Discovery of 2-aminopyrimidines as potent agonists for the bitter taste receptor TAS2R14

Lukas Waterloo[1], Harald Hübner[1], Fabrizio Fierro[2], Tara Pfeiffer[1], Regine Brox[1], Stefan Löber[1], Dorothee Weikert[1], Masha Y. Niv[2*], Peter Gmeiner[1*]

[1]Department of Chemistry and Pharmacy, Medicinal Chemistry, Friedrich-Alexander-Universität Erlangen-Nürnberg, Nikolaus-Fiebiger-Str. 10, 91058 Erlangen, Germany

[2]The Robert H. Smith Faculty of Agriculture, Food and Environment, Institute of Biochemistry, Food Science and Nutrition, The Hebrew University, Rehovot, Israel

* Corresponding authors: peter.gmeiner@fau.de; masha.niv@mail.huji.ac.il

ABSTRACT

The bitter taste receptor TAS2R14 is a G protein-coupled receptor that is found on the tongue as well as in the human airway smooth muscle and other extraoral tissues. Because its activation causes bronchodilatation, TAS2R14 is a potential target for the treatment of asthma or chronic obstructive pulmonary disease. Structural variations of flufenamic acid, a nonsteroidal anti-inflammatory drug, led us to 2-aminopyridines showing considerable efficacy and potency in an IP-One accumulation assay. In combination with a bioisosteric exchange of the carboxylic moiety by a tetrazole unit, a set of promising new TAS2R14 agonists was developed. The most potent ligand **28.1** (EC_{50} = 72 nM) revealed a six-fold higher potency than flufenamic acid and a maximum efficacy of 129%. Besides its unprecedented TAS2R14 activation, **28.1** revealed marked selectivity over a panel of 24 non-bitter taste human GPCRs.

INTRODUCTION

The superfamily of G protein-coupled receptors (GPCRs) are membrane proteins ubiquitously expressed in the human body, where they are involved in a plethora of physiological functions including nervous and endocrine systems as well as the sensing of exogenous signals.[1] Among those, the group of taste receptors (TASRs) are critically involved in the mediation of human senses including the sweet, umami (TAS1R), and bitter (TAS2R) subset of the taste modalities.[2] Besides their obvious presence in taste buds located in the oral cavity, TAS2Rs were found to be expressed in a number of extraoral tissues, such as the mammary epithelial, the heart, breast cancer and bone marrow cells, and human airway smooth muscles.[3] Among the subfamily of the 25 bitter taste GPCRs, the TAS2R14 subtype is one of the most highly expressed receptors in extraoral tissues.[3] TAS2R14 activation by bitter molecules causes bronchodilation and the agonistic effect turned out to be more prominent than bronchodilation by common β-adrenergic receptor agonists. Therefore, TAS2R14 is a potential target for the treatment of asthma or chronic obstructive pulmonary disease.[4, 5]

Several attempts to generate computational TAS2R14 models based on known ligands and mutational studies have been made but experimental validation from structural biology is still lacking.[6-8] Interestingly, most known TAS2R14 ligands are agonists, but with EC_{50} values mostly in the micromolar range, their potency remains relatively low. In general, these compounds differ strongly in their molecular size and do not show common structural motifs,[9, 10] leading to the assumption that TAS2R14 possesses a broadly tuned binding pocket which together with other bitter taste receptors may have evolved to cover a vast range of chemically varying ligands.[10, 11] Moreover, an endogenous agonist of TAS2R14 has not been identified yet. Selective, high-affinity ligands are thus needed to enable further investigation of the physiological functions of TAS2R14, elucidate its structure, and ultimately exploit its potential as a drug target. Among the known TAS2R14 ligands, flufenamic acid (2-{[3-(trifluoromethyl)phenyl]amino}benzoic acid, **Figure 1a**), a nonsteroidal anti-inflammatory drug, is one of the most potent and well-characterized agonists.[7-9, 12, 13] Using this molecule as a lead structure, we have previously developed a series of TAS2R14 ligands using a combination of

computational design and chemical synthesis. Most of these ligands shared the general diarylamine structure and the benzoic acid moiety. We could further show that bioisosteric replacement of the carboxylic acid by a tetrazole leads to TAS2R14 partial agonists with superior potency (**Figure 1b**).[7]

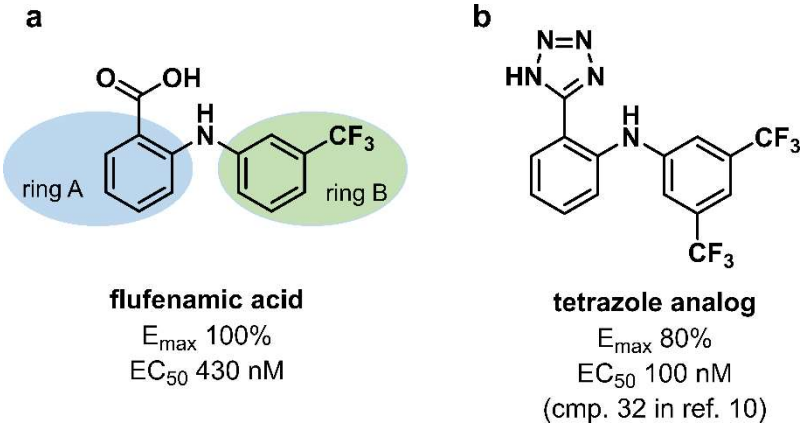


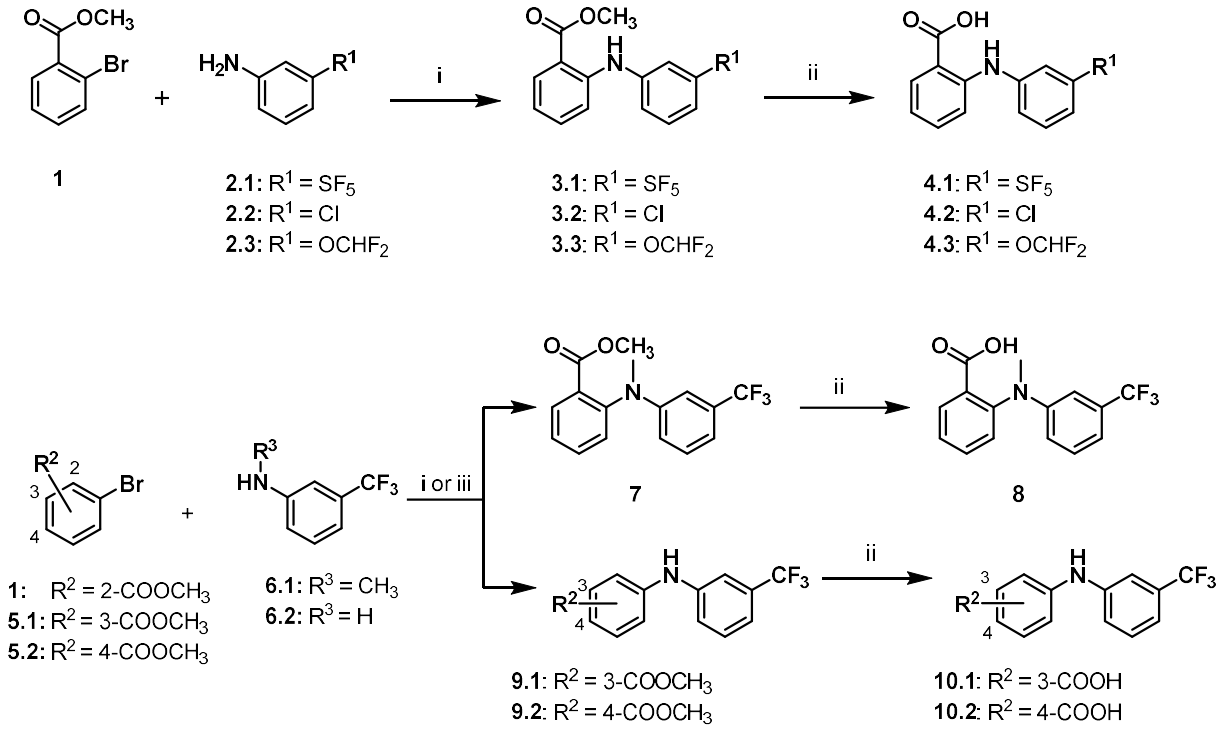
Figure 1. Chemical structure and TAS2R14 activity data derived from an IP-One accumulation assay for **a)** the reference agonist flufenamic acid and **b)** a recently reported potent tetrazole-containing partial agonist.[7]

Building on these findings, we herein expand the structure-activity relationships (SAR) of flufenamic acid analogs by employing a ligand-based design and synthesis strategy. Functional evaluation of the novel ligands in an IP-One accumulation assay reveals that incorporation of heterocyclic ring B moieties, especially the 2-aminopyrimidine scaffold, leads to highly potent TAS2R14 ligands with increased efficacy compared to flufenamic acid.

RESULTS

Chemistry. Our initial investigations were directed towards the trifluoromethyl substituent in the *meta*-(3')-position of flufenamic acids' phenyl ring B (**Figure 1**, **Scheme 1**). Following the already established synthesis route,[7, 14] we prepared a 3'-pentafluorosulfanyl- (**4.1**)[14], a 3'-chloro- (**4.2**)[15], and a 3'-difluoromethoxy-containing diarylamine analog (**4.3**)[16] of flufenamic acid by coupling the respective anilines with methyl 2-bromobenzoate (**1**) in a Pd-catalyzed Buchwald-Hartwig reaction. Subsequent saponification of the ester under basic conditions yielded the title compounds **4.1**-**4.3** in good to excellent yield.

Scheme 1. Synthesis of flufenamic acid analogs **4.1**-**4.3**, **8**, and **10.1**-**10.2**.[a]



[a] Reagents and conditions: i) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, dry toluene, 100 °C or 120 °C, 2-24 h, 68-96% or; ii) KOH, EtOH/H_2O or MeOH/H_2O, 80 °C, 100 °C or reflux, 1- 3.5 h, 51-85%; iii) for **7**: $Pd_2(dba)_3$, XPhos, K_3PO_4, dry toluene, 110 °C, 24 h, 35%.

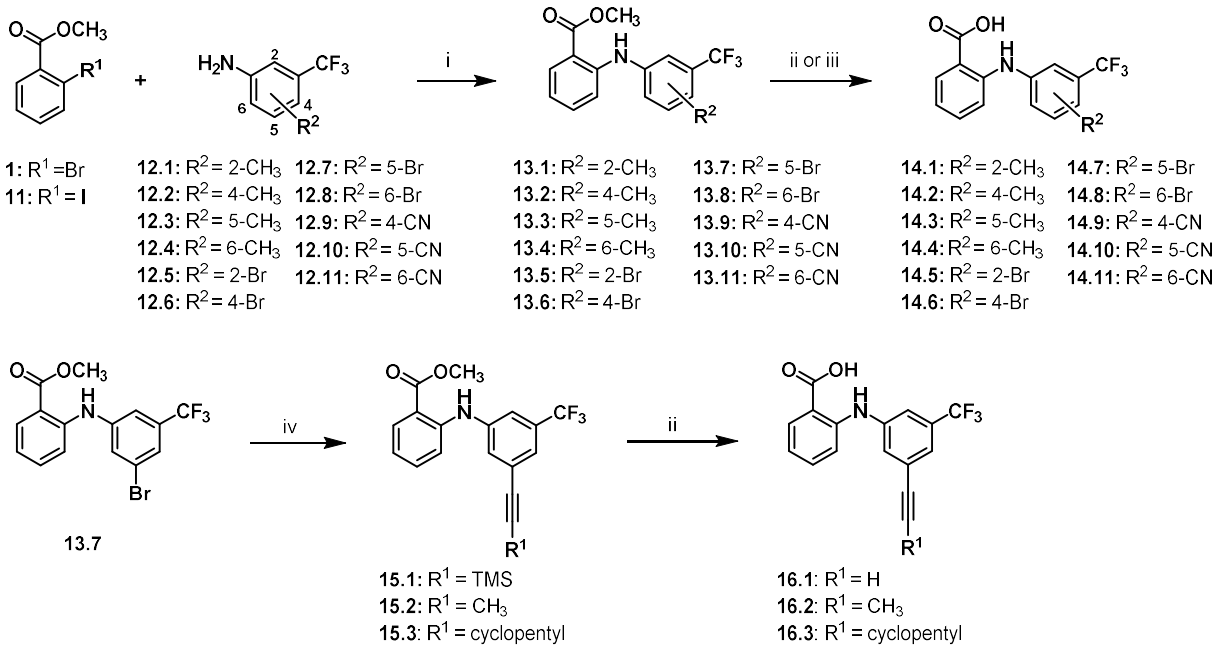
Additionally, we prepared *N*-methylated flufenamic acid (**8**) starting from *N*-methyl-3-(trifluoromethyl)aniline (**6.1**), to probe the importance of the H-bond donating properties of the central diarylamine. Previous SAR had also indicated the importance of the acidic functionality on ring A.[7] To further explore the relevance of the relative orientation of the carboxylic acid and the amine, we synthesized the *meta*- and *para*-substituted regioisomers of flufenamic acid (**10.1** and **10.2**) following the same strategy as above,[15] but starting from 3- and 4-bromobenzoic acid methyl esters (**5.1** and **5.2**, **Scheme 1**).

Our previous study also pointed towards a beneficial effect of a second *meta*-substituent on ring B for TAS2R14 agonist activity.[7] To further elucidate these findings, we planned to systematically investigate the effect of a combination of the 3'-trifluoromethyl group with an additional methyl- and bromine-substitution (**Scheme 2**). Title compounds **14.1** – **14.8** were prepared as described above, starting from the commercially available 2-, 4-, 5-, and 6-

substituted 3-(trifluoromethyl)anilines (**12.1** – **12.8**) which were connected with the halogen-substituted methyl benzoates (**1** or **11**) by Buchwald-Hartwig coupling, followed by basic ester hydrolysis. Likewise, the cyano-substituted analogs **14.9** and **14.11** could be obtained via the intermediates **13.9** and **13.11**. In the case of the 5'-cyano-diarylamine **13.10**, basic ester saponification was not possible, as the nitrile quickly hydrolyzed as well. Instead, the desired product **14.10** was afforded by treatment with TMSI (**Scheme 2**).

Since especially *bis-meta*-substitution proved successful in enhancing biological activity (see below), we further took advantage of the 5'-bromo-substituted intermediate **13.7** to introduce alkyne-containing sidechains of varying size by Pd-catalyzed Sonogashira coupling (**15.1**-**15.3**). For the propynyl derivative **15.2**, we employed butynoic acid as alkyne source to avoid the use of gaseous propyne. In combination with $PdCl_2(PPh_3)_2$, 1,4-bis(diphenylphosphino)butane (dppb) and DBU in DMSO, the carboxylic acid undergoes a decarboxylative cross-coupling reaction and forms the C(sp^2)-C(sp) bond.[17] In the final step, the resulting intermediates **15.1** – **15.3** were again hydrolyzed under basic conditions to give the target compounds **16.1** – **16.3**.

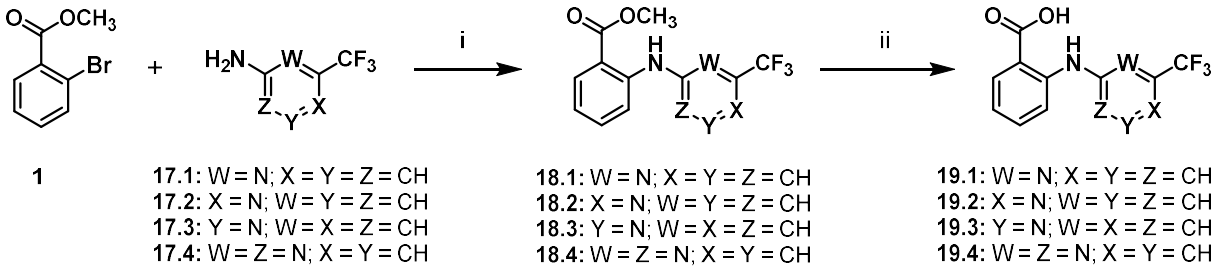
Scheme 2. Synthesis of flufenamic acid analogs **14.1** – **14.11** and **16.1** – **16.3** carrying additional B-ring substituents.[a]



[a] Reagents and conditions: i) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, dry toluene, 100 °C or 120 °C, 2-22 h; ii) KOH or NaOH, EtOH/H_2O or EtOH/THF or EtOH/THF/H_2O or MeOH/THF/H_2O, rt or 80 °C or reflux, 1-16 h, 34-94%; iii) TMSI, 70 °C, 23 h, 49%; iv) terminal alkyne, $Pd(PPh_3)_4$, CuI, $ZnBr_2$, Et_3N, dry THF, argon, 80 °C, 21-24 h, 92-93 % or butynoic acid, $PdCl_2(PPh_3)_2$, DBU, dry DMSO, argon, 110 °C, 1.5 h, 78%.

