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QSAR Studies of Some Synthetic Structurally Related Androstene Derivatives as Anti-Inflammatory Agents

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Abstract

The use of steroids in the acute and emergency conditions of inflammation is well established. Most of the time they are given chronically to the patients with arthritis. The present study focuses on developing substantial quantitative structure activity relationship models of certain steroidal derivatives reported to be as anti-inflammatory agents. The QSAR models of androstene derivatives were developed using ED_{50}, log ED_{50} and 1/log ED_{50} values of anti-inflammatory agents. The models developed have shown significant correlation between the anti-inflammatory activity and some of the structural parameters. The best fit model has shown r^2 of 0.9081, q^2 of 0.8310 and F-values of 29.6585.

Keywords: Steroids; Androstene; Anti-inflammatory; QSAR

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Introduction

Drug designing is a continuous and iterative process, which starts with some lead molecule of interesting biological profile and ends with the optimization of this lead, leading for the selection of candidate molecule for drug development [1]. Computer aided drug design has received considerable and justified attention in recent years. Quantitative structure-activity relationship is an area of research pioneered by Hansch and Fujita [2], is based on the concept that there is a relationship between properties of compounds (biological activity, etc.) and the structure of the molecules of those compounds. Since then QSARs methods have been extensively applied in a drug discovery, toxicity prediction and regulatory decisions. The increase in the use of QSAR early in the drug discovery process as a screening and enrichment tool helps in the elimination and further development those chemicals that lack drug-like properties. It attempts to model the activity of a series of compounds using measured or computed properties of the compound.

Since 1949, when Hansch described the use of coricosteroids in rheumatoid arthritis, they have become very useful in the management of many different rheumatic conditions. Corticosteoids like Beclomethasone, Betamethasone, and Cortisone etc. show complex antiinflammatry and immunomodulatory effects [3]. They inhibit the migration of leucocytes to the sites of inflammation and interfere with the function of leucocytes, endothelial cells and fibroblast. They also suppress the production and release of factors involved in inflammatory responses such as cytokines, prostaglandins and leukotrienes [4-6]. A large number of steroidal anti-inflammatory agents have been designed and developed by our group since a long time. It was planned to investigate in-silico prediction of activity, i.e., QSAR among these synthesized steroidal anti-inflammatory agents.

The original Hansch work used multi linear regression (MLR) analysis to combine different descriptors in data set. In our present study we have made use of BESERGMS (Best-multi linear regression) analysis. The activity of synthesized compounds was calculated experimentally using rat-paw odema method [7]. The lipophilic parameters were calculated theoretically using Pallas 20, Hyper Chem. Various other descriptors were explored using software like Chem 3D, codessa etc. The 3D descriptors were determined with the help of Dragon software. QSAR models were developed using BESREGMS option built in Codessa software and cross validation was done using Leave-one-out (LOO) method.

Experimental protocol

QSAR analysis

To develop a QSAR models for newly synthesized 16-(2-and 3-pyridylmethylene) androstene derivatives, Chem 3D, Dragon and Codessa software were used. The total of about 1897 different descriptors physicochemical, topological, geometrical, constitutional, 2D and 3D descriptors were calculated and these number of descriptors were reduced to final set of 97, by rationally stepwise elimination of lesser significant ones based on their one parameter and multiparameter r^2 values. In subset only those descriptors were choosen which were having $r^2 \geq 0.1$.

The heuristic method was used as final statistical tool for developing QSAR relations using the software Codessa. In case of heuristic method, a pre-selection of descriptors was accomplished. All the descriptors were checked to ensure that value of each descriptor was available for each structure and there is significant variation in these values. Descriptors for which values were not available for every structure in the data in question were discarded. Thereafter, the one parameter correlation equations for each descriptor were calculated.

The maximum number of descriptors involved in a correlation was choosen in accordance with the ratio of number of compounds to number of descriptors as 4:1. As a final result, the heuristic method yields a list of best ten correlations each with highest r^2 and F values. Many such attempts were carried out to obtain significant correlations for each congeneric series. The statistical significance of each correlation was determined on the basis of the value of F-criterion and magnitude of cross-validated r^2. In the next step, predictive ability of the equation is tested with the help of LOO method.

Results and Discussion

The structures of the series of androstene derivatives 54 DP, 59DP, 60DP, 62DP-72DP, 76RG, 87RG and 88RG which were synthesized in our laboratory [8-12] are given in **Figure 1**. The results of their anti-inflammatory activity, determined using rat-paw odema method in terms of ED_{50}, log ED_{50} and $1/ED_{50}$ values are given in **Table 1**. Despite having similar steroid backbone, changes in molecular structure among these therapeutic corticosteroids result in significant variability in activity.

