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QSAR Study of N-[3-(1,1,2,2-Tetrafluoroethoxy)benzyl]-N-(3-phenoxyphenyl)trifluoro-3-amino-2-propanol Derivatives as Antiatherogenic Agents

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Coronary heart disease is one of the dreaded diseases prevailing now a day, which can be treated by the use of more potent and selective agents. One of such agent is Cholesterol ester transfer protein inhibitors. N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]-N-(3-phenoxyphenyl)-trifluoro-3-amino-2-propanol derivatives has screened as antiatherogenic agents. So, N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]-N-(3-phenoxyphenyl)trifluoro-3-amino-2-propanol derivatives were selected for quantitative structure activity relationships, for the present study. QSAR studies with significant equations indicate that the molar refractivity in the R_3 position of the parent compound negatively contributed for activity.

Key Words: QSAR, Antiatherogenic agents, Coronary heart disease, Cholesterol ester transfer protein, Descriptors.

INTRODUCTION

Coronary heart disease (CHD) is one of the dreaded diseases prevailing now a day, which can be treated by the use of more potent and selective agents. One of such agent is cholesterol ester transfer protein (CETP) inhibitors[1]. CETP is a plasma glycoprotein that mediates the transfer of neutral lipids among various lipoproteins. CETP facilitates the transfer of cholesteryl ester (CE) from high density lipoprotein (HDL) to apolipoprotein-B, containing lipoproteins such as very low density lipoproteins (VLDL) and low density lipoproteins (LDL). CETP plays a potential proatherogenic role by moving CE from HDL to pro-atherogenic VLDL and LDL particle, thereby lowering atheroprotective HDL-cholesterol (HDLC) level. CETP also plays a potential antiatherogenic role in reverse cholesterol transport RCT pathway and CETP-mediated transfer of CE from peripheral tissuses to the liver by regulating HDL to LDL increases LDL-cholesterol (LDLS) and lowers HDLC level. So now a day, there is intense interest in identifying potent and selective CETP inhibitors

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to find out whether they could represent a new therapeutic approach to improve that HDLC/LDLC ratio and provide an important therapeutic benefit to CHD patient with low HDLC levels[2]. In view of this, N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]-N-(3-phenoxy phenyl)trifluoro-3-amino-2-propanol derivatives were selected for quantitative structure activity relationships (QSAR), for the present study. In addition, nowhere quantitative structure activity analysis has been reported for N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]-N-(3-phenoxyphenyl)trifluoro-3-amino-2-propanol derivatives as antiatherogenic agents.

EXPERIMENTAL

All computational work was performed on Pentium IV workstation-using software Openstate 4 version 6.5.1 statistical software developed by William G. Miller. Total of 30 compounds were selected for the present study (Table-1). Regression analysis correlates independent x variable (physico-chemical parameter) and dependent y variable (biological data). The correlation coefficient is a relative measure of the quality of fit to the mode, its value depend on the over all variance of the data, r^2 is a measure of the explained variance, most often given as a percentage value. The standard deviation is an absolute measure of the quality of fit. The F value is a measure of the statistical significance of the regression model. Often perfect correlations are obtained in PLS analysis, due to usually large numbers of x variables. A cross validation procedure was used to select the model having the highest predictive values, served PLS runs were performed in which one (leave one out technique) or several objects were eliminated from the data set. Only the excluded objects are predicted by the corresponding models.

The biological activity data for the QSAR analysis was obtained from Richard work[2] (Table-1). The biological activities of the N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]-N-(3-phenoxyphenyl)trifluoro-3-amino-2-propanol derivatives (Fig. 1) are given as IC_{50} for inhibitory action as antiatherogenic agents. The biological activities were converted in to -log IC_{50}. The physico-chemical descriptors were calculated from *The substituents constants for correlation analysis in chemistry and biology developed by Corwin Hansch and Albert Leo*. The physico-chemical parameters and -log IC_{50} values were loaded in to the MS excel worksheet and saved as coma delimited file. Openstat 4 version 6.5.1 software was used to derive the regression equations between physicochemical descriptors and biological activity of the compounds. The statistical parameters that were considered for the analysis are correlation coefficient (r), squared correlation coefficient (r^2), F test value and VIF. The selected significant equations were validated by leave one out method (LOO).

