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RESEARCH ARTICLE

Synthesis, Characterization and Antifungal Activity of Some Indolo [2-3-b] Quinoxaline Derivatives

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Abstract

In this research the focus was to synthesis new series of indolo [2-3-b] quinoxaline through the reaction of Isatin with 4-methyl-o-phenylenediamine in the presence of water to obtain 2-methyl-6H-indolo [2-3-b] quinoxaline (A_1). Compound (A_2) was prepared by refluxing of compound (A_1) with chloroacetyl chloride in the presence of triethylamine, compound (A_2) was treated with hydrazine hydrate to give 2-hydrazino-1-(2-methyl-indolo[2,3-b]quinoxalin-6-yl)-ethanone (A_3), While the Schiffe bases (A_4- A_8) were synthesized by the condensation of compounds (A_3) with aromatic aldehydes. The prepared compounds identified by spectral methods [FTIR, ^{1}H-NMR] and measurement some of its physical properties. Furthermore we were studied the effects of the preparing compounds on some strains of Antifungal activity.

Keywords: *Isatin, Indolo [2-3-b] quinoxaline, Antifungal Activity, Schiffe base.*

Introduction

Indole has a benzene ring fused with a pyrrole nucleus [1]. Indole is the parent substance of a large number of important compounds that occur in nature [2]. Indole chemistry began to develop with the study of the dye indigo. Indole derivatives have attracted special attention because their possessing various of pharmacological activities.

It's an important class of organic heterocyclic which are commonly found in nature and they have acquired more importance in the recent years due to their wide range of biological and pharmacological activities [3].

Schiff bases are significant class of compounds in medicinal and pharmaceutical fields as they have also been shown to exhibit wide-ranging biological activities, including antifungal [4], antibacterial [5], anti-inflammatory [6], anticancer [7], antimicrobial [8, 9], antiviral [10], anti-proliferative [11], analgesic [12], Antioxidants [13]. Schiff bases are additionally utilized as catalysts, dyes, polymers and corrosion inhibitors [14].

Materials and Methods

All chemicals and solvents used during synthesis compounds were purchased from a number of different companies such as Merck, BDH, Sigma Aldrich and Fulka.

They were used as obtained without further purification. The purity of the synthesized compounds was checked it by TLC sheet and the chemical structures were characterized by FT-IR, ^{1} H NMR .The Melting points of compounds were determined on GallenKamp(MFB-600) melting point apparatus and are uncorrected.

FT-IR spectra of compounds were recorded PERKIN ELMER SPEACTUM-65 within the range [5000-400] using KBr Disc in the Chemistry Department /Diyala University. The^{1}H-NMRspectra was recorded by Bruker 400 MHz spectrophotometer with TMS as internal standard and deuterated DMSO was used as a solvent.

Synthesis Methods

Synthesis of 2-methyl-6H-indolo [2, 3-b]quinoxaline [A_1]

Isatin (1.71 g, 11.6 mmol) was dissolved in

refluxing aqueous sodium bicarbonate hydrochloric solution (2.38 g, 28.3 mmol in 160 ml water).

4-methyl-o-Phenylenediamine (1.6 g, 13.29mmol) was added and the mixture was refluxed 4 h. The completion of the reaction was checked by using TLC (mobile phase: ethyl acetate: hexane 1:3). After cooling to room temperature 25 ° C, the solution was acidified with acetic acid and left to stay overnight. The solution is then deposited, filtered and washed with water, the precipitate appeared was dried and recrystallized from ethanol to give pure 2-methyl-6H-indolo [2, 3-b]quinoxaline. Yield 93%, m.p. 76-78 **° C**.

Synthesis of 2- Chloro-1-(2-methyl-indolo [2, 3-b] quinoxalin-6-yl)- ethanone [A_2]

A mixture of 2-Methyl-6H-indolo[2,3-b]quinoxaline (0.25g,1.07 mmol) and triethylamine (0.108g,1.07 mmol) in 50 ml benzene, then add chloroacetyl chloride (0.121g,1.07 mmol) in 25 ml benzene drop by drop for about 30 min. Then the reaction mixture was stirred at room temperature 25^0C for about 6 h and then refluxed for 10 h.

Progress of the reaction is monitored by TLC using 3:1 hexane:ethyl acetate mixture as mobile phase. After the completion of reaction, the reaction mass was quenched in ice cold water and filtered, the precipitate appeared was dried and recrystallized from ethanol to give pure 2-chloro-1-(2-methyl-indolo[2,3-b]quinoxalin-6-yl)-ethanone.Yield 98% , m.p. 132-134 **° C**.

Synthesis of 2-hydrazino-1-(2-methyl-indolo [2, 3-b] quinoxalin-6-yl)-ethanone [A_3]

A mixture of 2-Chloro-1-(2-methyl-indolo [2,3-b]quinoxalin-6-yl)- ethanone (0.5 g, 1.7mmol) in 50 ml ethanol ,hydrazine hydrate (0.15 g, 3mmol) was added with continuous stirring and the resulting mixture was re-poured into bath water for 7 h. Progress of the reaction is monitored by TLC using 3:1 hexane: ethyl acetate mixture as mobile phase.

After cooling the mixture, precipitate was formed. The precipitate appeared was filtered, dried and recrystallized from ethanol to give pure 2-Hydrazino-1-(2-methyl-indolo [2, 3-b] quinoxalin-6-yl)-ethanone. Yield 83%, m.p. above 300° C.

