Recent patents in the discovery of small molecule inhibitors of JAK3

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Importance of the field: Protein kinase enzymes have become increasingly important as the target of many disease modification drug discovery programs. Disruption of JAK3 function results in quantitative and qualitative deficiencies in both B- and T-cell compartments of the immune system of JAK3 deficient mice and development of severe combined immunodeficiency in humans with the JAK3 genetic aberration. JAK3 plays a specific role in immune function and lymphoid development and it only resides in the hematopoietic system, thus the rationale for selective targeting. Inhibitors of JAK3 have shown utility in many different autoimmune disorders, including allograft rejection during transplantation, acute lymphoblastic leukemia, Type 1 diabetes, rheumatoid arthritis and allergic and asthmatic diseases. These inhibitors are making their way into clinical trials with profound effects, thus, validating the target and strategy.

Areas covered in this review: A review that covers around 90 patents and patent applications made in the last 10 years in the area involving JAK3 inhibitors is provided. Specifically, what this content will provide is the genus, highlighted compounds of particular interest, filing organization and some biological measure of these compounds as inhibitors of this protein kinase or none if it is not provided. Some information from original research articles appearing in peer reviewed literature is provided, but this article is not a review of the literature. Furthermore, an overview of the current clinical status and future outcomes of this field is provided as summary.

What the reader will gain: A strong understanding for the current state of the art in patents dealing with inhibitors of JAK3 including genus and species designations, potential commercial interest of this target in the pharmaceutical community, depth of coverage by numbers of examples and selected proof of action against the target. Also, a brief understanding of the biology and pharmacology involved in the processes involving the research, discovery, characterization and clinical status of JAK3 inhibitors.

Take home message: This review is intended for medicinal chemists and patent agents who want to get a quick understanding of the state of the art in the field of JAK3 inhibitors. It further serves as a reference point to go into more depth on any series reported and to be able to evaluate any original research ideas in this area in the future.

Keywords: cytokines, IL-2, IL-4, immuno suppression, JAK1, JAK2, JAK3, JAK3 inhibitors, protein kinases, STATs, transplantation

Expert Opin. Ther. Patents (2010) ***20****(5):609-623*

1. Introduction

The Janus (JAK) protein tyrosine kinase (PTK) family are cytoplasmic PTKs that play a pivotal role in cytokine signal transduction pathways through association with various cytokine receptors by activation of the latent forms of STATs (signal transducers and activators of transcription). The members of the JAK family include

10.1517/13543771003709767 © 2010 Informa UK Ltd ISSN 1354-3776

Article highlights.

- JAK3 in a cytoplasmic protein kinase responsible for immune system signaling by cytokines through the JAK–STAT pathway.
- As a member of the JAK family which includes JAK1, JAK2 and Tyk2, this enzyme has unique functions that make it an attractive therapeutic target. It has been found within the cells that form the basis of the immune system, including T, B and mast cells. However, in some cases both JAK1 and JAK3 play dual roles in receptor phosphorylation events, making the action of both enzymes equivalent.
- JAK3 related defects are associated with a loss of immune system function including direct association with severe combined immunodeficiency disorder in both mice and humans.
- A JAK3 antagonist in a normal functioning immune system would be useful and effective as an immunosuppressant, finding uses in the many autoimmune and inflammatory based disease states such as, but not limited to, transplantation rejection, psoriasis, psoriatic arthritis, graft-versus-host disease, multiple sclorosis, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, allergic diseases and asthma.
- Inhibitors of this enzyme fall into several chemical classes, including fused 6,6 and 5,6 bicyclic and monocyclic pyrimidines and pyridines as well as strucutures with three or more fused ring systems.
- The current status of the field is provided in the context of the findings in the clinic. A perspective on the chances of success for the best compounds (CP-690,550, R-348 and VX-509) is given and it seems that side effects may be the only barrier. The significance of selectivity within the JAK family is discussed with reference to the JAK1/2 clinical compound INCB18424.

This box summarizes key points contained in the article.

JAK1, JAK2, JAK3 and Tyk2. Activated JAK kinases phosphorylate the intracellular domain of cytokine receptors creating docking sites for the STAT signaling proteins, and further phosphorylation by the JAK kinases of the STAT proteins takes place [1]. JAK3 is a key member of JAK family and was identified by three independent groups in 1994. JAK3 is highly restricted to the cells of hematopoietic lineage, unlike other members of the JAK family that are expressed ubiquitously [2]. Unlike the other members of the JAK family, which are widely expressed, JAK3 has limited tissue distribution and seems to interact uniquely with the common γ-subunit (γc) for the receptor of six specific IL cytokines: IL-2, -4, -7, -9, -15 and -21, thus, inducing the signaling response [3].

The IL cytokines selectively activate JAK3 due to its binding to the γc chain of the receptors [2]. The ILs play a crucial role in lymphoid development and function and are associated with many of the basic functions of normal immunity, including foreign pathogen recognition and self tolerance. The IL-2 cytokine plays a critical role in helper and memory T-cell development. Human genetic abnormalities, where either the changes to the JAK3 enzyme or the γc subunit have been identified, are associated with rare and inherited defects in primary immunity known as severe combined immunodeficiency [4]. Although the deficiency of JAK3 in humans typically results in the lack of T cells and NK cell development, the development of B cells is not affected [5]. JAK3 knockout mice that were generated by targeted disruption of the JAK3 gene exhibited profound immunological defects [6]. Unlike humans, these mice show the lack of B cells and have relatively small numbers of T cells.

The initial belief was that a primary function of JAK3 was to regulate proliferation of T and B cells through a cytokine-dependent pathway. In T cells, this is through IL-2, while in B cells it is IL-4. Recent studies, however, have shown that JAK3 can also transduce signals in non-cytokine-dependent biological responses. For example, mast cells have been shown to express JAK3 and the enzymatic activity of JAK3 is enhanced by IgE receptor crosslinking [7]. Studies with JAK3 knockout mice and JAK3 specific inhibitors have shown that JAK3 plays a key role in mast cell mediated inflammatory responses.

Therefore, a JAK3 antagonist in a normal functioning immune system would be useful and effective as an immunosuppressant, finding uses in the many autoimmune and inflammatory based disease states such as, but not limited to, transplantation rejection, psoriasis, psoriatic arthritis, graft-versus-host disease, multiple sclorosis, inflammatory bowel disease, systemic lupus erythematosus, rheumatoid arthritis, Type 1 diabetes, allergic diseases and asthma [8].

