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SYNTHESIS CHARACTERIZATION AND ANTI-MICROBIAL ACTIVITY OF QUINAZOLINONE COMPOUNDS

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Abstract:- Heterocyclic compounds have diverse biological properties due to which they are intensively studied and researched. Compounds. One of these compounds is quinazolinone which has been found to exhibit various medicinal properties. Activities. Quinazolinone with heterocyclic nucleus is a novel molecule that attracts chemists to make a new discovery. Therapeutic molecule. The current review article contains various quinazolinone and their various derivatives Substitution with antimicrobial activities.

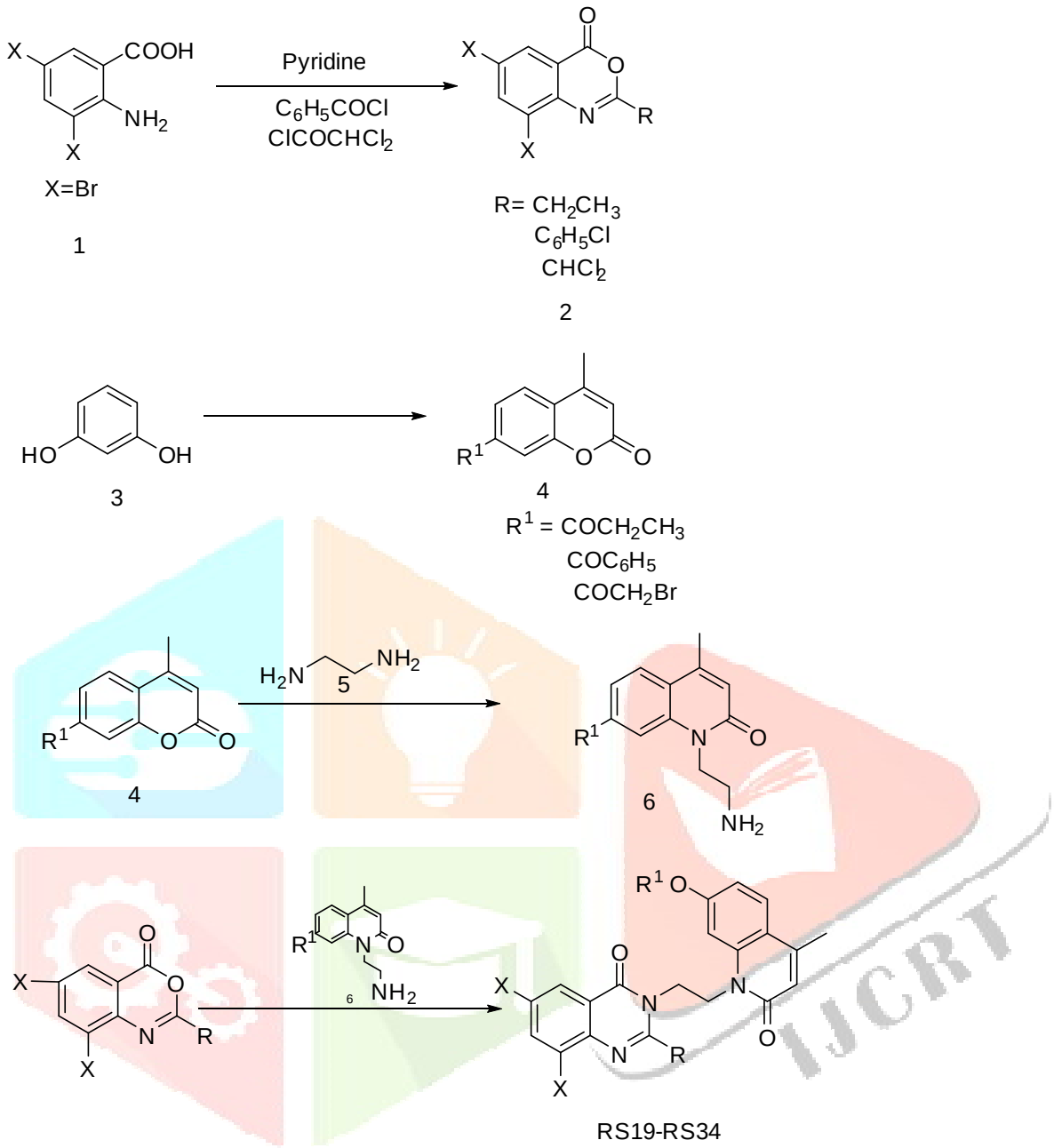
Introduction:- Heterocyclic chemistry is a chemical consisting of heterocyclic compounds that contain at least two atoms. Various elements such as ring number. The rhombus can be inorganic, although the compound contains carbon atoms. The term ring, hetero, is different from carbon and hydrogen. Nitrogen containing heterocyclic compounds Plays an important role in medicinal chemistry. Quinazolinone consists of two fused benzene and pyrimidinone rings. Quinazolinones are a large class of active chemical compounds exhibiting a broad spectrum of biological activities In animals as well as humans. Literature studies on quinazolinones have shown that these derivatives have a. Many biological activities like antioxidant [1], antifungal [2], antibacterial [3], anticonvulsant [4] antiinflammatory [5], antihyperlipidemic [4], anticancer [,], antimalarial [ar], antispasmodial [4] analgesic [10] Antiviral [11], antitubercular [12] and antimicrobial [13] activities. Quinazolinones fuses are heterocycle classes that are of great interest due to the diverse range of Their biological properties. Quinazolinones will be classified into the following five categories, based on Replacement pattern of ring system; They are 2-Substituted -

4 [3H] -Squinazolinone, 3-Substituted -4 [[3H] - Quinazoline, 4-substituted-quinazoline, 2,3-disubstituted-4 [3H] -quinazoline and 2,4-disubstituted-4 [3H] quinazolinones. Based on the position of the keto group, these compounds can be classified into three types. They are 2 [1H] quinazolinone, 4 [3H] quinazolinone and 2, 4 [1H, 3H] quinazolindione. Quinazolinone is one of the most important rhombic compounds, weak base with different biological activities. And still great scientific interest still a day. They are widely found in bio-inorganic and medicinal chemistry Application in drug discovery. This review was focused on quinazolinones and its various derivatives Occupies antimicrobial activities.

