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SYNTHESIS OF 1,2,4-TRISUBSTITUTED IMIDAZOLES AND 1,3,5-TRISUBSTITUTED 1,2,4-TRIAZOLES

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Dedicated to Prof. R. Noyori on the occasion of his 70th birthday

Abstract – We report synthetic strategies to easily access 1,2,4-trisubstituted imidazoles by introduction of different residues at C(2) and C(4) followed by substitution at N(1). Furthermore, a synthesis of trisubstituted 1,2,4-triazoles *via* a cyclization of hydrazonamides is described.

INTRODUCTION

Imidazoles and triazoles are important classes of heterocycles.[1] They are widely used as structural motifs in medicinal and crop protection chemistry[2] while imidazoles additionally are also present in a large number of biomolecules, spanning from the amino acid histidine to a variety of secondary metabolites.[3] We became interested in trisubstituted imidazoles and triazoles as non-peptidic, small-molecule ligands to inhibit the enzyme IspF[4] (2*C*-methyl-D-erythritol 2,4-cyclodiphosphate synthase, EC 4.6.1.12) and to prevent the dimerization of VZV TK[5] (varicella zoster virus thymidine kinase, EC 2.7.1.21). IspF is an enzyme in the non-mevalonate pathway of isoprenoid biosynthesis, which is responsible for the preparation of the essential precursor molecules isopentenyl diphosphate and dimethylallyl diphosphate.[4] Important parasites, such as the malaria-causing *Plasmodium falciparum* and *Mycobacterium tuberculosis*, use exclusively the non-mevalonate pathway, whereas isoprenoid synthesis in humans relies on the distinctly different mevalonate pathway. The enzymes of the non-mevalonate pathway have been validated as targets for the development of antimalarials with novel mechanisms of action.[6] Also, first series of synthetic inhibitors of IspF have recently been reported.[7] VZV TK on the other hand plays an important role in the reactivation of the varicella zoster virus in

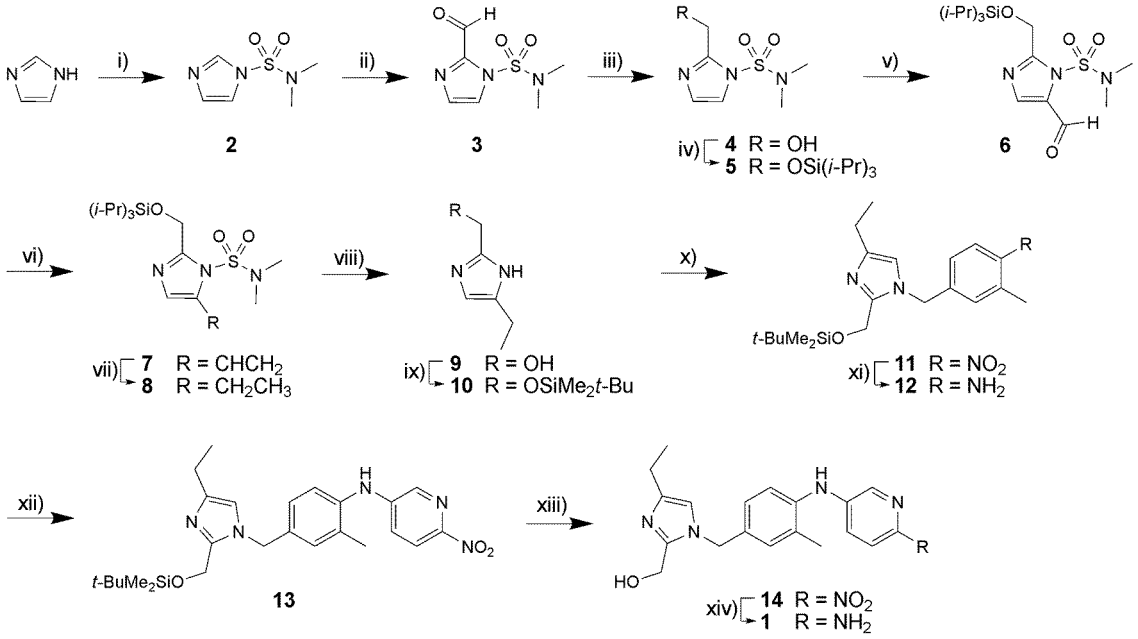
infected nerve cells, leading to the painful and, in rare cases, severe symptoms of shingles in immuno-compromised hosts. The enzyme has been identified as a target to study the disruption of a protein-protein interaction. While the heterocycles described herein were prepared with the objectives mentioned above, these highly decorated scaffolds could also constitute interesting starting points for hit and lead development in other medicinal chemistry and crop protection projects.

We report two strategies for the formation of 1,2,4-trisubstituted imidazoles bearing different residues whereas in both cases the substituent at N(1) is incorporated after the introduction of the desired residues at C(2) and C(4). In contrast, the synthesis of the trisubstituted 1,2,4-triazoles is based on a cyclization of highly substituted hydrazonamides.[8] The biological study of all of the synthesized molecules will be described elsewhere.

RESULTS AND DISCUSSION

Synthesis of Trisubstituted Imidazoles.

Structure-based design approaches[9] suggested that imidazole scaffolds, such as **1** (Scheme 1), bearing a polar hydroxymethyl group at C(2), a shorter alkyl chain at C(4), and a 2,5-diaminopyridyl terminus connected by a benzylic linker to N(1) would be potential ligands of IspF. We chose the 2,5-diaminopyridine scaffold as a substitute for cytosine, to bind into the highly conserved "Pocket III" in the active site of IspF.[7] Target compound **1** was obtained starting from *N*,*N*-dimethylsulfamoyl-protected imidazole **2** (Scheme 1).[10] This protecting group allows the regioselective functionalization of imidazole nuclei at C(2) and C(5) through sequential *ortho*-metallations.[10-14] Selective metallation of **2** at C(2) and *in situ* conversion with DMF provided the 2-formylated imidazole **3**.[13] Reduction of the aldehyde to the alcohol **4**, followed by silyl-protection, led to **5**. Selective metallation at C(5), followed by treatment with DMF, provided the desired 2,5-disubstituted imidazole **6** in good yield. The alkene **7** was prepared by a *Wittig* reaction with **6** and the commercially available methyltriphenylphosphonium bromide, which was converted to the ylide *in situ* with *n*-BuLi. Pd-catalyzed hydrogenation of the double bond yielded **8**, acidic cleavage of both the sulfamoyl and the silyl protecting groups led to **9**, and reprotection of the hydroxy group gave **10**. The 1,2,4-trisubstituted imidazole **11** was obtained as a single regioisomer by alkylation of **10** with 3-methyl-4-nitrobenzyl bromide. Pd-catalyzed hydrogenation yielded the amine **12**, and *Buchwald-Hartwig* cross-coupling with 5-bromo-2-nitropyridine, using $[Pd_2(dba)_3]$ as catalyst and (±)-BINAP as ligand, afforded **13**. Deprotection to the alcohol **14** and catalytic hydrogenation of the nitro group yielded the desired target molecule **1** (Scheme 1).

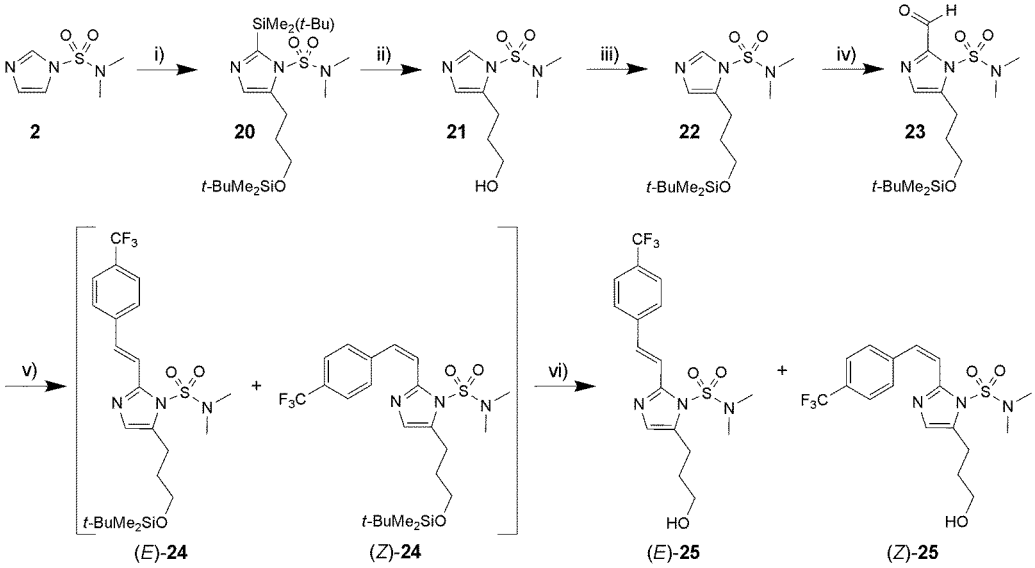


Reagents and conditions: i) Me_2NSO_2Cl, Et_3N, toluene, rt, 23 h; 93%. ii) a) *n*-BuLi, THF, -78 °C, 30 min; b) DMF, -78 °C, 30 min, rt, 1 h; 88%. iii) $NaBH_4$, MeOH, 0 °C, 1 h, rt, 1 h; 84%. iv) TIPSCl, DMAP, CH_2Cl_2, rt, 21 h; 97%. v) a) *n*-BuLi, THF, -78 °C, 30 min; b) DMF, -78 °C, 1 h, rt, 1 h; 91%. vi) a) $MePPh_3Br$, *n*-BuLi, THF, -78 °C, 1 h; b) **6**, THF, -78 °C, 30 min, rt, 17 h; 84%. vii) Pd/C, H_2, MeOH, rt, 3 h; 98%. viii) HCl/MeOH (1.4 M), rt, 4 d; 74%. ix) TBDMSCl, pyridine, rt, 1 h; 95%. x) NaH, 3-methyl-4-nitrobenzyl bromide, DMF, rt, 30 min; 37%. xi) Pd/C, H_2, MeOH, rt, 3 h; 79%. xii) 5-bromo-2-nitropyridine, $[Pd_2(dba)_3]$, (±)-BINAP, Cs_2CO_3, DME, 110 °C, 20 h; 56%. xiii) *n*-Bu_4NF, THF, rt, 2 h; 86%. xiv) Pd/C, H_2, MeOH, rt, 3 h; 85%. THF = tetrahydrofuran, DMF = dimethylformamide, TIPS = triisopropylsilyl, DMAP = 4-(dimethylamino)pyridine, TBDMS = *tert*-butyldimethylsilyl. dba = dibenzylideneacetone, BINAP = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, DME = 1,2-dimethoxyethane.

Scheme 1 Synthesis of trisubstituted imidazole **1** as a potential inhibitor of the enzyme IspF from the non-mevalonate pathway of isoprenoid biosynthesis.

1,2,4-Trisubstituted imidazoles with a pyrazole substituent at N(1) and a tertiary amine connected *via* a propyl linker to C(4), such as **15-17** (Scheme 3), were suggested by computer modeling to mimic the *i*, *i*+1, and *i*+3 residues of an α-helix, that have been suggested to be at the hot spot[15] responsible for the dimerization of VZV TK. Therefore, we prepared such compounds as small non-peptidic ligands to disrupt the protein-protein interaction. Earlier studies reported potent small molecule antagonists of MDM2 and the Bak BH3/Bcl-xL complex mimicking the *i*, *i*+3, *i*+4 and i+7 residues of an α-helix.[16] For the synthesis of **15-17**, the *N*,*N*-dimethylsulfamoyl-protected imidazole **2** was first silylated at C(2) (Scheme 2). Alkylation with *tert*-butyl(3-iodopropoxy)dimethylsilane (**18**), which was synthesized *via* 3-{[*tert*-butyl(dimethyl)silyl]oxy}-1-propanol (**19**) starting from 1,3-dihydroxypropane,[17,18] provided **20**. Double cleavage of the silyl groups afforded alcohol **21**, and silylation of the hydroxy group led to **22**. Selective formylation of **22** gave aldehyde **23**, and *Wittig* olefination with 4-(trifluoromethyl)benzyltriphenylphosphonium bromide, which was converted to the ylide *in situ* with

n-BuLi, provided a diastereomeric mixture of the 2,5-disubstituted imidazoles (*E*)-**24** and (*Z*)-**24**. Deprotection of the alcohol yielded (*E*)-**25** and (*Z*)-**25**, which were separated by column chromatography and assigned according to the coupling constants of the olefinic protons ((*E*)-**25** J = 16.0 Hz; (*Z*)-**25** J = 12.7 Hz) (Scheme 2).

