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Research Article

SOLUTIONS TO PHARMACEUTICAL ISSUES FOR ANTI-CANCER DRUGS BY ACCORD EXCEL

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ABSTRACT

Drug action involves the successful administration of the drug to the patient, the transport of the drug molecules to the vicinity of the target and the maintenance of the drug as an active species for a sufficient period of time to allow an effect to take place. The drug molecules must interact with the target receptor in defined ways and with sufficient affinity to perturb the dynamics of a series of molecular events and pathways, without residing within cells and organs for long enough to cause non-specific effects. All of these stages are influenced by different combinations of the chemical and physical features of a drug, which defines its Absorption, Distribution, Metabolism and Excretion (ADME) properties. The term 'drugability' describes a drug's performance with respect to cellular uptake, distribution, metabolism and retention. The Lipinski 'rule of five' is an empirical guide to the optimization of drug-like properties, especially oral absorption and distribution features, centered on the knowledge base of known drugs, over all therapeutic categories. The ability to reliably predict drug-like properties together with ADME/T information, which is all too often unavailable for many classes of anti-cancer drugs. So present study has been carried out to predict ADME/T properties and Lipinski Rule of Five of 150 anti- cancer drugs approved by FDA (Food and Drug Administration). We found that not all the 150 compounds obeyed Lipinski's Rule of Five and ADME/T properties as per Accord Excel. In future, we will trace out the above mentioned properties of all the other existing anticancer drugs.

Keywords: ADME/T, Lipinski Rule of Five, drugability, Accord Excel.

INTRODUCTION

The escalating cost of drug discovery has become a major concern in the recent years.

Discovering and bringing a new drug to the market has been estimated to cost in excess of US $ 800 million[1]. In the past, in a typical drug discovery setting, once an array of quality leads were generated, a series of tests were applied to evaluate the pharmacokinetic properties (Absorption, Distribution, Metabolism and Excretion) and Toxicity (together called as ADME/T). Failure of promising lead (s) to exhibit desirable ADME/T profile is now regarded as the major reason of late-stage attrition. According to a recent report, poor pharmacokinetics (39%) and preclinical toxicity (11%) were the major reasons for failures in the drug development, in addition to lack of efficacy, adverse effects in man and commercial reasons[2]. This scenario has changed in the current decade with more efforts focused on the early-stage ADME/T profiling. The process is streamlined with the introduction of medium-to-high throughput *in vitro* ADME/T assays to keep pace with the high numbers associated with combinatorial libraries and the high throughput screening. In addition to the experimental evaluation of ADME/T, *in silico* predictions of these properties have gained popularity in the industry in recent years for the obvious reasons. Various Quantitative Structure-Activity and Structure-Property Relationship (QSAR and QSPR) and related approaches have successfully made their way in the form of software in the field of predictive ADME/T. The sole purpose of all these recently evolved experimental and predictive ADME/T approaches is to reduce late-stage failures by focusing on the most promising lead(s) with desired ADME/T properties. Newer approaches and methods to predict ADME/T profile are continuously introduced to the drug discovery community[3]. The ability to reliably predict drug-like properties involves the incorporation of data from classic Quantitative Structure-Activity Relationships together with experimental ADME information[1], which is all too often unavailable for many classes of anticancer drugs. Anticancer drugs have traditionally been outliers from the Lipinski rule, many having a higher molecular weight than is common in other therapeutic areas.

The Lipinski 'rule of five'

A potential drug molecule will have poor absorption and distribution properties if the following criteria are met.

- Its molecular weight is over 500 Da
- The calculated log *P* is over 5.
- There are over 5 hydrogen-bond donors.
- There are over 10 hydrogen-bond acceptors.

This constitutes Lipinski Rule of Five. In this present study, we have taken 150 anti-cancer compounds approved by FDA, calculated its Lipinski's rule of five and ADME/T properties.

MATERIALS AND METHODS

In the current work, 150 anti-cancer compounds downloaded from Pubchem database and calculated its ADME/T properties and Lipinski's Rule of Five by using Accord Excel 6.1 version. But Accord Excel did not provide exact molecular weight and LogP value. If molecular weight less than 500, it gave the result as False, otherwise True. If logP value is less than 5, the result will be False otherwise True. So in order to overcome this difficulty we used Discovery studio 2.1 version, with the help of which we calculated the value of molecular weight and LogP. Accelrys Discovery Studio (2.1) is a life science modeling and simulation suite of application focused on optimizing the drug discovery process. It makes easier to examine the properties of large and small molecules. Accord for Excel allows scientists to display chemical structures and reactions, perform chemical calculations, analyze R-groups, and query by substructure or similarity directly within Excel.

RESULTS

Table 1 describes ADME/T properties of 150 anticancer compounds. Lipinski Rule of Five of those compounds were calculated and tabulated in Table 2. Both these calculations done through Accord Excel. But Accord Excel doesn't offer the exact value of molecular weight and log p. So we used Discovery studio 2.1 version and the results were shown inTable 3.

