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RESEARCH ARTICLE

Synthesis Characterisation and Antimicrobial Activity of *N′*-(2-Chloroquinolin-3-yl)methylene)-isonicotinohydrazide

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Abstract: A series of novel *N′*-(2-chloro-substituted quinolin-3-yl)methylene)isonicotinohydrazide (**3a-h**) were prepared by condensation of 2-chloro-3-formylquinoline (**1a-h**) with isonicotinohydrazide (**2**) in the presence of catalytic quantity of acetic acid in methanol under reflux in good yield. Newly synthesized compounds were characterized by IR, ^{1}H NMR and mass. The newly synthesized compound **(3a-h)** has been screened for their antibacterial and antifungal activities. All compounds exhibited significant antibacterial and antifungal activity.

Keywords: 2-Chloro-3-formylquinoline, Isonicotinohydrazide, Methanol, Antifungal activity

Introduction

One of the most frequently encountered heterocycle in medicinal chemistry is quinoline with wide applications including antibacterial[1], antifungal[2], anti-malarial[3], antiviral[4], antiasthamatic[5], antihypertensive[6], analgesic[7,] antiinflammatory[8], cytotoxic[9], anti-platelet[10], antiprion[11], H+/K+ATPase inhibitor[12], leukotrien[13] and biosynthesis inhibitor activity. Interesting pharmacological properties have been associated with 2-chloroquinoline-3-carbaldehydes and their derivatives[14,15]. Derivatives of 3-(quinolin-3-yl)acrylates and the corresponding reduced allylic alcohols that have been identified by Bristol-Myers Squibb (BMS) as novel and potent maxi-K channel openers are useful for the treatment of male erectile dysfunction[16]. The quinoline ring is a part of antibacterial ciprofloxacin, naldixic acid and fluoroquinoline. Reduced 1,2,3,4-tetrahydroquinoline derivatives oxamniquine is used to eradicate blood flukes (Schistosoma mansoni).

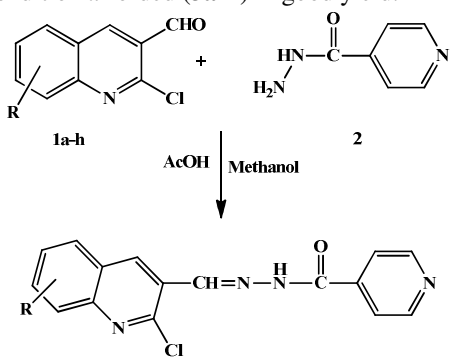
Quinaldic acid is carbolic acid; substituted quinoline at 2 positions is a catabolite of tryptophan aromatic side chain amino acid. It is a fundamental structure of some antihypertensive agents such as prazosin and doxazosin which are peripheral vasodilator. On the other hand isonicotinohydrazide (INH) is an antibiotic used for the treatment of tuberculosis it is bactericidal to rapidly dividing mycobacteria, but is bacteriostatic if the

mycobacteria are slow-growing[17]. It inhibits the cytochrome P450 system and hence acts as a source of free radicals. Isoniazid has been approved as prophylactic therapy for the people with HIV infection.

However, over the past few decades, health benefits are under threat as many commonly used antibiotics have become less and less effective, only because many of them produce toxic reactions, but also due to emergence of drug-resistant bacteria. In general, bacteria have the genetic ability to transmit and acquire resistance to synthetic drugs which are utilized as therapeutic agents. In an effort to expand the spectrum of antibacterial agents, it is essential to investigate newer drugs with lesser resistance.

Recently, Narang *et al.,*[18] developed a novel series of nicotinic acid hydrazide derivatives as potential antimycobacterial agents. Adhikari and co-workers reported two studies on the design, synthesis and biological evaluation of two different series of new quinoline-3-carbohydrazone derivatives, as potential antimycobacterial agents[19,20].

