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Design, Synthesis and Biological Screening of Novel 3-Amino Quinazolines as Antiulcer Agents

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ABSTRACT:

Quinazoline derivatives are associated with broad spectrum of biological activities. In view N-((3-Benzamido-4-oxo-3,4-dihydroquinolin-2-yl)methyl)-N-(substituted) phenylbenzamide derivatives were synthesized and tested for *in-vitro* antiulcer activity on isolated hog gastric mucosal H^+/K^+-ATPase, The synthetic scheme of the prepared compounds is given. All the synthesized compounds were characterized by using IR, MS and ^{1}H NMR spectroscopy. Compounds were screened for their antiulcer activity: compound 1e showed maximum inhibitory activity. Omeprazole is used used as standard.

Keywords: Synthesis; 4-quinazolinone; antiulcer activity, H^+/K^+-ATPase, Potassium-competitive acid blockers

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INTRODUCTION:

The presence of acid is a fundamental factor in the pathogenesis of gastric and duodenal ulcers, reflux esogastritis, and non steroidal antiinflammatory drug-induced lesions. Therefore, it is mandatory to control acid secretion for treatment of these diseases. Therefore, acid suppression is considered as the first-line therapy. [1] The conventional agents are histamine 2 receptor antagonists (H_2RAs) and proton pump inhibitors (PPIs). Presently, PPIs are recognized as the 'treatment of choice' in most countries. However, PPIs still continues to have their set of limitations. [2,3,19] The currently available PPIs require around 3–5 days to achieve maximum acid inhibition at existent therapeutic doses, primarily due to their chemical structures and irreversible inhibition of H^+/K^+ ATPase. [4,5] Failure to demonstrate a sustained acid inhibition throughout the day and night, in spite of twice daily administration, and nocturnal acid breakthrough (NAB) are found to be common in patients taking PPIs. [6,7] The long lasting inhibition of gastric secretion by proton pump inhibitors showed an indirect pharmacodynamic consequence i.e. ECL-cell hyperplasia and some apparent drawbacks such as extreme irreversible gastric acid suppression, achlorhydria, hypergastrenemia, carcinoma and affinity for cytochrome 450. [8,9,10]

Hence researchers have been attracted toward designing of reversible, shorter, and rapid acting acid pump antagonist. A research effort to identify reversible, short acting inhibitors of the gastric H^+/K^+-ATPase as an alternative antisecretory strategy to both histamine H_2-receptor antagonists and the long acting, irreversible inhibitors such as omeprazole has been conducted in a number of laboratories. [11,]

This has led to a class of compounds, the so called "K-site inhibitors", which inhibit the enzyme by binding competitively to potassium to the lumenal surface of the H^+/K^+-ATPase. Furthermore, the potential use of mildly basic molecules as pCABs (Potassium Competitive Acid Blockers) may lead to accumulation in the acidic parietal cell, leading to similar concentrations to those delivered by PPIs, affording additional opportunities for selectivity, potency and duration of action. Potassium-competitive acid blockers (pCABs), also known as acid pump antagonists (APAs), have become a focus of attention as a means of achieving rapid but potentially long-lasting inhibition of gastric acid secretion. Unlike the irreversible proton pump inhibitors (PPIs) they do not require acid activation and would be expected to be significantly more stable than PPIs under all physiological conditions. Thus, their pharmacokinetic half life can be significantly longer allowing active drug species to be present whenever parietal cells become activated. Therefore, full acid suppression from first dose together with long duration of action is expected to be key features of these reversible inhibitors. [12]

APAs are lipophilic and weak bases that have diverse structures such as, imidazopyridines, pyrimidines, imidazonaphthyridines, quinolines, etc. The APAs studied most extensively so far rely on substituted imidazo[1,2-a]pyridine derivatives . And they were shown to inhibit the gastric acid secretion by reversible and K^+ competitive binding to H+/K+ ATPase, and they also displayed excellent antisecretory properties. [13-16]

So, In the course of efforts to develop novel and potent APAs, It was thought to identify APAs that have a novel heterocyclic scaffold different from the well-known imidazo[1,2-a]pyridine. Hence 3-Quinazoline derivatives of the general formula (1) has been design to aquire good lipophilicity by two benzoyl substitution and high basicity due to presence of basic quinazoline moiety with amino moiety and different substituted amines. Amine moieties of the design molecule is thought to be undergo protonation reaction in acidic pH of stomach and that cationic derivative can inhibit the enzyme by binding competitively to potassium to the lumenal surface of the H^+/K^+-ATPase.

