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Synthesis, characterization and biological activity of some new pyrazino[2,1-b]quinazolinone derivatives

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ABSTRACT

*Amonalysis of 2-(chloromethyl)-4-oxo-benzoxainone(**1**) with ammonium acetate under fusion gave the corresponding 2-(aminomethyl)-4(3H)-quinazolinone(**2**). 4-Aryl-1H-pyrazino[2,1-b]quinazolin-6(2H)-ones(**3a-d**) were prepared via treatment of **3** with ω-bromomethyl arylketones in presence of fused sodium acetate in acetic acid. Acetylation and alkylation of **3** with acetic anhydride, acetic anhydride fused sodium acetate and alkyl halides yielded the corresponding monoacetyl, diacetyl derivatives(**4,5**) and N-alkyl derivatives(**6**).The mass spectral fragmentation patterns of some prepared compounds have been investigated in order to elucidate the structure of the synthesized compounds. Antimicrobial activities were assayed against test bacteria and fungi*

Keywords: pyrazino[2, 1-b]quinazolines, mass spectral, synthesis, biological activity.

INTRODUCTION

The quinazolinone core and its derivatives form an important class of compounds, as they are present in a large family of products with broad biological activities. They generally display useful therapeutic and pharmacological properties such as anticancer, anti inflammatory, anti-convulsant, antihypertensive and antimalarial activity[1-22]. Moreover, the 4(3H)–quinazolinone moiety is found in several bioactive natural products[23,24]. For these reasons their synthesis has received considerable attention. Several groups have reported conventional preparation methods which require reflux for several hours and the use of large volumes of solvent[25,26].

The electron impact (EI) ionization mass spectral fragmentations of some synthesized compounds were described.

MATERIALS AND METHODS

Melting points were determined in Capillaries with a Thomas Uni-melt apparatus uncorrected. NMR spectra were recorded on a general electric QE300 instrument and chemical shifts are given with respect to TMS. IR spectra were recorded on a Perkin-Elmer 1420 spectrometer and a Biorad FTS7 (KBr). Mass spectra were obtained on a Jeol JMSD-300 spectrometer operating at 70 eV. Microanalyses were conducted using an elemental analyzer 1106.

2-(Chloromethyl)-4-oxo-3,1-benzoxazinone (1)
A mixture of anthranilic acid (0.01 mole), chloroacetyl chloride (0.01 mole) and fused sodium acetate (0.03mole) in acetic acid (30 mL)was heated under reflux for 2 hr, then cooled and poured into ice-water . The solid formed was

filtered off, washed with water, dried and purified by recrystallization with ethanol to give **1** as colorless crystals, yield 87%, m.p: 165°C; **IR** (KBR): 1722(C=O), 1630(C=N), 1605, 1592(C=C), 1120, 1075(C-O) cm^{-1}. **^{1}H-NMR** (DMSO-d6): δ 3.41(s, 2H, CH_2, CH_2Cl), 7.13-7.91(m,4H,Ar-H) ppm. **MS** (m/z, %): 197(M_+2, 6.1), 196(M_+1, 14.2), 195(M^+, 51.3), 191(17.4), 160(48.7), 147(25.8), 146(17.0), 103(100), 92(25.2), 91(37.4), 90(14.8), 77(45.2), 63(22.6), 51(27.8). Anal. Calcd. For $C_9H_6ClNO_2$: C, 55.26; H, 3.09; Cl, 18.13; N, 7.16 . Found: C, 55.11; H, 2.89; Cl, 17.93; N, 7.12

2-Aminomethyl-4-oxo -quinazolinone (2)

A mixture of **1** (0.01 mole) and ammonium acetate (0.03 mole) was fused on a hot- plate for 1-2 hr. The reaction mixture was cooled and poured into water. The crude product was filtered off , washed with water, dried and purified by ethanol to give **2** as white crystals, yield 75%, m.p: 245°C; **IR** (KBR): 3320-3300(NH_2), 3296(NH), 1722(C=O), 1630(C=N), 1605, 1592(C=C) cm^{-1}. **^{1}H-NMR** (DMSO-d6): δ 3.01(s, 2H, CH_2NH_2), 6.31(s, 2H, NH_2), 7.16-7.91(m, 4H, Ar-H), 10.33(s, 1H, NH) ppm. Ms (m/z, %): 176(M_+1, 15.9), 175(M^+, 27.5), 159(31.1), 145(100), 105(35.6), 91(45.9), 77(83.8), 50(32.4). Anal. Calcd. For $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99 Found: C, 61.48; H, 4.98; N, 23.68

4-Aryl-6-oxo-1H-pyrazino[2,1-b]quinazolinone (3a-d)

