Tetrasubstituted Imidazole Inhibitors of Cytokine Release: Probing Substituents in the N-1 Position†

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We prepared novel 1,2,4,5-tetrasubstituted imidazole derivatives with high anti-inflammatory activity by using our previously described regiospecific synthesis. Systematic optimization of the imidazole N-1 substituent resulted in compound **9b** that potently inhibited the mitogen-activated protein kinase p38 (p38 $IC_{50} = 0.218\ \mu M$) as well as the release of the proinflammatory cytokines interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) from human whole blood after stimulation with LPS. Furthermore, compound **9b** exhibited reduced cytochrome P450 interaction in comparison with SB203580. This result is particularly important, since cytochrome P450 interaction is observed for some p38 inhibitors and in turn can potentially cause drug−drug interaction or lead to other hepatic changes such as P450 enzyme induction.

Introduction

Inflammation is a defense reaction initiated by tissue damage, injury, or infectious pathogens. The primary objective of inflammation is to localize and eradicate the irritant and to repair the surrounding tissue. Acute inflammation exhibits a rapid onset and is maintained only for a short duration. On the other hand, chronic inflammation is an inflammatory response of prolonged duration often leading to severe tissue damage. In some cases, the stimulus to chronic inflammation may be an endogenous tissue component, giving rise to a so-called *autoimmune disease*.

Elevated levels of proinflammatory cytokines, especially tumor necrosis factor α (TNFα) and interleukin-1β (IL-1β), are associated with several autoimmune diseases[1], including rheumatoid arthritis (RA)[2], toxic shock syndrome, osteoarthritis, and inflammatory bowel disease. For example, RA is a chronic inflammatory and destructive joint disease of unknown etiology. It affects about 1% of the population worldwide and is characterized by a chronic inflammation of the synovium (synovitis), which often leads to joint and bone destruction, to significant disability, and consequently to a reduction in quality of life. The cytokines mediate the inflammatory response in association with other related molecules.[3,4] It is well-established that TNFα and IL-1β are key cytokines in the process of chronic inflammation and the resulting tissue and bone destruction. Therefore, the regulation of proinflammatory cytokines, mainly TNFα and IL-1β, is of crucial importance in chronic inflammatory diseases such as RA.[5] The ongoing evaluation of the cytokine cascade and the steadily growing knowledge about cytokine-mediated processes seem to open striking therapeutical options in the fields of sepsis and autoimmune and chronic inflammatory diseases via modulation or inhibition of the cytokine cascade. Subsequently, anti-cytokine treatments can be efficiently used in the therapy of chronic inflammatory rheumatic diseases. Biological cytokine inhibitors, such as soluble TNFα receptors (Etanercept), IL-1 receptor antagonists (Anakinra), or anti-TNF antibodies (Infliximab, Adalimumab), provide new therapeutic strategies for these diseases.[6,7] However, limitations of these biologicals are adverse immunological reactions,[6,8] and the therapy is associated with high costs.[9] There is still a lack of new and effective small molecule disease modifying agents that are orally active and more safe.

A new therapeutic drug target for the treatment of inflammatory disorders is the mitogen-activated protein kinase (MAPK) p38.[10−13] P38 is a serine/threonine kinase that is part of the stress-activated signal transduction cascade that transduces extracellular signals to intracellular response, e. g. cytokine production.[11,14,15] The p38-MAPK is activated through bis-phosphorylation of Thr and Tyr within a Thr-Gly-Tyr motif, which is located in an activation or phosphorylation loop near the active site. Activated p38 phosphorylates other kinases or transcription factors, leading to mRNA stabilization or expression of certain target genes.[10,16−18]

Pyridinylimidazoles (i.e. SB203580) are potent and selective inhibitors of p38-MAPK[7,19,20] by competing with ATP for binding to the ATP pocket (Figure 1).[21−23] In contrast to ATP, which only interacts with the activated (bis-phosphorylated) kinase, pyridinylimidazoles also bind to the inactive form. The pyridinylimidazole pharmacophore is defined as the 4-aryl-5-(pyridin-4-yl)imidazole.[24] The 4-aryl substituent occupies an additional hydrophobic pocket generated mainly by the Thr106 side chain, which is replaced by a bulky hydrophobic residue in most other protein kinases. Therefore, this small hydrophobic pocket near the ATP-binding site is responsible for the selectivity of SB203580 for p38 compared to most other kinases.[22,25,26] The pyridin-4-yl moiety is essential for the inhibitory potency and generates a pivotal hydrogen bond with the amino backbone of Met109 through its pyridinium nitrogen.[27]

† Dedicated to Prof. Dr. Dannhardt on the occasion of his 60th birthday.

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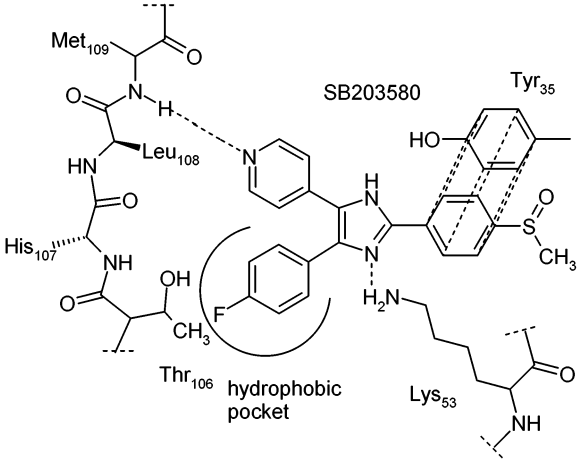


Figure 1. Representation of the active site interactions between SB203580 and p38-MAPK. (modified from refs 19, 24, and 27). The predicted hydrogen bonds and $\pi-\pi$-interaction are indicated by broken lines.

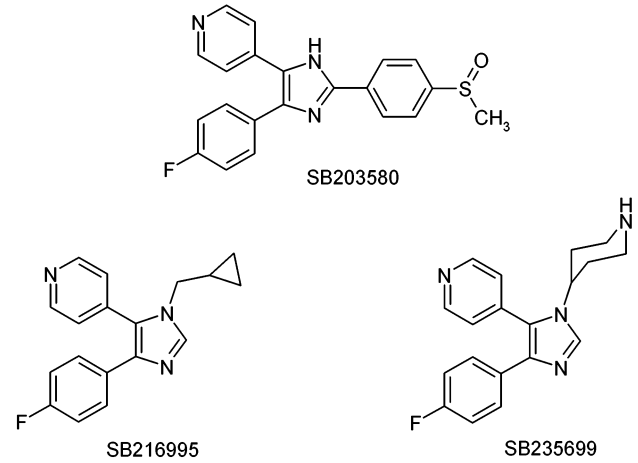


Figure 2. Pyridinylimidazole inhibitors of p38-MAP kinase. The piperidin-4-yl residue of SB235699 is supposed to interact with Lys53, whereas the cyclopropylmethyl residue is assumed to interact with Val30 and Val38.[22]

In general, substitutions at the imidazole N-1 (adjacent to the azaheteroaryl) and the C-2 position are both tolerated. However, substitution at the imidazole N-3 (adjacent to the aryl group) is not tolerated and causes a loss of potency.[24]

The major drawback of the therapeutical use of some pyridinylimidazoles is the occurrence of severe adverse effects. Some pyridinylimidazoles inhibitors have been associated with CYP450 inhibition.[24,28] Both the imidazole ring itself and the pyridinyl substituent seem to contribute to this adverse effect.[29] Thus, the work presented here aims to modify the pyridinylimidazole SB203580 at the N-1 position to enhance its inhibitory effects on p38-MAPK and to minimize its interference with the CYP450 pathway. The low CYP450 interaction potential can in theory be attained by changing electronic properties of both nitrogen heterocycles while retaining all essential interactions with the active site of p38. In a previous study,[30] we identified a methylsulfanyl residue as favorable substituent at the C-2 position. This group contributes low sterical hindrance, thus allowing deep penetration of the inhibitor into the ATP binding pocket and thereby leading to tighter binding. Nevertheless, we tested different residues at the imidazole C-2 in combination with our novel N-1 substituents to determine the importance of the C-2 substituent in combination with different N-1 substitutents. Acetylation of 2-aminopyridine increases the affinity of pyridinylimidazoles for p38-MAPK. This higher affinity is not detected for a simple amino group at the pyridine ring, suggesting that the amino group of the 2-acetylaminopyridine generates a second hydrogen bond with the carbonyl group of Met109.[31] Therefore, we used acetylated 2-aminopyridines in our study.

The key objective of our study was the synthesis of compounds with higher affinity for the p38-MAPK and improved in vitro and in vivo potency combined with reduced CYP450 interaction. We describe our investigation on the structure−activity relation of tetrasubstituted imidazoles, which led to the identification of the methoxyethyl moiety as an optimal N-1 substituent, combining significantly decreased CYP450 interference and highly efficient inhibition of p38-MAPK activity regardless of its C-2 substituent.

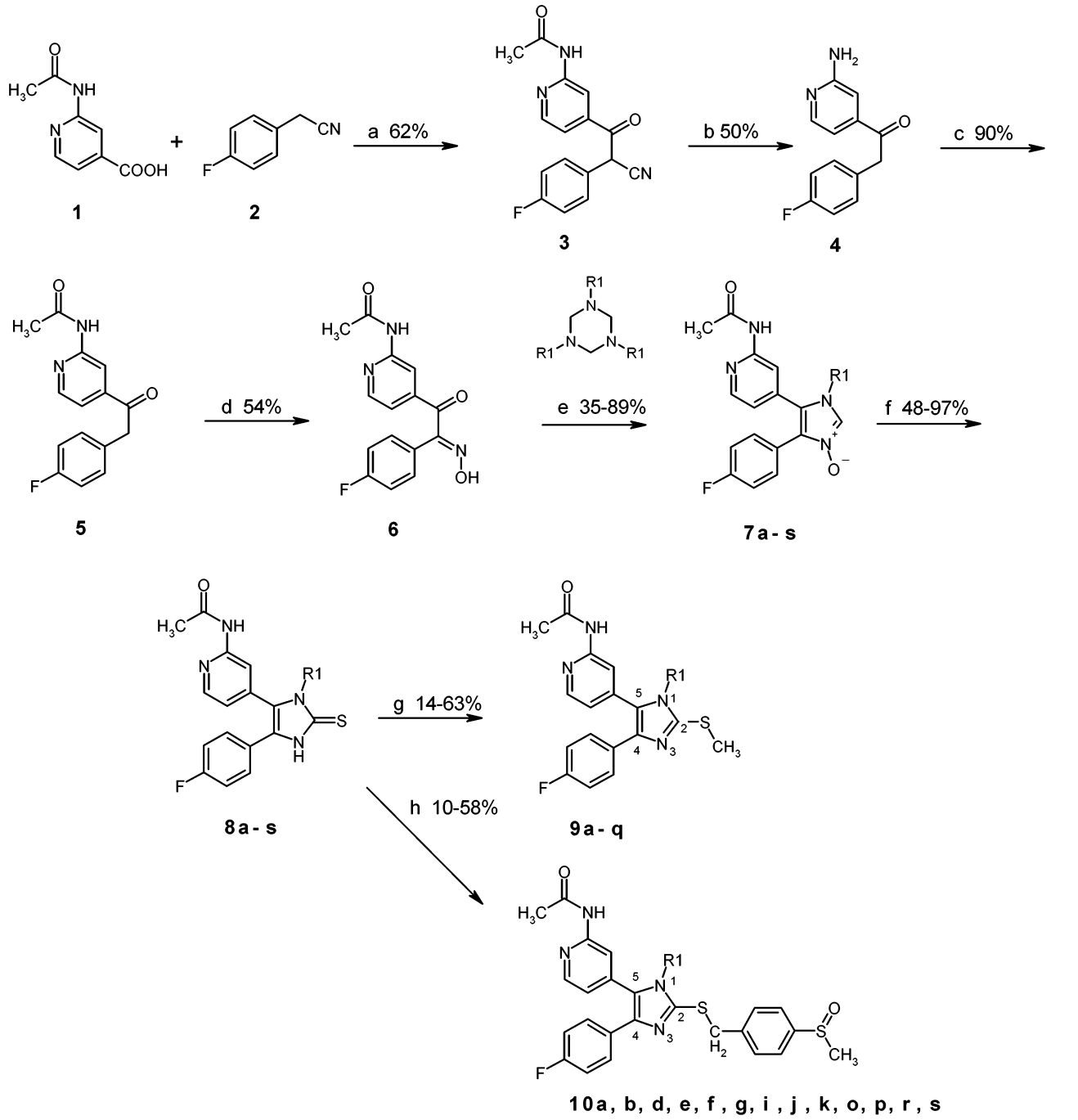
Chemistry

The general synthesis of regiospecific tetrasubstituted pyridin-4-ylimidazoles has previously been described (Scheme 1).[31−33] The starting material for all syntheses was α-hydroximinoketone **6**. Compound **6** was obtained in three steps from nitrile **3**. Condensation of activated 2-acetyl isonicotinic acid **1** with 4-fluorophenyl acetonitrile **2** in DMF produced **3** with 62% yield. The nitrile residue was hydrolyzed using 48% HBr. Due to this acidic environment, decarboxylation of **3** occurred concurrently with the cleavage of the acetyl moiety at the aminopyridine, producing compound **4**. Reintroduction of the acetyl group was achieved by refluxing **4** in acetic anhydride. Compound **6** was prepared by using isoamyl nitrite, sodium methoxide, and methanol at room temperature based on a standard procedure used in our laboratory. In the following step, different residues at the imidazole N-1 were introduced by using several substituted triazines. The triazines were prepared according to literature procedures.[34−36] (For example, we added paraformaldehyde to the stirred liquid primary amine. The resulted clear solution could be used without any purification step.) Depending on the corresponding residues at the triazines, the imidazole *N*-oxides **7a**−**s** were obtained, which were converted into the thiones **8a**−**s** by using 2,2,4,4-tetramethylcyclobutane-1,3-dithione[37] as sulfur donor. At this step, a second source of diversity was introduced by substituting the thiones **8a**−**s**. To generate compounds **9a**−**q**, iodomethane was used for the S-methylation. For compounds in the **10** series, 1-chloromethyl-4-methanesulfinylbenzene was used. In both cases, Na_2CO_3 catalyzed the S-substitution. To synthesize compounds **11a**−**e** starting from the thiones **8a**−**c**, tetramethylammonium iodide was utilized as catalytic agent in THF (Scheme 2).

Biological Results and Discussion

Recently, 1,4,5-trisubstituted imidazoles have been synthesized to demonstrate the effects of substitution at imidazole N-1 [i.e. piperidin-4-yl (SB235699) and cyclopropylmethyl (SB216995)] (Figure 2). The piperidin-4-yl residue was envisioned to interact with the carboxyl group of Asp168,[19] whereas the cyclopropylmethyl residue was assumed to interact with the phos-

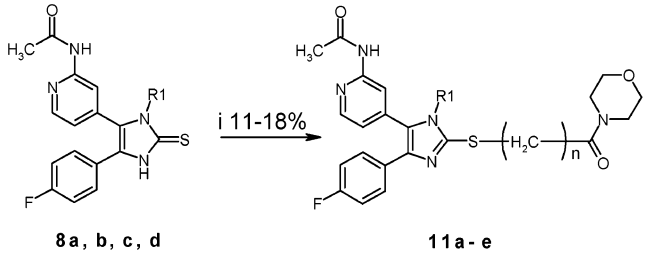
Scheme 1[a]



[a] Reagents: (a) carbonyldiimidazole, absolute DMF, potassium *tert*-butoxide, 120 °C; (b) 48% hydrobromic acid, reflux; (c) acetic anhydride, 4-(dimethylamino)pyridine, reflux; (d) isoamyl nitrite, sodium methoxide, methanol, rt; (e) substituted triazine, ethanol, reflux; (f) 2,2,4,4-tetramethylcyclobutane-1,3-dithione, DCM, rt; (g) iodomethane, Na_2CO_3, ethanol, reflux; (h) 1-chloromethyl-4-methylsulfinylbenzene, Na_2CO_3, ethanol, reflux.

