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Drugs, Leads, and Drug-Likeness: An Analysis of Some Recently Launched Drugs

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Abstract—An analysis of the origins of recently launched drugs reveals that most were derived by modification of known drug structures or from lead structures obtained from the scientific literature. High-throughput screening did not have a significant impact on the derivation of these drugs. The drug structures are very closely related to their leads.

There has been an ongoing debate over the past several years on the distinctions between drug-like and non drug-like molecules.[1] The debate is particularly appropriate as it relates to the identification or generation of tractable lead structures for medicinal chemistry optimization, and has been driven in part by the influence of high-throughput screening, combinatorial chemistry, and the nature of particular compound collections on the selection of such lead molecules. Given the pressures to rapidly convert lead structures into drug candidates it is important that lead structures be of high quality or 'drug-likeness', that is, possess some significant likelihood of transformation into a drug substance.

Teague et al. recently analyzed the relationship between a variety of lead structures and optimized compounds[2] and proposed guidelines for the design of combinatorial libraries with utility as lead sources. Although several of the optimized examples chosen, while useful as research tools, are not marketed drugs, the form of the analysis was interesting and provocative. A similar comparison of marketed drugs and lead structures could provide a basis for evaluating how drug-like a lead structure typically is in a successful discovery campaign. Such an analysis has been performed for the small molecule drugs first launched in 2000.[3]

These molecules are displayed in order of increasing molecular weight in Fig. 1. Lead structures, which are also shown in Fig. 1, were acknowledged, or can be proposed with reasonable certainty, for a majority of the drugs based on disclosures in the literature. Lead structures are disclosed for levetiracetam[4] **1**, cevimeline[5] **2**, frovatriptan[6] **5**, egualen sodium[7] **7**, artemotil[8] **12**, almotriptan[9] **14**, linezolid[10] **15**, bexarotene[11] **17**, taltirelin[12] **21**, maxacalcitol[13] **24**, perospirone[14] **25**, zofenopril[15] **26** and lopinavir[16] **29**. For ziprasidone[17] **22**, both tiospirone **22a** and structure **22b**[18] are indicated as leads. For zoledronic acid[19] **6**, levosimendan[20] **8**, exemestane[21] **11**, liranaftate[22] **13**, and lafudidine[23] **27**, the lead structures are not explicitly disclosed but are inferred from the literature or earlier closely related known structures. The starting points for alosetron **10**, bepotastine[24] **20**, ramatroban[25] **23**, and dofetilide[26] **28**, are not disclosed in the literature. Bulaquine[27] **19** is first described as a synthetic derivative of primaquine without reference to biological activity. Drospirenone[28] **18** appears first as a synthetic intermediate en route to a structure targeted in a related field—no lead structure is assigned. Three structures—dexmedetomidine **3**, levobupivacaine **9**, and esomeprazole **16**—are single enantiomers of previously marketed substances, and the racemic drug is shown as the lead structure. Melevodopa **4** is the methyl ester of levodopa. These latter four probably required no medicinal chemistry optimization and are shown for completeness.

In Table 1, the nature or source of the leads is shown along with some basic molecular properties of the lead and drug. Many of the lead structures are drugs or clinical candidates, and several are natural products, (i.e., vitamins, hormones, etc.) two traditionally successful

