International Journal of Scientific Research in Chemistry (IJSRCH)
© 2019 IJSRCH | Volume 4 | Issue 1 | ISSN : 2456-8457

Synthesis of Some New Quinazoline Derivatives Incorporating Sydnone Moiety and Evaluation of Their Antimicrobial and Antitubercular Activities

Dr. S. A. Patel*[1], Dr. K. C. Patel[2]

*[1]Department of Chemistry, Navjivan Science College, Dahod, Gujarat, India

[2]Department of Chemistry, Veer Narmad South Gujarat University, Gujarat, India

Corresponding Author : shrey.patel84@gmail.com[1]

ABSTRACT

In this study, we present the synthesis of a novel set of sydnone derivatives, specifically 3-(4-chlorophenyl)-4-N-[2-(substitutedphenyl)-4-oxoquinazoline-3(4H)-yl]sulfamoyl-sydnone 7a-i, derived from 3-(4-chlorophenyl)-4-(chlorosulfonyl) sydnone. The characterization of the recently synthesized compounds was conducted using infrared (IR), 1H nuclear magnetic resonance (NMR), 13C NMR, mass spectrometry, and elemental analysis. A screening was conducted to evaluate the antibacterial activity of the synthesized compounds against Gram-positive bacteria such as S. aureus and S. pyogenes, as well as Gram-negative bacteria including E. coli and P. aeruginosa. Additionally, the compounds were assessed for their antifungal activity against C. albicans and A. niger.

IndexTerms - Antimicrobial Activity, Mesoionic, Quinazoline, Sydnone.

I. INTRODUCTION

Mesoionic compounds, five membered heterocyclic conjugated betains which belong to the class of non-benzenoid aromatics, have gained importance due to their unusual structure, chemical properties and varied pharmacological properties.[1,2]The most extensively studied class of the mesoionic category is the sydnone ring and its chemical and physical properties are unique.[3]The aromatic and dipolar nature of sydnone have proved to be a challenge for researchers who intended to satisfactorily describe and define it.[4]Sydnone has played a crucial role in the development of theory in heterocyclic chemistry and occupy special position in organic synthesis.[5]The sydnone has a 1,2,3-oxadiazole skeleton containing an oxygen atom attached to the C-5 position.[6]Sydnones undergoes various electrophilic substitution reactions such as nitration,[7]sulphonation,[8]halogenation[9]and acylation[10]at the C-4 position of the ring.Sydnone derivatives show a variety of biological properties, such as antimalarial,[11,12] antiinflammatory,[13] analgesic,[14]antibacterial,[15]antifungal,[16] antitumor,[17]and antioxidant activity.[18]Sydnones show liquid crystalline properties.[19]

Quinazolinone is one of the most frequently encountered heterocyclic compounds in medicinal chemistry because of its wide range of biological applications including; antihypertensive,[20] CNS depressants, [21]analgesic,[22] antihistaminic,[23,24] anticoccidial,[25] antifolatesinhibitor,[26] anticancer,[27] anthelmintic,[28] antibacterial,[29] anti HIV,[30] antifungal,[31] antitubercular,[32] and anticonvulsant.[33]

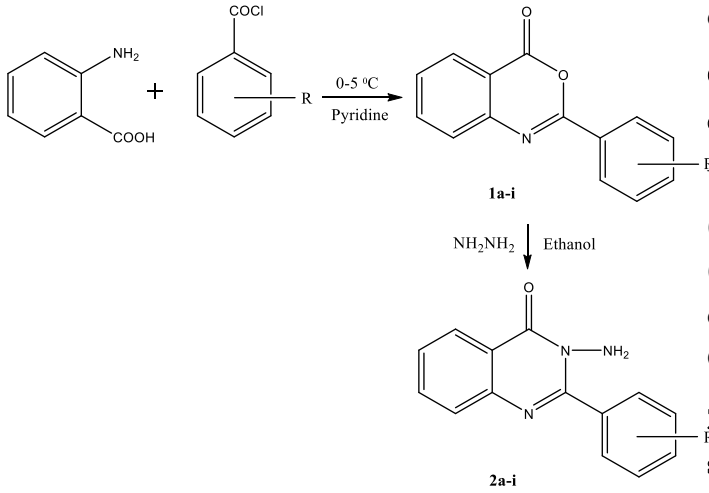
On the basis of these observations, we decided to undertake the synthesis of some new quinazoline

Received : 15 Jan 2019 | Accepted : 30 Jan 2019 | January-February-2019 [4 (1) : 57-66]

containing sydnone derivatives and evaluated their antimicrobial and antitubercular activities.

