ISATINS AS POTENTIAL BIOLOGICALLY ACTIVE AGENTS

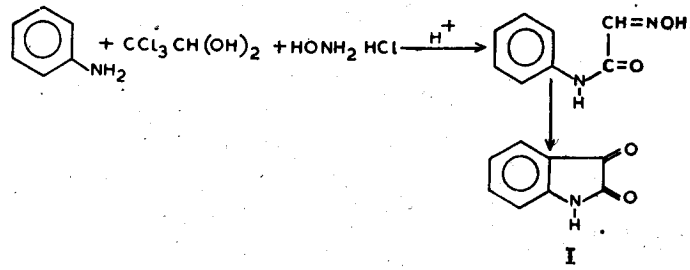
RAJENDRA S. VARMA & IFTIKHAR A. KHAN

Lucknow University, Lucknow

(*Received* 14 *April* 1977; *revised* 8 *Sept* 1977)

Various biological activities such as antiviral, antibacterial, fungicidal, antineoplastic, anti-hypotensive, analgesic, anti-inflammatory, excystment and cysticidal and others associated with isatins have been briefly discussed. Structure activity considerations have been taken into account.

Isatin (*I*) was discovered in 1941 independently by Erdmann[1] and Laurent[2] through the oxidation studies of indigo. It has been synthesised by various methods. The Sandmeyer isonitrosoacetanilide synthesis[3,4] is the most versatile amongst all.



I

Some isatin monooxime is formed during Sandmeyer synthesis presumably from isatin and some hydroxylamine liberated by hydrolysis of isonitrosoacetanilide[4].

The Sandmeyer synthesis has been applied to a variety of arylamines. Simple meta-substituted arylamines usually lead to two isomers having the expected structures *e.g.* *m*-toluidine gives both 4-methyl and 6-methyl isatins[5].

Isatins have generally been associated with antiviral activity[6]. Some isatin derivatives have also been found to exhibit antibacterial[7], anthelmintic[8] and hypotensive[9] activity. The synthesis of a large number of isatin derivatives have been described with a view to obtaining biologically potent compounds. Many such compounds have been found to be promising. A few even have clinical application also. Recently for the first time it has been found that certain isatin derivatives show cysticidal action and also cause excystment[10].

The literature abounds with various other types of biological responses associated with differentiation derivatives. The various types of biological activities shown by the isatin derivatives may be recorded as under:

ANTIVIRAL ACTIVITY

Rough estimates indicate that nearly fifty percent of the human ailments like small pox, poliomyelitis, influenza, measles etc. are caused by viruses. Besides these, the viruses are also responsible for mosaic diseases of tobacco and sandal wood in plants, and foot and mouth diseases, cowpox and rabies in animals. The structure of a virus consists of a central core of infective nucleic acid covered by a protein sheath. Viruses can only grow and exist inside a host cell. Consequently they are dependent for their growth on the enzymatic activity of the host cell. Therefore any interference with nucleic acid synthesis might help to inhibit viral synthesis, specifically without interfering with normal cell metabolism.

A number of isatin derivatives have been tested for their possible usefulness in the chemotherapy of viral infections. Isatins showing definite antiviral activity may be studied as under:

(*i*) Isatin-β-thiosemicarbazones and their derivatives.

(*ii*) Isothiosemicarbazones.

(*iii*) N-Mannich Bases.

(*iv*) Miscellaneous antiviral isatins.

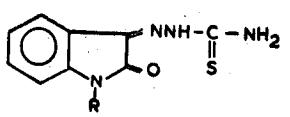
Isatin-β-thiosemicarbazones and their derivatives : The antiviral chemotherapeutic activity of isatin-β-thiosemicarbazone (II) has been reported by various workers[11–15]. It has been found effective against rabbit-pox, cowpox, alastrim and variola viruses. Bauer[13] was the first to investigate the antiviral chemotherapeutic activity of isatin-β-thiosemicarbazone(II) in mice infected intracerebrally with vaccinia-virus. It was found that mice infected with 100000 LD50 of neurovaccinia virus could be protected against death by the repeated subcutaneous administration of II in doses of 2 mg/ml. It is also known to have antiviral activity against certain other pox viruses[16, 17].

N-Methylisatin-β-thiosemicarbazone (III) which is also known as methisazone inhibited the multiplication of vaccinia[17] and small pox[18] viruses in mice and is effective in prophylaxis of small pox[19] and alastrim[20] in man as well as in the treatment of eczema vaccinatum[21] and vaccinia gangrenosa[22]. Methisazone had no apparent effect in mice that were infected intracerebrally with fifteen other viruses[17]. It is also highly active against certain types of adenoviruses[17,23]. It inhibited the multiplication of the types 3, 7, 9, 11, 14, 16, 17, 21 & 28 adenoviruses. SV[15] (a simian adenovirus) was also inhibited by methisazone[23]. A study of adenovirus type 11 under single cycle conditions showed that multiplication of virus was completely inhibited by 30 μM methisazone when addition of the compound was delayed until 13 hr after infection[23].

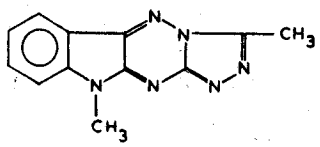
Thus the successful use of methisazone (III) in pox virus infections of man makes it reasonable to expect that this compound may find some application in prevention and treatment of adenovirus infections of man.

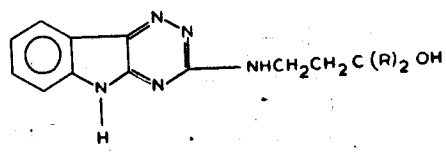
N-Ethylisatin-β-thiosemicarbazone (IV) has been reported as the most active antiviral compound, even forty percent more active than methisazone. It protected mice against a lethal neuro-vaccinia virus infection[15,17,25]. It also markedly reduced the inflammatory response in brain, elementary or inclusion bodies were not observed and antibody was not suppressed[24].

The compounds (III & IV) have also been found active against certain rhinoviruses[26]. This is an unexpected finding since the compound (II) was known only to have antiviral activity against certain pox viruses[16,17]. As a result, related heterocyclic compounds were tested, of which three (V, VI and VII), were found to have activity against rhinovirus strains used[26]. The strains used were rhinoviruses 2060, 33342, 1059 and strain H.G.P. The compounds II, III, IV and V inhibited only rhinovirus 1059 while the derivatives VI and VII were found to have activity against all the four strains of rhinoviruses used. The highest concentration for permitting normal cell maintenance was designated the well tolerated dose producing fifty percent or greater reduction in viral cytopathic effect as before[26].