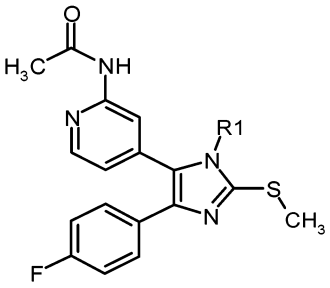
phate-binding ribbon in a cavity formed by Val30 and Val38.[27] Previous work has demonstrated that tetra-substituted imidazoles that were substituted with a methyl group at N-1 of the imidazole have improved selectivity and oral bioavailability.[38] Therefore, we studied the effects of substitution at N-1 in a much wider range. We analyzed both inhibitions of p38-MAPK and CYP450 and compared them to the inhibitory functions of SB203580. It has been demonstrated that 1,4,5-trisubstituted imidazoles can interact with Asp168 of p38-MAPK through the residue positioned at imidazole N-1.[19,22] Thus, a variety of substituents were

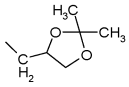
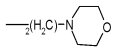
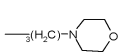
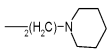
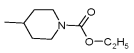
Scheme 2[a]



[a] Reagents: (i) Na_2CO_3, THF, chloro-1-morpholin-4-ylalkan-1-one, tetrabutylammonium iodide.

Table 1. Inhibition of P38-MAP Kinase by Acetylaminopyridines[a]



		$IC_{50} \pm$ SEM (μM)
compd	R^1	p38α
9a	-$(CH_2)_2$-OH	0.398 ± 0.037 (n=3)
9b	-$(CH_2)_2$-O-CH_3	0.218 ± 0.010 (n=3
9c	-$(CH_2)_3$-OH	0.813 ± 0.04 (n=3)
9d	-$(CH_2)_3$-O-CH_3	0.205 ± 0.027 (n=3)
9e	-$(CH_2)_2O(CH_2)_2$-OH	8.479 ± 0.384 (n=2)
9f	-CH_2-$CH(CH_3)OH$	8.692 ± 0.188 (n=2)
9g	-$(CH_2)_2$-NH-$COCH_3$	7.29 (n=1)
9h	-$(CH_2)_2$-$N(CH_3)_2$	2.409 ± 0.145 (n=3)
9i	-$(CH_2)_2OCH_2CH{=}CH_2$	1.85 ± 0.753 (n=3)
9j	-$(CH_2)_2OCH_2C{\equiv}CH$	0.666 ± 0.148 (n=3)
9k	-$(CH_2)_2$-S-CH_3	0.431 ± 0.1 (n=3)
9l	-(CH_2)-$CH(OCH_3)_2$	4.099 ± 1.690 (n=2)
9m		3.732 ± 2.116 (n=2)
9n		2.029 ± 0.686 (n=2)
9o		6.279 ± 1.510 (n=3)
9p		1.343 ± 0.576 (n=2)
9q		>10
SB203580		0.462 ± 0.025 (n=6)

[a] Results are given as mean of two independent experiments except stated otherwise.

introduced at N-1 (**10a**−**q**) and the the C-2 substituent (a methylsulfanyl group) was kept constant. Theoretically, substitution at the imidazole N-1 position with hydroxyalkyl residues (**9a**,**c**,**e**,**f**) should result in enhanced inhibitory potency compared to SB203580. This is due to the fact that alcohols could interact via a hydrogen bond to the carboxyl group of Asp168. Compound **9a** displayed a considerable inhibition of p38-kinase activity comparable to SB203580, whereas **9c** showed a decrease. Compounds **9e** and **9f** showed a loss of inhibitory potency (Table 1) compared to the reference compound SB203580. On one hand, it can be assumed that **9a** and **9c** have the ability to interact with Asp168 (Figure 3). On the other hand, the hydroxyalkyl substituent could force these compounds into a spatially unfavorable conformation hindering an optimal interaction of the compounds with the active side of the kinase (Figure 4). **9c** was more likely to take the unfavorable

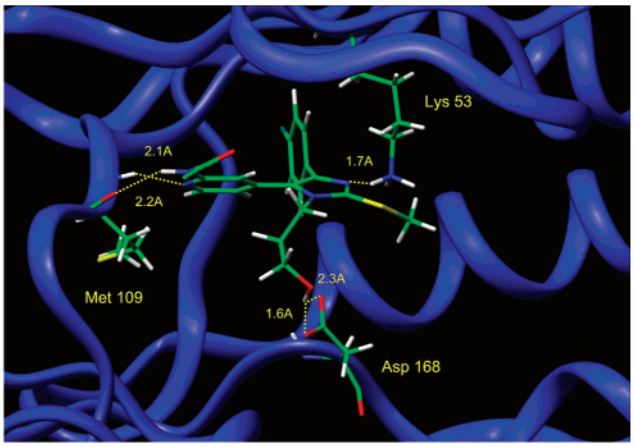


Figure 3. Model of **9c** bound to the ATP-binding side of p38-MAP kinase. The predicted hydrogen-bond interactions between **9c**, Met109, Lys53, and Asp168 are displayed by yellow dashed lines.

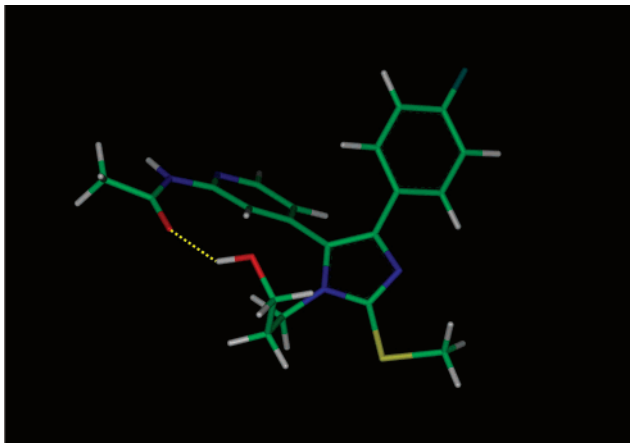
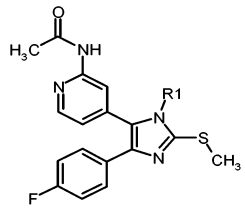


Figure 4. Model of a spatially unfavorable conformation of **9c**, hindering the compound to bind to the p38-MAPK. The expected intramolecular hydrogen bond is depicted by a yellow dashed line.

conformation than **9a** because of its elongated flexible alkyl side chain; hence, it has a lower inhibitory activity. Compound **9e** presumably lost its potency due to its elongated spacer, corroborating the assumption that biological activity depends on the length of the side chain in the case of our tetrasubstituted imidazoles. A possible explanation for the loss in potency of **9f** could be the sterical conformation of this branched residue at the imidazole N-1, thus hindering the compound to penetrate deeply into the ATP binding pocket. However, this conflicts with literature data, in which branching was tolerated in the case of some other pyridinylimidazoles.[39] Substitution of the hydroxyl groups of **9a** and **9c** with a methoxy group provided **9b** and **9d**, respectively. This resulted in a 2-fold improvement of p38 inhibition (Table 1) compared to SB203580. We assumed that the ether was not able to take the same spatial conformation as the alcohol (Figure 4) and could therefore possibly take a sterical conformation allowing the interaction of its oxygen atom with the hydroxyl hydrogen of Asp168. Contrarily, this improved inhibitory potency could not be observed in the whole blood assay in comparison to SB203580 (Table 2). Compounds **9a**−**d** inhibited the release of both cytokines with similar IC_{50} values. The different trends in the enzyme assay and

Table 2. Inhibition of Cytokine Release by Acetylaminopyridines[a]

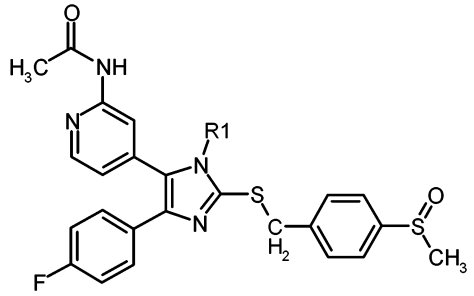


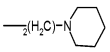
compd	R^1	IC_{50} ± SEM (μM) Whole Blood TNFα	IL-1β
9a	-$(CH_2)_2$-OH	35.75 ± 9.25	33.25 ± 5.75
9b	-$(CH_2)_2$-O-CH_3	32.75 ± 3.25	30.5 ± 2.9
9c	-$(CH_2)_3$-OH	20.5 ± 8.5	13.75 ± 2.25
9d	-$(CH_2)_3$-O-CH_3	17.75 ± 4.25	18.25 ± 3.25
9e	-$(CH_2)_2O(CH_2)_2$-OH	>100	>100
9f	-(CH_2)-$CH(CH_3)$OH	n.d.	n.d.
9g	-$(CH_2)_2$-NH-$COCH_3$	n.d.	n.d.
9h	-$(CH_2)_2$-$N(CH_3)_2$	n.d.	n.d.
9i	-$(CH_2)_2OCH_2CH{=}CH_2$	>100	48.495 ± 11.825
9j	-$(CH_2)_2OCH_2C{\equiv}CH$	40.0 ± 5.27	13.87 ± 7.49
9k	-$(CH_2)_2$-S-CH_3	44.235 ± 2.925	36.435 ± 1.625
9l	-(CH_2)-$CH(OCH_3)_2$	n.d.	n.d.
9m		n.d.	n.d.
9n		>10	>10
9o		n.d.	n.d.
9p		>10	>10
9q		n.d.	n.d.
SB203580		2.64 ± 0.769 (n=6)	1.117 ± 0.493 (n=6)

[a] Results are given as mean of two independent experiments except stated otherwise.

the whole blood assay could be ascribed to differences in transport, membrane penetration, intracellular distribution, or metabolic effects. Given the benefit in potency gained from the presence of the methoxyethyl residue in **9b**, we wanted to determine whether the oxygen atom was necessary for the improved inhibitory potency. Comparing **9b** and **9k**, we came to the conclusion that the loss of potency of **9k** (Table 1) can be attributed to the reduced electronegativity around the sulfur atom, leading to a weaker hydrogen bond with Asp168. In addition, it can also be explained by the larger atom radius of sulfur. The decreased inhibitory potency compared to SB203580 was not seen in the whole blood assay (Table 2) in which **9b** and **9k** showed comparable inhibition of cytokine release (Table 2). Substitution of the hydroxyl group of **9a** with an allyloxy residue (**9i**) led to decreased activity (Table 1), presumably due to sterical hindrance. In contrast, hydroxyl substitution in **9a** with a propynyloxy residue (compound **9j**) resulted in a 3-fold increased inhibition of p38 kinase compared to **9i** and only moderately decreased inhibition compared to SB203580 (Table 1). This could result from $\pi-\pi$ interactions immobilizing the flexible side chain in a favorable spatial conformation, thereby causing a tighter binding to the kinase. Similar to the p38 kinase values, **9i** showed less potency in the whole blood assay than **9j**, which was comparable to **9a**−**d** in the whole blood assay (Table 2). Compound **9g** was expected to be capable of forming two hydrogen bonds with Asp168. However, contrary to theory, there was

Table 3. Inhibition of P38-MAP Kinase by Methylsulfinylbenzylmethylsulfanyl-Substituted Imidazole Compounds[a]



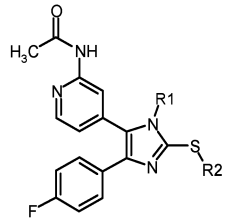
compd	R^1	IC_{50} ± SEM (μM) p38α
10r	-CH_3	5.849 ± 0.809 (n=2)
10a	-$(CH_2)_2$-OH	2.236 ± 0.126 (n=3)
10b	-$(CH_2)_2$-O-CH_3	0.15 (n=1)
10d	-$(CH_2)_3$-O-CH_3	1.306 ± 0.439 (n=3)
10e	-$(CH_2)_2O(CH_2)_2$-OH	>10
10f	-(CH_2)-$CH(CH_3)$OH	>10
10g	-$(CH_2)_2$-NH-$COCH_3$	>10
10i	-$(CH_2)_2OCH_2CH{=}CH_2$	>10
10j	-$(CH_2)_2OCH_2CC$-H	4.974 ± 0.007 (n=2)
10k	-$(CH_2)_2$-S-CH_3	2.377 ± 0.304 (n=2)
10s		>10
10o		>10
10p		4.435 ± 0.229 (n=2)
SB203580		0.462 ± 0.025 (n=6)

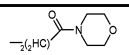
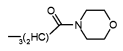
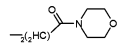
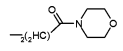
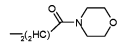
[a] Results are given as mean of two independent experiments except stated otherwise.

no improvement noted in p38 kinase inhibitory potency (Table 1). We supposed that this could be due to a sterical handicap that prevents the tight binding to p38 kinase. The compounds **9l** and **9m** possessed a branched side chain at imidazole N-1 and, in accordance with their assumed sterical hindrance, demonstrated decreased p38 kinase inhibitory potency (Table 1). The morpholinopropyl residue at imidazole N-1 in trisubstituted imidazoles has been described to give marginally better results than the morpholinoethyl residue.[40] In contrast, we found that the 2-carbon spacer in **9n** led to a 3-fold better result than the three-carbon spacer in compound **9o** (Table 1). Accordingly, compound **9p**, containing a two-carbon spacer, had approximately the same inhibitory potency as compound **9n** (Table 1). On the basis of the comparison between compounds **9p** and **9n,** it can be assumed that the oxygen in the morpholine ring is not necessary for the inhibitory potency. The compound with the weakest activity was **9q** (Table 1) substituted at N-1 with a piperidine-1-carboxylic acid ethyl ester. In an overall perspective, we found increased inhibitory potency in vitro only for the compounds **9b** and **9d**.

In the next step, we synthesized compounds in the **10** series with a 4-methylsulfinylbenzylsulfanyl residue at the C-2 position of the imidazole ring to analyze

Table 4. Inhibition of P38-MAP Kinase by Morpholine-Substituted Imidazoles[a]



compd	R^1	R^2	IC50 ± SEM (μM) p38α
11a	-$(CH_2)_2$-OH		2.512
11b	-$(CH_2)_2$-OH		2.001
11c	-$(CH_2)_3$-OH		9.501
11d	-$(CH_2)_2$-O-CH_3		0.460
11e	-$(CH_2)_3$-O-CH_3		>10
SB203580			0.277 ± 0.058 (n=3)

[a] Results of a single experiment are given except stated otherwise.

Table 5. Inhibition (%) of Five CYP450 Isoforms by Selected Compounds at 10 μM

compd	1A2	2C9	2C19	2D6	3A4
SB203580	61	75	85	67	61
9b	0	23.5	70.5	3.5	62
9e	0	18.5	19	0	38
9p	12	5	41	77.5	97

whether the combination of a large residue at C-2 and different residues at N-1 contributed to increased p38 inhibition. The result was a loss in potency for all tested substances, except for the methoxyethyl-substituted compound **10b** (Table 3).

In the last part of this study, we focused on novel residues at the C-2 position of the imidazole ring and synthesized the morpholin-4-ylalkan-1-ones **11a**−**e**. This moiety was reported to interact via a hydrogen bond with Arg173. The effect was the same as for the compounds in the **10** series. All compounds except **11d** presented a decreased inhibitory potency (Table 4). In conclusion, N-1 methoxyethyl substitution is superior, regardless of C-2 residues.