Present work:

From the literature survey it is evident that 7-substituted oxyquinolone attached quinazolinones exhibit promising type of antioxidant, anti-inflammatory, H_1antihistaminic and antitumor activity. In the present investigation it has been envisaged to introduce CH_3CO/ C_6H_5CO/ $ClCH_2CO$ in 7 th position of quinolone moiety and CH_3 at 2nd position of 4(3*H*) quinazolinones and to evaluate the resulting molecules for possible antioxidant, anti-inflammatory, H_1-antihistaminic and antitumor activities . Hence the synthesis of 6, 8-dibromo/ -3-(2-(7-acetyl/ benzoyl/ chloroacetyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl) ethyl)-2-methyl quinazolin-4(3*H*)-ones are taken up.Synthesis of the title compounds are shown in **scheme 2A** by adopting simple synthetic procedures. Six appropriate 6,8-dibromo/ -3-(2-(7-acetyl/benzoyl/ chloroacetyl oxy-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl)-2-methylquinazolin-4(3*H*)-ones (**RS19, RS22,RS25, X=H) (RS28, RS31, RS34, X=Br)** were synthesized from dibromo/ anthranilic acids by a known procedure reported from this laboratory. The details of the synthesis are drawn in scheme **4.1.2 and 4.1.3 (scheme 2A).** The IR, PMR and Mass spectrums are shown in **4.1.4 (Figure 4.1 and 4.2)**. The compounds profile of **RS19, RS22, RS25, RS28, RS31,** and **RS34**

General scheme of 3-(2-(7-subs. oxy-4-methyl-2-oxoquinolin-1-(2*H*)-yl) ethyl) 6,8-dibromo/unsubs.-2-subs. quinazolin-4(3*H*)-one



RS19-RS34

Experimental

General procedure for the synthesis of 7-hydroxy-4-methyl-2H-chromen-2-one (2A-II, step1):

A solution of resorcinol (0.1 mol) and ethyl acetoacetate (0.1 mol) was mixed with 160 g of polyphosphoric acid . The reaction mixture was stirred and heated at 75-80 ^{o}C for 20 min and then poured into ice-water. The resultant pale yellow solid mixture was collected by suction filtration, washed with a little cold water and dried at 60^{o}C. Recrystallisation from dilute ethanol yields pure and colorless compound.

[X=H, R= CH_3] Yield 76%; MP 187^{0}C; IR (KBr) cm^{-1}:3350(Ar-OH), 3052(Ar),1643(C=O); Anal. Calc'd for $C_{10}H_8O_3$: C, 68.18; H, 4.58; O, 27.25. Found: C, 668.08; H, 4.63; O, 27.30.

General procedure for the synthesis of 7-acetyloxy / benzoyloxy /chloroacetyloxy-4-methyl-2H-chromen-2-one (2A-II, step 2):

4-Methyl-7-hydroxycoumarin (0.1 mol) in acetic anhydride (0.12 mol) and a few drops of pyridine / benzoyl chloride (0.12 mol) in absolute ethanol (10 mL)/ chloro acetylchloride (0.12 mol) in absolute ethanol (10 mL) was refluxed for 2 h, and then poured into ice-water. The resultant product was collected by suction filtration, washed with a little cold water and dried at 60^{o}C and recrystallised from absolute ethanol.

[R= $COCH_3$] Yield 76%; M.P. 189^{o}C; IR (KBr) cm^{-1}:3050(Ar), 1645(C=O), 1510(Lactone); Anal. Calc'd for $C_{12}H_{10}O_2$: C, 66.05; H, 4.62; O, 29.33. Found: C, 66.05; H, 4.57; O, 29.28.

General procedure for the synthesis of 1-(2-aminoethyl)-7-substituted oxy-4-methylquinolin-2(1H)-one (2A-III):

Equalent moles of 7-acetyl/ benzoyl / chloroacetyl oxy-4-methyl-2*H*-chromen-2-ones (0.1mol) with diethyl amine (0.1 mol) in glacial acetic acid was refluxed for 6 h. The excess solvent was then distilled off under reduced pressure and poured into crushed ice (200 g) to get the solid. The product so obtained was filtered under suction and dried at room temperature. It was purified by recrystalization from absolute ethanol.

[R= $COCH_3$] Yield 79%; M.P. 179^{o}C; IR (KBr) cm$^{-1;}$3410(Ar-NH_2), 3054 (Ar) 1652(C=O); Anal. Calc'd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.20; N, 10.76; O, 18.44. Found: C, 64.50; H, 6.22; N, 10.74 ; O, 18.46.

