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SYNTHESIS CHARACTERIZATION AND EVOLUTION OF SOME DI BROMOQUINAZOLINONE COMPOUNDS

Kalpesh Barasara[1 *] Dr. Vinay Sharma[1]

1* Department of Chemistry Madhav University, Sirohi

1 Department of Chemistry Madhav University, Sirohi

Abstract:- Heterocyclic chemistry comprises at least half of all organic chemistry around the world. Quinazoline and its derivatives constitute an important class of heterocyclic compounds. The chemistry of quinazoline compounds has a centuries-old history; However, intensive exploration of biologically active substances in this series began only in the last few decades. This current communication attempts to cover the pharmacologically active compounds with recent discoveries that were made about these biological activities.

1. Introduction:-An introduction to Medicinal Chemistry gives us a very detailed look into the world of Medic1. Principles of medicinal chemistry are necessary to consider the physiological chemical properties used to develop new pharmacologically active components and their mechanisms of action, and many of them are characterized by their biological activity. . Pharmacological screening is performed to determine. This screening process has been inefficient, but has resulted in the identification of new lead compounds, whose composition has been adapted to produce diagnostic agents 2. A rich tradition of tailored design strategies has evolved to form new compounds within medicinal chemistry research for biological assessment 3. Heterocyclic chemistry is a chemical consisting of heterocyclic compounds, which contain atoms of at least two different elements as a ring number. Heterocyclic atoms may be inorganic, although the compound contains carbon atom in ring. In particular, heterocyclic structures form the basis of many pharmaceutical, agrochemical and veterinary products 4. Among the six-member heterocycles, quinazoline occupies an important position and is commonly found in a wide variety of natural products, synthetic pharmaceutical molecules, and other functional materials 5. The important role played by the heterocycle in drug design cannot be ruled out. Even where the natural substrate or ligand for a biological target does not contain heterocyclic6. Quinazolinone derivatives found Broad spectrum of activities such as antioxidant, antioxidant, antimicrobial, antipsychotic, antihypertensive 7-11 have been found. Quinazolinone (Figure 1) is a building block for approximately 150 naturally found alkaloids that are isolated from many families, animals, and

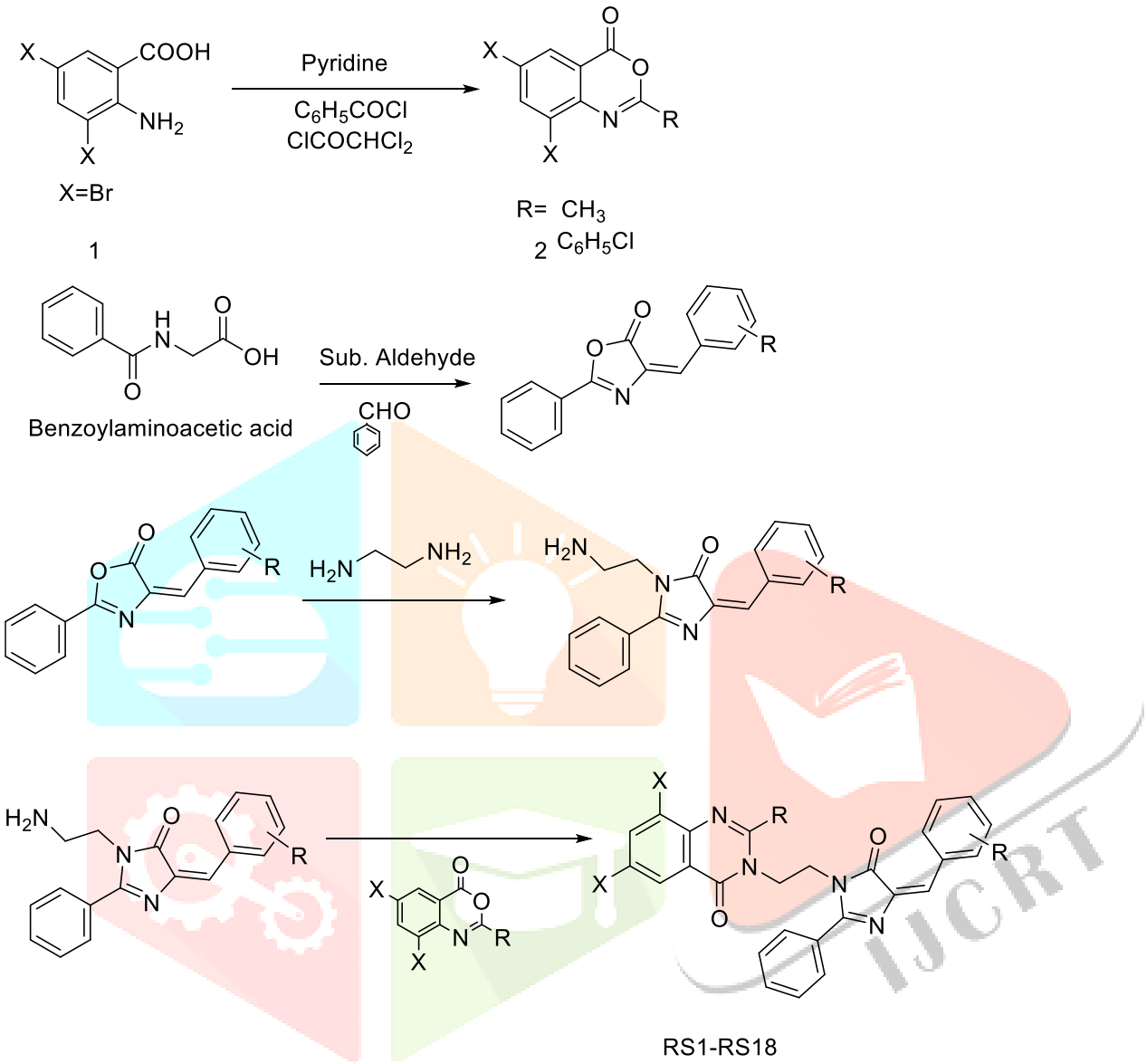
microorganisms such as Bacillus cereus *Bouchardatia neurococca, Dichroa febrifuga , and Peganum nigellastrum*[12-15]. in the plant kingdom.

