Nithya G. *et al.* / *International Journal of Pharmacy & Therapeutics*, 3(3), 2012, 243-246.

e- ISSN 0976-0342
Print ISSN 2229-7456

**International Journal of Pharmacy & Therapeutics**

Journal homepage: www.ijptjournal.com

IJPT

# SYNTHESIS & BIOLOGICAL EVALUATION OF SOME NOVEL SCHIFF BASES OF ISATIN DERIVATIVES

**Nithya G[1*], Panneerselvam P[2], Nepolean R[1], Selvakumar N[1], Jeyavalli A[1]**

[1]Thanthai Roever College of Pharmacy, Perambalur, Tamilnadu – 621212.
[2]CL Baid Metha College of Pharmacy, Chennai, Tamilnadu – 600097, India.

**ABSTRACT**

Novel substituted Nitrosoisatin derivatives were prepared by nitrosation with sodium nitrite in concentrated hydrochloric acid at 0-5 °c followed by schiff reaction with various aromatic amines. The structures were characterized by M.P, TLC, IR, $^1$H NMR and mass spectra. The synthesized compounds were evaluated *in vitro* anticonvulsant activity. Results of the activities reveal that, compounds exhibited significant reduction in seizers.

**Key words:** Isatin, Schiff bases, Maximal electrical shock method, Anticonvulsant activity.

## INTRODUCTION

Isatin derivatives display diverse biological activities such as antimicrobial, (Ankur Patel *et al*., 2006; Krishna C *et al*., 1990; Mashelkar U C *et al*., 2005; Krishna C *et al*., 1992; Anil K et al., 1982), anti cancer (Ashraf H *et al*., 2006; Lidia Matesic *et al*., 2008; Mohammad Mamun Hossain *et al*., 2007; Rolf Braun *et al*., 1977), anti plasmoidal, (Idan Chiyanzu *et al*., 2005), antiviral (Ny Sin *et al*., 2009) (eg. Melosatin A) activities. Schiff bases of Isatin derivatives have shown variety of biological activities like anticonvulsant, (Sridhar S K *et al*., 2002; *Olcay Bekircan et al*., 2008; Popp F D *et al*., 1982; *Prince P Sharma et al*., 2009), antimicrobial (Surendra N Pandya *et al*., 2000), antiHIV (Pandeya S N *et al*., 2005; Tao Jiang *et al*., 2005; Tanushree Ratan Bal *et al*., 2005), anti-inflammatory (Seshaiah Krishnan Sridhar *et al*., 2001) activities , In view of this observation we have synthesized some compounds that may exhibit potent anticonvulsant activity. As outlined in scheme I, Isatin on nitrosation with $NaNO_2$ in presence of conc HCl at 0°C to 5°C yielded N-nitroso isatin 1. Schiff reaction of 1 with various aromatic amines 2 in presence of ethanol under reflux for 4 hrs yielded the desired compounds (2a-2h) at ambient temperature in good yield (TLC). All the compounds synthesized were characterized on the basis of their analytical data and spectral data.

Corresponding Author

**Nithya G**
Email: nithyaprajesh19@gmail.com

## MATERIALS AND METHODS

All the melting points reported were determined in open capillary tube method and are uncorrected. The IR spectra of the compounds were recorded on ABB BOMEM FTIR spectrophotometer MB 104 and are expressed in cm-$^1$ .The $^1$H NMR and $^{13}$C NMR spectra of the compounds were recorded on Bruker spectrometer in DMSO and DMF with TMS as internal standard. The Mass spectra of the compounds were recorded on JOEL GC mate. The progress of the reaction was monitored on precoated silica gel F254 plates (Merck) using different chloroform: methanol (9.5: 0.5). Synthesis and analytical studies of the title compounds were carried out using laboratory grade and analytical grade reagents.

## GENERAL PROCEDURE

### Synthesis of N-NitrosoIsatin (1)

To a solution of isatin (14.7g, 0.1mol) in chloroform (200 ml), concentrated hydrochloric acid (30 ml) and water (30 ml) were added ,and while stirring, solid $NaNO_2$ (1.65 g, 0.024mol) was added in portions during 30 min. The stirring was continued for 4 h at 0 -5$^0$C. The organic layer was washed with water and saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. After removal of the chloroform, the residue was recrystallized from ethanol.

### Synthesis of Schiff bases of N-Nitrosoisatin compounds (2a -2h).

Equimolar quantity (0.01mol) of N-Nitrosoisatin and the aromatic primary amine were dissolved in 10 ml of warm ethanol and refluxed for 3 h and then checked for completion of reaction by TLC. After standing for approximately 24 h at room temperature, the products were separated by filtration, dried and recrystallized from warm ethanol.