CYP450 Affinity. Both pyridine and imidazole ring systems are known to be ligands for ferric heme iron in cytochrome P450. Compounds possessing these heterocyclic rings are often inhibitors of P450 enzymes. The reference compound SB203580 is a potent inhibitor of human liver P450 isozymes. At a concentration of 10 μM, it displayed more than 60% inhibition of five isoforms of cytochrome P450 (Table 5). Recently, successful modifications of the 4-pyridyl group have been described which established p38 inhibitors with significantly decreased CYP450 inhibition, including our (2-acetylaminopyridin-4-yl)imidazole.[33] Further modifications were made in this study to reduce affinity for CYP450 compared to SB203580. Therefore, we tested the most active compounds, **9b**, **9e**, **9p**, at a concentration of 10 μM for their inhibition of five CYP450 isoforms. These novel compounds showed on average significantly lower inhibition of CYP450. In general, CYP450 enzymes were predominantly inhibited by lipophilic compounds. Hence, the decreased inhibition demonstrated by **9e** (below 40%) for all the five tested isoforms was attributed to the increase in polarity resulting from the introduction of the hydroxyethoxyethyl side chain. Introduction of the more lipophilic methoxyethyl residue **9b** showed high affinity for only two of the five tested isoforms (Table 5) in contrast to SB203580, which is a potent inhibitor of all five tested isoforms.

Conclusion

A novel structural class of tetrasubstituted imidazoles of p38-MAPK was optimized by imidazole N-1 substitutions. We have shown that branched substituents, as well as spatially dispersed substituents, at the N-1 position resulted in reduced inhibitory potency. This is somewhat incongruent with literature data from Jackson.[39] A hypothetical explanation could be an unfavorable spatial conformation, which was suggested to hinder the compounds to fit deeply into the ATP pocket for tight binding. However, further investigations such as X-ray studies are necessary to clarify this point. Furthermore, our results demonstrate that in this class of compounds the unbranched hydroxyalkyl **9a** and **9c** and methoxyalkyl **9b** and **9d** containing two- or three-carbon spacers led to significant inhibition of cytokine release in comparison to SB203580. The methoxyethyl residue, assumed to build a hydrogen bond to Asp168, had good inhibitory potency independent from C-2 substitution. In addition, introduction of the methoxyethyl side chain caused loss of interaction with three of five tested CYP450 isoforms. Large polar substituents at imidazole N-1 (i.e. compound **9e**) were in this case unfavorable for p38-inhibition but showed diminished CYP450 interaction for all tested CYP450 isoforms.

In conclusion, we have synthesized novel tetrasubstituted imidazoles with higher inhibitory potency for p38-MAPK in vitro and lower inhibition of CYP450 isoforms than SB203580.

Experimental Section

Biological Evaluation. Biological profiles of compounds in this paper were evaluated according to the methods described as follows.

Whole Blood Assay.[41] Test compounds were prepared by serial dilution in Cremophor EL/ethanol (1:1). Blood of healthy human contributors was preincubated for 15 min (37 °C, 5% CO_2) with test compounds or 1% Cremophor EL/ethanol as control samples. Cytokine production was stimulated by addition of LPS (1 μg/mL) to each sample and adjacent incubation for 4 h (37 °C, 5% CO_2). The reaction was terminated by cooling in an ice bath. The concentrations of the proinflammatory cytokines TNFα and Il-1β were determined (after centrifugation) in the supernatant by using commercial ELISA (Beckman Coulter Immunotech). Anticytokine activity was determined by comparing the percent reduction of cytokine concentration in test samples to control samples. Results are given as IC_{50} values (μM).

p38-MAPK Assay.[42] The inhibitors were dissolved in DMSO, and the final maximal DMSO concentration was kept below 1%. An Immulon 4HBX plate was coated with ATF-2 (activating transcription factor 2) by filling each well with 50 μL of an ATF-2 solution (10 μg/mL) followed by incubation for 90 min (37 °C). The plate was thoroughly washed with ultrapure H_2O, then free capacities were blocked with blocking buffer (BB) containing Tween 20 (0.05%), BSA (0.25%), and NaN_3 (0.02%) in TBS and then washed again with ultrapure H_2O. A KB p38 solution was prepared by solution of p38-MAP

kinase (10 μL p38 parent solution) in KB1 buffer (8990 μL). The KB1 buffer contains 50 mM Tris (pH 7.5), 10 mM $MgCl_2$, 10 mM β-glycerophosphate, 100 μg/mL BSA, 1 mM DTT, 10 μM rATP, and 0.1 mM Na_3VO_4. Different concentrations of the test compounds were preincubated for 2 min (37 °C) in KB p38 buffer. The preincubated samples were transferred to the wells of the coated plate and incubated for 1 h (37 °C). The plate was thoroughly washed with ultrapure H_2O, blocked with BB, and washed with ultrapure H_2O. The wells were then incubated for 1 h with phospho-ATF-2-antibody solution (NEB Cell Signaling) composed of 7 mL of BB and 3.5 μL of antibody. The plate was washed with ultrapure H_2O and incubated for 1 h (37 °C) with anti-rabbit IgG-AP-antibody solution (Santa Cruz Biotechnology) containing 7 mL of BB and 3.5 μL of antibody. The plate was thoroughly washed with ultrapure H_2O. In each well, 100 μL of 4-nitrophenol phosphate was added and the plate was incubated for about 1.5 h. The optical density was measured at 405 nm. Inhibition of p38-MAP kinase was determined by comparing the percent reduction of the phospho-ATF-2 concentration in test samples to control samples. Control samples contained only KB p38 buffer without an inhibitor. Results are given as IC_{50} values (μM).

Cytochrome P450 Assay. The inhibition of cytochrome P450 isoenzymes by selected compounds was determined at a concentration of 10 μM in phosphate buffer (pH 7.4, 0.1% DMSO) as reported previously.[43]

General. All reagents and solvents were of commercial quality and used without further purification as received, unless noted otherwise. Melting points were measured on a Büchi B-545 melting point apparatus and were thermodynamically corrected. ^{1}H NMR spectra were collected on a Bruker Advance 200 Spectrospin at 200 MHz. Chemical shifts were reported in parts per million relative to TMS as internal standard. Infrared spectra were recorded by ATR technique on a Perkin-Elmer Spectrum One spectrometer.

***N*-{4-[2-Cyano-2-(4-fluorophenyl)acetyl]pyridin-2-yl}acetamide (3).** To a stirred solution of 2-acetylaminoisonicotinic acid **1** (18.0 g, 0.1 mol) in THF (50 mL) was added carbonyldiimidazole (17.0 g, 0.1 mol) over 30 min. The reaction was stirred at room temperature for 45 min. 4-Fluorophenylacetonitrile **2** (14.9 g, 0.11 mol) was added to the solution. At this point, potassium *tert*-butoxide (14.6 g, 0.13 mol) was added. The reaction was heated to 120 °C for 2 h, cooled to room temperature, and then stirred for an additional 12 h at room temperature. The addition of ice and neutralization with concentrated HCl led to the precipitation of crude **3**. The precipitate was collected by filtration; washed with cold H_2O, cold methanol, and petroleum ether; and dried to give **3** (8.43 g, 62%): mp 257 °C; ^{1}H NMR (DMSO-d_6) δ 2.12 (s, 3H, CO−CH_3), 7.19−7.31 (m, 3H, 4-Pyr und 4-F-Ph), 7.75−7.82 (m, 2H, 4-F-Ph), 8.27 (s, 1H, 4-Pyr), 8.42−8.45 (m, 1H, 4-Pyr); IR (ATR) 1707 (NHC=O), 1234 (C−F) cm^{-1}. $C_{16}H_{12}FN_3O_2$ (M_r 297.29)

1-(2-Aminopyridin-4-yl)-2-(4-fluorophenyl)ethanone (4). A solution of **3** (27.9 g, 93.9 mmol) in hydrobromic acid (48%) (500 mL) was heated under reflux for about 30 h. After cooling to room temperature, the reaction mixture was poured on ice and made basic with concentrated NH_3. The precipitated solids were filtered; washed with cold H_2O, cold methanol, and petroleum ether; and dried to give **4** (10.81 g, 50%): mp 157.0 °C; ^{1}H NMR (DMSO-d_6) δ 4.31 (s, 2H, $-CH_2-$), 6.32 (s, 2H, $-NH_2$), 6.94−6.99 (m, 2H, 4-Pyr), 7.09−7.18 (m, 2H, 4-F-Ph), 7.23−7.30 (m, 2H, 4-F-Ph), 8.06−8.09 (m, 1H, 4-Pyr); IR (ATR) 1697 (NHC=O), 1243 (C−F) cm^{-1}.

***N*-{4-[2-(4-Fluorophenyl)acetyl]pyridin-2-yl}acetamide (5).** To suspension of **4** (12.0 g, 52.2 mmol) in acetic anhydride (100 mL) was added a catalytic amount of 4-DMAP. The suspension was heated under reflux for 7 h. After cooling to room temperature, ice water was added to the suspension. The pH was adjusted with concentrated NH_3 to pH 8 with subsequent precipitation of **5**. The precipitate was filtered, washed with cold water and petroleum ether, and then dried to give **5** (12.79 g: 90%): mp 140.9 °C; ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 3H, CO−CH_3), 4.41 (s, 2H, $-CH_2-$), 7.09−7.17 (m, 2H, 4-F-Ph), 7.26−7.33 (m, 2H, 4-F-Ph), 7.61−7.64 (m, 1H, 4-Pyr), 8.5−8.55 (m, 2H, 4-Pyr), 10.72 (s, 1H, NH); IR (ATR) 1682 (NHC=O), 1224 (C−F), cm^{-1}.

***N*-{4-[2-(4-Fluorophenyl)-2-hydroxyiminoacetyl]pyridin-2-yl}acetamide (6).** A 30% sodium methoxide solution (8.4 g) was diluted with methanol (120 mL). Isoamyl nitrite (4.8 g, 41.0 mmol) was added to the solution. The reaction mixture was stirred at room temperature, at which point, **5** (12.0 g, 44.06 mmol) was added over 2 h in portions. After stirring the mixture for 2 h at room temperature, the reaction solvent was removed in vacuo and the resulting residue was dissolved in ice water. The aqueous solution was neutralized with 10% HCl to precipitate **6**. The precipitate was filtered, washed with diethyl ether, and dried in vacuo to give **6** (6.5 g, 54%): mp 162.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.11 (s, 3H, CO−CH_3), 7.24−7.33 (m, 2H, 4-F-Ph), 7.39−7.42 (m, 1H, 4-Pyr), 7.51−7.58 (m, 2H, 4-F-Ph), 8.39 (s, 1H, 4-Pyr), 8.42−8.45 (m, 1H, 4-Pyr), 10.68 (s, 1H, −NH)

Preparation of *N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-alkyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamides 7a−n, General Procedure A. A solution of **6** (1 equiv) and a 1,3,5-trialkyl-[1,3,5]triazinane (1 equiv) in absolute ethanol was heated under reflux for ca. 6 h. After cooling to room temperature, the mixture was evaporated in vacuo. Trituration with Et_2O gave compounds **7a**−**n**.

***N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-(2-hydroxyethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7a).** This compound was prepared from **6** (2.0 g, 6.64 mmol) and 3-[3,5-bis(2-hydroxyethyl)[1,3,5]triazinan-1-yl]ethan-1-ol (1.45 g, 6.64 mmol) according to general procedure A. Trituration with Et_2O yielded **7a** (1.69 g, 71%): mp 206.6 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H, CO−CH_3), 3.37 (t, 2H, J = Hz, O−CH_2), 3.91 (t, 2H, J = 5.06 Hz, N−CH_2), 7.04−7.27 (m, 3H, 4-F-Ph, 4-Pyr), 7.46−7.53 (m, 2H, 4-F-Ph), 8.03 (s, 1H, 4-Pyr), 8.35−8.37 (m, 1H, 4-Pyr), 8.53 (s, 1H, C^2-H), 10.69 (s, 1H, NH); IR (ATR) 1694 (HNC=O), 1220 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-(2-methoxyethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7b).** This compound was prepared from **6** (2.0 g, 6.64 mmol) and 1,3,5-tris(2-methoxyethyl)[1,3,5]triazinane (2.61 g, 6.64 mmol) according to general procedure A. Trituration with Et_2O yielded **7b** (2.03 g, 82%): mp 222.3 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H, CO−CH_3), 3.17 (s, 3H, O−CH_3), 3.50 (t, 2H, J = 4.98 Hz, O−CH_2), 4.01 (t, 2H, J = 4.98 Hz, N−CH_2), 7.02−7.05 (m, 1H, 4-Pyr), 7.10−7.19 (m, 2H, 4-F-Ph), 7.47−7.54 (m, 2H, 4-F-Ph), 8.04 (s, 1H, 4-Pyr), 8.35−8.37 (m, 1H, 4-Pyr), 8.53 (s, 1H, C^2-H), 10.69 (s, 1H, N−H)

***N*-{4-[5-(4-Fluorophenyl)-3-(hydroxypropyl)-1-oxy-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7c).** This compound was prepared from **6** (5.0 g, 16.6 mmol) and 1-[3,5-bis(3-hydroxypropyl)[1,3,5]triazinan-1-yl]propan-1-ol (4.38 g, 16.6 mmol) according to general procedure A. Trituration with Et_2O yielded **7c** (4.5 g, 73%): mp 214.2 °C; ^{1}H NMR (DMSO-d_6) δ 1.81 (quint, 2H, J = 6.43 Hz, $-CH_2-$), 2.08 (s, 3H, CO−CH_3), 3.19 (t, 2H, J = 5.98 Hz, O−CH_2), 3.92 (t, 2H, J = 6.94 Hz, N−CH_2), 7.01−7.07 (m, 1H, 4-Pyr), 7.09−7.19 (m, 2H, 4-F-Ph), 7.49−7.52 (m, 2H, 4-F-Ph), 8.04 (s, 1H, 4-Pyr), 8.36−8.37 (m, 1H, 4-Pyr), 8.35 (s, 1H, C^2-H), 10.69 (s, 1H, N−H)

***N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-(3-methoxypropyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7d).** This compound was prepared from **6** (2.0 g, 6.64 mmol) and 1,3,5-tris(3-methoxypropyl)[1,3,5]triazinane (2.01 g, 6.64 mmol) according to general procedure A. Trituration with Et_2O yielded **7d** (1.82 g, 71%): mp 213.2 °C; ^{1}H NMR (DMSO-d_6) δ 1.82 (quint, 2H, J = 6.42 Hz, $-CH_2-$), 2.06 (s, 3H, CO−CH_3), 3.09 (s, 3H, O−CH_3), 3.21 (t, 2H, J = 5.90 Hz, O−CH_2), 3.92 (t, 2H, J = 6.94 Hz, N−CH_2), 7.03−7.06 (m, 1H, 4-Pyr), 7.10−7.19 (m, 2H, 4-F-Ph), 7.47−7.54 (m, 2H, 4-F-Ph), 8.04 (s, 1H, 4-Pyr), 8.36−8.38 (m, 1H, 4-Pyr), 8.61 (s, 1H, C^2-H), 10.71 (s, 1H, N−H); IR (ATR) 2867 (O−CH_3), 1682 (HNC=O), 1555 (HNC=O), 1215 (C−F), 1157 (O−CH_3) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-[2-(2-hydroxyethoxy)ethyl]-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7e).** This compound was prepared from **6** (5.0 g, 16.61 mmol) and 2-(2-{3,5-bis[2-(2-hydroxyethoxy)ethyl][1,3,5]triazinan-1-yl}ethoxy)-

ethanol (5.0 g, 14.42 mmol) according to general procedure A. Trituration with Et_2O yielded **7e** (5.97 g, 89%): mp 210.3 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H, CO−CH_3), 2.54 (t, 2H, J = 5.88 Hz, O−CH_2−), 3.44 (t, 2H, J = 4.82 Hz, −CH_2−O), 3.61 (t, 2H, J = 4.78 Hz, −CH_2−O) 4.00 (t, 2H, J = 4.68 Hz, N−CH_2−), 7.04−7.07 (m, 1H, 4-Pyr), 7.10−7.20 (m, 2H, 4-F-Ph), 7.47−7.55 (m, 2H, 4-F-Ph), 8.04 (s, 1H, 4-Pyr), 8.35−8.37 (m, 1H, 4-Pyr), 8.58 (s, 1H, C^2-H), 10.70 (s, 1H, N−H); IR (ATR) 1699 (HNC=O), 1237 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-hydroxypropyl)-1-oxy-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7f).** This compound was prepared from **6** (3.0 g, 9.97 mmol) and 1-[3,5-bis(2-hydroxypropyl)[1,3,5]triazinan-1-yl]propan-2-ol (2.6 g, 9.97 g) according to general procedure A. Trituration with Et_2O yielded **7f** (2.5 g, 63%): mp 180.5 °C; ^{1}H NMR (DMSO-d_6) δ 1.21 (d, 3H, J = 5.98 Hz, −CH_3), 2.0 (s, 1H, −OH), 2.02 (s, 3H, CO−CH_3), 3.4 (quint, 1H, J = 6.43 Hz, −CH−),3.88 (t, 2H, J = 6.94 Hz, N−CH_2), 7.00−7.06 (m, 1H, 4-Pyr), 7.10−7.19 (m, 2H, 4-F-Ph), 7.49−7.51 (m, 2H, 4-F-Ph), 8.05 (s, 1H, 4-Pyr), 8.36−8.37 (m, 1H, 4-Pyr), 8.33 (s, 1H, C^2-H), 10.69 (s, 1H, N−H)

