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Synthesis and structure activity relationship of new antibacterial active multi substituted quinoline-azetidinone mannich bases

G. Madhu[1], K. N. Jayaveera[*1], L. K. Ravindra Nath[2], B. Santosh Kumar[2] and P. Nagarjuna Reddy[2]

[1]Department of Chemistry, JNTUA College of Engineering, Anantapur
[2]Department of Chemistry, S.K .University, Anantapur

ABSTRACT

Novel Mannich bases (Z)-2-(5-(3-chloro-2-oxo-4-p-tolylazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidine)acetohydrazides were synthesized by the condensation of 2-(5-(3-chloro-2-oxo-4-p-tolylazetidin-1-yl)quinolin-8-yloxy)acetohydrazide with Isatin afford corresponding (Z)-2-(5-(3-chloro-2-oxo-4-p-tolylazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxoindolin-3-ylidene)acetohydrazide. This was subjected to mannich reaction with cyclic secondary amines such as piperidine / morpholine / N-Methyl Piperazine in presence of formaldehyde in DMF to give corresponding Mannich bases (Z)-2-(5-(3-chloro-2-oxo-4-p-tolylazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidine)acetohydrazide in excellent yields. The structures of these newly synthesized compounds were characterized by ^{1}H-NMR, ^{13}C-NMR, Mass, IR and elemental analysis. The prepared compounds have been screened on some stains of bacteria and fungai.

Keywords: Azetidinones, Mannich bases, β-Lactums, Anti-microbial activity

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INTRODUCTION

β-lactumheterocyclics are most prescribed antibiotics used in medicine. The most widely used antibiotics such as penicillin,cephalosporins, azetreonam etc. contain β-lactum rings [1]. Azetidinones, which are part of antibiotic structure, are known to exhibit interesting biological activities [2]. Azetidinonesderivatives find a new variety of applications ranging from antibacterial, anti-microbial, anti-inflammatory, anticonvulsantand anti-tubercular activity [3-6,8,22,23]. They also function as enzyme inhibitors and are effective on CNS [7]. 8-hydroxy quninolines constitute another class of heterocyclics. A series of compounds derived from 8-hydroxy quninolines were recently synthesised as potential HIV-1integrase inhibitors [9-12]. Some new 8-hydroxy quinolines also possess interesting herbicidal, antimicrobial activities [13-18,24]. Some quinoline based azetidinones were recently synthesised as potential anti-microbialagents[21,22]. Mannich bases of azetidinones containing quinoline derivatives plays pivotal role in medicinal chemistry.

The areain which mannich bases of azetidinone-quinolinederivatives have not reported so far. Hence it was thought worthwhile to synthesise some new congenersβ-lactumheterocyclics by incorporating the 8-hydroxy quinoline and azetidinone moieties in a single molecular frame work. The present work deals with the synthesis of the title compounds using the synthon 5-amino-8-hydroxy quinoline followed by their antimicrobial screening.

MATERIALS AND METHODS

Melting points were determined on open capillaries using a cintex melting point apparatus. T.L.C analyses were performed on precoatedsilicagel (E-Merck Kieselgel 60F_{254}) plates and visualisation was done by exposing to iodine

vapour. Solvents were purified by standard procedures before use. Column chromatography was conducted by using silica gel with different solvent systems as elutes. IR Spectra were recorded in KBr on Perkin-Elmer Spectrum BX series FT-IR spectrometer. ^{1}H-NMR spectrum were recorded on Varian Gemini 300MHz and 200MHz spectrometers using TMS as internal standard (chemical shifts in δ ppm). ^{13}C-NMR Spectra were recorded on a Brucker 75MHz spectrometer. Mass spectra were scanned on a varian MATCH-7 and Jeol JMSD-300 mass spectrometer at 70ev. Elemental analyses were carried out on a carloerba 106 and Perkin-Elmer Analyser. All the chemicals used in the present investigation were purchased from Aldrich chemicals; U.S.A. 5-Amino-8-Hydroxy quinoline was prepared by a reported method [19]

RESULTS AND DISCUSSION

5-Amino-8-Hydroxy quinolone on condensation with 4-substituted benzaldehydes yielded 5-(benzylideneamino)quinolin-8-ol (A). Compound-A on treatment with chloroacetyl chloride afford a 3-chloro-1-(8-hydroxyquinolin -5-yl)-4-substituted phenyl azetidin-2-one (1) with yield of 58%. Compound (1) on reaction with chlroethyl acetate yielded compound-2 with 50% yield. Compound-2 on amination with hydrazine hydrate afford a 2-(5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yloxy) acetohydrazide (3a - f). The condensationreaction of compound-3 with isatin (4) yielded (Z)-2-(5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxoindolin-3-ylidene)acetohydrazide (5a-f). Compounds (5a-f) on reaction with formaldehyde and piperidine / morpholine / N-methyl piperazine afford compounds 6a-f. These reactions are summarised in the scheme-I. Yields were moderate to fair (40-70%). The purity of the compounds was monitored by TLC.

