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A CONVENIENT SYNTHESIS OF ETHOXYPHTHALIMIDE DERIVATIZED QUINAZOLINE ASSEMBLED PYRIMIDINE AND PYRIDINE VIA COMMON INTERMEDIATE CHALCONE AND THEIR ANTIMICROBIAL AGENTS

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ABSTRACT

In the present investigation, synthesis of 3-{4-[2-amino-6-(4-chlorophenyl)-1,6-dihydropyrimidin-4-yl]phenyl}-1 Nethoxyphthalimido quinazoline-2,4-dione 5a-d and 2-amino-6-(4-chlorophenyl)-4-[4-(2,4-dioxo-1,4-dihydroquinazolin-3-yl)phenyl] }-1-Nethoxyphthalimido pyridine-3-carbonitrile 6a-d is described. Nucleophilic aza substitution on isatoic anhydride with p-aminoacetophenone gave 3-(4-acetylphenyl) quinazoline-2, 4-dione (1). This on Claisen condensation with various aromatic aldehydes 2a-d yields the corresponding 3-{4-[3-(4-substitutedphenyl) prop-2-enoyl] phenyl}quinazoline-2,4-dione 3a-d derivateives.This was condensed by bromoethoxyphthalimide to afford - [4-{3-(4-subsitutedphenyl)prop-2-enoyl}phenyl]-1-N-ethoxyphthalimidoquinazoline-2,4-dione 4a-d. These compounds 4a-d were cyclized separately with guanidine nitrate and malononitrile in ammonium acetate to give two series of final compound 5a-d and 6a-d. Structures of synthesized compounds have been assigned on the basis of their analytical and spectral data. Antibacterial and antifungal activities of the final compounds have been evaluated. Some of the compounds have shown significant inhibition on bacterial and fungal growth.

KEYWORDS: Isatoic anhydride, pyrimidine, pyridine, Bromoethoxyphthalimide, Antimicrobial activity.

INTRODUCTION

Quinazoline derivatives, which belong to the N-containing heterocyclic compounds, have caused universal concerns due to their widely and distinct biopharmaceutical activities. Researchers have already determined many therapeutic activities of quinazoline derivatives, including anti-cancer, [1- 4] anti-inflammation, [5,6], anti-bacterial, [7-10] anal-gesia,[5,9] anti-virus, [11] anti-cytotoxin,[12] anti-spasm,[9,13] anti-tuberculosis,[14] anti-oxidation, [15] anti-malarial[16] anti-hypertension,[17] anti-obesity,[18] anti-psychotic,[19] anti-diabetes,[20] etc. Medicinal chemists synthesized a variety of quinazoline compounds with different biological activities by installing various active groups to the quinazoline moiety using develop-ing synthetic methods. And the potential applications of the quinazoline derivatives in fields of biology, pesti-cides and medicine have also been explored.In addition to being essential components of naturally occurring nucleic acids, pyrimidines are integral parts of biologically important compounds such as antiviral[21] antiherpes,[22] and cardiovascular agents.[23] On the other hand, acetamido derivatives, in general, have been found to possessfungicidal[24] and herbicidal[25] activities.

As the biological activities of pyridine derivatives are shown above, the pyridine is found to be a very versatile nucleus in the pharmaceutical field. The derivatives are very much used as anticancer,[26] antimicrobial[27-30] antiviral,[31] antidiabetic & antithrombic agents[32] Anti-oxidant,[33] Antichagasic,[34] Antitumer[35] etc. Thus the pyridine nucleus could be considered as the panacea for the management of various diseases.

MATERIALS AND METHODS

Melting points of all synthesized compounds were taken in open capillaries and are uncorrected. IR spectra (KBr) were recorded on a Perkin-Elmer 1300 FT IR spectrometer and 1H NMR were determined on a Bruker WM-400 (400 MHz FT NMR) spectrometer using TMS as internal standard. Purity of compounds was checked by TLC using silica gel-G as adsorbent and visualization was accomplished with iodine. Bromoalkoxyphthalimide[36] compound was synthesized by reported methods our previous research lab group.

Synthesis of 3-(4-acetylphenyl) quinazoline-2, 4-dione 1

To a solution of isatoic anhydride (0.01 mole) in absolute alcohol, *p* aminoacetophenone (0.01mole) was added. The reaction mixture was heated under reflux for 4 hrs. Excess of the solvent was distilled off under reduced pressure and after cooling crystalline product was obtained. It was filtered and recrystallized from ethanol to yield needle shaped crystals.

KBr IR: 3416 (N-H str.),3086 (C-H str., Ar-H), 2935 (C-H, str. CH_3), 1718, 1693 (C=Ostr.) ^{1}HNMR ($CDCl_3$) δ:8.6 (s, 1H, NH), 6.8-7.4 (m, 8H, Ar-H), 2.6 (s, 3H, CH_3).

Synthesis of 3-{4-[3-(4-chlorophenyl)prop-2-enoyl]phenyl}quinazoline-2,4-dione (3a)

To a stirred solution of (1**,** 0.01 mol) 4-chlorobenzaldehyde (0.01 mol) in ethanol (20 ml) NaOH (3 g dissolved in minimum amount of water) was added portion wise. The stirring was continued for next 1 hrs and then kept overnight. The contents of the flask were poured into water and neutralized with acetic acid. The separated solid was filtered, washed with water, dried and recrystallized from ethanol.

