kojima, T. Yamazaki and T. Sakurai, *Jpn. Kokai 75 84 579*(1975) [*Chem. Abstr., 84* (1976) 31 059q].
33 M. Sato, M. Arimoto and K. Ueno, *Jpn. Kokai 76 131 879*(1976) [*Chem. Abstr., 87* (1977) 5967b].
34 M. Sato, M. Arimoto and K. Ueno, *Jpn. Kokai 76 136 674*(1976) [*Chem. Abstr., 87* (1977) 53 289d].
35 M. Sato, M. Arimoto, K. Ueno, H. Kojima, T. Yamasaki, T. Sakurai and A. Kasahara, *J. Med. Chem., 21* (1978) 1116.
36 K. Sudo, H. Tachizawa and M. Sano, *Xenobiotica, 11* (1981) 685.
37 M. Sato, M. Arimoto, K. Ueno, H. Kojima, T. Yamazaki and T. Sakurai, *Jpn. Kokai 76 136 674*(1976) [*Chem. Abstr., 86* (1977) 189 933w].
38 G. Cascio, R. Erba, E. Manghis, A. Biazzi, G. Fermi and G. B. Fregnan, *Farmaco. Ed. Sci., 35* (1980) 605.
39 Sumitomo Chemical Co. Ltd., *Jpn. Kokai Tokkyo Koho 80 85 562*(1980) [*Chem. Abstr., 94* (1981) 83 949f].
40 K. Ono, *Jpn. Kokai 77 97 927*(1977) [*Chem. Abstr., 88* (1978) 105 329j].
41 K. Sasajima, K. Ono, Y. Motoi'ke, S. Inaba and H. Yamamoto, *Ger. Offen. 2 632 414*(1977) [*Chem. Abstr., 86* (1977) 155 373y].

42 K. Sasajima, M. Nakao, I. Maruyama, S. Katayama and H. Yamamoto, *Jpn. Kokai 73 00 474*(1973) [*Chem. Abstr.*, *78* (1973) 124 586a].

43 K. Sasajima, K. Ono, Y. Motoike, S. Inaba and H. Yamamoto, *Jpn. Kokai 77 12 173*(1977) [*Chem. Abstr.*, *87* (1977) 53 087m].

44 J. Vandenberk, L. E. J. Kennis, M J. M. C. van der Aa and A. H. M. T. van Heertum, *Ger. Offen. 2 645 125*(1977) [*Chem. Abstr.*, *87* (1977) 102 326z].

45 H. Yamamoto, M. Nakao, K. Sasajima, M. Kikuo, I. Masuyama and S. Katayama, *Ger. Offen. 2 052 537*(1971) [*Chem. Abstr.*, *75* (1971) 151 679c].

46 J. Katsube, M. Nakao, K. Sasajima, I. Maruyama, M. Takayama, K. Ono, S. Katayama, Y. Tanaka and S. Inaba, *Ger. Offen. 2 265 094*(1976) [*Chem. Abstr.*, *85* (1976) 33 016t].

47 K. Sasajima, M. Nakao, I. Maruyama, K. Ono, S. Katayama, M. Takayama, J. Katsube, S. Inaba and H. Yamamoto, *Ger. Offen. 2 313 258*(1973) [*Chem. Abstr.*, *79* (1973) 146 409t].

48 I. Maruyama, M. Nakao, K. Sasajima, S. Inaba and H. Yamamoto, *Jpn. Kokai 76 100 085*(1976) [*Chem. Abstr.*, *86* (1977) 16 553u].

49 I. Maruyama, M. Nakao, K. Sasajima, S. Inaba and H. Yamamoto, *Jpn. Kokai 76 43 764*(1976) [*Chem. Abstr.*, *86* (1977) 5456b].

50 I. Maruyama, M. Nakao, K. Sasajima, H. Yamamoto, S. Sakai and S. Kitagawa, *Jpn. Kokai 74 46 310*(1974) *Chem. Abstr.*, *83* (1975) 82 233r].

51 I. Maruyama, M. Nakao, K. Sasajima, S. Inaba, H. Yamamoto, S. Sakai and S. Kitagawa, *Jpn. Kokai 75 11 391*(1975) [*Chem. Abstr.*, *83* (1975) 193 320z].

52 W. I. Van, W. Soudijn, J. Vandenberk and J. F. Hens, *US Pat. 4 082 755*(1978) [*Chem. Abstr.*, *89* (1978) 197 539z].

53 L. D. Wise, I. C. Pattison, D. E. Buttler, H. A. Dewald, E. P. Lewis, S. J. Lobbestael, I. C. Nordin, B. P. H. Poschel and L. L. Coughenour, *J. Med. Chem.*, *28* (1985) 606.

54 G. Startz and M. Baboulene, *Ger. Offen. 2 303 862*(1973) [*Chem. Abstr.*, *79* (1973) 104 947m].

55 M. Baboulene, G. Sturtz and J. Hache, *Chim. Ther.*, *7* (1972) 493.

56 F. Uchimaru, M. Sato, H. Kojima and T. Yamazaki, *Jpn. Kokai 74 126 683*(1974) [*Chem. Abstr.*, *83* (1975) 43 009r].

57 M. Sato, M. Kitagawa, F. Uchimaru, K. Ueno, H. Kojima and T. Yamasaki, *Chem. Pharm. Bull.*, *27* (1979) 119.

58 K. Sasajima, M. Nakao, I. Maruyama, S. Katayama and H. Yamamoto, *Jpn. Kokai 73 00 476*(1973) [*Chem. Abstr.*, *78* (1973) 72 147m].

59 K. Sasajima, M. Nakao, I. Maruyama, S. Katayama and H. Yamamoto, *Jpn. Kokai 73 00 475*(1973) [*Chem. Abstr.*, *78* (1973) 72 141e.