## BIOLOGICAL ACTIVITY

### Anticonvulsant activity (MES method in mice)

The anticonvulsant activity was carried out for all the synthesized compounds by maximal electric shock method using phenytoin sodium as reference drug. Animals were weighed, numbered and divided into three groups each consisting of 6 rats. One group was used as normal control received dimethyl sulphoxide i.v., second group was standard control received phenytoin sodium at dose of 25mg/kg body wt i.v. and the third group received sample treatment at dose of 100 and 200mg/kg body wt. i.v. The corneal electrodes were placed on the cornea of the animal. The whole procedures were repeated with the animals of all the three groups. After 30 min of drug treatment, the animals were subjected to a electric shock of 150 M.A. by convulsiometer for 0.2 sec. The reduction in time or abolition of tonic extensor phase and flexion phase of MES- convulsions was noted.

% protection = [(Control-Test)/Control] X100

**Table 1. The physico-chemical data of synthesized compound**

| Comp. | m.f. | Mol. Wt. | Rf | m.p.($^0$C) | Yield % |
|---|---|---|---|---|---|
| **2a** | $C_{14}H_8ClN_3O_2$ | 285.69 | *0.8378* | 254 - 256 | 96.4 |
| **2b** | $C_{14}H_8BrN_3O_2$ | 330.14 | 0.8024 | 220 - 222 | 92.6 |
| **2c** | $C_{14}H_8FN_3O_2$ | 269.23 | 0.6040 | 156 -158 | 89.2 |
| **2d** | $C_{14}H_7ClFN_3O_2$ | 303.00 | 0.8918 | 210 - 212 | 66.6 |
| **2e** | $C_{15}H_{11}N_3O_2$ | 265.27 | 0.7837 | 216 - 218 | 37.7 |
| **2f** | $C_{15}H_{11}N_3O_3$ | 281.27 | 0.8648 | 225 - 227 | 61.3 |
| **2g** | $C_{14}H_8N_4O_4$ | 296.24 | *0.6046* | 88 - 90 | 95.4 |
| **2h** | $C_{14}H_7N_5O_6$ | 341.24 | 0.8024 | 120 - 122 | 76.4 |

*Solvent System: Chloroform: Methanol (9.5:0.5)*

**Table 2. Spectral data of the synthesized compounds**

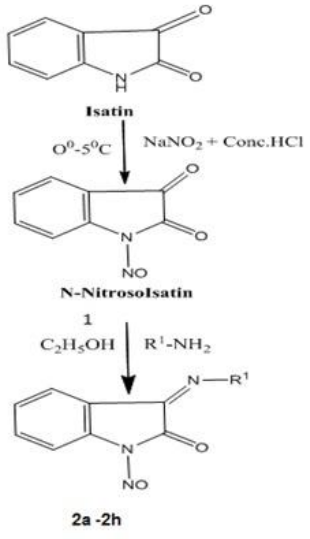
| Comp. | |
|---|---|
| **2a** | IR: 3178 (Ar-CH),1592 (C=C),1331 (C-N), 1461 (N-NO),1738 (C=O),1611(C=N),751(C-Cl) ; 1HNMR: 6.58 - 7.74 (8H, m, Ar-H) ; ($M^+$) m/z : 285 |
| **2b** | IR: 3268 (Ar-CH), 1592 (C=C), 1334 (C-N), 1460 (N-NO), 1739(C=O), 1610(C=N),582 (C-Br) ; 1HNMR: 6.42 - 7.71 (8H, m, Ar-H); (M+2) m/z : 332 |
| **2c** | IR: 2987 (Ar-CH),1497 (C=C), 1385 (C-N), 1463 (N-NO), 1728 (C=O), 1615 (C=N),1288 (C-F); 1HNMR: 6.41 - 7.61 (8H, m, Ar-H) ; ($M^+$) m/z : 270 |
| **2d** | IR: 3196 (Ar-CH), 1590 (C=C), 1334 (C-N), 1463 (N-NO), 1726 (C=O), 1611 (C=N),758 (C-Cl), 1204 (C-F); 1HNMR: 6.76 - 8.21 (7H, m, Ar-H) ; ($M^+$) m/z : 303 |
| **2e** | IR: 3257(Ar-CH), 1592 (C=C), 1333(C-N), 1463 (N-NO), 1742 (C=O), 1611 (C=N),2910 (C-$CH_3$); 1HNMR: 6.58 - 8.04 (8H, m, Ar-H), 2.2 (3H,s,$CH_3$);($M^+$)m/z : 265 |
| **2f** | IR: 3118 (Ar-CH), 1499 (C=C), 1332 (C-N), 1460 (N-NO), 1738 (C=O), 1611 (C=N), 2833 (CO-$CH_3$); 1HNMR: 6.78 - 8.21 (8H, m, Ar-H), 3.3 (3H,s, $OCH_3$);($M^+$)m/z :281 |
| **2g** | IR: 3370 (Ar-CH), 1584 (C=C), 1301 (C-N), 1471 (N-NO), 1734 (C=O), 1621 (C=N),1367 (C-$NO_2$); 1HNMR: 6.92 - 8.21 (8H, m, Ar-H) ; $^{13}$C -NMR δ(ppm):112.60 – 146.24 ( 11 C, Ar –C), 161.89 ( 1C, C-N ), 163.23 (1C C=N ), 166.66 ( 1C, C=O ); ($M^+$) m/z : 296 |
| **2h** | IR: 3335 (Ar-CH), 1584 (C=C), 1301 (C-N), 1464 (N-NO), 1732 (C=O), 1624 (C=N),1388 (C-$NO_2$); 1HNMR: 7.03 - 8.28 (7H, m, Ar-H); ($M^+$) m/z : 341 |

