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Synthesis of fluorine substituted pyrazolopyrimidines as potential leads for the development of PET-imaging agents for the $GABA_A$ receptors

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Abstract—Neuroimaging of $GABA_A$ receptors offers the potential for a better diagnosis of diseases related to a dysfunction of the GABAergic neurotransmission. A series of potent fluorinated analogues of the pyrazolopyrimidine Indiplon has been synthesized and evaluated in vitro as potential agents for imaging the $GABA_A$ receptor by means of positron emission tomography (PET). The most promising compound *N*-(3-fluoropropyl)-*N*-[3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-*a*]pyrimidin-7-yl]-phenyl]-acetamide (**5b**) showed an IC_{50} value of 2.78 ± 0.63 nM comparable to the lead compound Indiplon (IC_{50} 3.29 ± 0.37 nM), thus making it an interesting candidate for further investigations. In addition to the fluorinated reference compounds, suitable precursors for ^{18}F-radiolabelling studies have been synthesized.

1. Introduction

Impairment of GABAergic neurotransmission is assumed to be crucial in the pathogenesis of a variety of neurological disorders such as anxiety, sleep disorders, or epilepsy. The inhibitory neurotransmitter γ-aminobutyric acid (GABA) binds to three classes of receptors: $GABA_A$ and $GABA_C$ are ligand-gated ion channels and $GABA_B$ are G-protein coupled receptors. Molecular imaging of neuroreceptors, in particular by positron emission tomography (PET), is a powerful tool to study the pathology of brain diseases in vivo. To date, the majority of radiotracers suitable for $GABA_A$ receptor imaging are structurally related to benzodiazepines, with [^{11}C]flumazenil,[1,2] [^{18}F]flumazenil[3] and [^{18}F]fluoroethyl-flumazenil[4–8] as the most widely used tracers. However, benzodiazepine binding site ligands bind to a variety of $GABA_A$ receptor subtypes, which are characterized by a heterogeneity of expression and function. Therefore, a large number of structurally diverse compounds like pyrazolopyrimidines, imidazopyridines[9] and imidazolones[10] that act at these receptor sites as agonists,[11] inverse agonists[12] and antagonists[13] were developed (Fig. 1).

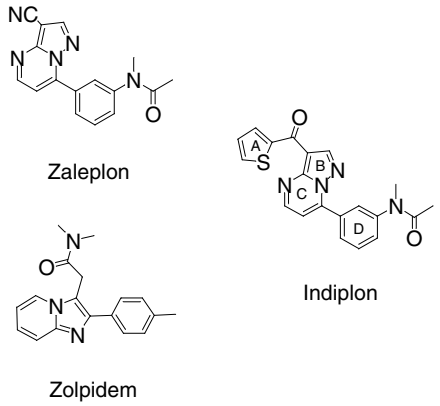

Figure 1. Selected structures of compounds with high affinity for the $GABA_A$ receptor.

Keywords: $GABA_A$; Indiplon; Fluorine-18; PET.
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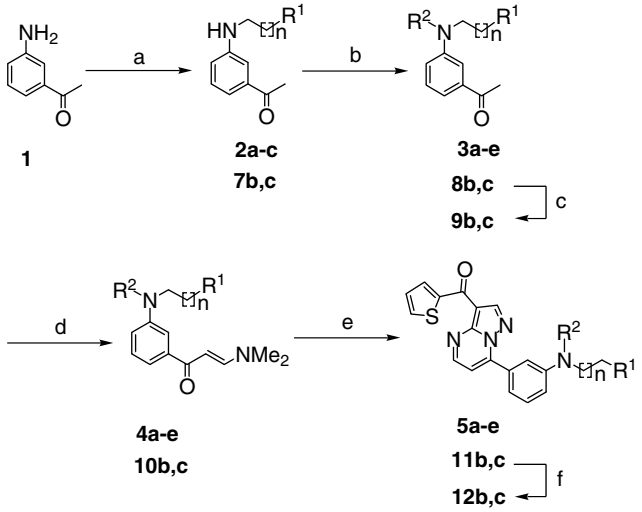
Novel 'nonbenzodiazepines' that exhibit high affinity to the $GABA_A$ receptor display a high selectivity for receptors containing the α1-subunit. Isoforms containing the α1-subunit constitute about 60% of the whole $GABA_A$ receptor population and represent an important pharmaceutical target since sedative and hypnotic effects are primarily mediated by these receptors.[14] Compounds that bind to the $GABA_A$-α1 receptor and were developed for the treatment of insomnia are the imidazopyridine Zolpidem, the cyclopyrrolone Zopiclone and the pyrazolopyrimidines Indiplon and Zaleplon. The subnanomolar binding affinity of Indiplon with K_i values of 0.55 and 0.45 nM measured at rat cerebellar and cerebral cortex membranes is a prerequisite for the development of imaging agents.[15] Therefore, we chose Indiplon as a lead structure for the development of PET-radiotracers. Due to the superior imaging properties of ^{18}F with $t_{1/2}$ = 109 min in contrast to $t_{1/2}$ = 20 min of ^{11}C we focused on the synthesis of fluorinated Indiplon derivatives.[16] Since Indiplon does not contain a fluorine atom, it has to be incorporated without altering the biological properties. Hence, we developed several fluorinated pyrazolopyrimidines as reference compounds to investigate their biological properties in terms of in vitro affinity and specificity. Furthermore, corresponding precursors for future ^{18}F-labelling have been synthesized.

2. Results and discussion

2.1. Chemical synthesis

The synthesis of the lead compound Indiplon and its demethyl derivative was performed according to literature methods.[17] With Demethylindiplon in hand, we envisioned a straightforward fluoroalkylation reaction for the preparation of various fluoroalkyl derivatives of Indiplon. However, yields of the corresponding fluoroalkyl derivatives were rather low due to the poor reactivity of the demethyl derivative, caused by the decreased nucleophilicity of the amide nitrogen. Thus, the introduction of the fluoroalkyl group had to be performed at an earlier stage of the reaction sequence (Scheme 1). 3-Aminoacetophenone (**1**) was reacted with various fluoroalkyl tosylates or halogenides to provide the fluoroalkyl acetophenones **2a**–**c** which were subsequently acylated with carboxylic acid anhydrides to yield the amides **3a**–**e**. Then the enaminones **4a**–**e** as the first key building block of the overall strategy were synthesized by reacting **3a**–**e** with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA). In analogy to the synthesis of Indiplon, the condensation of enaminones **4a**–**e** with the second key building block aminopyrazole **6**[17] yielded the respective fluoroalkyl derivatives **5a**–**e** under acidic conditions.

The synthesis of potential precursors for ^{18}F-labelling was performed in a similar manner (Scheme 1). Again, 3-aminoacetophenone (**1**) was used as a starting material. By reaction with various hydroxyalkyl halogenides, neat or in aqueous solution, the ω-hydroxyalkyl derivatives **7b**,**c** were obtained in good yields. Next, the ω-hydroxyalkyl derivatives were acylated with different acetic acid anhydrides. Since a selective monoacylation of the amino group was difficult to achieve, the *N*,*O*-bis-acyl derivatives **8b**,**c** were subjected to a mild *O*-deacylation using potassium carbonate in methanol. Compounds **9b**,**c** were then converted to the enaminones **10b**,**c** which upon reaction with the aminopyrazole **6**



	n	R^1	R^2
2a	1	F	-
2b	2	F	-
2c	3	F	-
3a - 5a	1	F	Acetyl
3b - 5b	2	F	Acetyl
3c - 5c	3	F	Acetyl
3d - 5d	2	F	Propionyl
3e - 5e	2	F	Isobutyroyl
7b	2	OH	-
7c	3	OH	-
8b	2	OAc	Acetyl
8c	3	OAc	Acetyl
9b - 11b	2	OH	Acetyl
9c - 11c	3	OH	Acetyl
12b	2	OTos	Acetyl
12c	3	OTos	Acetyl

Scheme 1. Reagents and conditions: (a) for **2a**: toluene-4-sulfonic acid 2-fluoroethyl ester, $CaCO_3$, water, reflux 3.5 h (42%); for **2b**: toluene-4-sulfonic acid 3-fluoropropyl ester, $CaCO_3$, water, reflux 3.5 h (51%); for **2c**: 1-chloro-4-fluorobutane, $CaCO_3$, water, reflux 3.5 h (13%); for **7b**: 3-bromo-1-propanol, $CaCO_3$, water, reflux 2 h (46%); for **7c**: 4-chloro-1-butanol, $CaCO_3$, water, reflux 2 h (7%); (b) for **3a**–**c**: acetic anhydride, DMAP, pyridine, 0 °C to rt 16 h (45%, 57% and 64%, resp.); for **3d**: propionic anhydride, DMAP, pyridine, 0 °C to rt 16 h (39%); for **3e**: isobutyryl chloride, DMAP, pyridine, 0 °C to rt 16 h (13%); for **8b**,**c**: acetic anhydride, DMAP, pyridine, rt 16 h (for **8b** 100%, for **8c** 97%); (c) K_2CO_3, methanol/water, rt 15 min (97%); (d) DMFDMA, reflux 16 h (for **4a** 92%, for **4b** 65%, for **4c** 81%, for **4d** 69%, for **4e** 84%, for **10b** 74% and for **10c** 71%); (e) acetic acid, **6**, 65 °C 1.5 h (for **5a** 44%, for **5b** 46%, for **5c** 47%, for **5d** 55%, for **5e** 41%, for **11b** 58% and for **11c** 56%); (f) toluene-4-sulfonic acid anhydride, pyridine, dichloromethane, 0 °C to rt 1.25 h (for **12b** 65%, for **12c** 55%).

yielded the ω-hydroxyalkyl derivatives **11b**,**c** of Indiplon. Potential labelling precursors **12b**,**c** were obtained by converting the ω-hydroxy group of these compounds into tosylate leaving groups.