DISCUSSION

The transformation of a lead molecule into a drug is a key step in the process of drug discovery, requiring the application of knowledge of the compound's absorption, distribution, metabolism and excretion (ADME) profile[1] to optimize its 'drugability'. Most compounds that fail to reach the clinic, even though they might be high-affinity *in vitro* inhibitors of the desired target, often do so because of insufficient attention to these issues. Therefore, there is now widespread agreement[2] that drug-like and ADME properties should be incorporated as early as possible in the discovery cycle, rather than, after the optimization of molecular recognition features.

Table.1.ADME/T properties of 150 anti-cancer compounds

S.I.No	Compounds	Fpsa	Aq.Sol.Lev	Bbb.Lev	Cyp206	Heptatox	Hia. Lev	Prtn.Bind.Lev
1	Pirenzepine	68.7303	3	3	1	0	0	1
2	Dicyclomine	29.5812	2	0	1	0	0	2
3	Oxybutynin	50	2	1	1	0	0	1
4	Cevimeline	12.2826	3	2	0	0	0	0
5	Aceclidine	29.58	4	2	0	0	0	0
6	Imidafenacin	60.45	3	2	1	0	2	2
7	Piperidolate	29.58	2	1	1	0	1	1
8	Scopolamine	59.329	3	3	0	0	0	0
9	Atropine	50.39	3	2	0	0	0	0
10	Tolterodine	24.16	2	0	1	0	0	2
11	Solifenacin	32.93	2	1	1	0	2	2
12	Xanomeline	34.80	2	1	1	0	0	0
13	Darifenacin	56.12	2	1	1	0	2	2
14	Teimoniumiodide	29.74	4	2	1	0	1	1
15	Alvameline Malate	42.48	4	3	0	0	2	0
16	Methantheline Bromide	35.16	3	1	1	0	2	2
17	Esoxybutynin Chloride	50.39	2	1	1	0	0	1
18	Talsaclidine Fumarate	12.28	3	1	0	0	0	0
19	Oxyphencylimine	61.72	3	2	0	0	0	0
20	Trimebutine	56.37	2	1	0	0	0	2
21	Cimetropium Bromide	55.97	4	3	0	0	2	2
22	Dexetimide	50.76	2	1	1	0	0	1
23	Pirenzepine Hydrochloride	68.73	3	3	1	0	0	0
24	Propantheline	35.16	2	1	1	0	0	2
25	Thiaton	0	2	0	1	0	0	0
26	Methylephdrine	24.16	4	1	0	0	0	0
27	Aptazapine	12.05	2	1	1	0	0	2
28	Atipamezole	26.31	3	1	0	0	0	2
29	Methylatropine	47.64	4	3	0	0	0	0
30	Nozinan Hydrochloride	15.63	2	0	1	0	0	2
31	Methylergonovine	69.33	3	3	1	0	0	1
32	Hexocyclium	24.16	3	1	1	1	0	0
33	Dipivefrin	86.08	2	2	0	0	0	2
34	Moxisylyte	38.51	3	1	0	0	0	2
35	Naphazoline	24.13	3	1	0	0	0	1
36	Methocholine Chloride	26.23	5	4	0	0	2	0
37	Fluotropium Chloride	47.03	3	2	1	0	0	2
38	Sunitinib	78.62	2	2	1	0	0	1
39	Midostaurin	46.59	2	1	1	1	0	2
40	Vatalamib	33.65	3	1	0	0	0	1
41	Metasanib Diphosphate	43.23	2	1	1	0	0	1
42	Semaxinib	34.51	2	1	0	0	0	1
43	Pazopanib	73.42	2	2	1	0	0	2
44	Eucatropine Hydrochloride	24.70	3	1	1	1	0	2
45	Alafuzosin	69.33	2	2	1	0	0	1
46	Metraminol	38.51	3	1	0	0	0	2
47	Glyceryl Phosphochloride	47.64	4	3	0	0	0	0
48	Glycopyrate	69.33	3	3	0	0	0	1
49	Sorafenib	35.16	2	1	1	0	0	2
50	Indromin	31.56	2	1	1	0	0	2
51	Dasatinib	29.43	2	1	1	0	0	1
52	Acythylcholine Chloride	26.231	5	4	0	0	2	0
53	Adatanserin hydrochloride	59.338	3	2	0	1	0	0
54	Benzatropine	12.283	2	0	1	0	0	2
55	Benzitimide Hydrochloride	50.764	2	1	1	0	0	2
56	Benztropine Mesilate	12.283	2	0	1	0	0	2
57	Bethanechol Chloride	52.771	5	4	0	0	1	0
58	Biperiden Hydrochloride	24.168	2	1	1	0	0	0
59	Biperiden Lactate	24.168	2	1	1	0	0	1
60	Butropium Bromide	55.977	3	2	0	0	0	1
61	Carbachol	52.771	5	4	0	0	1	0
62	Carpronium Chloride	26.231	5	4	0	0	2	0
63	Chlorpromazine Hydrochloride	13.41	1	4	0	1	3	2
64	Choline Alfoscerate	94.093	5	4	0	0	3	0
65	Chlorpromazine	13.41	1	4	0	1	3	2
66	Cyclopentolate Hydrochloride	50.399	3	2	0	0	0	0
67	Darifenacin Hydrobromide	56.123	2	1	1	0	0	2