Since heterocycles are frequently found in biologically active compounds[18], we explored nitrogen-containing ring systems as substitutes for phenyl ring B. The preparation of the respective pyridine- or pyrimidine-derived final compounds **19.1-19.4** followed the same synthesis strategy as above involving Buchwald-Hartwig coupling and subsequent ester hydrolysis (**Scheme 3**).

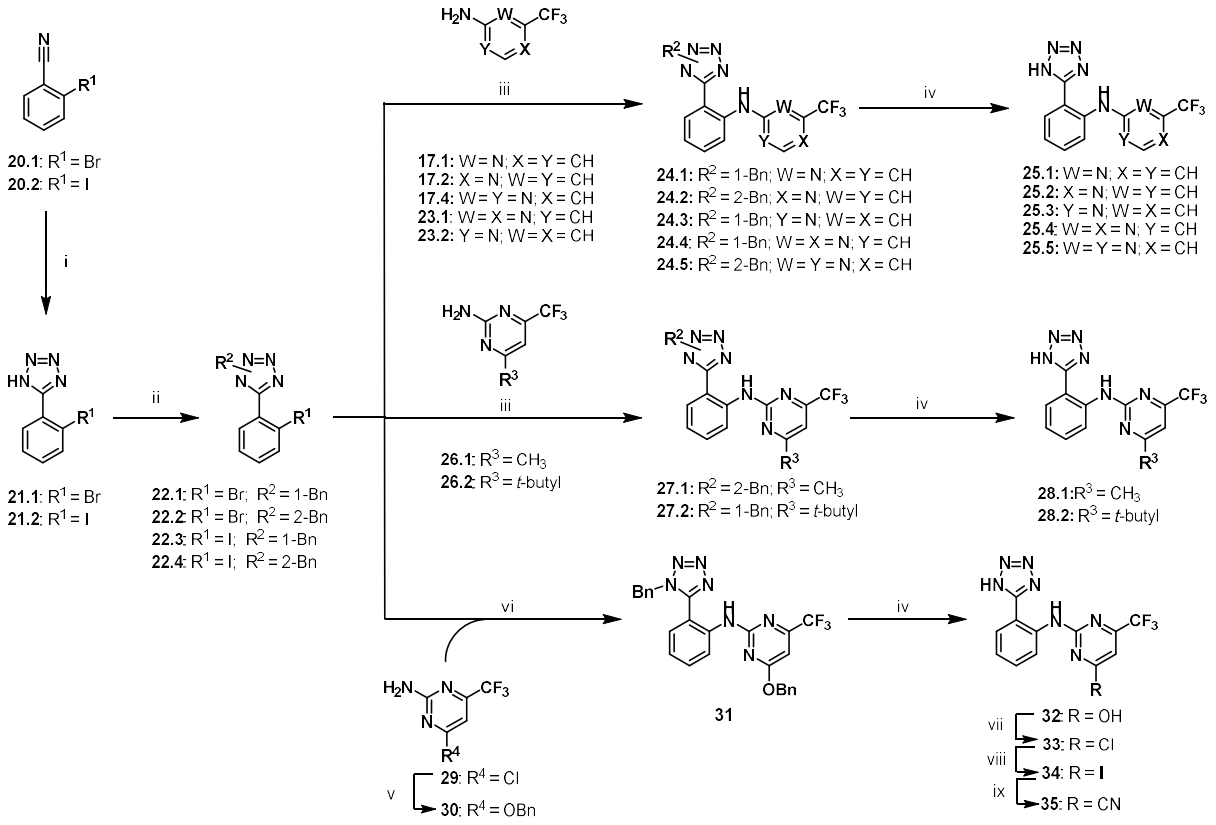
Scheme 3. Preparation of heteroaromatic flufenamic acid analogs. [a]



[a] Reagents and conditions: i) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, dry toluene,120 °C, 4-5 h, 44-79%; ii) KOH, EtOH/H_2O or EtOH/THF/H_2O, rt or 100 °C, 1-4 h, 36-84%;

We could previously show that tetrazoles are well-suited for a bioisosteric replacement of the carboxylic acid moiety of flufenamic acid, leading to the discovery of high-potency TAS2R14 (partial) agonists.[1] To efficiently explore the combination of heterocyclic ring B analogs and the tetrazole bioisostere, a synthetic route was established where the tetrazole was formed in the first step of the reaction sequence. Hence, we started from the respective 2-bromo- and 2-iodobenzonitriles **20.1** or **20.2** and obtained the tetrazoles **21.1** and **21.2** in one step by using neat $TMSN_3$ and TBAF · 3 H_2O. The target molecules could be easily recrystallized from a mixture of toluene and ethanol (**Scheme 4**). To prepare them for the subsequent Pd-catalyzed amination, a benzyl protective group was introduced by treatment with benzyl bromide under basic conditions, resulting in two regioisomers each (**22.1-22.4**). The benzyl-protected tetrazoles were coupled to the respective amino-substituted pyridines **17.1, 17.2**, and **23.2** and the amino-pyrimidines **17.4**, **23.1**, and **26.1**-**26.2**, respectively, resulting in the diarylamine intermediates **24.1-24.5** and **27.1-27.2**. Deprotection of **24.1-24.5** and **27.1-27.2** using H_2 on Pd/C gave the final compounds **25.1-25.5** and **28.1-28.2**. To introduce an additional chlorine atom at the C4-position of the pyrimidine scaffold (**33**), we started by treating 4-chloro-6-(trifluoromethyl)pyrimidin-2-amine (**29**) with benzyl alcohol and NaH in dry DMF to yield the benzyl ether **30**. This building block was then coupled under Pd-catalyzed conditions to **22.3** resulting in formation of the bisbenzyl-protected intermediate **31**. Both benzyl protective groups could be cleaved off simultaneously resulting in the pyrimidin-4-ol **32**. Treatment of **32** with $POCl_3$ led to the formation of the desired chlorinated compound **33**, which served as both, a target compound and valuable intermediate that could easily be transformed to further final compounds. Treatment of **33** with NaI and aqueous HI afforded the iodo-derivative **34** which underwent a Pd-catalyzed coupling with $Zn(CN)_2$ and $Pd(PPh_3)_4$ resulting in formation of the nitrile **35** (**Scheme 4**).

Scheme 4. Synthesis of tetrazole derivatives. [a]

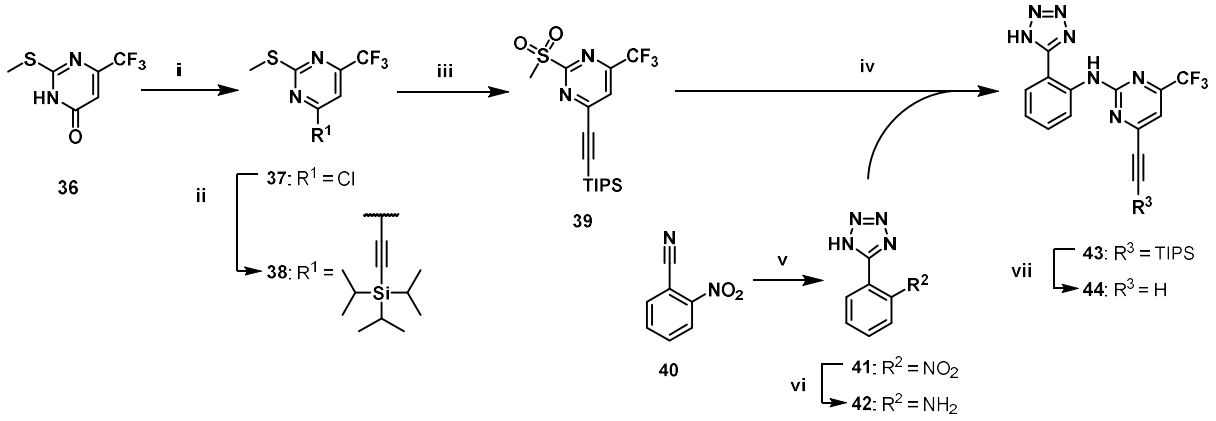


[a] Reagents and conditions: i) $TMSN_3$, TBAF · $3H_2O$, 85 °C, 17-21 h, 51-67%; ii) BnBr, K_2CO_3, reflux, 15-18 h, 35-49%; iii) $Pd(OAc)_2$, (±)-BINAP, Cs_2CO_3, dry toluene, 120 °C, 2-28 h, 66-85%; iv) Pd/C, H_2, EtOH or EtOH/CH_2Cl_2, rt 1 h - 6 d, 31-83 %; v) NaH, benzyl alcohol, dry DMF, argon, 90 °C, 2 h, 67%; vi) $Pd(OAc)_2$, XantPhos, Cs_2CO_3, dry toluene, 120 °C, 3 h; vii) $POCl_3$, 60 °C, 2 h, 83 %; viii) NaI, HI, rt, 3 h, 73 %; ix) $Pd(PPh_3)_4$, $Zn(CN)_2$, dry DMF, argon, 80 °C, 4 h, 65%.

Combining the bioisosteric replacement of the carboxylic acid with a heteroaromatic ring B and an additional acetylene substituent in *meta*-position to the amine, **44** was prepared employing an alternative syntheses route. First, the chlorination of 2-(methylthio)-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (**36**) with $POCl_3$ generated the pyrimidine **37**. Subsequently, a nucleophilic substitution was performed applying TIPS acetylene, $PdCl_2(PPh_3)_2$, and Et_3N to result in **38**. Oxidation of the thioether to the respective sulfonyl **39** was achieved with *m*CPBA in good yield. To introduce the tetrazole group as the bioisostere of the carboxylic acid, we first conducted a [3 + 2] cycloaddition on 2-nitrobenzonitrile (**40**) to give the 5-substituted tetrazole **41**. The nitro group was subsequently reduced to a primary amine by the application of H_2 on Pd/C affording **42** in excellent yield. To generate intermediate

43, **42** was coupled to **39** by nucleophilic aromatic substitution.[19] Deprotection of the crude compound with TBAF in combination with acetic acid gave the final product **44** in moderate yield over two steps (**Scheme 5**).

Scheme 5. Synthesis of tetrazole **44**.[a]



[a] Reagents and conditions: i) $POCl_3$, argon, 100 °C, 1 h; 73%; ii) TIPS acetylene, $PdCl_2(PPh_3)_2$, Et_3N, argon, dry ACN, 80 °C, 90 min, 79%; iii) mCPBA, dry CH_2Cl_2, rt, 15 h, 79%; iv) TFA, 2,2,2-trifluoroethanol, argon, 140 °C, microwave irradiation, 9 h; v) $TMSN_3$, TBAF · $3H_2O$, 85 °C, 17-21 h, 47%; vi) Pd/C, H_2, EtOH or EtOH/CH_2Cl_2, rt 1 h - 6 d, 94 %; vii) 1M TBAF in THF, AcOH, dry THF, rt, 1 h, 36%.

TAS2R14 activity and structure-activity relationship studies. To determine the impact of the structural modifications on the biological activity of the flufenamic acid derivatives, the activation of TAS2R14 was measured employing an IP_1 accumulation assay (IP-One-Gq Kit).[7] Specifically, HEK293T cells were transiently transfected with plasmids encoding TAS2R14 and a chimeric $G\alpha_{qi5}$ protein[20] to enable robust coupling of TAS2R14 to the $G\alpha_q$-type second messenger pathway. Surface expression of TAS2R14 was achieved as described previously by *N*-terminal addition of a cleavable HA-signal peptide followed by a FLAG-tag and the first 45 amino acids of the rat somatostatin receptor 3.[7, 21] **Tables 1-2** summarize the obtained functional responses of the newly synthesized derivatives in comparison to the reference agonist flufenamic acid.

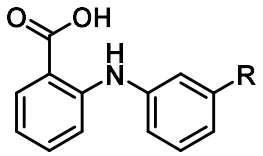
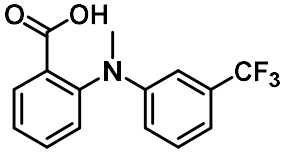
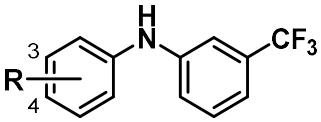
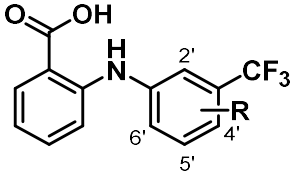
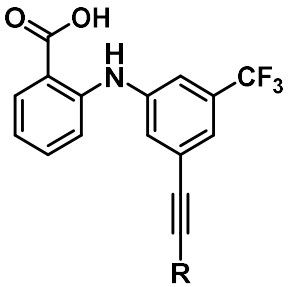
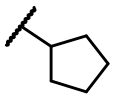
In agreement with its similar physicochemical properties and size, replacement of the 3'-trifluoromethyl substituent with $-SF_5$ resulting in ligand **4.1** was found to potently activate TAS2R14 (EC_{50} = 190 nM), albeit with a slightly reduced maximum efficacy (E_{max} = 77%)

compared to flufenamic acid (430 nM, 100%). The lipophilic chlorine (**4.2**) and acidic $OCHF_2$ substituent (**4.3**) were not beneficial for TAS2R14 agonism. Methylation of the diarylamine (**8**) or displacement of the carboxylic acid position from the *ortho*- (flufenamic acid) to the *meta*- (**10.1**) and *para*-position (**10.2**) of ring A strongly diminished or even abrogated the compounds' activity at TAS2R14 (**Figure 2a**). This highlights the importance of the H-bond donating properties of the central amine and the relative positioning of the acidic and basic functionalities for the receptor-activating properties of flufenamic acid. In agreement with these findings, our previous investigations revealed that a replacement of the central diarylamine by ethylamine or by oxygen, and the conformational restriction to a tricyclic system, are neither tolerated by TAS2R14.[7]

Generally, the addition of a methyl-, bromo- or cyano- to ring B of the lead compound preserved or even improved agonism at TAS2R14 (**Figure 2b**), with potencies (EC_{50}) ranging from 140 – 1,200 nM and maximum efficacies (E_{max}) between 48 and 102%. For the methyl- and bromo-substituted analogs, insertion of the functional group was found to be most favorable in the second *meta*-position (5'-position) leading to ~2-fold improved potencies for **14.3** (EC_{50} = 190 nM) and **14.7** (EC_{50} = 290 nM) and comparable efficacy relative to the reference agonist flufenamic acid. In the case of the cyano-derivatives, this second meta-position (**14.10**) was also well tolerated (EC_{50} = 180 nM, E_{max} = 81%), although the introduction of the substituent to the *para*-position (**14.9**) lead to even higher potency (140 nM) and nearly full agonist activity (92%).

Because the *meta*-position seemed to be most advantageous for a second substitution, we continued investigating the impact of different groups at this position. Intriguingly, the insertion of an acetylene moiety (**16.1**) lead to a similarly potent compound (EC_{50} = 150 nM) which at the same time exhibited a maximal activity (E_{max} = 110%) compared to our reference agent flufenamic acid. Further enlargement of the acetylene moiety with an additional methyl or cyclopentyl group did not further improve activity, as **16.2** and **16.3** both showed decreased potency and maximum activity ($E_{max} \leq 64\%$) in the investigated concentration range (up to 30 µM).

Table 1. Functional properties of flufenamic acid derivatives **4.1-4.3**, **8**, **10.1-10.2**, **14.1-14.11,** and **16.1-16.3**.[a]

			TAS2R14 activation	
Compound		**R**	**EC_{50} [nM]**	**E_{max}[b] [%]**
flufenamic acid		CF_3	430 ± 40	100 (10)
4.1		SF_5	190 ± 33	77 ± 8 (*3*)
4.2		Cl	950 ± 33	100 ± 6 (*3*)
4.3		$OCHF_2$	930 ± 170	66 ± 3 (*3*)
8		-	n.q.	59 ±10 (*5*)[c] @ 30 µM
10.1		3-COOH	n.q.	27 ± 4 (*3*)[c] @ 30 µM
10.2		4-COOH	n.q.	< 5 (*3*)
14.1		2'-CH_3	1,200 ± 700	82 ± 14 (*3*)
14.2		4'-CH_3	340 ± 79	67 ± 2 (*3*)
14.3		5'-CH_3	190 ± 30	101 ± 4 (*5*)
14.4		6'-CH_3	390 ± 3	102 ± 2 (*3*)
14.5		2'-Br	1,200 ± 650	48 ± 9 (*4*)
14.6		4'-Br	300 ± 27	81 ± 1 (*4*)
14.7		5'-Br	290 ± 84	96 ± 6 (*4*)
14.8		6'-Br	640 ± 110	79 ± 5 (*4*)
14.9		4'-CN	140 ± 44	92 ± 3 (*3*)
14.10		5'-CN	180 ± 16	81 ± 3 (*6*)
14.11		6'-CN	420 ± 22	65 ± 3 (*3*)
16.1		H	150 ± 26	110 ± 5 (*4*)
16.2		CH_3	540 ± 160	58 ± 3 (*6*)
16.3			n.q.	64 ± 12 (*3*)[c] @ 30 µM

[a] Data represent mean ± s.e.m. of (*n*) individual experiments, with n indicated in brackets. n.q.: not quantified. [b] maximum efficacy determined relative to reference agonist flufenamic acid. [c] No complete sigmoid concentration-response was obtained. Data represents maximal efficacy at the indicated compound concentration.

