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SYNTHESIS AND ANTIFUNGAL ACTIVITY SCREENING OF SOME NOVEL 7–SUBSTITUTED –2–HYDROXY–QUINOLINE SCHIFF BASES

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ABSTRACT

With an objective of synthesizing some novel, potent and broad spectrum antifungal activity having compounds, here some novel quinoline derivatives are reported. Initially 7-substituted-2-cholro-3-formylquinolines were prepared using well known Vilsemeir-Hack reagent method. These on microwave irradiation with 4M HCl yielded 7-substituted-2-hydroxy quinoline-3-carbaldehydes **I(a, b)**, which on further treatment with different substituted hydrazides yielded the novel Schiff bases of quinoline **II(a-f)**. The structure of all newly synthesized compounds was confirmed by spectral study such as IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. All the synthesized compounds were screened for *in-vitro* antifungal activity by two fold serial dilution method using fluconazole as the standard drug. Compounds **II a, II b and II d** showed significant antioxidant activity

INTRODUCTION

During last two decades, fungi have emerged as new life threatening agents, causing increased opportunistic infections in human and animals. In fact, overwhelming efforts of the medicinal chemists, it is not getting eradicated successfully. The unhygienic condition maintained by the people and dust induced infection being a prime reason for fungal infection to spread fast. Furthermore some of these organisms have earned a resistance to anti fungal drugs. In case of immuno compromised patients it spreads very fast. Thus there is a need to explore some novel antifungal agents. Quinoline ring system is a ubiquitous pharmacophore and an essential structural fragment of a large number of natural and synthetic compounds possessing versatile pharmacological activities like anti-inflammatory [1,2], antitubercular [3,4,5], antiviral [6], antimalarial [7,8], anticancer [9,10], antibacterial [11], antioxidant [12], tyrosine kinase inhibitor [13], anticonvulsant and antihypertensive [14] etc. These findings encouraged us for synthesizing some novel quinoline Schiff base compounds.

In this research work initially 7-substituted-2-cholro-3-formylquinolines on microwave irradiation with 4M HCl yielded 7-substituted-2-hydroxy quinoline-3-carbaldehydes **I (a, b).** IR spectra of these compounds showed characteristic peaks at around 3190 cm^{-1} (OH), 1680 cm^{-1} (C=O), 1620 cm^{-1} (C=N), Further a novel series of quinoline Schiff bases **II (a-f)** were synthesized by the reaction between 7-substituted-2-hydroxy quinoline-3-carbaldehydes **I(a, b)** and different hydrazides. IR spectra of these compounds showed characteristic peaks at around 3400 cm^{-1} (OH), 3100 cm^{-1} (NH), 1650 cm^{-1} (C=O), 1610 cm^{-1} (C=N).. ^{1}H NMR spectra of these compounds showed characteristic peaks at around δ 8.3 and 12.25 ppm due to protons of CH=N and OH respectively. ^{13} C NMR spectra of these compounds showed characteristic peaks at around δ 138 and 156 ppm due to carbon of CH=N and C=O respectively.

MATERIALS AND METHOD

General considerations

The various chemicals used in the synthesis of the titled compounds were purchased from, Sigma-Aldrich Pvt Ltd, S.D. Fine Chem Pvt Ltd. Absolute ethanol and DMF utilized were purified according to the literature.