KBr IR: 3408 (N-H str.), 3075 (C-H str., Ar-H),1658 (C=O str.), 740 (C-Cl), ^{1}HNMR ($CDCl_3$) δ: 9.20 (s, 1H, NH), 7.2-7.8 (m, 12H, Ar-H),6.8 (*d*, 1H, Ar-CH=CH), 7.5 (*d*, 1H, Ar-CH=CH),

Synthesis of 3-{4-[3-phenylprop-2-enoyl]phenyl}quinazoline-2,4-dione (3b)

KBr IR: 3420 (N-H str.), 3062 (C-H str., Ar-H),1682 (C=O str.), ^{1}HNMR ($CDCl_3$) δ: 9.05 (s, 1H, NH), 6.8-7.3 (m, 13H, Ar-H), 6.4 (*d*, 1H, Ar-CH=CH), 7.1 (*d*, 1H, Ar-CH=CH).

Synthesis of 3-{4-[(2E)-3-(4-methoxyphenyl)prop-2-enoyl]phenyl}quinazoline-2,4-dione(3c)

KBr IR: 3427 (N-H str.), 3068 (C-H str., Ar-H), 1690 (C=O str.), 1092 (C-O), ^{1}HNMR ($CDCl_3$) δ: 9.15 (s, 1H, NH), 6.9-7.5 (m, 12H, Ar-H), 6.6 (*d*, 1H, Ar-CH=CH), 7.3 (*d*, 1H, Ar-CH=CH), 3.40 (s, 3H, OCH_3).

Synthesis of 3-(4-{(2E)-3-[4-(N, N dimethylamino)phenyl]prop-2-enoyl}phenyl) quinazoline-2, 4(1H,3H)-dione(3d)

KBr IR: 3432 (N-H str.), 3083 (C-H str., Ar-H),1694 (C=O str.): ^{1}HNMR ($CDCl_3$) δ:9.25 (s, 1H, NH), 7.0-7.6 (m, 12H, Ar-H),6.9 (*d*, 1H, Ar-CH=CH), 7.7 (*d*, 1H, Ar-CH=CH), 2.97 (s, 6H, $N(CH_3)_2$).

Synthesis of 3-{4-[3-(4-chlorophenyl)prop-2-enoyl]phenyl}-1-N-ethoxyphthalimido quinazoline-2, 4-dione (4a)

Compound (**3a,** 0.01 mol) and bromoethoxyphthalimide (0.01 mol), were refluxed in dry acetone for 15-17 hrs. Containing K_2CO_3 (0.01 mol) as base. It was filtered and excess of solvent was removed under reduced pressure. The separated solid was filtered, washed and recrystallized from ethanol.

KBr IR: 3065 (C-H str., Ar-H), 2940 (C-H str.,CH_2),1762, 1694 (C=O str., CO-N-CO), 1667 (C=O str, COCH=CH),1355 (N-O str.), 1080 (C-O str.), 745 (C-Cl); ^{1}HNMR (CDCl3) δ: 7.3-7.8(m, 16H, Ar-H), 5.8 (*d*, 1H, =CH-Ar).3.95 (t, 2H, OCH_2), 3.10 (t, 2H, NCH_2).

Synthesis of 3-{4-[3-(phenyl) prop-2-enoyl]phenyl}-1-N-ethoxyphthalimidoquinazoline-2, 4-dione(4b)

KBr IR: 3053 (C-H str., Ar-H), 2934 (C-H str.,CH_2), 1754, 1676 (C=Ostr., CO-N-CO), 664 (C=O str, COCH=CH),1343 (N-O str.), 1076 (C-O str.);^{1}HNMR (CDCl3) δ: 7.0-7.6 (m, 17H, Ar-H),5.4 (*d*, 1H, =CH-Ar), 3.65 (t, 2H, OCH_2),2.95 (t , 2H, NCH_2).

Synthesis of 3-{4-[3-(4-methoxyphenyl) prop-2-enoyl]phenyl}-1-N-ethoxyphthalimido quinazoline-2, 4-dione(4c)

KBr IR: 3062 (C-H str., Ar-H),2938 (C-H str.,CH_2),1758, 1691 (C=Ostr., CO-N-CO), 1669 (C=O str, COCH=CH),1347 (N-O str.), 1073 (C-O str.);^{1}HNMR (CDCl3) δ: 6.8-7.4 (m, 16H, Ar-H), 5.9 (*d*, 1H, =CH-Ar),3.84 (t, 2H, OCH_2),3.05 (t , 2H, NCH_2), 3.30 (s, 3H, OCH_3).

Synthesis of 3-{4-[3-(4-(N,Ndimethyl)phenyl)prop-2-enoyl]phenyl}-1-N-ethoxy phthalimidoquinazoline-2, 4-dione(4d)

KBr IR: 3056 (C-H str., Ar-H), 2947 (C-H str.,CH_2), 1766, 1690 (C=Ostr., CO-N-CO), 1661 (C=O str, COCH=CH), 1351 (N-O str.), 1076 (C-O str.); ^{1}HNMR (CDCl3) δ: 6.6-7.2 (m, 16H, Ar-H),6.1 (*d*, 1H, =CH-Ar), 3.90 (t, 2H, OCH_2), 3.15 (t , 2H, NCH_2), 2.90 (s, 6H, $N(CH_2)_2$).