60 K. Sasajima, M. Nakao, I. Maruyama, S. Katayama and H. Yamamoto, *Jpn. Kokai 73 44 264*(1973) [*Chem. Abstr.*, *79* (1973) 66 192b].

61 S. Fielding, W. J. Novick, H. M. Geyer, W. W. Petko, J. C. Wilker, L. Davis, J. T. Klein and M. Cornfeldt, *Drug Dev. Res.*, *3* (1983) 233.

62 J. T. Strupczewski, R. C. Allen, B. A. Gardner, B. L. Schmid, U. Stache, E. J. Glamkowski, M. C. Jones, D. B. Ellis, F. P. Huger and R. W. Dunu, *J. Med. Chem.*, *28* (1985) 761.

63 F. E. Janssens, J. Torremans, G. Leo, J. F. Hens, O. T. Van and J. M. Theresia, *Eur. Pat. 144 101*(1985) [*Chem. Abstr.*, *104* (1986) 68 856e].

64 F. E. Janssens, J. Torremans, G. Leo, J. H. Hens, O. T. Van and J. M. Theresia, *Eur. Pat. 99 139*(1984) [*Chem. Abstr.*, *101* (1984) 23 473z].

65 F. E. Janssens, J. Torremans, G. Leo, J. F. Hens, O. T. Van and J. Theresia, *Eur. Pat. 151 824*(1985) [*Chem. Abstr.*, *104* (1986) 50 874z].

66 F. Janssens, M. Luyckx, R. Stokbroekx and J. Torremans, *US Pat. 4 219 559*(1980) [*Chem. Abstr.*, *94* (1981) 30 579d].

67 S. A. Synthelabo, *Neth. Appl. 79 04 755*(1979) [*Chem. Abstr.*, *93* (1980) 26 462x].

68 H. Najer, P. Manoury and J. P. Kaplan, *Br. UK Pat. 2 023 594*(1980) [*Chem. Abstr.*, *93* (1980) 114 564n].

69 S. Bahadur, R. S. Varma and M. Saxena, *J. Chem. Eng. Data*, *25* (1980) 291.

70 R. Imhof and E. Kyburz, *US Pat. 4 391 978*(1983) [*Chem. Abstr.*, *99* (1983) 139 803b].

71 N. B. Dyatkina, A. Aleksandrova, J. M. Von and P. Langen, *Z. Chem.*, *25* (1985) 180.

72 B. A. G. Farbenfabriken, *Neth. Appl. 6 516 360*(1966) [*Chem. Abstr.*, *66* (1967) 115 708s].

73 V. I. Troitskaya, V. I. Rudyk and L. M. Yagupol'skii, *USSR Pat. 371 263*(1973) [*Chem. Abstr., 79* (1973) 20 318u].
74 Shell International Research Maatschappij N. V., *Neth. Appl. 6 707 085*(1967) [*Chem. Abstr., 69* (1968) 27 419e].
75 K. I. Pashkevich, V. I. Saloutin and I. Ya. Postovskii, *Izv. Akad. Nauk SSSR, Ser. Khim., 5* (1980) 1172.
76 K. C. Eapen and C. Tamborski, *J. Fluorine Chem., 18* (1981) 243.
77 Q. F. Soper, *Fr. Pat. 1 509 499*(1968) [*Chem. Abstr., 70* (1969) 57 850b].
78 J. L. Miesel, *US Pat. 3 890 343*(1975) [*Chem. Abstr., 83* (1975) 164 176b].
79 K. H. Buechel, *Z. Naturforsch., Teil B, 25* (1970) 934.
80 E. Edzislaw, Z. Eckstein, E. Gradon, Z. Ochaal, D. Rusek and B. Stawska, *Pol. J. Chem., 57* (1983) 1037.
81 M. H. Fishar, *US Pat. 3 749 789*(1973) [*Chem. Abstr., 79* (1973) 115 580n].
82 B. C. Bishop, A. S. Jones and J. C. Tatlow, *J. Chem. Soc.*, (1964) 3076.
83 Fison Pest Control Ltd., *Fr. Pat. 1 469 504*(1967) [*Chem. Abstr., 69* (1968) 59 236j].
84 Fison Pest Control Ltd., *Br. Pat. 1 087 561*(1967) [*Chem. Abstr., 68* (1968) 95 817n].
85 Fison Pest Control Ltd., *Neth. Appl. 6 501 323*(1966) [*Chem. Abstr., 66* (1967) 28 771p].
86 Fison Pest Control Ltd., *Neth. Appl. 6 602 316*(1966) [*Chem. Abstr., 66* (1967) 27 985z].
87 Fison Pest Control Ltd., *Belg. Pat. 569 384*(1965) [*Chem. Abstr., 63* (1965) 18 102b].
88 E. S. Lane, *J. Chem. Soc.*, (1955) 534.
89 Daikin Kogyo Co. Ltd., *Jpn. Kokai Tokkyo Koho 57 150 669*(1982) [*Chem. Abstr., 98* (1983) 53 858r].
90 H. Harada, S. Mizutaki, S. Hayashi and N. Ishikawa, *J. Fluorine Chem., 12* (1978) 211.
91 N. Ishikawa and T. Muramatsu, *Nippon Kagaku Kaishi, 3* (1973) 563.
92 Daikin Kogyo Co. Ltd., *Jpn. Kokai Tokkyo Koho JP 57 150 670*(1982) [*Chem. Abstr., 98* (1983) 53 857q].
93 Daikin Kogyo Co. Ltd., *Jpn. Kokai Tokkyo Koho JP 59 46 276*(1984) [*Chem. Abstr., 101* (1984) 90 930j].
94 A. Takaoka, H. Iwakiri, N. Fujiwara and N. Iskikawa, *Nippon Kagaku Kaishi, 11* (1985) 2161.
95 H. Roechling, G. Hoerlein and L. Emmel, *Ger. Offen. 2 022 504*(1971) [*Chem. Abstr., 76* (1972) 59 629j].
96 K. D. Zwalhen, *S. Afr. Pat. 67 05 585*(1968) [*Chem. Abstr., 70* (1969) 47 461m].
97 K. D. Zwalhlen, *US Pat. 3 412 101*(1968) [*Chem. Abstr., 70* (1969) 47 451h].
98 J. H. Parsons, A. Percival and G. T. Newbold, *S. Afr. Pat. 67 07 059*(1968) [*Chem. Abstr., 70* (1969) 87 812h].
99 A. Takaoka, K. Iwamato, T. Kitazume and N. Ishikawa, *J. Fluorine Chem., 14* (1979) 421.
100 G. W. Adamson, D. Bawden and D. T. Saggers, *Pestic. Sci., 15* (1984) 31.
101 A. F. Kozhokaru, M. G. Fomkina, A. B. Berezhnew and G. I. Plyushcheko, *Deposited Doc.*, (1983) 18pp.
102 M. Alam, *FEMS Microbiol. Lett., 17* (1983) 291.
103 J. H. Stevenson, *Plant Pathol., 27* (1978) 38.
104 J. L. Miesel, *US Pat. 4 000 295*(1976) [*Chem. Abstr., 86* (1977) 140 050s].
105 J. L. Miesel, *US Pat. 3 927 020*(1975) [*Chem. Abstr., 85* (1976) 94 361y].
106 E. L. Samuel, *Aust. J. Chem., 25* (1972) 2725.
107 J. L. Miesel, *Ger. Offen. 2 029 753*(1970) [*Chem. Abstr., 74* (1971) 53 792u].
108 A. Chloroplasts, R. William and D. E. Moreland, *Pestic. Biochem. Physiol., 5* (1975) 163.
109 Farbwerke, Hoechst AG, *Fr. Demande 2 011 273*(1970) [*Chem. Abstr., 73* (1970) 130 998z].
110 R. K. Pfeiffer, *Proc. Br. Weed Contr. Conf. 8th, 2* (1966) 394.
111 R. K. Pfeiffer, *Br. Pat. 1 186 165*(1970) [*Chem. Abstr., 72* (1970) 131 364f].
112 G. O. P. Doherty, *Ger. Offen. 2 165 021*(1972) [*Chem. Abstr., 77* (1972) 164 700u].
113 Fisons Pest Control Ltd., *Fr. Pat. 1 502 294*(1967) [*Chem. Abstr., 70* (1969) 2677v].
114 M. F. Gaetano and G. C. Kenneth, *Boll. Ist. Sieroter. Milan, 42* (1963) 630.

