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Review of Chemical, Pharmacological, Biological Activities of Isatin and its Derivatives – Part-1 (1877 to 2002)

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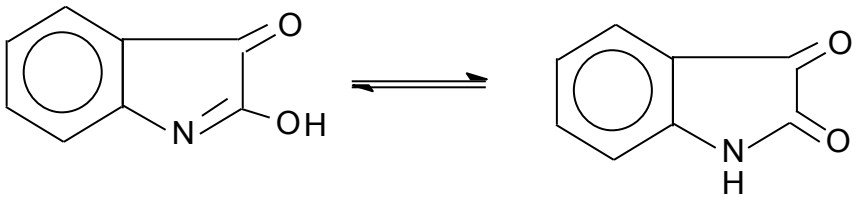
Abstract:*Isatin is a naturally occurring substance present in humans, animals, plants and coal tar. Isatin itself exhibits a variety of biological effects (invivo and invitro) and substituted isatins are reported to possess a wide range of pharmacological properties such as antimicrobial, antineoplastic, analgesic, anti-inflammatory, antipyretic, enzyme activity, CNS activity, antiprotozoal, antihelminthic and association with biomolecules. In this review article, we have attempted to compile the most signigicant reports (1877 to 2002) of biological and pharmacological activites of isatin and its derivatives.*

Keywords*: isatin, hydrazones, schiff base, mannich base*

I. Introduction

Isatin was discovered in 1841[1] independently by Erdmann and Laurent through oxidation studies on indigo and Kekule[2] proposed the lactam structure. Further Bayer[2] in 1869 established an empirical relationship between isatin - dioxindole, oxindole and indole as a result of various degradation reactions. The structure of isatin has been the subject of numerous investigations and considerable controversy since Bayer's realization in 1882 that isatin, in its reactions behaves both as a lactim and a lactam (**1**) (tautomerism). Isatin has the credit of being one of the first organic compound synthesized[3] and characterized as a derivative of indigo.



(1)

Even though isatin was discovered in 1841, isatin was only identified in human and rat tissue in 1988[4] by direct probe insertion mass spectrometry in an attempt to identify the endogenous non-peptide monoamine oxidase (MAO) inhibitor which was previously detected and called "Tribulin". Isatin was also reported in humans as a metabolic derivative of adrenaline[5,6]. Subsequently, a GC-MS method[7] was developed for its quantitative assay in human urine, rat brain and liver using 5-methyl isatin as an internal standard. Isatin was also reported to be quantified by HPLC (2 to 20 nMoles/ml) and capillary chromatography[8,9]. Isatin has been found in the secretion from the parotid gland of Bufo frogs[10]. Isatin is

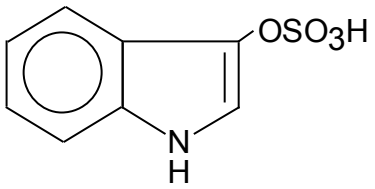
also found in many plants such as genus Isatis[11], *Calanthe discolour* Lindl[12] and *Couroupita guiane*[13]. Substituted isatins (melosatin alkaloids) is found in plants such as *Melochia tomentosa*[14-16]. Isatin compounds are also isolated in fungi: 6-(3'-Methylbuten2'-yl)isatin from *Streptomyces albus*[17-18] and 5- (3'-methylbuten-2'-yl)isatin from *Chaetomium globosum*[19]. Isatin has also been found in coal tar[20].

Tissue Distribution

Isatin[21] was reported as a major component of the endogenous MAO inhibitory activity of tribulin in many tissues and its concentration found to increase in certain circumstances associated with stress and anxiety.

Isatin has the distinct tissue distribution[21] in both rat tissues and different regions of rat brain (table 1). High concentrations have been found in the vas deferens and seminal vesicles for which reasons are yet to be established. The distinct tissue distribution does not seem to parallel any other biochemical system. The discontinuous distribution in the brain also suggests a possible function i.e. high level of isatin in hippocampus conceivably support link between isatin and anxiety. The concentrations present in certain brain regions and tissues are quite high, more comparable to monoamines such as 5-hydroxy tryptamine. Isatin level in CSF was reported to be elevated in bulimia nervosa[22].

Almost nothing is known about the biosynthetic or degradation pathways[23] of isatin. Because of the similarity of its structure with indican (indoxyl sulfate **2**), it is possible that a part of it is biosynthesized from the action of gut flora. The possibility that a part of the isatin may be derived from the action of gut flora was reported. There was a clear reduction of urinary isatin concentration in rats exposed to germ free environment[24].



(2)

Phamacological and Biological Properties of Isatin

Isatin exhibits several *invitro* and *invivo* activities (table 2 and 3). The relationship[96,97] between isatin, stress and water balance was studied since isatin interacts with atrial natriuretic peptide and arginine vasopressin which in turn are responsible for anxiolytic and anxiogenic states of the biological system.

Stress induced increase in urinary isatin[98] excretion in rats and reversal by dexamethasone and α-methyl p-tyrosine was studied. The stress applied was acute food deprivation and acute cold exposure. Both types of stress induced a marked increase in urinary isatin excretion during 24 hours. The administration of dexamethasone prevented the increase in urinary Isatin excretion induced by both stress stimuli. Administration of diazepam (benzodiazepine receptor agonist) or L-methyl-p-tyrosine (tyrosine hydroxylase inhibitor) prevented the increase of urinary isatin induced by acute food deprivation whereas diethyldithio-carbamate (dopamine-β-hydroxylase inhibitor) was ineffective.

The effect of various serotonergic compounds in anxiety and increase in the concentration of isatin[99] in rat urine was studied. m-Chlorophenyl-piperazine ($5HT_{1A/1B/2A/2C}$ receptor agonist) and (+/-)-1-(4-iodo-2,5-dimethoxy-phenyl)-2-amino- propane hydrochloride ($5HT_{2A/2C}$ agonist) which have anxiogenic properties induced a marked increase in 24 hours urinary isatin excretion. 1-(m-Chlorophenyl)-biguanide ($5HT_3$ agonist) and 2 methyl-5HT ($5HT_{3,4}$ agonist) did not affect isatin concentration.

Isatin was reported as a developing agent for the detection of imino acids by paper chromatography[100], determination of proline[101,102], fluorescent agent for eosinophil leukocyte granules[103], serum proline in hyperprotinemia patients[104], detection of 3,4- dehydroproline[105], developing agent in TLC

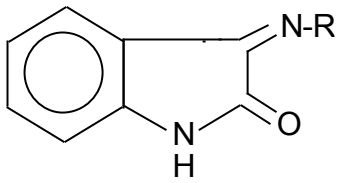
for determination of amino acids[106] in bone collagen and sketal remains. Isatin[107] was used as a marker for the measurement of estradiol and cortisone levels in material blood, foetal blood and amniotic fluid.

Chemical modifications of Isatin

The chemical modifications performed on isatin to synthesis a diverse variety of derivatives can be catagorized into 4 major types which are substitution at the benzene ring moiety, nitrogen heteroatom, 3rd position and co-ordination complexes of isatin and its derivations.

