SYNTHESIS, ANOREXIGENIC ACTIVITY AND QSAR OF SUBSTITUTED ARYLOXYPROPANOLAMINES

Shipra Srivastava, Kalpana Bhandari, Girija Shankar, H. K. Singh and Anil K. Saxena

Medicinal and Process Chemistry Division, Central Drug Research Institute, Lucknow-226001, India, Pharmacology Division, Central Drug Research Institute, Lucknow-226001, India

Abstract. Substituted aryloxypropanolamines (6-20) were synthesized and evaluated for their anorexigenic activity. Among them 4-cyanoaryloxy (7), 2-methylarylloxy (9), 2-methoxy aryloxy (10), 4-acetamidoarylloxy (15), 4-bromoarylloxy (16) and 4-ethylaminarylloxy (20) exhibited potent anorexigenic activity. According to QSAR studies, the electronic parameter \( \sigma \) plays an important role in describing the variance in activity.

Introduction

The obesity is a chronic and stigmatized disorder in both children and adults, it is widely prevalent in the developed as well as in the developing countries throughout the world.\(^1\)\(^2\) It is responsible for various adverse effects on health, being associated with an increase in morbidity and mortality from non-insulin dependent diabetes mellitus (NIDDM), hypertension, hypercholesterolemia, sleep apnea and other medical conditions.\(^3\) Currently available therapies\(^4\)\(^5\) for the treatment of obesity are effective only when they are being used and the ability to achieve long-term weight loss by behavioral modification (diet and exercise) is limited. These realizations have resulted in intensified effort to develop new pharmacological approaches for the treatment of obesity.
The three types of drugs\(^6\) for the treatment of obesity are: (i) ‘drugs’ which can reduce the amount of fat absorbed in the gut; (ii) ‘thermogenic’ drugs, which increase the amount of fat that is metabolized in the body; and (iii) ‘satiety’ drugs or ‘appetite suppressants’, which reduce the appetite. Orlistat\(^7\) and Sibutramine\(^8\) are the only two drugs that are currently available for the long term treatment of obesity. Sibutramine suppresses appetite by altering norepinephrine and 5HT metabolism in the brain where as the other drug, Orlistat, reduces fat absorption by inhibiting gastric, pancreatic and other gastrointestinal lipases. Both of these drugs are of limited efficacy. Therefore there is a need of drug with better efficacy and potency.

Selective optimization of side activities (SOSA)\(^9\) has been reported to be an approach for new lead. In view of the anorectic side effects\(^10,11\) of Fluoxetine,\(^12,13\) an antidepressant drug (a selective serotonin reuptake inhibitor), it appeared of interest to substitute the secondary NH group by other substructures so as to optimize the anorexigenic side effect and minimize the antidepressant effect. These studies involving the synthesis of substituted aryloxy propanolamines, their pharmacological evaluation and QSAR analysis are reported in this paper.

Chemistry

The synthetic route for substituted aryloxypropanolamines (6-20) is outlined in scheme 1.