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In Silico Adme and Toxicity Profile of Some Epalons Derived from Ganaxolone

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ABSTRACT

The present work involves the evaluation of drug-likeness of some epalons derived from Ganaxolone. Selected pharmacokinetic and toxicity properties were predicted by using ACD labs Chemsketch ver 12.0 and ADME& TOX boxes web version of Pharma Alogrithms. Almost all drugs like epalon derivatives were predicted to be less toxic(LD_{50} 920 to 1000 mg/kg) with an enhancement in lipophilicity (C log P 4.56 to 7.39, molar refractivity 105.22 to 117.89cm^3,parachor 865.1 to 983.3 cm^3),protein binding 64% to 90%) and oral bioavailability (64 to 85%). But, there is no marked change in type and rate of absorption, first pass metabolism, volume of distribution and refractive index. In conclusion, ADME and toxicity properties of these compounds suggest advantages over the Ganaxolone.

KEYWORDS: Ganaxolone, Epalons, ADME & TOX profile, *In silico* method.

INTRODUCTION

Epalons are defined as a unique class of synthetic and naturally occurring pregnane steroids with high specificity for a novel allosteric modulatory site on the $GABA_A$ receptor complex. Their ability to allosterically potentiate GABA action at $GABA_A$ receptor with high potency and specificity provides the basis and rationale for their potential use as CNS therapeutic agents. $GABA_A$ receptor regulates the influx of chloride ions in such a way that receptor activation causes hyperpolarisation of the cell membrane and thus, decreased sensitivity of the neurone to excitatory input (Enna SJ *et al.,* 1997 and Chebib M *et al.,* 2000). Animal and human studies suggest that epalons plays an important role in several disorders including premenstrual syndrome, anxiety, epilepsy, psychosis and memory impairment (Chieu Liang C *et al.,* 1999, King KB *et al.,* 2002, Chain GP *et al.,* 1997, Lupien SJ *et al.,* 1997 and Lupien SJ *et al.,* 1998).

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The four rings of the steroid molecule can be configured in different ways, forming rigid framework to which substituents can be attached stereo specifically at selected points. Thus, steroid molecules may be used as potent lipophilic carriers of specific physiological or pharmacological activities (Michael AS *et al.,* 1991). Substitution of the steroid nucleus at the 3β -position was initially explored to increase bioavailability by blocking metabolic oxidation of the critical 3α-OH group, preventing conversion to potentially hormonally active steroid metabolites and to slow metabolic conjugation at 3rd position. This approach resulted in ganaxolone (Hogenkamp DJ *et al.,* 1997 and Carter RB *et al.,* 1997). Ganaxolone is a synthetic analogue of the endogenous neurosteroid allopregnanolone, a metabolite of progesterone. Like allopregnanolone, ganaxolone is a potent, positive allosteric modulator of $GABA_A$ receptor. Ganaxolone has robust anticonvulsant effects in a variety of animal models of epilepsy, is orally active and lacks hormonal side effects. The most frequently reported side effect is somnolence,

which occurs with an acceptable therapeutic index (Reddy S *et al.,* 2004).

Epilepsy is a chronic neurologic condition that affects more than 50 million people worldwide. Epilepsy is characterised by recurrent unprovoked seizures. Seizures can last from a few seconds to several minutes. They can have many symptoms, from convulsions and loss of consciousness to some that are not always recognized as seizures by the person experiencing them but by healthcare professionals: blank staring, lip smacking or jerking movements of arms and legs. One in ten adults will have a seizure some time during his or her life. Despite nearly ten new antiepileptic drugs being introduced over the past decade, 30% or close to one million people continue to have seizures even while taking two or more antiepileptic drugs. Marinus pharmaceuticals (Branford, Connecticut) conducted phase-II clinical trials investigating the safety and efficacy of ganaxolone as adjunctive therapy in adults with partial onset seizures, a type of epilepsy. It was generally well tolerated with the majority of patients able to escalate and maintain the 1500 mg/day dose. The discontinuation rate due to adverse effects was 7%. Common adverse effects experienced by more than 5% of subjects included dizziness, fatigue, somnolence, headache, abnormal coordination, falls, nasopharyngitis and convulsion(Marinus pharmaceuticals, Inc. 2009). The clinical attraction of epalons includes the advantages of good overall safety, lack of toxicity and a relatively rapid metabolism by the liver that promotes a short duration of action. Their use in clinic has, however, been hampered by problems in formulation stemming from their solubility in water. Recently, we reported the application of *In silico* methods in enhancing the druglikeness of some xenobiotics (Rajasekhar KK *et al.,* 2009, Rajendra Prasad Y *et al.,* 2009 and Rajendra Prasad Y *et al.,* 2010). The present work was undertaken with an aim to enhance the drug likeness of epalons like ganaxolone by *In silico* methods.

