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Synthesis and Biological Evaluation of Some Tetrahydroquinoline Compounds Derived from 4- Aminobenzenesulfonamid

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ABSTRACT

In the present study, five compounds of 1,2,3,4-tetrahydroquinolines derivatives of 4- Aminobenzenesulfonamid were prepared through Imines – Diels – Alder reaction by reacting Schiff bases with cinnamic acid and Bf3 Et2O in ethanol. The Schiff bases were synthesized by treating various aromatic aldehydes with 4-Aminobenzenesulfonamid. The structures of the synthesized compounds were determined on the basis of their FTIR, UV and C.H.N spectral data. The in vitro antibacterial and antifungal activities of the compounds were evaluated by paper disc diffusion method. The synthesized compounds were determined by using the Minimum Inhibitory Concentration (MIC).Significant antimicrobial activities were observed for some compounds of the series.

Introduction :

The chemistry of 1,2,3,4-tetrahydroquinolines is of interest among many investigations during recent years. The growing interest in them can be explained by their biological activities. Substituted tetrahydroquinolines are the core structures in many important pharmacological agents, .(1-2) many relatively simple synthetic 1,2,3,4-tetrahydroquinolines are already in use or have been tested as potential drugs.(3-4) Besides pharmaceutical applications, tetrahydroquinoline derivatives are useful as pesticides.(5) antioxidants,(6) corrosion inhibitors, (7) and active components of various dyes. (8) In addition, they also have found application in modern recording technologies.(9-10) Consequently, synthesis methodologies for preparing tetrahydroquinoline derivatives have attracted considerable interest and several methods offering good results have been reported.(11) The nature, number, and relative location of the substituents are the key parameters to consider before choosing a method. Until now, much attention has been paid to the development of synthesis of mono functional 1,2,3,4 tetrahydroquinolins,but the bifunctional1 ,2,3,4tetrahydroquinoline derivatives have been seldom investigated. The present work is directed towards synthesis of some 1,2,3,4-tetrahydroquinolines of sulfonamides prepared through Imines – Diels – Alder reaction by use the derivatives of Schiff bases with cinnamic acid and Boron tri fluoride ethyl ether (Bf3 Et2O) as catalyst (scheme 1.). All the synthesized compounds have been characterized on the basis of their m.p, IR, UV and C.H.N data. The antimicrobial activity of these compounds was evaluated by Agar diffusion method.The main aim of the present work is to find new molecules such as these by synthesizing several 1,2,3,4-tetrahydroquinolines from sulphonamide.

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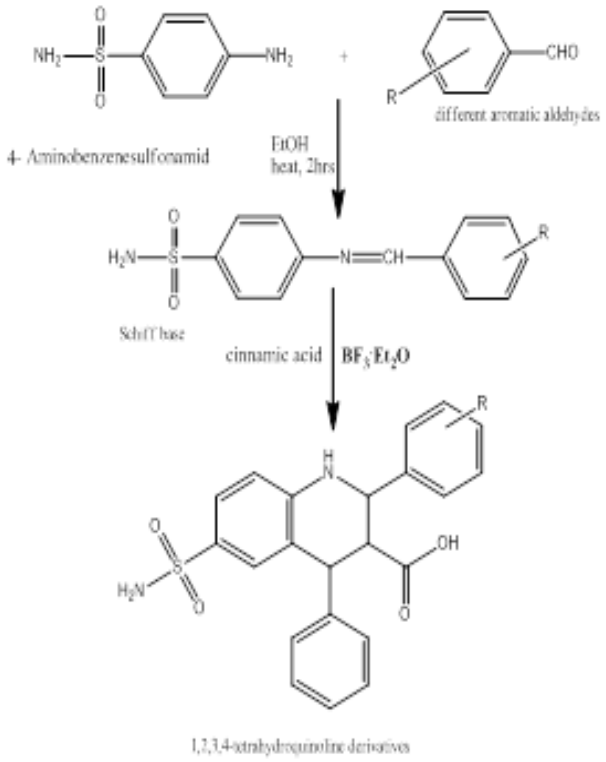


(scheme 1)

MATERIALS AND METHODS

Experimental:

Melting points of the synthesized compounds were determined by open capillary and are uncorrected.The developed chromatographic plates were visualized under UV at 254nm. IR spectra were recorded us KBr discs on FTIR 100 fishe C.H.N Analyzer Type 1106 Carlo Ferba spectrophotometer.

