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Rule of five violations among the FDA-approved small molecule protein kinase inhibitors

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ABSTRACT

Because genetic alterations including mutations, overexpression, translocations, and dysregulation of protein kinases are involved in the pathogenesis of many illnesses, this enzyme family is the target of many drug discovery programs in the pharmaceutical industry. Overall, the US FDA has approved 74 small molecule protein kinase inhibitors, nearly all of which are orally effective. Of the 74 approved drugs, thirty-nine block receptor protein-tyrosine kinases, nineteen target nonreceptor protein-tyrosine kinases, twelve are directed against protein-serine/threonine protein kinases, and four target dual specificity protein kinases. The data indicate that 65 of these medicinals are approved for the management of neoplasms (51 against solid tumors such as breast, colon, and lung cancers, eight against nonsolid tumors such as leukemia, and six against both types of tumors). Nine of the FDA-approved kinase inhibitors form covalent bonds with their target enzymes and they are accordingly classified as TCIs (targeted covalent inhibitors). Medicinal chemists have examined the physicochemical properties of drugs that are orally effective. Lipinski's rule of five (Ro5) is a computational procedure that is used to estimate solubility, membrane permeability, and pharmacological effectiveness in the drug-discovery setting. It relies on four parameters including molecular weight, number of hydrogen bond donors and acceptors, and the Log of the partition coefficient. Other important descriptors include the lipophilic efficiency, the polar surface area, and the number of rotatable bonds and aromatic rings. We tabulated these and other properties of the FDA-approved kinase inhibitors. Of the 74 approved drugs, 30 fail to comply with the rule of five.

1. The importance of therapeutic protein kinase inhibitors

As a result of genetic alterations including mutations, translocations and overexpression, the dysregulation of protein kinase activity plays a major role in the pathogenesis of inflammatory, autoimmune, nervous, and cardiovascular diseases as well as a number of malignancies. Accordingly, protein kinases are among the most prominent drug targets in the 21st century [1–4]. Perhaps 25–33% of drug discovery endeavors worldwide focus on these enzymes. The therapeutic effectiveness of imatinib in the treatment of Philadelphia chromosome-positive chronic myelogenous leukemia in 2001 prompted the search for orally bioavailable therapeutic protein kinase inhibitors [5–7]. This unparalleled success resulted from the imatinib blockade of the activated chimeric BCR-Abl protein-tyrosine kinase, the causative biochemical defect that produces these leukemias.

The existence of thousands of protein kinase X-ray crystal structures in the public domain aids in the discovery and development of new protein kinase antagonists. Moreover, additional proprietary structures are also used in the drug discovery process. About 250 orally bioavailable protein kinase antagonists are in clinical trials worldwide [8]. A complete listing of these agents, which is regularly updated, is posted at www.icoa.fr/pkidb/. There are 74 US FDA-approved medicinals in use today that target about two dozen different protein kinases (www.brimr.org/PKI/PKIs.htm). These targets, however, represent a small fraction of

Abbreviations: ADMET, absorption, distribution, metabolism, excretion, and toxicity; bRo5, beyond Lipinski's rule of five; BTK, Bruton protein-tyrosine kinase; CDK, cyclin-dependent protein kinase; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; Fsp^3, fraction of sp^3 carbon atoms/total carbon atoms; HA, hydrogen-bond acceptor; HD, hydrogen-bond donor; HTS, high throughput screening; JAK, Janus kinase; LE, ligand efficiency; LipE, lipophilic efficiency; MW, molecular weight; N, number of heavy (non-hydrogen) atoms; nAr, number of aromatic rings; nBnz, number of benzenes; nRng, number of rings; nRotB, number of rotatable bonds; NSCLC, non-small cell lung cancer; PDGFR, platelet-derived growth factor receptor; PI3-kinase, phosphatidylinositol 3-kinase; PSA, polar surface area; QED, quantitative estimate of drug-likeness; Ro5, Lipinski's rule of five; VEGFR, vascular endothelial growth factor receptor.

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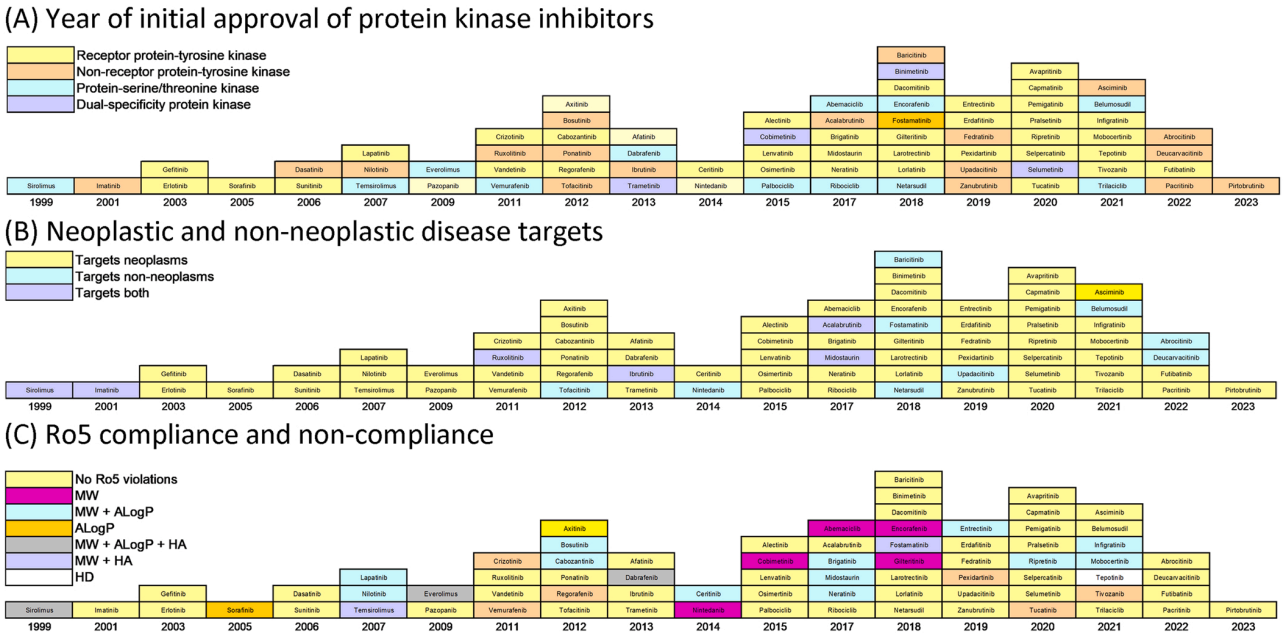

Fig. 1. (A) Year of approval of receptor and nonreceptor protein-tyrosine kinase inhibitors, protein-serine/threonine kinase blockers and dual specificity protein kinase antagonists. (B) Protein kinase inhibitors that target neoplastic diseases, nonneoplastic diseases, and both classes of disorder. (3) Ro5 compliant and non-compliant protein kinase antagonists. MW, molecular weight violation, AlogP, atom-based logarithm of the partition coefficient violation, HA, hydrogen bond acceptor infraction, HD, hydrogen bond donor noncompliance.

the 518-member protein kinase superfamily. Dozens of drugs directed against currently targeted and untargeted protein kinases are in clinical trials across the globe [6–8].

Manning et al. found that the human protein kinase family contains 478 typical and 40 atypical members [9] such as phosphatidylinositol 3-kinase (PI 3-kinase) [7,10]. Protein kinases mediate the following reaction;.

$$\mathrm{MgATP}^{1-} + \text{protein–O:H} \rightarrow \text{protein–O:PO}_3^{2-} + \mathrm{MgADP} + \mathrm{H}^+$$

Based upon the nature of the protein–OH groups, these catalysts are divided into protein-serine/threonine kinases (385 members), protein-tyrosine kinases (90), and protein-tyrosine kinase–like enzymes (43). The protein-tyrosine kinase family consists of both intracellular non-receptor (32) and transmembrane receptor (58) proteins. Furthermore, the protein kinase group includes a small cadre of intracellular enzymes such as MEK1/2 that catalyze the phosphorylation of both tyrosine and then threonine residues within the activation segment of their target protein kinases; because of this unique property, MEK1/2 and related enzymes are called dual specificity (DS) protein kinases. Another indication of the importance of the protein kinase lineage is the reckoning that one in every 40 human genes (518 protein kinase genes out of an estimated 20,000 human protein-encoding genes) corresponds to a protein kinase. Protein kinases therefore constitute approximately 2.5% of the human genome. An additional indication of the significance of protein kinases as drug targets is the work of Manning et al. that proposes that 244 protein kinases map to cancer amplicons and other disease loci [9]. Accordingly, as additional research on the pathogenesis of additional diseases is performed, it is quite likely that there will be a substantial increase in the number of protein kinase targets.

The US FDA has approved 74 small molecule therapeutic protein kinase antagonists as of April 2023, nearly all of which are orally effective. The exceptions include temsirolimus and trilaciclib (which are given intravenously) and netarsudil (an eye drop). Ruxolitinib is an orally effective JAK1/2 protein kinase inhibitor that was approved for the treatment of myelofibrosis and polycythemia vera in 2011. This medicinal is topically active as a cream and was approved in 2021 for the treatment of atopic dermatitis. Of the 74 approved drugs, thirty-nine block receptor protein-tyrosine kinases, nineteen target nonreceptor protein-tyrosine kinases, twelve are directed against protein-serine/threonine protein kinases, and four target dual specificity protein kinases (MEK1/2) (Fig. 1A).

The data indicate that 65 of these medicinals are approved for the management of neoplasms (51 against solid tumors such as breast, colon, and lung cancers, eight against nonsolid tumors such as leukemia, and six against both types of tumors: midostaurin, ibrutinib, imatinib, ruxolitinib, sirolimus, and acalabrutinib) (Fig. 1B). Oral medicinals have many advantages in comparison to other drug formulations. In contrast to liquids and suspensions, solid forms of oral drugs are more stable during storage [11]. Importantly, oral delivery is the patient-preferred method of drug administration. Compared with intravenous therapy, the quality of life for patients is increased owing to the ability to self-administer at home. Most drugs used in oncology are given intravenously, but most patients prefer the convenience of oral medicinals.