68	Alosetron hydrochloride	52.317	3	2	0	1	0	0
69	Esoxybutynin Chloride	50.399	2	1	1	0	0	1
70	Ethybentropine	12.283	2	0	1	0	0	2
71	Etileferine	54.441	4	3	0	0	0	1
72	Etomidoline	45.746	2	1	1	1	0	2
73	Alosetron	52.317	3	2	1	0	0	2
74	Flutropium Bromide	47.046	3	2	1	0	0	1
75	Homatropine Hydrobromide	50.399	3	2	0	0	0	0
76	Homatropine Methylbromide	47.046	4	3	0	0	0	0
77	Hyoscine Methyobromide	55.977	4	3	0	0	0	0
78	Azasetron hydrochloride	63.046	3	3	0	0	0	0
79	Mazaticol Hydrochloride Hydrate	50.399	2	1	0	0	0	0
80	Mazaticol	50.399	2	1	0	0	0	0
81	Methixene Hydrochloride	3.3525	1	0	1	0	1	2
82	Orphenadrine Hydrochloride	12.283	2	0	1	0	0	1
83	Orphenadrine Citrate	12.283	2	0	1	0	0	1
84	Oxitropium Bromide	55.977	4	3	0	0	0	0
85	Pilocarpine Borate	42.84	4	3	0	0	0	0
86	Pilocarpine Nitrate	42.84	4	3	0	0	0	0
87	Pimethixene	3.3525	1	0	1	0	0	1
88	Pipethanate	50.399	2	1	1	0	0	2
89	Piroheptine	3.3525	1	0	1	0	1	2
90	Procyclidine Hydrochloride	24.168	2	1	1	0	0	0
91	Procyclidine	24.168	2	1	1	0	0	0
92	Profenamine Hydrochloride	6.705	2	0	1	0	1	2
93	Profenamine	6.705	2	0	1	0	1	2
94	Propiverine	38.514	2	1	1	0	0	1
95	Sertindole	42.164	1	1	1	0	0	1
96	Tamsulosin	100.74	2	3	0	0	0	1
97	Trihexyphenidyl Chloride	24.168	2	0	1	0	0	1
98	Trihexyphenidyl	24.168	2	0	1	0	0	1
99	Tropicamide	52.73	4	3	1	0	0	2
100	Tropsium Chloride	47.046	3	2	1	0	0	2
101	Amosulalol	112.62	3	4	0	1	0	0
102	Arotinolol	88.727	2	3	0	0	0	0
103	Asenapine maleate	12.286	2	0	1	1	0	2
104	Bunazosin hydrochloride	90.928	2	3	1	0	0	0
105	Bunazosin	90.928	2	3	1	0	0	0
106	Carvedilo l phosphate hydrate	75.471	2	2	1	0	0	1
107	Carvedilol	75.471	2	2	1	0	0	1
108	Dapiprazole hydrochloride	34.572	2	1	0	0	0	1
109	Dipivefrin hydrochloride	86.08	2	2	0	0	0	1
110	Batanopride hydrochloride	86.234	3	3	1	0	0	1
111	Ergometrine	69.33	3	3	1	0	0	1
112	Ergonovine maleate	69.33	3	3	1	0	0	1
113	Guanadrel sulfate	82.263	4	3	0	0	0	0
114	Ifenprodil tartrate	44.983	2	1	0	0	0	1
115	Labetalol hydrochloride	98.281	3	3	0	1	0	2
116	Labetalol	98.281	3	3	0	1	0	2
117	Levomepromazine hydrochloride	15.63	2	0	1	0	0	2
118	Levomepromazine maleate	15.63	2	0	1	0	0	2
119	Levomepromazine	15.63	2	0	1	0	0	2
120	Medroxalol	116.142	3	4	0	1	0	2
121	Cilansetron hydrochloride	39.258	2	1	0	1	0	2
122	Methylergometrine	69.33	3	3	1	0	0	1
123	Methylergonovine maleate	69.33	3	3	1	0	0	1
124	Mianserin hydrochloride	6.705	2	0	1	0	0	2
125	Mianserin	6.705	2	0	1	0	0	2
126	Moxisylyte hydrochloride	38.513	3	1	0	0	0	2
127	Cilansetron	39.258	2	1	0	1	0	2
128	Naphazoline hydrochloride	24.133	3	1	0	0	0	1
129	Naphazoline nitrate	24.133	3	1	0	0	0	1
130	Cinanserin hydrochloride	33.463	2	1	1	1	0	0
131	Oxymetazoline hydrochloride	44.949	3	1	0	0	0	1
132	Oxymetazoline	44.949	3	1	0	0	0	1
133	Phenoxybenzamine hydrochloride	12.286	2	0	1	0	0	2