Synthesis of 3-{4-[2-amino-6-(4-chlorophenyl)-1, 6-dihydropyrimidin-4-yl]phenyl}-1-Nethoxyphthalimido quinazoline-2,4-dione (5a)

A mixture of compound IVa (0.01 mol) and guanidine nitrate (0.01 mol) were dissolved in absolute alcohol and refluxed for 1 hr. 20% NaOH solution was added dropwise to the reaction mixture and refluxing continued for 8 hrs. Reaction mixture was cooled and poured slowly into crushed ice. The solid obtained was filtered, washed, dried and recrystallised from ethanol.

IR (KBr) cm-^{1} : 3455–3210 (NH,NH_2), 3076 (C-H str., Ar-H), 2947 (C-H str.,CH_2), 1766, 1690 (C=Ostr., CO-N-CO), 1616-1425 (C=N,C=C str.), 1351 (N-O str.), 1076 (C-O str.), 756 (C-Cl); ^{1}HNMR ($CDCl_3$) δ : 10.44 (s, NH, exchangeable with D2O), 7.3-7.8(m, 16H, Ar-

H), 5.44 (s, NH_2, exchangeable with D_2O) , 5.56 (d, H, pyrimidine) 3.95 (t, 2H, OCH_2), 3.10 (t , 2H, NCH_2); ^{13}C-NMR ($CDCl_3$): 40, 58.2, 78.2 ($CDCl_3$) 127.1,130.4, 131.6, 133.3, 134.1, 136.4, 137.2, 138.3, 140.9, 141.2,142.6, 145.5, 148.2,150.0, 151.6, 152.5, 155.2, 156.5, 158.3, 160.2, 161.4, 205.2, 210.6,212.8 MS: (*m/z*) [M]+. 634, [M]+2. 636.Anal. calcd for $C_{34}H_{25}ClN_6O_5$: calcd for N, 13.29 %. Found.13.09%.

Synthesis of 3-{4-[2-amino-6-(phenyl)-1, 6-dihydropyrimidin-4-yl]phenyl}-1-Nethoxy phthalimido quinazoline-2,4-dione (5b)

IR (KBr) cm-^{1} : 3410–3240 (NH,NH_2), 3016 (C-H str., Ar-H), 2926 (C-H str.,CH_2), 1756, 1666 (C=O str., CO-N-CO), 1640-1415 (C=N,C=C str.), 1335 (N-O str.), 1067 (C-O str.)

^{1}HNMR ($CDCl_3$) δ : 10.12 (s, NH, exchangeable with D_2O), 6.8-7.2(m, 17H, Ar-H), 5.15 (s, NH_2, exchangeable with D_2O) , 5.46 (d, H, pyrimidine), 3.87 (t, 2H, OCH_2), 3.84 (t , 2H, NCH_2); ^{13}C-NMR ($CDCl_3$): 38, 56.3, 78.0 ($CDCl_3$) 123.4,125.3, 128.3, 129.4, 133.4, 134.4, 136.2, 137.3, 138.9, 140.2,141.2, 140.2, 144.2,148.5, 149.6, 150.5, 152.2, 154.4, 156.3, 157.4, 158.4, 202.9, 206.3,210.4 MS: (*m/z*) [M]+. 598.05. Anal. calcd for $C_{34}H_{26}N_6O_5$: calcd for N, 14.04 %. Found.13.85%.

Synthesis of 3-{4-[2-amino-6-(4-methoxyphenyl)-1,6-dihydropyrimidin-4-yl]phenyl}-1-Nethoxyphthalimido quinazoline-2,4-dione (5c)

IR (KBr) cm-^{1}: 3445–3254 (NH, NH_2), 3065 (C-H str., Ar-H), 2940 (C-H str.,CH_2), 1767, 1667 (C=O str., CO-N-CO), 1643-1410 (C=N,C=C str.), 1345 (N-O str.), 1080 (C-O str.)

^{1}HNMR ($CDCl_3$) δ: 10.20 (s, NH, exchangeable with D_2O), 7.45-7.80(m, 16H, Ar-H), 5.78 (s, NH_2, exchangeable with D_2O) , 5.76 (d, H, pyrimidine) 3.90 (t, 2H, OCH_2), 3.43 (s, OCH3), 3.12 (t , 2H, NCH_2); ^{13}C-NMR ($CDCl_3$): 41.6, 59.8, 60.5, 78.4 ($CDCl_3$) 128.7,131.3, 132.5, 134.8, 135.6, 138.4, 139.4, 140.7, 142.2, 143.4,144.8, 147.5, 148.2,151.3, 153.6, 154.6, 157.4, 158.3, 159.3, 162.4, 163.4, 212.3, 216.6, 222.8 : MS: (*m/z*) [M]+. 628.63. Anal. calcd for $C_{35}H_{28}N_6O_6$: calcd for N, 13.37 %. Found.13.19%.

Synthesis of 3-{4-[2-amino-6-(4-(N,Ndimethyl)phenyl)-1,6-dihydropyrimidin-4yl] phenyl}-1-Nethoxyphthalimido quinazoline-2,4-dione (5d)

IR (KBr) cm-^{1} : 3450–3234 (NH,NH_2), 3072 (C-H str., Ar-H), 2942 (C-H str.,CH_2), 1763, 1694 (C=Ostr., CO-N-CO), 1623-1442 (C=N,C=C str.), 1358 (N-O str.), 1083 (C-O str.)