***N*-{4-[3-(2-Acetylaminoethyl)-5-(4-fluorophenyl)-3-oxy-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7g).** This compound was prepared from **6** (3.0 g, 9.97 mmol) and *N*-{2-[3,5-bis(2-acetylaminoethyl)[1,3,5]triazinan-1-yl]ethyl}acetamide (3.41 g, 9.97 mmol) according to general procedure A. Trituration with Et_2O yielded **7g** (1.4 g, 35%): mp 137.3 °C; ^{1}H NMR (DMSO-d_6) δ 1.64 (s, 3H, CO−CH_3), 2.06 (s, 3H, CO−CH_3), 3.15 (q, 2H, −CH_2−N), 3.91 (t, 2H, N−CH_2−), 7.00−7.03 (m, 1H, 4-Pyr), 7.10−7.18 (m, 2H, 4-F-Ph), 7.48−7.59 (m, 2H, 4-F-Ph), 8.04 (s, 1H, NH−CO), 8.35−8.37 (m, 1H, 4-Pyr), 8.54 (s, 1H, 4-Pyr), 8.59 (s, 1H, C^2-H), 10.77 (s, 1H, N−H); IR (ATR) 1223 (C−F) cm^{-1}.

***N*-{4-[3-(2-Dimethylaminoethyl)-5-(4-fluorophenyl)-1-oxy-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7h).** This compound was prepared from **6** (5.0 g, 16.59 mmol) and {2-[3,5-bis(2-(dimethylamino)ethyl)[1,3,5]triazinan-1-yl]ethyl}-dimethylamine (5.0 g, 16.64 mmol) according to general procedure A. Trituration with Et_2O yielded **7h** (4.4 g, 69%): mp 149.3 °C; ^{1}H NMR (DMSO-d_6) δ 2.02 (s, 6H, N(CH_3)$_2$), 2.07 (s, 3H, CO−CH_3), 2.98 (q, 2H, −CH_2−N), 3.83 (t, 2H, N−CH_2−), 6.99−7.04 (m, 1H, 4-Pyr), 7.10−7.17 (m, 2H, 4-F-Ph), 7.50−7.59 (m, 2H, 4-F-Ph), 8.02 (s, 1H, NH−CO), 8.34−8.36 (m, 1H, 4-Pyr), 8.52 (s, 1H, 4-Pyr), 8.61 (s, 1H, C^2-H), 10.79 (s, 1H, N−H); IR (ATR) 1222 (C−F) cm^{-1}.

***N*-{4-[3-(2-Allyloxyethyl)-5-(4-fluorophenyl)-1-oxy-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7i).** This compound was prepared from **6** (5.0 g, 16.6 mmol) and 1,3,5-tris(2-allyloxyethyl)[1,3,5]triazinane (5.64 g, 16.61 mmol) according to general procedure A. Trituration with Et_2O yielded **7i** (4.9 g, 74%): mp 151.6 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H, CO−CH_3), 3.49 (t, 2H, J = 6.16 Hz, −CH_2−O), 3.85−3.87 (m, 2H, −O−CH_2−), 4.04 (t, 2H, J = 5.81 Hz, N−CH_2−), 5.07−5.17 (m, 2H, =CH_2), 5.69−5.87 (m, 1H, H−C=), 7.03−7.05 (m, 1H, 4-Pyr), 7.10−7.19 (m, 2H, 4-F-Ph), 7.47−7.60 (m, 2H, 4-F-Ph), 8.04 (s, 1H, 4-Pyr), 8.35−8.38 (m, 1H, 4-Pyr), 8.58 (s, 1H, C^2-H), 10.69 (s, 1H, N−H); IR (ATR) 1698 (HNC=O), 1605, 1226 (C−F) cm^{-1}.

***N*-{4-[5-(4-fluorophenyl)-1-oxy-3-(2-prop-2-ynyloxyethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7j).** This compound was prepared from **6** (4.0 g, 13.29 mmol) and 1,3,5-tris(2-prop-2-ynyloxyethyl)[1,3,5]triazinane (4.43 g, 13.29 mmol) according to general procedure A. Trituration with Et_2O yielded **7j** (3.9 g, 75%): mp 163.4 °C; H NMR (DMSO-d_6) δ 2.06 (s, 3H, CO−CH_3), 3.59 (t, 2H, J = 6.16 Hz, −CH_2−O), 3.94−4.10 (m, 4H, N−CH_2-, −O−CH_2−), 7.03−7.05 (m, 1H, 4-Pyr), 7.10−7.19 (m, 2H, 4-F-Ph), 7.47−7.60 (m, 2H, 4-F-Ph), 8.04 (s, 1H, 4-Pyr), 8.35−8.38 (m, 1H, 4-Pyr), 8.58 (s, 1H, C^2-H), 10.69 (s, 1H, N−H); IR (ATR) 1679 (NHC=O), 1226 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-methylsulfanylethyl)-1-oxy-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7k).** This compound was prepared from **6** (5.0 g, 16.6 mmol) and 1,3,5-tris(2-methylsulfanylethyl)[1,3,5]triazinane (5.2 g, 16.8 mmol) according to general procedure A. Trituration with diethyl ether yielded **7k** (4.5 g, 70%): mp 189.7 °C; ^{1}H NMR (DMSO-d_6) δ 2.04 (s, 3H, CO−CH_3), 3.19 (s, 3H, S−CH_3), 3.48 (t, 2H, J = 4.95 Hz, S−CH_2), 4.05 (t, 2H, J = 4.98 Hz, N−CH_2), 7.00−7.05 (m, 1H, 4-Pyr), 7.09−7.21 (m, 2H, 4-F-Ph), 7.46−7.55 (m, 2H, 4-F-Ph), 8.06 (s, 1H, 4-Pyr), 8.35−8.37 (m, 1H, 4-Pyr), 8.51 (s, 1H, C^2-H), 10.70 (s, 1H, N−H)

***N*-{4-[3-(2,2-Dimethoxyethyl)-5-(4-fluorophenyl)-1-oxy-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7l).** This compound was prepared from **6** (3.0 g, 9.97 mmol) and 1,3,5-tris(2,2-dimethoxyethyl)[1,3,5]triazinane (3.5 g, 9.97 mmol) according to general procedure A. Trituration with Et_2O yielded **7l** (2.5 g, 63%): mp 205.7 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H, CO−CH_3), 3.20 (s, 6H, −C(O−CH_3)$_2$), 3.95 (d, 2H, J = 2.5 Hz, >N−CH_2−), 4.37 (t, 1H, J = 5.41 Hz, >CH−), 7.04−7.07 (m, 1H, 4-Pyr), 7.10−7.20 (m, 2H, 4-F-Ph), 7.46−7.53 (m, 2H, 4-F-Ph), 8.04 (s, 1H, 4-Pyr), 8.36−8.38 (m, 1H, 4-Pyr), 8.52 (s, 1H, C^2-H), 10.67 (s, 1H, N−H); IR (ATR) 1693 (NHC=O), 1222 (C−F) cm^{-1}.

***N*-{4-[3-(2,2-Dimethyl[1,3]dioxolan-4-ylmethyl)-5-(4-fluorophenyl)-1-oxy-3*H*-imidazol-4-yl]pyridin-2-yl}-acetamide (7m).** This compound was prepared from **6** (3.0 g, 9.97 mmol) and 1,3,5-tris(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-[1,3,5]triazinane (4.28 g, 9.97 mmol) according to general procedure A. Trituration with Et_2O yielded **7m** (2.1 g, 49%): mp 220 °C; ^{1}H NMR (DMSO-d_6) δ 1.13 (d, 6H, J = 3.7 Hz, >C(CH_3)$_2$), 2.06 (s, 3H, CO−CH_3), 3.59−3.65 (m, 1H, >CH−), 3.80−4.24 (m, 4H, >N−CH_2, −CH_2−O), 7.03−7.07 (m, 1H, 4-Pyr), 7.10−7.19 (m, 2H, 4-F-Ph), 7.47−7.57 (m, 2H, 4-F-Ph), 8.01 (s, 1H, 4-Pyr), 8.25−8.35 (m, 1H, 4-Pyr), 8.55 (s, 1H, C^2-H), 10.64 (s, 1H, N−H); IR (ATR) 1694 (NHC=O), 1214 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-(2-morpholin-4-ylethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7n).** This compound was prepared from **6** (5.0 g, 16.6 mmol) and 1,3,5-tris(2-morpholin-4-ylethyl)[1,3,5]triazinane (6.0 g, 14.1 mmol) according to general procedure A. Trituration with Et_2O yielded **7n** (5.2 g, 73%): mp 226.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H, CO−CH_3), 2.27 (t, 4H, J = 3.82 Hz, −CH_2−O−CH_2−) 3.44 (t, 4H, J = 4,32 Hz, −CH_2−N−CH_2−), 3.53 (t, 2H, J = 5,94 Hz, N−CH_2), 3.96 (t, 2H, J = 5,88 Hz, N−CH_2−), 7.04−7.06 (m, 1H, 4-Pyr), 7.10−7.19 (m, 2H, 4-F-Ph), 7.48−7.55 (m, 2H, 4-F-Ph), 8.04 (s, 1H, 4-Pyr), 8.36−8.38 (m, 1H, 4-Pyr), 8.58 (s, 1H, C^2-H), 10.69 (s, 1H, NH), IR (ATR) 1691 (HNC=O), 1224 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-(3-morpholin-4-ylpropyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7o).** This compound was prepared from **6** (4.0 g, 13.0 mmol) and 1,3,5-tris(2-morpholin-4-ylpropyl)[1,3,5]triazinane (6.14 g, 13.0 mmol) according to general procedure A. Trituration with Et_2O yielded **7o** (3.8 g, 65%): mp 232.3 °C; ^{1}H NMR (DMSO-d_6) δ 1.72 (quint, 2H, J = 6.1 Hz, −CH_2−), 2.07 (s, 3H, CO−CH_3), 2.14−2.20 (m, 6H, N(CH_2)$_3$), 3.41 (t, 4H, J = 4.26 Hz, −CH_2−O−CH_2−), 3.92 (t, 2H, J = 6,48 Hz, N−CH_2), 7.03−7.06 (m, 1H, 4-Pyr), 7.10−7.19 (m, 2H, 4-F-Ph), 7.49−7.56 (m, 2H, 4-F-Ph), 8.05 (s, 1H, 4-Pyr), 8.36−8.38 (m, 1H, 4-Pyr), 8.62 (s, 1H, C^2-H), 10.71 (s, 1H, NH); IR (ATR) 1680 (NHC=O), 1222 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-(2-piperidin-1-ylethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7p).** This compound was prepared from **6** (4.0 g, 13.29 mmol) and 1,3,5-tris(2-piperidin-1-ylethyl)[1,3,5]triazinane (5.59 g, 13.29 mmol) according to general procedure A. Trituration with Et_2O yielded **7p** (4.3 g, 76%): mp 204.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.37−1.52 (m, 2H, −CH_2−), 1.54−1.73 (m, 4H, −CH_2−), 2.08 (s, 3H, CO−CH_3), 2.45−2.61 (m, 4H, −CH_2−N−CH_2−), 3.15 (t, 2H, J = 6.52 Hz, −CH_2−N<), 3.92 (t, 2H, J = 6.12 Hz, N−CH_2−), 7.00−7.04 (m, 1H, 4-Pyr), 7.09−7.15 (m, 2H, 4-F-Ph), 7.47−7.57 (m, 2H, 4-F-Ph), 8.04 (s, 1H, NH), 8.38−8.40 (m, 1H, 4-Pyr), 8.53 (s, 1H, 4-Pyr),8.58 (s, 1H, C^2-H); IR (ATR) 1685 (NHC=O), 1230 (C−F) cm^{-1}.

4-[5-(2-Acetylaminopyridin-4-yl)-4-(4-fluorophenyl)-3-oxyimidazol-1-yl]piperidin-1-carbonic Acid Ethyl Ester (7q). This compound was prepared from **6** (2.3 g, 7.6 mmol)

and tris(4-[1,3,5]triazinan-1-yl)piperidin-1-carbonic acid ethyl ester **7q** (6.9 g, 12.4 mmol) according to general procedure A. Trituration with Et_2O yielded **7q** (2.4 g, 67%): mp 254.8 °C; ^{1}H NMR (DMSO-d_6) δ 1.18 (t, 3H, J = 7.08 Hz, $-CH_3$), 1.75−1.87 (m, 4H, 2(CH_2)Pip), 2.07 (s, 3H, CO−CH_3), 2.77−2.86 (m, 2H, CH_2 Pip), 3.94−4.08 (m, 5H, CHPip, CH_2Pip, O−CH_2), 7.00−7.03 (m, 1H, 4-Pyr), 7.09−7.18 (m, 2H, 4-F-Ph), 7.44−7.56 (m, 2H, 4-F-Ph), 8.04 (s, 1H, 4-Pyr), 8.35−8.38 (m, 1H, 4-Pyr), 8.85 (s, 1H, C^2-H), 10.71 (s, 1H, N−H)

***N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-methyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7r).** This compound was prepared from **6** (4.68 g, 15.5 mmol) and 1,3,5-trimethyl[1,3,5]-triazinane (2.0 g, 15.5 mmol) according to general procedure A. Trituration with Et_2O yielded **7r** (3.5 g, 69%): mp 182.3 °C; ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H, CO−CH_3), 3.66 (s, 3H, N−CH_3), 6.74−6.77 (m, 1H, 4-Pyr), 6.98−7.07 (m, 2H, 4-F-Ph), 7.47−7.54 (m, 2H, 4-F-Ph), 8.16 (s, 1H, C^2-H), 8.22−8.25 (m, 1H, 4-Pyr), 8.28 (s, 1H, 4-Pyr), 10.69 (s, 1H, NH), IR (ATR) 1225 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-1-oxy-3-(2,2,6,6-tetramethylpiperidin-4-yl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (7s).** This compound was prepared from **6** (1.0 g, 3.32 mmol) and 1,3,5-tris(2,2,6,6-tetramethylpiperidin-4-yl)[1,3,5]triazinane (1.67 g, 3.32 mmol) according to general procedure A. Trituration with Et_2O yielded **7s** (1.2 g, 80%): mp 48.30 °C; ^{1}H NMR (DMSO-d_6) δ 0.83 (s, 6H, C((CH_3)$_2$), 1.02 (s, 6H, C((CH_3)$_2$), 1.44−1.70 (m, 4H, −CH−(CH_2)$_2$−), 2.05 (s, 3H, CO−CH_3) 4.18−4.30 (m, 1H, N−CH<), 6.96−7.12 (m, 2H, 4-F-Ph, 4-Pyr) 7.42−7.49 (m, 2H, 4-F-Ph), 8.06 (s, 1H, 4-Pyr), 8.30−8.33 (m, 1H, 4-Pyr), 8.65 (s, 1H, C^2-H), 10.65 (s,1H, NH), IR (ATR) 1697 (NHC=O), 1225 (C−F) cm^{-1}.