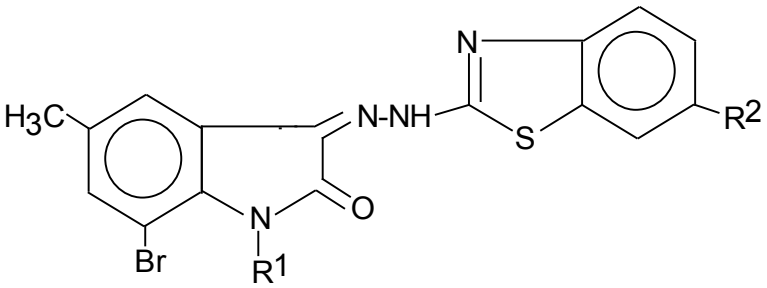
The most preferred position of substitution is 5th position but there are also reports of other substitutions. The imino group of isatin is highly reactive and can be subjected to mannich reaction, acylation, alkylation, halogenation, etc. Substitution at the 3rd position can be further classified into imino formation (schiff base, hydrazones and oximes), dioxindole and oxindole formation. Co-ordination complexes of isatin and its derivations with Cu(II), Zn(II), Pt(II), Pd(II), Ni(II), Co(II), Cd(II), Fe(III), Th(III) and Mo(VI) were reported to be synthesised. The synthesised complexes were either screened for antimicrobial or anticancer activity or enzyme activity.

The reaction of various alkyl-2-naphtyl-ketone[108], cycloalkyl-aminos[109] (**3**), 6-substituted-benzothiazolyl-hydrazine[110] (**4**), anodic methoxylation[111], isonicotinyl-hydrazine[112], aryloxy-magnesium bromide[113] (**5**), aromatic compounds to form oxindoles[114,115] (**6**) and aromatic amines[116] (**7**) with isatin at the 3rd position were reported. Mannich bases of isatin[117, 118] were synthesised and reported (**8**, **9**).



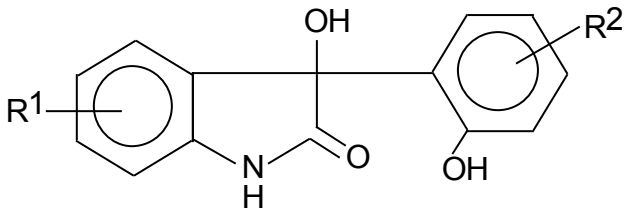
(3)

R = cyclopentyl, cyclohexyl, cycloheptyl



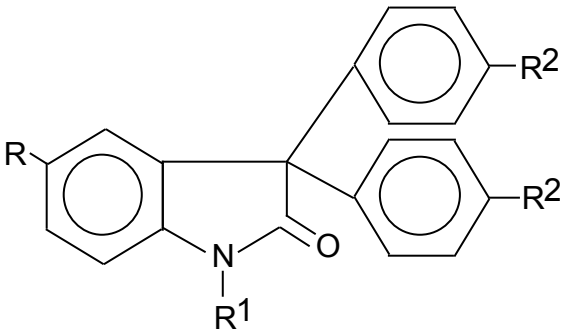
(4)

R[1] = H, CH_3, piperidyl, morpholinyl
R[2] = Cl, CH_3, OCH_3



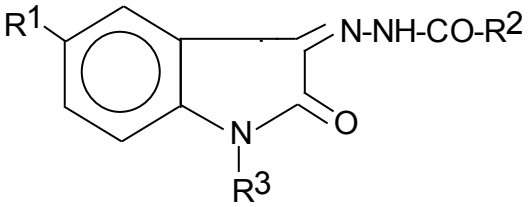
(5)

R[1] = H, 1-CH_3, 4-I, 5-I, 5-OCH_3,5-NO_2, 6-I, 6-CF_3, 6,7-benzo
R[2] = H, 2-Cl, 2-F, 2-CF_3, 2-napthyl, 3-Cl, 3-OCH_3, 3-NH_2, 4-Cl, 4-I, 4-CF_3, 4-OCH_3, 4-C_6H_5, 4-piperazinyl, 3,5-Cl_2



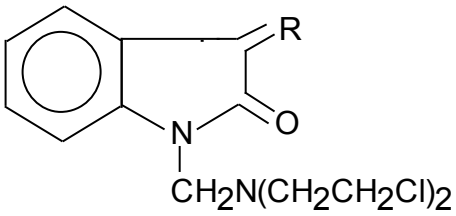
(6)

R = H, F, Cl, NO_2
R[1] = H, CH_3, C_6H_5
R[2] = H, Cl, F, CH_3, C_2H_5, C_3H_7, C_4H_9, -$(CH_2)_8$-CH_3, -$(CH_2)_3$-3-(4-pyridyl)



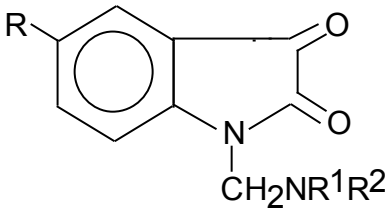
(7)

R[1] = H, CH_3
R[2] = CH_2-1-cyclohexenyl, CH_2-4-pyridyl
R[3] = H, CH_2-N(CH_3)$_2$, CH_2-N(C_2H_5)$_2$, CH_2-NHCO-(2-piperazinyl), CH_2-piperidyl, CH_2-morpholinyl



(8)

R = O, $NNHCSNH_2$



(9)

R = H, Br, CH_3,
NR^1R^2 = $N(CH_3)_2$, $N(C_2H_5)_2$, $N(C_2H_5)$-cyclohexyl, piperdino, morpholino, hexahydroazepino, 3-azabicyclo[3.2.1]octane, 3-azabicyclo[3.2.2]nonane

Several metal complexes of isatin[119-121], isatin-3-oxime[122], isatin-3-isothiosemicar-bazone[123,124], schiff bases of isatin[125-130], N^1(2-furfurylidence)-N^2-β-(isatin)-azine[131], N^1-(5-nitro-2-furfurylidene-N^2-β-(isatin)-azine[132], isatin-N,N'-dimethyl hydrazone[133], N (4') substituted-methisazone[134], isatin-β-thiosemicarbazone[135-140] and N-methyl-isatin-N^4-cyclohexyl-thiosemicarbazone[141] were reported.

The reaction of isatin with trialkyl phosphites[142], dialkyl phosphonites[142], alkoxy- carbonyl-methylene(triphenyl)-phosphoranes[143-144], dikene[145], o-phenylene hydrogen phosphites[146], diorganitinoxides[147], cyano-methylene(triphenyl)-phosphorane[148] and leading to spiro compounds[149-151] were also reported.

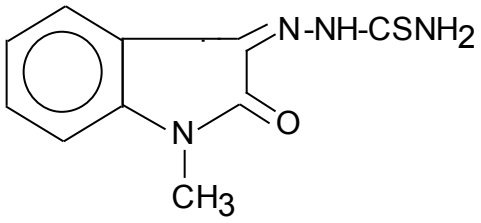
Pharmacological Properties and Application of Isatin Derivatives

The various pharmacological properties and application of isatin derivatives are classified into antimicrobial, antiprotozoal, antihelminthic, antineoplastic, analgesic, anti-inflammatory, antipyretic, enzyme activity, association with biomolecules and miscellaneous.