More than two dozen of the approved drugs are multikinase antagonists. Because the specificity of many of the protein kinase antagonists has not been thoroughly examined, it is likely that other FDA-approved drugs are multikinase inhibitors. The simultaneous inhibition of multiple protein kinases has potential advantages as well as disadvantages. For example, the therapeutic efficacy of multikinase antagonists may be related to the inhibition of two or more targets. For example, cabozantinib and sunitinib have potent off-target activity against the Axl receptor protein-tyrosine kinase and this characteristic may add to their clinical effectiveness [16]; Axl is the receptor for GAS6 (growth arrest-specific protein 6). Contrariwise, the blockade of off-target kinases may elicit unwanted side effects. Hence, we have the dilemma of whether a magic shotgun should be preferred to Paul Ehrlich's magic bullet [17].

Twelve of the FDA-approved protein kinase inhibitors are prescribed for the treatment of nonneoplastic diseases. For example, (i) deucravacitinib is used for the treatment of psoriasis, (ii) baricitinib and upadacitinib are employed for the treatment of rheumatoid arthritis, (iii) tofacitinib is used for the treatment of psoriatic arthritis, rheumatoid

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Table 1
FDA-approved small molecule protein kinase inhibitors, their protein kinase targets, and therapeutic indications[a].

Drug	Code	Company	Trade name	Year approved	Primary targets[b]	Therapeutic indications[c]
Abemaciclib	LY2835219	Lilly	Verzenio	2017	CDK4/6	Combination therapy with (i) an aromatase inhibitor or with (ii) fulvestrant or (iii) as a monotherapy for breast cancer
Abrocitinib	PF-04965842	Pfizer	Cibinqo	2022	JAK1	Atopic dermatitis
Acalabrutinib	ACP-196	Acerta Pharma	Calquence	2017	BTK	Mantle cell lymphomas, CLL, SLL
Afatinib	BIBW 2992	Boehringer Ingelheim	Tovok	2013	ErbB1/2/4	NSCLC
Alectinib	CH5424802	Roche	Alecensa	2015	ALK, RET	ALK-positive NSCLC
Asciminib	ABL001	Novartis	Scemblix	2021	BCR-Abl	Ph^+ CML
Avapritinib	BLU285	Blueprint Medicines	Ayvakit	2020	PDGFRα	GIST with a *PDGFRα* exon 18 mutations, systemic mastocytosis
Axitinib	AG-013736	Pfizer	Inlyta	2012	VEGFR1/2/3	RCC
Baricitinib	LY 3009104	Lilly	Olumiant	2018	JAK1/2	Rheumatoid arthritis
Belumosudil	KD025	Kadmon Pharma	Rezurock	2021	ROCK2	Graft vs. host disease
Binimetinib	MEK162	Array BioPharma	Mektovi	2018	MEK1/2	Combination therapy with encorafenib for $BRAF^{V600E/K}$ melanomas
Bosutinib	SKI-606	Pfizer	Bosulif	2012	BCR-Abl	Ph^+ CML
Brigatinib	AP 26113	Ariad Pharm	Alunbrig	2017	ALK	ALK-positive NSCLC
Cabozantinib	BMS-907351	Exelixis	Cometriq & Cabometyx	2012	RET, VEGFR2	Medullary thyroid cancer, RCC, HCC
Capmatinib	INC-280	Novartis	Tabrecta	2020	MET (HGFR)	NSCLC with MET exon 14 skipping
Ceritinib	LDK378	Novartis	Zykadia	2014	ALK	ALK-positive NSCLC resistant to crizotinib
Cobimetinib	GDC-0973	Genentech	Cotellic	2015	MEK1/2	$BRAF^{V600E/K}$ melanomas in combination with vemurafenib
Crizotinib	PF 2341066	Pfizer	Xalkori	2011	ALK, ROS1	ALK or ROS1-postive NSCLC
Dabrafenib	GSK2118436	GSK	Tafinlar	2013	B-Raf	$BRAF^{V600E/K}$ melanomas, $BRAF^{V600E}$ NSCLC, $BRAF^{V600E}$ anaplastic thyroid cancers
Dacomitinib	PF-00299804	Pfizer	Visimpro	2018	EGFR	*EGFR*-mutant NSCLC
Dasatinib	BMS-354825	Bristol Myers Squibb	Sprycel	2006	BCR-Abl	Ph^+ CML
Deucravacitinib	BMS-986165	Bristol Myers Squibb	Sotyktu	2022	TYK2	Psoriasis
Encorafenib	LGX818	Array BioPharma	Braftovi	2018	B-Raf	Combination therapy for $BRAF^{V600E/K}$ melanomas and colorectal cancer
Entrectinib	RXDX-101	Genentech	Rozlytrek	2019	TRKA/B/C, ROS1	Solid tumors with NTRK fusion proteins, ROS1-positive NSCLC
Erdafitinib	JNJ-42756493	Jansen Pharm	Balversa	2019	FGFR1/2/3/4	Urothelial bladder cancer
Erlotinib	OSI-774	Genentech	Tarceva	2004	EGFR	NSCLC, pancreatic cancer
Everolimus	RAD001	Novartis	Afinitor	2009	FKBP12/mTOR	HER2-negative breast cancer, pancreatic neuroendocrine tumors, RCC, angiomyolipomas, subependymal giant cell astrocytomas
Fedratinib	TG101348	Celgene	Inrebic	2019	JAK2	Myelofibrosis
Fostamatinib	R788	Rigel Pharma.	Tavalisse	2018	Syk	Chronic immune thrombocytopenia
Futibatinib	TAS_120	Tiaho Pharma	Lytgobi	2022	FGFR2	Bile duct cancers (cholangiocarcinomas) with FGFR2 fusions or rearrangements
Gefitinib	ZD1839	AstraZeneca	Iressa	2003	EGFR	NSCLC with *EGFR L858R* mutations or exon 19 deletions
Gilteritinib	ASP2215	Astellas Pharma	Xospata	2018	Flt3	AML with a *FLT3* mutation
Ibrutinib	PCI-32765	Johnson & Johnson	Imbruvica	2013	BTK	CLL, mantle cell lymphoma, marginal zone lymphoma, graft vs. host disease, Waldenström macroglobulinemia
Imatinib	STI571	Novartis	Gleevec	2001	BCR-Abl	Ph^+ CML or ALL, aggressive systemic mastocytosis, chronic eosinophilic leukemia, dermatofibrosarcoma protuberans, hypereosinophilic syndrome, GIST, myelodysplastic/myeloproliferative disease
Infigratinib	BGJ 398	QED Therapeutics	Truseltiq	2021	FGFR2	Cholangiocarcinomas with FGFR2 fusion or other rearrangement
Lapatinib	GW572016	GSK	Tykerb	2007	EGFR, ErbB2/HER2	HER2-positive breast cancer
Larotrectinib	LOXO-101	Bayer	Vitrakvi	2018	TRKA/B/C	Solid tumors with NTRK fusion proteins
Lenvatinib	AK175809	Easai Co.	Lenvima	2015	VEGFR, RET	Differentiated thyroid cancer
Lorlatinib	PF-06463922	Pfizer	Lorbrena	2018	ALK	ALK-positive NSCLC
Midostaurin	CPG 41251	Novartis	Rydapt	2017	Flt3	*FLT3* mutation positive AML, mastocytosis, mast cell leukemia
Mobocertinib	TAK-788	Takeda Pharm.	Exkivity	2021	EGFR	NSCLC for *EGFR*-positive exon 21 insertions
Neratinib	HKI-272	Puma Biotech	Nerlynx	2017	ErbB2/HER2	HER2-positive breast cancer
Netarsudil	AR11324	Aerie Pharma	Rhopressa	2018	ROCK1/2	Glaucoma
Nilotinib	AMN107	Novartis	Tasigna	2007	BCR-Abl	Ph^+ CML
Nintedanib	BIBF-1120	Boehringer Ingelheim	Vargatef	2014	FGFR1/2/3	Idiopathic pulmonary fibrosis
Osimertinib	AZD-9292	AstraZeneca	Tagrisso	2015	EGFR	NSCLC with *EGFR L858R* or *T790M* mutations or exon 19 deletions

(*continued on next page*)

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Table 1 (*continued*)