Preparation of *N*-{4-[5-(4-Fluorophenyl)-3-(2-alkyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}-acetamide 8a−m, General Procedure B. A solution of 2,2,4,4-tetramethylcyclobutan-1,3-dithione (1 equiv) in DCM (100 mL) was added dropwise to a stirred solution of **7a**−**m** (1 equiv) in DCM. The mixture was stirred for 2 h at room temperature. The solvent was evaporated in vacuo, and the solid residue was triturated with Et_2O.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-hydroxyethyl)-2-thioxo-2,3-dihydro-1*H*-imid azol-4-yl]pyridin-2-yl}acetamide (8a).** This compound was prepared from **7a** (1.6 g, 4.46 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (0.77 g, 4.46 mmol) according to general procedure B. Trituration with Et_2O yielded **8a** (1.5 g, 90%): mp 222.1 °C; ^{1}H NMR (DMSO-d_6) δ 2.08 (s, 3H, CO−CH_3), 3.50 (t, 2H, J = Hz, O−CH_2), 3.92 (t, 2H, J = Hz, N−CH_2), 7.11−7.32 (m, 5H, 4-F-Ph, 4-Pyr), 8.09 (s, 1H, 4-Pyr), 8.39−8.42 (m, 1H, 4-Pyr), 10.73 (s, 1H, CO−NH), 12.99 (s, 1H, NH); IR (ATR) 1226 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-methoxyethyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}acetamide (8b).** This compound was prepared from **7b** (2.0 g, 5.37 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (0.93 g, 5.37 mmol) according to general procedure B. Trituration with Et_2O yielded **8b** (1.7 g, 82%): mp 196.4 °C; ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 3H, CO−CH_3), 3.03 (s, 3H, O−CH_3), 3.50 (t, 2H, J = 5.54 Hz, O−CH_2), 4.02 (t, 2H, J = 5.36 Hz, N−CH_2), 7.10−7.31 (m, 5H, 4-F-Ph, 4-Pyr), 8.07 (s, 1H, 4-Pyr), 8.38−8.40 (m, 1H, 4-Pyr), 10.67 (s, 1H, CO−NH), 12.85 (s, 1H, NH); IR (ATR) 1224 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-(3-hydroxypropyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}acetamide (8c).** This compound was prepared from **7c** (4.0 g, 10.74 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (1.85 g, 10.74 mmol) according to general procedure B. Trituration with Et_2O yielded **8c** (2.2 g, 52%): mp 224.6 °C; ^{1}H NMR (DMSO-d_6) δ 1.59 (quint, 2H, J = 5.90 Hz, $-CH_2-$), 2.07 (s, 3H, CO−CH_3), 3.27 (t, 2H, J = 5.8 Hz, O−CH_2), 3.94 (t, 2H, J = 6.68 Hz, N−CH_2), 7.01−7.31 (m, 5H, 4-F-Ph, 4-Pyr), 8.06 (s, 1H, 4-Pyr), 8.39−8.41 (m, 1H, 4-Pyr), 10.71 (s, 1H, CO−NH), 12.96 (s, 1H, NH)

***N*-{4-[5-(4-Fluorophenyl)-3-(3-methoxypropyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}acetamide (8d).** This compound was prepared from **7d** (1.8 g, 4.66 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (0.80 g, 4.66 mmol) according to general procedure B. Trituration with Et_2O yielded **8d** (1.8 g, 95%): mp 227.4 °C; ^{1}H NMR (DMSO-d_6) δ 1.79 (quint, 2H, J = 5.84 Hz, $-CH_2-$), 2.08 (s, 3H, CO−CH_3), 3.05 (s, 3H, O−CH_3), 3.19 (t, 2H, J = 6.04 Hz, O−CH_2), 3.94 (t, 2H, J = 6.18 Hz, N−CH_2), 7.12−7.29 (m, 5H, 4-F-Ph, 4-Pyr), 8.07 (s, 1H, 4-Pyr), 8.40−8.43 (m, 1H, 4-Pyr), 10.71 (s, 1H, CO−NH), 12.96 (s, 1H, NH); IR (ATR) 1695 (NHC=O), 1220 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-[2-(2-hydroxyethoxy)ethyl]-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}-acetamide (8e).** This compound was prepared from **7e** (5.9 g, 14.66 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (2.51 g, 14.67 mmol) according to general procedure B. Trituration with Et_2O yielded **8e** (4.7 g, 77%): 232.5 °C; ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 3H, CO−CH_3), 3.22 (t, 2H, J = 4.62 Hz, O−CH_2−), 3.44 (t, 2H, J = 5.18 Hz, $-CH_2-$O), 3.58 (t, 2H, J = 4.18 Hz, $-CH_2-$O), 4.01 (t, 2H, J = 4.2 Hz, N−CH_2−), 7.05−7.19 (m, 3H, 4-F-Ph, 4-Pyr), 7.24−7.37 (m, 2H, 4-F-Ph), 8.04 (s, 1H, 4-Pyr), 8.37−8.40 (m, 1H, 4-Pyr), 10.67 (s, 1H, CO−NH), 12.96 (s, 1H, NH); IR (ATR) 1699 (NHC=O), 1122 (C−F), 1112 cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-hydroxypropyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}acetamide (8f).** This compound was prepared from **7f** (3.5 g, 9.45 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (1.63 g, 9.45 mmol) according to general procedure B. Trituration with Et_2O yielded **8f** (2.8 g, 77%): mp 224.8 °C; ^{1}H NMR (DMSO-d_6) δ 0.88 (d, 3H, J = 5.96 Hz, C−CH_3), 2.06 (s, 3H, CO−CH_3), 3.55−3.68 (m, 1H, −CH−), 3.90−4.02 (m, 2H, N−CH_2), 7.10−7.29 (m, 5H, 4-F-Ph, 4-Pyr), 8.01 (s, 1H, 4-Pyr), 8.36−8.39 (m, 1H, 4-Pyr), 10.65 (s, 1H, CO−NH), 12.85 (s, 1H, NH); IR (ATR) 1710 (NHC=O), 1228 (C−F) cm^{-1}.

***N*-{4-[3-(2-Acetylaminoethyl)-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}-acetamide (8g).** This compound was prepared from **7g** (1.2 g, 3.00 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (0.52 g, 3.0 mmol) according to general procedure B. Trituration with Et_2O yielded **8g** (1.2 g, 97%): mp 266.8 °C; ^{1}H NMR (DMSO-d_6) δ 1.44 (s, 3H, CO−CH_3), 2.05 (s, 3H, CO−CH_3), 3.22 (q, 2H, $-CH_2-$N), 3.95 (t, 2H, N−CH_2−), 7.10−7.29 (m, 5H, 4-F-Ph, 4-Pyr), 7.87 (t, 1H, NH−CO), 8.01 (s, 1H, 4-Pyr), 8.37−8.40 (m, 1H, 4-Pyr), 10.67 (s, 1H, CO−NH), 12.85 (s, 1H, NH); IR (ATR) 1222 (C−F) cm^{-1}.

***N*-{4-[3-(2-Dimethylaminoethyl)-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}-acetamide (8h).** This compound was prepared from **7h** (4.7 g, 12.19 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (2.1 g, 12.19 mmol) according to general procedure B. Trituration with Et_2O yielded **8h** (4.0 g, 82%): mp 234.7 °C; ^{1}H NMR (DMSO-d_6) δ 1.94 (s, 6H, N(CH_3)$_2$), 2.07 (s, 3H, CO−CH_3), 2.35 (t, 2H, J = 7.06 Hz, N−CH_2), 3.97 (t, 2H, J = 7.1 Hz, N−CH_2), 7.10−7.19 (m, 3H, 4-F-Ph, 4-Pyr), 7.24−7.32 (m, 2H, 4-F-Ph), 8.07 (s, 1H, 4-Pyr), 8.39−8.41 (m, 1H, 4-Pyr), 10.67 (s, 1H, CO−NH), 12.73 (s, 1H, NH); IR (ATR) 1698 (NHC=O) 1226 (C−F) cm^{-1}.

***N*-{4-[3-(2-Allyloxyethyl)-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}acetamide (8i).** This compound was prepared from **7i** (4.9 g, 12.36 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (2.12 g, 12.36 mmol) according to general procedure B. Trituration with Et_2O yielded **8i** (4.3 g, 84%): mp 193.7; ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H, CO−CH_3), 3.55 (t, 2H, J = 6.16 Hz, $-CH_2-$O), 3.72−3.74 (m, 2H, −O−CH_2−), 4.04 (t, 2H, J = 5.81 Hz, N−CH_2−), 4.99−5.07 (m, 2H, =CH_2), 5.59−5.75 (m, 1H, HC=), 7.02−7.37 (m, 5H, 4-F-Ph, 4-Pyr), 8.04 (s, 1H, 4-Pyr), 8.37−8.39 (m, 1H, 4-Pyr), 10.67 (s, 1H, CO−NH), 12.85 (s, 1H, NH); IR (ATR) 1699 (NHC=O), 1223 (C−F), 1085 cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-prop-2-ynyloxyethyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}-acetamide (8j).** This compound was prepared from **7j** (3.9 g, 9.94 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (1.71 g, 9.94 mmol) according to general procedure B. Trituration with Et_2O yielded **8j** (3.5 g, 86%): mp 207.8 °C; ^{1}H NMR

(DMSO-d_6) δ 2.05 (s, 3H, CO−CH_3), 3.53 (t, 2H, J = 6.16 Hz, −CH_2−O), 4.00−4.80 (m, 4H, N−CH_2−, O−CH_2−), 7.02−7.37 (m, 5H, 4-F-Ph, 4-Pyr), 8.04 (s, 1H, 4-Pyr), 8.37−8.39 (m, 1H, 4-Pyr), 10.67 (s, 1H, CO−NH), 12.85 (s, 1H, NH); IR (ATR) 1693 (HNC=O), 1218 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-methylsulfanylethyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}-acetamide (8k).** This compound was prepared from **7k** (5.1 g, 13.2 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (2.27 g, 13.2 mmol) according to general procedure B. Trituration with Et_2O yielded **8k** (3.6 g, 68%): mp 184.9 °C; ^{1}H NMR (DMSO-d_6) δ 2.07 (s, 3H, CO−CH_3), 2.09 (s, 3H, S−CH_3), 2.70 (t, 2H, J = 5.44 Hz, S−CH_2), 3.82 (t, 2H, J = 5.36 Hz, N−CH_2), 7.09−7.30 (m, 5H, 4-F-Ph, 4-Pyr), 8.05 (s, 1H, 4-Pyr), 8.38−8.41 (m, 1H, 4-Pyr), 10.67 (s, 1H, CO−NH), 12.83 (s, 1H, NH); IR (ATR) 1222 (C−F) cm^{-1}.

***N*-{4-[3-(2,2-Dimethoxyethyl)-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}-acetamide (8l).** This compound was prepared from **7l** (2.5 g, 6.24 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (1.07 g, 6.24 mmol) according to general procedure B. Trituration with Et_2O yielded **8l** (2.1 g, 81%): mp 209.7 °C; ^{1}H NMR (DMSO-d_6) δ 2.06 (s, 3H, CO−CH_3), 3.32 (s, 6H, >C(O−CH_3)$_2$), 3.96 (d, 2H, J = 2.61 Hz, >N−CH_2−), 4.65 (t, 1H, J = 5.40 Hz, >CH−), 7.07−7.35 (m, 5H, 4-F-Ph, 4-Pyr), 8.01 (s, 1H, 4-Pyr), 8.37−8.39 (m, 1H, 4-Pyr), 10.57 (s, 1H, CO−NH), 12.85 (s, 1H, NH)

***N*-{4-[3-(2,2-Dimethyl[1,3]dioxolan-4-ylmethyl)-5-(4-fluorophenyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]-pyridin-2-yl}acetamide (8m).** This compound was prepared from **7m** (2.1 g, 4.92 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (0.85 g, 4.92 mmol) according to general procedure B. Trituration with Et_2O yielded **8m** (2.1 g, 96%): mp 251.0 °C; ^{1}H NMR (DMSO-d_6) δ 0.9 (s, 3H, CH_3), 1.10 (s, 3H, S−CH_3), 2.06 (s, 3H, CO−CH_3), 3.50−3.59 (m, 1H, >CH−), 3.62−3.97 (m, 2H, −CH_2−O−), 4.23−4.39 (m, 2H, >N−CH_2−), 7.03−7.28 (m, 5H, 4-F-Ph, 4-Pyr), 8.01 (s, 1H, 4-Pyr), 8.38−8.40 (m, 1H, 4-Pyr), 10.55 (s, 1H, CO−NH), 12.85 (s, 1H, NH); IR (ATR) 1699 (NHC=O), 1222 (C−F), cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-morpholin-4-ylethyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}-acetamide (8n).** This compound was prepared from **7n** (5.0 g, 11.7 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (2.0 g, 11.7 mmol) according to general procedure B. Trituration with Et_2O yielded **8n** (4.9 g, 95%): mp 230.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, CO−CH_3), 2.37 (t, 4H, J = 4.48 Hz, −CH_2−O−CH_2−), 2.64 (t, 2H, J = 6.84 Hz, −CH_2−N−), 3.55 (t, 4H, J = 4.56 Hz, −CH_2−N−CH_2−), 4.19 (t, 2H, J = 7.32 Hz, N−CH_2−), 6.87−6.90 (m, 1H, 4-Pyr), 6.93−7.02 (m, 2H, 4-F-Ph), 7.17−7.27 (m, 2H, 4-F-Ph), 8.16−8.19 (m, 1H, 4-Pyr), 8.30 (s, 1H, 4-Pyr), 8.74 (s, 1H, NH−CO), IR (ATR) 1696 (NHC=O), 1225 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-(3-morpholin-4-ylpropyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}-acetamide (8o).** This compound was prepared from **7o** (3.75 g, 8.3 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (1.43 g, 8.3 mmol) according to general procedure B. Trituration with Et_2O yielded **8o** (2.46 g, 65%): mp 210.2 °C; ^{1}H NMR (DMSO-d_6) δ 1.86 (quint, 2H, J = 7.02 Hz, −CH_2−), 2.08 (s, 3H, CO−CH_3), 2.16−2.22 (m, 6H, N(CH_2)$_3$), 3.59 (t, 4H, J = 4.50 Hz, −CH_2−O−CH_2−), 3,92 (t, 2H, J = 7.46 Hz, N−CH_2), 7.11−7.32 (m, 5H, 4-F-Ph, 4-Pyr), 8.09 (s, 1H, 4-Pyr), 8.39−8.42 (m, 1H, 4-Pyr), 10.73 (s, 1H, CO−NH), 12.99 (s, 1H, NH), IR (ATR) 1699 (HNC=O), 1229 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-piperidin-1-ylethyl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}-acetamide (8p).** This compound was prepared from **7p** (4.3 g, 10.12 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (1.74 g, 10.12 mmol) according to general procedure B. Trituration with Et_2O yielded **8p** (4.0 g, 90%): mp 104.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.40−1.52 (m, 2H, −CH_2−), 1.57−1.72 (m, 4H, −CH_2−), 2.07 (s, 3H, CO−CH_3), 2.42−2.54 (m, 4H, −CH_2−N−CH_2−), 2.45 (t, 2H, J = 6.84 Hz, −CH_2−N<), 3.93 (t, 2H, J = 6.01 Hz, N−CH_2−), 7.10−7.30 (m, 5H, 4-F-Ph, 4-Pyr), 8.08 (s, 1H, 4-Pyr), 8.40−8.42 (m, 1H, 4-Pyr), 10.74 (s, 1H, CO−NH), 12.97 (s, 1H, NH); IR (ATR) 1695 (NHC=O), 1224 (C−F) cm^{-1}.