A mixture of **2** (0.01 mole) and ω-bromomethyl arylketones(such as phenacyl bromide, 4-methyl phenacyl bromide, 4-methoxy phenacyl bromide and 4-nitrophenacyl bromide) (0.01 mole) in presence of fused sodium acetate(0.03 mole) in acetic acid (30mL) was heated under reflux for 4 hr. The reaction mixture was cooled and poured into water. The crude product was filtered off, washed with water, dried and purified by ethanol to give compound (**3a-d**) *4-phenyl-6-oxo-1H-pyrazino[2,1-b]quinazolinone(**3a**)* as pale yellow crystals yield 80 %,m.p: 193 °C ; **IR**(KBr): 3296(NH), 1715(C=O), 1630(C=N), 1605, 1592(C=C) cm^{-1}

^{1}H-NMR (DMSO-d6): δ3.61(s, 2H, CH_2NH), 7.21-8.01(m, 10H, Ar-H and H-pyrazine), 10.36(s, 1H, NH) ppm. **MS** (m/z, %):276(M_+1, 8.1), 275(M^+, 47.6), 198(28.9), 174(29.5), 159(39.5), 145(100), 105(26.6), 92(47.3), 77(83.8), 50(32.4). Anal.Calcd. for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26 Found: C, 73.88; H, 4.37; N, 15.11

*4-(P-Tolyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**3b**)* as pale yellow crystals yield 73 %, m.p: 201 °C; **IR** (KBr): 3320(NH), 1723(C=O), 1658(C=N), 1620, 1580(C=C) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ2.21 (s, 3H, CH_3-Ar), 3.61(s, 2H, CH_2NH), 7.13-7.98(m, 9H, Ar-H and H-pyrazine), 10.38(s, 1H, NH)ppm. **MS** (m/z, %): 290(M^+1, 3.2), 289(M^+, 24.1), 274(25.9), 198(100), 174(28.5), 159(29.5), 145(58.0), 105(26.6), 91(40.6), 77(81.1), 60(65.1), 50(26.9). Anal.Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52 Found: C, 74.51; H, 5.09; N, 14.32

*4-(P-methoxyphenyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**3c**)* as pale yellow crystals yield 70 %, m.p: 220 °C; **IR** (KBr): 3285(NH), 1728(C=O), 1676(C=N), 1632, 1598(C=C), 1218-1077(C-O)cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ 3.58(s, 2H, CH_2NH), 3.96(s, 3H, OCH_3), 7.17-7.91(m, 9H, Ar-H and H-pyrazine), 10.37(s, 1H, NH) ppm. **MS** (m/z, %):306(M^+1, 13.2), 305(M^+, 67.8), 290(55.4), 274(45.0), 198(51.6), 174(40.7), 159(46.1), 145(100), 105(33.9), 91(31.9), 77(43.1), 64(33.3), 51(22.2). Anal.Calcd. for $C_{18}H_{15}N_3O_2$: C, 70.81; H, 4.95; N, 13.76. Found: C, 70.48; H, 4.59; N, 13.63

*4-(P-nitrophenyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**3d**)* as yellow crystals yield 62 %, m.p: 240 °C; **IR** (KBr): 3315(NH), 1720(C=O), 1605(C=N), 1612, 1583(C=C), 1530-1350(NO_2) cm^{-1}. **^{1}H-NMR** (DMSO-d6): δ3.41(s, 2H, CH_2-NH), 7.21-7.89(m, 9H, Ar-H and H-pyrazine), 10.34(s, 1H, NH) ppm. **MS** (m/z, %):321(M^+_+1, 13.5), 320(M^+, 49.2), 274(68.9), 198(56.5), 174(53.2), 159(100), 145(78.1), 105(37.3), 77(56.5), 50(33.9). Anal.Calcd. for $C_{17}H_{12}N_4O_3$: C, 63.75; H, 3.78; N, 17.49 . Found: C, 63.48; H, 3.52; N, 17.17

2-Acetyl-4-aryl-6-oxo-1H-pyrazino[2,1-b]quinazolinone (4a-d)

A solution of **3** (0.01 mole) in acetic anhydride (20 mL) was heated under reflux for 2 hr, then cooled and poured into ice-water. The solid obtained was filtered off, washed with water, dried and purified by ethanol to give **4**.