115 K. H. Buechel, W. Flucke and H. P. Schulz, *Ger. Offen. 2 016 622*(1971) [*Chem. Abstr., 76* (1972) 69 180v].
116 P. J. Booker, J. Goose and A. Percival, *Ger. Offen. 2 408 736*(1974) [*Chem. Abstr., 82* (1975) 51 781f].
117 J. R. Corbett and A. Percival, *Ger. Offen. 2 137 508*(1972) [*Chem. Abstr., 76* (1972) 140 831r].
118 P. J. Brooker, J. Goose and A. Percival, *Br. Pat. 1 464 553*(1977) [*Chem. Abstr., 87* (1977) 79 680z].
119 W. Traber and E. Aufderhaar, *Ger. Offen. 2 502 116*(1975) [*Chem. Abstr., 83* (1975) 209 408x].
120 J. Hannah, D. W. Graham and E. F. Rogers, *US Pat. 3 749 734*(1973) [*Chem. Abstr., 79* (1973) 78 802p].
121 E. F. Rogers, J. Hannah and D. W. Graham, *Fr. Demande 2 145 633*(1973) [*Chem. Abstr., 79* (1973) 53 322u].
122 J. R. Corbett and A. Percival, *Br. Pat. 1 356 246*(1974) [*Chem. Abstr., 81* (1974) 91 523j].
123 J. R. Corbett and A. Percival, *Br. Pat. 1 356 245*(1974) [*Chem. Abstr., 81* (1974) 91 521g].
124 K. H. Buechel and W. Stendel, *Ger. Offen. 2 242 785*(1974) [*Chem. Abstr., 80* (1974) 146 159g].
125 D. F. Weetman, K. Cain and A. J. Sweetman, *Arch. Int. Pharmacodyn. Ther., 203* (1973) 342.
126 H. F. W. Roechling, K. H. Buechel and F. A. G. K. Korte, *US Pat. 3 988 465*(1976) [*Chem. Abstr., 86* (1977) 72 641h].
127 M. H. Fisher, D. R. Hoff and R. J. Bochis, *US Pat. 3 705 174*(1972) [*Chem. Abstr., 78* (1973) 58 419v].
128 Fison Ltd., *Fr. Demande 2 188 957*(1974) [*Chem. Abstr., 81* (1974) 34 607r].
129 R. Anliker, A. Raeuchle and H. Hefri, *Proc. Int. Wolltextil-Forschiengskonf., 5th(1975), 5* (1976) 161.
130 Fisons Pest Control Ltd., *Fr. Pat. 1 513 599*(1968) [*Chem. Abstr., 70* (1969) 87 803f].
131 C. D. Ercegovich, N. L. Hartwig, S. Witkonton and P. Carroll, *Environ. Entomol., 1* (1972) 730.
132 Q. A. Greering, J. A. Bond and A. J. Jones, *Proc. Br. Insectic. Fungic. Conf., 4th, 1* (1967) 209.
133 Fison Ltd., *Fr. Demande 2 028 095*(1970) [*Chem. Abstr., 75* (1971) 19 102e].
134 J. Ilivicky and J. E. Casido, *Biochem. Pharmacol., 18* (1969) 1389.
135 J. R. Hardison, *Phytopathology, 62* (1972) 609.
136 G. B. Leslie and D. F. Weetman, *Arch. Int. Pharmacodyne. Ther., 177* (1969) 105.
137 T. Palosz, *Biul. Inst. Ochr. Rosl., 54* (1972) 461.
138 J. R. Corbett and B. J. Wright, *Pestic. Sci., 1* (1970) 120.
139 H. Roechling, L. Emmel and O. Scherer, *Ger. Offen. 2 022 505*(1971) [*Chem. Abstr., 76* (1972) 95 759k].
140 D. G. Ashby, *Meded. Rijksfac. Landbouwwet., Gent, 33* (1968) 839.
141 R. B. Jolmson, *Fla. Entomol., 52* (1969) 73.
142 Fisons Pest Control Ltd., *Fr. Addn. 93 257*(1969) [*Chem. Abstr., 72* (1970) 21 691c].
143 G. T. Newbold, A. Percival and M. B. Purdew, *Ger. Offen. 2 157 051* (1972) [*Chem. Abstr., 77* (1972) 88 505s].
144 H. Roechling and K. H. Buechel, *Z. Naturforsch., Teil, B, 25* (1970) 1103.
145 D. T. Saggers, *Ger. Offen. 1 960 159*(1970) [*Chem. Abstr., 73* (1970) 97 862a].
146 A. Mordhay, *Curr. Top. Bioenerg., 2* (1967) 1.
147 K. H. Buechel, W. Draber, A. Trebst and E. Pistorius, *Z. Naturforsch., 21* (1966) 243.
148 E. I. Barskii, M. V. Gussev, N. V. Kazennova and V. D. Samuilov, *Fiziol. Rast., 32* (1985) 688.
149 D. F. Weetman and N. Turner, *Arch. Int. Pharmacodyn. Ther., 210* (1974) 12.
150 I. R. Flockhart, R. L. Smith and R. T. Williams, *Proc. Eur. Soc. Study Drug Toxic., 14* (1973) 36.
151 R. P. Gupta, C. A. Larroquette and K. C. Agarwal, *J. Med. Chem., 25* (1982) 1342.

