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SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NOVEL QUINAZOLINE DERIVATIVES AS ACID PUMP ANTAGONISTS

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ABSTRACT: Gastric acid hypersecretion is a major cause of gastric complications like hypergastrinemia, hyperhistaminemia and Zollinger-Ellison syndrome. Out of various drug treatments used, H_2-receptor antagonists possess some limitations, such as the development of tolerance when used for a long period, having a short duration of action, and no complete inhibition of acid secretion in response to a meal. In the case of PPIs they are showing the slow onset of action, short half-life, incomplete acid suppression, and differences in effectiveness in patients due to CYP_2C_{19} (Cytochrome P_2C_{19}) metabolism To overcome these limitations, other alternative better therapeutic agents should be focused. Potassium-competitive acid blockers (P-CABs) or Acid pump antagonists (APAs) are new H^+/K^+-ATPase inhibitors that can exhibit almost complete inhibition of gastric acid secretion through reversible and K^+-competitive inhibition of the enzyme. In our research work, We are reporting the synthetic methods of novel Quinazoline derivatives and their preliminary gastric acid secretion suppression action. Proposed compounds belong to two Series of N-((3-Benzamido-4-oxo-3, 4-dihydroquinazolin 2-yl) methyl)-N- (substituted) phenyl-benzamides and were prepared, and structural was confirmed using different spectroscopic methods including Infrared spectroscopy, mass spectroscopy, and ^{1}HNMR. The primary antisecretory activity was evaluated by an *in-vitro* method using an isolated Hog gastric H^+/K^+-ATPase enzyme. All the compounds were found to be potent inhibitors of Isolated Hog stomach H^+/K^+-ATPase enzyme with variant efficacy, and amongst them, compound LMDP-15 was emerged out as a potent inhibitor with IC_{50} 7 µM. The proposed novel series of N-((3-Benzamido-4-oxo-3, 4-dihydroquinazolin-2-yl) methyl)-N-(substituted) phenylbenzamides (1) provides active and reversible inhibitors of the gastric H^+/K^+-ATPase.

INTRODUCTION:

Complications of High Gastric Acid Secretion: Hyper acid secretion is the root cause behind hypergastrinemia, hyperhistaminemia, Zollinger-Ellison syndrome, and other common and chronic gastric complications.

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Therefore, acid-suppressive therapy is a promising way to treat and cure such conditions, and many patients with these diseases also benefited by acid-suppressive therapy [1].

Choice of Treatment of High Gastric Acid Secretion: H^+/K^+ pump-targeted inhibitors are choice of drug as acid-suppressive agents, and there are two groups of these agents: covalent inhibitors (proton pump inhibitors, PPIs) and second new class of reversible inhibitors (acid pump antagonists, APAs or potassium competitive acid blockers, PCABs). The covalent inhibitors form a covalent bond with enzymes after activation in

acidic envirnment of gastric juice. Their structures are substituted pyridinemethylsulfinyl benzimidazoles. The reversible inhibitors are weak basic molecules and get protonated in gastric juice and bind with enzyme reversible at K^+ binding site [2].

Proton Pump Inhibitors (PPIs): Proton pump inhibitors (PPIs) are Conventional PPIs is a form of a prodrug, which must be activated in acidic pH, the PPI should be reached in parietal cells in which acid secretion must be activated after the meal. Considering the time taken for this process, 30 minutes before the meal is required [2]. The currently available PPIs require 4–5 consecutive days of therapy to achieve máximum activity due to the chemical structures and irreversible inhibition of H^+/K^+ ATPase. Even though sustained acid inhibition throughout 24 h period is not achieved, even when taken twice daily, nighttime acid secretion may cause symptoms in some patients. Therefore, it is needed to search for many novel strategies to address such limitations [3, 4, 21].

Reversible Inhibitors: Reversible H^+/K^+ ATPase inhibitors are K^+-competitive inhibitors in contrast to conventional PPIs. In the early 1980s, an imidazopyridine compound, SCH28080 of this class, was developed by Schering-Plough that inhibited gastric acid secretion in animals and humans in response to histamine, high K^+, methacholine and cyclic AMP. Kinetic studies indicated that the inhibition of H^+/K^+-ATPase was competitive with respect to K^+; however, clinical development of SCH28080 was stopped because repeated administration caused hepatic toxicity [5, 6, 7]. Revaprazan[10] was the first P-CAB introduced in the market of Korea. Many new reversible H^+/K^+ ATPase inhibitors such as Imidazopyridine [8] derivatives (*e.g.,* Linaprazan and BY841) [8, 13], imidazonaphthyridine derivatives (*e.g.,* Soraprazan) [11], imidazothienopyridines *(e.g.,* SPI-447) [11], quinolone derivatives (*e.g.,* SK&F96067 and SK&F97574) [9, 19], pyrrolopyridazine derivatives (*e.g.,* CS-526) [11], pyrimidine derivatives (*e.g.,* Revaprazan) [10] and pyrrole derivatives (*e.g.,* Vonoprazan (TAK-438) [12, 13, 15] had been investigated till now, However, in comparison with other agents Vonoprazan's absorption speed is rapid and can be taken regardless of meal. The T1/2 for Vonoprazan is 9 h compared to conventional PPs with T1/2 of 2 h [14, 15]. In 2014, Vonoprazan was developed and got approval in Japan, it is chemically different has higher pKa value, there is rapid onset of action and long duration of action as compared to other P-CABs[17, 19, 20].

The pKa values of SCH28080, Linaprazan and Vonoprazan are 5.6[6], 6.1[17], and 9.3[14]. Linaprazan inhibited acid secretion stimulated by K^+ with IC_{50} of 1.0 μM at pH 7.4, but was 8 times more potent at pH 6.4. They are weak bases, and the theoretical percent of protonated linaprazan is about 33% at pH 6.4 and less than 5% at pH 7.4. The inhibitory effect of linaprazan is also weaker in neutral conditions (IC_{50}=0.17 μM at pH 6.7 *vs.* IC_{50}=2.1μM at pH 7.2 [16, 17] suggesting that protonated forms of P-CABs inhibit H^+/K^+-ATPase. Linaprazan exerts high inhibition in ion-tight vesicles than in ion-leaky vesicles, therefore, it concentrates in regions of low pH owing to weak basic nature and produce action at luminal site.[11] vonoprazan's pKa value is 9.3, and protonated instantly and exert fast and potent inhibition (IC_{50}=19 nM at pH 6.5, IC_{50}=28 nM at pH 7.5).[15] As protonated derivatives can not cross membrane due to lack of lipophilicity, they tend to concentrate in the acidic secretory canaliculi of parietal cells and produce faster action of H^+, K^+-ATPase inhibition compared to conventional PPs were was the first P-CAB introduced in market of Korea.

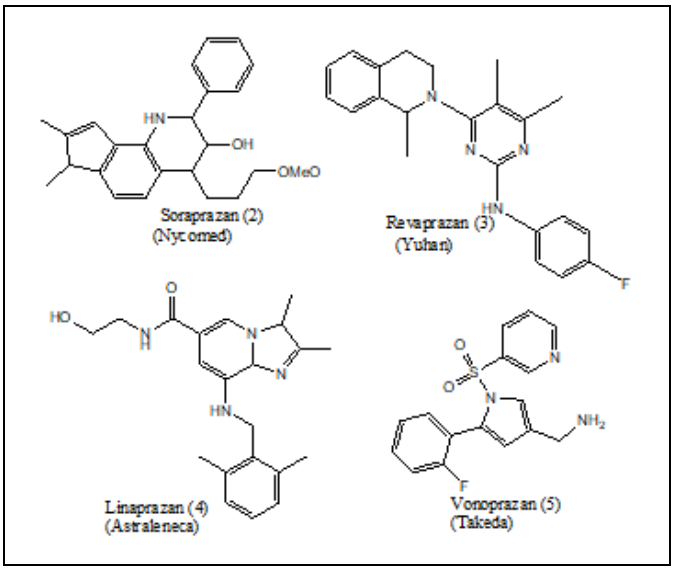

FIG. 1: EXAMPLES OF PCABs

We have proposed and synthesized a series of Quinazoline derivatives (1); they are weak basic compounds with the presence of aliphatic amines like other Potassium competitive acid blockers

Linaprazan (2), Vanaprazan (3), Soraprazan (4), and Revaprazan (5). Here, we have replaced Benzpiperidine ring of revaprazan and soraprazan with Quinazoline ring. The aliphatic amine undergoes protonation at acidic pH and resulted protonated derivatives can compete with potassium at binding site of H^+/K^+ ATPase enzyme to inhibit gastric acid secretion in a reversible manner. In addition to this the proposed synthesized Quinazoline derivatives are showing pKa values in range of 5 to 8, which is also parallel to the PKA value of Linaprazan, Vanaprazan, Soraprazan, and revaprazan.