2. JAK3 biology and pharmacology

In cells, JAK3 associates with cytokine receptors, which homo and heterodimerize on ligand binding and signal the appropriate STAT pathway (**Figure 1**). JAK3 is bound to the γc common chain which is shared by the cytokine receptors IL-2, -4, -7, -9, -15 and -21 [1]. The receptors form a heterodimer with a JAK1 associated domain in which both JAK1 and JAK3 act cooperatively in the recruitment and phosphorylation of their target proteins, the STATs. As such, it may be difficult to distinguish between an inhibitor of JAK1 and JAK3 in the phosphoryation of the STAT proteins when both enzymes are present. In T cells, this cytokine pathway is through IL-2 and STAT-5 and in B cells it is IL-4 and STAT-6 [9]. The presumed mechanism goes through several steps (**Figure 1**), the first in which the intracellular domain of the receptor is phosphorylated by JAK3. Transphosphorylation of the co-dimer/JAK1 complex occurs and then attracts two molecules of STAT to the receptor [10]. The STAT molecules undergo phosphorylation, dimerize and migrate to the nucleus where interaction with DNA results in transcription of the target genes.

The *in vitro* bioassays that are used to characterize JAK3 inhibitors can be first and foremost using the isolated enzyme and measuring displacement of ATP. Like most protein kinases, JAK3 uses ATP to phorphyrylate its substrates.

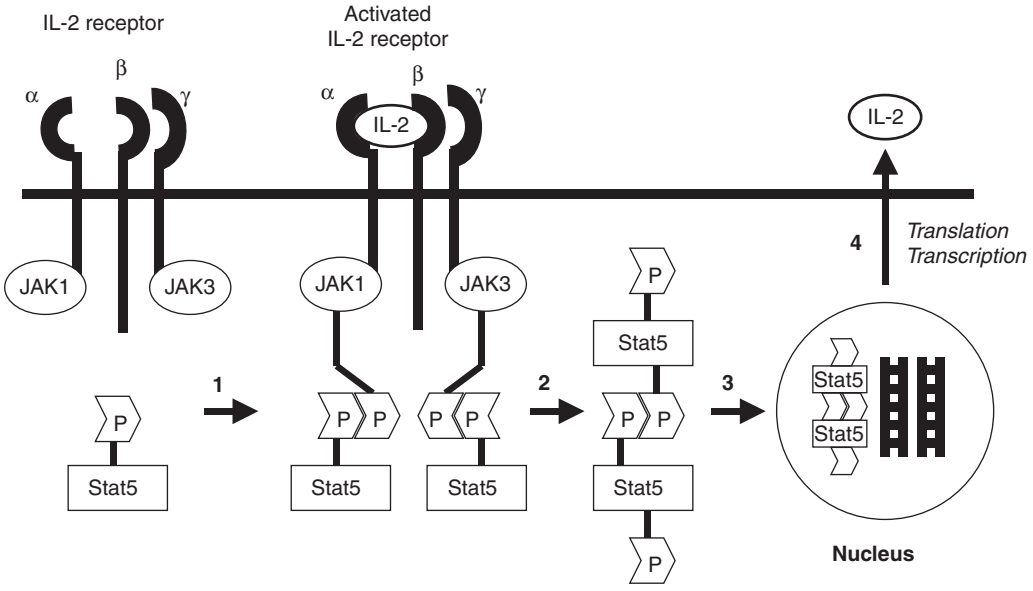


Figure 1. Schematic showing the role of JAK3 in IL-2 signal transduction within T cells. A resting receptor on the cell surface becomes activated by docking of IL-2 (step 1) and multiple phosphorylation events involving JAK1 and JAK3 lead to association of two molecules of Stat5. These molecules become further phosphorylated by both kinases and dimererize and dissociate from the receptor (step 2). The dimer migrates to the nucleus (step 3) and transcription and translation occur resulting in cell proliferation and cytokine (IL-2) production (step 4).

This assay will identify ATP-dependent inhibitors which either act by direct displacement or prevent binding of ATP through alosteric interactions. This assay will not measure inhibition of phosphorylation of the STAT molecules (the substrates of JAK3) because these reside in the cytoplasm of the cells. Nonetheless, it is usually used as a primary screen due to ease of operation and interpretation of results and can serve in combination with whole cell assays to confirm the action of compounds under evaluation. Furthermore, when used to screen for JAK3 versus JAK1 selectivity, it will provide the best possible way to determine how the compounds act.

Whole cell assays using the cells JAK3 resides in, such as T and B cells, provide a more complete measure of an inhibitor's effectiveness in blocking the signal pathway. These assays measure the ability of an inhibitor to prevent cell proliferation when the cells are exposed to the cytokine which stimulates the JAK3-dependent pathway, such as IL-2 and -4. Prevention of proliferation by cytokine stimulation is a measure of the ability of the inhibitor to block the JAK3 pathway in a functional setting. Furthermore, non-proliferation measures include quantification of STAT phosphorylation by cell lysis and western blot analysis. In addition to measuring the ability to block the signaling pathway, because the JAK3 enzyme resides in the cytoplasm, the whole cell assays measure the compound's ability to penetrate into the cell. However, and not undesirable, this assay will not distinguish between JAK3 and JAK1 inhibition due to the before mentioned joint function between the enzymes.

An important phenomenon that can accompany JAK3 inhibitors is that they may have significant pan JAK activity showing significant inhibition of other JAK family members, especially the JAK1 and JAK2 enzymes. In terms of JAK1, although it cooperates with JAK3 in the IL-2 receptor pharmacological response, inhibition may lead to potentially unknown undesirable responses. JAK1 knockout mice do not thrive as the pups fail to nurse presumably due to neurological defects [11]. However, it should be pointed out that any side effects associated with JAK1 inhibition have as yet not been observed. This is not the case with JAK2. This enzyme is found with in red blood cells and is coupled to the erythropoietin growth factor pathway. As such, inhibition of JAK2 may lead to potentially harmful side effects, including anemia, thrombocytopenia and generalized leucopenia during treatment [12].

Finally, *in vivo* measures of effectiveness to evaluate lead compounds can vary and provide strong support for a JAK3 based effect. Some animal models that have been reported with successful testing of JAK3 inhibitors include transplantation rejection, rheumatoid arthritis, asthma, IFN-γ release and IgE stimulation.

There are close to 90 applications which cover antagonists of the JAK3 enzyme. These documents describe and disclose chemical structures in both generic form and particular species reported to inhibit this enzyme. In general, the description of the biology varies widely, from specific data regarding inhibition by IC_{50} determinations to simply claiming that the described compounds have activity < 10 μM. Other

applications claim JAK3 activity vicariously and give biological details regarding JAK2 or some other non-JAK family protein kinase. Furthermore, some applications have claims that are specific to the target JAK3, while others claim acitivty in some or all JAK family members (JAK1, JAK2, JAK3 and Tyk2), For the purposes of completeness, this review covers applications that make any claims to JAK3 supported by specific biological data or not. As such, it is not a review of the overall field, and there are reports and publications that cover JAK3 inhibitor development that are outside the scope of this review [8].