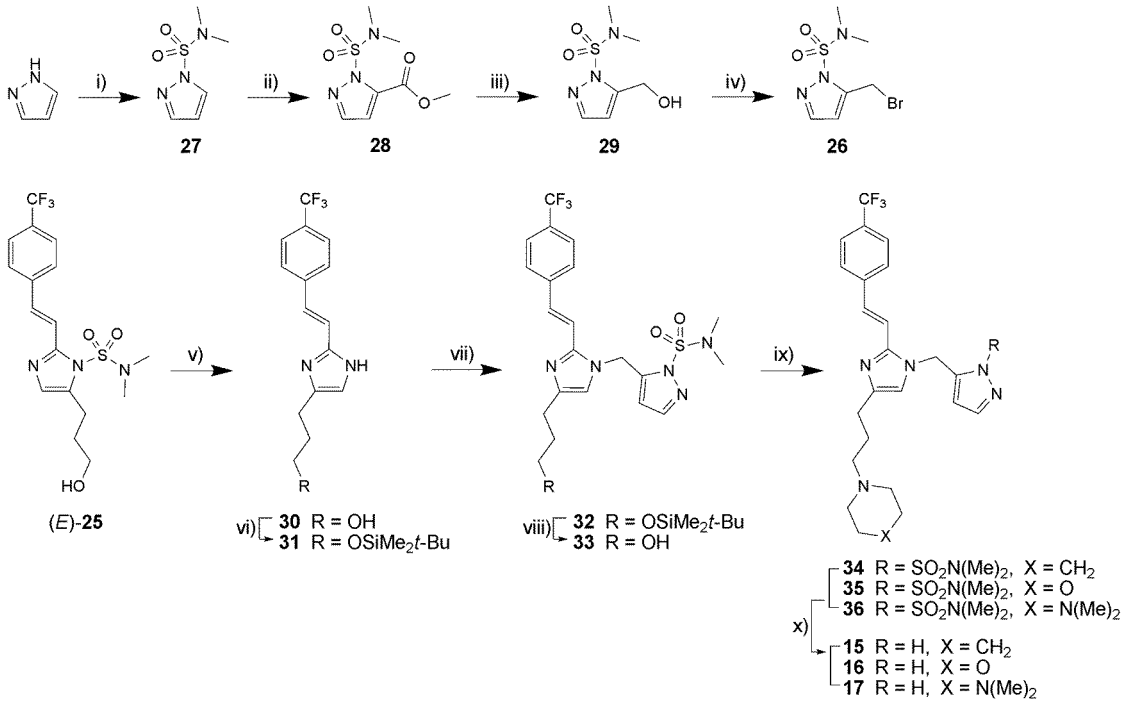


Reagents and conditions: i) a) *n*-BuLi, THF, -78 °C, 30 min; b) TBDMSCl, rt, 12 h; c) *s*-BuLi, -78 °C, 1 h; d) **18**, rt, 15 h; 67%. ii) *n*-Bu_4NF, THF, rt, 1 h; 92%. iii) TBDMSCl, imidazole, CH_2Cl_2, rt, 15 h; 97%. iv) a) *n*-BuLi, THF, -78 °C, 1 h; b) DMF, rt, 2 h; 89%. v) a) 4-(Trifluoromethyl)benzyltriphenylphosphonium bromide, *n*-BuLi, THF, -78 °C, 1 h; b) rt, 20 h; 96% (*E*:*Z* = 4:1). vi) *n*-Bu_4NF, THF, rt, 1 h; 70% ((*E*)-**25**), 21% ((*Z*)-**25**).

Scheme 2 Synthesis of (*E*)-**25** as a common intermediate towards trisubstituted imidazoles such as **15**-**17**.

The pyrazole building block **26** was synthesized starting from *N*,*N*-dimethylsulfamoyl-protected pyrazole **27**[19], which was converted to the ester **28** (Scheme 3). Migration of the *N*,*N*-dimethylsulfamoyl group of **28** to N(2) occurs by standing at room temperature, thus **28** was directly reduced to the alcohol **29**, and then transformed to the bromide **26**.

Acidic cleavage of the sulfamoyl and the silyl protecting groups in (*E*)-**25** led to **30**, and reprotection of the hydroxy group gave **31**. Alkylation of **31** with the pyrazole building block **26** at the sterically less hindered position afforded regioselectively the trisubstituted imidazole **32**. The constitution of **32** was assigned by ^{1}H-NOE NMR experiments. The proton at C(5) of the imidazole as well as the olefinic proton proximal to C(2) of the imidazole showed a signal in the NOE-spectrum with presaturation at the frequency of the methylene protons of the linker between the imidazole and the pyrazole rings. Deprotection of the alcohol in **32** provided **33**, which was mesylated and converted to the tertiary amines **34**-**36** by nucleophilic substitution. Finally, cleavage of the sulfamoyl protecting group gave the desired trisubstituted imidazoles **15**-**17** (Scheme 3).

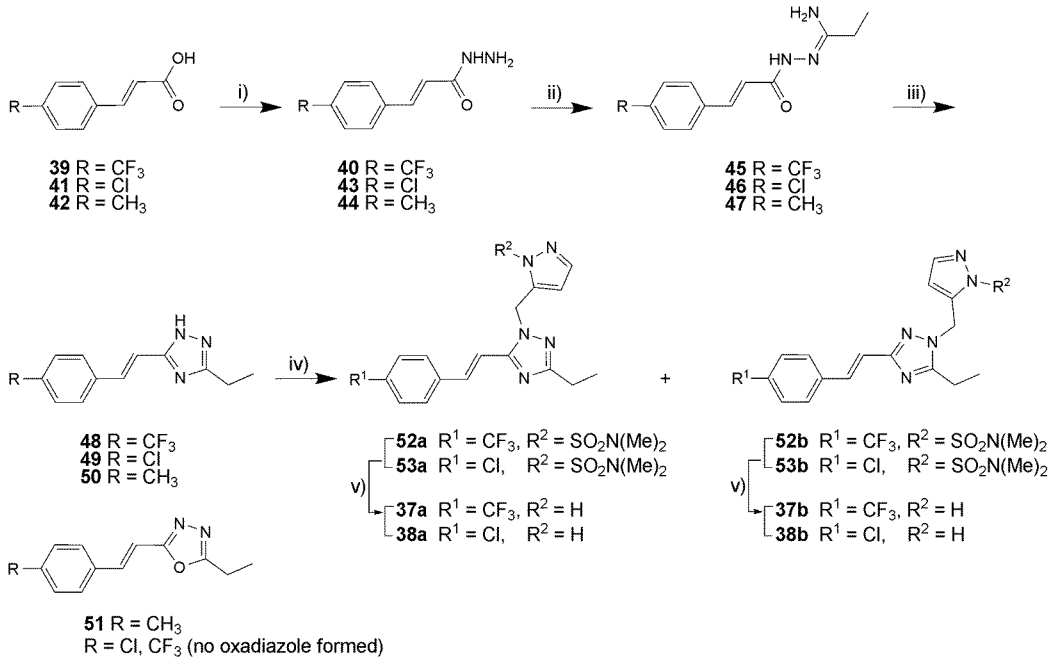


Reagents and conditions: i) Me_2NSO_2Cl, Et_3N, toluene, 80 °C, 18 h; 89%. ii) a) *n*-BuLi, THF, -78 °C, 1 h; b) $ClCO_2Me$, rt, 15 h; 71% (directly converted to alcohol **29**). iii) $LiAlH_4$, THF, -10 °C, 1 h; 99%. iv) PPh_3, Br_2, CH_2Cl_2, 0 °C, 2.5 h; 64%. v) HCl/MeOH (1.4 M), rt, 24 h; 83%. vi) TBDMSCl, imidazole, THF, rt, 2 h; 92%. vii) a) NaH, THF, 0 °C, 1 h; b) **26**, rt, 1 h; 74%. viii) *n*-Bu_4NF, THF, rt, 1 h; 94%. ix) a) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2.5 h; b) Piperidine, morpholine or 1-methylpiperazine, rt, 20 h; 95% (**34**), 56% (**35**), 75% (**36**). x) HCl/MeOH (1.4 M), rt, 24 h; 89% (**15**), 89% (**16**), 87% (**17**). Ms = mesyl, methylsulfonyl.

Scheme 3 Synthesis of trisubstituted imidazoles as potential inhibitors of the dimerization of VZV TK.

Synthesis of Trisubstituted Triazoles.

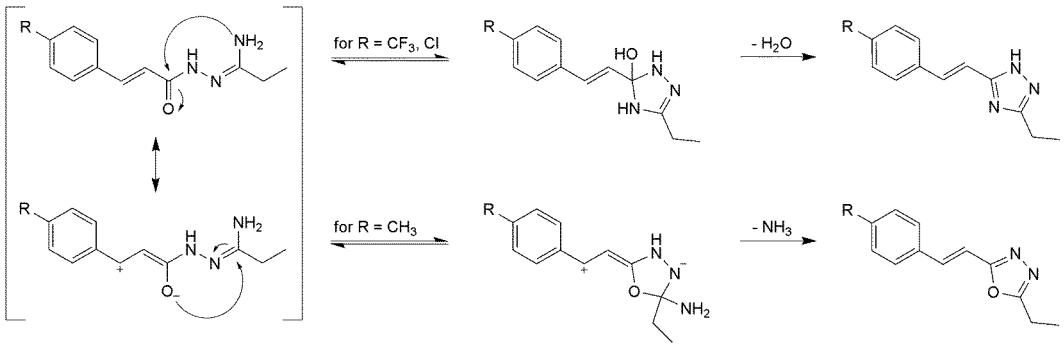
Another class of compounds of interest were 1,3,5-trisubstituted 1,2,4-triazoles, such as **37a** and **38a** (Scheme 4), with similar substituents to those in imidazoles **15-17**: pyrazolemethylene at N(1), *para*-substituted aryl residue at C(3), and alkyl residue at C(5). Thus (*E*)-3-[4-(trifluoromethyl)-phenyl]acrylic acid (**39**)[20] was converted to the cinnamic hydrazide **40** (Scheme 4). Accordingly, the cinnamic acids **41** and **42** were converted to the corresponding cinnamic hydrazides **43**[21] and **44**[22] following a known literature procedure.[8] The reaction of **40**, **43** and **44** with ethyl propaneimidoate hydrochloride[23] did not directly lead to triazoles as described in literature.[8] Instead, the hydrazonamides **45**-**47** were isolated. The cyclization to the desired disubstituted triazoles **48** and **49** was achieved under rather harsh conditions by stirring the hydrazonamides **45** and **46** in pyridine under reflux for 24 h. However, treating the hydrazonamide **47** under the same conditions formed the desired triazole **50** with only 6% yield. Instead, the 1,3,4-oxadiazole **51** was isolated in 56% yield (Scheme 4).



Reagents and conditions: i) a) Isobutylchloroformate, *N*-methylmorpholine, THF, rt, 15 min; b) H_2NNH_2, rt, 15 h; 82%. ii) Ethyl propaneimidoate hydrochloride, DMF, Et_3N, 60 °C, 24 h; 27% (**45**), 30% (**46**), 47% (**47**). iii) Pyridine, 115 °C, 24 h; 64% (**48**), 77% (**49**), 6% (**50**), 56% (**51**). iv) a) NaH, THF, 0 °C, 1 h; b) **26**, rt, 19 h; 41% (**52a**), 41% (**52b**), 35% (**53a**), 46% (**53b**). v) HCl/MeOH (1.4 M), rt, 1 h; 96% (**37a**), 99% (**37b**), 99% (**38a**), quant. (**38b**).

Scheme 4 Synthesis of 1,3,5-trisubstituted 1,2,4-triazoles as potential inhibitors of the dimerization of VZV TK.

The inductive effect of the *para*-substituent at the phenyl ring has an important influence on the chemoselectivity of the cyclization. An electron-withdrawing group such as CF_3 or Cl activates the carbonyl group for the nucleophilic attack of the amine and favors the ring closure to the desired triazole. But the presence of even a weak electron-donating group, such as CH_3, leads to a stabilization of the benzylic cation formed by nucleophilic attack of the carbonyl *O*-atom at the electrophilic hydrazonamide C-atom and therefore favors the formation of the undesired 1,3,4-oxadiazole (Scheme 5). Cyclizations of hydrazonamides to oxadiazoles under acidic conditions have been reported.[24]



Scheme 5 Proposed mechanism of the formation of triazoles and oxadiazoles starting from hydrazonamides.

Alkylation of **48** and **49** with the pyrazole building block **26** afforded the trisubstituted triazoles **52a/b** and **53a/b**, respectively. The regioisomers can be separated by column chromatography, and their constitution was assigned by ^{1}H-NOE NMR measurements. Presaturation of the methylene protons on the linker between the triazole and the pyrazole lead to NOE-signals of the olefinic proton proximal to the triazole (**53a**) or of the ethyl protons (**53b**). The constitution of **52a** and **52b** was assigned by comparison of their ^{1}H and ^{13}C-NMR spectra with the spectra from **53a** and **53b**. Finally, cleavage of the sulfamoyl protecting group gave the desired triazoles **37a** and **38a** as well as the 1,3,5-trisubstituted 1,2,4-triazoles **37b** and **38b** (Scheme 4).

CONCLUSIONS

Different routes are presented to access 1,2,4-trisubstituted imidazoles and 1,3,5-trisubstituted 1,2,4-triazoles that were designed as potential ligands to bind at the active site of the enzyme IspF or to disrupt the protein-protein interaction leading to the dimerization of the kinase VZV TK. The two heterocycles are attractive skeletons for the convenient attachment of multiple vectors reaching into protein sub-pockets. Besides yielding the specific target molecules reported here, the described methodology should be applicable to the generation of larger focused compound libraries, which could serve as source for potential hits in a variety of other medicinal chemistry or crop protection projects. From the viewpoint of heterocycle synthesis, the most notable result is the strong electronic effect of the *para*-substituent at the phenyl ring of cinnamic hydrazonamides on the nature of the formed product. The absence of an electron-withdrawing substituent leads to 1,3,4-oxadiazoles in moderate yield while substituents such as CF_3 and Cl induce cyclizations to the desired triazole derivatives.