In IR spectra compounds 6a-f showed broad band around 3190 cm^{-1}, strong bands in the region of 1613, 1693 and 1710 cm^{-1}, indicating the presence of characteristic peaks for –NH, -C=N, Azetidinone –C=O and amide –CONH groups respectively. In ^{1}H-NMR ($(CD)_2SO$) the compounds (6a-h) shown δ: 1.5-2.2(m,10H, -CH_2 of piperidine ring), 2.35 (s, 3H, Ar-CH_3), 4.0(s,2H,N-CH_2-N), 4.83(s,2H,-O-CH_2), 5.12(d,1H,-CH of azetidin attached to phenyl ring), 5.40(d,1H,-CH of azetidin attached to –Cl), 6.55(d, 1H, -CH), 6.7(d,1H,-CH), 7.1(m, 4H of C_6H_4),7.3-7.7(m,4H, for C_6H_4 of Indole) 8.0-8.8(m,3H of quinoline ring), 9.6(s, 1H, -NH). The ^{13}C-NMR spectrum of ($CDCl_3$) shown δ: 150, 107, 116, 134, 129, 121, 149, 140, 122, 144, 127, 129, 127 (Ar-C), 162(N-C=O), 62(C-Cl), 64(N-CH-Ar), 69(O-CH_2), 173(-CO-N), 132, 164, 122, 131, 125, 130, 147, 117(Indole-C), 71, 52, 26 (Piperidine-C). In mass spectrometry by ESI-MS showed the molecular ions $(M+1)^+$624.10, 638.13, 654.13, 658.55, 703.00, 669.10, 626.07 and 639.12. The spectral values are in good agreement with the structures of the compounds (6a-h).

3.1. Anti- Bacterial Activity

The anti-bacterial activity of 6a-h was determined by the disc diffusion method with Amoxicillin and Cefaclor as the reference antibiotics [20]. The newly synthesised compounds were examined, respectively, against *Staphylococcus aureus*, *Bacillus Cereus*, *Escherichia Coli* and *Pseudomonas aeruginosa*bacteria. The test results presented in the table-2, suggest that –Nitro, -Chloro and –Bromo exhibit high activity against the tested bacteria, the rest of the compounds were found to be either slightly active or inactive against the tested microorganisms.

3.2. Antifungal Activity

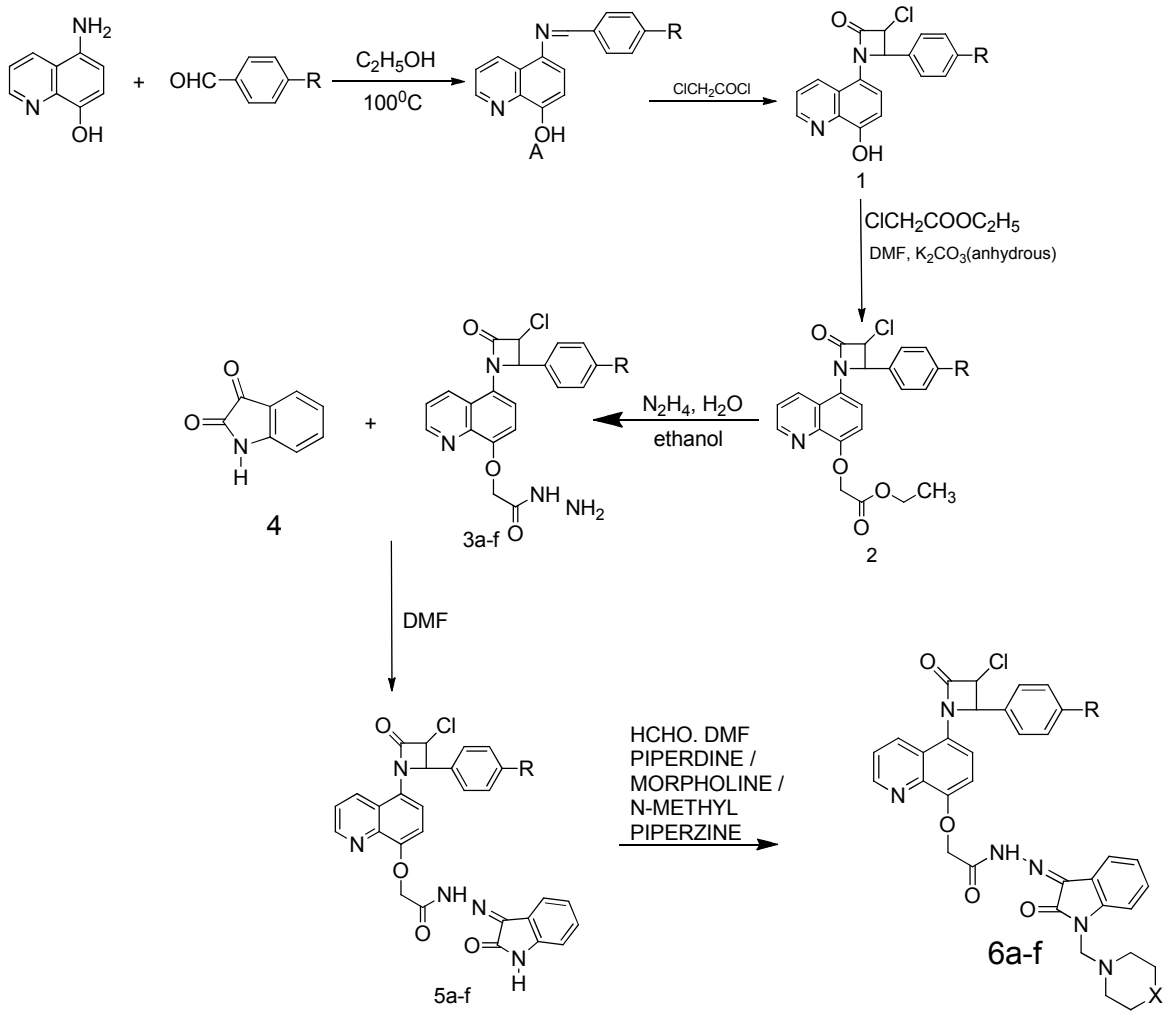
The antifungal activity of 6a-h were tested against two different fungi such as *Asperigillusniger* and *Candida albicans* by disc diffusion method[20], none of the compounds were found to be active against the fungi species tested.