The first quinazolinone (1) was synthesized in the late 1860s from anthranilic acid and cyanogens, so that 2-cyanoquinazolinone (2) methquaclone (3) was synthesized for the first time in 1951 and is the most well-known synthetic quinazoline drug . Its sedative-hypnotic effect 16. Proquazone, a derivative of quinazoline-2- , exhibits a potential NSAID potential that has been used in pathological conditions such as rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, musculoskeletal disorders, acute inflammatory conditions and acute pain conditions such as dysmenorrhea, postpartum pain. And headache 53. Quinazolinone is a heterocyclic chemical compound with two aromatic rings with two nitrogen-rich atoms and one of the oxidizing carbons with keto oxygen, also called quinazolindian, chemically known as quinazolin-4 (3H) - one17. in the form of. There are two structural isomers, 2- quinazoline (4) and 4-quinazolinone (5), 4- isomer is more common. The name quinazoline (German: chinazoline) was first proposed for this compound by Wedige, noting that the compound was isomeric with cinomoline quinoxaline. And many derivatives of the quinazoline system known so far, keto-quinazolines also known as quinazoline, are the most important compounds 18.

2. Present work: In view of the above observations, it is clear that quinazolinones nucleus has all the potentialities of a good pharmacophore. Hence we thought it would be interesting to investigate the effect of 6, 8-unsubstituted and/or 6, 8 - dibromosubstitution on the qunazolin-4(3*H*)-one nucleus and study their antioxidant, anti-inflammatory, H_1-antihistaminic and antitumor activities.In the present investigation, we have endeavored to introduce methyl at 2nd-position of methylquinazoline-4(3*H*)-one moiety and H/*o*-OH/*p*-$(CH_3)_2$N-benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol moiety with a view to evaluate them forpossible antioxidant, anti-inflammatory, H_1-antihistaminic and antitumor activities.Hence the synthesis of substituted 3-(2-((16Z)-4- H/OH/$(CH_3)_2$N benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-2-methylquinazolin-4(3*H*)-one (**RS1,RS3,RS5**) and 3-(2-((16Z)-4- H/ OH/ $(CH_3)_2$N-benzylidene-4,5-dihydro-5-oxo- 2-phenyl imidazol-1-yl)ethyl)-2-phenyl6,8-dibromo quinazolin-4(3*H*)-one (**RS10,RS13,RS16**) have been undertaken. As shown in scheme **1A** in **3.2.2** three different derivatives of 3-(2-((16Z)-4- H/ OH/ $(CH_3)_2$N benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-2-methyl quinazolin-4(3*H*)-one (**RS1,RS3,RS5**) and another three derivatives of 3-(2-((16Z)-4- H/ OH/ $(CH_3)_2$N benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-2-methyl 6,8-dibomo quina- zolin-4(3*H*)-one (**RS10,RS13,RS16**) were synthesized by simple chemical condensation reactions. The synthetic procedures along with their physical and spectral data have been discussed in detail in experimental section of this chapter. The details of the synthesis are drawn in scheme **3.2.2** and **3.2.3.** The IR, PMR and mass spectrums are shown in **3.2.4 (Figure 3.1** and **3.2)**. The compounds profile of **RS1, RS3,RS5, RS10, RS13, and RS16** are shown

3. Material and Method

General reaction scheme:-



3.2 Experimental:

General procedure for the synthesis of 2-methyl-4H-benzo[d] [1, 3] oxazin- 4-one (1A-I):

A mixture of disubstituted anthranilic acid (X=H, Br) (**1**) (0.12 mol), acetic anhydride (0.2 mol) and few drops of pyridine(0.02 mol) was taken in a dry round bottomed flask and refluxed for one hour under anhydrous condition. The excess solvent was then distilled off under reduced pressure. The crude product formed was filtered, washed, dried and re-crystallized from absolute ethanol.

[X=H, R= CH_3] Yield 81%; M.P. 187^0C; IR (KBr) cm^{-1}:3021(Ar), 1657(C=O);^{1}HNMR ($CDCl_3$): δ 0.9 (s, 3H, CH_3), 7.5-8.1 (m, 4H, heterocyc); Anal. Calc'd for $C_9H_7NO_2$: C, 67.07; H, 4.38; N, 8.69; O, 19.86. Found: C, 67.09; H, 4.36; N, 8.67; O, 19.88.

[X=Br_2, R= CH_3] Yield 80%; M.P. 189^0C; IR (KBr) cm^{-1}:3010(Ar), 1650(C=O);^{1}HNMR ($CDCl_3$): δ 0.92 (s, 3H, CH_3), 7.5-8.5 (m, 4H, heterocyc); Anal. Calc'd for $C_9H_5Br_2NO_2$: C, 33.89; H, 1.58; Br, 50.10; N, 4.39; O, 10.03 Found: C, 33.90; H, 1.57; Br, 50.12; N, 4.38; O, 10.02.

General procedure for the synthesis of (Z) - 2- substituted benzylidene -2- phenyl oxa-zolidin-4-one (1A-II & III):

mixture of redistilled substituted [H/OH/N(CH_3)$_2$]- benzaldehyde (0.25 mol), benzoyl glycine (0.25 mol) prepared from benzoyl chloride and glycine by standard procedure, acetic anhydride (0.75 mol) and anhydrous sodium acetate (0.25 mol) in a 500 mL conical flask and heated with constant shaking. As soon as the mixture has melted completely, the flask was transferred to a water bath and heated for 2 h. Then 100 mL of ethanol was added slowly to the contents of the flask and allowed the mixture to stand for overnight. The crystalline product was filtered with suction, washed with two 25 mL portions of ice cold alcohol and then washed with two 25 mL portions of boiling water. The resultant product was dried at 100 ºC, and recrystallised from benzene.

[X=0, R'=H] Yield 88%; M.P. 203^0C; IR (KBr) cm^{-1}:3021(Ar), 2945(C=C), 1655(C=O); ^{1}H NMR ($CDCl_3$): δ 7.6 (d, 1H, =CH-), 7.9-8.8 (m, 9H, heterocyc); Anal. Calc'd for $C_{16}H_{11}NO_2$: C, 77.10; H, 4.45; N, 5.62; O, 12.84. Found: C, 77.06; H, 4.49; N, 5.60; O, 12.85.

General procedure for the synthesis of (Z)-3 - (2- amino ethyl) -5-substituted benzy lidene -2-phenyl imidazolidin -4-one (1A-IV):

A mixture of (Z)-2-substituted (H/*o*-OH/ *p*-$(CH_3)_2$N- benzylidene -2- phenyl oxazolidine -4- one (**5**) (0.1 mol) and ethylene diamine (0.1 mol) in glacial acetic acid was refluxed under anhydrous conditions for 8 h. The reaction mixture was cooled to room temperature and the mixture was poured into crushed ice. The crude product obtained was recrystallized from absolute ethanol.