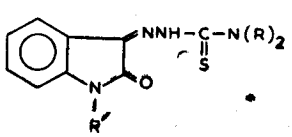
II (R=H)
III (R=Me)
IV (R=Et)





VI (R=H)
VII (R=CH_3)

The antiviral chemotherapeutic activity of isatin-β-thiosemicarbazone (II) in mice infected intracerebrally with neurovaccinia virus was investigated by Bauer[13] Bock[27] also studied the effect of the compound (II) in mice infected intr. cerebrally with vaccinia and made the additional observation that the compound had no antiviral effect in mice infected with ectromelia. In view of the close antigenic relationship between the two viruses, this finding was very surprising and cast the first doubt on the generally held view that antiviral compound would have to act by selectively affecting some host cell system which was required for the multiplication of the virus. Later on Bauer and associates[28] found that compound (II) is active also against ectromelia virus in tissue culture. Since the activity was very low and at the very limit of detectability, Bauer and Sadler [29] did certain changes in the structure of isatin-β-thiosemicarbazone (II) which resulted in a series of derivatives (VIII-XV) with high activity against ectromelia infection and with little or no effect against vaccinia[29].



VIII (R=CH_3, R′=H)
IX (R=CH_3, R′=CH_3)
X (R=CH_3, R′=C_2H_5)
XI (R=C_2H_5, R′=H)
XII (R=C_2H_5, R′=CH_3)
XIII(R=C_2H_5, R′=C_2H_5)
XIV (R=C_4H_9 R′=H).
XV (R=C_4H_9, R′=CH_3)

Thus compounds so far found to possess anti-ectromelia activity are all 4'4' -dialkyl-β-thiosemicar' bazones of isatin', *N*-methylisatin and *N*-ethylisatin[29,30]. N- methylisatin -β-4' 4'- debutyl thiosemicarbazone (XV) which is also familiar by the name of busatin, is the most active within this series of derivatives[29,30].

Busatin (XV) has also been found very much active against the polioviruses [31-33]. It blocked the polio-virus types, 1, 2, & 3 replication and viral RNA synthesis at any time in replication cycle[31]. It also directly inhibits cell- free polio RNA polymerase reaction which differentiates it from other polio inhibitors such as guanidine and 2-(α-hydroxybenzyl)—benzim

idazole. Thus busatin blocks poliovirus replication by causing a discrete lesion in viral RNA synthesis. The exact mechanism of the inhibition remains as yet unclear. The other dialkyl substituted isatin -β-thiosemicarbazones have also been found effective against poliovirus replication but most of them have been ruled out as drugs owing to their very high toxicity[30].

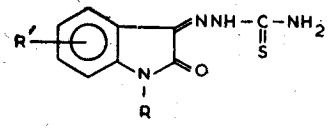
Following these reports, certain changes or modifications in the structure of (II) have been done by various workers with a view to achieve even more potent thiosemicarbazone derivatives of isatin. As a result these derivatives of isatin - β-thiosemicarbazone (XVI-XX) have been prepared and tested for their antiviral activity but none could exceed the antiviral activity shown by the methisazone (III) and busatin (XV). The 5- methoxyisatin - β thiosemicarbazone (XVI) and 6-bromoisatin - β- thiosemicarbazone (XVII) showed their antiviral activity even less than that of the compound (II)[34]. The derivatives (XVIII-XX) had antiviral activity at 20-50/μM/ml but they were toxic at all concentrations.[35]

It has also been found that *N*- methylisatin -β-4', 4 morpholino thiosemicarbazone and *N*-ethylisatin β-4', 4'- tetramethylene thiosemicarbazone are effective for viral inhibition in the early stage of granulocytemacrophage in culture.[36,37]

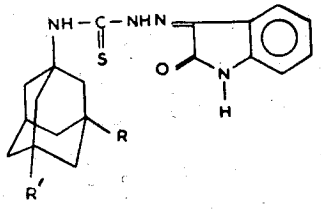
Several other variations in the structure of compound (III) have also been described. Varma and Nobles[38] have replaced *N*- methyl group in (III) with a substituted aminomethyl group to study the effect of such a group. They found that 1- piperidinomethyl- isatin - β- thiosemicarbazone was active against poliovirus, herpes simplex, measles and parainfluenza viruses.

Indole-*2*, *3*-dione-*3*-(*1*-adamantyl) -*3*- thiosemicarbazone derivatives, XXI (R = *Me*, R'=*H*) and XXIX (R = R' = *Me*) have also been found useful antagonists of herpes simplex and vaccinia viruses[39].

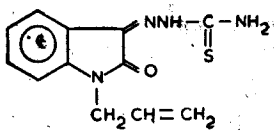
Bauer and associates[40] have also found that when some of the isatin- β-thiosemicarbazones (II,III,IV and XXIII) are heated with sodium or potassium hydroxide, they give water soluble salts of isatic acids (XXIV —XXVII) which have been found effective against various infections caused by small pox. eczema vaccinatum, vaccinia gangrenosa, herpes zoster, keratitis and conjunctivitis viruses[40].



XVI (R=H, R'=5-MeO)
XVII (R=H, R'=6-Br)
XVIII (R=isonicotinoyl, R'=H)
XIX (R=H, R'=5-Br)
XX (R=H, R'=5-HO_2C)

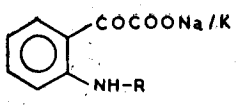


XXI (R=Me, R'=H)
XXII (R=R'=Me)

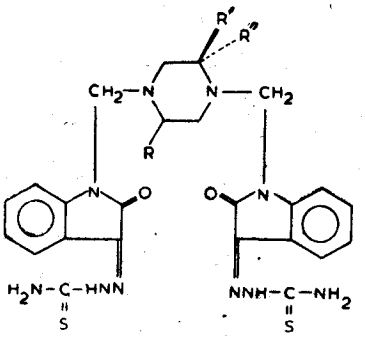


XXIII

Recently a few thiosemicarbazone derivatives have been prepared after certain unique variations in the basic structure of (II) and have been reported for their activity against the infection caused by the vaccinia viruses [41-43]. These thiosemicarbazone derivatives (XXVIII-XXX) inhibited the virus multiplication and thus showed their therapeutic importance. The compound (XXVIII) has been found most effective in inhibiting vaccinia virus [41-43].



