National Journal of Medical and Allied Sciences

[ISSN Online: 2319 – 6335, Print: 2393 – 9192|Original article |Open Access]

Website:-www.njmsonline.org

2D QSAR STUDY ON SERIES OF TACRINE AND RELATED COMPOUNDS WITH ACETYLCHOLINESTERASE INHIBITORY ACTIVITY

Zeeshan Fatima,[1] Anil K.Saxena[2]

1.Amity Institute of Pharmacy Amity University Uttar Pradesh Lucknow Campus, India 2 Medicinal and Process Chemistry Division. Central Drug Research Institute,Lucknow India

Abstract

Introduction: Acetylcholine esterase inhibitors are the drugs that provide symptomatic treatment for Alzheimer's disease. The AChE inhibitors, which interact with both, peripheral and active site of the enzyme,can also inhibit the formation of βA4-amyloid protein(βAP) in addition to AChE inhibition. In order to gain a deeper insight of drug receptor interaction QSAR study has been performed.

Material and Methods: Compounds reported in the literature has been taken up for the study. The physicochemical parameters were calculated and it was then correlated with the given acetylcholinesterase activity using Systat 7 statistical software.

Results: A series of 77 structurally diverse group AChE inhibitors reported in the literature have been investigated and a comprehensive QSAR study has been performed. A meaningful QSAR equation has been derived which explains the hydrophobic and molar refractivity as a key physicochemical parameters contributing towards activity.

Conclusion: The QSAR model developed in this study can provide a better insight of the physiochemical parameters and can be useful in designing novel acetylcholinestrae inhibitors.

Keywords: Alzheimers, Acetylcholinesterae inhibition, 2D QSAR, regression analysis.

Corresponding author: Zeeshan Fatima, Email: dr.dilshadali@yahoo.com

INTRODUCTION

Alzheimer's disease is a devastating degenerative disorder of the central nervous system that results in gradual deterioration of cognitive function and severe alteration of personality [1,2]Degeneration of neurons in the nucleus basalis Meynert, the origin of the major cholinergic projections to the neocortex, [3-6]occurs early in the course of the disease, and is correlated with the cognitive decline. The biochemical deficit also extends to other neurochemicals systems affecting the level of monamine transmitter,[7] but cholinergic neurotransmission is the one that is greatly affected. Using *in-vivo* rodent models, several cholinergic enhancement strategies including neuropharmacological approaches (acetylcholinesterase inhibitors), neurotrophic factor administration (nerve growth factor),[8]and transplantation of cholinergic-enriched fetal grafts have been developed and were proven to be effective in alleviating lesion-induced cognitive deficits. On the basis of preclinical and clinical studies cholinesterase inhibitors are the only approved drugs for the treatment of cognitive deficit associated with Alzheimers disease. [9] The AChE inhibitors restore deficient cholinergic neurotransmission. by increasing the available acetylcholine within the active synapse Increasing the level of acetylcholine has been regarded as one of the most promising methods for the palliative treatment of AD [10,11] Indeed, the three drugs (Donepezil, Rivastigmine, Galanthamine currently approved for the treatment of Alzheimer's disease are cholinomimetics with the pharmacological profile of acetylcholinesterase inhibitors[12,13] These drugs are prescribed to treat symptoms related to memory loss, thinking, language judgments and other thought processes. Beside these three acholinesterase inhibitors, another drug Memantine[14]has been approved to treat moderate to severe Alzheimer's. It is the first novel class of Alzheimer's disease medications acting on

the glutamatergic system by blocking NMDA-type glutamate receptors.

Extensive efforts by different researchers have led to discovery of a number of potent AChE inhibitors with structural diversity, such as xanthostigmine, physostigmine, phenserine, ,huperzine-A, bis-tacrine, bis-huperzin-B[15-20] Studies have shown that the AChE inhibitors, which interact with both, peripheral and active site of the enzyme,[21-24]can also inhibit the formation of βA4-amyloid protein(βAP) in addition to AChE inhibition. This could be achieve by blocking the active site of acetylcholnesterase enzyme. Tacrine was launched as the first drug for the treatment of Alzheimers related symptoms. Howeverit is no longer usebecause of its hepatotoxicity. In order to improve its efficacy, its several analogs have been synthesized and evaluated for their AChE inhibitory activity. The comparative QSAR studies on most of these compounds have been reported byHanch and Maurizino[25].However in these studies they could not draw any conclusion about the effect of steric and hydrophobiocparameters on activity because of high colinearity between these parameters. Therefore they suggested about the need of carefully designed analogs for filling the gap in the parameter space and for getting the sound basis for building more informative QSAR. Later Maurizinoetal[26] synthesized tetrahydroacridine analogs with non collinear substituents in terms of steric and hydrophobioc parameters. However the best 2D and 3D QSAR models developed for these and related 11H-Indeno [1, 2-b] quinolin-10ylamine analogs, did not include the N- 9-substituted compounds even though they had high activity. The reason given for their exclusion wasthat the conformational flexibility of both benzyl and heptyl groups at N-9 position ofacridine had made the choice of proper physicochemical parameter questionable. Moreover in these models as well as in the docking studies neither N- 9-substituted nor 1- hydroxy (velnacrine) analogs were considered. Hence it appeared of interest to relook into these studies for the development of comprehensive 2D models taking into consideration the issues of colinearity between the steric and hydrophobic parameter and the inclusion of N-9 substituted and 1-hydroxy analogs in the study .