The present attempt is to design new compounds, through the combination of 2-chloro-3-formylquinoline derivatives with isoniazid in one structure which may lead to new compounds with increased antimicrobial activity. In view of the above mentioned observations and in continuation of our interest in the synthesis of 2 chloro3-formylquinoline derivatives[21,22] we herein report the synthesis of *N*′-(-2-chloro-substitutedquinolin-3-yl)methylene) isonicotinohydrazide. The general synthetic pathway discussed hereafter is depicted in Scheme 1. The starting compounds 2-chloro-3-formylquinoline derivatives (**1a-h**) were prepared by Vilsmeier Haack reaction according to literature method[23]. Reaction between (**1a-h**) and isonicotinohydrazide (**2**) in methanol in the presence of catalytic quantity of glacial acetic acid under reflux condition afforded (**3a-h**) in good yield.



Scheme 1. General synthetic pathway

The purity of synthesized compounds is checked by TLC (ethyl acetate:benzene). All synthesized compounds (**3a-h**) were characterized by IR, ^{1}H NMR and mass spectrometric techniques Table 1.

Experimental

All melting points were determined in open capillary tubes and are uncorrected. The homogeneity of all the compounds were checked by TLC on silica gel coated plates. IR spectra were obtained in KBr on Perkin-Elmer FTIR spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ on Varian NMR spectrometer operating at 300 MHz. Chemical shifts are expressed in δ, with reference to TMS.

General procedure for the synthesis of 1-(2-chloroquinolin-3-yl)methylene)isonicotinohydrazide ***(3a-h)***

A solution of substituted 2-chloro-3-formylquinoline (0.01 mole) in methanol (20 mL) and isonicotinohydrazide (0.01 mole) was refluxed for 2 h. The reaction mixture was cooled; the solid separated was filtered, washed with water and recrystallized from methanol to furnish **3a-h** (Scheme 1). Physical and analytical data of compounds are given in Table 1.

Table 1. Physical and analytical data of compounds (**3a-h**)

Compd.	Molecular formula	M. P. ^{o}C	% Analysis found (calcd.)		
			C%	H%	N%
3a	$C_{17}H_{13}ClN_4O$	260	62.00(62.87)	4.02(4.03)	17.20(17.25)
3b	$C_{17}H_{13}ClN_4O$	252	62.05(62.87)	4.00(4.03)	17.10(17.25)
3c	$C_{17}H_{13}ClN_4O$	252	62.10(62.87)	3.99(4.03)	17.00(17.25)
3d	$C_{17}H_{13}ClN_4O_2$	264	63.13(63.63)	4.00(4.15)	16.40(16.44)
3e	$C_{16}H_{11}ClN_4O$	238	61.60(61.84)	3.00(3.57)	18.00(18.03)
3f	$C_{16}H_{10}ClBrN_4O$	254	49.01(49.32)	2.50(2.59)	14.30(14.38)
3g	$C_{17}H_{12}ClN_5O_3$	258-260	55.10(55.22)	3.00(3.27)	18.25(18.94)
3h	$C_{17}H_{12}ClN_5O_4$	250	52.70(52.93)	3.10(3.14)	18.01(18.15)

Spectral analysis of compounds

N´-(2-Chloro-6-methylquinolin-3-yl)methylene)isonicotinohydrazide **(3a)**

IR (KBr, cm^{-1}): 3310 (N-H stretching), 1676 (C=O stretching of carbonyl), 1615 (-N=CH-Ar stretching of aromatic ring), 822 (C-Cl stretching of chlorine). ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 2.71 (3H, s, CH_3), 8.78-8.80(2H, d, Py), 8.93-8.97 (2H, d, Py), 7.51-7.90 (4H, m, aromatic), 7.64 (1H, bs, -N=CH), 12.41(1H, s, NH). MS (*m/z*): 324[M]+(100%),326[M+2].