*2-Acetyl-4-phenyl-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**4a**)*as white crystals, yield 83%, m.p: 255°C; **IR** (KBr): 1733-1691(C=O), 1638(C=N), 1620, 1567(C=C) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ2.35(s, 3H, CO CH_3), 3.51(s, 2H, CH_2-N), 7.20-7.98(m, 10H, Ar-H and H-pyrazine)ppm. **MS** (m/z, %): 318(M^+_+1, 13.2), 317(M^+, 43.2), 302(26.8), 274(51.1), 197(48.9), 171(53.8), 145(100). Anal.Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.91; H, 4.76; N, 13.24. Found: C, 71.55; H, 4.37; N, 13.11

*2-Acetyl-4-(P-tolyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**4b**)* as pale yellow crystals yield 63 %, m.p: 232 ^{o}C; **IR** (KBr): 1738-1687(C=O), 1644(C=N), 1612, 1576(C=C) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ 2.22(s, 3H, CH_3), 2.35(s, 3H, $COCH_3$), 3.58(s, 2H, CH_2-N), 7.11-7.96(m, 9H, Ar-H and H-pyrazine)ppm. **MS** (m/z, %):332(M^++1, 8.9), 331(M^+, 43.7), 316(49.7), 288(45.6), 273(66.9), 197(65.0), 171(100). Anal.Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.49; H, 5.17; N, 12.68 . Found: C, 72.18; H, 4.87; N, 12.37

*2-Acetyl-4-(P-methoxyphenyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**4c**)* as pale yellow crystals yield 75 %, m.p: 241 ^{o}C; **IR** (KBr): 1738-1692(C=O), 1665(C=N), 1602, 1558(C=C),1212-1045(C-O)cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ2.35 (s, 3H, CO CH_3), 3.59(s, 2H, CH_2N), 3.98 (s, 3H, OCH_3), 7.13-7.91(m, 9H, Ar-H and H-pyrazine)ppm. **MS** (m/z, %):348(M^++1, 12.1), 347(M^+, 44.4), 332(48.9), 304(49.7), 289(49.6), 273(66.9), 197(100). Anal.Calcd. for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 68.82; H, 4.55; N, 11.89

*2-Acetyl-4-(P-nitrophenyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**4d**)* as yellow crystals yield 58 %, m.p: 221 ^{o}C; **IR** (KBr): 1709-1673(C=O), 1620(C=N), 1612, 1588(C=C), 1534-1371(NO_2) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ3.53 (s, 2H, CH_2N), 7.14-7.96 (m, 9H, Ar-H and H-pyrazine) ppm. **MS** (m/z, %): 363(M^++1, 5.7), 362(M^+, 35.7), 347(55.7), 319(35.7), 273(48.7), 197(46.1), 171(53.5), 145(100). Anal.Calcd. for $C_{19}H_{14}N_4O_4$: C, 62.98; H, 3.89; N, 15.46. Found: C, 62.64; H, 3.68; N, 15.22

1,2-Diacetyl-4-aryl-6-oxo-1H-pyrazino[2,1-b]quinazolinone (5a-d)

A mixture of **3** (0.01mole) and fused sodium acetate (0.03mole) in acetic anhydride (20mL) was heated under reflux for 4 hr, then cooled and poured into ice-water. The resulting product was filtered off, washed with water, dried and purified by ethanol to give compound **5**.

*1,2-Diacetyl-4-phenyl-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**5a**)*as pale yellow crystals yield 72 %, m.p: 230 ^{o}C; **IR** (KBr): 1725-1680(C=O), 1627(C=N), 1612, 1548(C=C) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ2.21(s, 3H, CO CH_3), 2.34(s, 3H, $COCH_3$), 5.89(s, 1H, COCHNH), 7.18-7.89(m, 10H, Ar-H and H-pyrazine) ppm. **MS** (m/z, %): 360(M^++1, 5.5), 359(M^+, 52.2), 344(37.8), 316(43.1), 273(45.0), 196(51.6), 171(100), 145(43.1). Anal.Calcd. for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69 Found: C, 69.88; H, 4.46; N, 11.53

*1,2-Diacetyl-4-(P-tolyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**5b**)* as pale yellow crystals yield 65 %, m.p: 219 ^{o}C; **IR** (KBr): 1728-1695(C=O), 1638(C=N), 1605, 1524(C=C) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ2.13(s, 6H, CH_3CO), 2.21(s, 3H, $COCH_3$), 2.36(s, 3H, $COCH_3$), 5.87(s, 1H, COCHNH), 7.13-7.89(m, 9H, Ar-H and H-pyrazine) ppm. **MS** (m/z, %):374(M^+1, 16.7), 373(M^+, 56.7), 358(52.2), 330(33.2), 287(57.0), 272(45.0), 196(51.6), 171(52.2), 145(100). Anal.Calcd. for $C_{22}H_{19}N_3O_3$: C, 70.76; H, 5.13; N, 11.25. Found: C, 70.22; H, 4.92; N, 11.08