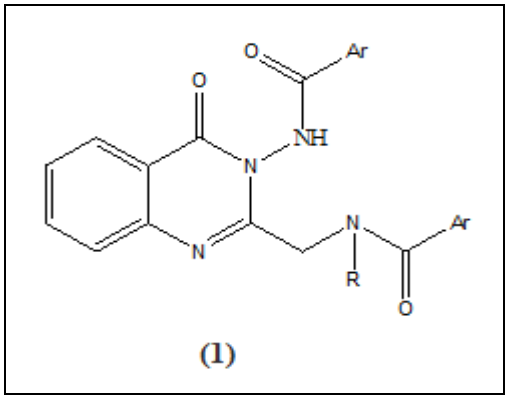

FIG. 2: DESIGNED SERIES STRUCTURE

MATERIALS AND METHODS: All compounds' IR spectra was recorded using FTIR-8400s SHIMADZU Spectrophotometer using KBr. Mass spectra were obtained on LCMS 2010 EV SHIMADZU Mass spectrometer. ^{1}HNMR spectra were obtained in DMSO-d_6 on BRUKER Advance-II 400 MHz instrument and chemical shift were measured as parts per million downfield from tetramethylsilane (TMS) as internal standard. ^{13}C NMR spectra were obtained in DMSO-d_6 on BRUKER Avance-II 400 MHz instrument and chemical shifts were measured in parts per million (ppm) using internal standard tetramethylsilane (TMS).

Synthesis of N-Chloroacetyl methyl anthranilate (7): A solution of Chloroacetyl chloride (12.5 ml, 0.15 mol) was added dropwise to a solution of Methyl anthranilate (20 ml, 0.15 mol) in Glacial acetic acid (100 ml) and temperature was maintained at 5-10 °C. Then the reaction mixture was stirred for 30 min. The progress of the reaction was monitored by thin layer chromatography. After attaining room temperature, the reaction mixture was slowly poured into 100 ml ice water. The white solid product was separated out which was washed successively with water until the filtrate became neutral; the product was dried and recrystallized from hexane [22]. M.P.: 90-92 °C.

Synthesis of N-(substituted phenyl)-aminoacetyl methyl anthranilate (8): N-Chloroacetyl methyl anthranilate (7) (1 gm, 0.0044mol), Aromatic amine (0.0066 mol), Triethylamine (0.6 ml, 0.0044 mol) and dioxane was taken in a round bottom flask and the mixture was refluxed for 8 hours. The progress of the reaction was monitored by thin-layer chromatography. After completion of the reaction, it was allowed to cool to room temperature and slowly added to 100 ml ice water and stirred continuously with the help of a glass rod for 15 minutes. The solid product was then filtered and dried [22].

Synthesis of 3-amino-2-(substituted phenyl)-amino methyl- quinazolin-4(3*H*)-one (9): N-(Substituted phenyl)-aminoacetyl methyl anthranilate (8) (0.0052mol) was mixed with Hydrazine hydrate (80% v/v) (1 ml, 0.046 mol) in absolute alcohol (20 ml) and then refluxed for 6-8 hours. The progress of the reaction was monitored by thin-layer chromatography. When there is the absence of starting material on thin-layer chromatography, the heating was stopped, and the reaction mixture was allowed to cool to room temperature. The solid crystalline product generated when standing for 15 minutes was filtered and washed properly with water and, after drying, recrystallized from absolute alcohol [22].

Synthesis of N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin -2-yl) methyl)-N-(substituted phenyl) benzamide (1) (Series-A): In round bottom flask 3-Amino-2-(substituted phenyl)-aminomethyl-quinazolin-4(3*H*)-one (9) (0.0018), Sodium hydroxide (0.14 gm, 0.0036 mol) and benzoyl chloride (0.23 ml, 0.0019) were taken in dioxane (20 ml) and mixed properly. Then the reaction mixture was refluxed for half hour. The progress of the reaction was monitored by thin-layer chromatography. The reaction mixture was allowed to cool to attain room temperature. The solid product formed was separated by filtration, washed successively with water, and then dried. The product was purified by recrystallization from ethyl acetate [22].

Synthesis of N-((3-4-Nitrobenzamido-4-oxo-3, 4-dihydroquinazolin-2-yl) methyl)-N-(substituted phenyl)-4- nitrobenzamide (1) (Series-B): In round bottom flask, 3-Amino-2-(substituted phenyl)-amino methyl-quinazolin-4(3h)-one (0.0018), Sodium hydroxide (0.14 gm, 0.0036 mol) and 4-nitro-benzoyl chloride (0.23 ml, 0.0019) and dioxane (20 ml) were taken and refluxed for half-hour. The progress of the reaction was monitored by thin-layer chromatography. The reaction mixture was allowed to cool to attain room temperature. The solid product formed was separated by filtration, washed with water, and then dried. The obtained product was purified by recrystallization from Ethyl acetate [22].

Spectral Data:

Synthesis of N-((3-benzamido-4-oxo-3, 4-dihydro-quinazolin-2-yl)methyl)-N–(pheny) benzamide (LMDP-1): Mass spectrum (in methanol) (m/z): 475 (M^{+1}), 473 (M-1). I.R (in KBr, cm^{-1}): 3201 (-NH stretching of CONH), 1697 (C=O stretching of CONH), 3000 (C-H stretching aliphatic), 3049 (C-H stretching aromatic), 1398 (C-H bending aliphatic) ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.6 (s, 1H, NHCO (D_2O exchangeable), δ 3.6 (s, 2H, CH_2), δ 7.2-7.4 (m, 10H, Ar-H), δ 7.5-7.9 (m, 6H, Ar-H), δ 8.0-8.3 (m, 3H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 53.3, 130.10, 124.6, 128.92, 160.5, 125.06, 133.05, 152.89, 126.41, 131.70, 131.70, 128.63, 128.63, 127.05, 129.5, 119.9, 162.2, 165.18, 124.72, 122.11, 122.11, 142.10, 129.25, 129.25, 140.5, 126.8, 134.7, 139.3, 145.89.

Synthesis of N-((3-Benzamido-4-oxo-3, 4-dihydro-quinazolin-2-yl)methyl)-N–(4-methyl phenyl) benzamide (LMDP-2): Mass spectrum (in methanol) (m/z): 489.4 (M+1), 487.4 (M-1). I.R (in KBr, cm^{-1}), 3193(N-H stretching of CONH), 2930 (C-H stretching Aliphatic), 1394 (C-H bending Aliphatic), 1683 (C=O stretching of CONH). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.6 (s, 1H, NHCO) (D_2O exchangeble), δ 3.6 (s, 2H, CH_2), δ 2.5 (s, 3H, CH_3) , δ 7.O (d, 2H, Ar-H), δ 7.2-7.4 (m, 7H, Ar-H), δ 7.5-7.8 (m, 5H, Ar-H), δ 7.9 (d, 1H, Ar-H), δ 8.1-8.2 (d, 1H, Ar-H), δ 8.1-8.2 (d, 2H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 130.10, 129.55, 132.46, 140.5, 124.6, 127.05, 134.7, 119.9, 125.06, 117.5, 117.5, 131.70, 131.70, 128.92, 139.3, 145.89, 142.10, 129.83, 129.83, 160.5, 21.26, 128.63, 128.63, 152.89, 53.3, 162.2, 133.05, 165.18, 126.41, 126.8.

Synthesis of N-((3-Benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)- N– (4-methoxy pheny) benzamide (LMDP-4): Mass spectrum (in methanol) (m/z): 505.4 (M+1) 503.4 (M-1). I.R (in KBr, cm^{-1}) 3195 (N-H stretching of CONH), 3000 (C-H stretching of Aliphatic), 1695 (C=O stretching of $CONH_2$), 1641 (N-H bending of $CONH_2$), 1450 (-CH_2- bending Aliphatic), 1328 (-CH_3- bending Aliphatic). ^{1}H NMR (DMSO-d_6, 400 MHz): δ11.7(s, 1H, NHCO), δ 3.6 (s, 2H, CH_2), δ 2.5 (s, 3H, OCH_3), δ 6.8 (d, 2H, Ar-H), δ 7.2-7.4(m, 7H, Ar, H), δ 7.6 (q, 3H, Ar-H), δ 7.7 (t, 1H, Ar-H), δ 7.2-7.9 (m, 4H, Ar-H), δ 7.8 (d, 1H, Ar-H), δ 7.9 (t, 1H, Ar-H), δ 8.0 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H), ^{13}C-NMR (DMSO-d_6, δ ppm): 131.70, 131.70, 124.6, 133.05, 152.89, 126.8, 142.10, 127.05, 162.2, 53.3, 156.89, 160.5, 139.3, 140.5, 128.92, 134.7, 128.63, 128.63, 119.9, 126.41, 129.55, 123.65, 123.65, 130.10, 125.06, 145.89, 114.63, 114.63, 55.46, 165.18

Synthesis of N-((3-benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)- N– (2-methoxy pheny) benzamide (LMDP-6): Mass spectrum (in methanol) (m/z): 505.4 (M+1) 503.4 (M-1). I.R (in KBr, cm^{-1}) : 3195 (N-H stretching of CONH), 3000 (C-H Stretching aliphatic, 1427 (-CH_2- bending), 1650 (C=O stretching of $CONH_2$). ^{1}H NMR (DMSO-d_6, 400 MHz): δ11.7(s, H, NHCO), δ 3.6 (s, 2H, CH_2), δ 2.5 (s, 3H, OCH_3), δ 6.8 (d, 2H, Ar-H), δ 7.2-7.4(m, 7H, Ar, H), δ 7.6 (q, 3H, Ar-H), δ 7.7 (t, 1H, Ar-H), δ 7.2-7.9 (m, 4H, Ar-H), δ 7.8 (d, 1H, Ar-H), δ 7.9 (t, 1H, Ar-H), δ 8.0 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H), ^{13}C-NMR (DMSO-d_6, δ ppm): 125.06, 142.10 133.05 128.92 152.89, 114.9, 128.63, 128.63, 127.05, 135.45, 126.41, 160.5, 119.9, 131.70, 131.70, 122.9, 128.63, 128.63, 133.26, 115.4, 53.3, 145.89, 128.45, 128.45, 162.2, 128.92, 123.28, 154.77, 165.18, 55.95