[X=H, R= H] Yield 87%; M.P 204^{0}C; IR (KBr) cm^{-1}:3401 (NH_2), 3021(Ar), 1657(C=O) ; ^{1}H NMR ($CDCl_3$): δ 2 (s, 2H, NH_2), 2.91 (s, 2H, CH_2), 3.22 (s, 2H, CH_2), 7.61 (d, 1H, =CH-) 7.14-7.6 (m, 10H, heterocyc); Anal. Calc'd for $C_{18}H_{17}N_3O$: C, 74.20; H, 5.88; N, 14.42; O, 5.49. Found: C, 74.22; H, 5.86; N, 14.41; O, 5.51.

General procedure for the synthesis of 3-(2-(17Z) - 5-substituted)-4-oxo-2-phenyl imidazol-1-yl) ethyl)-2-methylquinazolin-4(3H)-one (1A-V):

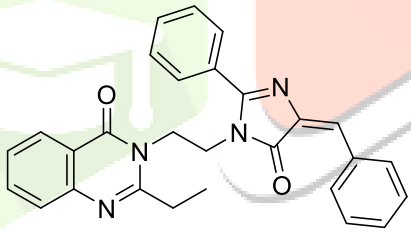
6,8-Dibromo/Unsubs.-2-methyl-4*H*-benzo[d](1,3)oxazin-4-one (**2**) (0.1 mol) and (Z)-3-(2-aminoethyl)-5-subs.[H/OH/N$(CH_3)_2$]-benzylidene-2-phenylimidazolidin-4-one (**6**) (0.1 mol) was dissolved in glacial acetic acid and refluxed under anhydrous conditions for 8 h. The reaction mixture was cooled to room temperature and the mixture was poured into crushed ice. The crude product obtained was recrystallized from absolute ethanol.

[RS1 *X=0, R= CH_3, R'=H*] Yield 72 %; M.P. 312^0C; IR (KBr) cm^{-1}:3120 (Ar-NH),3014 (Ar), 1658(C=O),1527 (CH); ^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H, CH_3), 3.26 , 3.46 (t, 2H, CH_2), 7.64(d, 1H, =CH-) 7.21-7.9 (m, 15H, heterocyc); MS(m/z): 434; Anal. Calc'd for $C_{32}H_2N_4O_2$: C, 74.64; H, 5.10; N, 12.89; O, 7.36. Found: C, 74.60; H, 5.14; N, 12.87; O, 7.38.

[RS 10 *X=Br, R= CH_3, R'=H*] Yield 79%; M.P. 315^0C; IR (KBr) cm^{-1}:3122 (Ar-NH),3017(Ar), 1653(C=O),1524 (CH); ^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H, CH_3), 3.26 ,3.46 (t, 2H, CH_2), 7.64(d, 1H, =CH-) 7.21-7.9 (m, 13H, heterocyc) 7.8, 8.1 (m, 2H,Br-Ar); MS (m/z): 592; Anal. Calc'd for $C_{27}H_{20}Br_2N_4O_2$: C, 54.75; H, 3.4; Br, 26.98; N, 9.46; O, 5.4. Found: C, 54.73; H, 3.6; Br, 26.96; N, 9.46; O, 5.6.

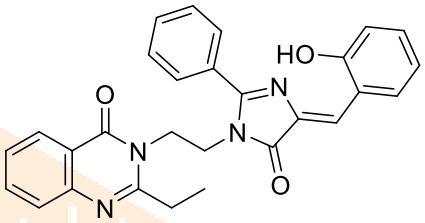
3.2 Compounds profile:

3-(2-((16E)-4-Benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-2-methyl quinazolin-4(3*H*)-one (RS1)



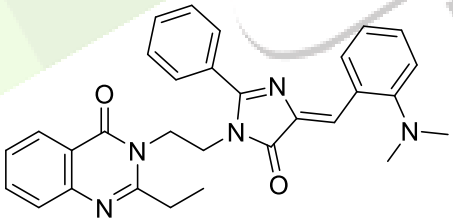
M.W. 434.49; M.F. $C_{27}H_{22}N_4O_2$;Yield 67% (3.5 g); M.P. 312^{o}C; R_f 0.48($CHCl_3$) ; IR(KBr)cm^{-1}:3120 (Ar-NH), 3014 (Ar), 1658(C=O),1527 (CH); ^{1}H NMR ($CDCl_3$): 0.9 (s, 3H, CH_3), 3.26 ,3.46 (t, 2H, CH_2), 7.64 (d, 1H, =CH-) 7.21-7.9 (m, 15H, heterocyc); EI-MS (70 eV) [m/z, %] :77, 90, 144, 159, 247, 434, 435, 436; Elem. Anal. Calc'd for $C_{27}H_{22}N_4O_2$: C, 74.64; H, 5.10; N, 12.89; O, 7.36. Found: C, 74.54; H, 5.20; N, 12.79; O, 7.46.

-(2-((16E)-4-(2-Hydroxybenzylidene)-4,5-dihydro-5-oxo -2-phenyl imidazol-1-yl)ethyl)-2-methylquinazolin-4(3*H*)-one (RS4)



M.W 450.49; M.W. $C_{27}H_{22}N_4O_3$;Yield 94 % (4.7 g); M.P. 331 ^{0}C ; R_f 0.51(CH_3Cl); IR (KBr cm^{-1}): 3122 (Ar-NH), 3010 (Ar-H), 1656 (C=O), 1510 (Lactone) ; Elem. Anal. Calc'd for $C_{27}H_{22}N_4O_3$: C, 71.99; H, 4.92; N, 12.44; O, 10.65. Found: C, 71.89; H, 5.02; N12.42; O, 10.67.

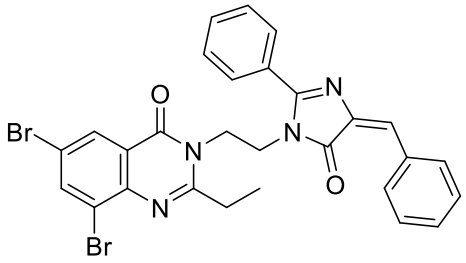
3-(2-((16E)-4-(2-(Dimethylamino) benzylidene)-4,5-dihydro-5-oxo- 2-phenylimidazol -1-yl) ethyl)-2-methylquinazolin-4(3*H*)-one (RS7)



N

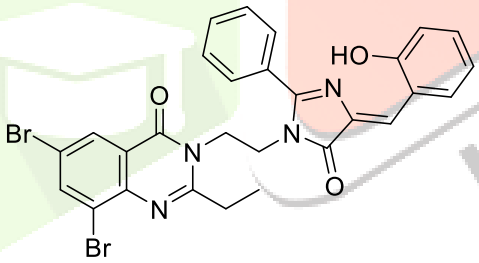
M.W. 477.56; M.F. $C_{29}H_{27}N_5O_2$. ; Yield 63% (2.96 g); M.P. 319 ^{0}C; R_f 0.46 (CH_3Cl) ; IR (KBr cm^{-1}): 3122(Ar-NH), 3010(Ar-H), 1656(C=O), 1510 (Lactone). Elem. Anal. Calc'd for $C_{29}H_{27}N_5O_2$: C, 72.94; H, 5.70; N, 14.66; O, 6.70. Found: C, 72.74; H, 5.90; N, 14.86; O, 6.50.

