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RESEARCH ARTICLE

Synthesis and Antimicrobial Activities of *N´*-[(2-Chloro-6-methoxy quinolin-3-yl)methylidene]-substituted Benzohydrazide

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Abstract: A number of *N´*-[(2-chloro-6-methoxyquinolin-3-yl) methylidene]-substituted benzohydrazide have been synthesized by the treatment of 2-chloro-6-methoxy-3-quinolinecarbaldehyde with the substituted benzohydrazides. The structures of the synthesized compounds have been characterized by using IR and ^{1}H NMR spectroscopy. These compounds were screened for their antibacterial as well as antifungal activity. Compounds show grater antibacterial activity as compare to antifungal activity.

Keywords: 2-Chloro-6-methoxy-3-quinolinecarbaldehyde, Benzohydrazides, Antimicrobial activities

Introduction

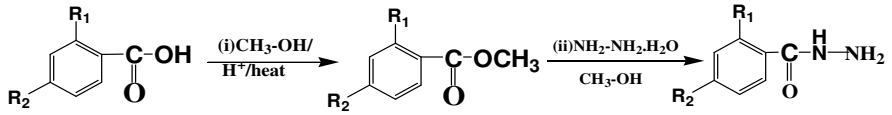
Hydrazide analogues having azomethine (–CONHN=CH-) group show antimicrobial activities and it also possess other biological activities like anticonvulsant, antidepressant, analgesic[1,2], anti-inflammatory[3], antimalarial, anticancer activities. It is also active against experimental tuberculosis in guinea pigs[4,5]. In *in-vitro* metabolism studies, it has been found that hydrazide-hydrazones undergo hydrolytic reactions and aromatic rings undergo aromatic hydroxylation reactions and give positive effect for cure of diseases[6,7]. Gökhan-Kelekçi *et al*. synthesized hydrazones containing 5-methyl-2-benzoxazoline[8]. The analgesic effects of 2-[2-(5-methyl-2-benzoxazoline-3-yl) acetyl]-4-chloro- /4-methyl benzylidene hydrazine were found to be higher than those of morphine and aspirin[8]. Hydrazide-hydrazones compounds are not only intermediates but they are also very effective organic compounds in their own right. When they are used as intermediates, coupling products can be synthesized by using the active hydrogen component of –CONHN=CH- azomethine group[9]. In continuation of this work to develop potential antimicrobial molecules[10], we report here the synthesis of some derivatives by combining two biological active compounds (3-formyl 2-chloro quinolines and substituted benzohydrazides) having azomethine group and characterized by spectral data with evaluation for their antimicrobial activity.

Experimental

All the reagents were obtained commercially and used with further purification. The melting points were determined on microprocessor MP apparatus, IR spectra were recorded with a FTIR spectrometer in KBr optics. ^{1}H NMR spectra were recorded on a DPX-300 MHz spectrometer in DMSO-d6 solutions. The chemical shifts were expressed in the ppm (δ scale) downfield from TMS. For purification of prepared compounds column chromatography was used as per requirement. Thin layer chromatography (TLC) was performed to check the purity of the compounds, spots being visualized under UV cabinet.

*General procedure for the preparation of benzohydrazides (**2a-2e**)*

The esterification of the substituted benzoic acids was performed by reported method[11]. It was carried out by refluxing acids (0.246 mol) with methanol in sulpuric acid for 4 h. Then esters were separated out and converted into benzoic acid hydrazides or benzohydrazides by hydrazinolysis process[11] (Scheme 1).



