Synthesis and Study of Some New Mannich Bases Derived From Isatin (1H - Indole – 2, 3 – Dione) with Substituted Sulfonamides and Their Antimicrobial Activity

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Abstract

A series of new amino – alkylated Mannich bases were prepared by reaction of substituted sulfonamides with formaldehyde and isatin (1H- indole – 2, 3- dione). Mannich bases 4(f-j) were prepared by reaction of isatin with formaldehyde and secondary amines. The structure of the newly synthesized compounds was confirmed by melting points, TLC, and FTIR, ^{1}H-NMR spectral data. All the newly synthesized Mannich bases are introduced for antimicrobial activity against the bacteria: ***B.subtillis , E.coli and K. pneumoniae***. All the Mannich bases showing better antibacterial activity to the corresponding sulfonamides, and therefore the results obtained showed available attempt for the drugs building.

Keywords: Isatin, Substituted Sulfonamides, Mannich bases, Antimicrobial activity

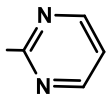
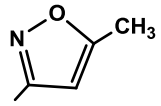
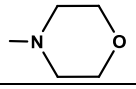
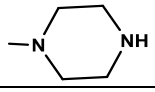
Introduction

Isatin is a synthetically versatile substrate that can be used to prepare a large variety of heterocyclic compounds, such as indoles and quinolines, and as a raw material for drug synthesis [(1)].Isatin, chemically know as 1H-indole – 2, 3-dione, has become a popular topic due to its various uses. The synthetic versatility of isatin has led to the extensive use of this compound in organic synthesis[(2)] .The NH group compounds of the isatin series are capable of entering into N-alkylation and N-acylation and into Mannich and Michael reaction [(3)].Mannich bases and its derivatives are of great importance in medicinal chemistry because of their wide variety of biological and pharmacological applications [(4,5)].A large number of Mannich bases of isatin derivatives have been found to exhibit various biological activities such as anti–inflammatory[(6)], antifungal[(7,8)], antibacterial[(9,10)], antiviral [(11,12)], anticancer[(13-15)], and anti HIV activities [(16)]. The sulfonamide is well know antibacterial [(17,18)]. Isatins are very important compounds due to their antifungal properties [(19)].

Experimental

Melting points of the newly synthesized compounds were determined in open capillary tubes.IR spectra were recorded on a Shimadzu 8400 spectrometer in KBr pellets and ^{1}H-NMR spectra on a Bruken Ultra Shield (300 MHZ FT NMR) spectrometer using TMS (Tetramethyl Silane) as internal reference (chemical shift in δ ppm).Purity of the compounds was checked by TLC (Thin Layer Chromatography) on silica gel plates and spots were visualized by exposure to iodine vapours.The physical data of the prepared compounds are listed in Table 1.

Table 1 Some physical data of the synthesized compounds

Comp. NO.	R	M.F	M.W	M.P^0(C)	R_f chloroform: methanol (9:1)	Yield %
4a		$C_{19}H_{15}N_5O_4S$	409	190-192	0.56	76
4b		$C_{19}H_{16}N_4O_5S$	412	135-137	0.60	83
4c	-H	$C_{15}H_{13}N_3O_4S$	331	198-200	0.69	70
4d	$-COCH_3$	$C_{17}H_{15}N_3O_5S$	373	168-170	0.55	77
4e	$-C=NHNH_2$	$C_{16}H_{15}N_5O_4S$	373	205-207	0.62	68
4f	$-N(C_2H_4OH)_2$	$C_{13}H_{16}N_2O_4$	264	115-117	0.41	81
4g	$-N(C_6H_5)_2$	$C_{21}H_{16}N_2O_2$	328	100-102	0.72	85
4h	$-N(CH_3)_2$	$C_{11}H_{12}N_2O_2$	204	110-112	0.70	62
4i		$C_{13}H_{14}N_2O_3$	246	155-157	0.71	67
4j		$C_{13}H_{15}N_3O_2$	245	160-162	0.55	88

Synthesis of Mannich bases from primary amines (Substituted Sulfonamides) 4(a-e)

General procedure for preparation of 4-[(2, 3-dioxoindolin-1-yl) methyl amino]-N-substituted benzene sulfonamide

Mannich bases of isatin were prepared by taken isatin (0.01mol) dissolved in 20 ml of ethanol with derivatives sulfonamide (0.01mol) and 2.5 ml (0.01mol) of formaldehyde solution (37 % v/v) was added slowly with constant stirring. The pH of the mixture was adjusted to 3.5 by adding 0.5 ml of HCl. The mixture was kept at efficient ice cooling for half an hour, and then refluxed on water bath. Reflux time varied with the sulfonamide used. The refluxed mixture was kept at 0^0C for 4 days when crystalline product was obtained. The product was crystallized from absolute ethanol and dioxane – water (1:1) (Table 1).