Although heterocycles are omnipresent in biologically active compounds, they have so far not been systematically included in flufenamic acid analogs serving as TAS2R14 ligands. Hence, we investigated the effect of the replacement of phenyl ring B by three trifluoromethylpyridine regioisomers (**19.1**-**19.3**) or a trifluoromethyl-substituted pyrimidine (**19.4**, **Table 2**). The three pyridine analogs **19.1**-**19.3** did not show superior agonist properties compared to the reference flufenamic acid as we observed maximum efficacies of 52-99% and at the same time a potency (EC_{50} > 670 nM) which was at least 1.5-fold reduced compared to reference. Interestingly, the introduction of the second nitrogen to the ring system (**19.4**) led to a similarly weak potency (EC_{50} = 1,600 nM) but at the same time enhanced the ligand's efficacy to 121% (**Table 2**).

In our previous study, the bioisosteric replacement of flufenamic acid's carboxylic acid by a tetrazole led to the discovery of three potent TAS2R14 partial agonists (E_{max} = 69-80%, EC_{50} = 100-640 nM as determined in the IP_1 accumulation assay).[1, 4] It was hence tempting to combine both modifications, the tetrazole bioisostere and the heteroaromatic ring B, as especially introduction of a pyrimidine scaffold seemed to increase the ligands' maximum efficacy.

In analogy to the trend observed with the carboxylic acid derivatives **19.1**-**19.3**, the 6-(trifluoromethyl)pyridin-2-amine scaffold **25.1** was preferred over both, the 2-(trifluoromethyl)pyridin-4-amine **25.2** and the 4-(trifluoromethyl)pyridin-2-amine-containing tetrazole **25.3**. With an EC_{50} of 98 nM, **25.1** was as potent as the best previously described tetrazole-containing TAS2R14 ligand, which was shown to be a partial agonist.[7] In contrast, **25.1** elicited an E_{max} of 112% compared to flufenamic acid. Formal insertion of a second nitrogen into the ring system of **25.1** yielded the 4-aminopyrimidine **25.4** and the 2-aminopyrimidine **25.5** which again slightly increased the efficacy (E_{max} = 117-121%), but did not further enhance potency (EC_{50} = 1,100 and 160 nM for **25.4** and **25.5**, respectively, **Figure 2c**).

To combine the favorable effects of substituents in position 5' of phenyl ring B as described above (**Table 1**), we probed the effect of the addition of different functional groups in the analogous position of the 2-aminopyrimidine scaffold of **25.5**. The introduction of a methyl

substituent (**28.1**) was found to be most favorable, leading to the best TAS2R14 agonist within our SAR study (**Figure 2c**). Compared to the parent molecule **25.5**, the methyl-pyrimidine derivative **28.1** possessed a further increased efficacy (E_{max} = 129%) and a 2.2-fold enhanced potency (EC_{50} = 72 nM). Similarly, the nitrile analog **35** showed promising biological activity (EC_{50} = 200 nM, E_{max} = 118%). However, further variations in size and polarity of the second substituent were not well tolerated by the receptor, as increasing the steric demand with a tertiary butyl group (**28.2**), adding polarity by a hydroxyl group (**32**), or lipophilicity by the halogens chlorine (**33**) and iodine (**34**) were found to decrease the potency and/or the efficacy for TAS2R14 activation (E_{max} = 62-106%, EC_{50} = 540-6,800 nM). In contrast to the results obtained for substitution of the phenyl-analogs, the introduction of an acetylene moiety (**44**) was not beneficial for potency either (EC_{50} = 1,400 nM) although it strongly enhanced the efficacy (E_{max} = 142 %) (**Table 2**).

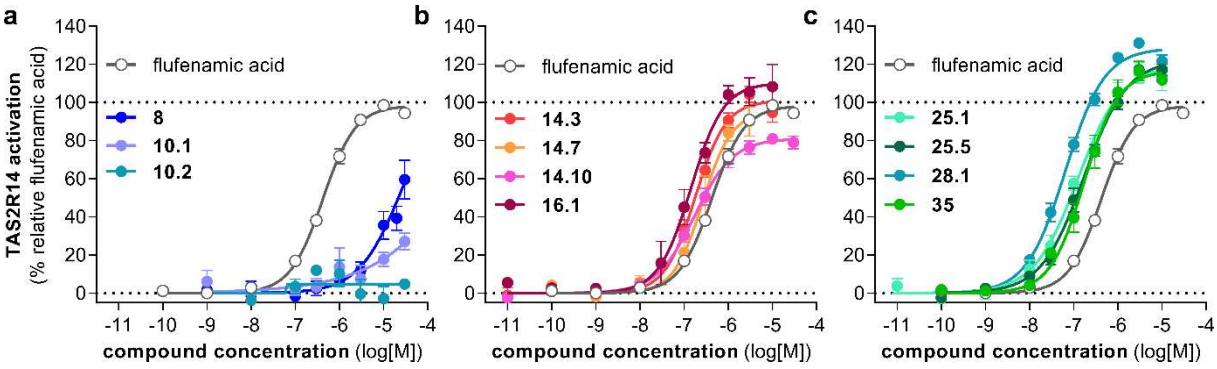
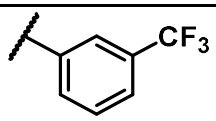
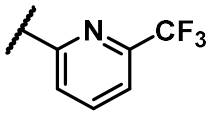
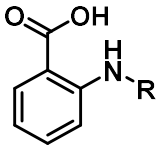
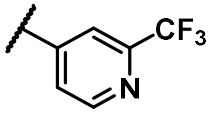
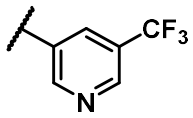
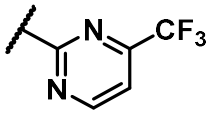
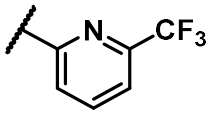
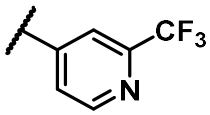
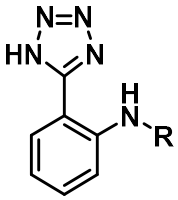
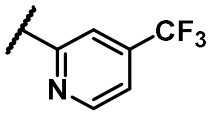
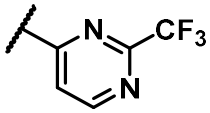
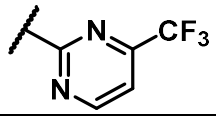
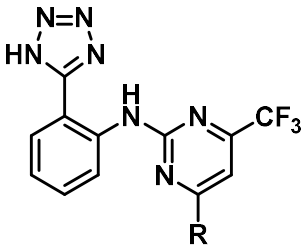
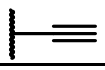


Figure 2. Concentration-response curves for ligand-mediated TAS2R14 activation were determined in an IP_1 accumulation assay. **a)** Alkylation of the central amine or shifting the position of the carboxylic acid strongly diminishes TAS2R14 activation. **b)** Small substituents (-CH_3, Br, -CN, acetylene) are well tolerated in the 5' position of flufenamic acid's phenyl ring B. **c)** The combination of the tetrazole as carboxylic acid bioisostere with a pyrimidine-substitute for phenyl ring B induces superior potency and efficacy for activation of TAS2R14 compared to flufenamic acid. Data show mean ± s.e.m. of 3-10 independent experiments.

Table 2: Functional properties of heterocyclic flufenamic acid analogs **19.1-19.4**. and tetrazole bioisosteres **25.1**-**25.5**, **28.1**-**28.2**, **32**-**35** and **44**.

			TAS2R14 activation[a]	
compound		**R**	**EC_{50} [nM]**	**E_{max}[b] [%]**
flufenamic acid			430 ± 40	100 (*10*)
19.1			670 ± 67	99 ± 5 (*5*)
19.2			n.q.	52 ± 4 (*5*)[c] @ 10 µM
19.3			1,200 ± 120	98 ± 2 (*3*)
19.4			1,600 ± 87	121 ± 2 (*4*)
25.1			98 ± 6	112 ± 3 (*7*)
25.2			3,500 ± 540	110 ± 5 (*6*)
25.3			350 ± 91	82 ± 4 (*4*)
25.4			1,100 ± 160	121 ± 2 (*6*)
25.5			160 ± 31	117 ± 3 (*10*)
28.1		CH_3	72 ± 8	129 ± 2 (*8*)
28.2			700 ± 160	115 ± 8 (*4*)
32		OH	6,800 ± 1,200	106 ± 13 (*4*)
33		Cl	540 ± 95	62 ± 4 (*5*)
34		I	700 ± 160	99 ± 2 (*6*)
35		CN	200 ± 63	118 ± 2 (*4*)
44			1,400 ± 240	142 ± 12 (*8*)

[a] Data represent mean ± s.e.m. of (*n*) individual experiments, with n indicated in brackets. n.q.: not quantified. [b] maximum efficacy determined relative to reference agonist flufenamic acid. [c] No complete sigmoid concentration-response was obtained. Data represents maximal efficacy at the indicated compound concentration.

Computational analysis. To gain insights into key interactions of TAS2R14 with the newly developed ligands and to further rationalize the underlying SAR, we analyzed the putative binding poses of representative ligands by molecular docking. As direct structural information on TAS2R14 is not available, we used I-TASSER to generate a model of the receptor that was further optimized by the integration of available data from mutational studies and functional analysis of TAS2R14 agonists (see Methods).[6-8, 23]

Flufenamic acid and derivatives usually dock within the TAS2R14 pocket with the trifluoromethyl group exposed toward the extracellular side. Key interactions involved in their recognition involve a stacking interaction with Trp89$^{3.82}$ (numbers in superscript refer to Ballesteros-Weinstein nomenclature[24]) and an H-bond between the ligands' carboxylic acid and Asn93$^{3.36}$ (**Figure 3a**). The diarylamine methylation leads to both a ligand electrostatic change and to an increased steric hindrance inside the binding pocket, precluding a proper fit of the ligands within the flufenamic acid binding site (like for compound **8**, see **Figure 3b**) and leading to a binding pose that does not overlap with the flufenamic acid.

On the other hand, the translation of the ring A carboxylic acid from the ortho to the *meta*- or *para*-position relative to the amine (**10.1** or **10.2**) also affects the diarylamine positioning in our docking. Indeed, the main difference between the two derivatives and flufenamic acid as the lead structure is a rotation of the diarylamine that, instead of facing transmembrane helix (TM) 7, is pointing towards TM4 and TM5. This rotation allows the ligand to fit inside the bottom region of the binding pocket and to interact with Asn93$^{3.36}$ (**Figure 3c**), while precluding potent TAS2R14 activation. Position 93$^{3.36}$ was found to be involved in receptor activation in other GPCRs [25-31]. An alteration of the orientation of Asn93$^{3.36}$ mediated by ligand interaction could, therefore, affect the activation level for this bitter taste receptor. Due to the different orientation of **10.1** observed within the binding site, we assume the different binding pose could alter the Asn93$^{3.36}$ positioning.

Among the SAR data generated within this study, the addition of a second substituent to ring B is generally well tolerated and in most cases does not significantly alter the receptor activation profile. In line with these findings, the main interactions typical of flufenamic acid as

well as the orientation of the molecules within the pocket are conserved, as illustrated for the derivative **14.2** (**Figure 3d**).

Replacement of flufenamic acid's ring A carboxylic acid with a tetrazole, as for compound **28.1**, the most potent identified within this study, increases the number of stacking interactions with the receptor (**Figure 3e**), The orientation of the docked molecule remains the same as flufenamic acid (**Figure 3f**).In addition to the stacking, despite the lack of H-bonds in the predicted complexes, the presence of this type of interaction between Asn93$^{3.36}$ and tetrazole can not be excluded and is compatible with the short distance between the two groups.

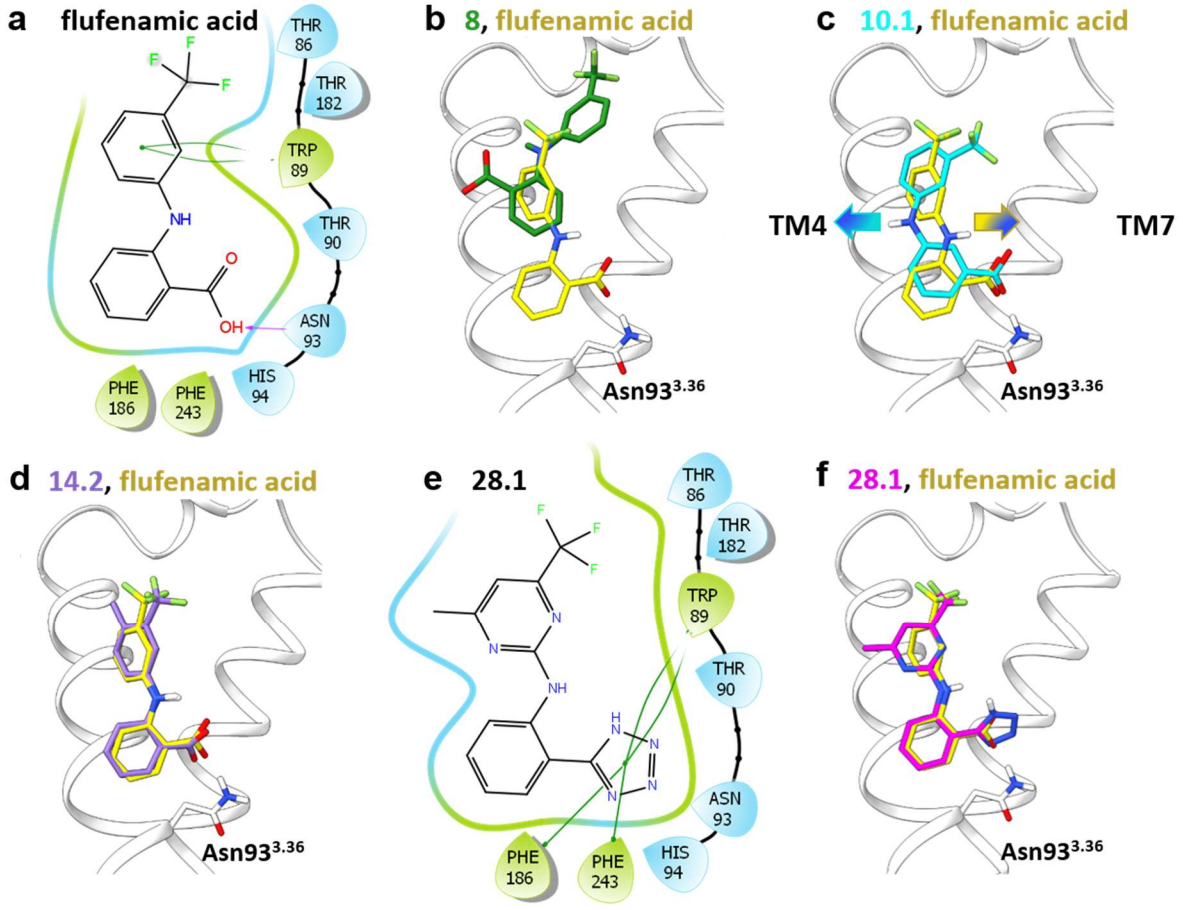


Figure 3: Docking results for the compounds analyzed in this study. **a)** Interaction diagram for flufenamic acid. **b)** Methylation of the diarylamine leads to a docking pose not overlapping with the potential flufenamic acid binding site. **c)** Modification of the carboxylic acid's position to the *para*- and *meta*-position of ring A cause a 90° rotation of the diarylamine, which moves away from TM7. This rotation allows the ligands to fit within the bottom part of the

binding site. **d)** Addition of a second small substituent to flufenamic acid ring B does not alter the binding pose. **e)** Interaction diagram for a tetrazole analog of flufenamic acid, a compound replacing the carboxylic acid with a tetrazole. **f)** Overlap of **28.1** with flufenamic acid binding poses show similar orientation within the pocket.

Together with the tetrazole group, the presence of a heterocyclic ring B, in particular those with at least one nitrogen, located in the 2'-position like in **28.1**, contributes to improved ligand potency and efficacy. Docking of this compound shows an identical orientation within the pocket compared to the flufenamic acid, while the presence of the tetrazole heterocycle can potentially allow the generation of additional H-bond interactions with binding site residues (e.g. Thr182$^{5.42}$, **Figure 3e**).

The CryoEM structure of a bitter taste receptor, TAS2R46, was published while this work was accomplished.[32] Due to the improved sequence identity between the TAS2R14 and the available GPCRs potential templates, which moved from the 11-13% at the beginning of this study till circa 45% with the new TAS2R46 structure, a homology model of the TAS2R14 was also generated based on this novel template. The docking of ligands to this structure gave results incompatible with the experimental data, probably due to the low refinement level of the binding site residues (**Supplementary Text**, **Supplementary Figure S2**).