Structure of the inhibitors Fig.1

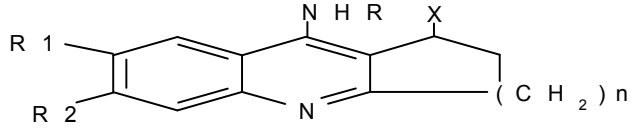

Fig.1

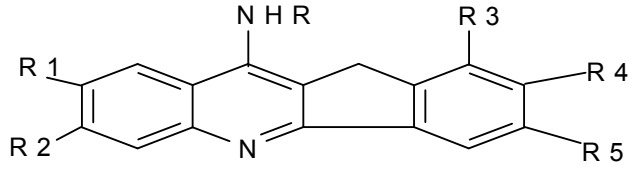

Fig. 2

This study was undertaken to develop a correlation between acetylcholineesterase activity of tacrine analogs with different physicochemical parameters.

MATERIAL AND METHODS

This study was conducted at Central Drug Research Institute for a period of six month. The reported data of 77 compounds from three different sources [35-37] was considered for QSAR analysis. The AChE inhibitory (IC50) activities of these compounds were from two different labs; however compounds from both the labs were tested using Ellmanetalprotocol.Since the activity of the standard drug tacrine was different in the dataset reported from two different groups being 0.319 μM in the dataset reported by Shustkeetal and 0.25 μM in the other two datasets. Hence the activities of the compounds reported in the latter two data sets were normalized by multiplying them by the factor of 1.27 (tac1\tac2m 0.319\0.25=1.27) (Table 1,2)

2D QSAR Development

The preliminarily 2D QSAR analysis was carried out using the AChE inhibitory activity of all the 77 compounds as dependent and thephysicochemical parameters such as hydrophobicity (π), steric (Es,MR) and electronic (R,F,σ) and the indicators variables as the independent parameters.The values of different physicochemical parameters were computed from the literature values[38]and the two indicator parameters I_1 and I_2 were used for the presence of hydroxyl group(I_1=1) and the tetrahydroacridine nucleus(I_2=1) respectively. The multiparameter analysis was carried using systat software 7.0

RESULTS

2D QSAR

The multiparameter regression analysis(MLR) using different permutation and combinations of the independent parameters viz hydrophobicity (π), steric (Es,MR) and electronic (R,F,σ) and the indicators variables led to the development of the 2D QSAR model (eq1 ,where the figures in parentheses describe the standard error of the regression coefficient, n represents the number of data points, r is the correlation coefficient, s is the standard error from the regression and F is the measure of statistical significance of the regression model.

$-\log IC_{50}$= 0.798(±0.220) πR_2-0.179(±0.042) MR_1-0.019(±0.005) MRR -1.284 (±0.171) I_1 + 1.251 (±0.215) I_2 –0.282

n=77, r=0.784, s=0.584, F= 22.760 eq1

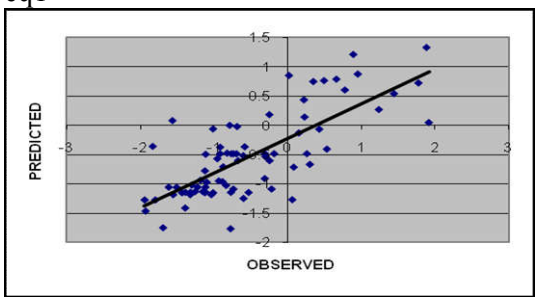

Fig 3 Graph showing linear relationship between the observed and predicted values.This model with moderate correlation coefficient value (0.784), low standard error (0.584 0), high statistical significance ($F_{5, 71\ \alpha\ 0.001}$ =5.08; $F_{5, 71}$ = 22.760) and with>99.9% values for regression coefficients well describes the variation in the observed acetylcholinesterase inhibitory activity of all the 77 compounds of the data set. as shown by comparison of observed and calculated acetylcholinesterase inhibitory activity of these molecules (table 3, fig.3). It is interesting to note that there is no intercorrelation between the independent parameters (r <0.5) (Table 4).