General procedure for the synthesis of 3-(2-(7-subs. oxy-4-methyl-2-oxoquinolin-1(2H)-yl)ethyl)-2-methyl-6,8-dibromo/unsubs.quinazolin-4(3H)-one (2A-IV, RS19):

The appropriate 1-(2-aminoethyl)-7-substituted oxy-4-methylquinolin-2(1*H*)-one (0.1 mol) and 2-methyl-4*H*- benzo[d][1,3]oxacin-4-one(0.1 mol) were taken in glacial acetic acid (40

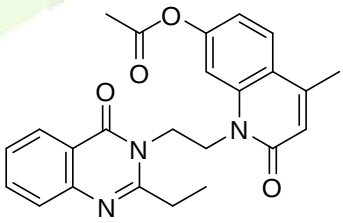
mL) and refluxed for 8 h. The course of the reaction was monitored every hour with the help of TLC. The excess solvent was then distilled off under reduced pressure and poured into crushed ice to get the solid. The final compounds were filtered, dried and purified by recrystalization from absolute ethanol.

The IR spectrum (KBr) of the compound had shown strong characteristic absorption bands (in cm^{-1}) at 3401 (NH_2), 3021(Ar) 1657 (C=O), 1597.6 (C=N). Its PMR spectrum showed strong signals at δ ppm **[RS19*X=H, R= CH_3, R'=H*]** Yield 69 %; M.P. 315^oC; IR (KBr)cm^{-1}:3345 (Ar-NH), 2919(Ar), 1676(C=O),1524 (CH); ^1H NMR ($CDCl_3$): δ 0.9,1.4,2.2 (s, 3H, CH_3), 3.3 ,3.5 (t, 2H, CH_2), 7-7.8 (m, 4H,Ar) 7.21-7.9 (m, 15H, heterocyc); MS(m/z): 403;Anal. Calc'd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N,10.42; O, 15.86 Found: C, 68.44; H, 5.28; N, 10.42; O, 15.82.

[RS28 X=*Br, R= CH_3, R'=H*] Yield 69%; M.P 245^0C; IR (KBr) cm^{-1}:3127(Ar),1677(C=O),1524 (CH); ^1H NMR ($CDCl_3$): δ 0.8,1.3,2.2 (s, 3H, CH_3), 3.3 ,3.5 (t, 2H, CH_2), 7-7.8(m, 4H, Ar), 6.8-7.4(m, 4H,Ar), 7.8, 8.1 (m, 2H,Br-Ar); MS(m/z): 561; Anal. Calc'd for $C_{23}H_{19}Br_2N_3O_4$: C, 49.22; H, 3.41; Br, 28.47; N, 7.49; O, 11.40. Found: C, 49.20; H, 3.43; Br, 28.50; N, 7.48; O, 11.38.

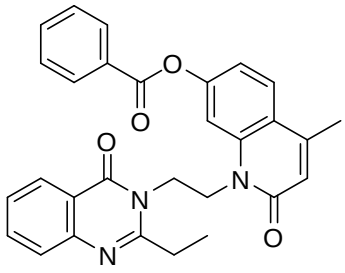
Compounds profile:

3-(2-(7-Acetyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl) ethyl)-2-methylquinazolin-4(3*H*)-one (RS19)



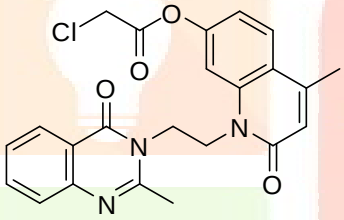
M.W. 403; M.F. $C_{23}H_{21}N_3O_4$.;Yield 69 % (3.7 g) ; M.P. 315 ^0C; IR (KBr) cm^{-1}:3345 (Ar-NH), 2919(Ar), 1676(C=O),1524 (CH); ^1H NMR ($CDCl_3$): δ 0.9,1.4,2.2 (s, 3H, CH_3), 3.3 ,3.5 (t, 2H, CH_2), 7-7.8 (m, 4H,Ar) 7.21-7.9 (m, 15H, heterocyc); MS(m/z): 403; Anal. Calc'd for $C_{23}H_{21}N_3O_4$: C, 68.47; H, 5.25; N, 10.42; O, 15.86. Found: C, 68.44; H, 5.28; N, 10.42; O, 15.82.

3-(2-(7-Benzoyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl) ethyl)-2methylquinazolin-4(3*H*)-one (RS22)



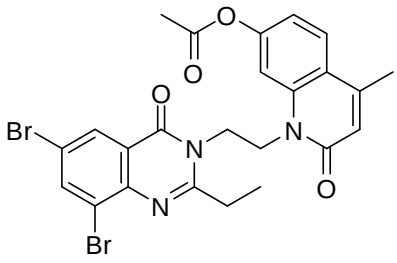
M.W. 465.17; M.F. $C_{28}H_{23}N_3O_4$; Yield 67 % (3.23 g) ; M.P. 265 ^{0}C; R_f 0.47; IR (KBr) cm^{-1}: 3344 (Ar-NH), 2912(Ar), 1671(C=O),1520 (CH);Anal. Calc'd for $C_{28}H_{23}N_3O_4$: C, 72.24; H, 4.98; N, 9.03; O, 13.75. Found: C, 72.34; H, 4.88; N, 9.13; O, 13.65.

3-(2-(7-Chloroacetyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl)-2-methyl quinazolin-4(3*H*)-one (RS 25)



M.W. 437.88; M.F. $C_{23}H_{20}ClN_3O_4$; Yield 67% (3.45 g); M.P 246 ^{0}C; R_f 0.49(CH_3Cl); IR (KBr) cm^{-1}: 3034 (Hetero), 2919 (Ar),1676(C=O), 1524 (CH); Anal. Calc'd for $C_{23}H_{20}ClN_3O_4$: C, 63.09; H, 4.60; Cl , 8.10; N, 9.60; O, 14.62. Found: C, 63.10; H, 4.59; Cl , 8.11; N, 9.59; O, 14.62.

