

SYNTHESIS, CHARACTERIZATION OF 7-AZAISATIN DERIVATIVES

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ABSTRACT

The synthesis of heterocyclic compounds in various ways while incorporating a range of known pharmacophores into their molecular systems and analyzing them for prospective pharmacological effects in the field of medicinal chemistry. Because of their diverse biological and pharmacological features, some of their derivatives and primary amines of azaisatin have been discovered to be of increasing interest. With this in mind, the goal is to synthesize new 7 azaisatin derivatives.

Keywords: 7-azaisatin, synthesis, characterization

1. INTRODUCTION

Although the chemistry of indole has been studied for over a century, novel indole derivatives such as 7-azaindole and azaisatin have recently been developed that show more powerful pharmacological activities [1-5]. Indole is a common scent component and a precursor to numerous medicines, with a wide spectrum of biological actions [6-15]. The substitution of heterocyclic compounds at different locations resulted in medicinally relevant analogs that are used to treat various diseases. Substituted indole and azaindole groups are being investigated as potential surrogates for the indole core, resulting in a new class of medicinal medicines with a wide range of pharmacological actions. Hypotensive [1], analgesic [2], anti-cancer [3], antibacterial [4], antifungal [4], and cardioprotective [5] properties have been described for azaindole derivatives. The goal of this study was to look at some new

7-azaisatin derivatives as pharmacological agents.

2. MATERIALS AND METHODS

The melting points were measured using the Toshniwal melting point instrument in open capillary tubes and are uncorrected. On an FTIR Bruker spectrophotometer, IR spectra were recorded in KBr, and frequencies were reported in cm^{-1} . Thin layer chromatography on Silica Gel precoated plates was used to assess the purity of the chemicals. CDCl_3 and DMSO were used as solvents in the $^1\text{H NMR}$ spectra obtained on a Bruker DPX-400MHz spectrometer. Chemical shift readings are expressed in parts per million (ppm) in comparison to TMS as the internal reference. EI-MS mode was used to record mass spectra on the VG AUTO SPEC.

2.1. Chemicals

All the chemicals used were of analytical grade only. 7-azaindole, Dimethyl sulphoxide, and Benzyl chloride were purchased from Merck chemicals Private Limited, Hyderabad, India. N-Bromosuccinamide, Hydrazine hydrate, Ethyl chloroformate, and Aromatic aldehydes were purchased from VSN lab, Hyderabad, India.

2.2. Chemistry

The compounds were synthesized by conventional methods and also methods

developed in our laboratory. General reactions were monitored by TLC using precoated silica gel (GF-245) and were visualized under ultraviolet light. 2-chloro-1-(1H-pyrrolo [2, 3-b] pyridine-1-

yl)ethanone was synthesized by the method available in the literature [2-5]. The synthetic strategies adopted to obtain target compounds are depicted in Figure 1.