EXPERIMENTAL

Solvents and reagents were reagent-grade, purchased from commercial suppliers, and used without further purification unless otherwise stated. The following known compounds were prepared according to literature procedures: *N*,*N*-dimethyl-1*H*-imidazole-sulfonamide (**2**),[10] 2-formyl-*N*,*N*-dimethyl-1*H*-imidazole-sulfonamide (**3**),[13] *tert*-butyl(3-iodopropoxy)dimethylsilane (**18**),[18] 3-{[*tert*-butyl(dimethyl)-silyl]oxy}-1-propanol (**19**),[17] *N*,*N*-dimethyl-1*H*-pyrazole-1-sulfonamide (**27**),[19] (2*E*)-3-(4-chlorophenyl)-acrylohydrazide (**43**),[8] and (*E*)-3-(4-tolyl)acrylohydrazide (**44**).[8] THF was freshly distilled from sodium and benzophenone, CH_2Cl_2 from CaH_2. Evaporation *in vacuo* was conducted at 30–70 °C and 600–15 mbar pressure. Products were dried under high vacuum (10^{-2} Torr) before analytical characterization. Column chromatography (CC): SiO_2-*60* (40–63 μm) from *Fluka*, 0-0.4 bar pressure. TLC: SiO_2-*60* F_{254} (on glass), *Merck*, visualization by UV light at 254 nm or staining with a solution of $KMnO_4$ (3 g) and K_2CO_3 (20 g) in 5% aqueous NaOH solution (5 mL) and H_2O (300 mL). Melting

points (mp): *Büchi B450* melting point apparatus; uncorrected. IR Spectra [cm^{-1}]: *Perkin-Elmer Spectrum BX FTIR System* spectrometer (*ATR-unit, Attenuated Total Reflection, Golden Gate*). NMR spectra (^{1}H, ^{13}C, ^{19}F): *Varian Gemini-300*, and *Bruker AMX-500*; spectra were recorded at rt, with solvent peak as reference. High resolution mass spectra (HRMS): MALDI: *IonSpec Ultima spectrometer*, 2,5-dihydroxybenzoic acid (DHB) as matrix; EI: *VG-TRIBRID* spectrometer at 70 eV. Elemental analyses were performed by the *Mikrolabor* at the *Laboratorium für Organische Chemie*, *ETH Zürich*.

General procedure for the reduction of an aromatic nitro group into an aromatic amine, for the reduction of an alkene into an alkane, or for the deprotection of a Cbz-protected amine (GP 1)

To a solution of a nitrobenzene derivative, an alkene or a Cbz-protected cytosine derivative (1.0 equivalent) in MeOH or CH_2Cl_2/MeOH, 10% Pd/C (10% w/w) was added under Ar. The flask was evacuated and refilled with H_2 (3 x). The black suspension was stirred at rt for 3 h under H_2. The mixture was filtered over Celite, and the Celite was washed with MeOH and CH_2Cl_2. The filtrate was concentrated *in vacuo*.

General procedure for the cleavage of the *N*,*N*-dimethylsulfamoyl-protecting group (GP 2)

A *N*,*N*-dimethylsulfamoyl-protected imidazole or pyrazole (1.0 equivalent) was dissolved in a 1.4 M solution of HCl in MeOH (30 equivalents), and the mixture was stirred at rt for 1 h. The solvent was concentrated *in vacuo*.

General procedure for the deprotection of a silyl-protected alcohol (GP 3)

To a solution of a silyl ether (1.0 equivalent) in THF, *n*-Bu_4NF (1 M in THF, 1.2 equivalents) was added and the mixture stirred at rt for 2 h. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo*.

General procedure for the protection of a primary alcohol with TBDMS (GP 4)

To a solution of an alcohol (1.0 equivalent) and imidazole (1.1 equivalents) in CH_2Cl_2 or THF, a solution of (*t*-Bu)Me_2SiCl (1.3 equivalents) in CH_2Cl_2 or THF was added at 0 °C. The mixture was stirred at 0 °C for 20 min and at rt for 2 h.

General procedure for the replacement of a hydroxy group by a secondary amine (GP 5)

To a solution of an alcohol (1.0 equivalent) and Et_3N (1.1 equivalents) in CH_2Cl_2, methanesulfonylchloride (1.1 equivalents) was added at 0 °C. The mixture was stirred until no starting

material was left. A secondary amine (10 equivalents) was added at 0 °C, and the mixture was allowed to reach rt for 20 h while stirring. The solvent was concentrated *in vacuo*.

General procedure for the synthesis of a hydrazonamide (GP 6)

Ethyl propaneimidoate hydrochloride[23] (1.0 equivalent) was suspended in Et_3N (20 min, ultrasonic bath). DMF and a hydrazide (0.9 equivalents) were added, and the mixture was stirred at 60 °C for 24 h. The resulting solid was filtered off, and the filtrate was concentrated *in vacuo*.

General procedure for the cyclization of a hydrazonamide to a 1,2,4-triazole (GP 7)

A suspension of a hydrazonamide (1.0 equivalent) in pyridine was stirred under reflux for 24 h. The solvent was concentrated *in vacuo*.

2-(Hydroxymethyl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (4)

To a solution of **3** (2.52 g, 12.4 mmol) in MeOH (40 mL), $NaBH_4$ (469 mg, 12.4 mmol) was added at 0 °C. The mixture was stirred at 0 °C for 1 h and at rt for 1 h. MeOH was concentrated *in vacuo*, the residue was taken up in CH_2Cl_2, and washed with 10% aqueous Na_2CO_3 solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo*, and the crude product was purified by CC (SiO_2; AcOEt → AcOEt/MeOH 95:5 → AcOEt/MeOH 9:1) to afford **4** as a white solid. Yield: 2.13 g (84%). mp: 118–120 °C. IR (neat): υ 3153, 3119, 2943, 1537, 1454, 1421, 1386, 1276, 1237, 1184, 1153, 1124, 1047, 1026, 961, 762, 725 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.94 (s, 6 H); 3.79 (brs, 1 H); 4.86 (s, 2 H); 7.02 (d, J = 1.6 Hz, 1 H); 7.25 (d, J = 1.6 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 38.4, 57.8, 120.0, 127.7, 148.5. EI-HRMS: 205.0516 (M^+, $C_6H_{11}N_3O_3S^+$; calcd 205.0516).

***N*,*N*-Dimethyl-2-{[(triisopropylsilyl)oxy]methyl}-1*H*-imidazole-1-sulfonamide (5)**

To a solution of **4** (2.31 g, 11.3 mmol) in CH_2Cl_2 (45 mL), (i-Pr)$_3$SiCl (3.6 mL, 16.9 mmol) and DMAP (2.34 g, 19.1 mmol) were added. The mixture was stirred at rt for 21 h. After addition of Et_2O, the mixture was washed with H_2O and saturated aqueous NaCl solution. The aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by CC (SiO_2, CH_2Cl_2/pentane 1:1 → CH_2Cl_2 → CH_2Cl_2/MeOH 98:2) to afford **5** as a white solid. Yield: 3.98 g (97%). mp: 43-45 °C. IR (neat): υ 2942, 2865, 1461, 1419, 1390, 1276, 1168, 1156, 1058, 1037, 967, 881, 815, 720 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.03-1.20 (m, 21 H); 2.95 (s, 6 H); 4.97 (s, 2 H); 7.02 (d, J = 1.6 Hz, 1 H); 7.24 (d, J = 1.6 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.1, 18.0, 38.4, 58.1, 120.1, 127.7, 147.3. EI-HRMS:

318.1301 ([M – C_3H_7]$^+$, $C_{12}H_{24}N_3O_3SSi^+$; calcd 318.1303).

5-Formyl-*N*,*N*-dimethyl-2-{[(triisopropylsilyl)oxy]methyl}-1*H*-imidazole-1-sulfonamide (6)

To a solution of **5** (3.29 g, 9.10 mmol) in THF (15 mL), *n*-BuLi (6.8 mL, 10.9 mmol, 1.6 M in hexane) was added at –78 °C. The mixture was stirred at –78 °C for 30 min. DMF (3.4 mL, 43.7 mmol) was dropped to the solution, and the mixture was stirred at –78 °C for 1 h and at rt for 1 h. The mixture was cooled to –78 °C, and saturated aqueous $NaHCO_3$ solution was added. H_2O was added at rt, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by CC (SiO_2, pentane/AcOEt 6:1 → 4:1) to afford **6** as a white solid. Yield: 3.21 g (91%). mp: 69-71 °C. IR (neat): υ 3119, 2943, 2864, 1672, 1534, 1464, 1420, 1409, 1389, 1268, 1224, 1183, 1164, 1093, 1054, 970, 881, 824, 759, 726, 659 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.04-1.25 (m, 21 H); 3.01 (s, 6 H); 5.05 (s, 2 H); 7.81 (s, 1 H); 10.05 (s, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.1, 18.0, 38.4, 59.3, 133.0, 138.4, 153.6, 179.7. EI-HRMS: 346.1250 ([M – C_3H_7]$^+$, $C_{13}H_{24}N_3O_4SSi^+$; calcd 346.1251). *Anal.* Calcd for $C_{16}H_{31}N_3O_4SSi$ (389.59): C, 49.33; H, 8.02; N, 10.79. Found: C, 49.52; H, 8.09; N 10.74.

***N*,*N*-Dimethyl-2-{[(triisopropylsilyl)oxy]methyl}-5-vinyl-1*H*-imidazole-1-sulfonamide (7)**

To a suspension of methyltriphenylphosphonium bromide (917 mg, 2.57 mmol) in THF (15 mL), *n*-BuLi (1.6 mL, 2.57 mmol, 1.6 M in hexane) was added at –78 °C and the mixture stirred at –78 °C for 1 h. A solution of **6** (1.00 g, 2.57 mmol) in THF (5 mL) was added and the mixture stirred at –78 °C for 30 min and at rt for 17 h. The solution was cooled to 0 °C, saturated aqueous NH_4Cl solution was added, and the mixture was stirred at 0 °C for 10 min. H_2O was added at rt and the aqueous layer extracted with CH_2Cl_2. The combined organic phases were washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by CC (SiO_2; pentane/AcOEt 9:1 → 4:1) to afford **7** as a white solid. Yield: 839 mg (84%). mp: 49-51 °C. IR (neat): υ 2942, 2866, 1616, 1558, 1459, 1420, 1389, 1338, 1281, 1218, 1180, 1160, 1101, 1051, 980, 967, 921, 883, 825, 770, 731, 683, 659 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.04-1.22 (m, 21 H); 2.91 (s, 6 H); 4.98 (s, 2 H); 5.29 (dd, *J* = 11.2, 1.2 Hz, 1 H); 5.63 (dd, *J* =17.4, 1.2 Hz, 1 H); 6.91 (dd, *J* = 17.4, 11.2 Hz, 1 H); 7.11 (s, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.2, 18.1, 38.3, 59.6, 117.2, 124.8, 126.6, 132.7, 149.6. MALDI-HRMS: 388.2084 ([M + H]$^+$, $C_{17}H_{34}N_3O_3SSi^+$; calcd 388.2085).

5-Ethyl-*N*,*N*-dimethyl-2-{[(triisopropylsilyl)oxy]methyl}-1*H*-imidazole-1-sulfonamide (8)

GP 1, starting from **7** (839 mg, 2.16 mmol) in MeOH (13 mL), afforded **8** after CC (SiO_2; pentane/AcOEt 9:1 → 6:1) as a colorless oil. Yield: 830 mg (98%). IR (neat): υ 2942, 2866, 1575, 1462, 1418, 1381,

1283, 1210, 1174, 1156, 1100, 1055, 968, 882, 816, 724, 681 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.03-1.24 (m, 21 H); 1.28 (t, *J* = 7.5 Hz, 3 H); 2.76 (dq, *J* = 7.5, 1.5 Hz, 2 H); 2.95 (s, 6 H); 4.96 (s, 2 H); 6.74 (t, *J* = 1.5 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.2, 18.1, 19.4, 38.0, 59.7, 125.4, 135.7, 149.0 (one aliph. signal missing due to overlap). MALDI-HRMS: 390.2229 ($[M + H]^+$, $C_{17}H_{35}N_3O_3SSi^+$; calcd 390.2241).

(4-Ethyl-1*H*-imidazole-2-yl)methanol (9)

GP 2, starting from **8** (830 mg, 2.13 mmol), but the mixture was stirred for 4 d. The crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1) to afford **9** as a white solid. Yield: 198 mg (74%). mp: 106-107 °C. IR (neat): υ 3164, 3135, 3108, 3020, 2966, 2864, 2864, 2770, 2594, 1576, 1537, 1464, 1393, 1346, 1305, 1255, 1215, 1126, 1061, 1037, 1001, 953, 816, 786, 768, 688 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$/CD_3OD 6:1): δ 1.10 (t, *J* = 7.5 Hz, 3 H); 2.45 (q, *J* = 7.5 Hz, 2 H); 4.44 (s, 2 H); 6.52 (s, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$/CD_3OD 6:1): δ 13.3, 19.7, 57.0, 116.4, 138.0, 146.6. EI-HRMS: 125.0708 ($[M – H]^+$, $C_6H_9N_2O^+$; calcd 125.0709).

2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-ethyl-1*H*-imidazole (10)

Compound **9** (198 mg, 1.57 mmol) was dissolved in pyridine (4.8 mL). (*t*-Bu)Me_2SiCl (402 mg, 2.67 mmol) was added and the mixture stirred at rt for 1 h. The solvent was concentrated *in vacuo*, the residue was taken up in CH_2Cl_2, and the organic phase was washed with saturated aqueous $NaHCO_3$ solution and with saturated aqueous NaCl solution. The organic phase was dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by CC (SiO_2, CH_2Cl_2/MeOH 98:2) to afford **10** as a pale yellow oil. Yield: 359 mg (95%). IR (neat): υ 2954, 2929, 2883, 2856, 1597, 1461, 1406, 1361, 1253, 1078, 1006, 938, 833, 774, 664 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.10-0.12 (m, 6 H); 0.92-0.94 (m, 9 H); 1.24 (t, *J* = 7.5 Hz, 3 H); 2.61 (dq, *J* = 7.5, 0.9 Hz, 2 H); 4.78 (s, 2 H); 6.68 (t, *J* = 0.9 Hz, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$): δ –5.3, 13.7, 18.6, 25.9, 60.0, 123.9, 147.0, 150.0 (one aliph. signal missing due to overlap). EI-HRMS: 225.1420 ($[M – CH_3]^+$, $C_{11}H_{21}N_2OSi^+$; calcd 225.1418). *Anal*. Calcd for $C_{12}H_{24}N_2OSi$ (240.42): C, 59.95; H, 10.06; N, 11.65. Found: C, 59.94; H, 10.00; N, 11.54.