Selectivity Screening. To further assess the specificity of our ligands and to exclude false-positive results in our biological model system, we performed an *in silico* screening for pan assay interfering structural motifs (PAINS screening, **Supplementary Table 1**)[33] and found no similarity to known aggregators or otherwise flagged liabilities of the compounds contained in our SAR study.

Moreover, we assessed the selectivity of the novel TAS2R14 full agonists **16.1**, **28.1**, and **35** over a panel of 24 non-bitter taste human GPCRs belonging to the pharmacologically relevant classes of adrenergic, dopaminergic, muscarinic, neurotensinergic, opioid and serotonergic receptors. For each of the ligands, we measured radioligand competition at 1, 10, and 30 µM in comparison to the reference agonist flufenamic acid (**Supplementary Figure 1**). Noteworthy, flufenamic acid and the tetrazole-analog **28.1** carrying the methyl-substituted

trifluoromethyl-pyrimidine did not substantially displace the radioligand at any of the investigated receptor subtypes, and thus show high selectivity for TAS2R14. This selectivity was also mostly retained for compound **16.1** carrying an additional acetylene substituent in the second meta (5'-)position of ring B. **16.1** competes with the radioligand [^{3}H]RX821002 to more than 50% at the adrenergic α_{2B} and α_{2C} receptor subtypes, but does not show a substantial affinity for any of the other receptors we investigated. When measuring concentration-response curves, affinity constants (K_i) in the two-digit micromolar range were determined for both receptor subtypes (16 ± 2 µM for α_{2B}; 17 ± 2 µM for α_{2C}; mean ± s.d., n = 2). Replacement of the methyl-substituent at the pyrimidine-ring of **28.1** by a cyano substituent (**35**) decreased the TAS2R-selectivity, as **35** can bind to D_2-like dopaminergic receptors and the M_2 muscarinic acetylcholine receptor with affinities in the low micromolar range (K_i 7.3 ± 3 µM for $D_{2S}R$, 16 ± 2 µM for $D_{2L}R$, 1.1 ± 0.6 µM for D_3R, 2.3 ± 0.8 µM for M_2R; mean ± s.d., n = 2).

CONCLUSION

The bitter taste receptor TAS2R14 is a potential target for the treatment of asthma or chronic obstructive pulmonary disease. Activation of TAS2R14 by bitter molecules causes bronchodilation and more prominent bronchodilation than common β-adrenergic receptor agonists. Flufenamic acid, a nonsteroidal anti-inflammatory drug, is one of the most potent and well-characterized agonists of TAS2R14. Starting from flufenamic acid, the synthesis of structural analogs, functional investigations and computationally assisted SAR studies led us to 2-aminopyridines showing considerable efficacy and potency in an IP_1 accumulation assay. In combination with a bioisosteric exchange of the carboxylic moiety by a tetrazole unit, a set of promising new TAS2R14 agonists was developed. The most potent ligand **28.1** (EC_{50} = 72 nM) revealed a six-fold higher potency than flufenamic acid and a maximum efficacy of 129 %. Besides its unprecedented TAS2R14 activation, **28.1** revealed marked selectivity over a panel of 24 non-bitter taste human GPCRs. Our newly described TAS2R14 agonists will serve as valuable tools to better understand the mechanism and the physiological function of bitter

taste receptors and guide the development of drug candidates targeting this intriguing family of membrane proteins.

EXPERIMENTAL SECTION

Chemistry. Dry solvents of high purity grade chemicals were used as purchased without further purification. Reactions were monitored by thin-layer chromatography (TLC) on Merck 60 F254 aluminum sheets. The spots were visualized under UV light at 254 nm. Further reaction monitoring was conducted by HPLC-MS using either a Thermo Scientific Dionex Ultimate 3000 HPLC system equipped with either a Kinetex 2.6u mesh C6 100A (2.1 x 75 mm, 2.6 µm) HPLC column or a Zorbax Eclipse XDB-C8 (4.6 x 150 mm, 5 µm) HPLC column using mass detection on a Bruker amaZon SL mass spectrometer. UV detection was carried out with a DAD (230 nm and 254 nm). Purification was performed using flash column chromatography with Silica 60 (40-63 µm mesh) from Merck as the stationary layer. NMR spectra were measured on a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 101 MHz) or a Bruker Avance 600 (^{1}H: 600 MHz, ^{13}C: 151 MHz) using the solvents indicated. Chemical shifts are described in the δ-scale as parts per million (ppm) relative to TMS or the respective deuterated solvent signal, coupling constants J given in Hertz (Hz) and integral. Splitting patterns are abbreviated as singlet (s), doublet (d), doublet of doublet (dd), doublet of doublet of doublet (ddd), doublet of doublet of doublet of doublet (dddd), triplet (t), quartet (q) and multiplet (m). High-resolution mass spectrometry (HR-MS) was performed on an AB Sciex Triple TOF660 Sciex, on a Bruker maXis MS or a Bruker timsTOF Pro using an electrospray ionization (ESI) or atmospheric pressure photoionization (APPI) source. Purification by preparative RP-HPLC was conducted on Agilent 1260 Preparative Series equipped with a Zorbax Eclipse XDB-C8 (21.1 x 150 mm, 5 µm) column using a flow rate of 10 ml/min. As mobile phase binary gradient solvent systems were used as indicated. in respective procedures Eluent systems are specified below. UV detection was carried out with a VDW detector (λ = 230 nm and 254 nm). Analytical HPLC purity experiments were performed on an Agilent 1200 and 1260 Series HPLC system equipped with a DAD (λ = 220, 254 and 280 nm). A Zorbax Eclipse XDB-C8 (4.6 mm x 150 mm, 5 µm) column with a flow rate of 0.5 ml/min was used in reversed-phase mode. Data analyses were conducted with ChemStation software. Binary systems of the following gradients were applied: (A) 10% methanol in 0.1% aqueous formic acid for 3 min, from 10% to 100% in 15 min, 100% for 6 min, 100% to 5% in 3 min, 10% for 3 min. (B) 5% acetonitrile in

0.1% aqueous formic acid for 3 min, 5% to 95% in 15 min, 95% for 6 min, 95% to 5% in 3 min, 5% for 3 min. All target compounds investigated for biological activity were confirmed to be at least 95% pure by HPLC.

General procedure for the coupling of aniline/aminopyridines/aminopyrimidines with aryl halides (GP1). The respective aryl halide (if solid), aniline / aminopyridine / aminopyrimidine (if solid), $Pd(OAc)_2$, and (±)-BINAP were dissolved in dry toluene. The reaction mixture was purged with argon and the aryl halide (if liquid), aniline / aminopyridine / aminopyrimidine (if liquid) were added under argon flow. Cs_2CO_3 was added before the mixture was purged with argon for two more minutes and stirred at 120 °C. When completed, the reaction mixture was diluted with EtOAc, washed with 2 M HCl (3x), brine (3x), dried over $MgSO_4$, filtered and evaporated. Purification occurred by flash column chromatography.

General procedure for the hydrolysis of phenylamino benzoates (GP2). The respective aryl phenylamino benzoate was dissolved in a mixture of EtOH/H_2O, EtOH/THF, EtOH/THF/H_2O, MeOH/H_2O or MeOH/THF/H_2O. After the addition of 2 M NaOH or KOH, the reaction was stirred at rt, reflux, 80 °C or 100 °C. After completion, the mixture was cooled to rt and diluted with H_2O before the organic solvent was evaporated. The aqueous remain was acidified using 2 M HCl to pH 1. The respective final compound was received by washing the formed precipitate with H_2O. If necessary, further purification steps were made. These are indicated for the respective compound.

General procedure for the synthesis of tetrazoles from their benzyl protected precursors (GP3). The respective benzyl-protected tetrazole was dissolved in EtOH or EtOH/CH_2Cl_2 in a dried Schlenk flask. The flask was evacuated and purged with argon. Palladium on carbon (10 wt%) was added before the flask was evacuated and filled with argon another three times. The reaction was purged with H_2 and stirred at rt. After completion, the mixture was filtered through a syringe filter and the solvent was evaporated. Purification of the respective tetrazole was conducted by flash column chromatography or preparative HPLC.

Methyl 2-((3-(pentafluoro-λ^6-sulfanyl)phenyl)amino)benzoate (3.1).[14] Compound **3.1** was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 100 µL, 711 µmol, 1.00 eq), 3-(pentafluoro-λ^6-sulfanyl)aniline (**2.1**, 188 mg, 858 µmol, 1.21 eq), $Pd(OAc)_2$ (10.0 mg, 44.5

µmol, 0.06 eq), (±)-BINAP (35.0 mg, 59.2 µmol, 0.08 eq) and Cs_2CO_3 (325 mg, 997 µmol, 1.40) in 5 mL dry toluene. The reaction was stirred for 4 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (*n*-hexane/EtOAc, 50:1) yielded **3.1** as a light orange oil (252 mg, 96%). R_f = 0.31 (*n*-hexane/EtOAc 50:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.62 (s, 1H), 8.00 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.64 – 7.62 (m, 1H), 7.44 – 7.35 (m, 4H), 7.29 – 7.25 (m, 1H), 6.84 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 155.3 – 154.5 (m), 146.6, 141.7, 134.5, 132.0, 129.6, 124.4, 120.6 – 1120.2 (m), 119.3 – 119.0 (m), 118.7, 114.3, 113.3, 52.2. LC-MS (ESI-MS): m/z 354.02 $[M+H]^+$.

Methyl 2-((3-chlorophenyl)amino)benzoate (3.2).[15] Compound **3.2** was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 100 µL, 711 µmol, 1.00 eq), 3-chloroaniline (**2.2**, 90 µL, 858 µmol, 1.21 eq), $Pd(OAc)_2$ (8.00 mg, 35.6 µmol, 0.05 eq), (±)-BINAP (37.0 mg, 59.4 µmol, 0.08 eq) and Cs_2CO_3 (327 mg, 1.00 mmol, 1.41 eq) in 5 ml dry toluene. The reaction was stirred for 4 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash column chromatography (*n*-hexane/EtOAc 20:1) yielded **3.2** as a green oil (154 mg, 78%). R_f = 0.41 (*n*-hexane/EtOAc 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 7.97 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.36 (ddd, *J* = 8.6, 7.0, 1.7 Hz, 1H), 7.29 (ddd, *J* = 8.5, 1.3, 0.5 Hz, 1H), 7.27 – 7.22 (m, 2H), 7.10 (ddd, *J* = 8.1, 2.1, 1.0 Hz, 1H), 7.03 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 1H), 6.79 (ddd, *J* = 8.1, 7.0, 1.3 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 147.0, 142.5, 135.0, 134.3, 131.8, 130.5, 123.3, 121.6, 119.9, 118.2, 114.6, 112.9, 52.1. LC-MS (ESI-MS): m/z 261.93 $[M+H]^+$.

Methyl 2-((3-(difluoromethoxy)phenyl)amino)benzoate (3.3). 3.3 was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 100 µL, 711 µmol, 1.00 eq), 3-(difluoromethoxy)aniline (**2.3**, 110 µL, 885 µmol, 1.24 eq), $Pd(OAc)_2$ (8.00 mg, 35.6 µmol, 0.05 eq), (±)-BINAP (36.0 mg, 57.8 µmol, 0.08 eq) and Cs_2CO_3 (325 mg, 997 mmol, 1.40 eq) in 5 ml dry toluene. The reaction was stirred for 21 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash column chromatography (toluene) yielded **3.3** as a yellow oil (147 mg, 71%). R_f = 0.31 (isohexane/EtOAc 25:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.53 (s, 1H), 7.98 (ddd, *J* = 8.0, 1.6, 0.5 Hz, 1H), 7.36 (ddd, *J* = 8.4, 6.8, 1.6 Hz, 1H), 7.35 – 7.26 (m, 2H), 7.08 (ddd, *J* = 8.1, 2.1, 0.9 Hz, 1H), 7.03 – 7.01 (m, 1H), 6.83 – 6.77 (m, 2H),

6.51 (t, *J* = 74.0 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 152.3, 146.9, 142.7, 134.3, 131.8, 130.6, 118.5, 118.2, 116.0 (t, *J* = 259.4 Hz), 114.7, 113.7, 112.9, 112.5, 52.1. LC-MS (ESI-MS): m/z 294.04 $[M+H]^+$.

2-((3-(Pentafluoro-λ^6-sulfaneyl)phenyl)amino)benzoic acid (4.1).[14] Compound **4.1** was synthesized according to **GP2** using **3.1** (91.0 mg, 258 µmol, 1.00 eq) and KOH (89.0 mg, 1.59 mmol, 6.16 eq) in a mixture of EtOH (4 mL) and H_2O (1 mL). The mixture was stirred at reflux for 1 h. Completion of the reaction was monitored via TLC and LC-MS. Precipitation, filtration and purification by flash chromatography (CH_2Cl_2/MeOH 50:1 + 0.1% HCOOH) yielded **4.1** as a yellow solid (66.0 mg, 76%). R_f = 0.23 (CH_2Cl_2/MeOH 50:1 + 0.1% HCOOH). RP-HPLC: 96% (t_R = 21.1 min, system A), > 99.9% (t_R = 18.8 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.17 (s, 1H), 9.66 (s, 1H), 7.94 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.73 – 7.70 (m, 1H), 7.56 – 7.44 (m, 4H), 7.29 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.92 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.4, 154.8 – 152.6 (m), 145.1, 142.2, 134.1, 132.0, 130.3, 123.4, 119.3, 119.2 – 118.9 (m), 117.2 – 116.9 (m), 115.2, 115.0. LC-MS (ESI-MS): m/z 339.98 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{13}H_{11}F_5NO_2S$: 340.0425, found: 340.0427.

2-((3-Chlorophenyl)amino)benzoic acid (4.2).[15] Compound **4.2** was synthesized according to **GP2** using **3.2** (82.0 mg, 313 µmol, 1.00 eq) and KOH (90.0 mg, 1.60 mmol, 5.12 eq) in a mixture of EtOH (4 mL) and H_2O (1 mL). The mixture was stirred at reflux for 1 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **4.2** as a yellow solid (40.0 mg, 52%). R_f = 0.23 (CH_2Cl_2/MeOH 50:1 + 0.1% HCOOH). RP-HPLC: 99% (t_R = 20.7 min, system A), > 99.9% (t_R = 18.2 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.17 (s, 1H), 9.63 (s, 1H), 7.93 (ddd, *J* = 7.9, 1.7, 0.4 Hz, 1H), 7.45 (ddd, *J* = 8.5, 7.1, 1.7 Hz, 1H), 7.39 – 7.26 (m, 3H), 7.21 (ddd, *J* = 8.1, 2.2, 0.9 Hz, 1H), 7.07 (ddd, *J* = 7.9, 2.0, 0.9 Hz, 1H), 6.87 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.7, 145.7, 142.6, 134.2, 133.8, 131.9, 131.0, 122.2, 119.9, 118.8, 118.6, 114.9, 114.0. LC-MS (ESI-MS): m/z 247.90 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{13}H_{11}ClNO_2$: 248.0473, found: 248.0475.

2-((3-(Difluoromethoxy)phenyl)amino)benzoic acid (4.3).[16] Compound **4.3** was synthesized according to **GP2** using **3.3** (86.0 mg, 293 µmol, 1.00 eq) and KOH (36.0 mg, 642

µmol, 2.19 eq) in a mixture of EtOH (3 mL) and H_2O (1 mL). The mixture was stirred at reflux for 1 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **4.3** as a light-yellow solid (69.0 mg, 84%). RP-HPLC: > 99.9% (t_R = 19.9 min, system A), 99% (t_R = 17.7 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.19 (s, 1H), 9.68 (s, 1H), 7.93 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.47 – 7.26 (m, 4H), 7.12 (ddd, *J* = 8.1, 2.2, 0.9 Hz, 1H), 7.04 (t, *J* = 2.2 Hz, 1H), 6.89 – 6.80 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.8, 152.0 (t, *J* = 3.2 Hz) 145.8, 142.5, 134.2, 131.9, 130.8, 118.5, 117.0, 116.4 (t, *J* = 257.1 Hz), 114.7, 112.4, 110.3. LC-MS (ESI-MS): m/z 280.00 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{14}H_{12}F_2NO_3$: 280.0780, found: 280.0782.