Table 4: Correlation matrix (r values) of physicochemical parameters

	- $LOGIC_{50}$	ΠR_2	MR_1	MRR	I_1	I_2
-$LOGIC_{50}$	1.000					
ΠR_2	0.389	1.000				
MR_1	0.004	0.059	1.000			
MRR	-0.323	0.029	-0.243	1.000		
I_1	-0.477	0.047	-0.318	0.469	1.000	
I_2	0.102	0.229	0.135	0.453	0.463	1

DISCUSSION

The issues of co-linearity between the steric and hydrophobic parameter and the inclusion of N-9 substituted and 1-hydroxy analogs of tacrine which was not reported in the earlier studies was resolved.[25-28] It is evident from the equation that hydrophobicity and steric effects play an important role in the variation of activity. Thus the hydrophobicity of the substituents(R_2) at 6th position for tacrine and velnacrine and 7th position of 11H-Indeno[1,2-b] quinolin-10ylamine analogs contributes positively while the increase in bulk at 7th position(R1) for tacrine and velnacrine and 8th position of11H-Indeno[1,2-b] quinolin-10ylamine contributes negatively for the activity. This indicates that for molecule to possess acetylcholinesterase inhibitory activity the molecule must be hydrophobic in nature.[30,31]The result also indicates that bulky substituents at the specified position will be detrimental for the activity.Further the presence of hydroxyl group in the nucleus in the prototypes (I_1=1) and tetrahydroacridine(I_2 =1) contributes negatively and positively respectively thus indicating that the tetyrahydroacridine nucleus devoid of the hydroxyl group best suits for activity.

CONCLUSION

The comprehensive QSAR performed in this study has given a better insight about the structural modification that can be incorporated, in order to produce novel molecule with acetylcholinestrase activity.Further exploration with different scaffold will enhance better understanding of contributing physicochemical parameters towards acetylcholinesterase activity.

Additional files

Additional File – 1: Table 1 – Data Set 1 Tacrine Related Molecules
Additional File – 2: Table 2 – Data Set 2 Tacrine Related Molecules
Additional File – 3: Table 3 – Physicochemical 2D Parameters

Acknowledgement: The author is thankful to CSIR-CDRI for carrying this study during her research.

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Conflicts of Interest: Nil Source of Funding: Nil

Citation: Fatima Z, Saxena AK. 2D QSAR Study on Series of Tacrine and Related Compounds With Acetylcholinesterase Inhibitory Activity. National Journal of Medical and Allied Sciences 2015; 5(1): 87-91.