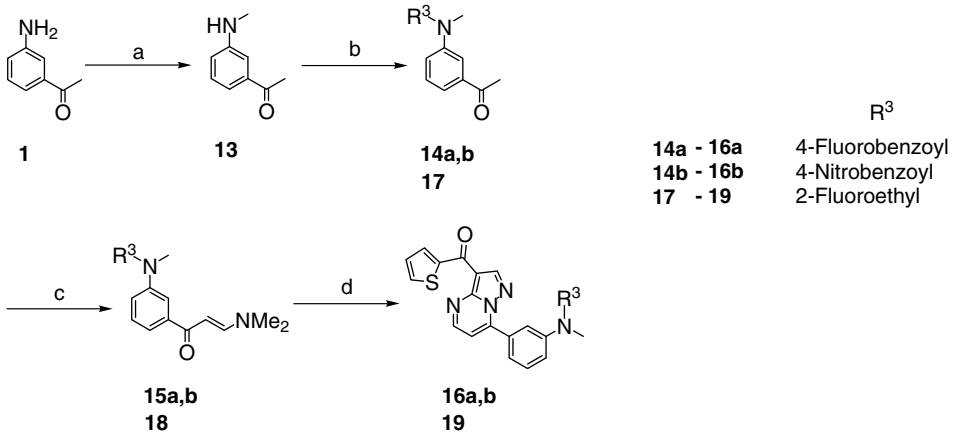
In a second approach the methyl group was maintained and the acetyl group was replaced by a 4-fluorobenzoyl group. Here we started again from 3-aminoacetophenone (**1**) which was *N*-methylated according to literature methods.[17] The methylamino acetophenone **13** was then acylated with the respective substituted benzoyl chlorides to yield the fluoro-derivative **16a** as reference and the nitro-derivative **16b** as the corresponding precursor compound (Scheme 2).

Eventually, the acetyl group in Indiplon was substituted by a fluoroethyl group. Thus, **13** was alkylated with bromofluoroethane to afford fluoroethyl aminoacetophenone **17**. Enaminone **18** was obtained by refluxing **17** in DMFDMA. Condensation with aminopyrazole **6** furnished **19** in good yields (Scheme 2).

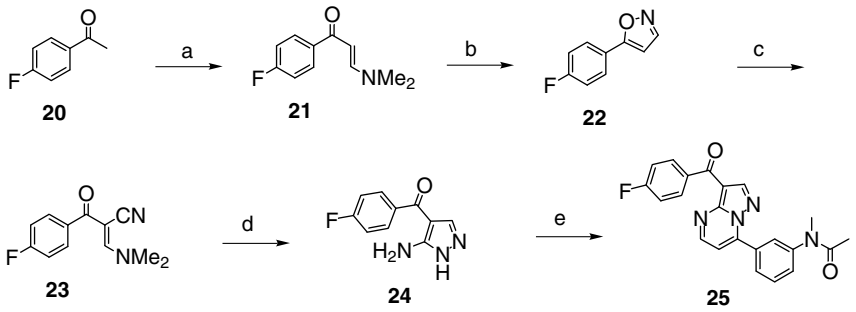
Another approach aimed at the replacement of the thiophene ring A in Indiplon by a fluorophenyl ring. Hence, the aminopyrazole building block had to be modified. Conversion of 4-fluoroacetophenone (**20**) with DMFDMA to the enaminone **21** and further to the isoxazole **22** proceeded quite smoothly. Ring opening of isoxazole **22** yielded the cyano-enaminone **23** which was converted to the benzoyl substituted aminopyrazole **24**. Aminopyrazole **24** was then condensed with compound *N*-[3-(3-dimethylamino-acryloyl)-phenyl]-*N*-methyl-acetamide to furnish the target compound **25** in good yields (Scheme 3).

2.2. In vitro binding assays

Different strategies for the synthesis of fluorinated pyrazolopyrimidines have been developed. First, we synthesized a series of fluoroalkyl derivatives of Indiplon by replacing the methyl group of the *N*-methylacetanilide part with an ω-fluorinated alkyl group. Three compounds have been tested for their binding affinity at $GABA_A$ receptor complexes (IC_{50} values are shown in Table 1). Compound **5b** has the highest affinity with an IC_{50} of 2.78 ± 0.63 nM on cerebellar $GABA_A$ receptors of the adult rat. However, differences in binding affinity between the fluoroethyl compound **5a** (IC_{50} 5.71 ± 0.95 nM) as the compound with the shortest alkyl chain and the fluorobutyl compound **5c** (IC_{50} 5.98 ± 0.98 nM) with the longest alkyl chain are rather small. The IC_{50} values for the fluoroalkyl compounds



Scheme 2. Reagents and conditions: (a) MeI, K_2CO_3, DMF; (b) for **14a**: 4-fluorobenzoyl chloride, DMF, triethylamine, rt 16 h (96%); for **14b**: 4-nitrobenzoyl chloride, DMF, triethylamine, rt 16 h (95%); for **17**: toluene-4-sulfonic acid 2-fluoroethyl ester, $CaCO_3$, water, reflux 3.5 h (41%); (c) DMFDMA, reflux, 16 h (for **15a** 80%, for **15b** 89%, and for **18** 86%); (d) acetic acid, **6**, 65 °C 1.5 h (for **16a** 78%, for **16b** 79% and for **19** 35%).



Scheme 3. Reagents and conditions: (a) DMFDMA, reflux 16 h (63%); (b) $NH_2OH \cdot HCl$, methanol, reflux 2.5 h (97%); (c) DMFDMA, reflux 16 h (60%); (d) aminoguanidine nitrate, NaOH, ethanol, reflux 4 h (62%); (e) acetic acid, *N*-[3-(3-dimethylamino-acryloyl)-phenyl]-*N*-methyl-acetamide, 65 °C 1.5 h (48%).

Table 1. Binding affinities of the newly synthesized Indiplon-derived compounds at $GABA_A$ receptors isolated from adult rat brain tissue (cerebellum) and labelled with [^{3}H]flunitrazepam (~0.3 nM)

Compound		IC_{50} (nM)
	Indiplon	3.29 ± 0.37
5a	ABX012	5.71 ± 0.95
5b	ABX016	2.78 ± 0.63
5c	ABX014	5.98 ± 0.98
5d	ABX017	5.26 ± 1.30
5e	ABX021	37.7 ± 15.4
16a	ABX006	14.1 ± 1.70
16b	ABX007	15.9 ± 7.04
19	ABX008	17.8 ± 1.75
25	ABX020	53.3 ± 18.3

The IC_{50} values were obtained from triplicates, estimated by nonlinear regression analyses, and are given as means ± SD ($n \geqslant 3$).

are in the same order of magnitude as the IC_{50} value for Indiplon (3.29 ± 0.37 nM). These excellent binding affinities make the fluoroalkyl compounds promising candidates for the development of radiotracers. Next, we investigated the influence of the alkanoic acid residue of the *N*-methylanilide in the propanamide **5d** and the isobutyramide **5e**. While the binding affinity of **5d** is comparable to that of the acetamides, it is nearly one order of magnitude lower for **5e** (IC_{50} 5.26 ± 1.3 nM and 37.7 ± 15.4 nM, respectively). Apparently, the binding affinity of the pyrazolopyrimidines is rather sensitive towards changes of the acid residue at the amide group for the fluoroalkyl compounds. On the other hand, the IC_{50} of 14.1 ± 1.7 nM for the fluorobenzamide **16a** does not show such a drastic decrease in binding affinity. This result is complemented by a similar IC_{50} value of 15.9 ± 7.0 nM obtained for the nitrobenzamide **16b**. Therefore, we assume that the overall steric bulk at the amide nitrogen contributes to the receptor binding. Another parameter affecting the receptor binding is probably the amide carbonyl. In compound **19** that lacks the carbonyl group we found a decreased binding affinity. Though this effect is not very strong, the binding affinity of **19** is decreased by a factor of about 6 in comparison to **5b** (IC_{50} 2.78 ± 0.63 nM for **5b** vs 17.8 ± 1.75 nM for **19**). We observed a very profound change in binding affinity by substituting the thiophene ring A in Indiplon with a 4-fluorophenyl ring in **25** (IC_{50} 2.78 ± 0.63 nM for **5b** vs 53.3 ± 18.3 nM for **25**). The introduction of an aromatic fluorine label is expected to be rather stable against biodegradation. Moreover, the carbonyl group in 4-position exerts an electron withdrawing effect that facilitates a nucleophilic substitution of a nitro or a trimethylammonium group by fluoride. However, the low binding affinity of this compound precludes a further development of a tracer based on this compound.