^{1}HNMR ($CDCl_3$) δ : 10.24 (s, NH, exchangeable with D_2O), 7.6-7.92 (m, 16H, Ar-H), 5.62 (s, NH_2, exchangeable with D_2O) , 5.46 (d, H, pyrimidine) 3.92 (t, 2H, OCH_2), 3.32 (s, 6H, $N(CH_3)_2$), 3.20 (t , 2H, NCH_2); ^{13}C-NMR ($CDCl_3$): 41.8, 58.9, 78.6 ($CDCl_3$) 128.5,129.4,

130.6, 132.3, 135.1, 137.2, 138.5, 139.4, 140.5, 142.4,143.7, 146.8, 145.3,148.4, 152.8, 153.4, 156.8, 157.6, 159.3, 162.2, 163.5, 208.3, 212.7,214.8 : (*m/z*) [M]+. 641.67. Anal. calcd for $C_{36}H_{31}N_7O_5$: calcd for N, 15.29 %. Found.14.9%.

Synthesis of 2-amino-6-(4-chlorophenyl)-4-[4-(2,4-dioxo-1,4-dihydroquinazolin-3-yl) phenyl] }-1-Nethoxyphthalimido pyridine-3-carbonitrile (6a)

A mixture of compound **3a** (0.01 mol), malononitrile (0.01 mol) and ammonium acetate (0.08 mol) were dissolved in ethanol (30 ml) and refluxed for 12 hrs. The mixture was cooled and poured over crushed ice. Solid was filtered, dried and recrystallised from ethanol. Similarly, compounds 4b-e also synthesized by changing reflux time. Yield (66%), m.p 268 ºC.

IR (KBr) cm-^{1}:3450-3331(NH_2), 3076 (C-H str., Ar-H), 2239 (C≡N), 2947 (C-H str.,CH_2), 1766, 1690 (C=O str., CO-N-CO), 1616-1425 (C=N,C=C str.), 1351 (N-O str.), 1076 (C-O str.), 740 (C-Cl). ^{1}HNMR ($CDCl_3$) δ: 7.3-7.8(m, 16H, Ar-H), 5.86 (s, NH_2, exchangeable with D_2O),3.95 (t, 2H, OCH_2), 3.10 (t , 2H, NCH_2); ^{13}C-NMR (CDCl3): 45.3, 56.9, 78.6 (CDCl3) 120.5, 125.2, 127.1, 128.4, 129.7, 130.4, 131.6, 132.6.134.5, 138.2, 140.4, 141.4, 143.2, 145.6, 148.2, 150.4, 152.3, 156.3, 159.5, 184, 206.6, 210.2, 214.6: MS: (*m/z*) [M]+. 655,) [M]+2. 657. Anal. calcd for $C_{36}H_{23}ClN_6O_5$: calcd for N, 12.82 %. Found.12.43%.

Synthesis of 2-amino-6-(phenyl)-4-[4-(2,4-dioxo-1,4-dihydroquinazolin-3-yl)phenyl] }-1-Nethoxyphthalimido pyridine-3-carbonitrile (6b)

IR (KBr) cm-^{1}:3423-3345(NH_2), 3072 (C-H str., Ar-H), 2230 (C≡N), 2924 (C-H str.,CH_2), 1732, 1643 (C=O str., CO-N-CO), 1620-1434 (C=N, C=C str.), 1346 (N-O str.), 1060 (C-O str.); ^{1}HNMR ($CDCl_3$) δ : 7.10-7.82(m, 17H, Ar-H), 5.82 (s, NH_2, exchangeable with D_2O),3.92 (t, 2H, OCH_2), 3.08 (t , 2H, NCH_2); ^{13}C-NMR (CDCl3): 43.8, 54.4, 78.2 (CDCl3) 119.5, 122.3, 123.4, 125.6, 126.2, 128.3, 129.6, 130.6. 132.4, 134.2, 138.6, 140.2, 142.3, 144.8, 146.2, 148.4, 151.3, 153.3, 155.5, 178, 202.3, 208.2, 210.2: MS: (*m/z*) [M]+. 620. Anal. calcd for $C_{36}H_{24}N_6O_5$: calcd for N, 13.54 %. Found.13.02%.

Synthesis of 2-amino-6-(4-methoxyphenyl)-4-[4-(2,4-dioxo-1,4-dihydroquinazolin-3-yl) phenyl] }-1-Nethoxyphthalimido pyridine-3-carbonitrile (6c)

IR (KBr) cm-^{1}:3447-3343(NH_2), 3078 (C-H str., Ar-H), 2220 (C≡N), 2963 (C-H str.,CH_2), 1762, 1668 (C=Ostr., CO-N-CO), 1623-1416 (C=N,C=C str.), 1367 (N-O str.), 1023 (C-O str.); ^{1}HNMR ($CDCl_3$) δ: 7.3-7.8(m, 16H, Ar-H), 5.86 (s, NH_2, exchangeable with D_2O),3.95 (t, 2H, OCH_2), 3.24 (s,OCH_3), 3.10 (t , 2H, NCH_2); ^{13}C-NMR (CDCl3): 41.8, 58.9,64.3,78.6

(CDCl3) 120.3, 125.8, 127.6, 128.2, 129.4, 130.8, 131.2, 133.2.136.5, 139.2, 140.2, 141.8, 143.8, 145.2, 149.4, 151.3, 132.5, 157.4, 158.5, 184.5, 208.4, 214.2, 218.4: MS: (*m/z*) [M]+. 650. Anal. calcd for $C_{37}H_{26}N_6O_6$: calcd for N, 12.92 %. Found.12.48%.