Methyl 2-(methyl(3-(trifluoromethyl)phenyl)amino)benzoate (7). In a microwave tube, methyl 2-bromobenzoate (**1**, 65.4 µL, 465 µmol, 1.00 eq), N-methyl-3-(trifluoromethyl)aniline (**6.1**, 164 mg, 936 µmol, 2.01 eq), $Pd_2(dba)_3$ (35.0 mg, 38.2 µmol, 0.07 eq) and XPhos (71.0 mg, 149 µmol, 0.32 eq) were dissolved in dry toluene (2 mL). Then, K_3PO_4 (201 mg, 947 µmol, 2.04 eq) was added under constant argon flow, the tube was sealed with a crimp cap with rubber septum and stirred at 110°C for 24 h. Completion of the reaction was monitored via TLC and LC-MS. After cooling to rt, the mixture was diluted with EtOAc, washed with 2 M HCl (3x), brine (3x), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (isohexane/EtOAc 20:1) yielded **7** as a yellow oil (50.0 mg, 35%). R_f = 0.26 (isohexane/ EtOAc 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (ddd, *J* = 7.8, 1.7, 0.5 Hz, 1H), 7.58 (ddd, *J* = 7.9, 7.4, 1.7 Hz, 1H), 7.37 – 7.32 (m, 1H), 7.29 (ddd, *J* = 8.0, 1.2, 0.5 Hz, 1H), 7.24 – 7.18 (m, 1H), 6.98 – 6.93 (m, 1H), 6.81 (dd, *J* = 2.1 Hz, 1H), 6.68 (dd, *J* = 8.4, 2.5 Hz, 1H), 3.63 (s, 3H), 3.30 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.8, 149.3, 147.1, 133.7, 131.8, 131.2 (q, *J* = 31.6 Hz), 129.8, 129.4, 129.2, 126.4, 124.4 (q, *J* = 272.3 Hz), 116.7 – 116.4 (m), 113.9 (q, *J* = 3.9 Hz), 109.4 (q, *J* = 4.0 Hz), 52.2, 40.3. LC-MS (ESI-MS): m/z 309.98 $[M+H]^+$.

2-((3-(Prop-1-yn-1-yl)-5-(trifluoromethyl)phenyl)amino)benzoic acid (8). Compound **8** was synthesized according to **GP2** using **7** (40.0 mg, 129 µmol, 1.00 eq) and KOH (26.0 mg, 463 µmol, 3.58 eq) in a mixture of MeOH (2 mL) and H_2O (0.5 mL). The mixture was stirred at 80°C for 3.5 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration

yielded **8** as a yellow solid (48.0 mg, 85%). RP-HPLC: > 99.9% (t_R = 20.1 min, system A), > 99.9% (t_R = 18.2 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.82 (s, 1H), 7.84 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.67 (ddd, *J* = 7.7, 1.7 Hz, 1H), 7.44 (ddd, *J* = 7.6, 1.2 Hz, 1H), 7.36 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34 – 7.28 (m, 1H), 6.97 – 6.91 (m, 1H), 6.73 – 6.67 (m, 2H), 3.24 (s, 3H).). ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.2, 149.2, 145.7, 133.5, 131.1, 130.6, 130.0 – 129.0 (m), 126.8, 123.0 (q, *J* = 272.3 Hz), 116.3 – 116.0 (m), 112.5 (q, *J* = 3.8 Hz), 108.0 (q, *J* = 4.1 Hz), 39.8. LC-MS (ESI-MS): m/z 295.98 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{15}H_{13}F_3NO_2$: 296.0893, found: 296.0893.

Methyl 3-((3-(trifluoromethyl)phenyl)amino)benzoate (9.1).[15] Compound **9.1** was synthesized according to **GP1** using methyl 3-bromobenzoate (**5.1**, 101 mg, 470 µmol, 1.00 eq), 3-(trifluoromethyl)aniline (**6.2**, 70.4 µL, 564 µmol, 1.20 eq), $Pd(OAc)_2$ (7.00 mg, 31.2 µmol, 0.07 eq), (±)-BINAP (25.0 mg, 40.2 µmol, 0.09 eq) and Cs_2CO_3 (223 mg, 684 µmol, 1.46 eq) in 5 mL dry toluene. The reaction was finished after 16 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 10:1) yielded **9.1** as a white solid (111 mg, 80%). R_f = 0.40 (isohexane/EtOAc 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 – 7.66 (m, 1H), 7.59 (ddd, *J* = 7.6, 1.6, 1.1 Hz, 1H), 7.34 – 7.28 (m, 2H), 7.22 (ddd, *J* = 8.1, 2.4, 1.1 Hz, 1H), 7.20 – 7.14 (m, 2H), 7.13 – 7.09 (m, 1H), 5.86 (s, 1H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.8, 142.3, 141.2, 130.9 (q, *J* = 32.1 Hz), 130.5, 129.0, 128.6, 127.1 – 118.7 (m), 122.1, 121.6, 119.4 – 119.0 (m), 118.4, 116.7 (q, *J* = 3.8 Hz), 113.0 (q, *J* = 3.9 Hz), 51.2. LC-MS (ESI-MS): m/z 295.98 $[M+H]^+$.

Methyl 4-((3-(trifluoromethyl)phenyl)amino)benzoate (9.2).[15] Compound **9.2** was synthesized according to **GP1** using methyl 4-bromobenzoate (**5.2**, 105 mg, 488 µmol, 1.00 eq), 3-(trifluoromethyl)aniline (**6.2**, 73.2 µL, 564 µmol, 1.20 eq), $Pd(OAc)_2$ (6.00 mg, 26.7 µmol, 0.05 eq), (±)-BINAP (24.0 mg, 38.5 µmol, 0.08 eq) and Cs_2CO_3 (242 mg, 743 µmol, 1.52 eq) in 5 mL dry toluene. The reaction was finished after 16 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/CH_2Cl_2 1:1 to 100% CH_2Cl_2) yielded **9.2** as a yellow solid (98.0 mg, 68%). R_f = 0.43 (isohexane/CH_2Cl_2 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 – 7.87 (m, 2H), 7.36 (dd, *J* = 7.9 Hz, 1H), 7.32 – 7.30 (m, 1H), 7.28 – 7.24 (m, 1H), 7.23 – 7.18 (m, 1H), 6.99 – 6.94 (m, 2H), 6.06 (s, 1H), 3.82 (s, 3H).

^{13}C NMR (101 MHz, $CDCl_3$): δ 165.7, 145.7, 140.7, 131.0 (q, *J* = 32.4 Hz), 130.6, 129.0, 122.8 (q, *J* = 272.3 Hz), 121.4 – 121.2 (m), 121.4, 118.1 (q, *J* = 3.9 Hz), 115.0 (q, *J* = 3.9 Hz), 114.5, 50.8. LC-MS (ESI-MS): m/z 296.01 $[M+H]^+$. RP-HPLC: 100% (t_R = 20.1 min, system A), 100% (t_R = 18.2 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.82 (s, 1H), 7.84 (dd, *J* = 7.7, 1.6 Hz, 1H), 7.67 (ddd, *J* = 7.7, 1.7 Hz, 1H), 7.44 (ddd, *J* = 7.6, 1.2 Hz, 1H), 7.36 (dd, *J* = 8.0, 1.2 Hz, 1H), 7.34 – 7.28 (m, 1H), 6.97 – 6.91 (m, 1H), 6.73 – 6.67 (m, 2H), 3.24 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 167.2, 149.2, 145.7, 133.5, 131.1, 130.6, 130.0 – 129.0 (m), 126.8, 123.0 (q, *J* = 272.3 Hz), 116.3 – 116.0 (m), 112.5 (q, *J* = 3.8 Hz), 108.0 (q, *J* = 4.1 Hz), 39.8. LC-MS (ESI-MS): m/z 295.98 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{15}H_{12}F_3NO_2$: 296.0893, found: 296.0894.

3-((3-(Trifluoromethyl)phenyl)amino)benzoic acid (10.1).[15] Compound **10.1** was synthesized according to **GP2** using **9.1** (50.0 mg, 169 µmol, 1.00 eq) and KOH (23.0 mg, 410 µmol, 2.42 eq) in a mixture of EtOH (2 mL) and H_2O (1 mL). The mixture was stirred at 100°C for 1 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **10.1** in a brownish solid (28.0 mg, 59%). RP-HPLC: 98% (t_R = 19.7 min, system A), > 99.9% (t_R = 17.4 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.96 (s, 1H), 8.76 (s, 1H), 7.68 (dd, *J* = 1.8 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.41 (dd, *J* = 7.7 Hz, 1H), 7.38 – 7.33 (m, 2H), 7.30 (dd, *J* = 1.9 Hz, 1H), 7.19 – 7.14 (m, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 167.1, 143.9, 142.4, 131.8, 130.4, 130.0 (q, *J* = 31.3 Hz), 129.5, 124.1 (q, *J* = 272.3 Hz), 121.5, 121.5, 119.6 – 119.5 (m), 117.8, 115.8 (q, *J* = 3.9 Hz), 112.3 (q, *J* = 3.9 Hz). LC-MS (ESI-MS): m/z 281.96 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{14}H_{11}F_3NO_2$: 282.0736, found: 282.0737.

4-((3-(Trifluoromethyl)phenyl)amino)benzoic acid (10.2).[15] Compound **10.2** was synthesized according to **GP2** using **9.2** (48.0 mg, 163 µmol, 1.00 eq) and KOH (19.0 mg, 339 µmol, 2.08 eq) in a mixture of EtOH (2 mL) and H_2O (1 mL). The mixture was stirred at 100°C for 1 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **10.2** as a white solid (25.0 mg, 55%). RP-HPLC: > 99.9% (t_R = 19.6 min, system A), > 99.9% (t_R = 17.2 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.47 (s, 1H), 9.04 (s, 1H), 7.87 – 7.82 (m, 2H), 7.55 – 7.46 (m, 2H), 7.39 (dd, *J* = 2.0 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.16 – 7.10 (m, 2H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 166.9, 146.7, 142.6, 131.1, 130.4, 130.0 (q, *J* =

31.4 Hz), 124.0 (q, *J* = 272.4 Hz), 121.7, 121.3 – 121.2 (m), 117.1 (q, *J* = 3.9 Hz), 115.1, 114.0 (q, *J* = 3.9 Hz). LC-MS (ESI-MS): m/z 281.96 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{14}H_{11}F_3NO_2$: 282.0736, found: 282.0737.

Methyl 2-((2-methyl-3-(trifluoromethyl)phenyl)amino)benzoate (13.1). Compound **13.1** was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 100 µL, 711 µmol, 1.00 eq), 2-methyl-3-(trifluoromethyl)aniline (**12.1**, 150 mg, 856 µmol, 1.20 eq), $Pd(OAc)_2$ (8.00 mg, 35.6 µmol, 0.05 eq), (±)-BINAP (36.0 mg, 57.8 µmol, 0.08 eq) and Cs_2CO_3 (325 mg, 997 mmol, 1.40 eq) in 5 ml dry toluene. The reaction was stirred for 21 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash column chromatography (isohexane/EtOAc 50:1) yielded **13.1** as a light-yellow solid (167 mg, 76%). %). R_f = 0.40 (isohexane/EtOAc 50:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.34 (s, 1H), 7.99 (ddd, *J* = 8.1, 1.7, 0.4 Hz, 1H), 7.52 (d, *J* = 8.0 Hz, 1H), 7.47 – 7.44 (m, 1H), 7.32 – 7.24 (m, 2H), 6.82 (ddd, *J* = 8.5, 1.1, 0.5 Hz, 1H), 6.75 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 3.92 (s, 3H), 2.41 – 2.38 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.2, 148.4, 140.9, 134.4, 131.9, 131.8, 130.7 (q, *J* = 29.5 Hz), 127.7, 126.4, 124.5 (q, *J* = 273.9 Hz), 122.2 (q, *J* = 5.8 Hz), 117.4, 114.0, 112.00, 52.0, 13.9 (q, *J* = 2.4 Hz). LC-MS (ESI-MS): m/z 310.06 $[M+H]^+$.

Methyl 2-((4-methyl-3-(trifluoromethyl)phenyl)amino)benzoate (13.2). Compound **13.2** was synthesized according to **GP1** using methyl 2-bromobenzoate (**1**, 100 µL, 815 µmol, 1.00 eq), 4-methyl-3-(trifluoromethyl)aniline (**12.2**, 123 µL, 857 µmol, 1.20 eq), $Pd(OAc)_2$ (10.0 mg, 44.5 µmol, 0.06 eq), (±)-BINAP (37.0 mg, 59.4 µmol, 0.08 eq) and Cs_2CO_3 (329 mg, 1.01 mmol, 1.42 eq) in 5 mL dry toluene. The reaction was finished after 2 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 20:1) yielded **13.2** as a yellow oil (189 mg, 86%). R_f = 0.53 (isohexane/EtOAc 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.49 (s, 1H), 8.00 – 7.95 (m, 1H), 7.48 (d, *J* = 2.3 Hz, 1H), 7.34 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.30 (dd, *J* = 8.2, 2.4 Hz, 1H), 7.24 (d, *J* = 8.2 Hz, 1H), 7.20 – 7.14 (m, 1H), 6.77 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 3.91 (s, 3H), 2.45 (q, *J* = 1.9 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 147.5, 138.7, 134.3, 132.9, 131.7, 131.3 (q, *J* = 1.6 Hz), 129.8 (q, *J* = 30.0 Hz), 125.4 – 125.1 (m), 124.3 (q, *J* = 273.9 Hz), 119.9 (q, *J* = 5.7 Hz), 117.6, 113.8, 112.2, 51.9, 18.7. LC-MS (ESI-MS): m/z 310.04 $[M+H]^+$.

Methyl 2-((3-methyl-5-(trifluoromethyl)phenyl)amino)benzoate (13.3). Compound **13.3** was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 100 µL, 711 µmol, 1.00 eq), 3-methyl-5-(trifluoromethyl)aniline (**12.3**, 160 mg, 913 µmol), $Pd(OAc)_2$ (8.00 mg, 35.6 µmol), (±)-BINAP (38.0 mg, 61.0 µmol) and Cs_2CO_3 (325 mg, 997 µmol) in 5 mL dry toluene. The reaction was finished after 22 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 20:1) yielded **13.3** as a brown oil (95.0 mg, 43%). R_f = 0.44 (isohexane/EtOAc 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.54 (s, 1H), 7.99 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.37 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.32 – 7.30 (m, 1H), 7.29 – 7.26 (m, 1H), 7.22 – 7.20 (m, 1H), 7.13 – 7.10 (m, 1H), 6.81 (ddd, *J* = 8.1, 7.0, 1.2 Hz, 1H), 3.91 (s, 3H), 2.39 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ δ 169.0, 147.0, 141.6, 140.3, 134.4, 132.4 – 131.2 (m), 131.9, 124.2 (q, *J* = 272.8 Hz), 120.5 (q, *J* = 3.8 Hz), 118.2, 115.4 (q, *J* = 3.8 Hz), 114.5, 112.9, 52.1, 21.6. LC-MS (ESI-MS): m/z 310.03 $[M+H]^+$.

Methyl 2-((2-methyl-5-(trifluoromethyl)phenyl)amino)benzoate (13.4). Compound **13.4** was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 100 µL, 711 µmol, 1.00 eq), 2-methyl-5-(trifluoromethyl)aniline (**12.4**, 150 mg, 856 µmol, 1.20 eq), $Pd(OAc)_2$ (11.0 mg, 49.0 µmol, 0.07 eq), (±)-BINAP (40.0 mg, 64.2 µmol, 0.09 eq) and Cs_2CO_3 (330 mg, 1.01 mmol, 1.42 eq) in 5 mL dry toluene. The reaction was finished after 7 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 50:1) yielded **13.4** as a light-yellow solid (166 mg, 75%). R_f = 0.35 (isohexane/EtOAc 50:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.40 (s, 1H), 8.00 (ddd, *J* = 8.1, 1.7, 0.5 Hz, 1H), 7.63 – 7.60 (m, 1H), 7.38 – 7.32 (m, 2H), 7.30 – 7.26 (m, 1H), 7.00 (ddd, *J* = 8.6, 1.1, 0.5 Hz, 1H), 6.79 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 3.92 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.0, 147.5, 139.8, 135.8, 134.4, 131.7, 131.5, 129.10 (q, *J* = 32.2 Hz), 124.12 (q, *J* = 271.9 Hz), 120.4 (q, *J* = 3.9 Hz), 118.9 (q, *J* = 3.8 Hz), 117.7, 114.0, 112.3, 51.9, 18.2. LC-MS (ESI-MS): m/z 310.06 $[M+H]^+$.

Methyl 2-((2-bromo-3-(trifluoromethyl)phenyl)amino)benzoate (13.5). Compound **13.5** was synthesized according to **GP1** using methyl 2-iodobenzoate (**11**, 210 µL, 1.39 mmol, 1.00 eq), 2-bromo-3-(trifluoromethyl)aniline (**12.5**, 402 mg, 1.67 mmol, 1.21 eq), $Pd(OAc)_2$ (22.0 mg, 98.0 µmol, 0.07 eq), (±)-BINAP (71.0 mg, 114 µmol, 0,08 eq) and Cs_2CO_3 (698 g, 2.14 mmol,

1.55 eq) in 5 mL dry toluene at 100°C. The reaction was finished after 15 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 40:1) yielded **13.5** as an off-white solid (444 mg, 86%). R_f = 0.39 (isohexane/EtOAc 40:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.74 (s, 1H), 8.02 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.68 – 7.63 (m, 1H), 7.42 – 7.30 (m, 3H), 7.26 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.89 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 168.5, 145.4, 141.6, 134.0, 131.88, 131.87 (q, *J* = 30.8 Hz), 127.5, 123.5, 123.0 (q, *J* = 273.5 Hz), 121.3 (q, *J* = 5.7 Hz), 119.3, 115.3, 114.5, 114.1 – 114.0 (m), 52.1. LC-MS (ESI-MS): m/z 374.15 $[M+H]^+$, 376.06 $[M+H]^+$.