3. 6,6-Fused bicyclic heterocycles

One of the first JAK3 inhibitors to be reported was the quinazolines by the Parker Hughes Medical Institute (**Figure 2**). Several applications cover a series of analogues with a variety of *in vitro* and *in vivo* biological data [13-15]. The inventions provide novel quinoline JAK3 kinase inhibitors **1** that are useful for treating a variety of disorders, including leukemia, lymphoma, prevent skin cancer, as well as sunburn and UVB-induced skin inflammation, allergic disorders and asthma, prevent autoimmune diseases, inflammation and transplant rejection (**Figure 1**). The inventions also provide pharmaceutical compositions comprising compounds of the invention, as well as therapeutic methods for their use. Overall, 17 examples are given, and the most studied compound of these patents is WHI-P131 (**2**). This compound has a reported IC_{50} against the JAK3 enzyme of 9 μM. For example, treatments with 50 or 75 mg/kg of the quinazoline derivative WHI-P131 were as effective as cyclosporin A treatment in prolongation of islet allograft survival in mice. More extensive *in vitro* and *in vivo* biological data are given for WHI-P131 [15].

Other 6,6-fused heterocycles of similar type were reported by other groups. AstraZeneca reported on a series of quinoline-3-carboxamides in two applications with 222 and 274 examples given (**3**, **Figure 3**) [16,17]. No data were reported in either filing. Both Vertex and Novartis reported on a series of related quinoxalines (**Figure 3**). In the first case, 47 examples (**4**) were provided with no specific biological data [18]. In the second, 171 examples (**5**, **Figure 3**) were provided and all were tested against JAK3 [19]. The best compound had an IC_{50} value of 77 nM. The last heterocycle of note in this series was a series of chromen-4-one oximes reported by Vertex (**6**). Here, there were 37 examples provided with no biological data [20].

4. 5,6-Fused bicyclic heterocycles

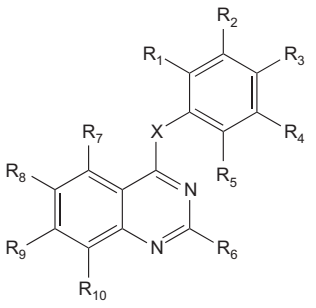
4.1 Pyrrolo-pyrimidines, pyrrolo-pyridines and pyrrolo-pyrazines

This series is by far the most covered in the patent literature for JAK3 activity. In this section there are > 30 patents covering a wide array of fused systems, with the most prevalent being the pyrrole fused to either a pyridine or pyrimidine ring. Pfizer provided a novel series of pyrrolo-pyrimidine compounds (**7**, **Figure 4**). The title compounds are inhibitors of the enzyme PTKs such as JAK3 and as such useful as immunosuppressive agents for organ transplants, lupus, multiple sclerosis, rheumatoid arthritis, psoriasis, type 1 diabetes and complications from diabetes, cancer, asthma, atopic dermatitis, autoimmune thyroid disorders, ulcerative colitis, Crohn's disease, Alzheimer's disease, leukemia and other autoimmune diseases. There are numerous examples (101, 78, 26 and 298) for each application [21-24]. However, no specific JAK3 data for any compound are described. Furthermore, a method patent describes the stereo selective synthesis of the best substitution [25]. This identifies the most significant compound from these patents as CP-690,550 (**8**). This and other examples have been the subject of study in the organ transplant rejection [26,27]. Furthermore, CP-690,550 (**8**) is the most advanced compound in the clinic for JAK3. Phase II clinical studies for this compound are ongoing or have been completed including rheumatoid arthritis, kidney transplant, psoriasis, Crohn's disease and dry-eye syndrome. This is further discussed later in the text.

Incyte reported on a similar series, but included a fused pyridine ring (**9**). A compound similar to CP-690,550 was described (123 examples), but no biological data were given [28]. For the pyrrolopyrimidines and pyridines, the piperidine ring substituted with 5 member nitrogen heterocycles provided numerous compounds (**10**, 745 and 750 examples) but with no biological data [29,30]. The clinical candidate, INCB18424 (**11**), is included in this application series. More recently, in the pyrrolopyrimidine series, an application with an N-cyclobutyl or N-azetidine substituted azapyrrole attached at the 3-position (83 examples) appeared with JAK2 data indicating single digit nanomolar inhibition for several analogues [31].

Recently, Targegen reported a series alkynyl linked pyrrolopyrimidines (**12**, **Figure 4**). The application provided 112 examples where the alkynyl is substituted with various aryl and bicyclic heteroaryl groups [32]. Biological data were provided for 54 compounds. The best compounds had a benzimidazole on the alkyne with an aryl amine on the pyridine ring (one compound had an IC_{50} of 103 nM against JAK3 and 12 nM against JAK2). Merck recently reported on a series of 3-pyrazinyl-pyrrolo-pyridines (**13**, **Figure 4**). Various substitutions on the pyridine and pyrazine rings are provided (34 examples) [33]. The majority of examples contain a pyrrazole on the pyridine ring and an alkoxy group on the pyrazine. No biological data are given. Novartis reported on a series of pyrrolopyrimidines with an aryl-amino substituent on the pyrimidine ring and an aryl group on the pyrrole nitrogen (**14**, **Figure 4**) [34]. In this application, 522 examples were provided, along with JAK2 data.

Roche recently reported on a series of pyrrolo-1,4-pyrazines with a substituent on the pyrazine ring, and a ketone substitution at the 3-position on the pyrrole ring (**15**, **Figure 5**). Four applications provide various types of groups at the two



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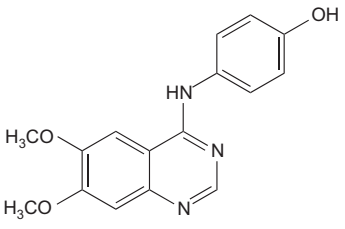
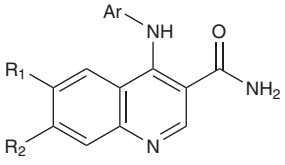


2 (WHI-P131)

Figure 2. Parker Hughes' quinazolines.



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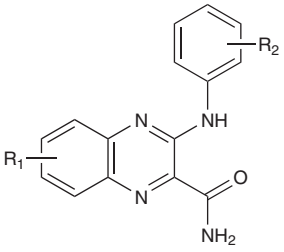

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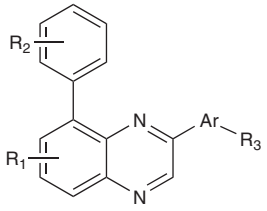

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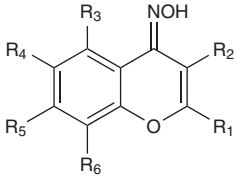
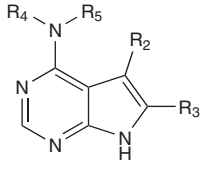


6 (US2004198750A1)

Figure 3. Quinolines, quinoxalines and chromenones.