3-(2-((16E)-4-Benzylidene-4,5-dihydro-5 -oxo-2- phenylimidazol-1-yl)ethyl)-6,8-dibromo-2-methylquinazolin-4(3*H*)-one (RS10)



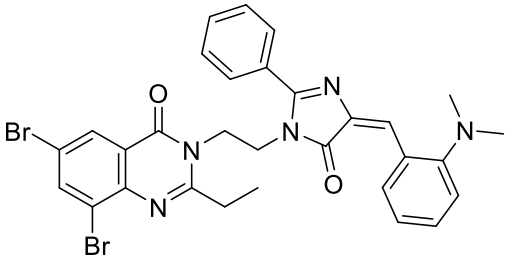
M.W. 592.28; M.F. $C_{27}H_{20}Br_2N_4O_2$;.Yield 79% (13.8 g); M.P. 315^{o}C; R_f 0.48(CH_3Cl); IR (KBr) cm^{-1}:3322 (Ar-NH), 3013(Ar), 1650(C=O),1520 (CH); ^{1}H NMR ($CDCl_3$): 0.85 (s, 3H, CH_3), 3.6 , 3.8 (t, 2H, CH_2), 7.1(d, 1H, =CH-) 7.21-7.9 (m, 15H, heterocyc) ; EI-MS (70 eV) [m/z, %] : 77, 79, 125, 275, 300, 314, 342, 573, 590, 594, 595; Elem.Anal. Calc'd for $C_{27}H_{20}Br_2N_4O_2$: C, 54.75; H, 3.40; Br, 26.98; N, 9.46; O, 5.40. Found: C, 54.45; H, 3.70; Br, 26.98; N, 9.26; O, 5.60.

3-(2-((16E)-4-(2-Hydroxybenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-6,8-dibromo-2-methylquinazolin-4(3*H*)-one(RS 13)



M.W. 608.28; M.F. $C_{27}H_{20}Br_2N_4O_3$; .Yield 84% (12.85 g); M.P. 301 ^{0}C; R_f 0.46; IR (KBr cm^{-1}): 3323 (Ar-NH), 3350 (Ar-H), 3013 (Ar)1650(C=O), 1520 (Lactone); Elem. Anal. Calc'd for $C_{27}H_{20}Br_2N_4O_3$: C, 53.31; H, 3.31; Br, 26.57; N, 9.21; O, 7.89. Found: C, 53.11; H, 3.51; Br, 26.47, N, 9.01; O, 7.89.

3-(2-((16E)-4-(2-(Dimethylamino) benzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-6,8-dibromo-2-methylquinazolin-4(3*H*)-one (RS 16):



M.W. 635.35; M.F. $C_{29}H_{25}Br_2N_5O_2$; Yield 78% (12.88 g); M.P. 307 ^{0}C; R_f 0.48 (CH_3Cl); IR (KBr cm^{-1}): 3333 (Ar-NH), 3013 (Ar-H), 3013 (Ar), 1638(C=O), 1520 (Lactone); Elem.Anal. Calc'd for $C_{29}H_{25}Br_2N_5O_2$:C, 54.82; H, 3.97; Br, 25.15; N, 11.02; O, 5.04. Found: C, 54.62; H, 4.17; Br, 25.05; N, 11.10; O, 5.06.

General procedure for the synthesis of 2-phenyl-4H-benzo[d] [1, 3]oxazin- 4-one (1B-I):

Dibromo/Unsubs.anthranilic acid (0.1 mol) was dissolved in 50 mL dry pyridine. To this, solution of benzoyl chloride (0.3 mol) was added dropwise with constant stirring. While adding temperature was maintained at 15^{o}C. The reaction mixture was cooled when the addition of benzoyl chloride was completed; the resultant reaction mixture was treated with 10% $NaHCO_3$ solution (15 mL). After the effervecessence ceased, the reaction mixture was filtered and washed repeatedly with water to remove inorganic materials. The crude resulting product was recrystallized from absolute ethanol.

[X=H, R= C_6H_5] Yield 81%; M.P. 187^{0}C: IR (KBr) cm^{-1}:3275 (NH), 3021(Ar), 1653 C=O); ^{1}H NMR ($CDCl_3$): δ 7.14-7.25(m, 5H, Ar), 7.5-8.1 (m, 4H, heterocyc); Anal. Calc'd for $C_{14}H_9NO_2$: C, 75.33; H, 4.06; N, 6.27; O, 14.33. Found: C, 75.23; H, 4.16; N, 6.17; O, 14.44.

[X=Br_2, R= C_6H_5] Yield 80%; M.P. 189^{0}C; IR (KBr) cm^{-1}:3021(Ar), 1657(C=O);^{1}HNMR ($CDCl_3$): δ7.13-7.26 (m, 5H, Ar), 7.5-8.5 (m, 4H, heterocyc); Anal. Calc'd for $C_9H_5Br_2NO_2$: C, 33.89; H, 1.58; Br, 50.10; N, 4.39; O, 10.03. Found: C, 33.90; H, 1.57; Br, 50.12; N, 4.38; O, 10.02.

General procedure for the synthesis of 3-(2-((16E)-4-benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-2-phenylquinazolin-4(3H)-one (1B-V):

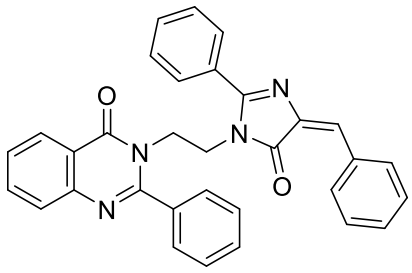
6, 8-Dibromo- 2-phenyl-4*H*-benzo[d](1,3)oxazin-4-one (2) (0.1 mol) was mixed with (Z)-3-(2-aminoethyl)-5-substituted [H/OH/N(CH_3)$_2$]benzylidene-2-phenyl imida-zolidin-4-one (6) (0.1 mol) in glacial acetic acid and refluxed under anhydrous conditions for 8 h. The reaction mixture was cooled to room temperature and the mixture was poured into crushed ice. The crude product obtained was recrystallized from absolute ethanol.