3.3. Synthesis of 3-chloro-1-(8-hydroxyquinolin-5-yl)-4-phenylazetidin-2-one (1)

Equimolar quantity of 5-Amino-8-hydroxyquinoline and 4-substituted benzaldehydes were dissolved in absolute alcohol, to this one drop of acetic acid is added then heated on a steam bath for 5-6h at 100^{o}C. After standing for 24h at room temperature, the product was dried and recrystallized from warm absolute alcohol.

Monochloroacetyl chloride (0.01mol) was added drop wise to schiff's base (0.01mol) and triethyl amine (0.02mol) in dioxane (25ml) at room temperature. The mixture was stirred for 8h and left at room temperature for 3 days. Pour the contents on crushed ice. The product thus formed was filtered and washed with sodium bicarbonate solution. The dried product was recrystallized with absolute alcohol. The M,P was182-184^{0}C with a yield of 58%.

IR(KBr)3340cm^{-1}, 1690 cm^{-1} and 677 cm^{-1}. **^{1}H NMR(300MHz, $(CD)_2SO$, TMS) Spectra:** δ=4.6(s,1H,-OH),5.16(d,1H,-CH of azetidin attached to phenyl ring), 5.44(d,1H,-CH of azetidin attached to –Cl), 6.76(d, 1H, -CH), 6.57(d,1H,-CH), 7.12-7.21(m, 5H of C_6H_5), 7.9-8.8(m,3H of quinolinne ring).



SCHEME-I

Comp	6a	6b	6c	6d	6e	6f	6g	6h
R	H	4-CH_3	4-OCH_3	4-Cl	4-Br	4-NO_2	H	H
X	CH_2	CH_2	CH_2	CH_2	CH_2	CH_2	O	N-CH_3

3.4. Synthesis of 2-(5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yloxy) acetohydrazide (3a)

A mixture of 3-chloro-1-(8-hydroxyquinolin-5-yl)-4-phenylazetidin-2-one **(1)** (0.02M) anhydrous K_2CO_3 (0.03M),Chloroethyl acetate (0.02M) and DMF was added and the mixture is stirred at room temperature for 8 hours, the reaction mixture was diluted with ice-cold water. The separated solid was identified as **(2)**.

A solution of **(2)** (0.01M) and hydrazine hydrate (0.015M) in ethanol 20 mL was refluxed for 5 hours. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford **(3)**. Other compounds of the series were similarly prepared (3a-f).

3.4.1. 2-((5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yl)oxy)acetohydrazide(3a)

IR(KBr): 1620(-C=N), 1690(-C=O), 3205(-NH), 3496,3413(-NH_2), 677^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ= 2.10(s,2H,-NH_2), 5.16(d,1H,-CH of azetidin attached to phenyl ring), 5.44(d,1H,-CH of azetidin attached to –Cl), 4.8(s,2H,-O-CH_2), 7.12-7.21(m, 5H of C_6H_5), 6.76(d, 1H, -CH), 6.57(d,1H,-CH), 7.9-8.8(m,3H of quinolinne ring), 10.10(s, 1H, -NH). ^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 151, 107, 116, 133, 128, 120, 149, 139, 123, 143, 127, 128, 126 (Ar-C), 162(N-C=O), 62(C-Cl), 63(N-CH-Ar), 69(O-CH_2), 166(-CO-N).

3.4.2. 2-(5-(3-chloro-2-oxo-4-p-tolylazetidin-1-yl)quinolin-8-yloxy)acetohydrazide (3b)

IR(KBr): 1618(-C=N), 1685(-C=O), 3206(-NH), 3498,3412(-NH_2), 674^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ= 2.10(s,2H,-NH_2), 2.35(s,3H,Ar-CH_3), 5.16(d,1H,-CH of azetidin attached to phenyl ring), 5.44(d,1H,-CH of azetidin attached to –Cl), 4.75(s,2H,-O-CH_2), 7.01(m, 4H of C_6H_4), 6.6 (d, 1H, -CH), 6.8(d,1H,-CH), 8.0-8.8(m,3H of quinolinne ring), 10.10(s, 1H, -NH).). ^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 152, 106, 116, 134, 129,

119, 148, 139, 122, 140, 127, 129, 136 (Ar-C), 163(N-C=O), 63(C-Cl), 64(N-CH-Ar), 68(O-CH_2), 167(-CO-N), 24(Ar-CH_3).