152 Z. Ya. Molchanova, *Vinodel. Vinograd. SSSR*, *7* (1974) 30.
153 A. Shinohara, S. Kusano, S. Matsui, N. Muramatsu and S. Kawada, *Jpn. Kokai 78 29 934*(1978) [*Chem. Abstr.*, *89* (1978) 101 871c].
154 P. Rohrbach and I. Karadavidoff, *Ger. Offen. 2 049 377*(1971) [*Chem. Abstr.*, *75* (1971) 20 398n].
155 S. A. Fuveau, *Fr. Demande 2 092 648*(1972) [*Chem. Abstr.*, *77* (1972) 118 208s].
156 S. Ram, D. S. Wise and L. B. Townsend, *J. Heterocycl. Chem.*, *23* (1986) 1109.
157 Merck & Co. Inc., *Belg. Pat. 621 596*(1963) [*Chem. Abstr.*, *59* (1963) 11 505b].
158 V. A. Lopyrev, I. A. Titova, E. F. Shibanova, T. I. Yushmanova and M. G. Voronkov, *Otkrytiya Izobret.*, *33* (1986) 112.
159 Sandoz AG, *Neth. Appl. 78 10 821*(1980) [*Chem. Abstr.*, *93* (1980) 173 761x].
160 W. J. Houlihan, *S. Afr. Pat. 78 05 778*(1980) [*Chem. Abstr.*, *94* (1981) 71 484n].
161 Sandoz AG, *Jpn. Kokai Tokkyo Koho 79 41 331*(1979) [*Chem. Abstr.*, *91* (1979) 9500z].
162 D. Hoff, *Fr. Pat. 1 510 330*(1968) [*Chem. Abstr.*, *70* (1969) 77 967y].
163 C. Fauran, J. Eberle, A. Y. Lecloaree, G. Raynaud and N. Dorme, *Fr. Demande 2 160 719*(1973) [*Chem. Abstr.*, *79* (1973) 137 156f].
164 A. V. Fokin, E. I. Astashkin, A. Z. Prikhodko, V. V. Ryabichenko, I. S. Nikolaeva, Yu. V. Slavich and A. F. Kolomiets, *Dokl. Akad. Nauk SSSR*, *284* (1985) 1492.
165 C. Fauran, M. Turin, G. Raynaud and B. Pourrias, *Fr. Demande 2 259 590*(1975) [*Chem. Abstr.*, *84* (1976) 59 477y].
166 N. A. Malichenko, *USSR Pat. 505 639*(1976) [*Chem. Abstr.*, *85* (1976) 108 638h].
167 N. A. Malichenko, A. P. Krasnoshchek, T. P. Medvedeva and L. M. Yagupol'skii, *Khim. Geterotsikl. Soedin.*, *9* (1976) 1262.
168 N. A. Malichenko and L. M. Yagupol'skii, *Khim. Geterotsikl. Soedin.*, *3* (1978) 388.
169 V. P. Borisenko, N. A. Malichenko and N. I. Zhuravskaya, *Fiziol. Akt. Veshchestva*, *13* (1981) 26.
170 C. Fauran, J. Eberle, M. Turin and G. Raynaud, *Ger. Offen. 2 444 194*(1975) [*Chem. Abstr.*, *83* (1975) 114 426n].
171 K. Rao, V. B. Charles, S. Elizabeth, S. Sharma, R. N. Iyer, S. Gupta and J. C. Katiyar, *Eur. J. Med. Chem. Chim. Ther.*, *16* (1981) 35.
172 F. Merchan, J. Garin, V. Martinez and E. Melendez,, *Synthesis*, *6* (1982) 482.
173 X. Zhang and F. He, *Beijing Daxue Xuebaoziran Kexueban*, *6* (1982) 85.
174 S. Giri and H. C. Gupta, *Bokin Bobai*, *7* (1979) 557.
175 M. Winn and J. Kyncl, *US Pat. 4 093 726*(1978) [*Chem. Abstr.*, *89* (1978) 197 600n].
176 F. Janssens, J. Torremans, M. Janssen, R. A. Stokbrockx, A. Raymond, M. Luycks and P. A. J. Janssen, *J. Med. Chem.*, *28* (1985) 1925.
177 C. Tamborski *et al.*, *US Pat 4 100 301*(1980) [*Chem. Abstr.*, *94* (1981) 30 756j].
178 J. B. Christian, *US Pat. 4 233 277*(1981) [*Chem. Abstr.*, *96* (1982) 145 877h].
179 A. Sykes and J. C. Tatlow, *J. Chem. Soc.*, (1952) 4078.
180 R. R. Smolders, A. Wacfelaer and D. Francart, *Ing. Chim. (Brussels)*, *64* (1982) 3.
181 A. Rosegay, *Drug Metab. Dispos.*, *8* (1980) 136.
182 H. Kimoti, S. Fujii and L. A. Cohen, *J. Org. Chem.*, *47* (1982) 2867.
183 K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, *34* (1969) 384.
184 E. Aufderhaar, J. J. Gallay, M. Kuehne, A. Meyer, O. Rechsteiner, M. Schellenbaum and J. P. Funeaux, *Ger. Offen. 2 815 675*(1978) [*Chem. Abstr.*, *90* (1979) 54 939q].
185 Ciba-Geigy AG, *Belg. Pat. 865 871*(1978) [*Chem. Abstr.*, *90* (1979) 103 957e].
186 Ciba-Geigy AG, *Belg. Pat. 865 870*(1978) [*Chem. Abstr.*, *90* (1979) 137 817z].
187 W. Gauss, *Ger. Offen. 3 340 932*(1985) [*Chem. Abstr.*, *103* (1985) 196 082r].
188 W. E. Frick and T. Wenger, *US Pat. 3 686 411*(1972) [*Chem. Abstr.*, *77* (1972) 140 079x].
189 D. Henri, J. Marcel, G. Libeer, M. Van and M. N. Jean, *Belg. Pat 595 980*(1961) [*Chem. Abstr.*, *58* (1963) 14 171g].
190 L. M. Yagupol'skii and G. I. Matyushecheva, *Zh. Obshch. Khim.*, *33* (1963) 3031.
191 United States Borax and Chemical Corp., *Br. Amend. 1 015 937*(1971) [*Chem. Abstr.*, *75* (1971) 151 788n].
192 D. L. Hunter and W. S. Belles, *US Pat. 4 177 057*(1979) [*Chem. Abstr.*, *92* (1980) 111 017e].