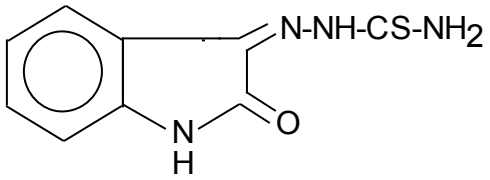
1. Antimicrobial Activity

The antimicrobial activity of isatin derivatives were reported against gram(+), gram(-), acid fast bacteria, fungi and virus. The reported compounds can be broadly classified into thiosemicarbazones, hydrazones, schiff, mannich bases and other derivatives.

Thiosemicarbazone moiety in the 3rd position seems to play a vital role in the antimicrobial property of isatin derivatives. Methisazone[152] (**10**) was an official antiviral drug (N-methyl-isatin-β-thiosemicarbazone) used in the prophylactic treatment of small pox in risk groups.



(10)

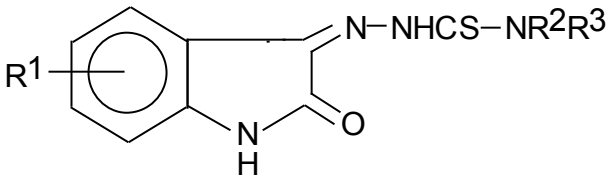


(11)

Isatin-β-thiosemicarbozone[153-159] (**11**) has been reported to possess antiviral properties. Isatin-β-thiosemicarbozone derivatives[160-200] (**12**) was reported to possess antibacterial, antiviral and antifungal properties. The effects of various substituents on the imino moiety of isatin, amido and imino moiety of thiosemicarbazone moiety and on the benzenoid moiety are extensively reported.

Hydrazones and schiff bases (**13**) of isatin[201-206] were reported to possess antimicrobial activity. The biological effects of various hydrazones and 3rd position are reported.

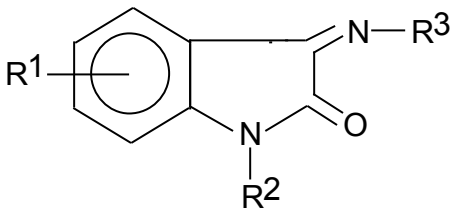
N-mannich bases (**14**) of various substituted isatin derivatives[207-217] were reported to possess antibacterial activity. The effect of various secondary amines in the 1st position has been reported.



(12)

R^{1} = H, 1-CH_3, 1-C_2H_5, 1-*i*-C_3H_7, 1-C_3H_7, 1-C_5H_{11}, 1-CH_2OH, 1-CH_2-C_6H_5, 1-CH_2CH_2OH, 1-$COOCH_3$, 1-$COCH_3$, 1-$COCH_2OC_2H_5$, 1-O-$(CH_2)_2$-O-$(CH_2)_2$-$COCH_3$, 1-$(CH_2)_2$-CN, 1-CH_2-$N(CH_3)_2$, 1-CH_2-$N(i\text{-}C_3H_7)_2$, 1-$(CH_2)_2$-$N(CH_3)_2$, 1-$(CH_2)_2$-$N(C_2H_5)_2$, 1-CH_2-$CH{=}CH_2$, 1-CH_2-piperidino, 1-CH_2-3-methylpiperidino, 1-CH_2-morpholino, 1-CH_2-3-azabicyclo[3.2.2]nonane, 4-Cl, 4-Br, 4-I, 5-CH_3, 5-OCH_3, 5-Cl, 5-Br, 5-F, 5-I, 5-NH_2, 5-OH, 5-$COOCH_3$, 5-sulphonamido, 6-F, 6-I, 6-Cl, 6-Br, 7-Cl, 7-F, 7-Br, 7-I, 7-CH_3, 4,5-CH_2-C_6H_5; 6,7-CH_2-C_6H_5-5-O$(CH_2)_2COCH_3$; 5-$COOCH_3$-1-CH_3; 5-O$(CH_2)_2$-$COCH_3$, 1-CH_3-4-CF_3-5-COOH-7-COOH.

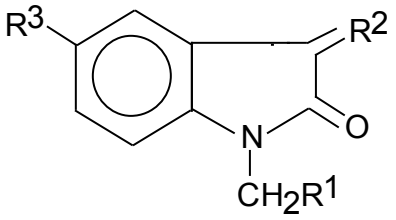
NR^{2}**R**^{3} = NH_2, $N(CH_3)_2$, $N(C_2H_5)_2$, $N(C_2H_5)_2$, $N(C_3H_7)_2$, $N(i\text{-}C_3H_7)_2$; -$N(CH_2$-$CH{=}CH_2)_2$, $N(C_4H_9)_2$, $NHCH_3$, $NH(CH_2$-$CH{=}CH_2)$, NHC_6H_5, pyrrolidino, piperdino, piperidino-4-one, piperidino-3-one, morpholino, hexahydroazepino



(13)

R$_1$ = H, 5-Br, 5-CH_3, 7-Cl, 7-CH_3
R$_2$ = H, 4-methoxyphenyl

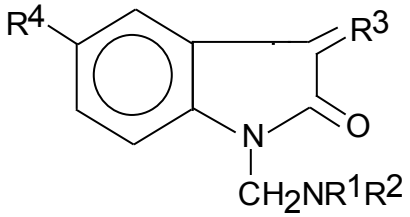
R_3 = N-aryl-furfurylidino-amino, 2-alkyl-benzoxazole-5-carbonyl-amino, phenyl-amino; 2,4-dinitrophenyl-amino, 3-pyridine-amido, 5-substituted phenyl-3,4-thiazolin-2-ylidene, 2-phenyl-3,4-dihydro-4-oxo-quinazolin-3-yl, (3,4-dihydro-3-oxo-1,4-benoxazin-2-yl)- acetyl-hydrazino.



(14)

R^1 = $N(CH_2CH_2OH)_2$, $N(CH_2CH_2Cl)_2$, $N(CH_3)_2$, $N(C_2H_5)_2$, $N(i\text{-}C_3H_7)$, N-pyrrolidino, N-piperidino, N-morpholino, N-4-methyl-morpholino, hexahydroazepino, 3-azabicyclo [3.2.1]octane, 3-azabicyclo[3.2.2]nonane.
R^2 = O, N-$NHCOCH_3$, $NNHCH_3$, $NNHCSNH_2$, $NNHCO(4\text{-}NO_2\text{-}C_6H_4)$, $N(3\text{-}OCH_3\text{-}C_6H_4)$, N-$(3\text{-}Cl\text{-}C_6H_4)$, N-$(3\text{-}NO_2\text{-}C_6H_4)$, N-$(4\text{-}OCH_3\text{-}C_6H_4)$, N- $(4\text{-}Cl\text{-}C_6H_4)$
R^3 = H, Cl, CH_3, NO_2

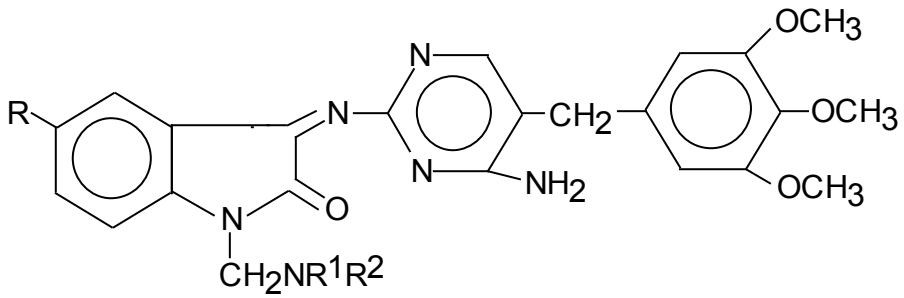
Varma *et al*[218-221] reported the synthesis of a series of hydrazones, anils, N-mannich bases of isatin derivatives (**15**) and their antimicrobial properties.