XXIV (R=*H*)
XXV (R=*Me*)
XXVI (R= *Et*)
XXVII (R=$CH_2CH=CH_2$)



XXVIII (R=*Me*, R'=R''=*H*)
XXIX (R=*Me*, R'=*Me*, R''=*H*)
XXX (R=*Me*, R'=H, R''=*Me*)

The study of structure- activity- relations of isatin -β- thiosemicarbazone derivatives may be summed up briefly as follows :

The substitution at position-1 in the structure II(*R-H*) by *Cl, F, Br* and *I*, atoms resulted in diminished activity[25] of the compound. The substitution by ethyl group at position-1 in (II) has been reported responsible for the highest antiviral activity[25]. The activity has been shown to be reduced to one half by the removal of 1-methyl group and reduced still further by the substitution[25] at the position-5. The antiviral activity in the order of amyl < Pr< -CH_2 OH < iso-pr < Ac < Me < 2-hydroxyethyl < Et- substituent at position-1 has been reported by Sadler[25]. Introduction of substituents into (II) at positions 2 or 4 and replacement of S by O atom virtually abolished the original activity against vaccinia virus[23,24] and substituents at positions 4 & 7 have diminished the activity lest[44]. Substitution at positions 5 & 6 in (II) as in XVI (R = *H*, & R' = *5 — OMe*) and XVII (R=*H*, R^1=*6-Br*) also decreased the virustatic activity[34]. The cyanamethyl or carboxymethyl function at position-1 also abolished all the activity[44]. Thus the original activity abolished by the replacement of S by O-atom indicates that=*NNHC(S)-NH_2* grouping is essential for the antiviral activity and substitution of *H*-atom at position -1 by methyl or ethyl groups results in the enhancement of activity but activity seems to be decreased in the presence of the large sized or any other function at position-1.

The addition of dialkyl group to the terminal *N*-atom of isatin -β- thiosemicarbazone in the thiosemicarbazide moiety confers a wide antiviral spectrum, embracing both DNA and RNA -containing animal viruses[29-31]. The basis for the extended range of activity appears to be the dialkyl-substituted compounds which inhibit both cellular and viral DNA synthesis as well as viral RNA dependent synthesis.

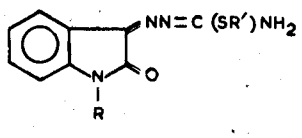
The exact mechanism of action of the viral inhibition by these thiosemicarbazone derivatives of isatin remains as yet unclear. It is understood that they interfere with viral multiplication by blocking the viral RNA or DNA synthesis.

I sothiosemicarbazones : Recently some isothiosemicarbazone derivatives of isatin (XXXI-XXXIII) have been reported as antiviral agents[34, 35].

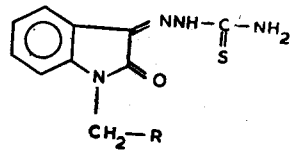
The *1*-ethylisatin-*S*-ethyliso-thiosemicarbazone derivative (XXXIV) has been found effective in mengo virus inhibition[46]. It is all due to the suppression of the viral replication[46]. The *1*-ethylisatin-*S*-*n*-butylisothiosemicarbazone (XXXV) and *1*-ethylisatin-*S*-benzylisothiosemicarbazone (XXXVI) at 15 μM/ml dose caused 99 % plaque reduction in mengo-virus infected FL-cells[47].

The virustatic activity of a series of isatin-β-isothio-semicarbazones (XXXIII-XXXVI) has been found to be more strongly influenced by the substitutions in position R than in position *R'*[48]. Substitution at the position-*1*-of isatin residue by ethyl group resulted in maximum antiviral activity[46]. The same results were obtained by ethyl, *n*-propyl or *n*-butyl-substituents at 'S' atom[46] in isothiosemicarbazones (XXXIII-XXXVI).

N-Mannich Bases: *N*-Mannich bases of isatins have also been reported to exhibit a wide range of antiviral activity. Many *N*-Mannich bases have been formed in combination with the thiosemicarbazones which have been found active against viruses. *N*-Mannich bases (XXXVII, R=dibenzylamino), XXXVIII (R=*N*-methyl-*N*-benzylamino), XXXIX (R=hexamethyleneimino) and XL (R=octahydrazocino) of isatin-β-thiosemicarbazone (II) have been reported as potential antiviral agents by Arya[49]. They have also been found water soluble and least toxic.



XXXI (R=*H*, R'=*Pr*)
XXXII (R=*Me*, *R'*=*Et*)
XXXIII (R=*Et*, *R'*=CH_2-*Ph*)
XXXIV (R=*Et*, *R'*=*Et*)
XXXV (R=*Et*, *R'*=*butyl*)
XXXVI (R=*Et*, *R'*=*benzyl*)



XXXVII (*R=dibenzylamino*)
XXXVIII (*R=N-methyl-N-benzylamino*)
XXXIX (*R=hexamethyleneimino*)
XL (*R=octahydroazocino*)

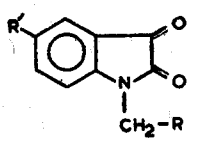
Varma and Nobles[38] replaced *N*-methyl group with a substituted aminomethyl group in isatin (I) and thus obtained *N*-piperidinomethylisatin (XLI) which showed greater activity against polio, herpes simplex, measle and parainfluenza viruses[38]. Various other *N*-Mannich bases (XLII-XLVII) have also been prepared[50] by Varma and Nobles and reported as antiviral agents[7,38].

Miscellaneous Antiviral Isatins : A number of different isatins and its hydrazone derivatives have also been introduced as antiviral agents.

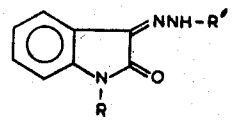
5-Nitroisatin showed its effectiveness for inhibition of vaccina virus[51], and naphthisatin formed by the ring fusion at 4, 5 or 5, 6-or 6, 7-position had also a little activity against pox virus and enterovirus infections[44].

Isatin-3-amidinohydrazone-hydrochloride and *N*-methylmorpholinoisatin-3-(anthraniloyl) hydrazone have been reported to inhibit polio virus type I growth by 88-99 % *in vitro* without being toxic to KD host cells during 24 hr[52]. Replacement of *N*-atom of isatin by *S*-atom enhanced the antiviral activity to some extent.

Following these reports Kontz[53], [54] prepared many hydrazone derivatives and studied them for their antiviral activity. Some of these derivatives (XLVIII-LI) have been found responsible for their antiviral activity[54].