193 S. Robev, *Dokl. Bolg. Akad. Nauk, 34* (1981) 663.
194 G. Paglietti, G. Grella, M. Pirisi, F. Sparatore, P. Manca and M. Satta, *Studi Sassar, 60* (1982) 329.
195 G. Grella, G. Paglietti, F. Sparatore, P. Manca and M. Satto, *Farmaco, Ed. Sci., 42* (1987) 475.
196 D. L. Hunter, R. A. Smith and W. S. Belles, *US Pat. 3 954 438*(1976) [*Chem. Abstr., 86* (1976) 21 374v].
197 D. L. Hunter and R. A. Smith, *US Pat. 3 954 788*(1976) [*Chem. Abstr., 88* (1978) 22 903r].
198 D. L. Hunter, R. A. Smith and W. S. Belles, *S. Afr. Pat. 74 009 93*(1974) [*Chem. Abstr., 83* (1975) 179 059q].
199 D. L. Hunter, R. A. Smith and W. S. Belles, *Ger. Offen. 2 405 070*(1974) [*Chem. Abstr., 81* (1974) 169 546r].
200 D. L. Hunter, R. A. Smith and W. S. Belles, *US Pat. 3 901 910*(1975) [*Chem. Abstr., 84* (1976) 4964z].
201 K. K. W. Shen, *US Pat. 3 954 792*(1976) [*Chem. Abstr., 86* (1977) 106 628b].
202 D. L. Hunter, R. A. Smith and W. S. Belles, *US Pat. 3 954 438*(1976) [*Chem. Abstr., 85* (1976) 21 374v].
203 K. J. Bannert and D. J. Fry, *Br. Pat. 1 111 905*(1968) [*Chem. Abstr., 69* (1968) 52 139w].
204 P. M. G. Bavin, *Br. Pat. 1 094 903*(1967) [*Chem. Abstr., 69* (1968) 19 159e].
205 G. A. Bistocchi, M. G. De, M. Pedini, A. Ricci and P. Jacquignon, *Collect. Czech. Chem. Commun., 59* (1985) 1959.
206 B. G. Alunni, M. G. De, M. Pedini, A. Ricci, M. Pitzurra, R. Cavallo, T. Sposini, C. Riccardin and P. Jacquignon, *Farmaco, Ed. Sci., 37* (1984) 660.
207 M. Pedini, B. G. Alunni, M. G. De, A. Ricci, P. Jacquignon, C. Riccardi, L. Bastianini and T. Sposini, *Farmaco, Ed. Sci., 42* (1987) 541.
208 Merck & Co. Inc., *Fr. Pat. M4234*(1966) [*Chem. Abstr., 68* (1968) 68 990g].
209 Merck & Co. Inc., *Neth. Appl. 6 413 475*(1965) [*Chem. Abstr., 64* (1965) 8191h].
210 P. Strehlke and U. Redmann, *Ger. Offen. 2 142 585*(1973) [*Chem. Abstr., 78* (1973) 136 284p].
211 B. G. Alunni, M. G. De, T. Pedini and P. Jacquignon, *Farmaco, Ed. Sci., 37* (1982) 597.
212 L. D. George, *US Pat. 3 322 783*(1967) [*Chem. Abstr., 67* (1967) 64 399c].
213 A. V. Zeiger and M. M. Joullie, *Synth. Commun., 6* (1976) 457.
214 A. V. Zeiger and M. M. Joullie, *J. Org. Chem., 42* (1977) 542.
215 J. Y. Lew, T. Miyamoto and M. Goldstein, *Biochem. Pharmacol., 25* (1976) 1433.
216 R. Giraudon and G. Santini, *Eur. Pat. Appl. EP 152 360*(1985) [*Chem. Abstr., 104* (1986) 34 080g].
217 D. W. S. Latham, O. Methcohn and H. Suschitzky, *J. Chem. Soc., Chem. Commun.*, (1973) 41.
218 F. Sparatore, U. Boido and F. Fanelli, *Farmaco, Ed. Sci., 23* (1968) 344.
219 H. Loewe, J. Urbanietz, R. Kirsch and D. Duewel, *Ger. Offen. 2 332 487*(1975) [*Chem. Abstr., 82* (1975) 156 301c].
220 J. Urbanietz, R. Kirsch and D. Duewel, *Can. Pat. 1 031 780*(1978) [*Chem. Abstr., 90* (1979) 72 183t].
221 M. Michiels, R. Hendiiks, J. Heykants and B. H. Vandess, *Arch. Int. Pharmacodyn. Ther., 256* (1982) 180.
222 Nippon Shinyaku Co. Ltd., *Jpn. kokai Tokkyo 801 105 615*(1980) [*Chem. Abstr., 97* (1982) 17 116t].
223 H. H. Lautenschlaeger, H. Betzing, B. Stoll and M. Probst, *Eur. Pat. Appl. 51 827*(1982) [*Chem. Abstr., 97* (1982) 182 413v].
224 D. G. O'Sullivan, C. M. Ludlow and A. K. Wallis, *Experientia, 27* (1971) 1025.
225 D. G. O'Sullivan, C. M. Ludlow, D. Pantic and A. K. Wallis, *Antimicrob. Agents Chemother.*, (1969) 153.
226 S. A. Agripat, *Neth. Appl. 6 611 087*(1967) [*Chem. Abstr., 68* (1968) 29 699z].
227 C. J. Paget and J. L. Sands, *US Pat. 4 088 768*(1978) [*Chem. Abstr., 90* (1979) 137 814w].
228 G. Paglietti, V. Boido and F. Sparatore, *Farmaco, Ed. Sci., 30* (1975) 505.