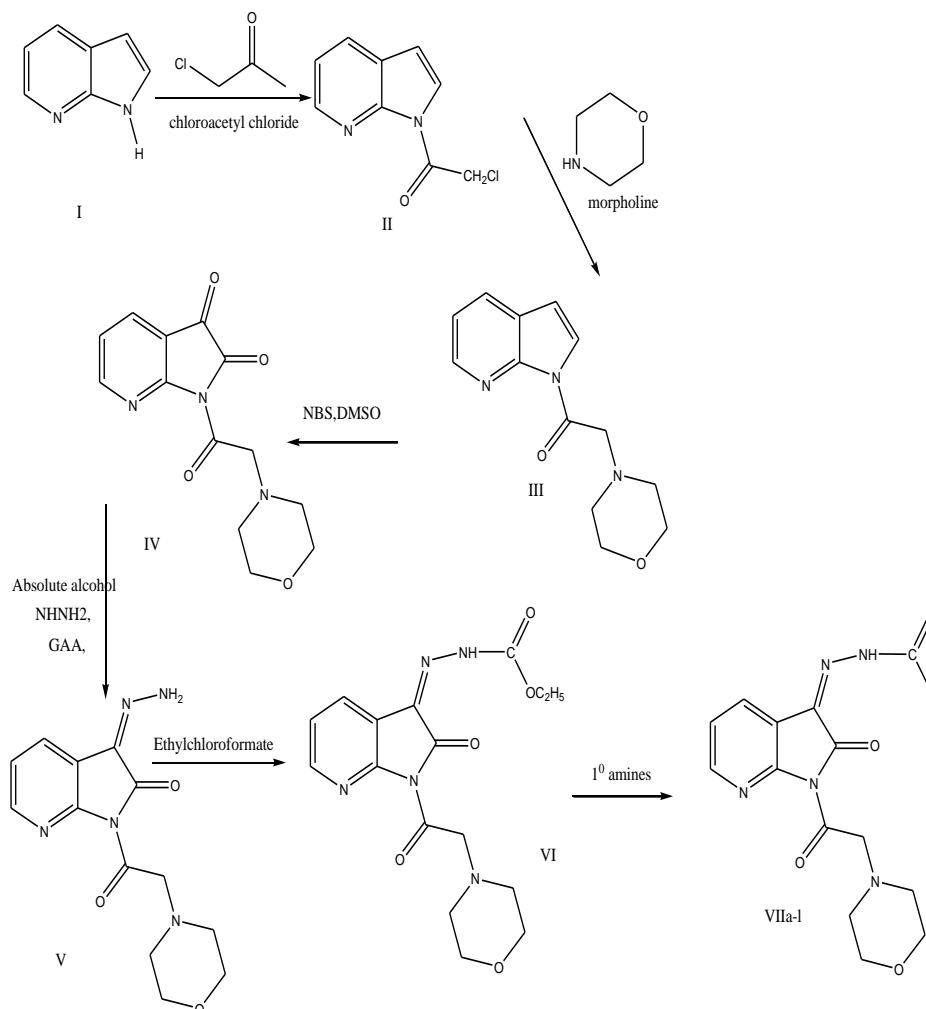


Figure -1: Experimental scheme-I for the synthesis of 7-azaisatin derivatives

Synthesis of 2-chloro-1-(1H-pyrrolo [2, 3-b] pyridin-1-yl)ethanone (Compound-II):

Taken 250ml conical flask and added dimethyl sulphoxide (50ml), Potassium hydroxide (5.5gm) shaken it for 5mints. To this solution, added 3g of 7-Azaindole and stirred for 50min. Then the reaction mixture was placed in an ice bath, added chloro acetyl chloride (3.55gm, 5.05ml), and stirred again for 50min. Water (50ml) was added and the reaction was partitioned

with 100ml of ether and repeated three times, taken dryness by rotary evaporation. **2-morpholino-1-(1H-pyrrolo[2, 3-b]pyridin-1-yl)ethanone - (Compound-III):**

An 0.01mol of 2-chloro-1-(1H-pyrrolo[2,3-b]pyridin-1-yl)ethanone/2-chloro acetyl 7-azaindole was heated under reflux with morpholine (0.01mol) in dry acetone in presence of potassium carbonate under anhydrous condition using calcium chloride guard tube for 90mint.

The product thus formed was filtered and it was purified by recrystallization from ethanol.

Synthesis of 1-(2-morpholinoacetyl)-1H-pyrrolo pyridin-2, 3-dione (Compound - IV):