N´-(2- Chloro-7-methylquinolin-3-yl)methylene)isonicotinohydrazide **(3b)**

IR (KBr, cm^{-1}): 3315 (N-H stretching), 1670 (C=O stretching of carbonyl), 1610 (-N=CH-Ar stretching of aromatic ring), 820 (C-Cl stretching of chlorine). ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 2.74 (3H, s, CH_3), 8.75-8.78(2H, d, Py), 8.92-8.96 (2H, d, Py), 7.50-7.89 (4H, m, aromatic), 7.64 (1H, bs, -N=CH), 12.38 (1H, s, NH). MS (*m/z*): 324[M]+ (100%), 326 [M+2] [33%].

N´-(2-Chloro-8-methylquinolin-3-yl)methylene)isonicotinohydrazide **(3c)**

IR (KBr, cm^{-1}): 3313 (N-H stretching), 1674 (C=O stretching of carbonyl), 1615 (-N=CH-Ar stretching of aromatic ring), 824 (C-Cl stretching of chlorine). ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 2.71 (3H, s, CH_3), 8.76-8.79(2H, d, Py), 8.92-8.96 (2H, d, Py), 7.50-7.89 (4H, m, aromatic), 7.60 (1H, s, -N=CH), 12.36 (1H, s, NH). MS (*m/z*): 324.01[M]+ (100%), 326.01 [M+2][33%].

N´-(2-Chloro-6-methoxyquinolin-3-yl)methylene)isonicotinohydrazide **(3d)**

IR (KBr, cm^{-1}): 3310 (N-H stretching), 1669(C=O stretching of carbonyl), 1615 (-N=CH-Ar stretching of aromatic ring), 821 (C-Cl stretching of chlorine). ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 3.31 (3H, s, CH_3), 8.80-8.83(2H, d, Py), 8.95-8.99 (2H, d, Py), 7.50-7.89 (4H, m, aromatic), 7.55 (1H, s, -N=CH), 12.30 (1H, s, NH). MS (*m/z*): 340.02[M]+ (100%), 342.02 [M+2][33%].

N´-(2-Chloroquinolin-3-yl)methylene)isonicotinohydrazide (**3e)**

IR (KBr, cm^{-1}): 3320 (N-H stretching), 1665(C=O stretching of carbonyl), 1615 (-N=CH-Ar stretching of aromatic ring), 824 (C-Cl stretching of chlorine). ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.74-8.78 (2H, d, Py), 8.90-8.94(2H, d, Py), 7.50-7.89 (5H, m, aromatic), 7.50(1H, s, -N=CH), 12.20 (1H, s, NH), MS (*m/z*): 310.06[M]+(100%), 312.06[M+2][33%].

N´-(2-Chloro-6-bromoquinolin-3-yl)methylene)isonicotinohydrazide (**3f)**

IR (KBr, cm^{-1}): 3310 (N-H stretching), 1669(C=O stretching of carbonyl), 1615 (-N=CH-Ar stretching of aromatic ring), 821 (C-Cl stretching of chlorine). ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 8.80-8.83 (2H, d, Py), 8.95-8.99 (2H, d, Py), 7.50-7.89 (4H, m, aromatic), 7.55 (1H, s, -N=CH), 12.25 (1H, s, NH). MS (*m/z*): 389.97[M]+(100%), 387.97[M+2][77%].

N´-(2-Chloro-8-methyl-7-nitroquinolin-3-yl)methylene)isonicotinohydrazide (**3g)**

IR (KBr, cm^{-1}): 3315 (N-H stretching), 1665(C=O stretching of carbonyl), 1610 (-N=CH-Ar stretching of aromatic ring), 1555 (NO_2), 1352 (NO_2),825(C-Cl stretching of chlorine), ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 3.34(3H,s,CH_3), 8.82-8.85(2H, d, Py), 8.95-8.99 (2H, d, Py), 7.50-7.79 (3H, m, aromatic), 7.45 (1H, s, -N=CH), 11.92 (1H, s, NH). MS (*m/z*): 385.02[M]+ (100%), 387.02[M+2][33%].