XLI (*R'=H, R=piperidino*)
XLII (*R'=H, R=4-methylpiperidino*)
XLIII (*R'=H, R=2, 6-dimethylmorpholino*)
XLIV (*R'=Br, R'=-NMe₂*)
XLV (*R'=Br, R=morpholino*)
XLVI (*R'=Br, R=hexamethyleneimino*)
XLVII (*R'=Br, R'= 3-azabicyclo (3.2.2) nonano*)



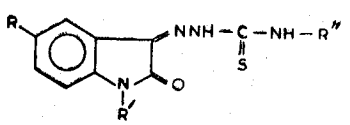
XLVIII (*R=cetyl, R'=isonicotinoyl*)
XLIX (*R=cetyl, R'=sulfanilyl*)
L (*R=cetyl, R'=H_2NCS*)
LI (*R=alkyl, R'=$NCCH_2CO$*)

Thus a number of isatin derivatives have been found to be very much useful against the infections caused by a wide range of viruses. A few have shown promising results and also have undergone extensive clinical trials.

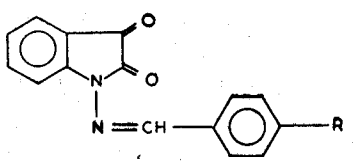
ANTIBACTERIAL ACTIVITY

Isatin itself is inhibitory to growth of Tubercle bacillus[55]. Isatin-β-thiosemicarbazone (II) has been described as antibacterial by various workers. This compound (II) has also been found effective against Tubercle bacillus to some extent[56–58].

The other many isatin-β-thiosemicarbazone derivatives (LII, R=*H*, Me, *Br*; R'=*H*, piperidinomethyl, morpholinomethyl and R''=cyclohexyl, naphthyl, NH_2) have been prepared with a view to getting more potent antibacterial agents[59]. Out of these LII (R=*H*, R'=piperidinomethyl and R''=cyclohexyl) showed greater antibacterial activity against *Staphylococcus aureus* at 10μ g/ml concentration[59].



LII (*R=H, R'=Piperidinomethyl & R''=cyclohexyl*)



LIII (*R=Cl or OMe*)

Some other isatin derivatives (LIII) have also been found to exhibit antibiotic activity[60].

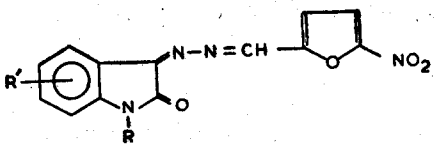
The inhibition of the bacterial growth by 1-isatinylmethyl-phenoxymethyl penicillate has also been established[61].

Antibacterial activity of a few 5-nitrofurfurylideneisatin-β-hydrazone derivatives (LIV-LVII) has been reported by Johnston and Kidd[62]. They found that *N*-ethylisatin derivative (LVII) to be the most promising of the compounds studied by them.

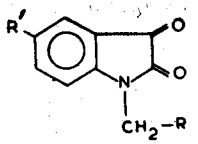
Padhya *et. al.*[63] studied the effect of alkyl and halogen substituents in the isatin moiety on the antibacterial properties of 5-nitrofurfurylideneisatin-β-hydrazone (LIV). Thus ten 5-nitrofurfurylideneisatin-β-hydrazones (LIV, LV, LVI and LVIII to LXIV) have been prepared and studied for their antibacterial properties. Out of these 5-nitrofurfurylidene-(5-bromoisatin)-β-hydrazone (LXIV) has been found to be the most active followed by the 6-chloro derivative LIX[63].

No significant change is noticed in the antibacterial properties of the parent azines by introducing *Cl* or CH_3 in the isatin moiety. The *N*-hydroxymethylation expected to confer some water solubility on the compounds (otherwise sparingly soluble in water) and thereby increase the potency of the compounds, actually brought about a reduction in the antibacterial potency of the compounds[63].

Recently *M*-Mannich bases (XLV, XLVII, LXV) have also been reported as antibacterial agents by Varma and Nobles[7].



LIV ($R'=R'=H$)
LV ($R'=CH_3, R'=H$)
LVI ($R=CH_2CH, R'=H$)
LVII ($R=Et, R'=H$)
LVIII ($R=H, R'=5\text{-}Cl$)
LIX ($R=H, R'=6\text{-}Cl$)
LX ($R=H, R'=7\text{-}Cl$)
LXI ($R=H, R'=5\text{-}CH_3$)
LXII ($R=H, R'=7\text{-}CH_3$)
LXIII ($R=CH_2OH, R'=7\text{-}Cl$)
LXIV ($R=H, R'=5\text{-}Br$)

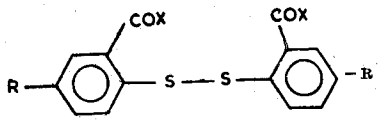


LXV ($R^4=H$, $R=$*4-(3-phenyl propyl) piperidine*

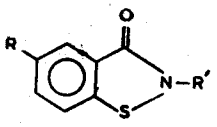
Thus a number of different isatin derivatives have also been reported to exhibit the antibacterial action against a number of pathogenic bacteria which cause many serious diseases like tuberculosis, typhoid, pneumonia etc. in humans.

FUNGICIDAL ACTIVITY

Bis-(2-carboxyphenyl)-disulphide derivatives (LXVI-LXXI) have been prepared from substituted isatins after various steps. Each such derivative after treatment with chlorine gas and ammonia gas in respective manner gave benzisothia-zolinone derivatives (LXXII-LXXXIV). All these derivatives (LXVI—LXXXIV) thus prepared, were tested for their antifungal activity. They have been found effective against *Candida albicans, C. tropicalis, Saccharomyces cervisiae* and *Trichophyton mentagrophytes*[64].



LXVI (X=*Cl*, R=*n*-butyl)
LXVII (X=*Cl*, R=*sec*-butyl)
LXVIII (X=*Cl*, R=*tert*-butyl)
LXIX (X=NH_2, R=*sec*-butyl)
LXX (X=NH_2, R=*tert*-butyl)
LXXI (X=BuNH, R=*tert*-butyl)

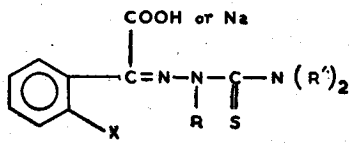


LXXII ($R=sec\text{-}Bu, R'=H$)
LXXIII ($R=tert\text{-}Bu, R'=H$)
LXXIV ($R=Bu, R'=Bu$)
LXXV ($R=sec\text{-}Bu, R'=Bu$)
LXXVI ($R=tert\text{-}Bu, R\|=Bu$)
LXXVII ($R=Bu, R'=Me$)
LXXVIII ($R=Bu, R'=Et$)
LXXIX ($R=Bu, R'=Pr$)
LXXX ($R=Bu, R'=amyl$)
LXXXI ($R=Bu, R'=hexyl$)
LXXXII ($R=Bu, R'=heptyl$)
LXXXIII ($R=Bu, R'=isopr$)
LXXXIV ($R=Bu, R'=isoamyl$)

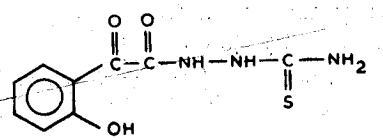
The antifungal activity of sulfenylindole derivative prepared from isatin or its sodium or potassium salt and trichloro-sulfenyl chloride has been reported by Claude[65] and also by Chimetron[66].