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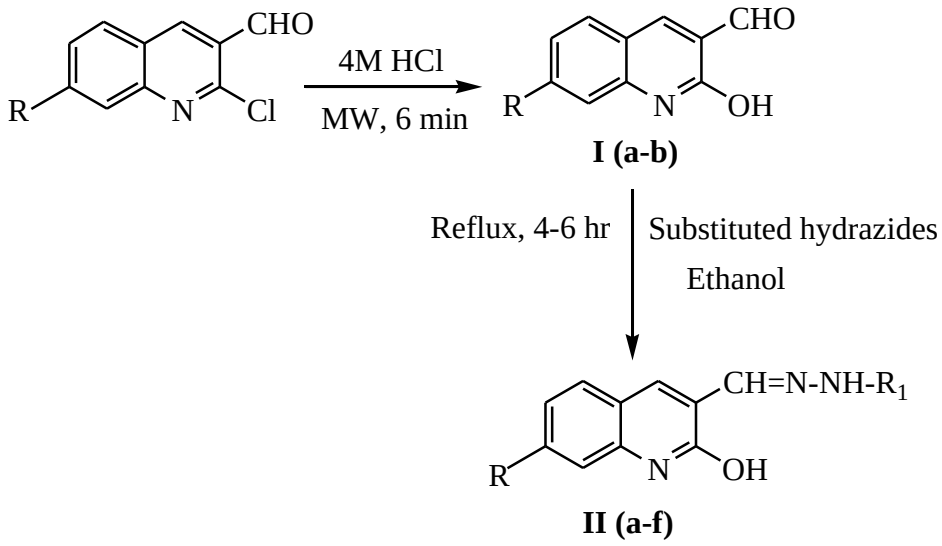
Melting points of all synthesized compounds were determined by open capillary method and are uncorrected. FTIR spectra were recorded on Bruker Alpha-T by using KBr pellets. The ^{1}HNMR were recorded on Bruker Avance II NMR 400 MHz instruments using DMSO as solvent and TMS as internal standard, chemical shifts are expressed as δ values (ppm). Elemental analysis was carried out for the synthesized compounds. All the physicochemical data are given in table 1.

Antifungal activity

In vitro anti fungal activity of the synthesized compounds was evaluated by two fold serial dilution method[25]. Media used was Potato Dextrose Broth (PDB). Initially, the stock culture of *Aspergillus niger*, *Aspergillus flavus*, *Aspergillus terrius* and *Candida albicans* were revived by inoculating in broth media and grown at 37^{0}C for 48 hrs. The tubes of the above media PDB (5 ml) were prepared and each tube was added with compounds (10-500 µg) and inoculated with 100 µl of 48 hr old cultures. The control tubes with fluconazole and DMSO were also prepared. All the tubes were incubated at 37^{0}C for 48 h with constant shaking and the absorbance of biomass were measured at 660 nm using shimadzu UV-Visible spectrophotometer against autoclaved, uninoculated media as blank. The result of i*n vitro* anti fungal activity is expressed as Minimum Inhibitory concentration (MIC). Compounds **II a, II b** and **II d** showed significant antifungal activity. Table 2 reveals antifungal activity (MIC) data for all the synthesized compounds.

Scheme:



Where,

	R	R_1
II a =	F	—C(=O)—pyridin-4-yl
II b =	F	—C(=O)—pyridin-3-yl
II c =	NO_2	—C(=S)—NH_2
II d =	F	—C(=S)—NH_2
II e =	NO_2	—C(=O)—pyridin-4-yl
II f =	NO_2	—C(=O)—pyridin-3-yl

Table 1: Physico-chemical data of the synthesized compounds II (a-f)

Compound	Molecular formula	M.P°C	%Yield	Elemental Analysis Found (Calcd) %			Solubility
				C	H	N	
II a	$C_{16}H_{11}FN_4O_2$	246-248	71	61.95 (61.92)	3.57 (3.51)	18.06 (18.03)	DMSO
II b	$C_{16}H_{11}FN_4O_2$	258-260	68	61.95 (61.93)	3.57 (3.53)	18.06 (18.02)	DMSO
II c	$C_{11}H_9N_5O_3S$	232-234	64	45.36 (45.32)	3.11 (3.08)	24.04 (24.91)	DMSO
II d	$C_{11}H_9FN_4OS$	274-276	76	49.99 (49.95)	3.43 (3.42)	21.20 (21.16)	DMSO
II e	$C_{16}H_{11}N_5O_4$	224-226	70	56.98 (56.95)	3.29 (3.26)	20.76 (20.73)	DMSO
II f	$C_{16}H_{11}N_5O_4$	248-250	66	56.98 (56.97)	3.29 (3.27)	20.76 (20.75)	DMSO

Table 2: Antifungal activity screening results of newly synthesized compounds II (a-f)

Compound	MIC values (µg/ ml)			
	A.niger	***A.flavus***	***A.terrius***	***C.albicans***
II a	25	50	12.5	50
II b	12.5	25	12.5	>100
II c	50	>100	50	>100
II d	50	100	12.5	25
II e	12.5	50	>100	12.5
II f	50	>100	100	12.5
DMSO (Solvent)	--	--	--	--
Fluconazole	6.25	6.25	6.25	6.25

RESULTS

General procedure for the synthesis of 7-substituted-2-hydroxyquinoline-3-carbaldehyde I(a,b)

A mixture of 7-substituted-2-chloro-3-formylquinolines (0.01 mol) and 4M HCl solution (30 ml) was subjected for MW irradiation (120 W) for 6 min. Yellow solid precipitated on cooling. This was poured into a beaker containing crushed ice (100 g), filtered, dried and recrystallised from glacial acetic acid.