Substituted Benzoic Acid Comp. 1a-1e **Comp. 2a-2e**

1a: R_1=R_2=H, 1b: R_1=H; R_2=CH_3, 1c: R_1=H; R_2=OCH_3, Id: R_1=H; R_2=CI; 1e: R_1=R_2=CI
2a: R_1=R_2=H; 2b: R_1=H; R_2=CH_3, 2c: R1=H; R_2=OCH_3, 2d: R_1=H; R_2=CI; 2e: R_1=R_2=CI

Scheme 1. Synthesis of benzohydrazides from substituted benzoic acid

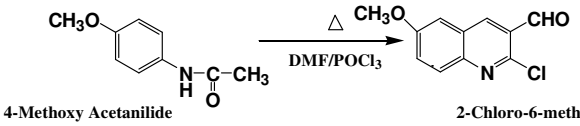
*General procedure for the synthesis of 2-chloro-6-methoxy-3-quinoline carbaldehyde (**4**)*

These compounds were prepared by modified reported method[12]. *N, N*-Dimethylformamide (9.1 g, 9.6 mL and 0.125 mol) was cooled to 0 ^{0}C and phosphoryl chloride (53.7 g, 32.2 mL, 0.35 mol) was added drop wise with stirring. To this solution 4-methoxy acetanilide (0.05 mol) (**3**) was added and the temperature of the reaction mixture was raised to 80 ^{0}C for 18 h. The cooled reaction mixture was poured into ice water (300 mL) and stirred for 1 h at 0–10 ^{0}C. The precipitated 2-chloro-3-quinolinecarbaldehyde was filtered off, dried, and recrystallized from ethyl acetate to give the 2-chloro-6-methoxy-3-quinoline carbaldehyde (4) product[12,13] (Scheme 2).

Yield: 49%, mp. 143–144 ^{0}C; IR (KBr) cm^{-1}: 1693 (C=O), 1619 (C=C), 1595 C=N), 751 (C-Cl). ^{1}H NMR (300MHz, DMSO-d6, δ, ppm): 10.50 (s, 1H, CHO), 8.57 (s, 1H, H-4), 7.91 (d, 1H, J ¼ 9.0 Hz, H-8); 7.46 (dd, 1H, J ¼ 9.0 Hz and 2.8 Hz, H-7), 7.17 (d, 1H, J ¼ 2.8 Hz, H-5), 3.94 (s, 3H, OCH3); Mol. formula $C_{11}H_8C1NO_2$ .Calcd. Mol.wt. 221.02.

*General procedure for the synthesis of N'-[(2-chloro-6-methoxyquinolin-3-yl) methyl-lidene]benzohydrazide (**5a-5e**)*

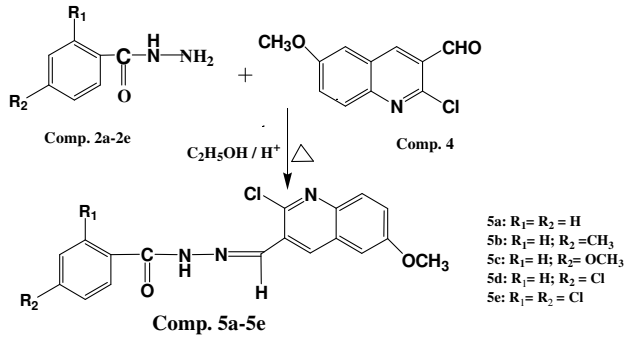
Benzohydrazides (0.01 mol)**,** 2-chloro-6-methoxy-3-quinolinecarbaldehyde **(**0.01 mol) were taken in ethanol with catalytic amount of acetic acid (20 mL) and heated to refluxed for 3-4 h. After completion of the reaction (reaction monitored by TLC method), the reaction mixture was poured into crushed ice. The solid mass thus separated out was filtered, washed with water and dried to give the desired compounds with good yields. IR and ^{1}H NMR analysis were performed for the compounds (Scheme 3).



4-Methoxy Acetanilide
Comp. 3

2-Chloro-6-methoxy-3-quinolinecarbaldehyde
Comp. 4

Scheme 2. Synthesis of 2-chloro-6-methoxy-3-quinolinecarbaldehyde



Comp. 5a-5e

Scheme 3. Synthesis of *N´*-[(2-chloro-6-methoxyquinolin-3yl)methylidene]benzohydrazides