2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-ethyl-1-(3-methyl-4-nitrobenzyl)-1*H*-imidazole (11)

To a solution of **10** (359 mg, 1.49 mmol) in DMF (15 mL), NaH (60 mg, 1.49 mmol, as a 60% dispersion in mineral oil) was added. The mixture was stirred at rt for 15 min. 3-Methyl-4-nitrobenzyl bromide (378 mg, 1.64 mmol) was added portionwise, and the solution was stirred at rt for 30 min. After addition of cold H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed

with saturated aqueous NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by CC (SiO_2, CH_2Cl_2/Et_2O 95:5) to afford **11** as a pale yellow solid. Yield: 217 mg (37%). mp: 66-68 °C. IR (neat): υ 2958, 2930, 2857, 1613, 1590, 1566, 1517, 1461, 1438, 1382, 1342, 1249, 1182, 1143, 1040, 1003, 989, 938, 836, 774, 758, 737, 722 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.01-0.03 (m, 6 H); 0.79-0.83 (m, 9 H); 1.21 (t, *J* = 7.5 Hz, 3 H); 2.56-2.59 (m, 5 H); 4.71 (s, 2 H); 5.22 (s, 2 H); 6.53 (s, 1 H); 7.07 (d, *J* = 8.4 Hz, 1 H); 7.09 (s, 1 H); 7.95 (d, *J* = 8.1 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ –5.3, 13.7, 18.3, 20.7, 21.7, 25.9, 48.8, 58.8, 116.0, 125.2, 130.9, 134.2, 142.5, 143.5, 145.8, 148.4 (one arom. signal missing due to overlap). MALDI-HRMS: 390.2202 ($[M + H]^+$, $C_{20}H_{32}N_3O_3Si^+$; calcd 390.2207). *Anal*. Calcd for $C_{20}H_{31}N_3O_3Si$ (389.57): C, 61.66; H, 8.02; N, 10.79. Found: C, 61.88; H, 7.91; N, 10.71.

4-{[2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-ethyl-1*H*-imidazole-1-yl]methyl}-2-methyl-aniline (12)

GP 1, starting from **11** (209 mg, 0.54 mmol) in MeOH (20 mL), afforded **12** after CC (SiO_2; CH_2Cl_2/MeOH 98:2) as a beige solid. Yield: 153 mg (79%). mp: 61-63 °C. IR (neat): υ 2932, 2850, 1703, 1600, 1510, 1466, 1368, 1326, 1296, 1256, 1143, 1134, 1086, 1060, 878, 844, 810, 759, 744, 635 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.06-0.07 (m, 6 H); 0.88-0.90 (m, 9 H); 1.18 (t, *J* = 7.5 Hz, 3 H); 2.14 (s, 3 H); 2.54 (q, *J* = 7.5 Hz, 2 H); 3.62 (brs, 2 H); 4.72 (s, 2 H); 5.01 (s, 2 H); 6.49 (s, 1 H); 6.63 (d, *J* = 8.7 Hz, 1 H); 6.87 (d, *J* = 6.9 Hz, 1 H); 6.88 (s, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ –5.3, 13.8, 17.5, 18.4, 21.7, 26.0, 49.4, 58.8, 115.1, 116.1, 122.7, 126.6, 126.8, 130.1, 142.7, 144.4, 145.6. MALDI-HRMS: 360.2461 ($[M + H]^+$, $C_{20}H_{34}N_3OSi^+$; calcd 360.2466). *Anal*. Calcd for $C_{20}H_{33}N_3OSi$ (359.59): C, 66.80; H, 9.25; N, 11.69. Found: C, 66.98; H, 9.28; N, 11.60.

***N*-(4-{[2-({[*tert*-Butyl(dimethyl)silyl]oxy}methyl)-4-ethyl-1*H*-imidazole-1-yl]methyl}-2-methyl-phenyl)-6-nitro-3-pyridineamine (13)**

$[Pd_2(dba)_3]$ (5 mol%), BINAP (10 mol%), 5-bromo-2-nitropyridine (70 mg, 0.34 mmol), and Cs_2CO_3 (277 mg, 0.85 mmol) were added to an oven-dried sealed tube. The flask was evacuated and refilled with Ar. Compound **12** (148 mg, 0.41 mmol) and DME were added, and the mixture was stirred at 110 °C for 20 h. The suspension was cooled to rt and taken up in CH_2Cl_2. The organic phase was washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by CC (SiO_2, pentane/AcOEt 1:1) to afford **13** as an orange-yellow solid. Yield: 91 mg (56%). IR (neat): υ 2956, 2928, 2856, 1736, 1573, 1507, 1470, 1381, 1330, 1306, 1288, 1261, 1156, 1106, 1067, 1006, 990, 835, 777, 698 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.04-0.07 (m, 6 H); 0.85-0.88 (s, 9 H); 1.21 (t, *J* = 7.5 Hz, 3 H); 2.24 (s, 3 H); 2.58 (dq, *J* = 7.5,

0.9 Hz, 2 H); 4.73 (s, 2 H); 5.17 (s, 2 H); 6.16 (s, 1 H); 6.56 (s, 1 H); 7.05 (brd, *J* = 8.1 Hz, 1 H); 7.09 (brs, 1 H); 7.10 (dd, *J* = 9.0, 2.8 Hz, 1 H); 7.22 (d, *J* = 8.1 Hz, 1 H); 8.06 (d, *J* = 2.5 Hz, 1 H); 8.13 (d, *J* = 9.0 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ –5.3, 13.7, 18.1, 18.4, 21.7, 25.9, 49.0, 58.7, 116.0, 120.1, 120.2, 124.4, 126.1, 130.3, 133.4, 134.7, 135.4, 136.2, 143.0, 145.6, 146.4, 148.6. MALDI-HRMS: 482.2592 ($[M + H]^+$, $C_{25}H_{35}N_5O_3Si^+$; calcd 482.2582).

(4-Ethyl-1-{3-methyl-4-[(6-nitro-3-pyridinyl)amino]benzyl}-1*H*-imidazole-2-yl)methanol (14)

GP 3, starting from **13** (81 mg, 0.17 mmol), afforded **14** after CC (SiO_2; CH_2Cl_2/MeOH 9:1) as an orange-yellow solid. Yield: 54 mg (86%). mp: > 81 °C (dec.). IR (neat): υ 2964, 2926, 2856, 1663, 1572, 1504, 1469, 1383, 1328, 1306, 1286, 1262, 1218, 1160, 1105, 1007, 907, 844, 796, 727, 696 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.16 (t, *J* = 7.5 Hz, 3 H); 2.21 (s, 3 H); 2.51 (dq, *J* = 7.5, 0.9 Hz, 2 H); 4.62 (s, 2 H); 5.15 (s, 2 H); 6.57 (s, 1 H); 6.71 (s, 1 H); 7.02 (dd, *J* = 8.1, 1.9 Hz, 1 H); 7.10 (brs, 1 H); 7.10 (dd, *J* = 9.0, 2.8 Hz, 1 H); 7.20 (d, *J* = 8.1 Hz, 1 H); 8.03 (d, *J* = 2.8 Hz, 1 H); 8.10 (d, *J* = 9.0 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 13.6, 18.1, 21.3, 49.1, 55.8, 115.9, 120.1, 120.2, 124.6, 126.0, 130.3, 133.7, 134.7, 134.7, 136.6, 142.6, 146.6, 147.0, 148.4. MALDI-HRMS: 368.1723 ($[M + H]^+$, $C_{19}H_{22}N_5O_3^+$; calcd 368.1717).

(1-{4-[(6-Amino-3-pyridinyl)amino]-3-methylbenzyl}-4-ethyl-1*H*-imidazole-2-yl)methanol (1)

GP 1, starting from **14** (52 mg, 0.14 mmol) in MeOH (3 mL), afforded **1** after CC (SiO_2; CH_2Cl_2/MeOH 9:1) as a beige solid. Yield: 40 mg (85%). mp: > 62 °C (dec.). IR (neat): υ 2966, 2930, 1618, 1498, 1381, 1340, 1283, 1162, 1121, 1018, 907, 807, 730 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$/CD_3OD 6:1): δ 1.07 (t, *J* = 7.5 Hz, 3 H); 2.13 (s, 3 H); 2.41 (q, *J* = 7.5 Hz, 2 H); 4.48 (s, 2 H); 4.93 (s, 2 H); 6.46 (s, 1 H); 6.46 (d, *J* = 8.7 Hz, 1 H); 6.61 (d, *J* = 7.9 Hz, 1 H); 7.02 (brd, *J* = 8.4 Hz, 1 H); 6.87 (brs, 1 H); 7.22 (dd, *J* = 8.7, 2.8 Hz, 1 H); 7.68 (d, *J* = 2.5 Hz, 1 H). ^{13}C-NMR (125 MHz, $CDCl_3$/CD_3OD 6:1): δ 9.5, 13.7, 17.1, 45.6, 51.8, 105.9, 109.8, 112.3, 121.0, 122.4, 122.8, 126.3, 130.8, 137.7, 137.8, 140.2, 142.3, 151.2 (one arom. signal missing due to overlap). MALDI-HRMS: 338.1981 ($[M + H]^+$, $C_{19}H_{23}N_5O^+$; calcd 338.1975).

2-[*tert*-Butyl(dimethyl)silyl]-5-(3-{[*tert*-butyl(dimethyl)silyl]oxy}propyl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (20)

To a solution of **2** (7.34 g, 41.9 mmol) in THF (210 mL), *n*-BuLi (28.8 mL, 46.1 mmol, 1.6 M in hexane) was added at –78 °C. The mixture was stirred at –78 °C for 1 h. (*t*-Bu)Me_2SiCl (6.94 g, 46.1 mmol) was added, and the mixture was allowed to reach rt for 15 min. *s*-BuLi (38.7 mL, 50.3 mmol, 1.3 M in cyclohexane) was added at –78 °C to the brown solution, and the mixture was stirred at –78 °C for 1 h.

The solution was transferred slowly *via* a cannula to a solution of the iodide **18** (18.2 g, 60.7 mmol) in THF (100 mL) that was cooled to –78 °C. The mixture was stirred at –78 °C for 1 h, allowed to reach rt, and stirred for 15 h. The mixture was cooled to –78 °C, and saturated aqueous NH_4Cl solution was added. The suspension was stirred at –78 °C for 1 h and then allowed to reach rt slowly. H_2O was added, and the aqueous layer was extracted with AcOEt. The organic phase was washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by CC (SiO_2, hexane/AcOEt 9:1) to afford **20** as a white solid. Yield: 13.0 g (67%). mp: 49 °C. IR (neat): υ 2956, 2929, 2896, 2856, 1566, 1470, 1459, 1416, 1384, 1282, 1249, 1181, 1140, 1125, 1082, 964, 832, 811, 771, 723 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6 H); 0.38 (s, 6 H); 0.89 (s, 9 H); 1.00 (s, 9 H); 1.89 (m, 2 H); 2.79 (td, J = 7.8, 1.2 Hz, 2 H); 2.83 (s, 6 H); 3.70 (t, J = 6.0 Hz, 2 H); 6.93 (t, ^2J = 1.2 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ –5.2, –3.4, 18.4, 18.5, 21.7, 26.0, 27.4, 30.1, 37.2, 62.3, 129.1, 134.6, 155.0. MALDI-HRMS: 462.2629 ($[M + H]^+$, $C_{20}H_{44}N_3O_3SSi^+$; calcd 462.2636).

5-(3-Hydroxypropyl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (21)

GP 3, starting from **20** (12.4 g, 26.9 mmol), but the solvent was concentrated *in vacuo* and the crude product purified by CC (SiO_2, AcOEt/MeOH 95:5) to afford **21** as a white solid. Yield: 5.78 g (92%). mp: 68 °C. IR (neat): υ 3287, 3134, 2929, 2857, 1672, 1570, 1477, 1419, 1387, 1267, 1174, 1145, 1091, 1068, 960, 926 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.93 (m, 2 H); 2.30 (brs, 1 H); 2.85 (td, J = 7.8, 0.9 Hz, 2 H); 2.88 (s, 6 H); 3.71 (m, 2 H); 6.84 (d, J = 1.1 Hz, 1 H); 7.85 (d, J = 1.1 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 21.4, 31.3, 38.1, 61.5, 128.2, 132.1, 138.1. MALDI-HRMS: 234.0907 ($[M + H]^+$, $C_8H_{16}N_3O_3S^+$; calcd 234.0907). *Anal*. Calcd for $C_8H_{15}N_3O_3S$ (233.29): C, 41.19; H, 6.48; N, 18.01. Found: C, 41.37; H, 6.56; N, 17.95.

5-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}propyl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (22)

GP 4, starting from **21** (6.28 g, 26.9 mmol) in CH_2Cl_2, afforded **22** after CC (SiO_2; AcOEt) as a white solid. Yield: 9.11 g (97%). mp: 39 °C. IR (neat): υ 3132, 2952, 2929, 2896, 2858, 1654, 1561, 1463, 1420, 1384, 1255, 1172, 1159, 1088, 1049, 960, 826, 774, 720 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.05 (s, 6 H); 0.89 (s, 9 H); 1.88 (m, 2 H); 2.82 (td, J = 7.9, 0.9 Hz, 2 H); 2.88 (s, 6 H); 3.69 (t, J = 6.0 Hz, 2 H); 6.83 (d, J = 0.8 Hz, 1 H); 7.86 (d, J = 0.8 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ –5.2, 18.4, 21.5, 26.0, 31.0, 38.0, 62.0, 128.0, 132.2, 138.1. EI-HRMS: 332.1463 ($[M – CH_3]^+$, $C_{13}H_{26}N_3O_3SSi^+$; calcd 332.1459). *Anal*. Calcd for $C_{14}H_{29}N_3O_3SSi$ (347.55): C, 48.38; H, 8.41; N, 12.09. Found: C, 48.44; H, 8.44; N, 12.20.