General procedure for the synthesis of Schiff bases (1-5).

The Schiff base was prepared by reaction of equimole of4-aminobenzenesulphonamide and substituted aromatic aldehydes. Each reactant was dissolved in a minimum amount of ethanol, then mixed together. The solution was refluxed for 8 hrs. then cool to room temperature and poured into ice cold water. The solid product was collected through filtration and then dried using drying oven at 80 ºC. The product was redissolved in ethanol for recrystalliziation and then dried to give a product. (12)

Preparation of Tetrahydro quinoline compounds (6-10)

(0.019mol) of the Schiff base was Melted in a solvent toluene (2ml) with cinnamic acid (3 gm , 0.013 mol) . As the mixture was heated to complete the solubility . Then ,(3 ml) of Bf3 Et2O was added gradually to the mixture with continuous stirring by magnetic stirrer for five hrs. with room temperature 25 oC . The mixture was cooled and the solid product was filtrated and then dried and recrystalized by using the ethanol solvent .

ANTIMICROBIAL ACTIVITY

The antibacterial activity of the synthesized compounds was tested against Staphylococcus aureus, Staphylococcu epidermidis, Klebsiella pneumonia and Escherichia coli using nutrient agar medium. The antifungal activity of the compounds was tested against Candida albicans and Aspergillus niger using sabouraud dextrose agar medium .

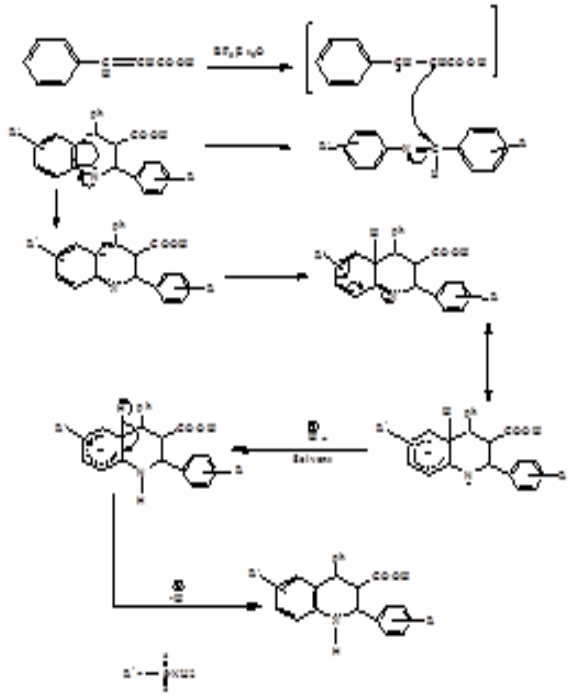
Paper Disc Diffusion Medium

A suspension of the organisms were added to sterile nutrient agar media at 45oC and the mixture was transferred to sterile Petri dishes and allowed to solidify. Sterile discs 6mm in diameter (made from Wattmann filter paper previously sterilized in U.V. lamp) dipped in specified concentration solutions of synthesized compounds and standard were placed on the surface of agar plates. A disc dipped in DMF was also used as control. The plates were left for 1 hour at room temperature as a period of preoccupation diffusion to minimize the effects to variation in time between the applications of the different solutions. The plates were then incubated at 37 oC for 24 hours and observed for antibacterial activity. The diameters of zone of inhibition were measured and compared with that of the standard, the values were tabulated. Ciprofloxacin (50 µg g/disc) and Ketoconazole (50 µg g/disc) were used as standard for antibacterial and antifungal activity respectively. The observed zone of inhibition is presented in Table4.