3.4.3. 2-((5-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)quinolin-8-yl)oxy) acetohydrazide (3c)
IR(KBr): 1621(-C=N), 1687(-C=O), 3208(-NH), 3496,3412(-NH_2), 677^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ= 2.10(s,2H,-NH_2), 5.1(d,1H,-CH of azetidin attached to phenyl ring), 5.44(d,1H,-CH of azetidin attached to –Cl), 3.73(s,3H,Ar-O-CH_3),4.83(s,2H,-O-CH_2), 6.9-7.1(m, 4H of C_6H_4), 6.5 (d, 1H, -CH), 6.7(d,1H,-CH), 7.3-8.8(m,3H of quinolinne ring), 10.10(s, 1H, -NH).^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 150, 108, 116, 133, 129, 120, 148, 140, 123, 136, 128, 114, 159 (Ar-C), 162(N-C=O), 62(C-Cl), 63(N-CH-Ar), 68(O-CH_2), 166(-CO-N), 55.9(O-CH_3).

3.4.4. 2-((5-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)quinolin-8-yl)oxy)acetohydrazide (3d)
IR(KBr): 1617(-C=N), 1680(-C=O), 3210(-NH), 3495,3413(-NH_2), 677^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ= 2.10(s,2H,-NH_2), 5.16(d,1H,-CH of azetidin attached to phenyl ring), 5.44(d,1H,-CH of azetidin attached to –Cl), 4.8(s,2H,-O-CH_2), 7.1-7.2(m, 4H of C_6H_4), 6.57 (d, 1H, -CH), 6.76(d,1H,-CH), 7.3-8.8(m,3H of quinolinne ring), 10.12(s, 1H, -NH).^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 153, 107, 116, 134, 128, 121, 149, 140, 122, 141, 128, 129, 132 (Ar-C), 162(N-C=O), 62(C-Cl), 64(N-CH-Ar), 68(O-CH_2), 167(-CO-N).

3.4.5. 2-((5-(2-(4-bromophenyl)-3-chloro-4-oxoazetidin-1-yl)quinolin-8-yl)oxy) acetohydrazide (3e)
IR(KBr): 1620(-C=N), 1683(-C=O), 3209(-NH), 3498,3414(-NH_2), 676^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ= 2.10(s,2H,-NH_2), 5.16(d,1H,-CH of azetidin attached to phenyl ring), 5.44(d,1H,-CH of azetidin attached to –Cl), 4.8(s,2H,-O-CH_2), 7.1-7.4(m, 4H of C_6H_4), 6.57 (d, 1H, -CH), 6.76(d,1H,-CH), 7.3-8.8(m,3H of quinolinne ring), 10.12(s, 1H, -NH).^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 151, 107, 116, 133, 128, 129, 148, 139, 122, 142, 129, 131, 121 (Ar-C), 162(N-C=O), 62(C-Cl), 63(N-CH-Ar), 69(O-CH_2), 166(-CO-N).

3.4.6. 2-((5-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)quinolin-8-yl)oxy) acetohydrazide (3f)
IR(KBr): 1615(-C=N), 1682(-C=O), 3210(-NH), 3495,3413(-NH_2), 677^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ= 2.10(s,2H,-NH_2), 5.16(d,1H,-CH of azetidin attached to phenyl ring), 5.44(d,1H,-CH of azetidin attached to –Cl), 4.83(s,2H,-O-CH_2), 7.4-8.1(m, 4H of C_6H_4), 6.57 (d, 1H, -CH), 6.76(d,1H,-CH), 7.3-8.8(m,3H of quinolinne ring), 10.12(s, 1H, -NH).^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 154, 107, 116, 133, 128, 120, 149, 139, 122, 150, 128, 121, 146 (Ar-C), 163(N-C=O), 63(C-Cl), 64(N-CH-Ar), 69(O-CH_2), 166(-CO-N).

3.5. Synthesis of (Z)-2-((5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxoindolin-3-ylidene) acetohydrazide (5)
Equimolar quantities (0.01 mol) of Isatin(4)and the corresponding amino compound **(**3a-f**)** were dissolved in warm ethanol (40 mL) containing DMF (0.5 mL). The reaction mixture was refluxed for 1-4 hours and then kept at room temperature overnight. The resulting solid was filtered and washed with ethanol, dried and recrystallized from ethanol to afford compounds (5a-f).

3.5.1. (Z)-2-((5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxoindolin-3-ylidene) acetohydrazide (5a)
IR(KBr): 1617(-C=N), 1705(NH-C=O), 1690(Azetidinone-C=O), 3226(-NH), 677^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ= 4.8(s,2H,-O-CH_2), 5.16(d,1H,-CH of azetidin attached to phenyl ring), 5.44(d,1H,-CH of azetidin attached to –Cl), 6.57(d, 1H, -CH), 6.76(d,1H,-CH), 7.12-7.21(m, 5H of C_6H_5),7.3-7.7(m,4H, for C_6H_4 of Indole) 7.9-8.4 (m,3H of quinoline ring), 9.52(s, 1H, -NH), 10.10(s,1H,-NH of Indole).^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 150, 107, 116, 133, 128, 120, 148, 139, 122, 143, 127, 128, 126 (Ar-C), 162(N-C=O), 62(C-Cl), 63(N-CH-Ar), 69(O-CH_2), 166(-CO-N), 132, 167, 121, 131, 124, 129, 146, 117(Isatin-C).