Table 1

Compd no	R	R1	R2	n	X	IC_{50} ®	$IC_{50}^{\#(N)}$	-log
1	H	H	H	2	OH	4.00	4.00	-0.602
2	H	Cl	H	2	OH	24.70	24.70	-1.393
3	H	H	Cl	2	OH	0.0117	0.0117	1.921
4	H	H	CH_3O	2	OH	2.00	2.00	-0.301
5	H	H	CF_3	2	OH	1.77	1.77	-0.248
6*	H	H	F	2	OH	0.292	0.292	0.535
7*	H	H	H	1	OH	5.97	5.97	-0.776
8*	CH_3	H	H	2	OH	1.76	1.76	-0.245
9*	N-C_3H_7	H	H	2	OH	13.3	13.3	-1.124
10	$(CH_3)_2N(CH_3)_2$	H	H	2	OH	7.68	7.68	-0.885
11	$(CH_2)_2C_6H_5$	H	H	2	OH	3.39	3.39	-0.53
12*	$(CH_2)_2OC_6H_5$	H	H	2	OH	3.98	3.98	-0.599
13	$(CH_2)_2CH(C_6H_5)_2$	H	H	2	OH	49.3	49.3	-1.693
14*	$(CH_2)_2CH(4FC_6H_4)_2$	H	H	2	OH	87.8	87.8	-1.943
15	$(CH_2)_2CH(3-$	H	H	2	OH	63.0	63.0	-1.799
16	$CH_2C_6H_5$	H	H	2	OH	32.2	32.2	-1.508
17	$CH_2(2\text{-}ClC_6H_4)$	H	H	2	OH	10.3	10.3	-1.013
I8*	$CH_2(3\text{-}ClC_6H_4)$	H	H	2	OH	13.3	13.3	-1.124
19	$CH_2(4\text{-}ClC_6H_4)$	H	H	2	OH	27.2	27.2	-1.435
20	$CH_2(2\text{-}FC_6H_4)$	H	H	2	OH	41.3	41.3	-1.616
21	$CH_2(3\text{-}FC_6H_4)$	H	H	2	OH	13.1	13.1	-1.117
22	$CH_2(4\text{-}FC_6H_4)$	H	H	2	OH	16.7	16.7	-1.223
23	$CH_2(2\text{-}CH_3OC_6H_4)$	H	H	2	OH	36.0	36.0	-1.556
24	$CH_2(3\text{-}CH_3OC_6H_4)$	H	H	2	OH	21.1	21.1	-1.324
25*	$CH_2(4\text{-}CH_3OC_6H_4)$	H	H	2	OH	10.9	10.9	-1.037
26*	$CH_2(2\text{-}CH_3C_6H_4)$	H	H	2	OH	5.89	5.89	-0.77
27*	$CH_2(3\text{-}CH_3C_6H_4)$	H	H	2	OH	24.5	24.5	-1.389
28	$CH_2(4\text{-}CH_3C_6H_4)$	H	H	2	OH	21	21	-1.322
29	$CH_2(2\text{-}CF_3C_6H_4)$	H	H	2	OH	13.3	13.3	-1.124
30	$CH_2(2\text{-}CF_3C_6H_4)$	H	H	2	OH	14.2	14.2	-1.152
31	$CH_2(4\text{-}CF_3C_6H_4)$	H	H	2	OH	18.1	18.1	-1.258
32	$CH_2C_6F_5$	H	H	2	OH	12.6	12.6	-1.1
33	$CH_2(2\text{-}C_4H_3S)$	H	H	2	OH	15.3	15.3	-1.185
34	$CH_2C_6H_5$	H	Cl	2	OH	1.30	1.30	-1.114
35	$CH_2(4\text{-}FC_6H_4)$	H	Cl	2	OH	0.823	0.823	0.084
36	$CH_2C_6H_5$	H	F	2	OH	8.63	8.63	-0.936
37*	$CH_2(2\text{-}CFC_6H_4)$	H	F	2	OH	20.1	20.1	-1.303
38	$CH_2C_6H_5$	H	CF_3	2	OH	68.2	68.2	-1.834
39	H	CH_3	H	2	H	8.1	10.33	-1.014
40	H	H	CH_3	2	H	0.1	0.127	0.894
41	H	Cl	H	2	H	0.55	0.7018	0.154
42	H	H	Cl	2	H	0.0099	0.126	1.889
43	H	NO_2	H	2	H	3	3.828	-0.583
44*	H	H	NO_2	2	H	0.028	0.0357	1.447
45	H	H	OCH_3	2	H	0.35	0.4466	0.35
46*	H	NH_2	H	2	H	3.8	4.8488	-0.686
47	H	H	F	2	H	0.087	0.1110	0.955
48	H	Cl	Cl	2	H	0.47	0.5997	0.222
49	H	OCH_3	OCH_3	2	H	5.2	6.6352	-0.822
50	$CH_2C_6H_5$	CH_3	H	2	H	3.7	4.7212	-0.674
51	$CH_2C_6H_5$	H	CH_3	2	H	0.75	0.957	0.019
52	$CH_2C_6H_5$	H	Cl	2	H	0.17	0.2169	0.664
53	$CH_2C_6H_5$	NO_2	H	2	H	1.6	2.0416	-0.31
54	$CH_2C_6H_5$	H	NO_2	2	H	4.8	6.1248	-0.787
55	C_7H_{15}	CH_3	H	2	H	0.39	0.4976	0.303
56*	C_7H_{15}	H	CH_3	2	H	0.13	0.1658	0.78
57	C_7H_{15}	H	Cl	2	H	0.013	0.01658	1.78
58*	C_7H_{15}	H	NO_2	2	H	0.29	0.37	0.431
59	C_7H_{15}	H	OCH_3	2	H	0.46	0.5869	0.231
60	C_7H_{15}	H	F	2	H	0.045	0.0574	1.241
61(tacrine)	H	H	H	2	H	0.28	.319	0.498