4-[5-(2-Acetylaminopyridin-4-yl)-4-(4-fluorophenyl)-2-thioxo-2,3-dihydroimidazol-1-yl]piperidin-1-carbonic Acid Ethyl Ester (8q). This compound was prepared from **7q** (2.4 g, 5.11 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (0.88 g, 5.11 mmol) according to general procedure B. Trituration with Et_2O yielded **8q** (1.19 g, 48%): mp 225.5 °C; ^{1}H NMR (DMSO-d_6)δ 1.16 (t, 3H, J = 7.17 Hz, −CH_3), 1.75−1.86 (m, 4H, 2(CH_2)Pip), 2.07 (s, 3H, CO−CH_3), 2.76−2.86 (m, 2H, CH_2 Pip), 3.94−4.06 (m, 5H, CHPip, CH_2Pip, O−CH_2), 6.82−6.84 (m, 1H, 4-Pyr), 7.06−7.28 (m, 5H, 4-F-Ph, 4-Pyr), 8.09 (s, 1H, 4-Pyr), 8.39−8.42 (m, 1H, 4-Pyr), 10.68 (s, 1H, CO−NH), 12.99 (s, 1H, NH); IR (ATR) 1228 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-methyl-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}acetamide (8r).** This compound was prepared from **7r** (2.0 g, 6.13 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (1.1 g, 6.39 mmol) according to general procedure B. Trituration with Et_2O yielded **8r** (1.36 g, 65%): mp 266.10 °C; ^{1}H NMR (DMSO-d_6) δ 2.09 (s, 3H, CO−CH_3), 3,38 (s, 3H, N−CH_3), 6.83−6.86 (m, 1H, 4-Pyr), 7.08−7.27 (m, 5H, 4-F-Ph, 4-Pyr), 8.10 (s, 1H, 4-Pyr), 8.39−8.44 (m, 1H, 4-Pyr), 10.69 (s, 1H, CO−NH), 12.96 (s, 1H, NH), IR (ATR) 1711(HNC=O), 1228 (C−F) cm^{-1}.

***N*-{4-[5-(4-Fluorophenyl)-3-(2,2,6,6-tetramethylpiperidin-4-yl)-2-thioxo-2,3-dihydro-1*H*-imidazol-4-yl]pyridin-2-yl}acetamide (8s).** This compound was prepared from **8s** (1.2 g, 2.66 mmol) and 2,2,4,4-tetramethylcyclobutan-1,3-dithione (0.46 g, 2.66 mmol) according to general procedure B. Trituration with Et_2O yielded **8s** (1.16 g, 93%): mp 212.5 °C; ^{1}H NMR (DMSO-d_6) δ 0.97 (s, 6H, C(CH_3)$_2$), 1.08 (s, 6H, C(CH_3)$_2$), 1.51−1.84 (m, 4H, −(CH_2)$_2$−), 2.08 (s, 3H, CO−CH_3), 4.26−4.38 (m, 1H, N−CH<), 7.10−7.29 (m, 5H, 4-F-Ph, 4-Pyr), 8.12 (s, 1H, 4-Pyr), 8.41−8.43 (m, 1H, 4-Pyr), 10.70 (s, 1H, CO−NH), 12.96 (s, 1H, NH), IR (ATR) 1683 (HNC=O), 1557 (HNC=O), 1239 (C−F) cm^{-1}.

Preparation of *N*-{4-[5-(4-Fluorophenyl)-3-alkyl-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide 9a−m, General Procedure C. To a solution of **8a**−**m** (1 equiv) in ethanol were added a catalytic amount of Na_2CO_3 and iodomethane. This mixture was heated under reflux for about 3 h under an inert atmosphere of argon. The solution was cooled to room temperature and filtered. The filtrate was concentrated in vacuo. The solid residue was purified by column chromatography or recrystallization.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-hydroxyethyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9a).** According to the general procedure C, compound **9a** was obtained from **8a** (0.8 g, 2.15 mmol) and iodomethane (0.31 g, 2.20 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **9a** (0.12 g, 14%): mp 195.7 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, CO−CH_3), 2.73 (s, 3H, S−CH_3), 3.92 (t, 2H, J = 5.01 Hz, O−CH_2), 4.04 (t, 2H, J = 5.33 Hz, N−CH_2), 6.90−6.98 (m, 3H, 4-F-Ph, 4-Pyr), 7.27−7.45 (m, 2H, 4-F-Ph), 8.19−8.26 (m, 2H, 4-Pyr), 8.34 (s, 1H, CO−NH); IR (ATR) 1665 (HNC=O), 1542 (HNC=O), 1223 (C−F) cm^{-1}. Anal. ($C_{19}H_{19}FN_4O_2S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-methoxyethyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9b).** According to the general procedure C, compound **9b** was obtained from **8b** (0.6 g, 1.55 mmol) and iodomethane (0.43 g, 3.05 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **9b** (0.24 g, 38%): mp 154.5 °C; H NMR ($CDCl_3$) δ 2.24 (s,3H, CO−CH_3), 2.74 (s, 3H, S−CH_3), 3.26 (s, 3H, O−CH_3), 3.52 (t, 2H, J = 5.89 Hz, O−CH_2), 4.10 (t, 2H, J = 6.07 Hz, N−CH_2), 6.89−6.99 (m, 3H, 4-F-Ph, 4-Pyr), 7.39−7.46 (m, 2H, 4-F-Ph), 8.16 (s, 1H, CO−NH), 8.27−8.30 (m, 2H, 4-Pyr); IR (ATR) 1667 (HNC=O), 1542 (HNC=O), 1120 (C−F) cm^{-1}. Anal. ($C_{20}H_{21}FN_4O_2S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-(3-hydroxypropyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9c).** According to the general procedure C, compound **9c** was obtained from **8c** (2.15 g, 5.56 mmol) and iodomethane (0.99

g, 7.0 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOAc/EtOH 9:2.5:0.5) yielded **9c** (0.45 g, 20%): mp 101,3 °C; ^{1}H NMR ($CDCl_3$) δ 2.12 (quint, 2H, J = 5.13 Hz, $-CH_2-$), 2.26 (s, 3H, $CO-CH_3$), 2.75 (s, 3H, $S-CH_3$), 3.70 (t, 2H, J = 5.67 Hz, $O-CH_2$), 4.04 (t, 2H, J = 5.808 Hz, $N-CH_2$), 6.87−6.98 (m, 3H, 4-F-Ph, 4-Pyr), 7.37−7.44 (m, 2H, 4-F-Ph), 8.18−8.24 (m, 2H, 4-Pyr), 8.81 (s, 1H, CO−NH); IR (ATR) 1675 (HNC=O), 1550 (HNC=O), 1217 (C−F) cm^{-1}. Anal. ($C_{20}H_{21}FN_4O_2S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-(3-methoxypropyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9d).** According to the general procedure C, compound **9d** was obtained from **8d** (0.8 g, 2.0 mmol) and iodomethane (0.28 g, 1.98 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **9d** (0.45 g, 54%): mp 164.3 °C; ^{1}H NMR ($CDCl_3$) δ 1.86 (quint, 2H, J = 5.80 Hz, $-CH_2-$), 2.23 (s, 3H, $CO-CH_3$), 2.73 (s, 3H, $S-CH_3$), 3.21 (s, 3H, $O-CH_3$), 3.27 (t, 2H, J = 5.86 Hz, $O-CH_2$), 4.01 (t, 2H, J = 6.64 Hz, $N-CH_2$), 6.88−6.96 (m, 3H, 4-F-Ph, 4-Pyr), 7.39−7.45 (m, 2H, 4-F-Ph), 8.26−8.28 (m, 3H, 4-Pyr, CO−NH); IR (ATR) 1693 (HNC=O), 1547 (HNC=O), 1214 (C−F) cm^{-1}. Anal. ($C_{21}H_{23}FN_4O_2S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-[2-(2-hydroxyethoxy)ethyl]-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9e).** According to the general procedure C, compound **9e** was obtained from **8e** (4.0 g, 9.6 mmol) and iodomethane (1.5 g, 10.56 mmol). Purification by recrystallization (EtOH) yielded **9e** (2.6 g, 63%): mp 181.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, $CO-CH_3$), 2.74 (s, 3H, $S-CH_3$), 3.13 (t, 2H, J = 6.23 Hz, $O-CH_2-$), 3.52 (t, 2H, J = 5.5 Hz, $-CH_2-O$), 3.76 (t, 2H, J = 5.6 Hz, $-CH_2-O$), 4.10 (t, 2H, J = 5.66 Hz, $N-CH_2-$), 6.87−6.97 (m, 3H, 4-F-Ph, 4-Pyr), 7.38−7.45 (m, 2H, 4-F-Ph), 8.21−8.23 (m, 1H, 4-Pyr), 8.38−8.40 (m, 2H, 4-Pyr, CO−NH); IR (ATR) 1693 (HNC=O), 1219 (C−F) cm^{-1}. Anal. ($C_{21}H_{23}FN_4O_3S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-hydroxypropyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9f).** According to the general procedure C, compound **9f** was obtained from **8f** (2.0 g, 5.18 mmol) and iodomethane (0.8 g, 5.63 mmol). Purification by recrystallization yielded **9f** (0.9 g, 43%): mp 239.1 °C; ^{1}H NMR (DMSO-d_6) δ 0.87 (d, 3H, J = 5.86 Hz, $C-CH_3$), 2.07 (s, 3H, $CO-CH_3$), 2.63 (s, 3H, $S-CH_3$), 3.64−3.74 (m, 3H, $-CH-$, $N-CH_2$), 4.98 (d, 1H, J = 4.62 Hz, $-OH$), 7.02−7.13 (m, 3H, 4-F-Ph, 4-Pyr), 7.32−7.40 (m, 2H, 4-F-Ph), 8.04 (s, 1H, 4-Pyr), 8.38−8.40 (m, 1H, 4-Pyr), 8.66 (s, 1H, NH), IR (ATR) 1671 (HNC=O), 1216 (C−F) cm^{-1}. Anal. ($C_{20}H_{21}FN_4O_2S$) C, H, N.

***N*-{4-[3-(2-Acetylaminoethyl)-5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9g).** According to the general procedure C, compound **9g** was obtained from **8g** (0.8 g, 1.93 mmol) and iodomethane (0.3 g, 2.11 mmol). Purification by recrystallization (EtOH) yielded **9g** (0.3 g, 36%): mp 206.7 °C; ^{1}H NMR ($CDCl_3$) δ 1.88 (s, 3H, $CO-CH_3$), 2.20 (s, 3H, $CO-CH_3$), 2.73 (s, 3H, $S-CH_3$), 3.52 (q, 2H, J = 6.5 Hz, $-CH_2-N$), 4.05 (t, 2H, J = 6.54 Hz, $N-CH_2-$), 6.32 (t, 1H, J = 5.72 Hz, NH−CO), 6.62−6.99 (m, 3H, 4-F-Ph, 4-Pyr), 7.36−7.46 (m, 2H, 4-F-Ph), 8.17 (s, 1H, 4-Pyr), 8.24−8.27 (m, 1H, 4-Pyr), 8.71 (s, 1H, NH); IR (ATR) 1214 (C−F), cm^{-1}. Anal. ($C_{21}H_{22}FN_5O_2S$) C, H, N.

***N*-{4-[3-(2-Dimethylaminoethyl)-5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9h).** According to the general procedure C, compound **9h** was obtained from **8h** (4.5 g, 11.26 mmol) and iodomethane (1.6 g, 11.27 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **9h** (0.8 g, 17%): mp 159.3 °C; ^{1}H NMR (DMSO-d_6) δ 1.97 (s, 6H, $N(CH_3)_2$), 2.07 (s, 3H, $CO-CH_3$), 2.31 (t, 2H, J = 6.88 Hz, $-CH_2-N<$), 2.63 (s, 3H, $S-CH_3$), 3.85 (t, 2H, J = 6.68 Hz, $N-CH_2$), 7.02−10 (m, 3H, 4-F-Ph, 4-Pyr), 7.33−7.40 (m, 2H, 4-F-Ph), 8.05 (s, 1H, 4-Pyr), 8.38−8.41 (m, 1H, 4-Pyr), 10.64 (s, 1H, CO−NH); IR (ATR) 1694 (NHC=O), 1219 (C−F) cm^{-1}. Anal. ($C_{21}H_{24}FN_5OS$) C, H, N.

***N*-{4-[3-(2-Allyloxyethyl)-5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9i).** According to the general procedure C, compound **9i** was obtained from **8i** (2.5 g, 6.06 mmol) and iodomethane (0.9 g, 6.33 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **9i** (0.7 g, 27%): mp 127.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H, $CO-CH_3$), 2.73 (s, 3H, $S-CH_3$), 3.55 (t, 2H, J = 5.93 Hz, $-CH_2-O$), 3.87 (dt, 2H, J_1 = 1.36 Hz, J_2 = 2.73 Hz, J_3 = 4.14 Hz, 4.11 (t, 2H, J = 6.19 Hz, $N-CH_2$), 5.09−5.20 (m, 2H, $=CH_2$), 5.70−5.83 (m, 1H, HC=), 6.87−6.98 (m, 3H, 4-F-Ph, 4-Pyr), 7.38−7.45 (m, 2H, 4-F-Ph), 7.98 (s, 1H, NH), 8.25−8.31 (m, 2H, 4-Pyr); IR (ATR) 1698 (NHC=O), 1217 (C−F) cm^{-1}. Anal. ($C_{22}H_{23}FN_4O_2S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3-(2-prop-2-ynyloxyethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9j).** According to the general procedure C, compound **9j** was obtained from **8j** (1.8 g, 4.39 mmol) and iodomethane (0.7 g, 4.93 mmol). Purification by recrystallization (EtOH) yielded **9j** (0.7 g, 38%): mp 163.3 °C; ^{1}H NMR ($CDCl_3$) δ 2.18 (s, 3H, $CO-CH_3$), 2.38 (t, 1H, J = 2.4 Hz, C−H), 2.73 (s, 3H, $S-CH_3$), 3.62 (t, 2H, J = 6.04 Hz, $-CH_2-O$), 4.06 (d, 2H, J = 2.38 Hz, $O-CH_2-$), 4.12 (t, 2H, J = 5.8 Hz, $N-CH_2-$), 6.87−6.99 (m, 3H, 4-F-Ph, 4-Pyr), 7.39−7.46 (m, 2H, 4-F-Ph), 8.02 (s, 1H, NH), 8.26−8.31 (m, 2H, 4-Pyr); IR (ATR) 1683 (NHC=O), 1216 (C−F) cm^{-1}. Anal. ($C_{22}H_{21}FN_4O_2S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3-(2-methylsulfanylethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9k).** According to the general procedure C, compound **9k** was obtained from **8k** (2.5 g, 6.21 mmol) and iodomethane (0.89 g, 6.26 mmol). Purification by recrystallization (EtOH) yielded **9k** (1.5 g, 58%): mp 160.6 °C; ^{1}H NMR ($CDCl_3$) δ 1.97 (s, 3H, $S-CH_3$), 2.18 (s, 3H, $CO-CH_3$), 2.64 (t, 2H, J = 7.6 Hz, $-CH_2-S$), 2.74 (s, 3H, $S-CH_3$), 4.06 (t, 2H, J = 7.74 Hz, $>N-CH_2-$), 6.82−6.97 (m, 3H, 4-F-Ph, 4-Pyr), 7.35−7.45 (m, 2H, 4-F-Ph), 8.20 (s, 1H, NH), 8.27−8.42 (m, 2H, 4-Pyr); IR (ATR) 1696 (NHC=O), 1212 (C−F) cm^{-1}. Anal. ($C_{20}H_{21}FN_4OS_2$) C, H, N.