3.5.2. (Z)-2-(5-(3-chloro-2-oxo-4-p-tolylazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxoindolin-3-ylidene) acetohydrazide (5b)
IR(KBr): 1620(-C=N), 1696(NH-C=O), 1685(Azetidinone-C=O), 3225(-NH), 675^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ2.35 (s, 3H, Ar-CH_3), 4.83(s,2H,-O-CH_2), 5.12(d,1H,-CH of azetidin attached to phenyl ring), 5.40(d,1H,-CH of azetidin attached to –Cl), 6.55(d, 1H, -CH), 6.7(d,1H,-CH), 7.1(m, 4H of C_6H_4),7.3-7.7(m,4H, for C_6H_4 of Indole) 7.9-8.8(m,3H of quinoline ring), 9.6(s, 1H, -NH), 10.12(s,1H,-NH of Indole).^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 152, 108, 116, 134, 129, 121, 149, 140, 123, 141, 126, 129, 136 (Ar-C), 163(N-C=O), 62(C-Cl), 64(N-CH-Ar), 68(O-CH_2), 171(-CO-N), 133, 168, 122, 132, 125, 130, 147, 118(Indole-C), 25(Ar-CH_3).

3.5.3. (Z)-2-((5-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxoindolin-3-ylidene)acetohydrazide (5c)

IR(KBr): 1615(-C=N), 1695(NH-C=O), 1687(Azetidinone-C=O), 3226(-NH), 675^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ 3.73 (s, 3H, Ar-O-CH_3), 4.78(s,2H,-O-CH_2), 5.15(d,1H,-CH of azetidin attached to phenyl ring), 5.46(d,1H,-CH of azetidin attached to –Cl), 6.5 (d, 1H, -CH), 6.7(d,1H,-CH), 6.8-7.0(m, 4H of C_6H_4),7.3-7.7(m,4H, for C_6H_4 of Indole) 8.0-8.6(m,3H of quinoline ring), 9.6(s, 1H, -NH), 10.12(s,1H,-NH of Indole). ^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 154, 108, 116, 134, 129, 121, 149, 140, 123, 136, 128, 114, 159 (Ar-C), 162(N-C=O), 62(C-Cl), 64(N-CH-Ar), 69(O-CH_2), 172(-CO-N), 132, 167, 122, 132, 124, 130, 147, 118(Indole-C), 56(-O-CH_3).

3.5.4. (Z)-2-((5-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxoindolin-3-ylidene)acetohydrazide (5d)

IR(KBr): 1620(-C=N), 1698(NH-C=O), 1680(Azetidinone-C=O), 3126(-NH), 677^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ 4.78(s,2H,-O-CH_2), 5.15(d,1H,-CH of azetidin attached to phenyl ring), 5.46(d,1H,-CH of azetidin attached to –Cl), 6.57 (d, 1H, -CH), 6.8(d,1H,-CH), 7.1-7.2(m, 4H of C_6H_4),7.4-7.7(m,4H, for C_6H_4 of Indole) 7.8-8.5(m,3H of quinoline ring), 9.8(s, 1H, -NH), 10.12(s,1H,-NH of Indole).^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 151, 108, 116, 133, 128, 121, 149, 139, 122, 142, 128, 129, 132 (Ar-C), 162(N-C=O), 62(C-Cl), 63(N-CH-Ar), 69(O-CH_2), 173(-CO-N), 132, 168, 121, 131, 124, 129, 146, 116(Indole-C).

3.5.5. (Z)-2-((5-(2-(4-bromophenyl)-3-chloro-4-oxoazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxoindolin-3-ylidene)acetohydrazide (5e)

IR(KBr): 1617(-C=N), 1703(NH-C=O), 1683(Azetidinone-C=O), 3126(-NH), 676^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ 4.83(s,2H,-O-CH_2), 5.15(d,1H,-CH of azetidin attached to phenyl ring), 5.46(d,1H,-CH of azetidin attached to –Cl), 6.57 (d, 1H, -CH), 6.8(d,1H,-CH), 7.0-7.3(m, 4H of C_6H_4),7.4-7.7(m,4H, for C_6H_4 of Indole) 7.9-8.4(m,3H of quinoline ring), 9.8(s, 1H, -NH), 10.12(s,1H,-NH of Indole).^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 153, 108, 116, 133, 128, 121, 149, 139, 122, 143, 129, 131, 121 (Ar-C), 163(N-C=O), 62(C-Cl), 63(N-CH-Ar), 69(O-CH_2), 173(-CO-N), 132, 168, 121, 131, 124, 129, 146, 116(Indole-C).

3.5.6. (Z)-2-((5-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxoindolin-3-ylidene)acetohydrazide (5f)

IR (KBr): 1622(-C=N), 1695(NH-C=O), 1682(Azetidinone-C=O), 3126(-NH), 672^{-1}cm(-Cl). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ 4.83(s,2H,-O-CH_2), 5.15(d,1H,-CH of azetidin attached to phenyl ring), 5.46(d,1H,-CH of azetidin attached to –Cl), 6.57 (d, 1H, -CH), 6.8(d,1H,-CH), 7.8-8.1(m, 4H of C_6H_4),7.4-7.7(m,4H, for C_6H_4 of Indole) 7.8.8.4(m,3H of quinoline ring), 9.8(s, 1H, -NH), 10.12(s,1H,-NH of Indole).^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 154, 107, 116, 133, 128, 120, 148, 139, 122, 150, 128, 121, 146 (Ar-C), 161(N-C=O), 64(C-Cl), 65(N-CH-Ar), 71(O-CH_2), 171(-CO-N), 134, 168, 121, 131, 124, 129, 146, 119(Indole-C).