**Table 3. Anticonvulsant activity**

| Compounds | Dose (mg/kg) | Flexion phase | | Extensor phase | |
|---|---|---|---|---|---|
| | | Mean±SEM | %protection | Mean±SEM | %protection |
| **2a** | 100 | 5.00+0.40** | 28.57 | 6.25+0.85*** | 48.97 |
| | 200 | 4.75+0.47** | 32.14 | 5.50+0.64*** | 55.10 |
| **2b** | 100 | $5.50+0.28^{NS}$ | 21.42 | 9.25+0.25* | 24.48 |
| | 200 | 5.25+0.47* | 25.00 | 8.50+0.86** | 30.61 |
| **2c** | 100 | $5.5+0.28^{NS}$ | 21.42 | 9.50+0.28* | 22.44 |
| | 200 | 5.25+0.47* | 25.00 | 8.25+0.47** | 32.65 |
| **2d** | 100 | 5.25+0.25* | 25.00 | 9.50+0.28* | 22.44 |
| | 200 | 5.00+0.40* | 28.57 | 8.50+0.64** | 30.61 |
| **2e** | 100 | 4.50+0.64*** | 35.17 | 8.00+0.81*** | 34.69 |
| | 200 | 4.25+0.47*** | 39.28 | 7.5+0.25*** | 38.77 |
| **2f** | 100 | $6.00+0.40^{NS}$ | 14.28 | 9.25+1.17* | 24.48 |
| | 200 | $5.75+0.25^{NS}$ | 17.85 | 9.00+0.47* | 26.53 |
| **2g** | 100 | 4.75+0.25** | 32.14 | 9.00+0.40** | 26.53 |
| | 200 | 4.50+0.28*** | 35.17 | 8.5+0.64** | 30.61 |
| **2h** | 100 | 5.00+0.40** | 28.57 | 9.25+0.47* | 24.48 |
| | 200 | 4.75+0.47** | 32.14 | 8.25+0.85** | 32.65 |
| **PHENYTOIN** | 25 | 4.5+0.28 | 35.71 | 0.00+0.00*** | 100 |
| **CONTROL** | - | 7.00+0.40 | - | 12.25+0.85 | - |

Significant differences with respect to control was evaluated by (ANOVA), Dunnet's t test *P< 0.05, **P<0.01, ***P<0.001, NS (Non significant).

**SCHEME 1**




$R^1$ = p-chlorophenyl, p-bromophenyl, p-fluorophenyl
3-chloro-4-fluorophenyl, p-methylpenyl, p-methoxyphenyl,
p -nitrophenyl, 2,4-dinitrophenyl.

## RESULTS AND DISCUSSION

All the synthesized title compounds were subjected for *in-vivo* anticonvulsant activity. The results showed that substitution with electron donating moiety favors significant reduction in the seizures than substitution with electron withdrawing moiety. Compound 2a exhibit better activity among the series of compounds synthesized.

## ACKNOWLEDGEMENT

Authors are thankful to Head, Department of Chemistry. C.L. Baid Metha College of pharmacy,

Chennai for providing laboratory facilities to carry out the research work. Authors are grateful to Sasthra University, Tanjore for NMR spectral analysis, DR .CEEAL Analytical lab, Chennai for IR spectroscopy, IIT MADRAS for MASS spectroscopy and EUMIC LAB, Trichy for anti microbial activity.

**REFERENCES**

Anil K Sen Gupta, Anitha Rastogi. Synthesis of some new 1-substituted 5- bromo-3-aryloxy acetylhydrazono-2-indolinones as potential anti-bacterial agents. *J Indian Chem. Soc*., 59, 1982, 1102-1104.

*Ankur Patel, Sanjay Baria, Gokul Talele, Jitendra Patel, Manda Sarangapani B. Synthesis and antimicrobial activity of some new Isatin Derivatives. Iranian. J. Pharm. Research, 4, 2006, 249-254.*

Ashraf H Abadi. Sahar M.Abou-Seri, Christian Klein. Synthesis of 3-substituted -2-oxoindole analogues and their evaluation of kinase inhibitors, anti-cancer and anti-angiogenic agents. *Eur J Med Chem*., 41, 2006, 296-305.