134	Phenoxybenzamine	12.286	2	0	1	0	0	2
135	Pimozide	36.816	1	1	1	0	0	2
136	Pseudoephedrine hydrochloride	33.625	4	2	0	0	0	0
137	Pseudophedrine sulfate	33.625	4	2	0	0	0	0
138	Pseudophedrine	33.625	4	2	0	0	0	0
139	Quetiapine fumarate	47.773	3	2	1	0	0	1
140	Silodosin	98.679	3	3	0	1	0	1
141	Terazosin hydrochloride hydrate	98.858	3	3	0	0	0	0
142	Terazosin	98.858	3	3	0	0	0	0
143	Tetrahydrozoline hydrochloride	24.133	3	1	0	0	0	0
144	Tetrahydrozoline nitrate	24.13349	3	1	0	0	0	0
145	Tetryzoline	24.133	3	1	0	0	0	0
146	Tolazoline hydrochloride	24.133	4	2	0	0	0	2
147	Tramazoline	36.943	3	1	0	0	0	0
148	Bunitrolol hydrochloride	52.68	4	3	0	0	0	0
149	Tolazoline	24.133	4	2	0	0	0	2
150	Tramazoline hydrochloride	36.943	3	1	0	0	0	0

Table.2.Lipinski Rule of five of 150 anti-cancer compounds

S.i.	Compound	Hydrogen bond acceptor	Hydrogen bond Donor	Molecular weight	A logp
1	Pirenzepine	7	1	False	False
2	Dicyclomine	3	0	False	False
3	Oxybutynin	4	1	False	False
4	Cevimeline	2	0	False	False
5	Aceclidine	3	0	False	False
6	Imidafenacin	4	2	False	False
7	Piperidolate	3	0	False	False
8	Scopolamine	5	1	False	False
9	Atropine	2	1	False	False
10	Tolterodine	2	1	False	False
11	Solifenacin	4	0	False	False
12	Xanomeline	4	0	False	False
13	Darifenacin	4	2	False	False
14	Teimoniumiodide	3	1	False	False
15	Alvameline Malate	9	2	False	False
16	Methantheline Bromide	4	0	False	False
17	Esoxybutynin Chloride	4	1	False	False
18	Talsaclidine Fumarate	6	2	False	False
19	Oxyphencylimine	5	1	False	False
20	Trimebutine	6	0	False	False
21	Cimetropium Bromide	5	1	False	False
22	Dexetimide	4	1	False	False
23	Pirenzepine Hydrochloride	8	3	False	False
24	Propantheline	4	0	False	False
25	Thiaton	1	0	False	False
26	Methylephdrine	2	1	False	False
27	Aptazapine	7	2	False	False
28	Atipamezole	2	1	False	False
29	Methylatropine	8	1	False	False
30	Nozinan Hydrochloride	3	0	False	False
31	Methylergonovine	9	5	False	False
32	Hexocyclium	7	1	False	False
33	Dipivefrin	6	2	False	False
34	Moxisylyte	4	0	False	False
35	Naphazoline	2	1	False	False
36	Methocholine Chloride	3	0	False	False
37	Fluotropium Chloride	4	1	False	False
38	Sunitinib	6	3	False	False
39	Midostaurin	4	1	False	False
40	Vatalamib	3	1	False	False
41	Metasanib Diphosphate	2	1	False	False
42	Semaxinib	4	0	False	False
43	Pazopanib	3	1	False	False
44	Eucatropine Hydrochloride	2	1	False	False
45	Alafuzosin	3	0	False	False
46	Metraminol	6	1	False	False
47	Glyceryl Phosphochloride	4	2	False	False
48	Glycopyrate	3	2	False	False
49	Sorafenib	2	1	False	False
50	Indromin	3	0	False	False