Table 2

Comp.	R	R1	R2	R3	R4	R5	IC50 µM	IC_{50} #	-log IC_{50}
62	H	H	H	H	H	H	0.68	0.8636	0.064
63	H	NH_2	H	H	H	H	5.9	7.493	-0.875
64	H	H	NO_2	H	H	H	67.5	85.34	-1.931
65	H	H	NH_2	H	H	H	29	36.83	-1.566
66	H	H	Cl	H	H	H	6.5	8.255	-0.917
67	H	H	F	H	H	H	1.2	1.524	-0.183
68	H	H	H	OCH_3	H	H	1.6	2.002	-0.308
69	H	H	H	H	OCH_3	H	6.5	8.255	-0.917
70	H	H	H	H	H	OCH_3	4.3	5.461	-0.737
71	H	H	H	CH_3	H	H	3.9	4.953	-0.695
72	H	H	H	H	H	CH_3	4.6	5.842	-0.766
73	H	H	H	H	F	H	0.43	0.5461	0.263
74	H	H	H	H	Cl	H	5.4	6.858	-0.836
75	$CH_2C_6H_5$	H	H	H	H	H	7.1	9.017	-0.955
76	CH_3	H	H	H	H	H	1.3	1.651	-0.218
77	C_7H_{15}	H	H	H	H	H	4.3	5.461	-0.737

Normalized IC_{50} values

Table 3

Comp no	IIR2	MRR1	MRR	I_1	I_2
1	0	1.03	1.03	1	1
2	0	6.03	1.03	1	1
3	0.71	1.03	1.03	1	1
4	-0.02	1.03	1.03	1	1
5	0.88	1.03	1.03	1	1
6	0.14	1.03	1.03	1	1
7	0	1.03	1.03	1	0
8	0	1.03	5.65	1	1
9	0	1.03	14.96	1	1
10	0	1.03	24.83	1	1
11	0	1.03	34.74	1	1
12	0	1.03	40.2	1	1
13	0	1.03	67.05	1	1
14	0	1.03	41.58	1	1
15	0	1.03	41.58	1	1
16	0	1.03	30.1	1	1
17	0	1.03	35	1	1
18	0	1.03	35	1	1
19	0	1.03	35	1	1
20	0	1.03	29.89	1	1
21	0	1.03	29.89	1	1
22	0	1.03	29.89	1	1
23	0	1.03	36.84	1	1
24	0	1.03	36.84	1	1
25	0	1.03	36.84	1	1
26	0	1.03	34.62	1	1
27	0	1.03	34.62	1	1
28	0	1.03	34.62	1	1
29	0	1.03	33.99	1	1
30	0	1.03	33.99	1	1
31	0	1.03	33.99	1	1
32	0	1.03	25.402	1	1
33	0	1.03	23.54	1	1
34	0.71	1.03	30.1	1	1
35	0.71	1.03	41.88	1	1
36	0.14	1.03	30.1	1	1
37	0.14	1.03	33.99	1	1
38	0.88	1.03	30.1	1	1
39	0	5.65	1.03	0	1
40	0.56	1.03	1.03	0	1
41	0	6.03	1.03	0	1
42	0.71	1.03	1.03	0	1
43	0	7.36	1.03	0	1
44	-0.28	1.03	1.03	0	1
45	-0.02	1.03	1.03	0	1
46	0	5.42	1.03	0	1
47	0.14	1.03	1.03	0	1
48	0.71	6.03	1.03	0	1
49	-0.02	7.87	1.03	0	1
50	0	5.65	30.1	0	1
51	0.56	0	30.1	0	1
52	0.71	1.03	30.1	0	1
53	0	7.36	30.1	0	1
54	-0.28	1.03	30.1	0	1
55	0	5.65	33.53	0	1
56	0.56	1.03	33.53	0	1
57	0.71	1.03	33.53	0	1
58	-0.28	1.03	33.53	0	1
59	-0.02	1.03	33.53	0	1
60	0.14	1.03	33.53	0	1
61	0	1.03	1.03	0	1
62	0	1.03	1.03	0	0
63	0	5.42	1.03	0	0
64	-0.28	1.03	1.03	0	0
65	-1.23	1.03	1.03	0	0
66	0.71	1.03	1.03	0	0
67	0.14	1.03	1.03	0	0
68	0	1.03	1.03	0	0
69	0	1.03	1.03	0	0
70	0	1.03	1.03	0	0
71	0	1.03	1.03	0	0
72	0	1.03	1.03	0	0
73	0	1.03	1.03	0	0
74	0	1.03	1.03	0	0
75	0	1.03	30.1	0	0
76	0	1.03	5.65	0	0
77	0	1.03	33.35	0	0