Krishna C Joshi, Anushu Dandia, Sangeeta Khanna. Synthesis and antibacterial activity of some new fluorine containing spiro-3-indolines. *Indian J Chem*., 29b, 1990, 1125-1128.

Krishna C Joshi, Anshu Dandia,Sangeetha Khanna. Synthesis of some new fluorin containing bioactive heterocycles derived from fluorinated isatins and evaluation of their anti-bacterial activity. *Indian J Chem*., 31b, 1992, 105-108.

Idan Chiyanzu, Cailean Clarkson, Peter J. Smith, Julie Lehman, Jiri Gut, Philip J. Rosenthal, Kelly Chibale. Design,synthesis and anti-plasmodial evaluation *in vitro* of new 4-Aminoquinoline isatin derivatives. *Bio org & Med Chem,* 13, 2005, 3249-3261.

Lidia Matesic, Julie M. Locke, John B. Bremner, Stephen G Pyne, Danielle Skropeta, Marie Ranson, Kara L. Vine. N-Phenethyl and N-Naphthylmethyl isatins and analogues as invitro cytotoxic agents. *Bio org & Med Chem*, 13, 2008, 3118-3124.

Mohammad Mamun Hossain, Nazrul Islam, Rahat Khan,Md. Rabiul Islam. Cytotoxicity study of dimethylisatin and its heterocyclic derivatives. *Bangladesh J Pharmacol*, 2, 2007, 66-70.

Mashelkar UC, Deepak M Rane. Synthesis of some isatin based novel spiroheterocycles and their biological activity studies. *Indian J Chem*., 44b, 2005, 1937-1939.

Ny Sin, Brian L Venables, Keith D Combrink, H Belgin Gulgeze, Kuo-Long Yu, Rita L Civiello, Jan Thuring. Respiratory syncytial virus fusion inhibitors. Part 7: Structure–activity relationships associated with a Series of isatin oximes that demonstrate antiviral activity *in Vivo*. *Bio org & Med Chem Lett*, 19, 2009, 4857-4862.

*Olcay Bekircan, Hakan Bektas. Synthesis of schiff and mannich bases of isatin derivatives with 4-amino-4,5-dihydro-1h-1,2,4-triazole-5-ones. Molecules, 13, 2008, 2126-2135.*

Pandeya SN, Sriram D, Nath G. Synthesis, anti-bacterial and anti-HIV evaluation of schiff and mannich bases of isatin derivatives with – 3- amino-2-methyl mercapto quinazolin-4(3H)-one. *Pharmaceutica Acta Helvetiae*, 74, 1999, 11-17.

Popp FD. Potential anti-convulsants. V. The condensation of isatins with acetyl heterocyclic compounds. *J Hetero Chem*., 19, 1982, 589 -592.

*Prince P Sharma, Pandeya SN, Roy RK, Anurag, Krishan Verma, S Gupta. Synthesis and anticonvulsant activity of some novel Isatin Schiff's Bases. International J .Chemtech Research, 1, 2009, 758-763.*

Rolf Braun, Dieter Ziebarth. *In vivo* formation of N-Nitroso compounds and detection of their mutagenic activity in the Host-Mediated Assay. *Cancer Research*, 37, 1977, 4572-4579.

*Seshaiah Krishnan Sridhar and Atmakuru Ramesh. Synthesis and pharmacological* activities of hydrazones, schiff and mannich bases of isatin derivatives. *Biol. Pharm. Bull*., 24, 2001, 1149-1152.

Sridhar SK, Surendra N Pandeya, Atmakuri Ramesh. Anticonvulsant activity of hydrazones, Schiff and mannich bases of isatin derivatives. *Eur J Pharm Sci*., 16, 2002, 129-132.

Surendra N Pandya, Dham rajan Sriram and Gopalnath. Synthesis, anti-bacterial, anti-fungal and anti-HIV activities of Nofloxacin mannich bases. *Eur J Med Chem*., 35, 2000, 249-255.

Tanushree Ratan Bal, Balasubramani Anand, Perumal Yoge Eswari, Dharmarajan Sriram. Synthesis and evaluation of anti-HIV ativity of isatin β-thiosemicarbazone derivatives. *Bio Org & Med Chem*, 15, 2005, 4451-4455.

Tao Jiang, Kelli L Kuhen, Karen Wolff, Hong Yin, Kimberly Bieza, Jeremy Caldwell, Badry Bursulaya, Tom Yao-Hsing Wu, Yun He. Design, synthesis and biological evaluations of novel oxindoles as HIV-1 non-nucleoside reverse transcriptase inhibitors. Part I" *Bio org & Med Chem Lett*, 16, 2006, 2105-2108.