2. Materials and methods

All the melting points were determined in open capillaries in microprocessor based melting point apparatus model VMP-D (Veego make) and are uncorrected. Infrared spectra were recorded in KBr on 8400S Shimadzu Fourier Transform spectrophotometer. Proton Nuclear Magnetic Resonance spectra were taken on Bruker Avance 400 spectrophotometer

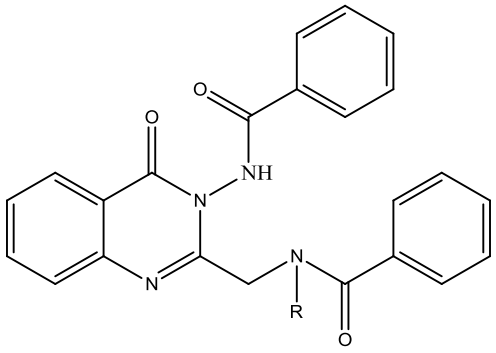


Figure-1: N-((3-Benzamido-4-oxo-3,4-dihydroquinolin-2-yl)methyl)-N-(substituted) phenyl benzamide (1)

at 400 MHz and the chemical shifts are given as parts per million (ppm) downfield from tetramethylsilane (TMS) as internal standard. Mass spectra were obtained on Perkin-Elmer LC-MS PE Sciex API/65. The reactions were monitored by thin layer chromatography (TLC) using silica gel-G (Hexane:Ethyl acetate, 1 : 1). TLC was performed on microscopic slides (2 × 7.5cms) coated with silica-gel-G and pre-coated silica gel 60 F_{254} strip. Spots were visualized under UV light and by exposure to iodine vapour.

2.2 GENERAL METHOD FOR SYNTHESIS OF COMPOUNDS SYNTHESIS OF N-CHLOROACETYL METHYL ANTHRANILATE (3)

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) at 5-10 ˚C temperature. The reaction mixture was stirred for 30 minutes. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to stand to attain room temperature and slowly poured into 100 ml ice water. The product formed was separated by filtration and washed successively with water till filterate showed neutral pH and then product was dried. The obtained product was purified by recrystallization from hexane.

synthesis of n-(3- methyl phenyl)-aminoacetyl methyl anthranilate (4)

The mixture of N-Chloroacetyl methyl anthranilate (1 gm, 0.0044mol) m-Toluidine (0.35 gm 0.0066 mol), Triethylamine (0.6 ml, 0.0044 mol) in dioxane was refluxed for 7 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature and slowly poured into 100 ml ice water and stirred with the help of glass rod for 15 minutes. The solid product formed was separated by filtration and washed successively with water and then dried. The obtained product was purified by recrystallization from Benzene.

synthesis of 3-amino-2-(3- methyl phenyl)-amino methyl-quinazolin-4(3h)-one (5)

The mixture of N-(3-methyl phenyl)-aminoacetyl methyl anthranilate (1.5 gm, 0.0052mol) and Hydrazine hydrate (80% v/v) (1 ml, 0.046 mol) was refluxed in absolute alcohol (20 ml) for 6-8 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature. The solid crystalline product was separated out on standing. The solid product formed separated was filtrated and washed successively with absolute alcohol and then dried.

synthesis of n-((3-benzamido-4-oxo-3,4-dihydroquinolin-2-yl)methyl)-n–(3-methyl pheny) benzamide (1a)

3-Amino-2-(3- methyl phenyl)-amino methyl-quinazolin-4(3h)-one (1 gm, 0.0035 mol), Sodium hydroxide (0.28 gm, 0.007 mol) and benzoyl chloride (0.82 ml, 0.007) was refluxed in dioxane (20 ml) for half hour. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature. The solid product formed was separated by filtration and washed successively with water and then dried. The obtained product was purified by recrystallization from Ethyl acetate.