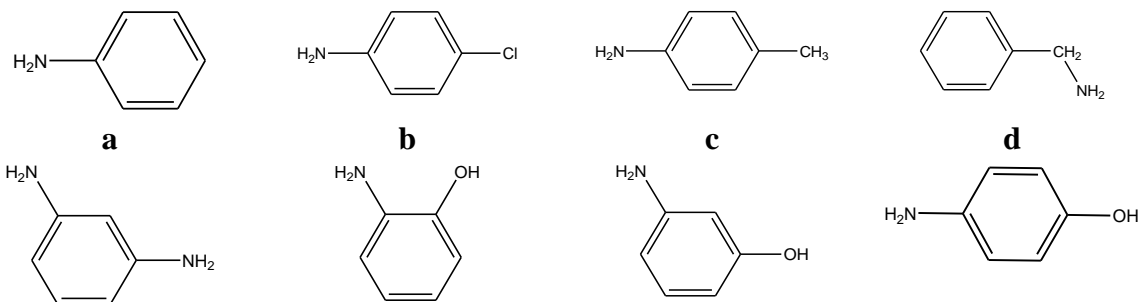
A mixture of 0.1 mol of 2-morpholino-1-(1H-pyrrolo[2,3-b]pyridin-1-yl)ethanone, N-bromosuccinimide (0.90gm, 5.0 mmol) in 20ml of anhydrous dimethyl sulphoxide were stirred at 60°C for 5h and then above 80°C for 10 h under reduced pressure. Poured the reaction mixture into 50ml water and the residue was purified with dichloromethane.

Synthesis of (Z) 3-hydrazonoe-1-(2-morpholinoacetyl)-1H-pyrrolo[2,3-b]pyridin-2(3H)-one (Compound -V):

Placed 100ml of absolute alcohol, equimolar quantities of 1-(2-morpholinoacetyl)-1H-pyrrolo pyridine-2, 3-dione, and hydrazine hydrate in a cleaned dry round-bottomed flask, followed by dropwise addition of glacial acetic acid. Refluxed the mixture for about 3 h. During the heating period itself, the crystals of compound-5 started separating. Then the reaction mixture was cooled to room temperature and poured on crushed ice with stirring and the product was purified by recrystallization from ethanol.

Where,

R= (1⁰amines) & code

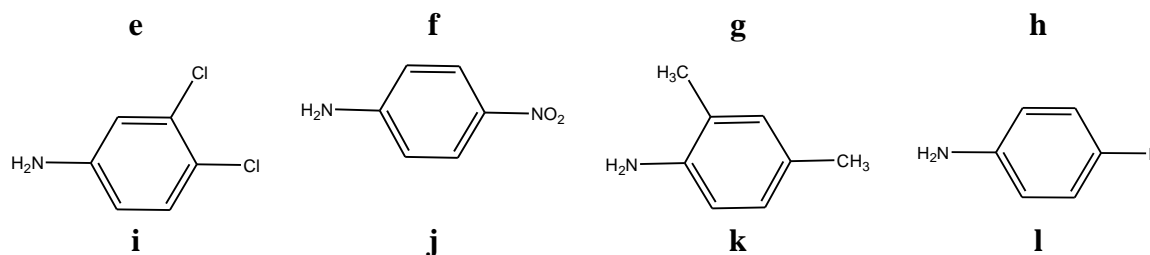


Synthesis of ethyl-2-(1-(2-morpholinoacetyl)-1H-pyrrolo [2,3-b] pyridin-2(3H)-one) hydrazine carboxylate (Compound-VI):

An 0.01mol of 1-(2-morpholinoacetyl)-1H-pyrrolo pyridine-2, 3-dione was heated under reflux with ethyl chloroformate (0.01mol) in dry acetone in presence of potassium carbonate under anhydrous condition using calcium chloride guard tube for 3h. The product thus formed was filtered and washed with small portions of acetone to remove any unreacted ethyl chloroformate. It was purified by recrystallization from ethanol.

Synthesis of 1-(1'-benzyl-1,2'-dihydro-2'-oxopyrrolo pyridin-3'-ylidene)-4-substituted semicarbazide (Compound -VII a-l).

Taken 0.1mol of ethyl-2-(1-(2-morpholinoacetyl)-1H-pyrrolo[2,3-b]pyridin-2(3H)-one) hydrazine carboxylate was heated under reflux with various primary amines (0.1mol) in dry acetone under anhydrous condition using calcium chloride guard tube for 3h. The product thus formed was filtered and washed with small portions of acetone to remove any unreacted primary amines. It was purified by recrystallization from ethanol.