Synthesis of 4- {[2- (2-methyl-indolo [2, 3-b] quinoxalin- 6- yl)- 2- oxo- ethyl]-hydrazonomethyl}-benzaldehyde [A_4]

A mixture of 2-hydrazino-1-(2-methyl-indolo[2,3-b]quinoxalin-6-yl)-ethanone (0.2g , 0.65m mol) in ethanol 25ml. Benzene-1,4-dicarbaldehyde (0.087g.,0.65 mmol) was added with 3-4drops of glacial acetic acid. The reaction mixture was refluxed to (70-80) °C for 16 h in water bath. Progress of the reaction is monitored by TLC using 3:1 hexane: ethyl acetate mixture as mobile phase. Then cooled the resultant solution to room temperature, precipitate formed, filtered washed and recrystallized from (Ethanol/water). Yield 94%, m.p a bove300° **C**.

Synthesis of 2- [N'-(4-hydroxy- 3-methoxy-benzylidene) - hydrazino]-1- (2-methyl-indolo [2, 3-b] quinoxalin-6-yl)-ethanone [A_5]

A mixture of 2-hydrazino-1-(2-methyl-indolo[2,3-b]quinoxalin-6-yl)-ethanone (0.1g., 0.32m mol) in ethanol 20ml, then add 4-hydroxy-3-methoxy-benzaldehyde (0.049g, 0.32mmol) with 3-4drops of glacial acetic acid. The reaction mixture was refluxed to (70-80) °C for 15 h in water bath. Progress of the reaction is monitored by TLC using 3:1 hexane: ethyl acetate mixture as mobile phase. Then cooled the resultant solution to room temperature, precipitate formed, filtered washed and recrystallized from (Ethanol/water). Yield 71%, m.p 138-140° **C**.

Synthesis of 2-[N'-(4-hydroxy-benzylidene)-hydrazino]-1-(2-methyl-indolo [2, 3-b] quinoxalin-6-yl)-ethanone [**A_6**]

A mixture of 2-hydrazino-1-(2-methyl-indolo[2,3-b]quinoxalin-6-yl)-ethanone (0.1g, 0.32mmol) in ethanol 25ml, 4-hydroxy-benzaldehyde (0.04g.,0.32mmol) was added with 3-4drops of glacial acetic acid. The reaction mixture was refluxed to (70-80) °C for 10 h in water bath. Progress of the reaction is monitored by TLC using 3:1 hexane: ethyl acetate mixture as mobile phase. Then cooled the resultant solution to room temperature, precipitate formed, filtered washed and recrystallized from (Ethanol/water). Yield 89%, m.p 236-238° **C.**

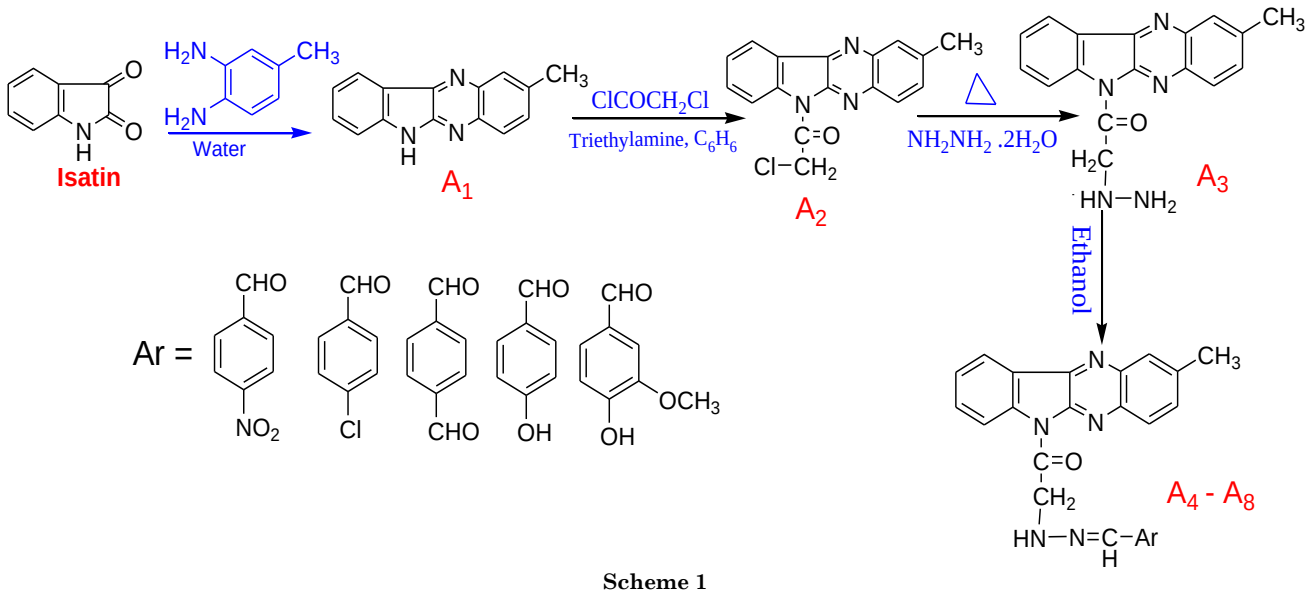
Synthesis of 2-[N'- (4- chloro-benzylidene)- hydrazino]- 1- (2- methyl-indolo [2, 3-b] quinoxalin-6-yl)- ethanone [A_7]

A mixture of 2-hydrazino-1-(2-methyl-indolo [2, 3-b] quinoxalin-6-yl)-ethanone (0.1g, 0.32 mmol) in ethanol 20ml, 4-Chloro-benzaldehyde (0.04g , 0.32 mmol) was added with 3-4 drops of glacial acetic acid.