[RS1 X=*H*, *R*= C_6H_5, *R'*=*H*] Yield 72 %; M.P. 312^{0}C; IR (KBr) cm^{-1}:3120 (Ar-NH),3014 (Ar), 1658(C=O),1527 (CH); ^{1}H NMR ($CDCl_3$): δ 0.9 (s, 3H, CH_3), 3.26 ,3.46 (t, 2H, CH_2), 7.64(d, 1H, =CH-) 7.21-7.9 (m, 15H, heterocyc); MS(m/z): 434; Anal. Calc'd for $C_{32}H_2N_4O_2$: C, 74.64; H, 5.10; N, 12.89; O, 7.36. Found: C, 74.60; H, 5.14; N, 12.87; O, 7.38.

[RS 11 *X*=*Br*, *R*= C_6H_5, *R'*=*H*] Yield 79%; M.P 297^{0}C; IR (KBr) cm^{-1}:3365 (Ar-NH),3081(Ar), 1710 (C=O),1534 (CH); ^{1}H NMR ($CDCl_3$): δ 3.6 ,3.9 (t, 2H, CH_2), 7.4-7.9 (m, 4H,Ar) 7.29-7.62(m, 5H, Ar), 7.14-7.3 (m, 5H, Ar); MS(m/z): 654; Anal. Calc'd for $C_{32}H_{22}Br_2N_4O_2$: C, 58.74; H, 3.39; Br, 24.42; N, 8.56; O, 4.89 Found: C, 58.54; H, 3.59; Br, 24.22; N, 8.56; O, 5.09.

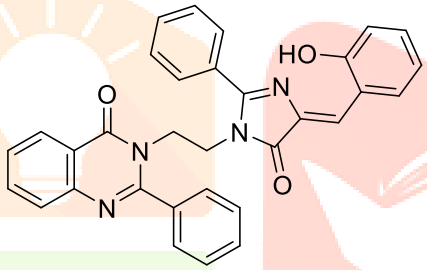
Compounds profile:

3-(2-((16E)-4-Benzylidene-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-2-phenyl quinazolin-4(3*H*)-one (RS2)



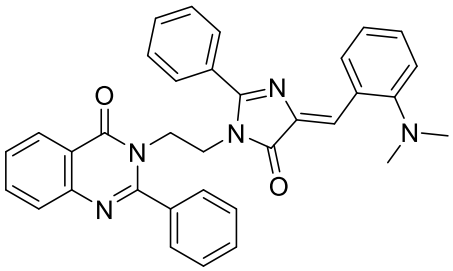
M.W. 496.56; M.F. $C_{32}H_{24}N_4O_2$;. Yield 72% (3.25 g); M.P. 314^{o}C; R_f 0.49; IR (KBr) cm^{-1}:3120 (Ar-NH), 3014(Ar), 1658(C=O),1527 (CH); ^{1}H NMR ($CDCl_3$): 0.85 (s, 3H, CH_3), 3.6 , 3.8 (t, 2H, CH_2), 7.64(d, 1H, =CH-); EI-MS (70 eV) [m/z, %] : 77,79,144, 221, 247, 249, 419, 496, 495, 498. Elem. Anal. Calc'd for $C_{32}H_{24}N_4O_2$: C, 57.33; H, 3.31; Br, 23.84 N, 8.16; O, 7.36. Found: C, 57.53; H, 3.11; Br, 23.84; N, 8.16; O, 7.36.

3-(2-((16E)-4-(2-Hydroxybenzylidene)-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl) -2-phenylquinazolin-4(3*H*)-one (RS5)



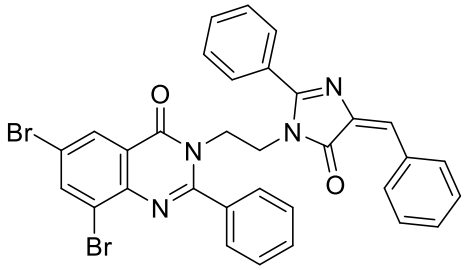
M.W. 512.56; M.F. $C_{32}H_{24}N_4O_3$; Yield 79% (3.48 g); M.P. 317 ^{0}C; R_f 0.48; IR (KBr cm^{-1}):3380 (Ar-OH), 3010(Ar-H), 3013(Ar)1657(C=O), 1521 (Lactone). Elem. Anal. Calc'd for $C_{32}H_{24}N_4O_3$: C, 74.99; H, 4.72; N, 10.93; O, 9.36. Found: C, 74.79; H, 4.92; N, 10.63; O, 9.66.

3-(2-((16E)-4-(2-(Dimethylamino)benzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol 1-yl) ethyl)-2-phenylquinazolin-4(3*H*)-one (RS8)



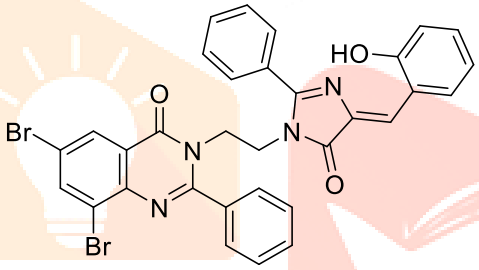
M.W. 539.63; M.F. $C_{34}H_{29}N_5O_2$;Yield 79% (3.3 g); M.P. 314^{0}C; R_f 0.51; IR (KBr cm^{-1}): 3322 (Ar-NH), 3013(Ar), 1656(C=O), 1523 (Lactone); Elem. Anal. Calc'd for $C_{34}H_{29}N_5O_2$: C, 75.68; H, 5.42; N, 12.98; O, 5.93. Found: C, 75.48; H, 5.63; N, 12.78; O,6.13.

3-(2-((16E)-4-Benzylidene-4,5-dihydro-5-oxo-2- phenylimidazol-1 yl)ethyl) 6,8-dibromo-2-phenylquinazolin-4(3*H*)-one (RS11)



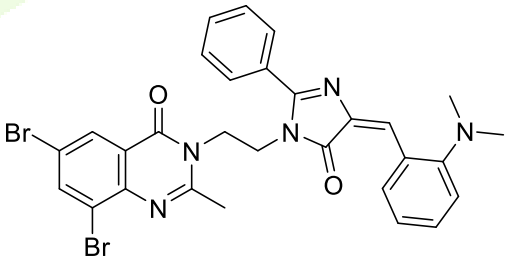
M.W.654; M.F. $C_{32}H_{22}Br_2N_4O_2$; Yield 94% (14.9 g); M.P. 297 ^{0}C; R_f 0.44; IR (KBr cm^{-1}): 3332 (Ar-NH), 3012(Ar), 1652(C=O), 1522(Lactone); Elem. Anal. Calc'd for $C_{32}H_{22}Br_2N_4O_2$: C, 58.74; H, 3.39; Br, 24.42; N, 8.56; O, 4.89. Found: C, 58.54; H, 3.59; Br, 24.22; N, 8.36; O, 5.09.

