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Pharmacophore Modeling of Janus Kinase Inhibitors: Tools for Drug Discovery and Exposition Prediction

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Abstract: Pesticides are essential in agriculture for protecting crops and boosting productivity, but their widespread use may pose significant health risks. Farmworkers face direct exposure through skin contact and inhalation, which may lead to hormonal imbalances, neurological disorders, and elevated cancer risks. Moreover, pesticide residues in food and water may affect surrounding communities. One of the lesser investigated issues is immunotoxicity, mostly because the chronic effects of compound exposure are very complex to study. As a case study, this work utilized pharmacophore modeling and virtual screening to identify pesticides that may inhibit Janus kinases (JAK1, JAK2, JAK3) and tyrosine kinase 2 (TYK2), which are pivotal in immune response regulation, and are associated with cancer development and increased infection susceptibility. We identified 64 potential pesticide candidates, 22 of which have previously been detected in the human body, as confirmed by the Human Metabolome Database. These results underscore the critical need for further research into potential immunotoxic and chronic impacts of the respective pesticides on human health.

Keywords: pesticides; JAK1; JAK2; JAK3; TYK2; immunosuppression; pharmacophore modeling

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1. Introduction

According to the European Commission (EC) (https://food.ec.europa.eu/plants/pesticides_en, accessed on 14 April 2025), pesticides are used to prevent, destroy, or control harmful organisms ('pests') or diseases, and to protect plants or plant products during production, storage, and transport. This category includes various agents, such as herbicides, fungicides, insecticides, and biocides. In daily agriculture, pesticides play a vital role in safeguarding crops from insects, weeds, and other detrimental organisms, which ultimately profoundly enhances agricultural yields and food security. However, the extensive application of these agrochemicals may have notable consequences, particularly for farmworkers, who are the most exposed group [1–3]. This exposure can occur through various pathways, with dermal contact being a prevalent route. When substances touch the skin, they can be absorbed into the bloodstream, potentially causing localized or systemic effects. Inhalation of pesticide vapors or aerosols represents another significant exposure route, which can lead to respiratory issues and further systemic absorption [1,4,5].

Moreover, the broad and often uncontrolled use of biocides can lead to significant bioaccumulation and persistent residues in key environmental matrices, including food, feed, animal-derived products, soil, and water [6,7]. These chemicals can persist in crops and animal products, entering the food chain and posing a potential public health risk. As

a result, even urban consumers who are not directly involved in agriculture can be exposed to pesticides through contaminated food and water. Over time, this indirect exposure can accumulate and contribute to various health problems, including endocrine disruptions, neurological disorders, and an elevated risk of cancers, such as prostate, lung, liver, breast, and colon cancer, as well as non-Hodgkin lymphoma and leukemia [5,8–12]. Experimental studies have also reported that exposure to pesticides can exert damaging effects on the immune system [13,14].

Our immune system is a highly sophisticated network that coordinates various pathways and specialized cells to defend the organism against pathogens and cancerous cells. Cytokines, produced by immune cells, are crucial for regulating immune functions, inflammation, and hematopoiesis. They exert their effects by binding to specific receptors, which in turn activate JAKs. These intracellular enzymes consist of four subtypes: Janus kinase 1 (JAK1), Janus kinase 2 (JAK2), Janus kinase 3 (JAK3), and tyrosine kinase 2 (TYK2). Each of these kinases contributes to the complex signaling pathways that manage immune responses and other vital biological processes [15–17].

Cytokines bind to the extracellular domains of their receptors, triggering conformational changes that activate associated JAK proteins. These JAKs undergo mutual transphosphorylation, enhancing their catalytic function. Subsequently, activated JAKs phosphorylate specific tyrosine residues on the receptor, creating binding sites for signal transducer and activator of transcription proteins (STATs). The STAT family involves seven subtypes: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6, each with distinct roles in cellular processes, such as immune regulation, growth, and differentiation. Once phosphorylated, STAT proteins form dimers, translocate to the nucleus, and bind to gene promoter regions, initiating transcriptional changes in target cells [18].

By intervening in this system, for example with approved JAK inhibitors (jakibs) such as tofacitinib, baricitinib, and filgotinib, a state of immunosuppression can be induced. This mechanism is therapeutically exploited in treating conditions like rheumatoid arthritis and ulcerative colitis, where effectively controlling inflammation can lead to significant improvements in patient health and quality of life [19].

However, interfering with this signaling cascade can also lead to various health risks. The inhibition of JAKs may disrupt the regulation of blood cell production and immune response, resulting in complications such as increased susceptibility to infections, thrombosis, and potentially the development of malignancies [20].

This prospective computational study was based on the hypothesis that some pesticides, though designed for agricultural use, may interfere with the JAK signaling pathways akin to jakibs. In general, the health effects of pesticide exposure are difficult to assess, mainly due to the lack of long-term exposure data. Addressing this gap is crucial, since it could provide valuable insights into the broader activity spectra and to the risks of pesticides.

Assessing the effects of pesticide exposure poses considerable challenges, as in vitro and in vivo experiments are not only expensive, but raise ethical concerns. To address these issues, in silico methods, such as pharmacophore modeling and virtual screening, can offer a highly effective complement. These computational approaches provide predictive insights, allowing for the early identification of potential hazards. By enabling the targeted prioritization of biological tests, they reduce the reliance on animal experiments and promote efficient resource deployment.

In this study, we developed and optimized pharmacophore-based models for potential jakibs, leveraging known jakibs from the literature as training data. These models are designed to identify compounds with structural features that align with the binding site of the target protein, allowing for the efficient virtual screening of large compound databases.

By prioritizing compounds that match the pharmacophore model, the likelihood of testing compounds that exhibit the desired biological activity is increased.

Moreover, pharmacophore-based virtual screening (PBVS) facilitates the discovery of biologically active compounds by enabling early-stage predictions of both the desired biological activities and the potential off-target effects or toxicological risks. This approach is not limited to pharmaceutical research but is equally valuable in the development and monitoring of agrochemicals, such as herbicides or insecticides, where high target specificity and minimal impact on non-target organisms are essential. PBVS aids in the prioritization of candidates for biological testing, thereby accelerating the overall development process and lowering costs in both pharmaceutical and agrochemical contexts [21].

2. Results

2.1. Datasets

As a basis for model development, literature-based datasets were assembled. In order to train a model to distinguish active and inactive compounds, data sets of active compounds (ACs) and inactive compounds (IAs) were collected. To qualify a model's performance in a larger database, sets of probable inactive compounds, so-called decoys (DCs), were generated. The dataset sizes of ACs, IAs, and DCs corresponding to the assigned kinase subtype are shown in Table 1. Exemplary 2D structures of representative ACs used in this project are shown in Figure 1.

Table 1. Theoretical evaluation results of the overall generated pharmacophore models of JAK1, JAK2, JAK3, and TYK2 focused on model EF, YoA, along with TPs, FPs, TNs, and FNs.

Overall Evaluation	JAK1 TOTAL (8 Models)	JAK2 TOTAL (10 Models)	JAK3 TOTAL (10 Models)	TYK2 TOTAL (9 Models)
active hits/TPs	95	167	116	68
inactive hits	0	15	2	40
decoy hits	79	75	292	136
FPs	79	90	294	176
TNs	3232	2799	4247	2935
number of ACs in database	105	185	129	75
number of IAs in database	48	49	42	61
number of DCs in database	3263	2840	4499	3050
Model Accuracy	0.97	0.96	0.93	0.94
YoA	0.55	0.65	0.28	0.28
EF	17.76	10.80	10.24	11.84
sensitivity	0.90	0.90	0.86	0.91
specificity	1.00	0.99	1.00	1.00

2.2. Pharmacophore Modeling

"A pharmacophore is the ensemble of steric and electronic features that is necessary to ensure the optimal supramolecular interactions with a specific biological target and to trigger (or block) its biological response" [22]. Therefore, pharmacophore modeling is based on the theory that shared chemical functionalities and similar localization of features lead to

biological activity on the same target. The chemical properties of a molecule that is able to interact with its ligand are shown in the pharmacophore model as geometric features, such as spheres and vectors, as illustrated in Figures 2–5, and in the Supplementary Materials (Figures S1–S29).

In this project, we use structure-based (SB) and ligand-based (LB) pharmacophore modeling as part of the virtual screening approach [23]. SB modeling involves generating models based on the 3D structure of the target protein, identifying key binding sites and interactions. LB pharmacophore modeling, on the other hand, is based on the alignment of known ligands' structures to identify common features critical for binding to the target. Both approaches are used to predict potential interactions between compounds and the target protein during virtual screening [23].

The models in this project consist of hydrogen bond donors (HBDs), hydrogen bond acceptors (HBAs), aromatic interactions (AIs), hydrophobic contacts (HCs), residue bonding points (RBPs), and exclusion volumes (Xvols). For better clarity, Xvols are specified numerically in this publication instead of being shown graphically.

Multiple pharmacophore models are used to capture the diversity of compounds in the training set. In this project, both structure-based (SB) and ligand-based (LB) pharmacophore models were generated [24]. In total, eight models for JAK1 (four SB + four LB), ten models for JAK2 (two SB + eight LB), ten models for JAK3 (three SB + seven LB), and nine models for TYK2 (three SB + six LB) were generated. Examples of SB- and LB-based models in complex with identified training set hits are presented in Figures 2–5.

The 2D structures of the literature-known Janus kinase inhibitors, used specifically for the generation of the pharmacophore models presented in the manuscript, are shown in Figure 1.

These molecules served as the basis for the generation of the displayed pharmacophore models. The complete datasets used for the development and training of the models are provided in the Supplementary Materials section (Tables S1–S8). The remaining pharmacophore models, along with the structures they are based on, are presented in the Supplementary Materials (Figures S1–S29).

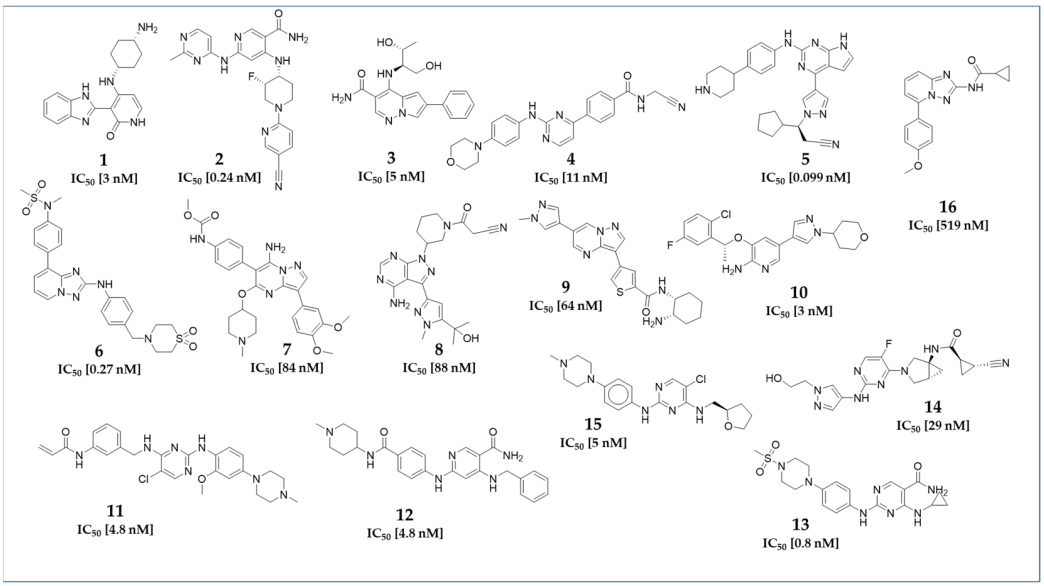

Figure 1. 2D structures of the pharmacophore modeling training compounds for JAK1 (**1** [25], **2** [26], **3** [27], **4** [28]) JAK2 (**5** [29], **6** [30], **7** [31], **8** [32], **9** [33], **10** [34]), JAK3 (**11** [35], **12** [36], **13** [30]), and TYK2 (**14** [37], **15** [38], **16** [39]) used to develop the shown pharmacophore models, along with their corresponding IC_{50} values.

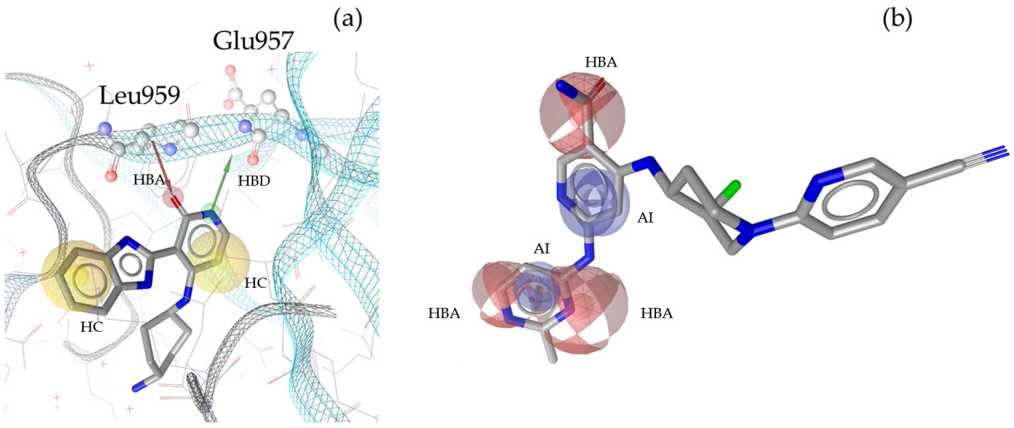

Figure 2. Two exemplary pharmacophore models for JAK1, illustrating key interactions and structural features. (**a**) JAK1_SB1 developed from the X-ray structure PDB: 5HX8 [25] in complex with its co-crystallized ligand compound **1** [25]. The model consists of one HBD with Glu957 and one HBA with Leu959, as well as two HCs. Furthermore, the model includes 66 Xvols. (**b**) Shows LB pharmacophore model JAK1_LB1 in complex with compound **2** [26]. This model was generated through alignment and merging of features from compound **2** [26], compound **3** [27], and compound **4** [28] JAK1_LB1 includes three HBAs, two AIs, and forty-seven Xvols. Chemical features are color-coded: HBDs—green, HBAs red, HCs—yellow, AIs—blue.

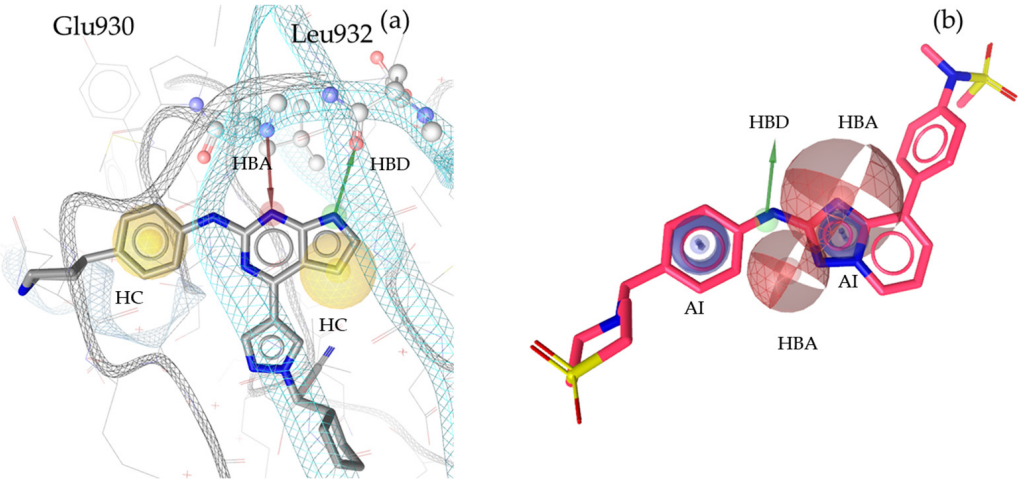

Figure 3. Two exemplary pharmacophore models for JAK2, illustrating key interactions and structural features. (**a**) JAK2_SB1, developed from the X-ray structure PDB: 6VNB [29] in complex with its co-crystallized ligand compound **5** [29]. This model consisted of one HBD with Leu932, one HBA with Glu930, two HCs, and nine Xvols. (**b**) Shows the LB pharmacophore model JAK2_LB1 in complex with compound **6** [30]. This model was generated through alignment and merging of features from compound **7** [31], compound **8** [32], compound **9** [33], and compound **10** [37]. JAK2_LB1 includes one HBD, two HBAs, two AIs, and nine Xvols. Chemical features are color-coded: HBDs—green, HBAs red, HCs—yellow, AIs—blue.

2.3. Theoretical Evaluation of the Generated Pharmacophore Models

Each model was optimized to maximize the identification of ACs from the training set while excluding a high number of IAs and DCs. Table 1 presents the results of the theoretical evaluation for the overall models of JAK1, JAK2, JAK3, and TYK2. The theoretical evaluation of the generated pharmacophore models focused on key performance metrics, such as model accuracy, enrichment factor (EF), and yield of active compounds (YoA). These metrics were derived from the classification of compounds into true positives (TPs), false positives (FPs), true negatives (TNs), and false negatives (FNs). Each pharmacophore model was systematically optimized to ensure the highest possible identification

of active ACs from the training set. Simultaneously, the models were refined to maximize their ability to distinguish IAs and DCs, ensuring both robustness and precision in virtual screening. Figure 6a–d show the overall receiver operating characteristic (ROC) curves for these models, illustrating their predictive performance as well as the area under the curve (AUC). The results for each individual model from this evaluation process are provided in the Supplementary Materials (Tables S11–S14). The ROC curves of the individual models are shown in the Supplementary Materials (Figures S30–S33).

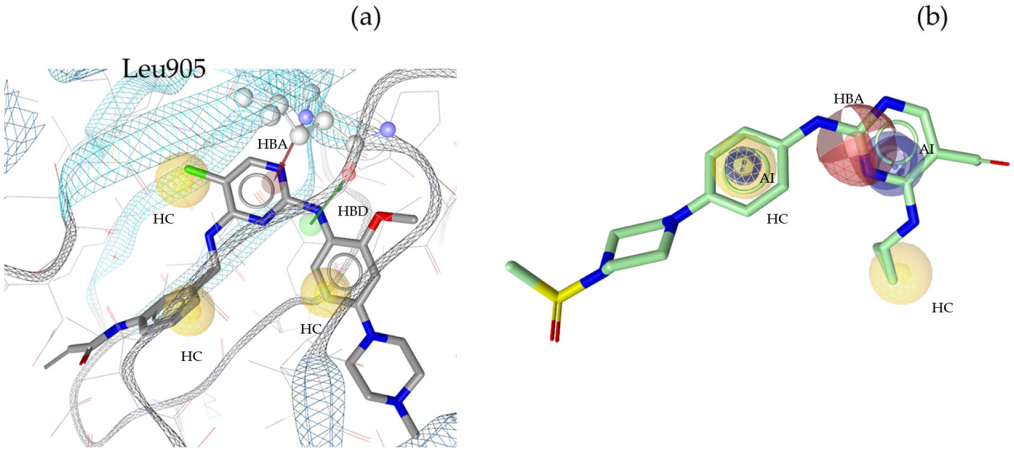

Figure 4. Two pharmacophore models for JAK3, illustrating key interactions and structural features. (**a**) JAK3_SB1, developed from the X-ray structure PDB: 4Z16 [35] in complex with its co-crystallized ligand compound **11** [35]. This model includes one HBD with Leu905, one HBA, three HCs, and twenty Xvols. (**b**) Shows LB pharmacophore model JAK3_LB1 in complex with compound **12**. This model was generated through alignment and merging of features from compound **12** [36] and compound **13** [40]. JAK3_LB1 includes one HBA, two AIs, two HCs, and twenty-nine Xvols. Chemical features are color-coded: HBDs—green, HBAs red, HCs—yellow, AIs—blue.