*1,2-Diacetyl-4-(P-methoxyphenyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**5c**)* as pale yellow crystals yield 81 %, m.p: 248 ^{o}C ; **IR**(KBr): 1722-1683(C=O), 1675(C=N), 1605, 1567(C=C),1210-1035(C-O)cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ2.21(s, 3H, CO CH_3), 2.36(s, 3H, $COCH_3$),3.97(s, 1H, COCHN), 7.18-7.93 (m, 9H, Ar-H and H-pyrazine)ppm. **MS** (m/z, %): 390(M^+1, 8.1), 389(M^+, 45.6), 374(55.6), 346(68.1), 303(44.8), 288(45.6), 272(68.9), 196(100). Anal.Calcd. for $C_{22}H_{19}N_3O_4$: C, 67.86; H, 4.92; N, 10.79 Found: C, 67.65; H, 4.53; N, 10.39

*1,2-Diacetyl-4-(P-nitrophenyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**5d**)* as yellow crystals yield 60 %, m.p: 236 ^{o}C; **IR** (KBr): 1719-1683(C=O), 1618(C=N), 1600, 1562(C=C), 1514-1362(NO_2) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ2.21(s, 3H, CO CH_3), 2.33 (s, 3H, $COCH_3$), 5.87(s, 1H, COCHN), 7.13-7.93(m, 9H, Ar-H and H-pyrazine) ppm. **MS** (m/z, %):405 (M^++1, 10.4), 404 (M^+, 50.6), 389(29.9), 361(33.6), 318(31.6), 272(100), 196(29.9), 171(31.7), 145(32.0). Anal.Calcd. for $C_{21}H_{16}N_4O_5$: C, 62.37; H, 3.99; N, 13.86. Found: C, 62.12; H, 3.63; N, 13.38

2-Alkyl-4-aryl-6-oxo-1H- pyrazino[2,1-b]quinazolinone (6a-h)

A mixture of **3** (0.01 mole) and alkyl halide (namely, methyl iodide and ethyl iodide) (0.01 mole) in pyridine (25mL) was heated under reflux for 2 hr. The reaction mixture was cooled and acidified with dilute hydrochloric acid (2 mole/L). The solid formed was filtered off, washed with water, dried and purified by ethanol to give **6**.

*2-Methyl-4-phenyl-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**6a**)*as pale yellow crystals yield 74 %, m.p: 215 ^{o}C; **IR** (KBr): 1722(C=O), 1665(C=N), 1612, 1598(C=C) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ2.01(s, 3H, NCH_3), 3.58(s, 2H, CH_2-N), 7.44-7.87(m, 10H, Ar-H and H-pyrazine) ppm. **MS** (m/z, %): 289(M^+, 44.5), 274(28.6), 198(50.3),

172(59.1), 145(100), 105(45.2), 77(65.3),60(53.2). Anal.Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.52. Found: C, 74.55; H, 5.19; N, 14.23

*2-Ethyl-4-phenyl-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**6b**)*as pale yellow crystals yield 65 %, m.p: 228 ^oC; **IR** (KBr): 1719(C=O), 1654(C=N), 1640, 1595(C=C) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ1.35 (t, 3H, CH_3), 3.01(q, 2H, NCH_2), 3.53(s, 2H, CH_2N), 7.20-793(m, 10H, Ar-H and H-pyrazine)ppm. **MS** (m/z, %): 303(M^+, 33.5), 288(42.8), 274(37.5), 197(55.4), 172(100), 145(78.2), 105(45.2), 77(51.2), 50(24.3). Anal.Calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.11; H, 5.48; N, 13.64

*2-Methyl-4-(P-tolyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**6c**)* as yellow crystals yield 85 %, m.p: 219 ^oC ; **IR**(KBr): 1728(C=O), 1678(C=N), 1618, 1597(C=C) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ2.03(s, 3H, NCH_3), 2. 21 (s, 3H, CH_3-Ar), 3.53(s, 2H, CH_2-N), 7.12-7.46(m, 9H, Ar-H and H-pyrazine)ppm. **MS** (m/z, %): 303 (M^+, 28.5), 288(51.5), 197(76.3), 171(82.4), 145(100), 105(61.5), 77(45.7), 51(28.5). Anal.Calcd. for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85 Found: C, 75.18; H, 5.51; N, 13.67

*2-Ethyl-4-(P-tolyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**6d**)* as pale yellow crystals yield 70 %, m.p: 230 ^oC; **IR** (KBr): 1717(C=O), 1668(C=N), 1634, 1597(C=C) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ1.33 (t, 3H, CH_3), 2.21(s, 3H, CH_3-Ar), 3.03(q, 3H, NCH_2), 3.52 (s, 2H, CH_2N), 7.13-7.97(m, 9H, Ar-H and H-pyrazine)ppm. **MS** (m/z, %): 317(M^+, 29.5), 302(45.7), 288(57.5), 274(46.2), 198(72.8), 172(54.2), 145(100), 104(37.5), 77(45.6), 50(25.6). Anal.Calcd. for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.46; H, 5.95; N, 13.21