(15)

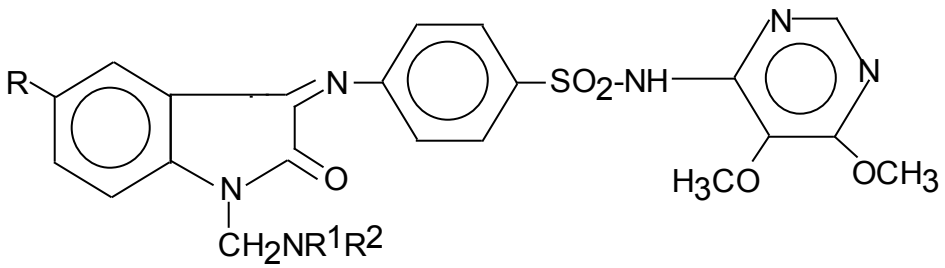
NR^1R^2 = $N(CH_3)_2$ piperidino, 4-methylpiperidino, 3-methylpiperidino, 4-phenyl propyl-piperidino, morpholino, 3,5-dimethyl morpholino, 2,6-dimethyl morpholino, hexahydroazepino, 3-azabicyclo [3.2.1]octane, 3-azabicyclo[3.2.2]nonane.
R^3 = O, $NNHCSNH_2$
R^4 = H, Br, CH_3

Pandeya *et al* followed a novel strategy of synthesis of N-mannich and schiff bases of trimethoprim[222,223] (**16**), sulphadoxime[224,225] (**17**), ciprofloxacin[226] (**18**), lomefloxacin[226] (**19**) and norfloxacin[227,228] (**20**) with isatin. The synthesised compounds were evaluated against gram(+), gram(-) bacteria, fungi and HIV. They also reported that certain compounds of the series were more potent than the parent antimicrobial agent. Pandeya *et al* also reported schiff bases and mannich bases of isatin with pyrimidine[216] (**21**), thiazole[230] (**22**), quinazoline[231] (**23**), benzthiazole[232] (**24**) and triazole[233] (**25**) derivatives.



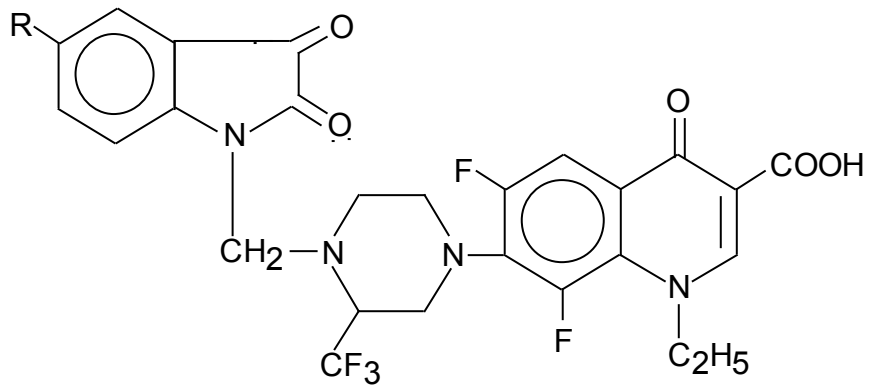
(16)

R = H, Br, CH_3
NR^1R^2 = pyrrolidino, piperidino, morpholino, sulphomethoxazole



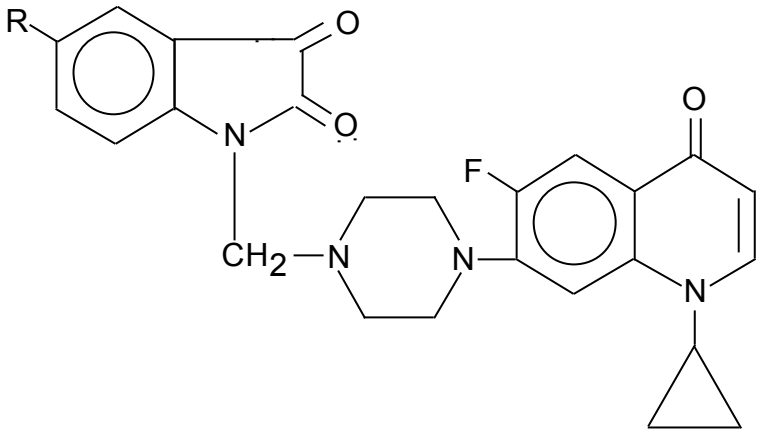
(17)

R = H, CH_3
NR^1R^2 = H, $N(CH_3)_2$, $N(C_2H_5)_2$, pyrrolidino, piperidino, morpholino



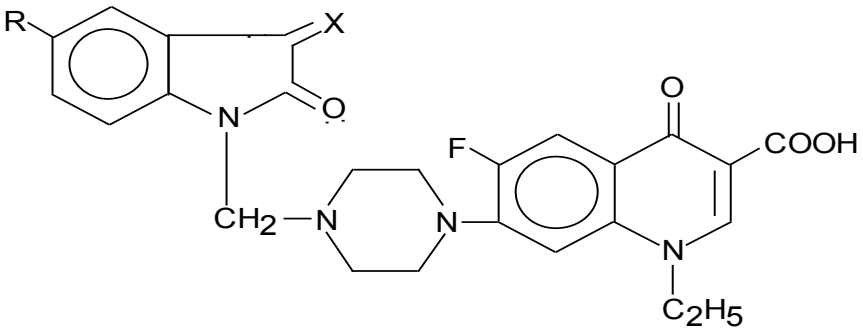
(18)

R = H, CH_3



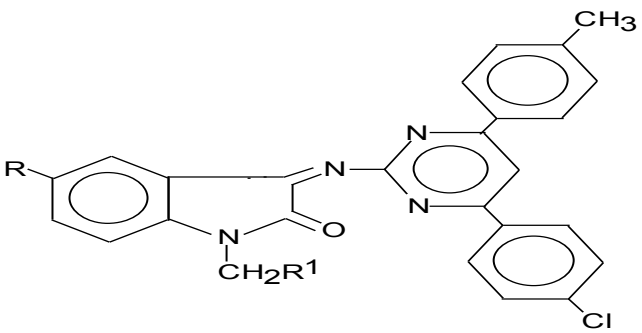
(19)