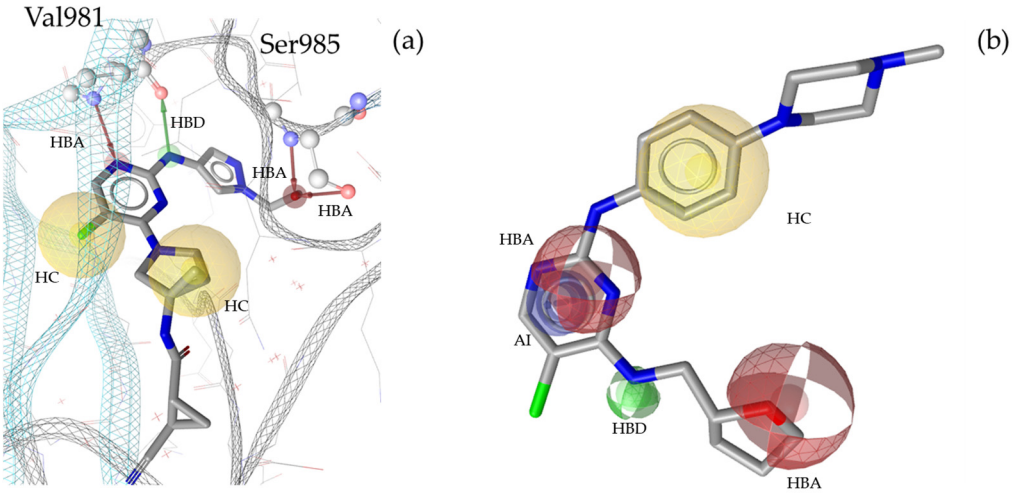

Figure 5. Two pharmacophore models for TYK2, illustrating key interactions and structural features. (**a**) TYK2_SB1, based on the X-ray structure PDB: 6VNS [37] in complex with the co-crystallized ligand compound **14** [37]. This model consists of one HBD with Val981, one HBA and two HBAs directed to Ser985, two HCs, and twenty-six Xvols. (**b**) Shows LB pharmacophore model TYK2_LB1 in complex with compound **15** [38]. This model was generated through alignment and merging of features from compound **15** [38] and compound **16** [39] TYK2_LB1 includes one HBD, two HBAs, one HC, one AI, and thirty-five Xvols. Chemical features are color-coded: HBDs—green, HBAs red, HCs—yellow, AIs—blue.

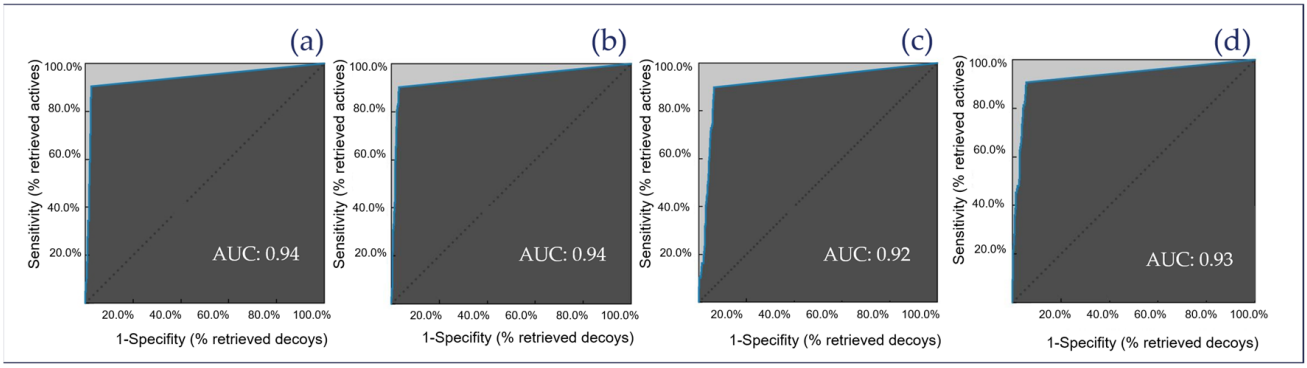

Figure 6. ROC curves of the overall models, including the AUC. Panel (**a**) shows JAK1, panel (**b**) shows JAK2, panel (**c**) shows JAK3, and panel (**d**) shows TYK2.

2.4. Identified Pesticides During Virtual Screening Campaign

The pharmacophore models identified 64 pesticides potentially inhibiting one or more JAKs by virtually screening the LUXPEST database [41]. A subsequent comparison with the Human Metabolome Database [42] revealed that 22 substances identified in the virtual screening have been qualitatively detected in the human body. The 2D structures of these substances are presented in Figure 7. Examples of identified pesticides in complex with their respective models, as described in detail in Section 2.2, are illustrated in Figures 8–11. The comprehensive list of all 64 identified pesticides obtained from the virtual screening of the LUXPEST [41] database assigned to the corresponding JAK model, is provided in the Supplementary Materials in Tables S15–S18.

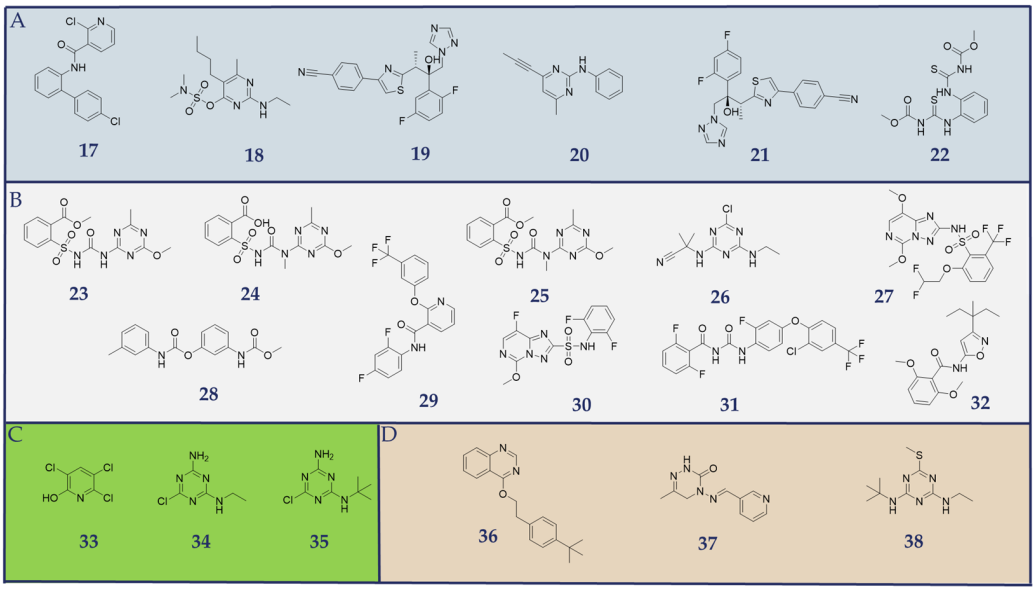

Figure 7. Identified pesticides from the virtual screening that are listed as qualitatively detected in the Human Metabolome Database. The hit list included fungicides (Section (**A**)), such as boscalid (**17**), bupirimate (**18**), isavuconazole (**19**), mepanipyrim (**20**), ravuconazole, (**21**), thiophanate-methyl (**22**). (Section (**B**)) comprises herbicides, including metsulfuron-methyl (**23**), tribenuron (**24**), tribenuron-methyl (**25**), cyanazine (**26**), penoxsulam (**27**), phenmedipham (**28**), diflufenican (**29**), florasulam (**30**), flufenoxuron (**31**), and isoxaben (**32**). (Section (**C**)) represents metabolites, such as 3,5,6-trichloro-2-pyridinol (**33**), deisopropylatrazine (**34**), and desethylterbutylazine (**35**). (Section (**D**)) includes insecticides, such as fenazaquin (**36**), pymetrozine (**37**), and terbutryn (**38**).

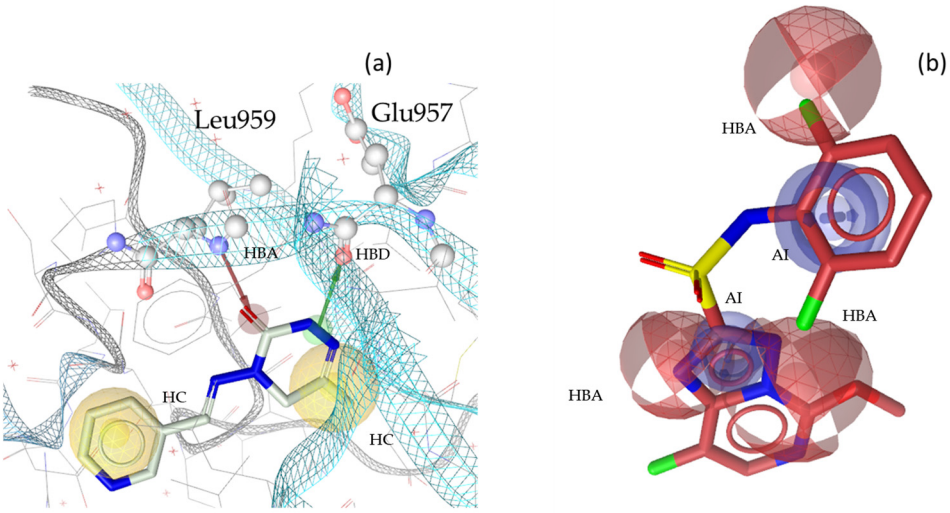

Figure 8. Exemplary virtual hits for JAK1. (**a**) Identified insecticide **36** (pymetrozine) in complex with model JAK1_SB1. (**b**) Identified herbicide **30** (florasulam) in model JAK1_LB1. Chemical features are color-coded: HBDs—green, HBAs red, HCs—yellow, AIs—blue.

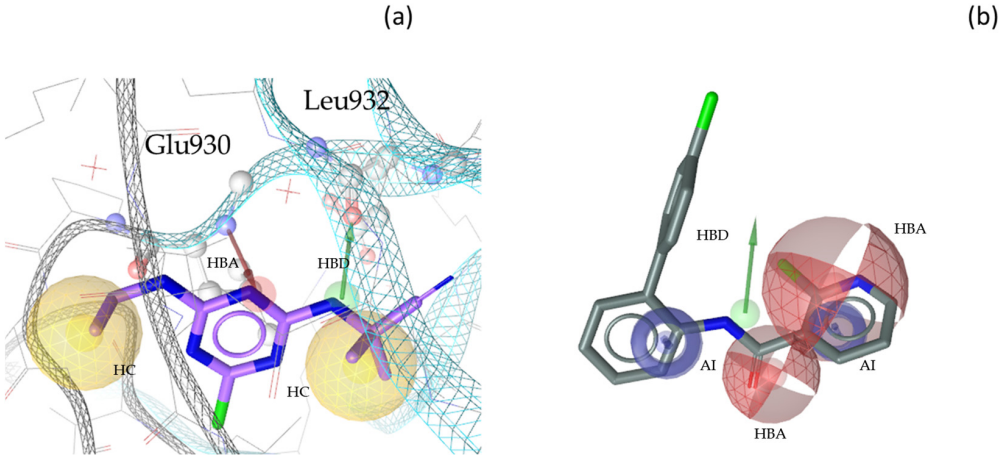

Figure 9. Exemplary virtual hits for JAK2. (**a**) Identified insecticide **27** (cynacine) in complex with model JAK2_SB1. (**b**) The fungicide **17** (boscalid) mapping model JAK2_LB1. Chemical features are color-coded: HBDs—green, HBAs red, HCs—yellow, AIs—blue.

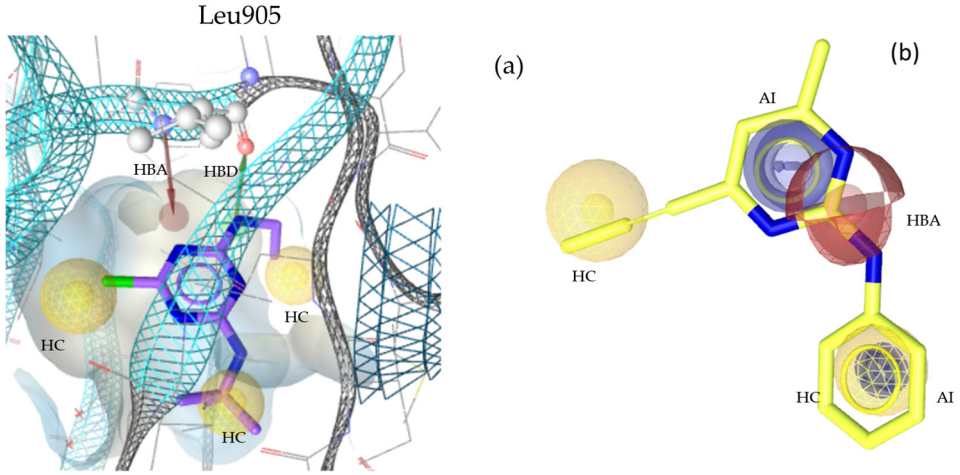

Figure 10. Exemplary virtual hits for JAK3. (**a**) The identified herbicide **26** (cyanazine) in complex with model JAK3_SB1. (**b**) The fungicide **20** (mepanipyrim) in model JAK3_LB1. Chemical features are color-coded: HBDs—green, HBAs red, HCs—yellow, AIs—blue.

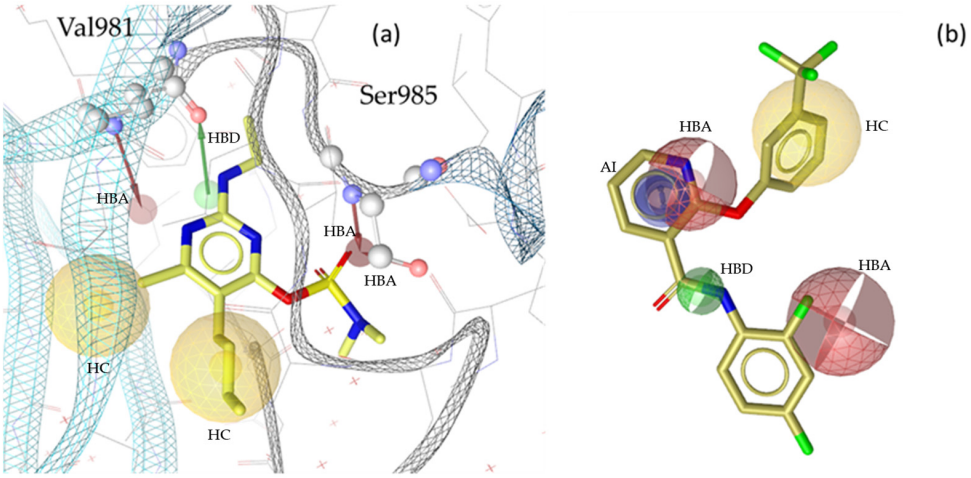

Figure 11. Exemplary virtual hits for TYK2. (**a**) The identified fungicide **18** (bupirimate) fitting into model TYK2_SB1. (**b**) The herbicide **28** (diflufenican) mapping to model TYK2_LB1. Chemical features are color-coded: HBDs—green, HBAs red, HCs—yellow, AIs—blue.

3. Discussion

PBVS offers a rapid and cost-efficient approach to early drug discovery, providing significant advantages over traditional high-throughput screening (HTS). By leveraging pharmacophore models, PBVS allows for the efficient prioritization of promising compounds from vast chemical libraries, reducing both time and costs while minimizing environmental impact. This approach filters out inactive or toxic substances before they reach experimental evaluation, streamlining the drug discovery process [43].

High-quality pharmacophore models can swiftly screen large, chemical databases, facilitating the identification of potential active compounds and enhancing the exploration of chemical space. This enables researchers to prioritize compounds for further experimental validation, significantly reducing resource consumption and time compared to conventional methods [44].

However, the accuracy of PBVS is highly dependent on the careful construction of well-validated models and the use of high-quality training datasets, as the reliability of pharmacophore models is intrinsically linked to the data from which they are derived.

Jakibs are widely recognized for their ability to suppress the immune system. Patients taking these inhibitors display increased risks of infections, including herpes, influenza, and fungal infections like pneumocystis. Respiratory and urinary tract infections are also more frequent, along with adverse events, such as joint and musculoskeletal disorders. Reports of malignant neoplasms, including hematopoietic, skin, and respiratory cancers, are also more prevalent. Additionally, this substance class is associated with an increased risk of venous thromboembolism compared to placebo or tumor necrosis factor (TNF) inhibitors [20,45–48].

In Europe, the risk assessment of pesticides is hindered by significant shortcomings within the regulatory framework. Despite the EU Pesticide Regulation 1107/2009 (http://data.europa.eu/eli/reg/2009/1107/oj, accessed on 14 April 2025) being one of the strictest globally, there is still room for improvement considering chronic toxicity and long-term effects [49]. However, there is much to consider. A 2024 U.S. study examined the link between agricultural pesticide use and cancer incidence by analyzing county-level data on pesticides, cancer rates, and factors like smoking and population demographics. Using latent class analysis, the researchers identified pesticide use profiles and assessed their impact on cancer incidence, while considering factors like land use and social vulnerability. The study highlighted regional trends between pesticide exposure and cancer. Atrazine,

an herbicide with a 1,3,5-triazine core structure, was consistently identified as a major contributor to increased cancer risk, particularly for colon cancer. These findings emphasize the varied effects of pesticides on different cancer types across regions [50]. Atrazine was also identified as a virtual hit for JAK2, JAK3, and TYK2; however, it was not present in the HMD. The JAK model collection identified similar pesticides from this structural scaffold, including cyanazine (**26**), metsulfuron-methyl (**23**), tribenuron (**24**), tribenuron-methyl (**25**), and terbutryn (**37**). Additionally, the virtual hit and fungicide boscalid (**17**) is associated with higher risks for leukemia, non-Hodgkin lymphoma, and pancreatic cancer [50].

The Food Safety Commission of Japan assessed the anilinopyrimidine fungicide mepanipyrim (**20**) based on various studies. Results showed hepatocellular hypertrophy, liver degeneration, and increased kidney weight in rats. A genotoxic mechanism was ruled out, and the exact mechanism of cancer development remains unclear; therefore, based on our findings, further investigations into the inhibition of JAKs are recommended [51].

Diflufenican (**29**) is a selective herbicide widely used in agriculture to control broadleaf weeds in crops such as corn and soybeans. As a phenyl ether herbicide, it exhibits moderate toxicity at high exposure levels, potentially leading to liver issues in animals. While current data suggests no increased cancer risk or immune-related effects, further studies are recommended due to its identification by pharmacophore models of all four JAK subtypes in this project. Additionally, the degradation product TFA (trifluoroacetic acid) raised concerns because of its persistence in the environment, acting as a "forever chemical" that can accumulate in both ecosystems and human tissues, potentially posing long-term environmental and health risks [52].

Counter to the immune-suppressive hypothesis, there are also studies suggesting that certain pesticides, such as thiophanate-methyl (**22**), activate immune responses rather than suppressing them. These substances stimulate inflammatory pathways, enhance macrophage proliferation, and promote cytokine production, including interleukins (IL) IL-1β, IL-6, TNF-α, and interferon-gamma. This underscores the dual nature of pesticide impacts, highlighting their capacity to both suppress and activate immune functions depending on specific mechanisms of action and exposure contexts [53].

Penoxsulam (**27**) is a herbicide from the sulfonamide class that inhibits acetolactate synthase in various weeds, aquatic plants, and grasses [54]. The EPA classifies it as having potential carcinogenicity, based on the observation of mononuclear cell leukemia in rats during carcinogenicity testing. A study conducted by D.M. Patel et al. examined the relationship between agricultural pesticides and the risk of childhood leukemia in Denmark. The herbicides phenmedipham (**28**) and tribenuron-methyl (**25**) were identified as potential risk factors. While higher applications of phenmedipham (**28**) were associated with an increased risk of childhood leukemia, the findings were not statistically significant. Both herbicides are classified as possible human carcinogens, highlighting concerns about their use in residential areas [55].

Interesting anti-inflammatory effects were reported for the herbicide cyanazine (**23**). It effectively suppressed lipopolysaccharide-induced increases in key pro-inflammatory cytokines, including TNF-α and IL-6, thereby inhibiting gonadal inflammation [56]. As the relevant cytokines are also prominently involved in the JAK signaling pathway, it would be interesting to follow up with in vitro experiments on this compound.

Significant knowledge gaps remain in understanding the off-target effects of pesticides, particularly in their interaction with molecular pathways, such as JAK signaling. While computational approaches, like pharmacophore-based virtual screening, offer valuable insights into potential risks, biological validation of these models is essential to confirm their accuracy. The next step is the biological validation of the virtual hits through a single protein assay, providing evidence for these predictions. Additional steps, such as

cell-based assays, may offer more comprehensive insights, improving our understanding of the broader impacts of pesticide exposure. It could also be that pesticides applied in mixtures act synergistically, amplifying their biological effects. Such synergistic effects have already been observed in salmon, where mixtures of pesticides in the water led to severe disruptions in their behavior and survival. Similar effects may also occur in humans, particularly with prolonged or repeated exposure. However, this remains an area requiring further research, as pesticides will be still essential in the future to enhance crop yields and food safety [57].

It takes a long time for the effects of pesticide use to manifest in epidemiological studies, like the ones mentioned above. It would therefore be desirable to anticipate potential chronic interference with human, animal, and crop organisms already in the discovery process. Computational methods, as presented in this study, could aid in identifying potentially problematic molecules.