The reaction mixture was refluxed to (70-80) °C for 12 h in water bath. Progress of the reaction is monitored by TLC using 3:1 hexane: ethyl acetate mixture as mobile phase. Then cooled the resultant solution to room temperature, precipitate formed, filtered washed and recrystallized from (Ethanol/water). Yield 89%, m.p 260-262° **C.**

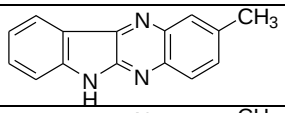
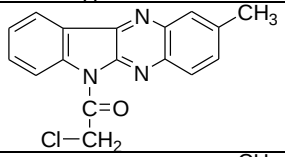
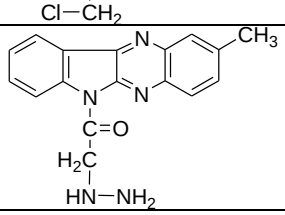
Synthesis of 1- (2-methyl-indolo [2, 3-b] quinoxalin-6-yl)- 2-[N'-(4- nitro-benzylidene)-hydrazino]-ethanone [A_8]

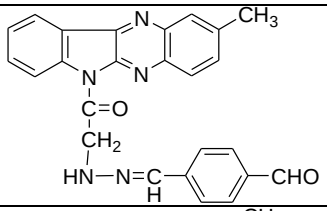
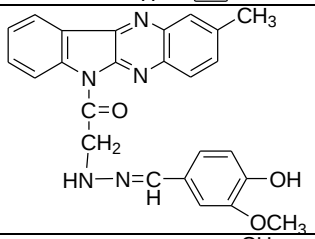
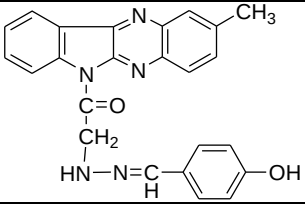
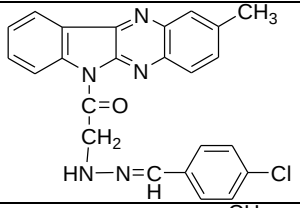
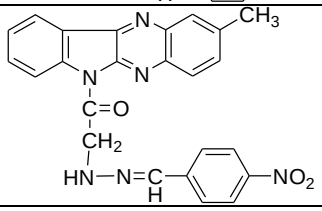
A mixture of 2-hydrazino-1-(2-methyl-indolo [2,3-b]quinoxalin-6-yl)-ethanone (0.2g, 0.65 mmol) in ethanol 25ml, 4-nitro-benzaldehyde (0.09g, 0.65mmol) was added with 3-4drops of glacial acetic acid. The reaction mixture was refluxed to (70-80) °C for 6 h in water bath. Progress of the reaction is monitored by TLC using 3:1 hexane: ethyl acetate mixture as mobile phase. Then cooled the resultant solution to room temperature, precipitate formed, filtered washed and recrystallized from (Ethanol/water). Yield 87%, m.p 180-182 °C. (Table-1) shows the physical properties and chemical structure for the compounds (A_1-A_8). They showed different melting points, yielded ratio of the prepared compound.



Scheme 1

Table 1: Physical Properties of the Prepared Compounds

Comp. symbol	Comp. Structure	Molecular Formula	M.P. ° C	% Yield
A_1		$C_{15}H_{11}N_3$	76-78	93
A_2		$C_{17}H_{12}N_3OCl$	132-134	98
A_3		$C_{17}H_{15}N_5O$	Above300	83

A_4		**$C_{25}H_{19}N_5O_2$**	**Above300**	**94**
A_5		**$C_{25}H_{22}N_5O_3$**	**138-140**	**71**
A_6		**$C_{24}H_{19}O_2N_5$**	**236-238**	**89**
A_7		**$C_{24}H_{18}ClN_5O$**	**260-262**	**89**
A_8		**$C_{24}H_{18}N_6O_3$**	**180-182**	**87**

Antifungal Activity

Antifungal susceptility testing was done by agar well diffusion method to detect anti fungal effect for yeasts fumigates isolate and mold (*Cryptococccus Neoformans, Candida Albicans, Rhodotorula rubra, Aspergilus parasiticus, Penicilium sp., Rhizopus arrhizus*) the moulds were grown on at 25°C for 7 days. Stock solution was prepared by mixing 0.05g of compound with 1ml DMSO (solvent). The solid appeared at the petri plate which poisoned agar plates were inoculated at the centre with fungal plugs (10 mm) obtained from actively growing colony and incubated at 25°C for 7 days. Diameter of the fungal colonies was measured.

Table 2: Antifungal activities for some compounds: inhibition zones in mm

Comp.	No.	Cryptococccus neoformans	Candida albicans	Rhodotorularubra	Aspergilusparasiticus	Penicilium sp.	Rhizopusarrhizus
A_1	**7**	**21**	**16**	**24**	**22**	**0**	0
A_2	**2**	**30**	**16**	**25**	**0**	**0**	0
A_3	**3**	**24**	**21**	**25**	**16**	**20**	22
A_8	**6**	**11**	**18**	**30**	**0**	**17**	0

Results and Discussion

The 2-methyl-6H-indolo [2, 3-b] quinoxaline was prepared in this work by the reaction of isatin with 4-methyl-o-Phenylenediamine. The structure of the compound (A_1) was identified by its melting point, TLC, FT- IR, and ^{1}H-NMR spectroscopy. The FT-IR spectrum of compound (**A_1**) (Figure 1-1) showing absorption band at 3327cm^{-1} was attributed to bonding of N-H group. Absorption band at 3023 cm^{-1} was due to C-H aromatic. Absorption band at 2919 cm^{-1} was due to C-H aliphatic .Bond absorption at 1610 cm^{-1} was due to C=N stretching. The sharp bands at 1513 cm^{-1} and 1434 cm^{-1} are due to the C=C aromatic[15]. All these absorption bands are approved to the formation of this compound. The ^{1}H-NMR spectra of the Compound (A_1), (Figure 1-6) showed the following chemical shifts (DMSO-d_6, ppm): 10.04(s, 1H, N-H), 6.5-8.04 (m, 7H,

Ar-H), 1.21 (s, 3H, CH_3). The FT-IR spectrum of compound A_2 (Figure1-2) showing absorption bands at 3437 cm^{-1} was attributed to bonding of O-H (tuat.) group. Bond absorption at 1617 cm^{-1} was due to C=N stretching. . Bond absorption at 1679 cm^{-1} was due to C=O stretching. The band at 1516 cm^{-1} is due to the C=C aromatic. The ^{1}H-NMR spectrum of Compound (A_2) showed the chemical shifts (DMSO-d_6, ppm): 9. 93 (s, 1H, O-H), 7.00-7.63 (m, 7H, Ar-H), 4.30 (s, 1H, CH_2) and 1.22 (s, 3H, CH_3).