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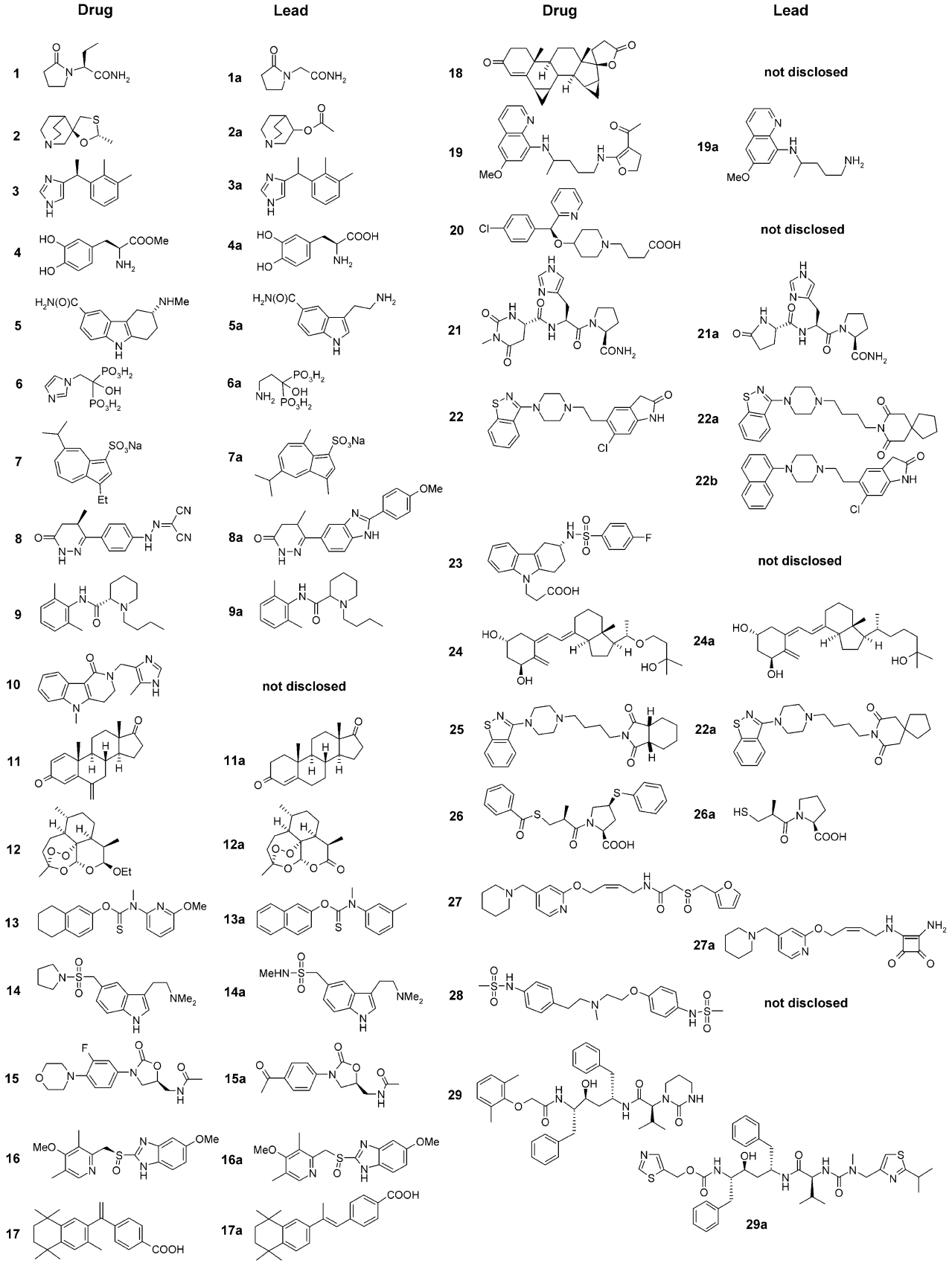
Drug
Lead
Drug
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22b
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not disclosed
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24a
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22a
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26a
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27a
28
not disclosed
29
29a

Figure 1.

Table 1. Comparison of drug and lead properties[a,b,c]