*2-Methyl-4-(P-methoxyphenyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**6e**)* as pale yellow crystals yield 63 %, m.p: 238 ^oC; **IR** (KBr): 1731(C=O), 1687(C=N), 1635, 1584(C=C), 1211-1085(C-O) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ2.02 (s, 3H, N-CH_3), 3.53(s, 2H, CH_2-N), 3.96(s, 3H, O-CH_3), 7.18-7.91(m, 9H, Ar-H and H-pyrazine)ppm. **MS** (m/z, %): 319(M^+, 25.1), 304(68.3), 290(46.4), 274(45.5), 197(33.7), 171(50.8), 145(100), 105(44.6), 77(50.3), 51(26.1). Anal.Calcd. for $C_{19}H_{17}N_3O_2$: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.28; H, 5.29; N, 13.09

*2-Ethyl-4-(P-methoxyphenyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**6f**)*as pale yellow crystals yield 65 %, m.p: 247 ^oC; **IR** (KBr): 1725(C=O), 1682(C=N), 1622, 1567(C=C), 1208-1095(C-O)cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ1.32(t, 3H, CH_3), 3.13(q, 2H, NCH_2), 3.54(s, 2H, CH_2-N), 3.98(s, 3H, O-CH_3), 7.20-7.93(m, 9H, Ar-H and H-pyrazine)ppm. **MS** (m/z, %): 333(M^+,35.5), 318(30.2), 304(50.3), 290(37.6), 274(47.4), 197(38.5), 174(28.2), 159(31.7), 145(100), 105(29.4), 91(33.1), 77(47.5), 51(24.6). Anal.Calcd. for $C_{20}H_{19}N_3O_2$: C, 72.05; H, 5.74; N, 12.60. Found: C, 71.88; H, 5.68; N, 12.54

*2-Methyl-4-(P-nitrophenyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**6g**)* as yellow crystals yield 71 %, m.p: 256 ^oC; **IR** (KBr): 1722(C=O), 1609(C=N), 1634, 1588(C=C), 1542-1370(NO_2) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ2.12(s,3H,NCH_3), 3.53(s, 2H, CH_2N), 7.20-7.91(m, 9H, Ar-H and H-pyrazine) ppm. **MS** (m/z, %): 334(M^+,33.5), 319(22.5), 288(54.6), 274(74.5), 197(57.2), 171(100), 144(84.2), 104(45.5), 76(34.6), 61(23.7), 51(22.4). Anal.Calcd. for $C_{18}H_{14}N_4O_3$: C, 64.66; H, 4.22; N, 16.76. Found: C, 64.51; H, 4.17; N, 16.58

*2-Ethyl-4-(P-nitrophenyl)-6-oxo-1H-pyrazino[2,1-b]quinazolinone (**6h**)* as yellow crystals yield 57 %, m.p: 265 ^oC; **IR** (KBr): 1718(C=O), 1615(C=N), 1618, 1563(C=C), 1525-1333(NO_2) cm^{-1}. **^{1}H-NMR** (DMSO-d_6): δ 1.31(t, 3H, CH_3), 3.15(q, 2H, NCH_2), 3.55(s, 2H, N-CH_2), 7.18-7.89(m, 9H, Ar-H and H-pyrazine) ppm. **MS** (m/z, %): 348(M^+,28.5), 333(44.2), 320(51.5), 274(75.2), 198(54.8), 173(44.1), 145(100), 107(33.5), 77(47.5), 51(27.4). Anal.Calcd. for $C_{19}H_{16}N_4O_3$: C, 65.51; H, 4.63; N, 16.08 Found: C, 65.43; H, 4.55; N, 15.87

RESULTS AND DISCUSSION

Chemistry

2-Chloromethyl-4-oxo-3,1-benzoxazinone(**1**) was prepared via the reaction of anthranilic acid with chloroacetyl chloride in presence of fused sodium acetate in acetic acid. A monolysis of 2-chloromethyl-4-oxo-3,1-benzoxazinone(**1**) with ammonia from ammonium acetate and/or formamide under fusion led to the formation of 2-aminomethyl-4-oxo-quinozolinone(**2**). Treatment of compound **2** with ω-bromomethyl aryl ketones(such as phenacyl bromide, 4-methyl phenacyl, 4-methoxy phenacyl bromide and 4-nitrophenacyl bromide) in presence of fused sodium acetate in acetic acid under reflux, yielded the corresponding 4-aryl-6-oxo-1H-pyrazino[2,1-b]quinazolinone(**3a-d**).

Acetylation of compound **3** with acetic anhydride under reflux led to the formation of 2-acetyl-4-aryl-6-oxo-1Hpyrazino[2,1-b]quinazolinones(4a-d), while the Acylation of compound **3** with acetic anhydride in presence of fused sodium acetate under reflux led to the formation of 1,2-diacetyl-4-aryl-6-oxo-1H-pyrazino[2,1-b]quinazolinones(**5a-d**).