3. RESULTS & DISCUSSION

The structures of synthesized compounds (II-VII) were Physico-chemical and elemental analyses shown in table-1. A series of 7- azaisatin derivatives (VII a-1) were obtained 1-(1'-benzyl-1,2'-dihydro-2'-oxopyrrolo pyridine-3'-ylidene)-4-substituted semicarbazide was synthesized by using dimethylformamide,

formaldehyde and various primary amines. The structures of synthesized compounds (VIIa-i) were characterized based on spectral data. The compounds were purified by recrystallization from suitable solvents [16-22]. The chemical structures and purity of synthesized compounds were confirmed by IR, ¹H NMR, and Mass. The data is expressed in table-2.

Table-1 Physico-chemical and elemental analysis

Compound	MF	MW	% Yield	M.P(°C)	Rf*	Elemental Analysis (Calculated/ Found) %
II	C ₉ H ₇ ClN ₂ O	194	83	210-213	0.68	C, 55.54/56.66; H, 3.63/4.00; Cl, 18.22/18.05; N, 14.39/14.22; O, 8.22/8.20.
III	C ₁₃ H ₁₅ N ₃	245	74	180-183	0.58	C, 63.66/63.67; H, 6.16/6.17; N, 17.13/17.00; O, 13.05/13.08.
IV	C ₁₃ H ₁₃ N ₃ O ₄	275	74	169-170	0.66	C, 56.72/56.73; H, 4.76/4.78; N, 15.27/15.25; O, 23.25/23.20.
V	C ₁₃ H ₁₅ N ₅ O ₃	289	78	190-191	0.62	C, 53.97/53.99; H, 5.23/5.66; N, 24.21/24.24; O, 16.59/16.55.
VI	C ₁₆ H ₁₉ N ₅ O ₅	361	64	155-157	0.58	C, 53.18/53.20; H, 5.30/5.31; N, 19.38/19.36; O, 22.14/22.15.
VIIa	C ₂₀ H ₂₀ N ₆ O ₄	408	76	165-167	0.68	C, 58.82/58.66; H, 4.94/4.95; N, 20.58/20.60; O, 15.67/15.65
b	C ₂₀ H ₁₉ ClN ₆ O ₄	442	78	160-162	0.50	C, 54.24/54.30; H, 4.32/4.30; Cl, 8.01/8.00; N, 18.98/18.99; O, 14.45/14.44
c	C ₂₁ H ₂₂ N ₆ O ₄	422	66	134-135	0.47	C, 59.71/59.71; H, 5.25/5.26; N, 19.89/19.90;

						O, 15.15/15.16
d	$C_{21}H_{22}N_6O_4$	422	69	130-131	0.49	C, 59.71/59.70; H, 5.25/5.26; N, 19.89/19.90; O, 15.15/15.15
e	$C_{20}H_{21}N_7O_4$	423	66	145-146	0.52	C, 56.73/56.74; H, 5.00/5.00; N, 23.16/23.17; O, 15.11/15.10
f	$C_{20}H_{20}N_6O_5$	424	72	143-145	0.55	C, 56.60/56.66; H, 4.75/4.77; N, 19.80/19.81; O, 18.85/18.88
g	$C_{20}H_{20}N_6O_5$	424	77	125-126	0.54	C, 56.60/56.66; H, 4.75/4.75; N, 19.80/19.81; O, 18.85/18.86
h	$C_{20}H_{20}N_6O_5$	424	69	133-134	0.49	C, 56.60/56.61; H, 4.75/4.75; N, 19.80/19.81; O, 18.85/18.86
i	$C_{20}H_{18}Cl_2N_6O_4$	477	78	120-123	0.48	C, 50.33/50.32; H, 3.80/3.82; Cl, 14.86/14.85; N, 17.61/17.60; O, 13.41/13.41
j	$C_{20}H_{19}N_7O_6$	453	69	160-162	0.50	C, 52.98/53.00; H, 4.22/4.20; N, 21.62/21.66; O, 21.17/21.18
k	$C_{22}H_{24}N_6O_4$	436	79	174-175	0.47	C, 60.54/60.55; H, 5.54/5.52; N, 19.25/19.23; O, 14.66/14.65
l	$C_{20}H_{19}FN_6O_4$	426	77	146-148	0.49	C, 56.34/56.35; H, 4.49/4.50; F, 4.46/4.48; N, 19.71/19.70; O, 15.01/15.00