Synthesis of Mannich bases from secondary amines 4(f-j)

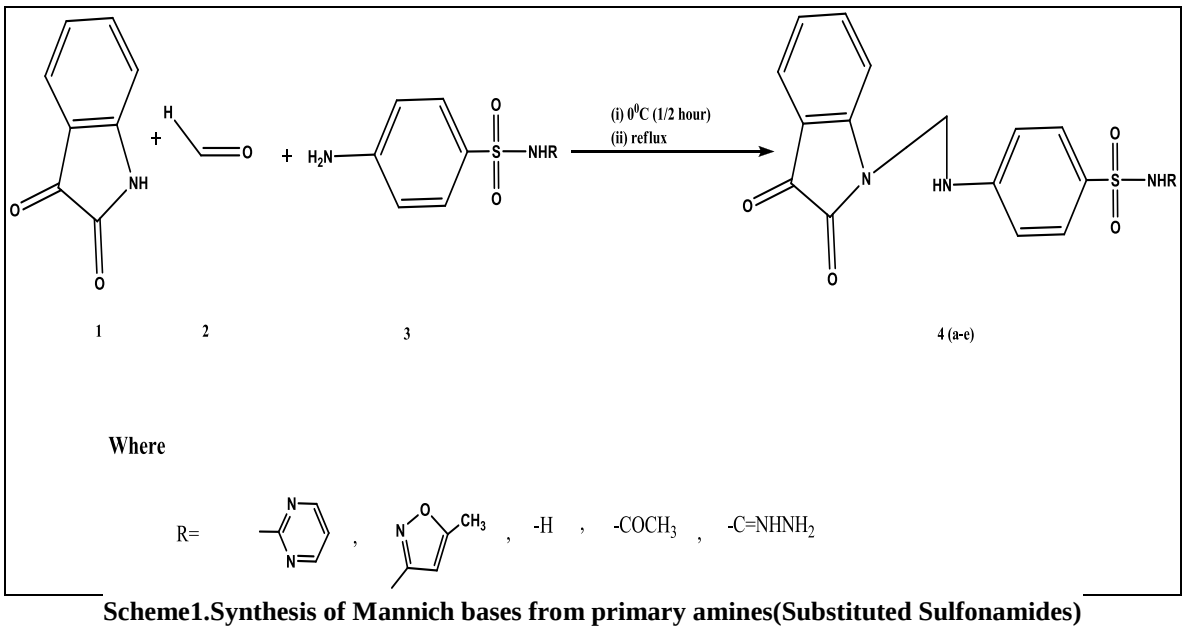
General procedure for preparation of 1-[(bis substituted amino) methyl] indoline-2, 3- dione

Secondary amine (0.01 mol) was added to an ethanolic solution (50 ml) of isatin (0.01 mol) in a flat bottom flask. Amount of 0.4 ml (0.015 mol) of formaldehyde solution (37 % v/v) was added slowly with constant stirring .The reaction mixture was stirred at 70 – 75 ^{0}C for 3 -8 hours , depending upon the secondary amine .The remaining portion of formaldehyde solution was added in two installments after 2 hours , respectively . The reaction mixture was kept overnight in the refrigerator. The excess of solvent was distilled off from the reaction mixture under reduced pressure. It was again kept for crystallization in the refrigerator. The product was crystallized from absolute ethanol (Table 1).