Alkylation of 4- aryl-6-oxo-1H-pyrazino[2,1-b]quinazolinones(**3**)with alkyl halides (such as methyl iodide and ethyl iodide) in pyridine under reflux gave the corresponding 2-alkyl-4-aryl-6-oxo-1H-pyrazino[2,1-b]quinazolinones(**6a-h**).

Mass spectrometry:
The mass spectral decomposition modes [27-29] of the pyrazino[2,1-b]quinazolinone derivatives have been investigated.

Compounds 3a-d
The mass spectra of the 4-aryl-6-oxo-1H-pyrazino[2,1-b]quinazolinones(3a-d) showed intense molecular ion peaks at m/z 275, 289, 305 and 320, consistent with the molecular formula $C_{17}H_{13}N_3O$, $C_{18}H_{15}N_3O$, $C_{18}H_{15}N_3O_2$ and $C_{17}H_{12}N_4O_3$, respectively. The molecular ion of compounds **3a-d** fragmented further and involved two pathways as illustrated in scheme 2

The molecular ion of compounds 3a-d fragment via the pathway A to produce the peak at m/z 198. The ion at m/z 198 underwent loss of C_2 to give peak at m/z 174, which further broke to give an ion at m/z 145 by losing methylene amino (CH_2=NH) . The loss of cyano group(CN) from the ion with m/z 145 resulted in an ion at m/z 119. The ion at m/z 119 underwent loss nitrogen atom and carbonyl group to give peaks at m/z 105 and 77, respectively.

Also, the ion at m/z 198 underwent fragmentation to produce peaks at m/z 159. It further underwent loss of isocyanate group and methyl nitrile molecule to give peaks at m/z 117 and 76.

Accordingly, the same molecular ion of compounds 3a-d fragmented via pathway B to produce the aryl cation radical depending on the structure of compounds **3**.

Compounds **4, 5** and **6**
From the mass spectra of monoacetyl derivatives (**4a-d**) showed an intense molecular ion peaks at m/z 317, 331, 347 and 362, corresponding to the molecular formula $C_{19}H_{15}N_3O_2$, $C_{20}H_{17}N_3O_2$, $C_{20}H_{17}N_3O_3$ and $C_{19}H_{14}N_4O_4$, respectively.

The loss of keton molecule(CH_2CO) from the molecular ion peaks for the compounds 3a-d gave a peak at m/z 275, 289, 305 and 320, corresponding to the molecular ions of compounds 3a-d.