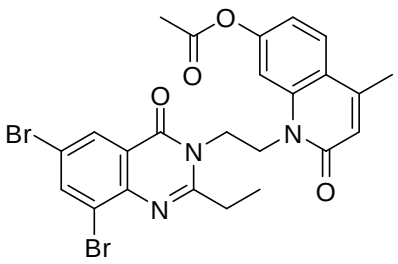
6, 8-Dibromo-3-(2-(7-acetyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl)-2-methyl quinazolin-4(3*H*)-one (RS 28)



M.W. 561.22; M.F. $C_{23}H_{19}Br_2N_3O_4$; Yield 69% (12.8 g); M.P. 247 ^{0}C; R_f 0.48; IR (KBr) cm^{-1}:3127 (Ar), 1677 (C=O),1524 (CH); ^{1}H NMR ($CDCl_3$): δ 0.8,1.3,2.2 (s, 3H,

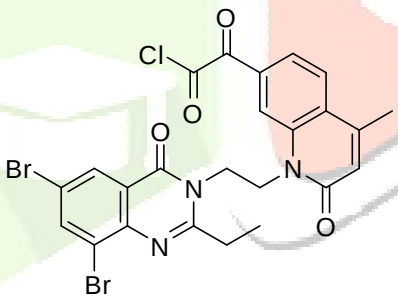
CH_3), 3.3 ,3.5 (t, 2H, CH_2), 7-7.8 (m, 4H, Ar), 6.8-7.4 (m, 4H,Ar), 7.8, 8.1 (m, 2H,Br-Ar); MS(m/z): 561; Anal. Calc'd for $C_{23}H_{19}Br_2N_3O_4$: C, 49.22; H, 3.41; Br, 28.47; N, 7.49; O, 11.40. Found: C, 49.20; H, 3.43; Br, 28.50; N, 7.48; O, 11.38.

6,8-Dibromo-3-(2-(7-acetyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl)-2-methyl quinazolin -4(3*H*)-one (RS 31)



M.W. 623.29; M.F. $C_{28}H_{21}Br_2N_3O_4$;. Yield 68% (11.3 g); M.P. 258 ^{0}C; R_f 0.49 (CH_3Cl); IR (KBr) cm^{-1}: 3123(Ar),1670(C=O), 1521 (CH); Anal. Calc'd for $C_{28}H_{21}Br_2N_3O_4$: C, 53.96; H, 3.40; Br, 25.64 ; N, 6.74; O, 10.27. Found: C, 53.98; H, 3.38; Br, 25.66 ; N, 6.72; O, 10.27.

6,8-Dibromo-3-(2-(7-oxychloroacetyl-4-methyl-2-oxoquinolin-1(2H)-yl)ethyl)-2-methyl quinazolin-4(3*H*)-one (RS 34)



M.W. 595.67; M.F. $C_{23}H_{18}Br_2ClN_3O_4$; Yield 68% (11.8g); M.P. 274 ^{0}C; R_f 0.49(CH_3Cl); IR (KBr) cm^{-1}: 3123(Ar),1670(C=O), 1521 (CH); Anal. Calc'd for $C_{28}H_{21}Br_2N_3O_4$: C, 46.38; H, 3.05; Br, 26.83; Cl, 5.95; N,7.05; O, 10.74. Found: C, 46.40; H, 3.07; Br, 26.85; Cl, 5.93; N, 7.06; O, 10.73.

General procedure for the synthesis of 3-(2-(7-subs. oxy-4-methyl-2-oxoquinolin-1(2H)-yl)ethyl)-2-phenyl-6,8-dibromo/unsubs.quinazolin-4(3H)-one (2B-IV) [130]**:**

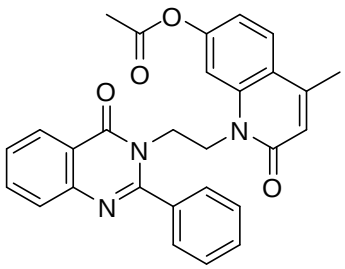
The appropriate 1-(2-aminoethyl)-7-substituted oxy-4-methylquinolin-2(1*H*)-one (0.1 mol) and 2-phenyl-4*H*- benzo[d][1,3]oxacin-4-one(0.1 mol) were taken in glacial acetic acid (40 mL) and was refluxed for 8 h. The course of the reaction was monitored every hour with the help of TLC. The excess solvent was then distilled off under reduced pressure and poured into crushed ice to get the solid. The resultant compounds were filtered, dried and purified by recrystalization from absolute ethanol.

[RS 20 *X=H, R= C_6H_5, R'=H*] Yield 69 %; M.P. 294^{0}C: IR (KBr) cm^{-1}:3495 (Ar-NH), 2927(Ar), 1669(C=O),1452 (CH); ^{1}H NMR ($CDCl_3$): δ 0.9,2.2 (s, 3H, CH_3), 3.3 ,3.5 (t, 2H, CH_2), 6.8-7.5 (m, 4H,Ar) 7.21-7.9 (m, 15H, heterocyc); MS(m/z): 465; Anal. Calc'd for $C_{28}H_{23}N_3O_4$: C, 72.24; H, 4.98; N, 19.03; O, 13.75. Found: C, 72.26; H, 4.96; N, 19.06; O, 13.72.