R = H, CH_3



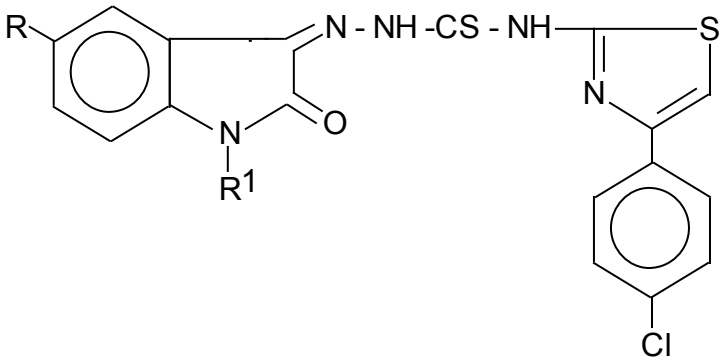
(20)

R = H, Cl, Br
X = O, $NNHCONH_2$, $NNHCSNH_2$



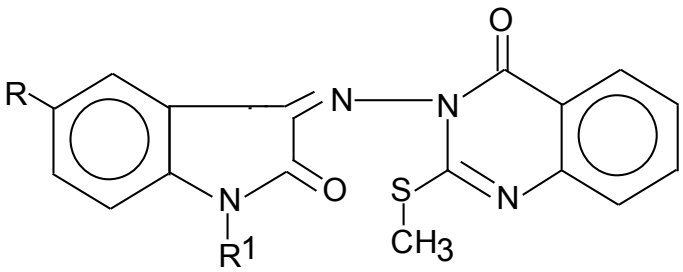
(21)

R = H, Cl, Br
R^1 = $N(CH_3)_2$, piperidino, morpholino



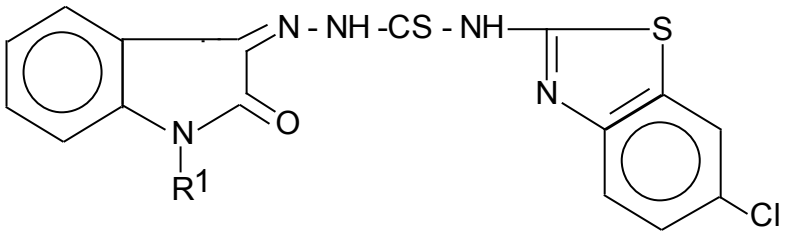
(22)

R = H, Cl, Br
R^1 = $N(CH_3)_2$, piperidino, morpholino



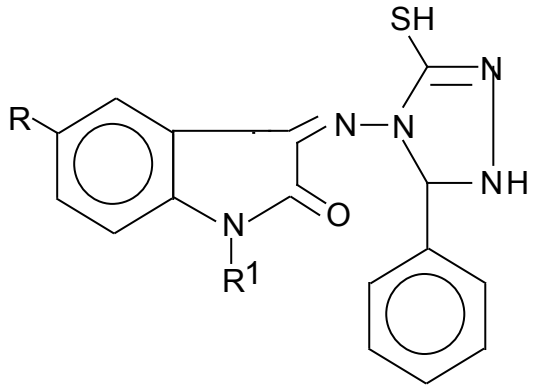
(23)

R = H, Cl, Br
R^1 = $N(CH_3)_2$, piperidino, morpholino



(24)

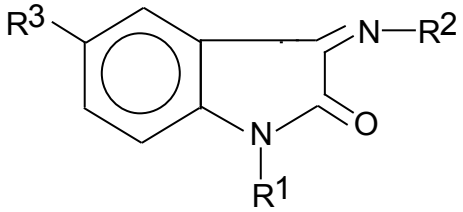
R^1 = $N(CH_3)_2$, piperidino, morpholino



(25)

R = H, Cl, Br
R[1] = $N(CH_3)_2$, piperidino, morpholino

Our team[234-236] has also reported the synthesis, antibacterial and anti-HIV activity of hydrazones, schiff bases, mannich bases (diphenylamine) of isatin derivatives (**26**).

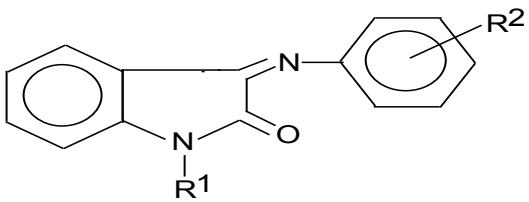


(26)

R[1] = $COCH_3$, CH_2-piperidino, CH_2-$N(C_6H_5)_2$
R[2] = $NHCSNH_2$, 2-thiazolyl, 2-pyridyl, 1-naphthyl, 4-Cl-C_6H_4, 4-CH_3-C_6H_4, 4-OCH_3-C_6H_4, NHC_6H_5, $NH(2,4(NO_2)_2$-$C_6H_3)$
R[3] = H, Cl, Br, NO_2, OCH_3, OC_2H_5

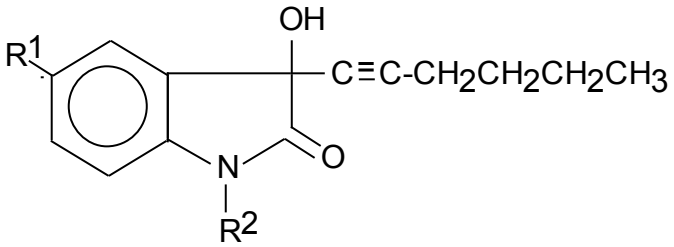
2. Antiprotozal and Antihelminthic Activity

Isatin-3-anils[237,238] and their mannich bases (**27**) were reported to possess cysticidal activity against *Schizopyrenus russelli*. Propargylic alcohol derivatives of isatin (**28**) were reported to possess inhibitory activity of *Echinococcus multicularis* metacestodes (causative agent of alveolar hydatid disease) in *Merion unguiculatus*.



(27)

R^1 = 2-OCH_3, 3-CH_3, 4-Cl, 4-CH_3, 4-OCH_3, 4-C_6H_5
R^1 = H, CH_2-piperidino, CH_2-morpholino



(28)

R^1 = H, NO_2
R^2 = H, CH_3

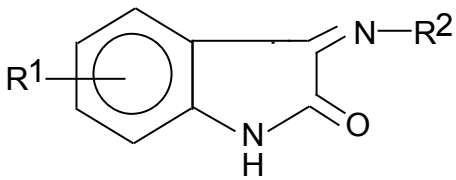
3. Antineoplastic Activity

Several isatin derivatives[219,220,239-246] (**29**) were reported to possess antineoplastic activity against hela cell lines, walker carcino sarcoma, L_{1210} lymphoid leukemia cell line, P_{388} lymphocytic leukemia cell line, human cervix carcinoma cells and murine melanoma B_{16} cells.

4. CNS Activity

Sarangapani *et al*[247,248] reported the potentiation of pentobarbitone induced narcosis of N-mannich bases of isatin (**30**). Varma *et al*[249] reported the gross CNS effects of schiff and mannish bases of isatin (**31**). Pajouesh *et al*[250] reported the anticonvulsant activity of the addition products of isatin with cycloketone and its derivatives (**32**). Popp *et al*[251-254] reported the anticonvulsant properties of addition products of isatin with ketones and its derivatives (**33**). Our team has also reported anticonvulsant activity of isatin derivatives[255] by maximum electro shock and metrozol induced convulsions method (**26**).