MinimumInhibitory Concentration:

Minimum Inhibitory Concentration (MIC) of the test compounds were determined by agar streak dilution method. 1 mg/ml stock solution of the synthesized compounds were made using DMF as the solvent. From this stock solution, required quantities of drug solutions were mixed with the known quantities of molten sterile agar media aseptically to provide the following concentrations1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45, 50 and100 g/ml. About 20 ml of the media containing the drug was dispensed into each sterile Petri dish. Then the media were

allowed to get solidified. Microorganisms were then streaked one by one on the agar plates aseptically. After streaking all the plates were incubated at 37oC for 24 hours/48 hours for bacterial and fungus activity respectively. Then the plates were observed for the growth of microorganisms. The lowest concentration of the synthesized compounds inhibiting the growth of the given bacteria/fungus was considered as minimum inhibitory concentration (MIC) of the test compounds against that bacteria or fungi on the plate. The MIC values of each compound against various bacteria and fungus were tabulated in Table 4.



(Scheme2)

RESULTS AND DISCUSSION

It is possible to clarify the mechanism of preparation of compounds tetrahydroquinolines as shown below.

The newly prepared tetrahydroquinolines were characterized by spectral (UV, IR and C.H.N). The absorption bands of novel tetrahydroquinolines are totally agree with the anticipated structure. The physical characterization and spectral data are presented in Tables 1 ,2,All the synthesized compounds were evaluated for in vitro antibacterial and significant antifungal activities. Among the compounds, compounds 2 and 4 posscess significant activity against bacterial organisms whereas 3 showed very less activity.

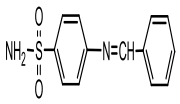
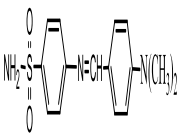
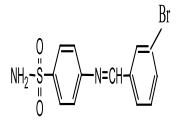
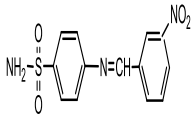
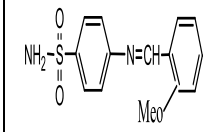
Other compounds showed moderantibacterial activity. Compoundand 3 and 5,showed Zone of inhibition (for 50µg g/ml) and MIC of the synthesized compounds have been summarized in Table4

Table 1. Physical characterization data of the synthesized compounds (6-10)

No.	Compounds	Molecular Weight	Molecular formula	M.P °C	Elemental Analysis found (calcd.)		
					C	H	N
6	2,4-diphenyl-6-sulfamoyl-1,2,3,4-tetrahydroquinoline-3-carboxylic acid	408.47	C22H20N2O4S	278-276	64.69 (64.48)	4.94 (4.65)	6.86 (6.66)
7	2-(4-(dimethylamino)phenyl)-4-phenyl-6-sulfamoyl-1,2,3,4-tetrahydroquinoline-3-carboxylic acid	451.54	C24H25N3O4S	230-228	63.84 63.64)	5.58 (5.48)	9.3 (9.19)
8	2-(3-bromophenyl)-4-phenyl-6-sulfamoyl-1,2,3,4-tetrahydroquinoline-3-carboxylic acid	487.37	C22H19BrN2O4S	244-242	54.22 (54.15)	3.93 (3.74)	5.75 (5.54)

9	2-(3-nitrophenyl)-4-phenyl-6-sulfamoyl-1,2,3,4-tetrahydroquinoline-3-carboxylic acid	453.47	C22H19N3O6S	210-208	58.2 (58.18)	4.22 (4.10)	9.27 (9.05)
10	2-(2-methoxyphenyl)-4-phenyl-6-sulfamoyl-1,2,3,4-tetrahydroquinoline-3-carboxylic acid	38.50	C23H22N2O5S	234-232	63.00 (62.96)	5.06 (4.94)	6.39 (6.17)

Table 2:- characteristic IR spectral data (υ cm^{-1}) of shiff bases (1 – 5)