Methyl 2-((4-bromo-3-(trifluoromethyl)phenyl)amino)benzoate (13.6). Compound **13.6** was synthesized according to **GP1** using methyl 2-iodobenzoate (**11**, 300 µL, 488 µmol, 1.00 eq), 4-bromo-3-(trifluoromethyl)aniline (**12.6**, 573 mg, 2.39 mmol, 1.22 eq), $Pd(OAc)_2$ (23.0 mg, 102 µmol, 0.05 eq), (±)-BINAP (102 mg, 164 µmol, 0.09 eq) and Cs_2CO_3 (917 mg, 2.81 mmol, 1.41 eq) in 5 mL dry toluene. The reaction was finished after 16 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 20:1) yielded **13.6** as a white solid (580 mg, 78%). R_f = 0.37 (isohexane/EtOAc 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.52 (s, 1H), 7.93 (ddd, *J* = 8.1, 1.7, 0.5 Hz, 1H), 7.54 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.47 (d, *J* = 2.7 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.23 – 7.15 (m, 1H), 6.78 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 146.0, 140.7, 135.7, 134.3, 131.9, 131.0 (q, *J* = 31.3 Hz), 124.9, 122.7 (q, *J* = 273.5 Hz), 120.4 (q, *J* = 5.5 Hz), 118.8, 114.4, 113.3, 111.9 (q, *J* = 1.6 Hz), 52.0. LC-MS (ESI-MS): m/z 374.03 $[M+H]^+$, 375.98 $[M+H]^+$.

Methyl 2-((3-bromo-5-(trifluoromethyl)phenyl)amino)benzoate (13.7).[34] Compound **13.7** was synthesized according to **GP1** using methyl 2-iodobenzoate (**11**, 500 µL, 3.40 mmol, 1.00 eq), 3-bromo-5-(trifluoromethyl)aniline (**12.7**, 528 µL, 3.74 mmol, 1.10 eq), $Pd(OAc)_2$ (38.0 mg, 169 µmol, 0.06 eq), (±)-BINAP (170 mg, 273 µmol, 0.08 eq) and Cs_2CO_3 (1.55 g, 4.75 mmol, 1.42 eq) in 7 mL dry toluene. The reaction was finished after 16 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/CH_2Cl_2 7:1) yielded **13.7** as a white solid (898 mg, 71%). R_f = 0.44 (isohexane/CH_2Cl_2 7:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.65 (s, 1H), 8.01 (ddd, *J* = 8.1, 1.7, 0.5 Hz, 1H), 7.55 (dd, *J* = 2.0 Hz,

1H), 7.43 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.40 – 7.38 (m, 2H), 7.32 (ddd, *J* = 8.5, 1.2, 0.5 Hz, 1H), 6.89 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 145.5, 143.3, 134.3, 133.2 (q, *J* = 32.9 Hz), 131.9, 126.2 – 126.0 (m), 123.3, 123.1 (q, *J* = 273.0 Hz), 122.0 (q, *J* = 3.8 Hz), 119.3, 115.9 (q, *J* = 3.8 Hz), 114.9, 113.8, 52.1. LC-MS (ESI-MS): m/z 375.83 $[M+H]^+$.

Methyl 2-((2-bromo-5-(trifluoromethyl)phenyl)amino)benzoate (13.8). Compound **13.8** was synthesized according to **GP1** using methyl 2-iodobenzoate (**11**, 100 µL, 660 µmol, 1.00 eq), 2-bromo-5-(trifluoromethyl)aniline (**12.8**, 104 µL, 726 µmol, 1.10 eq), $Pd(OAc)_2$ (16.0 mg, 71.3 µmol,0.11 eq), (±)-BINAP (65.0 mg, 104 µmol, 0.16 eq) and Cs_2CO_3 (302 mg, 927 µmol, 1.40 eq) in 5 mL dry toluene. The reaction was finished after 3 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 50:1) yielded **13.8** as an off-white solid (133 mg, 54%). R_f = 0.40 (isohexane/EtOAc 50:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.72 (s, 1H), 8.03 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.75 – 7.67 (m, 2H), 7.44 (ddd, *J* = 7.1, 1.7, 0.5 Hz, 1H), 7.32 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.11 (ddd, *J* = 8.3, 2.2, 0.7 Hz, 1H), 6.92 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.5, 144.9, 140.3, 134.2, 134.0, 131.9, 130.4 (q, *J* = 32.8 Hz), 127.9 – 119.6 (m), 119.5 (q, *J* = 3.8 Hz), 116.1 (q, *J* = 3.8 Hz), 115.2, 114.6, 100.0, 52.2. LC-MS (ESI-MS): m/z 373.99 $[M+H]^+$, 375.98 $[M+H]^+$.

Methyl 2-((4-cyano-3-(trifluoromethyl)phenyl)amino)benzoate (13.9). Compound **13.9** was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 100 µL, 711 µmol, 1.00 eq), 4-amino-2-(trifluoromethyl)benzonitrile (**12.9**, 160 mg, 860 µmol, 1.21 eq), $Pd(OAc)_2$ (8.00 mg, 35.6 µmol, 0.05 eq), (±)-BINAP (37.0 mg, 59.4 µmol, 0.08 eq) and Cs_2CO_3 (330 mg, 1.01 mmol, 1.42 eq) in 4 mL dry toluene. The reaction was finished after 16 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 10:1) yielded **13.9** as a white solid (209 mg, 92%). R_f = 0.23 (isohexane/EtOAc 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.90 (s, 1H), 8.05 (ddd, *J* = 8.0, 1.6, 0.5 Hz, 1H), 7.70 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.53 – 7.48 (m, 2H), 7.46 (ddd, *J* = 8.4, 1.5, 0.5 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.03 (ddd, *J* = 8.0, 6.9, 1.5 Hz, 1H), 3.93 (s, 3H).). ^{13}C NMR (151 MHz, $CDCl_3$): δ 168.6, 146.1, 143.5, 136.3, 134.3, 134.6 (q, *J* = 32.5 Hz), 132.1, 122.4 (q, *J* = 274.1 Hz), 121.4, 119.9, 116.8,

116.3, 116.99, 115.96 (q, *J* = 4.9 Hz), 100.8, 52.4. LC-MS (ESI-MS): m/z 321.05 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{13}H_{10}ClNO_2$: 248.0473, found: 248.0475.

Methyl 2-((3-cyano-5-(trifluoromethyl)phenyl)amino)benzoate (13.10). 13.10 was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 130 µL, 925 µmol, 1.00 eq), 4-amino-2-(trifluoromethyl)benzonitrile (**12.10**, 211 mg, 1.13 mmol, 1.20 eq), $Pd(OAc)_2$ (12.0 mg, 53.5 µmol, 0.05 eq), (±)-BINAP (50.0 mg, 80.3 µmol, 0.08 eq) and Cs_2CO_3 (430 mg, 1.32 mmol, 1.40 eq) in 5 ml dry toluene. The reaction was stirred for 5 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash column chromatography (isohexane/EtOAc 50:1) yielded **13.10** as a white solid (256 mg, 86%). R_f = 0.20 (isohexane/EtOAc 50:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.78 (s, 1H), 8.04 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.68 – 7.66 (m, 1H), 9.78 (s, 1H), 8.04 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.68 – 7.66 (m, 1H), 7.65 – 7.62 (m, 1H), 7.51 – 7.45 (m, 2H), 7.34 (ddd, *J* = 8.4, 1.1, 0.5 Hz, 1H), 6.97 (ddd, *J* = 8.0, 7.2, 1.1 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 144.5, 143.4, 134.4, 133.3 (q, *J* = 33.6 Hz), 132.1, 125.0, 122.8 (q, *J* = 273.0 Hz), 121.6 (q, *J* = 3.9 Hz), 120.5 (q, *J* = 3.7 Hz), 120.3, 117.5, 115.2, 114.7, 114.3, 52.3. LC-MS (ESI-MS): m/z 321.07 $[M+H]^+$.

Methyl 2-((2-cyano-5-(trifluoromethyl)phenyl)amino)benzoate (13.11). Compound **13.11** was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 100 µL, 711 µmol, 1.00 eq), 2-amino-4-(trifluoromethyl)benzonitrile (**12.11**, 169 mg, 908 µmol, 1.28 eq), $Pd(OAc)_2$ (9.00 mg, 40.1 µmol, 0.06 eq), (±)-BINAP (38.0 mg, 61.0 µmol, 0.09 eq) and Cs_2CO_3 (325 mg, 997 µmol, 1.40 eq) in 5 mL dry toluene. The reaction was finished after 22 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 20:1) yielded **13.11** as a yellow solid (205 mg, 90%). R_f = 0.21 (isohexane/EtOAc 20:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.15 (s, 1H), 8.07 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.78 – 7.76 (m, 1H), 7.74 – 7.70 (m, 1H), 7.55 – 7.45 (m, 1H), 7.40 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.27 – 7.19 (m, 1H), 7.04 (ddd, *J* = 8.0, 7.2, 1.2 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.2, 145.5, 143.4, 135.4 (q, *J* = 32.9 Hz), 134.3, 134.2, 132.1, 123.1 (q, *J* = 273.4 Hz), 121.3, 117.8 (q, *J* = 3.7 Hz), 116.3, 115.99, 115.97, 114.3 (q, *J* = 3.9 Hz), 106.2 – 106.1 (m), 52.5. LC-MS (ESI-MS): m/z 321.05 $[M+H]^+$.

2-((2-Methyl-3-(trifluoromethyl)phenyl)amino)benzoic acid (14.1).[35] Compound **14.1** was synthesized according to **GP2** using **13.1** (87.0 mg, 281 µmol, 1.00 eq) and KOH (32.0 mg, 570 µmol, 2.03 eq) in a mixture of EtOH (4 mL) and H_2O (1 mL). The mixture was stirred at reflux for 1 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **14.1** as a light -yellow solid (78.0 mg, 94%). RP-HPLC: > 99.9% (t_R = 21.2 min, system A), 99% (t_R = 19.0 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.18 (s, 1H), 9.61 (s, 1H), 7.93 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.64 (d, *J* = 7.9 Hz, 1H), 7.53 – 7.48 (m, 1H), 7.46 – 7.35 (m, 2H), 6.86 – 6.78 (m, 2H), 2.33 – 2.30 (m, 3H).). ^{13}C NMR (151 MHz, DMSO-d_6): δ 170.1, 147.3, 140.8, 134.3, 131.8, 130.1 – 130.0 (m), 129.0 (q, *J* = 28.8 Hz), 127.3 – 121.6 (m), 121.4 (q, *J* = 5.7 Hz), 117.6, 113.6, 112.6, 13.5 – 13.4 (m). LC-MS (ESI-MS): m/z 296.06 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{15}H_{13}F_3NO_2$: 296.0893, found: 296.0889.

2-((4-Bromo-3-(trifluoromethyl)phenyl)amino)benzoic acid (14.2). Compound **14.2** was synthesized according to **GP2** using **13.2** (60.0 mg, 194 µmol, 1.00 eq) and KOH (24.0 mg, 428 µmol, 2.21 eq) in a mixture of EtOH (2 mL), THF (1 mL) and H_2O (1 mL). The mixture was stirred at reflux for 2 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **14.2** as a yellow solid (41.0 mg, 72%). RP-HPLC: > 99.9% (t_R = 21.4 min, system A), > 99.9% (t_R = 19.0 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (s, 1H), 9.63 (s, 1H), 7.92 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.49 (d, *J* = 2.3 Hz, 1H), 7.47 – 7.37 (m, 3H), 7.21 (dd, *J* = 8.5, 0.9 Hz, 1H), 6.84 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 2.40 (q, *J* = 1.9 Hz, 3H).). ^{13}C NMR (151 MHz, DMSO-d_6): δ 169.6, 146.1, 139.0, 134.1, 133.2, 131.8, 129.7 – 129.6 (m), 128.2 (q, *J* = 29.3 Hz), 124.2 (q, *J* = 273.9 Hz), 118.1 (d, *J* = 11.6 Hz), 114.1, 113.5, 18.0 (q, *J* = 1.7 Hz). LC-MS (ESI-MS): m/z 296.02 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{15}H_{13}F_3NO_2$: 296.0893, found: 296.0890.

2-((3-Methyl-5-(trifluoromethyl)phenyl)amino)benzoic acid (14.3). Compound **14.3** was synthesized according to **GP2** using **13.3** (59.0 mg, 191 µmol, 1.00 eq) and KOH (27.0 mg, 481 µmol, 2.52 eq) in a mixture of EtOH (3 mL) and H_2O (1 mL). The mixture was stirred at reflux for 1 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **14.3** as a yellow solid (45.0 mg, 80%). RP-HPLC: > 99.9% (t_R = 21.3 min, system A), 99% (t_R = 19.1 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.20 (s, 1H), 9.67 (s, 1H),

7.93 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.50 – 7.42 (m, 1H), 7.35 (s, 1H), 7.33 (s, 1H), 7.30 (d, *J* = 8.6 Hz, 1H), 7.17 (s, 1H), 6.92 – 6.85 (m, 1H), 2.37 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.7, 145.6, 141.8, 140.6, 134.2, 132.0, 130.1 (q, *J* = 31.3 Hz), 124.3 – 124.2 (m), 124.2 (q, *J* = 272.4 Hz), 119.3 (q, *J* = 3.8 Hz), 118.8, 114.9, 114.2, 113.6 (q, *J* = 4.0 Hz), 20.9.). LC-MS (ESI-MS): m/z 295.96 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{15}H_{13}F_3NO_2$: 296.0893, found: 296.0893.

2-((2-Methyl-5-(trifluoromethyl)phenyl)amino)benzoic acid (14.4). Compound **14.4** was synthesized according to **GP2** using **13.4** (93.0 mg, 301 µmol, 1.00 eq) and KOH (41.0 mg, 731 µmol, 2.43 eq) in a mixture of EtOH (3 mL) and H_2O (1 mL). The mixture was stirred at reflux for 2 h. Completion of the reaction was monitored via TLC and LC-MS. Precipitation, filtration and purification by flash chromatography (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH) yielded 75.0 mg (254 µmol, 85%) of an off white solid. R_f = 0.13 (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH). RP-HPLC: > 99.9% (t_R = 20.8 min, system A), 99% (t_R = 18.9 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.23 (s, 1H), 9.66 (s, 1H), 7.94 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.61 – 7.60 (m, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.43 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.40 – 7.34 (m, 1H), 7.01 – 6.95 (m, 1H), 6.84 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 2.29 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.0, 146.6, 139.9, 135.6 – 134.9 (m), 134.4, 132.0, 127.6 (q, *J* = 31.7 Hz), 124.2 (q, *J* = 272.1 Hz), 119.8 (q, *J* = 4.0 Hz), 118.1, 117.2 (q, *J* = 3.7 Hz), 114.0, 113.3, 17.8. LC-MS (ESI-MS): m/z 295.99 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{15}H_{13}F_3NO_2$: 296.0893, found: 296.0892.

2-((2-Bromo-3-(trifluoromethyl)phenyl)amino)benzoic acid (14.5).[36] Compound **14.5** was synthesized according to **GP2** using **13.5** (52.0 mg, 139 µmol, 1.00 eq) and KOH (32.0 mg, 570 µmol, 4.10 eq) in a mixture of EtOH (2 mL) and H_2O (0.5 mL). The mixture was stirred at reflux for 2 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **14.5** as a white powder (44.0 mg, 88%). RP-HPLC: > 99.9% (t_R = 21.0 min, system A), 99% (t_R = 18.7 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.38 (s, 1H), 9.99 (s, 1H), 7.97 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.80 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.57 – 7.45 (m, 3H), 7.24 (dd, *J* = 8.5, 1.0 Hz, 1H), 6.95 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.6, 144.7, 141.2, 134.1, 131.8, 129.8 (q, *J* = 30.1 Hz), 128.7, 127.4 – 118.1 (m), 124.3, 121.4 (q,

J = 5.6 Hz), 119.4, 115.0, 114.6, 112.7 – 112.4 (m). LC-MS (ESI-MS): m/z 360.32 $[M+H]^+$, 362.24 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{14}H_{10}BrF_3NO_2$: 359.9842, found: 359.9837.