3-(2-((16E)-4-(2-Hydroxybenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-6,8-dibromo-2-phenylquinazolin-4(3*H*)-one (RS 14)



M.W. 670.35; M.F. $C_{32}H_{22}Br_2N_4O_3$;Yield 94% (14.6 g); M.P. 302^{0}C ; R_f 0.49; IR (KBr cm^{-1}): 3332 (Ar-NH), 3012(Ar), 1652(C=O), 1522(Lactone). Elem. Anal. Calc'd for $C_{32}H_{22}Br_2N_4O_3$: C, 57.33; H, 3.31; Br, 23.84; N, 8.36; O, 7.16. Found: C, 5753; H, 3.11; Br, 23.84; N, 8.16; O, 7.36.

3-(2-((16E)-4-(2-(Dimethylamino)benzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol 1-yl)ethyl)-6,8-dibromo-2-methylquinazolin -4(3*H*)-one (RS17)



M.W. 635.35; M.F. $C_{29}H_{25}Br_2N_5O_2$; .Yield 94% (13.97 g); M.P. 307^{0}C; R_f 0.48; IR (KBr cm^{-1}): 3321 (Ar-NH), 3011(Ar), 1658(C=O), 1522(Lactone). Elem. Anal. Calc'd for $C_{29}H_{25}Br_2N_5O_2$: C, 54.82; H, 3.97; Br, 25.15; N, 11.02; O, 5.04. Found: C, 54.62; H, 4.17; Br, 25.05; N, 11.12; O, 5.04.

General procedure for the preparation of 2-(chloromethyl)-4H-benzo[d][1,3]oxazin-4-one(IC-I):

6,8-Dibromo /Unsubs.anthranilic acid **(**0.1 mol**)** was taken in dry benzene (60 mL), warmed and stirred to get a homogenous suspension. The mixture was cooled and bromoacetyl bromide (0.12 mol) was added. The reaction mixture was shaken for 2 h. The solvent along with the unreacted chloroacetyl chloride was distilled off under reduced pressure and then 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 recrystallization from a mixture of chloroform and ethyl acetate.

6,8 Dibromo/ unsubs.chloroacetyl anthranilic acid **(**0.01 mol**)** was taken in a dry round bottomed flask and acetic anhydride (0.02 mol) was added. The reaction mixture was refluxed for one hour under anhydrous condition. Excess of acetic anhydride was distilled off to the possible extent and on cooling, the reaction mixture gets solidified. The resultant product was dried and purified by recrystallization from ethanol.

[IC-Ia X=H, R= CH_2Cl] Yield 84%; M.P182^{0}C; IR (KBr) cm^{-1}:3265(NH), 3010(Ar), 1657(C=O), 1512(CH_2); ^{1}H NMR ($CDCl_3$): δ 7.5-8.1(m, 4H, Ar), 3.4 (s, 2H, CH_2); Anal. Calc'd for $C_9H_6ClNO_2$: C, 55.26; H, 3.09; Cl, 18.13; N, 7.16; O, 16.36. Found: C, 55.22; H, 3.13; Cl, 18.17; N, 7.14; O, 16.34. **[IC-Ib X=Br_2, R= CH_2Cl]** Yield 82%; M.P. 191^{0}C; IR (KBr) cm^{-1}: 3266 (NH), 3023 (Ar), 1653(C=O); ^{1}H NMR ($CDCl_3$): δ7.9-8.1(m, 2H, Ar), 3.4 (s, 2H, CH_2); Anal. Calc'd for $C_9H_4Br_2ClNO_2$: C, 30.59; H, 1.14; Br, 45.22; Cl, 10.03; N, 3.96; O, 9.05. Found: C, 30.60; H, 1.13; Br, 45.21; Cl, 10.04; N, 3.98; O, 9.03.

General procedure for the synthesis of3-(2-((16Z)-4-subs. benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)- 6,8-dibromo / -2-bromomethyl quinazolin-4(3H)-one (1C-V) (RS 3):

2-(Bromomethyl)-4*H*-benzo[d][1,3]oxazin-4-one (0.1 mol) was mixed with (4Z)-1-(2-aminoethyl)-4- H/ OH/ CH_2Cl benzylidene-2-phenyl-1*H*-imidazol-5(4*H*)-one (0.1 mol) in glacial acetic acid and refluxed under anhydrous conditions for 8 h. The reaction mixture was cooled to room

temperature and the mixture was poured into crushed ice. The crude product was recrystallized from absolute ethanol.

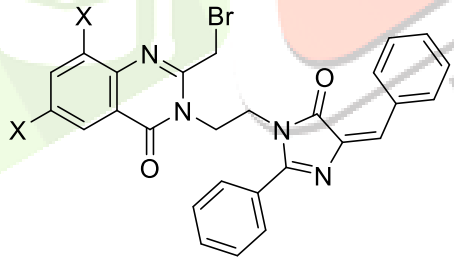
[RS 3 X=*H*, *R*= *CH_2Cl*, *R'=H*] Yield 79 %; M.P 315^{0}C; IR (KBr) cm^{-1}:3279 (Ar-NH),2925 (Ar), 1683 (C=O),1535 (CH); ^{1}H NMR ($CDCl_3$): δ3.7,3.9, 4.2(t, 2H, CH_2),), 7.64 (d, 1H, =CH-) 7.21-7.9 (m, 15H, heterocyc), 7.14-7.30 (m, 4H, Ar); MS(m/z): 468; Anal. Calc'd for $C_{27}H_{21}ClN_4O_2$: C, 69.15; H, 4.51; Cl, 7.56; N, 11.95; O, 6.82. Found: C, 69.17; H, 4.49; Cl, 7.60; N, 11.93; O, 6.80.

[RS 12 X=*Br*, *R*= *CH_2Cl*, *R'=H*] Yield 68%; M.P 295^{0}C; IR (KBr) cm^{-1}:3122 (Ar-NH),3017 (Ar), 1653 (C=O),1524 (CH); ^{1}H NMR ($CDCl_3$): δ 3.26 ,3.46, 4.2 (t, 2H, CH_2),

7.64 (d, 1H, =CH-) 7.14-7.3 (m, 13H, heterocyc) 7.8, 8.1 (m, 2H,Br-Ar); MS(m/z): 626;
Anal. Calc'd for $C_{27}H_{19}Br_2ClN_4O_2$: C, 51.74; H, 3.06; Br, 25.50; Cl, 5.66; N, 8.94; O, 5.11. Found: C, 51.70; H, 3.10; Br, 25.52; Cl, 5.64; N, 8.96; O, 5.09.