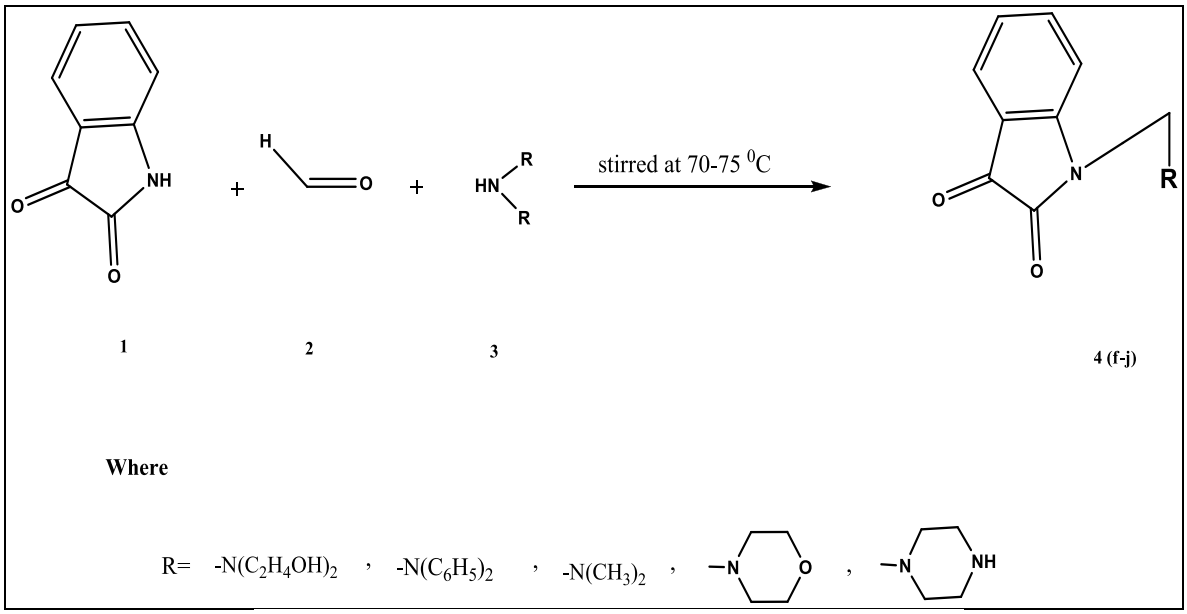
Results and Discussion

The first part of the research includes the preparation of a series of mannich bases 4(a-e) by the reaction of substituted sulfonamides with formaldehyde and isatin (1H-indole –2, 3-dione), and the second part includes preparation of compounds 4(f-j) by the reaction of isatin with formaldehyde and secondary amines.The structures of the synthesized compounds was confirmed by melting point, TLC, and FTIR, ^{1}H-NMR spectral data.

In vitro antimicrobial activity which was evaluated by disc diffusion method for newly synthesized compounds against, *B.subtillis* , *E.coli and K. pneumoniae*, at varying concentrations 40, 80, 160, mg/ml. The inhibitory effects of the samples were measured against the bacteria after incubation for 24 hours at 37^{0}C.The newly synthesized Mannich bases appeared to be very potent and outstanding antibacterial agents with promising activity and are found safer. Mannich base 4d, 4e was found to be most significantly active over others against *E.coli*. Compounds 4a, 4b, 4c, 4d, 4g were found to be significantly active over others against *K.pneumonie*. *B.Subtilis* was significantly inhibited by Mannich bases 4b, 4c, 4d, 4e fallowed by over other Mannich bases.All the Mannich bases 4(a-j) showed better antibacterial activity to the corresponding sulfonamides 3(a-e).



Scheme1.Synthesis of Mannich bases from primary amines(Substituted Sulfonamides)