N-(1-Isatinylmethylphthalimide) derivative of isatin prepared by treating 1-chloromethylisatin with phthalimide has also been reported to possess antifungal activity[67].

Another series of compounds (LXXXV-LXXXVIII) synthesised from isatin-β-thiosemicarbazones have shown fungistatic behaviour against most of the species of *Trichophyton* and also against *M. lapnosum* and *Candida albicans*[68]. Amongst these (LXXXVI- LXXXVII and LXXXVIII) were found effective against one or more of the above molds[65].



LXXXV ($X=NH_2$, $R'=Me$, $R=H$)
LXXXVI ($X=NO_2$, $R'=H$, $R=Me$)
LXXXVII ($X=OH$, $R=R'=H$)



LXXXVIII

Recently Maksudov[69] reported isatin (I), 5-methylisatin and isonitrosoaceto-*p*-chloroaniline as highly effective fungicides. These isatins have been reported to have their ability to inhibit *V. dahliae* growth *in vitro* to the same extent as B. M. K.[69].

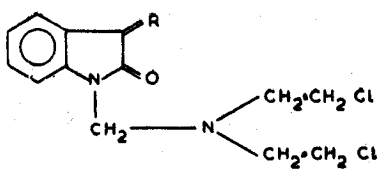
ANTINEOPLASTIC ACTIVITY

In search of chemotherapeutic agents for selectively interfering with the growth of neoplastic cells as compared to the normal cells, the idea of incorporating alkylating function into a derivative of indole has attractive implications[70,71]. It was concluded by Undenfriend and coworkers that the carcinoid tumour is parasitic on the tryptophan stores of the patients and as a result of this,less of aminoacid may be available for the formation of metabolites.[72]

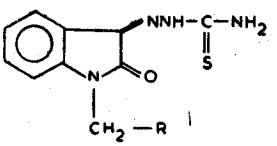
It is therefore strongly suggested that tryptophan pyrrolase or one or of the other enzymes associated with tryptophan (or indole) metabolism may be available to deoxify an indole *N*-mustard in normal cells while the toxic properties of the *N*-mustard remain substantially undiminished in tumour system. On the basis of this hypotheses Mannich-base nitrogen mustards (LXXXIX—XC) of isatin have been prepared and tested. They showed antineoplastic activity to some extent.[70,71]

Some isatin-β-thiosemicarbazone derivatives (XCI—XCIV) of isatin have also been found to exhibit antitumour activity[73].

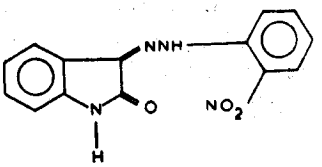
A series of 3 orthonitrophenylhydrazone derivatives (XCV) of isatin have also been synthesised and tested for their antineoplastic activity. Amongst these only one derivative (XCV) showed the highest activity[74] again t Walker carcinosarcoma-256.[74]



LXXXIX ($R=O$)
XC ($R=NNH-CNH_2$ ‖ S)



XCI $R=p$-ClC_6H_4NH)
XCII ($R=NHPh$)
XCIII ($R=p$-FC_6H_4NH)
XCIV ($R=3,4,Cl_2C_6H_3NH$)



XCV

ANTIHYPOTENSIVE ACTIVITY

Many derivatives of isatin were prepared and tested for their hypotensive activity. LIII (R=*Cl,OMe*) have been found to possess hypotensive activity[60].

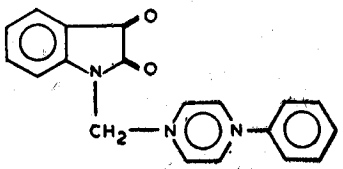
A number of *N*-substituted isatins have also been prepared and tested. One of these XCVI lowered the blood pressure in anaesthesised rats and thus may be useful as a hypotensive agent[9].

ANALGESIC ACTIVITY

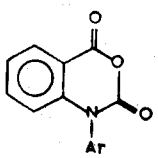
N-Arylisatoic anhydrides (XCVII—CII) prepared from the corresponding *N*-arylisatins have been found to possess the analgesic property[75].

The isatin-β-thiosemicarbazone derivatives (XCI-XCIV) described earlier as antitumour agents have also shown analgesic activity[73].

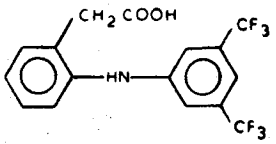
A highly substituted isatin, i.e., 1-(*aaa*, *a'* *a'* *a'* -hexafluora)-3,5-xylindole-2, 3-dione has been reacted with hydrazine hydrate and sodium ethoxide in ethanol to give [*C*—(*aaa*, *a'a'a'*—hexafluoro-3, 5-xylidinophenyl)-acetic acid (CIII) which together with its salts showed analgesic behaviour[76].



XCVI.



XCVII (*Ar*=2, 3-dimethylphenyl)
XCVIII (*Ar*=2, 3-dichlorophenyl)
XCIX (*Ar*=2, 6-dimethyl-3-ethylphenyl)
C (*Ar*=2, 6-dichloro-3-methylphenyl)
CI (*Ar*=2, 6-dichloro-3-methoxyphenyl)
CII (*Ar*-3-trifluoromethylphenyl).



CIII.

Recently 5-bromoisatin has been found as a good analgesic and sedative agent, even stronger than aspirin[77]. It also showed the potentiation of barbiturate-narcosis[77]. It has no side effects associated with aspirin e.g.it never lengthened the blood clotting time which has generally been the case with the analgesic agents such as aspirin[77].

ANTIINFLAMMATORY ACTIVITY

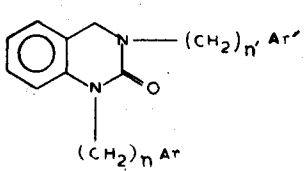
N-Arylisatoic anhydride derivatives (XCVII—CII) have also been tested for their antiinflammatory activity and found to be so[75]. The isatin amide derivatives LIII (R=*Cl*) and (R=*OMe*) also showed their antiinflammatory behaviours[60].

Another compound (CIII) with its salts, derived from isatin showed a high degree of antiinflammatory activity[76].

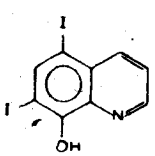
Some other antiinflammatory agents, e.g., aryl and aralkyl 3, 4-dihydro-2 (IH)-quinazolinones (CIV) have been derived from *N*-phenylisatin[78].