	Drug lead or lead source	MW	Δ MW	M Log P	Δ M Log P
1	Levetiracetam	170		−0.1	
1a	Piracetam (drug)	142	28	−0.8	0.7
2	Cevimaline	199		1.6	
2a	Literature	169	30	0.7	0.9
5	Frovatriptan	243		1.2	
5a	Literature	203	40	0.3	0.9
6	Zoledronic acid	272		−3.1	
6a	Pamidronate (drug)	235	25	−3.1	0
7	Egualen sodium	278		c	
7a	Guaiazulene sulfonate (drug)	278	0	c	0
8	Levosimendan	280		0.6	
8a	Pimobendan (drug)	334	−54	2.3	−1.7
11	Exemestane	296		3.7	
11a	Natural product	286	10	3.6	0.1
12	Artemotil	312		3.1	
12a	Natural product	282	30	2.4	0.7
13	Liranaftate	328		3.4	
13a	Tolnaftate (sreening)	307	11	4.4	1.0
14	Almotriptan	335		1.2	
14a	Sumatriptan (drug)	295	40	0.4	0.8
15	Linezolid	337		1.3	
15a	Clinical candidate	276	61	1.1	0.2
17	Bexarotene	348		5.0	
17a	Literature	348	0	5.0	0
19	Bulaquine	369		2.0	
19a	Primaquine	259	110	1.9	0.1
21	Taltirelin	405		−1.6	
21a	Natural product	362	43	−1.5	0.1
22	Ziprasidone	412		3.0	
22a	Tiospirone (drug)	440	−28	2.6	0.3
22b	In-house generated	406	6	4.0	−1.0
24	Maxacalcitol	418		3.5	
24a	Natural product	416	2	4.5	−1.0
25	Perospirone	426		2.4	
22a	Tiospirone (drug)	440	−14	2.6	−0.2
26	Zofenopril	429		2.4	
26a	Captopril (drug)	217	212	0.2	2.2
27	Lafutidine	431		1.0	
27a	Pibutidine (clinical candidate)	356	75	1.2	−0.2
29	Lopinavir	628		3.3	
29a	Ritonavir (drug)	720	−92	2.3	1.0

[a]An sdf file of the drug and lead structures is available from the author upon request.
[b]Calculated using SimulationsPlus QMPRPlus.
[c]Calculated Log P values are not meaningful for these structures.

lead sources in drug discovery.[29] For only one drug, **13**, was it indicated that screening played a role in the discovery of the lead structure.

Despite the varied objectives (improving potency, selectivity, chemical stability, etc.) driving the optimization of these drugs, the drug and lead structures are generally remarkably similar. All but two (**19** and **26**) of the drugs are within 25% of the lead with regard to molecular weight, and nearly all are within one calculated M Log P unit. Structurally, most of the drugs are derived by quite limited modification of the lead. For **1**, introduction of an ethyl group sufficed; for **2**, a ring constraint and replacement of an oxygen with a sulfur atom led to success; for **5** a ring constraint and introduction of two carbon atoms, and so on. In all cases the greater part of the lead structure remains unchanged. From these comparisons it appears that high quality, effective lead structures are already closely related to the final drug.

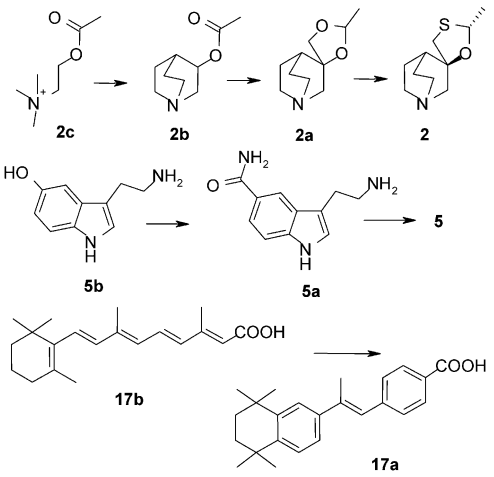

Figure 2.

The transformation of these leads into drug structures is best described as drug optimization rather than lead optimization. Most of the lead structures, aside from natural products, are drugs or clinical candidates and already the products of optimization. This is also true for those leads derived from the literature. Discovery of **2**, **5**, and **17** proceeded as shown in Fig. 2, and all three derived from natural products as progenitors.

Approaches to the evaluation drug likeness often compare large collections of 'drug-like' molecules with large collections of non drug-like molecules. These analyses can give the impression that drug-like molecules are quite abundant, and high quality lead structures are easy to find, whether by high throughput screening, combinatorial chemistry or rational processes.

The analysis above shows that, at least for the successful discovery campaigns that resulted in the new drugs launched last year, the lead structures were very closely related to the marketed drug. Successful, timely drug discovery campaigns require high quality lead structures and these lead structures may need to be much more drug-like than is commonly accepted.

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