II. MATERIAL AND METHOD

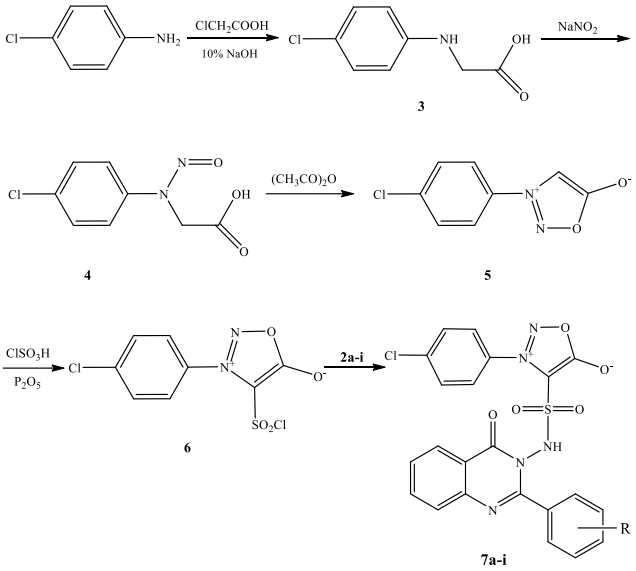
The structures of the synthesized compounds were confirmed by 1H and 13C nuclear magnetic resonance and Fourier transform infrared. 1H NMR spectra were recorded with a Bruker Avance II 400 MHz NMR spectrometer at SAIF, Chandigarh, in DMSO-d6 using TMS as internal standard and chemicalshifts are expressed in δ ppm. 13C NMR spectra of the compounds were recorded with a Bruker Avance II 400 MHz NMR spectrometer at SAIF (Sophisticated Analytical Instrument Facilities), Chandigarh. The IR spectra were recorded on a Shimadzu, Japan FTIR spectrometer using KBr disc. Elemental analyses (C, H, N) were performed on a Thermo Scientific FLASH 2000 at G.N.F.C. (Gujarat Narmada Valley Fertilizer Company Ltd., Bharuch). Mass spectra Electron Ionization (EI) of the compounds were recorded with a Firmegan MAT-8230 mass spectrometer also at SAIF, Chandigarh. The progress of reactions and the purity of synthesized compounds were checked by TLC on E-Merck precoated 60 F254 plates and the spots were examined under short-wave UV light.



a R = H;b R = 3,4-$(Cl)_2$;c R = 4-OCH_3;d R = 3-NO_2-4-OCH_3;eR = 3-NO_2;

f R = 4-NO_2; g R = 3-Cl; hR = 4-Cl; i R = 3-Br

Scheme 1. Synthetic pathway for compounds 2a-i.



Scheme 2. Synthetic pathway for compounds 7a-i.

2.1. General procedure for the synthesis of compounds (1a-i)

A solution of substituted benzoyl chloride (0.05 mol) was added dropwise to the stirred solution of anthranilic acid (0.05 mol) in pyridine (60 mL) at 0-5 °C for 1 h. Then the reaction mixture was stirred for 2 h at room temperature until a solid product was formed. The reaction mixture was neutralized with saturated sodium bicarbonate solution. Separated solid was filtered off, washed with water, driedandrecrystallised from ethanol.

Compound 1a; 2-phenyl-4H-benzo[d][1,3]oxazin-4-one

Yield: 9.25 g (83 %); m.p.-113-114 °C; IR spectrum (KBr, ν, cm^{-1}): 1728 (CO), 1596 (C=N); 1H NMR (DMSO-d_6, δ ppm): 7.45-8.10 (m, 9H, Ar-H). Anal. calcd. for $C_{14}H_9NO_2$: C, 75.25; H, 4.01; N, 6.21; found: C, 75.33; H, 4.06; N, 6.27.