Drug	Code	Company	Trade name	Year approved	Primary targets[b]	Therapeutic indications[c]
Pacritinib	SB1518	CTI BioPharma	Vonjo	2022	JAK2	Myelofibrosis
Palbociclib	PD-0332991	Parke-Davis	Ibrance	2015	CDK4/6	Combination therapy for estrogen-receptor positive and HER2-negative breast cancers
Pazopanib	GW786034	GSK	Votrient	2009	VEGFR1/2/3	RCC, soft tissue sarcomas
Pemigatinib	INCB054828	Incyte Corp.	Pemazyre	2020	FGFR2	Advanced cholangiocarcinoma with a FGFR2 fusion or rearrangement
Pexidartinib	PLX3397	Plexxikon Inc	Turalio	2019	CSF1R	Tenosynovial giant cell tumors
Pirtobrutinib	LOXO-305	Lilly	Jaypirca	2023	BTK	Mantle cell lymphoma
Ponatinib	AP 24534	Ariad Pharm	Iclusig	2012	BCR-Abl	Ph^+ CML or ALL
Pralsetinib	Blu-667	Blueprint Medicines	Gavreto	2020	RET	RET-fusion (i) NSCLC, (ii) medullary thyroid cancer, (iii) differentiated thyroid cancer
Regorafenib	BAY 73–4506	Bayer	Stivarga	2012	VEGFR1/2/3	Colorectal cancer, HCC, GIST
R406 active metabolite of fostamatinib		Rigel Pharma.		2018	Syk	Chronic immune thrombocytopenia
Ribociclib	LEE011	Novartis	Kisqali	2017	CDK4/6	Combination therapy with an aromatase inhibitor for HR-positive HER2-negative breast cancer
Ripretinib	DCC-2618	Decipera Pharma.	Qinlock	2020	Kit, PDGFRα	Fourth-line treatment for GIST
Ruxolitinib	INCB-018424	Incyte Corp.	Jakafi	2011	JAK1/2/3, Tyk	Myelofibrosis, polycythemia vera, graft vs. host disease, topically for atopic dermatitis
Selpercatinib	CEGM9YBNG	Lilly	Retevmo	2020	RET	RET fusion NSCLC, solid tumors, thyroid cancers and *RET* mutant medullary thyroid cancer
Selumetinib	AZD6224	AstraZeneca	Koselugo	2020	MEK1/2	Neurofibromatosis type I
Sirolimus	AY 22989	Wyeth, LLC	Rapamycin	1999	FKBP12/mTOR	Kidney transplants, lymphangioleiomyomatosis
Sorafenib	BAY 43–9006	Bayer	Nexavar	2005	VEGFR1/2/3	HCC, RCC, differentiated thyroid cancer
Sunitinib	SU11248	Pfizer	Sutent	2006	VEGFR2	GIST, pancreatic neuroendocrine tumors, RCC
Temsirolimus	CCI-779	Wyeth, LLC	Torisel	2007	FKBP12/mTOR	RCC
Tepotinib	EMD 1214063	EMD SeronoInc.	Tepmetko	2021	MET (HGFR)	NSCLC with *MET* mutations
Tivozanib	AV951	AVEO Pharma	Fotvida	2021	VEGFR2	Third-line treatment of RCC
Tofacitinib	CP-690550	Pfizer	Tasocitinib	2012	JAK3	Rheumatoid arthritis
Trametinib	GSK1120212	GSK	Mekinist	2013	MEK1/2	$BRAF^{V600E/K}$ melanomas, $BRAF^{V600E}$ NSCLC
Trilaciclib	G1T28	G1 Therapeutics	Cosela	2021	CDK4/6	Chemotherapy-induced myelosuppression
Tucatinib	ONT-380	Seattle Genetics	Tukysa	2020	ErbB2/HER2	Combination second-line treatment for HER2-positive breast cancer
Upadacitinib	ABT-494	AbbVie	Rinvoq	2019	JAK1	Second-line treatment for rheumatoid arthritis, psoriatic arthritis, atopic dermatitis
Vandetanib	ZD6474	Sanofi	Zactima	2011	VEGFR2	Medullary thyroid cancer
Vemurafenib	PLX-4032	Genentech	Zelboraf	2011	B-Raf	$BRAF^{V600E}$ melanomas, Erdheim-Chester disease
Zanubrutinib	BGB3111	BeiGene	Brukinsa	2019	BTK	Mantle cell lymphomas

[a] Data from Refs. [2–4,12–15].
[b] Although many of these drugs are multikinase inhibitors, only the primary therapeutic targets are given here.
[c] ALL, acute lymphoblastic leukemias; AML, acute myelogenous leukemias; CLL, chronic lymphocytic leukemias; CML, chronic myelogenous leukemias; ErbB2/HER2, human epidermal growth factor receptor-2; GIST, gastrointestinal stromal tumors; HCC, hepatocellular carcinomas; MET (HGFR), hepatocyte growth factor receptor; HR, hormone receptor; NSCLC, non-small cell lung cancers; Ph^+, Philadelphia chromosome positive; RCC, renal cell carcinomas; SLL, small lymphocytic leukemias.

arthritis, and ulcerative colitis, (iv) abrocitinib and ruxolitinib are prescribed for the management of atopic dermatitis, (v) upadacitinib is prescribed for the treatment of psoriatic arthritis, rheumatoid arthritis, and atopic dermatitis, (vi) sirolimus and belumosudil are prescribed for the management of graft vs. host disease, (vii) nintedanib is used for the treatment of idiopathic pulmonary fibrosis, (viii) fostamatinib is prescribed for the management of chronic immune thrombocytopenia, (ix) and netarsudil is employed for the treatment of glaucoma [3,12–15,18,19]. Moreover, acalabrutinib, ibrutinib, imatinib, midostaurin, ruxolitinib, and sirolimus are approved therapeutics for both neoplastic and nonneoplastic diseases.

Nine of the FDA-approved kinase inhibitors form covalent bonds with their target enzymes and they are accordingly classified as TCIs (targeted covalent inhibitors) [18]. These agents include acalabrutinib (inhibiting BTK in mantle cell lymphoma), afatinib (targeting EGFR in NSCLC), dacomitinib (inhibiting mutant *EGFR* in NSCLC), futibatinib (inhibiting FGFR2 in bile duct cancers), ibrutinib (blocking BTK in chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone lymphoma, chronic graft vs. host disease, and Waldenström macroglobulinemia), mobocertinib (inhibiting *EGFR* in NSCLC), neratinib (targeting ErbB2 in HER2-positive breast cancer), osimertinib (blocking *EGFR T970M* mutants in NSCLC), and zanubrutinib (targeting BTK in mantle cell lymphoma). The most common mutant protein kinases in all cancers are the closely related EGFR and ErbB4 of the ErbB1/2/3/4 epidermal growth factor receptor family [3]. For a summary of the characteristics of small molecule protein kinase antagonists that were FDA-approved by 2023, see Refs. [2–4,12–15,18,19].

Of the 74 FDA-approved protein kinase blockers, twenty are used in the treatment of more than one disease. For example, imatinib is approved for the treatment of eight distinct disorders (Table 1). This medicinal inhibits the nonreceptor protein-tyrosine kinase Abl (and the BCR-Abl chimera – responsible for the pathogenesis of chronic myelogenous leukemia), Kit (the stem cell factor receptor), PDGFRα/β, Abl2, and epithelial discoidin domain-containing receptor-1 (DDR1) and

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Table 2
Properties of FDA-approved small molecule inhibitors.