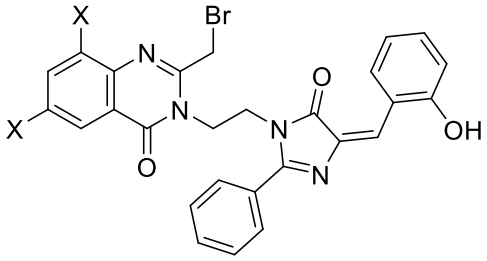
Compounds profile:

3-(2-((16E)-4-Benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-2-(bromo-methyl)quinazolin-4(3*H*)-one (RS 3)



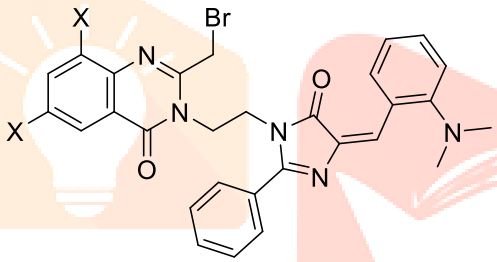
M.W. 468.93; M.F. $C_{27}H_{21}ClN_4O_2$; Yield 72 % (3.45 g); M.P 315 ^{0}C; R_f 0.49 (CH_3Cl); IR (KBr) cm^{-1}:3279 (Ar-NH), 2925 (Ar), 1683(C=O),1535 (CH); ^{1}H NMR ($CDCl_3$): δ3.7, 3.9, 4.2(t, 2H, CH_2),), 7.64(d, 1H, =CH-) 7.21-7.9 (m, 15H, heterocyc), 7.14-7.30 (m, 4H, Ar); MS (m/z): 468.93; Anal. Calc'd for $C_{27}H_{21}ClN_4O_2$: C, 69.15; H, 4.51; Cl, 7.56; N, 11.95; O, 6.82. Found: C, 69.17; H, 4.49; Cl, 7.60; N, 11.93; O, 6.80.

3-(2-((16E)-4-(2-Hydroxybenzylidene)-4, 5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-2-(bromomethyl) quinazolin-4(3*H*)-one (RS 6)



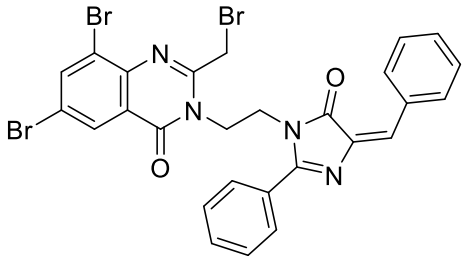
M.W. 484.93; M.F. $C_{27}H_21ClN_4O_3$; Yield 75 % (4.65 g); M.P 318 ^{0}C; R_f 0.49 (CH_3Cl);IR (KBr) cm^{-1}: 3120 (Ar-NH), 3014(Ar), 1658(C=O), 1527 (CH) ; Anal. Calc'd for $C_{27}H_21ClN_4O_3$: C, 66.87; H, 4.36; Cl, 7.31; N, 11.55; O, 9.92 Found: C, 66.77; H, 4.46; Cl, 7.51; N, 11.55;O, 9.90.

3-(2-((16E)-4-(2-(Dimethylamino) benzylidene)- 4,5-dihydro-5-oxo- phenylimidazol-yl)ethyl)-2-(bromomethyl)quinazolin-4(3*H*)-one (RS 9)



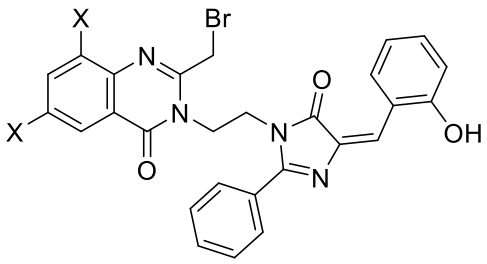
M.W. 512; M.F. $C_{29}H_{26}ClN_5O_2$;Yield 74 % (3.25 g); M.P 316 ^{0}C; R_f 0.49 (CH_3Cl);IR (KBr) cm^{-1}: 3122 (Ar-NH), 3012 (Ar), 1653(C=O),1525 (CH); Anal. Calc'd for$C_{29}H_{26}ClN_5O_2$: C, 69.15; H, 4.51; Cl, 7.56; N, 11.95; O, 6.82. Found: C, 69.17; H, 4.49; Cl, 7.60; N, 11.93 ; O, 6.80.

3-(2-((16E)-4-Benzylidene-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl)ethyl)-6,8-dibromo-2-(bromomethyl)quinazolin-4(3*H*)-one (RS 12)



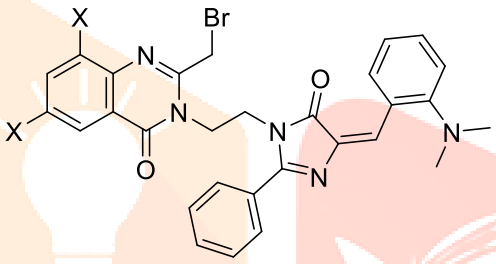
M.W. 623.96; M.F. $C_{27}H_{19}Br_2ClN_4O_2$;Yield 68% (11.3 g); M.P 295 ^{0}C; R_f 0.47 (CH_3Cl); IR (KBr) cm^{-1}: 3127 (Ar-NH), 3010 (Ar), 1650 (C=O),1520 (CH); Anal. Calc'd for $C_{27}H_{19}Br_2ClN_4O_2$: C, 51.74; H, 3.06; Br, 25.50; Cl, 5.66; N, 8.94; O, 5.11. Found: C, 51.54; H, 3.26; Br, 25.40; Cl, 5.76; N, 8.84; O, 5.21.

3-(2-((16E)-4-(2-Hydroxybenzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol-1-yl) ethyl)-6,8-dibromo-2-(bromoomethyl) quinazolin-4(3*H*)-one (RS 15)



M.W. 642.73; M.F. $C_{27}H_{19}Br_2ClN_4O_3$; Yield 72% (11.9 g); M.P. 304 ^{0}C; R_f 0.49; IR (KBr) cm^{-1}: 3120 (Ar-NH), 3014(Ar), 1658(C=O), 1527 (CH); Anal. Calc'd for $C_{27}H_{19}Br_2ClN_4O_3$: C, 50.46; H, 2.98; Br, 24.86; Cl, 5.52; N, 8.72; O, 7.47. Found: C, 50.40; H, 3.02; Br, 24.80; Cl, 5.56; N, 8.70; O, 7.49.