Scheme 2. Synthesis of Mannich bases from Secondary amines

Table 2 Some spectroscopic data of the synthesized compounds

Comp. NO.	IR (KBr ,υ cm^{-1})	^{1}H-NMR (DMSO - d_6 ,δ ppm)
4a	3340 (N-H str.of SO_2NH), 3050 (Ar-H str.), 2914 (C-H str. $_{(as)}$ in CH_2), 1620(C=N str.), 1715 (C=O str. in isatin), 1342(S=O str.$_{(as)}$ in SO_2NH) , 835 out of plane(C-H str. in disubstituted aromatic ring)	
4b	3337 (N-H str.of SO_2NH), 3060 (Ar-H str.), 2918 (C-H str. $_{(as)}$ in CH_2), 1623(C=N str.), 1721(C=O str. in isatin) , 1348(S=O str.$_{(as)}$ in SO_2NH) , 833 out of plane(C-H str. in disubstituted aromatic ring)	
4c	3379, 3350 (N-H str.of SO_2NH), 3116 (Ar-H str.), 2962(C-H str. $_{(as)}$ in CH_2), 1726 (C=O str. in isatin) , 1326(S=O str.$_{(as)}$ in SO_2NH) , 821 out of plane (C-H str. in disubstituted aromatic ring)	
4d	3350 (N-H str.of SO_2NH), 3070 (Ar-H str.), 2922 (C-H str. $_{(as)}$ in CH_2),1650(C=O str.in acetamide), 1713(C=O str. in isatin) , 1344(S=O str.$_{(as)}$ in SO_2NH) , 844 out of plane (C-H str. in disubstituted aromatic ring)	1.91(m,3H,CH_3); 2.5 (S,DMSO); 3.3 (S,H_2O in DMSO); 4.38 (S, 2H, CH_2); 6.5 – 8.8 (m , Ar-H); 10.14 (S, 1H , NH) ; 11.9 (S , 1H , SO_2NH)
4e	3333, 3305 (N-H str.of SO_2NH), 3100 (Ar-H str.), 2923 (C-H str. $_{(as)}$ in CH_2), 1615(C=N str.), 1732(C=O str. in isatin) , 1331(S=O str.$_{(as)}$ in SO_2NH) , 841 out of plane(C-H str. in disubstituted aromatic ring)	
4f	3200(O-H str.), 3088 (Ar-H str.), 2961 (C-H str. $_{(as)}$ in CH_2), 1724(C=O str. in isatin) , 860out of plane(C-H str. in disubstituted aromatic ring)	
4g	3035 (Ar-H str.), 2922 (C-H str. $_{(as)}$ in CH_2), 1705(C=O str. in isatin) , 844 out of plane(C-H str. in disubstituted aromatic ring)	3.3 (S , H_2O in DMSO);2.5 (S,DMSO); 4.83 (S,2H,CH_2) ; 6.5-9(m, Ar-H)
4h	3069 (Ar-H str.), 2932 (C-H str. $_{(as)}$ in CH_2), 1727(C=O str. in isatin) , 829 out of plane(C-H str. in disubstituted aromatic ring)	
4i	3059 (Ar-H str.), 2944 (C-H str. $_{(as)}$ in CH_2), 1716(C=O str. in isatin) , 863 out of plane(C-H str. in disubstituted aromatic ring)	
4j	3337 (N-H str.), 3044 (Ar-H str.), 2936 (C-H str. $_{(as)}$ in CH_2), 1245, 1080(C-O-C str.) 1713(C=O str. in isatin), 845 out of plane(C-H str. in disubstituted aromatic ring)	