Drug	PubMED CID	Formula	MW (Da)	HD[a]	HA[b]	ALogP[c]	Log $D_{7.4}$[d]	PSA ($Å^2$)[e]	Fsp^3[f]	nStereo[g]	Cplx[h]
Abemaciclib	46220502	$C_{27}H_{32}F_2N_8$	507	1	9	4.94	3.76	75	0.41	0	723
Abrocitinib	78323835	$C_{14}H_{21}N_5S$	323	2	6	1.3	0.79	99.4	0.57	0	474
Acalabrutinib	71226662	$C_{26}H_{23}N_7O_2$	466	2	6	3.31	2.56	119	0.19	1	845
Afatinib	10184653	$C_{24}H_{25}ClFN_5O_3$	486	2	8	4.39	2.34	88.6	0.29	1	702
Alectinib	49806720	$C_{30}H_{34}N_4O_2$	483	1	5	4.77	4.75	72.4	0.47	0	867
Asciminib	72165228	$C_{20}H_{18}ClF_2N_5O_3$	450	3	8	3.46	3.86	103	0.25	1	626
Avapritinib	118023034	$C_{26}H_{27}FN_{10}$	499	1	9	2.61	2.12	106	0.27	1	752
Axitinib	6450551	$C_{22}H_{18}N_4OS$	386	2	4	4.64	4.15	96	0.05	0	557
Baricitinib	44205240	$C_{16}H_{17}N_7O_2S$	371	1	7	1.10	-0.19	129	0.19	0	678
Belumosudil	11950170	$C_{26}H_{24}N_6O_2$	452	3	6	4.82	4.02	105	0.15	0	678
Binimetinib	10288191	$C_{17}H_{15}BrF_2N_4O_3$	441	3	7	3.01	3.81	88.4	0.18	0	521
Bosutinib	5328940	$C_{26}H_{29}Cl_2N_5O_3$	530	1	8	5.19	3.37	82.9	0.23	0	734
Brigatinib	68165256	$C_{29}H_{39}ClN_7O_2P$	584	2	9	5.09	2.49	85.9	0.28	0	835
Cabozantinib	25102847	$C_{28}H_{24}FN_3O_5$	501	2	7	5.54	4.65	98.8	0.18	0	795
Capmatinib	25145656	$C_{23}H_{17}FN_6O$	412	1	6	3.43	2.96	81.5	0.09	0	637
Ceritinib	57379345	$C_{28}H_{36}ClN_5O_3S$	558	3	8	6.36	3.38	114	0.25	0	835
Cobimetinib	16222096	$C_{21}H_{21}F_3IN_3O_2$	531	3	7	3.78	2.73	64.6	0.33	1	624
Crizotinib	11626560	$C_{21}H_{22}Cl_2FN_5O$	450	2	6	5.04	0.95	78	0.29	1	558
Dabrafenib	44462760	$C_{23}H_{20}F_3N_5O_2S_2$	520	2	11	5.36	5.10	148	0.17	0	817
Dacomitinib	11511120	$C_{24}H_{25}ClFN_5O_2$	470	2	7	5.16	3.53	79.4	0.29	0	665
Dasatinib	3062316	$C_{22}H_{26}ClN_7O_2S$	488	3	9	3.31	3.74	135	0.32	0	642
Deucravacitinib	134821691	$C_{20}H_{22}N_8O_3$	426	3	8	1.78	2.10	136	0.45	0	648
Encorafenib	50922675	$C_{22}H_{27}ClFN_7O_4S$	540	3	10	3.91	2.61	149	0.36	1	836
Entrectinib	25141092	$C_{31}H_{34}F_2N_6O_2$	561	3	8	5.03	4.87	85.5	0.35	0	847
Erdafitinib	67462786	$C_{25}H_{30}N_6O_2$	446	1	7	4.18	1.25	77.3	0.32	0	583
Erlotinib	176870	$C_{22}H_{23}N_3O_4$	393	1	7	3.41	3.20	74.7	0.27	0	525
Everolimus	6442177	$C_{53}H_{83}NO_{14}$	958	3	14	6.20	7.40	205	0.75	15	1810
Fedratinib	16722836	$C_{27}H_{36}N_6O_3S$	525	3	9	4.82	3.23	117	0.41	0	787
Fostamatinib	11671467	$C_{23}H_{26}FN_6O_9P$	580	4	15	3.09	-0.52	187	0.30	0	904
Futibatinib	71621331	$C_{22}H_{22}N_6O_3$	418	1	7	1.78	1.54	108	0.23	1	723
Gefitinib	123631	$C_{22}H_{24}ClFN_4O_3$	447	1	8	4.28	3.64	68.7	0.36	0	545
Gilteritinib	49803313	$C_{29}H_{44}N_8O_3$	552	3	10	2.70	1.69	121	0.62	0	785
Ibrutinib	24821094	$C_{25}H_{24}N_6O_2$	441	1	6	4.22	3.63	99.2	0.16	1	678
Imatinib	5291	$C_{29}H_{31}N_7O$	494	2	7	4.59	3.80	86.3	0.24	0	706
Infigratinib	53235510	$C_{26}H_{31}Cl_2N_7O_3$	560	2	8	5.35	3.99	95.1	0.31	0	724
Lapatinib	208908	$C_{29}H_{26}ClN_4O_4S$	580	2	9	6.14	4.40	115	0.17	0	898
Larotrectinib	46188928	$C_{21}H_{22}F_2N_6O_2$	428	2	7	2.95	2.44	86	0.38	2	659
Lenvatinib	9823820	$C_{21}H_{19}ClN_4O_4$	427	3	5	4.07	2.52	116	0.19	0	634
Lorlatinib	71731823	$C_{21}H_{19}FN_6O_2$	406	1	7	2.80	1.62	110	0.19	1	700
Midostaurin	9829523	$C_{35}H_{30}N_4O_7$	571	1	4	5.91	5.43	77.7	0.20	4	1140
Mobocertinib	118607832	$C_{32}H_{39}N_7O_4$	586	2	9	5.08	3.79	114	0.31	0	935
Neratinib	9915743	$C_{30}H_{29}ClN_6O_3$	557	2	8	5.93	3.05	112	0.17	0	881
Netarsudil	66599893	$C_{28}H_{27}N_3O_3$	454	2	5	4.89	3.42	94.3	0.14	1	678
Nilotinib	644241	$C_{28}H_{22}F_3N_7O$	530	2	9	6.36	5.35	97.6	0.11	0	817
Nintedanib	135423438	$C_{31}H_{33}N_5O_4$	540	2	7	3.62	2.57	102	0.26	0	892
Osimertinib	71496458	$C_{28}H_{33}N_7O_2$	500	2	7	4.51	3.01	87.6	0.25	0	752
Pacritinib	46216796	$C_{28}H_{32}N_4O_3$	473	1	7	4.96	3.11	68.7	0.29	0	644
Palbociclib	5330286	$C_{24}H_{29}N_7O_2$	448	2	8	2.97	1.30	103	0.42	0	775
Pazopanib	10113978	$C_{21}H_{23}N_7O_2S$	438	2	8	3.14	3.55	127	0.19	0	717
Pemigatinib	86705695	$C_{24}H_{27}F_2N_5O_4$	487	1	8	3.66	1.80	83.2	0.38	0	731
Pexidartinib	25151352	$C_{20}H_{15}ClF_3N_5$	417	2	7	5.23	3.35	66.5	0.15	0	537
Pirtobrutinib	129269915	$C_{22}H_{21}F_4N_5O_3$	479	3	9	3.43	4.55	125	0.23	1	719
Ponatinib	24826799	$C_{29}H_{27}F_3N_6O$	533	1	8	4.46	4.54	65.8	0.14	0	910
Pralsetinib	129073603	$C_{27}H_{32}FN_9O_2$	534	3	9	4.20	3.64	136	0.37	1	816
Regorafenib	11167602	$C_{21}H_{15}ClF_4N_4O_3$	483	3	8	5.69	4.49	92.4	0.10	0	686
Ribociclib	44631912	$C_{23}H_{30}N_8O$	435	2	7	2.80	0.91	91.2	0.48	0	636
Ripretinib	71584930	$C_{24}H_{21}BrFN_5O_2$	510	3	5	5.67	4.38	86.4	0.13	0	746
Ruxolitinib	25126798	$C_{17}N_{18}N_6$	306	1	4	3.47	2.48	83.2	0.41	1	453
Selpercatinib	134436906	$C_{29}H_{31}N_7O_3$	526	1	9	3.28	3.11	112	0.38	0	885
Selumetinib	10127622	$C_{17}H_{15}BrClF_4O_3$	458	3	6	3.53	4.27	88.4	0.18	0	523
Sirolimus	5284616	$C_{51}H_{79}NO_{13}$	914	3	13	6.18	7.45	195	0.75	15	1760
Sorafenib	216239	$C_{21}H_{16}ClF_3N_4O_3$	465	3	7	5.55	4.34	92.4	0.10	0	646
Sunitinib	5329102	$C_{22}H_{27}FN_4O_2$	398	3	4	3.33	1.28	77.2	0.36	0	636
Temsirolimus	6918289	$C_{56}H_{87}NO_{16}$	1030	4	16	4.39	?	242	0.75	15	2010
Tepotinib	25171648	$C_{29}H_{28}N_6O_2$	493	0	7	4.01	2.26	94.7	0.28	0	880
Tivozanib	9911830	$C_{22}H_{19}CLIN_4O_5$	455	2	7	5.64	4.16	108	0.14	0	631
Tofacitinib	9926791	$C_{16}H_{20}N_6O$	312	1	5	1.54	1.19	88.9	0.50	2	488
Trametinib	11707110	$C_{26}H_{23}FlN_5O_4$	615	2	6	3.94	3.18	102	0.23	0	1090
Trilaciclib	68029831	$C_{24}H_{30}N_8O$	447	2	7	2.72	2.29	91.2	0.46	0	707
Tucatinib	51039094	$C_{26}H_{24}N_8O_2$	481	2	8	5.09	5.25	111	0.19	0	796
Upadacitinib	58557659	$C_{17}H_{19}F_3N_6O$	380	2	6	2.91	0.85	78.3	0.47	2	561
Vandetanib	3081361	$C_{22}H_{24}BrFN_4O_2$	475	1	7	5.00	2.81	59.5	0.32	0	539
Vemurafenib	42611257	$C_{23}H_{18}ClF_2N_3O_3S$	490	2	7	5.54	4.61	100	0.09	0	790
Zanubrutinib	135565884	$C_{27}H_{27}N_5O_3$	472	2	5	4.22	3.42	103	0.30	0	756

[a] HD, no. of hydrogen bond donors.

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[b] HA, no. of hydrogen bond acceptors.
[c] ALogP, values for atom-based log of the partition coefficient from https://www.ebi.ac.uk/chembl/.
[d] Log $D_{7.4}$, values for the log of the distribution coefficients at pH 7.4 obtained from https://www.ebi.ac.uk/chembl/.
[e] PSA, polar surface area.
[f] Fraction of sp^3 carbon atoms.
[g] Defined atom stereocenter count.
[h] Complexity values obtained from https://pubchem.ncbi.nlm.nih.gov/.

receptor-2 (DDR2). DDR1/2, which are activated by collagen, participate in cell migration, proliferation, differentiation, and the remodeling the extracellular matrix. Imatinib is FDA-approved for (i) the first-line treatment of Philadelphia chromosome-positive chronic myelogenous leukemia, (ii) acute lymphoblastic leukemia, (iii) *KIT* mutation-positive gastrointestinal stromal tumors, (iv) myelodysplastic/myeloproliferative diseases with *PDGFR* gene-rearrangements, (v) dermatofibrosarcoma protuberans, (vi) hypereosinophilic syndrome, (vii) chronic eosinophilic leukemia, and (viii) as a second-line treatment for aggressive systemic mastocytosis without the *KIT* ^{D816V} mutation [2,3]. Furthermore, imatinib is used off-label for the treatment of chordomas, desmoid tumors, advanced *KIT*-mutant melanomas, and chronic myelogenous leukemia following allogeneic stem cell transplantation. Imatinib is thus a broad-spectrum inhibitor.

2. Physicochemical properties of orally bioavailable drugs

2.1. Lipinski's rule of five (Ro5)

Pharmacologists and medicinal chemists have examined the physicochemical properties of drugs that are orally effective. Lipinski's rule of five (Ro5) is an experimental and computational procedure that is used to estimate water and lipid solubility, membrane permeability, and pharmacological effectiveness in the drug-discovery setting [20]. This methodology is a rule of thumb that determines whether a substance with specific pharmacological activities has properties indicating that it would be orally bioavailable. The Lipinski benchmarks are based on data demonstrating that most orally effective compounds are relatively small and moderately lipophilic substances. Ro5 compliance is used during drug development as (i) effective hits discovered during high throughput screening and (ii) lead compounds are systematically optimized to improve their potency while maintaining specificity and selectivity.

The Ro5 criteria indicate that less than ideal oral bioavailability is more likely to occur when (i) the atom-based calculated Log P (ALogP) is larger than 5, when (ii) there are more than 5 hydrogen-bond donors, when (iii) there are greater than 5 × 2 or 10 hydrogen-bond acceptors, and when (iv) the molecular weight exceeds 5 × 100 or 500 [20]. The partition coefficient (P) is the ratio of the solubility of the un-ionized drug in the organic phase divided by its solubility in the aqueous phase of water-saturated *n*-octanol. The P value parallels the hydrophobicity of a compound; the larger the P value, the greater the hydrophobicity. The number of hydrogen-bond donors represents the sum of NH and OH groups. The number of hydrogen-bond acceptors is more complicated to assess; these are the number of uncharged heteroatoms excepting the halogens, heteroaromatic oxygen and sulfur atoms, pyrrole nitrogen atoms, and higher oxidation states of phosphorus, sulfur, and nitrogen, but it includes the oxygen atoms bonded to them. In the original paper [20], the number of hydrogen bond acceptors equaled the sum of nitrogens and oxygens. The Ro5 criteria were based on the physicochemical properties of 2245 reference compounds that had reached phase II clinical trials or higher and the final values were at the 90th percentile for the distribution of the four components in the original Ro5 criteria [20]. If any two of the four conditions were violated, the molecule was deemed less likely to result in an orally bioavailable drug. Natural products and actively transported molecules were excluded from this analysis.