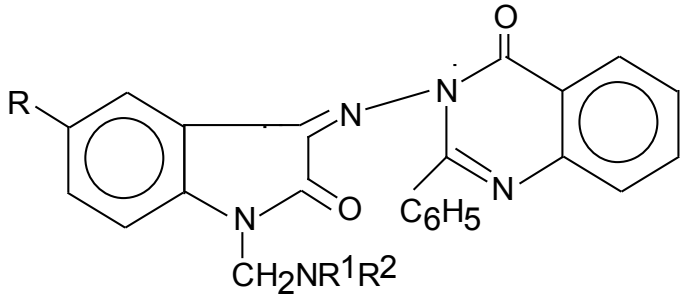
3-(Thiosemicarbazino)-2-indolinones[256], 3-(4-thiazolidone-2-hydrazino)-2-indolin-ones[256], 1-morpholino-methyl-3-aryloxy-aryl-thioacetyl-hydrazono-2-indolinones[257] and furfurylidene derivatives of isatin[258] have been reported to possess anticonvulsant activity.



(29)

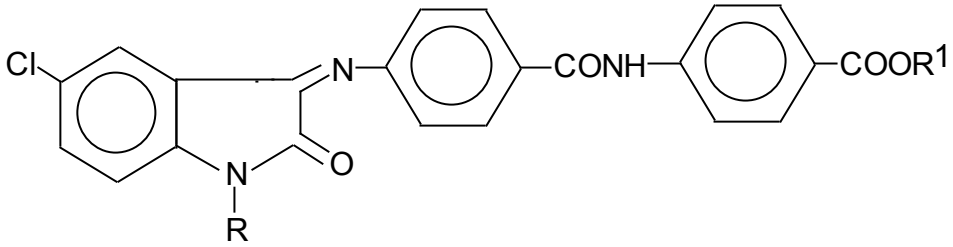
R^1 = H , 1-CH_3, 1-$COCH_3$, 1-CH_2-$N(CH_3)_2$, 1-CH_2-(3-CH_3-piperidino), 1-CH_2-piperdino, 1-CH_2-morpholino, 4-CF_3, 5-Br, 5-Cl, 5-F, 5-OCH_3, 5-CH_3, 5-NO_2, 5-SO_3H, 7-Cl, 7-CH_3; 4-Cl-7-OCH_3; 6-Cl-5-OCH_3; 4-Cl-7-CH_3; 5-Cl-7-CH_3; 6-Cl-7-CH_3; 4-7-Cl_2; 5,7-Cl_2; 4,7-$(CH_3)_2$; 5,7-$(CH_3)_2$; 6,7-$(CH_3)_2$

R^2 = $NHCSNH_2$, NH(2-Cl-C_6 H_4), NH-(2-CH_3-C_6H_4), NH-(2-OCH_3-C_6H_4), NH(2-NO_2-C_6H_4), 4-F-C_6H_4, 2-C_6H_5-C_6H_4, pentafluorophenyl-amino, 2-amino-pyridine, 2-amino-4-methyl-6-hydroxy-pyridine, ethyl carbazate, Indole-3-acetic acid, 5-quinolinyl, cyclopentyl, 3-amino-carbazole, 3-amino-4-ethyl carbazole.



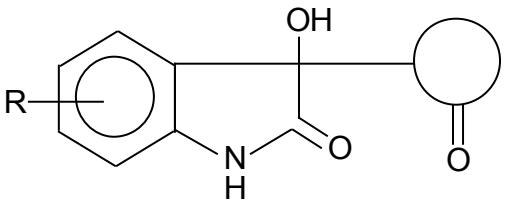
(30)

R = H, Br, CH_3
NR^1R^2 = H, $N(CH_2CH_2OH)_2$, N(cyclohexyl)$_2$, pyrrolidino, piperidino, morpholino



(31)

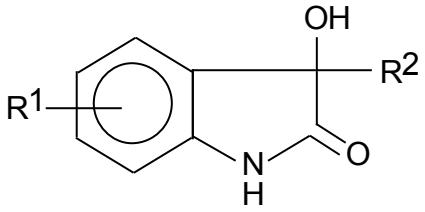
R = H, CH_3, piperidino, morpholino
R^1 = CH_3, C_2H_5, C_3H_7, C_4H_9



(32)

R^1 = H, 1-CH_3, 1-CH_2-C_6H_5, 4-Cl, 5-Br, 5-Cl, 5-NO_2, 5-CH_3, 5-OCH_3, 7-CH_3, 4-Cl-7-CH_3; 4-Cl-7-OCH_3; 5-OCH_3-6-Cl; 5-Cl-7-CH_3; 4,7-Cl ; 5,7-Cl ; 6-Cl-7-CH_3

R_2(Ketone) = acetone, isopropyl methyl acetone, cyclopentanone, cylcohexanone, 2-methyl cylcohexanone, 4-methyl cyclohexanone, 4-isopropyl cylcohexanone 4-*t*-butyl cyclohexanone, benzyl acetone, acetyl adamantane, 1-methyl piperidone, 1-tetratone; 1,3,4,6,7,11b-hexadro-9,10-dimethoxy-benzo(a)-quinolizin-2-one; 3-ethyl-1,3,4,6,7,11b-hexadro-9,10-dimethoxy-benzo(a)-quinolizin-2-one, 5α-androsten-3β-ol-17-one, 5β-androsten-3β-ol-17-one, 5α-androsten-3β-ol-17-one acetate, androstanolone benzoate, 5α- chlolestan-3-one ; CH_2COAr (**Ar** = 2-pyridine, 4-pyridine, 2-furan, 2-benzofuran, 2-thiophene, 2-(5-bromo)thiophene, 2-(5-chloro)thiophene, 2-(3-methyl)thiophene, 3-thiophene, 3-(2,5-dichloro)thiophene, 2-pyrrole, 2-(1-methyl)pyrrole, 4(5-methyl-1-phenyl pyrrole, 2-phenothiazine, 2(3-dimethyl amino)-1-oxo-propyl)-indole; $CH_2(COR_4)$-COR_3 (**R_3** = CH_3, C_6H_5, $CH_2C_6H_5$, cyclohexanone, O-ethyl-2-acetyl-cyclonexanone, $COCH_2$-3- oxindole;



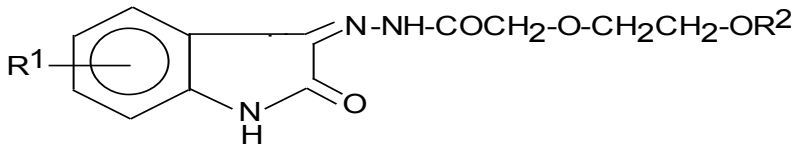
(33)

R_1 = H, 1-CH_3, 1-CH_2-C_6H_5, 1-CH_2-NH(4-Br-C_6H_4), 1-CH_2-piperidino, 1-CH_2-morpholino, 4-CF_3, 5-Br, 5-Cl, 5-I, 5-NO_2, 5-CH_3, 6-Cl, 7-Cl, 7-CF_3, 4-Cl-7-OCH_3; 4-Cl-7-OCH_3; 4-Cl-7-CH_3; 4,7-Cl; 5,7-Cl; 6-Cl-7-CH_3