2-Formyl-5-(3-{[*tert*-butyl(dimethyl)silyl]oxy}propyl)-*N*,*N*-dimethyl-1*H*-imidazole-1-sulfonamide (23)

To a solution of **22** (9.09 g, 26.2 mmol) in THF (130 mL), *n*-BuLi (18.0 mL, 28.8 mmol, 1.6 M in hexane) was added at –78 °C. The mixture was stirred at –78 °C for 1 h. DMF (2.2 mL, 28.8 mmol) was dropped to the solution. The mixture was stirred at –78 °C for 30 min and then allowed to reach rt for 2 h. The mixture was cooled to –78 °C, and saturated aqueous $NaHCO_3$ solution was added. H_2O was added at rt and the aqueous layer extracted with AcOEt. The combined organic phases were dried (Na_2SO_4) and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by CC (SiO_2, hexane/AcOEt 3:2) to afford **23** as a yellow solid. Yield: 8.78 g (89%). mp: 74 °C. IR (neat): υ 2928, 2857, 1681, 1550, 1462, 1433, 1393, 1255, 1096, 1053, 965, 834, 797, 770, 727, 666 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6 H); 0.90 (s, 9 H); 1.88-1.98 (m, 2 H); 2.95 (t, *J* = 7.9 Hz, 2 H); 2.97 (s, 6 H); 3.71 (t, *J* = 5.9 Hz, 2 H); 7.09 (s, 1 H); 10.01 (s, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ –5.2, 18.4, 23.0, 26.0, 31.3, 38.4, 61.9, 129.8, 139.2, 145.2, 179.1. MALDI-HRMS: 376.1728 ($[M + H]^+$, $C_{15}H_{30}N_3O_4SSi^+$; calcd 376.1721).

5-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}propyl)-*N*,*N*-dimethyl-2-{(*E*)-2-[4-(trifluoromethyl)phenyl]-vinyl}-1*H*-imidazole-1-sulfonamide ((*E*)-**24**) and
5-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}propyl)-*N*,*N*-dimethyl-2-{(*Z*)-2-[4-(trifluoromethyl)phenyl]-vinyl}-1*H*-imidazole-1-sulfonamide ((*Z*)-**24**)

To a suspension of 4-(trifluoromethyl)benzyltriphenylphosphonium bromide (1.38 g, 2.75 mmol) in THF (23 mL), *n*-BuLi (1.65 mL, 2.63 mmol, 1.6 M in hexane) was added at –78 °C and the mixture stirred at –78 °C for 1.5 h. A solution of **23** (860 mg, 2.30 mmol) in THF (10 mL) was added and the mixture stirred at –78 °C for 1 h and at rt for 20 h. The solution was cooled to –78 °C, saturated aqueous NH_4Cl solution was added, and the mixture was allowed to reach rt slowly while stirring. The solvent was concentrated *in vacuo*, H_2O was added, and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were washed with saturated aqueous NaCl solution, dried (Na_2SO_4), and filtered. The filtrate was concentrated *in vacuo*, and the crude product was purified by CC (SiO_2; hexane/AcOEt 3:2) to afford a white solid of (*E*)-**24** and (*Z*)-**24** as a diastereomeric mixture (*E*:*Z* = 4:1). Yield: 1.14 g (96%). mp: 73 °C. IR (neat): υ 2955, 2932, 2859, 1611, 1565, 1472, 1417, 1389, 1318, 1255, 1164, 1122, 1110, 1094, 1064, 1012, 958, 776, 731, 712 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD): δ 0.08 (s, 6 H); 0.91 (s, 9 H); 1.86-1.96 (m, 2 H); 2.89 (s, 6 H, (*E*)-isomer); 2.91 (s, 6 H, (*Z*)-isomer); 2.94 (t, *J* = 7.9 Hz, 2 H); 3.74 (t, *J* = 5.9 Hz, 2 H); 6.78 (s, 1 H, (*Z*)-isomer); 6.79 (d, *J* = 12.5 Hz, 1 H, (*Z*)-isomer); 6.91 (d, *J* = 12.5 Hz, 1 H, (*Z*)-isomer); 6.92 (s, 1 H, (*E*)-isomer); 7.44 (d, *J* = 7.7 Hz, 2 H, (*Z*)-isomer); 7.51 (d, *J* = 7.7 Hz, 2 H, (*Z*)-isomer); 7.53 (d, *J* = 16.0 Hz, 1 H, (*E*)-isomer); 7.68 (d, *J* = 8.6 Hz, 2 H, (*E*)-isomer);

7.70 (d, J = 16.0 Hz, 1 H, (*E*)-isomer); 7.73 (d, J = 8.6 Hz, 2 H, (*E*)-isomer). MALDI-HRMS: 518.2107 ($[M + H]^+$, $C_{23}H_{35}F_3N_3O_3SSi^+$; calcd 518.2115).

5-(3-Hydroxypropyl)-*N*,*N*-dimethyl-2-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-imidazole-1-sulfonamide ((*E*)-25) and

5-(3-Hydroxypropyl)-*N*,*N*-dimethyl-2-{(*Z*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-imidazole-1-sulfonamide ((*Z*)-25)

GP 3, starting from the diastereomeric mixture of (*E*)-**24** and (*Z*)-**24** (4.92 g, 9.5 mmol), but the solvent was concentrated *in vacuo* and the crude product purified by CC (SiO_2, AcOEt → AcOEt/MeOH 95:5) to afford (*E*)-**25** as a white solid and (*Z*)-**25** as a colorless oil.

(*E*)-**25**: Yield: 2.70 g (70%). mp: 130 °C. IR (neat): υ 3270, 2937, 2864, 1612, 1570, 1468, 1420, 1391, 1325, 1159, 1107, 1066, 1014, 971, 824, 741, 718 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.86-1.97 (m, 2 H); 2.93 (s, 6 H); 2.94 (t, J = 7.6 Hz, 2 H); 3.65 (t, J = 6.2 Hz, 2 H); 6.94 (s, 1 H); 7.54 (d, J = 16.0 Hz, 1 H); 7.69 (d, J = 8.6 Hz, 2 H); 7.71 (d, J = 16.0 Hz, 1 H); 7.74 (d, J = 8.6 Hz, 2 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –63.01. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 23.1, 31.8, 38.2, 61.9, 118.0, 125.6 (q, $^3J_{CF}$ = 3.7 Hz), 127.0, 127.8, 130.1 (q, $^2J_{CF}$ = 32.5 Hz), 133.1, 134.8, 139.6, 147.0 (CF_3 signal not visible). MALDI-HRMS: 404.1244 ($[M + H]^+$, $C_{17}H_{21}F_3N_3O_3S^+$; calcd 404.1250).

(*Z*)-**25**: Yield: 820 mg (21%). IR (neat): υ 3347, 2933, 2872, 1615, 1568, 1457, 1389, 1320, 1160, 1110, 1064, 1016, 966, 875, 833, 722 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.50 (brs, 1 H); 1.90-2.00 (m, 2 H); 2.87 (s, 6 H); 2.89-2.96 (m, 2 H); 3.74 (t, J = 5.9 Hz, 2 H); 6.76 (d, J = 12.7 Hz, 1 H); 6.81 (s, 1 H); 6.83 (d, J = 12.7 Hz, 1 H); 7.52 (d, J = 8.5 Hz, 2 H); 7.58 (d, J = 8.5 Hz, 2 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.52. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 22.9, 31.5, 38.1, 61.6, 120.0, 123.9 (q, J_{CF} = 271.6 Hz), 125.0 (q, $^3J_{CF}$ = 3.7 Hz), 126.9, 129.2, 129.7 (q, $^2J_{CF}$ = 32.2 Hz), 133.7, 134.5, 138.9, 144.5. MALDI-HRMS: 404.1244 ($[M + H]^+$, $C_{17}H_{21}F_3N_3O_3S^+$; calcd 404.1250).

5-(Hydroxymethyl)-*N*,*N*-dimethyl-1*H*-pyrazole-1-sulfonamide (29)

To a solution of **27** (8.82 g, 50.0 mmol) in THF (190 mL), *n*-BuLi (35 mL, 55.0 mmol, 1.6 M in hexane) was added at –78 °C. The suspension was stirred at –78 °C for 1 h and then transferred slowly *via* a cannula (Ø 1.0 mm) to a solution of methyl chloroformate (7.8 mL, 100 mmol) in THF (100 mL) that was cooled to –78 °C. The mixture was allowed to reach rt for 15 h while stirring. Saturated aqueous NH_4Cl solution was added, and the solvent was concentrated *in vacuo*. H_2O was added to the residue, and the aqueous layer was extracted with CH_2Cl_2. The organic phase was dried ($MgSO_4$), filtered, and the filtrate was concentrated *in vacuo*. Et_2O and hexane were added to the crude product, the resulting suspension filtered, and the residue was washed with hexane to afford **28** as a white solid. Yield: 9.24 g

(71%). mp: 55 °C. IR (neat): υ 3128, 2958, 1728, 1521, 1449, 1373, 1319, 1280, 1245, 1178, 1157, 1125, 978, 759, 721 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.12 (s, 6 H); 3.93 (s, 3 H); 6.82 (d, *J* = 1.7 Hz, 1 H); 7.59 (d, *J* = 1.7 Hz, 1 H). EI-HRMS: 202.0278 ($[M - CH_3O]^+$, $C_7H_8N_3O_3S^+$; calcd 202.0281). *Anal*. Calcd for $C_7H_{11}N_3O_4S$ (233.24): C, 36.05; H, 4.75; N, 18.02. Found: C, 36.21; H, 4.76; N, 17.97.

Because the ester **28** was not stable at rt, it was directly converted to the alcohol **29**:

To a suspension of $LiAlH_4$ (1.53 g, 38.0 mmol) in THF (150 mL), a solution of **28** (8.95 g, 38.0 mmol) in THF (50 mL) was added at –10 °C and the mixture stirred at –10 °C for 1 h. Aqueous 1 M NH_4Cl solution, H_2O, AcOEt, and Rochelle's salt were added, and the suspension was stirred vigorously for 30 min. The aqueous layer was extracted with AcOEt, the organic phase was dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by CC (SiO_2; hexane/AcOEt 1:1) to afford **29** as a colorless oil. Yield: 7.81 g (99%) IR (neat): υ 3385, 2941, 1732, 1548, 1456, 1417, 1376, 1285, 1169, 1129, 1084, 1049, 1015, 967, 918, 909, 724 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 3.00 (s, 6 H); 4.79 (s, 2 H); 6.33 (d, *J* = 1.6 Hz, 1 H); 7.59 (d, *J* = 1.6 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 38.9, 56.0, 108.0, 142.1, 146.4. EI-HRMS: 205.0515 ($[M]^+$, $C_6H_{11}N_3O_3S^+$; calcd 205.0516). *Anal*. Calcd for $C_6H_{11}N_3O_3S$ (205.24): C, 35.11; H, 5.40; N, 20.47. Found: C, 35.23; H, 5.40; N, 20.21.

5-(Bromomethyl)-*N*,*N*-dimethyl-1*H*-pyrazole-1-sulfonamide (26)

To a solution of PPh_3 (6.40 g, 24.4 mmol) in CH_2Cl_2 (75 mL), Br_2 (1.2 mL, 23.6 mmol) was added dropwise at 0 °C and the mixture stirred at rt for 30 min. To this suspension, a solution of the alcohol **29** (3.13 g, 15.3 mmol) in CH_2Cl_2 (75 mL) was added and the mixture stirred until the starting material had disappeared. The mixture was washed with 1 M aqueous K_2CO_3 solution. The organic phase was dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo*, and the crude product was purified by CC (SiO_2; hexane/AcOEt 4:1) to afford **26** as a white solid. Yield: 2.63 g (64%). mp: 71 °C. IR (neat): υ 3134, 2985, 2929, 1543, 1474, 1456, 1429, 1382, 1310, 1278, 1225, 1170, 1127, 966, 916, 827, 726, 710, 668 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 2.99 (s, 6 H); 4.70 (s, 2 H); 6.40 (d, *J* = 1.6 Hz, 1 H); 7.56 (d, *J* = 1.6 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 20.4, 39.2, 109.7, 141.8, 142.5. MALDI-HRMS: 267.9751 ($[M + H]^+$, $C_6H_{11}BrN_3O_2S^+$; calcd 267.9750). *Anal*. Calcd for $C_6H_{10}BrN_3O_2S$ (268.13): C, 26.88; H, 3.76; N, 15.67. Found: C, 27.17; H, 3.87; N, 15.75.

3-(2-{(*E*)-2-[4-(Trifluoromethyl)phenyl]vinyl}-1*H*-imidazole-5-yl)-1-propanol (30)

GP 2, starting from (*E*)-**25** (2.69 g, 6.70 mmol), but the mixture was stirred for 24 h. The crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1) to afford **30** as a colorless foam. Yield: 1.63 g (83%). IR (neat): υ 3142, 2935, 2872, 1613, 1568, 1437, 1415, 1320, 1161, 1107, 1064, 1014, 964, 866,

819, 751, 718 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.88 (m, 2 H); 2.70 (t, *J* = 7.7 Hz, 2 H); 3.61 (t, *J* = 6.4 Hz, 2 H); 6.88 (s, 1 H); 7.06 (d, *J* = 16.6 Hz, 1 H); 7.30 (d, *J* = 16.6 Hz, 1 H); 7.64 (d, *J* = 8.6 Hz, 2 H); 7.69 (d, *J* = 8.6 Hz, 2 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.30. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 23.5, 32.9, 61.8, 118.9, 119.8, 126.3 (q, $^3J_{CF}$ = 3.9 Hz), 127.5, 129.8, 130.3 (q, $^2J_{CF}$ = 32.2 Hz), 138.5, 141.2, 145.3 (CF_3 signal not visible). MALDI-HRMS: 297.1204 ($[M + H]^+$, $C_{15}H_{16}F_3N_2O^+$; calcd 297.1209).