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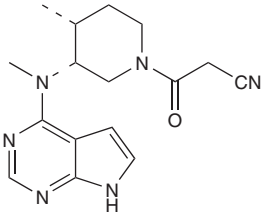
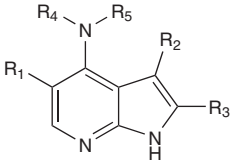


8 (CP-690,550)



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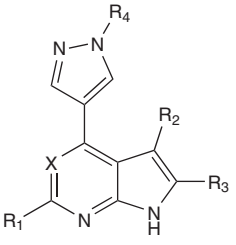

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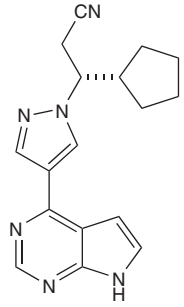
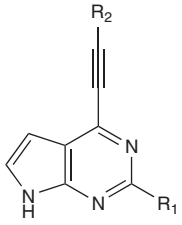


11 (INCB18424)



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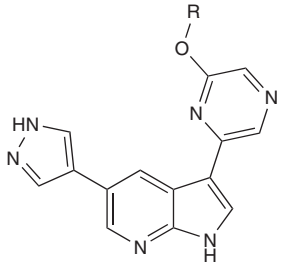

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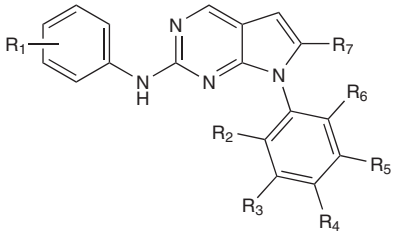
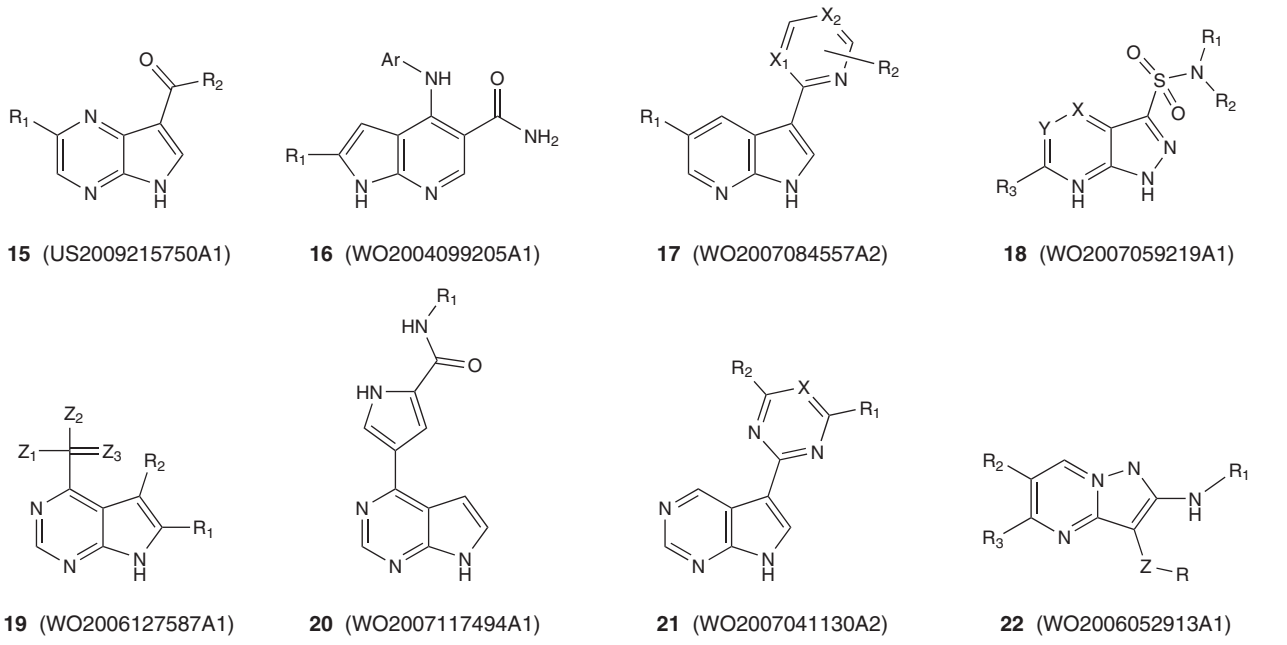


14 (WO2009098236A1)

Figure 4. Pyrrolo-pyrimidines and pyridines.



15 (US2009215750A1) **16** (WO2004099205A1) **17** (WO2007084557A2) **18** (WO2007059219A1)

19 (WO2006127587A1) **20** (WO2007117494A1) **21** (WO2007041130A2) **22** (WO2006052913A1)

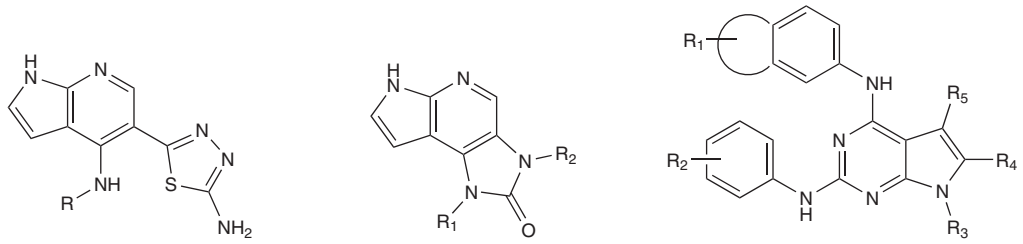
Figure 5. More fused pyrrolo pyridines, pyrimidines and pyazines.

specified positions with ample examples provided (54, 171, 32 and 39 compounds, respectively) [35-38]. A limited amount of biological activity is provided amounting to about 3 – 5 compounds per application (for example, one compound had an IC_{50} of 32 nM against JAK3). AstraZeneca recently reported on a series of pyrrolopyridine compounds with a primary carboxamide (**16**, **Figure 5**) [39]. There were 19 examples given and no specific biological data. Vertex reported on a series of pyrrolopyridine derivatives with substitution on the pyridine ring and the 3-position on the pyrrole ring (**17**, **Figure 5**, four applications). One series was with amino-pyrimidines (469 examples) and compounds were found to have IC_{50} values < 500 nM against JAK3 [40]. Another series involved amino-thiazole substitution (75 examples) with no biological data [41]. A third application was provided where the pyrimidine on the pyrrole had a different substitution pattern than the first example (405 examples), and no biological data were provided [42]. Finally, the fourth application provided a series of pyrrazolopyridines with a sulfonamide group substituted at the 3-position on the pyrrazole ring (**18**, 107 examples) [43]. Again, no data were provided for these compounds. Further examples were provided in the pyrrolo pyrimidine series (**19**), with 426 examples and no biological data given [44,45]. Continuing in the deazapurine series, which is structurally identical, this was followed with 254 examples (**20**) and 113 examples (**21**) where compounds were reported to have IC_{50} values < 100 nM [46,47]. The last disclosure by Vertex in this area was a series of pyrazolo[1,5-a]pyrimidines (**22**) with 353 examples given and a number of compounds with activity < 500 nM against JAK3 [48].