MATERIALS AND METHODS

Selection of lead molecule

Developing new neuroactive steroidal agonist and antagonists, and understanding their mechanism of action are active areas of research in the quest for an ideal medicinal agent. The mechanisms by which neuroactive steroids affect neuronal activity are not clear, but it should be noted that they may regulate neuronal excitability (Baulieu EE *et al.,* 1998). In an effort to develop an effective steroidal CNS medicinal agent, we selected ganaxolone as lead molecule to generate drug-like molecules with anticipated CNS activity.

Generation of drug-like epalons

It is usual to start with molecules that appear to be dug-like at the outset rather than to make a hit drug-like later (Lester AM *et al.,* 2002). Therefore, 12 drug like epalons were generated from ganaxolone by replacing 3-OH group with simple alkoxy and alkyl ester functionalities. Structures of these drug-like molecules were drawn through Chemsketch software (ACD labs Chem sketch ver 12.0.2008). Each 2D chemical structure was systematically built, that is, the basic nucleus was kept unaltered and the above mentioned substituents were added accordingly. All these chemical structures were saved and exported to ADME&TOX boxes web version of Pharma Alogrithms (Pharma Alogrithms 2008).

In silico ADME and TOX profile

Unfavourable ADME and toxicity properties have been identified as a major cause of failure for candidate molecules in drug development. Consequently, there is increasing interest in the early prediction of these properties, with the objective of increasing the success rate of compounds reaching development. The Pharmacokinetic and toxicity properties of drug like epalons were calculated through ACD labs Chem sketch and ADME & TOX boxes of Pharma Alogrithm.

RESULTS AND DISCUSSION

Tables 1&2 shows the structural details and the predicted ADME & Toxicity properties of 12 drugs- like molecules derived from ganaxolone. Replacement of alcoholic hydroxy group with alkoxy and alkyl ester functionalities shows much impact on pharmacokinetic properties. As number of carbon atoms increases from 1 to 3, lipophilicity also increases in all 12 drugs like molecules. Branching of these carbon atoms further increases lipophilicity. For example, presence of isopropyl group has much positive impact on lipophilicity than n-propyl group. This is reflected in some lipophilic parameters like Clog P, Parachor and Molar refractivity. Polarisability also increases as number of carbon atoms increases from 1-3. But, there seems to be an inverse correlation between refractive index and number of carbon atoms. Structural modification do not shows much influence on type of absorption and metabolism. All the12 drugs like molecules were predicted to be absorbed via passive diffusion and metabolised via first pass. Volume of distribution is slightly increased whereas protein binding, oral bioavailability and toxicity (LD_{50} in mice) are varied.

Drug discovery and development are expensive undertakings. The research cost for a compound increase dramatically as it progress through clinical development, and therefore, there are economic reasons for identifying and discontinuing the development of poor drug candidates at the earliest possible time. Even compounds that do eventually reach the market sometimes have less than ideal characteristics, complicating patient management. Poor pharmacokinetic properties are one of the main reasons for terminating the development of drug candidates. The application of computational technology during drug discovery and development offers considerable potential for reducing the number of experimental studies required for compound selection and development and for improving the success rate. In this context, *In silico* approaches are being