5-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}propyl)-2-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-imidazole (31)

GP 4, starting from **30** (1.55 g, 5.23 mmol) in THF, afforded **31** after CC (SiO_2; hexane/AcOEt 4:1 → 1:1) as a colorless oil. Yield: 1.98 g (92%). IR (neat): υ 2930, 2857, 1614, 1588, 1471, 1436, 1415, 1321, 1254, 1164, 1122, 1107, 1066, 1015, 962, 950, 834, 820, 774 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.06 (s, 6 H); 0.91 (s, 9 H); 1.82-1.92 (m, 2 H); 2.68 (t, *J* = 7.6 Hz, 2 H); 3.69 (t, *J* = 6.2 Hz, 2 H); 6.82 (s, 1 H); 7.06 (d, *J* = 16.6 Hz, 1 H); 7.27 (d, *J* = 16.6 Hz, 1 H); 7.63 (d, *J* = 8.6 Hz, 2 H); 7.68 (d, *J* = 8.6 Hz, 2 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.27. ^{13}C-NMR (125 MHz, $CDCl_3$): δ –6.4, –1.2, 18.0, 25.2, 32.2, 62.6, 118.9, 124.5 (q, J_{CF} = 270.8 Hz), 125.5 (q, $^3J_{CF}$ = 3.9 Hz), 126.7, 128.2, 129.4 (q, $^2J_{CF}$ = 32.3 Hz), 140.7, 144.9 (two arom. signals missing due to overlap). MALDI-HRMS: 411.2076 ($[M + H]^+$, $C_{21}H_{30}F_3N_2OSi^+$; calcd 411.2074). *Anal*. Calcd for $C_{21}H_{29}F_3N_2OSi$ (410.55): C, 61.44; H, 7.12; N, 6.82. Found: C, 61.73; H, 7.07; N, 6.85.

5-{[4-(3-{[*tert*-Butyl(dimethyl)silyl]oxy}propyl)-2-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-imidazole-1-yl]methyl}-*N*,*N*-dimethyl-1*H*-pyrazole-1-sulfonamide (32)

To a solution of **31** (1.89 g, 4.60 mmol) in THF (46 mL), NaH (276 mg, 6.90 mmol, as a 60% dispersion in mineral oil) was added at 0 °C. The mixture was stirred at 0 °C for 1 h. The bromide **26** (1.48 g, 5.50 mmol) was added and the solution stirred at rt for 2 h. After addition of NH_4Cl, MeOH, and SiO_2, the solvent was concentrated *in vacuo*. The crude product was purified by CC (SiO_2, hexane/AcOEt 4:1 → 7:3) to afford **32** as a yellow solid. Yield: 2.05 g (74%). mp: 99 °C. IR (neat): υ 3073, 2955, 2931, 2858, 1611, 1556, 1472, 1456, 1416, 1392, 1324, 1257, 1166, 1125, 1098, 1067, 987, 960, 921, 834, 715 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 0.03 (s, 6 H); 0.88 (s, 9 H); 1.82-1.93 (m, 2 H); 2.66 (t, *J* = 8.1 Hz, 2 H); 3.02 (s, 6 H); 3.67 (t, *J* = 6.3 Hz, 2 H); 5.43 (s, 2 H); 5.88 (d, *J* = 1.7 Hz, 1 H); 6.72 (s, 1 H); 6.88 (d, *J* = 15.8 Hz, 1 H); 7.52 (d, *J* = 1.7 Hz, 1 H); 7.53 (brs, 4 H); 7.54 (d, *J* = 15.8 Hz, 1 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.35. ^{13}C-NMR (75 MHz, $CDCl_3$): δ –5.11, 18.5, 25.0, 26.1, 32.4, 39.1, 42.0, 62.6, 108.0, 114.9, 117.3, 125.5 (d, $^3J_{CF}$ = 3.8 Hz), 126.8, 129.6 (q, $^2J_{CF}$ = 32.4 Hz), 130.9, 139.9, 142.1, 142.2, 143.5, 144.1 (CF_3 signal not visible). MALDI-HRMS: 598.2480 ($[M + H]^+$,

$C_{27}H_{39}F_3N_5O_3SSi^+$; calcd 598.2490). *Anal.* Calcd for $C_{27}H_{38}F_3N_5O_3SSi$ (597.78): C, 54.25; H, 6.41; N, 11.72. Found: C, 54.30; H, 6.40; N, 11.66.

5-{[4-(3-Hydroxypropyl)-2-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-imidazole-1-yl]methyl}-*N*,*N*-dimethyl-1*H*-pyrazole-1-sulfonamide (33)

GP 3, starting from **32** (1.90 g, 3.18 mmol), but the solvent was concentrated *in vacuo* and the crude product purified by CC (SiO_2, AcOEt). The colorless oil was taken up in Et_2O, and the solvent was concentrated *in vacuo* to afford **33** as a white solid. Yield: 1.44 g (94%). mp: 126 °C. IR (neat): υ 3136, 2934, 1614, 1558, 1455, 1433, 1414, 1367, 1323, 1284, 1170, 1108, 1064, 982, 919, 824, 731, 709 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.87-1.96 (m, 2 H); 2.75 (t, *J* = 6.7 Hz, 2 H); 3.06 (s, 6 H); 3.79 (t, *J* = 5.7 Hz, 2 H); 4.32 (brs, 1 H); 5.45 (s, 2 H); 5.92 (d, *J* = 1.6 Hz, 1 H); 6.75 (s, 1 H); 6.87 (d, *J* = 15.9 Hz, 1 H); 7.52 (d, *J* = 15.9 Hz, 1 H); 7.56-7.59 (m, 5 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.39. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 26.0, 31.9, 39.2, 42.0, 62.9, 108.1, 114.5, 117.5, 125.6 (q, $^3J_{CF}$ = 3.7 Hz), 126.9, 129.8 (q, $^2J_{CF}$ = 32.8 Hz), 131.6, 139.6, 141.8, 142.0, 142.8, 144.0 (CF_3 signal not visible). MALDI-HRMS: 484.1618 ($[M + H]^+$, $C_{21}H_{25}F_3N_5O_3S^+$; calcd 484.1625). *Anal.* Calcd for $C_{21}H_{24}F_3N_5O_3S$ (483.51): C, 52.17; H, 5.00; N, 14.48. Found: C, 51.88; H, 5.18; N, 14.29.

***N*,*N*-Dimethyl-5-({4-[3-(1-piperidinyl)propyl]-2-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-imidazole-1-yl}methyl)-1*H*-pyrazole-1-sulfonamide (34)**

GP 5, starting from **33** (400 mg, 0.83 mmol) and piperidine (0.82 mL, 8.30 mmol), afforded **34** after CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1) as a colorless oil. Yield: 434 mg (95%). IR (neat): υ 2935, 2853, 2767, 1613, 1551, 1455, 1412, 1385, 1321, 1284, 1164, 1065, 968, 908, 821, 727 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.28-1.39 (m, 2 H); 1.45-1.55 (m, 4 H); 1.71-1.86 (m, 2 H); 2.26-2.35 (m, 6 H); 2.53 (t, *J* = 7.7 Hz, 2 H); 2.94 (s, 6 H); 5.36 (s, 2 H); 5.82 (d, *J* = 1.7 Hz, 1 H); 6.66 (s, 1 H); 6.83 (d, *J* = 15.9 Hz, 1 H); 7.46 (d, *J* = 1.7 Hz, 1 H); 7.47 (brs, 4 H); 7.48 (d, *J* = 15.9 Hz, 1 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.38. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 24.4, 25.9, 26.6, 39.0, 41.9, 54.5, 59.0, 108.0, 114.9, 117.2, 125.4 (d, $^3J_{CF}$ = 3.7 Hz), 126.7, 129.4 (q, $^2J_{CF}$ = 32.4 Hz), 130.6, 139.8, 142.0, 142.1, 143.4, 143.9 (CF_3 signal not visible, one aliph. signal missing due to overlap). MALDI-HRMS: 551.2403 ($[M + H]^+$, $C_{26}H_{34}F_3N_6O_2S^+$; calcd 551.2411).

***N*,*N*-Dimethyl-5-({4-[3-(4-morpholinyl)propyl]-2-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-imidazole-1-yl}methyl)-1*H*-pyrazole-1-sulfonamide (35)**

GP 5, starting from **33** (400 mg, 0.83 mmol) and morpholine (0.73 mL, 8.30 mmol), afforded **35** after CC (SiO_2; CH_2Cl_2/MeOH 95:5) as a colorless oil. Yield: 255 mg (56%). IR (neat): υ 2942, 2855, 2810,

1613, 1552, 1456, 1412, 1386, 1322, 1284, 1165, 1110, 1013, 968, 917, 821, 728 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.77-1.89 (m, 2 H); 2.34-2.45 (m, 6 H); 2.60 (t, *J* = 7.9 Hz, 2 H); 3.01 (s, 6 H); 3.67 (t, *J* = 4.7 Hz, 4 H); 5.41 (s, 2 H); 5.87 (d, *J* = 1.2 Hz, 1 H); 6.71 (s, 1 H); 6.86 (d, *J* = 15.9 Hz, 1 H); 7.51 (brs, 5 H); 7.52 (d, *J* = 15.9 Hz, 1 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.39. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 26.4, 39.1, 42.0, 53.7, 58.5, 67.0, 108.0, 114.9, 117.2, 125.5 (d, $^3J_{CF}$ = 3.7 Hz), 126.7, 129.5 (q, $^2J_{CF}$ = 32.3 Hz), 130.9, 139.7, 141.9, 142.0, 143.3, 144.0 (CF_3 signal not visible, one aliph. signal missing due to overlap). MALDI-HRMS: 553.2212 ($[M + H]^+$, $C_{25}H_{32}F_3N_6O_3S^+$; calcd 553.2203).

_N_,_N_-Dimethyl-5-({4-[3-(4-methyl-1-piperazinyl)propyl]-2-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-imidazole-1-yl}methyl)-1*H*-pyrazole-1-sulfonamide (36)

GP 5, starting from **33** (400 mg, 0.83 mmol) and 1-methylpiperazine (0.93 mL, 8.30 mmol), afforded **36** after CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1) as a colorless resin. Yield: 350 mg (75%). IR (neat): υ 2938, 2796, 1613, 1551, 1457, 1412, 1386, 1321, 1283, 1162, 1110, 1065, 1011, 968, 820, 728 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.79-1.91 (m, 2 H); 2.26 (s, 3 H); 2.31-2.56 (m, 10 H); 2.60 (t, *J* = 7.8 Hz, 2 H); 3.04 (s, 6 H); 5.43 (s, 2 H); 5.87 (d, *J* = 1.5 Hz, 1 H); 6.72 (s, 1 H); 6.87 (d, *J* = 15.8 Hz, 1 H); 7.54 (d, *J* = 15.8 Hz, 1 H); 7.55 (brs, 5 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.37. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 26.6, 26.8, 39.2, 42.0, 46.2, 53.3, 55.2, 58.2, 108.0, 114.9, 117.2, 125.6 (d, $^3J_{CF}$ = 3.8 Hz), 126.8, 129.6 (q, $^2J_{CF}$ = 32.1 Hz), 130.7, 139.8, 142.0, 142.1, 143.5, 144.8 (CF_3 signal not visible). MALDI-HRMS: 566.2514 ($[M + H]^+$, $C_{26}H_{35}F_3N_7O_2S^+$; calcd 566.2520).

1-{3-[1-(1*H*-Pyrazole-3-ylmethyl)-2-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-imidazole-4-yl]-propyl}piperidine (15)

GP 2, starting from **34** (434 mg, 0.79 mmol), and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1) to afford **15** as a white solid. Yield: 310 mg (89%). mp: 140 °C. IR (neat): υ 3059, 2923, 2852, 2812, 2733, 1610, 1556, 1464, 1432, 1456, 1320, 1269, 1159, 1110, 1014, 951, 822, 756 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.39-1.49 (m, 2 H); 1.52-1.64 (m, 4 H); 1.81-1.94 (m, 2 H); 2.35-2.45 (m, 6 H); 2.60 (t, *J* = 7.8 Hz, 2 H); 5.20 (s, 2 H); 6.15 (d, *J* = 2.4 Hz, 1 H); 6.76 (s, 1 H); 7.07 (d, *J* = 15.9 Hz, 1 H); 7.52 (d, *J* = 2.4 Hz, 1 H); 7.54 (d, *J* = 15.9 Hz, 1 H); 7.56 (brs, 4 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.33. ^{13}C-NMR (125 MHz, CD_3OD/TFA): δ 21.5, 21.6, 22.7, 23.0, 44.8, 53.2, 55.8, 104.3, 110.2, 120.1, 124.2 (q, J_{CF} = 271.3 Hz), 125.9 (q, $^3J_{CF}$ = 3.8 Hz), 128.3, 130.7, 131.7 (q, $^2J_{CF}$ = 32.5 Hz), 133.0, 138.3, 138.8, 142.8, 145.3. MALDI-HRMS: 444.2364 ($[M + H]^+$, $C_{24}H_{29}F_3N_5^+$; calcd 444.2370).