51	Cisapride	8	5	False	False
52	Acythylcholine Chloride	3	0	False	False
53	Adatanserin hydrochloride	6	1	False	False
54	Benzatropine	2	0	False	False
55	Benzitimide Hydrochloride	4	1	False	False
56	Benztropine Mesilate	5	1	False	False
57	Bethanechol Chloride	4	2	False	False
58	Biperiden Hydrochloride	2	1	False	True
59	Biperiden Lactate	5	3	False	False
60	Butropium Bromide	5	1	True	False
61	Carbachol	4	2	False	False
62	Carpronium Chloride	3	0	False	False
63	Chlorpromazine Hydrochloride	7	2	False	False
64	Choline Alfoscerate	4	0	True	True
65	Chlorpromazine	4	1	False	False
66	Cyclopentolate Hydrochloride	4	2	True	True
67	Darifenacin Hydrobromide	4	1	False	False
68	Alosetron hydrochloride	5	1	False	False
69	Esoxybutynin Chloride	2	0	False	False
70	Ethybentropine	7	2	False	False
71	Etileferine	3	3	False	False
72	Etomidoline	5	1	False	False
73	Alosetron	5	1	False	False
74	Flutropium Bromide	5	3	False	False
75	Homatropine Hydrobromide	4	1	False	False
76	Homatropine Methylbromide	4	1	False	False
77	Hyoscine Methyobromide	5	1	False	False
78	Azasetron hydrochloride	6	1	False	False
79	Mazaticol Hydrochloride Hydrate	5	3	False	False
80	Mazaticol	4	1	False	False
81	Methixene Hydrochloride	2	2	False	False
82	Orphenadrine Hydrochloride	2	0	False	False
83	Orphenadrine Citrate	9	4	False	False
84	Oxitropium Bromide	5	1	False	False
85	Pilocarpine Borate	7	3	False	False
86	Pilocarpine Nitrate	8	1	False	False
87	Pimethixene	1	0	False	False
88	Pipethanate	4	1	False	False
89	Piroheptine	1	0	False	True
90	Procyclidine Hydrochloride	2	1	False	False
91	Procyclidine	2	1	False	False
92	Profenamine Hydrochloride	2	0	False	True
93	Profenamine	2	0	False	True
94	Propiverine	4	0	False	False
95	Sertindole	5	1	False	False
96	Tamsulosin	7	3	False	False
97	Trihexyphenidyl Chloride	2	1	False	False
98	Trihexyphenidyl	2	1	False	False
99	Tropicamide	4	1	False	False
100	Trospium Chloride	4	1	False	False
101	Amosulalol	7	4	False	False
102	Arotinolol	5	4	False	False
103	Asenapine maleate	2	0	False	False
104	Bunazosin hydrochloride	8	2	False	False
105	Bunazosin	8	2	False	False
106	Carvedilo l phosphate hydrate	4	2	False	False
107	Carvedilol	6	3	False	False
108	Dapiprazole hydrochloride	6	3	False	False
109	Dipivefrin hydrochloride	5	0	False	False
110	Batanopride hydrochloride	6	3	False	False
111	Ergometrine	6	2	False	False
112	Ergonovine maleate	5	3	False	False
113	Guanadrel sulfate	9	5	False	False
114	Ifenprodil tartrate	14	10	True	False
115	Labetalol hydrochloride	3	2	False	False
116	Labetalol	5	5	False	False
117	Levomepromazine hydrochloride	5	5	False	False
118	Levomepromazine maleate	3	0	False	False
119	Levomepromazine	3	0	False	False
120	Medroxalol	3	0	False	False
121	Cilansetron hydrochloride	5	2	False	False
122	Methylergometrine	2	1	False	False
123	Methylergonovine maleate	5	3	False	False
124	Mianserin hydrochloride	9	5	False	False

125	Mianserin	2	0	False	False
126	Moxisylyte hydrochloride	2	0	False	False
127	Cilansetron	4	0	False	False
128	Naphazoline hydrochloride	4	0	False	False
129	Naphazoline nitrate	2	1	False	False
130	Cinanserin hydrochloride	3	1	False	False
131	Oxymetazoline hydrochloride	2	1	False	False
132	Oxymetazoline	3	2	False	False
133	Phenoxybenzamine hydrochloride	3	2	False	False
134	Phenoxybenzamine	2	0	False	True
135	Pimozide	2	0	False	False
136	Pseudoephedrine hydrochloride	4	1	False	True
137	Pseudophedrine sulfate	2	2	False	False
138	Pseudophedrine	4	4	False	False
139	Quetiapine fumarate	2	2	False	False
140	Silodosin	5	1	False	False
141	Terazosin hydrochloride hydrate	7	4	False	False
142	Terazosin	9	2	False	False
143	Tetrahydrozoline hydrochloride	9	2	False	False
144	Tetrahydrozoline nitrate	2	1	False	False
145	Tetryzoline	2	1	False	False
146	Tolazoline hydrochloride	2	1	False	False
147	Tramazoline	2	1	False	False
148	Bunitrolol hydrochloride	4	3	False	False
149	Tolazoline	1	1	False	False
150	Tramazoline hydrochloride	1	2	False	False