4. Materials and Methods

4.1. Generation of Databases

A dataset of ACs and IAs was compiled for the individual targets JAK1, JAK2, JAK3, and TYK2, using data from ChEMBL (European Bioinformatics Institute, EMBL-EBI, Hinxton, United Kingdom; https://www.ebi.ac.uk/chembl/, accessed on 14 April 2025) PubChem (National Center for Biotechnology Information, Bethesda, MD, USA; https://pubchem.ncbi.nlm.nih.gov/, accessed on 14 April 2025), and the Protein Data Bank (Research Collaboratory for Structural Bioinformatics, RCSB, Piscataway, NJ, USA; https://www.rcsb.org/, accessed on 14 April 2025) [58–60]. Additionally, a decoy set was generated using the online tool Directory of Useful Decoys (DOCK group, University of California San Francisco, San Francisco, CA, USA; https://dude.docking.org/, accessed on 14 April 2025) [61], comprising random structures assumed to be inactive but with similar physicochemical properties to the active compounds, used to evaluate model restrictiveness. Active compounds were limited to those with an $IC_{50} \leq 1000$ nM, while inactive compounds were defined as those with an $IC_{50} > 40.000$ nM for JAK1 and >50.000 for JAK2, JAK3, and TYK2. Compounds with IC_{50} values in this intermediate range were subsequently excluded from the dataset. Lists detailing the manually selected ACs as well as IAs is given in the Supplementary Materials (Tables S1–S8) [19,23–27,29–34,36–38,62–312]. Due to the large number of references [70–312], those that exclusively concern compounds of the training sets are separately continued and mentioned in the bibliography to the Supplementary Materials. The 3D structures for pharmacophore model training and virtual screening were generated from the isomeric SMILES codes, with a maximum of 200 conformers generated for each compound using the iCon BEST [313] algorithm in LigandScout 4.4.5 (Inte:Ligand GmbH, Vienna, Austria) [314].

4.2. Pharmacophore Model Generation

All models were generated and optimized using LigandScout software version 4.4.5 [314]. SB models were generated using protein–ligand complex structures, while LB models were created by aligning multiple bioactive compounds [24]. For SB modeling, X-ray crystal structures of the protein–ligand complexes were used, including JAK1 (PDB: 4FK6 [62], 6SMB [63], 5WO4 [64], 5HX8 [25]), JAK2 (PDB: 6VNB [29], 7TEU [65]), JAK3 (PDB: 3ZEP [66], 4Z16 [35], 5TTV [67], 5LWM [68]), and TYK2 (PDB: 6VNS [37], 3LXN [315], 3NZ0 [316]). The selection of crystal structures was guided by quality criteria, including a resolution below 3 Å and highly defined electron density within the binding pocket. Crystal structures that generated three or fewer features using automatic generation with standard settings [314] were excluded. For LB modeling, the merged feature mode was

applied to align the selected molecules in 3D from the active compound data set. During the optimization process, each pharmacophore feature was individually refined to maximize the detection of ACs, while minimizing the identification of IAs and DCs. To optimize the models, each feature was manually optimized and adjusted during subsequent screening stages. Features that did not enhance model selectivity were discarded, while Xvols were added or removed as needed, and feature tolerances were fine-tuned to maximize model performance.

4.3. Theoretical Validation

The assessment metrics calculated in this study encompassed sensitivity (a), specificity (b), accuracy (c), YoA (d), EF (e), and (ROC) curve. The ROC curve is a plot used to evaluate the performance of a classification model. It depicts the relationship between the true positive rate (TPR) and the false positive rate (FPR), with TPR on the y-axis and FPR on the x-axis. AUC is a metric derived from the ROC curve that represents a model's ability to distinguish between positive and negative classes. AUC values range from 0 to 1, with higher values indicating better classification performance.

Continuous monitoring of these metrics facilitated the refinement process [21]. Pharmacophore models that did not meet performance criteria (EF < 4) were excluded. The overall performance of all JAK models, according to their subtype, is presented in Table 1, while the results of the individual models for each kinase are provided Tables S11–S14.

(a) Sensitivity = number of ACs identified by the model/number of ACs in the dataset
(b) Specificity = number of ACs not identified by the model/number of IAs in the dataset
(c) Accuracy = (number of TP/number of TN)/number of all the compounds in the database
(d) YoA = number of TP/number of total hits
(e) EF = YoA/(number of ACs in the database/number of all compounds in the database)

4.4. Virtual Screening

The LUXPEST S69 a Pesticide Screening List for Luxembourg (https://www.norman-network.com/nds/SLE/) Les Garennes sur Loire, France (28 May 2020) [41], containing 386 pesticides, was screened after being converted into a 3D database using LigandScout 4.4.5. Using iCon BEST [313], 400 conformers were generated per pesticide, following the same approach used in the creation of the training sets, as outlined in Section 4.1. An overview of all identified hits is included in the Tables S15–S18.

The identified pesticides were cross-referenced with the Human Metabolome Database to determine whether these compounds have been qualitatively detected in the human body [42].

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules30102183/s1. Figure S1: JAK1_SB2; Figure S2: JAK1_SB3; Figure S3: JAK1_SB4; Figure S4: JAK1_LB2; Figure S5: JAK1_LB3; Figure S6: JAK1_LB4; Figure S7: JAK2_SB2; Figure S8: JAK2_LB2; Figure S9: JAK2_LB3; Figure S10: JAK2_LB4; Figure S11: JAK2_LB5; Figure S12: JAK2_LB6; Figure S13: JAK2_LB7; Figure S14: JAK2_LB8; Figure S15: JAK3_SB2; Figure S16: JAK3_SB3; Figure S17: JAK3_SB4; Figure S18: JAK3_LB2; Figure S19: JAK3_LB3; Figure S20: JAK3_LB4; Figure S21: JAK3_LB5; Figure S22: JAK3_LB6; Figure S23: TYK2_SB2; Figure S24: TYK2_SB3; Figure S25: TYK2_LB2; Figure S26: JAK2_LB3; Figure S27: TYK2_LB4; Figure S28: TYK2_LB5; Figure S29: TYK2_LB6; Figure S30: ROC-curves JAK1; Figure S31: ROC-curves JAK2; Figure S32: ROC-curves JAK3; Figure S33: ROC-curves TYK2. Table S1: JAK1 active compounds; Table S2: JAK1 inactive compounds; Table S3: JAK2 active compounds; Table S4: JAK2 inactive compounds; Table S5: JAK3 active compounds; Table S6: JAK3 inactive compounds; Table S7: TYK2 active compounds; Table S8: TYK2 inactive compounds; Table S9: Pharmacophore features

overview; Table S10: Amino acid interactions of structure-based models; Table S11: Theoretical evaluation results JAK1; Table S12: Theoretical evaluation results JAK2; Table S13: Theoretical evaluation results JAK3; Table S14: Theoretical evaluation results TYK2; Table S15: Pesticide Hits JAK1; Table S16: Pesticide Hits JAK2; Table S17: Pesticide Hits JAK3; Table S18: Pesticide Hits TYK2.

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References

1. Macfarlane, E.; Carey, R.; Keegel, T.; El-Zaemay, S.; Fritschi, L. Dermal exposure associated with occupational end use of pesticides and the role of protective measures. *Saf. Health Work* **2013**, *4*, 136–141. [CrossRef]
2. Zhang, X.; Wu, M.; Yao, H.; Yang, Y.; Cui, M.; Tu, Z.; Stallones, L.; Xiang, H. Pesticide poisoning and neurobehavioral function among farm workers in Jiangsu, People's Republic of China. *Cortex* **2016**, *74*, 396–404. [CrossRef]
3. Wang, L.; Liu, Z.; Zhang, J.; Wu, Y.; Sun, H. Chlorpyrifos exposure in farmers and urban adults: Metabolic characteristic, exposure estimation, and potential effect of oxidative damage. *Environ. Res.* **2016**, *149*, 164–170. [CrossRef] [PubMed]
4. Damalas, C.A.; Koutroubas, S.D. Farmers' Exposure to Pesticides: Toxicity Types and Ways of Prevention. *Toxics* **2016**, *4*, 1. [CrossRef] [PubMed]
5. Kim, K.H.; Kabir, E.; Jahan, S.A. Exposure to pesticides and the associated human health effects. *Sci. Total Environ.* **2017**, *575*, 525–535. [CrossRef] [PubMed]
6. Syafrudin, M.; Kristanti, R.A.; Yuniarto, A.; Hadibarata, T.; Rhee, J.; Al-Onazi, W.A.; Algarni, T.S.; Almarri, A.H.; Al-Mohaimeed, A.M. Pesticides in Drinking Water—A Review. *Int. J. Environ. Res. Public Health* **2021**, *18*, 468. [CrossRef]
7. Jensen, B.H.; Petersen, A.; Petersen, P.B.; Christensen, T.; Fagt, S.; Trolle, E.; Poulsen, M.E.; Andersen, J.H. Cumulative dietary risk assessment of pesticides in food for the Danish population for the period 2012–2017. *Food Chem. Toxicol.* **2022**, *168*, 113359. [CrossRef]
8. Fucic, A.; Duca, R.C.; Galea, K.S.; Maric, T.; Garcia, K.; Bloom, M.S.; Andersen, H.R.; Vena, J.E. Reproductive Health Risks Associated with Occupational and Environmental Exposure to Pesticides. *Int. J. Environ. Res. Public Health* **2021**, *18*, 6576. [CrossRef]
9. Richardson, J.R.; Fitsanakis, V.; Westerink, R.H.S.; Kanthasamy, A.G. Neurotoxicity of pesticides. *Acta Neuropathol.* **2019**, *138*, 343–362. [CrossRef]
10. Alavanja, M.C.; Ross, M.K.; Bonner, M.R. Increased cancer burden among pesticide applicators and others due to pesticide exposure. *CA Cancer J. Clin.* **2013**, *63*, 120–142. [CrossRef]
11. Purdue, M.P.; Hoppin, J.A.; Blair, A.; Dosemeci, M.; Alavanja, M.C. Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. *Int. J. Cancer* **2007**, *120*, 642–649. [CrossRef]
12. Mahajan, R.; Blair, A.; Lynch, C.F.; Schroeder, P.; Hoppin, J.A.; Sandler, D.P.; Alavanja, M.C. Fonofos exposure and cancer incidence in the agricultural health study. *Environ. Health Perspect.* **2006**, *114*, 1838–1842. [CrossRef]
13. Mokarizadeh, A.; Faryabi, M.R.; Rezvanfar, M.A.; Abdollahi, M. A comprehensive review of pesticides and the immune dysregulation: Mechanisms, evidence and consequences. *Toxicol. Mech. Methods* **2015**, *25*, 258–278. [CrossRef]
14. Costa, C.; Rapisarda, V.; Catania, S.; Di Nola, C.; Ledda, C.; Fenga, C. Cytokine patterns in greenhouse workers occupationally exposed to α-cypermethrin: An observational study. *Environ. Toxicol. Pharmacol.* **2013**, *36*, 796–800. [CrossRef] [PubMed]

15. Takeuchi, T. Cytokines and cytokine receptors as targets of immune-mediated inflammatory diseases—RA as a role model. *Inflamm. Regen.* **2022**, *42*, 35. [CrossRef]
16. Gadina, M.; Le, M.T.; Schwartz, D.M.; Silvennoinen, O.; Nakayamada, S.; Yamaoka, K.; O'shea, J.J. Janus kinases to jakinibs: From basic insights to clinical practice. *Rheumatology* **2019**, *58*, i4–i16. [CrossRef] [PubMed]
17. Zarrin, A.A.; Bao, K.; Lupardus, P.; Vucic, D. Kinase inhibition in autoimmunity and inflammation. *Nat. Rev. Drug Discov.* **2021**, *20*, 39–63. [CrossRef]
18. Xue, C.; Yao, Q.; Gu, X.; Shi, Q.; Yuan, X.; Chu, Q.; Bao, Z.; Lu, J.; Li, L. Evolving cognition of the JAK-STAT signaling pathway: Autoimmune disorders and cancer. *Signal Transduct. Target. Ther.* **2023**, *8*, 204. [CrossRef] [PubMed]
19. Clark, J.D.; Flanagan, M.E.; Telliez, J.B. Discovery and development of Janus kinase (JAK) inhibitors for inflammatory diseases. *J. Med. Chem.* **2014**, *57*, 5023–5038. [CrossRef]
20. Hoisnard, L.; Lebrun-Vignes, B.; Maury, S.; Mahevas, M.; El Karoui, K.; Roy, L.; Zarour, A.; Michel, M.; Cohen, J.L.; Amiot, A.; et al. Adverse events associated with JAK inhibitors in 126,815 reports from the WHO pharmacovigilance database. *Sci. Rep.* **2022**, *12*, 7140. [CrossRef]
21. Giordano, D.; Biancaniello, C.; Argenio, M.A.; Facchiano, A. Drug Design by Pharmacophore and Virtual Screening Approach. *Pharmaceuticals* **2022**, *15*, 646. [CrossRef]
22. Wermuth, C.G.; Ganellin, C.R.; Lindberg, P.; Mitscher, L.A. Glossary of terms used in medicinal chemistry (IUPAC Recommendations 1998). *Pure Appl. Chem.* **1998**, *70*, 1129–1143. [CrossRef]
23. Kaserer, T.; Beck, K.R.; Akram, M.; Odermatt, A.; Schuster, D. Pharmacophore Models and Pharmacophore-Based Virtual Screening: Concepts and Applications Exemplified on Hydroxysteroid Dehydrogenases. *Molecules* **2015**, *20*, 22799–22832. [CrossRef]
24. Schuster, D.; Wolber, G. Identification of bioactive natural products by pharmacophore-based virtual screening. *Curr. Pharm. Des.* **2010**, *16*, 1666–1681. [CrossRef] [PubMed]
25. Simov, V.; Deshmukh, S.V.; Dinsmore, C.J.; Elwood, F.; Fernandez, R.B.; Garcia, Y.; Gibeau, C.; Gunaydin, H.; Jung, J.; Katz, J.D.; et al. Structure-based design and development of (benz)imidazole pyridones as JAK1-selective kinase inhibitors. *Bioorganic Med. Chem. Lett.* **2016**, *26*, 1803–1808. [CrossRef]
26. Nakajima, Y.; Aoyama, N.; Takahashi, F.; Sasaki, H.; Hatanaka, K.; Moritomo, A.; Inami, M.; Ito, M.; Nakamura, K.; Nakamori, F.; et al. Design, synthesis, and evaluation of 4,6-diaminonicotinamide derivatives as novel and potent immunomodulators targeting JAK3. *Bioorganic Med. Chem.* **2016**, *24*, 4711–4722. [CrossRef] [PubMed]
27. Spergel, S.H.; Mertzman, M.E.; Kempson, J.; Guo, J.; Stachura, S.; Haque, L.; Lippy, J.S.; Zhang, R.F.; Galella, M.; Pitt, S.; et al. Discovery of a JAK1/3 Inhibitor and Use of a Prodrug To Demonstrate Efficacy in a Model of Rheumatoid Arthritis. *ACS Med. Chem. Lett.* **2019**, *10*, 306–311. [CrossRef]
28. Raghuvanshi, R.; Bharate, S.B. Recent Developments in the Use of Kinase Inhibitors for Management of Viral Infections. *J. Med. Chem.* **2022**, *65*, 893–921. [CrossRef]
29. Davis, R.R.; Li, B.; Yun, S.Y.; Chan, A.; Nareddy, P.; Gunawan, S.; Ayaz, M.; Lawrence, H.R.; Reuther, G.W.; Lawrence, N.J.; et al. Structural Insights into JAK2 Inhibition by Ruxolitinib, Fedratinib, and Derivatives Thereof. *J. Med. Chem.* **2021**, *64*, 2228–2241. [CrossRef]
30. Mesaros, E.F.; Dugan, B.J.; Dorsey, B.D.; Milkiewicz, K.L.; Curry, M.A.; Gingrich, D.E. Preparation and Uses of 1,2,4-triazolo [1,5a] Pyridine Derivatives. U.S. Patent 8633173-B2, 5 June 2009.
31. Mathison, C.J.N.; Chianelli, D.; Rucker, P.V.; Nelson, J.; Roland, J.; Huang, Z.; Yang, Y.; Jiang, J.; Xie, Y.F.; Epple, R.; et al. Efficacy and Tolerability of Pyrazolo[1,5-*a*]pyrimidine RET Kinase Inhibitors for the Treatment of Lung Adenocarcinoma. *ACS Med. Chem. Lett.* **2020**, *11*, 558–565. [CrossRef]
32. Yin, Y.; Chen, C.J.; Yu, R.N.; Shu, L.; Zhang, T.T.; Zhang, D.Y. Discovery of novel selective Janus kinase 2 (JAK2) inhibitors bearing a 1H-pyrazolo[3,4-d]pyrimidin-4-amino scaffold. *Bioorganic Med. Chem.* **2019**, *27*, 1562–1576. [CrossRef] [PubMed]
33. Sloman, D.L.; Noucti, N.; Altman, M.D.; Chen, D.; Mislak, A.C.; Szewczak, A.; Hayashi, M.; Warren, L.; Dellovade, T.; Wu, Z.; et al. Optimization of microtubule affinity regulating kinase (MARK) inhibitors with improved physical properties. *Bioorganic Med. Chem. Lett.* **2016**, *26*, 4362–4366. [CrossRef] [PubMed]
34. Ma, X.; Diao, Y.; Ge, H.; Xu, F.; Zhu, L.; Zhao, Z.; Li, H. Discovery and optimization of 2-aminopyridine derivatives as novel and selective JAK2 inhibitors. *Bioorganic Med. Chem. Lett.* **2020**, *30*, 127048. [CrossRef]
35. Tan, L.; Akahane, K.; McNally, R.; Reyskens, K.M.S.E.; Ficarro, S.B.; Liu, S.; Herter-Sprie, G.S.; Koyama, S.; Pattison, M.J.; Labella, K.; et al. Development of Selective Covalent Janus Kinase 3 Inhibitors. *J. Med. Chem.* **2015**, *58*, 6589–6606. [CrossRef] [PubMed]
36. Bhide, R.S.; Keon, A.; Weigelt, C.; Sack, J.S.; Schmidt, R.J.; Lin, S.; Xiao, H.-Y.; Spergel, S.H.; Kempson, J.; Pitts, W.J.; et al. Discovery and structure-based design of 4,6-diaminonicotinamides as potent and selective IRAK4 inhibitors. *Bioorganic Med. Chem. Lett.* **2017**, *27*, 4908–4913. [CrossRef]