Astellas Pharma report on a series of pyrrolopyridines that were substituted mainly on the pyridine ring (**Figure 6**). This series contained an amino group at the 4-position on the pyridine and an appropriate group such as a heterocycle at the 3-position (**23**, 579 examples) [49]. The second disclosure was with a fused pyrimidinone ring (**24**) and 114 examples were provided [50,51]. Biological activity was provided for selected examples (one compound gave an IC_{50} value of 0.17 nM against the JAK3 enzyme). Palau Pharma reported on a series of pyrrolopyrimidines (13 examples) [52]. Portola reported a series of biarylamino pyrrolopyrimidines (**25**) which had 27 examples and no data given [53].

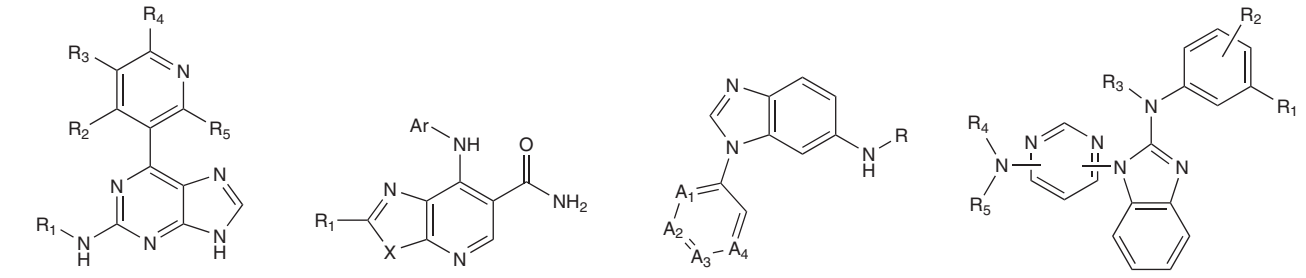
4.2 Purines, imidazo-pyrimidines, imidazo-pyridines, benzimidazoles and purinones

In the expanded area beyond pyrroles fused to various pyridine and pyrimidine heterocycles, there are numerous reports of other configurations including imidazoles (**Figure 7**). First, Palau pharma showed a series of pyridine-amino substituted imidazo-pyrimidines (**26**) with 237 examples, and no biological data given [54]. AstraZeneca reported a series of imidazole (**27**) and thiazole (**28**) fused carboxamide pyridines with 93 examples and no data [55]. Cytopia reported a series of benzimidazoles (**29**) with 48 examples and some compounds being active against JAK3 < 10 μM [56]. Another set of benzimidazole based compounds (**30**) was reported by IRM with 120 examples and no biological data [57]. Last, Pharmacopeia reported on a series of imidazopyrimidines (**31**) and pyrimidine-imidazinones (**32**) in six filings with 269, 326,

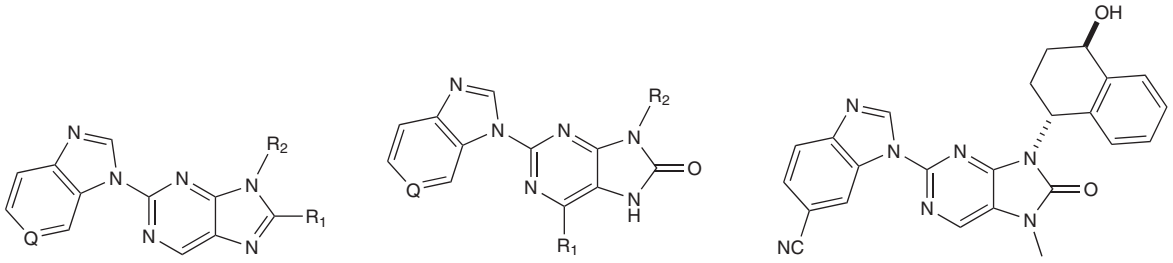


23 (WO2007077949A1) **24** (WO2007007919A2) **25** (WO2009026107A1)

Figure 6. More pyrrolo pyridines and pyrimidines.



26 (WO2008090181A1) **27** (X = NH); **28** (X = S) (WO2004099204A1) **29** (WO2005066156A1) **30** (WO2007005673A1)



31 (WO2008043019A1) **32** (WO2008043031A1) **33** (WO2009048474A1)

Figure 7. Purines, imidazo-pyrimidines, imidazo-pyridines, benzimidazoles and pyrimidine-imidazones.

112, 141, 138 and 57 examples reported in sequential publications [58-63]. There were biological data for most compounds with many < 100 nM against the JAK3 enzyme. One compound (**33**) had reported activity better than CP-690,550 (**8**) in an *in vivo* model of IFN-γ release [63].

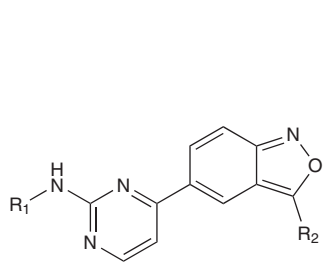
4.3 Oxygen and sulfur containing 5,6-fused heterocycles

In addition to the sulfur containing heterocycle reported earlier (**28**), there were other reports of oxygen and sulfur containing heterocycles. Vertex reported a series of benzisoxazoles (**34**, **Figure 8**) with 38 examples and no biological data [64]. Novartis reported a series of amino-benzoxazoles (**35**) with 185 examples and only JAK2 activity listed [65]. Last, Cytopia reported on a thienopyrimidine series (**36**) with 101 examples, and reported JAK3 activity on several compounds < 1 μM [66].