Synthesis of N-((3-Benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)- N– (4-chloro pheny) benzamide (LMDP-7): Mass spectrum (in methanol) (m/z): 509.3 (M+1), 507.3 (M-1) 511.3 (M+2). I.R (in KBr, cm^{-1}): 3274 (N-H stretching of CONH), 3000 (C-H stretching Aliphatic), 1390 (-CH2- bending), 1680 (C=O stretching of $CONH_2$), 1639 (N-H bending of $CONH_2$) ,690 (C-Cl stretching) ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.9 (s, 1H, NHCO) (D_2O exchangeable), δ 4.8 (s, 2H, CH_2), δ 2.5 (s, 3H, OCH_3), δ 6.8 (d, 2H, Ar-H), δ

7.2-7.4 (m, 7H, Ar-H), δ 7.6 (q, 3H, Ar-H), δ 7.7 (t, 1H, Ar-H), δ 7.2-7.9 (m, 4H, Ar-H) , δ 7.8 (d, 1H, Ar-H), δ 7.9 (t, 1H, Ar-H), δ 8.0 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H), 13C-NMR (DMSO-d_6, δ ppm): 128.92, 165.18, 129.18, 142.10, 128.63, 128.63, 128.63, 128.63, 53.1, 125.06, 126.4, 135.45, 128.45, 128.45, 131.70, 131.70, 152.89, 128.92, 160.5, 127.05, 140.5, 133.052, 125.39, 125.39, 162.2, 145.89, 119.9, 129.23, 129.23

Synthesis of N-((3-Benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)- N– (3-chloropheny) benzamide (LMDP-9): Mass spectrum (in methanol) (m/z): 507.3 (M-1), 509.3 (M+1), 511.3 (M+2): I.R (in KBr, cm^{-1}) 3211 (-NH stretching of CONH), 3000 (C-H stretching Aliphatic), 1471 (-CH_2- bending), 1703 (C=O stretching of $CONH_2$), 690 (C-Cl stretching). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.9 (s,1H, NHCO) (D_2O exchangeable), δ 4.8 (s, 2H, CH_2), δ 2.5 (s, 3H, OCH_3), δ 6.8 (d, 2H, Ar-H), δ 7.2-7.4 (m, 7H, Ar-H), δ 7.6 (q, 3H, Ar-H), δ 7.7 (t, 1H, Ar-H), δ 7.2-7.9 (m,4H,Ar-H) , δ 7.8 (d, 1H, Ar-H), δ 7.9 (t, 1H, Ar-H), δ 8.0 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 152.89, 160.5, 142.10, 119.9, 125.06, 125.53, 144.89, 128.63, 128.63, 128.63, 128.63, 133.052,162.2, 130.56, 128.45, 128.45, 128.24, 135.45, 131.70, 131.70, 128.92, 165.18, 126.41, 128.34, 127.05, 53.3, 125.10, 145.89, 128.92

Synthesis of N-((3-benzamido-4-oxo-3, 4-dihydro-quinazolin-2-yl) methyl)- N–(4-Flouro pheny) benzamide (LMDP-10): Mass spectrum (in methanol) (m/z): 491.4 (M-1) 492.4 (M+) 493.4 (M+1) 494.4 (M+2). I.R (in KBr, cm^{-1}): 3217 (-NH stretching of CONH), 1710 (C=O stretching of $CONH_2$), 3000 (C-H stretching Aliphatic), 1384 (-CH_2- bending).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.9 (s, 1H, NHCO) (D_2O exchangeable), δ 4.8 (s, 2H, CH_2), δ 2.5 (s, 3H, OCH_3), δ 6.8 (d, 2H, Ar-H), δ 7.2-7.4 (m, 7H, Ar-H), δ 7.6 (q, 3H, Ar-H), δ 7.7 (t, 1H, Ar-H), δ 7.2-7.9 (m, 4H, Ar-H), δ 7.8 (d, 1H, Ar-H), δ 7.9 (t, 1H, Ar-H), δ 8.0 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H), ^{13}C-NMR (DMSO-d_6, δ ppm): 145.89, 133.052, 135.457, 162.2, 128.63, 128.63, 165.18, 130.06, 152.89, 126.41, 131.70, 131.70, 127.05, 125.06, 53.3, 128.92, 118.33, 144.73, 128.92, 122.11, 134.4, 123.34, 119.9, 142.10, 128.45, 128.45, 160.5, 128.63551, 128.63.

Synthesis of N-((3-Benzamido-4-oxo-3, 4-dihydro-quinazolin-2-yl) methyl)- N– (4-Triflouromethyl pheny) benzamide (LMDP-11): Mass spectrum (in methanol) (m/z): 541.3 (M-1), 542.3 (M+), 543.3 (M+1), 544.3 (M+2). I.R (in KBr, cm^{-1}): 3330 (-NH stretching of CONH), 1606 (C=O stretching of $CONH_2$), 3195 (C-H stretching Aromatic), 3064 (C-H stretching Aliphatic), 1471 (-CH_2- bending), 1334 (C-F Stretching). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.73 (s, 1H, NHCO), δ 3.6 (s, 2H, CH_2), δ 7.2-7.4 (m, 5H, Ar-H), δ7.4-7.5(d, 2H, Ar-H), δ7.6-7. 8 (m, 7H, Ar-H), δ 7.9-8.0 (t, 1H, Ar-H), 8.0-8.1 (m, 2H, Ar-H) 8.2 (d, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 129.10, 133.052, 128.92, 131.70, 131.70, 128.92, 126.4, 53.3, 128.63, 128.63, 165.18, 127.53, 127.53, 140.5, 125.06, 160.5, 113.84, 113.84, 142.10, 128.63, 128.63, 145.89, 152.89, 124.01, 119.9, 135.45, 162.2, 127.05, 128.45, 128.45

Synthesis of N-((3-Benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)-n– (3-Triflouro methyl pheny) benzamide (LMDP-12): Mass spectrum (in methanol) (m/z): 541.3 (M-1), 542.3 (M+), 543.3 (M+1), 544.3 (M+2). I.R (in KBr, cm^{-1}): 3309 (-NH stretching of CONH), 1693 (C=O stretching of $CONH_2$), 2950 (C-H stretching Aliphatic), 1471 (-CH_2- bending). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.73 (s, 1H, NHCO), δ 3.6 (s, 2H, CH_2) δ 7.2-7.4 (m, 5H, Ar-H), δ 7.4-7.5 (d, 2H, Ar-H), δ 7.6-7. 8 (m, 7H, Ar-H), δ 7.9-8.0 (t, 1H, Ar-H), 8.0-8.1 (m, 2H, Ar-H) 8.2 (d, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 165.18, 131.70, 131.70, 128.63, 128.63, 128.92, 124.09, 129.58, 119.9, 131.41, 162.2, 135.45, 128.92, 160.5, 142.10, 122.1, 125.06, 53.3, 144.73, 133.05, 112.15, 152.89, 127.05, 126.41, 128.63, 128.63, 145.89, 117.78, 128.45, 128.45.

Synthesis of N-((3-Benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl)methyl)- N– (3-Chloro4-Flouro pheny) benzamide (LMDP-13): Mass spectrum (in methanol) (m/z): 541.3 (M-1), 542.3 (M+), 543.3 (M+1), 544.3 (M+2). I.R (in KBr, cm^{-1}): 3220 (N-H stretching of CONH), 3100 (C-H stretching Aromatic), 3000 (C-H stretching Aliphatic), 1712 (C=O stretching of $CONH_2$), 713 (C-Cl stretching). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.8 (s, 1H, NHCO), δ 3.5 (d, 2H, CH2), δ7.3-7.5(m, 7H, Ar-H), δ 7.5-7.7 (d, 5H, Ar-H), δ 7.7-7.8 (t, 2H, Ar-H), δ 7.9-8.0 (t, 1H, Ar-H), δ 8.0-8.1 (d, 2H, Ar-H), δ 8.1-8.2 (d, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ

ppm): 117.12, 127.05, 128.63, 128.63, 53.3, 160.5, 125.06, 142.10, 119.1, 126.41, 133.052, 135.45, 162.2, 145.89, 144.73, 165.18, 128.63, 128.63, 128.92, 152.10, 128.92, 119.9, 115.93, 126.23, 131.70, 131.70, 128.45, 128.45, 152.89.