Mass spectrum (in methanol) (*m/z)*: 489 (M + 1), 487 (M-1) **I.R (in KBr, cm^{-1}):** 3197 (-NH stretching of $CONH_2$), 1710 (C=O stretching of $CONH_2$) **^{1}H NMR (DMSO-d_6, 400 MHz):** 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*),δ 11.7 (s,1H, N*H*CO), δ 4.8 (s, 2H, CH_2), δ 2.5 (s, 3H, CH_3)

synthesis of n-(3- methoxy phenyl)-aminoacetyl methyl anthranilate

The mixture of N-Chloroacetyl methyl anthranilate (3 gm, 0.0132 mol) m-Anisidine (2.4 gm 0.0198 mol), Triethylamine (1.85 ml, 0.0132 mol) in dioxane was refluxed for 7 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature and slowly poured into 100 ml ice water and stirred with the help of glass rod for 15 minutes. The solid product formed was separated by filtration and washed successively with water and then dried. The obtained product was purified by recrystallization from Benzene.

synthesis of 3-amino-2-(3- methoxy phenyl)-amino methyl-quinazolin-4(3h)-one (4c)

The mixture of N-(4-methoxy phenyl)-aminoacetyl methyl anthranilate (1.7 gm, 0.0052mol) and Hydrazine hydrate (80% v/v) (1 ml, 0.046 mol) was refluxed in absolute alcohol (20 ml) for 6-8 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature. The solid crystalline product was separated out on standing. The solid product formed separated was filtrated and washed successively with absolute alcohol and then dried.

synthesis of n-((3-benzamido-4-oxo-3,4-dihydroquinolin-2-yl)methyl)-n–(3-methoxy phenyl) benzamide (1b)

3-Amino-2-(3- methoxy phenyl)-amino methyl-quinazolin-4(3H)-one (1 gm, 0.0035 mol), Sodium hydroxide (0.26 gm, 0.0066 mol) and benzoyl chloride (0.77 ml, 0.0066) was refluxed in dioxane (20 ml) for half hour. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature. The solid product formed was separated by filtration and washed successively with water and then dried. The obtained product was purified by recrystallization from Ethyl acetate.

Mass spectrum (in methanol) (*m/z)*: 505 (M + 1), 503 (M-1) **I.R (in KBr, cm^{-1}):** 3195(-NH stretching of $CONH_2$), 1695 (C=O stretching of $CONH_2$)

synthesis of n-(4- methoxy phenyl)-aminoacetyl methyl anthranilate

The mixture of N-Chloroacetyl methyl anthranilate (3 gm, 0.0132 mol) p-Anisidine (2.4 gm 0.0198 mol), Triethylamine (1.85 ml, 0.0132 mol) in dioxane was refluxed for 7 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature and slowly poured into 100 ml ice water and stirred with the help of glass rod for 15 minutes. The solid product formed was separated by filtration and washed successively with water and then dried. The obtained product was purified by recrystallization from Benzene.

synthesis of 3-amino-2-(4- methoxy phenyl)-amino methyl-quinazolin-4(3h)-one

The mixture of N-(4-methoxy phenyl)-aminoacetyl methyl anthranilate (1.7 gm, 0.0052mol) and Hydrazine hydrate (80% v/v) (1 ml, 0.046 mol) was refluxed in absolute alcohol (20 ml) for 6-8 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature. The solid crystalline product was separated out on standing. The solid product formed separated was filtrated and washed successively with absolute alcohol and then dried.

synthesis of n-((3-benzamido-4-oxo-3,4-dihydroquinolin-2-yl)methyl)-n–(4-methoxy phenyl) benzamide (1c)

3-Amino-2-(4- methoxy phenyl)-amino methyl-quinazolin-4(3H)-one (1 gm, 0.0035 mol), Sodium hydroxide (0.26 gm, 0.0066 mol) and benzoyl chloride (0.77 ml, 0.0066) was refluxed in dioxane (20 ml) for half hour. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature. The solid product formed was separated by filtration and washed successively with water and then dried. The obtained product was purified by recrystallization from Ethyl acetate.