[RS 29 *X=Br, R= C_6H_5, R'=H*] Yield 69%; M.P 245^{0}C; IR (KBr) cm^{-1};3494 (Ar-NH_2),1677 (C=O),1524 (CH); ^{1}H NMR ($CDCl_3$): δ 0.9, 1.3, 2.1 (s, 3H, CH_3), 3.3 ,3.5 (t, 2H, CH_2), 6.8-7.00 (m,4H,Ar), 7.3-7.8(m, 4H,Ar); MS(m/z): 623; Anal. Calc'd for $C_{28}H_{21}Br_2N_3O_4$: Cal: C, 53.96; H, 3.40; Br, 25.64; N, 6.74; O, 10.27. Found: C, 53.93; H, 3.43; Br, 25.64; N, 6.72; O, 10.29.

Compounds profile:

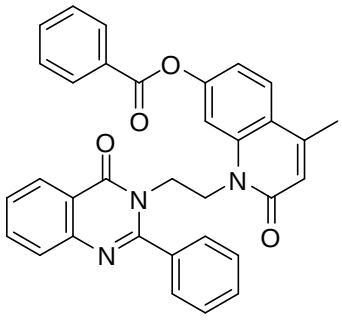
3-(2-(7-Acetyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl) ethyl)-2-phenylquinazolin-4(3*H*) -one (RS20)



M.W. 465; M.F. $C_{28}H_{23}N_3O_4$; Yield 69% (3.85 g); M.P. 294^{0}C; R_f 0.52 (CH_3Cl) ; IR (KBr) cm^{-1}: 3345 (Ar-NH), 2919 (Ar), 1676(C=O), 1524 (CH); ^{1}H NMR ($CDCl_3$): δ 1.4, 2.2, (s,3H, CH_3)3.3, 3.5(t, 2H, CH2),7-7.8 (m,4H,Ar),6.8- 7.4(m, 4H, Ar). MS (m/z): 465; Anal.

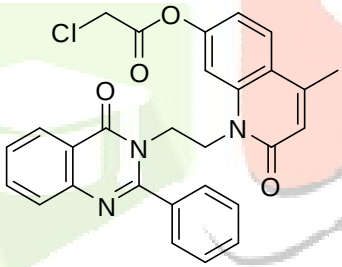
Calc'd for $C_{28}H_{23}N_3O_4$: C, 72.24; H, 4.98; N, 19.03; O, 13.75. Found: C, 72.26; H, 4.96; N, 19.06; O, 13.72.

3-(2-(7-Benzoyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl) ethyl)- phenylquinazolin-4(3*H*)-one (RS 23)



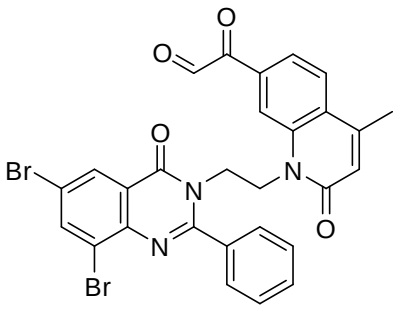
M.W. 527; M.F. $C_{33}H_{25}N_3O_4$;. Yield 72% (3.7 g); M.P 246 ^{0}C; R_f 0.50; IR (KBr) cm^{-1}: 3030 (Ar), 1672 (C=O), 1521 (CH). Anal. Calc'd for $C_{33}H_{25}N_3O_4$: C, 75.13; H, 4.78; N, 7.96; O, 12.13. Found: C, 75.23; H, 4.88; N, 7.93; O, 12.16.

3-(2-(7-Chloroacetyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl)-2-phenylquina-zolin-4(3*H*)-one (RS 26)



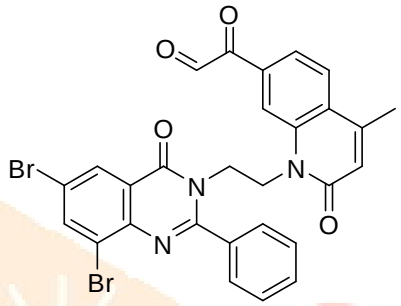
M.W. 499; M.F. $C_{28}H_{22}ClN_3O_4$; Yield 68% (3.06 g); M.P. 248 ^{0}C; R_f 0.51; IR (KBr) cm^{-1}: 3031(Hetero), 2911(Ar), 1672(C=O), 1521 (CH); Anal. Calc'd for $C_{28}H_{22}ClN_3O_4$: C, 67.27; H, 4.44; Cl, 7.09; N, 8.40; O, 12.80. Found: C, 67.37; H, 4.34; Cl, 7.09; N, 8.30; O, 12.90.

6,8-Dibromo-3-(2-(7-oxyacetyl-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl)-2-phenyl quinazolin-4(3*H*)-one (RS29)



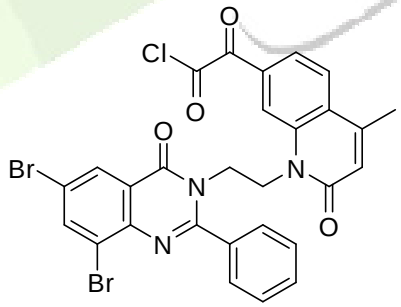
M.W. 623; M.F. $C_{28}H_{21}Br_2N_3O_4$; Yield 69% (11.5 g); M.P 245 ^{0}C; IR (KBr) cm^{-1}:3494(Ar-NH_2), 1677 (C=O),1524 (CH); ^{1}H NMR ($CDCl_3$): δ 0.9, 1.3, 2.1 (s, 3H, CH_3), 3.3 ,3.5 (t, 2H, CH_2), 6.8-7.00(m, 4H, Ar), 7.3-7.8(m, 4H,Ar); MS(m/z): 623; Anal. Calc'd for $C_{28}H_{21}Br_2N_3O_4$: Cal: C, 53.96; H, 3.40; Br, 25.64; N, 6.74; O, 10.27 Found: C, 53.93; H, 3.43; Br, 25.64; N, 6.72; O, 10.29.