2.3. Measurement of log *D* values

A high brain uptake is important for radiotracers designed to monitor neuroreceptor distribution and density. The log *P* value gives a first estimate of the ability of a compound to cross the blood–brain barrier. Although not to be taken as an absolute criterion, log *P* values within a range of 0.9–2.5 indicate a good brain penetration of tracer compounds.[18] Therefore, we determined the log *D* values of the Indiplon-derived compounds by means of HPLC and compared these data with calculated log *P* values (ChemOffice, Table 2).[19] The log *D* values were found to be in the range between 2.2 and 2.7. Calculated log *P* values differ somewhat from the measured values, the differences are probably due to difficulties in fragmentation of these rather complex compounds and protonation at physiological pH. However, based on our experimental data we assume that our newly synthesized compounds are able to cross the blood–brain barrier in a sufficient amount.

3. Conclusion

In conclusion, we present here the synthesis of a new series of fluorinated pyrazolopyrimidines as potential PET imaging agents for $GABA_A$ receptors. Some of these compounds displayed excellent binding affinities in vitro. In addition to these fluorinated reference compounds we have synthesized suitable precursor compounds. The latter provide a basis for a straightforward ^{18}F-labelling currently under investigation in our laboratories.

Table 2. Calculated log *P* and measured log *D* values (standard deviation given in parentheses)

Compound		log *P*		log *D*	
		Calculated[a]	Calculated[b]	Measured[c]	Measured[d]
	Indiplon	2.57 (0.47)	2.68 (0.49)	2.26 (0.23)	2.23 (0.18)
5a	ABX012	2.76 (0.47)	2.84 (0.49)	2.62 (0.26)	—
5b	ABX016	2.87 (0.47)	2.90 (0.47)	2.35 (0.24)	2.38 (0.18)
5c	ABX014	3.32 (0.47)	3.35 (0.49)	2.48 (0.25)	—
5d	ABX017	3.52 (0.47)	3.52 (0.47)	—	—
5e	ABX021	4.09 (0.47)	4.09 (0.49)	2.55 (0.25)	2.68 (0.41)
16a	ABX006	4.46 (0.47)	4.46 (0.47)	2.64 (0.25)	2.63 (0.24)
16b	ABX007	—	—	2.51 (0.25)	2.64 (0.23)
19	ABX008	4.63 (0.47)	4.74 (0.49)	2.66 (0.26)	2.69 (0.25)
25	ABX020	2.75 (0.47)	2.80 (0.49)	2.34 (0.24)	2.38 (0.24)

[a] Crippen's fragmentation.[20]
[b] Viswanadhan's fragmentation.[21]
[c] HPLC method 1 (C-18 reversed phase).
[d] HPLC method 2 (alkyl amide reversed phase).

4. Experimental

4.1. Chemical synthesis

Chemicals were purchased from Sigma–Aldrich, Germany, and used without further purification. Indiplon, Demethylindiplon, (5-amino-1*H*-pyrazol-4-yl)-thiophen-2-yl-methanone (**6**), 3-*N*-methylaminoacetophenone (**13**), and *N*-[3-(3-dimethylamino-acryloyl)-phenyl]-*N*-methyl-acetamide were synthesized according to literature procedures.[17] Reactions were routinely monitored by TLC on precoated silica gel plates (ALUGRAM sheets SIL G/UV254, Macherey-Nagel, Düren). Flash chromatography was conducted on silica gel (0.040–0.063 mm, VWR International) columns. All melting points were determined in open glass capillaries using a Büchi apparatus and are uncorrected. ^{1}H NMR spectra were recorded at a Bruker AV500 Ultra Shielded spectrometer, using the hydrogenated residue of deuterated solvents as internal standards. Chemical shifts are reported in ppm, downfield from TMS (s, d, t, dd, td and br for singlet, doublet, triplet, doublet of doublets, triplet of doublets and broad, respectively). Elemental analyses were performed on a EL analyser (Elementar Analysensysteme, Germany) and were within ±0.4% of the theoretical values for C, H, and N. High-resolution mass spectra were recorded with a Bruker Daltonics 7 Tesla APEX II spectrometer.

4.2. In vitro binding assays

Adult female Sprague–Dawley rats (8–10 weeks old; University of Leipzig) were used. Animal care and handling through experimental procedures were in accordance with the national regulations for animal research. Rats were anaesthetised and sacrificed by decapitation, their brains were rapidly dissected on ice, and the cerebella were collected in 30 volumes of ice-cold 50 mM Tris–HCl, pH 7.4, at 4 °C, homogenised with a glass–Teflon Potter (1000 rpm), and the crude membrane fraction was collected by centrifugation at 20,000*g* at 4 °C for 15 min. The resulting pellet was washed two times by resuspending in the same volume of fresh buffer and recentrifugation, and stored at 0.1 g wet weight/mL fresh buffer at −25 °C until the day of the assay. For homogenate binding assays, the frozen membranes were thawed, recentrifuged, washed another two times according to the described protocol, and resuspended at ∼0.05 g wet weight/mL 50 mM Tris–HCl, pH 7.4, at 21 °C (incubation buffer). [^{3}H]Flunitrazepam binding was measured in a final volume of 1 mL, consisting of 100 μL membrane suspension (∼5 mg wet weight = ∼100 μg protein), 100 μl *N*-methyl-[^{3}H]flunitrazepam (specific activity 3600 GBq/mmol; Amersham, GE Healthcare; final concentration in the assay ∼0.3 nM), 100 μL of drug solution and incubation buffer. Solutions of the test drugs were prepared by diluting a 10 mM DMSO-stock with incubation buffer, and non-specific binding of [^{3}H]flunitrazepam was determined in the presence of 10 μM Zolpidem (TOCRIS; 100 μM stock in incubation buffer). Specific binding of the radioligand (about 85%) was calculated by subtracting the nonspecific from the total binding (about 5% of the total radioactivity). The incubation started with the application of the membrane solution and was performed at 21 °C for 60 min. The incubation was terminated by rapid filtration through glass–fibre filters (GF/B, Whatman; presoaked in 0.3% polythyleneimine solution at 4 °C for 90 min) on a cell harvester manifold (Brandel). The filters were washed four times with ice-cold 50 mM Tris–HCl, pH 7.4, at 4 °C, and filter-bound radioactivity was measured by liquid scintillation spectrometry.

The concentration of the test compounds that inhibited [^{3}H]flunitrazepam binding by 50%, IC_{50}, was determined by nonlinear regression analyses with 10–12 concentrations of the compound, each in triplicate. Each compound was assayed in at least three independent experiments and the respective IC_{50} values were given as means ± standard deviation (SD).

4.3. Measurement of log *D* values

log *D* values were determined with HPLC methods and were performed according to the European guideline.[22] HPLC system: Agilent Hewlett Packard 1100 with a binary pump, auto sampler, variable wavelength UV detector (228, 344; 220, 254 nm). Column for method 1: Multisorb RP18-7 column (250 × 4 mm, 7 μm, CS Chromatography Service, Germany); for method 2: Supelcosil™ ABZ$^+$Plus (250 × 4 mm, 5 μm, Sigma–Aldrich, Germany). Mobile phase: Solvent A: 5% acetonitrile + 20 mM ammonium acetate; solvent B: 80% acetonitrile + 20 mM ammonium acetate. Gradient 1: 0–5 min (solvent A), 5–40 min (solvent B); Gradient 2: 0–5 min (solvent A), 5–50 min (solvent B), Gradient 3: 0–5 min (solvent A), 5–65 min (solvent B); flow rate 1 mL/min. The sample (2–20 μg/mL) was injected in a volume of 1–5 μL of solvent C (25% acetonitrile + 20 mM ammonium acetate). All runs were done in triplicate. A good reproducibility was obtained ($\Delta t_R < 0.07$ min). Before running test samples, the system was validated by running standard samples. The following standard compounds were used for referencing[23,24]: acetophenone (log *P* = 1.7–1.6), aniline (0.9), anisole (2.11), benzene (2.13), benzonitrile (1.56), benzyl alcohol (1.1), benzyl chloride (2.13), indole (2.14), nitrobenzene (1.9), 2-nitrophenol (1.79) and toluene (2.73) either as single standard or mixture of three (1: aniline, nitrobenzene, toluene; 2: anisole, benzyl chloride, toluene; 3: benzyl alcohol, indole, toluene). Analysis was performed by determination of capacity factors k' and linear regression of log k'/log *P*. Linear regression with $n = 32$ (number of runs) showed $R < 0.94667$ with $p < 0.0001$ independent from the method and gradient.