Mass spectrum (in methanol) (*m/z*): 505 (M + 1), 503 (M-1) **I.R (in KBr, cm^{-1}):** 3195(-NH stretching of $CONH_2$), 1695 (C=O stretching of $CONH_2$). **^{1}H NMR (DMSO-d_6, 400 MHz):** 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*), 7.8 (d, 1H, Ar-*H*), 7.9 (t, 1H, Ar-*H*), δ 8.0 (d, 2H, Ar-*H*), δ 8.2 (d, 1H, Ar-*H*),δ 11.7 (s,1H, *NHCO*), δ 4.8 (s, 2H, CH_2), δ 2.5 (s, 3H, OCH_3)

synthesis of n-(2-chloro phenyl)-aminoacetyl methyl anthranilate

The mixture of N-Chloroacetyl methyl anthranilate (3 gm, 0.0132 mol) o-chloro Aniline (2.5 ml 0.0198 mol), Triethylamine (1.85 ml, 0.0132 mol) in dioxane was refluxed for 7 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature and slowly poured into 100 ml ice water and stirred with the help of glass rod for 15 minutes. The solid product formed was separated by filtration and washed successively with water and then dried. The obtained product was purified by recrystallization from Benzene.

synthesis of 3-amino-2-(2-chloro phenyl)-amino methyl-quinazolin-4(3h)-one

The mixture of N-(2- Chloro phenyl)-aminoacetyl methyl anthranilate (1.5 gm, 0.0047mol) and Hydrazine hydrate (80% v/v) (1.5 ml, 0.028 mol) was refluxed in absolute alcohol (20 ml) for 6-8 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature. The solid crystalline product was separated out on standing. The solid product formed separated was filtrated and washed successively with absolute alcohol and then dried.

synthesis of n-((3-benzamido-4-oxo-3,4-dihydroquinolin-2-yl)methyl)-n–(2-chloro phenyl) benzamide (1d)

3-Amino-2-(2- chloro phenyl)-amino methyl-quinazolin-4(3H)-one (1.5 gm, 0.0050 mol), Sodium hydroxide (0.4 gm, 0.01 mol) and benzoyl chloride (1.17 ml, 0.01) was refluxed in dioxane (20 ml) for half hour. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature. The solid product formed was separated by filtration and washed successively with water and then dried. The obtained product was purified by recrystallization from Ethyl acetate.

Mass spectrum (in methanol) (*m/z*): 509.4 (M + 1), 507 (M-1), 511 (M+2) **I.R (in KBr, cm^{-1}):** 3274 (-NH stretching of CONH), 1712 (C=O stretching of $CONH_2$), 3066 (C-H stretching Aromatic) **^{1}H NMR (DMSO-d_6, 400 MHz):** δ 7.1-7.3 (m, 5H, Ar-*H*), δ 7.4-7.8 (m, 9H, Ar-*H*), δ 7.9 (m, 1H, Ar-*H*), 8.0 (m, 1H, Ar-*H*), δ 8.2 (m, 1H, Ar-*H*),δ 12.0 (s,1H, *NHCO*), δ 4.0 (s, 2H, CH_2)

synthesis of n-(2, 4-dimethyl phenyl)-aminoacetyl methyl anthranilate

The mixture of N-Chloroacetyl methyl anthranilate (3 gm, 0.0132mol) 2,4-Dimethyl Aniline (2.44 ml 0.0198 mol), Triethylamine (1.85ml, 0.0132 mol) in dioxane was refluxed for 7 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature and slowly poured into 100 ml ice water and stirred with the help of glass rod for 15 minutes. The solid product formed was separated by filtration and washed successively with water and then dried. The obtained product was purified by recrystallization from Benzene.