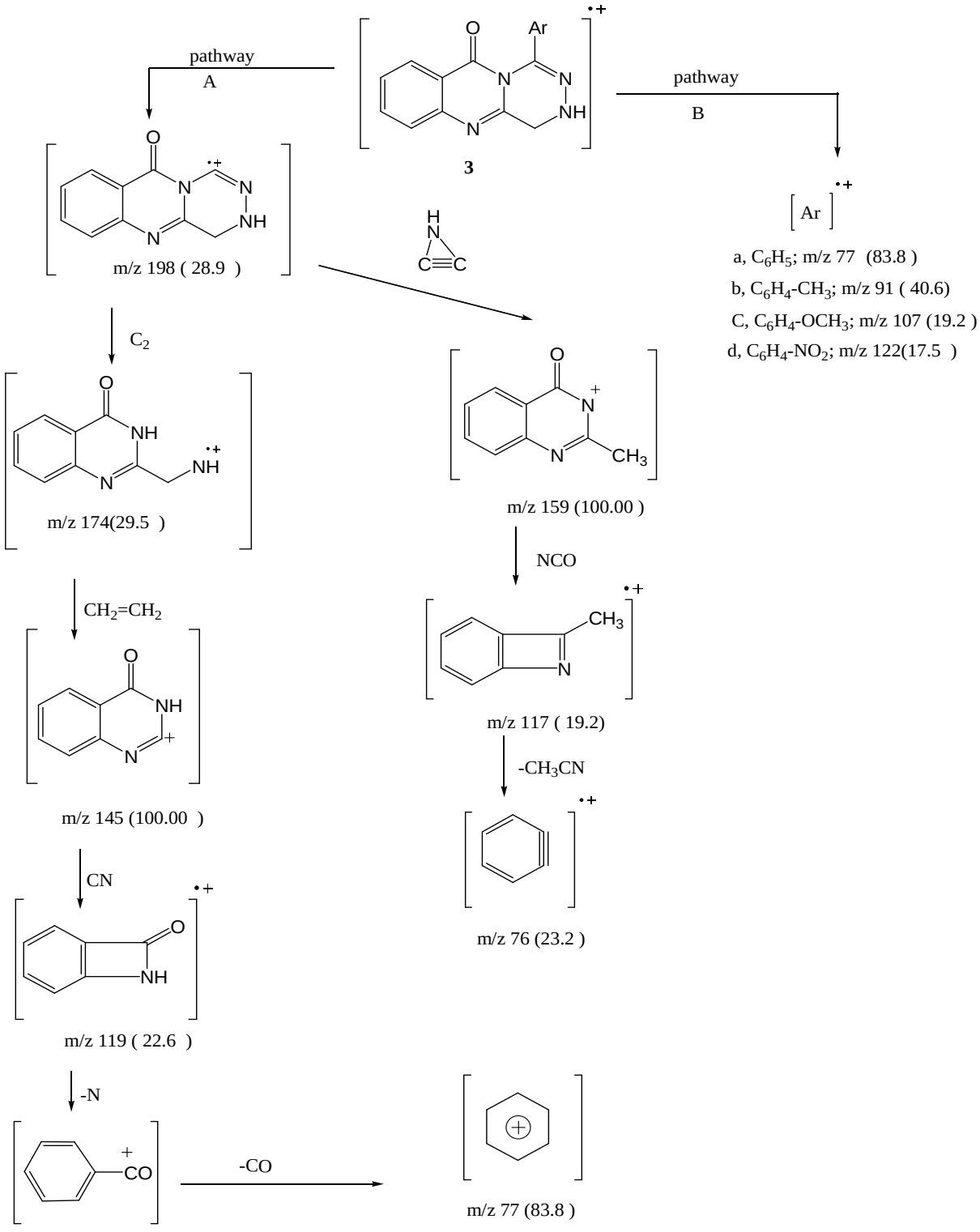
The molecular ion peaks of diacetyl derivatives (**5a-d**) were observed at m/z 359, 373, 389 and 404, corresponding to the molecular formula $C_{21}H_{16}N_3O_3$, $C_{22}H_{19}N_3O_3$, $C_{22}H_{19}N_3O_4$ and $C_{21}H_{16}N_4O_5$. The loss of keton molecule(CH_2CO) from the molecular ion peaks of compounds 5a-d gave a fragment ion peaks at m/z 317, 331, 347 and 362, corresponding to the molecular ion peaks of compounds **4a-d.**

The fragmentation peaks at m/z 317, 331, 347 and 362 underwent fragmentations to produce peaks at m/z 275, 289, 305 and 320 (molecular ion peaks of compounds 3a-d) by losing ketene molecule(CH_2CO).

The mass spectra of compounds **6a-h** are fully consistent with the assigned structures. In most cases, intense molecular ion peaks were observed.
The molecular ion peaks of compounds 6a-h underwent fragmentation to produce peak at m/z 198 and/or 197. The loss of CH≡C and HCN from the ion of m/z 198 or 197 resulted in an stable ion of m/z 145. The ion at m/z 145 underwent loss of CN, N and CO to give peaks at m/z 119, 105 and 77, respectively.

The molecular ions of [3a]; (Fig.3), [$6a_1$]; (fig.6), [$6c_1$]; (fig.7) and [$6c_2$]; (Fig.8) fragmented further and involved pathway as illustrated in Scheme III, Where the molecular ion of [$6c_2$] at m/z 333 fragmented to give the molecular ion of [$6c_1$]at m/z 319 by losing CH_2 that broken and lose $OCH_2$to give the molecular ion of [$6a_1$] at m/z 289. The later fragmented to give [3a] at m/z 275 by losing CH_2 which fragmented to give the fragment of m/z 187 by losing

CO. The fragment of m/z 187, which broken to give the fragment of m/z 145 (the base peak) by losing CH2-CH=NH. The fragment of m/z 145 was broken to give an ion of m/z 105 which further broke to give an ion at m/z 77. The later loss CH_2=CH to form the fragment of m/z 50.