6,8-Dibromo-3-(2-(7-oxyacetyl-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl)-2-phenyl quinazolin-4(3*H*)-one (RS32)



M.W. 685; M.F. $C_{33}H_{23}Br_2N_3O_4$; Yield 74%(11.2 g) ; M.P 267 ^{0}C; R_f 0.51(CH_3Cl); IR (KBr) cm^{-1}: 3121(Ar),1672(C=O), 1524 (CH). Anal. Calc'd for $C_{28}H_{22}ClN_3O_4$: C, 57.83; H, 3.38; Br, 23.32;N, 6.13; O, 9.34. Found: C, 57.81; H, 3.40; Br, 23.34; N, 6.11; O, 9.34.

6,8-Dibromo-3-(2-(7-oxychloroacetyl -4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl)-2-phenyl quinazolin-4(3*H*)-one (RS35)



M.W. 657; M.F. $C_{28}H_{20}Br_2ClN_3O_4$; Yield 79% (12.5 g) ; M.P 235 ^{0}C; R_f 0.47(CH+Cl); IR (KBr) cm^{-1}: 3121(Ar),1671(C=O), 1522 (CH). Anal. Calc'd for $C_{28}H_{22}ClN_3O_4$: C, 51.13; H, 3.06; Br, 24.30; Cl, 5.39;N, 6.39; O, 9.73. Found: C, 51.15; H, 3.04; Br, 24.33; Cl, 5.36; N, 6.36; O, 9.76.

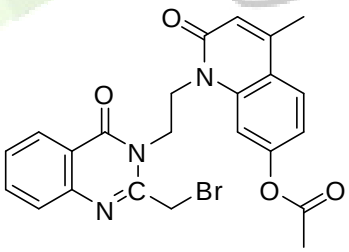
General procedure for the synthesis of 3-(2-(7-subs.oxy-4-methyl-2-oxoquinolin-1(2H)-yl)ethyl)-2-methylchloro-6,8-dihaloquinazolin-4(3H)-one

The appropriate 1-(2-aminoethyl)-7-substituted oxy-4-methylquinolin-2(1*H*)-one (0.1 mol) and 2-methylchloro-4*H*- benzo[d][1,3]oxacin-4-one(0.1 mol) were taken in glacial acetic acid (40 mL) and refluxed for 8 h. The course of the reaction was monitored every hour with the help of TLC. The excess solvent was then distilled off under reduced pressure and poured into crushed ice to get the solid. The final compounds were filtered, dried and purified by recrystalization from absolute ethanol.

[RS 21 *X=H, R= CH_2Cl, R'=H*] Yield 67 %; M.P 278^{0}C; IR (KBr) cm^{-1}: 3441 (Ar-NH), 2925(Ar), 1671(C=O),1529 (CH); ^{1}H NMR ($CDCl_3$): δ 0.9,2.2, 2.4 (s, 3H, CH_3), 3.3 ,3.5(t, 2H, CH_2), 6.8-7.00 (m, 4H,Ar) 7.3-7.8 (m, 8H, heterocyc); MS(m/z): 437; Anal. Calc'd for $C_{23}H_{20}ClN_3O_4$ Cal: C, 63.09; H, 4.60; Cl, 8.10; N, 9.60; O, 14.62 Found:C, 63.07; , 4.62; Cl, 8.06; N, 9.620; O, 14.64 .

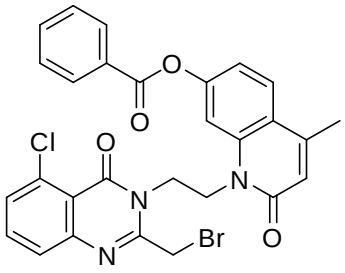
[RS 30 *X=Br, R= CH_2Cl, R'=H*] Yield 69%; M.P 245^{0}C; IR (KBr) cm^{-1}: 3493(Ar-NH_2), 2925(Ar),1683(C=O),1537 (CH); ^{1}H NMR ($CDCl_3$): δ 0.9, 2.3, 2.4 (s, 3H, CH_3), 3.3 ,3.5 (t, 2H, CH_2), 6.8-7.00(m, 4H, Ar), 7.3-8.1(m, 4H,Ar); MS(m/z): 595; Anal. Calc'd for $C_{23}H_{18}Br_2ClN_3O_4$: Cal: C, 46.38; H, 3.05; Br, 26.83; Cl, 5.95; N, 7.05; O, 10.74 Found: C, 46.40; H, 3.07; Br, 26.85; Cl, 5.93; N, 7.05; O, 10.74.

3-(2-(7-Acetyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl)-2-ethyl chloroquinazolin-4(3*H*)-one (RS21)



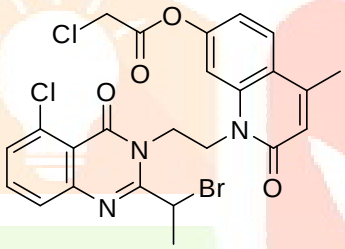
M.W. 437; M.F $C_{23}H_{20}ClN_3O_4$; Yield 67% (3.45 g) ; M.P. 278 ^{0}C; R_f 0.51 (CH_3Cl); IR (KBr) cm^{-1}: 3441 (Ar-NH), 2925(Ar), 1671(C=O),1529 (CH); ^{1}H NMR ($CDCl_3$): δ 0.9,2.2, 2.4 (s, 3H, CH_3), 3.3 ,3.5 (t, 2H, CH_2), 6.8-7.00 (m, 4H,Ar) 7.3-7.8 (m, 8H, heterocyc); MS(m/z): 437; Anal. Calc'd for $C_{23}H_{20}ClN_3O_4$ Cal:C, 63.09; H, 4.60; Cl, 8.10; N, 9.60; O, 14.62. Found:C, 63.07; , 4.62; Cl, 8.06; N, 9.620; O, 14.64 .