2-((4-Bromo-3-(trifluoromethyl)phenyl)amino)benzoic acid (14.6). Compound **14.6** was synthesized according to **GP2** using **13.6** (57.0 mg, 152 µmol, 1.00 eq) and KOH (18.0 mg, 321 µmol, 2.11 eq) in a mixture of EtOH (2 mL), THF (1 mL) and H_2O (1 mL). The mixture was stirred at reflux for 2 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **14.6** as an off-white solid (25.0 mg, 64%). RP-HPLC: 98% (t_R = 21.0 min, system A), 98% (t_R = 19.0 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.24 (s, 1H), 9.62 (s, 1H), 7.93 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 2.7 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.34 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.94 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 169.8, 145.0, 142.0, 136.3, 134.5, 132.4, 129.7 (q, *J* = 30.5 Hz), 124.6, 123.3 (q, *J* = 273.3 Hz), 120.1, 119.4 (q, *J* = 5.6 Hz), 116.3, 116.1 – 115.9 (m), 109.9. LC-MS (ESI-MS): m/z 360.06 $[M+H]^+$, 362.0306 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{14}H_{10}BrF_3NO_2$: 359.9842, found: 359.9842.

2-((3-Bromo-5-(trifluoromethyl)phenyl)amino)benzoic acid (14.7).[34] Compound **14.7** was synthesized according to **GP2** using **13.7** (86.0 mg, 230 µmol, 1.00 eq) and KOH (24.0 mg, 428 µmol, 1.86 eq) in a mixture of EtOH (2 mL), THF (2 mL) and H_2O (1 mL). The mixture was stirred at 80°C for 1 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **14.7** as a white powder (63.0 mg, 76%) of a white powder. RP-HPLC: 99% (t_R = 21.8 min, system A), > 99.9% (t_R = 19.6 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.15 (s, 1H), 9.64 (s, 1H), 7.94 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.68 (dd, *J* = 1.9 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.48 – 7.44 (m, 1H), 7.38 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.00 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.2, 144.4, 143.8, 134.1, 132.3 – 131.3 (m), 127.5 – 118.9 (m), 124.5, 123.0, 120.4, 120.1 (q, *J* = 3.8 Hz), 116.8, 116.6, 114.2 (q, *J* = 3.8 Hz). LC-MS (ESI-MS): m/z 359.85 $[M+H]^+$, 361.85 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{14}H_{10}BrF_3NO_2$: 359.9842, found: 359.9844.

2-((2-Bromo-5-(trifluoromethyl)phenyl)amino)benzoic acid (14.8). Compound **14.8** was synthesized according to **GP2** using **13.8** (62.0 mg, 166 µmol, 1.00 eq) and KOH (34.0 mg,

606 µmol, 3.66 eq) in a mixture of EtOH (3 mL), THF (1 mL) and H_2O (1 mL). The mixture was stirred at 80°C for 1.5 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **14.8** as a white solid (20.0 mg, 34%). RP-HPLC: >99.9% (t_R = 21.4 min, system A), >99.9% (t_R = 19.0 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.41 (s, 1H), 9.95 (s, 1H), 7.98 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.94 (dd, *J* = 8.4, 0.9 Hz, 1H), 7.75 – 7.72 (m, 1H), 7.52 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.31 (ddd, *J* = 8.3, 2.2, 0.5 Hz, 1H), 7.28 (dd, *J* = 8.5, 0.8 Hz, 1H), 6.98 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.5, 144.3, 140.0, 134.4, 134.2, 131.9, 129.1 (q, *J* = 32.2 Hz), 123.6 (q, *J* = 272.6 Hz), 119.8 – 119.7 (m), 119.5 – 119.3 (m), 115.8 (q, *J* = 3.9 Hz), 115.1, 115.0.). LC-MS (ESI-MS): m/z 359.96 $[M+H]^+$, 361.96 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{14}H_{10}BrF_3NO_2$: 359.9842, found: 359.9841.

2-((4-Cyano-3-(trifluoromethyl)phenyl)amino)benzoic acid (14.9). Compound **14.9** was synthesized according to **GP2** using **13.9** (74.0 mg, 231 µmol, 1.00 eq) and KOH (30.0 mg, 535 µmol, 2.31 eq) in a mixture of EtOH (4 mL) and H_2O (1 mL). The mixture was stirred at rt for 4 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **14.9** as a light-yellow solid (56.0 mg, 79%). RP-HPLC: > 99.9% (t_R = 19.7 min, system A), > 99.9% (t_R = 17.6 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.32 (s, 1H), 9.75 (s, 1H), 7.96 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.91 (d, *J* = 8.6 Hz, 1H), 7.61 – 7.56 (m, 2H), 7.52 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.44 (dd, *J* = 8.6, 2.3 Hz, 1H), 7.17 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H).). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.9, 148.1, 141.7, 137.2, 134.2, 133.7 – 132.0 (m), 123.3, 123.1 (q, *J* = 273.7 Hz), 120.8, 120.6, 118.6, 117.0, 114.9 (q, *J* = 4.9 Hz), 97.4 – 97.2 (m). LC-MS (ESI-MS): m/z 307.06 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{15}H_{10}F_3N_2O_2$: 307.0689, found: 307.0690.

2-((3-Cyano-5-(trifluoromethyl)phenyl)amino)benzoic acid (14.10). In a flame dried microwave tube, **13.10** (84.0 mg, 262 µmol, 1.00 eq) was dissolved in neat TMSI (1.00 mL, 7.05 mmol, 26.9 eq). The tube was sealed with a crim cap with rubber septum and stirred at 70°C for 23 h. Completion of the reaction was monitored via TLC and LC-MS. The reaction mixture was cooled to rt, quenched with 2 M HCl and extracted with EtOAc. The combined organic fractions were dried over $MgSO_4$, filtered and evaporated. Initial purification by flash

chromatography (CH_2Cl_2/MeOH + 0.1% HCOOH 50:1) followed by preparative HPLC (flow: 20% acetonitrile in 0.1% aqueous formic acid for 3 min, 20% to 95% in 15 min, 95% for 5 min, 95% to 20% in 3 min, 20% for 3 min, t_R = 17.08 min) yielded **14.10** as a white lyophilizate (39.0 mg, 49%). R_f = 0.25 (CH_2Cl_2/MeOH + 0.1% HCOOH 50:1). RP-HPLC: 96% (t_R = 20.4 min, system A), > 99.9% (t_R = 18.0 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ δ 9.86 (s, 1H), 7.95 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.91 – 7.89 (m, 1H), 7.82 – 7.80 (m, 1H), 7.80 – 7.77 (m, 1H), 7.51 (ddd, *J* = 8.6, 7.1, 1.5 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.05 – 6.99 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.2, 143.9, 143.4, 133.9, 132.2 – 130.8 (m), 124.7, 123.1 (q, *J* = 273.0 Hz), 120.8 – 120.7 (m), 119.4 (q, *J* = 3.7 Hz), 117.6, 116.9, 113.6. LC-MS (ESI-MS): m/z 306.90 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{15}H_{10}F_3N_2O_2$: 307.0689, found: 307.0688.

2-((2-Cyano-5-(trifluoromethyl)phenyl)amino)benzoic acid (14.11). Compound **14.11** was synthesized according to a slightly modified **GP2** using **13.11** (69.0 mg, 215 µmol, 1.00 eq) and KOH (28.0 mg, 499 µmol, 1.82 eq) in a mixture of EtOH (2.5 mL), THF (0.5 mL) and a drop of H_2O. The mixture was stirred at rt for 1 h. Completion of the reaction was monitored via TLC and LC-MS. After the reaction was finished, H_2O was added and the mixture was lyophilized. The resulting lyophilisate was dissolved in H_2O, acidified to pH 1 and the formed precipitated was filtered off. Final purification by flash chromatography (CH_2Cl_2/MeOH 50:1 + 0.1% HCOOH) yielded **14.11** as an off-white solid (37.0 mg, 56%). R_f = 0.07 CH_2Cl_2/MeOH 50:1 + 0.1% HCOOH). RP-HPLC: 99% (t_R = 20.4 min, system A), > 99.9% (t_R = 18.1 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.53 (s, 1H), 10.27 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 8.00 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.76 (d, *J* = 1.7 Hz, 1H), 7.57 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.45 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.41 (dd, *J* = 8.4, 1.1 Hz, 1H), 7.08 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.0, 145.7, 143.7, 135.7, 134.7, 134.3 (q, *J* = 32.3 Hz), 132.4, 123.6 (q, *J* = 273.4 Hz), 121.7, 118.6 (q, *J* = 3.7 Hz), 117.3, 117.0, 116.5, 115.2 (q, *J* = 4.3 Hz), 107.0 – 106.1 (m). LC-MS (ESI-MS): m/z 306.88 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{15}H_{10}F_3N_2O_2$: 307.0689, found: 307.0688.

Methyl 2-((3-(trifluoromethyl)-5-((trimethylsilyl)ethynyl)phenyl)amino)benzoate (15.1). In a microwave tube, **13.7** (103 mg, 275 µmol, 1.00 eq) and $ZnBr_2$ (101 mg, 449 µmol, 1.63 eq)

were dissolved in dry THF (1 mL), purged with argon, sealed with a crimp cap with rubber septum and stirred at 80°C for 30 minutes. After cooling to rt, TMS-acetylene (157 µL, 1.10 mmol, 4.00 eq), CuI (10.0 mg, 52.5 µmol, 0.19 eq), $Pd(PPh_3)_4$ (16.0 mg, 13.9 µmol, 0.05 eq) and NEt_3 (382 µL, 2.76 mmol, 10.0 eq) were added under constant argon flow. The tube was then sealed and stirred at 80°C for 24 h. Completion of the reaction was monitored via TLC and LC-MS. After cooling to rt, the mixture was diluted with EtOAc and filtered over a pad of celite. After evaporation of the solvent, purification by flash chromatography (isohexane/CH_2Cl_2 5:1) yielded **15.1** as a yellow oil (99.0 mg, 92%). R_f = 0.38 (isohexane/CH_2Cl_2 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ δ 9.59 (s, 1H), 8.00 (ddd, *J* = 8.0, 1.7, 0.4 Hz, 1H), 7.49 (dd, *J* = 1.7 Hz, 1H), 7.44 – 7.37 (m, 3H), 7.29 (dd, *J* = 8.5, 0.9 Hz, 1H), 6.85 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 3.91 (s, 3H), 0.26 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.7, 146.1, 141.8, 134.3, 132.0 (q, *J* = 32.7 Hz), 131.8, 127.0 – 126.8 (m), 125.1, 123.5 (q, *J* = 272.8 Hz), 122.9 (q, *J* = 3.9 Hz), 118.7, 117.6 (q, *J* = 3.8 Hz), 114.6, 113.3, 103.1, 96.2, 52.0, -0.2. LC-MS (ESI-MS): m/z 392.11 $[M+H]^+$.

Methyl 2-((3-(prop-1-yn-1-yl)-5-(trifluoromethyl)phenyl)amino)benzoate (15.2). In a microwave tube, **13.7** (102 mg, 273 µmol, 1.00 eq), butynoic acid (53.0 mg, 630 µmol, 2.31 eq), $PdCl_2(PPh_3)_2$ (14.0 mg, 20.0 µmol, 0.07 eq) and 1,4-bis(diphenylphosphino)butane (16.0 mg, 37.5 µmol, 0.14 eq) were dissolved in dry DMSO (1 mL). Then, DBU (81.4 µL, 545 µmol, 2.00 eq) was added under constant argon flow, the tube was sealed with a crimp cap with rubber septum and stirred at 110°C for 1.5 h. Completion of the reaction was monitored via TLC and LC-MS. After cooling to rt, the mixture was quenched with NH_4Cl, extracted with EtOAc (3x), the combined organic fractions were washed with brine (3x), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (isohexane/CH_2Cl_2 7:1 to 4:1) yielded **15.2** as a clear oil (71.0 mg, 78%). R_f = 0.30 (isohexane/CH_2Cl_2 7:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 7.99 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.44 – 7.35 (m, 3H), 7.32 – 7.27 (m, 2H), 6.84 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 3.91 (s, 3H), 2.05 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.8, 146.3, 141.7, 134.3, 132.5 – 131.3 (m), 126.8 – 126.5 (m), 126.0, 123.6 (q, *J* = 271.9 Hz), 122.5 (q, *J* = 3.8 Hz), 118.6, 116.9 (q, *J* = 3.8 Hz), 114.6, 113.2, 87.8, 78.4, 52.0, 4.3. LC-MS (ESI-MS): m/z 334.08 $[M+H]^+$.

Methyl 2-((3-(cyclopentylethynyl)-5-(trifluoromethyl)phenyl)amino)benzoate (15.3). In a microwave tube, **13.7** (80.0 mg, 214 µmol, 1.00 eq) and $ZnBr_2$ (75.0 mg, 333 µmol, 1.56 eq) were dissolved in dry THF (2 mL), purged with argon, sealed with a crimp cap with rubber septum and stirred at 80°C for 10 minutes. After cooling to rt, ethynylcyclopentane (49.6 µL, 428 µmol, 1.50 eq), CuI (3.00 mg, 15.8 µmol, 0.08 eq), $Pd(PPh_3)_4$ (12.0 mg, 10.4 µmol, 0.05 eq) and NEt_3 (30 µL, 214 µmol, 1.00 eq) were added under constant argon flow. The tube was then sealed and stirred at 80°C for 21 h. After cooling to rt, the mixture was diluted with EtOAc and filtered over a pad of celite. After evaporation of the solvent, purification by flash chromatography (isohexane/EtOAc 40:1) yielded **15.3** as a clear oil (77.0 mg, 93%). R_f = 0.47 (isohexane/EtOAc 40:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.56 (s, 1H), 7.99 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.43 – 7.37 (m, 2H), 7.36 – 7.34 (m, 1H), 7.32 – 7.30 (m, 1H), 7.30 – 7.26 (m, 1H), 6.83 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H), 3.91 (s, 3H), 2.82 (dddd, *J* = 7.5 Hz, 1H), 2.06 – 1.95 (m, 2H), 1.84 – 1.57 (m, 6H). ^{13}C NMR (101 MHz $CDCl_3$): 168.8, 146.3, 141.6, 134.3, 131.9 (q, *J* = 32.5 Hz), 131.8, 127.2 – 126.5 (m), 126.2, 123.6 (q, *J* = 272.6 Hz), 122.6 (q, *J* = 3.8 Hz), 118.5, 116.8 (q, *J* = 3.8 Hz), 114.6, 113.1, 96.5, 78.71, 52.0, 33.8, 30.7, 25.1. LC-MS (ESI-MS): m/z 388.08 $[M+H]^+$.

2-((3-Ethynyl-5-(trifluoromethyl)phenyl)amino)benzoic acid (16.1). Compound **16.1** was synthesized according to **GP2** using **15.1** (51.0 mg, 130 µmol, 1.00 eq) and 2 M NaOH (261 µL, 522 µmol, 4.01 eq) in a mixture of EtOH (1 mL) and THF (0.5 mL). The mixture was stirred at rt for 2 h. Completion of the reaction was monitored via TLC and LC-MS. Precipitation, filtration and purification by flash chromatography (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH) yielded **16.1** as a white solid (25.0 mg, 63%). R_f = 0.22 (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH). RP-HPLC: > 99.9% (t_R = 21.2 min, system A), > 99% (t_R = 18.8 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.25 (s, 1H), 9.61 (s, 1H), 7.94 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.58 – 7.56 (m, 2H), 7.50 (ddd, *J* = 8.4, 7.2, 1.7 Hz, 1H), 7.38 – 7.33 (m, 2H), 6.96 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 4.39 (s, 1H). ^{13}C NMR (151 MHz, DMSO-d_6): δ 169.2, 144.3, 142.8, 134.0, 131.8, 130.7 (q, *J* = 32.0 Hz), 125.1, 123.8, 123.4 (q, *J* = 272.8 Hz), 120.7 (q, *J* = 3.8 Hz), 119.8, 116.1 – 115.9 (m), 115.7, 82.4, 81.8. LC-MS (ESI-MS): m/z 306.03 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{16}H_{11}F_3NO_2$: 306.0736, found: 306.0737.

2-((3-(Prop-1-yn-1-yl)-5-(trifluoromethyl)phenyl)amino)benzoic acid (16.2). Compound **16.2** was synthesized according to **GP2** using **15.2** (59.0 mg, 177 µmol, 1.00 eq) and KOH (47.0 mg, 838 µmol, 4.73 eq) in a mixture of MeOH (2 mL), THF (0.5 mL) and H_2O (0.5 mL). The mixture was stirred at 80°C for 3.5 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **16.2** as a white solid (48.0 mg, 85%). RP-HPLC: 99% (t_R = 21.9 min, system A), > 99.9% (t_R = 19.4 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.24 (s, 1H), 9.61 (s, 1H), 7.94 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.53 – 7.45 (m, 3H), 7.33 (dd, *J* = 8.4, 1.0 Hz, 1H), 7.28 – 7.26 (m, 1H), 6.95 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H), 2.06 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.2, 144.5, 142.6, 134.0, 131.8, 130.6 (q, *J* = 31.9 Hz), 125.4, 124.7, 123.5 (q, *J* = 272.8 Hz), 120.4 (q, *J* = 3.8, 3.3 Hz), 119.6, 115.8, 115.4, 115.2 (q, *J* = 3.8 Hz), 88.5, 78.2, 3.8. LC-MS (ESI-MS): m/z 320.04 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{17}H_{13}F_3NO_2$: 320.0893, found: 320.0894.