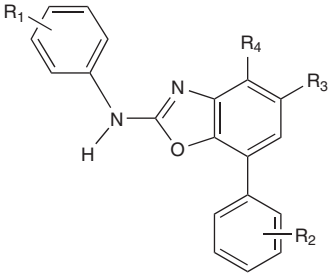
5. Monocyclic 5 and 6 member heterocycles: pyrimidines, pyridines, pyrazines, triazines and thiophenes

5.1 Six member heterocycles: pyridines, pyrimidines and pyrazines

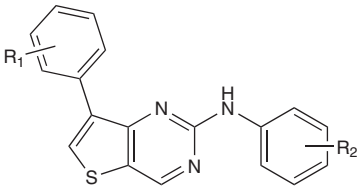
The second largest area with applications is with monocyclic containing compounds where the core is defined as either a pyridine or pyrimidine. This area has about 20 filings with a large variety of structural types and examples. Vertex had several filings covering both pyridine and pyrimidine compounds (**Figure 9**). Three filings covered aminophenyl pyridines and pyrimidines (**37** and **38**) with 144, 189 and 95 examples



34 (WO2004058749A1)

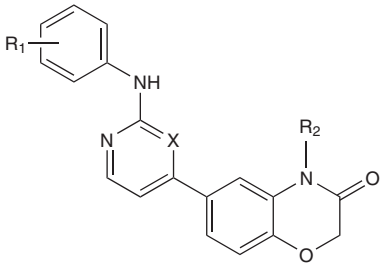


35 (WO2008031594A1)

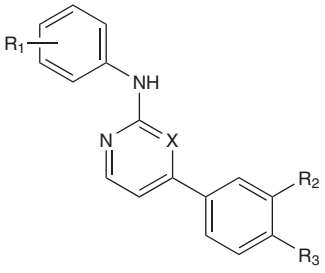


36 (WO2009062258A1)

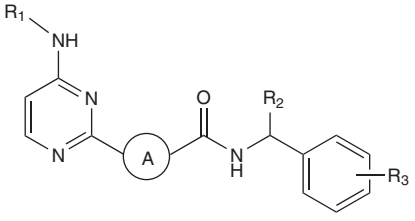
Figure 8. Oxygen and sulfur containing 5,6-fused heterocycles.



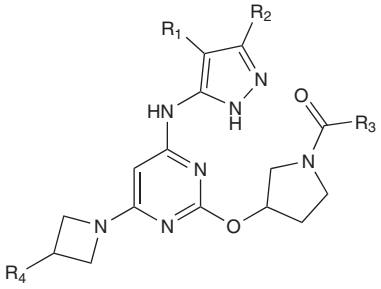
37 (X = CH and N)
(US2004097504A1)



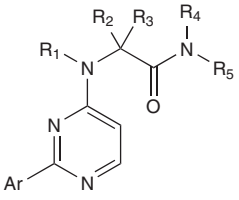
38 (X = CH and N)
(WO2004041810A1)



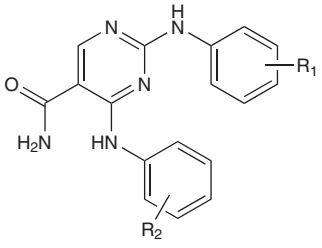
39 (WO2005068468A2)



40 (WO2007059299A1)



41 (WO2008116139A2)



42 (WO2008009458A1)

Figure 9. Pyridines and pyrimidines.

each [67-69]. No biological data were provided. Two applications covered slightly more complicated substitutions (**39** and **40**) with 12 and 3 examples each [70,71]. The last application (**40**) listed one compound with a K_i of < 10 nM against JAK3. The final application in this series listed a series of pyrimidine amides (**41**) with 168 examples [72]. This application listed 20 compounds with K_i values < 1 μM against JAK3. Novartis provided one application in this area involving diaryl-pyrimidine carboxamides (**42**). There were 96 examples listed and the best compound had an IC_{50} value of 26 nM against the JAK3 enzyme [73].

The next biggest contribution in this part of the patent literature is that from Rigel (**Figure 10**). There are eight applications in all covering many examples. These applications all focus on the 2,4-pyrimidinediamine structure (**43**) with a focus on both Syk and JAK3 kinase activity. Often, the biological activity was provided in whole cell assays using both IL-2/T and IL-4/B cytokine–cell combinations. Two generic representations are **43** and **44**, both of which in essence cover the first five applications of 89, 726, 235, 549 and 202 examples [74-78]. Many compounds from these applications have IC_{50} values < 100 nM in both the T- and B-cell assays. Many of these compounds contain a primary sulfonamide as in **44**. The other three applications contain 45, 509 and 311 examples [79-81]. Although the generic structures **43** and **44** still apply in these cases, so does an expansion in the aromatic ring systems to other cyclic structures with the generic representation of **45**. For example, compound **46** was

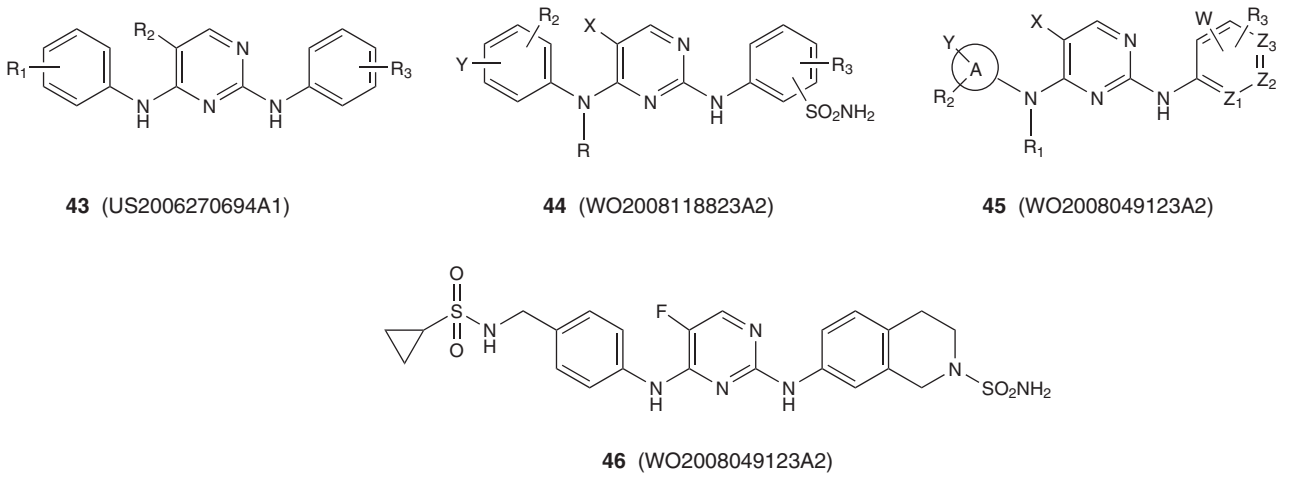


Figure 10. Pyrimidines from Rigel.

3 nM in the IL-2/T-cell assay. Rigel has reported a compound of unknown structure that is in Phase I clinical trials (R-348). The significance of the status of this compound is discussed later, but it is likely that R-348 is contained in one of these applications.