A total of about 1700 different descriptors physiocochemical, topological, electrotopological, geometrical, constitutional, 2D and 3D descriptors were calculated by the software: Pallas 20, hyperchem, Chem3D, Dragon and Codesssa. The Number of descriptors was reduced to final set of 64, by rationally stepwise elimination of the insignificant ones based on their one parameter and multiparameter r^2 values. In sub set only those descriptors were chosen which were having $r^2 \geq 0.1$. The heuristics and multi linear regression analysis (MLRA) was used as final statistical tool for developing QSAR relations using the software Codessa. The final QSAR models, along with their respective q^2, r^2, F-value and probability factor are given in **Tables 2-4**. These relations

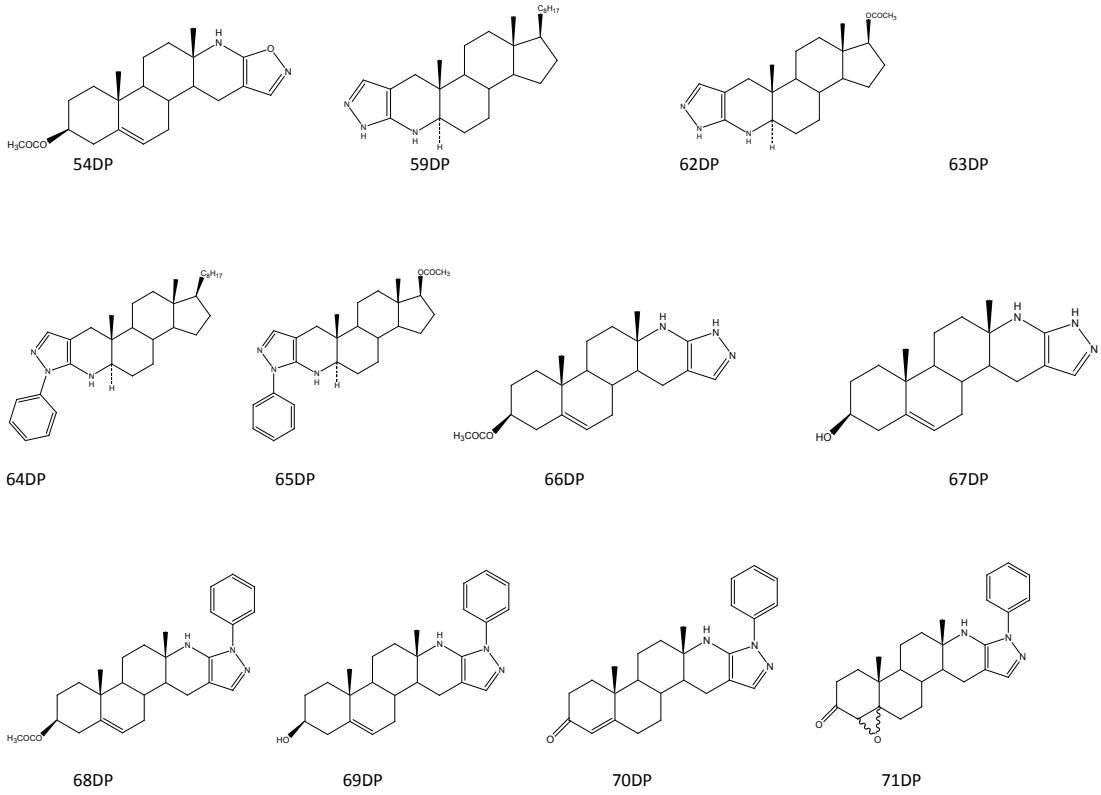

Figure 1 The structures of the compounds whose QSAR was performed.

Table 1 Showing the ED_{50}, log ED_{50} and $1/ED_{50}$ values of the compounds.

Compounds	Activity (ED_{50})	Log Activity	1\A
54DP	5.67	0.753583	0.176367
59DP	2.97	0.4727564	0.3367
62DP	1.39	0.1430148	0.71942
63DP	2.65	0.4232458	0.37736
64DP	0.63	-0.2006594	1.5873
65DP	0.36	-0.4436975	2.7777
66DP	1.57	0.1958996	0.63694
67DP	1.52	0.1818435	0.65789
68DP	0.59	-0.2291479	1.69492
69DP	0.65	-0.1870866	1.53846
70DP	0.37	-0.4317982	2.7027
71DP	0.35	-0.4559319	2.85714
72DP	1.95	0.2900346	0.51282
60DP	2.61	0.4166405	0.383142
76RG	2.93	0.4668676	0.341297
87RG	3.67	0.564666	0.27248
88RG	1.41	0.1492191	0.70922

Table 2 Significant linear and logarithmic QSAR polynomial equations along with the statistical parameters for a series of steroids using anti-inflammatory activity as property parameter.