Excluding the macrolides (everolimus, sirolimus, and temsirolimus), the average molecular weight (MW) of the orally effective FDA-approved protein kinase inhibitors is 477 with a range of 306 (ruxolitinib) to 615 (trametinib) (Table 2). The compounds with a molecular weight greater than 500 include the three macrolides and 19 other drugs. Although this data suggests that there is a propensity for orally bioavailable small molecule protein kinase blockers to exceed the 500 Da molecular-weight criterion, the masses of most of the larger compounds excepting the macrolides are near 500 Da. Moreover, 20 of the 74 approved drugs have an ALogP of greater than five. Additionally, tepotinib has seven hydrogen bond donors and dabrafenib and fostamatinib have 11 and 15 hydrogen bond acceptors, respectively. Overall, a total of 30 of the 74 FDA-approved small molecule protein kinase inhibitors fail to conform to Lipinski's Ro5 (Fig. 1C). Of these 30, bosutinib, brigatinib, cabozantinib, entrectinib, fostamatinib, infigratinib, lapatinib, midostaurin, mobocertinib, neratinib, nilotinib, ripretinib have two Ro5 deficiencies with a molecular weight greater than 500 and a partition coefficient greater than 5. Fostamatinib has two Ro5 violations with a molecular weight of 580 and 15 hydrogen bond acceptors. Furthermore, dabrafenib has three Ro5 deficiencies with a molecular weight of 520, an ALogP greater than five (5.36), and 11 hydrogen bond acceptors. These are FDA-approved medicines, but finding drug candidates at the end of the discovery process with two or three Ro5 criteria exceptions is typically an undesirable finding. Medicinals with Ro5 noncompliance are labeled bRo5 (beyond the rule of five) compounds.

2.2. The importance of lipophilicity and ligand efficiency

2.2.1. Lipophilic efficiency, LipE

Both before and after the emergence of Lipinski's Ro5 in 2001 [20], other reports on the physical and chemical properties of orally bioavailable medicines were published [21–28]. For example, LipE (lipophilic efficiency) is a property that is used in drug development and discovery that combines potency and lipophilic-driven binding as an approach to increase binding efficiency. The following formulas are used to calculate lipophilic efficiency:

$$\mathrm{LipE} = \mathrm{p}K_i - \mathrm{ALogP};\ \mathrm{LipE} = \mathrm{pIC}_{50} - \mathrm{ALogP}$$

Paralleling the practice to express the molar hydrogen ion concentration as pH, the operator p denotes the negative of the Log_{10} of the K_i or IC_{50}. Moreover, ALogP is the atom-based computed Log_{10} of the partition coefficient; this factor reflects the ratio of the drug solubility in the organic phase divided by its solubility in the aqueous phase of immiscible *n*-octanol/water.

The second term of the equation (– ALogP or minus ALogP) denotes the lipophilicity of a compound and the value is calculated using an algorithm based upon the properties of thousands of reference organic chemicals. The greater the solubility of a compound in the organic phase when compared with the aqueous phase of a *n*-octanol/water mixture, the greater is its lipophilicity. Leeson and Springthorpe stated that drug lipophilicity, as assessed by its – ALogP value, is one of the more important properties that should be considered during the drug discovery process [22]. Their use of – ALogP was based upon calculations performed before the evaluation of the distribution coefficient (D) became more common. The distribution coefficient ($\mathrm{LogD}_{7.4}$) represents the ratio of the solubility of the ionized and un-ionized compound in the organic phase over the aqueous phase of immiscible *n*-octanol/water at a specified pH of the aqueous phase, which is usually 7.4. As a practical matter, either ALogP or $\mathrm{LogD}_{7.4}$ can be used to screen several

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Table 3
Properties of FDA-approved small molecule protein kinases inhibitors.

Drug	Target, kinase family[a]	K_i nM[b]	pK_i	LipE[c]	N[d]	LE[e]	Dose[f]	pDose[g]	Sol[h]	pSol[i]	nRotB[j]	nRng[k]	nAr[l]	nBnz[m]	QED[n]
Abemaciclib	CDK4, S/T	0.6	9.22	4.28	37	0.351	400 *	4.50	15.9	3.10	7	5	4	0	0.38
Abrocitinib	JAK1, NRY	5.1	8.29	7.04	22	0.531	100	2.89	420	3.51	6	3	2	0	0.83
Acalbrutinib	BTK, NRY	3.1	8.51	5.20	35	0.343	200 *	4.63	10.9	3.37	4	5	4	1	0.45
Afatinib	EGFR, RY	0.5	9.33	4.94	34	0.387	40	4.58	12.8	4.08	8	4	3	1	0.46
Alectinib	ALK, RY	1.9	8.72	3.95	36	0.342	1200 *	4.66	10.5	2.60	3	6	3	0	0.58
Asciminib	BCR-Abl, NRY	0.5	9.3	5.84	31	0.300	80	3.91	55	3.75	6	4	3	1	0.50
Avapritinib	PDGFRα, RY	0.18	9.7	7.09	37	0.370	300	4.22	30.1	3.22	5	6	5	1	0.39
Axitinib	VEGFR2, RY	0.25	9.6	4.96	28	0.483	300	5.85	0.55	3.11	5	4	4	1	0.52
Baricitinib	JAK2, NRY	7	8.15	7.05	26	0.442	2	3.02	357	5.27	5	4	3	0	0.72
Belumosudil	ROCK2, S/T	53.9	7.3	2.48	34	0.303	200	5.19	2.89	3.35	7	5	5	1	0.33
Binimetinib	MEK1, DS	12	7.92	4.91	27	0.414	90 *	3.95	49.9	3.69	6	3	3	1	0.40
Bosutinib	BCR-Abl, NRY	20	7.7	2.51	36	0.302	500	4.75	9.5	3.03	9	4	3	1	0.38
Brigatinib	ALK, RY	0.398	9.4	4.31	40	0.331	180	4.42	22	3.51	8	5	3	2	0.35
Cabozantinib	RET, RY	5	8.3	2.76	37	0.316	40	5.40	1.99	4.10	8	5	4	2	0.31
Capmatinib	MET, RY	0.13	9.89	6.46	31	0.450	800 *	4.89	5.29	2.71	4	5	5	1	0.49
Ceritinib	ALK, RY	0.2	9.7	3.34	38	0.360	750	5.40	2.22	2.87	9	4	3	2	0.28
Cobimetinib	MEK1, DS	0.79	9.1	5.32	30	0.428	60	4.10	42.2	3.95	4	4	2	2	0.53
Crizotinib	ALK, RY	0.63	9.2	4.16	30	0.432	500 *	4.87	6.11	2.95	5	4	3	1	0.53
Dabrafenib	B-Raf, S/T	0.4	9.4	4.04	35	0.379	300 *	5.20	3.27	3.24	6	4	4	2	0.37
Dacomitinib	EGFR, RY	2	8.7	3.54	33	0.372	45	4.73	8.74	4.02	7	4	3	1	0.47
Dasatinib	BCR-Abl, NRY	0.16	9.8	6.49	33	0.419	100	4.58	12.8	3.69	7	4	3	1	0.47
Deucravacitinib	TYK2	0.2	9.69	7.96	31	0.441	6	6.43	0.159	4.85	7	4	3	1	0.52
Encorafenib	B-Raf, S/T	0.3	9.52	5.61	36	0.373	450	4.68	11.2	3.08	10	3	3	1	0.37
Entrectinib	TRKA, RY	1	9	3.97	41	0.310	600	4.80	8.9	2.97	7	6	4	2	0.29
Erdafitinib	FGFR1, RY	2	8.7	4.52	33	0.372	8	4.54	13	4.75	9	4	4	1	0.41
Erlotinib	EGFR, RY	0.32	9.5	6.09	29	0.462	150	4.64	8.91	3.42	11	3	3	1	0.42
Everolimus	FKBP12/mTOR, S/T	?	?	?	68	?	10	5.77	1.63	4.98	9	3	0	0	0.13
Fedratinib	JAK2, NRY	6	8.22	3.40	37	0.313	400	4.74	9.49	3.12	11	4	3	2	0.35
Fostamatinib	Syk, NRY	17	7.77	4.68	40	0.274	300 *	4.05	52	3.29	10	4	3	1	0.26
Futibatinib	FGFR2, RY	4	8.4	6.62	31	0.382	20	4.02	40	4.32	6	4	3	1	0.51
Gefitinib	EGFR, RY	0.5	9.3	5.02	31	0.423	250	4.22	27	3.25	8	4	3	1	0.52
Gilteritinib	Flt3, RY	0.41	9.39	6.69	40	0.331	120	4.39	22.3	3.66	9	5	2	1	0.43
Ibrutinib	BTK, NRY	12.6	7.9	3.68	33	0.338	560	4.34	20.3	2.90	5	5	4	2	0.47
Imatinib	BCR-Abl, NRY	1	9	4.41	37	0.343	600	4.53	14.6	2.92	7	5	4	2	0.39
Infigratinib	FGFRs	5	8.3	2.95	38	0.308	125	4.27	29.9	3.65	8	4	3	2	0.38
Lapatinib	EGFR, RY	1	9	2.86	40	0.317	1250	4.42	22.3	2.67	11	5	5	2	0.18
Larotrectinib	TRK, RY	9.7	8.01	5.06	31	0.364	200 *	3.25	238	3.33	3	5	3	1	0.67
Lenvatinib	VEGFR2, RY	3.98	8.4	4.33	30	0.395	24	4.84	6.22	4.25	6	4	3	1	0.55
Lorlatinib	ALK, RY	9	8.05	5.25	30	0.378	100	3.58	108	3.61	0	3	3	1	0.61
Midostaurin	Flt3, RY	37	7.43	1.52	43	0.244	200 *	4.56	15.7	3.46	3	7	4	1	0.29
Mobocertinib	EGFR, RY	60	7.22	2.14	43	0.237	160	4.63	13.6	3.56	13	4	4	1	0.17
Neratinib	ErbB2/HER2, RY	59	7.23	1.30	40	0.255	240	4.92	6.74	3.37	11	4	4	1	0.22
Netarsudil	ROCK1/2, S/T	1	9	4.11	34	0.373	0.01	6.30	0.23	7.66	8	4	4	2	0.39
Nilotinib	BCR-Abl, NRY	12.5	7.9	1.54	39	0.286	600 *	5.42	2.01	2.95	6	5	5	2	0.27
Nintedanib	FGFR, RY	39.8	7.4	3.78	40	0.261	300 *	4.24	30.9	3.26	8	5	4	2	0.35
Osimertinib	EGFR, RY	7	8.15	3.64	37	0.311	80	4.35	22.4	3.80	10	4	4	1	0.31
Pacritinib	JAK2, NRY	19	7.72	2.21	35	0.289	100	4.10	38	3.67	4	4	2	1	0.54
Palbociclib	CDK4, S/T	10	8	5.03	33	0.342	125	4.41	17.4	3.55	5	5	3	0	0.58
Pazopanib	VEGFR2, RY	30	7.52	4.38	31	0.342	800	4.00	43.3	2.74	5	4	4	1	0.49
Pemigatinib	FGFR, RY	0.5	9.3	5.64	35	0.375	13.5	3.53	144	4.56	6	5	3	1	0.57
Pexidartinib	CSF1R, RY	13	7.89	2.66	29	0.384	800 *	5.18	3.15	2.78	5	3	4	0	0.47
Pirtobrutinib	BTK, NRY	0.5	9.3	5.87	34	0.386	200	5.04	3.84	3.32	7	4	3	2	0.45
Ponatinib	BCR-Abl, NRY	1	9	4.54	39	0.325	45	5.26	2.95	4.07	8	5	4	2	0.39
Pralsetinib	RET	0.5	9.3	5.10	39	0.336	400	4.72	10.1	3.13	8	5	4	0	0.31
Regorafenib	VEGFR2, RY	4.2	8.4	2.71	33	0.359	160	5.68	1.02	3.48	5	3	3	2	0.41
Ribociclib	CDK4, S/T	10	8	5.20	32	0.353	600	3.27	231	2.86	5	5	3	0	0.64
Ripretinib	RET	3	8.52	2.85	33	0.364	150	4.94	5.83	3.53	5	4	4	2	0.32
Ruxolitinib	JAK1, NRY	1.2	8.92	5.45	23	0.547	20 *	3.42	116	4.18	4	4	3	0	0.8
Selpercatinib	RET, RY	1	9	5.72	39	0.325	320 *	4.25	29.9	3.22	8	4	4	0	0.37
Selumetinib	MEK1, DS	14	7.85	4.32	27	0.410	80 *	4.34	21	3.76	6	3	3	1	0.39
Sirolimus	FKBP12/mTOR, S/T	?	?	?	65	?	2	5.72	1.73	5.66	6	3	0	0	0.16
Sorafenib	VEGFR1, RY	15.8	7.8	2.25	32	0.344	800 *	5.43	1.71	2.76	5	3	3	2	0.46
Sunitinib	VEGFR2, RY	3.98	8.4	5.07	29	0.408	50	4.11	30.8	3.90	7	3	2	0	0.63
Temsirolimus	FKBP12/mTOR, S/T	?	?	?	73	?	25 * *	5.64	2.35	4.61	11	4	0	0	?
Tepotinib	MET, RY	1	9	4.99	37	0.343	450	?	?	3.04	7	5	4	2	0.38
Tivozanib	VEGFR2	6.5	8.19	2.55	32	0.312	1.34	3.94	52.1	5.53	6	4	4	1	0.39
Tofacitinib	JAK1, NRY	0.79	9.1	7.56	23	0.558	10 *	3.02	299	4.49	3	3	2	0	0.93
Trametinib	MEK1, DS	3.4	8.47	4.53	37	0.323	2	4.30	30.7	5.49	5	5	3	2	0.33
Trilaciclib	CDK4/6, S/T	1	9	6.28	33	0.385	480	3.24	260	2.97	3	6	3	0	0.64
Tucatinib	ErbB2/HER2, RY	8	8.1	3.01	36	0.317	600 *	5.08	4	2.90	6	6	5	1	0.36
Upadacitinib	JAK1, NRY	43	7.37	4.46	27	0.385	15	3.73	70.7	4.40	3	4	3	0	0.73
Vandetanib	RET, RY	50	7.3	2.30	30	0.343	300	4.67	10.2	3.20	6	4	3	1	0.54
Vemurafenib	B-Raf, S/T	3.98	8.4	2.86	33	0.359	1920 *	6.13	0.36	2.41	7	4	4	2	0.33
Zanubrutinib	BTK, NRY	0.3	9.52	5.30	35	0.384	320 *	4.66	10.3	3.17	6	5	3	2	0.52