EXCYSTMENT AND CYSTICIDAL ACTIVITY

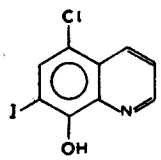
Generally relapses have been encountered in the treated cases of chronic amoebiasis. This ha' been attributed to the fact that the drugs discovered so far have little or no effect on the cystic stage of amoeba. Quinolines (e.g., CV and CVI) show amoebicidal action but have little or no effect on the cystic stage of amoeba.



CIV.



CV.



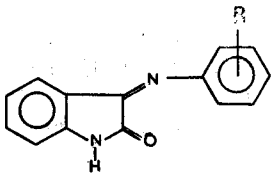
CVI.

The structural similarity between quinoline and isatin (*I*) led us to examine certain isatin derivatives (CVII and CIX) for their cysticidal activity.

Thus for the first time it has been observed by us that certain isatin derivatives do show cysticidal activity and also cause excystment[10]. It is also interesting to note that certain such compounds have shown cysticidal activity and also caused excystment simultaneously. This type of behaviours in a single substance has perhaps not been reported earlier.

These results encouraged us to synthesise other isatin analogs. We have recently reported some isatin-3-arylimino-2-indolinones (CVIII) and their *N*-morpholino/piperidinomethyl analogs (CX) which have been tested for cysticidal and excystment activity[79].

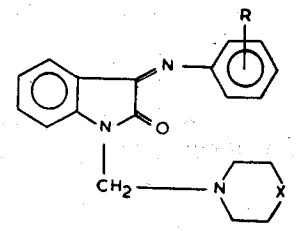
The isatin analogs (CVII & CVIII) showed their cysticidal effect to some extent and also caused excystment. The compounds (CVIII & CX) have caused a very high percentage of excystment. Compounds (CVIII & CX) have also been tested for their cysticidal action in conjunction with emetine (1 : 4000). Amongst these only *N*-Mannich bases (CX) showed a high percentage of cysticidal action which indicates that morpholino/piperidinomethyl moiety is essential for the cysticidal activity. The presence of 3-methoxy-carbonyl and 3-ethoxycarbonyl groups in 3-arylimino moiety enhance the percentage of excystment. The cysticidal activity shown by (CX) in conjunction with emetine, may be explained on the basis that these isatin derivatives render the cyst wall permeable to emetine which then kills the cysts inside. The cysts from a pure line culture of *Schizopyrenus russelli* have been used in this work.



CVII (*R*=*H*, 4-*Br*, 4-CH_3, 4-*Cl*, OCH_3 4-*Ph* & 3-*Cl*)

CVIII (*R*=4-CO_2Me, 4-CO_2Et, 4-CO_2Pr, 3-CO_2Me, 3-CO_2Et).

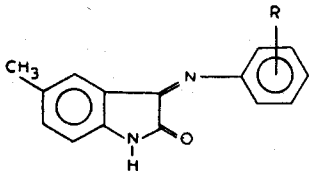
Fig. —



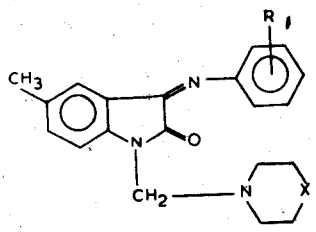
CIX (*R*=*H*, 4-*Br*, 4-CH_3, 4-*Cl*, 4-OCH_3, 4-*Ph*, 3-*Cl* & *X*=CH_2 /*O*)

CX (*R*=4-CO_2Me, 4-CO_2Et, 4-CO_2Pr, 3-CO_2Me, 3-CO_2Et & *X*=CH_2/*O*).

Varma and Khan[80] further synthesised another series of 3-arylimino-2-indolinones (CXI) and their *N*-morpholino/piperidinomethyl analogs (CXII) with a view to study the effect of methyl group in isatin at position-5 on the excystment and cysticidal activity. Most of these compounds have shown the excystment activity but could not exceed the activity shown by CVII—CX.



CXI (*R*=*H*, 4-*Br*, 4-*I*, 4-*Cl*, 4-CH_3, 4-*F*, 4-*Ph*, 2-*Cl*, 3-*Cl*, 4-OCH_3 & 2-*Ph*.).



CXII (*R*=*H*, 4-*Br*, 4-*I*, 4-*Cl*, 4-CH_3, 4-*F*, 4-*Ph*, 2-*Cl*, 3-*Cl*, 4-OCH_3, & 2-*Ph*, *X*=CH_2 or *O*).

The replacement of *H* at *N*-atom of isatin by methyl group did not cause any enhancement in activity. A methyl group at position-5 also did not cause any remarkable increase in activity. The *N*-morpholino/piperidino methyl grouping seems to be responsible for the cysticidal action.

Thus isatin derivatives may be useful also to develop new drugs that will effectively control the amoebiasis in the cystic stage. These drugs may also cause excystment to some extent on the present showing. This would enable the medical profession to deal with the excysted cysts with the aid of other agents.

OTHER BIOLOGICAL RESPONSES

Besides the above described biological activities shown by the isatin derivatives, various other derivatives of isatins have also been found responsible for other types of biological responses. These are described herein,

Anthelmintic Activity

5-Nitroisatin has been reported to exhibit anthelmintic activity[8]. It acted against *Hymenolepis nana* deparasitizing them in the infected mice. Another isatin derivative, *N*-(1-isatinmethyl)-saccharin prepared in 77—96% yield from 1-chloromethylisatin and sacharin, has also been described as an anthelmintic agent[67].

Herbicidal Activity

Isatin (*1*) has also been patented as a selective herbicide, both for pre-and post-emergence for the dicotylednou plants[81]. It is apparently without deleterious effects on grasses. Alkyl and halogen-substituted isatins are especially effective, 5, 7-dichloroi atin , 4-chloroisatin, 6-chloroisatin and 5-bromoisatin are well known selective herbicides for killing the dicotylednous plants[81].

The complex amide derivatives LIII (R=*Cl*, *OMe*) have also been described to inhibit the germination of seeds[60]. Thus the e derivatives may al o help in the protection of the crop to some extent.

Pesticidal Activity

N-Trichlorosulfenylmethyl derivative of isatin has also been found to have a broad spectrum of pesticidal activity[82].

Thus the literature abounds with the description of the various biological responses of variously substituted isatins. Besides these responses which have already been described above, isatin alters blood sugar levels in mice[84], prolongs the effect of hexabarbiturate narcosis[84] and protects the animals against electrically and chemically elicited convulsions[85]. It also inhibits monoamine oxidase[84] which may be the biochemical basis for several of the physiological effects discussed in this article.