synthesis of 3-amino-2-(2, 4- dimethyl phenyl)-amino methyl-quinazolin-4(3h)-one

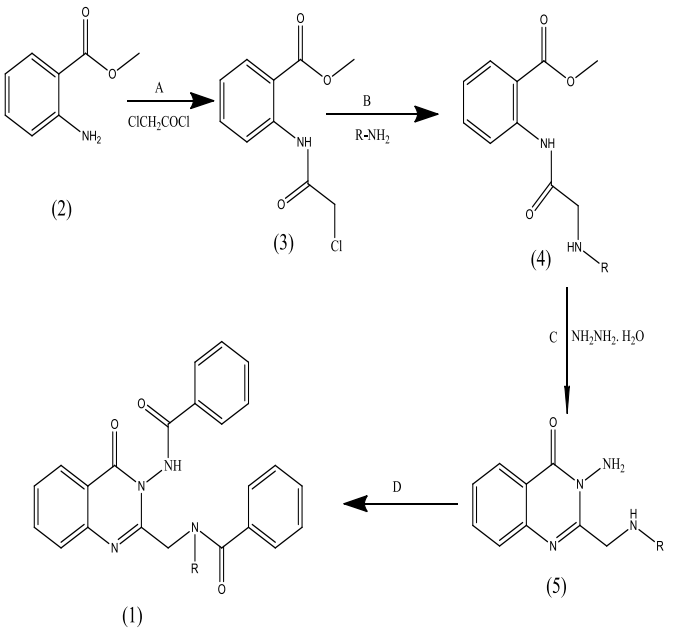
The mixture of N-(2,4-dimethyl phenyl)-aminoacetyl methyl anthranilate (3 gm, 0.0106 mol) and Hydrazine hydrate (80% v/v) (1.02 ml, 0.0063 mol) was refluxed in absolute alcohol (20 ml) for 6-8 hours. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature. The solid crystalline product was separated out on standing. The solid product formed separated was filtrated and washed successively with absolute alcohol and then dried.

synthesis of n-((3-benzamido-4-oxo-3,4-dihydroquinolin-2-yl)methyl)-n–(2,4- dimethyl phenyl) benzamide (1e)

3-Amino-2-(2,4-dimethyl phenyl)-amino methyl-quinazolin-4(3h)-one (0.9 gm, 0.003 mol), Sodium hydroxide (0.24 gm, 0.006 mol) and benzoyl chloride (0.84 ml, 0.006) was refluxed in dioxane (20 ml) for half hour. The progress of the reaction was monitored by thin layer chromatography. The reaction mixture was allow to cool to attain room temperature. The solid product formed was separated by filtration and washed successively with water and then dried. The obtained product was purified by recrystallization from Ethyl acetate.

Mass spectrum (in methanol) (*m/z*): 503.4 (M + 1), 501.4 (M-1) **I.R (in KBr, cm^{-1}):** 3242 (-NH stretching of $CONH_2$), 1687 (C=O stretching of $CONH_2$) **^{1}H NMR (DMSO-d$_6$, 400 MHz):** δ 6.8-7.0 (m, 3H, Ar-*H*), δ 7.4-7.8 (m, 9H, Ar-*H*), δ 7.9 (m, 1H, Ar-*H*), 8.0 (m, 1H, Ar-*H*), δ 8.2 (m, 1H, Ar-*H*),δ 12.0 (s,1H, N*H*CO), δ 4.0 (s, 2H, *CH$_2$*), δ 2.1 (s, 3H, *CH$_3$*), δ 2.4 (s, 3H, *CH$_3$*)

REACTION SCHEME:



R= 3-METHYL PHENYL, 3-METHOXY PHENYL, 4-METHOXY PHENYL, O-CHLORO ANILINE, 2,4-DIMETHYL ANILINE

A= Stirring at room temperature in glacial acetic acids. **B=** Heating under reflux condition in 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.

3. BIOLOGICAL ACTIVITY

The *in vitro* inhibitory activity of the N-((3-Benzamido-4-oxo-3,4-dihydroquinolin-2-yl)methyl)-N-(substituted) phenybenzamide derivatives on gastric H^+/K^+-ATPase were examined. The IC_{50} values were determined by average of triplicate experiments and the results are presented in Table 1. Omeprazole gastric H^+/K^+-ATPase inhibitor, were included as a reference compound. Several compounds exhibited potent inhibitory activity on gastric H^+/K^+-ATPase.