TABLE-1
SUBSTITUTION ON THE PARENT NUCLEUS AND
BIOLOGICAL DATA OF THE SERIES

Compd. No.	R^1	R^2	R^3	R^4	Cytotoxicity -log IC_{50}
1	H	H	H	H	-0.778
2	H	*i*-pr	H	H	-0.361
3	H	Tri fluoro methoxy	H	H	-0.579
4	H	H	F	H	-0.612
5	Cl	Cl	H	H	0.220
6	H	Et	Cl	H	0.045
7	H	Et	H	H	0.000
8	H	Me	H	H	-0.041
9	H	*t*-but	H	H	-0.579
10	H	Me	Me	H	-0.812
11	H	Me	F	H	-0.491
12	H	Cl	Cl	H	-0.892
13	H	Et	H	Me	-0.531
14	H	Me	H	H	-1.123
15	H	*n*-but	N But	H	-0.716
16	H	H	Trifluoromethoxy	H	-0.838
17	H	H	Me	H	-1.056
18	H	Tri fluoro methoxy	H	H	-1.012
19	H	H	Npr	H	-1.328
20	H	F	H	F	-1.060
21	H	H	Pr	H	-1.434
22	H	H	H	H	-0.986
23	H	H	Cl	H	-1.000
24	H	H	OC_3H_7	H	-1.530
25	H	H	Pr	H	-1.496
26	H	H	Trifluoromethoxy	H	-1.478
27	H	H	NH_2	H	-0.950
28	H	OMe	H	H	-1.193
29	NO_2	F	H	H	-0.748
30	H	H	NO_2	H	-1.466

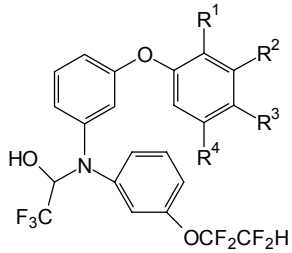

Fig. 1. Parent structure of the N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]-N-(3-phenoxy phenyl)-trifluoro-3-amino-2-propanol derivatives series

RESULTS AND DISCUSSION

30 Compounds belonging to N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]-N-(3-phenoxy phenyl)-trifluoro-3-amino-2-propanol category were taken for this study. The biological activities data for N-[3-(1,1,2,2-tetrafluoroethoxy)benzyl]-N-(3-phenoxy phenyl)-trifluoro-3-amino-2-propanol derivatives were taken from literature. The IC_{50} values were transformed into -log IC_{50}. Stepwise regression analysis was performed by taking -log IC_{50} as dependent variable and descriptors as independent variables. From the analysis significant equations were selected which were validated by leave one out method. The significant regression equations are:

$$-\log IC_{50} = -0.044 (\pm 0.014) R^3 MR-0.603 \quad (1)$$

$$n = 30, F = 10.489, r = 0.822, r^2 = 0.644, VIF = 1$$

$$-\log IC_{50} = -0.071 (\pm 0.013) R^3 MR + 0.303 (\pm 0.074) R_{..} \text{sum-}0.756 \quad (2)$$

$$n = 30, F = 16.64, r = 0.828, R^2 = 0.685, VIF = 1$$

$$-\log IC_{50} = -0.0839 (\pm 0.013) R^2 MR + 0.367 (\pm 0.074) R_{..} \text{sum-}0.846 (\pm 0.366) R^3R -0.827\text{-}(3) \quad (3)$$

$$n = 30, F = 14.65, r = 0.993, r^2 = 0.625, VIF = 1$$

Total 30 compounds are taken for the study. From above equations it is clear that group at position 2 effects biological activity of the parent compound significantly. Descriptors effects the biological activity significantly are lipophilicity, molar refractivity in the pool of descriptors, taken for study.

Conclusion

QSAR studies with significant equations indicate that the molar refractivity in the R^3 position of the parent compound negatively contributed for activity. Eqn. 1 with monoparameter regression analysis has least significant with activity. But along with positive contributor hydrophobic descriptors, value of the correlation coefficient was increased significantly. In eqn. 3, electronic parameter also negatively contributed for the activity. From this study it is concluded that the compound with hydrophobicity along with molar refractivity is important for the activity.

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