Eqn. No.	Equation	r^2	q^2	s^2	F-value
1	A= -16.569 + 5.4989*R6u + 11.322*DISPe + 0.016351*mp + 0.59686*No. of double bonds	0.9081	0.8310	0.2551	29.6585
2	A= 1.9444 – 1.2398*T(N-N) + 4.5989*E1s – 3.2262*Mor24M + 77.454*Relative no. of F atoms	0.9081	0.8120	0.2551	29.6576
3	A= -33.307 – 1.1272*T(N-N) + 9.0278*E1m – 3.1350*Mor24m + 67.042*Relative no. of F atoms	0.9063	0.8300	0.2601	29.0308
4	A= -2.4126 – 1.0104*T(N-N) + 11.695*E1m – 2.4212*Mor24m + 2.5748*DISPe	0.9024	0.7938	0.2710	27.7397
5	A= -16.107 + 5.9397*R6u + 10.311*DISPe + 1.6523*Av. Information content (order2) + 13.305*Max partial charge for N atom	0.8976	0.8335	0.2842	26.3078
6	A= -7.6514 – 1.0383*T(N-N) + 16.448*E1m – 4.1936*Mor24m + 2.4477*RDF55v	0.8996	0.8022	0.2870	26.0233
7	A= 0.38444 – 1.1502*T(N-N) + 6.1507*E1s – 2.3837*Mor24m + 2.8594*DISPe	0.8926	0.7184	0.2982	24.9344
8	A= 2.3040 – 1.2149*T(N-N) + 16.013*E1m – 2.9251*Mor24m - 40.723*G3u	0.8916	0.7974	0.3011	24.6637
9	A= 2.4332 – 1.1931*T(N-N) + 7.7234*E1m – 2.1698*Mor16e + 3.0528*DISPe	0.8904	0.7652	0.3044	24.3701
10	A= -16.370 + 6.0823*R6u + 10.649*DISPe + 1.6708* Av. Information content (order2) – 1.1041*No. of N atoms	0.88890	0.8050	0.3082	24.0250
11	A= -2.0256 – 1.2077*T(N-N) + 12.831*E1m – 2.2541*Mor24m	0.8676	0.7821	0.3393	28.3986
12	A= 2.3865 – 1.2109*T(N-N) + 11.384*E1m – 11.510*GNar	0.8496	0.6955	0.3855	24.4758
13	A= -11.974 + 8.2322*DISPe + 6.3140*R6u	0.7423	0.6531	0.6531	20.1666
14	A= 5.6996 – 2.4489*Mor16e – 1.4089*T(N-N) + 35.370*R1m+	0.8958	0.8060	0.2672	37.2339
15	A= 10.414 – 3.1131*Mor16e – 1.4800*T(N-N) + 42.446*$R1m^+$ - 1.6720*R4e	0.9215	0.8375	0.2178	35.2405

Table 3 Significant linear and logarithmic QSAR polynomial equations along with the statistical parameters for a series of steroids using logarithm of anti-inflammatory activity as property parameter.

Eqn. No.	Equation	r^2	q^2	s^2	F-value
1	*LOG A= -0.11079 + 3.0027*DISPe + 1.1310*R6u – 0.39859*X5v	0.8394	0.7514	0.0289	22.6532
2	LOG A= -1.7721 + 1.5440*Mor26m – 39.029*FNSA-3 + 0.0040713*mp	0.8718	0.7493	0.0230	29.4624
3	LOG A= -1.5121 + 1.363*Mor26m – 40.969*FNSA-3 + 0.0029662*mp – 0.33457*Mor24m	0.8930	0.7665	0.0208	25.0465
4	LOG A= -0.25577 + 2.0047*Mor26m – 29.508*FNSA-3 + 1.1953 Mor23v + 0.62199 Mor15v	0.8968	0.7791	0.0201	26.0762
5	LOG A= -0.7864 + 1.6072*Mor26m – 35.105*FNSA-3 + 0.0034184*mp – 0.12515*X5v	0.8973	0.7535	0.0200	26.2022
6	LOG A= -0.21524 + 4.5257*E1m + 1.4150*Mor26m + 0.0049426*mp – 7.8277*E1e	0.8980	0.7535	0.0199	26.3980
7	LOG A= -2.1967 + 1.7250*Mor26m – 38.127*FNSA-3 + 0.0047030*mp + 0.082489* No. of double bonds	0.8985	0.7661	0.0198	26.5562
8	LOG A= -2.4539 + 2.28295*E1m + 2.0142*Mor26m + 1.3862*Mor23v + 0.32186*Ui	0.8992	0.8097	0.0196	26.7539
9	LOG A= -2.1098 + 3.1448*E1m + 1.7032*Mor26m + 1.0871*Mor23v + 0.072236*PCR	0.98084	0.8356	0.017	29.7382
10	LOG A= -2.5669 + 1.9666*Mor26m – 36.388*FNSA-3 + 0.0051370*mp – 0.45770*Mor8p	0.9104	0.8035	0.0174	30.4748
11	LOG A= 3.4897 + 2.6011*E1m + 2.0443*Mor26m + 1.3211*Mor23v – 5.4851*relative no. of single bonds	0.9162	0.8492	0.0163	32.8137
12	LOG A= 2.4903 + 1.9027*Mor26m – 39.719*FNSA-3 + 0.0054865*mp – 2.2155*R2e	0.9195	0.8286	0.0157	34.2712
13	*LOG A= -0.74051 + 2.7214*DISPe – 0.83321*Mor16e – 31.662*$R1v^+$ + 3.4346*Av structural information content (order2)	0.9200	0.8427	0.0156	34.4771