3.6. (Z)-2-(5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl) indolin-3-ylidene)acetohydrazide (6)

A mixture of **(5a)(**0.1 mol), piperidine (0.15 mol) and water (20 mL) was stirred to obtain a clear solution. To this solution, HCHO (0.05mol) and DMF were added in ice-cold condition and stirred for 2 hours in an ice-bath and left overnight at room temperature. The obtained white solid was isolated and crystallized from ethanol to give Compound **(6a).** The reaction procedure leading to **(6a)** was then extended for the syntheses of **(6b-h).**

3.6.1. (Z)-2-(5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl) indolin-3-ylidene)acetohydrazide (6a)

IR (KBr): 3190(NH), 1613(-C=N), 1693 (Azetidinone-C=O), 1710(CO-NH), 2947(-CH_2). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ 1.5-2.2(m,10H, -CH_2 of piperidine ring), 4.0(s,2H,N-CH_2-N),4.8(s,2H,-O-CH_2), 5.16(d,1H,-CH of azetidin attached to phenyl ring), 5.44(d,1H,-CH of azetidin attached to –Cl), 6.57(d, 1H, -CH), 6.76(d,1H,-CH), 7.12-7.21(m, 5H of C_6H_5),7.3-7.7(m,4H, for C_6H_4 of Indole) 7.9-8.8(m,3H of quinoline ring), 9.52(s, 1H, -NH).^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 150, 107, 116, 134, 129, 121, 149, 140, 122, 144, 127, 129, 127 (Ar-C), 162(N-C=O), 62(C-Cl), 64(N-CH-Ar), 69(O-CH_2), 173(-CO-N), 132, 164, 122, 131, 125, 130, 147, 117(Indole-C), 71(-N-CH_2-N), 52, 26 (Piperidine-C).

3.6.2. (Z)-2-(5-(3-chloro-2-oxo-4-p-tolylazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl) indolin-3-ylidene)acetohydrazide (6b)

IR (KBr): 3189(NH), 1604(-C=N), 1692(Azetidinone-C=O), 1702(CO-NH), 2933(-CH_2). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ 1.5-2.2(m,10H, -CH_2 of piperidine ring), 2.35 (s, 3H, Ar-CH_3), 4.0(s,2H,N-CH_2-N), 4.83(s,2H,-O-CH_2), 5.12(d,1H,-CH of azetidin attached to phenyl ring), 5.40(d,1H,-CH of azetidin attached to –Cl), 6.55(d, 1H, -CH), 6.7(d,1H,-CH), 7.1(m, 4H of C_6H_4),7.3-7.7(m,4H, for C_6H_4 of Indole) 8.0-8.8(m,3H of quinoline ring), 9.6(s, 1H, -NH).^{13}C NMR (75 MHz, $CDCl_3$,TMS) δ = 153, 107, 116, 133, 128, 120, 148, 139, 122, 141, 127, 129, 136

(Ar-C), 162(N-C=O), 62(C-Cl), 64(N-CH-Ar), 69(O-CH_2), 172(-CO-N), 133, 163, 122, 132, 125, 130, 147, 117(Indole-C), 70(-N-CH_2-N), 52, 26 (Piperidine-C), 24(Ar-CH_3).

3.6.3. (Z)-2-(5-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)quinolin-8-yloxy)-N'-(2-oxo-1-(piperidin-1-yl methyl)indolin-3-ylidene)acetohydrazide (6c)

IR (KBr): 3130(NH), 1609(-C=N), 1690(Azetidinone-C=O), 1696(CO-NH), 2938(-CH_2). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ 1.5-2.2(m,10H, -CH_2 of piperidine ring), 3.73 (s, 3H, Ar-O-CH_3), 4.0(s,2H,N-CH_2-N), 4.78(s,2H,-O-CH_2), 5.15(d,1H,-CH of azetidin attached to phenyl ring), 5.46(d,1H,-CH of azetidin attached to –Cl), 6.5 (d, 1H, -CH), 6.7(d,1H,-CH), 6.8-7.0(m, 4H of C_6H_4),7.3-7.7(m,4H, for C_6H_4 of Indole) 8.0-8.8(m,3H of quinoline ring), 9.6(s, 1H, -NH).^{13}C NMR (75MHz, $CDCl_3$,TMS) δ = 151, 107, 116, 133, 128, 121, 149, 140, 122, 136, 128, 114, 158 (Ar-C), 161(N-C=O), 62(C-Cl), 63(N-CH-Ar), 69(O-CH_2), 171(-CO-N), 132, 162, 121, 131, 124, 129, 147, 118(Indole-C), 70(-N-CH_2-N), 52, 25 (Piperidine-C), 55(O-CH_3).

3.6.4. (Z)-2-((5-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetohydrazide (6d)

IR (KBr): 3185(NH), 1602(-C=N), 1696(Azetidinone-C=O), 1704(CO-NH), 2931(-CH_2). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ 1.5-2.2(m,10H, -CH_2 of piperidine ring),4.0(s,2H,N-CH_2-N), 4.78(s,2H,-O-CH_2), 5.15(d,1H,-CH of azetidin attached to phenyl ring), 5.46(d,1H,-CH of azetidin attached to –Cl), 6.57 (d, 1H, -CH), 6.8(d,1H,-CH), 7.1-7.2(m, 4H of C_6H_4),7.4-7.7(m,4H, for C_6H_4 of Indole) 8.0-8.8(m,3H of quinoline ring), 9.8(s, 1H, -NH). ^{13}C NMR (75MHz, $CDCl_3$,TMS) δ = 150, 107, 116, 133, 128, 121, 148, 139, 122, 141, 128, 132, 121 (Ar-C), 163(N-C=O), 62(C-Cl), 63(N-CH-Ar), 69(O-CH_2), 171(-CO-N), 132, 163, 121, 131, 124, 129, 147, 118(Indole-C), 71(-N-CH_2-N), 52, 25 (Piperidine-C).