The FT-IR spectrum of compound A_3 (Figure1-3) showing absorption bands at 3226, 3196 cm^{-1} was attributed to bonding of NH_2 groups. Absorption bands at 3105 cm^{-1} was attributed to bonding of N-H groups, absorption band at 3034 cm^{-1} was due to C-H aromatic, absorption band at 2924 cm^{-1} was due to C-H aliphatic .Bond absorption at 1684 cm^{-1} was due to C=O stretching and bonds absorption at 1610 cm^{-1} and 1593 cm^{-1} was due to C=N stretching.

The ^{1}H -NMR spectrum of Compound (A_3), (Figure 1-7) showed the chemical shifts (DMSO-d_6, ppm): 9.95 (bro, 1H, N-H) [16], 7.55-8.48 (m, 7H, Ar-H), 5.71 (bro, 2H, NH_2), 4.11(d, 2H, CH_2) and 1.22 (s, 3H, CH_3). The FT-IR spectrum of compound A_4 (Figure 1-4) showing absorption bands at 3345 cm^{-1} was attributed to bonding of N-H group. Absorption bands at 2998 cm^{-1} and 2935 cm^{-1} was due to C-H aliphatic.

Bond absorption at 1689 cm^{-1} was due to C=O stretching. Bonds absorption at 1641 cm^{-1} and 1620 $cm^{-1}$was due to C=N stretching vibration. The ^{1}H -NMR spectrum of Compound (A_4), showed showed the chemical shifts (DMSO-d_6, ppm): 10.46 (bro,1H,N-H), 9.42(s,1H,CH=O), 8.7 (s,1H,N=CH), 6.21-7.63 (m,11H,Ar-H), 4.41 (d, 2H, CH_2) and 1.15 (s,3H, CH_3). The FT-IR spectrum of compound A_5 (Figure 1-5) showing absorption band at 3136 cm^{-1} was attributed to bonding of NH group. Absorption band at 3038 cm^{-1} was due to C-H aromatic. Bond absorption at 1662 cm^{-1} was due to C=O stretching and bonds absorption at 1640 cm^{-1} and 1599 cm^{-1} was due to C=N stretching vibration. The ^{1}H -NMR spectrum of Compound (**A_5**), (Figure 1-8) showed the chemical shifts (DMSO-d_6, ppm): 11.05 (s,1H,O-H) 9.42 (bro,1H,N-H), 8.70 (s,1 H,N=CH), 6.36-8.19 (m,10 H, Ar-H), 4.43 (d, 2H, CH_2) 2.22 (s,3H, OCH_3), and 1.46 (s,3H, CH_3). The FT-IR spectrum of compound A_6 showing absorption bands at 3306 cm^{-1} was attributed to bonding of O-H group. An absorption band at 3195 cm^{-1} was attributed to bonding of N-H group.

Bond absorption at 1654 cm^{-1} was due to C=O stretching and bond absorption at 1601 cm^{-1} was due to C=N stretching. The ^{1}H -NMR spectrum of Compound (A_6), showed the chemical shifts (DMSO-d_6, ppm): 10.81(s,1H,O-H) 10.01 (bro, 1H,N-H), 8.48 (s,1H,N=CH), 6.27-7.79 (m,11 H, Ar-H), 3.88 (d, 2H, CH_2) and 1.22 (s,3H, CH_3). The FT-IR spectrum of compound A_7 showing absorption bands at 3378 cm^{-1} was attributed to bonding of N-H group, absorption band at 3053 cm^{-1} was due to C-H aromatic. Bond absorption at 1669 cm^{-1} was due to C=O stretching. Bonds absorption at 1624 cm^{-1} and 1598 cm^{-1} was due to C=N stretching.

The sharp bands at 1528 cm^{-1} and 1486 cm^{-1} are due to the C=C aromatic. The ^{1}H -NMR spectrum of Compound (A_7), (Figure 1-9) showed the chemical shifts (DMSO-d_6, ppm): 9.90 (bro, 1H, N-H), 8.72 (s, 1H, N=CH), 6.77-7.49 (m, 11 H, Ar-H), 4.38 (d, 2H, CH_2) and 1.85(s, 3H, CH_3). The FT-IR spectrum of compound A_8 showing absorption bands at 3175 cm^{-1} was attributed to bonding of N-H group. Bond absorption at 1664 cm^{-1} was due to C=O stretching.

Bonds absorption at 1628 cm^{-1} and 1598 cm^{-1} was due to C=N stretching vibration. The sharp bands at 1347 cm^{-1} and 1526 cm^{-1} are due to the NO_2. The ^{1}H -NMR spectrum of Compound (A_8), showed the chemical shifts (DMSO-d_6, ppm): 9.64 (bro, 1H, N –H), 8.83 (s, 1H, N=CH), 7.1-8.3 (m, 11 H, Ar-H), 4.33 (d, 2H, CH_2) and 1.22(s, 3H, CH_3). The FT-IR data for each compound are given in (Table-3).