229 H. Goldsmith and R. F. Crawford, *US Pat. 3 317 555*(1967) [*Chem. Abstr., 67* (1967) 21 914z].
230 E. H. Gold, *US Pat. 3 987 182*(1976) [*Chem. Abstr., 86* (1977) 72 638n].
231 V. Boido and F. Sparatore, *Farmaco, Ed. Sci., 29* (1974) 517.
232 I. Maruyama, M. Nakao, K. Sasajima, S. Inaba and H. Yamamoto, *Jpn. Kokai 75 108 264*(1975) [*Chem. Abstr., 84* (1976) 59 466u].
233 M. Sato, M. Arimoto and K. Ueno, *Jpn. Kokai 77 00 278*(1977) [*Chem. Abstr., 87* (1977) 68 356x].
234 T. Kawakita, M. Setoguchi and T. Moro, *PCT Int. Appl. WO 81 01 554*(1981) [*Chem. Abstr., 96* (1982) 6712n].
235 R. A. Stokbroekx, J. J. M. Willems and M. G. M. Luyckx, *Eur. Pat. Appl. EP 35 902*(1981) [*Chem. Abstr., 96* (1982) 104 237f].
236 F. Janssens, R. Stokbroekx, J. Torremans and M. Luyckx, *Eur. Pat. Appl., 5 318*(1979) [*Chem. Abstr., 92* (1980) 215 439k].
237 M. Bianchi, A. Butti, S. Rossi,F. Barzaghi and V. Marcaria, *Eur. J. Med. Chem. Chim. Ther., 18* (1983) 495.
238 L. Kennis, *Eur. Pat. 5 610*(1979) [*Chem. Abstr., 93* (1980) 26 439v].
239 H. C. Newson and W. G. Woods, *J. Agric. Food Chem., 21* (1973) 598.
240 P. C. Kearney and D. D. Kaufman, *Pestic. Biochem. Physiol., 3* (1973) 271.
241 J. L. Allen and J. W. Hogan, *J. Agric. Food Chem., 25* (1977) 554.
242 V. I. Troitskaya, V. I. Popov, V. I. Rudyk, N. V. Kondrotenka and L. M. Yagupolshii, *Ukr. Khim. Zh., 46* (1980) 1181.
243 N. V. Kondratenko, L. G. Yurchenko and L. M. Yagupol'skii, *Ukr. Khim. Zh., 44* (1978) 1192.
244 J. F. Bolanos, W. G. Overend, A. Sykes, J. C. Tatlow and E. H. Wiseman, *J. Chem. Soc.*, (1960) 4003.
245 A. J. Cleaver, A. B. Foster and W. G. Overend, *J. Chem. Soc.*, (1959) 407.
246 Gevaert Photo-production N. V., *Belg. Pat. 640 453*(1964) [*Chem. Abstr., 63* (1965) 1924h].
247 J. C. Allen, J. Burdon and J. C. Tatlow, *J. Chem. Soc.*, (1965) 6329.
248 Y. Inukai, T. Sonoda and H. Kobayashi, *Bull. Chem. Soc. Jpn., 52* (1979) 2657.
249 Y. Inukai, Y. Oono, T. Sonoda and H. Kobayashi, *Bull. Chem. Soc. Jpn., 52* (1979) 516.
250 J. Perronnet and J. P. Demoute, *Gazz. Chim. Ital., 112* (1982) 507.
251 B. J. Senn, H. Scheffer, V. Figala, K. Kurt, K. Klemm and S. Hartmann, *S. Afr. Pat. ZA 84 03 288*(1984) [*Chem. Abstr., 103* (1985) 160 504r].
252 B. J. Senn, H. Schaeffer, V. Figala, K. Klemm, G. Rainer, R. Riedel, C. Schudt and W. Simon, *Ger. Offen. 3 240 248*(1983) [*Chem. Abstr., 99* (1983) 70 734k].
253 M. Vchida, S. Morita and M. Chihiro, *Jpn. Kokai Tokyo Koho 62 61 978*(1987) [*Chem. Abstr., 107* (1987) 39 827c].
254 Z. Kazimierczuk, L. Dudycz, R. Stolarski and D. Shugar, *J. Carbohydr. Nucleosides Nucleotides, 8* (1981) 101.
255 F. J. Weigert, *J. Org. Chem., 38* (1973) 1316.
256 R. Henning, R. Latterell, H. J. Gerhards and M. Leven, *J. Med. Chem., 30* (1987) 814.
257 P. Rohrbach and J. Blum, *Br. Pat. 1 174 493*(1969) [*Chem. Abstr., 72* (1970) 90 473v].
258 S. Janiak and O. Rohr, *Ger. Offen. 1 803 728*(1969) [*Chem. Abstr., 70* (1969) 70 603p].
259 N. Tsuda, M. Arita, T. Hamasaki, T. Tsukane and T. Kenjo, *Jpn. Kokai 77 97 978*(1977) [*Chem. Abstr., 88* (1978) 89 666j].
260 N. Tsuda, M. Arita, T. Hamasaki, T. T. Tsumagari and T. Kenjo, *Jpn. Kokai 78 05 174*(1978) [*Chem. Abstr., 88* (1978) 190 828p].
261 L. Davis and J. T. Klein, *US Pat. 4 390 544*(1983) [*Chem. Abstr., 99* (1983) 122 458v].
262 L. Davis and J. T. Klein, *Eur. Pat. 91 511*(1983) [*Chem. Abstr., 100* (1984) 85 680c].
263 P. A. J. Janssen, H. Van, H. M. T. Albert, J. Vandenberk, A. Vander and J. M. C. Marcel, *Ger. Offen. 2 527 261*(1976) [*Chem. Abstr., 84* (1976) 13 565z].
264 J. Vandenberk, L. E. J. Kennis, A. Vander, J. M. C. Marcel, H. Van and H. M. T. Albert, *Ger. Offen. 2 714 437*(1977) [*Chem. Abstr., 88* (1978) 50 920n].