N´-(2-Chloro-6-methoxy-5-nitroquinolin-3-yl)methylene)isonicotinohydrazide (**3h)**

IR (KBr, cm^{-1}): 3310 (N-H stretching), 1669(C=O stretching of carbonyl), 1615 (-N=CH-Ar stretching of aromatic ring), NO_2 (1550), 1350 (NO_2), 821(C-Cl stretching of chlorine); ^{1}H NMR (300 MHz, $CDCl_3$, δ/ppm): 3.31(3H,s,CH_3), 8.80-8.83(2H, d, Py), 8.95-8.99 (2H, d, Py), 7.30-7.69 (3H, m, aromatic), 7.50 (1H, s, -N=CH), 12.02 (1H, s, NH); MS (*m/z*): 385.02[M]+(100%), 387.02[M+2][33%].

Results and Discussion

The structures of the synthesized compounds **(3a-h)** were confirmed on the basis of spectral and elemental analysis. The IR spectrum of **3a-h** exhibited a band at 1610-1615 (C=N), 1670, 3310 cm^{-1} due to C=N, C=O, N-H functions respectively. Further, in their ^{1}H NMR ($CDCl_3$) spectrum, the appearance of a singlet at δ 7.50 and at δ 12.00 due to protons of CH=N and amide NH function respectively. Multiplet observed in the region 7.50-7.80 is due to aromatic protons. A doublet observed in region δ 8.80-8.83 and δ 8.90-8.99 is due to protons of pyridine ring. Mass spectrum of compounds displayed M^+(100%), M^++2(33%) respectively.

Antimicrobial activity

The compounds **3a-h** were screened for their antibacterial activity against *E coli*, *Salmonella typhi*, *Staphylococcus aureus* and *Bacillus subtilis* by using paper disc diffusion method[24], using Penicillin (100 µb/disc) as reference standard and antifungal activity against *Aspergillus niger*, *Aspergillus flavus*, *Penicillium chrysogenum* and *Fusuriummoneliforme* by using Greseofulvin (100 µb/disc) as reference standard by poison plate method[25]. The observed minimum inhibitory concentrations (MIC) values for all the synthesized compounds are presented in Table 2 and 3.

The investigation of antibacterial screening results indicate that compounds **3a-h** shows promising activity against all bacterial strains (Table 2) as well as fungal strains (Table 3). The good activity is attributed due to the presence of pharmacologically active isoniazid moiety.

Table 2. Antibacterial screening results of the compounds (**3a-h**) (Zone of inhibition in mm)

Compound	*E. coli*	*Salmonella typhi*	*Staphylococcus aureus*	*Bacillus subtilis*
3a	12	17	25	16
	11	16	27	16
3b	12	15	26	15
	10	14	28	14
3c	13	17	24	15
	12	14	22	17
3d	10	15	25	16
3e	Not tested	Not tested	Not tested	Not tested
DMSO	-ve	-ve	-ve	-ve
Penicillin	13	18	36	18

-ve no antibacterial activity

Table 3. Antifungal screening results of the compounds **(3a-f)**

Compound	*E. coli*	*Salmonella typhi*	*Staphylococcus aureus*	*Bacillus subtilis*
3a	-ve	-ve	-ve	-ve
3b	-ve	-ve	-ve	-ve
3c	-ve	-ve	-ve	-ve
3d	-ve	-ve	-ve	-ve
3e	-ve	-ve	-ve	-ve
3f	-ve	-ve	-ve	-ve
3g	-ve	-ve	-ve	-ve
3h	-ve	-ve	-ve	-ve
DMSO	+ve	+ve	+ve	+ve
Greseofulvin	-ve	-ve	-ve	-ve

+ve no antifungal activity –ve no growth antifungal activity observed

Conclusion

We have synthesized various *N´*-(2-chloroquinolin-3-yl)methylene)isonicotinohydrazide with the objective of developing better antimicrobial agents. A common result was obtained, which showed good activity against all pathogenic bacteria and fungal strains. In conclusion, the isoniazid incorporated hydrazone derivatives can be regarded as a newer class of antibacterial and antifungal agent.

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