Table.3. Molecular weight and LogP value of 150 anti-cancer compounds

S.I.No	Compounds	Mol.wgt	LogP
1	Pirenzepine	351.412	1.04
2	Dicyclomine	309.496	5.106
3	Oxybutynin	357.497	4.646
4	Cevimeline	438.366	0.289
5	Aceclidine	169.226	0.557
6	Imidafenacin	319.409	2.551
7	Piperidolate	323.438	4.192
8	Scopolamine	303.362	0.824
9	Atropine	289.378	1.721
10	Tolterodine	325.497	5.662
11	Solifenacin	362.475	4.03
12	Xanomeline	281.425	3.961
13	Darifenacin	426.562	4.558
14	Teimonium iodide	445.368	0.954
15	Alvameline Malate	309.33	0.912
16	Methantheline Bromide	420.35	2.427
17	Esoxybutynin Chloride	393.958	4.646
18	Talsaclidine Fumarate	281.313	1.779
19	Oxyphencylimine	344.458	2.627
20	Trimebutine	387.481	4.116
21	Cimetropium Bromide	438.366	0.289
22	Dexetimide	362.475	3.559
23	Pirenzepine Hydrochloride	405.889	1.04
24	Propantheline	448.404	3.182
25	Thiaton	410.444	3.384
26	Methylephdrine	179.264	1.77
27	Aptazapine	369.425	2.8
28	Atipamezole	212.296	3.012
29	Methylatropine	366.42	0.366
30	Nozinan Hydrochloride	364.942	4.508
31	Methylergonovine	339.441	2.063
32	Hexocyclium	428.599	2.04
33	Dipivefrin	351.448	3.485
34	Moxisylyte	279.383	3.4
35	Naphazoline	246.741	2.06
36	Methocholine Chloride	195.692	-0.817
37	Fluotropium Chloride	313.159	-2.513
38	Sunitinib	398.484	2.998
39	Midostaurin	570.637	4.7
40	Vatalamib	346.821	4.705
41	Metasanib Diphosphate	535.441	2.721
42	Semaxinib	238.291	2.748
43	Pazopanib	437.53	3.741

44	Eucatropine Hydrochloride	327.855	2.139
45	Alafuzosin		
46	Metraminol	317.302	0.561
47	Glyceryl Phosphochloride	257.229	-2.987
48	Glycopyrate	398.344	1.457
49	Sorafenib	464.834	4.176
50	Indromin	347.463	3.347
51	Cisapride	483.97	2.786
52	Acythylcholine chloride	181.665	-1.195
53	Adatanserin hydrochloride	405.975	2.44
54	Benzatropine	307.438	3.875
55	Benzitimide hydrochloride	398..936	3.559
56	Benztropine mesilate	403.547	3.875
57	Bethanechol chloride	196.68	-1.027
58	Biperiden hydrochloride	347.931	3.649
59	Biperiden lactate	401.551	3.649
60	Butropium bromide	311.47	3.649
61	Carbachol	182.653	-1.405
62	Carpronium chloride	195.692	-0.758
63	Chlorpromazine hydrochloride	636.736	8.568
64	Chlorpromazine	636.736	8.568
65	Choline alfoscerate	257.229	-2.987
66	Cyclopentolate hydrochloride	327.855	2.489
67	Darifenacin hydrobromide	291.394	2.489
67	Darifenacin hydrobromide	507.474	4.558
68	Alosetron hydrochloride	330.82	1.654
69	Esoxybutynin chloride	393.958	4.646
70	Ethybenztropine	321.465	4.224
71	Etilefrine	181.	0.964
72	Etomidoline	379.506	4.043
73	Alosetron	294.359	1.654
74	Flutropium bromide	496.421	2.289
75	Homatropine hydrobromide	356.263	1.697
76	Homatropine methylbromide	370.29	0.342
77	Hyoscine methobromide	398.301	-0.531
78	Azasetron hydrochloride	386.282	1.235
79	Mazaticol hydrochloride hydrate	460.063	3.745
80	Mazaticol	405.586	3.745
81	Methexene hydrochloride	363.954	5.074
82	Orphenadrine citrate	461.519	3.871
83	Orphenadrine hydrochloride	305.85	3.871
84	Oxitropium bromide	412.328	-0.182
85	Pilocarpine borate	270.097	0.966
86	Pilocarpine nitrate	271.278	0.966
87	Pimethexene	293.434	4.495
88	Pipethanate	339.438	3.67
89	Piroheptine	303.449	5.212
90	Procyclidine hydrochloride	323.909	3.961
91	Procyclidine	287.448	3.961
92	Profenamine hydrochloride	348.942	5.088
93	Profenamine	312.481	5.088
94	Propiverine	367.492	4.006
95	Sertindole	440.951	4.68
96	Tamulosin	408.524	2.72
97	Trihexyphenidyl hydrochloride	337.936	4.418
98	Trihexyphenidyl	301.475	4.418
99	Tropicamide	284.361	1.432
100	Trospium Chloride	427.96	2.35
101	Amosulalol	380.141	1.664
102	Arotinolol	371.552	2.689
103	Asenapine maleate	285.775	3.879
104	Bunazosine hydrochloride	409.921	2.234
105	Bunazosin	373.46	2.234
106	Bunitrolol hydrochloride	284.789	0.485
107	Carvedilol phosphate hydrate	406.486	4.015
108	Carvedilol	406.486	4.015
109	Dapiprazole hydrochloride	361.921	3.003
110	Dipivefrin hydrochloride	387.909	3.485
111	Batanopride hydrochloride	392.33	1.842
112	Ergometrine	325.414	1.539
113	Ergonovine maleate	441.49	1.539
114	Guanadrel sulphate	524.648	0.294
115	Ifenprodil tartrate	325.454	4.186
116	Labetalol hydrochloride	364.876	2.356