4-{3-[1-(1*H*-Pyrazole-5-ylmethyl)-2-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-imidazole-4-yl]-

propyl}morpholine (16)

GP 2, starting from **35** (255 mg, 0.46 mmol), and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1) to afford **16** as a white solid. Yield: 182 mg (89%). mp: 132 °C. IR (neat): υ 3109, 2836, 1662, 1614, 1557, 1456, 1435, 1416, 1325, 1162, 1110, 1067, 1011, 969, 912, 868, 859 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.80-1.92 (m, 2 H); 2.38-2.48 (m, 6 H); 2.62 (t, *J* = 7.9 Hz, 2 H); 3.72 (t, *J* = 4.7 Hz, 4 H); 5.21 (s, 2 H); 6.16 (d, *J* = 2.4 Hz, 1 H); 6.76 (s, 1 H); 7.07 (d, *J* = 15.9 Hz, 1 H); 7.53 (d, *J* = 2.4 Hz, 1 H); 7.54 (d, *J* = 15.9 Hz, 1 H); 7.56 (s, 4 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.33. ^{13}C-NMR (125 MHz, CD_3OD/TFA): δ 21.4, 22.3, 44.8, 52.0, 56.0, 63.8, 104.3, 110.2, 120.2, 124.2 (q, J_{CF} = 271.4 Hz), 125.9 (q, $^3J_{CF}$ = 3.8 Hz), 128.3, 130.7, 131.7(q, $^2J_{CF}$ = 32.5 Hz), 133.0, 138.3, 138.8, 142.8, 145.3. MALDI-HRMS: 446.2155 ($[M + H]^+$, $C_{23}H_{27}F_3N_5O^+$; calcd 446.2162).

1-Methyl-4-{3-[1-(1*H*-pyrazole-3-ylmethyl)-2-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-imidazole-4-yl]propyl}piperazine (17)

GP 2, starting from **36** (350 mg, 0.62 mmol), and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1) to afford **17** as a colorless resin. Yield: 247 mg (87%). IR (neat): υ 3144, 2939, 2804, 1612, 1557, 1458, 1411, 1320, 1283, 1160, 1108, 1012, 819, 754 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.81-1.94 (m, 2 H); 2.30 (s, 3 H); 2.35-2.55 (m, 10 H); 2.62 (t, *J* = 7.7 Hz, 2 H); 5.20 (s, 2 H); 6.15 (d, *J* = 2.4 Hz, 1 H); 6.75 (s, 1 H); 7.06 (d, *J* = 15.8 Hz, 1 H); 7.53 (d, *J* = 2.4 Hz, 1 H); 7.54 (d, *J* = 15.8 Hz, 1 H); 7.57 (brs, 4 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.33. ^{13}C-NMR (125 MHz, CD_3OD/TFA): δ 21.4, 23.0, 23.1, 42.3, 48.8, 50.8, 55.4, 104.3, 110.2, 120.2, 124.2 (q, J_{CF} = 271.3 Hz), 125.9 (q, $^3J_{CF}$ = 3.9 Hz), 128.3, 130.7, 131.7 (q, $^2J_{CF}$ = 32.6 Hz), 133.2, 138.3, 138.7, 142.7, 145.3 (one aliph. signal missing due to overlap). MALDI-HRMS: 459.2472 ($[M + H]^+$, $C_{24}H_{30}F_3N_6^+$; calcd 459.2479).

(*E*)-3-[4-(Trifluoromethyl)phenyl]acrylohydrazide (40)

To a solution of **39** (22.6 g, 0.105 mol) in THF (348 mL) and *N*-methylmorpholine (12.0 mL, 0.110 mol), isobutyl chloroformate (15.6 mL, 0.110 mol) was added at 0 °C over 10 min. The mixture was allowed to reach rt for 20 min while stirring. The mixture was then transferred *via* a cannula (Ø 1.0 mm) to a solution of hydrazine (1 M in THF, 523 mL, 0.523 mol), and the solution was stirred at rt for 20 h. The solvent was concentrated *in vacuo* to the half of the volume, AcOEt was added, and the organic phase was washed with H_2O. The combined aqueous layers were extracted with AcOEt. The combined organic phases were washed with saturated aqueous NaCl solution, dried ($MgSO_4$), and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by crystallization (AcOEt) to afford **40** as colorless crystals. Yield: 19.65 g (82%). mp: 165 °C. IR (neat): υ 3318, 3219, 1649, 1609, 1577,

1531, 1416, 1350, 1315, 1238, 1162, 1125, 1107, 1060, 1016, 985, 960, 827 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD): δ 6.66 (d, *J* = 15.9 Hz, 1 H); 7.59 (d, *J* = 15.9 Hz, 1 H); 7.66 (d, *J* = 8.6 Hz, 2 H); 7.72 (d, *J* = 8.6 Hz, 2 H). ^{19}F-NMR (282 MHz, CD_3OD): δ –62.52. ^{13}C-NMR (75 MHz, CD_3OD): δ 122.1, 125.0 (q, J_{CF} = 270.7 Hz), 126.4 (q, $^3J_{CF}$ = 3.8 Hz), 127.8, 131.7 (q, $^2J_{CF}$ = 32.4 Hz), 139.2, 139.6, 166.6. EI-HRMS: 230.0663 ($[M]^+$, $C_{10}H_9F_3N_2O^+$; calcd 230.0662).

_N_'-[(2_E_)-3-(4-Chlorophenyl)prop-2-enoyl]propanehydrazonamide (46)

GP 6, starting from **43** (12.9 g, 65.4 mmol), and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1). The yellow oil was taken up in *i*-PrOH, Et_2O was added, the resulting solid was filtered off, and dried to afford **46** as a pale yellow solid. Yield: 5.50 g (30%). mp: 196 °C. IR (neat): υ 3454, 3174, 2973, 1654, 1634, 1584, 1562, 1556, 1488, 1403, 1340, 1212, 1085, 818 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD): δ 1.23 (t, *J* = 7.7 Hz, 3 H); 2.33 (q, *J* = 7.7 Hz, 2 H); 6.64 (d, *J* = 16.2 Hz, 1 H); 7.36 (d, *J* = 8.5 Hz, 2 H); 7.48 (d, *J* = 16.2 Hz, 1 H); 7.53 (d, *J* = 8.5 Hz, 2 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): δ 11.8, 26.9, 119.4, 128.8, 128.9, 129.2, 138.6, 150.4, 156.1, 164.7. *Anal*. Calcd for $C_{12}H_{14}ClN_3O$ (251.71): C, 57.26; H, 5.61; N, 16.69. Found: C, 57.21; H, 5.49; N, 16.60.

_N_-((_E_)-3-_p_-Tolylacryloyl)propanehydrazonamide (47)

GP 6, starting from **44** (10.0 g, 72.7 mmol), and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1). The yellow oil was taken up in MeOH, Et_2O was added, the resulting solid was filtered off, and dried to afford **47** as a white solid. Yield: 7.97 g (47%). mp: 188 °C. IR (neat): υ 3403, 3188, 3022, 2974, 2879, 1630, 1574, 1548, 1511, 1456, 1464, 1404, 1338, 1282, 1260, 1220, 1208, 1179, 1116, 1028, 984, 864, 810, 719, 646 cm^{-1}. ^{1}H-NMR (300 MHz, $(CD_3)_2SO$): δ 1.09 (t, *J* = 7.6 Hz, 3 H); 2.11 (q, *J* = 7.6 Hz, 2 H); 2.32 (s, 3 H); 6.10 (brs, 2 H); 6.57 (d, *J* = 15.9 Hz, 1 H); 7.22-7.51 (m, 5 H); 9.47 (brs, 1 H). ^{13}C-NMR (75 MHz, $(CD_3)_2SO$): δ 11.9, 21.0, 27.0, 117.3, 127.1, 129.3, 132.4, 138.6, 139.9, 149.9, 155.4. *Anal*. Calcd for $C_{13}H_{17}N_3O$ (231.29): C, 67.51; H, 7.41; N, 18.17. Found: C, 76.55; H, 7.52; N, 17.88.

(_E_)-3-Ethyl-5-(4-(trifluoromethyl)styryl)-1_H_-1,2,4-triazole (48)

GP 6, starting from **40** (15.1 g, 65.4 mmol), and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1). The product was dissolved in CH_2Cl_2, hexane was added, the resulting solid was filtered off, washed with Et_2O, and dried to afford **45** as a yellow solid. Yield: 5.68 g (27%). mp: 68 °C. IR (neat): υ 3204, 2980, 1652, 1579, 1464, 1414, 1319, 1286, 1216, 1163, 1107, 1065, 1015, 976, 954, 873, 828 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD): δ 1.25 (t, *J* = 7.6 Hz, 3 H); 2.36 (q, *J* = 7.6 Hz, 2 H); 6.76 (d, *J* = 15.8 Hz, 1 H); 7.55 (d, *J* = 15.8 Hz, 1 H); 7.67 (d, *J* = 8.7 Hz, 2 H); 7.73 (d, *J* = 8.7 Hz,

2 H). EI-HRMS: 285.1086 ($[M]^+$, $C_{12}H_{14}F_3N_3O^+$; calcd 285.1084).

45 was directly converted to **48**:

GP 7, starting from **45** (5.68 g, 19.9 mmol), and the crude product was taken up in Et_2O. The resulting solid was filtered off, and dried to afford **48** as a white solid. Yield: 3.41 g (64%). mp: 190 °C. IR (neat): υ 2718, 1617, 1500, 1430, 1415, 1397, 1324, 1264, 1157, 1105, 1067, 1054, 1016, 970, 957, 870, 840, 826, 755 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD): δ 1.35 (t, *J* = 7.8 Hz, 3 H); 2.82 (q, J = 7.8 Hz, 2 H); 7.17 (d, *J* = 16.8 Hz, 1 H); 7.55 (d, *J* = 16.8 Hz, 1 H); 7.66 (d, *J* = 8.2 Hz, 2 H); 7.75 (d, *J* = 8.2 Hz, 2 H). ^{13}C-NMR (75 MHz, CD_3OD/TFA): δ 11.9, 20.0, 116.5, 123.2, 126.4 (q, $^3J_{CF}$ = 3.5 Hz), 128.3 (q, $^2J_{CF}$ = 32.3 Hz), 135.9, 140.0, 156.6, 159.9 (CF_3 signal not visible). EI-HRMS: 266.0901 ($[M - H]^+$, $C_{13}H_{11}F_3N_3^+$; calcd 266.0900).

5-[(*E*)-2-(4-Chlorophenyl)vinyl]-3-ethyl-1*H*-1,2,4-triazole (49)

GP 7, starting from **46** (5.00 g, 19.8 mmol), and the crude product was taken up in Et_2O. The resulting solid was filtered off, and dried to afford **49** as a white solid. Yield: 3.59 g (77%). mp: 202 °C. IR (neat): υ 3110, 2983, 2668, 1644, 1551, 1492, 1427, 1395, 1261, 1086, 1054, 1012, 966, 824, 807 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD): δ 1.34 (t, *J* = 7.6 Hz, 3 H); 2.80 (q, *J* = 7.6 Hz, 2 H); 7.02 (d, *J* = 16.3 Hz, 1 H); 7.37 (d, *J* = 8.6 Hz, 2 H); 7.46 (d, *J* = 16.3 Hz, 1 H); 7.54 (d, *J* = 8.6 Hz, 2 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): δ 12.1, 19.7, 118.6, 128.4, 128.6, 130.8, 132.5, 135.1, 158.4, 160.0. EI-HRMS: 232.0639 ($[M - H]^+$, $C_{12}H_{11}ClN_3^+$; calcd 232.0642). *Anal.* Calcd for $C_{12}H_{12}ClN_3$ (233.70): C, 61.67; H, 5.18; N, 17.98. Found: C, 61.52; H, 5.40; N, 17.82.

(*E*)-3-Ethyl-5-(4-methylstyryl)-1*H*-1,2,4-triazole (50) and

(*E*)-2-Ethyl-5-(4-methylstyryl)-1,3,4-oxadiazole (51)

GP 7, starting from **47** (3.26 g, 14.1 mmol), and the crude product was taken up in Et_2O. The resulting solid was filtered off, and dried to afford **50** and **51** as white solids.

50: Yield 180 mg (6%). mp: 174 °C. IR (neat): υ 3142, 3030, 2975, 2853, 2762, 1650, 1556, 1499, 1438, 1259, 1054, 974, 966, 799 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.33 (t, *J* = 7.8 Hz, 3 H); 2.34 (s, 3 H); 2.79 (q, *J* = 7.8 Hz, 2 H); 6.49 (d, *J* = 16.5 Hz, 1 H); 7.19 (d, *J* = 7.8 Hz, 2 H); 7.40-7.52 (m, 3 H). ^{13}C-NMR (125 MHz, $(CD_3)_2SO$): δ 12.7, 20.0, 21.5, 118.5, 127.3, 130.0, 132.5, 134.2, 138.2, 158.7, 161.3. EI-HRMS: 213.1261 ($[M]^+$, $C_{13}H_{15}N_3^+$; calcd 213.1261).

51: Yield: 1.67 g (56%). mp: 173 °C. IR (neat): υ 3146, 3033, 2975, 2855, 1651, 1562, 1495, 1438, 1259, 1053, 977, 801, 750 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.42 (t, *J* = 7.7 Hz, 3 H); 2.38 (s, 3 H); 2.91 (q, *J* = 7.7 Hz, 2 H); 6.96 (d, *J* = 15.3 Hz, 1 H); 7.20 (d, *J* = 7.0 Hz, 2 H); 7.43 (d, *J* = 7.0 Hz, 2 H) 7.47 (d, *J* = 15.3 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.0, 19.3, 21.6, 109.1, 127.3, 129.6, 132.0,

138.4, 140.1, 164.4, 167.0. EI-HRMS: 213.1025 ($[M - H]^+$, $C_{13}H_{13}N_2O^+$; calcd 213.1028). *Anal*. Calcd for $C_{13}H_{14}N_2O$ (213.28): C, 72.87; H, 6.59; N, 13.07; O, 7.47. Found: C, 72.71; H, 6.77; N, 13.15.