Synthesis of N-((3-Benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)- N– (2, 3- Dichloro pheny) benzamide (LMDP-14): Mass spectrum (in methanol) (m/z): 541.4 (M-1), 543.4 (M+1), 545.4 (M+2). I.R (in KBr, cm^{-1}): 3392 (N-H stretching of CONH), 1606 (C=O stretching of $CONH_2$), 3064 (C-H stretching Aromatic), 2956 (C-H stretching Aliphatic) 1471 (-CH_2- bending), 713 (C-Cl stretching). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.8 (s, 1H, NHCO), δ 3.5 (d, 2H, CH_2), δ 7.2-7.4 (m, 5H, Ar-H), δ 7.4 (d, 1H, Ar-H), δ 7.5-7.8 (m, 7H, Ar-H), δ 7.9 (q, 1H, Ar-H), δ 8.0 (d, 2H, Ar-H) 8.2 (d, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 128.98, 125.53, 165.18, 128.63, 128.63, 125.06, 128.92, 162.2, 125.39, 130.13, 126.41, 128.92, 145.89, 128.45, 128.45, 127.05, 133.05, 128.63, 128.63, 144.73, 117.12, 135.45, 152.89, 53.3, 160.5, 119.9, 142.10, 131.70, 131.70**.**

Synthesis of N-((3-Benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl)methyl)-N–(benzyl) benzamide (LMDP-15): Mass spectrum (in methanol) (m/z): 487.4 (M-1), 488.4(M^+), 489.4 (M+1). I.R (in KBr, cm^{-1}): 3218 (-NH stretching of $CONH_2$), 3000 (C-H stretching Aliphatic), 1710 (C=O stretching of $CONH_2$), 1467 (-CH_2- bending), ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.5 (d,1H, NHCO), δ 2.5 (s, 2H, CH_2), δ 3.9 (s, 2H, CH_2), δ 6.5-7.5(m, 16H, Ar-H), δ 7.8-8.0 (m, 3H, Ar-H), 8.2 (m, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 128.92, 133.05, 170.08, 131.70, 131.70, 127.05, 160.5, 128.45, 128.45, 135.55, 137.30, 128.6, 128.63, 119.9, 125.06, 126.4, 142.10, 128.92, 128.9, 127.9, 127.97, 152.89, 53.3, 128.63, 128.63, 145.89, 128.59, 128.59, 50.865, 162.2.

Synthesis of N-((3-Benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)- N– (3, 4- Dichloro pheny) benzamide (LMDP-16): Mass spectrum (in methanol) (m/z): 541.4 (M-1), 543.4 (M+1) 545.4 (M+2). I.R (in KBr, cm^{-1}): 3392 (N-H stretching of CONH), 1606 (C=O stretching of $CONH_2$), 3064 (C-H stretching, Aromatic), 2956 (C-H stretching, Aliphatic) 1471 (-CH_2- bending), 713 (C-Cl stretching). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.8 (s, 1H, NHCO), δ 3.5 (d, 2H, CH_2), δ 7.2-7.4 (m, 5H, Ar-H), δ 7.4 (d, 1H, Ar-H), δ 7.5-7.8 (m, 7H, Ar-H), δ 7.9 (q, 1H, Ar-H), δ 8.0 (d, 2H, Ar-H) 8.2 (d, 1H, Ar-H).^{13}C-NMR (DMSO-d_6, δ ppm): 128.98, 125.53, 165.18, 128.63, 128.63, 125.06, 128.92, 162.2, 125.39, 130.13, 126.41, 128.92, 145.89, 128.45, 128.45, 127.05, 133.05, 128.63, 128.63, 144.73, 117.12, 135.45, 152.89, 53.3, 160.5, 119.9, 142.10, 131.70, 131.70.

Synthesis of N-((3-Benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)- N– (2-methyl pheny) benzamide (LMDP-17): Mass spectrum (in methanol) (m/z): 489.4 (M+1) 487.4 (M-1): I.R (in KBr, cm^{-1}): 3251 (-NH stretching of CONH), 1714 (C=O stretching of $CONH_2$), 3064 (C-H stretching Aromatic), 2941 (C-H stretching Aliphatic). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.7 (s, 1H, NHCO), δ 3.7 (s, 2H, CH2), δ 2.3 (s, 3H, CH3) δ 6.9 (d, 1H, Ar-H), δ 7.1-7.4 (m, 8H, Ar-H), δ 7.6-7.8 (m, 5H, Ar-H), δ 7.9 (t, 1H, Ar-H), 8.0 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): δ 125.06, 142.10, 133.05, 128.92, 152.89, 114.95, 128.63, 128.63, 127.05, 135.45, 126.41, 160.5, 119.9, 131.70, 131.70, 122.96, 128.63, 128.63, 133.26, 115.45, 53.3, 145.89, 128.45, 128.45, 162.2, 128.92, 123.28, 154.77, 165.18, 55.95**.**

Synthesis of N-((3-Benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)- N– (3, 6- Dichloro pheny) benzamide (LMDP-18): Mass spectrum (in methanol) (m/z): 541.4 (M-1), 543.4 (M+1), 545.4 (M+2). I.R (in KBr, cm^{-1}): 3245 (-NH stretching of CONH), 1693 (C=O stretching of $CONH_2$), 3070 (C-H stretching Aromatic), 3000 (C-H stretching Aliphatic). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.8(s,1H, NHCO), δ 3.5 (d, 2H, CH_2), δ 7.2-7.4 (m, 5H, Ar-H), δ 7.4 (d, 1H, Ar-H), δ 7.5-7.8 (m, 7H, Ar-H), δ 7.9 (q, 1H, Ar-H), δ 8.0 (d, 2H, Ar-H) 8.2 (d, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 128.98, 125.53, 165.18, 128.63, 128.63, 125.06, 128.92, 162.2, 125.39, 130.13, 126.41, 128.92, 145.89, 128.45, 128.45, 127.05, 133.05, 128.63, 128.63, 144.73, 117.12, 135.45, 152.89, 53.3, 160.5, 119.9, 142.10, 131.70, 131.70

Synthesis of N-((3-Benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)- N– (2, 4- Dichloro pheny) benzamide (LMDP-19): Mass spectrum (in methanol) (m/z): 541.4 (M-1), 543.4 (M+1),

545.4 (M+2), I.R (in KBr, cm^{-1}): (-NH stretching of CONH), 1714 (C=O stretching of CONH2), 3000 (C-H stretching Aliphatic), 1423 (-CH_2- Bending), 767 (C-Cl Stretching). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.8 (s, 1H, NHCO), δ 3.5 (d, 2H, CH), 7.2-7.4 (m, 5H, Ar-H), δ 7.4 (d, 1H, Ar-H), δ 7.5-7.8 (m, 7H, Ar-H), δ 7.9 (q, 1H, Ar-H), δ 8.0 (d, 2H, Ar-H) 8.2 (d, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 162.2, 127.05, 128.92, 128.63, 128.63, 165.18, 145.89, 119.9, 53.3, 128.75, 131.70, 131.70, 128.92, 128.45, 128.45, 128.63, 128.63, 142.10, 126.41, 160.5, 128.9, 122.71, 135.45, 125.06, 133.05, 117.29, 130.2, 144.89, 152.89**.**

Synthesis of N-((3-benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)- N– (3-Bromo pheny) benzamide (LMDP-20): Mass spectrum (in methanol) (m/z): 551.4 (M-1) 553.4 (M+1), 554.4 (M+2), 556.4 (M+4), I.R (in KBr, cm^{-1}): 3195 (-NH stretching of CONH), 3000 (C-H stretching Aliphatic), 1739 (C=O stretching of $CONH_2$), 1641 (N-H bending of $CONH_2$).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.3 (d,1H, NHCO), δ 2.5 (s, 2H, CH_2), δ 3.4 (s, 2H, CH_2), δ 7.1-7.3 (m, 5H, Ar, H), δ 6.8-7.4 (m, 5H, Ar-H), δ 7.4-7.8 (m, 5H, Ar-H), δ 8.0-8.2 (s, 2H, Ar-H), δ 7.8 (m, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 142.10, 160.5, 128.45, 128.45, 145.89, 128.92, 122.11, 127.05, 131.70, 131.70, 144.73, 128.63, 128.63, 125.06, 152.89, 128.92, 123.5, 135.45, 119.9, 128.63, 128.63, 123.4, 165.18, 126.41, 127.12, 53.3, 133.05, 162.2, 130.8.

Synthesis of N-((3-benzamido-4-oxo-3,4-dihydro-quinazolin- 2- yl) methyl)- N–(Phenyethyl) benzamide (LMDP-21): Mass spectrum (in methanol) (m/z): 501.4 (M-1) 502.4 (M+), 503.4 (M+1). I.R (in KBr, cm^{-1}): 3205 (-NH stretching of CONH), 1606 (C=O stretching of $CONH_2$), 3195 (C-H stretching Aromatic), 2931 (C-H stretching Aliphatic). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.3 (d, 1H, NHCO), δ 2.5 (s, 2H, CH_2), δ 3.4 (s, 2H, CH_2), δ 7.1-7.3 (m, 5H, Ar-H), δ 6.8-7.4 (m, 5H, Ar-H), δ 7.4-7.8 (m, 5H, Ar-H), δ 8.0-8.2 (s, 2H, Ar-H), δ 7.8 (m, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 142.10, 160.5, 128.45, 128.45, 145.89, 128.92, 122.11, 127.05, 131.70, 131.70, 144.73, 128.63, 128.63, 125.06, 152.89, 128.92, 123.5, 135.45, 119.9, 128.63, 128.63, 123.4, 165.18, 126.41, 127.53.3, 133.05, 162.2 130.8.