117	Labetalol	328.415	2.356
118	Levomepromazine hydrochloride	364.942	4.508
119	Levomepromazine maleate	328.421	4.508
120	Levomepromazine	328.481	4.508
121	Medroxalol	372.426	2.124
122	Cilansetron hydrochloride	373.886	3.165
123	Methylergometrine	339.441	2.063
124	Methylergonovine maleate	455.517	2.063
125	Mianserine hydrochloride	300.833	3.706
126	Mianserine	264.372	3.706
127	Moxisylyte hydrochloride	315.844	3.4
128	Cilansetron	319.409	3.165
129	Naphazoline hydrochloride	246.741	2.06
130	Naphazoline nitrate	210.28	2.06
131	Cinanserin hydrochloride	376.953	3.825
132	Oxymetazoline hydrochloride	296.843	3.283
133	Oxymetazoline	260.382	3.283
134	Phenoxybenzamine hydrochloride	340.295	4.579
135	Phenoxybenzamine	303.834	4.579
136	Pimozide	461.557	5.522
137	Pseudoephedrine hydrochloride	201.698	1.235
138	Pseudoephedrine sulfate	330.474	1.235
139	Pseudoephedrine	165.237	1.235
140	Quetiapine fumarate	383.518	2.657
141	Silodosin	459.566	2.845
142	Terasozin hydrochloride hydrate	387.444	1.381
143	Terasozin	387.444	1.381
144	Tetrahydrozoline hydrochloride	236.746	2.185
145	Tetrahydrozoline	200.285	2.185
146	Tetryzoline	200.285	2.185
147	Tolazoline hydrochloride	196.681	1.152
148	Tolazoline	160.22	1.152
149	Tramazoline hydrochloride	215.3	2.539
150	Tramazoline	215.3	2.539

Physicochemical properties of drug molecules play an important role throughout the processes from the site of oral administration to the site of its action[3]. Undesirable physicochemical properties point to the potentially undesirable pharmacokinetic behavior. Measurement of such properties in the ADME/T profiling of NCEs (New Chemical Entities) has become commonplace in the industry. Predictions of these properties using *in silico* models have gained popularity in the recent years due to the availability of reliable methods, models and the related commercial softwares [4].

ADME/T properties

ADME/T properties of 150 anti-cancer compounds have been calculated and the results were shown in Table (1). FPSA is Fast Polar Surface Area and the molecules whose FPSA is greater than 140Å exhibited poor permeability. All the 150 compounds taken for the present study had FPSA value less than 140, which indicated that these compounds possessed high permeability. For orally administered drugs, adequate aqueous solubility is of paramount importance since dissolution of the active drug (or its prodrug form) in the GI fluids precedes its oral absorption from the GIT. Oral bioavailability (fraction of the active form of an orally administered drug that reaches systemic circulation) is, thus, largely dependent on the aqueous solubility and membrane permeability.

Aqueous solubility level and mode of solubility is as follows (5,6)

0- Extremely low
1- Very low
2- Low
3- Good, slightly soluble to soluble
4- Optimal
5- Very soluble

Aqueous solubility, in turn, is dependent on several factors such as size and shape of the molecule, hydrophobicity, hydrogen bonding, crystalline/amorphous state and others[7]. A detailed account on solubility prediction has been provided by[8] and [9].From the table 1, it was clear that 6 compounds are very soluble in water, 22 had optimal solubility and 51 exhibited good or slightly soluble to soluble character.

Two main types of permeability, namely human intestinal permeability (important for the absorption of oral drugs) and blood-brain barrier (BBB) permeability (important for the distribution of CNS active agents and toxicity of non-CNS drugs) are calculated. For orally administered drugs, several factors affect the oral absorption and ultimately, bioavailability of such drugs. Of these, permeability across human intestinal membrane represented the major step in the process of oral absorption of xenobiotics. Most of the drugs cross intestinal epithelia by passive diffusion mechanism, which in turn, largely depended on the physicochemical properties of the drug. Hence, developing predictive *in silico* models of human intestinal permeability was thought of great significance for ADME/T profiling of the NCEs. BBB permeability is a crucial factor which needs careful consideration in the ADME/T profiling. CNS drugs must cross BBB to exhibit therapeutic effect whereas non CNS drugs are expected not to cross the BBB to avoid unwanted side effects.