R_2(ketone) = acetone, isopropyl methyl acetone, cyclopentanone, cylcohexanone, 2-methyl cylcohexanone, 4-methyl cyclohexanone, 4-isopropyl cylcohexanone 4-*t*-butyl cyclohexanone, benzyl acetone, acetyl adamantane, 1-methyl piperidone, 1-tetratone; 1,3,4,6,7,11b-hexadro-9,10-dimethoxy-benzo(a)-quinolizin-2-one; 3-ethyl-1,3,4,6,7,11b-hexadro-9,10-dimethoxy-benzo(a)-quinolizin-2-one, 5α-androsten-3β-ol-17-one, 5β-androsten-3β-ol-17-one, 5α-androsten-3β-ol-17-one acetate, androstanolone benzoate, 5α- chlolestan-3-one ; CH_2COAr (Ar = 2-pyridine, 4-pyridine, 2-furan, 2-benzofuran, 2-thiophene, 2-(5-bromo)thiophene, 2-(5-chloro)thiophene, 2-(3-methyl)thiophene, 3-thiophene, 3-(2,5-dichloro)thiophene, 2-pyrrole, 2-(1-methyl)pyrrole, 4(5-methyl-1-phenyl pyrrole, 2-phenothiazine, 2(3-dimethyl amino)-1-oxo-propyl)-indole; $CH_2(COR_4)$-COR_3 (R_3 = CH_3, C_6H_5, $CH_2C_6H_5$, cyclohexanone, O-ethyl-2-acetyl-cyclonexanone, $COCH_2$-3- oxindole; R_4 = CH_3, C_6H_5, CH_2-C_6H_5, cyclohexanone, O-ethyl-2-acetyl-cyclohexanone, $COCH_2$-3-oxindole)

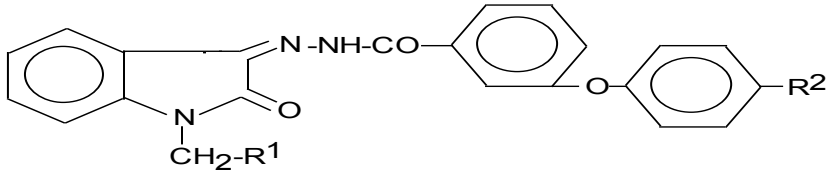
5. Analgesic, Anti-Inflammatory And Antipyretic Activity

Sarangapani *et al*[247,259] reported a series of isatin derivatives (**34**) possessing analgesic activity. Lingaiah *et al*[260] reported the anti-inflammatory activity of N-mannich bases of hydrazones of isatin (**35**). Our team has reported analgesic, anti-inflammatory and antipyretic activity of hydrazones, schiff and mannich bases (**26**) of isatin derivatives[261-263].



(34)

R^1 = H, 5-Br, 5-CH_3, 7-CH_3, 7-Cl
R^2 = CH_3, C_2H_5, C_4H_9



(35)

R^1 = piperidino, morpholino, 4-methyl-morpholino
R^2 = H, Cl, CH_3

6. Enzyme Activity

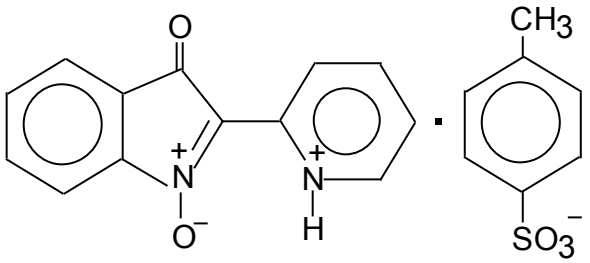
Methisazone[264] and isatin analogues[265,266] were reported for their inhibitory action of phosphodiesterase in human lymphocytes, reversible competative monoamine oxidase enzyme and inhibition of serine proteases[267].

7. Association with Biomolecules

The asosication of isatin[268], mustard-N-mannich bases of isatin[269], complexes [Co (II) and Cu (II)] of methisazone[270] with nucleic acids and proteins were reported.

8. Miscellaneous

The effect of oxyphen isatogen and its derivatives[271] on glucose and tyrosine absorption in rat small intestine was reported. The protective action of isatin compounds[272] was studied in hypoxic hypoxia. Isatogen derivatives[273,274] were reported to relax smooth muscles, inhibit ADP stimulated respiration in isolated mitochondria, inhibtiory effects of ATP on smooth muscles and block ATP receptor sites. 5-Bromo isatin[275] was reported to possess positive ionotropic activity. Isatin-3-oxime derivatives[276] was reported as ion channel activating agents specifically SKC and IKC channels. Various pharmacological, biochemical properties and applications have been reported to be associated (table 4) with 2,2-pyridyl-isatogen (**36**).



(36)

Table 1. Distribution of Isatin in Rat Brain and Tissue

Region	**Concentration (µg/g) Mean ± SD**
Whole Brain	0.04 ± 0.005
Hippocampus	0.13 ± 0.03
Cerebellum	0.11 ± 0.03
Frontal cortex	0.04 ± 0.003
Striatum	0.09 ± 0.03
Vas deferens	0.10 ± 0.02
Seminal Vesicles	1.60 ± 0.10
Heart	0.16 ± 0.10
Liver	0.16 ± 0.10
Testis	0.04 ± 0.03

Table 2. Invitro effects of Isatin

S.No	Effect	ED_{50} Dose
1.	Inhibits rat liver xanthine oxidase[25]	
2.	Potentiates the response of frog rectus abdominis muscle to acetylcholine[26]	
3.	Increase chick brain acid & alkaline phosphatases[27]	
4.	Inhibits rat brain Acid Phosphatase (57%)[28]	10mM
5.	Activates rat liver acid phosphate[28]	-
6.	Species difference on effects on liver acid Phosphatase[29] (i) Inhibits sheep and hedgehog (ii) Activates rat, goat and pig	10mM
7.	Weak inhibition of rat testicular Hyaluronidase (18%)[30,31]	K_i - 12.5 mM
8.	Inhibits rat testicular alkaline Phosphatase[32,33]	K_i - 9.5 mM
9.	Inhibits rat kidney alkaline phosphatase[34-36]	K_i - 11.4 mM
10.	Effect on Alkaline Phosphatase of various organs of rat[37]	-
11.	Inhibits Na^+ dependent glucose uptake into rat Intestine non-competitively[38,39]	K_i - 7.5 mM
12.	Inhibits Na^+ dependent glucose transport[40]	K_i - 7.2 mM
13.	Inhibits amino acid transport[40]	K_i > 6mM
14.	Spasmogenic effect on smooth muscle such as guinea pig ileum[41], rat ileum, rabbit ileum and rat fundus[42].	
15.	Cardio inhibitory property on Isolated perfused frog heart[42].	
16.	Inhibits Monoamine oxidase(MAO)-A [4,43,44]	IC_{50} = 3μM
17.	Inhibits acetyl cholinesterase activity in rat brain[45,46]	K_i -0.833 mM
18.	Inhibits Brush border Sucrase in rat intestine[47,48]	15 - 25 mM
19.	Inhibits glucose transport in human erythrocytes[49]	10 μM
20.	Increases plasma norepinephrine and decreases MAO activity in stroke prone spontaneously hypertensive rats[50]	
21.	Inhibits Monoamine oxidase-B [4, 44, 46, 51, 52]	IC_{50} = 63μM
22.	Antagonizes guanylate cyclase coupled Atrial Natriuretic Peptide receptors[53]	$IC_{50}=4x10^{-7}$ μM
23.	Inhibits Na^+ dependent L-lysine uptake in rat intestine[54]	
24.	Inhibits Na^+ K^+ ATPase activity in Intestine[46,54]	
25.	Inhibits central Benzodiazepine receptor[4]	IC_{50} = 123μM
26.	Inhibits glucose influx in human erythrocytes[4]	10 μM