Synthesis of N-((3-benzamido-4-oxo-3,4-dihydro-quinazolin- 2-yl) methyl)- N– (3, 6 Dimethyl pheny) benzamide (LMDP-23): Mass spectrum (in methanol) (m/z): 501.5 (M-1), 502.5 (M+), 503.4 (M+1), 504.4 (M+2). I.R (in KBr, cm^{-1}): 3242 (-NH stretching of CONH), 2950 (C-H stretching Aliphatic), 1720 (C=O stretching of $CONH_2$), 1421 (-CH_2- Bending), ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.7 (d, 1H, NHCO), δ 2.3 (s, 3H, CH_3), δ 2.5 (s, 2H, CH_2), δ 6.9-7.1 (m, 3H, Ar-H), δ 7.2-7.4 (m, 5H, Ar-H), δ 7.5-7.7 (m, 5H, Ar-H), δ 7.9 (t, 1H, Ar-H), δ 8.0-8.1 (d, 2H, Ar-H) δ 8.2 (d, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 17.7, 53.3, 142.10, 165.18, 119.9, 162.2, 145.89, 131.7, 131.70, 125.06, 116.35, 128.92, 128.63, 128.63, 133.05, 135.45, 128.6, 21.22, 141.65, 128.38, 152.89, 135.51, 127.05, 160.5, 128.45, 128.45, 134.76, 128.92, 126.41, 128.63, 128.63**.**

Synthesis of N-((3-benzamido-4-oxo-3, 4-dihydro-quinazolin- 2- yl) methyl)- N– (4-Iodopheny) benzamide (LMDP-24): Mass spectrum (in methanol) (m/z): 599.4, (M-1), 600.4(M+), 601.3 (M+1), 602.3 (M+2). I.R (in KBr, cm^{-1}): 3218 (-NH stretching of CONH), 1695 (C=O stretching of CONH2), 1325 (-CH_2- Bending), ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.7 (d, 1H, NHCO), δ 2.5 (s, 2H, CH_2), δ 7.0-7.2 (d, 2H, Ar, H), δ 7.2-7.5 (m, 4H, Ar-H), δ 7.5-7.7 (m, 5H, Ar-H), δ 7.7-7.8 (m, 2H, Ar-H), δ 7.9 (t, 1H, Ar-H), δ 8.0-8.1 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H), ^{13}C-NMR (DMSO-d_6, δ ppm): 162.2, 126.41, 135.45, 131.70, 131.70, 125.06 128.63, 128.63, 138.95, 138.95, 53.3, 133.05, 152.89, 165.18, 128.92, 145.89, 119.9, 160.5, 128.92, 90.72, 128.63, 128.63 128.45, 128.45, 127.05, 124.4, 124.4, 142.10, 140.5.

Synthesis of N-((3-benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl)methyl)- N–(5-Chloro 2-methyl pheny) benzamide (LMDP-26): Mass spectrum (in methanol) (m/z): 521.4 (M-1), 523.4 (M+1), 525.4 (M+2). I.R (in KBr, cm^{-1}): 3209 (-NH stretching of CONH), 1699 (C=O stretching of $CONH_2$), 3066 (C-H stretching Aromatic), 3000 (C-H stretching Aliphatic), 1488 (-CH_2- Bending), 1365 (CH_3- Bending), 1H NMR (DMSO-d6, 400 MHz): δ 11.7 (d,1H, NHCO), δ 2.5 (s, 2H, CH_2), δ 7.0-7.2 (d, 2H, Ar, H), δ 7.2-7.5 (m, 4H, Ar- H), δ 7.5-7.7 (m, 5H, Ar-H), δ 7.7-7.8 (m, 2H, Ar-H), δ 7.9 (t, 1H, Ar-H), δ 8.0-8.1 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H), ^{13}C-NMR (DMSO-d_6, δ ppm): 126.41,

138.3, 152.89, 135.45, 17.75, 114.95, 162.2, 142.10, 125.06, 128.27, 165.18, 128.8, 133.05, 128.45, 128.45, 128.92, 134.76, 160.5, 145.89, 141.65, 128.63, 128.63, 119.9, 131.70, 131.70, 128.92, 128.63, 128.63,127.05, 53.3.

Synthesis of N-((3-benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl)methyl)- N– (5-Bromo, 2-methyl pheny) benzamide (LMDP-27): Mass spectrum (in methanol) (m/z): 565.4(M-1) 567.4 (M+1) 569.4 (M+2). I.R (in KBr, cm^{-1}): 3209 (-NH stretching of CONH), 1699 (C=O stretching of $CONH_2$), 3066 (C-H stretching Aromatic), 3000 (C-H stretching Aliphatic), 1488 (-CH_2- Bending), 1365 (CH_3- Bending).

^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.7 (d, 1H, NHCO), δ 2.5 (s, 2H, CH_2), δ 7.0-7.2 (d, 2H, Ar-H), δ 7.2-7.5 (m, 4H, Ar- H), δ 7.5-7.7 (m, 5H, Ar-H), δ 7.7-7.8 (m, 2H, Ar-H), δ 7.9 (t, 1H, Ar-H), δ 8.0-8.1 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H), 13C-NMR (DMSO-d6, δ ppm): 117.84, 133.05, 53.3, 128.9, 128.63, 128.63, 165.18, 131.70, 131.70, 145.89, 135.45, 119.42, 141.65, 142.10, 152.89, 127.82, 128.92, 128.63, 128.63, 119.9, 131.75, 160.5, 162.2, 17.75, 134.76, 125.06, 127.0, 126.4, 128.45, 128.45.

Synthesis of N-((3- 4-Nitro benzamido-4-oxo-3,4-dihydroquinazolin-2-yl) methyl)- N– (4-Bromo pheny) 4-Nitro benzamide (LMDP-28): Mass spectrum (in methanol) (m/z): 551.4 (M-1), 553.4 (M+1), 554.4 (M+2), I.R (in KBr, cm^{-1}): 3207 (-NH stretching of CONH), 3066 (C-H stretching Aromatic), 3000 (C-H stretching Aliphatic), 1714 (C=O stretching of $CONH_2$), 1485 (-CH_2- Bending), ^{1}H NMR (DMSO-d^6, 400 MHz): δ 11.9 (s,1H, NHCO) (D_2O exchangeable), δ 4.8 (s, 2H, CH_2), δ 2.5 (s, 3H, OCH_3), δ 6.8 (d, 2H, Ar-H), δ 7.2-7.4 (m, 7H, Ar-H), δ 7.6 (q, 3H, Ar-H), δ 7.7 (t, 1H, Ar-H), δ 7.2-7.9 (m,4H,Ar-H), δ 7.8 (d, 1H, Ar-H), δ 7.9 (t, 1H, Ar-H), δ 8.0 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H). 13C-NMR (DMSO-d_6, δ ppm): 133.05, 128.45, 128.45, 132.15, 132.15, 152.89, 142.10, 162.2, 135.45, 131.70, 131.70, 125.06, 126.41, 53.3, 126.17, 126.17, 127.05, 117.93, 140.5, 128.63, 128.63, 128.92, 128.92, 145.89, 128.63, 128.63, 160.5, 119.9, 165.18, 2.10, 125.06, 128.27, 165.18, 128.8, 133.05, 128.45, 128.45, 128.92, 134.76, 160.5, 145.89, 141.65, 128.63, 128.63, 119.9, 131.70, 131.70, 128.92, 128.63, 128.63, 127.05, 53.3.

Synthesis of N-((3-benzamido-4-oxo-3,4-dihydro-quinazolin-2-yl) methyl)- N– (4-Nitropheny) benzamide (LMDP-29): Mass spectrum (in methanol) (m/z): 518.4 (M-1), 519.4 (M+), 520.4 (M+1), 521.4 (M+2). I.R (in KBr, cm^{-1}): 3280 (-NH stretching of CONH), 3050 (C-H stretching Aliphatic), 1606 (C=O stretching of $CONH_2$), 1471 (-CH_2- Bending), ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.9 (s,1H, NHCO) (D2O exchangeable), δ 4.8 (s, 2H, CH_2), δ 2.5 (s, 3H, OCH_3), δ 6.8 (d, 2H, Ar-H), δ 7.2-7.4 (m, 7H, Ar-H), δ 7.6 (q, 3H, Ar-H), δ 7.7 (t, 1H, Ar-H), δ 7.2-7.9 (m, 4H, Ar-H) , δ 7.8 (d, 1H, Ar-H), δ 7.9 (t, 1H, Ar-H), δ 8.0 (d, 2H, Ar-H), δ 8.2 (d, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 142.10, 117.29, 117.29, 53.3, 133.05, 128.63, 128.63, 127.05, 128.92, 160.5, 165.18, 119.9, 126.41, 128.45, 128.45, 131.70, 131.70, 125.06, 128.6, 128.63, 140.5, 135.45, 162.2, 140.47, 145.89, 117.66, 117.66 128.92, 152.89.