Blood Brain Barrier level of a compound varies from 0 to 4 indicated (10)

0- Very high
1- High
2- Medium
3- Low
4- Undefined penetration level.

Among the 150 compounds, nature of only 4 of them were undefined, 24 possessed very high penetration capacity, 55 have high level of penetration, 27 exhibited medium and 31 showed low penetration. Compounds those showed penetration to BBB can be used as CNS drugs. CNS active drugs can cross BBB by several mechanisms, including passive diffusion. This assumption formed the basis for developing earlier BBB prediction models[11].

HIA indicated the Human Intestinal Absorption. Intestinal absorption is defined as a percentage absorbed rather than as a ratio of concentrations. According to[13], ADMET predicts the Human Intestinal Absorption (HIA) after oral administration. A well-absorbed compound is one that is absorbed at least 90% into the bloodstream in humans.

As per Accord Excel, If HIA LEVEL is [12]

0- Good absorption
1- Moderate
2- Low
3- Very low

It was interesting to see that majority of the compounds i.e, 132 were showed good absorption, only 3 compounds had very low, 8 members exhibited low absorption and 7 compounds will absorb moderately.

This can be used for the classification of compounds with high or low fractional absorption. Overall, HIA represents a complex phenomenon highly dependent on the physicochemical properties of the compounds.

Hepatotoxicity plays a crucial role in drug discovery. In Accord Excel, if the[14]
Heptox = 0 (non-toxic)
Heptox = 1 (toxic)
In the present study of 150 compounds, only 13 compounds were toxic in nature. These compounds can be undergone some modifications in order to become potential drugs.

Plasma protein binding level is very important factor for finding the distribution rate of the compound. Human Plasma Protein Binding (PPB) involves reversible association of drugs with plasma proteins such as albumin and others. Drugs are in equilibrium between their protein-bound and free forms. Since only free drug exhibited the intended therapeutic effect, the PPB affinity of drugs or NCEs becomes a crucial property. Thus, PPB is significant with respect to the toxicity, pharmacology and pharmacokinetics of the drugs. For these reasons, development of the *in silico* models for the prediction of extent of PPB is an active area of predictive ADME/T.

Plasma protein binding level is [15]

0 = ≤90%
1 ≥ 90%
2 ≥ 95%

From table 1, it was clear that 54 compounds showed greater than or equal to 95% of binding affinity towards plasma protein, 45 of them had greater than or equal to 90% of binding range, whereas 51 constitutes less than 90% affinity.

Drug Blood-to-Plasma Concentration Ratio (Rb) is a measure of drug distribution within blood (binding to plasma protein and/or blood cells). It is related to either the volume of distribution or clearance of the drug. Even though the determination of Rb is relatively simple, such data is absent in most pharmacokinetic studies[16].

Inhibition or Non-inhibition of CYP450 2D6 [14, 17]
Non inhibitors of CYP450 2D6=0
Inhibitors of CYP450 2D6= 1

Chemical transformations of xenobiotics by liver (and other tissues and organs), i.e., metabolism, are central to the ADME/T profiling. It is extremely difficult to predict metabolic rate of drugs due to the complex nature of the processes involved. Of the two sets of metabolic transformations, oxidation(s) by CYP enzymes (phase I reactions) are crucial. Majority of the oxidative metabolism is brought about by three CYP isoforms 3A4, 2D6 and 2C9. Majority of the drugs are either substrates or inhibitors of the CYP enzymes. Some drugs also act as CYP inducers thereby speeding up metabolism of the co-administered drugs. The most important implication of either inhibition/induction of CYP family proteins is clinically significant and at times, potentially fatal due to drug-drug interactions. Hence, CYP inhibition assays are routinely performed for NCEs to identify problematic candidates during the early phases.

Here, in this work we also found the CYP protein affinity of the same 150 compounds. It is clearly given in table 1 that 74 compounds showed non-inhibition and rest inhibited CYP.

Lipinski's Rule of Five

According to Johnson and Wolfgang [18], compounds should possess certain properties to be accepted as drug. Those properties were formulated by Lipinski in 1997. It is a rule of thumb to evaluate drug likeness, or to determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely active drug.

Lipinski's Rule of Five for all the 150 compounds were calculated and tabulated in table2. Among the 150 drugs, only one compound was violating the rule. In order to access molecular weight and LogP of the compounds, whose value was not available from Accord Excel, we depended on Discovery studio 2.1 version. The results were shown in table3.

With the dawn of new century, major technological advances in the drug discovery field have revolutionized absorption, distribution, metabolism, excretion and toxicity (ADME/T) profiling of new chemical entities (NCEs) among others. The present work establishes ADME/T and Lipinski properties and its usefulness in screening, through which efficiency or side effects of drugs can be determined at early stages in drug discovery. We will predict these properties of all the existing anticancer compounds and also other compounds in future.

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