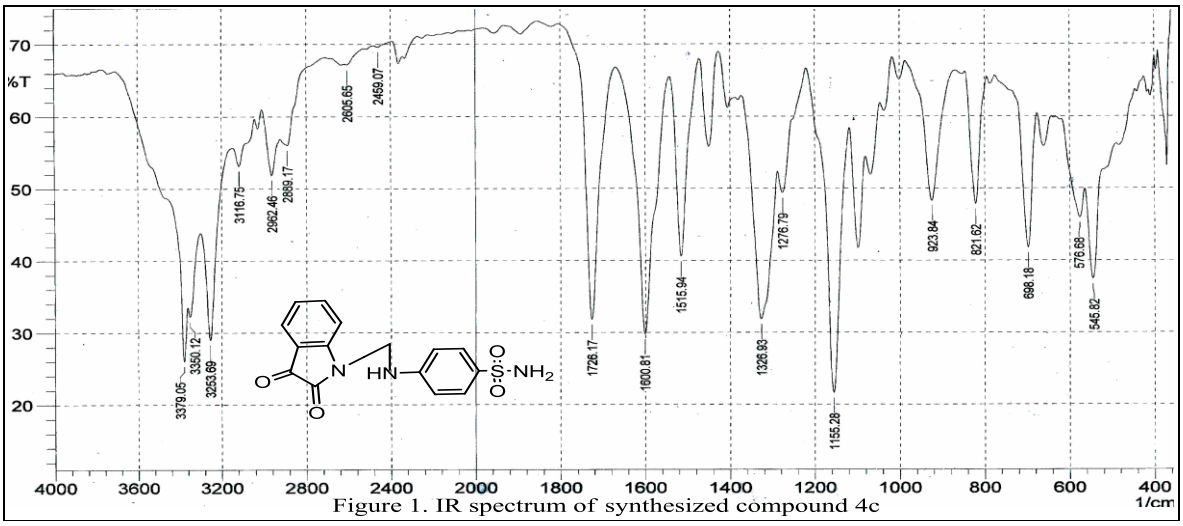


Figure 1. IR spectrum of synthesized compound 4c

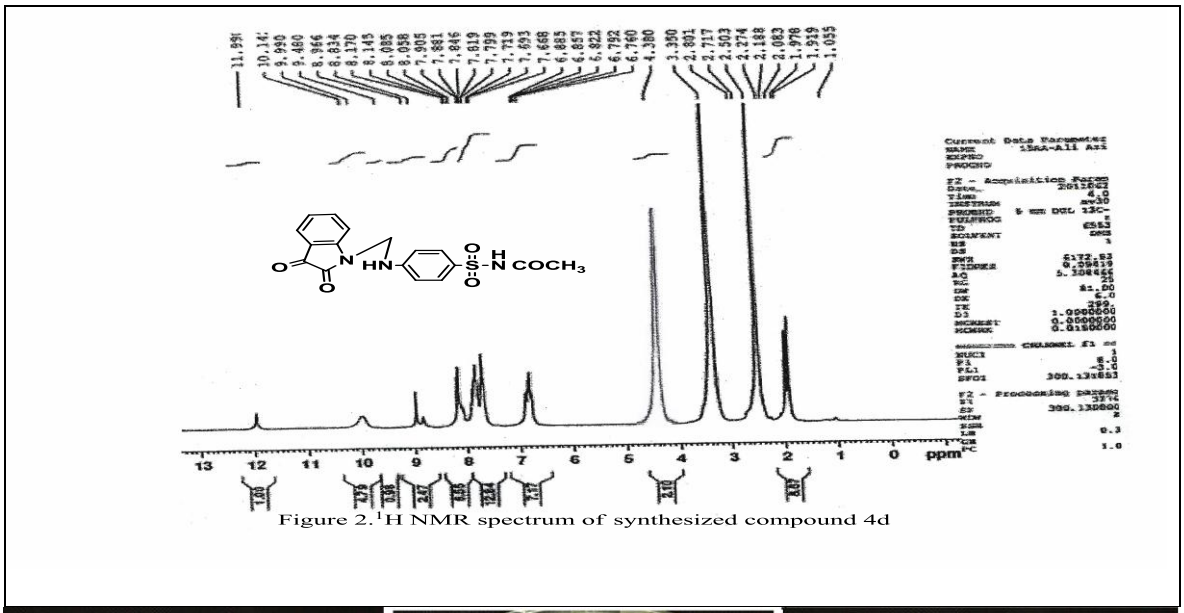


Figure 2.^{1}H NMR spectrum of synthesized compound 4d

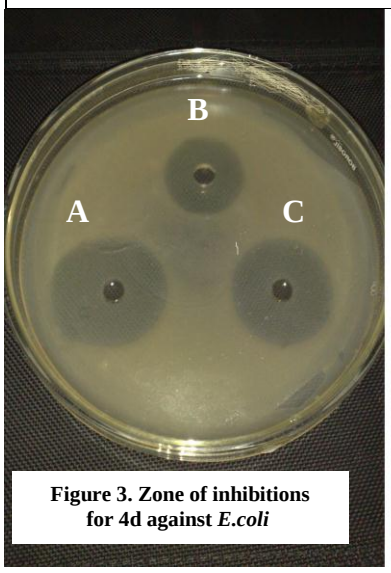


Figure 3. Zone of inhibitions for 4d against *E.coli*

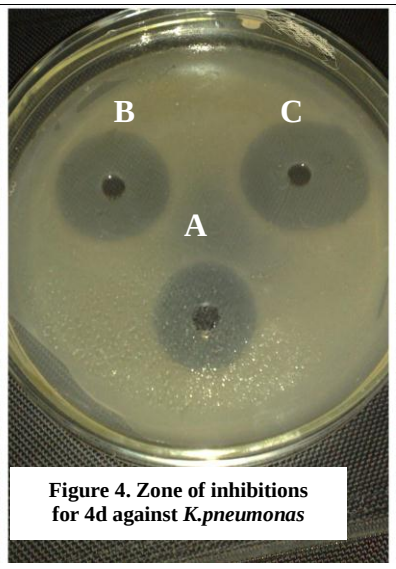


Figure 4. Zone of inhibitions for 4d against *K.pneumonas*

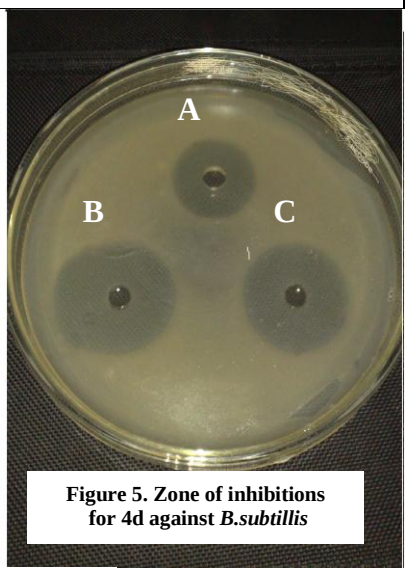


Figure 5. Zone of inhibitions for 4d against *B.subtillis*

160mg /ml Conc. in C= , 80mg /ml Conc. in B= ، Conc. in 40mg /ml A=

Table 3 Antimicrobial activity of the Sulfonamides 3(a-e) and Mannich bases 4(a-j)

Comp. NO.	*E.coli* (Zone of inhibition in mm)				*K.pneumonas* (Zone of inhibition in mm)				*B.subtillis* (Zone of inhibition in mm)			
	Concentration in mg / ml				Concentration in mg / ml				Concentration in mg / ml			
	40	*80*	*160*	*Avg.*	*40*	*80*	*160*	*Avg.*	*40*	*80*	*160*	*Avg.*
3a	++	++	++	++	+	+	+	+	–	–	–	–
3b	+	+	++	+	–	–	–	–	++	++	++	++
3c	+	++	++	++	+	+	+	+	++	++	++	++
3d	++	++	++	++	++	++	++	++	–	–	–	–
3e	++	++	+++	++	–	–	–	–	+++	+++	+++	+++
4a	++	++	+++	++	++	+++	+++	+++	++	++	++	++
4b	+	++	+++	++	++	+++	+++	+++	++	+++	+++	+++
4c	++	++	+++	++	++	+++	+++	+++	+++	+++	+++	+++
4d	+++	+++	+++	+++	+++	+++	++	+++	+++	+++	+++	+++
4e	+++	+++	+++	+++	++	++	+++	++	+++	+++	+++	+++
4f	++	++	++	++	++	++	++	++	++	++	+++	++