Synthesis of 2-amino-6-(4-(N,N-dimethyl)phenyl)-4-[4-(2,4-dioxo-1,4-dihydro quinazolin-3-yl)phenyl] }-1-Nethoxyphthalimido pyridine-3-carbonitrile (6d)

IR (KBr) cm-^{1}: 3442-3336(NH_2), 3070 (C-H str., Ar-H), 2223 (C≡N), 2934(C-H str.,CH_2), 1750, 1680 (C=O str., CO-N-CO), 1623-1434 (C=N,C=C str.), 1345 (N-O str.), 1087 (C-O str.); ^{1}HNMR ($CDCl_3$) δ : 7.3-7.8(m, 16H, Ar-H), 5.86 (s, NH_2, exchangeable with D_2O),3.95 (t, 2H, OCH_2), 3.45 (s, 6H, $N(CH_3)_2$),3.10 (t , 2H, NCH_2); ^{13}C-NMR (CDCl3): 44.6, 63.9, 78.8 (CDCl3) 120.4, 123.8, 125.6, 126.4, 127.4, 128.7, 130.4, 131.6, 133.6.134.5, 138.2, 140.3, 142.4, 144.2, 145.6, 149.6, 150.4, 156.8, 156.3, 159.5, 184, 208.6, 213.2, 223.7: MS: (*m/z*) [M]+. 663. Anal. calcd for $C_{38}H_{29}N_7O_5$: calcd for N, 14.78 %. Found.14.20%.

RESULT AND DISCUSSION

The synthetic route for obtaining the final product is presented in scheme I. The required intermediate 3-(4-acetylphenyl) quinazoline-2,4-dione (1) was prepared by reaction of isatoic anhydride with p-aminoacetophenone by refluxing in ethanol. Formation of (1) was confirmed by IR absorption spectra at 1693 cm^{-1} due to carbonyl group. This is further supported by appearance of ^{1}H NMR signal at 8.6 δ ppm for NH proton. Compounds (I) was converted to chalcones 3-{4-[3-(4-substitutedphenyl) prop-2-enoyl]phenyl}quinazoline-2,4-dione (3a-d) by treating with corresponding aromatic aldehyde in NaOH/ethanol. IR and ^{1}H NMR spectral data established the structure of these compounds. IR absorption band at 1665 cm^{-1} indicated the presence of α, β-unsaturated carbonyl functionalities and disappearance of singlet at 2.6 δ ppm of -CH_3 proton. Compounds (3a-d) were condensed with bromoethoxyphthalimide in acetone in the presence of K_2CO_3 as a base to furnish 3-[4-{3-(4-subsitutedphenyl)prop-2-enoyl}phenyl]-1-N-ethoxyphthalimidoquinazoline-2,4-dione (4a-d). Structure of 4a was confirmed by disappearance of IR peak for NH functionality , appetence of C-O and N-O stretching band at 1080 and 1355 cm-1 respectively and two triplets at δ 3.10 and and 3.95 for N-CH_2 and O-CH_2 of ethoxyphthalimide moiety in the ^{1}H NMR spectrum.

Compounds 4a-d when treated with guanidine nitrate in alkohalic solution and malanonitrile with CH_3COONH_4 separately, afforded 3-{4-[2-amino-6-(4-chlorophenyl)-1,6-

dihydropyrimidin-4-yl]phenyl}-1-Nethoxyphthalimido quinazoline-2,4-dione (5a-d) and 2-amino-6-(4-chlorophenyl)-4-[4-(2,4-dioxo-1,4-dihydroquinazolin-3-yl)phenyl]-1-Nethoxy phthalimido pyridine-3-carbonitrile (4a-d) respectively. Formation of these ccompounds has been confirmed by disappearance C=O stretching band at 1665 cm^{-1} for α, β-unsaturated carbonyl group in the both case. Structure of 5a-d was further confirmed by the presence of singlet with two spikes for NH_2 group, which appearance at 3455, 3210 δppm. Formation of 5a-d was also established on the basis of IR stretching at 3450, 3331 cm-1 and 2239 cm-1 which is confirmed that NH_2 and CN group present.

For antibacterial activity, compounds 5a,6a are considered to be good active against *E. Coli, P. aeruginosa*, and *S. aureus* while 5c, are considered as very good active against *E. Coli and S. aureus* while 5b for *P. aeruginosa*. Compounds 5a, 5c, 5d, 6a, 6c are considered as excellent active against *S. aureus*. For the antifungal activity compounds 5a, 5b, 6a, 6c are considered as good active against *C. albicans, A niger and A. clavatus*. The discussion and comparison of antibacterial and antifungal activities have been compared with ampicillin and griseofulvin, respectively.

Antibacterial Activity

For the antibacterial activity, the newly synthesized compounds were screened for their antibacterial activity against gram positive bacteria *S. Aureus* (MTCC-96) and gram negative *E. coli* (MTCC-443) and *Pseudomonas aeruginosa* (MTCC- 1688)]. Antibacterial activity was carried out by serial broth dilution method. The standard strains used for the antimicrobial activity was procured from Institute of Microbial Technology, Chandigarh. The compounds (3a–e) were screened for their antibacterial activity in triplicate against *E. coli, S. aureus* and *P. aeruginosa*, at different concentrations of 1000, 500, 200, 100, 50, 25, 12.5 µg/ml as shown in (Table 2). The drugs which were found to be active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5 µg/ml concentrations. 10 µg/ml suspensions were further inoculated on appropriate media and growth was noted after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture was considered as MIC for each drug. The highest dilution showing at least 99% inhibition is taken as (MIC). The test mixture should contain 108cells/ml. The standard drug used in this study was 'ampicillin' for evaluating antibacterial activity which showed (50,100, and 50 µg/ml) MIC against *E. coli, P. aeruginosa* and *S. aureus* respectively.