Table 3. Invivo Effects of Isatin

S.No	Effect	Dose (/kg)
1.	Anticonvulsant effect against maximal electroshock seizures in rats(33-100% effective)[55]	50-400 mg
2.	LD_{50} in rats[56]	>800 mg I.V.
3.	Neurotoxic dose[56]	1.3 kg
4.	Anticonvulsant effect against supramaximal electroshock seizure[56]	430 mg
5.	Anticonvulsant in Hypernatraemic Electro shock seizure threshold test[56]	183 mg
6.	LD_{50} in Mice[57]	580 mg
7.	Prolongs Hexobarbital Narcosis[57]	50-80 mg
8.	Antagonizes electrical convulsions[57]	86 mg

9.	Hypoglycemic effect[58]	
10.	Anti extension effect by Electro physiologic studies[59]	
11.	Depression of amplitude of ventricular contraction and cardiac output of frog heart (perfused)[60]	0.1-6 mg
12.	No effect on cardiovascular system of mammals[60]	10-100 mg
13.	Induced changes in photically evolved potentials[61]	
14.	Effect of extinction of passive avoidance reaction[62]	
15.	Potentiates beneficial effect of GABA on myocardial ischemia in dogs[63]	
16.	Increased amplitude of EEG in rats[64] producing typical spindles. Also increased number of photic after discharge and facilitation effect on photic recruting. * All these effects inhibited by Atropine * Weak inhibition of Acetyl cholinesterase	160 mg
17.	Reduced Audiogenic seizures in rats[64,65]	80-160 mg
18.	Slow wave sleep diminished & onset delayed[66]	40-160 mg
19.	Blocked behavioral syndrome and letharlity induced by pargyline and tryptamine[67]	100-200 mg
20.	Decreased in Triglycerides – raised palmitic acid oxidation. Increased activity of Malic enzyme and Glucose-6-phosphate dehydrogenase and 6-Phosphogluconate dehydrogenase[68]	200 mg
21.	Action on Echinococcus granulosus[69]	50 mg
22.	Less potent glucokinase inhibitor than ninhydrin[70]	
23.	Killed Echinococcus multicularis metacestodes - ultra structural and Biochemical effects including decrease in alkaline Phosphatase, Lactate dehydrogenase and reduced Glucose and Glycogen storage[71]	50 mg
24.	Potentiated anticonvulsant effect of propranolol in maximal electroshock model in mice[72]	80 mg

Table 3 (cont.) Invivo Effects of Isatin

S.No	Effect	Dose (/kg)
25.	Antifungal effect on shrimps[73]	200 ug/ml
26.	Antagonizes pentylene tetrazole convulsions and 3-mercapto propionic acid convulsions[74,75]	199 mg
27.	Inhibits Liver monoamine oxidase (50%)[76]	70 mg
28.	Sedative and Anxiogenic activity in mice and rats[42,73,77-83]	15&20mg I.p
29.	Increased Rat hypothalamic and cortical 5-hydroxytryptamine concentration without affecting 5-hydroxy Indole acetic acid levels. Synaptosomal 5HT uptake not affected but ^{3}H-Ketanserin binding sites ($5HT_2$-receptors) tended to decrease[84]	80 mg
30.	Increased levels of serotonin in brain[84-86]	
31.	Inhibition of alkaline phosphatases ofEchinococcus multicularis, Metacustodes and livers of infected gerbils[87]	
32.	Behavioural effects of Isatin in open field activity and immobility in forced swim test in rats[88]	
33.	Effect on conditioned flight reflex in rats[89]	
34.	Induces Memory dysfunction in rats[90]	100, 200 mg
35.	Chromic administration of Isatin increased systolic blood pressure[91]	200 mg/day
36.	The relationship between Isatin and Natriuretic Peptides[92]	
37.	Inhibits food intake in mice[93]	
38.	Antagonizes generation of secondary messenger on rat brain particulate	

	guanylate cyclase[94]	
39.	Inhibition of ANP stimulated guanyl cyclase[95]	
40.	Effect on rat Testicular Hyaluronidase[31] * 153% increase after 2 hrs * 59% decrease after 24 hrs	200 mg
41.	Lowered Kidney alkaline phosphatase after 5 hrs. Enhanced Rat duodenal and Jejunal enzyme after 2 and 5 hours[37]	200 mg
42.	Decreased blood pressure in mongrel dogs[42]	20-80 mg I.v
43.	Increased acid and pepsin output[42]	10,50,100mg
44.	Protective effect against Histamine aerosol induced bronchospasm on guinea pig[42]	50mg I.p
45.	Reduced the time of drowning on exhaustive swim test in mice[42]	50 mg I.p
46.	Effect on Renal function[42] a) Elevated urine volume after 24 hrs b) Reduced urine volume after 48 hrs	20 mg
47.	No significant effect against carragennan induced paw inflammation[42]	10,50 & 200 mg I.p
48.	No effect against adjuvant arthritis[42]	50 mg I.p
49.	Proconvulsant and anticonvulsant activity[22]	

Table 4. Pharmacological actions and applications of 2,2-pyridyl-Isatogen

S.No	Pharmacological properties and applications
1.	Antagonizes the inhibitory action of ATP in taenia caeci[277-280]
2.	Potentiates vasoconstriction to electrical stimulation at 2-32 Hz in a concentration dependent manner[280-282]
3.	Blocked the effects[283] of ATP, ADP and weak activity against AMP.
4.	Increases capillary permeability produced by ATP[284]
5.	Effect on calcium stimulated respiration in mitochondria from guinea pig liver[285]
6.	Modifies ATP response and neural stimulation of the rat gastric corpus[286]
7.	Influences particulate immune complex binding (IgG) to Peritoneal cells[287]
8.	Inhibits[288] NADPH dependent and independent hydroxylation of aniline, cyclochrome-C-reductase and stimulates NADPH oxidation.
9.	Exhibited vasoconstrictor effect of ATP of pancreatic vascular bed of the rat[289].
10.	Reduces the higher first phase of glucose utilization from glucose deprivation in glucose induced insulin responses[290]
11.	Potentiates the response to ATP and exhibits low affinity towards α_1, α_2, $5HT_{1A}$, $5HT_{1B}$, $5HT_2$, $5HT_3$, D_1, D_2, Muscarinic, Central benzodiazepine, H_1, μ-opiod, Dihydropyridine and Batrachotoxin receptors determined by radio ligand binding assay[291]
12.	Employed as a spin trapping agent for superoxide and hydroxy radicals[292]

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