Synthesis of N-((3-(4-Nitro benzamido)-4-oxo-3, 4-dihydroquinazolin-2-yl) methyl)- N– (pheny) 4-nitro benzamide (LMDP-30N): Mass spectrum (in methanol) (m/z): 563.4 (M-1), 564.4 (M+), I.R (in KBr, cm^{-1}): 3195 (-NH stretching of CONH), 3050 (C-H stretching Aromatic), 1681(C=O stretching of CONH2), 2950 (C-H stretching Aliphatic). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.14 (s, 1H, NHCO), δ 2.0 (s, 2H, CH_2), δ 6.6-6.8 (d, 1H, Ar, H), δ 6.8-7.0 (m, 2H, Ar, H), δ 7.0-7.2 (t, 1H, Ar, H), δ 7.6-7.8 (m, 4H, Ar-H), δ 7.9- 8.0 (t, 1H, Ar-H), δ 8.1-8.4 (m, 5H, Ar-H), δ 8.4-8.6 (d, 2H, Ar-H) ^{13}C-NMR (DMSO-d_6, δ ppm): 160.5, 122.1, 122.1, 117.29, 117.29, 117.29, 117.29, 133.0, 135.45, 133.82, 140.47, 145.89, 140.47, 162.2, 119.9, 125.06, 127.0, 128.69, 128.69, 124.72, 53.3, 165.18, 129.25, 129.25, 126.4, 140.5, 128.69, 128.69, 152.89.

Synthesis of N-((3-(4-Nitro benzamido)-4-oxo-3, 4-dihydroquinazolin-2-yl) methyl)-N–(4-Flouro pheny) 4-nitro benzamide (LMDP-31N): Mass spectrum (in methanol) (m/z): 581.4 (M-1), 583.4 (M+1), 584.4 (M+2), I.R (in KBr, cm^{-1}): 3230 (-NH stretching of CONH), 3050 (C-H stretching Aromatic), 2990 (C-H stretching Aliphatic), 1712 (C=O stretching of $CONH_2$), 1639 (N-H Bending of $CONH_2$), ^{1}H NMR (DMSO-d_6, 400 MHz): δ 12.14 (s, 1H, NHCO), δ 2.0 (s, 2H, CH_2), δ 6.6-6.8 (d, 1H, Ar-H), δ 6.8-7.0 (m, 2H, Ar-H), δ 7.0-7.2 (t, 1H, Ar, H), δ 7.6-7.8 (m, 4H, Ar-H), δ 7.9- 8.0 (t,

1H, Ar-H), δ 8.1-8.4 (m, 5H, Ar-H), δ 8.4-8.6 (d, 2H, Ar-H).^{13}C-NMR (DMSO-d_6, δ ppm): 160.5, 122.11, 122.11, 117.29, 117.29, 117.29, 117.29, 133.0, 135.45, 133.82 140.47, 145.89, 140.47, 162.2, 119.9, 125.06, 127.0, 128.69, 128.69, 124.72, 53.3, 165.18 , 129.25, 129.25, 126.41, 140.5, 128.69, 128.69, 152.89.

Synthesis of N-((3-(4-Nitro benzamido)-4-oxo-3, 4-dihydroquinazolin-2-yl)methyl)-N–(3-methoxy pheny) 4-Nitro benzamide (LMDP-32N): Mass spectrum (in methanol) (m/z): 593.4 (M-1), 594.4 (M+), 595.4 (M+1), 596.4 (M+2). I.R (in KBr, cm^{-1}): 3350 (-NH stretching of CONH), 3050 (C-H stretching Aromatic), 1714 (C=O stretching of $CONH_2$), 2977 (C-H stretching Aliphatic), δ 12.14 (s, 1H, NHCO), δ 2.0 (s, 2H, CH_2), δ 3.5 (s, 3H, CH_3), δ 6.6-6.8 (d, 1H, Ar, H), δ 6.8-7.0 (m, 2H, Ar, H), δ 7.0-7.2 (t, 1H, Ar, H), δ 7.6-7.8 (m, 4H, Ar-H), δ 7.9- 8.0 (t, 1H, Ar-H), δ 8.1-8.4 (m, 5H, Ar-H), δ 8.4-8.6 (d, 2H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 128.69, 128.69, 162.2, 145.89, 127.05, 160.5, 140.47, 125.06, 135.45, 152.89, 117.29, 117.29, 160.5, 144.73, 126.41, 128.69, 128.69, 119.9, 108.26, 53.3, 55.46, 122.1, 165.1, 140.47, 133.82, 133.05, 129.8, 117.29, 117.29, 103.9.

Synthesis of N-((3-(4-Nitro benzamido)-4-oxo-3, 4-dihydroquinazolin-2-yl)methyl)-N–(2-methoxy pheny) 4-nitro benzamide (LMDP-33N): Mass spectrum (in methanol) (m/z): 590.9 (M-1), 592.4 (M+), 593.4 (M+1)). I.R (in KBr, cm^{-1}): δ 12.14 (s,1H, NHCO),δ 5.5 (s, 2H, CH_2), δ 3.6 (s, 3H, CH3), δ 6.6-6.8 (d, 1H, Ar, H), δ 6.8-7.0 (m, 2H, Ar, H), δ 7.0-7.2 (t, 1H, Ar, H), δ 7.6-7.8 (m, 4H, Ar-H), δ 7.9- 8.0 (t, 1H, Ar-H), δ 8.1-8.4 (m, 5H, Ar-H), δ 8.4-8.6 (d, 2H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 160.5, 127.05, 128.69, 128.69, 114.95, 154.77, 152.89, 162.2, 117.29, 117.29, 122.96, 140.47, 123.28, 53.3, 135.45, 165.18, 140.47, 145.89, 115.45, 117.29, 117.29, 125.06, 126.4, 119.9, 55.95, 133.26, 128.69,128.69, 133.82, 133.05.

Synthesis of N-((3-(4-Nitrobenzamido)-4-oxo-3, 4-dihydroquinazolin-2-yl)methyl)-N–(Benzyl) 4-Nitrobenzamide (LMDP-34N): Mass spectrum (in methanol) (m/z): 487.4 (M-1), 488.4 (M+), 489.4. I.R (in KBr, cm^{-1}): 3218 (-NH stretching of $CONH_2$), 3000 (C-H stretching Aliphatic), 1710 (C=O stretching of $CONH_2$), 1467 (-CH_2-bending). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 11.5 (d, 1H, NHCO), δ 2.5 (s, 2H, CH_2), δ 3.9 (s, 2H, CH2), δ 6.5-7.5(m, 16H, Ar-H), δ 7.8-8.0 (m, 3H, Ar-H), 8.2 (m, 1H, Ar-H). ^{13}C-NMR (DMSO-d_6, δ ppm): 128.92, 133.05, 170.08, 131.70, 131.70, 127.05, 160.5, 128.45, 128.45, 135.55, 137.30, 128.63, 128.63, 119.9, 125.06, 126.4, 142.10, 128.92, 128.9, 127.9, 127.97, 152.89, 53.3, 128.63, 128.63, 145.89, 128.59, 128.59, 50.865, 162.2.

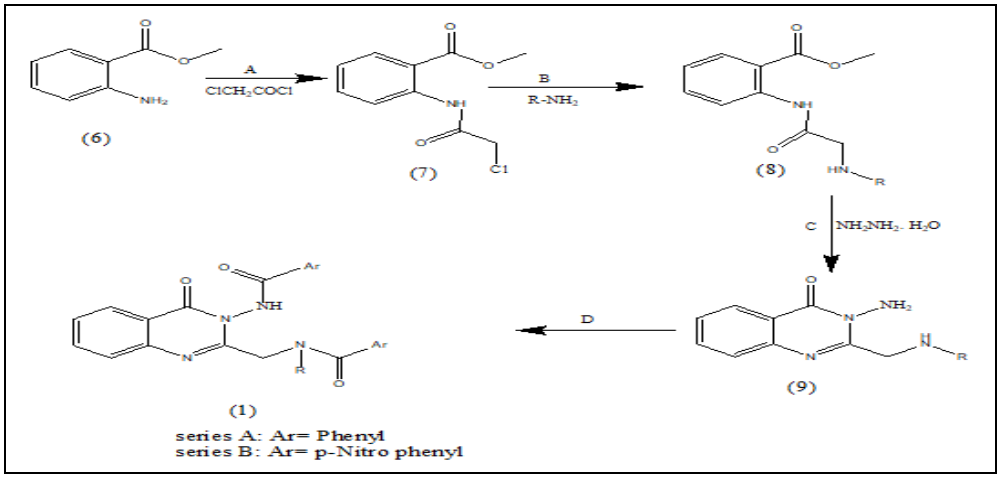

FIG. 3: SYNTHETIC SCHEME OF DESIGNED SERIES

Series A: R= Phenyl, 2-Methyl phenyl, 4-Methyl phenyl, 2-Methoxy phenyl, 4-Methoxy phenyl, 3-Chloro Phenyl, 4-Chloro phenyl, 4-Flouro phenyl 4-Iodo phenyl, 3-Bromo Phenyl, 3,6-Dimethyl phenyl, 2,4-Dichloro phenyl, 2,3-Dichloro phenyl, 3-Chloro 4-Flouro phenyl, 3, 4-Dichloro phenyl, 4-Trifluoromethyphenyl, 3-Trifluoromethyphenyl, 3,6-Dichlorophenyl, Benzyl, Phenylethyl, 5-Chloro 2-methyl Phenyl, 5-Bromo 2-methyl Phenyl, p-Nitrophenyl, 2,3 Dichlorophenyl, 3,4 Dichlorophenyl 3,6 Dichlorophenyl, 4-Bromophenyl. Series B: Phenyl, 4-Flourophenyl, Phenylethyl, 3-Methoxylphenyl, 2-Methylphenyl, 3-Methylphenyl. A= Stirring at room temperature in glacial acetic acids. B= Heating under reflux condition in the presence of Triethylamine and substituted amines in dioxane for 8-10. C= Heating under reflux condition with hydrazine hydrate in absolute Alcohol for 7-8 hr. D= Heating under reflux condition with Benzoyl chloride in dioxane for 7-8 hr.