3.6.5. (Z)-2-((5-(2-(4-bromophenyl)-3-chloro-4-oxoazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetohydrazide (6e)

IR (KBr): 3178(NH), 1600(-C=N), 1691(Azetidinone-C=O), 1710(CO-NH), 2920(-CH_2). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ1.5-2.2(m,10H, -CH_2 of piperidine ring),4.0(s,2H,N-CH_2-N), 4.78(s,2H,-O-CH_2), 5.15(d,1H,-CH of azetidin attached to phenyl ring), 5.46(d,1H,-CH of azetidin attached to –Cl), 6.57 (d, 1H, -CH), 6.8(d,1H,-CH), 7.0-7.3(m, 4H of C_6H_4),7.4-7.7(m,4H, for C_6H_4 of Indole) 8.0-8.8(m,3H of quinoline ring), 9.8(s, 1H, -NH).^{13}C NMR (75MHz, $CDCl_3$,TMS) δ = 152, 107, 116, 133, 128, 121, 148, 139, 122, 143, 130, 132, 121 (Ar-C), 163(N-C=O), 62(C-Cl), 63(N-CH-Ar), 69(O-CH_2), 171(-CO-N), 132, 163, 121, 131, 124, 129, 147, 118(Indole-C), 71(-N-CH_2-N), 52, 25 (Piperidine-C).

3.6.6. (Z)-2-((5-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetohydrazide (6f)

IR (KBr): 3186(NH), 1600(-C=N), 1664(Azetidinone-C=O), 1724(CO-NH), 2929(-CH_2). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ1.5-2.2(m,10H, -CH_2 of piperidine ring),4.0(s,2H,N-CH_2-N), 4.83(s,2H,-O-CH_2), 5.15(d,1H,-CH of azetidin attached to phenyl ring), 5.46(d,1H,-CH of azetidin attached to –Cl), 6.57 (d, 1H, -CH), 6.8(d,1H,-CH), 7.8-8.1(m, 4H of C_6H_4),7.4-7.7(m,4H, for C_6H_4 of Indole) 7.9-8.8(m,3H of quinoline ring), 9.8(s, 1H, -NH), 10.12(s,1H,-NH of Indole).^{13}C NMR (75MHz, $CDCl_3$,TMS) δ = 151, 108, 116, 134, 129, 121, 149, 140, 123, 150, 128, 121, 146 (Ar-C), 162(N-C=O), 62(C-Cl), 64(N-CH-Ar), 70(O-CH_2), 173(-CO-N), 132, 164, 122, 131, 124, 130, 148, 117(Indole-C), 70(-N-CH_2-N), 52, 26 (Piperidine-C).

3.6.7. (Z)-2-((5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yl)oxy)-N'-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)acetohydrazide (6g)

IR (KBr): 3183(NH), 1604(-C=N), 1689(Azetidinone-C=O), 1694(CO-NH), 2939(-CH_2). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ2.3-3.7(m,8H, -CH_2 of piperidine ring), 4.0(s,2H,N-CH_2-N),4.8(s,2H,-O-CH_2), 5.16(d,1H,-CH of azetidin attached to phenyl ring), 5.44(d,1H,-CH of azetidin attached to –Cl), 6.57(d, 1H, -CH), 6.76(d,1H,-CH), 7.12-7.21(m, 5H of C_6H_5),7.3-7.7(m,4H, for C_6H_4 of Indole) 7.9-8.8(m,3H of quinoline ring), 9.52(s, 1H, -NH).^{13}C NMR (75MHz, $CDCl_3$,TMS) δ = 150, 107, 116, 134, 129, 121, 149, 140, 122, 143, 127, 129, 127 (Ar-C), 162(N-C=O), 62(C-Cl), 64(N-CH-Ar), 69(O-CH_2), 173(-CO-N), 132, 164, 122, 131, 125, 130, 147, 117(Indole-C), 70(-N-CH_2-N), 51, 66 (Morpholine-C).

3.6.8. (Z)-2-((5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yl)oxy)-N'-(1-((4-methylpiperazin-1-yl)methyl)-2-oxoindolin-3-ylidene)acetohydrazide (6h)

IR (KBr): 3188(NH), 1678(-C=N), 1684(Azetidinone-C=O), 1698(CO-NH), 2942(-CH_2). ^{1}HNMR(300MHZ, $(CD)_2SO$, TMS): δ2.2(s,3H,-N-CH3 of piperazine ring), 2.46(m,8H, -CH_2 of piperazine ring), 4.1(s,2H,N-CH_2-N),4.8(s,2H,-O-CH_2), 5.16(d,1H,-CH of azetidine attached to phenyl ring), 5.44(d,1H,-CH of azetidine attached to–Cl), 6.57(d, 1H, -CH), 6.76(d,1H,-CH), 7.12-7.21(m, 5H of C_6H_5),7.3-7.7(m,4H, for C_6H_4 of Indole) 7.9-8.8(m,3H of quinoline ring), 9.52(s, 1H, -NH).^{13}C NMR (75MHz, $CDCl_3$,TMS) δ = 154, 107, 116, 134, 129, 121, 149, 140,

122, 143, 127, 129, 127 (Ar-C), 162(N-C=O), 62(C-Cl), 64(N-CH-Ar), 69(O-CH_2), 173(-CO-N), 132, 164, 122, 131, 125, 130, 147, 117(Indole-C), 70(-N-CH_2-N), 50, 55 (Piperazine-C).