***N*-{4-[3-(2,2-Dimethoxyethyl)-5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9l).** According to the general procedure C, compound **9l** was obtained from **8l** (2.1 g, 5.04 mmol) and iodomethane (0.71 g, 5.04 mmol). Purification by recrystallization (EtOH) yielded **9l** (0.9 g, 41%): mp 146.8 °C; ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H, $CO-CH_3$), 2.72 (s, 3H, $S-CH_3$), 3.28 (s, 6H, $>C(O-CH_3)_2$), 4.01 (d, 2H, J = 2.69 Hz, $>N-CH_2-$), 4.43 (t, 1H, J = 5.46 Hz, $>CH-$), 6.87−6.99 (m, 3H, 4-F-Ph, 4-Pyr), 7.37−7.47 (m, 2H, 4-F-Ph), 7.98 (s, 1H, NH), 8.22−8.30 (m, 2H, 4-Pyr); IR (ATR) 1692 (NHC=O), 1212 (C−F) cm^{-1}. Anal. ($C_{21}H_{23}FN_4O_3S$) C, H, N.

***N*-{4-[3-(2,2-Dimethyl[1,3]dioxolan-4-ylmethyl)-5-(4-fluorophenyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9m).** According to the general procedure C, compound **9m** was obtained from **8m** (2.1 g, 4.75 mmol) and iodomethane (0.67 g, 4.75 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **9m** (0.4 g, 18%): mp 142.4 °C; ^{1}H NMR ($CDCl_3$) δ 1.23 (d, 6H, J = 2.38 Hz, $>C(CH_3)_2$), 2.18 (s, 3H, $CO-CH_3$), 2.73 (s, 3H, $S-CH_3$), 3.73 (quint, 1H, J = 5.98 Hz, $>CH-$), 3.92−3.99 (m, 2H, $-CH_2-O$), 4.07−4.22 (m, 2H, $>N-CH_2$), 6.88−6.99 (m, 3H, 4-F-Ph, 4-Pyr), 7.37−7.44 (m, 2H, 4-F-Ph), 7.98 (s, 1H, NH), 8.21 (s, 1H, 4-Pyr), 8.26−8.29 (m, 1H, 4-Pyr); IR (ATR) 1708 (NHC=O), 1225 (C−F) cm^{-1}. Anal. ($C_{23}H_{25}FN_4O_3S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-morpholin-4-ylethyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9n).** According to the general procedure C, compound **9n** was obtained from **8n** (4.5 g, 10.19 mmol) and iodomethane (1.48 g, 10.49 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **9n** (1.6 g, 34%): mp 218.3 °C; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H, $CO-CH_3$), 2.39 (t, 4H, J = 3.78 Hz, $-CH_2-O-CH_2-$), 2.54 (t, 2H, J = 7.12 Hz, $-CH_2-N<$), 2.73 (s, 3H, $S-CH_3$), 3.62 (t, 4H, J = 4.26 Hz, $-N(CH_2)_2$), 4.03 (t, 2H, J = 7.16 Hz, $>N-CH_2-$), 6.88−6.96 (m, 3H, 4-F-Ph, 4-Pyr), 7.36−7.44 (m, 2H, 4-F-Ph),8.06 (s, 1H, CO−NH) 8.26−8.34 (m, 2H, 4-Pyr), IR (ATR) 1698 (HNC=O), 1214 (C−F) cm^{-1}. Anal. ($C_{23}H_{26}FN_5O_2S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-(3-morpholin-4-ylpropyl)-2-methylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}-**

acetamide (9o). According to the general procedure C, compound **9o** was obtained from **8o** (2.4 g, 5.27 mmol) and iodomethane (1.48 g, 10.49 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **9o** (0.45 g, 18%): mp 215.1 °C; ^{1}H NMR ($CDCl_3$) δ 1.81 (quint, 2H, J = 7.44 Hz, $-CH_2-$), 2.23 (s, 3H, $CO-CH_3$), 2.30−2.36 (m, 6H, $N(CH_2)_3$), 2.73 (s, 3H, $S-CH_3$), 3.66 (t, 2H, J = 6.79 Hz, $O-CH_2$), 3.98 (t, 2H, J = 7.73 Hz, $N-CH_2$), 6.85−6.96 (m, 3H, 4-F-Ph, 4-Pyr), 7.37−7.44 (m, 2H, 4-F-Ph), 8.28−8.35 (m, 2H, 4-Pyr), 8.54 (s, 1H, CO−NH), IR (ATR) 1694 (HNC=O), 1544 (HNC=O), 1220 (C−F) cm^{-1}, Anal. ($C_{24}H_{28}FN_5O_2S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-methylsulfanyl-3-(2-piperidin-1-ylethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (9p).** According to the general procedure C, compound **9p** was obtained from **8p** (2.0 g, 4.55 mmol) and iodomethane (0.7 g, 4.39 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **9p** (0.67 g, 32%): mp 104.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.42−1.58 (m, 2H, $-CH_2-$), 1.61−1.79 (m, 4H, $-CH_2-$), 2.19 (s, 3H, $CO-CH_3$), 2.52−2.65 (m, 4H, $-CH_2-N-CH_2-$), 2.73 (s, 3H, $S-CH_3$), 2.78 (t, 2H, J = 6.52 Hz, $-CH_2-N<$), 4.19 (t, 2H, J = 6.12 Hz, $N-CH_2-$), 6.86−6.97 (m, 3H, 4-F-Ph, 4-Pyr), 7.37−7.45 (m, 2H, 4-F-Ph), 8.14 (s, 1H, NH), 8.28−8.31 (m, 2H, 4-Pyr), IR (ATR) 1689 (NHC=O), 1218 (C−F) cm^{-1}. Anal. ($C_{24}H_{28}FN_5OS$) C, N, H.

4-[5-(2-Acetylaminopyridin-4-yl)-4-(4-fluorophenyl)-2-methylsulfanylimidazol-1-yl]piperidin-1-carbonic Acid Ethyl Ester (9q). According to the general procedure C, compound **9q** was obtained from **8q** (0.3 g, 0.62 mmol) and iodomethane (0.2 g, 1.41 mmol). Purification by recrystallization (EtOH) yielded **9q** (0.01 g, 3%): mp 190.1 °C; ^{1}H NMR ($CDCl_3$) δ 1.28 (t, 3H, J = 7.10 Hz, $-CH_3$), 1.82−1.88 (m, 2H, $-CH_2-$Pip), 2.24 (s, 3H, $CO-CH_3$), 2.41−2.58 (m, 2H, $-CH_2-$Pip), 2.65−2.78 (m, 4H, $(CH_2)_2$Pip) 2.75 (s, 3H, $S-CH_3$), 4.03−4.18 (m, 1H, N−CH), 4.15 (q, 2H, J = 7.12 Hz, $CO-CH_2$), 6.87−6.95 (m, 3H, 4-F-Ph, 4-Pyr), 7.32−7.39 (m, 2H, 4-F-Ph), 8.11 (s, 1H, CO−NH), 8.17 (s, 1H, 4-Pyr), 8.27−8.29 (m, 1H, 4-Pyr), IR (ATR) 1673 (NHC=O), 1228 (C−F) cm^{-1}. Anal. ($C_{25}H_{28}FN_5O_3S$) C, H, N.

Preparation of *N*-{4-[5-(4-Fluorophenyl)-2-(4-methylsulfinylbenzylsulfanyl)-3-alkyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide 10a,b,d−g,i−k,o,p,r,s. General Procedure D. To a solution of **8** (1 equiv) in EtOH (100 mL) were added a catalytic amount of Na_2CO_3 and 1-chloromethyl-4-methylsulfinylbenzene. This mixture was heated under reflux for about 3 h under an inert atmosphere of argon. The solution was cooled to room temperature and filtered. The filtrate was concentrated in vacuo. The solid residue was purified by column chromatography or recrystallization.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-hydroxyethyl)-2-(4-methylsulfinylbenzylsulfanyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10a).** According to the general procedure D, compound **10a** was obtained from **8a** (0.6 g, 1.61 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.32 g, 1.69 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **10a** (0.1 g, 12%): mp 159.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.22 (s, 3H, $CO-CH_3$), 2.71 (s, 3H, $SO-CH_3$), 3.71 (t, 2H, J = 5.84 Hz, $-O-CH_2$), 3.79 (t, 2H, J = 5.72 Hz, $N-CH_2$), 4.42 (s, 2H, $S-CH_2$), 6.83−6.86 (m, 1H, 4-Pyr), 6.90−6.99 (m, 2H, 4-F-Ph), 7.35−7.45 (m, 2H, 4-F-Ph), 7.48−7.62 (m, 4H, 4-MeS(O)-Ph, AA′BB′), 8.14 (s, 1H, 4-Pyr), 8.19−8.22 (m, 1H, 4-Pyr), 8.46 (s, 1H, CO−NH); IR (ATR) 1690 (HNC=O), 1224 (C−F), 1056 (S=O), 838 cm^{-1}. Anal. ($C_{26}H_{25}FN_4O_3S_2$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-(4-methylsulfinylbenzylsulfanyl)-3-(2-methoxyethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10b).** According to the general procedure D, compound **10b** was obtained from **8b** (0.5 g, 1.29 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.48 g, 2.6 mmol). Purification by recrystallization (EtOH) yielded **10b** (0.07 g, 10%): mp 130.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H, $CO-CH_3$), 2.71 (s, 3H, $SO-CH_3$), 3.14 (s, 3H, $O-CH_3$), 3.31 (t, 2H, J = 5.92 Hz, $O-CH_2$), 3.86 (t, 2H, J = 5.86 Hz, $N-CH_2$), 4.41 (s, 2H, $S-CH_2-$), 6.88−6.96 (m, 3H, 4-F-Ph, 4-Pyr), 7.36−7.43 (m, 2H, 4-F-Ph), 7.46−7.63 (m, 4H, 4-MeS(O)-Ph, AA′BB′), 8.15 (s, 1H, 4-Pyr), 8.25−8.28 (m, 1H, 4-Pyr), 8.53 (s, 1H, CO−NH); IR (ATR) 1695 (HNC=O), 1535 (HNC=O), 1264 (C−F), 1050 (S=O) cm^{-1}. Anal. ($C_{27}H_{27}FN_4O_3S_2$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-(4-methylsulfinylbenzylsulfanyl)-3-(3-methoxypropyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10d).** According to the general procedure D, compound **10d** was obtained from **8d** (0.6 g, 1.49 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.3 g, 1.59 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **10d** (0.25 g, 30%): mp 149.2 °C; ^{1}H NMR ($CDCl_3$), δ 1.66 (quint, 2H, J = 5.93 Hz, $-CH_2-$), 2.23 (s, 3H, $CO-CH_3$), 2.73 (s, 3H, $SO-CH_3$), 3.16 (t, 2H, J = 6.53 Hz, $O-CH_2$), 3.17 (s, 3H, $O-CH_3$), 3.81 (t, 2H, J = 7.41 Hz, $N-CH_2$), 4.45 (s, 2H, $S-CH_2$), 6.88−6.99 (m, 3H, 4-F-Ph, 4-Pyr), 7.38−7.45 (m, 2H, 4-F-Ph), 7.50−7.65 (m, 4H, 4-MeS(O)-Ph, AA′BB′), 8.15 (s, 1H, 4-Pyr), 8.22 (s, 1H, CO−NH), 8.27−8.29 (m, 1H, 4-Pyr); IR (ATR) 1694 (HNC=O), 1543 (HNC=O), 1219 (C−F), 1047 (S=O) cm^{-1}. Anal. ($C_{28}H_{29}FN_4O_3S_2$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-[2-(2-hydroxyethoxy)ethyl]-2-(4-methylsulfinylbenzylsulfanyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10e).** According to the general procedure D, compound **10e** was obtained from **8e** (0.5 g, 1.2 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.48 g, 2.6 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **10e** (0.30 g, 44%): mp 113.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, $CO-CH_3$), 2.72 (s, 3H, $SO-CH_3$), 3.41 (t, 2H, J = 4.77 Hz, $O-CH_2-$), 3.60 (t, 2H, J = 4.14 Hz, $-CH_2-OH$), 3.72 (t, 2H, J = 4.52 Hz, $-CH_2-O-$), 3.92 (t, 2H, J = 5.34 Hz, $N-CH_2-$), 4.48 (s, 2H, $S-CH_2-$), 6.84−6.88 (m, 1H, 4-Pyr), 6.90−6.99 (m, 2H, 4-F-Ph), 7.38−7.45 (m, 2H, 4-F-Ph), 7.50−7.64 (m, 4H, 4-MeS(O)-Ph, AA′BB′), 8.22−8.25 (m, 1H, 4-Pyr), 8.28 (s, 1H, 4-Pyr), 8.38 (s, 1H, CO−NH); IR (ATR) 1690 (HNC=O), 1219 (C−F), 1085 (S=O), cm^{-1}. Anal. ($C_{28}H_{29}FN_4O_4S_2$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-hydroxypropyl)-2-(4-methylsulfinylbenzylsulfanyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10f).** According to the general procedure D, compound **10f** was obtained from **8f** (0.7 g, 1.81 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.48 g, 2.6 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **10f** (0.3 g, 31%): mp 140.4 °C; ^{1}H NMR ($CDCl_3$) δ 1.07 (d, 3H, J = 6.00 Hz, $C-CH_3$), 2.23 (s, 3H, $CO-CH_3$), 2.71 (s, 3H, $SO-CH_3$), 3.65−3.74 (m, 3H, $N-CH_2-$, $-CH-$), 4.39 (s, 2H, $S-CH_2-$), 6.87−6.98 (m, 3H, 4-F-Ph, 4-Pyr), 7.36−7.43 (m, 2H, 4-F-Ph), 7.47−7.63 (m, 4H, 4-MeS(O)-Ph, AA ′BB′), 8.15 (s, 1H, 4-Pyr), 8.22−8.25 (m, 1H, 4-Pyr), 8.31 (s, 1H, CO−NH); IR (ATR) 1689 (HNC=O), 1219 (C−F), cm^{-1}. Anal. ($C_{27}H_{27}FN_4O_3S_2$) C, H, N.

***N*-{4-[3-(2-Acetylaminoethyl)-5-(4-fluorophenyl)-2-(4-(methylsulfinyl)benzylsulfanyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10 g).** According to the general procedure D, compound **10g** was obtained from **8g** (0.4 g, 0.97 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.2 g, 1.06 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **10g** (0.2 g, 37%): mp 245.8 °C; ^{1}H NMR ($CDCl_3$) δ 1.86 (s, 3H, $CO-CH_3$), 2.24 (s, 3H, $CO-CH_3$), 2.72 (s, 3H, $SO-CH_3$), 3.35 (q, 2H, J = 6.3 Hz, $-CH_2-N$), 3.85 (t, 3H, J = 6.68 Hz, $N-CH_2-$), 4.46 (s, 2H, $S-CH_2-$), 6.21 (t, 1H, J = 6.16 Hz, NH−CO), 6.86−6.89 (m, 1H, 4-Pyr), 6.91−7.00 (m, 2H, 4-F-Ph), 7.38−7.43 (m, 2H, 4-F-Ph), 7.46−7.63 (m, 4H, 4-MeS(O)-Ph, AA′BB′), 8.09 (s, 1H, 4-Pyr), 8.25−8.28 (m, 1H, 4-Pyr), 8.39 (s, 1H, CO−NH); IR (ATR) 1691 (C=O−NH), 1214 (C−F) cm^{-1}. Anal. ($C_{28}H_{28}FN_5O_3S_2$) C, H, N.