4.4. General procedure for the synthesis of the fluoroalkyl acetophenones (2a–c)

3-Aminoacetophenone (**1**) (3.95 g, 29.2 mmol) and calcium carbonate (1.32 g, 13.2 mmol) were suspended in water (100 mL) in an ultrasonic bath. The alkylating agent (26.3 mmol, toluene-4-sulfonic acid 2-fluoroethyl ester for **2a**, toluene-4-sulfonic acid 3-fluoropropyl ester for **2b** and 1-chloro-4-fluorobutane for **2c**) was added, and the mixture was heated under reflux for 3.5 h. After

cooling to room temperature, aqueous (aq) 10% potassium carbonate (50 mL) was added. The mixture was extracted with dichloromethane (3× 100 mL). The combined organic phases were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography.

4.4.1. 1-[3-(2-Fluoroethylamino)-phenyl]-ethanone (2a). Yield: 42%, yellow oil, R_f (ethyl acetate/dichloromethane 1:25) = 0.41. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.34–7.26 (m, 2H, H_{AR}), 7.23 (m, 1H, H_{AR}), 6.87–6.83 (m, 1H, H_{AR}), 4.65 (td, 2H, J = 4.7 Hz, J_{2F} = 47.2 Hz, CH_2F), 3.51 (td, 2H, J = 4.9 Hz, J_{2F} = 26.7 Hz, NCH_2), 2.58 (s, 3H, CH_3).

4.4.2. 1-[3-(3-Fluoropropylamino)-phenyl]-ethanone (2b). Yield: 51%, yellow oil, R_f (dichloromethane) = 0.36. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.30–7.24 (m, 2H, H_{AR}), 7.20 (m, 1H, H_{AR}), 6.83–6.80 (m, 1H, H_{AR}), 4.60 (td, 2H, J = 5.6 Hz, J_{2F} = 47.2 Hz, CH_2F), 3.37 (t, 2H, J = 6.7 Hz, NCH_2), 2.58 (s, 3H, CH_3), 2.09–1.97 (m, 2H, CH_2).

4.4.3. 1-[3-(4-Fluorobutylamino)-phenyl]-ethanone (2c). Yield: 13%, yellow oil, R_f (ethyl acetate/dichloromethane 1:25) = 0.33. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.32–7.22 (m, 2H, H_{AR}), 7.29 (m, 1H, H_{AR}), 6.82–6.78 (m, 1H, H_{AR}), 4.51 (td, 2H, J = 5.8 Hz, J_{2F} = 47.3 Hz, CH_2F), 3.24 (t, 2H, J = 6.9 Hz, NCH_2), 2.58 (s, 3H, CH_3), 1.89–1.74 (m, 4H, CH_2).

4.5. General procedure for the synthesis of the fluoroalkyl acetophenones (3a–e)

A solution of **2a**–**c** (14.8 mmol) and DMAP (183 mg, 1.5 mmol) in dry pyridine (75 mL) was cooled in an ice bath and the acylating agent was added (22.2 mmol, acetic anhydride for **3a**–**c**, propionic anhydride for **3d**, isobutyryl chloride for **3e**). After complete addition, the ice bath was removed and the mixture was stirred for 16 h at room temperature. The mixture was poured onto ice/water and was adjusted to pH 1 with hydrochloric acid and extracted with dichloromethane. The combined organic phases were washed with aq sodium bicarbonate solution, dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (dichloromethane/ethyl acetate 5:1).

4.5.1. *N*-(3-Acetyl-phenyl)-*N*-(2-fluoroethyl)-acetamide (3a). Yield: 45%, yellow oil, R_f (dichloromethane/ethyl acetate 10:1) = 0.21. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.95 (m, 1H, H_{AR}), 7.84 (m, 1H, H_{AR}), 7.55 (m, 1H, H_{AR}), 7.47 (m, 1H, H_{AR}), 4.64 (td, 2H, J = 4.8 Hz, J_{2F} = 47.4 Hz, CH_2F), 4.00 (t, 2H, J = 4.8 Hz, J_{3F} = 26.3 Hz, NCH_2), 2.63 (s, 3H, CH_3), 1.89 (br s, 3H, CH_3).

4.5.2. *N*-(3-Acetyl-phenyl)-*N*-(3-fluoropropyl)-acetamide (3b). Yield: 57%, yellow oil, R_f (dichloromethane/ethyl acetate 5:1) = 0.31. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.94 (m, 1H, H_{AR}), 7.79 (m, 1H, H_{AR}), 7.56 (m, 1H, H_{AR}), 7.40 (m, 1H, H_{AR}), 4.50 (td, 2H, J = 5.8 Hz, J_{2F} = 47.1 Hz, CH_2F), 3.87 (t, 2H, J = 7.3 Hz, NCH_2), 2.64 (s, 3H, CH_3), 2.03–1.91 (m, 2H, CH_2), 1.85 (br s, 3H, CH_3).

4.5.3. *N*-(3-Acetyl-phenyl)-*N*-(4-fluorobutyl)-acetamide (3c). Yield: 64%, yellow oil, R_f (dichloromethane/ethyl acetate 5:1) = 0.24. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.94 (m, 1H, H_{AR}), 7.77 (m, 1H, H_{AR}), 7.56 (m, 1H, H_{AR}), 7.39 (m, 1H, H_{AR}), 4.45 (td, 2H, J = 5.8 Hz, J_{2F} = 47.0 Hz, CH_2F), 3.78 (t, 2H, J = 7.3 Hz, NCH_2), 2.65 (s, 3H, CH_3), 1.85 (br s, 3H, CH_3), 1.78–1.61 (m, 4H, CH_2).

4.5.4. *N*-(3-Acetyl-phenyl)-*N*-(3-fluoropropyl)-propionamide (3d). Yield: 39%, yellow oil, R_f (dichloromethane/ethyl acetate 5:1) = 0.42. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.94 (m, 1H, H_{AR}), 7.78 (m, 1H, H_{AR}), 7.56 (m, 1H, H_{AR}), 7.39 (m, 1H, H_{AR}), 4.51 (td, 2H, J = 5.8 Hz, J_{2F} = 47.0 Hz, CH_2F), 3.87 (t, 2H, J = 7.3 Hz, NCH_2), 2.65 (s, 3H, CH_3), 2.10–1.92 (m, 4H, CH_2), 1.06 (t, J = 7.3 Hz, 3H, CH_3).

4.5.5. *N*-(3-Acetyl-phenyl)-*N*-(3-fluoropropyl)-isobutyramide (3e). Yield: 94%, yellow oil, R_f (dichloromethane/ethyl acetate 5:1) = 0.44. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.95 (m, 1H, H_{AR}), 7.79 (m, 1H, H_{AR}), 7.56 (m, 1H, H_{AR}), 7.40 (m, 1H, H_{AR}), 4.51 (td, 2H, J = 5.9 Hz, J_{2F} = 47.2 Hz, CH_2F), 3.84 (t, 2H, J = 7.3 Hz, NCH_2), 2.64 (s, 3H, CH_3), 2.44–2.34 (m, 1H, CH), 2.03–1.91 (m, 2H, CH_2), 1.03 (d, 6H, CH_3).

4.6. General procedure for the synthesis of the enaminones (4a–e)

A solution of **3a**–**e** (8.5 mmol) in *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA, 30 mL) was heated at 120 °C overnight. After evaporation of the solvent, the residue was purified by flash chromatography (ethyl acetate/methanol 9:1).

4.6.1. *N*-[3-(3-Dimethylamino-acryloyl)-phenyl]-*N*-(2-fluoroethyl)-acetamide (4a). Yield: 92%, yellow solid, mp 89.6–90.4 °C, R_f (ethyl acetate/methanol 9:1) = 0.27. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.90–7.82 (m, 2H, H_{AR}), 7.76 (br s, 1H, H_{AR}), 7.47 (t, 1H, J = 7.8 Hz, H_{AR}), 7.33 (m, 1H, H_{AR}), 5.67 (d, 1H, J = 12.3 Hz, CH), 4.62 (td, 2H, J = 4.9 Hz, J_{2F} = 47.4 Hz, CH_2F), 4.01 (td, 2H, J = 5.0 Hz, J_{3F} = 25.6 Hz, CH_2F), 3.18 (br s, 3H, NCH_3), 2.96 (br s, 3H, NCH_3), 1.89 (s, 3H, CH_3).

4.6.2. *N*-[3-(3-Dimethylamino-acryloyl)-phenyl]-*N*-(3-fluoropropyl)-acetamide (4b). Yield: 65%, yellow solid, mp 119–120 °C, R_f (ethyl acetate/methanol 9:1) = 0.37. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.90–7.82 (m, 2H, H_{AR}), 7.72 (br s, 1H, H_{AR}), 7.47 (t, 1H, J = 7.8 Hz, H_{AR}), 7.26 (m, 1H, H_{AR}), 5.67 (d, 1H, J = 12.3 Hz, CH), 4.50 (td, 2H, J = 5.9 Hz, J_{2F} = 47.2 Hz, CH_2F), 3.86 (m, 2H, NCH_2), 3.19 (br s, 3H, NCH_3), 2.96 (br s, 3H, NCH_3), 2.03–1.91 (m, 2H, CH_2), 1.86 (s, 3H, CH_3). HRMS *m*/*z* calculated for $C_{16}H_{22}FN_2O_2$ (M+H) 293.1660, found 293.1661.