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[a] NRY, non-receptor protein-tyrosine kinase; RY, receptor protein-tyrosine kinase; S/T, protein-serine/threonine kinase; DS; dual specificity protein kinase (catalyzes protein-tyrosine and then threonine phosphorylation of target kinase activation segments but evolutionarily in the protein-serine/threonine kinase family).
[b] Representative values obtained from www.ebi.ac.ug/chembl/ and from klifs.net.
[c] LipE (lipophilic efficiency) = pIC_{50} – ALogP
[d] N, Number of heavy (nonhydrogen) atoms.
[e] LE (ligand efficiency) = – 2.303 RT Log_{10} K_i/N where N is the number of heavy (non-hydrogen) atoms in the drug
[f] Dosage in mg/day from FDA label; * , one-half of total daily dose taken twice per day; * *, once weekly.
[g] pDose, – Log_{10} dose in moles
[h] Sol, solubility (μg/ml) in water
[i] pSol, – Log_{10} solubility in moles/liter
[j] nRotB, number of Rotatable bonds.
[k] nRng, number of rings
[l] nAr, number of Aromatic rings
[m] nBnz, number of benzene moieties
[n] QED, summed, weighted desirability (scores using MW + ALogP + HBD + HBA + PSA + nRotB + nAr) obtained from https://www.ebi.ac.uk/chembl/; see Ref. [28] for a full explanation.

compounds in the same study. Note that a highly lipophilic substance with a large negative – ALogP value decreases the lipophilic efficiency. The goal in drug development is to maximize lipophilic efficiency.

A high lipophilicity may promote the binding of a ligand to adventitious targets and this process may increase toxicity and lead to adverse events. A desirable goal during drug discovery and development is to increase potency without simultaneously increasing lipophilicity. Using lipophilic efficiency facilitates the optimization of lead compounds by directly comparing a series of drug congeners; moreover, the same protocols for establishing the lipophilic efficiency (determining the pIC_{50} and calculating the AlogP) should be used to ensure that such comparisons are valid [24,25]. To mention a cogent example, Cui et al. described the optimization of lead compounds using lipophilic efficiency as an index of binding effectiveness during the development of crizotinib [29]; crizotinib is FDA-approved for the management of ALK-positive and ROS1-positive NSCLC.

The ALogP of various compounds can be calculated in a matter of seconds. Because the experimental determination of LogP is labor intensive, such measurements are performed only in select cases. Hopkins et al. suggested that acceptable values for LogP are less than ~ 3 and those of lipophilic efficiency are greater than ~ 5 [24]. Johnson et al. reported that possessing a $logD_{7.4}$ in the range of 1 − 3 provides the best chance of achieving the overlap of low hepatic oxidative clearance, low renal clearance, high solubility, and high passive permeability [30]. The average value for ALogP for the 71 FDA-approved drugs (excluding the three macrolides) was 4.12 with a range from 1.1 (baricitinib) to 6.36 (nilotinib) and a standard deviation of 1.23. Only 13 of the approved protein kinase antagonists have an ALogP in the 1–3 range and 30 have a value in the 1–4 range. Decreasing the lipophilicity and increasing the potency during drug development generally produces medicinals with improved pharmacological properties. The average value of lipophilic efficiency (LipE) for 71 FDA-approved small molecule protein kinase blockers (omitting the macrolides) is 4.43 with a range from 1.3 (neratinib) to 7.56 (tofacitinib) and a standard deviation of 0.74 (Table 3).

2.2.2. Ligand efficiency, LE

The ligand efficiency (LE) relates the binding affinity, or potency, to the number of heavy (nonhydrogen) atoms of a drug. The following formula is used to compute this property:

$$LE = \Delta G^{\circ\prime}/N = -RT \ln K_{eq}/N = -2{\cdot}303RT \text{ Log } K_{eq}/N$$

$\Delta G^{\circ\prime}$ is the standard free energy change of a drug binding to its target at neutral pH, R denotes the universal energy-temperature coefficient or gas constant (1.98×10^{-3} kcal/degree-mol), T is the temperature in degrees Kelvin, K_{eq} represents the value of the equilibrium constant, and N is the number of heavy atoms in the drug. The K_i or IC_{50} values are surrogates for the equilibrium constant. At a physiological temperature of 37 °C (310 K), this equation becomes – ($2.303 \times (1.98 \times 10^{-3}$/K) × 310 K Log K_{eq})/N or – 1.41 Log K_{eq}/N [24]. At a temperature of 300 K, the multiplication factor is – 1.37 [28]. Ligand efficiency represents the affinity based on the average binding energy per atom. Moreover, ligand efficiency is useful in fragment-based drug discovery efforts and, like lipophilic efficiency, it aids in the selection of promising derivatives of lead compounds for further development [25].

Ligand efficiency represents the binding affinity per heavy atom of the drug or ligand of interest. The value of N is a proxy for the size or molecular weight of the drug. The equation used to compute ligand efficiency indicates that its value is directly proportional to – Log K_{eq} (minus Log K_{eq}, a positive number) or the binding affinity and is inversely proportional to the number of nonhydrogen atoms. Hopkins et al. reported that optimal values for ligand efficiency (LE) should be greater than 0.3 kcal per mol of heavy atom [21,24]. Ligand efficiency values for the FDA-approved small molecule protein kinase blockers based upon representative K_i or IC_{50} values are included in Table 3. The average value for ligand efficiency for 71 of the FDA-approved protein kinase inhibitors (excluding the three macrolides) was 0.363 with a range from 0.237 (mobocertinib) to 0.558 (tofacitinib) and a standard deviation of 0.064. Seven drugs had values of less than 0.3 kcal including fostamatinib, mobocertinib, midostaurin, neratinib, nilotinib, nintedanib, and pacritinib. The values for ligand efficiency (LE) and lipophilic efficiency (LipE) listed in Table 3 are based on data acquired under different conditions. Consequently, these values cannot be used to make a direct comparison of these agents because different methods were used to obtain the data. These findings were mined from various drug discovery projects and indicate typical values.