Cytopia reported on both pyridines and pyrimidines as different monocyclic series (**Figure 11**) in four applications. The first structural example involves nicotinamide derivatives (**47**) and there are two applications that cover 137 and 18 examples [82,83]. Only a few compounds are indicated with activity < 10 μM in the JAK3 assay. The second structural type involves arylthio and aniline based 2,4-substituted pyrimidines (**48**) in two applications with 394 and 64 examples, respectively [84,85]. There are many examples where JAK3 activity is < 1 μM, and a few with IC_{50} values < 100 nM. Targegen reported on a series of thiophenyl-aniline pyrimidines (**49**) with 100 examples [86]. The best compound had an IC_{50} value of 13 nM against the JAK3 enzyme. Cytopia reported two variations of 2,5-substituted 1,4-pyrazines (**50**, **Figure 11**). The first involves imidazo substitution with 84 examples, and the second as just a phenyl substitution with 55 examples [87,88]. Many compounds show > 50% inhibition at 10 μM against the JAK3 enzyme.

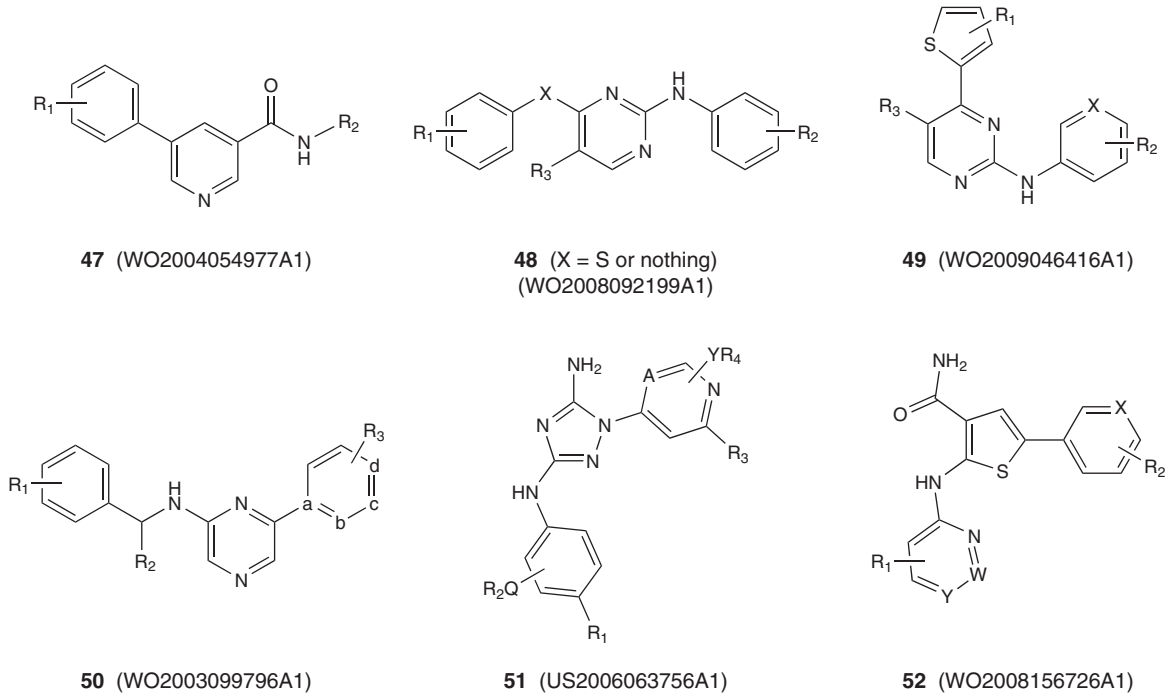
5.2 Five member heterocycles, triazoles and thiophenes

The last area to mention in the monocyclic series is that of five member heterocycles. Here, there are only a few developments. The first by Vertex discloses a series of diaminotriazoles (**Figure 11**, **51**) with 176 examples [89]. Most compounds had IC_{50} values < 50 nM in the JAK3 enzyme assay. The second is from Merck and discloses a series of aminothiophene carboxamides (**52**). There are 624 examples in this application with no specific biological data given [90].

6. Fusedmulticyclic heterocycles (more than two fused rings)

The applications that cover compounds with more than two fused rings is the last section of this review and have numerous examples, but about the same in number as the 6,6 fused heterocyclic class. These examples cover several classes of nitrogen based heterocycles. The first example is provided by Johnson & Johnson and covers a series of indole carbazoles similar in structure to the natural product staurosporine (**53**, **Figure 12**) [91]. Here, there are 223 examples with IC_{50} values as low as 1 nM in the JAK3 assay. In the next example, Merck reported four applications (**Figure 12**) covering tri and tetracyclic heterocycles. The first two contain a pyrimidinone ring fused at the end (**54** and **55**). Here, there are 127 and 189 examples for **54** and **55**, respectively [92,93]. No specific biological data were given. The next two applications focus on tricyclic carboxamides (**56**). There are 50 and 47 examples given where the parent ring can be either a pyridyl-carboline or pyridyl-benzthiophene [94,95]. Again, no specific biological data were given.

Vertex provided two separate series in this area (**Figure 13**). The first is a series of fused tricylic amino pyrimidines (**57**) where 235 examples are provided with diverse heterocyclic substitutions [96]. No data were given. The next discloses a series of fused azepine-pyrrolopyridine and pyrimidine series (**58**) [97]. There are 162 examples given here, with IC_{50} values < 250 nM in the JAK3 enzyme assay for 10 compounds. The next series was disclosed by IRM and provides a series of fused tricyclic napthyridines (**59**). There are 61 examples given with no data [98]. The last company to report in this area is Incyte. They provide two separate series (**Figure 13**). The first are fused pyrimidinones (**60**) similar to the Merck compounds (**54** and **55**) but more diverse in the ring systems [99]. There are 357 examples given and no specific



47 (WO2004054977A1)

48 (X = S or nothing) (WO2008092199A1)

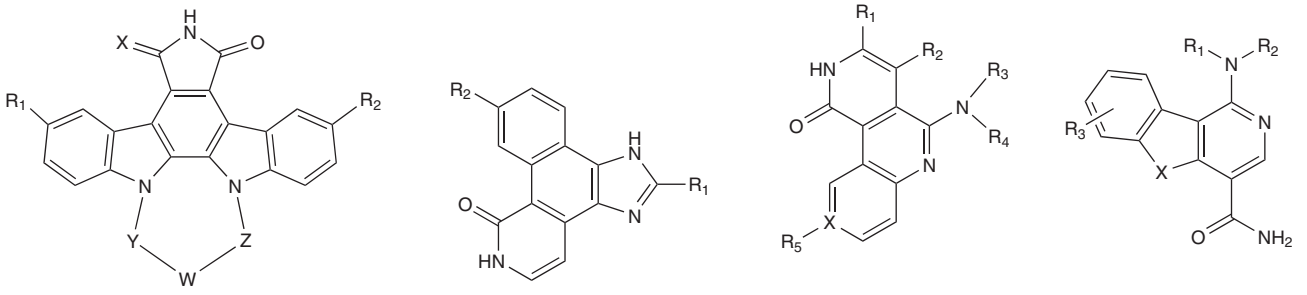
49 (WO2009046416A1)

50 (WO2003099796A1)

51 (US2006063756A1)

52 (WO2008156726A1)

Figure 11. Pyridines, pyrimidines, pyrazines, triazoles and thiophenes.