I a: IR (KBr) cm^{-1}: 3192.54 (OH), 1681.35 (C=O), 1620.68 (C=N) . ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.18 (d, 1H, C_6-H of quinoline), 7.46-7.51 (m, 1H, C_8-H of quinoline), 7.85 (d, 1H, C_5-H of quinoline), 8.32 (s, 1H, C_4-H of quinoline), 10.23 (s, 1H, CHO), 12.57 (s, 1H, OH).

I b: IR (KBr) cm^{-1}: 3189.11 (OH), 1684.76 (C=O), 1621.17 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.21 (d, 1H, C_6-H of quinoline), 7.49-7.57 (m, 1H, C_8-H of quinoline), 7.85 (d, 1H, C_5-H of quinoline), 8.29 (s, 1H, C_4-H of quinoline), 10.46 (s, 1H, CHO), 12.29 (s, 1H, OH).

General procedure for the synthesis of compounds II (a-f)

A mixture of compound **I (a, b)** (0.005 mol) in 25 ml of absolute ethanol, equimolar amount of substituted hydrazides (0.005 mol) and catalytic amount of glacial acetic acid were added. The mixture was refluxed for 6 h. Solid compound was obtained on cooling the reaction mixture. This was filtered, dried and recrystallized from ethanol and DMF mixture to get the final compounds **II (a-f).**

II a: IR (KBr) cm^{-1}: 3401.02 (OH), 3161.32 (NH), 1652.56 (C=O), 1607.89 (C=N). ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.24 - 8.31 (m, 9H, C_4, C_5, C_6, C_8-H of quinoline, CH=N & C_2, C_3, C_5, C_6-H of pyridine), 12.02 (s, 1H, NH), 12.25 (s, 1H, OH). Mass (m/z): 310.68

II b: IR (KBr) cm^{-1}: 3408.19 (OH), 3162.79 (NH), 1648.25 (C=O), 1612.31 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.30 (s, 2H, C_3 & C_4-H of pyridine), 7.45 (s, 1H, C_8-H of quinoline), 7.73 (s, 2H, C_2 & C_5-H of pyridine), 7.89 (s, 1H, C_6-H of quinoline), 8.02 (s, 1H, C_5-H of quinoline), 8.36 (s, 1H, CH=N), 8.59 (s, 1H, C_4-H of quinoline), 11.66 (s, 1H, NH), 12.18 (s, 1H, OH). ^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 162.46 (quinoline- C_2), 160.23 (C=O), 151.02 (quinoline C_9), 144.22 (CH=N), 140.67 (pyridine- C_4), 135.46 (quinoline- C_4), 132.65 (quinoline- C_7), 127.63 (pyridine- C_3 and -C_5), 125.32 (quinoline- C_5), 123.16 (pyridine- C_2 and -C_6), 121.44 (quinoline- C_8), 120.19 (quinoline- C_6), 118.21 (quinoline- C_{10}), 115.44 (quinoline- C_3).
Mass (m/z): 310.02

II c: IR (KBr) cm^{-1}: 3409.14 (OH), 3104.41 (NH), 1681.74 (C=O), 1615.22 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.31 (d, 1H, C_8-H of quinoline), 7.43 (d, 1H, C_6-H of quinoline), 7.59 (s, 1H, C_5-H of quinoline), 8.32(s, 1H, C_4-H of quinoline), 8.62(s, 2H, NH_2), 8.78(s, 1H, CH=N), 11.13 (s, 1H, NH), 12.17 (s, 1H, OH).
Mass (m/z): 291.06