3-(2-(7-Benzoyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl) ethyl)-2-methylchloro quina-zolin-4(3*H*)-one (RS24)



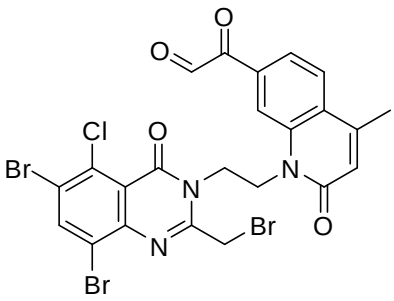
M.W. 499; M.F. $C_{28}H_{22}ClN_3O_4$; Yield 72% (3.25 g); M.P. 278 ^{0}C; R_f 0.52 (CH_3Cl); IR (KBr) cm^{-1}: 3031(Ar), 1671(C=O),1520 (CH);Anal. Calc'd for $C_{28}H_{22}ClN_3O_4$: C, 67.27; H, 4.44; Cl,7.09;N, 8.40; O, 12.80. Found C, 67.25; H, 4.46; Cl, 7.08;N, 8.41; O, 12.80.

3-(2-(7-Chloro acetyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl) ethyl)-2-methylchloro quinazolin-4(3*H*)-one (RS27)



M.W. 472; M.F. $C_{23}H_{19}C_{l2}N_3O_4$; Yield 77% (3.66 g); M.P. 249 ^{0}C; R_f 0.52(CH_3Cl); IR (KBr) cm^{-1}: 3036 (Hetero), 2912 (Ar), 1673 (C=O), 1526 (CH); Anal. Calc'd for $C_{28}H_{22}ClN_3O_4$: C, 58.49; H, 4.05; Cl, 15.01; N, 8.90; O, 13.55. Found C, 58.59; H, 3.95; Cl, 15.01; N, 8.80; O, 13.65.

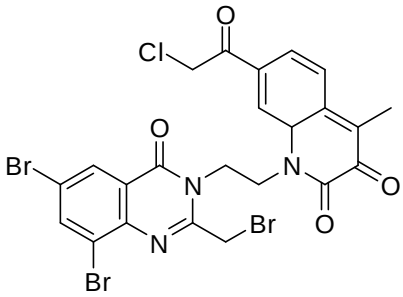
6,8-Dibromo-3-(2-(7-oxyacetyl-4-methyl-2-oxoquinolin-1(2*H*)-yl)ethyl)-2-methyl chloro quinazolin-4(3*H*)-one (RS30)



M.W. 595; M.F $C_{23}H_{18}Br_2ClN_3O_4$; Yield 69% (12 g); M.P. 245 ^{0}C; IR (KBr) cm^{-1}: 3493(Ar-NH_2), 2925 (Ar),1683 (C=O),1537 (CH); ^{1}H NMR ($CDCl_3$): δ 0.9, 2.3, 2.4 (s, 3H, CH_3), 3.3 ,3.5 (t, 2H,

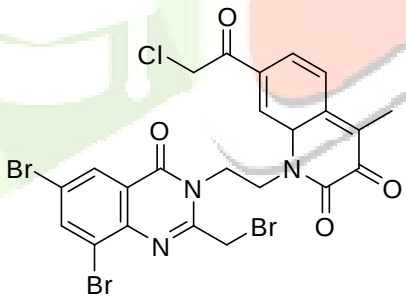
CH_2), 6.8-7.00 (m, 4H, Ar), 7.3-8.1(m, 4H,Ar); MS(m/z): 595; Anal. Calc'd for $C_{23}H_{18}Br_2ClN_3O_4$Cal: C, 46.38; H, 3.05; Br, 26.83; Cl, 5.95; N, 7.05; O, 10.74. Found: C, 46.40; H, 3.07; Br, 26.85; Cl, 5.93; N, 7.05; O, 10.74.

6, 8-Dibromo-3-(2-(7-acetyloxy-4-methyl-2-oxoquinolin-1(2*H*)-yl) ethyl)-2-methyl chloroquinazolin-4(3*H*)-one (RS33)



M.W. 657; M.F. $C_{28}H_{20}Br_2ClN_3O_4$; Yield 66% (10.4 g); M.P. 249 ^{0}C; R_f 0.43(CH_3Cl); IR (KBr) cm^{-1}: 3124 (Ar),1675(C=O), 1527 (CH); Anal. Calc'd for $C_{28}H_{22}ClN_3O_4$: C, 51.13; H, 3.06; Br, 24.30; Cl, 5.39; N, 6.39; O, 9.73. Found C, 51.16; H, 3.03; Br,24.34;Cl, 5.35; N, 6.33; O, 9.8.