Antifungal Activity

While for the antifungal activity, same compounds were tested for antifungal activity in triplicate against *Candida albicans*, *A. niger*, and *A. clavatus* at various concentrations of 1000, 500, 200, and 100 µg/ml as shown in (Table 3). The results were recorded in the form of primary and secondary screening. The synthesized compounds were diluted at 1000 µg/ml concentration, as a stock solution. The synthesized compounds which were found to be active in this primary screening were further tested in a second set of dilution against all microorganisms. The lowest concentration, which showed no growth after spot subculture was considered as (MIC) for each drug. The highest dilution showing at least 99% inhibition is taken as MIC. The test mixture should contain 108spores/ml MIC. 'griseofulvin' was used as a standard drug for antifungal activity, which showed (100, 100, and 100 µg/ml) MIC against *C. albicans*, *A. niger*, and *A. clavatus*, respectively.

The results of antimicrobial evaluation of derivatives (5a-d and 6a-d) are collected in Table 1 and 2.

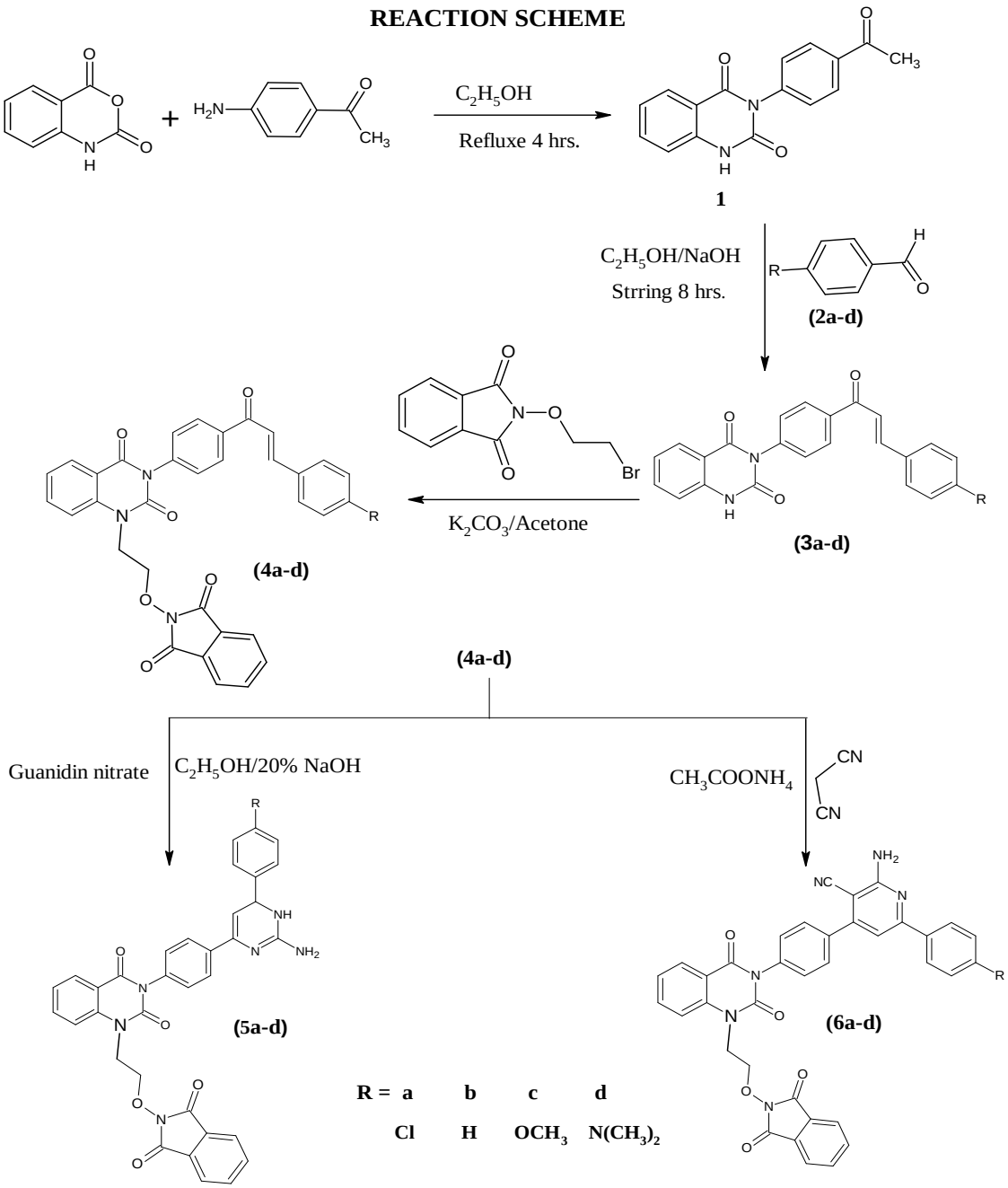
Table no.1 Antibacterial activity of synthesized compounds (4a-d and 6a-d).