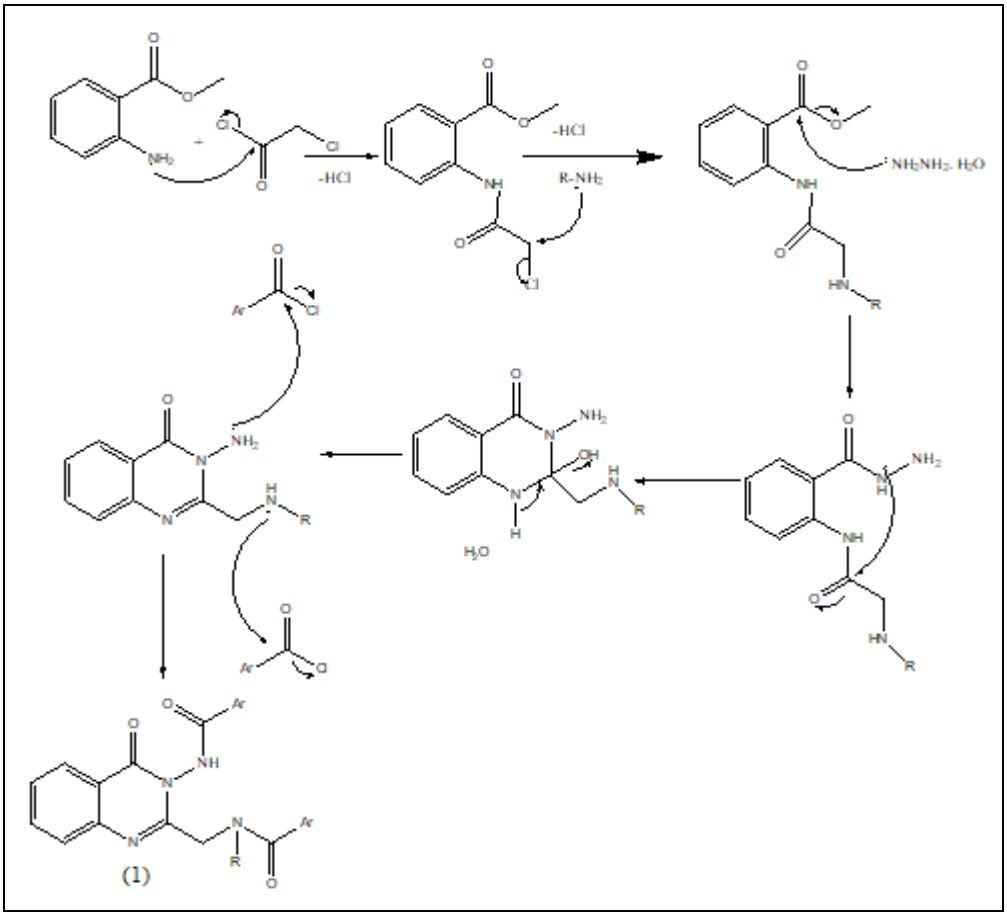

FIG. 4: MECHANISM OF SYNTHESIS

Biological Evaluation:

Animals: For *the in-vitro* study, isolated Hog stomach was obtained from Ahmedabad Municipal Corporation (registered slaughterhouse), Jamalpura, Ahmedabad, India. The study was approved by the ethical committee of our institute, CPCSCA (Committee for the Purpose of Control And Supervision of Experiments on Animals), according to its guideline.

Experimental Design: *In-vitro* H^+/K^+-ATPase Assay: [20]

***In-vitro* H^+/K^+-Atpase Inhibition Activity in Membrane Vesicles of Stomach Mucosa:** Histamine, acetylcholine, and gastrin stmulate the parietal cell of the stomach. Gastrin and Acetylcholine produce direct action on the parietal cell; in addition to this, they may also release histamine from histamine storage in the gastric mucosa. In this manner, histamine would act as the final mediator of acid secretion [21].

Upon stimulation, the expanded secretory canaliculus forms by fusion of the tubulovesicles in the cytoplasma of the cell in the apical membrane of the stomach where the enzyme H^+/K^+-ATPase is located. The enzyme H^+/K^+-ATPase is the ultimate mediator of acid secretion that transports hydrogen in exchange for potassium. So, the specific inhibitors of this enzyme to suppress acid secretion helps in ulcer formation as ulcers only exist in acidic medium [20].

Preparation of Hog Gastric H^+/K^+-ATPase Activity (Membrane Vesicles Preparation): The fundus part of the stomach was separated, washed with tap water, and then with 3M NaCl to remove dust, superficial cells, cell debris, and mucus. Then the mucosa was scraped off to obtain oxyntic cell-rich contents. Homogenizing buffer containing 0.25 M sucrose, 5 mM PIPES/Tris, pH 6.8, 1 mM EDTA, and 1 mM EGTA was prepared and then scraped content was homogenized. The homogenate obtained was centrifuged at 20,000 g for 30 min, and the supernatant was further centrifuged at 1,00,000 g for 90 min. The pellet separated at the bottom of centrifuge tubes was resuspended in homogenizing buffer, and it was layered over 7.5% (w/w) Ficoll in the homogenizing buffer again centrifuged at 1,00,000

g for 60 min. The middle layer was concentrated in the microsomal fraction was collected and diluted with homogenizing buffer. It was centrifuged again at 1,00,000 g for 90 min. The pellet was separated at the bottom of the centrifuge tube, which was collected and suspended in homogenizing buffer at a final protein concentration of 0.5 mg/mL, the suspension was stored at –80°C, and its protein content was determined with a Lowry protein assay method [23, 24, 25].

Measurement of H^+/K^+-ATPase Activity: Gastric H^+/K^+-ATPase activity can be correlated with the amount of release of inorganic phosphate from ATP[153] in a 96 well plate. The plate was containing reaction mixture with 50 µL containing 2.5 mg/L vesicles, 50 mM Hepes-Tris (pH 7.4), 5 mM $MgCl_2$, 8 mM KCl, 10-µM valinomycin in the presence of the test compound or vehicle. The mixture was pre-incubated at 37 °C for 30 min, then on the addition of ATP reaction was initiated at a final concentration of 0.2 mM at 37 °C for 20 min. After 20 minutes, the reaction was stopped by adding the mixture containing 15 µL of dye reagent with 0.1% w/v malachite green, 1.5% w/v hexaammonium molybdate, and 0.2% v/v Tween 20 in 4 N H_2SO_4. The absorbance of the resulting mixture was measured at 620 nm with an ELISA reader. K^+-dependent inhibition of ATPase was calculated as the difference between the activity in the presence and absence of KCl. For the controls with 0% inhibition of 1% DMSO and for 100% inhibition, reactions were carried out in the presence of omeprazole (0.56-14 µM) [18, 19, 20].

Inorganic phosphate (Pi) liberated in mg from ATP was due to ATPase activity per mg protein.

In the case of evaluation of the activity of test compounds, Reaction mixtures were incubated in the presence or absence of different test compounds. The experiments were performed in triplicate using at least three different concentrations, which include 4 µM, 12 µM, and 25 µM.[25]

Percentage inhibition of the H^+/K^+ ATPase activity was determined using the following formula.[20, 25]

% inhibition= [Pi concentration (control) - Pi concentration (test)] × 100 / Pi concentration (control)

RESULT AND DISCUSSION:

Antiulcer Activity Evaluation: All the compounds tested showed a decrease in amount of release of inorganic phosphate, which can be correlated with decrease in H^+/K^+-ATPase activity (mg Pi liberated/mg protein) with variable potency, compared with Omeprazole (standard). Effect of the compounds determined as the concentration needed to inhibit 50% (IC_{50}) of the activity of the enzyme. IC_{50} values of test compounds and Omeprazole is depicted in **Table 1**.