2.2. Compound 2a-i; General procedure for the synthesis of compounds

A mixture of Compound 1a-j (0.01 mol) and hydrazine hydrate (0.03 mol) in ethanol (10 mL) was refluxed for 4 h. The solid that separated out on

cooling was collected by filtration, washed with water, dried and recrystallized from ethanol.

Compound 2a; 3-amino-2-phenylquinazolin-4(3H)-one

Yield: 2.21g (88%); m.p.-177-178˚C; IR spectrum (KBr, ν, cm^{-1}): 3319, 3451 (NH_2), 1678 (CO), 1598 (C=N); ^1H NMR (DMSO-d_6, δ ppm): 7.50-8.15 (m, 9H, Ar-H), 5.49 (s, 2H, NH_2). Anal. calcd. for $C_{14}H_{11}N_3O$: C, 70.81; H, 4.75; N, 17.80; found: C, 70.87; H, 4.67; N, 17.71.

2.3. Compound 3;N-(4-chlorophenyl) glycine

4-chloroaniline (0.011 mol) was added to an ice-cold solution of chloroacetic acid(0.01 mol) and water (2 mL) which was neutralized by sodium hydroxide solution (10%). The reaction mixture was refluxed for 20 minand after cooling sodium hydroxide (0.5 gm) was added, and the mixture was extracted with methylene dichloride to remove the unreacted aniline. Acidification with concentrated HCl until complete precipitation gave the product which was collected by filtration, washed with water, dried and recrystallised from ethanol. Yield: 1.64g, (80%); m.p.-145˚C.IR spectrum (KBr, ν, cm^{-1}): 3420-3313 (NH_2); ^{1}NMR spectrum ($CDCl_3$, δ ppm): 7.49 (d, 1H, CH), 7.71 (d, 1H, CH), 6.85 (s, 2H, NH_2), 8.47 (s, 1H, CH). Anal. calcd. for $C_8H_8ClNO_2$: C, 51.66; H, 4.43; N, 7.62; found: C, 51.77; H, 4.34; N, 7.55.

2.4. Compound 4; N-Nitroso-N-(4-chlorophenyl) glycine

A cold solution of sodium nitrite (0.01 mol) in water (5 mL) was added dropwise to a suspension of compound 3 (0.01 mol) in water (40 ml) at 0-5˚C with stirring. After complete addition stirring was continued for 2 h and then overnight, whenupon the reaction mixture was filtered and the nitroso compound was precipitated by addition of concentrated HCl. The product was collected by filtration, washed with water, dried and recrystallised from methanol. Yield: 0.62 g (78 %); m.p.-104 ˚C. IR spectrum (KBr, ν, cm^{-1}): 3435 (NH), 1636 (CONH); ^1H NMR spectrum ($CDCl_3$, δ ppm): 4.31 (s, 2H, CH_2), 7.50 (d, 1H, CH), 7.70 (d, 1H, CH), 7.98 (s, 1H, CONH), 8.45 (s, 1H, CH). Anal. calcd. for $C_8H_7ClN_2O_3$: C, 44.62; H, 3.35; N, 13.16; found: C, 44.77; H, 3.29; N, 13.05.

2.5. Compound 5; 3-(4-chlorophenyl) sydnone

Compound 4 and acetic anhydride were taken in a ratio of 1: 5 by weight and stirred for 10 h. The solution was poured slowly in to cold water which was very well stirred. The pH was adjusted to neutrality with 10% sodium bicarbonate solution. The product was collected by filtration, washed with water, dried and recrystallised from benzene-petroleum ether. Yield: 1.54 g (78 %); m.p.-140-145 ˚C. IR spectrum (KBr, ν, cm^{-1}): 3455 (NH), 3350 ($NHNH_2$), 2888 (CH_2), 1648 (CONH); 1H NMR ($CDCl_3$, δ ppm): 2.01 (brs, 2H, NH2, D_2O exchangeable), 2.21 (brs, 1H, NH, D^2O exchangeable), 3.60 (s, 2H, CH_2), 7.52 (d, 1H, CH), 7.73 (d, 1H, CH), 8.01 (s, 1H, CONH), 8.51 (s, 1H, CH). Anal. calcd. for $C_8H_5ClN_2O_2$: C, 48.80; H, 2.46; N, 14.37; found: C, 48.88; H, 2.56; N, 14.25.

