QSAR Modeling of CCK2 Receptor Antagonists Utilizing Computed Structural Indices: A Case Study

Sisir Nandi, Department of Pharmaceutical Chemistry, Global Institute of Pharmaceutical Education and Research, Affiliated to Uttarakhand Technical University, Kashipur, India
Mridula Saxena, Department of Chemistry, Amity University, Lucknow, India
Anil Kumar Saxena, Division of Medicinal and Process Chemistry, CSIR-Central Drug Research Institute, Lucknow, India

ABSTRACT
In the present case study, a QSAR model has been developed to identify CCK2 receptor antagonists. The earlier reported 3D pharmacophore modeling of these molecules involved commercial software. Since the reduction in the cost involved in the drug discovery phase is very crucial, in the present study, QSAR models based on the structural indices including 1D, 2D and 3D indices computed from the structures of CCK2 receptor antagonists has been developed utilizing NanoBRIDGES software which is openly accessible (http://nanobridges.eu/software/). This QSAR model is not only comparable to the earlier reported model, but it also reasonably predicts the external set of nine compounds including the drug benzotript and the most active 6a described in earlier work on structure-based homology model CCK2 receptor antagonists as antiulcer agents and thus may be useful in virtual screening for the identification of new CCK2 receptor antagonists.

KEYWORDS
Benzotript Compounds, Binding Affinity Prediction, Calculated Structural Indices, CCK-2R Antagonists, Drug Design, Freely Accessible Internet Resources, GA-MLR, QSAR

INTRODUCTION
CCK represents cholecystokinin, which is one of the members of the gastrin/cholecystokinin family of peptide hormones. CCK acts on CCK1 and CCK2 receptors. The CCK1 receptor is present in the gallbladder and pancreas and is involved in the regulation of enzyme secretion by the pancreas, secretion of gastric acid in the stomach, intestinal motility and signaling of satiety. The CCK2 receptor is expressed in the brain and the gastric fundus (Innis and Snyder, 1980). CCK occupies the CCK2 receptor present in the brain and mediates anxiety, panic, and pain which are correlated with the stimulation of gastric acid secretion via activation of cholecystokinin. It may produce rebound hyperacidity and gastroesophageal reflux via pentagastrin mediated CCK2 receptor stimulation in

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peripheral tissues. If this problem persists for a long time, it may cause gastrointestinal adenocarcinoma cancer and death of the patients (Wank 1995). Therefore, significant attempts have been made to develop small molecule CCK2 receptor antagonists having beneficial antisecretory actions as well as in therapy anxiety, pain and sleep disorders (Sandvik and Waldum, 1991; Walish, 1990; Jensen, 1996; Crespi, 1990). Potent CCK2 receptor antagonists include glutamic acid derivatives such as spiroglumide (CR2194), itriglumide and CR2622; 1,4 benzodiazepines analogues: L-365260, L-369466, L-736380, L-740093, YM-022 and YF476; dipeptoids: CI-988; benzobicyclooctane analogues: JB95008, JB93182; 1,5 benzodiazepine-2,4-dione analogues: GV191869X, GR199114X and GV 150013X; 1-benzazepine-2-one analogues:CP310713 and CP212454; ureidoacetamide analogues: RP73870 RP69758 and DA-3934; quinazoline-based analogues: LY-202769; pyrazolidinone and related heterocyclic analogues: LY288513; indol-2-one analogue: AG-041R, and tetronothiodin (Berna et al. 2007; McDonald 2001). But most of these compounds have poor bioavailability and the limitation of physicochemical data, including solubility and ligand selectivity towards receptor binding (McDonald, 2001).

1,3,4-benzotriazepines were developed from the core nucleus of 1,4-BDZ CCK2 receptor antagonists and were shown to produce a higher affinity towards CCK2 receptors than the parent compound. The 1,4-BDZ CCK2 receptor antagonists are chiral with lower affinity to bind the receptor and are difficult to synthesize whereas 1,3,4-benzotriazepine analogs are achiral with higher specificity towards the CCK2 target and are relatively easy to synthesize. Therefore, McDonald and colleagues synthesized a number of 1,3,4-benzotriazepine analogs and performed an in-vivo biological activity on CCK2 receptor antagonism by inhibiting pentagastrin stimulation in isolated, lumen-perfused immature rat stomachs (McDonald et al. 2007). Further, Spencer and co-workers prepared many 1H-1,3,5-benzotriazepine-2,4(3H,5H)-diones compounds which were achiral and produced higher biological activity than 1,4-BDZ CCK2 receptor antagonists (Spencer et al. 2008). Further, anthranilic sulfonamide based CCK-2R antagonists were reported with better CCK-2R selectivity with promising pharmacokinetics and in vivo activity in inhibiting pentagastrin-stimulated gastric acid secretion in the rat (Pippel et al., 2009a, 2009b).

The drug discovery and development is a complex process and very expensive both in terms of time and money. The two major phases are drug discovery phase and clinical development phase. The discovery phase involves laboratory synthesis, structural elucidation, in vitro and in vivo biological activity evaluation, SAR studies, followed by animal toxicity studies. The clinical development involves phase I, phase II and phase III clinical trials. The pharmacoinformatics based rational drug design helps to accelerate the progress in the drug discovery phase with the application of computer algorithm in the design and discovery of a lead by making quantitative correlations between structures and activity-property-toxicities in terms of QSAR, QSPR and QSTR through virtual screening which is used to predict the activity, property and toxicities of chemicals prior to experimental analyses thus minimizing the cost of a drug discovery (Dearden, 2012; Roy et al., 2015). Since the major thrust in the drug discovery process has been on reducing the money and the time where computer-aided drug design (CADD) approaches, including virtual screening play a major role, the use of inexpensive or free internet resources instead of expensive and sophisticated software has a key importance particularly for the academic research in the developing countries.

In view of the above, our group (Gupta et al., 2012), developed a pharmacophore model on a data set of 92 compounds using the Hypogen algorithm of DS 2.0 and later (Gupta et al., 2013) performed the homology modeling, design, and synthesis of some CCK-2R antagonists. Both these works involved the use of commercial DS 2.0 and Schrodinger software and the activity of the newly designed and synthesized molecules were not predicted from the model (Gupta et al., 2012) but were of course well explained by the structure-based homology model. Thus, in search of devising a simple QSAR model, an attempt has been made in the present study to utilize freeware accessible through the Internet resources for making the drug discovery phase cost effective in terms of input and output.
Significance of Molecular Surfaces and Different Visualization Tools in Drug Designing: A Review

Molecular Spaces Quantum Quantitative Structure-Properties Relations (QQSPR): A Quantum Mechanical Comprehensive Theoretical Framework