Compound No.	Minimal Bactericidal Concentrations (MBC) in µg / ml		
	E. coli MTCC-443	*P. aeruginosa* MTCC-1688	*S. aureus* MTCC-96
5a	500	500	500
5b	100	250	150
5c	500	250	500
5d	100	100	250
6a	500	500	500
6b	100	100	100
6c	250	250	250
6d	100	100	100

Table no. 2 Antifungal activity of synthesized compounds (5a-d and 6a-d).

Compound No.	Minimal fungicidal concentrations (MFC) in µg / ml		
	C. albicans MTCC-227	*A. niger* MTCC-282	*A. clavatus* MTCC-1323
5a	500	500	500
5b	250	250	250
5c	100	250	100
5d	100	100	100
6a	500	250	250
6b	250	250	250
6c	500	500	500
6d	250	100	100

REACTION SCHEME



CONCLUSION

A series of Isatoic anhydride contending ethoxyphthalimide derivatives (5a-d and 6a-d) were synthesized and characterized by analytical and spectral studies. The newly synthesized compounds were evaluated for antibacterial & antifungal. The present study showed that the antimicrobial activity of newly synthesized compounds may change by introduction or elimination of a specific group. Hence further structural modifications and screening is to be required to confirm the more and still better activity.

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REFERENCES

1. Chandregowda V, Kush AK, Chandrasekara Reddy G: Synthesis and in vitro antitumor activities of novel 4-anilinoquinazoline derivatives. Eur J Med Chem, 2009; 44: 3046–3055.
2. Al-Rashood ST, Aboldahab IA, Nagi MN, Abouzeid LA, Abdel-Aziz AA, Abdel-Hamide SG, Youssef KM, Al-Obaid AM, El-Subbagh HI: Synthesis, dihydrofolate reductase inhibition, antitumor testing, and molecular modeling study of some new 4(3H)-quinazolinone analogs. Bioorg Med Chem, 2006; 14: 8608–8621.
3. Vasdev N, Dorff PN, Gibbs AR, Nandanan E, Reid LM, Neil JPO', VanBrocklin HF: Synthesis of 6-acrylamido-4-(2-[18F] fluoroanilino) quinazoline: A prospective irreversible EGFR binding probe. J Lablelled Compd Rad, 2005; 48: 109–115.
4. Wakeling AE, Guy SP, Woodburn JR, Ashton SE, Curry BJ, Barker AJ, Gibson KH: ZD1839 (Iressa): an orally active inhibitor of epidermal growth factor signaling with potential for cancer therapy. Cancer Res, 2002; 62: 5749–5754.
5. Alagarsamy V, Solomon VR, Dhanabal K: Synthesis and pharmacological evaluation of some 3-phenyl-2-substituted-3H -quinazolin-4-one as analgesic, anti-inflammatory agents. Bioorg Med Chem, 2007; 15: 235–241.
6. Baba A, Kawamura N, Makino H, Ohta Y, Taketomi S, Sohda T: Studies on disease-modifying antirheumatic drugs: synthesis of novel quinoline and quinazoline derivatives and their anti-inflammatory effect1. J Med Chem, 1996; 39: 5176–5182.
7. Rohini R, Muralidhar Reddy P, Shanker K, Hu A, Ravinder V: Antimicrobial study of newly synthesized 6-substituted indolo[1,2-c]quinazolines. Eur J Med Chem, 2010; 45: 1200–1205.
8. Antipenko L, Karpenko A, Kovalenko S, Katsev A, Komarovska-Porokhnyavets E, Novikov V, Chekotilo A: Synthesis of new 2-thio-[1,2,4]triazolo[1,5-c] quinazoline derivatives and its antimicrobial activity. Chem Pharm Bull, 2009; 57: 580–585.
9. Jatav V, Kashaw S, Mishra P: Synthesis and antimicrobial activity of some new 3–[5-(4-

substituted)phenyl-1,3,4-oxadiazole-2yl]-2-styrylquinazoline-4(3H)-ones. Med Chem Res, 2008; 17: 205–211.