5-[(3-Ethyl-5-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-1,2,4-triazole-1-yl)methyl]-*N*,*N*-dimethyl-1*H*-pyrazole-1-sulfonamide (52a) and
5-[(5-Ethyl-3-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-1,2,4-triazole-1-yl)methyl]-*N*,*N*-dimethyl-1*H*-pyrazole-1-sulfonamide (52b)

To a solution of **48** (500 mg, 1.90 mmol) in THF (10 mL), NaH (112 mg, 2.80 mmol, as a 60% dispersion in mineral oil) was added at 0 °C. The mixture was stirred at 0 °C for 1 h. The bromide **26** (602 mg, 2.20 mmol) was added, and the mixture was allowed to reach rt for 19 h while stirring. After addition of H_2O, the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and filtered. The filtrate was concentrated *in vacuo* and the crude product purified by CC (SiO_2, hexane/AcOEt 1:1 → AcOEt) to afford **52a** and **52b** as white solids.

52a: Yield: 346 mg (41%). mp: 121 °C. IR (neat): υ 2969, 2937, 1611, 1558, 1501, 1444, 1394, 1318, 1283, 1259, 1204, 1165, 1111, 1066, 975, 955, 828, 727, 710 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.35 (t, *J* = 7.6 Hz, 3 H); 2.78 (q, *J* = 7.6 Hz, 2 H); 3.04 (s, 6 H); 5.69 (s, 2 H); 6.04 (m, 1 H); 7.01 (d, *J* = 15.8 Hz, 1 H); 7.59 (m, 1 H); 7.64 (s, 4 H); 7.74 (d, *J* = 15.8 Hz, 1 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.54. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.9, 22.0, 39.2, 44.2, 108.7, 112.7, 125.7 (q, $^3J_{CF}$ = 3.5 Hz), 127.5, 130.7 (q, $^2J_{CF}$ = 32.4 Hz), 136.0, 138.7, 141.0, 142.2, 152.6, 165.7 (CF_3 signal not visible). MALDI-HRMS: 455.1465 ($[M + H]^+$, $C_{19}H_{22}F_3N_6O_2S^+$; calcd 455.1472).

52b: Yield: 353 mg (41%). mp: 155 °C. IR (neat): υ 2988, 1613, 1544, 1519, 1475, 1449, 1386, 1320, 1285, 1173, 1161, 1119, 1109, 1065, 1054, 972, 960, 919, 831, 808, 734 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.6 Hz, 3 H); 2.80 (q, *J* = 7.6 Hz, 2 H); 3.03 (s, 6 H); 5.57 (d, ^2J = 0.9 Hz, 2 H); 5.93 (dt, *J* = 1.8, 0.9 Hz, 1 H); 7.11 (d, *J* = 16.3 Hz, 1 H); 7.59 (d, *J* = 16.3 Hz, 1 H); 7.60 (d, *J* = 1.8 Hz, 1 H); 7.61 (s, 4 H). ^{19}F-NMR (282 MHz, $CDCl_3$): δ –62.45. ^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.8, 19.2, 39.0, 44.5, 108.0, 119.9, 125.6 (q, $^3J_{CF}$ = 3.5 Hz), 126.9, 132.1, 141.1, 142.3, 158.3, 160.2 (CF_3 and *C*CF_3 signals not visible). MALDI-HRMS: 455.1464 ($[M + H]^+$, $C_{19}H_{22}F_3N_6O_2S^+$; calcd 455.1472).

5-({5-[(*E*)-2-(4-Chlorophenyl)vinyl]-3-ethyl-1*H*-1,2,4-triazole-1-yl}methyl)-*N*,*N*-dimethyl-1*H*-pyrazole-1-sulfonamide (53a) and
5-({3-[(*E*)-2-(4-Chlorophenyl)vinyl]-5-ethyl-1*H*-1,2,4-triazole-1-yl}methyl)-*N*,*N*-dimethyl-1*H*-pyrazole-1-sulfonamide (53b)

To a solution of **49** (500 mg, 2.10 mmol) in THF (10 mL), NaH (128 mg, 3.20 mmol, as a 60% dispersion in mineral oil) was added at 0 °C. The mixture was stirred at 0 °C for 1 h. The bromide **26** (688 mg,

2.60 mmol) was added, and the mixture was allowed to reach rt for 19 h while stirring. After addition of MeOH and SiO_2, the solvent was concentrated *in vacuo*. The crude product was purified by CC (SiO_2, hexane/AcOEt 1:1 → AcOEt) to afford **53a** and **53b** as white solids.

53a: Yield: 317 mg (35%). mp: 138 °C. IR (neat): υ 2969, 2932, 1646, 1505, 1488, 1441, 1386, 1283, 1169, 1122, 1086, 964, 907, 899, 814, 728, 715 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.34 (t, *J* = 7.6 Hz, 3 H); 2.77 (q, *J* = 7.6 Hz, 2 H); 3.03 (s, 6 H); 5.66 (d, ^2J = 0.8 Hz, 2 H); 5.99 (dt, *J* = 1.7, 0.8 Hz, 1 H); 6.87 (d, *J* = 15.9 Hz, 1 H); 7.34 (d, *J* = 8.5 Hz, 2 H); 7.46 (d, *J* = 8.5 Hz, 2 H); 7.58 (d, *J* = 1.7 Hz, 1 H); 7.67 (d, *J* = 15.9 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 12.7, 21.5, 39.0, 44.1, 108.5, 110.8, 128.5, 129.0, 133.8, 135.1, 136.4, 141.2, 142.3, 153.0, 165.6. MALDI-HRMS: 421.1202 ($[M + H]^+$, $C_{18}H_{22}ClN_6O_2S^+$; calcd 421.1208). *Anal*. Calcd for $C_{18}H_{21}ClN_6O_2S$ (420.92): C, 51.36; H, 5.03; N, 19.97. Found: C, 51.26; H, 5.07; N, 19.74.

53b: Yield: 410 mg (46%). mp: 141 °C. IR (neat): υ 2984, 1544, 1494, 1474, 1418, 1384, 1287, 1171, 1132, 1089, 1054, 969, 919, 822, 806, 736, 720 cm^{-1}. ^{1}H-NMR (300 MHz, $CDCl_3$): δ 1.36 (t, *J* = 7.6 Hz, 3 H); 2.79 (q, *J* = 7.6 Hz, 2 H); 3.03 (s, 6 H); 5.55 (d, ^2J = 0.9 Hz, 2 H); 5.92 (dt, *J* = 1.8, 0.9 Hz, 1 H); 7.00 (d, *J* = 16.3 Hz, 1 H); 7.32 (d, *J* = 8.5 Hz, 2 H); 7.45 (d, *J* = 8.5 Hz, 2 H); 7.52 (d, *J* = 16.3 Hz, 1 H); 7.59 (d, *J* = 1.8 Hz, 1 H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 11.9, 19.2, 39.0, 44.5, 108.0, 118.0, 128.0, 128.8, 132.3, 133.9, 134.8, 141.2, 142.3, 158.2, 160.5. MALDI-HRMS: 421.1201 ($[M + H]^+$, $C_{18}H_{22}ClN_6O_2S^+$; calcd 421.1208). *Anal*. Calcd for $C_{18}H_{21}ClN_6O_2S$ (420.92): C, 51.36; H, 5.03; N, 19.97. Found: C, 51.44; H, 5.14; N, 19.70.

3-Ethyl-1-(1*H*-pyrazole-5-ylmethyl)-5-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-1,2,4-triazole (37a)

GP 2, starting from **52a** (300 mg, 0.66 mmol), and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1) to afford **37a** as a white solid. Yield: 300 mg (96%). mp: 161 °C. IR (neat): υ 3164, 3068, 2984, 2916, 1614, 1503, 1441, 1324, 1158, 1105, 1067, 1048, 970, 951, 867, 822, 757, 717 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD): δ 1.31 (t, *J* = 7.6 Hz, 3 H); 2.72 (q, *J* = 7.6 Hz, 2 H); 5.51 (s, 2 H); 6.27 (d, *J* = 2.3 Hz, 1 H); 7.42 (d, *J* = 16.2 Hz, 1 H); 7.61 (d, *J* = 2.3 Hz, 1 H); 7.65 (d, *J* = 16.2 Hz, 1 H); 7.69 (d, *J* = 8.2 Hz, 2 H); 7.82 (d, *J* = 8.2 Hz, 2 H). ^{19}F-NMR (282 MHz, CD_3OD): δ –63.03. ^{13}C-NMR (75 MHz, CD_3OD/TFA): δ 12.0, 21.2, 47.1, 105.0, 112.3, 126.5 (q, $^3J_{CF}$ = 3.8 Hz), 129.0, 131.5, 132.0 (q, $^2J_{CF}$ = 32.4 Hz), 139.2, 139.5, 146.2, 152.0, 162.0 (CF_3 signal not visible). MALDI-HRMS: 348.1426 ($[M + H]^+$, $C_{17}H_{17}F_3N_5^+$; calcd 348.1431).

5-Ethyl-1-(1*H*-pyrazole-5-ylmethyl)-3-{(*E*)-2-[4-(trifluoromethyl)phenyl]vinyl}-1*H*-1,2,4-triazole (37b)

GP 2, starting from **52b** (311 mg, 0.68 mmol), and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1) to afford **37b** as a white solid. Yield: 235 mg (99%). mp: 115 °C. IR (neat): υ 3354, 3133, 2970, 2915, 1615, 1514, 1482, 1452, 1366, 1322, 1271, 1169, 1106, 1066, 1050, 1016, 967, 825, 762, 720 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD): δ 1.29 (t, *J* = 7.6 Hz, 3 H); 2.88 (q, *J* = 7.6 Hz, 2 H); 5.39 (s, 2 H); 6.27 (d, *J* = 2.3 Hz, 1 H); 7.15 (d, *J* = 16.4 Hz, 1 H); 7.55 (d, *J* = 16.4 Hz, 1 H); 7.62 (d, *J* = 2.3 Hz, 1 H); 7.66 (d, *J* = 8.3 Hz, 2 H); 7.74 (d, *J* = 8.3 Hz, 2 H). ^{19}F-NMR (282 MHz, CD_3OD): δ –62.36. ^{13}C-NMR (75 MHz, CD_3OD/TFA): δ 11.6, 19.6, 47.0, 104.9, 118.5, 126.3 (q, $^3J_{CF}$ = 3.8 Hz), 128.1, 130.9 (q, $^2J_{CF}$ = 32.4 Hz), 131.5, 134.4, 140.5, 146.2, 157.8, 158.4 (CF_3 signal not visible) MALDI-HRMS: 348.1423 ($[M + H]^+$, $C_{17}H_{17}F_3N_5^+$; calcd 348.1431).

5-[(*E*)-2-(4-Chlorophenyl)vinyl]-3-ethyl-1-(1*H*-pyrazole-5-ylmethyl)-1*H*-1,2,4-triazole (38a)

GP 2, starting from **53a** (299 mg, 0.71 mmol), and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1) to afford **38a** as a white solid. Yield: 220 mg (99%). mp: 164 °C. IR (neat): υ 3116, 3052, 2912, 2813, 1637, 1542, 1505, 1435, 1372, 1302, 1265, 1182, 1087, 1047, 965, 905, 840, 812, 752 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD): δ 1.31 (t, *J* = 7.6 Hz, 3 H); 2.71 (q, *J* = 7.6 Hz, 2 H); 5.48 (s, 2 H); 6.26 (d, *J* = 2.3 Hz, 1 H); 7.27 (d, *J* = 16.1 Hz, 1 H); 7.40 (d, *J* = 8.6 Hz, 2 H); 7.57 (d, *J* = 16.1 Hz, 1 H); 7.59-7.62 (m, 1 H); 7.63 (d, *J* = 8.6 Hz, 2 H). ^{13}C-NMR (75 MHz, CD_3OD/TFA): δ 11.9, 21.1, 47.1, 105.1, 109.9, 129.8, 130.0, 131.5, 134.4, 136.8, 140.1, 146.2, 152.1, 161.7. MALDI-HRMS: 314.1158 ($[M + H]^+$, $C_{16}H_{17}ClN_5^+$; calcd 314.1167).

3-[(*E*)-2-(4-Chlorophenyl)vinyl]-5-ethyl-1-(1*H*-pyrazole-5-ylmethyl)-1*H*-1,2,4-triazole (38b)

GP 2, starting from **53b** (326 mg, 0.77 mmol), and the crude product was purified by CC (SiO_2; CH_2Cl_2/MeOH/NH_3 9:0.9:0.1) to afford **38b** as a white solid. Yield: 243 mg (quant.). mp: 138 °C. IR (neat): υ 3132, 3047, 2975, 2933, 1651, 1494, 1475, 1450, 1425, 1403, 1361, 1269, 1183, 1082, 1049, 1010, 961, 809, 756 cm^{-1}. ^{1}H-NMR (300 MHz, CD_3OD): δ 1.28 (t, *J* = 7.6 Hz, 3 H); 2.86 (q, *J* = 7.6 Hz, 2 H); 5.37 (s, 2 H); 6.26 (d, *J* = 2.3 Hz, 1 H); 7.00 (d, *J* = 16.4 Hz, 1 H); 7.36 (d, *J* = 8.7 Hz, 2 H); 7.46 (d, *J* = 16.4 Hz, 1 H); 7.53 (d, *J* = 8.7 Hz, 2 H); 7.61 (d, *J* = 2.3 Hz, 1 H). ^{13}C-NMR (75 MHz, CD_3OD/TFA): δ 11.5, 19.5, 47.1, 104.9, 115.8, 129.2, 129.6, 131.5, 135.3, 135.4, 146.0, 157.5, 158.0 (one arom. signal missing due to overlap). MALDI-HRMS: 314.1162 ($[M + H]^+$, $C_{16}H_{17}ClN_5^+$; calcd 314.1167).)

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