Table 4 Significant linear and logarithmic QSAR polynomial equations along with the statistical parameters for a series of steroids using reciprocal of anti-inflammatory activity as property parameter.

Eqn. No.	Equation	r^2	q^2	s^2	F-value
1	*1/A= 4.8406 – 3.1351*Mor26m – 4.4874*E1s	0.7002	0.6011	0.3004	16.3475
2	*1/A= 1.5545 – 2.1602*Mor26m + 1.555*Mor16e – 20.413*R1m$^+$	0.8209	0.6644	0.1932	19.8669
3	1/A= 4.9436 – 3.999Mor26m + 97.493*FNSA-3 – 18.224*RPCG	0.8549	0.7651	0.1566	25.5255
4	1/A = 3.9438 – 4.0403*Mor26m + 100.37*FNSA-3 – 3.1429*Polarity parameter/square distance	0.8714	0.8097	0.1388	29.3535
5	1/A = 2.6426 – 3.7620*Mor26m + 90.182*FNSA-3 – 2.8379*Polarity parameter/square distance + 0.060245*RDF55v	0.8887	0.8219	0.1301	23.9578
6	1/A = 6.6042 – 4.8252*Mor26m + 128.27*FNSA-3 – 20.225*RPCG + 0.63912*Mor18e	0.8900	0.7585	0.1286	24.2692
7	1/A = -6.8155 – 5.005*Mor26m + 69.629*FNSA-3 + 1.3294*X5 + 100.04*Moment of inertia A	0.8952	0.8038	0.1225	25.6283
8	1/A = 0.53565 – 5.1695*Mor26m + 118.28*FNSA-3 + 0.71793*X5 + 0.77602*Mor18e	0.8952	0.7395	0.1225	25.6289
9	1/A = 3.5984 – 3.4324*Mor26m + 94.131*FNSA-3 – 3.011* Polarity parameter/square distance -0.69436*Mor18m	0.8983	0.8018	0.1189	26.4849
10	1/A = 2.8273 – 3.6304*Mor26m + 85.507*FNSA-3 – 2.4059*Polarity parameter/square distance -0.73357*Mor16e	0.9038	0.8306	0.1124	28.1925
11	1/A = 3.7188 – 3.7838*Mor26m + 95.643*FNSA-3 – 3.0874*Polarity parameter/square distance -0.80094*Mor23m	0.9051	0.8122	0.1110	28.6012
12	1/A = 3.1600 – 3.8070*Mor26m + 79.803*FNSA-3 – 3.6137*Polarity parameter/square distance -0.92430*DISPp	0.9094	0.8396	0.1059	30.1110
13	1/A = 3.7869 – 3.4404*Mor26m + 101.79*FNSA-3 – 2.5672* Polarity parameter/square distance + 1.0379*Mor24m	0.9158	0.8530	0.0984	32.6454
14	1/A = 3.3955 – 3.9501*Mor26m + 86.671*FNSA-3 – 2.8389* Polarity parameter/square distance -1.0518*Mor23v	0.9159	0.8553	0.0983	32.6779
15	1/A= 8.4700 – 4.0093*DISPe + 1.6553*Mor16e – 3.2610*Mor26m – 9.9243*Av. Structural Information content (order 2)	0.9250	0.8573	0.0876	37.0234

all appeared to show significant correlations (r^2 range 0.7002 to 0.98084) and good predictivity performance (q^2 range 0.6011 to 0.8573).

Conclusion

The steroids represent a class of compounds with numerous and widespread biological effects, anti-inflammatory activity being one such important effect. Among themselves steroids can vary markedly in their efficacy, adverse effect, pharmacokinetics and pharmacodynamics. There is a continued interest in the development of potent anti-inflammatory steroid.

In our present study, QSAR models have been developed that are based on molecular, submolecular, physicochemical, 2D and 3D properties obtained from the various software. In contrast to using the entire the matrix of structural parameters as in PLS analysis and automatic forward inclusion MLR technique was used to arrive at the primary property determinants with minimal number of independent variables or descriptors.

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