4.6.3. *N*-[3-(3-Dimethylamino-acryloyl)-phenyl]-*N*-(4-fluorobutyl)-acetamide (4c). Yield: 81%, yellow oil, R_f (ethyl acetate/methanol 9:1) = 0.25. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.89–7.83 (m, 2H, H_{AR}), 7.70 (br s, 1H, H_{AR}), 7.47 (t, 1H, J = 7.8 Hz, H_{AR}), 7.24 (m, 1H, H_{AR}), 5.68 (d, 1H, J = 12.3 Hz, CH), 4.43 (td, 2H, J = 5.8 Hz, J_{2F} = 47.1 Hz, CH_2F), 3.77 (m, 2H, NCH_2), 3.18 (br s, 3H, NCH_3), 2.96 (br s, 3H, NCH_3), 1.84 (s, 3H, CH_3), 1.77–1.60 (m, 4H, CH_2). HRMS *m*/*z* calculated for $C_{17}H_{24}FN_2O_2$ (M+H) 307.1816, found 307.1818.

4.6.4. *N*-[3-(3-Dimethylamino-acryloyl)-phenyl]-*N*-(3-fluoropropyl)-propionamide (4d). Yield: 69%, yellow solid, mp 95.3–96.0 °C, R_f (ethyl acetate/methanol 9:1) = 0.46. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.89–7.82 (m, 2 H, H_{AR}), 7.70 (br s, 1H, H_{AR}), 7.47 (t, 1H, J = 7.8 Hz, H_{AR}), 7.25 (m, 1H, H_{AR}), 5.67 (d, 1H, J = 12.3 Hz, CH), 4.50 (td, 2H, J = 5.9 Hz, J_{2F} = 47.2 Hz, CH_2F), 3.86 (m, 2H, NCH_2), 3.19 (br s, 3H, NCH_3), 2.96 (br s, 3H, NCH_3), 2.07–1.92 (m, 4H, CH_2), 1.04 (t, 3H, J = 7.4 Hz, CH_3). HRMS *m*/*z* calculated for $C_{17}H_{24}FN_2O_2$ (M+H) 307.1816, found 307.1818.

4.6.5. *N*-[3-(3-Dimethylamino-acryloyl)-phenyl]-*N*-(3-fluoropropyl)-isobutyramide (4e). Yield: 84%, yellow solid, mp 102.4–106.1 °C, R_f (ethyl acetate/methanol 9:1) = 0.48. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.89–7.84 (m, 2H, H_{AR}), 7.71 (br s, 1H, H_{AR}), 7.47 (t, 1H, J = 7.8 Hz, H_{AR}), 7.26 (m, 1H, H_{AR}), 5.68 (d, 1H, J = 12.3 Hz, CH), 4.50 (td, 2H, J = 5.9 Hz, J_{2F} = 47.1 Hz, CH_2F), 3.84 (m, 2H, NCH_2), 3.19 (br s, 3H, NCH_3), 2.97 (br s, 3H, NCH_3), 2.46 (m, 1H, CH), 2.04-1.92 (m, 2H, CH_2), 1.03(d, 6H, J = 6.7 Hz, CH_3). HRMS *m*/*z* calculated for $C_{18}H_{25}FN_2O_2$ (M+H) 321.1973, found 321.1972.

4.7. General procedure for the synthesis of the fluoroalkyl pyrazolopyrimidines (5a–e)

A suspension of **4a**–**e** (2.74 mmol) and (5-amino-1*H*-pyrazol-4-yl)-thiophen-2-yl-methanone (**6**) (2.74 mmol) in acetic acid (20 mL) was heated to 65 °C for 1.5 h. After cooling to room temperature the mixture was poured onto ice/water and adjusted to pH 8 with sodium bicarbonate before extraction with dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography.

4.7.1. *N*-(2-Fluoroethyl)-*N*-[3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-*a*]pyrimidin-7-yl]-phenyl]-acetamide (5a). Yield: 44%, yellow solid, mp 179–180 °C, R_f (ethyl acetate/dichloromethane/methanol 10:10:1) = 0.39. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.84 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 8.72 (s, 1H, H_{AR}), 8.1 (m, 1H, H_{AR}), 8.03 (m, 2H, H_{AR}), 7.73–7.66 (m, 2H, H_{AR}), 7.52 (m, 1H, H_{AR}), 7.21 (m, 1H, H_{AR}), 7.16 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 4.69 (td, 2H, J_{2F} = 47 Hz, J_{3H} = 4.7 Hz, CH_2F), 4.05 (td, 1H, J_{3F} = 26 Hz, J_{3H} = 4.8 Hz, N–CH_2), 2.02 (s, 3H, CH_3). ^{19}F NMR ($CDCl_3$, 470 MHz): δ = −222.24 ppm. Calculated C: 61.75, H: 4.20, N: 13.72, found C: 61.45, H: 4.04, N: 13.50.

4.7.2. *N*-(3-Fluoropropyl)-*N*-[3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-*a*]pyrimidin-7-yl]-phenyl]-acetamide (5b). Yield: 46%, yellow solid, mp 194–195 °C, R_f (ethyl acetate) = 0.30. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.84 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 8.72 (s, 1H, H_{AR}), 8.1 (m, 1H, H_{AR}), 8.00 (m, 2H, H_{AR}), 7.73–7.67 (m, 2H, H_{AR}), 7.47 (m, 1H, H_{AR}), 7.21 (m, 1H, H_{AR}), 7.17 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 4.53 (dt, 2H, J_{2F} = 47 Hz, J_{3H} = 5.8 Hz, CH_2F), 3.92 (t, 2H, J_{3H} = 7.3 Hz, N–CH_2), 2.09–1.95 (m, 5H, CH_2 and CH_3). ^{19}F NMR ($CDCl_3$, 470 MHz): δ = −219.99 ppm. Calculated C: 62.54, H: 4.53, N: 13.26, found C: 62.36, H: 4.52, N: 13.14.

4.7.3. *N*-(4-Fluorobutyl)-*N*-[3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-*a*]pyrimidin-7-yl]-phenyl]-acetamide (5c). Yield: 47%, yellow solid, mp 151–152 °C, R_f (ethyl acetate) = 0.26. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.87 (d, 1H, J_{3H} = 4.3 Hz, H_{AR}), 8.73 (s, 1H, H_{AR}), 8.11 (m, 1H, H_{AR}), 8.03–7.99 (m, 2H, H_{AR}), 7.73–7.66 (m, 2H, H_{AR}), 7.45 (m, 1H, H_{AR}), 7.23 (m, 1H, H_{AR}), 7.18 (d, 1H, J_{3H} = 4.3 Hz, H_{AR}), 4.47 (dt, 2H, J_{2F} = 41.5 Hz, J_{3H} = 5.7 Hz, CH_2F), 3.84 (t, 2H, J_{3H} = 7.1 Hz, N–CH_2), 1.97 (s, 3H, CH_3) 1.81–1.68 (m, 4H, CH_2). ^{19}F NMR ($CDCl_3$, 470 MHz): δ = −218.57 ppm. Calculated C: 63.29, H: 4.85, N: 12.84, found C: 63.16, H: 4.91, N: 12.67.

4.7.4. *N*-(3-Fluoropropyl)-*N*-[3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-*a*]pyrimidin-7-yl]-phenyl]-propionamide (5d). Yield: 55%, yellow solid, mp 171.0–171.8 °C, R_f (ethyl acetate/dichloromethane 1:1) = 0.50. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.85 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 8.73 (s, 1H, H_{AR}), 8.11 (m, 1H, H_{AR}), 8.04–7.97 (m, 2H, H_{AR}), 7.73–7.67 (m, 2H, H_{AR}), 7.45 (m, 1H, H_{AR}), 7.22 (m, 1H, H_{AR}), 7.17 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 4.54 (td, 2H, J_{2F} = 47.1 Hz, J_{3H} = 5.8 Hz, CH_2F), 3.92 (t, 2H, J_{3H} = 7.1Hz, N–CH_2), 2.18 (m, 2H, CH_2), 2.14 (m, 2H, CH_2) 1.11 (m, 3H, CH_3). ^{19}F NMR ($CDCl_3$, 470 MHz): δ = −219.89 ppm. Calculated C: 63.29, H: 4.85, N: 12.84, found C: 63.02, H: 4.88, N: 12.66.