3.1 Treatment Procedure:

3.1.1 Preparation of Gastric H^+/K^+-ATPase from hog stomach[17,18]

Gastric H^+/K^+-ATPase was prepared from hog gastric mucosa as described previously (Shin et al., 2011). All operations were carried out at 1 to 4°C. The crude gastric mucosal membranes were collected from the stomach and homogenized in a solution of 0.25 M sucrose, 5 mM PIPES/Tris, pH 6.8, 1 mM EDTA, and 1 mM EGTA. The homogenate was centrifuged at 20,000*g* in a Sorvall GSA rotor (Thermo Fisher Scientific, Waltham, MA) for 45 min. The pellet was discarded, and the supernatant was centrifuged at 134,000*g* in a Beckman type 35 rotor (Beckman Coulter, Fullerton, CA) for 1 h. The microsomal membrane pellet was resuspended in a solution of 0.25 M sucrose, 5 mM PIPES/Tris, pH 6.8, 1 mM EDTA, and 1 mM EGTA and was purified on a step gradient sucrose solution composed of 34% (w/v) sucrose, 5 mM PIPES/Tris, pH 6.8, 1 mM EDTA, and 1 mM EGTA overlaid by a solution composed of 7.5% Ficoll, 0.25 M sucrose, 5 mM PIPES/Tris, pH 6.8, 1 mM EDTA, and 1 mM EGTA, using a SW 28 rotor (Beckman Coulter) at 130,000*g* for 2 h. The vesicles above the 7.5% Ficoll gradient step were collected and diluted by adding 3 volumes excess of a solution of 5 mM PIPES/Tris, pH 6.8, 1 mM EDTA, and 1 mM EGTA. The suspension was centrifuged at 130,000*g* for 1 h, and the pellet was resuspended in a solution of 0.25 M sucrose and 5 mM PIPES/Tris, pH 6.8.

3.1.2. Measurement of H^+,K^+-ATPase activity[17,18]

Gastric H^+/K^+-ATPase activity was measured by quantifying the release of inorganic phosphate from ATP in a 96 well format. Reactions were performed in a reaction mixture of 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. After preincubation at 37 °C for 30 min, the reaction was initiated by the addition of ATP at a final concentration of 0.2 mM and incubation at 37 °C for 20 min. The reaction was stopped by adding 15 µL of dye reagent containing 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, after which the absorbance was measured at 620 nm

with a ELISA reader. K^+-dependent ATPase activity was calculated as the difference between the activity in the presence and absence of KCl. For the controls with 0% inhibition and 100% inhibition, enzymatic reactions were carried out in the presence of 1% DMSO and omeprazole (0.56-14 µM), respectively.

4. RESULT AND DISCUSSION:

Table-1 H^+/K^+-ATPase inhibitory activity of compounds.

Sr. No.	Compd No.	R	pIC_{50} (µM)
1	1a	m-Methylphenyl	3.823909
2	1b	m-Methoxylphenyl	4.019691
3	1c	p-Methoxylphenyl	4. 57577
4	1d	o-Chlorophenyl	4.30103
5	1e	2,4-Dimethylphenyl	5.10103
6		Omeprazole	6.3

The H^+/K^+- ATPase inhibition activity of few 3-aminoquinazoline derivatives are reported in Table I. Compound-1a with methyl substituent on aromatic ring was found to inhibit H^+/K^+- ATPase enzyme considerable extend. However the compound was still to inferior than standard compound Omeprazole. Finally we decided to replace methyl group with more electron rich moiety methoxy to improve bacisity of compound by which there was considerable improvement of inhibitory activity. Comparison between position of methoxy on aromatic ring. Para substituted compound (1c) showed better inhibitory activity compare to meta substitution (1b). Introduction of Chlorine moiety (1d) on aromatic ring caused decrease in activity as basicity of molecule decrease by electron withdrawal effect. Compound with two methyl group on aromatic ring (1e) was most active with maximum inhibitory activity.

5. CONCLUSION

From the above study we conclude that in the series of 3-aminoquinazoline derivatives introduction of more electron rich substituent make compound more basic which leads to improvement of inhibitory activity on H^+/K^+-ATPase enzyme.