37. Fensome, A.; Ambler, C.M.; Arnold, E.; Banker, M.E.; Clark, J.D.; Dowty, M.E.; Efremov, I.V.; Flick, A.; Gerstenberger, B.S.; Gifford, R.S.; et al. Design and optimization of a series of 4-(3-azabicyclo[3.1.0]hexan-3-yl)pyrimidin-2-amines: Dual inhibitors of TYK2 and JAK1. *Bioorganic Med. Chem.* **2020**, *28*, 115481. [CrossRef]
38. Lawrence, H.R.; Mahajan, K.; Luo, Y.; Zhang, D.; Tindall, N.; Huseyin, M.; Gevariya, H.; Kazi, S.; Ozcan, S.; Mahajan, N.P.; et al. Development of novel ACK1/TNK2 inhibitors using a fragment-based approach. *J. Med. Chem.* **2015**, *58*, 2746–2763. [CrossRef]
39. Menet, C.J.; Fletcher, S.R.; Van Lommen, G.; Geney, R.; Blanc, J.; Smits, K.; Jouannigot, N.; Deprez, P.; van der Aar, E.M.; Clement-Lacroix, P.; et al. Triazolopyridines as selective JAK1 inhibitors: From hit identification to GLPG0634. *J. Med. Chem.* **2014**, *57*, 9323–9342. [CrossRef]
40. Bauer, S.M.; Pandey, A. National Center for Biotechnology Information (2024). PubChem Patent Summary for US-9868729-B2, Inhibitors of Protein Kinases. United States. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-9868729-B2 (accessed on 16 December 2024).
41. Krier, J.; Singh, R.R.; Kondić, T.; Lai, A.; Diderich, P.; Zhang, J.; Thiessen, P.A.; Bolton, E.E.; Schymanski, E.L. Discovering pesticides and their TPs in Luxembourg waters using open cheminformatics approaches. *Environ. Int.* **2022**, *158*, 106885. [CrossRef]
42. Wishart, D.S.; Guo, A.; Oler, E.; Wang, F.; Anjum, A.; Peters, H.; Dizon, R.; Sayeeda, Z.; Tian, S.; Lee, B.L.; et al. HMDB 5.0: The Human Metabolome Database for 2022. *Nucleic Acids Res.* **2022**, *50*, D622–D631. [CrossRef]
43. Ghosh, S.; Nie, A.; An, J.; Huang, Z. Structure-based virtual screening of chemical libraries for drug discovery. *Curr. Opin. Chem. Biol.* **2006**, *10*, 194–202. [CrossRef]
44. Sun, H. Pharmacophore-based virtual screening. *Curr. Med. Chem.* **2008**, *15*, 1018–1024. [CrossRef]
45. Xin, P.; Xu, X.; Deng, C.; Liu, S.; Wang, Y.; Zhou, X.; Ma, H.; Wei, D.; Sun, S. The role of JAK/STAT signaling pathway and its inhibitors in diseases. *Int. Immunopharmacol.* **2020**, *80*, 106210. [CrossRef] [PubMed]
46. Cohen, S.; Radominski, S.C.; Gomez-Reino, J.J.; Wang, L.; Krishnaswami, S.; Wood, S.P.; Soma, K.; Nduaka, C.I.; Kwok, K.; Valdez, H.; et al. Analysis of infections and all-cause mortality in phase II, phase III, and long-term extension studies of tofacitinib in patients with rheumatoid arthritis. *Arthritis Rheumatol.* **2014**, *66*, 2924–2937. [CrossRef] [PubMed]
47. Russell, M.D.; Stovin, C.; Alveyn, E.; Adeyemi, O.; Chan, C.K.D.; Patel, V.; Adas, M.A.; Atzeni, F.; Ng, K.K.H.; Rutherford, A.I.; et al. JAK inhibitors and the risk of malignancy: A meta-analysis across disease indications. *Ann. Rheum. Dis.* **2023**, *82*, 1059–1067. [CrossRef] [PubMed]
48. Zhang, J.; Li, W.; Gong, M.; Gu, Y.; Zhang, H.; Dong, B.; Guo, Q.; Pang, X.; Xiang, Q.; He, X.; et al. Risk of venous thromboembolism with janus kinase inhibitors in inflammatory immune diseases: A systematic review and meta-analysis. *Front. Pharmacol.* **2023**, *14*, 1189389. [CrossRef]
49. Robinson, C.; Portier, C.J.; Čavoški, A.; Mesnage, R.; Roger, A.; Clausing, P.; Whaley, P.; Muilerman, H.; Lyssimachou, A. Achieving a High Level of Protection from Pesticides in Europe: Problems with the Current Risk Assessment Procedure and Solutions. *Eur. J. Risk Regul.* **2020**, *11*, 450–480. [CrossRef]
50. Gerken, J.; Vincent, G.T.; Zapata, D.; Barron, I.G.; Zapata, I. Comprehensive assessment of pesticide use patterns and increased cancer risk. *Front. Cancer Control Soc.* **2024**, *2*, 1368086. [CrossRef]
51. Yamazoe, Y.; Yamamoto, S.; Yoshida, M.; Kawanishi, T.; Kumagai, S. Mepanipyrim (Pesticides). *Food Saf.* **2016**, *4*, 28–29. [CrossRef]
52. Zweigle, J.; Schmidt, A.; Bugsel, B.; Vogel, C.; Simon, F.; Zwiener, C. Perfluoroalkyl acid precursor or weakly fluorinated organic compound? A proof of concept for oxidative fractionation of PFAS and organofluorines. *Anal. Bioanal. Chem.* **2024**, *416*, 6799–6808. [CrossRef]
53. Weis, G.C.C.; Assmann, C.E.; Cadoná, F.C.; Bonadiman, B.D.S.R.; de Oliveira Alves, A.; Machado, A.K.; Duarte, M.M.M.F.; da Cruz, I.B.M.; Costabeber, I.H. Immunomodulatory effect of mancozeb, chlorothalonil, and thiophanate methyl pesticides on macrophage cells. *Ecotoxicol. Environ. Saf.* **2019**, *182*, 109420. [CrossRef]
54. Jabusch, T.W.; Tjeerdema, R.S. Partitioning of penoxsulam, a new sulfonamide herbicide. *J. Agric. Food Chem.* **2005**, *53*, 7179–7183. [CrossRef] [PubMed]
55. Patel, D.M.; Gyldenkærne, S.; Jones, R.R.; Olsen, S.F.; Tikellis, G.; Granström, C.; Dwyer, T.; Stayner, L.T.; Ward, M.H. Residential proximity to agriculture and risk of childhood leukemia and central nervous system tumors in the Danish national birth cohort. *Environ. Int.* **2020**, *143*, 105955. [CrossRef] [PubMed]
56. Abarikwu, S.O.; Mgbudom-Okah, C.J.; Ndufeiya-Kumasi, L.C.; Monye, V.E.; Aruoren, O.; Ezim, O.E.; Omeodu, S.I.; Charles, I.A. Influence of triazines and lipopolysaccharide coexposure on inflammatory response and histopathological changes in the testis and liver of BalB/c mice. *Heliyon* **2024**, *10*, e24431. [CrossRef] [PubMed]
57. Laetz, C.A.; Baldwin, D.H.; Collier, T.K.; Hebert, V.; Stark, J.D.; Scholz, N.L. The synergistic toxicity of pesticide mixtures: Implications for risk assessment and the conservation of endangered Pacific salmon. *Environ. Health Perspect.* **2009**, *117*, 348–353. [CrossRef]
58. Berman, H.M.; Westbrook, J.; Feng, Z.; Gilliland, G.; Bhat, T.N.; Weissig, H.; Shindyalov, I.N.; Bourne, P.E. The Protein Data Bank. *Nucleic Acids Res.* **2000**, *28*, 235–242. [CrossRef]

59. Gaulton, A.; Bellis, L.J.; Bento, A.P.; Chambers, J.; Davies, M.; Hersey, A.; Light, Y.; McGlinchey, S.; Michalovich, D.; Al-Lazikani, B.; et al. ChEMBL: A large-scale bioactivity database for drug discovery. *Nucleic Acids Res.* **2012**, *40*, D1100–D1107. [CrossRef]
60. Kim, S.; Chen, J.; Cheng, T.; Gindulyte, A.; He, J.; He, S.; Li, Q.; A Shoemaker, B.; A Thiessen, P.; Yu, B.; et al. PubChem 2023 update. *Nucleic Acids Res.* **2023**, *51*, D1373–D1380. [CrossRef]
61. Mysinger, M.M.; Carchia, M.; Irwin, J.J.; Shoichet, B.K. Directory of useful decoys, enhanced (DUD-E): Better ligands and decoys for better benchmarking. *J. Med. Chem.* **2012**, *55*, 6582–6594. [CrossRef]
62. Labadie, S.; Dragovich, P.S.; Barrett, K.; Blair, W.S.; Bergeron, P.; Chang, C.; Deshmukh, G.; Eigenbrot, C.; Ghilardi, N.; Gibbons, P.; et al. Structure-based discovery of C-2 substituted imidazo-pyrrolopyridine JAK1 inhibitors with improved selectivity over JAK2. *Bioorganic Med. Chem. Lett.* **2012**, *22*, 7627–7633. [CrossRef]
63. Su, Q.; Banks, E.; Bebernitz, G.; Bell, K.; Borenstein, C.F.; Chen, H.; Chuaqui, C.E.; Deng, N.; Ferguson, A.D.; Kawatkar, S.P.; et al. Discovery of (2*R*)-*N*-[3-[2-[(3-Methoxy-1-methyl-pyrazol-4-yl)amino]pyrimidin-4-yl]-1*H*-indol-7-yl]-2-(4-methylpiperazin-1-yl) propenamide (AZD4205) as a Potent and Selective Janus Kinase 1 Inhibitor. *J. Med. Chem.* **2020**, *63*, 4517–4527. [CrossRef] [PubMed]
64. Siu, T.; Brubaker, J.; Fuller, P.; Torres, L.; Zeng, H.; Close, J.; Mampreian, D.M.; Shi, F.; Liu, D.; Fradera, X.; et al. The Discovery of 3-((4-Chloro-3-methoxyphenyl)amino)-1-((3R,4S)-4-cyanotetrahydro-2H-pyran-3-yl)-1H-pyrazole-4-carboxamide, a Highly Ligand Efficient and Efficacious Janus Kinase 1 Selective Inhibitor with Favorable Pharmacokinetic Properties. *J. Med. Chem.* **2017**, *60*, 9676–9690. [CrossRef] [PubMed]
65. Arwood, M.L.; Liu, Y.; Harkins, S.K.; Weinstock, D.M.; Yang, L.; Stevenson, K.E.; Plana, O.D.; Dong, J.; Cirka, H.; Jones, K.L.; et al. New scaffolds for type II JAK2 inhibitors overcome the acquired G993A resistance mutation. *Cell Chem. Biol.* **2023**, *30*, 618–631.e12. [CrossRef] [PubMed]
66. Jaime-Figueroa, S.; De Vicente, J.; Hermann, J.; Jahangir, A.; Jin, S.; Kuglstatter, A.; Lynch, S.M.; Menke, J.; Niu, L.; Patel, V.; et al. Discovery of a series of novel 5H-pyrrolo[2,3-b]pyrazine-2-phenyl ethers, as potent JAK3 kinase inhibitors. *Bioorganic Med. Chem. Lett.* **2013**, *23*, 2522–2526. [CrossRef]
67. Thorarensen, A.; Dowty, M.E.; Banker, M.E.; Juba, B.; Jussif, J.; Lin, T.; Vincent, F.; Czerwinski, R.M.; Casimiro-Garcia, A.; Unwalla, R.; et al. Design of a Janus Kinase 3 (JAK3) Specific Inhibitor 1-((2S,5R)-5-((7H-Pyrrolo[2,3-d]pyrimidin-4-yl)amino)-2-methylpiperidin-1-yl)prop-2-en-1-one (PF-06651600) Allowing for the Interrogation of JAK3 Signaling in Humans. *J. Med. Chem.* **2017**, *60*, 1971–1993. [CrossRef]
68. Forster, M.; Chaikuad, A.; Bauer, S.M.; Holstein, J.; Robers, M.B.; Corona, C.R.; Gehringer, M.; Pfaffenrot, E.; Ghoreschi, K.; Knapp, S.; et al. Selective JAK3 Inhibitors with a Covalent Reversible Binding Mode Targeting a New Induced Fit Binding Pocket. *Cell Chem. Biol.* **2016**, *23*, 1335–1340. [CrossRef]
69. Adams, C.; Aldous, D.J.; Amendola, S.; Bamborough, P.; Bright, C.; Crowe, S.; Eastwood, P.; Fenton, G.; Foster, M.; Harrison, T.K.P.; et al. Mapping the kinase domain of janus kinase 3. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3105–3110. [CrossRef]
70. Burns, C.J.; Bourke, D.G.; Andrau, L.; Bu, X.; Charman, S.A.; Donohue, A.C.; Fantino, E.; Farrugia, M.; Feutrill, J.T.; Joffe, M.; et al. Phenylaminopyrimidines as inhibitors of Janus kinases (JAKs). *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5887–5892. [CrossRef]
71. Cole, A.G.; Bohnstedt, A.C.; Paradkar, V.; Kingsbury, C.; Quintero, J.G.; Park, H.; Lu, Y.; You, M.; Neagu, I.; Diller, D.J.; et al. 2-Benzimidazolyl-9-(chroman-4-yl)-purinone derivatives as JAK3 inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6788–6792. [CrossRef]
72. Gerspacher, M.; Furet, P.; Pissot-Soldermann, C.; Gaul, C.; Holzer, P.; Vangrevelinghe, E.; Lang, M.; Erdmann, D.; Radimerski, T.; Regnier, C.H.; et al. 2-Amino-aryl-7-aryl-benzoxazoles as potent, selective and orally available JAK2 inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1724–1727. [CrossRef]
73. Pissot-Soldermann, C.; Gerspacher, M.; Furet, P.; Gaul, C.; Holzer, P.; McCarthy, C.; Radimerski, T.; Regnier, C.H.; Baffert, F.; Drueckes, P.; et al. Discovery and SAR of potent, orally available 2,8-diaryl-quinoxalines as a new class of JAK2 inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2609–2613. [CrossRef] [PubMed]
74. Fidanze, S.D.; Erickson, S.A.; Wang, G.T.; Mantei, R.; Clark, R.F.; Sorensen, B.K.; Bamaung, N.Y.; Kovar, P.; Johnson, E.F.; Swinger, K.K.; et al. Imidazo[2,1-*b*]thiazoles: Multitargeted inhibitors of both the insulin-like growth factor receptor and members of the epidermal growth factor family of receptor tyrosine kinases. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2452–2455. [CrossRef]
75. Dart, M.L.; Machleidt, T.; Jost, E.; Schwinn, M.K.; Robers, M.B.; Shi, C.; Kirkland, T.A.; Killoran, M.P.; Wilkinson, J.M.; Hartnett, J.R.; et al. Homogeneous Assay for Target Engagement Utilizing Bioluminescent Thermal Shift. *ACS Med. Chem. Lett.* **2018**, *9*, 546–551. [CrossRef] [PubMed]
76. National Center for Biotechnology Information (2024). PubChem Bioassay Record for AID 1699, S.T.S.R.I.M.S.C.R.D., 2024. Available online: https://pubchem.ncbi.nlm.nih.gov/bioassay/1699 (accessed on 25 February 2025).
77. Xu, P.; Shen, P.; Yu, B.; Xu, X.; Ge, R.; Cheng, X.; Chen, Q.; Bian, J.; Li, Z.; Wang, J. Janus kinases (JAKs): The efficient therapeutic targets for autoimmune diseases and myeloproliferative disorders. *Eur. J. Med. Chem.* **2020**, *192*, 112155. [CrossRef]

78. Belanger, D.B.; Williams, M.J.; Curran, P.J.; Mandal, A.K.; Meng, Z.; Rainka, M.P.; Yu, T.; Shih, N.Y.; Siddiqui, M.A.; Liu, M.; et al. Discovery of orally bioavailable imidazo[1,2-a]pyrazine-based Aurora kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 6739–6743. [CrossRef]
79. Siu, T.; Kozina, E.S.; Jung, J.; Rosenstein, C.; Mathur, A.; Altman, M.D.; Chan, G.; Xu, L.; Bachman, E.; Mo, J.R.; et al. The discovery of tricyclic pyridone JAK2 inhibitors. Part 1: Hit to lead. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7421–7425. [CrossRef] [PubMed]
80. Wityak, J.; Das, J.; Moquin, R.V.; Shen, Z.; Lin, J.; Chen, P.; Doweyko, A.M.; Pitt, S.; Pang, S.; Shen, D.R.; et al. Discovery and initial SAR of 2-amino-5-carboxamidothiazoles as inhibitors of the Src-family kinase p56(Lck). *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4007–4010. [CrossRef]
81. Ma, H.; Filip, S.V.; Stent, M.A.H.; Dolan, J.A.; Dietrich, B. JAK3 Inhibitors for the Treatment of Autoimmune and Inflammatory Disorders. U.S. Patent 8592415-B2, 26 November 2013.
82. Ren, X.; Duan, L.; He, Q.; Zhang, Z.; Zhou, Y.; Wu, D.; Pan, J.; Pei, D.; Ding, K. Identification of Niclosamide as a New Small-Molecule Inhibitor of the STAT3 Signaling Pathway. *ACS Med. Chem. Lett.* **2010**, *1*, 454–459. [CrossRef]
83. Flanagan, M.E.; Blumenkopf, T.A.; Brissette, W.H.; Brown, M.F.; Casavant, J.M.; Shang-Poa, C.; Doty, J.L.; Elliott, E.A.; Fisher, M.B.; Hines, M.; et al. Discovery of CP-690,550: A potent and selective Janus kinase (JAK) inhibitor for the treatment of autoimmune diseases and organ transplant rejection. *J. Med. Chem.* **2010**, *53*, 8468–8484. [CrossRef]
84. Ioannidis, S.; Lamb, M.L.; Wang, T.; Almeida, L.; Block, M.H.; Davies, A.M.; Peng, B.; Su, M.; Zhang, H.J.; Hoffmann, E.; et al. Discovery of 5-chloro-N^2-[(1*S*)-1-(5-fluoropyrimidin-2-yl)ethyl]-N^4-(5-methyl-1*H*-pyrazol-3-yl)pyrimidine-2,4-diamine (AZD1480) as a novel inhibitor of the Jak/Stat pathway. *J. Med. Chem.* **2011**, *54*, 262–276. [CrossRef]
85. McDonnell, M.E.; Bian, H.; Wrobel, J.; Smith, G.R.; Liang, S.; Ma, H.; Reitz, A.B. Anilino-monoindolylmaleimides as potent and selective JAK3 inhibitors. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1116–1121. [CrossRef]
86. Harikrishnan, L.S.; Kamau, M.G.; Wan, H.; Inghrim, J.A.; Zimmermann, K.; Sang, X.; Mastalerz, H.A.; Johnson, W.L.; Zhang, G.; Lombardo, L.J.; et al. Pyrrolo[1,2-*f*]triazines as JAK2 inhibitors: Achieving potency and selectivity for JAK2 over JAK3. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1425–1428. [CrossRef]
87. Kim, M.H.; Kim, M.; Yu, H.; Kim, H.; Yoo, K.H.; Sim, T.; Hah, J.M. Structure based design and syntheses of amino-1H-pyrazole amide derivatives as selective Raf kinase inhibitors in melanoma cells. *Bioorg. Med. Chem.* **2011**, *19*, 1915–1923. [CrossRef]
88. Medina, J.R.; Blackledge, C.W.; Heerding, D.A.; Campobasso, N.; Ward, P.; Briand, J.; Wright, L.; Axten, J.M. Aminoindazole PDK1 Inhibitors: A Case Study in Fragment-Based Drug Discovery. *ACS Med. Chem. Lett.* **2010**, *1*, 439–442. [CrossRef] [PubMed]
89. Wang, T.; Ioannidis, S.; Almeida, L.; Block, M.H.; Davies, A.M.; Lamb, M.L.; Scott, D.A.; Su, M.; Zhang, H.J.; Alimzhanov, M.; et al. In vitro and in vivo evaluation of 6-aminopyrazolyl-pyridine-3-carbonitriles as JAK2 kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2958–2961. [CrossRef]
90. Thomas, M.; Huang, W.S.; Wen, D.; Zhu, X.; Wang, Y.; Metcalf, C.A.; Liu, S.; Chen, I.; Romero, J.; Zou, D.; et al. Discovery of 5-(arenethynyl) hetero-monocyclic derivatives as potent inhibitors of BCR-ABL including the T315I gatekeeper mutant. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3743–3748. [CrossRef] [PubMed]
91. Shu, L.; Chen, C.; Huan, X.; Huang, H.; Wang, M.; Zhang, J.; Yan, Y.; Liu, J.; Zhang, T.; Zhang, D. Design, synthesis, and pharmacological evaluation of 4- or 6-phenyl-pyrimidine derivatives as novel and selective Janus kinase 3 inhibitors. *Eur. J. Med. Chem.* **2020**, *191*, 112148. [CrossRef] [PubMed]
92. Qiu, Q.; Chi, F.; Zhou, D.; Xie, Z.; Liu, Y.; Wu, H.; Yin, Z.; Shi, W.; Qian, H. Exploration of Janus Kinase (JAK) and Histone Deacetylase (HDAC) Bispecific Inhibitors Based on the Moiety of Fedratinib for Treatment of Both Hematologic Malignancies and Solid Cancers. *J. Med. Chem.* **2023**, *66*, 5753–5773. [CrossRef]
93. Lim, J.; Taoka, B.; Otte, R.D.; Spencer, K.; Dinsmore, C.J.; Altman, M.D.; Chan, G.; Rosenstein, C.; Sharma, S.; Su, H.P.; et al. Discovery of 1-amino-5H-pyrido[4,3-b]indol-4-carboxamide inhibitors of Janus kinase 2 (JAK2) for the treatment of myeloproliferative disorders. *J. Med. Chem.* **2011**, *54*, 7334–7349. [CrossRef]
94. Giraud, F.; Marchand, P.; Carbonnelle, D.; Sartor, M.; Lang, F.; Duflos, M. Synthesis of N-aryl-3-(indol-3-yl)propanamides and their immunosuppressive activities. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 5203–5206. [CrossRef]
95. Gao, C.; Cahya, S.; Nicolaou, C.A.; Wang, J.; Watson, I.A.; Cummins, D.J.; Iversen, P.W.; Vieth, M. Selectivity data: Assessment, predictions, concordance, and implications. *J. Med. Chem.* **2013**, *56*, 6991–7002. [CrossRef] [PubMed]
96. Liosi, M.E.; Krimmer, S.G.; Newton, A.S.; Dawson, T.K.; Puleo, D.E.; Cutrona, K.J.; Suzuki, Y.; Schlessinger, J.; Jorgensen, W.L. Selective Janus Kinase 2 (JAK2) Pseudokinase Ligands with a Diaminotriazole Core. *J. Med. Chem.* **2020**, *63*, 5324–5340. [CrossRef] [PubMed]
97. Poulsen, A.; Blanchard, S.; Soh, C.K.; Lee, C.; Williams, M.; Wang, H.; Dymock, B. Structure-based design of PDK1 inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 305–307. [CrossRef] [PubMed]
98. Zificsak, C.A.; Gingrich, D.E.; Breslin, H.J.; Dunn, D.D.; Milkiewicz, K.L.; Theroff, J.P.; Thieu, T.V.; Underiner, T.L.; Weinberg, L.R.; Aimone, L.D.; et al. Optimization of a novel kinase inhibitor scaffold for the dual inhibition of JAK2 and FAK kinases. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 133–137. [CrossRef]