4.7.5. *N*-(3-Fluoropropyl)-*N*-[3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-*a*]pyrimidin-7-yl]-phenyl]-isobutyramide (5e). Yield: 41%, yellow solid, mp 155.4–157.0 °C, R_f (ethyl acetate/dichloromethane 1:2) = 0.41. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.86 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 8.72 (s, 1H, H_{AR}), 8.11 (m, 1H, H_{AR}), 8.05–7.97 (m, 2H, H_{AR}), 7.74–7.68 (m, 2H, H_{AR}), 7.46 (m, 1H, H_{AR}), 7.23 (m, 1H, H_{AR}), 7.17 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 4.55 (td, 2H, J_{2F} = 47.2 Hz, J_{3H} = 5.8 Hz, CH_2F), 3.90 (t, 2 H, J_{3H} = 7.2 Hz, N–CH_2), 2.59 (m, 1H, CH), 2.10–1.98 (m, 2H, CH_2), 1.10 (d, 6H, J_{3H} = 6.6 Hz, CH_3). ^{19}F NMR ($CDCl_3$, 470 MHz): δ = −219.70 ppm. Calculated C: 63.98, H: 5.15, N: 12.44, found C: 63.88, H: 5.81, N: 12.31.

4.8. General procedure for the synthesis of the alcohols (7b,c)

3-Aminoacetophenone (**1**) (24.33 g, 180 mmol) and calcium carbonate (8.1 g, 81 mmol) were suspended in

water (300 mL) in an ultrasonic bath under inert gas atmosphere. The alkylating agent (162 mmol, 3-bromo-1-propanol for **7b**, 4-chloro-1-butanol for **7c**) was added and the mixture was heated under reflux for 2 h. After cooling to room temperature 10% aq potassium carbonate (250 mL) was added before extraction with dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography.

4.8.1. 1-[3-(3-Hydroxy-propylamino)-phenyl]-ethanone (7b). Yield: 46%, yellow oil, R_f (ethyl acetate/dichloromethane/triethylamine 50:50:1) = 0.25. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.30–7.20 (m, 3H, H_{AR}), 6.83 (m, 1H, H_{AR}), 3.83 (t, J = 5.9 Hz, 2H, CH_2), 3.33 (t, J = 6.5 Hz, 2H, CH_2), 2.57 (s, 3H, CH_3), 1.91 (m, 2H, CH_2).

4.8.2. 1-[3-(4-Hydroxy-butylamino)-phenyl]-ethanone (7c). Yield: 7.4%, yellow oil, R_f (ethyl acetate) = 0.38. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.29–7.18 (m, 3H, H_{AR}), 6.80 (m, 1H, H_{AR}), 3.72 (m, 2H, CH_2), 3.21 (m, 2H, CH_2), 2.57 (s, 3H, CH_3), 1.78–1.66 (m, 4H, CH_2).

4.9. General procedure for the synthesis of the acetamides (8b,c)

To a solution of **7b**,**c** (41.4 mmol) and DMAP (1.01 g, 8.3 mmol) in dry pyridine (40 mL), acetic anhydride (12.8 g; 11.8 mL, 124 mmol) was added dropwise and the mixture was stirred at room temperature for 16 h. The mixture was added to ice/water and adjusted to pH 1–2 with 3 N HCl before extraction with dichloromethane. The combined organic phases were washed with 1 N HCl, saturated aq sodium bicarbonate and brine. The solution was dried over sodium sulfate, the solvent was evaporated and the product was dried in vacuum.

4.9.1. Acetic acid 3-[acetyl-(3-acetyl-phenyl)-amino]-propyl ester (8b). Yield: 100%, yellow oil, R_f (ethyl acetate/dichloromethane 1:1) = 0.33. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.95 (m, 1H, H_{AR}), 7.79 (m, 1H, H_{AR}), 7.55 (m, 1H, H_{AR}), 7.40 (m, 1H, H_{AR}), 4.10 (t, J = 6.5 Hz, 2H, CH_2), 3.82 (m, 2H, CH_2), 2.64 (s, 3H, CH_3), 2.01 (s, 3H, CH_3), 1.90–1.83 (m, 5H, $CH_{2/3}$).

4.9.2. Acetic acid 3-[acetyl-(3-acetyl-phenyl)-amino]-butyl ester (8c). Yield: 96%, yellow oil, R_f (ethyl acetate) = 0.44. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.94 (m, 2H, H_{AR}), 7.77 (m,1H, H_{AR}), 7.56 (m, 1H, H_{AR}), 7.38 (m, 1H, H_{AR}), 4.04 (m, 2H, CH_2), 3.75 (m, 2H, CH_2), 2.64 (s, 3H, CH_3), 2.02 (s, 3H, CH_3), 1.84 (br s, 3H, CH_3), 1.68–1.53 (m, 4H, CH_2).

4.10. General procedure for the synthesis of the alcohols (9b,c) (Deacetylation)

To a solution of **8b**,**c** (42 mmol) in methanol (100 mL), an aq 4 M potassium carbonate solution was added. The mixture was stirred for 15 min at room temperature and adjusted to pH 8 by adding saturated aq ammonium chloride before extracting with dichloromethane. The combined organic phases were dried over sodium sulfate, the solvent was evaporated and the product was dried in vacuum.

4.10.1. *N*-(3-Acetyl-phenyl)-*N*-(3-hydroxy-propyl)-acetamide (9b). Yield: 97%, white solid, mp 51.4-53.2 °C, R_f (ethyl acetate) = 0.16. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.96 (m, 1H, H_{AR}), 7.77 (m, 1H, H_{AR}), 7.57 (m, 1H, H_{AR}), 7.37 (m, 1H, H_{AR}), 3.90 (m, 2 H, CH_2), 3.69–3.64 (m, 3H, CH_2,OH), 2.64 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 1.67 (m, 2H, CH_2).

4.10.2. *N*-(3-Acetyl-phenyl)-*N*-(4-hydroxy-butyl)-acetamide (9c). Yield: 97%, yellow oil, R_f (ethyl acetate) = 0.13. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.94 (m, 2H, H_{AR}), 7.77 (m,1H, H_{AR}), 7.55 (m, 1H, H_{AR}), 7.39 (m, 1H, H_{AR}), 3.77 (m, 2H, CH_2), 3.66 (m, 2H, CH_2), 2.64 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.65–1.55 (m, 4H, CH_2).

4.11. General procedure for the synthesis of the enaminones (10b,c)

A solution of **9b**,**c** (41 mmol) in DMFDMA (70 mL) was heated at 120 °C overnight. After evaporation of the solvent, the residue was purified by flash chromatography (ethyl acetate/methanol 9:1–8:2).

4.11.1. *N*-[3-(3-Dimethylamino-acryloyl)-phenyl]-*N*-(3-hydroxy-propyl)-acetamide (10b). Yield: 74%, yellow solid, mp 143.4–144.7 °C, R_f (ethyl acetate/methanol 9:1) = 0.16. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.90–7.83 (m, 2H, H_{AR}), 7.70 (m, 1H, H_{AR}), 7.48 (m, 1H, H_{AR}), 7.22 (m, 1H, H_{AR}), 5.67 (d, 1H, J_{3H} = 12.2 Hz, CH), 3.92-3.73 (m, 3H, CH_2, OH), 3.67 (m, 2H, CH_2), 3.19 (br s, 3H, NCH_3), 2.96 (br s, 3H, NCH_3), 1.89 (s, 3H, CH_3), 1.67 (m, 2H, CH_2).

4.11.2. *N*-[3-(3-Dimethylamino-acryloyl)-phenyl]-*N*-(4-hydroxy-butyl)-acetamide (10c). Yield: 71%, yellow oil, R_f (ethyl acetate/methanol 9:1) = 0.12. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.86 (m, 2H, H_{AR}), 7.71 (m,1H, H_{AR}), 7.46 (m, 1H, H_{AR}), 7.25 (m, 1H, H_{AR}), 5.68 (d, 1H, J_{3H} = 12.3 Hz, H_{AR}), 3.77 (m, 2H, CH_2), 3.65 (m, 2H, CH_2), 3.19 (br s, 3H, NCH_3), 2.96 (br s, 3H, NCH_3), 1.96 (m, 3H, CH_3), 1.73–1.58 (m, 4H, CH_2).

4.12. General procedure for the synthesis of the ω-hydroxyalkyl derivatives of Indiplon (11b,c)

A suspension of **10b**,**c** (8.5 mmol) and (5-amino-1*H*-pyrazol-4-yl)-thiophen-2-yl-methanone (**6**) 1.65 g (8.5 mmol) in acetic acid (50 mL) was heated to 65 °C for 1.5 h. After cooling to room temperature the mixture was poured onto ice/water and adjusted to pH 8 with sodium bicarbonate before extraction with dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography.

4.12.1. *N*-(3-Hydroxy-propyl)-*N*-[3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-*a*]-pyrimidin-7-yl]-phenyl]-acetamide (11b). Yield: 58%, yellow solid, mp 210–211 °C, R_f (ethyl acetate/methanol 9:1) = 0.32. ^{1}H NMR ($CDCl_3$,

500 MHz): δ = 8.85 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 8.73 (s, 1H, H_{AR}), 8.1 (m, 1H, H_{AR}), 8.00 (m, 2H, H_{AR}), 7.74–7.68 (m, 2H, H_{AR}), 7.44 (m, 1H, H_{AR}), 7.22 (m, 1H, H_{AR}), 7.17 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 3.96 (t, 2H, J_{3H} = 6.2 Hz, CH_2), 3.73–3.59 (m, 3H, CH_2, OH), 2.01 (s, 3H, CH_3), 1.75 (m, 2H, CH_2). HRMS *m*/*z* calculated for $C_{22}H_{20}N_4O_3S$ (M+H) 421.1329, found 421.1335.