265 J. Vanderberk, L. E. J. Kennis, A. Vander, J. M. C. Marcel, H. Van and H. M. T. Albert, *Ger. Offen. 2 632 870*(1977) [*Chem. Abstr., 87* (1977) 23 274c].
266 J. Vanderberk, L. E. J. Kennis, H. Van, H. M. T. Albert, A. Vander and J. M. C. Marcel, *US Pat. 4 254 127*(1981) [*Chem. Abstr., 95* (1981) 25 063x].
267 R. A. Stokbrockx, J. J. M. Willems and M. G. M. Luyckx, *US Pat. 4 329 353*(1982) [*Chem. Abstr., 97* (1982) 92 279b].
268 Sumitomo Chemical Co. Ltd., *Ger. Offen. 2 065 426*(1973) [*Chem. Abstr., 79* (1973) 92 021q].
269 I. Maruyama, M. Nakao, K. Sasajima, S. Inaba, I. Yanagihara and H. Yamamoto, *Jpn. Kokai 74 31 673*(1974) [*Chem. Abstr., 81* (1974) 105 507w].
270 I. Maruyama, M. Nakao, K. Sasajima, S. Inaba and H. Yamamoto, *Jpn. Kokai 74 133 380*(1974) [*Chem. Abstr., 83* (1975) 43 320k].
271 A. Kojima, J. Katsube, S. Inaba and H. Yamamoto, *Jpn. Kokai 75 142 574*(1975) [*Chem. Abstr., 84* (1976) 150 662r].
272 A. Kojima, J. Katsube, M. Nakao and S. Inaba, *Jpn. Kokai 75 157 376*(1975) [*Chem. Abstr., 85* (1976) 77 849u].
273 H. Koeppe, A. Mentrup, E. O. Renth, K. Schromn, W. Hoefke and G. Muaceivic, *Can. Pat. 1 126 271*(1982) [*Chem. Abstr., 98* (1983) 72 091b].
274 W. I. Van, W. Soeidign, J. Vandenberk and J. F. Hens, *Ger. Offen. 2 806 233*(1978) [*Chem. Abstr., 90* (1979) 72 184u].
275 R. Belcher, A. Sykes and J. C. Tatlow, *J. Chem. Soc.*, (1954) 4759.
276 G. M. Booke, J. Burdon and J. C. Tatlow, *J. Chem. Soc.*, (1961) 802.
277 T. I. Cherepenko, I. R. Sapozhnikova, M. L. Pelt's, V. I. Rudyk and V. I. Troitskaya, *Fiziol. Akt. Veshchestva, 10* (1978) 24.
278 G. Hoerlein, A. Studeneer, P. Langelueddeke and F. Schwerdtle, *Ger. Offen. 2 326 624*(1974) [*Chem. Abstr., 83* (1975) 164 175a].
279 Eli Lilly & Co., *Br. Pat. 1 268 000*(1972) [*Chem. Abstr., 76* (1976) 153 746s].
280 Q. F. Soper, *US Pat. 3 443 015*(1969) [*Chem. Abstr., 71* (1969) 30 472p].
281 G. O. P. O'Doherty and J. L. Micsel, *Belg. Pat. 829 630*(1975) [*Chem. Abstr., 85* (1976) 160 092q].
282 G. O. P. O'Doherty and J. L. Miesel, *Jpn. Kokai 76 141 870*(1976) [*Chem. Abstr., 87* (1977) 53 304e].
283 L. G. Peterson, *Belg. Pat. 832 291*(1976) [*Chem. Abstr., 85* (1976) 172 820j].
284 Eli Lilly & Co., *Neth. Appl. 75 06 589*(1976) [*Chem. Abstr., 88* (1978) 1613f].
285 G. O. P. O'Doherty and J. L. Miesel, *Fr. Demande 2 312 495*(1976) [*Chem. Abstr., 87* (1977) 85 009d].
286 Q. F. Soper, *US Pat. 4 122 184 (1978) [Chem. Abstr., 90* (1979) 67 751x].
287 Q. F. Soper, *Ger. Offen. 1 922 572*(1969) [*Chem. Abstr., 72* (1970) 66 935b].
288 J. L. Miesel and D. I. Wickiser, *US Pat. 3 937 166*(1976) [*Chem. Abstr., 84* (1976) 150 630d].
289 G. O. P. O'Doherty, *US Pat. 4 265 901*(1981) [*Chem. Abstr., 95* (1981) 62 213s].
290 R. J. Boisvenue, *Br. UK Pat. 2 110 933*(1983) [*Chem. Abstr., 100* (1984) 152 498q].
291 G. O. P. O'Doherty, *Eur. Pat. 113 945*(1983) [*Chem. Abstr., 101* (1984) 230 522e].
292 H. R. Meyer and K. Weber, *Ger. Offen. 2 733 156*(1978) [*Chem. Abstr., 89* (1978) 61 044b].
293 Ciba-Geigy AG, *Neth. Appl. 78 03 886*(1978) [*Chem. Abstr., 90* (1979) 152 187n].
294 J. J. Gallay, M. Kuehne, A. Meyer, O. Rechsteiner and M. Schellenbaum, *Ger. Offen. 2 815 621*(1978) [*Chem. Abstr., 90* (1979) 38 919c].
295 E. S. Lazer, M. R. Matteo and G. J. Possanza, *J. Med. Chem., 30* (1987) 726.
296 E. S. Lazer, *US Pat. 4 608 381*(1985) [*Chem. Abstr., 106* (1987) 18 551x].
297 S. Okabe, T. Yamakawa, Y. Nomura, M. Hayashi and H. Matsukura, *Jpn. Kokai Tokkyo Koho 62 167 726*(1987) [*Chem. Abstr., 108* (1988) 112 449h].
298 S. Okabe, M. Sato, T. Yamakawa, Y. Nomura and M. Hayashi, *Jpn. Kokai Tokkyo Koho 62 192 366*(1987) [*Chem. Abstr., 108* (1988) 21 899p].
299 R. J. Ife, *Eur. Pat. 246 774* (1987) [*Chem. Abstr., 108* (1988) 112 458k].
300 A. Nohara and Y. Maki, *Eur. Pat. 208 452*(1987) [*Chem. Abstr., 106* (1987) 138 448r].