NO.	Structure	υ(C=N)	υ (C=C)	Y(NH_2)	υ(SO_2)	Others υ
1		1630	1500	3120	1110	-
2		1596	1540	3210	1150	-
3		1640	1584	3200	1154	Ar-Br (570)
4		1646	1578	3310	1200	Ar-NO2 (1260)
5		1620	1600	3115	1158	C-H methoxy (2910)

Tsble3:- characteristic IR spectral data (υ cm^{-1}) of tetrahydroquinolines compounds (6 – 10)

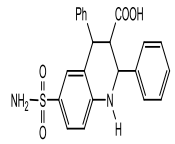
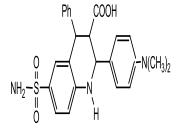
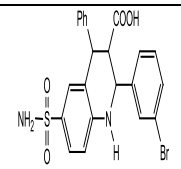
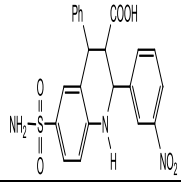
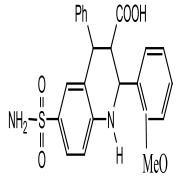
COM. NO.	Structure	υ(N-H) hetero	υ (C-N)	υ(C=O) carboxyl	υ(OH) carboxyl	υ(C-H) romatic
6		3420	1220	1630	3400	3073
7		3500	1210	1660	3420	3020
8		3320	1260	1656	3510	3100
9		3510	1260	1646	3500	3210
10		3400	1240	1666	3110	3100

Table 4. Antimicrobial activity of compounds 6 -10

Comp. NO.		Zone of inhibition (mm)				MIC (µg/disc)					
		Antibacterial activity			Antifungal activity		Antibacterial activity			Antifungal activity	
		S.A.	S.E.	K.P.	E.C.	A.N.	C.A.	S.A.	S.E.	K.P	E.C.	A.N	C.A.
6	12	12	16	16	23	18	10	17	13	14	10	10

7	18	16	26	19	25	18	11	12	10	10	14	12
8	20	17	17	16	28	17	15	16	11	12	15	13
9	20	18	22	23	16	15	12	13	13	10	10	10
10	11	16	18	14	15	22	10	11	11	17	12	14
C.P.	22	23	28	29	-	-						
K.C.	-	-	-	-	30	24						
C.	-	-	-	-	-	-						

S.A. - *Staphylococcus aureus*; S.E. - *Staphylococcus epidermidis*; K.P. *Klebsiella- pneumonia*
E.C. - *Escherichia coli*; A.N. - *Aspergillus niger*; C.A. - *Candida albicans*;
C.P. - Ciprofloxacin (50µg/ml); K.C. - Ketaconazole (50µg/ml);
C - Control
Concentration of the synthesized compounds: 50µg/ml

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تحضير ودراسة الفعالية البايولوجية لبعض مركبات رباعي هيدروكوينولين المشتقة من 4-امينوبنزين سلفون أمايد.

محمد عبد كاظم سميعة جمعة خماس

الخلاصة

في هذه الدراسة تم تحضير خمسة مركبات من 4,3,2,1- رباعي هيدروكوينولين المشتقة من 4- امينو بنزين سلفونمايد و قد حضرت من خلال طريقة تفاعل Imines – Diels – Alder بوساطة تفاعل قواعد شيف مع حامض السينامك بوجود Bf3 Et2O في الايثانول . قواعد شيف قد حضرت بوساطة تفاعل كميات متساوية المولات من الالديهيدات الاروماتية مع 4- امينو بنزين سلفونمايد . شخصت المركبات المحضرة باستخدام C.H.N , UV , FTIR.. تم تقدير نشاطها الحيوي تجاه البكتريا و الفطريات باستخدام طريقة الانتشار حول القرص حيث قدرت المركبات المحضرة باستخدام طريقة التركيز المثبط الأدنى فيما أعطت بعض المركبات فعالية جيدة تجاه البكتريا.