2.6. Compound 6; 3-(4-chlorophenyl)-4-(chlorosulfonyl) sydnone

Chlorosulphonic acid (0.3 mol) was added dropwise to a mixture of compound 5 (0.1 mol) and a catalytic amount of P_2O_5 over 30 min with constant stirring at 0-5 ˚C. When all the chlorosulphonic acid was added, the reaction mixture was stirred for 2 h and kept overnight at room temperature or heated on a water bath for 1 h to complete the reaction. The reaction was allowed to cool andthe oily mixture was poured into crushed ice with stirring. Any lumps of solid were broken up and the mixture was stirred for several min in order to obtain a greenish-yellow solid product. The product was collected by filtration, washed with water, dried and recrystallized from ethanol. Yield: 3.34 g (87 %); m.p.-175-178 ˚C. IR spectrum (KBr, ν, cm^{-1}): 1742 (CO), 1395, 1180 (SO_2); 1H NMR ($CDCl_3$, δ ppm): 7.67-7.96 (m, 4H, Ar-H).

Anal. calcd. for $C_8H_4Cl_2N_2O_4S$: C, 32.48; H, 1.43; N, 9.40; found: C, 32.56; H, 1.37; N, 9.49.

2.7. Compound 7a-i; General procedure for the synthesis of compounds (7a-i)

A solution of compound 2a-j (0.01 mol) in acetone was added dropwise into a solution of compound 6(0.01 mol) in acetone with constant stirring over a period of 5 h at room temperature. Pyridine (1 mL) was added to the well stirred solution after 1 h and the solution was poured into ice-cold water with stirring. The solid was collected by filtration, washed with water, dried and recrystallized from ethanol.

Compound 7a; 3-(4-chlorophenyl)-4-(N-(4-oxo-2-phenylquinazolin-3(4H)-yl) sulfamoyl)sydnone

Yield: 3.69 g (86%); m.p.-119-121˚C; IR spectrum (KBr, ν, cm^{-1}): 3319 (NH), 1730 (CO of sydnone), 1660 (CO of quinazoline), 1332, 1160 (SO_2); ^{1}H NMR (DMSO-d_6, δ ppm): 7.11-8.03 (m, 13H, Ar-H), 9.15 (s, 1H, SO_2NH);^{13}C NMR (DMSO-d_6, δ ppm): 108.96, 120.60, 124.40, 127.01, 127.72, 128.06, 128.86, 129.24, 129.87, 130.15, 130.58, 131.00, 132.49, 135.11, 137.69, 139.34, 152.85, 156.31, 166.52, 168.89; MS (m/z): 495.31 (M^+) 100%. Anal. calcd. for $C_{22}H_{14}ClN_5O_5S$: C, 53.32; H, 2.80; N, 14.13; found: C, 53.28; H, 2.85; N, 14.12.

Compound 7b;3-(4-chlorophenyl)-4-(N-(2-(3,4-dichlorophenyl)-4-oxoquinazolin-3(4H)-yl) sulfamoyl)sydnone

Yield: 3.67 g (75 %); m.p.-231-233 ˚C; IR spectrum (KBr, ν, cm^{-1}): 3330 (NH), 1737 (CO of sydnone), 1655 (CO of quinazoline), 1326, 1166 (SO_2), 750 (C-Cl); ^{1}H NMR (DMSO-d_6, δ ppm): 7.25-8.00 (m, 11H, Ar-H), 9.17 (s, 1H, SO_2NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.90, 120.61, 124.45, 127.03, 127.31, 127.45, 128.13, 128.96, 129.84, 130.21, 133.50, 134.05, 134.27, 135.15, 137.73, 139.39, 152.88, 156.37, 166.54, 168.98;MS (m/z): 564.98 (M^+) 100%. Anal. calcd. for $C_{22}H_{12}Cl_3N_5O_5S$: C, 46.75; H, 2.08; N, 12.45; found: C, 46.79; H, 2.14; N, 12.40.