*chloroform: ethylacetate 3:2

Table-2: Spectrum analysis of compound VII (a-j)

compound 7 (a-l)	IR	NMR	MASS
a	NH- 3346, ArCH- 3016, -CHstretch-2962, C=O-1718, 1630, C=N-1587, C-OC- 1062, C-N-1124	doublet at 8.8, 8.4(2H), 7.3, 8.0 (4H); triplet at 3.5, 1.4(8H), at 7.8, 7.5(2H); singlet at 3.0(2H, -CH ₂); singlet at 6.0, 7.0 (2H, -NH)	M ⁺ 409
b	NH- 3529, ArCH- 3084, -CHstretch-2925, C=O-1624, C=N-1534, C-OC- 1106, C-N-1144, CH-CH-828, C=C-1272, C-Cl-828	doublet at 8.1(1H)&7.4 (3H), 7.1(2H); triplet at 0.9, 1.4(8H) at 7.8(1H); singlet at 3.3(2H, -CH ₂); singlet at 6.0, 5.0 (2H-NH)	M ⁺ 442
c	NH- 3259, ArCH- 2944, -CHstretch-2626, C=O-1750, 1636 C=N-1573, C-O-C- 1106, C-N-	Doublet at 8.0, 7.8(2H), 7.0 (2H), 6.5(2H); triplet at 7.5(1H), 1.0, 2.4(8H); singlet at 3.0(5H, -CH ₂ -	M ⁺ 422