4g	++	++	+++	++	++	+++	+++	+++	+	+	++	+
4h	++	++	++	++	++	++	++	++	+	+	+	+
4i	++	++	++	++	++	++	+++	++	++	++	++	++
4j	++	++	++	++	++	++	++	++	++	++	+++	++

Key to symbols:
Inactive = - (inhibition zone <6mm), **Moderately active** = ++ (inhibition zone 9 - 12mm)
Slightly active = + (inhibition zone 6 - 9 mm), **Highly active** = +++ (inhibition zone >12mm)

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تخليق ودراسة بعض قواعد مانخ الجديدة المشتقة من ايزاتين (١ H – اندول – ٣،٢ – دايون) مع مشتقات السلفونواميدات ونشاطها المضادة للميكروبات

خلف احمد جاسم البياتي

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(تاريخ الاستلام: ٧ / ٢ / ٢٠١٢ ---- **تاريخ القبول:** ١٣ / ٣ / ٢٠١٢)

الملخص

تم تحضير سلسلة جديدة من قواعد مانخ ، حيث تم تفاعل الايزاتين (١ H – *اندول* – ٣،٢ – *دايون*) مع الفورمالديهايد و مشتقات السلفونواميدات للحصول على معوضات الايزاتين (4(a-e)4 ، اما قواعد مانخ (4(f-j فقد تم تحضيرها من خلال مفاعلة الايزاتين مع امينات ثانوية مختلفة والفورمالديهايد ، تم تشخيص المركبات المحضرة بواسطة الطرق الطيفية IR، ^{1}H-NMR بالاضافة الى قياس درجة الانصهار والنقاوة (TLC) كذلك درست الفعالية البايولوجية للمركبات المحضرة ضد انواع مختلفة من البكتيريا لفعاليتهم المضادة باستخدام ***B.subtillis , E.coli , K. pneumoniae*** . جميع قواعد مانخ بينت نشاطا مضادا للبكتيريا افضل من السلفونواميدات المقابلة ، وبالتالي النتائج المستحصلة هي محاولة جيدة لبناء عقاقير جديدة