Compound 7c;3-(4-chlorophenyl)-4-(N-(2-(4-methoxyphenyl)-4-oxoquinazolin-3(4H)-yl) sulfamoyl)sydnone

Yield: 3.19g (70%); m.p.-147-149˚C; IR spectrum (KBr, ν, cm^{-1}): 3300 (NH), 1760 (CO of sydnone), 1647 (CO of quinazoline), 1321, 1175 (SO_2), 1250, 1030 (C-O-C); ^{1}H NMR (DMSO-d_6, δ ppm): 3.87 (s, 3H, OCH_3), 6.69-7.95 (m, 12H, Ar-H), 9.22 (s, 1H, SO_2NH); ^{13}C NMR (DMSO-d_6, δ ppm): 55.94, 108.99, 114.35, 120.70, 124.48, 127.04, 128.09, 128.96, 129.81, 130.15, 131.41, 135.16, 137.64, 139.38, 152.88, 156.33, 161.59, 166.59, 168.86;MS (m/z): 525.75 (M^+) 100%. Anal. calcd. for $C_{23}H_{16}ClN_5O_6S$:C, 52.56; H, 3.04; N, 13.36; found: C, 52.53; H, 3.07; N, 13.32.

Compound 7d; 3-(4-chlorophenyl)-4-(N-(2-(4-methoxy-3-nitrophenyl)-4-oxoquinazolin-3(4H)-yl) sulfamoyl)Sydnone

Yield: 3.36g (68%); m.p.-128-130˚C; IR spectrum (KBr, ν, cm^{-1}): 3315 (NH), 1745 (CO of sydnone), 1650 (CO of quinazoline), 1556, 1345 (NO_2), 1333, 1169 (SO_2), 1236, 1020 (C-O-C); ^{1}H NMR (DMSO-d_6, δ ppm): 3.80 (s, 3H, OCH_3), 6.95-7.99 (m, 11H, Ar-H), 9.16 (s, 1H, SO_2NH); ^{13}C NMR (DMSO-d_6, δ ppm): 55.83, 108.95, 116.78, 120.63, 121.76, 124.49, 127.06, 128.01, 128.13, 129.89, 130.23, 135.15, 136.52, 137.77, 138.52, 139.41, 152.81, 153.09, 156.34, 166.59, 168.82; MS (m/z): 570.76 (M^+) 100%. Anal. calcd. for $C_{23}H_{15}ClN_6O_8S$:C, 48.43; H, 2.59; N, 14.68; found: C, 48.39; H, 2.65; N, 14.72.

Compound 7e; 3-(4-chlorophenyl)-4-(N-(2-(3-nitrophenyl)-4-oxoquinazolin-3(4H)-yl) sulfamoyl)sydnone

Yield: 3.51g (75%); m.p.-177-179˚C; IR spectrum (KBr, ν, cm^{-1}): 3327 (NH), 1744 (CO of sydnone), 1652 (CO of quinazoline), 1533, 1342 (NO_2), 1325, 1176 (SO_2); ^{1}H NMR (DMSO-d_6, δ ppm): 7.31-8.37 (m, 12H, Ar-H), 9.18 (s, 1H, SO_2NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.84, 119.96, 120.66, 124.39, 124.56, 127.10, 128.09, 129.76, 129.88, 130.21, 133.07, 133.94, 135.22, 137.69, 139.37, 148.10, 152.82, 156.39, 166.53, 168.84;

MS (m/z): 540.77 (M^+) 100%. Anal. calcd. for $C_{22}H_{13}ClN_6O_7S$: C, 48.90; H, 2.39; N, 15.59; found: C, 48.85; H, 2.42; N, 15.54.