6. REFERENCES:

1. Roberts S and McDonald M. Burger's Medicinal Chemistry and Drug Discovery, John Wiley Publication, New Jersey, 6th edition (2003):Vol.42003: 86–121.
2. Larner AJ and Lendrum R. Oesophageal candidiasis after omeprazole therapy, Gut, 1992; 33**:**860–861.
3. Michetti P, Dorta G and Wiesel. pH Effect of whey-based culture supernatant of Lactobacillus acidophilus (johnsonii) La1 on Helicobacter pylori infection in humans, Digestion. 1999; 60(3):203-209
4. Lamberts R, Creutzfeldt W, Stockmann F, Jacubaschke U, Maas S, and Brunner G. Long-term omeprazole treatment in man: effects on gastric endocrine cell populations, Digestion, 1988; 39**:**126–135.
5. Lamberts R, Creutzfeldt W, Struber HG, Brunner G, and Solcia E. Long-term omeprazole therapy in peptic ulcer disease: gastrin, endocrine cell growth, and gastritis, Gastroenterology, 1993; 104**:**1356–1370.
6. Freston JW, Borch K, Brand SJ, Carlsson E, Creutzfeldt W, Hakanson R, Olbe L, Solcia E, Walsh JH, and Wolfe MM. Effects of hypochlorhydria and hypergastrinemia on structure and function of gastrointestinal cells: A review and analysis, Digestive diseases and sciences, 1995; 40**:**50s–62s.
7. Tytgat GN. Shortcomings of the first-generation proton pump inhibitors, European journal of gastroenterology and Hepatology, 2001; 13**:**S29–S33.
8. Goto Y and Kishi S. Experimental model of acute esophagitis in the rat and comparison of effectiveness of antiulcer drugs including H_2-antagonists and omeprazole. The Japanese journal of Pharmacology, 1989; 49**:**193P.
9. Inatomi N, Nagaya H, Takami K, Shino A, and Satoh H. Effects of a proton pump inhibitor, AG-1749 (lansoprazole), on reflux esophagitis and experimental ulcers in rats, The japanese journal of Pharmacology, 1991; **55:**437–451.
10. Wallmark B, Briving C, Fryklund J, Munson K, Jackson R, Mendlein J, Rabon E, and Sachs G. Inhibition of gastric H^+/K^+-ATPase and acid secretion by SCH28080, a substituted pyridyl(1,2*a*)imidazole, Journal of biological Chemistry, 1987; **262:**2077–2084.
11. Kromer W, Postius S, and Riedel R. Animal pharmacology of reversible antagonism of the gastric acid pump, compared to standard antisecretory principles, Pharmacology, 2000; 60**:**179–187.

12. Gedda K, Briving C, Svensson K, Maxvall I, and Andersson K. Mechanism of action of AZD0865, a K^+-competitive inhibitor of gastric H^+/K^+-ATPase. Biochemical Pharmacology, 2007; 73:198–205.
13. Keeling DJ, Taylor AG, and Schudt C. The binding of a K^+ competitive ligand, 2-methyl, 8-(phenylmethoxy)imidazo(1,2-a)pyridine 3-acetonitrile, to the gastric H^+/K^+-ATPase. Journal of Biological Chemistry, 1989; **264:**5545–5551.
14. Pope AJ, Boehm MK, Leach C, Ife RJ, Keeling D, and Parsons ME. Properties of the reversible, K^+-competitive inhibitor of the gastric H^+/K^+-ATPase, SK&F 97574. *In vitro* activity, BiochemIcal Pharmacol, 1995; **50:**1543–1549.
15. 15. Pope AJ and Parsons ME. Reversible inhibitors of the gastric H^+/K^+-transporting ATPase: a new class of anti-secretory agent. Trends in Pharmacological Science, 1993; 14:323–325.
16. Cheon HG, Lim H, and Lee DH. Biochemical properties of a newly synthesized H^+/K^+-ATPase inhibitor, 1-(2-methyl-4-methoxyohenyl)-4-[(3-hydroxypropyl) amino]-6-methyl-2,3-dihydropyrrolo[3,2-*c*]quinoline. European Journal of Pharmacology, 2001; 411:181–186.
17. Munson K and Sachs G. Inactivation of H^+/K^+-ATPase by a K^+ competitive photo affinity inhibitor. Biochemistry, 1988; 27:3932–3938.
18. Sachs, G. Physiology of the Gastrointestinal Tract, Raven Press, New York, Second edition (1987): chapter 28, 865.
19. Lindberg P, Brandstrom A, Wallmark B, Mattsson H, Rikner L, and Hoffmann K. Omeprazole: the first proton pump inhibitor, Medicinal research reviews, 1990; 10:1–54.