99. Schenkel, L.B.; Huang, X.; Cheng, A.; Deak, H.L.; Doherty, E.; Emkey, R.; Gu, Y.; Gunaydin, H.; Kim, J.L.; Lee, J.; et al. Discovery of potent and highly selective thienopyridine Janus kinase 2 inhibitors. *J. Med. Chem.* **2011**, *54*, 8440–8450. [CrossRef]
100. Sonawane, Y.A.; Taylor, M.A.; Napoleon, J.V.; Rana, S.; Contreras, J.I.; Natarajan, A. Cyclin Dependent Kinase 9 Inhibitors for Cancer Therapy. *J. Med. Chem.* **2016**, *59*, 8667–8684. [CrossRef]
101. William, A.D.; Lee, A.C.; Goh, K.C.; Blanchard, S.; Poulsen, A.; Teo, E.L.; Nagaraj, H.; Lee, C.P.; Wang, H.; Williams, M.; et al. Discovery of kinase spectrum selective macrocycle (16*E*)-14-methyl-20-oxa-5,7,14,26-tetraazatetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8(27),9,11,16,21,23-decaene (SB1317/TG02), a potent inhibitor of cyclin dependent kinases (CDKs), Janus kinase 2 (JAK2), and fms-like tyrosine kinase-3 (FLT3) for the treatment of cancer. *J. Med. Chem.* **2012**, *55*, 169–196. [CrossRef]
102. Menichincheri, M.; Ardini, E.; Magnaghi, P.; Avanzi, N.; Banfi, P.; Bossi, R.; Buffa, L.; Canevari, G.; Ceriani, L.; Colombo, M.; et al. Discovery of Entrectinib: A New 3-Aminoindazole As a Potent Anaplastic Lymphoma Kinase (ALK), c-ros Oncogene 1 Kinase (ROS1), and Pan-Tropomyosin Receptor Kinases (Pan-TRKs) inhibitor. *J. Med. Chem.* **2016**, *59*, 3392–3408. [CrossRef]
103. Liu, Z.; Wang, P.; Chen, H.; Wold, E.A.; Tian, B.; Brasier, A.R.; Zhou, J. Drug Discovery Targeting Bromodomain-Containing Protein 4. *J. Med. Chem.* **2017**, *60*, 4533–4558. [CrossRef]
104. Hoemann, M.; Wilson, N.; Argiriadi, M.; Banach, D.; Burchat, A.; Calderwood, D.; Clapham, B.; Cox, P.; Duignan, D.B.; Konopacki, D.; et al. Synthesis and optimization of furano[3,2-d]pyrimidines as selective spleen tyrosine kinase (Syk) inhibitors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5562–5567. [CrossRef]
105. Oza, V.; Ashwell, S.; Brassil, P.; Breed, J.; Ezhuthachan, J.; Deng, C.; Grondine, M.; Horn, C.; Liu, D.; Lyne, P.; et al. Synthesis and evaluation of triazolones as checkpoint kinase 1 inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2330–2337. [CrossRef] [PubMed]
106. Yang, E.G.; Mustafa, N.; Tan, E.C.; Poulsen, A.; Ramanujulu, P.M.; Chng, W.J.; Yen, J.J.; Dymock, B.W. Design and Synthesis of Janus Kinase 2 (JAK2) and Histone Deacetlyase (HDAC) Bispecific Inhibitors Based on Pacritinib and Evidence of Dual Pathway Inhibition in Hematological Cell Lines. *J. Med. Chem.* **2016**, *59*, 8233–8262. [CrossRef]
107. Dugan, B.J.; Gingrich, D.E.; Mesaros, E.F.; Milkiewicz, K.L.; Curry, M.A.; Zulli, A.L.; Dobrzanski, P.; Serdikoff, C.; Jan, M.; Angeles, T.S.; et al. A selective, orally bioavailable 1,2,4-triazolo[1,5-a]pyridine-based inhibitor of Janus kinase 2 for use in anticancer therapy: Discovery of CEP-33779. *J. Med. Chem.* **2012**, *55*, 5243–5254. [CrossRef]
108. Mitton-Fry, M.J.; Berlinski, P.J.; Birchmeier, M.J.; Bowman, J.W.; Gonzales, A.J.; Kamerling, S.G.; Mann, D.W. Pyrrolo[2,3-d]pyrimidine Compounds. U.S. Patent US-9161939-B2, 20 October 2015.
109. Yogo, T.; Nagamiya, H.; Seto, M.; Sasaki, S.; Shih-Chung, H.; Ohba, Y.; Tokunaga, N.; Lee, G.N.; Rhim, C.Y.; Yoon, C.H.; et al. Structure-Based Design and Synthesis of 3-Amino-1,5-dihydro-4*H*-pyrazolopyridin-4-one Derivatives as Tyrosine Kinase 2 Inhibitors. *J. Med. Chem.* **2016**, *59*, 733–749. [CrossRef] [PubMed]
110. Kim, M.K.; Shin, H.; Park, K.S.; Kim, H.; Park, J.; Kim, K.; Nam, J.; Choo, H.; Chong, Y. Benzimidazole Derivatives as Potent JAK1-Selective Inhibitors. *J. Med. Chem.* **2015**, *58*, 7596–7602. [CrossRef]
111. Chen, X.; Wilson, L.J.; Malaviya, R.; Argentieri, R.L.; Yang, S.M. Virtual screening to successfully identify novel janus kinase 3 inhibitors: A sequential focused screening approach. *J. Med. Chem.* **2008**, *51*, 7015–7019. [CrossRef] [PubMed]
112. Fedorov, O.; Marsden, B.; Pogacic, V.; Rellos, P.; Müller, S.; Bullock, A.N.; Schwaller, J.; Sundström, M.; Knapp, S. A systematic interaction map of validated kinase inhibitors with Ser/Thr kinases. *Proc. Natl. Acad. Sci. USA* **2007**, *104*, 20523–20528. [CrossRef]
113. DiMauro, E.F.; Newcomb, J.; Nunes, J.J.; Bemis, J.E.; Boucher, C.; Buchanan, J.L.; Buckner, W.H.; Cee, V.J.; Chai, L.; Deak, H.L.; et al. Discovery of aminoquinazolines as potent, orally bioavailable inhibitors of Lck: Synthesis, SAR, and in vivo anti-inflammatory activity. *J. Med. Chem.* **2006**, *49*, 5671–5686. [CrossRef]
114. Wang, T.; Lamb, M.L.; Block, M.H.; Davies, A.M.; Han, Y.; Hoffmann, E.; Ioannidis, S.; Josey, J.A.; Liu, Z.Y.; Lyne, P.D.; et al. Discovery of Disubstituted Imidazo[4,5-*b*]pyridines and Purines as Potent TrkA Inhibitors. *ACS Med. Chem. Lett.* **2012**, *3*, 705–709. [CrossRef]
115. Liu, M.; Ju, X.; Zou, J.; Shi, J.; Jia, G. Recent researches for dual Aurora target inhibitors in antitumor field. *Eur. J. Med. Chem.* **2020**, *203*, 112498. [CrossRef]
116. Lawrence, H.R.; Martin, M.P.; Luo, Y.; Pireddu, R.; Yang, H.; Gevariya, H.; Ozcan, S.; Zhu, J.Y.; Kendig, R.; Rodriguez, M.; et al. Development of o-chlorophenyl substituted pyrimidines as exceptionally potent aurora kinase inhibitors. *J. Med. Chem.* **2012**, *55*, 7392–7416. [CrossRef]
117. Hanan, E.J.; van Abbema, A.; Barrett, K.; Blair, W.S.; Blaney, J.; Chang, C.; Eigenbrot, C.; Flynn, S.; Gibbons, P.; Hurley, C.A.; et al. Discovery of potent and selective pyrazolopyrimidine janus kinase 2 inhibitors. *J. Med. Chem.* **2012**, *55*, 10090–10107. [CrossRef] [PubMed]
118. William, A.D.; Lee, A.C.; Blanchard, S.; Poulsen, A.; Teo, E.L.; Nagaraj, H.; Tan, E.; Chen, D.; Williams, M.; Sun, E.T.; et al. Discovery of the macrocycle 11-(2-pyrrolidin-1-yl-ethoxy)-14,19-dioxa-5,7,26-triaza-tetracyclo[19.3.1.1(2,6).1(8,12)]heptacosa-1(25),2(26),3,5,8,10,12(27),16,21,23-decaene (SB1518), a potent Janus kinase 2/fms-like tyrosine kinase-3 (JAK2/FLT3) inhibitor for the treatment of myelofibrosis and lymphoma. *J. Med. Chem.* **2011**, *54*, 4638–4658. [CrossRef] [PubMed]

119. Forsyth, T.; Kearney, P.C.; Kim, B.G.; Johnson, H.W.; Aay, N.; Arcalas, A.; Brown, D.S.; Chan, V.; Chen, J.; Du, H.; et al. SAR and in vivo evaluation of 4-aryl-2-aminoalkylpyrimidines as potent and selective Janus kinase 2 (JAK2) inhibitors. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 7653–7658. [CrossRef]
120. Chen, J.J.; Thakur, K.D.; Clark, M.P.; Laughlin, S.K.; George, K.M.; Bookland, R.G.; Davis, J.R.; Cabrera, E.J.; Easwaran, V.; De, B.; et al. Development of pyrimidine-based inhibitors of Janus tyrosine kinase 3. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5633–5638. [CrossRef]
121. Liang, X.; Huang, Y.; Zang, J.; Gao, Q.; Wang, B.; Xu, W.; Zhang, Y. Design, synthesis and preliminary biological evaluation of 4-aminopyrazole derivatives as novel and potent JAKs inhibitors. *Bioorg. Med. Chem.* **2016**, *24*, 2660–2672. [CrossRef]
122. Yu, R.N.; Chen, C.J.; Shu, L.; Yin, Y.; Wang, Z.J.; Zhang, T.T.; Zhang, D.Y. Structure-based design and synthesis of pyrimidine-4,6-diamine derivatives as Janus kinase 3 inhibitors. *Bioorg. Med. Chem.* **2019**, *27*, 1646–1657. [CrossRef] [PubMed]
123. Elsayed, M.S.A.; Nielsen, J.J.; Park, S.; Park, J.; Liu, Q.; Kim, C.H.; Pommier, Y.; Agama, K.; Low, P.S.; Cushman, M. Application of Sequential Palladium Catalysis for the Discovery of Janus Kinase Inhibitors in the Benzo[c]pyrrolo[2,3- h][1,6]naphthyridin-5-one (BPN) Series. *J. Med. Chem.* **2018**, *61*, 10440–10462. [CrossRef]
124. Uckun, F.M.; Dibirdik, I.; Qazi, S.; Vassilev, A.; Ma, H.; Mao, C.; Benyumov, A.; Emami, K.H. Anti-breast cancer activity of LFM-A13, a potent inhibitor of Polo-like kinase (PLK). *Bioorg. Med. Chem.* **2007**, *15*, 800–814. [CrossRef]
125. Van Epps, S.; Fiamengo, B.; Edmunds, J.; Ericsson, A.; Frank, K.; Friedman, M.; George, D.; George, J.; Goedken, E.; Kotecki, B.; et al. Design and synthesis of tricyclic cores for kinase inhibition. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 693–698. [CrossRef]
126. Soth, M.; Hermann, J.C.; Yee, C.; Alam, M.; Barnett, J.W.; Berry, P.; Browner, M.F.; Frank, K.; Frauchiger, S.; Harris, S.; et al. 3-Amido pyrrolopyrazine JAK kinase inhibitors: Development of a JAK3 vs JAK1 selective inhibitor and evaluation in cellular and in vivo models. *J. Med. Chem.* **2013**, *56*, 345–356. [CrossRef] [PubMed]
127. Yang, S.M.; Malaviya, R.; Wilson, L.J.; Argentieri, R.; Chen, X.; Yang, C.; Wang, B.; Cavender, D.; Murray, W.V. Simplified staurosporine analogs as potent JAK3 inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 326–331. [CrossRef]
128. Lynch, S.M.; DeVicente, J.; Hermann, J.C.; Jaime-Figueroa, S.; Jin, S.; Kuglstatter, A.; Li, H.; Lovey, A.; Menke, J.; Niu, L.; et al. Strategic use of conformational bias and structure based design to identify potent JAK3 inhibitors with improved selectivity against the JAK family and the kinome. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 2793–2800. [CrossRef]
129. Guan, H.; Lamb, M.L.; Peng, B.; Huang, S.; Degrace, N.; Read, J.; Hussain, S.; Wu, J.; Rivard, C.; Alimzhanov, M.; et al. Discovery of novel Jak2-Stat pathway inhibitors with extended residence time on target. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 3105–3110. [CrossRef] [PubMed]
130. Marsilje, T.H.; Pei, W.; Chen, B.; Lu, W.; Uno, T.; Jin, Y.; Jiang, T.; Kim, S.; Li, N.; Warmuth, M.; et al. Synthesis, structure-activity relationships, and in vivo efficacy of the novel potent and selective anaplastic lymphoma kinase (ALK) inhibitor 5-chloro-N2-(2-isopropoxy-5-methyl-4-(piperidin-4-yl)phenyl)-N4-(2-(isopropylsulfonyl)phenyl)pyrimidine-2,4-diamine (LDK378) currently in phase 1 and phase 2 clinical trials. *J. Med. Chem.* **2013**, *56*, 5675–5690. [CrossRef]
131. Martin, M.W.; Newcomb, J.; Nunes, J.J.; Bemis, J.E.; McGowan, D.C.; White, R.D.; Buchanan, J.L.; DiMauro, E.F.; Boucher, C.; Faust, T.; et al. Discovery of novel 2,3-diarylfuro[2,3-*b*]pyridin-4-amines as potent and selective inhibitors of Lck: Synthesis, SAR, and pharmacokinetic properties. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2299–2304. [CrossRef]
132. Siu, M.; Pastor, R.; Liu, W.; Barrett, K.; Berry, M.; Blair, W.S.; Chang, C.; Chen, J.Z.; Eigenbrot, C.; Ghilardi, N.; et al. 2-Amino-[1,2,4]triazolo[1,5-*a*]pyridines as JAK2 inhibitors. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5014–5021. [CrossRef]
133. Brasca, M.G.; Mantegani, S.; Amboldi, N.; Bindi, S.; Caronni, D.; Casale, E.; Ceccarelli, W.; Colombo, N.; De Ponti, A.; Donati, D.; et al. Discovery of NMS-E973 as novel, selective and potent inhibitor of heat shock protein 90 (Hsp90). *Bioorg. Med. Chem.* **2013**, *21*, 7047–7063. [CrossRef] [PubMed]
134. DiMauro, E.F.; Newcomb, J.; Nunes, J.J.; Bemis, J.E.; Boucher, C.; Buchanan, J.L.; Buckner, W.H.; Cheng, A.; Faust, T.; Hsieh, F.; et al. Discovery of 4-amino-5,6-biaryl-furo[2,3-*d*]pyrimidines as inhibitors of Lck: Development of an expedient and divergent synthetic route and preliminary SAR. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2305–2309. [CrossRef]
135. Côté, B.; Boulet, L.; Brideau, C.; Claveau, D.; Ethier, D.; Frenette, R.; Gagnon, M.; Giroux, A.; Guay, J.; Guiral, S.; et al. Substituted phenanthrene imidazoles as potent, selective, and orally active mPGES-1 inhibitors. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6816–6820. [CrossRef]
136. Seerden, J.P.; Leusink-Ionescu, G.; Woudenberg-Vrenken, T.; Dros, B.; Molema, G.; Kamps, J.A.; Kellogg, R.M. Synthesis and structure-activity relationships of 4-fluorophenyl-imidazole p38α MAPK, CK1δ and JAK2 kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3412–3418. [CrossRef]
137. Zhong, Y.; Qiu, R.Z.; Sun, S.L.; Zhao, C.; Fan, T.Y.; Chen, M.; Li, N.G.; Shi, Z.H. Small-Molecule Fms-like Tyrosine Kinase 3 Inhibitors: An Attractive and Efficient Method for the Treatment of Acute Myeloid Leukemia. *J. Med. Chem.* **2020**, *63*, 12403–12428. [CrossRef]
138. Zhao, H.; Caflisch, A. Discovery of ZAP70 inhibitors by high-throughput docking into a conformation of its kinase domain generated by molecular dynamics. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5721–5726. [CrossRef] [PubMed]

139. Su, Q.; Ioannidis, S.; Chuaqui, C.; Almeida, L.; Alimzhanov, M.; Bebernitz, G.; Bell, K.; Block, M.; Howard, T.; Huang, S.; et al. Discovery of 1-methyl-1H-imidazole derivatives as potent Jak2 inhibitors. *J. Med. Chem.* **2014**, *57*, 144–158. [CrossRef] [PubMed]
140. Siu, T.; Kumarasinghe, S.E.; Altman, M.D.; Katcher, M.; Northrup, A.; White, C.; Rosenstein, C.; Mathur, A.; Xu, L.; Chan, G.; et al. The discovery of reverse tricyclic pyridone JAK2 inhibitors. Part 2: Lead optimization. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1466–1471. [CrossRef] [PubMed]
141. Huang, Q.; Johnson, T.W.; Bailey, S.; Brooun, A.; Bunker, K.D.; Burke, B.J.; Collins, M.R.; Cook, A.S.; Cui, J.J.; Dack, K.N.; et al. Design of potent and selective inhibitors to overcome clinical anaplastic lymphoma kinase mutations resistant to crizotinib. *J. Med. Chem.* **2014**, *57*, 1170–1187. [CrossRef]
142. Shen, P.; Wang, Y.; Jia, X.; Xu, P.; Qin, L.; Feng, X.; Li, Z.; Qiu, Z. Dual-target Janus kinase (JAK) inhibitors: Comprehensive review on the JAK-based strategies for treating solid or hematological malignancies and immune-related diseases. *Eur. J. Med. Chem.* **2022**, *239*, 114551. [CrossRef]
143. Wang, S.; Zhang, R.H.; Zhang, H.; Wang, Y.C.; Yang, D.; Zhao, Y.L.; Yan, G.Y.; Xu, G.B.; Guan, H.Y.; Zhou, Y.H.; et al. Design, synthesis, and biological evaluation of 2,4-diamino pyrimidine derivatives as potent FAK inhibitors with anti-cancer and anti-angiogenesis activities. *Eur. J. Med. Chem.* **2021**, *222*, 113573. [CrossRef]
144. Haidle, A.M.; Zabierek, A.A.; Childers, K.K.; Rosenstein, C.; Mathur, A.; Altman, M.D.; Chan, G.; Xu, L.; Bachman, E.; Mo, J.R.; et al. Thiophene carboxamide inhibitors of JAK2 as potential treatments for myleoproliferative neoplasms. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1968–1973. [CrossRef]
145. Costales, A.; Mathur, M.; Ramurthy, S.; Lan, J.; Subramanian, S.; Jain, R.; Atallah, G.; Setti, L.; Lindvall, M.; Appleton, B.A.; et al. 2-Amino-7-substituted benzoxazole analogs as potent RSK2 inhibitors. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 1592–1596. [CrossRef]
146. Park, E.; Lee, S.J.; Moon, H.; Park, J.; Jeon, H.; Hwang, J.S.; Hwang, H.; Hong, K.B.; Han, S.H.; Choi, S.; et al. Discovery and Biological Evaluation of. *J. Med. Chem.* **2021**, *64*, 958–979. [CrossRef] [PubMed]
147. Ren, J.; Shi, W.; Zhao, D.; Wang, Q.; Chang, X.; He, X.; Wang, X.; Gao, Y.; Lu, P.; Zhang, X.; et al. Design and synthesis of boron-containing diphenylpyrimidines as potent BTK and JAK3 dual inhibitors. *Bioorg. Med. Chem.* **2020**, *28*, 115236. [CrossRef]
148. Brasca, M.G.; Nesi, M.; Avanzi, N.; Ballinari, D.; Bandiera, T.; Bertrand, J.; Bindi, S.; Canevari, G.; Carenzi, D.; Casero, D.; et al. Pyrrole-3-carboxamides as potent and selective JAK2 inhibitors. *Bioorg. Med. Chem.* **2014**, *22*, 4998–5012. [CrossRef] [PubMed]
149. Hanan, E.J.; Eigenbrot, C.; Bryan, M.C.; Burdick, D.J.; Chan, B.K.; Chen, Y.; Dotson, J.; Heald, R.A.; Jackson, P.S.; La, H.; et al. Discovery of selective and noncovalent diaminopyrimidine-based inhibitors of epidermal growth factor receptor containing the T790M resistance mutation. *J. Med. Chem.* **2014**, *57*, 10176–10191. [CrossRef]
150. Goodwin, N.C.; Cianchetta, G.; Burgoon, H.A.; Healy, J.; Mabon, R.; Strobel, E.D.; Allen, J.; Wang, S.; Hamman, B.D.; Rawlins, D.B. Discovery of a Type III Inhibitor of LIM Kinase 2 That Binds in a DFG-Out Conformation. *ACS Med. Chem. Lett.* **2015**, *6*, 53–57. [CrossRef]
151. Duan, J.J.; Lu, Z.; Jiang, B.; Yang, B.V.; Doweyko, L.M.; Nirschl, D.S.; Haque, L.E.; Lin, S.; Brown, G.; Hynes, J.; et al. Discovery of pyrrolo[1,2-b]pyridazine-3-carboxamides as Janus kinase (JAK) inhibitors. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 5721–5726. [CrossRef] [PubMed]
152. Henderson, J.L.; Kormos, B.L.; Hayward, M.M.; Coffman, K.J.; Jasti, J.; Kurumbail, R.G.; Wager, T.T.; Verhoest, P.R.; Noell, G.S.; Chen, Y.; et al. Discovery and preclinical profiling of 3-[4-(morpholin-4-yl)-7H-pyrrolo[2,3-d]pyrimidin-5-yl]benzonitrile (PF-06447475), a highly potent, selective, brain penetrant, and in vivo active LRRK2 kinase inhibitor. *J. Med. Chem.* **2015**, *58*, 419–432. [CrossRef]
153. Brasca, M.G.; Gnocchi, P.; Nesi, M.; Amboldi, N.; Avanzi, N.; Bertrand, J.; Bindi, S.; Canevari, G.; Casero, D.; Ciomei, M.; et al. Novel pyrrole carboxamide inhibitors of JAK2 as potential treatment of myeloproliferative disorders. *Bioorg. Med. Chem.* **2015**, *23*, 2387–2407. [CrossRef]
154. Wan, H.; Schroeder, G.M.; Hart, A.C.; Inghrim, J.; Grebinski, J.; Tokarski, J.S.; Lorenzi, M.V.; You, D.; Mcdevitt, T.; Penhallow, B.; et al. Discovery of a Highly Selective JAK2 Inhibitor, BMS-911543, for the Treatment of Myeloproliferative Neoplasms. *ACS Med. Chem. Lett.* **2015**, *6*, 850–855. [CrossRef]
155. Zimmermann, K.; Sang, X.; Mastalerz, H.A.; Johnson, W.L.; Zhang, G.; Liu, Q.; Batt, D.; Lombardo, L.J.; Vyas, D.; Trainor, G.L.; et al. 9H-Carbazole-1-carboxamides as potent and selective JAK2 inhibitors. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 2809–2812. [CrossRef]
156. Yamagishi, H.; Shirakami, S.; Nakajima, Y.; Tanaka, A.; Takahashi, F.; Hamaguchi, H.; Hatanaka, K.; Moritomo, A.; Inami, M.; Higashi, Y.; et al. Discovery of 3,6-dihydroimidazo[4,5-d]pyrrolo[2,3-b]pyridin-2(1H)-one derivatives as novel JAK inhibitors. *Bioorg. Med. Chem.* **2015**, *23*, 4846–4859. [CrossRef] [PubMed]
157. Nakajima, Y.; Inoue, T.; Nakai, K.; Mukoyoshi, K.; Hamaguchi, H.; Hatanaka, K.; Sasaki, H.; Tanaka, A.; Takahashi, F.; Kunikawa, S.; et al. Synthesis and evaluation of novel 1H-pyrrolo[2,3-b]pyridine-5-carboxamide derivatives as potent and orally efficacious immunomodulators targeting JAK3. *Bioorg. Med. Chem.* **2015**, *23*, 4871–4883. [CrossRef] [PubMed]
158. Jang, W.D.; Kim, J.T.; Son, H.Y.; Park, S.Y.; Cho, Y.S.; Koo, T.S.; Lee, H.; Kang, N.S. Discovery of Tyk2 inhibitors via the virtual site-directed fragment-based drug design. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3947–3952. [CrossRef]