REFERENCES

1. ERDMANN, *J. prakt. Chem.*, **24** (1841), 1.
2. LAURENT, *J. prakt. Chem.*, **25** (1842), 430.
3. SANDMEYER *Helv. Chim. Acta.*, **3** (1919), 234.
4. MARVEL, C.E.S. & HIERS, G.S., *Org. Synth.* Col. **1** (1941), 321.
5. MAYER, F. & SCHULZE, R., *Ber.*, **58** (1925), 1465.
6. OSDENE, T.S. in "Medicinal Chemistry" 3rd Ed., Edited by A. Burger, (Wiley Interscience, New York, 1970, 662.
7. VARMA, R.S., & NOBLES, W.L., *J. Pharm. Sci.*, **64** (1975), 881.
8. CAVIER, R., ROYER, R., RIPS, R., & RENE, L. *Chim. Ther.*, **4** (1969), 21., *Chem. Abstr.*, **70** (1969), 113686.
9. WYETH, JOHN & BROTHER Ltd., Brit. Pat. 1,240,648 (1971); *Chem. Abstr.*, **75** (1971), 118342.
10. IMAM, S.A. & VARMA, R.S., *Experientia*, **31** (1975), 1287.
11. HOLZBECHER, *Z., Chem. Listy*, **44** (1950), 126; *Chem. Abstr.*, **45** (1951), 8005.
12. THOMPSON, R.L., DAVIS, J., RUSSEL, P.B. & HICHINGS, G.H., *Proc. Soc. Exptl. Biol., Med.*, **84** (1953), 496.
13. BAUER, D.J., *Brit. J. Exptl. Pathol.*, **36** (1955), 105; *Chem. Abstr.*, **49** (1955), 11869.
14. BACH, M.K. & MAGEE, W.E., *Proc. Soc. Exptl. Biol. Med.*, **110** (1962), 565.
15. SADLER, P.W., *Ann. N.Y. Acad. Sci.*, **130** (1965), 71; *Chem Abstr., 63* (1965), 18908.
16. THOMPSON, R.L., MINTONJUN, S.A. & OFFICER, J.E., *J. Immunol*, **70** (1953), 229.
17. BAUER, D.J. & SADLER, P.W., *Brit. J. Pharmacol.*, **15** (1960), 101.
18. PRUSOFF, W.H., *Pharmacol. Rev.*, **19** (1967), 209.
19. BAUER, D.J., ST. VINCENT, L.S., KEMPE, C.H. & BOWNIE, A.W., *Lancet*, **2** (1963), 494.
20. RIBELRO DO VALLE, L.A., *Lancet*, **2** (1965), 976.
21. ADELS, B.R. & OPPE, T.E., *Lancet*, **1** (1966) 18.
22. BAUER, D.J., *Ann. N.Y. Acad. Sci.*, **130** (1965), 110.

23. BAUER, D.J., APOSTOLOV, K., *Science*, **154** (1966), 796.

24. LIEBERMANN, M. & POLLIKOFF, R., *Proc. Soc. Exptl. Biol. Med.*, **122** (1966), 484.

25. SADLER, p.W., Drug parasites Hosts. Symp. Midleson Hosp. Medical School (1962), 286; *Chem. Abstr.*, **61** (1964) 6090.

26. GLADYCH, J.M.Z. & HUNT. J.H., *Nature*, **221** (1969), 286.

27. BOCK, M.Z., *Hyg.*, **143** (1957), 480.

28. SHEFFIELD, F.W., BAUER, D.J. & STEPHENSON, S.M., *Brit. J. Exptl. Pathol.*, **41** (1960), 638.

29. BAUER, D.J. & SADLER, P.W., *Nature*, **190** (1961), 1167.

30. ROBERT, W., SIDEWELL, G. & DIXON, J., *Appl. Microbiol.*, **16** (1968), 370; *Chem. Abstr.*, **64** (1966), 20416.

31. PEARSON, G.D. & ZIMMERMAN ,E.F., *Virology*, **38**, (1969), 641; *Chem. Abstr.*, **71** (1969), 58123.

32. PEARSON, G.D. & ZIMMERMAN ,E.F., *Biochim. Biophys. Acta*, **195** (1969), 246; *Chem. Abstr.*, **72** (1970), 40097.

33. BAUER, D.J., *Brit. J. Exptl. Pathol.*, **44** (1963), 233; *Chem. Abstr.*, **59** (1963), 15814.

34. FRANKS, R., *Acta. Biol. Med. Ger.*, **30** (1973), 467; *Chem. Abstr.* **80** (1974), 10265.

35. ALEXANDRESCU, M., MURGESCU, C., HANDRACHE, L., IONESCU, L., & DUCA, M., *Stud. Cerect. Inframicrobiol.*, **20**, (1969), 263; *Chem. Abstr.*, **72** (1970), 98804.

36. HEINSCH, L., KRAMAR, C., K., *J. Prakt. Chem;* **314** (1972), 682; *Chem. Abstr.*, **78** (1973), 71832.

37. MCNEILL, T.A., *Antimicrob. Agts. Chemother.*, **4** (1973), 105; *Chm. Abstr.*, **80** (1974), 33757.

38. VARMA, R.S. & NOBLES, W.L., *J. Med. Chem.*, **10** (1967), 510.

39. SALLAY, S. & CHILDRESS, S.J., *U.S. Pat.*, 3,406,180 (1968); *Chem. Abstr.*, **70** (1969), 11223.

40. BAUER, D.J. & EVERETTE, A.J., *Brit. Pat.*, 1,293,192 (1972); *Chem. Abstr.*, **78** (1973), 111119.

41. ZJORN AK, N.I., MARCISZEWSKA, M., PASTUSZAK, J. & LUCKA, S.B., *Acta. Microbiol. Pol. Ser.*, **A5** (1973), 199; *Chem. Abstr.*, **81** (1974), 33165.

42. BORYSIEWICZ, J., POREBSKA, A. & POTEC, Z., *Acta. Microbiol. Pol. Ser.*, **A5** (1973), 205; *Chem. Abstr.*, **80** (1974), 128738.

43. POREBSKA, A., POTEC, Z. & BORYSIEWICZ, J., *Acta. Microbiol. Pol. Ser*, **A5** (1973), **208**; *Chem. Abstr.*, **80** (1974), 116641.

44. SADLER, P.W., SULLIVAN, D.G.O., & BAUER, D.J., *Intern. Symp. Chemotherapy* pt. 2, (1963), 403; *Chem. Abstr.*, **60** (1964), 8496.