4.12.2. *N*-(4-Hydroxy-butyl)-*N*-[3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-*a*]-pyrimidin-7-yl]-phenyl]-acetamide (11c). Yield: 56%, yellow solid, mp 178–180 °C, R_f (ethyl acetate/methanol 9:1) = 0.29. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.85 (d, 1H, J_{3H} = 4.3 Hz, H_{AR}), 8.73 (s, 1H, H_{AR}), 8.10 (m, 1H, H_{AR}), 8.03–7.97 (m, 2 H, H_{AR}), 7.74–7.67 (m, 2H, H_{AR}), 7.45 (m, 1H, H_{AR}), 7.22 (m, 1H, H_{AR}), 7.18 (d, 1H, J_{3H} = 4.3 Hz, H_{AR}), 3.84 (t, 2H, J_{3H} = 7.3 Hz, CH_2), 3.69 (m, 2H, CH_2), 1.85 (m, 3H, CH_3), 1.65–1.54 (m, 4H, CH_2). HRMS *m*/*z* calculated for $C_{23}H_{22}N_4O_3S$ (M+H) 435.1485, found 435.1486.

4.13. General procedure for the synthesis of the ω-tosyloxy precursors (12b,c)

A solution of **11b**,**c** (2.4 mmol) and pyridine (0.57 mL, 7.1 mmol) in dry dichloromethane (100 mL) was cooled in an ice bath under argon atmosphere. Toluene-4-sulfonic acid anhydride (1.0 g, 3.1 mmol) was added and stirring was continued for 30 min. The cooling bath was removed and stirring was continued for 45 min. The mixture was successively washed with 1 N hydrochloric acid, aq sodium bicarbonate and brine. The organic phase was dried over sodium sulfate and concentrated (bath temperature <30 °C). The residue was purified by flash chromatography (ethyl acetate). After evaporation of the solvent the product was washed with diethyl ether and pentane, and dried in vacuum. Compounds **12b**,**c** are sensitive to heat, handle below 25 °C and store at −20 °C.

4.13.1. Toluene-4-sulfonic acid 3-(acetyl-[3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-*a*]-pyrimidin-7-yl]-phenyl]-amino)-propyl ester (12b). Yield: 65%, yellow solid, mp 123–127 °C (dec.) R_f (ethyl acetate) = 0.26. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.86 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 8.73 (s, 1H, H_{AR}), 8.12 (m, 1H, H_{AR}), 8.06–7.96 (m, 2 H, H_{AR}), 7.76–7.66 (m, 4H, H_{AR}), 7.42 (m, 1H, H_{AR}), 7.32 (d, 1H, 1H, J_{3H} = 8.1 Hz, H_{AR}), 7.22 (m, 2H, H_{AR}), 4.11 (t, 2H, J_{3H} = 6.3 Hz, CH_2), 3.83 (m, 2H, CH_2), 2.43 (s, 3H, CH_3), 2.05–1.92 (m, 5H, CH_2, CH_3). Calculated C: 60.61, H: 4.56, N: 9.75, found C: 60.28, H: 4.56, N: 9.74.

4.13.2. Toluene-4-sulfonic acid 4-(acetyl-[3-[3-(thiophene-2-carbonyl)-pyrazolo[1,5-*a*]-pyrimidin-7-yl]-phenyl]-amino)-butyl ester (12c). Yield: 55%, yellow solid, mp 83–85 °C (dec.), R_f (ethyl acetate) = 0.28. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.86 (d, 1H, J_{3H} = 4.4 Hz, H_{AR}), 8.74 (s, 1H, H_{AR}), 8.12 (m, 1H, H_{AR}), 8.04–7.95 (m, 2 H, H_{AR}), 7.76–7.67 (m, 4H, H_{AR}), 7.42 (m, 1H, H_{AR}), 7.31 (d, 1H, 1H, J_{3H} = 8.1 Hz H_{AR}), 7.22 (m, 2H, H_{AR}), 4.04 (t, 2H, J_{3H} = 5.9 Hz, CH_2), 3.78 (t, 2H, J_{3H} = 6.9 Hz, CH_2), 2.43 (s, 3H, CH_3), 1.95 (m, 3H, CH_3), 1.76–1.61 (m, 4H, CH_2). Calculated C: 61.21, H: 4.79, N: 9.52, found C: 60.52, H: 4.82, N: 9.29.

4.14. General procedure for the synthesis of the benzamides (14a,b)

To a solution of 3-*N*-methylaminoacetophenone (**13**) (13.4 mmol) in DMF (50 mL), the appropriate benzoyl chloride (13.4 mmol) and triethylamine (14.7 mmol) were added and the mixture was stirred at room temperature overnight. The solution was poured onto ice/water and extracted with ethyl acetate (3× 30 mL). The combined organic phases were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (light petroleum/ethyl acetate: 4:1).

4.14.1. *N*-(3-Acetylphenyl)-*N*-methyl-4-fluorobenzamide (14a). Yield: 96%, yellow solid, mp 64.8–67.1 °C, R_f (light petroleum/ethyl acetate 1:1) = 0.43. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.73 (dt, 1H, J = 7.7, 1.2 Hz), 7.67 (t, 1H, J = 1.9 Hz), 7.35–7.25 (m, 3H), 7.18 (m, 1H), 6.86(m, 2H), 3.51 (s, 3H), 2.51 (s, 3H).

4.14.2. *N*-(3-Acetylphenyl)-*N*-methyl-4-nitrobenzamide (14b). Yield: 95%, off-white solid, mp 117–118 °C, R_f (light petroleum/ethyl acetate 2:1) = 0.17. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.04 (d, 1H, J = 7.8 Hz), 7.76 (m, 1H), 7.70 (m, 1H), 7.45 (d, 1H, J = 8.6 Hz), 7.35 (t, 1H, J = 7.8 Hz), 7.19 (m, 1H), 3.54 (s, 1H), 2.53 (s, 1H).

HRMS *m*/*z* calculated for $C_{16}H_{14}N_2O_4$ (M+H) 299.1026, found 299.1029.

4.15. General procedure for the synthesis of the enaminones (15a,b)

A solution of **14a**,**b** (4 mmol) in DMFDMA (5 mL) was heated at 120 °C overnight. After evaporation of the solvent, the residue was purified by flash chromatography (ethyl acetate/methanol 9:1).

4.15.1. (*E*)-*N*-(3-(3-(Dimethylamino)acryloyl)phenyl)-*N*-methyl-4-fluoro-benzamide (15a). Yield: 80%, yellow solid, mp 105–121 °C, R_f (ethyl acetate/methanol 9:1) = 0.43. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 7.78 (d, 1H, J = 12.3 Hz), 7.66 (m, 1H), 7.61 (t, 1H, J = 1.8 Hz), 7.31 (m, 2H), 7.25 (t, 1H, J = 7.8 Hz), 7.05 (s, 1H), 6.84 (s, 2H), 5.48 (d, 1H, J = 12.5), 3.52 (s, 1H), 3.16 (s, 3H), 2.91 (s, 3H).

4.15.2. (*E*)-*N*-(3-(3-(Dimethylamino)acryloyl)phenyl)-*N*-methyl-4-nitrobenzamide (15b). Yield: 89%, brownish oil, R_f (ethyl acetate/methanol 9:1) = 0.44. ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 8.02 (d, 2H, J = 8.6 Hz), 7.79 (d, 1H, J = 12.2 Hz), 7.68–7.65 (m, 2H), 7.46 (d, 1H, J = 8.7 Hz), 7.26 (m, 1H), 7.05 (d, 1H, J = 7.2 Hz), 5.50 (d, 1H, J = 12.2 Hz), 3.55 (s, 3H), 3.17 (s, 3H), 2.92 (s, 3H).

4.16. General procedure for the synthesis of the pyrazolopyrimidines (16a,b)

A suspension of **15a**,**b** (5 mmol) and (5-amino-1*H*-pyrazol-4-yl)-thiophen-2-yl-methanone (**6**) (5 mmol) in acetic

acid (50 mL) was heated at 65 °C for 1.5 h. After cooling to room temperature the mixture was poured onto ice/water and adjusted to pH 8 with sodium bicarbonate before extraction with dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography (ethyl acetate/methanol 9:1).

4.16.1. 4-Fluoro-*N*-methyl-*N*-(3-(3-(thiophene-2-carbonyl)pyrazolo[1,5-*a*]pyrimidin-7-yl)phenyl)benzamide (16a). Yield: 78%, yellow solid, mp 170.7–171.8 °C, R_f (ethyl acetate) = 0.30. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.77 (d, 1H, J = 4.4 Hz), 8.65 (s, 1H), 8.07 (dd, 1H, J = 3.7, 1.0 Hz), 7.80 (m, 2H), 7.71 (dd, 1H, J = 4.9, 1.1 Hz), 7.50 (t, 1H, J = 7.9 Hz), 7.39 (m, 2H), 7.30 (m, 1H), 7.20 (dd, 1H, J = 4.9, 3.8 Hz), 6.92 (m, 3H), 3.57 (s, 3H).