6, 8-Dibromo-3-(2-(7-chloroacetyl oxy-4-methyl-2-oxoquinolin -1(2*H*)-yl) ethyl)-2-chloromethylquinazolin-4(3*H*)-one (RS36)



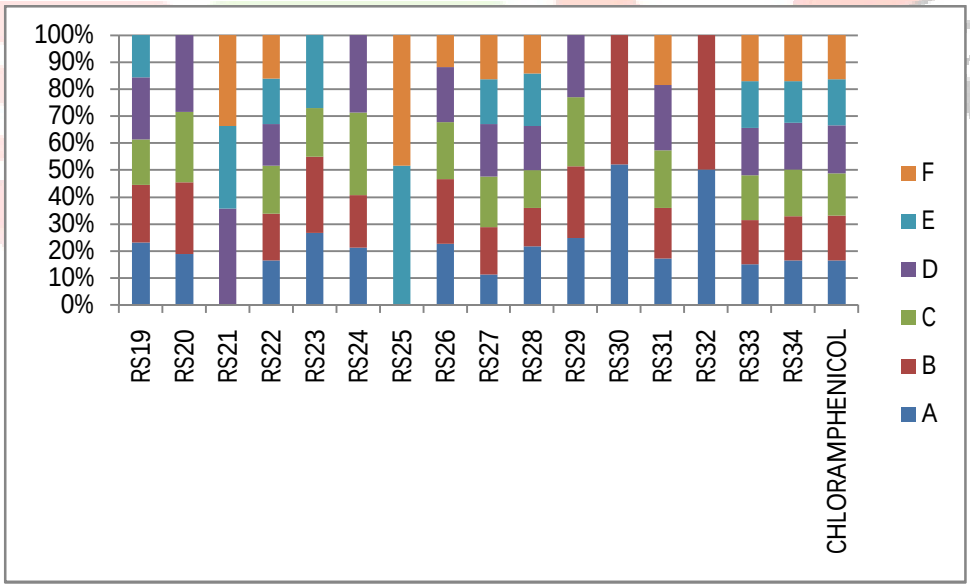
M.W. 630; M.F. $C_{23}H_{17}Br_2Cl_2N_3O_4$; Yield 66% (10.9 g); M.P. 267 ^{0}C; R_f 0.42 (CH_3Cl); IR (KBr) cm^{-1}: 3122 (Ar), 1674 (C=O), 1525 (CH); Anal. Calc'd for $C_{23}H_{17}Br_2Cl_2N_3O_4$: C, 43.84; H, 2.72; Br, 25.36; Cl, 11.25; N, 6.67; O, 10.16. Found C, 43.86; H, 2.70; Br, 25.40; Cl, 11.21; N, 6.65; O, 10.18.

Biological evolution

COMPOUND	MICROORGANISM					
	A	B	C	D	E	F
RS19	19.06	17.54	13.97	19.06	12.98	-†
RS20	13.76	19.63	19.05	20.97	-†	-†
RS21	-†	-†	-†	20.04	17.09	18.98
RS22	18.45	19.26	20.08	17.09	19.00	18.00
RS23	17.64	18.67	11.90	-†	18.00	-†
RS24	13.02	12.05	19.05	17.76	-†	-†
RS25	-†	-†	-†	-†	19.07	18.00
RS26	18.90	20.04	17.67	16.87	-†	10.00
RS27	11.56	18.09	19.05	20.06	17.07	16.94
RS28	20.05	12.98	13.09	15.06	18.09	13.09
RS29	18.24	19.67	19.09	17.05	-†	-†
RS30	19.57	18.00	-†	-†	-†	-†
RS31	12.09	13.03	15.06	17.08	-†	13.00
RS32	18.02	18.00	-†	-†	-†	-†
RS33	17.06	18.98	19.03	20.01	19.98	19.66
RS34	18.96	19.08	19.98	20.00	17.98	19.77
CHLORAMPHENICOL	22.08	22.64	21.24	23.88	23.28	22.13

*(A) *E. coli*; (B) *P. aeruginosa*; (C) *B. subtilis*; (D) *S. pyogenes*; (E) *K. pneumonia*; (F) *S. aureus* † (-) Inactive

Graphical comparison



5. ADME study

Product code	$CaCo_2$	BBB+	HERG	Plogs	AMES Toxicity	Carcinogenicity
RS19	0.5976	0.8405	0.8942	-4.1269	0.6654	0.6568
RS20	0.5102	0.8150	0.9585	-3.5990	0.7089	0.6293
RS21	0.5630	0.7612	0.9132	-3.9191	0.6223	0.6325
RS22	0.6062	0.8016	0.9015	-3.8908	0.6895	0.6534
RS23	0.5058	0.8335	0.9443	-3.5607	0.7013	0.6185
RS24	0.5522	0.7336	0.7900	-4.3035	0.6424	0.5842
RS25	0.5229	0.8394	0.9367	-3.8947	0.6610	0.6128
RS26	0.5000	0.8423	0.9325	-3.9848	0.6945	0.5934
RS27	0.5053	0.8112	0.8995	-4.0287	0.7083	0.5621
RS28	0.5606	0.7423	0.9033	-4.3497	0.6281	0.6184
RS29	0.5090	0.8173	0.9570	-3.6685	0.6281	0.5955
RS30	0.5404	0.8004	0.8175	-3.9181	0.5853	0.5907
RS31	0.5251	0.7849	0.9487	-4.0671	0.6477	0.5948
RS32	0.5118	0.8494	0.9013	-3.7181	0.6860	0.6013
RS33	0.5392	0.7525	0.6246	-3.5644	0.6227	0.5650
RS34	0.5340	0.7898	0.8850	-3.9683	0.5928	0.6057

Docking Study

Compound ID	PDB1Gos_1	PDB1Gos_2
RS19	-68.458	-67.362
RS20	-57.117	-59.800
RS21	-63.693	-58.444
RS22	-63.900	-65.849
RS23	-75.912	-72.453
RS24	-54.998	-55.382
RS25	-69.646	-68.459
RS26	-54.998	-58.717
RS27	-68.459	-67.391
RS28	-65.628	-66.840
RS29	-75.912	-72.161

RS30	-65.628	-66.702
RS31	-60.270	-59.657
RS32	-71.325	-69.942
RS33	-54.438	-53.420
RS34	-66.702	-65.628