159. Liu, Q.; Batt, D.G.; Lippy, J.S.; Surti, N.; Tebben, A.J.; Muckelbauer, J.K.; Chen, L.; An, Y.; Chang, C.; Pokross, M.; et al. Design and synthesis of carbazole carboxamides as promising inhibitors of Bruton's tyrosine kinase (BTK) and Janus kinase 2 (JAK2). *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4265–4269. [CrossRef]
160. Hart, A.C.; Schroeder, G.M.; Wan, H.; Grebinski, J.; Inghrim, J.; Kempson, J.; Guo, J.; Pitts, W.J.; Tokarski, J.S.; Sack, J.S.; et al. Structure-Based Design of Selective Janus Kinase 2 Imidazo[4,5-d]pyrrolo[2,3-b]pyridine Inhibitors. *ACS Med. Chem. Lett.* **2015**, *6*, 845–849. [CrossRef]
161. Gehringer, M.; Laufer, S.A. Emerging and Re-Emerging Warheads for Targeted Covalent Inhibitors: Applications in Medicinal Chemistry and Chemical Biology. *J. Med. Chem.* **2019**, *62*, 5673–5724. [CrossRef]
162. ChEMBL Database, EMBL-EBI (2024). ChEMBL Document: Affinity Phenotypic Cellular Literature for EUbOPEN Chemogenomic Library (CHEMBL5444388)-ChEMBL(20 January 2022). Available online: https://www.ebi.ac.uk/chembl/explore/document/CHEMBL5444388 (accessed on 25 February 2025).
163. Choi, J.S.; Hwang, H.J.; Kim, S.W.; Lee, B.I.; Lee, J.; Song, H.J.; Koh, J.S.; Kim, J.H.; Lee, P.H. Highly potent and selective pyrazolylpyrimidines as Syk kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4441–4446. [CrossRef]
164. Curry, M.A.; Dorsey, B.D.; Dugan, B.J.; Gingrich, D.E.; Mesaros, E.F.; Milkiewicz, K.L. Preparation and Uses of 1,2,4-triazolo[1,5a]pyridine Derivatives. U.S. Patent US-8633173-B2, 21 January 2014.
165. Jones, P.; Storer, R.I.; Sabnis, Y.A.; Wakenhut, F.M.; Whitlock, G.A.; England, K.S.; Mukaiyama, T.; Dehnhardt, C.M.; Coe, J.W.; Kortum, S.W.; et al. Design and Synthesis of a Pan-Janus Kinase Inhibitor Clinical Candidate (PF-06263276) Suitable for Inhaled and Topical Delivery for the Treatment of Inflammatory Diseases of the Lungs and Skin. *J. Med. Chem.* **2017**, *60*, 767–786. [CrossRef]
166. Casimiro-Garcia, A.; Trujillo, J.I.; Vajdos, F.; Juba, B.; Banker, M.E.; Aulabaugh, A.; Balbo, P.; Bauman, J.; Chrencik, J.; Coe, J.W.; et al. Identification of Cyanamide-Based Janus Kinase 3 (JAK3) Covalent Inhibitors. *J. Med. Chem.* **2018**, *61*, 10665–10699. [CrossRef] [PubMed]
167. Bauer, S.M.; Jia, Z.J.; Mehrotra, M.; Song, Y.; Xu, Q.; Huang, W.; Venkataramani, C.; Rose, J.W.; Pandey, A. Inhibitors of Syk and/or JAK Kinase. U.S. Patent US-8501944-B2, 6 August 2013.
168. Purandare, A.V.; Batt, D.G.; Liu, Q.; Johnson, W.L.; Mastalerz, H.; Zhang, G.; Zimmermann, K. Carbazole and Carboline Kinase Inhibitors. U.S. Patent US-8815840-B2, 26 August 2014.
169. Woo, H.C.; Cash, B.; Ahearn, S.P.; Dinsmore, C.; Jung, J.; Pu, Q.; Rivkin, A.; Scott, M.E.; Witter, D.J.; Woo, H.C.; et al. Pyrrolopyrimidines as Janus Kinase Inhibitors. U.S. Patent US-8993756-B2, 31 March 2015.
170. Forster, M.; Gehringer, M.; Laufer, S.A. Recent advances in JAK3 inhibition: Isoform selectivity by covalent cysteine targeting. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4229–4237. [CrossRef]
171. Promo, M.A.; Xie, J.; Acker, B.A.; Hartmann, S.J.; Wolfson, S.G.; Huang, H.-C.; Jacobsen, E.J. Pyrrolo[2,3-d]pyrimidine Compounds as Janus Kinase Inhibitors. U.S. Patent US-8633206-B2, 21 January 2014.
172. Brown, M.F.; Fenwick, A.E.; Flanagan, M.E.; Gonzales, A.; Johnson, T.A.; Kaila, N.; Mitton-Fry, M.J.; Strohbach, J.W.; TenBrink, R.E.; Trzupek, J.D.; et al. Pyrrolo[2,3-D]pyrimidine Derivatives. U.S. Patent US-9035074-B2, 19 May 2015.
173. McAllister, A.; Murone, M.; Sengupta, S.; Shetty, S.J. Bicyclic Compounds and Their Uses as Dual c-SRC/JAK Inhibitors. U.S. Patent US-8440679-B2, 21 May 2013.
174. Davies, A.; Ioannidis, S.; Lamb, M.; Su, M.; Wang, T.; Zhang, H. 9-(Pyrazol-3-yl)-9H-purine-2-amine and 3-(pyrazol-3-yl)-3H-imidazo[4,5-B] Pyridin-5-Amine Derivatives and Their Use for the Treatment of Cancer. U.S. Patent US8486966B2, 16 July 2013.
175. De Vicente Fidalgo, J.; Hermann, J.C.; Lemoine, R.; Li, H.; Lovey, A.J. Inhibitors of JAK for the Treatment of Autoimmune and Inflammatory Diseases. U.S. Patent US-8618103-B2, 31 December 2013. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-8618103-B2 (accessed on 25 February 2025).
176. Hynes, J.; Wu, H.; Kempson, J.; Duan, J.J.; Lu, Z.; Jiang, B.; Stachura, S.; Tokarski, J.S.; Sack, J.S.; Khan, J.A.; et al. Discovery of potent and efficacious pyrrolopyridazines as dual JAK1/3 inhibitors. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 3101–3106. [CrossRef] [PubMed]
177. Wrobleski, S.T.; Brown, G.D.; Doweyko, L.M.; Duan, J.; Guo, J. Pyrrolopyridazine JAK3 Inhibitors and Their Use for the Treatment of Inflammatory and Autoimmune Diseases. U.S. Patent US-8921368-B2, 30 December 2014.
178. Allen, S.; Andrews, S.W.; Condroski, K.R.; Haas, J.; Huang, L. Substituted Pyrazolo[1,5-a]pyrimidine Compounds as Trk Kinase Inhibitors. U.S. Patent US-8791123-B2, 29 July 2014.
179. Noji, S.; Shiozaki, M.; Miura, T.; Hara, Y.; Yamanaka, H.; Maeda, K.; Hori, A.; Inoue, M.; Hase, Y. Nitrogen-Containing Spirocyclic Compounds and Pharmaceutical Uses Thereof. U.S. Patent US-8609647-B2, 17 December 2013.
180. Combs, A.P.; Sparks, R.B.; Yue, E.W.T.; Feng, H.; Bower, M.J. Macrocyclic Compounds and Their Use as Kinase Inhibitors. U.S. Patent US8765727B2, 1 July 2014.
181. Brubaker, J.; Close, J.T.; Jung, J.; Martinez, M.; White, C. Acyclic Cyanoethylpyrazoles as Janus Kinase Inhibitors. U.S. Patent US9493441B2, 15 November 2016.

182. Hansen, B.B.; Jepsen, T.H.; Larsen, M.; Sindet, R.; Vifian, T.; Burhardt, M.N.; Larsen, J.; Seitzberg, J.G.; Carnerup, M.A.; Jerre, A.; et al. Fragment-Based Discovery of Pyrazolopyridones as JAK1 Inhibitors with Excellent Subtype Selectivity. *J. Med. Chem.* **2020**, *63*, 7008–7032. [CrossRef] [PubMed]
183. Vasbinder, M.M.; Alimzhanov, M.; Augustin, M.; Bebernitz, G.; Bell, K.; Chuaqui, C.; Deegan, T.; Ferguson, A.D.; Goodwin, K.; Huszar, D.; et al. Identification of azabenzimidazoles as potent JAK1 selective inhibitors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 60–67. [CrossRef]
184. Stauffer, F.; Cowan-Jacob, S.W.; Scheufler, C.; Furet, P. Identification of a 5-[3-phenyl-(2-cyclic-ether)-methylether]-4-aminopyrrolo[2,3-*d*]pyrimidine series of IGF-1R inhibitors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2065–2067. [CrossRef]
185. Wang, T.; Liu, X.; Hao, M.; Qiao, J.; Ju, C.; Xue, L.; Zhang, C. Design, synthesis and evaluation of pyrrolo[2,3-d]pyrimidine-phenylamide hybrids as potent Janus kinase 2 inhibitors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 2936–2941. [CrossRef]
186. Kim, H.; Kim, M.K.; Choo, H.; Chong, Y. Novel JAK1-selective benzimidazole inhibitors with enhanced membrane permeability. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3213–3215. [CrossRef]
187. Cee, V.J.; Albrecht, B.K.; Geuns-Meyer, S.; Hughes, P.; Bellon, S.; Bready, J.; Caenepeel, S.; Chaffee, S.C.; Coxon, A.; Emery, M.; et al. Alkynylpyrimidine amide derivatives as potent, selective, and orally active inhibitors of Tie-2 kinase. *J. Med. Chem.* **2007**, *50*, 627–640. [CrossRef]
188. Martin, M.W.; Newcomb, J.; Nunes, J.J.; McGowan, D.C.; Armistead, D.M.; Boucher, C.; Buchanan, J.L.; Buckner, W.; Chai, L.; Elbaum, D.; et al. Novel 2-aminopyrimidine carbamates as potent and orally active inhibitors of Lck: Synthesis, SAR, and in vivo antiinflammatory activity. *J. Med. Chem.* **2006**, *49*, 4981–4991. [CrossRef]
189. Phuangsawai, O.; Beswick, P.; Ratanabunyong, S.; Tabtimmai, L.; Suphakun, P.; Obounchoey, P.; Srisook, P.; Horata, N.; Chuckowree, I.; Hannongbua, S.; et al. Evaluation of the anti-malarial activity and cytotoxicity of 2,4-diamino-pyrimidine-based kinase inhibitors. *Eur. J. Med. Chem.* **2016**, *124*, 896–905. [CrossRef]
190. Hou, W.; Ren, Y.; Zhang, Z.; Sun, H.; Ma, Y.; Yan, B. Novel quinazoline derivatives bearing various 6-benzamide moieties as highly selective and potent EGFR inhibitors. *Bioorg. Med. Chem.* **2018**, *26*, 1740–1750. [CrossRef]
191. Narayan, S.; Ramisetti, S.; Jaiswal, A.S.; Law, B.K.; Singh-Pillay, A.; Singh, P.; Amin, S.; Sharma, A.K. ASR352, A potent anticancer agent: Synthesis, preliminary SAR, and biological activities against colorectal cancer bulk, 5-fluorouracil/oxaliplatin resistant and stem cells. *Eur. J. Med. Chem.* **2019**, *161*, 456–467. [CrossRef]
192. Vankayalapati, H.; Yerramreddy, V.K.; Gangireddy, P.; Appalaneni, R.P. National Center for Biotechnology Information (2024). PubChem Patent Summary for US-9206188-B2, Substituted Pyrrolo[2,3-b]pyridines as ITK and JAK Inhibitors. United States, 8 December 2015. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-9206188-B2 (accessed on 25 February 2025).
193. Wang, Y.; Huang, W.; Xin, M.; Chen, P.; Gui, L.; Zhao, X.; Tang, F.; Wang, J.; Liu, F. Identification of 4-(2-furanyl)pyrimidin-2-amines as Janus kinase 2 inhibitors. *Bioorg. Med. Chem.* **2017**, *25*, 75–83. [CrossRef] [PubMed]
194. Batt, D.G.; Bertrand, M.B.; Delucca, G.; Galella, M.A.; Ko, S.S. Substituted Tetrahydrocarbazole and Carbazole Carboxamide Compounds. United States Patent US-9334290-B2, 10 May 2016. Assignee: Bristol Myers Squibb Co. Available online: https://patents.google.com/patent/US9334290B2 (accessed on 25 February 2025).
195. Hayashi, K.; Watanabe, T.; Toyama, K.; Kamon, J.; Minami, M. Substituted Pyrrolo[2,3-h][1,6]naphthyridines and Compositions Thereof as JAK Inhibitors. United States Patent US-9216999-B2, 22 December 2015. Available online: https://patents.google.com/patent/US9216999B2 (accessed on 25 February 2025).
196. Yang, B.V.; Brown, G.D.; Gupta, A.K.; Pitts, W.J. National Center for Biotechnology Information (2024). PubChem Patent Summary for US-9428511-B2, Imidazopyridazine JAK3 Inhibitors and Their Use for the Treatment of Inflammatory and Autoimmune Diseases. United States. 30 August 2016. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-9428511-B2 (accessed on 25 February 2025).
197. Czodrowski, P.; Mallinger, A.; Wienke, D.; Esdar, C.; Pöschke, O.; Busch, M.; Rohdich, F.; Eccles, S.A.; Ortiz-Ruiz, M.J.; Schneider, R.; et al. Structure-Based Optimization of Potent, Selective, and Orally Bioavailable CDK8 Inhibitors Discovered by High-Throughput Screening. *J. Med. Chem.* **2016**, *59*, 9337–9349. [CrossRef]
198. Clark, M.P.; George, K.M.; Bookland, R.G.; Chen, J.; Laughlin, S.K.; Thakur, K.D.; Lee, W.; Davis, J.R.; Cabrera, E.J.; Brugel, T.A.; et al. Development of new pyrrolopyrimidine-based inhibitors of Janus kinase 3 (JAK3). *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1250–1253. [CrossRef]
199. Mitton-Fry, M.J.; Berlinski, P.J.; Birchmeier, M.J.; Bowman, J.W.; Gonzales, A.J. National Center for Biotechnology Information (2024). PubChem Patent Summary for US-9161939-B2, Pyrrolo[2,3-d]pyrimidine compounds. United States. 20 October 2015. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-9161939-B2 (accessed on 25 February 2025).
200. Smaill, J.B.; Gonzales, A.J.; Spicer, J.A.; Lee, H.; Reed, J.E.; Sexton, K.; Althaus, I.W.; Zhu, T.; Black, S.L.; Blaser, A.; et al. Tyrosine Kinase Inhibitors. 20. Optimization of Substituted Quinazoline and Pyrido[3,4-d]pyrimidine Derivatives as Orally Active, Irreversible Inhibitors of the Epidermal Growth Factor Receptor Family. *J. Med. Chem.* **2016**, *59*, 8103–8124. [CrossRef] [PubMed]
201. Huang, T.; Xue, C.-B.; Li, H.-Y.; Li, Q. Piperidin-4-yl Azetidine Derivatives as JAK1 Inhibitors. U.S. Patent US-8765734-B2, 1 July 2014. Available online: https://patents.google.com/patent/US8765734B2 (accessed on 25 February 2025).