*N'-[(2-Chloro-6-methoxyquinolin-3-yl)methylidene]benzohydrazide (**5a**)*

Yield: 71%, M.P.183 ^{o}C. IR (KBr) cm^{-1}: 3261 (N-H), 1655 (C=O), 1627 (C=N), 1589 (C=C), 759 (C-Cl). ^{1} H NMR (300 MHz, DMSO-*d* $_{6}$): δ 3.89 (s, 3H, OCH $_{3}$), 7.57-7.64 (m, 3H, H-3', 4' and 5'), 7.67-7.73 (d, 1H, H-7, *J* = 8.49 Hz), 7.68-7.88 (d, 1H, H-8, *J* = 8.52 Hz), 7.79-8.01 (m, 3H, H-2', 6'and 5), 8.81 (s, 1H, H-4), 8.93 (s, 1H, CH=N), 12.26 (s, 1H, CONH). Mol.formula $C_{18}H_{14}ClN_3O_2$ Calcd.Mol.wt. 339.75.

*N'-[(2-Chloro-6-methoxyquinolin-3-yl)methylidene]-4-ethylbenzohydrazide (**5b**)*

Yield: 65%, M.P.173 ^{o}C. IR (KBr) cm^{-1}: 3223 (N-H), 1668 (C=O), 1622 (C=N), 1597 (C=C), 751 (C-Cl). ^{1} H NMR (300 MHz, DMSO-*d* $_{6}$): δ 3.84(s, 3H, OCH $_{3}$),, 2.52 (s, 3H, CH $_{3}$), 7.35-7.38 (d, 2H, H-3' and 5', *J* = 7.68 Hz), 7.66-7.72 (d, 1H, H-7, *J* = 8.43 Hz), 7.83-7.89 (d, 3H, H- 2', 6' and 8, *J* = 8.07 Hz), 7.78 (s, 1H, H-5), 8.84 (s, 1H, H-4), 8.91 (s, 1H, CH=N), 12.19 (s, 1H, CONH). Mol.formula $C_{19}H_{16}ClN_3O_2$ Calcd.Mol.wt. 353.78.

*N'-[(2-Chloro-6-methoxyquinolin-3-yl)methylidene]-4-methoxybenzohydrazide (**5c**)*

Yield: 62%, M.P.183-186 ^{o}C. IR (KBr) cm^{-1} : 3223 (N-H), 1673 (C=O), 1629 (C=N), 1588 (C=C), 761 (C-Cl). ^{1}H NMR (300 MHz, DMSO-*d*$_{6}$); δ 3.89 (s, 3H, OCH $_{3}$), 3.82 (s, 3H, OCH $_{3}$), 7.31-7.34 (d, 2H, H-3' and 5', *J* = 7.72 Hz), 7.69-7.72 (d, 1H, H-7, *J* = 8.51 Hz), 7.85-7.88 (d, 1H, H-8, *J* = 8.42 Hz), 7.77-8.02 (m, 3H, H-2', 6' and 5), 8.82 (s, 1H, H-4), 8.92 (s, 1H,CH=N),12.17(s,1H,CONH). Mol. formula $C_{19}H_{16}ClN_3O_3$ Calcd.Mol.wt. 369.78.

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*4-Chloro-N´-[(2-chloro-6-methoxyquinolin-3-yl)methylidene]benzohydrazide (**5d**)*

Yield: 67%, M.P.211-214 ^{o}C. IR (KBr) cm^{-1} : 3264 (N-H), 1683 (C=O), 1630 (C=N), 1589 (C=C), 757 (C-Cl). ^{1} H NMR (300 MHz, DMSO-*d* $_{6}$): δ 3.92 (s, 3H, OCH $_{3}$), 7.63-7.65 (d, 2H, H-3' and 5' *J* = 8.38 Hz), 7.56-7.72 (d, 1H, H-7, *J* = 8.56 Hz), 7.82-7.88 (d, 1H, H-8, *J* = 8.59 Hz), 7.98-8.01 (m, 3H, H-2', 6' and 5), 8.82(s, 1H, H-4), 8.91 (s, 1H, CH=N), 12.25 (s, 1H, CONH). Mol.formula $C_{18}H_{13}Cl_2N_3O_2$ Calcd.Mol.wt. 374.20.