53 (US2007249590A1)

54 (WO2007145957A1)

55 (X = C,N) (WO2009035575A1)

56 (X = S,NH) (WO2007061764A2)

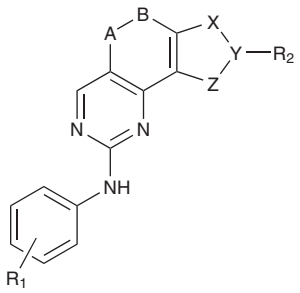
Figure 12. Multicyclic compounds from Johnson & Johnson and Merck.

data are provided. The second is a series of tetracyclic compounds with a fused imidazo-azepine ring system (**61**) [100]. Here, there are 382 examples with no specific data given.

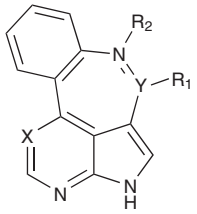
7. Expert opinion

The last decade has seen an increasing amount of resources dedicated to the discovery, characterization and development of JAK3 inhibitors [8,101]. There are now almost 90 patents and patent applications which describe thousands of examples with a wide diversity of heterocyclic structures that have been claimed as JAK3 inhibitors. The applications vary in the biological data presented, with some applications providing IC_{50} values and animal data, while others are absent of any specific biological data. Furthermore, while some cover JAK3 specifically, others claim acitivty in all JAK family members (JAK1, JAK2, JAK3 and Tyk2). This latter approach may be more prudent given the current development status of compounds that are active against several of these enzymes, especially JAK1 and JAK2. The significance of this is still unfolding. However, it seems clear that in addition to JAK3, the other JAKs may become useful therapeutic targets.

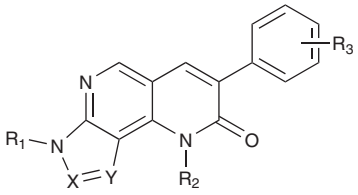
The early compounds identified as active against JAK3 have moved on to further evaluation. The clinical candidate CP-690,550 (**8**) is the most significant compound in the field and has been tested in Phase II trials in various diseases that verify the drug target, including kidney transplantation, psoriasis and rheumatoid arthritis [102]. Compound **8** has an



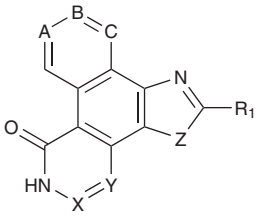
57 (US2005148603A1)



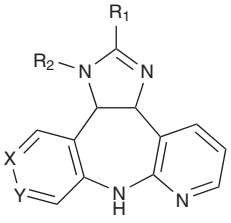
58 (WO2008079521A2)



59 [X = Y = C(R); X = C(R), Y = N; X = N, Y = C(R)] (WO2007134259A2)



60 (WO2005105814A1)



61 (X = Y = C(R); X = CH, Y = N; X = N, Y = CH) (WO2007038215A1)

Figure 13. Multicyclic compounds from Vertex, IRM and Incyte.

IC_{50} value of 1 nM against JAK3, but also inhibits JAK1 and JAK2 at higher concentrations (JAK2 IC_{50} = 20 nM, JAK1 IC_{50} = 112 nM) and it is concluded that the anemia seen as a side effect in primate studies of kidney allograft rejection is due to the inhibition of JAK2 [103,104]. Even though there is only a 10-fold difference in the enzyme inhibition between JAK3 and JAK2, the true therapeutic window may be larger because JAK3 and JAK1 act cooperatively in the receptor response giving an enhanced therapeutic window. The compound has been efficacious in humans during intermediate term studies lasting up to 12 weeks. In dose escalation studies in renal transplant, rheumatoid arthritis and psoriasis, improvement is seen at all doses [105]. At the higher doses some minor side effects have been observed and slight decreases in hemoglobin were seen, while a few reports of serious infections appeared. The side effects that are thought to be associated with JAK1 inhibition (neurologic effects) have not yet surfaced [12].

To date, there are two others that have reached Phase I clinical trials, R-348 (Rigel) [106,107] and VX-509 (Vertex) [108] (structures not disclosed). The Rigel compound R-348 is likely to be contained in the pyrimidine class (**43 – 46**) because these are the only recorded filings that have appeared for this company. It is labeled as a dual JAK3–Syk kinase inhibitor and has shown positive results in a rat cardiac allograft model [107]. The Vertex compound (VX-509) is more difficult to assign because there were multiple chemical series that appeared (**4**, **6**, **17 – 22**, **34**, **37 – 42**, **51**, **57**, **58**). As these potential drugs continue to be studied, they will provide insight to the pending issues, merits and potential improvements in the continuing development of inhibitors in this field. It is likely given the current pipeline of intellectual property outlined here, more compounds (such as **33**) will enter clinical trials and one or more will eventually gain marketing approval within the next 5 years or soon thereafter. However, the challenges remain in the search for a truly selective JAK3 inhibitor, which will continue to present itself as an attractive target.

Another concept that may result in potentially successful therapeutic agents includes compounds that are pan JAK inhibitors, which includes those compounds that inhibit either two or all three enzymes (JAK1, JAK2, JAK3). As such, although more selective for JAK3, CP-690,550 is effectively a pan JAK inhibitor. In fact, INCB18424 (**11**), a characterized JAK1/JAK2 inhibitor (IC_{50} values for JAK1, JAK2 and JAK3 are 3, 5 and 332 nM, respectively), has reached clinical trials for oncology indications, rheumatoid arthritis, and psoriasis. This compound is worth noting due to its opposite potency profile in the inhibition of the JAK enzymes when compared to CP-690,550 [109,110]. If these trials demonstrate low or reasonable side effect levels, it will make the pathway for further JAK3 inhibitor development less cumbersome. Furthermore, a dual JAK1/JAK3 inhibitor that has a larger therapeutic window against JAK2 than

CP-690,550 (**8**) will be an important development as JAK1 related side effects have not yet been observed. These trials and those ongoing for JAK3/pan JAK inhibitors such as CP-690,550 and INCB18424 may demonstrate that inhibiting the JAK2 pathway is tolerable during treatment and blocking this pathway is beneficial in the eradication of leukemia and other related JAK2 disorders. Although the context of this review focused on JAK3, ultimately, the pan JAK activity for compounds that make their way through clinical trials may generate interest in all JAK enzymes as therapeutic targets.

Declaration of interest

The author states no conflict of interest and has received no payment in preparation of this manuscript.

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