Table 3: FT-IR absorption spectra data $(cm)^{-1}$ of the prepared compounds

Comp. symbol	N-H	C-H Aro.	C-H Aliph	C=O	C=N	C=C Aro.	Others
A_1	3327	3023	2919	---	1610	1434-1513	--------
A_2	----	---	2930	1679	1617	1516	3437(OH) tuat.
A_3	3105	3034	2972 2924	1684	1610 1593	1525	v $NHNH_2$ 3226, 3196
A_4	3345	3030	2998	1689	1641	1414-1528	

			2935		1620		
A_5	3136	3038	2936	1662	1640 1599	1411-1505	v OH broad band
A_6	3195			1654	1601	1446-1513	3306 O-H
A_7	3378	3053	2928	1669	1624 1598	1486-1528	--------
A_8	3175	3109	2923	1664	1628 1596	1404	NO_2 1347-sym. 1526-asym.

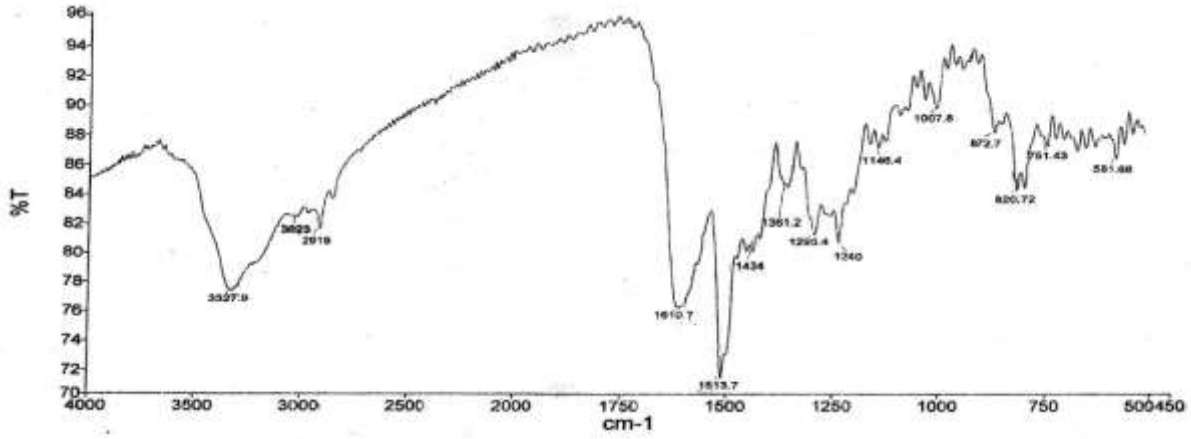


Figure 1.1: FT-IR spectrum in $cm^{-1}$of (A_1) compound

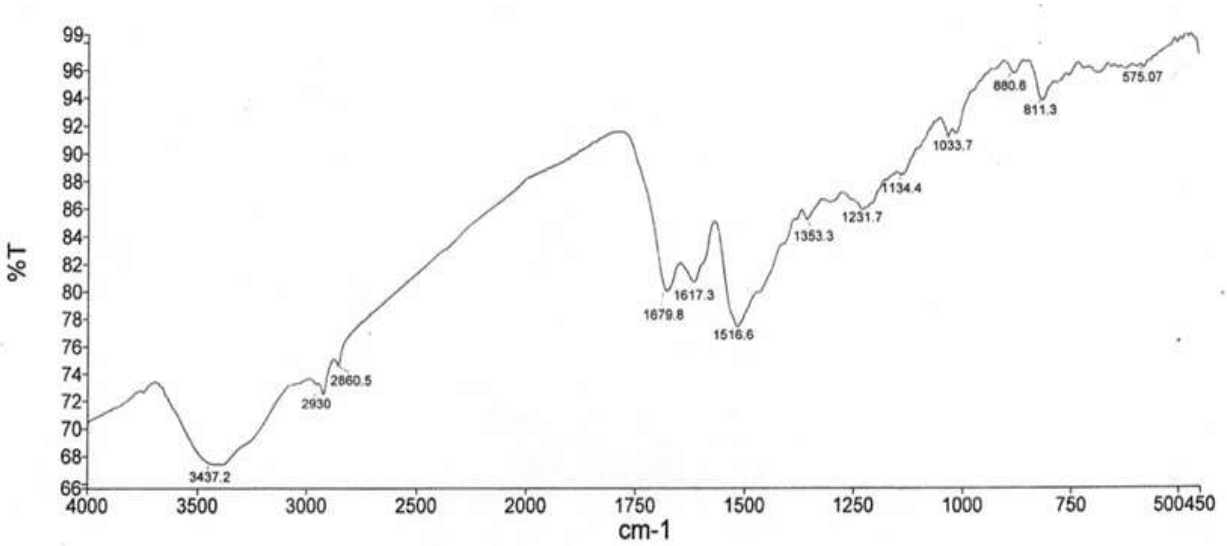


Figure 1.2: FT-IR spectrum in $cm^{-1}$of (A_2) compound

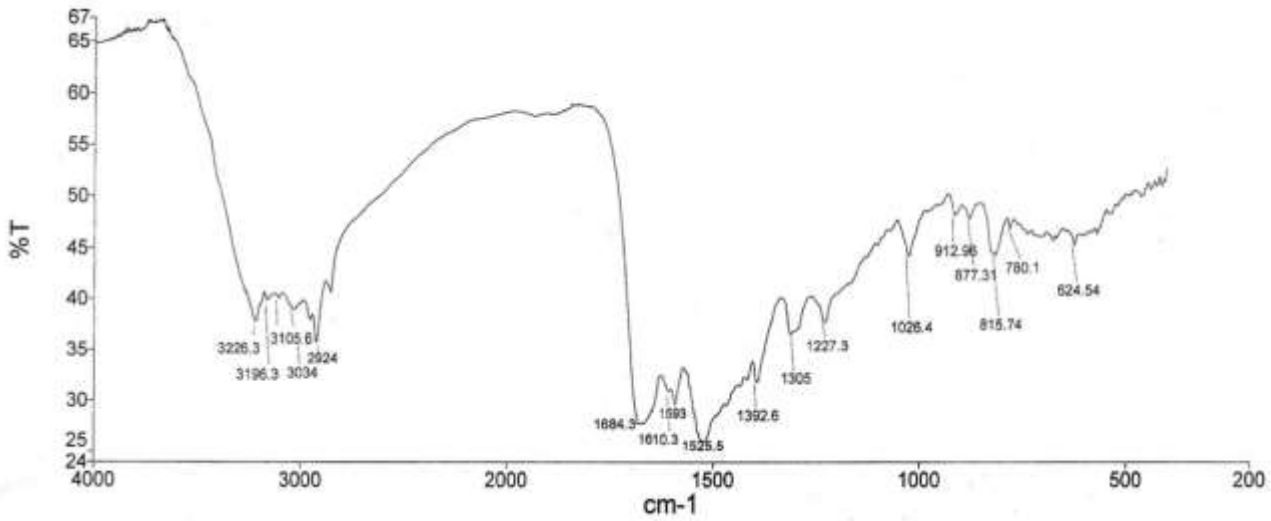


Figure 1.3: FT-IR spectrum in $cm^{-1}$of (A_3) compound

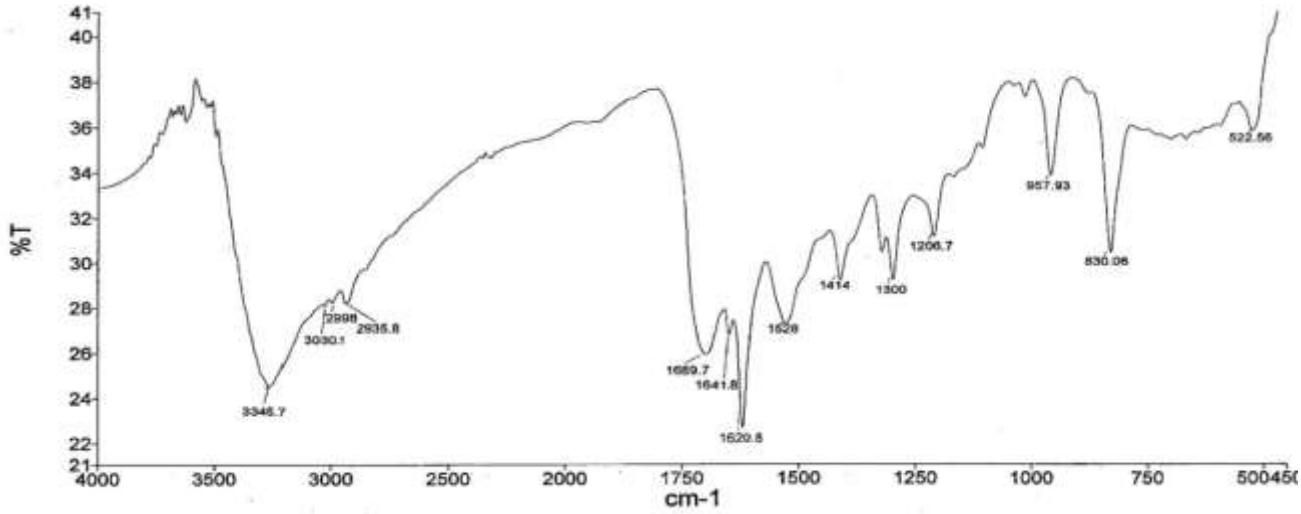