202. Takahashi, K.; Watanabe, T.; Hayashi, K.; Kurihara, K.; Nakamura, T.; Yamamoto, A.; Nishimura, T.; Kamiyama, T.; Hidaka, Y. National Center for Biotechnology Information (2024). PubChem Patent Summary for US-9475813-B2, Tricyclic Pyrrolopyridine Compound, and JAK Inhibitor. United States. 25 October 2016. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-9475813-B2 (accessed on 25 February 2025).
203. Xi, N.; Li, M.; Hu, H.; Dai, W. National Center for Biotechnology Information (2024). PubChem Patent Summary for US-9403801-B2, Substituted Heteroaryl Compounds and Methods of Use. United States. 2 August 2016. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-9403801-B2 (accessed on 25 February 2025).
204. Goldstein, D.M.; Brameld, K.A.; Verner, E. National Center for Biotechnology Information (2024). PubChem Patent Summary for US-9187487-B2, Azaindole Derivatives as Tyrosine Kinase Inhibitors. United States. 17 November 2015. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-9187487-B2 (accessed on 25 February 2025).
205. Ge, Y.; Jin, Y.; Wang, C.; Zhang, J.; Tang, Z.; Peng, J.; Liu, K.; Li, Y.; Zhou, Y.; Ma, X. Discovery of Novel Bruton's Tyrosine Kinase (BTK) Inhibitors Bearing a *N*,9-Diphenyl-9*H*-purin-2-amine Scaffold. *ACS Med. Chem. Lett.* **2016**, *7*, 1050–1055. [CrossRef] [PubMed]
206. Li, Y.-L.; Rodgers, J.D. National Center for Biotechnology Information (2024). PubChem Patent Summary for US-9216984-B2, 3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]octanenitrile and Heptanenitrile as JAK Inhibitors. United States. 22 December 2015. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-9216984-B2 (accessed on 25 February 2025).
207. Su, W.-G.; Deng, W.; Li, J.; Ji, J. National Center for Biotechnology Information (2024). PubChem Patent Summary for US-9346810-B2, Pyrrolopyrimidine Compounds and Uses Thereof. United States. 24 May 2016. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-9346810-B2 (accessed on 25 February 2025).
208. Brubaker, J.; Childers, M.L.; Christopher, M.; Close, J.T.; Katz, J.D. National Center for Biotechnology Information (2024). PubChem Patent Summary for US-9328099-B2, Cyanomethylpyrazole Carboxamides as Janus kinase Inhibitors. United States. 3 May 2016. Available online: https://pubchem.ncbi.nlm.nih.gov/patent/US-9328099-B2 (accessed on 25 February 2025).
209. Reddy, E.P.; Reddy, M.V.R. Substituted Pyrido[2,3-d]pyrimidin-7(8H)-ones and Therapeutic Uses Thereof. US8889696B2, 18 November 2014.
210. Lam, B.; Arikawa, Y.; Cramlett, J.; Dong, Q.; de Jong, R.; Feher, V.; Grimshaw, C.E.; Farrell, P.J.; Hoffman, I.D.; Jennings, A.; et al. Discovery of TAK-659 an orally available investigational inhibitor of Spleen Tyrosine Kinase (SYK). *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5947–5950. [CrossRef]
211. Blomgren, P.; Chandrasekhar, J.; Di Paolo, J.A.; Fung, W.; Geng, G.; Ip, C.; Jones, R.; Kropf, J.E.; Lansdon, E.B.; Lee, S.; et al. Discovery of Lanraplenib (GS-9876): A Once-Daily Spleen Tyrosine Kinase Inhibitor for Autoimmune Diseases. *ACS Med. Chem. Lett.* **2020**, *11*, 506–513. [CrossRef]
212. Abdel-Magid, A.F. Janus-Associated Kinase 1 (JAK1) Inhibitors as Potential Treatment for Immune Disorders. *ACS Med. Chem. Lett.* **2017**, *8*, 598–600. [CrossRef]
213. Kempson, J.; Ovalle, D.; Guo, J.; Wrobleski, S.T.; Lin, S.; Spergel, S.H.; Duan, J.J.; Jiang, B.; Lu, Z.; Das, J.; et al. Discovery of highly potent, selective, covalent inhibitors of JAK3. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 4622–4625. [CrossRef]
214. Hanan, E.J.; Liang, J.; Wang, X.; Blake, R.A.; Blaquiere, N.; Staben, S.T. Monomeric Targeted Protein Degraders. *J. Med. Chem.* **2020**, *63*, 11330–11361. [CrossRef] [PubMed]
215. Brameld, K.A.; Owens, T.D.; Verner, E.; Venetsanakos, E.; Bradshaw, J.M.; Phan, V.T.; Tam, D.; Leung, K.; Shu, J.; LaStant, J.; et al. Discovery of the Irreversible Covalent FGFR Inhibitor 8-(3-(4-Acryloylpiperazin-1-yl)propyl)-6-(2,6-dichloro-3,5-dimethoxyphenyl)-2-(methylamino)pyrido[2,3-d]pyrimidin-7(8H)-one (PRN1371) for the Treatment of Solid Tumors. *J. Med. Chem.* **2017**, *60*, 6516–6527. [CrossRef]
216. Data for DCP Probe TP-030-2. Available online: https://www.ebi.ac.uk/chembl/explore/document/CHEMBL4507326 (accessed on 2 February 2023).
217. Yao, L.; Mustafa, N.; Tan, E.C.; Poulsen, A.; Singh, P.; Duong-Thi, M.D.; Lee, J.X.T.; Ramanujulu, P.M.; Chng, W.J.; Yen, J.J.Y.; et al. Design and Synthesis of Ligand Efficient Dual Inhibitors of Janus Kinase (JAK) and Histone Deacetylase (HDAC) Based on Ruxolitinib and Vorinostat. *J. Med. Chem.* **2017**, *60*, 8336–8357. [CrossRef]
218. Fischer, T.; Krüger, T.; Najjar, A.; Totzke, F.; Schächtele, C.; Sippl, W.; Ritter, C.; Hilgeroth, A. Discovery of novel substituted benzo-anellated 4-benzylamino pyrrolopyrimidines as dual EGFR and VEGFR2 inhibitors. *Bioorg. Med. Chem. Lett.* **2017**, *27*, 2708–2712. [CrossRef]
219. Vazquez, M.L.; Kaila, N.; Strohbach, J.W.; Trzupek, J.D.; Brown, M.F.; Flanagan, M.E.; Mitton-Fry, M.J.; Johnson, T.A.; Ten-Brink, R.E.; Arnold, E.P.; et al. Identification of N-{cis-3-[Methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino]cyclobutyl}propane-1-sulfonamide (PF-04965842): A Selective JAK1 Clinical Candidate for the Treatment of Autoimmune Diseases. *J. Med. Chem.* **2018**, *61*, 1130–1152. [CrossRef] [PubMed]
220. Brubaker, J.; Close, J.; Siu, T.; Smith, G.F.; Torres, L.E. Pyrazole Carboxamides as Janus Kinase Inhibitors. U.S. Patent US9394282B2, 19 July 2016.

221. Juillerat-Jeanneret, L.; Aubert, J.D.; Mikulic, J.; Golshayan, D. Fibrogenic Disorders in Human Diseases: From Inflammation to Organ Dysfunction. *J. Med. Chem.* **2018**, *61*, 9811–9840. [CrossRef] [PubMed]
222. Huang, Y.; Dong, G.; Li, H.; Liu, N.; Zhang, W.; Sheng, C. Discovery of Janus Kinase 2 (JAK2) and Histone Deacetylase (HDAC) Dual Inhibitors as a Novel Strategy for the Combinational Treatment of Leukemia and Invasive Fungal Infections. *J. Med. Chem.* **2018**, *61*, 6056–6074. [CrossRef]
223. Grimster, N.P.; Anderson, E.; Alimzhanov, M.; Bebernitz, G.; Bell, K.; Chuaqui, C.; Deegan, T.; Ferguson, A.D.; Gero, T.; Harsch, A.; et al. Discovery and Optimization of a Novel Series of Highly Selective JAK1 Kinase Inhibitors. *J. Med. Chem.* **2018**, *61*, 5235–5244. [CrossRef]
224. Chough, C.; Joung, M.; Lee, S.; Lee, J.; Kim, J.H.; Kim, B.M. Development of selective inhibitors for the treatment of rheumatoid arthritis: (R)-3-(3-(Methyl(7*H*-pyrrolo[2,3-*d*]pyrimidin-4-yl)amino)pyrrolidin-1-yl)-3-oxopropanenitrile as a JAK1-selective inhibitor. *Bioorg. Med. Chem.* **2018**, *26*, 1495–1510. [CrossRef]
225. Yu, T.; Zhang, Y.; Kerekes, A.D.; Tagat, J.R.; Doll, R.J.; Xiao, Y.; Esposite, S.; Hruza, A.; Belanger, D.B.; Voss, M.; et al. Discovery of a highly potent orally bioavailable imidazo-[1, 2-a]pyrazine Aurora inhibitor. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 1397–1403. [CrossRef]
226. El-Gamal, M.I.; Al-Ameen, S.K.; Al-Koumi, D.M.; Hamad, M.G.; Jalal, N.A.; Oh, C.H. Recent Advances of Colony-Stimulating Factor-1 Receptor (CSF-1R) Kinase and Its Inhibitors. *J. Med. Chem.* **2018**, *61*, 5450–5466. [CrossRef] [PubMed]
227. Wang, Y.; Huang, W.; Xin, M.; Chen, P.; Gui, L.; Zhao, X.; Zhu, X.; Luo, H.; Cong, X.; Wang, J.; et al. Discovery of potent anti-inflammatory 4-(4,5,6,7-tetrahydrofuro[3,2-*c*]pyridin-2-yl) pyrimidin-2-amines for use as Janus kinase inhibitors. *Bioorg. Med. Chem.* **2019**, *27*, 2592–2597. [CrossRef] [PubMed]
228. Zheng, J.; Wu, J.; Ding, X.; Shen, H.C.; Zou, G. Small molecule approaches to treat autoimmune and inflammatory diseases (Part I): Kinase inhibitors. *Bioorg. Med. Chem. Lett.* **2021**, *38*, 127862. [CrossRef]
229. Yao, L.; Ramanujulu, P.M.; Poulsen, A.; Ohlson, S.; Dymock, B.W. Merging of ruxolitinib and vorinostat leads to highly potent inhibitors of JAK2 and histone deacetylase 6 (HDAC6). *Bioorg. Med. Chem. Lett.* **2018**, *28*, 2636–2640. [CrossRef]
230. Liu, Q.; Batt, D.G.; Chaudhry, C.; Lippy, J.S.; Pattoli, M.A.; Surti, N.; Xu, S.; Carter, P.H.; Burke, J.R.; Tino, J.A. Conversion of carbazole carboxamide based reversible inhibitors of Bruton's tyrosine kinase (BTK) into potent, selective irreversible inhibitors in the carbazole, tetrahydrocarbazole, and a new 2,3-dimethylindole series. *Bioorg. Med. Chem. Lett.* **2018**, *28*, 3080–3084. [CrossRef] [PubMed]
231. Pippione, A.C.; Sainas, S.; Federico, A.; Lupino, E.; Piccinini, M.; Kubbutat, M.; Contreras, J.M.; Morice, C.; Barge, A.; Ducime, A.; et al. *N*-Acetyl-3-aminopyrazoles block the non-canonical NF-kB cascade by selectively inhibiting NIK. *Medchemcomm* **2018**, *9*, 963–968. [CrossRef]
232. Yin, L.; Li, H.; Liu, W.; Yao, Z.; Cheng, Z.; Zhang, H.; Zou, H. A highly potent CDK4/6 inhibitor was rationally designed to overcome blood brain barrier in gliobastoma therapy. *Eur. J. Med. Chem.* **2018**, *144*, 1–28. [CrossRef]
233. Chough, C.; Lee, S.; Joung, M.; Lee, J.; Kim, J.H.; Kim, B.M. Design, synthesis and evaluation of (R)-3-(7-(methyl(7H-pyrrolo[2,3-d]pyrimidin-4-yl)amino)-5-azaspiro[2.4]heptan-5-yl)-3-oxopropanenitrile as a JAK1-selective inhibitor. *Medchemcomm* **2018**, *9*, 477–489. [CrossRef]
234. Chu-Farseeva, Y.Y.; Mustafa, N.; Poulsen, A.; Tan, E.C.; Yen, J.J.Y.; Chng, W.J.; Dymock, B.W. Design and synthesis of potent dual inhibitors of JAK2 and HDAC based on fusing the pharmacophores of XL019 and vorinostat. *Eur. J. Med. Chem.* **2018**, *158*, 593–619. [CrossRef]
235. Zhang, K.; Ye, K.; Tang, H.; Qi, Z.; Wang, T.; Mao, J.; Zhang, X.; Jiang, S. Development and Therapeutic Implications of Tyrosine Kinase 2 Inhibitors. *J. Med. Chem.* **2023**, *66*, 4378–4416. [CrossRef]
236. Henry, S.P.; Jorgensen, W.L. Progress on the Pharmacological Targeting of Janus Pseudokinases. *J. Med. Chem.* **2023**, *66*, 10959–10990. [CrossRef] [PubMed]
237. Ge, Y.; Wang, C.; Song, S.; Huang, J.; Liu, Z.; Li, Y.; Meng, Q.; Zhang, J.; Yao, J.; Liu, K.; et al. Identification of highly potent BTK and JAK3 dual inhibitors with improved activity for the treatment of B-cell lymphoma. *Eur. J. Med. Chem.* **2018**, *143*, 1847–1857. [CrossRef] [PubMed]
238. Moslin, R.; Gardner, D.; Santella, J.; Zhang, Y.; Duncia, J.V.; Liu, C.; Lin, J.; Tokarski, J.S.; Strnad, J.; Pedicord, D.; et al. Identification of imidazo[1,2-. *Medchemcomm* **2017**, *8*, 700–712. [CrossRef]
239. Noji, S.; Hara, Y.; Miura, T.; Yamanaka, H.; Maeda, K.; Hori, A.; Yamamoto, H.; Obika, S.; Inoue, M.; Hase, Y.; et al. Discovery of a Janus Kinase Inhibitor Bearing a Highly Three-Dimensional Spiro Scaffold: JTE-052 (Delgocitinib) as a New Dermatological Agent to Treat Inflammatory Skin Disorders. *J. Med. Chem.* **2020**, *63*, 7163–7185. [CrossRef]
240. Li, Y.; Ye, T.; Xu, L.; Dong, Y.; Luo, Y.; Wang, C.; Han, Y.; Chen, K.; Qin, M.; Liu, Y.; et al. Discovery of 4-piperazinyl-2-aminopyrimidine derivatives as dual inhibitors of JAK2 and FLT3. *Eur. J. Med. Chem.* **2019**, *181*, 111590. [CrossRef]
241. EUbOPEN. Selectivity Literature for EUbOPEN Chemogenomic Library. Available online: https://www.ebi.ac.uk/chembl/explore/document/CHEMBL5465560 (accessed on 2 July 2023).

242. Miao, Q.; Ma, K.; Chen, D.; Wu, X.; Jiang, S. Targeting tropomyosin receptor kinase for cancer therapy. *Eur. J. Med. Chem.* **2019**, *175*, 129–148. [CrossRef] [PubMed]
243. Moslin, R.; Zhang, Y.; Wrobleski, S.T.; Lin, S.; Mertzman, M.; Spergel, S.; Tokarski, J.S.; Strnad, J.; Gillooly, K.; McIntyre, K.W.; et al. Identification of *N*-Methyl Nicotinamide and N-Methyl Pyridazine-3-Carboxamide Pseudokinase Domain Ligands as Highly Selective Allosteric Inhibitors of Tyrosine Kinase 2 (TYK2). *J. Med. Chem.* **2019**, *62*, 8953–8972. [CrossRef]
244. Bryan, M.C.; Rajapaksa, N.S. Kinase Inhibitors for the Treatment of Immunological Disorders: Recent Advances. *J. Med. Chem.* **2018**, *61*, 9030–9058. [CrossRef]
245. Zhang, C.; Qi, W.; Li, Y.; Tang, M.; Yang, T.; Liu, K.; Chen, Y.; Deng, D.; Xiang, M.; Chen, L. Discovery of 3-(4-(2-((1*H*-Indol-5-yl)amino)-5-fluoropyrimidin-4-yl)-1*H*-pyrazol-1-yl)propanenitrile Derivatives as Selective TYK2 Inhibitors for the Treatment of Inflammatory Bowel Disease. *J. Med. Chem.* **2021**, *64*, 1966–1988. [CrossRef]
246. Shi, C.; Wang, Q.; Liao, X.; Ge, H.; Huo, G.; Zhang, L.; Chen, N.; Zhai, X.; Hong, Y.; Wang, L.; et al. Discovery of 6-(2-(dimethylamino)ethyl)-N-(5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzo[d]imidazole-6-yl)pyrimidin-2-yl)-5,6,7,8-tetrahydro-1,6-naphthyridin-2-amine as a highly potent cyclin-dependent kinase 4/6 inhibitor for treatment of cancer. *Eur. J. Med. Chem.* **2019**, *178*, 352–364. [CrossRef]
247. Liang, X.; Zang, J.; Li, X.; Tang, S.; Huang, M.; Geng, M.; Chou, C.J.; Li, C.; Cao, Y.; Xu, W.; et al. Discovery of Novel Janus Kinase (JAK) and Histone Deacetylase (HDAC) Dual Inhibitors for the Treatment of Hematological Malignancies. *J. Med. Chem.* **2019**, *62*, 3898–3923. [CrossRef]
248. Liang, X.; Zang, J.; Zhu, M.; Gao, Q.; Wang, B.; Xu, W.; Zhang, Y. Design, Synthesis, and Antitumor Evaluation of 4-Amino-(1*H*)-pyrazole Derivatives as JAKs Inhibitors. *ACS Med. Chem. Lett.* **2016**, *7*, 950–955. [CrossRef]
249. Bach, J.; Eastwood, P.; González, J.; Gómez, E.; Alonso, J.A.; Fonquerna, S.; Lozoya, E.; Orellana, A.; Maldonado, M.; Calaf, E.; et al. Identification of 2-Imidazopyridine and 2-Aminopyridone Purinones as Potent Pan-Janus Kinase (JAK) Inhibitors for the Inhaled Treatment of Respiratory Diseases. *J. Med. Chem.* **2019**, *62*, 9045–9060. [CrossRef] [PubMed]
250. Tang, G.; Liu, L.; Wang, X.; Pan, Z. Discovery of 7H-pyrrolo[2,3-d]pyrimidine derivatives as selective covalent irreversible inhibitors of interleukin-2-inducible T-cell kinase (Itk). *Eur. J. Med. Chem.* **2019**, *173*, 167–183. [CrossRef]
251. CoE, J.W.; Dehnhardt, C.M.; Jones, P.; Korturn, S.W.; Sabnis, Y.A.; Wakenhut, F.M.; Whitlock, G.A. JAK Inhibitors for the Treatment of Inflammatory Diseases. U.S. Patent US8895544B2, 25 November 2014.
252. Garton, N.S.; Barker, M.D.; Davis, R.P.; Douault, C.; Hooper-Greenhill, E.; Jones, E.; Lewis, H.D.; Liddle, J.; Lugo, D.; McCleary, S.; et al. Optimisation of a novel series of potent and orally bioavailable azanaphthyridine SYK inhibitors. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 4606–4612. [CrossRef] [PubMed]
253. Leonard, K.A.; Madge, L.A.; Krawczuk, P.J.; Wang, A.; Kreutter, K.D.; Bacani, G.M.; Chai, W.; Smith, R.C.; Tichenor, M.S.; Harris, M.C.; et al. Discovery of a Gut-Restricted JAK Inhibitor for the Treatment of Inflammatory Bowel Disease. *J. Med. Chem.* **2020**, *63*, 2915–2929. [CrossRef] [PubMed]
254. Shi, L.; Zhong, Z.; Li, X.; Zhou, Y.; Pan, Z. Discovery of an Orally Available Janus Kinase 3 Selective Covalent Inhibitor. *J. Med. Chem.* **2019**, *62*, 1054–1066. [CrossRef]
255. National Center for Biotechnology Information. PubChem Substance Record for SID 395763535, S., Source: PATENTSCOPE (WIPO). 2024. Available online: https://pubchem.ncbi.nlm.nih.gov/substance/395763535 (accessed on 18 December 2024).
256. Yuan, X.; Wu, H.; Bu, H.; Zhou, J.; Zhang, H. Targeting the immunity protein kinases for immuno-oncology. *Eur. J. Med. Chem.* **2019**, *163*, 413–427. [CrossRef]
257. Ritzén, A.; Sørensen, M.D.; Dack, K.N.; Greve, D.R.; Jerre, A.; Carnerup, M.A.; Rytved, K.A.; Bagger-Bahnsen, J. Fragment-Based Discovery of 6-Arylindazole JAK Inhibitors. *ACS Med. Chem. Lett.* **2016**, *7*, 641–646. [CrossRef]
258. Fensome, A.; Ambler, C.M.; Arnold, E.; Banker, M.E.; Brown, M.F.; Chrencik, J.; Clark, J.D.; Dowty, M.E.; Efremov, I.V.; Flick, A.; et al. Dual Inhibition of TYK2 and JAK1 for the Treatment of Autoimmune Diseases: Discovery of ((S)-2,2-Difluorocyclopropyl) ((1 R,5 S)-3-(2-((1-methyl-1 H-pyrazol-4-yl)amino)pyrimidin-4-yl)-3,8-diazabicyclo[3.2.1]octan-8-yl)methanone (PF-06700841). *J. Med. Chem.* **2018**, *61*, 8597–8612. [CrossRef]
259. Chen, P.; Norris, D.; Das, J.; Spergel, S.H.; Wityak, J.; Leith, L.; Zhao, R.; Chen, B.C.; Pitt, S.; Pang, S.; et al. Discovery of novel 2-(aminoheteroaryl)-thiazole-5-carboxamides as potent and orally active Src-family kinase p56(Lck) inhibitors. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 6061–6066. [CrossRef]
260. Yang, T.; Hu, M.; Qi, W.; Yang, Z.; Tang, M.; He, J.; Chen, Y.; Bai, P.; Yuan, X.; Zhang, C.; et al. Discovery of Potent and Orally Effective Dual Janus Kinase 2/FLT3 Inhibitors for the Treatment of Acute Myelogenous Leukemia and Myeloproliferative Neoplasms. *J. Med. Chem.* **2019**, *62*, 10305–10320. [CrossRef]
261. National Center for Biotechnology Information. PubChem Bioassay Record for AID 1791642, N.S.F.J., Source: ChEMBL. 2024. Available online: https://pubchem.ncbi.nlm.nih.gov/bioassay/1791642 (accessed on 25 December 2024).
262. Lee, S.M.; Yoon, K.B.; Lee, H.J.; Kim, J.; Chung, Y.K.; Cho, W.J.; Mukai, C.; Choi, S.; Kang, K.W.; Han, S.Y.; et al. The discovery of 2,5-isomers of triazole-pyrrolopyrimidine as selective Janus kinase 2 (JAK2) inhibitors versus JAK1 and JAK3. *Bioorg. Med. Chem.* **2016**, *24*, 5036–5046. [CrossRef] [PubMed]