***N*-{4-[3-(2-Allyloxyethyl)-5-(4-fluorophenyl)-2-(4-methylsulfinylbenzylsulfanyl)-3*H*-imidazol-4-yl]pyridin-2-yl}-acetamide (10i).** According to the general procedure D, compound **10i** was obtained from **8i** (1.8 g, 4.36 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.9 g, 5.34 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **10i** (0.9 g, 37%): mp 68.4 °C; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H, $CO-CH_3$), 2.73 (s, 3H, $SO-CH_3$), 3.38 (t, 2H, J = 5.84 Hz, $-CH_2-O$), 3.79 (dt, 2H, J_1 = 1.35 Hz, J_2 = 2.83 Hz, J_3 = 4.19 Hz, $=CH_2$), 3.90 (t, 2H, J = 6.02 Hz, $N-CH_2$), 4.44 (s, 2H, $S-CH_2-$), 5.06−5.15 (m, 2H, $=CH_2$), 5.64−5.78 (m, 1H, HC=), 6.90−6.98 (m, 3H, 4-F-Ph, 4-Pyr), 7.38−7.43 (m, 2H,

4-F-Ph), 7.45−7.52 (m, 2H, 4-MeS(O)-Ph, AA′), 7.61−7.65 (m, 2H, MeS(O)-Ph, BB′), 8.04 (s, 1H, CO−NH) 8.14 (s, 1H, 4-Pyr), 8.27−8.30 (m, 1H, 4-Pyr); IR (ATR) 1694 (NHC=O), 1219 (C−F) cm^{-1}. Anal. ($C_{29}H_{29}FN_4O_3S_2$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-(4-methylsulfinylbenzylsulfanyl)-3-(2-prop-2-ynyloxyethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10j).** According to the general procedure D, compound **10j** was obtained from **8j** (1.6 g, 3.90 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.7 g, 4.15 mmol). Purification by recrystallization (EtOH) yielded **10j** (0.6 g, 27%): mp 136.0 °C; ^{1}H NMR ($CDCl_3$) δ 2.23 (s, 3H, CO−CH_3), 2.35 (t, 1H, J = 2.34 Hz, C−H), 2.73 (s, 3H, SO−CH_3), 3.48 (t, 2H, J = 5.82 Hz, −CH_2−O), 3.92 (t, 2H, J = 5.52 Hz, N−CH_2−), 3.98 (d, 2H, J = 1.18 Hz, O−CH_2−), 4.44 (s, 2H, S−CH_2−), 6.75−6.98 (m, 3H, 4-F-Ph, 4-Pyr), 7.38−7.45 (m, 2H, 4-F-Ph), 7.49−7.56 (m, 2H, 4-MeS(O)-Ph, AA′), 7.61−7.65 (m, 2H, MeS(O)-Ph, BB′), 8.03 (s, 1H, CO−NH), 8.16 (s, 1H, 4-Pyr), 8.28−8.31 (m, 1H, 4-Pyr); IR (ATR) 1693 (NHC=O), 1213 (C−F) cm^{-1}. Anal. ($C_{29}H_{27}FN_4O_3S_2$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-(4-methylsulfinylbenzylsulfanyl)-3-(2-methylsulfanylethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10k).** According to the general procedure D, compound **10k** was obtained from **8k** (2.0 g, 4.97 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (1.0 g, 5.93 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **10k** (1.6 g, 58%): mp 119.3 °C; ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3H, S−CH_3), 2.23 (CO−CH_3), 2.39 (t, 2H, J = 7.82 Hz, −CH_2−S), 2.74 (s, 3H, SO−CH_3), 3.87 (t, 2H, 7.24 Hz, >N−CH_2−), 4.38 (s, 2H, S−CH_2−), 6.90−6.99 (m, 3H, 4-F-Ph, 4-Pyr), 7.39−7.47 (m, 2H, 4-F-Ph), 7.51−7.55 (m, 2H, 4-MeS(O)-Ph, AA′), 7.61−7.66 (m, 2H, MeS(O)-Ph, BB′), 8.09 (s, 1H, CO−NH), 8.16 (s, 1H, 4-Pyr), 8.22−8.25 (m, 1H, 4-Pyr); IR (ATR) 1707 (NHC=O), 1219 (C−F) cm^{-1}. Anal. ($C_{27}H_{27}FN_4O_2S_3$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-(4-methylsulfinylbenzylsulfanyl)-3-(3-morpholin-4-yl-propyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10o).** According to the general procedure D, compound **10o** was obtained from **8o** (1.2 g, 2.63 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.67 g, 3.55 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **10o** (0.2 g, 13%): mp 120.9 °C; ^{1}H NMR ($CDCl_3$) δ 1.56 (quint, 2H, J = 7.56 Hz, −CH_2−), 2.12−2.23 (m, 6H, N(CH_2)$_3$), 2.23 (s, 3H, CO−CH_3), 2.73 (s, 3H, SO−CH_3), 3.55−3.60 (m, 4H, −CH_2−O−CH_2−), 3.77 (t, 2H, J = 7.63 Hz, N−CH_2), 6.86−6.98 (m, 3H, 4-F-Ph, 4-Pyr), 7.37−7.45 (m, 2H, 4-F-Ph), 7.48−7.65 (m, 4H, 4-MeS(O)-Ph, AA′BB′), 8.17 (s, 1H, 4-Pyr), 8.26−8.29 (m, 1H, 4-Pyr), 8.43 (s, 1H, CO−NH); IR (ATR) 1694 (HNC=O), 1544 (HNC=O), 1218 (C−F), 1035 (S=O) cm^{-1}. Anal. ($C_{31}H_{34}FN_5O_3S_2$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-(4-methylsulfinylbenzylsulfanyl)-3-(2-piperidin-1-ylethyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10p).** According to the general procedure D, compound **10p** was obtained from **8p** (1.9 g, 4.32 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.8 g, 4.75 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **10p** (0.7 g, 27%): mp 121.2 °C; ^{1}H NMR ($CDCl_3$) δ 1.19 (m, 6H, −CH_2−CH_2−CH_2−), 2.09−2.21 (m, 4H, −CH_2−N−CH_2−), 2.23 (s, 3H, CO−CH_3), 2.27 (t, 2H, J = 7.5 Hz, −CH_2−N), 2.73 (s, 3H, SO−CH_3), 3.78 (t, 2H, J = 7.2 Hz, N−CH_2−), 4.44 (s, 2H, S−CH_2−), 6.87−6.98 (m, 3H, 4-F-Ph, 4-Pyr), 7.38−7.43 (m, 2H, 4-F-Ph), 7.45−7.52 (m, 2H, 4-MeS(O)-Ph, AA′), 7.60−7.65 (m, 2H, MeS(O)-Ph, BB′), 8.04 (s, 1H, CO−NH), 8.15 (s, 1H, 4-Pyr), 8.27−8.30 (m, 1H, 4-Pyr); IR (ATR) 1694 (NHC=O), 1219 (C−F) cm^{-1}. Anal. ($C_{31}H_{34}FN_5O_2S_2$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-(4-methylsulfinylbenzylsulfanyl)-3-methyl-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10r).** According to the general procedure D, compound **10r** was obtained from **8r** (1.0 g, 2.92 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.5 g, 2.92 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **10r** (0.25 g, 17%): mp 190.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H, CO−CH_3), 2.65 (s, 3H, SO−CH_3), 3.18 (s, 3H, N−CH_3), 4.30 (s, 2H, S−CH_2−), 6.77−6.90 (m, 3H, 4-F-Ph, 4-Pyr), 7.32−7.42 (m, 4H, 4-F-Ph, 4-MeS(O)-Ph), 7.53−7.57 (m, 2H, 4-MeS(O)-Ph), 8.09 (s, 1H, 4-Pyr), 8.16−8.19 (m, 1H, 4-Pyr), 9.05 (s, 1H, CO−NH); IR (ATR) 1698 (HNC=O), 1546 (HNC=O), 1220 (C−F), 1035 (S=O) cm^{-1}. Anal. ($C_{25}H_{23}FN_4O_2S_2$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-2-(4-methylsulfinylbenzylsulfanyl)-3-(2,2,6,6-tetramethyl-piperidin-4-yl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (10s).** According to the general procedure D, compound **10s** was obtained from **8s** (0.6 g, 1.55 mmol) and 1-chloromethyl-4-methylsulfinylbenzene (0.33 g, 1.70 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **10s** (0.15 g, 16%): mp 218.8 °C; ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 6H, C(CH_3)$_2$), 1.08 (s, 6H, C(CH_3)$_2$), 1.52−1.57 (m, 2H, −CH_2− equatorial), 1.84−1.97 (m, 2H, −CH_2−axial), 2.21 (s, 3H, CO−CH_3), 2.79 (s, 3H, SO−CH_3), 4.26−4.38 (m, 1H, NCH<), 4.55 (s, 2H, S−CH_2), 6.88−6.97 (m, 3H, 4-F-Ph, 4-Pyr), 7.36−7.52 (m, 2H, 4-F-Ph), 7.57−7.64 (m, 4H, 4-MeS(O)-Ph, AA′BB′), 8.07 (s, 1H, CO−NH), 8.22 (s, 1H, 4-Pyr), 8.31−8.33 (s, 1H, 4-Pyr); IR (ATR) 1699 (HNC=O), 1546 (HNC=O), 1231 (C−F), 1037 (S=O) cm^{-1}. Anal. ($C_{33}H_{38}FN_5O_2S_2$) C, H, N.

Preparation of 11a−e. General Procedure E. To a solution of **8** (1 equiv) in THF (30 mL) was added Na_2CO_3 (1 equiv), tetrabutylammonium iodide (1 equiv), and 4-chloro-1-morpholin-4-yl-alkan-1-one (1 equiv). This mixture was heated under reflux for about 6 h under an inert atmosphere of argon. The solution was cooled to room temperature and filtered. The filtrate was concentrated in vacuo. The solid residue was purified by column chromatography or recrystallization.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-hydroxyethyl)-2-(3-morpholin-4-yl-3-oxopropylsulfanyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (11a).** According to the general procedure E, compound **11a** was obtained from **8a** (0.6 g, 1.61 mmol) and 3-chloro-1-morpholin-4-ylpropan-1-one (0.3 g, 1.69 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **11a** (0.09 g, 11%): mp 219.6 °C; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, CO−CH_3), 2.95 (t, 2H, J = 6.62 Hz, −CH_2−CON), 3.45−3.66 (m, 10H, morpholino, S−CH_2−), 3.88 (t, 2H, J = 6.08 Hz, −CH_2−O), 4.07 (t, 2H, J = 5.98 Hz, N−CH_2), 6.89−6.97 (m, 3H, 4-F-Ph, 4-Pyr), 7.35−7.42 (m, 2H, 4-F-Ph), 8.07 (s, 1H, CO−NH), 8.24−8.26 (m, 2H, 4-Pyr); IR (ATR) 1693 (NHC=O), 1112 (C−F) cm^{-1}. Anal. ($C_{25}H_{28}FN_5O_4S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-hydroxyethyl)-2-(4-morpholin-4-yl-4-oxobutylsulfanyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (11b).** According to the general procedure E, compound **11b** was obtained from **8a** (0.5 g, 1.34 mmol) and 4-chloro-1-morpholin-4-ylbutan-1-one (0.3 g, 1.56 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **11b** (0.08 g, 11%): mp 169.7 °C; ^{1}H NMR ($CDCl_3$) δ 2.15 (quint, 2H, J = 7.4 Hz, −CH_2−), 2.25 (s, 3H, CO−CH_3), 2.55 (t, 2H, J = 7.28 Hz, −CH_2−CON<), 3.31 (t, 2H, J = 7.02 Hz, S−CH_2−), 3.47 (t, 2H, J = 4.9 Hz, −CH_2−morpholino), 3.61−3.65 (m, 6H, −CH_2−morpholino), 3.90 (t, 2H, J = 5.52 Hz, −CH_2−O), 4.09 (t, 2H, J = 5.62 Hz, N−CH_2−), 6.90−6.98 (m, 3H, 4-F-Ph, 4-Pyr), 7.36−7.43 (m, 2H, 4-F-Ph), 8.16 (s, 1H, CO−NH), 8.23−8.25 (m, 2H, 4-Pyr); IR (ATR) 1682 (NHC=O), 1217 (C−F) cm^{-1}. Anal. ($C_{26}H_{30}FN_5O_4S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-(3-hydroxypropyl)-2-(4-morpholin-4-yl-3-oxopropylsulfanyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (11c).** According to the general procedure E, compound **11c** was obtained from **8c** (0.5 g, 1.29 mmol) and 3-chloro-1-morpholin-4-ylpropan-1-one (0.3 g, 1.69 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **11c** (0.12 g, 18%): mp 193.9 °C; ^{1}H NMR ($CDCl_3$) δ 2.05 (quint, 2H, J = 7.45 Hz, −CH_2−), 2.25 (s, 3H, CO−CH_3), 2.96 (t, 2H, J = 6.97 Hz, −CH_2−CON), 3.50−3.67 (m, 12H, morpholino, S−CH_2−, −CH_2−O), 4.03 (t, 2H, J = 7.43 Hz, N−CH_2), 6.86−6.98 (m, 3H, 4-F-Ph, 4-Pyr), 7.33−7.40 (m, 2H, 4-F-Ph), 8.15 (s, 1H, CO−NH), 8.22−8.24 (m, 2H, 4-Pyr); IR (ATR) 1683 (NHC=O), 1220 (C−F) cm^{-1}. Anal. ($C_{26}H_{30}FN_5O_4S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-(2-methoxyethyl)-2-(3-morpholin-4-yl-3-oxopropylsulfanyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamide (11d).** According to the general proce-

dure E, compound **11d** was obtained from **8b** (0.6 g, 1.55 mmol) and 3-chloro-1-morpholin-4-ylpropan-1-one (0.3 g, 1.69 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **11d** (0.11 g, 13%): mp 171.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.23 (CO−CH_3), 2.96 (t, 2H, J = 7.11 Hz, −CH_2−CON), 3.22 (s, 3H, O−CH_3), 3.44−3.67 (m, 12H, morpholino, S−CH_2−, −CH_2−O), 4.07 (t, 2H, J = 6.01 Hz, N−CH_2), 6.87−6.99 (m, 3H, 4-F-Ph, 4-Pyr), 7.33−7.41 (m, 2H, 4-F-Ph), 8.10 (s, 1H, CO−NH), 8.26−8.30 (m, 2H, 4-Pyr); IR (ATR) 1696 (NH-C=O), 1224 (C−F) cm^{-1}. Anal. ($C_{26}H_{30}FN_5O_4S$) C, H, N.

***N*-{4-[5-(4-Fluorophenyl)-3-(3-methoxypropyl)-2-(3-morpholin-4-yl-3-oxopropylsulfanyl)-3*H*-imidazol-4-yl]pyridin-2-yl}acetamid (11e).** According to the general procedure E, compound **11e** was obtained from **8d** (0.6 g, 1.5 mmol) and 3-chloro-1-morpholin-4-ylpropan-1-one (0.3 g, 1.69 mmol). Purification by column chromatography (SiO_2 60, DCM/EtOH 9:1) yielded **11e** (0.1 g, 12%): mp 145.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.81 (quint, 2H, J = 7.53 Hz, −CH_2−), 2.23 (s, 3H, CO−CH_3), 2.95 (t, 2H, J = 7.20 Hz, −CH_2−CON), 3.18 (s, 3H, O−CH_3), 3.24 (t, 2H, J = 5.92 Hz, O−CH_2), 3.51 (t, 2H, J = 7.22 Hz, S−CH_2−), 3.56−3.66 (m, 8H, morpholino), 3.98 (t, 2H, J = 6.27 Hz, N−CH_2−), 6.87−6.96 (m, 3H, 4-F-Ph, 4-Pyr), 7.33−7.40 (m, 2H, 4-F-Ph), 8.06 (s, 1H, NHC=O), 8.23 (s, 1H, 4-Pyr), 8.26−8.29 (m, 1H, 4-Pyr); IR (ATR) 1225 (C−F) cm^{-1}. Anal. ($C_{27}H_{32}FN_5O_4S$) C, H, N.

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Supporting Information Available: Analysis data for compounds **9**−**11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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