Figure 1.4: FT-IR spectrum in cm^{-1}of (A_4) compound

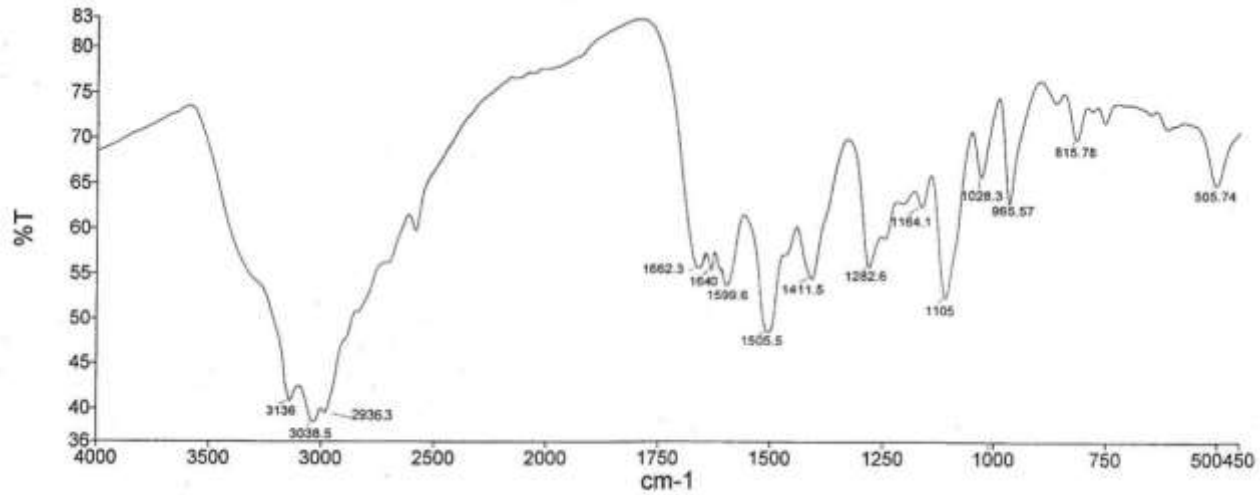


Figure 1.5: FT-IR spectrum in cm^{-1}of (A_5) compound

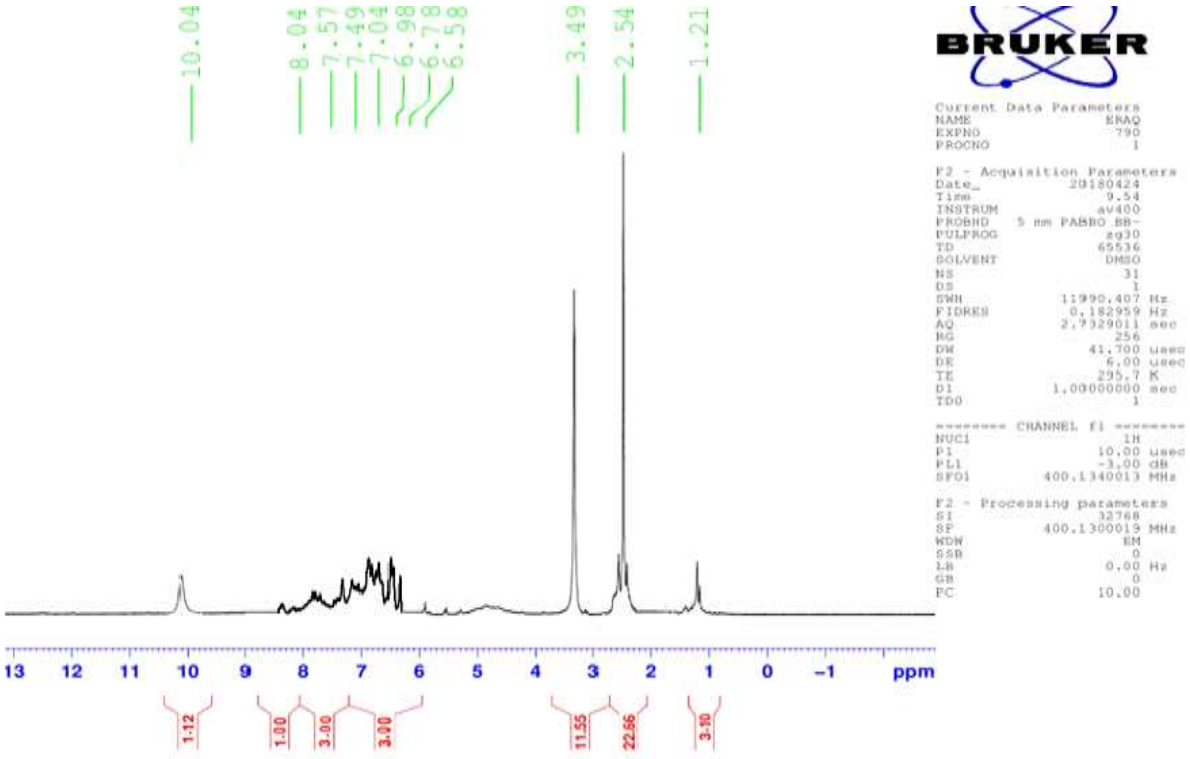


Figure 1.6: ^{1}H NMR spectrum of compound 2-methyl-6H-indolo [2, 3-b]quinoxaline[A_1]

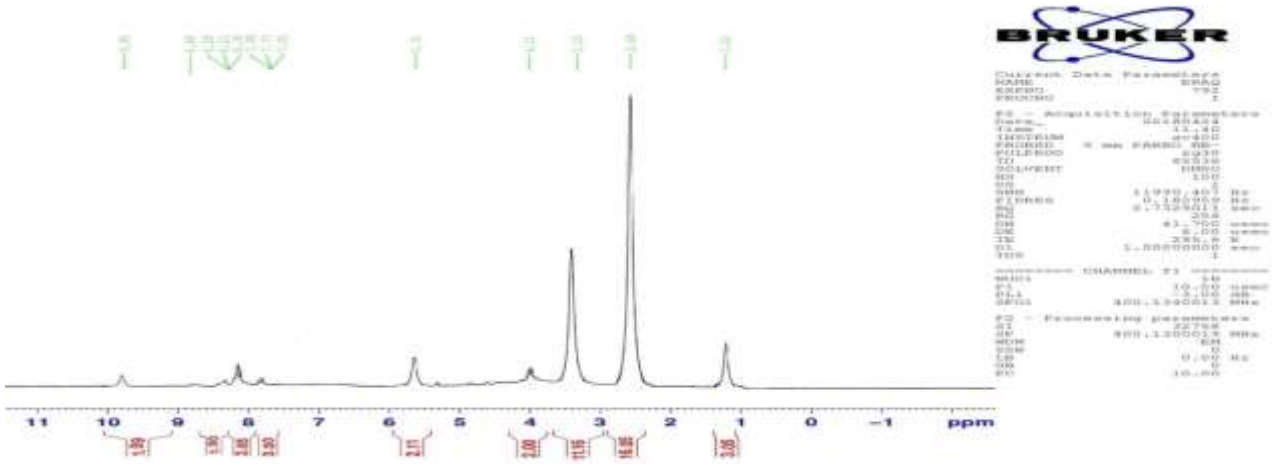


Figure 1.7: ^{1}H NMR to spectrum of compound2-hydrazino-1-(2-methyl-indolo [2, 3-b] quinoxalin-6-yl)-ethanone [A_3]