Compound 7f; 3-(4-chlorophenyl)-4-(N-(2-(4-nitrophenyl)-4-oxoquinazolin-3(4H)-yl) sulfamoyl)sydnone

Yield: 3.89 g (83 %); m.p.-199-201 °C; IR spectrum (KBr, ν, cm^{-1}): 3325 (NH), 1758 (CO of sydnone), 1659 (CO of quinazoline), 1547, 1333 (NO_2), 1324, 1171 (SO_2); ^{1}H NMR (DMSO-d_6, δ ppm): 7.19-8.20 (m, 12H, Ar-H), 9.18 (s, 1H, SO_2NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.90, 120.67, 124.43, 124.69, 127.10, 128.11, 129.01, 129.86, 130.18, 135.15, 136.70, 137.65, 139.36, 148.96, 152.85, 156.35, 166.58, 168.85; MS (m/z): 540.66 (M^+) 100%. Anal. calcd. for $C_{22}H_{13}ClN_6O_7S$: C, 48.78; H, 2.45; N, 15.48; found: C, 48.85; H, 2.42; N, 15.54.

Compound 7g; 3-(4-chlorophenyl)-4-(N-(2-(3-chlorophenyl)-4-oxoquinazolin-3(4H)-yl) sulfamoyl)sydnone

Yield: 3.45 g (75 %); m.p.-164-166 °C; IR spectrum (KBr, ν, cm^{-1}): 3328 (NH), 1749 (CO of sydnone), 1652 (CO of quinazoline), 1335, 1170 (SO_2), 754 (C-Cl); ^{1}H NMR (DMSO-d_6, δ ppm): 7.23-7.98 (m, 12H, Ar-H), 9.23 (s, 1H, SO_2NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.91, 120.64, 124.48, 125.96, 126.05, 127.07, 128.03, 129.81, 130.20, 130.37, 130.95, 131.16, 134.75, 135.19, 137.61, 139.34, 152.83, 156.38, 166.60, 168.86; MS (m/z): 530.63 (M^+) 100%. Anal. calcd. for $C_{22}H_{13}Cl_2N_5O_5S$: C, 49.88; H, 2.42; N, 13.26; found: C, 49.82; H, 2.47; N, 13.21.

Compound 7h; 3-(4-chlorophenyl)-4-(N-(2-(4-chlorophenyl)-4-oxoquinazolin-3(4H)-yl) sulfamoyl)sydnone

Yield: 2.99 g (65 %); m.p.-171-173 °C; IR spectrum (KBr, ν, cm^{-1}): 3333 (NH), 1738 (CO of sydnone), 1650 (CO of quinazoline), 1333, 1169 (SO_2), 752 (C-Cl); ^{1}H NMR (DMSO-d_6, δ ppm): 7.21-7.99 (m, 12H, Ar-H), 9.20 (s, 1H, SO_2NH); ^{13}C NMR (DMSO-d_6, δ ppm): 108.99, 120.69, 124.43, 127.09, 128.05, 129.15, 129.56, 129.80, 130.15, 132.33, 135.22, 136.22, 137.67, 139.31, 152.90, 156.43, 166.56, 168.82; MS (m/z): 530.54 (M^+) 100%. Anal. calcd. for $C_{22}H_{13}Cl_2N_5O_5S$: C, 49.76; H, 2.43; N, 13.25; found: C, 49.82; H, 2.47; N, 13.21.

Compound 7i; 4-(N-(2-(3-bromophenyl)-4-oxoquinazolin-3(4H)-yl) sulfamoyl)-3-(4-chlorophenyl) sydnone

Yield: 4.18g (84%); m.p.-179-181°C; IR spectrum (KBr, ν, cm-1): 3321 (NH), 1735 (CO of sydnone), 1666 (CO of quinazoline), 1335, 1162 (SO2), 594 (C-Br); 1H NMR (DMSO-d6, δ ppm): 7.18-8.03 (m, 12H, Ar-H), 9.16 (s, 1H, SO2NH); 13C NMR (DMSO-d6, δ ppm): 108.97, 120.71, 122.92, 124.41, 127.04, 127.17, 128.08, 129.85, 130.02, 130.20, 130.67, 131.82, 133.56, 135.19, 137.69, 139.39, 152.87, 156.31, 166.54, 168.90; MS (m/z): 574.95 (M+) 100%. Anal. calcd. for C22H13ClN5O5SBr: C, 45.92; H, 2.31; N, 12.16; found: C, 45.97; H, 2.28; N, 12.18.