263. Luo, Z.; Wang, L.; Fu, Z.; Shuai, B.; Luo, M.; Hu, G.; Chen, J.; Sun, J.; Wang, J.; Li, J.; et al. Discovery and optimization of selective RET inhibitors via scaffold hopping. *Bioorg. Med. Chem. Lett.* **2021**, *47*, 128149. [CrossRef] [PubMed]
264. Egyed, A.; Bajusz, D.; Keserű, G.M. The impact of binding site waters on the activity/selectivity trade-off of Janus kinase 2 (JAK2) inhibitors. *Bioorg. Med. Chem.* **2019**, *27*, 1497–1508. [CrossRef] [PubMed]
265. Chen, Y.; Li, H.; Yen, R.; Heckrodt, T.J.; McMurtrie, D.; Singh, R.; Taylor, V.; Masuda, E.S.; Park, G.; Payan, D.G. Optimization of Pyrimidine Compounds as Potent JAK1 Inhibitors and the Discovery of R507 as a Clinical Candidate. *ACS Med. Chem. Lett.* **2022**, *13*, 1805–1811. [CrossRef]
266. Liu, L.; Norman, M.H.; Lee, M.; Xi, N.; Siegmund, A.; Boezio, A.A.; Booker, S.; Choquette, D.; D'Angelo, N.D.; Germain, J.; et al. Structure-based design of novel class II c-Met inhibitors: 2. SAR and kinase selectivity profiles of the pyrazolone series. *J. Med. Chem.* **2012**, *55*, 1868–1897. [CrossRef]
267. Schlapbach, A.; Feifel, R.; Hawtin, S.; Heng, R.; Koch, G.; Moebitz, H.; Revesz, L.; Scheufler, C.; Velcicky, J.; Waelchli, R.; et al. Pyrrolo-pyrimidones: A novel class of MK2 inhibitors with potent cellular activity. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6142–6146. [CrossRef]
268. Bauer, D.; Whittington, D.A.; Coxon, A.; Bready, J.; Harriman, S.P.; Patel, V.F.; Polverino, A.; Harmange, J.C. Evaluation of indazole-based compounds as a new class of potent KDR/VEGFR-2 inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4844–4848. [CrossRef]
269. Zhou, H.; McGowan, M.A.; Lipford, K.; Christopher, M.; Fradera, X.; Witter, D.; Lesburg, C.A.; Li, C.; Methot, J.L.; Lampe, J.; et al. Discovery and optimization of heteroaryl piperazines as potent and selective PI3Kδ inhibitors. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 126715. [CrossRef]
270. Shah, R.R.; Redmond, J.M.; Mihut, A.; Menon, M.; Evans, J.P.; Murphy, J.A.; Bartholomew, M.A.; Coe, D.M. Hi-JAK-ing the ubiquitin system: The design and physicochemical optimisation of JAK PROTACs. *Bioorg. Med. Chem.* **2020**, *28*, 115326. [CrossRef] [PubMed]
271. Zhu, Y.; Zheng, X.; Wang, C.; Sun, X.; Sun, H.; Ma, T.; Li, Y.; Liu, K.; Chen, L.; Ma, X. Synthesis and biological activity of thieno[3,2-*d*]pyrimidines as potent JAK3 inhibitors for the treatment of idiopathic pulmonary fibrosis. *Bioorg. Med. Chem.* **2020**, *28*, 115254. [CrossRef]
272. Sasaki, Y.; Tokuhara, H.; Ohba, Y.; Okabe, A.; Nakayama, M.; Nakagawa, H.; Skene, R.; Hoffman, I.; Zou, H.; Yoshida, M. Efficient synthesis of tert-butyl 3-cyano-3-cyclopropyl-2-oxopyrrolidine-4-carboxylates: Highly functionalized 2-pyrrolidinone enabling access to novel macrocyclic Tyk2 inhibitors. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 126963. [CrossRef]
273. Lu, K.; Wu, W.; Zhang, C.; Liu, Z.; Xiao, B.; Yuan, Z.; Li, A.; Chen, D.; Zhai, X.; Jiang, Y. Discovery of triazolo [1,5-a] pyridine derivatives as novel JAK1/2 inhibitors. *Bioorg. Med. Chem. Lett.* **2020**, *30*, 127225. [CrossRef]
274. Zhu, Y.; Ma, Y.; Zu, W.; Song, J.; Wang, H.; Zhong, Y.; Li, H.; Zhang, Y.; Gao, Q.; Kong, B.; et al. Identification of. *J. Med. Chem.* **2020**, *63*, 6748–6773. [CrossRef] [PubMed]
275. Wang, X.; Xue, G.; Pan, Z. Design, synthesis and structure-activity relationship of indolylindazoles as potent and selective covalent inhibitors of interleukin-2 inducible T-cell kinase (ITK). *Eur. J. Med. Chem.* **2020**, *187*, 111918. [CrossRef]
276. Gerstenberger, B.S.; Ambler, C.; Arnold, E.P.; Banker, M.E.; Brown, M.F.; Clark, J.D.; Dermenci, A.; Dowty, M.E.; Fensome, A.; Fish, S.; et al. Discovery of Tyrosine Kinase 2 (TYK2) Inhibitor (PF-06826647) for the Treatment of Autoimmune Diseases. *J. Med. Chem.* **2020**, *63*, 13561–13577. [CrossRef] [PubMed]
277. Zak, M.; Hanan, E.J.; Lupardus, P.; Brown, D.G.; Robinson, C.; Siu, M.; Lyssikatos, J.P.; Romero, F.A.; Zhao, G.; Kellar, T.; et al. Discovery of a class of highly potent Janus Kinase 1/2 (JAK1/2) inhibitors demonstrating effective cell-based blockade of IL-13 signaling. *Bioorg. Med. Chem. Lett.* **2019**, *29*, 1522–1531. [CrossRef]
278. Baillache, D.J.; Unciti-Broceta, A. Recent developments in anticancer kinase inhibitors based on the pyrazolo[3,4-*d*]pyrimidine scaffold. *RSC Med. Chem.* **2020**, *11*, 1112–1135. [CrossRef]
279. Thoma, G.; Blanz, J.; Bühlmayer, P.; Drückes, P.; Kittelmann, M.; Smith, A.B.; van Eis, M.; Vangrevelinghe, E.; Zerwes, H.G.; Che, J.J.; et al. Syk inhibitors with high potency in presence of blood. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 2278–2282. [CrossRef]
280. Luo, L.; Jia, J.J.; Zhong, Q.; Zhong, X.; Zheng, S.; Wang, G.; He, L. Synthesis and anticancer activity evaluation of naphthalene-substituted triazole spirodienones. *Eur. J. Med. Chem.* **2021**, *213*, 113039. [CrossRef] [PubMed]
281. Yang, T.; Hu, M.; Chen, Y.; Xiang, M.; Tang, M.; Qi, W.; Shi, M.; He, J.; Yuan, X.; Zhang, C.; et al. *N*-(Pyrimidin-2-yl)-1,2,3,4-tetrahydroisoquinolin-6-amine Derivatives as Selective Janus Kinase 2 Inhibitors for the Treatment of Myeloproliferative Neoplasms. *J. Med. Chem.* **2020**, *63*, 14921–14936. [CrossRef] [PubMed]
282. Matheson, C.J.; Coxon, C.R.; Bayliss, R.; Boxall, K.; Carbain, B.; Fry, A.M.; Hardcastle, I.R.; Harnor, S.J.; Mas-Droux, C.; Newell, D.R.; et al. 2-Arylamino-6-ethynylpurines are cysteine-targeting irreversible inhibitors of Nek2 kinase. *RSC Med. Chem.* **2020**, *11*, 707–731. [CrossRef]
283. Liu, C.; Lin, J.; Langevine, C.; Smith, D.; Li, J.; Tokarski, J.S.; Khan, J.; Ruzanov, M.; Strnad, J.; Zupa-Fernandez, A.; et al. Discovery of BMS-986202: A Clinical Tyk2 Inhibitor that Binds to Tyk2 JH2. *J. Med. Chem.* **2021**, *64*, 677–694. [CrossRef]

284. Zheng, Y.G.; Wang, J.A.; Meng, L.; Pei, X.; Zhang, L.; An, L.; Li, C.L.; Miao, Y.L. Design, synthesis, biological activity evaluation of 3-(4-phenyl-1H-imidazol-2-yl)-1H-pyrazole derivatives as potent JAK 2/3 and aurora A/B kinases multi-targeted inhibitors. *Eur. J. Med. Chem.* **2021**, *209*, 112934. [CrossRef]
285. Sanachai, K.; Aiebchun, T.; Mahalapbutr, P.; Seetaha, S.; Tabtimmai, L.; Maitarad, P.; Xenikakis, I.; Geronikaki, A.; Choowongkomon, K.; Rungrotmongkol, T. Discovery of novel JAK2 and EGFR inhibitors from a series of thiazole-based chalcone derivatives. *RSC Med. Chem.* **2021**, *12*, 430–438. [CrossRef] [PubMed]
286. Wu, L.; Zhang, C.; He, C.; Qian, D.; Lu, L.; Sun, Y.; Xu, M.; Zhuo, J.; Liu, P.C.C.; Klabe, R.; et al. Discovery of Pemigatinib: A Potent and Selective Fibroblast Growth Factor Receptor (FGFR) Inhibitor. *J. Med. Chem.* **2021**, *64*, 10666–10679. [CrossRef]
287. Xu, P.; Shen, P.; Wang, H.; Qin, L.; Ren, J.; Sun, Q.; Ge, R.; Bian, J.; Zhong, Y.; Li, Z.; et al. Discovery of imidazopyrrolopyridines derivatives as novel and selective inhibitors of JAK2. *Eur. J. Med. Chem.* **2021**, *218*, 113394. [CrossRef]
288. Rao, D.; Li, H.; Ren, X.; Sun, Y.; Wen, C.; Zheng, M.; Huang, H.; Tang, W.; Xu, S. Discovery of a potent, selective, and covalent ZAP-70 kinase inhibitor. *Eur. J. Med. Chem.* **2021**, *219*, 113393. [CrossRef]
289. Howard, S.; Berdini, V.; Boulstridge, J.A.; Carr, M.G.; Cross, D.M.; Curry, J.; Devine, L.A.; Early, T.R.; Fazal, L.; Gill, A.L.; et al. Fragment-based discovery of the pyrazol-4-yl urea (AT9283), a multitargeted kinase inhibitor with potent aurora kinase activity. *J. Med. Chem.* **2009**, *52*, 379–388. [CrossRef]
290. Pollard, J.R.; Mortimore, M. Discovery and development of aurora kinase inhibitors as anticancer agents. *J. Med. Chem.* **2009**, *52*, 2629–2651. [CrossRef]
291. Yang, T.; Cui, X.; Tang, M.; Qi, W.; Zhu, Z.; Shi, M.; Yang, L.; Pei, H.; Zhang, W.; Xie, L.; et al. Identification of a Novel 2,8-Diazaspiro[4.5]decan-1-one Derivative as a Potent and Selective Dual TYK2/JAK1 Inhibitor for the Treatment of Inflammatory Bowel Disease. *J. Med. Chem.* **2022**, *65*, 3151–3172. [CrossRef]
292. Liang, X.; Tang, S.; Liu, X.; Liu, Y.; Xu, Q.; Wang, X.; Saidahmatov, A.; Li, C.; Wang, J.; Zhou, Y.; et al. Discovery of Novel Pyrrolo[2,3-. *J. Med. Chem.* **2022**, *65*, 1243–1264. [CrossRef] [PubMed]
293. Wellaway, C.R.; Baldwin, I.R.; Bamborough, P.; Barker, D.; Bartholomew, M.A.; Chung, C.W.; Dümpelfeld, B.; Evans, J.P.; Fazakerley, N.J.; Homes, P.; et al. Investigation of Janus Kinase (JAK) Inhibitors for Lung Delivery and the Importance of Aldehyde Oxidase Metabolism. *J. Med. Chem.* **2022**, *65*, 633–664. [CrossRef] [PubMed]
294. Wu, S.; Liao, M.; Li, M.; Sun, M.; Xi, N.; Zeng, Y. Structure-based discovery of potent inhibitors of Axl: Design, synthesis, and biological evaluation. *RSC Med. Chem.* **2022**, *13*, 1246–1264. [CrossRef] [PubMed]
295. Mao, W.; Wu, H.; Guo, Q.; Zheng, X.; Wei, C.; Liao, Y.; Shen, L.; Mi, J.; Li, J.; Chen, S.; et al. Synthesis and evaluation of hydrazinyl-containing pyrrolo[2,3-*d*]pyrimidine series as potent, selective and oral JAK1 inhibitors for the treatment of rheumatoid arthritis. *Bioorg. Med. Chem. Lett.* **2022**, *74*, 128905. [CrossRef]
296. Cascioferro, S.; Parrino, B.; Spanò, V.; Carbone, A.; Montalbano, A.; Barraja, P.; Diana, P.; Cirrincione, G. An overview on the recent developments of 1,2,4-triazine derivatives as anticancer compounds. *Eur. J. Med. Chem.* **2017**, *142*, 328–375. [CrossRef]
297. Asati, V.; Anant, A.; Patel, P.; Kaur, K.; Gupta, G.D. Pyrazolopyrimidines as anticancer agents: A review on structural and target-based approaches. *Eur. J. Med. Chem.* **2021**, *225*, 113781. [CrossRef]
298. Soltan, O.M.; Shoman, M.E.; Abdel-Aziz, S.A.; Narumi, A.; Konno, H.; Abdel-Aziz, M. Molecular hybrids: A five-year survey on structures of multiple targeted hybrids of protein kinase inhibitors for cancer therapy. *Eur. J. Med. Chem.* **2021**, *225*, 113768. [CrossRef]
299. Yamagishi, H.; Inoue, T.; Nakajima, Y.; Maeda, J.; Tominaga, H.; Usuda, H.; Hondo, T.; Moritomo, A.; Nakamori, F.; Ito, M.; et al. Discovery of tricyclic dipyrrolopyridine derivatives as novel JAK inhibitors. *Bioorg. Med. Chem.* **2017**, *25*, 5311–5326. [CrossRef]
300. Kiss, R.; Polgár, T.; Kirabo, A.; Sayyah, J.; Figueroa, N.C.; List, A.F.; Sokol, L.; Zuckerman, K.S.; Gali, M.; Bisht, K.S.; et al. Identification of a novel inhibitor of JAK2 tyrosine kinase by structure-based virtual screening. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3598–3601. [CrossRef] [PubMed]
301. Wilson, L.J.; Malaviya, R.; Yang, C.; Argentieri, R.; Wang, B.; Chen, X.; Murray, W.V.; Cavender, D. Synthetic staurosporines via a ring closing metathesis strategy as potent JAK3 inhibitors and modulators of allergic responses. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3333–3338. [CrossRef]
302. Ioannidis, S.; Lamb, M.L.; Davies, A.M.; Almeida, L.; Su, M.; Bebernitz, G.; Ye, M.; Bell, K.; Alimzhanov, M.; Zinda, M. Discovery of pyrazol-3-ylamino pyrazines as novel JAK2 inhibitors. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6524–6528. [CrossRef] [PubMed]
303. Ledeboer, M.W.; Pierce, A.C.; Duffy, J.P.; Gao, H.; Messersmith, D.; Salituro, F.G.; Nanthakumar, S.; Come, J.; Zuccola, H.J.; Swenson, L.; et al. 2-Aminopyrazolo[1,5-a]pyrimidines as potent and selective inhibitors of JAK2. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6529–6533. [CrossRef] [PubMed]
304. Wang, T.; Ledeboer, M.W.; Duffy, J.P.; Salituro, F.G.; Pierce, A.C.; Zuccola, H.J.; Block, E.; Shlyakter, D.; Hogan, J.K.; Bennani, Y.L. A novel chemotype of kinase inhibitors: Discovery of 3,4-ring fused 7-azaindoles and deazapurines as potent JAK2 inhibitors. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 153–156. [CrossRef]

305. Wei, H.; Myers, M.R.; Hanney, B.; Spada, A.P.; Bilder, G.; Galzcinski, H.; Amin, D.; Needle, S.; Page, K.; Jayyosi, Z.; et al. Potent Quinoxaline-Based Inhibitors of PDGF Receptor Tyrosine Kinase Activity. Part 2: The Synthesis and Biological Activities of RPR127963, an Orally Bioavailable Inhibitor. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3097–3100. [CrossRef]
306. Serafim, R.A.M.; Sorrell, F.J.; Berger, B.T.; Collins, R.J.; Vasconcelos, S.N.S.; Massirer, K.B.; Knapp, S.; Bennett, J.; Fedorov, O.; Patel, H.; et al. Discovery of a Potent Dual SLK/STK10 Inhibitor Based on a Maleimide Scaffold. *J. Med. Chem.* **2021**, *64*, 13259–13278. [CrossRef]
307. Ruel, R.; Thibeault, C.; L'Heureux, A.; Martel, A.; Cai, Z.W.; Wei, D.; Qian, L.; Barrish, J.C.; Mathur, A.; D'Arienzo, C.; et al. Discovery and preclinical studies of 5-isopropyl-6-(5-methyl-1,3,4-oxadiazol-2-yl)-*N*-(2-methyl-1*H*-pyrrolo[2,3-*b*]pyridin-5-yl) pyrrolo[2,1-*f*][1,2,4]triazin-4-amine (BMS-645737), an in vivo active potent VEGFR-2 inhibitor. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2985–2989. [CrossRef]
308. Das, J.; Moquin, R.V.; Pitt, S.; Zhang, R.; Shen, D.R.; McIntyre, K.W.; Gillooly, K.; Doweyko, A.M.; Sack, J.S.; Zhang, H.; et al. Pyrazolo-pyrimidines: A novel heterocyclic scaffold for potent and selective p38 alpha inhibitors. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2652–2657. [CrossRef]
309. Bhide, R.S.; Cai, Z.W.; Zhang, Y.Z.; Qian, L.; Wei, D.; Barbosa, S.; Lombardo, L.J.; Borzilleri, R.M.; Zheng, X.; Wu, L.I.; et al. Discovery and preclinical studies of (*R*)-1-(4-(4-fluoro-2-methyl-1*H*-indol-5-yloxy)-5- methylpyrrolo[2,1-*f*][1,2,4]triazin-6-yloxy)propan- 2-ol (BMS-540215), an in vivo active potent VEGFR-2 inhibitor. *J. Med. Chem.* **2006**, *49*, 2143–2146. [CrossRef]
310. Borzilleri, R.M.; Bhide, R.S.; Barrish, J.C.; D'Arienzo, C.J.; Derbin, G.M.; Fargnoli, J.; Hunt, J.T.; Jeyaseelan, R.; Kamath, A.; Kukral, D.W.; et al. Discovery and evaluation of *N*-cyclopropyl- 2,4-difluoro-5-((2-(pyridin-2-ylamino)thiazol-5-ylmethyl)amino)benzamide (BMS-605541), a selective and orally efficacious inhibitor of vascular endothelial growth factor receptor-2. *J. Med. Chem.* **2006**, *49*, 3766–3769. [CrossRef] [PubMed]
311. Liu, C.; Wrobleski, S.T.; Lin, J.; Ahmed, G.; Metzger, A.; Wityak, J.; Gillooly, K.M.; Shuster, D.J.; McIntyre, K.W.; Pitt, S.; et al. 5-Cyanopyrimidine derivatives as a novel class of potent, selective, and orally active inhibitors of p38alpha MAP kinase. *J. Med. Chem.* **2005**, *48*, 6261–6270. [CrossRef] [PubMed]
312. Sugimoto, Y.; Sawant, D.B.; Fisk, H.A.; Mao, L.; Li, C.; Chettiar, S.; Li, P.K.; Darby, M.V.; Brueggemeier, R.W. Novel pyrrolopyrimidines as Mps1/TTK kinase inhibitors for breast cancer. *Bioorg. Med. Chem.* **2017**, *25*, 2156–2166. [CrossRef] [PubMed]
313. Poli, G.; Seidel, T.; Langer, T. Conformational Sampling of Small Molecules With iCon: Performance Assessment in Comparison With OMEGA. *Front. Chem.* **2018**, *6*, 229. [CrossRef]
314. Wolber, G.; Langer, T. LigandScout: 3-D pharmacophores derived from protein-bound ligands and their use as virtual screening filters. *J. Chem. Inf. Model.* **2005**, *45*, 160–169. [CrossRef]
315. Chrencik, J.E.; Patny, A.; Leung, I.K.; Korniski, B.; Emmons, T.L.; Hall, T.; Weinberg, R.A.; Gormley, J.A.; Williams, J.M.; Day, J.E.; et al. Structural and thermodynamic characterization of the TYK2 and JAK3 kinase domains in complex with CP-690550 and CMP-6. *J. Mol. Biol.* **2010**, *400*, 413–433. [CrossRef]
316. Tsui, V.; Gibbons, P.; Ultsch, M.; Mortara, K.; Chang, C.; Blair, W.; Pulk, R.; Stanley, M.; Starovasnik, M.; Williams, D.; et al. A new regulatory switch in a JAK protein kinase. *Proteins* **2011**, *79*, 393–401. [CrossRef]