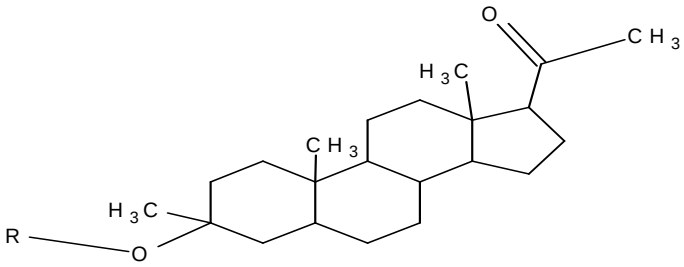
being used today in drug discovery to assess the ADME and toxicity properties of compounds at the early stages of discovery and development. This early assessment of pharmacokinetic and toxicity properties will help pharmaceutical scientists to select the best candidate for further development as well as to reject those with a low probability of success. *In silico* tools enabling the prediction of the pharmacokinetic profile would be invaluable for high-throughput screening and selection of compounds for in vivo testing.

Table.1 Predicted Biopharmaceutical properties of 12 drug-like Epalons

S.No	Code	R	Molar refractivity (cm^3)	Parachor (cm^3)	Refractive index	Polarisability x 10^{-24}(cm^3)	C log P
1.	Ganaxolone	- H	97.18	794.2	1.517	38.52	5.43
2.	1 a	$-CH_3$	105.22	865.1	1.516	40.26	6.07
3.	1 b	$-C_2H_5$	106.77	877.6	1.514	42.32	6.60
4.	1 c	$-C_3H_7$	111.38	915.7	1.511	44.15	6.95
5.	1 d	$-CH(CH_3)_2$	111.40	917.7	1.512	44.16	7.13
6.	2 a	$-COCH_3$	106.89	882.8	1.520	42.37	6.33
7.	2 b	$-COCH_2CH_3$	111.52	922.9	1.518	44.21	6.86
8.	2 c	$-COC_3H_7$	116.12	960.9	1.516	46.03	7.21
9.	2 d	$- COCH(CH_3)_2$	116.15	963.4	1.517	46.04	7.39
10.	3 a	$- COOCH_3$	108.63	903.1	1.519	43.06	6.30
11.	3 b	$-COOCH_2CH_3$	113.26	943.2	1.518	44.90	6.83
12.	3 c	$-COOC_3H_7$	117.87	981.3	1.515	46.72	7.18
13.	3 d	$-COOCH(CH_3)_2$	117.89	983.3	1.516	46.73	7.36

Table.2 Predicted Pharmacokinetic And Toxicity Parameters of 12 Drugs-Like Epalons

S.No	Code	Absorption	Rate of Absorption K_a(min^{-1})	Percentage Protein binding	Metabolism	LD_{50} in Mice (mg/kg)	Oral bioavailability	Volume of Distribution V_d (L/ Kg)
1.	Ganaxolone	Passive	0.093	55%	First pass	960	50%	2.14
2.	1 a	Passive	0.062	84%	First pass	1000	70%	2.16
3.	1 b	Passive	0.070	72%	First pass	940	70%	2.30
4.	1 c	Passive	0.08	90%	First pass	930	85%	2.61
5.	1 d	Passive	0.074	74%	First pass	950	70%	2.48
6.	2 a	Passive	0.067	64%	First pass	1000	60%	2.52
7.	2 b	Passive	0.08	76%	First pass	960	70%	2.16
8.	2 c	Passive	0.07	72%	First pass	920	68%	2.4
9.	2 d	Passive	0.072	70%	First pass	970	68%	2.7
10.	3 a	Passive	0.064	64%	First pass	950	64%	2.13
11.	3 b	Passive	0.082	80%	First pass	970	76%	2.19
12.	3 c	Passive	0.09	84%	First pass	960	80%	2.7
13.	3 d	Passive	0.084	80%	First pass	900	70%	2.60



CONCLUSION

From the present study, it can be concluded that some of the drugs like epalons derived from ganxolone were predicted to be more lipophilic and safe with an enhancement in oral bioavailability, plasma protein binding and volume of distribution. Further studies are necessary to establish the CNS activity of these epalons as possible antiepileptic agents.