301 K. Hirai and T. Mizushima, *Jpn. Kokai Tokkyo Koho 62 185 078*(1987) [*Chem. Abstr., 108* (1988) 21 895j].
302 Z. Kazimierezuk, R. Stolarski, L. Dudycz and D. Shugar, *Nucleosides Nucleotides, 1* (1982) 275.
303 V. I. Troitskaya, V. I. Rudyk, E. V. Konovalov and L. M. Yagupol'skii, *Zh. Org. Khim., 10* (1974) 1524.
304 V. P. Borisenko, V. I. Gridasova, L. S. Kudinova, V. I. Rudyk and V. I. Troitskaya, *Fiziol. Akt. Veshchestva, 7* (1975) 31.
305 T. I. Cherepenko, I. R. Sapozhnikova, M. L. Pel'ts, V. I. Rudyk and V. I. Troitskaya, *Fiziol. Akt. Veshchestva, 10* (1978) 24.
306 H. Kishida and T. Yano, *Jpn. Kokai Tokkyo Koho 61 17 569*(1986) [*Chem. Abstr., 104* (1986) 186 419n].
307 C. Fauran, M. Turin, G. Raynaud and M. Sergant, *Fr. Demande 2 251 312*(1975) [*Chem. Abstr., 84* (1976) 135 655x].
308 Fisons Pest Control Ltd., *Fr. Adnn. 93 257*(1969) [*Chem. Abstr., 72* (1970) 21 691c].
309 V. I. Troitskaya and V. I. Rudyk, *Ukr. Khim. Zh., 43* (1977) 729.
310 V. I. Troitskaya, V. I. Rudyk, E. B. Lifshits and L. M. Yagupol'skii, *Zh. Org. Khim., 9* (1973) 1051.
311 L. M. Yagupol'skii, V. I. Troitskaya, B. E. Gruz and N. V. Kondratenko, *Zh. Obshch. Khim., 35* (1965) 1644.
312 L. M. Yagupol'skii and V. I. Troitskaya, *Zh. Obshch. Khim., 29* (1959) 2409.
313 V. I. Trotskaya, V. I. Rudyk, G. G. Yakobson and L. M. Yagupol'skii, *Khim. Geterotsikl Soedin., 12* (1981) 1675.
314 V. I. Troitskaya, A. I. Burmakov, L. S. Kudryavtseva and L. M. Yagupol'skii, *Ukr. Khim. Zh., 37* (1971) 808.
315 V. I. Toitskaya and L. M. Yagupol'skii, *Khim. Geterotsikl. Soedin., 2* (1974) 275.
316 K. J. Bannert and D. J. Fry, *Br. Amand. 1 121 211*(1970) [*Chem. Abstr., 76* (1972) 60 966y].
317 H. Balli and R. Maul, *Helv. Chim. Acta, 59* (1976) 148.
318 U. Pintschovius, E. Schnizel and G. Roesch, *Ger. Offen. 2 750 947*(1979) [*Chem. Abstr., 91* (1979) 92 995h].