*2,4-Dichloro-N'-[(2-chloro-6-methoxyquinolin-3-yl)methylidene]benzohydrazide (**5e**)*

Yield: 56%, M.P.233-237 ^{o}C. IR (KBr) cm^{-1}: 3220 (N-H), 1672 (C=O), 1629 (C=N), 1582 (C=C), 763 (C-Cl). ^{1}H NMR (300 MHz, DMSO-d_6); δ 3.93 (s, 3H, OCH_3), 7.53-7.72 (m, 3H-3' and 5', 7), 7.86-7.89 (m, 2H, H- 6' and 8), 7.79 (s, 1H, H-5), 8.82 (s, 1H, H-4), 8.94 (s, 1H, CH=N), 12.18(s, 1H, CONH). Mol.form. $C_{18}H_{12}Cl_3N_3O_2$ Calcd. Mol. wt. 409.64.

Results and Discussion

We have synthesized series of *N´*-[(2-chloro-6-methoxyquinolin-3-yl)methylidene]-substituted benzohydrazide by a simple and efficient method. The reaction sequence for different synthesized compounds is outlined in Scheme 1. The synthesized compounds *N*'-[(2-chloro-6-methoxyquinolin-3-yl) methylidene]-substituted benzohydrazide (**5a-e**) were characterized by IR and ^{1} H NMR. The IR spectrum of (**5a-e**) exhibit absorption band at about 1596 - 1636 cm $^{-1}$ due to -C=N and amide stretching frequency remain at about 1655-1696 cm $^{-1}$. ^{1}H NMR of (**5a-e**) all synthesized compounds exhibits two most important signal, first was singlet for one proton at about δ values between 11.23 and 12.26 which indicates the CONH proton and second was the singlet varying from δ values 8.79 - 9.11, which indicates the presence of CH=N azomethine group. Aldehyde proton gets converted in to azomethine proton so singlet at δ value 10.52 due to aldehyde proton was absent in final product .It is the proof for completion of reaction. Reactions were assessed by TLC technique and all these prepared compounds were purified by column chromatography as per requirement and characterized on the basis of spectral studies.

Antimicrobial activity

The antimicrobial activity was assayed by cup plate agar diffusion method by measuring minimum inhibition zone in mm[14]. All the synthesized compounds (**5a-e**) were screened *in vitro* for antimicrobial activities against bacterial strains such as *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* and fungal strains such as *Aspergillus Niger, Candida albicans,* and *penicillium cetrinum* at a concentration of 2 mg/mL in DMSO. Potato dextrose agar and nutrient agar were used as the culture mediums for the antifungal and antibacterial activity, respectively. Chloramphenicol and fluconazole were used as standards for comparison purpose. On the basis of the observed zone of inhibition values, it can be concluded that there is a significant differences in the antibacterial and anti fungal potentials of the compounds. The difference among the responses of different prepared compounds is also significant.

Table 1. Antimicrobial activities for synthesized compounds

	Minimum inhibition zone in mm					
	Antibacterial activity			Antifungal activity		
Compd. No.	*E.coli*	*S. aureus*	*P. aerug-inosa*	*A. niger*	*C. albicans*	*P. citrinum*
5a	09	08	-	05	-	-
5b	06	02	-	-	-	-
5c	09	08	06	-	08	-
5d	12	11	10	08	08	-
5e	14	11	11	07	07	-
Chloramphenicol	24	23	22	NT	NT	NT
Fluconazole	NT	NT	NT	25	26	24

'–' *No sensitivity;* NT- *Not tested*

Conclusion

Among the synthesized benzohydrazides with azomethiene group, compounds with CH_3, OCH_3, Cl, Cl_2 were found to be active for antibacterial as well as antifungal screening. Compounds like *N'*-[(2-chloro-6-methoxyquinolin-3-yl)methylidene]-4-methoxybenzohydrazide 4-chloro-*N'*-[(2-chloro-6-methoxyquinolin-3-yl)methylidene] benzohydrazide and 2,4-dichloro-*N'*-[(2-chloro-6-methoxyquinolin-3-yl) methylidene] benzohydrazide show prominent activities. These compounds show grater antibacterial activity as compare to antifungal activity.

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