III. Antimicrobial activity and Antitubercular activity

3.1. Antimicrobial activity

The newly synthesized compounds 7a-i has been screened for antimicrobial activity using the broth dilution method (Table 1). The antibacterial activity of the compounds was tested against S.aureusandS.pyogenesas Gram-positive and P.aeruginosa and E.coli as Gram-negative bacterial strains. The antifungal activity of the compounds was tested against A.nigerandC.albicansasfungal strains. Ampicillin and Chloramphenicol were used as standard antibacterial drugs and Nystatin and Griseofulvin were used as standard antifungal drugs. Standard strains were procured from the Institute of Microbial Technology, Chandigarh.

Broth dilution method

In the present work, Minimum Inhibition Concentrations (MIC) was determined by the Broth dilution method. The lowest concentration inhibiting

growth of the organism was recorded as the MIC and the DMSO was used as a diluent.Serial dilutions were prepared in primary and secondary screening. Each synthesized drug was diluted obtaining 2000 µg/ml concentration, as a stock solution. Mueller Hinton Broth was used as a nutrient medium to grow and dilute the drug suspension for the test bacteria, and sabaourausdextrose broth was used for fungal nutrition. The inoculums size for the test strain was adjusted to 108 CFU [Colony Forming Unit] per milliliter by comparing the turbidity with McFarland standards. The control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and incubated at 37˚Cfor 24 hrs for bacteria and 22°C for 74 hrs for fungal. The MIC of the control organism is read to check the accuracy of the drug concentrations. The amount of growth from the control tube before incubation, which represents the original inoculums was compared.

3.2. Antitubercular activity

Tuberculosis (TB) is infectious disease and potentially serious disease caused by Mycobacterium tuberculosis. Tuberculosis (TB), disproportionally affecting the world's humblest populations, remains one of the biggest public health problems in the 21st century. It is responsible for nearly 3 million deaths worldwide every year. Current tuberculosis treatment is a long course of combination of 3-4 antibiotic drugs, which have one or the other toxic side effects and led to poor patient compliance. Mycobacterium tuberculosis is a significant public health concern because most of the anti-TB drugs that have been in use for over 40 years are no longer effective for the treatment of these infections. Antitubercular drugs such as isoniazid (INH), rifampicin (RIF), pyrazinamide, ethambutol, streptomycin etc. have been a mainstay in the treatment of tuberculosis. The occurrence of multidrug-resistant MDR-TB is the infection caused by M. tuberculosis which is resistant to at least isoniazid and rifampicin, the two key anti-TB drugs.

IV. Results and discussion

As evident from Table 1, the antimicrobial activity of the synthesized compounds was highly dependent on the nature of the substituted functional groups. In the series7a–i, it is observed that the non-substituted phenyl ring present at the 2nd position in quinazoline analogs suchas compound 7aprovided much less activity towards all microbial organisms, confirming the importance of a substituent at that position on phenyl ring.The presence ofelectron withdrawing nitro group at the 3-position of the phenyl ring attached to the C-2 position of the quinazoline moiety, such as in compound 7e, plays an important role in eliciting inhibition of both Gram-positive bacteria S.aureus and S.pyogenes compared with standard drugs Ampicillin. The replacement of the nitro group from the 3-position of the phenyl ring to the 4-position, as in compound 7f, retained some of the activity against Gram-positive bacteria S.aureus. An electron withdrawing chloro group present at the 3-position of the phenyl ring,such as in compound 7g, imparted good antibacterial activity against both Gram-negative bacteria, while a chloro group present at the 4-position of the phenyl ring,such in compound 7h provided good antibacterial activity against both Gram-positive bacteria. On the other hand, additional chloro groups at the 3- and 4-positions of the phenyl ring, such as in compound 7b witnessed a decrease in the antibacterial activity. It was shown thatmethoxy substitution at the para position of the phenyl ring, as in compound 7c, revealed the potent as against S.pyogeneswhile nitro and methoxy groups at 3- and 4-positions of the phenyl ring, as in compound 7d, providedgood antibacterial activity against S.aureus as Gram-positive bacteria and E.coli as Gram-negative bacteria. The presence of a bromo group at the 3-position of the phenyl ring, as in compound 7i, produced weak antimicrobial activity against tested microbial strains. The antifungal screening result for