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Table 1. Analytical data of the compounds 3a-f, 5a-f and 6a-f

Compound	Moleular formula	Yield (%)	M.P. * (^{0}C)	% Analysis						$(M+1)^+$
				C		H		N		
				Cald	Found	Cald	Found	Cald	Found	
3a	$C_{20}H_{17}ClN_4O_3$	45	156-7	60.53	60.38	4.32	4.31	8.93	8.85	397.83
3b	$C_{21}H_{19}ClN_4O_3$	50	163-4	61.39	61.05	4.66	4.68	8.63	7.98	411.11
3c	$C_{21}H_{19}ClN_4O_4$	45	173-4	59.09	58.95	4.49	4.37	8.31	8.12	427.11
3d	$C_{20}H_{16}Cl_2N_4O_3$	55	145-6	55.70	54.92	3.74	3.68	12.99	12.27	432.27
3e	$C_{20}H_{16}BrClN_4O_3$	45	151-2	50.49	50.59	3.39	3.31	11.78	11.64	477.01
3f	$C_{20}H_{16}ClN_5O_5$	50	185-6	54.37	54.26	3.65	3.59	15.85	15.05	442.08
5a	$C_{28}H_{20}ClN_5O_4$	45	172-3	63.94	63.92	3.83	3.79	13.32	13.31	526.12
5b	$C_{29}H_{22}ClN_5O_4$	50	165-6	64.51	64.48	4.11	4.14	12.97	12.85	540.97
5c	$C_{29}H_{22}ClN_5O_5$	50	188-9	62.65	62.72	3.99	3.89	12.60	12.38	556.37
5d	$C_{28}H_{19}Cl_2N_5O_4$	55	178-9	60.01	58.97	3.42	3.41	12.50	11.52	561.39
5e	$C_{28}H_{19}BrClN_5O_4$	45	153-4	55.60	55.52	3.17	3.15	11.58	12.58	605.84
5f	$C_{28}H_{19}ClN_6O_6$	40	152-3	58.90	57.86	3.35	3.39	14.72	14.61	571.94
6a	$C_{34}H_{31}ClN_6O_4$	45	185-6	65.54	65.51	5.01	5.04	13.49	13.43	624.10
6b	$C_{35}H_{33}ClN_6O_4$	50	190-1	65.98	65.86	5.22	5.22	13.19	13.18	638.13
6c	$C_{35}H_{33}ClN_6O_5$	45	201-2	64.36	64.32	5.09	4.98	12.87	12.69	654.13
6d	$C_{34}H_{30}Cl_2N_6O_4$	50	183-4	62.10	62.22	4.60	4.51	12.78	12.66	658.55
6e	$C_{34}H_{30}BrClN_6O_4$	45	208-9	58.17	58.52	4.31	4.19	11.97	11.87	703.00
6f	$C_{34}H_{30}ClN_7O_6$	55	218-19	61.12	61.05	4.53	4.41	14.68	14.59	669.10
6g	$C_{33}H_{29}ClN_6O_5$	40	195-6	63.41	63.36	4.68	4.53	13.44	13.32	626.07
6h	$C_{34}H_{32}ClN_7O_4$	45	202-3	64.00	63.29	5.05	5.12	15.37	15.31	639.12

Table 2.Antibacterial Activity by the disc diffusion method

S.No	Compound	Zone of Inhibition			
		Staphylococcus aureus	*Bacillus Cereus*	*Escherichia Coli*	*Pseudomonas aeruginosa*
1	(Z)-2-((5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene) acetohydrazide (6a)	9	13	11	8
2	(Z)-2-((5-(3-chloro-2-oxo-4-(p-tolyl)azetidin-1-yl)quinolin-8-yl)oxy) -N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetohydrazide(6b)	7	11	9	6
3	(Z)-2-((5-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)quinolin-8-yl)oxy) -N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene) acetohydrazide(6c)	6	10	8	7
4	(Z)-2-((5-(3-chloro-2-(4-chlorophenyl)-4-oxoazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene) acetohydrazide (6d)	12	16	14	13
5	(Z)-2-((5-(2-(4-bromophenyl)-3-chloro-4-oxoazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetohydrazide (6e)	11	15	13	12
6	(Z)-2-((5-(3-chloro-2-(4-nitrophenyl)-4-oxoazetidin-1-yl)quinolin-8-yl)oxy)-N'-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetohydrazide (6f)	14	18	16	15
7	(Z)-2-((5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yl)oxy)-N'-(1-(morpholinomethyl)-2-oxoindolin-3-ylidene)acetohydrazide (6g)	13	15	14	13
8	(Z)-2-((5-(3-chloro-2-oxo-4-phenylazetidin-1-yl)quinolin-8-yl)oxy)-N'-(1-((4-methylpiperazin-1-yl)methyl)-2-oxoindolin-3-ylidene)acetohydrazide (6h)	14	16	15	14
	Amoxycillin	21	27	24	22
	Cefaclor	19	22	19	20

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