45. HEINISCH. L., TONEW, M., & TONEW, E., *Ger Offen.*, 2,034,644 (1971); *Chem. Abstr.*, **75** (1971), 151669.

46. TONEW, M., TONEW, E., & HEINISCH, L., *Acta. Virol. (Eng. Ed.)*, **18** (1974), 17.

47. TONEW, E., LOEBER, G., TONEW, M., & HEINISCH, L., *Acta. Vir.* (Eng. Ed.), **18** (1974), 185.

48. FRANKE, R., LABES, D., TONEW, M. & ZSCHIESCHE, W., *Acta. Biol. Med. Ger.*, **34** (1975), 491; *Chem. Abstr.*, **83** (1976), 91496.

49. ARYA, V.P., Ciba Ltd., *Swiss.* 491,106 (1970); *Chem. Abstr.*, **73** (1970), 109673.

50. VARMA, R.S. & NOBLES, W.L., *J. Heterocyclic Chem.*, **3** (1966), 462.

51. ALLEXANDRESCU, M.. HANDRACHE, L., MURGESCU, C. & DUCA, M.. *Rev Roum. inframicrobiol* **6** (1969), 219; *Chem Abstr.* **73** (1970), 11669.

52. MICHELE, S., MICHELE, M.& JACQUELINE, P., *Chim. Ther.*, **5** (1970), 216; *Chem. Abstr.*, **73** (1970), 95728.

53. KONTZ, F., *Sci. Pharm.*, **38** (1970), 222; *Chem. Abstr.*, **74** (1971), 99770.

54. KONTZ, F., *Sci. Pharm.*, **38** (1970), 98; *Che.n. Abstr.*, **73** (1970), 55911.

55. KOSHIMURA, S., HAMADA– A., OTAKI, T., & DEGUCHI, K., *Ann. Rept. Research Inst. Tuberc. Kanazawa. Univ.*, **12** (1954), 9; *Chem. Abstr.*, **49** (1955), 9159.

56. LIEBERMANN, D., MOYEUX, M., ROUSAIX, A., MAILLARD, J., HENGL, L. & HIMBERT, J., *Bull. Soc. Chim. France*, (1953), 957; *Chem. Abstr.*, **49** (1955), 224.

57. MITRA, G.N. & GUHA SIRCAR, S.S., *J. Ind. Chem. Soc.*, **32** (1955), 435.

58. BEHNISCH, R., MIETZSCH, F., & SCHMIDT, H. *U.S. Pat.* 2,775,593 (1956); *Chem. Abstr.*, **51** (1957), 8804.

59. CHOUGH, Y.S., KANG, K. II; *Yakhak Hoeji.*, **17** (1973), 141; *Chem. Abstr.*– **81** (1974), 151896.

60. HARMANS, L., *U.S. Pat.* 3,297,694 (1967); *Chem. Abstr.*, **66** (1967), 76020.

61. KGNTZ, F., *Sci. Pharm., 30* (1970), 227; *Chem. Abstr.*, **74** (1971), 125548.

62. JOHNSTON, R.G. & KIDD, D., *J. Chem. Soc.*, (1964), 4734.

63. PADHYA, A.C., MEHTA, H.J., DIGHE, V.S. & SOMASEKHARA, S., *Sci. Cult.* **39** (1973), 55.

64. PONCI, R., VITALI, T., MOSSINI, F., & AMORETTI., L., *Faramaco. Ed. Sci.*, 22, (1967), 999; *Chem. Abstr.*, 68 (1968), 114493

65. CLAUDE, H., *Fr.* 1,497,492 (1967)., *Chem. Abstr.*, 69 (1968), 106555.

66. CHIMETRON. S. *a.r.l. Belg.*, 696,711 (1967); *Chem. Abstr.*, 71 (1969), 101891.

67. KONTZ, F., *Sci. Pharm.*, 41 (1973), 123; *Chem. Abstr.*, 79 (1973), 92152.

68. TOMOHIN, A.B., KHARIT, Y.A. & KUTSENKO, A.K., *Khim. Farm. Zh.*, 7 (1973), 10, *Chem. Abstr.*, 79, (1973), 104894.

69. MAKSUDOV, N. KH., AVEZOV, K. & K MUKUSUMOVA, Kh. G., *Uzb. Biol. Zh.*, 19 (1975), 13; *Chem. Abstr.*, 83 (1976), 53878.

70. PETTIT, G.R. & SETTEPIN, J.A., *J. Org. Chem.*, 27 (1962), 1714.

71. ELDERFIELD, R.C. & WOOD, J.R., *J. Org. Chem.*, 27 (1962), 2463.

72. UDENFRIEND, S., WEISSBACH, H. & SJOERDSMA, A., *Science*, 123 (1956), 669.

73. *CIBA Ltd., Neth.* 6507, 422 (1965); *Chem. Abstr.*, 65 (1966), 2227.

74. POPP., F.D., *J. Med. Chem.*, 12 (1969), 182; *Chem. Abstr.*, 70 (1969), 47209.

75. SCHERRER, R.A., *U.S. Pat.* 3,238,201 (1966); *Chem. Abstr.*, 64 (1966), 17614.

76. SALLMANN, A. & PFISTER, R., *Ger. Offen*, 1,815,807 (1969); *Chem. Abstr.*, 71 (1969), 101552.

77. DEBAT, J., *Ger. Offen*, 1,935,697 (1970); *Chem. Abstr.*, 72 (1970), 125053.

78. CUSIC, J.W., COYME, W.E., *U.S. Pat.* 3,509,149 (1970); *Chem. Abstr.*, 73 (1970), 3931.

79. VARMA, R.S. & KHAN, I.A., *Polish J. Pharmacol. Pharm.* 29 (1977) , 549.

80. VARMA, R.S. & KHAN, I.A., *Indian J. Med. Res.* 67 (1978), 315.

81. HAMBSCH, E., *German Pat*, 1013,459 (1957); *Chem. Abstr.*, 54 (1960), 16733.

82. ARIES, R., *Fr.* 1,492,948 (1967), *Chem. Abstr.* 69, (1968) 59240.

83. GAEDE, K. & GRETA, K.F.G., *Klin. Wochscher.*, 26 (1948), 720; *Chem. Abstr.*, 44 (1950), 8542.

84. MUELLER, M., *Med. Exptl.*, 7 (1962), 155; *Chem. Abstr.*, 58 (1963), 7262.

85. SAREEN, K.N., KOHLI, R.P., AMMA, M.K.P. & GUJRAL, M.L., *Ind. J. Physiol. Pharmacol.*, 6 (1962), 87.

78-M/S99—425—21-12-78—GIPS