II d: IR (KBr) cm^{-1}: 3416.10 (OH), 3133.21 (NH), 1659.04 (C=O), 1606.72 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.29 (d, 1H, C_8-H of quinoline), 7.47 (d, 1H, C_6-H of quinoline), 7.59 (s, 1H, C_5-H of quinoline), 8.24 (s, 1H, C_4-H of quinoline), 8.59 (s, 2H, NH_2), 8.77 (s, 1H, CH=N), 11.54 (s, 1H, NH), 12.17 (s, 1H, OH).
Mass (m/z): 264.85

II e: IR (KBr) cm^{-1}: 3411.78 (OH), 3103.61 (NH), 1642.20 (C=O), 1610.32 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.21 (s, 2H, C_3 & C_4-H of pyridine), 7.34 (s, 1H, C_8-H of quinoline), 7.61 (s, 2H, C_2 & C_5-H of pyridine), 7.79 (s, 1H, C_6-H of quinoline), 7.98 (s, 1H, C_5-H of quinoline), 8.56 (s, 1H, CH=N), 8.81 (s, 1H, C_4-H of quinoline), 11.39 (s, 1H, NH), 12.11 (s, 1H, OH).
Mass (m/z): 337.31

II f: IR (KBr) cm^{-1}: 3418.76 (OH), 3146.22 (NH), 1644.82 (C=O), 1619.29 (C=N), ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 7.44-8.85 (m, 9H, C_4, C_5, C_6, C_8-H of quinoline, CH=N & C_2, C_3, C_5, C_6-H of pyridine), 11.18 (s, 1H, NH), 12.35 (s, 1H, OH).^{13}C NMR (400 MHz, DMSO-d_6, δ ppm): 162.44 (quinoline- C_2), 161.53 (C=O), 151.32 (quinoline C_9), 141.85 (CH=N), 139.88 (pyridine- C_4), 136.66 (quinoline- C_4), 131.04 (quinoline- C_7), 128.11 (pyridine- C_3 and -C_5), 123.38 (quinoline- C_5), 122.76 (pyridine- C_2 and -C_6), 121.02 (quinoline- C_8), 120.77 (quinoline- C_6), 118.59 (quinoline- C_{10}), 116.63 (quinoline- C_3).
Mass (m/z): 337.57

DISCUSSION

A novel series of quinoline Schiff bases **II (a-f)** have been synthesized by reacting 7-substituted/unsubstituted-2-hydroxy-3-formylquinolines **I (a, b)** with substituted hydrazides. The purity of the synthesized compounds was confirmed by TLC. The structure of all the newly synthesized compounds was confirmed by physicochemical and spectral data. All the compounds were screened for their antifungal activities using two fold serial dilution method, Among the series **II (a-f),** **c**ompound **II a** showed significant antifungal activity against ***A.terrius***. Compound **II b** showed significant antifungal activity against ***A.niger*** and ***A.terrius*** Compound **II d** showed significant antifungal activity against ***A.terrius***, Compounds **II e** and **II f** showed significant antifungal activity against ***C.albicans***. Compounds **II c** has showed moderate antifungal activity against ***A.niger*** and ***A.terrius***. Compounds **II a**, **II b** and **II d** containing fluorine at the 7th position of quinoline shown significant antifungal activity against the tested organisms

CONCLUSION

In the series **II (a-f)** it is evidently observed that the antifungal activity of the compounds has been greatly influenced by the presence of fluorine as a substituent on the quinoline nucleus. Quinoline moiety and its Schiff bases do contribute for the observed activity but the presence of fluorine at 7th position of quinoline contributed for its significant antifungal activity. The preliminary antifungal activity screening result of these compounds depicted them as potential antifungal leads endowed with moderate to excellent activity. Further enhancement in the activity can be achieved by slight modifications in the ring substituent

ABBREVIATIONS

Term	Expansion/ Full form
UV	Ultra violet
FTIR	Fourier Transform Infrared Radiation
NMR	Nuclear Magnetic Resonance
TMS	Tetra Methyl Silane
DMSO	Dimethyl sulfoxide
nm	Nanometer
DMSO-d_6	Deuterated Dimethyl sulfoxide
MW irradiation	Microwave irradiation

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CONFLICT OF INTEREST: No any conflict of interest

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