TABLE 1: IC_{50} VALUES OF TEST COMPOUNDS AND OMEPRAZOLE

S. no.	Compound No.	R	IC_{50} (µM)
1	LMDP-1	Phenyl	12
2	LMDP-3	4-Methylphenyl	12
3	LMDP-4	4-Methoxylphenyl	22
4	LMDP-6	2-Methoxylphenyl	10
5	LMDP-7	4-Chlorophenyl	13
6	LMDP-9	3-Chlorophenyl	13
7	LMDP-10	4-Fluorophenyl	13
8	LMDP-11	4-Trifluoromethyphenyl	15
9	LMDP-12	3- Trifluoromethylphenyl	18
10	LMDP-13	3-Chloro,4-Fluoro phenyl	20
11	LMDP-14	2,3 Dichlorophenyl	22
12	LMDP-15	Benzyl	7
13	LMDP-16	3,4 dichlorophenyl	11
14	LMDP-17	2-Methyl phenyl	10
15	LMDP-18	3,6 dichlorophenyl	21
16	LMDP-19	2,4 dichlorophenyl	18
17	LMDP-20	3-Bromophenyl	14
18	LMDP-21	Phenylethyl	9
19	LMDP-23	3,6 Dimethylphenyl	8
20	LMDP-24	4-Iodophenyl	11
21	LMDP-25	3,4 dichlorophenyl	10

22	LMDP-26	5-Chloro 2-methyl Phenyl	25
23	LMDP-27	5-Bromo 2-methyl Phenyl	23
24	LMDP-28	4-Bromophenyl	22
25	LMDP-29	4-Nitrophenyl	19
26	LMDP-30N (series-B)	Phenyl	14
27	LMDP-31N (series-B)	4-Flourophenyl	24
28	LMDP-32N (series-B)	3-Methoxylphenyl	18
29	LMDP-33N (series-B)	2-Methoxylphenyl	17
30	LMDP-34N (series-B)	Benzyl	22
31	Omeprazole	-----	6

As can be seen from **Table 1**, three compounds out of all synthesized compounds, *viz*. LMDP-15, LMDP-21, and LMDP-23 showed IC_{50} values of 07 µM, 09 µM, and 08 µM, respectively. IC_{50} values of these three were found comparable with that of Omeprazole (IC_{50}=06). Although, maximum inhibition of the H^+/K^+ ATPase enzyme is shown by LMDP-15. A result of screening of all compounds in the form of a bar graph has presented in **Fig. 5-8**.

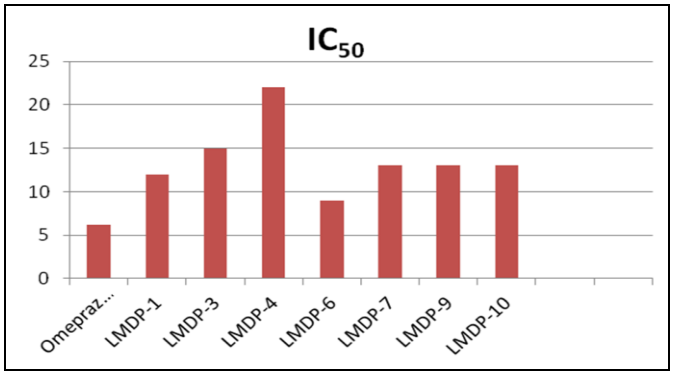

FIG. 5: GRAPHICAL REPRESENTATION OF IC_{50} VALUE OF LMDP-1 TO LMDP-10 AND OMEPRAZOLE

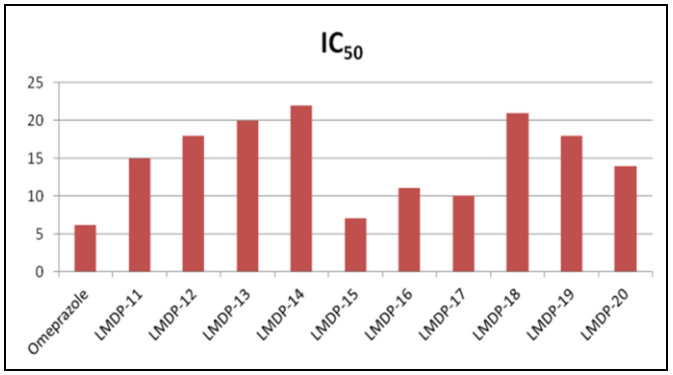

FIG. 6: GRAPHICAL REPRESENTATION OF IC_{50} VALUE OF LMDP-11 TO LMDP-20 AND OMEPRAZOLE

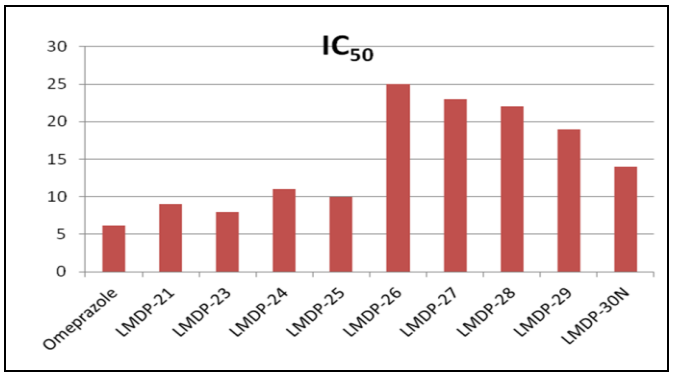

FIG. 7: GRAPHICAL REPRESENTATION OF IC_{50} VALUE OF LMDP-21 TO LMDP-30 AND OMEPRAZOLE

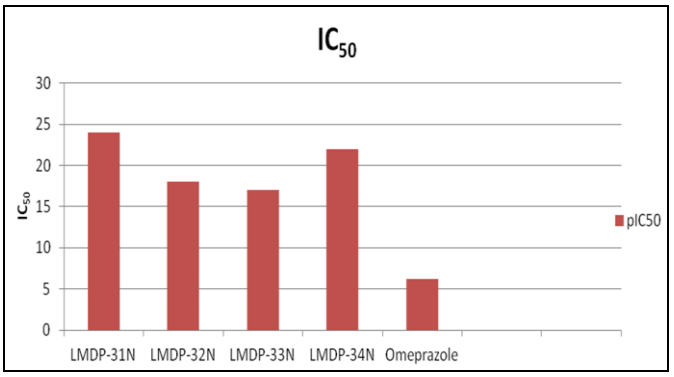

FIG. 8: GRAPHICAL REPRESENTATION OF IC_{50} VALUE OF LMDP-31 TO LMDP-37 AND OMEPRAZOLE

A number of new drugs have been introduced for peptic ulcer diseases (PUD) in last decades through intensive research in this field. However, widely used PPIs by the consequence of their covalent interaction, of the [(pyridylmethyl) sulfinyl] benz imidazoles (PSBs) such as omeprazole show a long duration of action *in-vivo* but may be responsible for the elevated levels of circulating gastrin observed after repeated administration of these compounds which is also responsible for rebound acidity in gastrointestinal tract.

In the present study, we have focused on developing effective H^+/K^+-ATPase inhibitors by designing novel series possessing weak basic pharmacophore, N-((3-Benzamido-4-oxo- 3, 4-dihydroquinazolin-2-yl) methyl) – N - (substituted) phenyl benzamide (1), which can be protonated in gastric acidic pH and resulting quaternary cation can bind with the enzyme at the binding site of K^+ and inhibit gastric acid secretion reversibly. The $H^{+/}K^+$-ATPase inhibition activities of this designed novel series have been studied under the present

section. The proposed novel series of compounds provide active inhibitors of the gastric H^+/K^+-ATPase. Differences in *in-vitro* inhibitory potency between the various Quinazoline derivatives with different substituents (R) on the phenyl ring of aromatic amine have been tested. The 2-methoxy derivative (LMDP-6) (IC_{50}-10) is more active than the 4-Methyl derivative (LMDP-3) (IC_{50}-12). This suggests that Compounds with substituted amine (R) carrying strong electron-donating groups are significantly more active compare to less electron-donating groups. Further decrease in activity has seen when the compound is substituted with electron-withdrawing groups. Eventually, it can also be correlated that Compounds with mono halogenated substitution (LMDP-4, LMDP-7, LMDP-9) are showing relatively similar inhibitory activity but more active than dihalogenated derivatives (LMDP-13, LMDP-14, LMDP-18, LMDP-19), owing to further decrease in basicity. Highly basic compounds are more stable by protonation in gastric pH as well as these protonated derivatives are competitive with the K^+ at binding site. Series-A are Benzoylated derivatives whereas Series-B are p-Nitrobenzoylated derivatives. However, Series-A compounds shows good inhibitory activity than Series-B which indicates that high degree of lipophilicity in series-B decreases the tendency of protonation in acidic pH.

Out of all synthesized compounds, three compounds namely LMDP-6 with 2-Methoxy group (IC_{50}-10), LMDP-15 with Benzyl group (IC_{50}-7), LMDP-21 with Phenylethyl group (IC_{50}-9), and LMDP-23 with 3,6 Dimethyl phenyl group (IC_{50}-8), were found highly effective as compared to standard, that further indicates, electron-rich groups carrying derivatives are more promising. Further, IC_{50} of LMDP-15 has been found very close to that of Omeprazole.

As a part of future work, we can go for more simple and effective molecules with said pharmacophoric requirements with more promising results to overcome the barrier of chronic gastrointestinal problems which are yet unsolved. Even though high efficiency and safety of the PPIs, there is a gradual onset of effect and does not provide complete symptoms relief in all patients. However, the potassium-competitive acid blockers (P-CABs), is under clinical investigation in GERD and other acid-related diseases.

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CONFLICTS OF INTEREST: The authors have declared no conflict of interest

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