3-(2-((16E)-4-(2-(Dimethylamino) benzylidene)-4,5-dihydro-5-oxo-2-phenylimidazol- 1-yl)ethyl)-6,8-dibromo-2-(bromomethyl)quinazolin-4(3*H*)-one (RS 18)

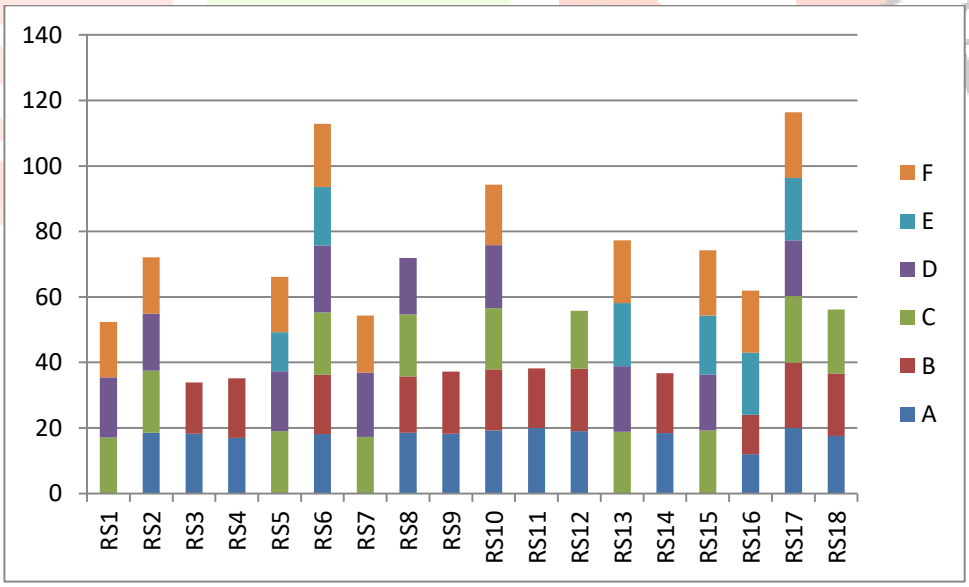


M.W. 669.79; M.F. $C_{29}H_{24}Br_2ClN_5O_2$;. Yield 72% (11.2 g); M.P. 307^{0}C; R_f 0.49; IR (KBr) cm^{-1}: 3120 (Ar-NH), 3014(Ar), 1658(C=O), 1527 (CH); Anal. Calc'd for $C_{29}H_{24}Br_2ClN_5O_2$: C, 52.00; H, 3.61; Br, 23.86; Cl, 5.29; N, 10.46; O, 4.78. Found: C,52.20; H, 3.41; Br, 23.76; Cl, 5.39; N, 10.56; O, 4.68.

4. Biological evolution

COMPOUND	MICROORGANISM					
	A	B	C	D	E	F
RS1	- †	-†	17.08	18.32	- †	16.97
RS2	18.56	-†	18.97	17.33	-†	17.22
RS3	18.25	15.67	-†	-†	-†	-†
RS4	16.96	18.24	-†	-†	-†	-†
RS5	-†	-†	19.03	18.26	11.94	16.94
RS6	18.11	18.14	19.05	20.38	17.94	19.24
RS7	-†	-†	17.25	19.64	-†	17.43
RS8	18.50	17.21	19.00	17.21	-†	-†
RS9	18.24	19.00	-†	-†	-†	-†
RS10	19.25	18.60	18.71	19.22	-†	18.53
RS11	19.97	18.24	-†	-†	-†	-†
RS12	19.05	19.05	17.64	-†	-†	-†
RS13	-†	-†	18.84	20.06	19.22	19.14
RS14	18.45	18.24	-†	-†	-†	-†
RS15	-†	-†	19.24	17.06	18.05	19.94
RS16	11.94	12.05	-†	-†	18.94	19.03
RS17	20.05	19.87	20.31	17.08	19.04	20.06
RS18	17.56	18.96	19.65	-†	-†	-†

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



5. ADME study

Product code	$CaCo_2$	BBB+	HERG	Plogs	AMES Toxicity	Carcinogenicity
RS1	0.5561	0.9326	0.7196	-3.1932	0.5827	0.6479
RS2	0.5094	0.9562	0.8207	-2.9303	0.5659	0.6300
RS3	0.5910	0.9272	0.7184	-3.5599	0.5959	0.6439
RS4	0.5911	0.5399	0.8135	-3.1493	0.5576	0.6205
RS5	0.5689	0.7241	0.8860	-2.8669	0.5591	0.6086
RS6	0.5870	0.5827	0.8128	-3.5009	0.5907	0.6155
RS7	0.5528	0.9144	0.6608	-3.1775	0.5496	0.6336
RS8	0.5169	0.9053	0.7684	-2.7999	0.5000	0.6078
RS9	0.5551	0.8776	0.6477	-3.3335	0.5296	0.6248
RS10	0.5705	0.8982	0.7389	-3.5964	0.5950	0.6409
RS11	0.5478	0.9362	0.8341	-3.4374	0.6036	0.6328
RS12	0.5910	0.9272	0.7184	-3.5599	0.5959	0.6439
RS13	0.5733	0.5482	0.8281	-3.5366	0.5744	0.6075
RS14	0.5643	0.6458	0.8953	-3.3648	0.6007	0.6020
RS15	0.5574	0.5875	0.7503	-3.3239	0.5744	0.6119
RS16	0.5675	0.8821	0.6857	-3.4841	0.5462	0.6209
RS17	0.5122	0.8841	0.8172	-3.2962	0.5581	0.6067
RS18	0.5658	0.8778	0.6306	-3.3787	0.5316	0.6159

Docking Study

Compound ID	PDB1Gos_1	PDB1Gos_2
RS1	-57.12	-53.867
RS2	-72.941	-69.759
RS3	-63.799	-67.203
RS4	-72.109	-67.981
RS5	-69.517	-68.617
RS6	-60.753	-63.906
RS7	-59.419	-59.568
RS8	-68.790	-68.418
RS9	-66.338	-65.866
RS10	-59.470	-66.386
RS11	-62.616	-66.222
RS12	-58.567	-55.661
RS13	-67.470	-69.202
RS14	-54.683	-51.069
RS15	-58.932	-56.313
RS16	-60.811	-61.389
RS17	-65.544	-67.629
RS18	-72.478	-71.870