	1144,C=C-1273, N-N-1098,C-N-1161	CH ₃); singlet at 5.0,5.9 (2H-NH).	
d	NH- 3259,ArCH- 2944,- CHstretch-2626,C=O-1750, 1636 C=N-1573, C-O-C- 1106, C-N- 1144,C=C-1273, N-N-1098,C-N- 1161	Doublet at 8.3,7.6(2H),6.5(2H); triplet at 8.0,7.0(2H) ,1.0,2.4(8H); singlet at 3.0(2H,-CH ₂)2.5(2H,-CH ₂); singlet at 5.0,6.1 (2H-NH), 7.5(1H,).	M ⁺ 422
e	-OH-3436, NH- 3219, ArCH- 3088,-CHstretch-2753,C=O-1639, 1628,C=N-1547, C-O-C- 1083, C-N-1298.	Doublet at 8.0, 8.5(2H),7.4, 7.6 (2H),7.0(1H); triplet at 7.6,6.8(2H) , 1.3,2.2(8H); singlet at 5.0(1H,0H), 3.3(2H,-CH ₂); 5.0,6.6 (2H-NH), 4.7 (2H,NH ₂),	M ⁺ 424
f	-OH-3528, NH- 3193, ArCH- 3018,-CHstretch-2923,C=O-1730, 1628,C=N-1547, C-O-C- 1083, C-N-1098.	Doublet at 8.0,8.7(2H),7.4 (2H), 6.5(1H); triplet at 8.3,7.0(2H) , 1.3,4.2(8H); singlet at 4.2(1H,0H), 3.2(2H,-CH ₂); 5.3,6.3 (2H-NH).	M ⁺ 424
g	-OH-3638, NH- 3286, ArCH- 3123,-CHstretch-2921, C=O- 1557, 1680, C=N-1196, C-O-C- 1119, C-N-1083.	Doublet at 8.2, 8.6(2H), 7.4 (2H),7.07.6(2H); triplet at 7.4(2H) , 1.3,4.2(8H); singlet at 4.3(1H,0H), 3.6(2H,-CH ₂); 5.0,6.0 (2H-NH).	M ⁺ 424
h	-OH-3398, NH- 3219, ArCH- 3055,-CHstretch-2853,C=O-1739, 1658,C=N-1547, C-O-C- 1093, C-N-1198.	Doublet at 8.2,8.6(2H),7.4 (2H),7.07.6(2H); triplet at 7.4(1H) , 1.3,4.2(8H); singlet at 4.3(1H,0H), 3.6(2H,-CH ₂); 5.0,6.0 (2H-NH).	M ⁺ 424
i	NH- 3398,ArCH- 3055,- CHstretch-2647,C=O-1658, C=N- 1549, C=C-1267,C-O-C- 1196, C=C-1547, C-N-1093	Doublet at 8.4,8.8(2H),7.6 (2H); triplet at 7.0(1H) , 1.5,3.6(8H); singlet at 4.3,6.0(2H,-NH), 3.6(2H,-CH ₂); 8.0 (1H-Ar).	M ⁺ 477
j	NH- 3388,ArCH- 3032,- CHstretch-2841,C=O-1703, 1633,C=N-1587,C-O-C- 1091, C=C-1547, C-N-1168, NO ₂ -1554.	Doublet at 8.3(1H),7.0 (4H),4.3(1H); triplet at 7.0(1H) , 2.4,2.8(8H); singlet at 3.0(2H,-CH ₂), 4.3,5.6(2H,-NH),	M ⁺ 453
k	NH- 3388, ArCH- 3032,- CHstretch-2841,C=O-1703, 1633,C=N-1587,C-O-C- 1091, C=C-1547, C-N-1168, NO ₂ -1554.	Doublet at 8.5,8.6(2H),7.8,6.0,4.5(3H); triplet at 7.0(1H) , 2.4,2.8(8H); singlet at 3.0(2H,-CH ₂),1.6(6H-CH ₃ , -CH ₃) 5.0.4.7(2H,-NH),	M ⁺ 436
l	NH- 3423,ArCH- 3058,- CHstretch-2985,C=O-1638, C=N- 1527, C-OC- 1106, C-N-1281, C=C-1272,C-F-1400	doublet at 8.0(1H)&7.4 (3H),7.2(2H); triplet at 1.9,1.4(8H) at 7.6(1H); singlet at 3.0(2H,-CH ₂); singlet at 6.0,5.0 (2H- NH)	M ⁺ 426

4. CONCLUSION

With an aim synthesis of 7-Azaisatin derivatives were synthesized from

azaindole, molecular structures, purity of compounds was confirmed.