compounds 7a-i have shown that compounds 7c, 7g and 7h exhibited excellent activity against fungal strain C.albicans while the remaining compounds showed good to moderate antifungal activity against both fungal species.

As illustrated in Table 2, most of the synthesized compoundsshowed moderate to significant activity to the tested anti tuberculosis activity against M.Tuberculsis. The excellent antitubercular activity was that of compound 7b, in which 3,4-dichloro was condensed with quinoline hetero system. The lower antitubercular activity was observed for derivatives in which phenyl group contain 4-methoxy, 3-nitro-4-methoxy, 4-nitro and 3-chloro groups.

V. Conclusions

Various quinazoline based sydnone derivatives were characterized by IR, 1H NMR, 13C NMR, mass spectra, and elemental analysis and evaluated for their antimicrobial activity. Most of the synthesized compounds showed good antibacterial activity compared with antifungal activity. Compounds 7d, 7e, 7f and7hwere found to be most active against S.aureas, whereas 7c, 7e and 7h showed good activity against S.pyogenus as Gram-positive bacteria. Compounds 7d and 7g showed better antibacterial activity against E.coli and compounds 7g exhibited good antibacterial activity against P.aeruginosa as Gram-negative bacteria. In the case of antifungal activity, compounds 7c, 7g and7h showed excellent activity against C.albicans.While chloro groups at the 3 and 4- positions of the phenyl ring, as in compound 7b enhance the antitubercular activity against M.Tuberculsis.

VI. Acknowledgment

The authors would like to acknowledge Department of Chemistry, Veer Narmad South Gujarat University, Surat for providing laboratory facilities and D. Rajani, Micro care Laboratory, Surat, for help in antimicrobial activity work. The authors also thank to SAIF, Chandigarh for analytical analysis.

Table 1. Antimicrobial activity (MIC µg/ml) of some synthesized compounds **7a-i.**

Compounds	Minimum Inhibitory Concentration (µg/ml)					
	Gram-positive		Gram-negative		Antifungal	
	S.aureus ATCC-96	*S.pyogenes* ATCC-443	*E.coli* ATCC-442	*P.aeruginosa* ATCC-441	*C.albicans* ATCC-227	*A.niger* ATCC-282
7a	250	250	200	250	250	500
7b	250	500	250	500	500	1000
7c	125	100	125	250	200	1000
7d	100	200	100	200	250	1000
7e	62.5	100	250	500	500	1000
7f	100	200	500	500	500	1000
7g	200	200	100	100	200	500
7h	100	100	250	250	200	1000
7i	250	250	250	500	500	1000
Ampicillin	250	100	100	100	-	-
Nystatin	-	-	-	-	100	100

Table 2. Antitubercular activity (MIC μg/ml) of synthesized compounds **7a-i**.

Compounds	Minimum Inhibitory Concentration (μg/ml)
	M.Tuberculsis(MTCC-96)
7a	100
7b	12.5
7c	500
7d	250
7e	100
7f	>1000
7g	250
7h	125
7i	100
Rifampicin	40

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Cite this

Dr. S. A. Patel, Dr. K. C. Patel, "Synthesis of Some New Quinazoline Derivatives Incorporating Sydnone Moiety and Evaluation of Their Antimicrobial and Antitubercular Activities", International Journal of Scientific Research in Chemistry (IJSRCH), ISSN : 2456-8457, Volume 4 Issue 1, pp. 57-66, January-February 2019.
URL : https://ijsrch.com/IJSRCH19462