Scheme **2**. Main fragmentation pathway of compound **3**

Table 1: Antibacterial activity of prepared compounds

Comp.	Gram Positive Bacteria									Gram NegativeBacteria					
	Bacillus Subtilis			***Streptococcus Penumonia***			***Staphylococcu Aureas***			***E. Coli***			***Pseudomonas Sp.***		
	10 mg	50 mg	100 mg	10 mg	50 mg	100 mg	10 mg	50 mg	100 mg	10 mg	50 mg	100 mg	10 mg	50 mg	100 mg
1	-	1	5	-	3	6	-	-	5	-	-	3	-	-	1
2	-	6	9	-	5	10	-	-	9	-	1	8	-	1	8
3a	2	8	16	3	10	16	5	15	18	6	15	18	5	11	25
3b	4	9	17	3	13	18	7	17	20	5	17	20	6	10	28
3c	15	21	34	11	23	31	14	21	35	14	25	32	12	21	30
3d	11	22	37	15	24	33	16	23	34	15	28	37	13	24	33
4a	5	10	16	5	10	19	6	14	19	8	15	21	7	12	26
4b	3	11	18	3	13	17	5	15	21	6	17	19	5	10	25
4c	11	18	28	14	22	34	11	26	33	15	28	38	13	26	33
4d	21	30	43	19	28	46	15	29	40	11	24	39	14	28	38
5a	5	8	15	4	11	18	5	16	19	9	19	21	6	11	23
5b	4	10	18	2	13	17	6	15	20	7	16	22	7	12	29
5c	20	29	48	19	35	49	18	33	41	19	30	48	21	38	51
5d	18	30	45	16	30	48	22	38	50	17	33	51	25	40	55
6a	5	7	18	1	11	16	4	17	21	8	19	23	6	11	25
6b	6	9	16	3	14	20	6	16	19	6	16	21	5	13	26
6c	4	8	19	5	13	17	5	15	18	9	15	19	5	12	24
6d	3	6	17	3	10	19	4	18	21	10	17	20	8	10	27
6e	9	19	28	10	21	35	11	23	35	14	25	34	11	25	34
6f	11	20	31	12	25	37	15	21	39	16	27	33	13	22	39
6g	15	22	35	9	26	42	12	25	37	13	26	38	15	26	40
6h	18	21	38	14	29	44	10	28	33	15	29	35	13	21	44
Streptomycin	3	7	18	2	11	17	4	16	20	8	17	22	6	12	27

Table2: Antifungal activity of prepared compounds

Comp.	Table (2) Antifungal Activity								
	Aspergillus Niger			**Penicillium Sp.**			**Candia albicans**		
	10mg	50mg	100 mg	10 mg	50 mg	100 mg	10 mg	50mg	100 mg
1	-	-	-	-	1	3	-		3
2	-	1	5	-	7	9	-	1	9
3a	7	12	17	6	15	19	5	15	20
3b	8	13	16	8	18	20	8	18	18
3c	13	20	33	12	25	28	15	25	32
3d	15	22	31	14	26	30	16	28	35
4a	9	11	18	9	16	21	8	19	20
4b	8	12	19	7	18	20	6	15	21
4c	18	24	33	15	29	35	18	30	38
4d	15	27	40	16	30	39	17	32	39
5a	9	15	20	7	18	19	5	18	19
5b	7	12	19	8	20	21	6	17	20
5c	20	28	35	18	39	42	20	39	43
5d	21	29	39	20	40	48	22	40	47
6a	9	14	16	7	16	20	5	19	20
6b	7	13	19	9	19	19	7	20	22
6c	8	15	20	6	17	21	6	16	25
6d	9	14	18	8	18	22	8	18	23
6e	15	26	30	15	25	35	12	30	33
6f	14	28	28	12	29	33	16	28	31
6g	17	30	31	15	31	37	13	24	38
6h	16	27	29	13	33	39	18	29	35
Ketoconazole	8	13	18	7	17	21	6	17	21

Antimicrobial activity

Antibacterial evaluation

Applying the agar plate diffusion technique [30, 31] all of the compounds were screened in Vitro for antibacterial activity against *Bacillus subtilis*, *Streptococcus Penumonia*, *Staphylococcus Aureas*, *E.Coli* and *Pseudomonas Solanarium*. The compounds were tested at (10mg, 50mg and 100mg) concentrations and the activity was

determined by measuring the zone of inhibition. The screening results given in table (1) where, the activities of compounds were compared with *streptomycin* as antibacterial standard. The compounds 5c and 5d showed maximum antibacterial potency. Compounds **3c**, **3d**, **4c**, **4d**, **5c**, **5d**, **6c** and 6d have more activity, Compounds **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, **6a** and **6b** have nearly activity and compounds **1** and **2** have less activity compared with *streptomycin* against all bacterial organisms.

Antifungal assay

The compounds were evaluated for their in vitro antifungal activity against *Aspergillus Nigaer*, *Candia albicans*, and *Penicillium Sp*. using an agar dilution method [32]. The screening results

Given in table (2) where, the activities of compounds were compared with Ketoconazole as antifungal standard. The compounds **5c** and **5d** showed maximum antifungal potency. Compounds **3c**,**3d**,**4c**, **4d**, **5c**, **5d**, **6c** and 6d have more activity, Compounds **3a**, **3b**, **4a**, **4b**, **5a**, **5b**, **6a** and **6b** have nearly activity and compounds **1** and **2** have less activity compared with *Ketoconazole* against all fungal organisms

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