REFERENCES

1. Ajmer Singh Grewal., *Isatin Derivatives with Several Biological Activities. International Journal of Pharmaceutical Research*, 6 (1), (2014).
2. Jarrahpour A., Khalili A., *Synthesis of 3,3'- [methylene bis (3,1-phenylenenitrilo)] bis[1,3-dihydro]-2H-indol-2-one as a novel bis-Schiff base D. Molbank*, 4, M437, (2005).
3. Chinnasamy Rajaram Prakash a, Sundararajan Raja *Synthesis, characterization and in vitro Antimicrobial activity of some novel 5-substituted Schiff and Mannich base of isatin derivatives. Journal of Saudi Chemical Society*, 17, 337–344, (2013).
4. Ermut.G, Karal. N, Cetin. I, Topcul.M, Birteksoz, S. *Marmara, A Review on Recent Advances and Applications of 5-Chloroisatin and its Derivatives in Design and Synthesis of New Organic Compounds, Pharm. J.*, 17, 147, (2013).
5. Sriram D, Bal TR, Yogeewari P, *Synthesis, Antiviral and Antibacterial Activities of Isatin Mannich Bases, Medicinal Chemistry Research*; 14(4): 211-228, (2005).
6. Havrylyuk.D., Zimenkovsky.B., Vasylenko.O., *Synthesis of New 4-Thiazolidinone-, Pyrazoline-, and Isatin-Based Conjugates with Promising Antitumor Activity, J. Med. Chem.*, 55, 8630, (2012).
7. Viramgama P, *Synthesis and Reactivity of New versatile Heterocyclic compound Izatin and its derivatives, Indian Journal of Applied Research*; 2(3): 9-11, (2012).
8. Mondal. P., Jana.S., Balaji.A., Ramakrishna.R., Kanthal., *Synthesis of Some New Isoxazoline Derivatives of Chalconised Indoline 2-one as a Potential Analgesic, Antibacterial and Anthelmintic Agents J. Young Pharm.*, 4, 38, (2013).
9. Raj R., Singh P., Singh P., Gut J., Rosenthal P.J., Kumar V., *Azide-alkyne cycloaddition to 1H-1,2,3-triazole-tethered 7-chloroquinoline-isatin chimeras Synthesis and antimalarial evaluation, Eur. J. Med. Chem.*; 62, 590, (2013).
10. Pandeya SN., Sriram D., Nath G., DeClercq E., *Synthesis, antibacterial, antifungal and anti-HIV evaluation of Schiff and Mannich bases of isatin derivatives with 3-amino-2-methylmercapto quinazolin-4(3H)-one. Pharmaceutica Acta Helvetiae*, 74(1): 11-17, (1999).
11. Kiran G., Sarangapani M., Gouthami T., Reddy ARN., *Synthesis, characterization, and antimicrobial and antioxidant activities of novel bis-isatin carbohydrazone derivatives. Toxicological & Environmental Chemistry*, 95(3), 367-378, (2013).
12. Singh UK., Pandeya SN., Singh A., Srivastava BK., Pandey M., *Synthesis and Antimicrobial Activity of Schiff's and N-Mannich Bases of Isatin and Its Derivatives with 4- Amino-N-Carbamimidoyl Benzene Sulfonamide. International Journal of Pharmaceutical Sciences and Drug Research*, 2(2): 151-154, (2010).
13. Varma RS., Nobles WL., *Antiviral, Antibacterial and Antifungal Activities Of Isatin N-mannich bases. Journal of Pharmaceutical Sciences*, 64(5): 881-882, (1975).
14. Shmidt MS, Reverdito AM, Kremenchuzky L, Perillo IA, Blanco MM, *Simple and efficient microwave assisted Nalkylation of isatin. Molecules*; 13(4): 831-840, (2008).
15. Breinholt J., Demuth H., *(5-(3-methyl-2-butenyl) indole-2, 3-dione): an antifungal isatin derivative from Chaetomium globosum. Acta Chem Scand.*, 50, 443, (1996).
16. Kumar A., Kaur H., Kumar S., *Synthesis, Antipsychotic and Anticonvulsant Activity of some new pyrazolinyl/ isoxazolinyndol-2-ones. Int J ChemTech Res.*, 2(2); 1010-1019, (2010).
17. Varma RS., Nobles WL, *Antiviral, antibacterial and antifungal activities of isatin N-mannich bases. Journal of Pharmaceutical Sciences*; 64(5): 881-882, (1975).



18. Malawska B., *New Anticonvulsant Agents. Current Topics in Medicinal Chemistry*, 5(1): 69-85, (2005).
19. Qing He., Gu Zhan., Wei Du and Ying-Chun Chen., *Application of 7-azaisatins in enantioselective Morita– Baylis–Hillman reaction. Beilstein J. Org. Chem*, 12, 309–313, (2016).
20. A.M. Amani., *Synthesis, characterization and biological activities of some novel isatin derivatives. Bulgarian Chemical Communications*, Volume 46, Number 4, 795- 800, (2014).
21. A.W. Bauer., W.M. Kirby., J.C. Sherris., M. Turck., *Antibiotic Susceptibility Testing by a Standardized Single Disk Method. Am. J. Clin. Pathol.*, 45, 493, (1996).
22. Sulthan, K., Ibrahim, S., Syed Ali Padusha, M., & Abdul Jameel, A. *Synthesis, Characterization and Antimicrobial Activity Of Some Novel Mannich bases derived from N-Methyl Piperazine. Int J ChemTech Res*, 3(4), 1974-7 (2011).