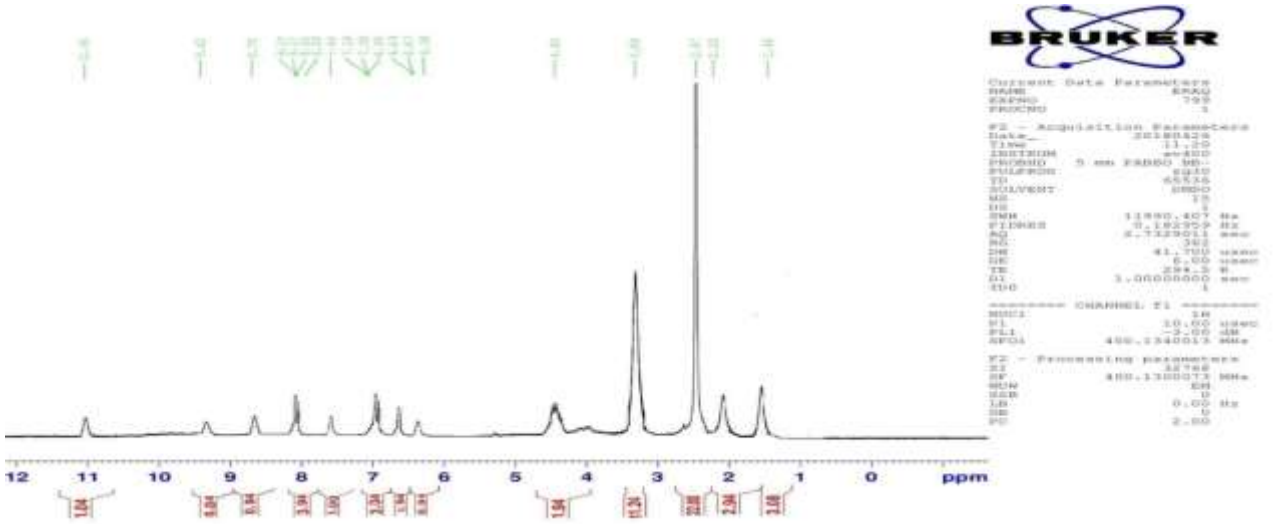


Figure 1.8: ^{1}H NMR spectrum of compound 2-[N'-(4-hydroxy-3-methoxy-benzylidene)-hydrazino]-1-(2-methyl-indolo [2, 3-b] quinoxalin-6-yl)-ethanone [A_5]

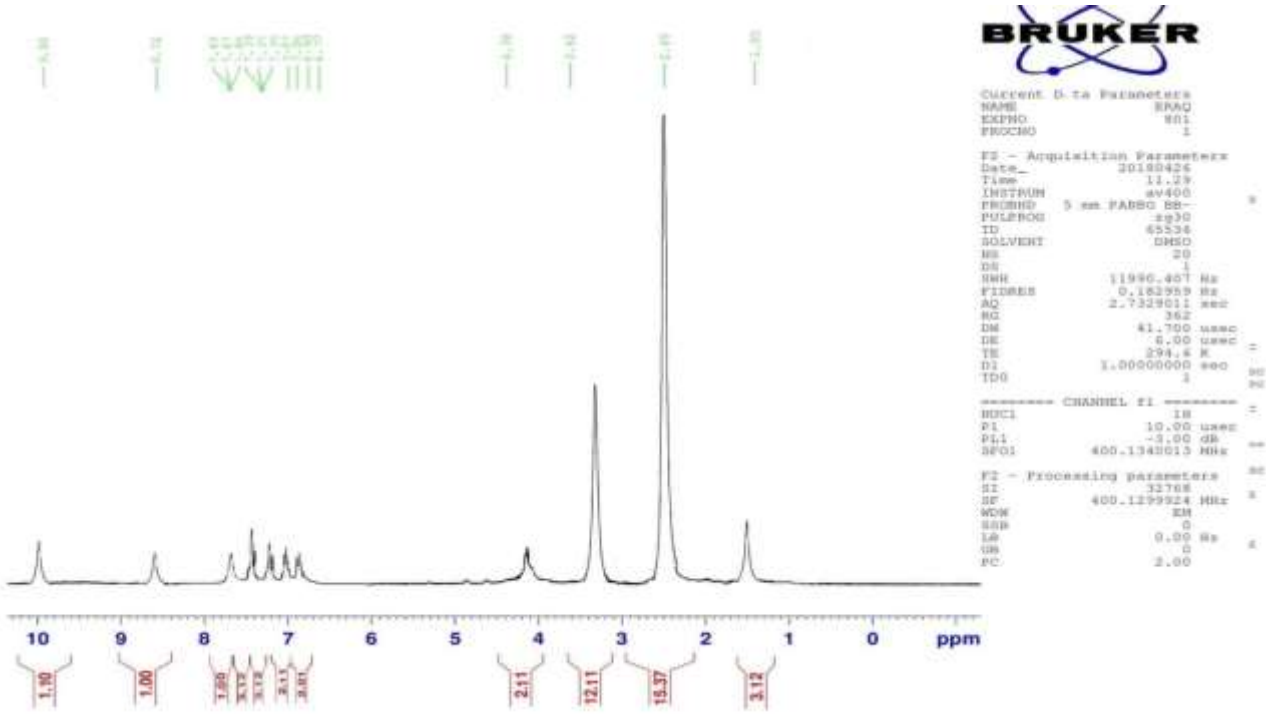


Figure 1.9: ^{1}H NMR spectrum of compound2-[N'-(4-chloro-benzylidene)-hydrazino]-1-(2-methyl-indolo [2, 3-b] quinoxalin-6-yl)-ethanone [A_7]

Conclusion

In the present work, new derivatives of indolo [2-3-b] quinoxaline compounds labeled 1-8 have been synthesized and characterized using various spectroscopic methods "(FT-IR, 1H-NMR)". The pharmacological study was performed to determine the effects of substituent on the antifungal activity, most of the derivatives showed good to moderate activity toward (*Cryptococccus Neoformans, Candida Albicans, Rhodotorula rubra, Aspergilus parasiticus, Penicilium sp., Rhizopus arrhizus*).

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