10. Aly AA: Synthesis of novel quinazoline derivatives as antimicrobial agents. Chin J Chem, 2003; 21: 339–346.
11. Li H, Huang R, Qiu D, Yang Z, Liu X, Ma J, Ma Z: Synthesis and bioactivity of 4-quinazoline oxime ethers. Prog Nat Sci, 1998; 8: 359–365.
12. Chandrika PM, Yakaiah T, Narsaiah B, Sridhar V, Venugopal G, Rao JV, Kumar KP, Murthy USN, Rao ARR: Synthesis leading to novel 2,4,6-trisubstituted quinazoline derivatives, their antibacterial and cytotoxic activity against THP-1, HL-60 and A375 cell lines. Indian J Chem, 2009; 48B: 840–847.
13. Paneersalvam P, Raj T, Ishar PS M, Singh B, Sharma V, Rather BA: Anticonvulsant activity of Schiff bases of 3-amino-6,8-dibromo-2-phenyl-quinazolin-4(3H)-ones. Indian J Pharm Sci, 2010; 72: 375–378.
14. Nandy P, Vishalakshi MT, Bhat AR: Synthesis and antitubercular activity of Mannich bases of 2-methyl-3H-quinazolin-4-ones. Indian J Heterocycl Chem, 2006; 15: 293–294.
15. Saravanan G, Alagarsamy V, Prakash CR: Synthesis and evaluation of antioxidant activities of novel quinazoline derivatives. Int J Pharm Pharm Sci, 2010; 2: 83–86.
16. Lakhan R, Singh OP, Singh-J RL: Studies on 4 (3H)-quinazolinone derivatives as anti-malarials. J Indian Chem Soc, 1987; 64: 316–318.
17. Hess HJ, Cronin TH, Scriabine A: Antihypertensive 2-amino-4(3H)-quinazolinones. J Med Chem, 1968; 11: 130–136.
18. Sasmal S, Balaji G, Kanna Reddy HR, Balasubrahmanyam D, Srinivas G, Kyasa S, Sasmal PK, Khanna I, Talwar R, Suresh J, Jadhav VP, Muzeeb S, Shashikumar D, Harinder Reddy K, Sebastian VJ, Frimurer TM, Rist Ø, Elster L, Högberg T: Design and optimization of quinazoline derivatives as melanin concentrating hormone receptor 1 (MCHR1) antagonists. Bioorg Med Chem Lett, 2012; 22: 3157–3162.
19. Alvarado M, Barceló M, Carro L, Masaguer CF, Raviña E: Synthesis and biological evaluation of new quinazoline and cinnoline derivatives as potential atypical antipsychotics. Chem Biodivers, 2006; 3: 106–117.
20. Malamas MS, Millen J: Quinazolineacetic acids and related analogs as aldose reductase inhibitors. J Med Chem, 1991; 34: 1492–1503.
21. Kumar, R. 5-(1-Substituted)alkyl pyrimidine nucleosides as antiviral (herpes) agents. Curr. Med. Chem. 2004; 11, 2749–2766.
22. Holy A, Gunter J, Structure–antiviral activity relationship in theseries of pyrimidine and

purine N-[2-(2-phosphonomethoxy)ethyl] nucleotideanalogues, 1: Derivatives substituted at the carbon atoms of the base. J. Med.Chem, 1999; 42: 2064–2086.

23. Xiang M X, Suh B C, Synthesis and biological examination of new pyrimidinetype derivatives as potential phosphodiesterase (PDE) V: Inhibitors.Korean J. Med. Chem. 1998; 8: 6–9.
24. Brandes W, Daum W, Krauss P, Fungicidal oxime ethers. Ger. Patent 2,623,847, 1977; Chem. Abstr, 1978; 88: 120822h.
25. Doherty, G. O. P. N-(2,2-Difluroalkanoyl)-2,3-pyridinediamine. U.S. Patent 3,962,263; Chem. Abstr, 1976; 85: 159901w.
26. KC Nicolaou, "Chemical synthesis and biological properties of pyridineepothilones, Chemistry & Biology", 2000; 7: 593-599.
27. Alexandre V, Ivachtchenko , Sergiy M, Kovalenko, "Synthesis and antimicrobial activity of 5-hydroxymethyl-8-methyl-2-(N-arylimino)-pyrano[2,3-c]pyridine-3-(N-aryl) carboxamides", Bioorganic & Medicinal Chemistry Letters, 2005; 15: 5483.
28. Ahmet Ozdemir, Fatih Demirci, "synthesis and the selective antifungal activity of 5,6,7,8-tetrahydroimidazo[1,2-a]pyridine derivatives" E.journal of medicinal chemistery, 2010; 45:2080-2084.
29. Bhatia M.S, "Synthesis and QSAR analysis of 5-substituted (arylmethylene)pyridin-2-amine derivatives as potential antibacterials", International Journal of Drug Discovery, 2009; 1: 1-9.
30. Bruno Leal, Carlos R. Rodrigues, "Antibacterial profile against drug-resistant Staphylococcus epidermidis clinical strain and structure–activity relationship studies of 1H-pyrazolo[3,4-b]pyridine and thieno[2,3-b]pyridine derivatives", Bioorganic & Medicinal Chemistry, 2008; 16: 8196–8204.
31. Alice Maria Rolim Bernardino, Helena Carla Castro,et al; "Design, synthesis, SAR, and biological evaluation of new 4-(phenylamino)thieno[2,3-b]pyridine derivatives", Bioorganic & Medicinal Chemistry, 2006; 14: 5765–5770.
32. Rajesh H. Bahekar, Mukul R. Jain, Pradip A. Jadav, Vijay M. Prajapati, Dipam N. Patel, Arun A. Gupta, Ajay Sharma, Robby Tom, Debdutta Bandyopadhya,Honey Modi and Pankaj R. Patel, "Synthesis and antidiabetic activity of 2,5-disubstituted- 3-imidazol-2-yl-pyrrolo[2,3-b]pyridines and thieno[2,3-b]pyridines", Bioorganic & Medicinal Chemistry, 2007; 15: 6782–6795.
33. Feng Shi, SSNing Ma, "Green chemoselective synthesis of thiazolo[3,2-a]pyridine derivatives and evaluation of their antioxidant and cytotoxic activities", Bioorganic &

Medicinal Chemistry Letters, 2009; 19: 5565–5568.

34. Luiza R. S. Dias, "Synthesis, in vitro evaluation, and SAR studies of a potential antichagasic 1H-pyrazolo[3,4-b]pyridine series", Bioorganic & Medicinal Chemistry, 2007; 15: 211–219.
35. Jong-Keun Son, Eung-Seok Lee,Synthesis of 2,6-diaryl-substituted pyridines and their antitumor activities, European Journal of Medicinal Chemistry, 2008; 43: 675-682.
36. L. Bauer, K. S. Suresh, J. Org. Chem, 1963; 28: 1604.