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QSAR Study of N-((3-Benzamido-4-oxo-3,4-Dihydroquinazolin 2-yl) methyl)-N-(Substituted) Phenyl Benzamide as Antiulcer Agents

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ABSTRACT

Suppression of gastric acid secretion by use of proton pump inhibitors is an efficient way to control hyperacidity complications. An inhibitory activity of N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin -2-yl) methyl)-N-(substituted phenyl) benzamides on H+/K+-ATPase was established and reported earlier. Thus, it is significant to develop more promising agents by quantitative structure-activity relationship (QSAR) study of 37 ligands by multi-linear regression method to link the structures of molecules with inhibitory activity on H+/K+-ATPase (pIc50). QSAR model was built using genetic function approximation protocol of the software Discovery Studio Version 2.1 using training set carrying 23 compounds. The remaining 14 compounds were used as a test set. The generated model was showing satisfying statistical qualities, r2=0.84 and predicted correlation coefficient r2pred=0.88. The theoretical approach indicates that an increase in Log D, Shadow_XZ and SC 2, and reduction of Shadow_Z length causes more inhibition of enzyme by molecule.

KEYWORDS

Antisecretory Agents, Antiulcer Activity, H+/K+-ATPase, H+/K+-ATPase Inhibitors, QSAR, Quinazolines

INTRODUCTION

Maximum people worldwide experience acidity occasionally. The prevalence of hyperacidity is increasing day by day due to multiple factors like, frequent use of Nonsteroidal anti-inflammatory drugs, by H-pylori infection, life style and daily habits of the people, which include eating high amount of meal and lying down after taking meal, food with high fat amount, types of food that can tend to increases acidity in stomach, family history of GERD, drinks like alcohol, smoking, high body mass index (BMI), less physical activity and age (Matsuura et al., 2013; Ter et al., 1998). The continuous experience of acidity symptoms on a regular basis can produce countable effects on quality of life (Dean et al., 2004; Tack et

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al., 2012; Pilotto et al., 2016; Maekawa et al., 1998). Additionally Gastric hyperacidity eventually may precipitates into Gastroesophageal reflux disease (GERD) (Craven et al., 2018, Johnson et al., 2004). It is a state of gastric hyperacidity where acid content from the stomach reverse back into the esophagus (Ness-Jensen et al., 2012). If GERD is left untreated, it may lead to life-threatening complications, like peptic ulcer, perforation and bleeding of GIT due to ulcer, Failure of esophageal peristalsis (Achem. Et al, 2003) and laryngopharyngeal carcinoma (Jarosz et al., 2014;). The worldwide prevalence of GERD is about 8.8–25.9% in Europe, 18.1–27.8% in North America, 11.6% in Australia, 8.7–33.1% in the Middle East, 2.5–7.8% in East Asia and 23.0% in South America (El-Serag et al., 2014, Mahadeva et al., 2005; Eusebi et al., 2018). Simultaneously, there is also an increase in economic burden of health care system by rise in prevalence of the GERD and other complications (Becher et al., 2011). In most of such cases of gastric hyperacidity, people are not consulting with health care provider, but there are the cases were people are needed to be hospitalized as well as have to go though invasive surgeries when there are complications due to high GIT (Gastrointestinal system) damage (Thukkani et al., 2010; Sonnenberg et al., 1994). Despite of high research and discovery of different class of new drugs till date in this area, there is no promising agent to deal with the chronic hyper gastric acidity, GERD and Gastric ulcer (Vaezi et al., 2017; Fass et al., 2001). The drugs like antacids and other present antisecretory agents can deal with Hyperacidity and neutralize it or decrease the acid secretion. But even though people are getting temporary relief from the symptoms on taking available drugs and relapse of acidity is frequently seen in many cases. Therefore the permanent solution is needed to be searched to address this situation. In addition, many patients are required to take medicines for longer time to deal with gastric disturbance generated by treatment of different types of cancers or while undergoing long term treatment of some infections like Tuberculosis. So, drug induced Hyperacidity is also the matter of concern.

As a part of our affords to improve the quality of life of people suffering from gasric hyperacidity and to prevent other complications, in our earlier work, We have synthesized and reported the Antisecretory activity of N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin -2-yl) methyl)-N-(substituted phenyl) benzamides by inhibition of H^+/K^+ ATPase. The activity was measured 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 (parmar, 2014;Parmar & suhagia, 2021). It is significant to discover new molecules of the same series with high inhibitory action on H^+ /K^+ -ATPase enzyme with the help of QSAR (Quantitative Structure Activity Relationship) (Kenard et al., 1969; Bhadoriya et al., 2015; Hansch et al., 2004).

In continuation of our affords, in this present work we are proposing QSAR model which can be used to get more efficient agents of the series of N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin -2-yl) methyl)-N-(substituted phenyl) benzamides. QSAR remains an efficient method for building mathematical models to search out a statistically significant correlation between the chemical structure and continuous (pIC_{50}, pEC_{50}, Ki, etc.) or categorical/binary (active, inactive, toxic, nontoxic, etc.) toxicological/biological property using classification and regression techniques, respectively (Eriksson et al., 2003; Hernandez et al., 2009; Worachartcheewan et al., 2014, Hanch et al., 1995). QSAR methods are important tool for prediction of biological effect of chemical compounds based on mathematical and statistical relations (Hansch et., 1964; Hansch et., 2004; Chtita et al., 2016, Abraham et al., 2000). QSAR being one of the Computer added drug design (CADD) method which can help to find out more active and novel agent of known series of molecules that can be synthesized and screened subsequently (Sabet et al., 2010; Chen et al., 2015; Zhang et al., 2011). Here, we present a quantitative structure–activity relationship (QSAR) study of 37 legands to rationalize the relationship between the structural and physicochemical features of a series of N-((3-Benzamido-4-oxo-3, 4 dihydro quinazolin-2-yl) methyl)-N-(substituted phenyl) benzamide with biological activity, which would help to discover more efficient and promising Antiulcer agents. (Talele et al., 2010)

Moreover, it was reported earlier in QSAR study of schiff bases of quinazolinones as H^+ /K^+ ATP-ase inhibitors, it was proposed that compounds must have high value of polar surface area, hydrophobic constant, and polarizablity. These properties was playing crucial role in the activity of the designed

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