2.2.3. Additional chemical descriptors of orally bioavailable drugs

To characterize pharmaceutical properties linked to oral bioavailability, not-unexpectedly, the Ro5 has generated many corollaries and variations. For example, Veber et al. found that the number of rotatable bonds and the topological polar surface area (PSA) differentiates between orally active and inactive agents for a large series of compounds in rats [26]. They reported that the optimal number of rotatable bonds is 10 or fewer. This parameter regulates passive membrane permeation and reflects molecular flexibility or degrees of freedom. Furthermore, degrees of freedom are related to the entropy change that occurs with ligand binding. With the exceptions of four drugs with 11 rotatable bonds (erlotinib, fedratinib, lapatinib, neratinib) and mobocertinib with 13 rotatable bonds, the remaining 66 drugs (the macrolides were excluded) have 10 or fewer of these bonds. The average value is 6.48 and the number of rotatable bonds ranges from 0 (lorlatinib) to 13 (mobocertinib) and a standard deviation of 2.34. Moreover, Veber et al. reported that drugs with a polar surface area less than or equal to 140 $Å^2$ are orally effective [26]. This parameter represents the sum of the surface over all polar atoms, primarily oxygen and nitrogen, but it also includes any connected hydrogen atoms. Excluding the three macrolides, the average value for the surface area is 98.7 $Å^2$ with a range from 59.5 (vandetanib) to 187 (fostamatinib) and a standard deviation of 22.7. Dabrafenib, encorafenib, and fostamatinib are the only FDA-approved protein kinases blockers with a polar surface area

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exceeding 140 $Å^2$ (Table 2). Furthermore, Oprea reported that the number of ring structures (both aromatic and nonaromatic) in most orally effective drugs is three or greater [27]. All approved small molecule protein kinase antagonists have three or more rings with an average value of 4.30, a range from three to six, and a standard deviation of 0.83. Except for trilaciclib and temsirolimus (which are given intravenously) and netarsudil (an eye drop), all of the FDA-approved drugs listed are orally effective.

Ritchie and Macdonald examined aromaticity as a factor in the drug development process [31]. Aromaticity refers to cyclically conjugated compounds with significantly greater stability than is found in a localized Kekulé structure owing to electron delocalization. They classified bicyclic and tricyclic structures as those containing two and three aromatic rings, respectively. The aromatic ring count includes structures containing carbon and heteroatom components. These investigators found that increasing the number of carboaromatic rings (benzene moieties) had a detrimental effect on drug effectiveness by decreasing water solubility, increasing binding to serum albumin, and blocking cytochrome P450. We find that the average number of aromatic rings in the 74 FDA-approved protein kinase inhibitors was 3.27 and the mean number of benzene moieties was 1.00. All of the FDA-approved kinase antagonists with the exception of the three macrolides have at least two aromatic rings; moreover, midostaurin had the largest number of aromatic rings with six. Fifteen of the drugs lacked benzene moieties and the number of drugs possessing one or two benzenes was about evenly distributed among the remainder (Table 3).

Bayliss et al. evaluated the lipophilicity, dosage, and solubility properties of orally effective drug and drug candidates [32]. Their findings suggest that daily doses of 100 mg or less reduces the risk of toxicity. The range of dosages for protein kinase blockers given orally is from 1.34 mg to 1920 mg daily with an average of about 300 mg. The daily doses range from 1.34, 2, 2, and 2 mg for tivozanib, trametinib, sirolimus, and baricitinib and 1200, 1250, and 1920 mg for alectinib, lapatinib, and vemurafenib, respectively. Only 29 of the FDA-approved protein kinase blockers have doses of 100 mg or less. Bayliss et al. reported that agents with a solubility in water of 100 μg/ml or less are associated with increased risk of failure during clinical trials and drug development [32]. We tallied the solubility of the approved protein kinase antagonists in water and found a range from 0.36 μg/ml (vemurafenib) to 420 μg/ml for abrocitinib with a mean value of about 45 μg/ml. Tepotinib is an outlier in that its solubility is below the limits of measurement. The range in solubilities and dosages among the FDA-approved drugs is nearly three orders of magnitude. For convenience and ease of use, we calculated the pSol (pSolubility) and the pDose for each of the FDA-approved protein kinase blockers where pSol is the $-\text{Log}_{10}$ of the solubility in mols/liter and the pDose is the $-\text{Log}_{10}$ of the molar dose (Table 3).

The molecular complexity of a substance is based upon the elements it contains, its structural features, and its symmetry. This parameter is calculated using the Bertz/Hendrickson/Ihlenfelt rules [33,34]. The calculation is based upon the number and identity of the constituent atoms, the bonding pattern, and the nature of the chemical bonds (single, double, triple, aromatic). Molecular complexity ranges from 0 for simple ions to several thousand for complex natural products. Ionic lithium, with a complexity of 0 and a molecular weight of 3, is used in the treatment of manic-depressive disorder as lithium carbonate (Li_2CO_3). Larger compounds generally have a greater molecular complexity value than smaller ones. In contrast, materials containing fewer elements and those that are highly symmetrical have a smaller molecular complexity value. The molecular complexity values for the drugs in this article were acquired from PubChem (https://pubchem.ncbi.nlm.nih.gov/). For the 74 FDA-approved small molecule protein kinase antagonists, the mean complexity value is 763 with a range from 453 (pralsetinib) to 2010 (temsirolimus) with a standard deviation of 264 (Table 2). As expected, the three large macrolides have the greatest molecular complexity values. There are no recommended or optimal molecular complexity values for orally bioavailable drugs; however, this parameter may be of use in predicting the ease or difficulty of drug synthesis, an important consideration in the commercial production of therapeutic agents.

Lovering et al. considered the fraction of sp^3 carbon atoms (Fsp^3) and the number of chiral carbon atoms as two additional measures of molecular complexity [35]. Fsp^3 represents the number of sp^3 carbon atoms in the drug divided by the total number of carbon atoms. A larger value corresponds to (i) an increase in saturation of the compound and (ii) a decrease in the number of unsaturated linkages including double and triple bonds and aromatic rings. Increased saturation allows for the preparation of architecturally more complex molecules resulting in the exploration of a more diverse chemical space without significantly increasing the molecular weight. The authors also suggest that increasing saturation will allow for the out-of-plane substituents to increase receptor-ligand complementarity and increase solubility. Excluding the three macrolides, the mean Fsp^3 was 0.27 with a range of 0.05 (axitinib) to 0.62 (gilteritinib) and a standard deviation of 0.12. The corresponding average number of stereocenters was 0.37 (excluding the macrolides). More than half of the FDA-approved kinases inhibitors (51) lacked a stereocenter and midostaurin had the maximum of 4 (Table 3).

Leeson reported that higher Fsp^3 values were associated with decreased drug-induced liver injury (DILI) [36]. Based upon the FDA labels, we found that 33 of the 74 FDA-approved protein kinase blockers mention hepatoxicity and elevated liver enzymes in the list of warnings and precautions (45%). Moreover, pazopanib (Fsp^3 of 0.19), pexidartinib (0.15), ponatinib (0.14), pralsetinib (0.37), and sunitinib (0.36) have strongly-worded black box hepatotoxicity warnings. Three of these drugs have Fsp^3 values below the median, but two of them have values that are above the median. The average Fsp^3 value for protein kinase blockers associated with liver toxicity was 0.25 while the value for drugs not associated with liver toxicity was 0.32, a trend going in the direction reported by Leeson [36]. The latter data excluded the three macrolides, compounds not associated with hepatotoxicity.

From the data submitted herein, it is clear that medicinal chemists have drawn from compounds outside of the traditional Ro5 space to target an expanding number of protein kinases. It has been argued that a too strict implementation of the Ro5 may have hampered the pharmaceutical industry from exploring opportunities involving novel but more difficult targets [37,38]. Additional properties such as polar surface area and the number of rotatable bonds have been used to extend correlations with absorption, distribution, metabolism, excretion, and toxicity (ADMET) parameters. There has been a recent focus on decreasing the emphasis of a hard-cutoff rule-based classification of compounds along with the emergence of composites such as the quantitative estimate of drug-likeness (QED). The QED (Table 3) includes weighted parameters of molecular weight, AlogP, number of hydrogen-bond donors and acceptors, polar surface area, number of rotatable bonds, and number of aromatic rings. The values for QED range from 0 (all properties unfavorable) to 1 (all properties favorable); the higher the value, the greater the drug-likeness. The mean value of QED for the approved kinase inhibitors was 0.52 with a minimum of 0.33 (everolimus) and a maximum of 0.93 (tofacitinib). Leeson et al. reported that the median QED for drugs was 0.62 for the 1990 – 2009 time frame and 0.49 for the 2010 – 2020 time frame [28], a unfavorable trend.

Leeson et al. reported that the molecular weight and lipophilicity of all FDA-approved drugs increased from the 1990 – 2009 to the 2010 – 2020 time frame [28]. We compared the averages of selected properties of FDA-approved protein kinase inhibitors over two time frames: 2001 – 2011 and 2012 – 2023. This analysis excluded the three large macrolides. The average molecular weight increased from 458 to 481 (5%) during this period as well as the heavy atom count (32.1–34.4; 7%), the polar surface area (91.9–100.2 $Å^2$; 9%), the lipophilic efficiency (4.07–4.51; 11%), and the molecular complexity (651–731; 12%). However, the average number of hydrogen bond donors and acceptors,

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Table 4
Principal FDA-approved protein kinase inhibitor drug targets [a].