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REFERENCES

ACD labs Chem sketch ver 12.0, Advanced Chemistry Development Inc, Toronto,Canada, 2008.

Baulieu EE, Neurosteroids, A novel function of the brain.Psychoendocrinology, 1998;23:963-987.

Chebib M and Johnston GAR, GABA activated ligand gated ion channels: Medicinal chemistry and molecular biology, *J.med.chem.* 2000;43:1427-1447.

Chieu-Liang C, Yea-Ru Y and Tsai-Hsien C, Potentiation of propofol by alphaxalone and inturn activation of $GABA_A$ receptors by the former, *Eur.J.Pharmacol.* 1999;386: 201-210.

Chain GP, Yakov P, Lior P, Shaul S, Moshe G and Ronit W, Pregnane-related neurosteroids as potent antipsychotic agents, *Brain Research.* 1997;765:129-134.

Carter RB, Wood PL, Wieland S, Hawkinson JE, Belelli D, Lambert JJ, White HS, Wolf HH, Mirsadeghi S, Tahir SH, Bolger MB, Lan NC and Gee KW, Characterisation of the anticonvulsant properties of ganaxolone-a selective, high affinity, steroid modulator of $GABA_A$ receptor.*J.Pharmacol.Exp.Ther.*1997;280:1284-1295.

Enna SJ and Bowery NG (eds)., The GABA receptors,(New Jersey). Humana press Inc: 1997.

Hogenkamp DJ, Tahir SH, Hawkinson JE, Upasani RB, Alauddin M, Kimbrough CL, Acosta BM, Whittemore ER, Woodward RM, Lan NC, Gee KW and Bolger MB, Synthesis and invitro activity of 3β- substituted -3α-hydroxy pregnan-20-ones, Allosteric modulators of the $GABA_A$ receptor. *J.Med.Chem.*1997;40:61-72.

King KB, Marek Z, Marivsz SW, Aneta K, Zaxzislaw K and Stainslaw JC, Neuroactive steroid induced neuroprotection in antiepileptics, *Eur. J. Pharmacol.* 2002;449:85-90.

Lupien SJ and Mc Ewen BS, The acute effects of corticosteroids on cognition: integration of animal and human model studies, *Brain-Res. Rev.* 1997;24:1-27.

Lupien SJ, de Leon M, de santi S, Convit A, Tarshish C, Nair N.P, Thakur M, Mc Ewen BS, Hauger RL and Meaney MJ, Cortisol levels during human aging predict hippocampal atrophy and memory deficits, *Nat. Neurosci.* 1998;1:3-4.

Lester AM, Krogsgaard Larsen P, Liljefors T and Madsen U, Drug design and discovery.An overview.3rd edition.Taylor and Francis(London and Newyork): 2002;1-53.

Michael AS, Modulation of the $GABA_A$ receptor by steroids, *The Neurosciences,* 1991;3:231-239.

Marinus pharmaceuticals,Inc.Announces positive results of its phase II clinical trials of Ganaxolone as adjunctive therapy. Epilepsy News,Medical News Today; March 4th 2009.

Pharma Alogrithms, Toronto, Canada, 2008.

Reddy S and Woodward R, Ganaxolone,A prospective Overview. Drugs of the future, 2004;29(3):227-242.

Rajasekhar KK, Ranganayakulu D, Shankarananth V, Rekharani K, Swetha harika K and Srividya K, *In silico* prediction of selected pharmacokinetic and toxicity properties of some neuro active steroids. *Drug Invention Today,* 2009;1(1):35-38.

Rajendra Prasad Y, Rajasekhar K.K, Shankarananth V,Sowjanya S, Saisravani D and Kothakota vandana, *In silico* ADME and TOX profile of some excitotoxins derived from Glutamic acid. *Drug Invention Today,* 2009;1(2):126-129.

Rajendra Prasad Y, Bhagavan raju M, Rajasekhar KK and Sowjanya S, *In silico* prodrug designing of MMPIs derived from Tanomastat. *Asian Journal of Research in Chemistry,* 2010;3(2):In press.