Calculated C: 65.78, H: 3.75, N: 12.27, found C: 65.51, H: 3.70, N: 11.98.

4.16.2. *N*-Methyl-4-nitro-*N*-(3-(3-(thiophene-2-carbonyl)-pyrazolo[1,5-*a*]pyrimidin-7-yl)phenyl)benzamide (16b). Yield: 79%, yellow solid, mp 159–161 °C, R_f (ethyl acetate/light petroleum 4:1) = 0.28. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 8.87 (d, 1H, J = 4.4 Hz), 8.74 (s, 1H), 8.19 (dd, 1H, J = 1.0, 3.8 Hz), 8.14 (d, 1H, J = 8.5 Hz), 8.05 (dd, 1H, J = 4.9 Hz, 1.0 Hz), 8.01 (s, 1H), 7.93 (m, 1H), 7.63 (d, 1H, J = 8.2 Hz), 7.54 (m, 1H), 7.42 (d, 1H, J = 4.4 Hz), 7.30 (dd, 1H, J = 4.9 Hz, 3.9 Hz), 3.48 (s, 1H).

Calculated C: 62.10, H: 3.54, N:14.48, found C: 61.96, H: 3.30, N: 14.35.

4.16.3. 1-[3-[(2-Fluoroethyl)methylamino]phenyl]ethanone (17). It was prepared according to the general procedure for acetophenones **6a**–**c**. Yield: 41%, yellow oil, R_f (dichloromethane) = 0.41. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.35-7.28 (m, 3H, H_{AR}), 7.23 (m, 1H, H_{AR}), 6.93 (m, 1H, H_{AR}), 4.62 (td, 2H, J = 5.1 Hz, J_{2F} = 47.2 Hz, CH_2F), 3.71 (td, 2H, J = 5.1 Hz, J_{2F} = 24.8 Hz, NCH_2), 2.98 (s, 3H, CH_3), 2.60 (s, 3H, CH_3). HRMS m/z calculated for $C_{11}H_{14}FNO$ (M+Na) 218.0951, found 218.0950.

4.16.4. 3-Dimethylamino-1-[3-[(2-fluoroethyl)methylamino]phenyl]propenone 18. It was prepared according to the general procedure for enaminones **4a**–**e**. Yield: 86%, yellow oil, R_f (ethyl acetate/methanol 9:1) = 0.42. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.79 (m, 1H, H_{AR}), 7.30–7.18 (m, 3H, H_{AR}), 6.83 (m, 1 H, H_{AR}), 5.70 (d, 1H, J = 12.4 Hz, CH), 4.62 (td, 2H, J = 45.2 Hz, J_{2F} = 47.2 Hz, CH_2F), 4.70 (td, 2H, J = 5.2 Hz, J_{3F} = 24.5 Hz, CH_2F), 3.20–2.85 (m, 9 H, CH_3). HRMS m/z calculated for $C_{14}H_{19}FN_2O$ (M+H) 251.1554, found 251.1553.

4.16.5. (7-[3-[(2-Fluoroethyl)methylamino]phenyl]pyrazolo[1,5-*a*]pyrimidin-3-yl)-thiophen-2-yl-methanone (19). It was prepared according to the general procedure for pyrazolopyrimidines **5a**–**e**. Yield: 35%, orange solid, mp 126.7–127.5 °C, R_f (ethyl acetate) = 0.75. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.80 (m, 1H, H_{AR}), 8.72 (s, 1H, H_{AR}), 8.12 (m, 1H, H_{AR}), 7.71 (m, 1H, H_{AR}), 7.45 (m, 1H, H_{AR}), 7.35 (m, 1H, H_{AR}), 7.27 (m, 1H, H_{AR}), 7.22 (m, 1H, H_{AR}), 7.13 (m, 1H, H_{AR}), 6.96 (m, 1H, H_{AR}), 4.67 (td, 2H, J_{2F} = 47.1 Hz, J_{3H} = 5.1 Hz, CH_2F), 3.74 (td, 1 H, J_{3F} = 24.6 Hz, J_{3H} = 5.1 Hz, N–CH_2), 3.11 (s, 3H, CH_3). Calculated C: 63.14, H: 4.50, N: 1214.73, found C: 62.90, H: 4.45, N: 14.34.

4.16.6. 3-(Dimethylamino)-1-(4-fluorophenyl)prop-2-en-1-one (21). A solution of 4-fluoroacetophenone (**20**) (1.5 g, 10.8 mmol) in DMFDMA (10 mL) was heated at 120 °C overnight. After evaporation of the solvent, the residue was purified by flash chromatography (ethyl acetate). Yield: 63%, yellow solid, mp 77.5–79.3 °C, R_f (ethyl acetate) = 0.28. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.91 (m, 2H), 7.80 (d, 1H, J = 12.3 Hz), 7.07 (m, 2H), 5.67 (d, 1H, J = 12.3), 3.15 (s, 3H), 2.93 (s, 3H).

4.16.7. 5-(4-Fluorophenyl)isoxazole (22). A solution of **21** (1.17 g, 6.04 mmol) and hydroxylamine hydrochloride (420 mg, 6.04 mmol) in methanol (10 mL) was heated at 65 °C for 2.5 h. After cooling to room temperature the mixture was diluted with water (10 mL) and extracted with dichloromethane (3× 10 mL). The combined organic phases were dried over sodium sulfate and concentrated. Yield: 97%, white solid, mp 53.4–54.2 °C, R_f (ethyl acetate) = 0.86. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.28 (d, 1H, J = 1.8 Hz), 7.79 (m, 2H), 7.17 (m, 2H), 6.47 (d, 1H, J = 1.9 Hz).

4.16.8. 3-(Dimethylamino)-2-(4-fluorobenzoyl)acrylonitrile (23). A solution of **22** (1.8 g, 11.0 mmol) in DMFDMA (10 mL) was heated at 120 °C overnight. After cooling to room temperature the mixture was diluted with a mixture of dichloromethane/diethyl ether 1/10 (40 mL). The product precipitates and was collected by suction filtration. Yield: 60%, yellow solid, mp 150.8–151.4 °C. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 7.96 (s, 1 H), 7.83 (m, 2H), 7.10 (s, 2H), 3.49 (s, 3H), 3.40 (s, 3H).

4.16.9. (5-Amino-1*H*-pyrazol-4-yl)(4-fluorophenyl)methanone (24). To a solution of **23** (1.96 g, 9 mmol) and aminoguanidinium nitrate (1.54 g, 11.2 mmol) in ethanol (15 mL) was added sodium hydroxide (1.25 mL, 10 M). The mixture was refluxed for 4 h and the solvent was removed. Then water (16 mL) was added and the solution was stored at 2–8 °C overnight. The precipitate was collected by suction filtration and dissolved in ethyl acetate (50 mL). The solution was dried over sodium sulfate and filtered. The filtrate was concentrated and dissolved in ethyl acetate (30 mL). Hexane was added and the solution was allowed to crystallize. The precipitate was collected and dried in vacuum. Yield: 62%, yellow solid, mp 155.7–156.3 °C. ^{1}H NMR (DMSO-d_6, 500 MHz): δ = 12.09 (br s, 1H, NH), 7.80 (m, 2H, H_{AR}), 7.62 (br s, 1H), 7.32 (m, 2H, H_{AR}), 6.71 (br s, 2H). HRMS m/z calculated for $C_{10}H_8FN_3O$ (M+H) 206.0724, found 206.0726.

4.16.10. *N*-(3-(3-(4-Fluorobenzoyl)pyrazolo[1,5-*a*]pyrimidin-7-yl)phenyl)-*N*-methylacetamide (25). A suspension of *N*-[3-(3-dimethylamino-acryloyl)-phenyl]-*N*-methyl-acetamide (0.50 g, 2 mmol) and (5-amino-1*H*-pyrazol-

4-yl)(4-fluorophenyl)methanone (**24**) (416 mg, 2 mmol) in acetic acid (10 mL) was heated to 65 °C for 1.5 h. After cooling to room temperature the mixture was poured onto ice/water and adjusted to pH 8 with sodium bicarbonate before extraction with dichloromethane. The combined organic phases were dried over sodium sulfate and concentrated. The residue was purified by flash chromatography. Yield: 48%, white solid, mp 121.5–123.2 °C, R_f (ethyl acetate) = 0.30. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.81 (d, 1H, J = 4.3 Hz), 8.57 (s, 1H), 7.99 (m, 4H), 7.67 (t, 1H, J = 7.8 Hz), 7.47 (d, 1H, J = 7.7 Hz), 7.18 (m, 1H), 3.35 (s, 3H), 2.00 (s, 3H). Calculated C: 68.03, H: 4.41, N: 14.43, found C: 67.65, H: 4.36, N: 14.32.

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