Kinase family	No.	Class of Kinase	RY	NRY	S/T	Y/T
ErbB	9	RY	9			
VEGFR	8	RY	8			
JAK	7	NRY		7		
BCR-Abl	6	NRY		6		
ALK	5	RY	5			
FGFR	5	RY	5			
CDK4/6	4	S/T			4	
MEK1/2	4	Y/T				4
BTK	4	NRY		4		
B-Raf	3	S/T			3	
FKBP	3	S/T			3	
MET	3	RY	3			
Flt3	2	RY	2			
RET	2	RY	2			
ROCK	2	S/T			2	
TRKA	2	RY	2			
CSF1	1	RY	1			
Kit	1	RY	1			
PDGFR	1	RY	1			
Syk	1	NRY		1		
TYK2	1	NRY		1		
	74		39	19	12	4

[a] NYR, nonreceptor protein-tyrosine kinase; RY, receptor protein-tyrosine kinase; S/T, protein-serine/threonine kinase; Y/T, Dual specificity protein kinase – tyrosine phosphorylation followed by threonine phosphorylation of target kinase activation segments.

the ALopP, the number of rotatable bonds, the ring count, the ligand efficiency, the fraction of sp^3 carbon atoms, and the potency (K_i values) were essentially unchanged (Tables 2 and 3). Leeson et al. reported that the molecular weight of all approved drugs, including protein kinase antagonists, has increased over time [28].

3. Epilogue and perspective

Although significant progress has been made in the development of low molecular weight protein kinase inhibitors since the FDA-approval of imatinib in 2001, this line of work is still in its infancy. Oprea et al. suggested that the heightened expression of many understudied protein kinases may play an important role in the pathogenesis of cancer [39]. Furthermore, these understudied proteins may be effective drug targets. Examples of enzymes that are frequently altered in breast cancer include eukaryotic elongation factor 2 kinase (*EEF2K*), cyclin-dependent protein kinase 12 (*CDK12*), mitogen-activated protein kinase kinase kinase 1 (*MAP3K1*), and ribosomal protein S6 kinase δ1 (*RPS6KC1*). Diseases of the central nervous system and several respiratory and metabolic disorders may also be the result of altered activity of understudied and uncharacterized protein kinases.

Most of the FDA-approved kinase blockers are antineoplastic and others function as immunomodulators [40–42]. Because of the inherent genetic changes in cancer cells, resistance to protein kinase antagonists is the rule rather than the exception. This resistance stimulated the discovery of second, third, and later generation antagonists that target the same enzyme and disease. Moreover, acquired drug resistance is often the result of gatekeeper mutations in the initial protein kinase target [5]. The gatekeeper residue controls access to a hydrophobic pocket in protein kinases that is next to the adenine binding pocket [43, 44], a pocket that regularly interacts with numerous small molecule protein kinase antagonists. A gatekeeper mutation in *EGFR* (*T790M*) is a relevant example and this is the third most common protein kinase mutation [5]. Furthermore, this change is responsible for about half of all acquired *EGFR* inhibitor resistance mutations.

Because 244 protein kinase genes map to cancer amplicons and disease loci [9], it is likely that (i) a substantial increase in the number of drugs blocking understudied protein kinases will be developed and (ii) new drugs will be developed for the treatment of additional illnesses [45–48]. Adding new protein kinase targets to the pharmacological armamentarium will require the elucidation of signaling networks and pathways in addition to the phosphatidylinositol 3-kinase-AKT and RAS-Raf-MEK MAP kinase signaling modules and protein kinases leading to these pathways [49]. Besides the 74 approved protein kinase blockers considered in this article, the FDA has approved six drugs that inhibit phosphatidylinositol 3-kinases (PI 3-kinases are members of the atypical protein kinase family) [10]. These include alpelisib – an orally bioavailable PI 3-kinase-α inhibitor that is used for the treatment of breast cancer – and copanlisib, duvelisib, umbralisib, and idelalisib that are orally effective PI 3-kinase-δ inhibitors that are approved for the third-line treatment of follicular lymphomas and other hematological disorders. Leniolisib is a PI 3-kinase-δ inhibitor that was approved for the treatment of APDS (activated PI 3-kinase delta syndrome) in 2023. As the protein kinase antagonist discipline progresses, it is expected that protein kinase inhibitors with new scaffolds, pharmacophores, and chemotypes will be devised [50]. Asciminib, cobimetinib, deucravacitinib, everolimus, selumetinib, sirolimus, temsirolimus, and trametinib are currently FDA-approved allosteric protein kinase blockers. Asciminib is a STAMP (specifically targeting the Abl myristoyl pocket) inhibitor. One can expect that additional allosteric antagonists will be developed that block (i) well known and (ii) understudied enzymes that are components of protein kinase signal transduction modules [51].

Of the 74 FDA-approved drugs, receptor protein-tyrosine kinases are the chief targets of 39 of them followed by nonreceptor protein-tyrosine kinases (19), protein-serine/threonine kinases (12), and dual-specificity protein kinases (4) (Table 4). Members of the EGFR/ErbB family represent the top-ranked targets followed by the VEGFR, JAK, BCR-Abl, ALK, and the FGFR families. CDK4/6 is inhibited by four of the FDA-approved antagonists that are prescribed for the treatment of breast cancer. The dual specificity (MEK1/2) protein kinases, which inhibit the RAS-Raf-MEK MAP kinase pathway, include trametinib (prescribed for the treatment of melanoma and NSCLC), selumetinib (prescribed for neurofibromatosis I or Von Recklinghausen disease), cobimetinib (used in combination with vemurafenib for the treatment of melanoma) and binimetinib (used in combination with encorafenib for the treatment of melanoma).

Osimertinib was approved by the FDA in 2015 for the first-line treatment of patients with metastatic NSCLC with *EGFR* exon-21 *L858R* mutations or exon-19 deletions [12,52,53]. It is therapeutically advantageous that this agent has almost two hundred times greater affinity for the *EGFR L858R/T790M* mutant than it has for the wildtype enzyme [12]. The drug is also approved for the second-line treatment of individuals with *EGFR T790M* mutation-positive metastatic NSCLC whose disease became resistant to prior EGFR inhibitor therapy. Moreover, osimertinib was the first drug approved for the treatment of patients with the *EGFR T790M* gatekeeper mutation. This agent irreversibly inhibits EGFR by forming a covalent bond with C797 of the protein target. Osimertinib was one of the top selling drugs in 2021 with sales of $3.3 billion [54]. Alectinib is FDA-approved for the treatment of ALK mutation-positive NSCLC; this medicine targets ALK and RET [55–59]. Alectinib had $910 million in sales in 2021. The cost for one month's supply of each of these drugs is about $18,000. Such prices contribute to the financial toxicity associated with essentially all protein kinase inhibitors [12].

Pfizer began the process of high throughput screening (HTS) in 1986 using 96-well plates and assay volumes of 50–100 μL [60]. By 1992 HTS produced hits as starting materials for about 40% of the drug discovery portfolio. By 1999 ADMET HTS was fully integrated into the drug discovery cycle. It was about this time that Ro5 compliance was introduced in an attempt to maximize the development of effective drugs and the minimize the failure or attrition of drug candidates that were identified by HTS. Gefitinib, erlotinib, sorafenib, dasatinib, and lapatinib are FDA-approved protein kinase antagonists that resulted from HTS hits. Prior to the advent of high throughput screening, drug discovery was based upon experiments performed in animals in vivo. Although the

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Table 5
Drug properties and descriptors [a].

Category	Properties and descriptons
Size	Molecular weight (MW) and heavy atom count (N)
Lipophilicity	Calculated octanol–water partition coefficients (ALogP and Log $D_{7.4}$)
Polarity	Polar surface area (PSA), hydrogen-bond donors (HD) and hydrogen-bond acceptors (HA)
Aromatic and aliphatic descriptors	Number of rings (nRng), number of aromatic rings (nAr), number of benzene rings (nBnz), fraction of carbon toms that are sp^3 hypridized (Fsp3), number of stereocenters (nStereo)
Flexibility	Number of rotatable bonds (nRotB)
Potency	– Log_{10} molar concentration IC_{50} or K_i as pIC_{50} or pK_i
Ligand efficiency metrics	Lipophilic ligand efficiency or LipE = pIC_{50} – AlogP or pIC_{50} – Log $D_{7.4;}$ Ligand efficiency or LE =– 2.303 RT Log_{10} K_i/N
Composite physicochemical descriptors	Quantitative estimate of drug-likeness or QED = summed, weighted desirability (scores using MW + ALogP + HD + HA + PSA + nRotB + nAr)

[a] Adapted from Ref. [28].

definitions of drug and drug-likeness are intuitive, in the 1970s I learned from Professor JP Long, a classical pharmacologist at the University of Iowa, that "A drug is a substance, that when injected into an animal, produces a paper."

The commonly used drug properties and descriptors used by medicinal chemists and pharmacologists are listed in Table 5. bRo5 descriptors include the heavy atom count, $LogD_{7.4}$, polar surface area, number of rings (total, aromatic, carboaromatic), number of rotatable bonds, potency, and composite metrics such as the quantitative estimate of drug likeness (QED). Low solubility, poor passive cell permeability, and issues related to metabolism are associated with increased molecular weight and lipophilicity. These drawbacks need to be overcome when working in the bRo5 space. Increased molecular complexity oftentimes improves solubility and reduces adventitious binding to off-targets. On the other hand, increased molecular complexity increases the difficulty of synthesis. The protein kinase inhibitor field is a relatively new one and 30 of the 74 FDA-approved drugs (40.5%) have a least one Ro5 violation. As stated by Hartung et al. "Playing by the rules is thus not always advisable when pushing for success in drug discovery. Rather, successful drug hunters must follow a mindset of pushing the limits of what is possible. Now, 25 years after the publication of the Ro5, small-molecule drug discovery is looking at an exciting future of clinical impact that must not be restricted by the number 5″ [61].

Conflict of interest

The author is unaware of any affiliations, memberships, or financial holdings that might be perceived as affecting the objectivity of this review.

Data Availability

No data was used for the research described in the article.

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