2-((3-(Cyclopentylethynyl)-5-(trifluoromethyl)phenyl)amino)benzoic acid (16.3). Compound **16.3** was synthesized according to **GP2** using **15.3** (47.0 mg, 121 µmol, 1.00 eq) and KOH (15.0 mg, 267 µmol, 2.20 eq) in a mixture of EtOH (2 mL), THF (1 mL) and H_2O (1 mL). The mixture was stirred at rt for 16 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **16.3** as an off-white solid (19.0 mg, 42%). RP-HPLC: 98% (t_R = 22.9 min, system A), > 99.9% (t_R = 21.5 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.24 (s, 1H), 9.58 (s, 1H), 7.93 (dd, J = 7.9, 1.6 Hz, 1H), 7.53 – 7.40 (m, 3H), 7.34 – 7.29 (m, 1H), 7.24 (s, 1H), 6.97 – 6.91 (m, 1H), 2.93 – 2.79 (m, 1H), 2.03 – 1.88 (m, 2H), 1.77 – 1.51 (m, 6H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 172.8, 147.3, 141.2, 135.4, 132.8, 131.9 (q, *J* = 32.6 Hz), 127.9 – 119.3 (m), 126.3, 123.2 (q, *J* = 3.6 Hz), 118.6, 117.5 (q, *J* = 3.5 Hz), 114.4, 111.6, 96.8, 78.6, 33.8, 30.7, 25.1. LC-MS (ESI-MS): m/z 374.11 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{21}H_{19}F_3NO_2$: 374.1362, found: 374.1364.

Methyl 2-((6-(trifluoromethyl)pyridin-2-yl)amino)benzoate (18.1). Compound **18.1** was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 97.9 µL, 698 µmol, 1.00 eq), 6-(trifluoromethyl)pyridin-2-amine (**17.1**, 135 mg, 833 µmol, 1.20 eq), $Pd(OAc)_2$ (8.00 mg, 35.6 µmol, 0.05 eq), (±)-BINAP (36.0 mg, 57.8 µmol, 0.08 eq) and Cs_2CO_3 (327 mg, 1.00 mmol, 1.45 eq) in 5 mL dry toluene. The reaction was finished after 5 h. Completion of the reaction

was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 10:1) yielded **18.1** as an off-white solid (164 mg, 79%). R_f = 0.39 (isohexane/EtOAc 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.87 (s, 1H), 8.91 (dd, *J* = 8.5, 1.3 Hz, 1H), 8.04 (ddd, *J* = 8.0, 1.8, 0.5 Hz, 1H), 7.71 – 7.61 (m, 1H), 7.59 – 7.53 (m, 1H), 7.17 (d, *J* = 7.4 Hz, 1H), 7.03 – 6.88 (m, 2H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 169.3, 154.8, 146.0 (q, *J* = 34.4 Hz), 143.9, 138.2, 134.7, 131.1, 121.6 (q, *J* = 273.6 Hz), 120.1, 118.6, 115.8 – 115.3 (m), 113.5, 111.9 (q, *J* = 3.1 Hz), 52.2. LC-MS (ESI-MS): m/z 296.91 $[M+H]^+$.

Methyl 2-((6-(trifluoromethyl)pyridin-2-yl)amino)benzoate (18.2).[37] Compound **18.2** was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 97.9 µL, 698 µmol, 1.00 eq), 2-(trifluoromethyl)pyridin-4-amine (**17.2**, 136 mg, 839 µmol, 1.20 eq), $Pd(OAc)_2$ (8.00 mg, 35.6 µmol, 0.05 eq), (±)-BINAP (35.0 mg, 56.2 µmol, 0.08 eq) and Cs_2CO_3 (329 mg, 1.01 mmol, 1.45 eq) in 5 mL dry toluene. The reaction was finished after 5 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 10:1) yielded **18.2** as a light-yellow solid (146 mg, 71%). R_f = 0.19 (isohexane/EtOAc 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.47 (d, *J* = 5.6 Hz, 1H), 8.09 – 8.02 (m, 1H), 7.56 – 7.50 (m, 2H), 7.42 (d, *J* = 2.2 Hz, 1H), 7.21 (dd, *J* = 5.6, 2.3 Hz, 1H), 7.09 – 7.02 (m, 1H), 3.94 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.4, 150.9, 150.1 – 148.6 (m), 142.8, 134.1, 132.0, 121.6, 121.5 (q, *J* = 274.4 Hz)117.6, 116.4, 113.6 – 113.3 (m), 108.8 (q, *J* = 3.0 Hz), 52.4. LC-MS (ESI-MS): m/z 296.90 $[M+H]^+$.

Methyl 2-((5-(trifluoromethyl)pyridin-3-yl)amino)benzoate (18.3). Compound **18.3** was synthesized according to **GP1** using methyl 2-bromo benzoate (**1**, 100 µL, 712 µmol, 1.00 eq), 5-(trifluoromethyl)pyridin-3-amine (**17.3**, 144 mg, 888 µmol, 1.25 eq), $Pd(OAc)_2$ (9.00 mg, 40.1 µmol, 0.06 eq), (±)-BINAP (36.0 mg, 57.8 µmol, 0.08 eq) and Cs_2CO_3 (325 mg, 997 µmol, 1.40 eq) in 5 mL dry toluene. The reaction was finished after 5 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 10:1) yielded **18.3** as a yellow oil (153 mg, 72%). R_f = 0.24 (isohexane/EtOAc 10:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.71 (s, 1H), 8.71 (d, *J* = 2.5 Hz, 1H), 8.54 – 8.51 (m, 1H), 8.03 (dd, *J* = 8.0, 1.6 Hz, 0H), 7.79 (dd, *J* = 2.3 Hz, 1H), 7.44 (ddd, *J* = 8.7, 7.1, 1.7 Hz, 1H), 7.29 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.92 (ddd, *J* = 8.2, 7.2, 1.1 Hz, 1H), 3.93 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ

168.8, 145.8, 145.4, 139.8 (q, *J* = 4.2 Hz), 138.0, 134.5, 132.0, 127.1 (q, *J* = 32.8 Hz), 123.5 (q, *J* = 3.6 Hz), 123.3 (q, *J* = 272.8 Hz), 119.7, 114.3, 114.0, 52.2. LC-MS (ESI-MS): m/z 296.93 $[M+H]^+$.

Methyl 2-((4-(trifluoromethyl)pyrimidin-2-yl)amino)benzoate (18.4). Compound **18.4** was synthesized according to **GP1** using methyl 2-bromobenzoate (**1**, 100 µL, 815 µmol, 1.00 eq), 4-(trifluoromethyl)pyrimidin-2-amine (**17.4**, 145 mg, 889 µmol, 1.25 eq), $Pd(OAc)_2$ (12.0 mg, 53.5 µmol, 0.08 eq), (±)-BINAP (56.0 mg, 90.0 µmol, 0.13 eq) and Cs_2CO_3 (330 mg, 1.01 mmol, 1.42 eq) in 5 mL dry toluene. The reaction was finished after 4 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 7:1) yielded **18.4** as an off-white sold (92.0 mg, 44%). R_f = 0.53 (isohexane/EtOAc 7:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.34 (s, 1H), 8.83 (dd, *J* = 8.6, 1.1 Hz, 1H), 8.69 (d, *J* = 4.9 Hz, 1H), 8.07 (ddd, *J* = 8.0, 1.7, 0.5 Hz, 1H), 7.63 – 7.54 (m, 1H), 7.09 – 7.02 (m, 2H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 168.6, 160.4, 159.9, 156.2 (q, *J* = 36.1 Hz), 142.2, 134.4, 131.1, 121.2, 119.3, 120.4 (q, *J* = 275.2 Hz), 114.8, 108.3 (q, *J* = 2.7 Hz), 52.3. LC-MS (ESI-MS): m/z 298.02 $[M+H]^+$.

2-((6-(Trifluoromethyl)pyridin-2-yl)amino)benzoic acid (19.1). Compound **19.1** was synthesized according to **GP2** using **18.1** (70.0 mg, 236 µmol, 1.00 eq) and KOH (35.0 mg, 624 µmol, 2.64 eq) in a mixture of EtOH (2 mL), THF (0.5 mL) and H_2O (1 mL). The mixture was stirred at rt for 4 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **19.1** as an off-white solid (56.0 mg, 84%). RP-HPLC: > 99.9% (t_R = 20.3 min, system A), 99% (t_R = 18.1 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.63 (s, 1H), 10.99 (s, 1H), 8.63 (dd, *J* = 8.6, 1.1 Hz, 1H), 8.01 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.89 (ddd, *J* = 8.3, 7.4, 0.8 Hz, 1H), 7.60 (ddd, *J* = 8.7, 7.2, 1.8 Hz, 1H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 7.04 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 1H).). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.5, 155.0, 144.6 (q, *J* = 33.7 Hz), 143.4, 139.9, 134.5, 131.9, 122.1 (q, *J* = 273.9 Hz), 120.9, 118.7, 116.8, 115.6, 112.7 (q, *J* = 3.2 Hz). LC-MS (ESI-MS): m/z 282.88 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{13}H_{10}BrF_3N_2O_2$: 283.0689, found: 283.0690.

2-((2-(Trifluoromethyl)pyridin-4-yl)amino)benzoic acid (19.2).[37] Compound **19.2** was synthesized according to **GP2** using **18.2** (71.0 mg, 240 µmol, 1.00 eq) and KOH (34.0 mg,

606 µmol, 2.53 eq) in a mixture of EtOH (2 mL), THF (0.5 mL) and H_2O (1 mL). The mixture was stirred at rt for 3 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **19.2** as an off-white solid (54.0 mg, 80%). RP-HPLC: > 99.9% (t_R = 18.8 min, system A), > 99.9% (t_R = 16.1 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.34 (s, 1H), 9.69 (s, 1H), 8.39 – 8.36 (m, 1H), 7.97 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.60 (ddd, *J* = 8.6, 7.1, 1.6 Hz, 1H), 7.55 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.45 (d, *J* = 2.2 Hz, 1H), 7.25 (dd, *J* = 5.7, 2.3 Hz, 1H), 7.19 (ddd, *J* = 8.1, 7.1, 1.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 168.9, 151.4, 151.2, 148.0 (q, *J* = 32.9 Hz), 141.3, 134.1, 132.2, 123.5, 122.2 (q, *J* = 274.2 Hz), 121.3, 121.1, 112.6, 108.0 (q, *J* = 2.7 Hz). LC-MS (ESI-MS): m/z 282.88 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{13}H_{10}BrF_3N_2O_2$: 283.0689, found: 283.0690.

2-((5-(Trifluoromethyl)pyridin-3-yl)amino)benzoic acid (19.3). Compound **19.3** was synthesized according to **GP2** using **18.3** (74.0 mg, 250 µmol, 1.00 eq) and KOH (42.0 mg, 535 µmol, 3.00 eq) in a mixture of EtOH (2 mL), THF (0.5 mL) and H_2O (1 mL). The mixture was stirred at rt for 3 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **19.3** as an off-white solid (56.0 mg, 79%). RP-HPLC: > 99.9% (t_R = 19.8 min, system A), 97% (t_R = 16.8 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.26 (s, 1H), 9.71 (s, 1H), 8.79 (d, *J* = 2.5 Hz, 1H), 8.57 – 8.52 (m, 1H), 8.01 – 7.95 (m, 1H), 7.95 (dd, *J* = 7.9, 1.7 Hz, 1H), 7.50 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.36 (dd, *J* = 8.4, 1.0 Hz, 1H), 6.97 (ddd, *J* = 8.1, 7.2, 1.1 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 169.3, 145.5, 144.4, 138.6 (q, *J* = 4.3 Hz), 138.4, 134.2, 131.9, 125.6 (q, *J* = 32.0 Hz), 123.6 (q, *J* = 272.9 Hz), 122.5 (q, *J* = 3.7 Hz), 120.0, 115.8, 115.6. LC-MS (ESI-MS): m/z 282.88 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{13}H_{10}BrF_3N_2O_2$: 283.0689, found: 283.0689.

2-((4-(Trifluoromethyl)pyrimidin-2-yl)amino)benzoic acid (19.4). Compound **19.4** was synthesized according to **GP2** using **18.4** (46.0 mg, 155 µmol, 1.00 eq) and KOH (16.0 mg, 285 µmol, 1.84 eq) in a mixture of EtOH (2 mL) and H_2O (0.5 mL). The mixture was stirred at 100°C for 1 h. Completion of the reaction was monitored via LC-MS. Precipitation and filtration yielded **19.4** as a yellowish solid (27.0 mg, 36%). RP-HPLC: > 99.9% (t_R = 20.4 min, system A), > 99.9% (t_R = 17.6 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.67 (s, 1H), 11.52 (s, 1H), 8.91 (d, *J* = 4.9 Hz, 1H), 8.69 (dd, *J* = 8.6, 1.1 Hz, 1H), 8.05 (dd, *J* = 7.9, 1.7 Hz, 1H),

7.66 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.43 (d, *J* = 4.9 Hz, 1H), 7.13 (ddd, *J* = 8.2, 7.3, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 170.3, 162.4, 159.7, 155.0 (q, *J* = 35.3 Hz), 142.0, 134.6, 131.9, 122.0, 120.9 (q, *J* = 275.1 Hz), 119.3, 116.2, 109.3 (q, *J* = 2.8 Hz). LC-MS (ESI-MS): m/z 284.01 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{12}H_9F_3N_3O_2$: 284.0641, found: 284.0638.

5-(2-Bromophenyl)-1*H*-tetrazole (21.1).[38] In a microwave tube, 2-bromobenzonitrile (**20.1**, 2.00 g, 11.0 mmol, 1.00 eq) TBAF · 3 H_2O (1.77 g, 5.61 mmol, 0.51 eq) were suspended in neat $TMSN_3$ (2.17 mL, 16.5 mmol, 1.50 eq), sealed with a crimp cap with rubber septum and stirred at 85°C for 19 h. Completion of the reaction was monitored via LC-MS. After cooling to rt, the mixture was dissolved in EtOAc, washed with 2 M HCl (5x), H_2O (3x), dried over $MgSO_4$, filtered and evaporated. The compound was then recrystallized (toluene/EtOH 5:1) to yield **21.1** as white needles (1.65 g, 67%). ^{1}H NMR (400 MHz, CD_3CN): δ 7.82 (ddd, *J* = 7.9, 1.4, 0.4 Hz, 1H), 7.77 (dd, *J* = 7.6, 1.8 Hz, 1H), 7.59 – 7.54 (m, 1H), 7.53 – 7.48 (m, 1H). ^{13}C NMR (151 MHz, CD_3CN): δ 155.5, 134.8, 133.7, 133.0, 129.2, 127.1, 122.6. LC-MS (ESI-MS): m/z 224.72 $[M+H]^+$, 226.72 $[M+H]^+$.

5-(2-Iodophenyl)-1*H*-tetrazole (21.2).[38] In a microwave tube, 2-iodobenzonitrile (**20.2**, 3.05 g, 13.3 mmol, 1.00 eq) TBAF · 3 H_2O (2.10 g, 6.66 mmol, 0.35 eq) were suspended in neat $TMSN_3$ (3.94 mL, 30.0 mmol, 2.25 eq), sealed with a crimp cap with a rubber septum and stirred at 85°C for 21 h. Completion of the reaction was monitored via LC-MS. After cooling to rt, the mixture was dissolved in EtOAc, washed with 2 M HCl (5x), H_2O (5x), dried over $MgSO_4$, filtered, and evaporated. The compound was then recrystallized (toluene/EtOH 3:1) to yield **21.2** as white needles (1.85 g, 51%). ^{1}H NMR (400 MHz, CD_3OD): δ 8.09 (ddd, *J* = 8.1, 1.2, 0.3 Hz, 1H), 7.61 – 7.52 (m, 2H), 7.33 (ddd, *J* = 8.0, 7.1, 2.1 Hz, 1H). ^{13}C NMR (101 MHz, CD_3OD): δ 158.23, 141.5, 133.56, 132.3, 131.9, 129.7, 97.2. LC-MS (ESI-MS): m/z 272.93 $[M+H]^+$.

1-Benzyl-5-(2-bromophenyl)-1*H*-tetrazole (22.1)[39] **and 2-benzyl-5-(2-bromophenyl)-2*H*-tetrazole (22.2).** In a round bottom flask, **21.1** (1.48 g, 6.58 mmol, 1.00 eq) and K_2CO_3 (1.82 g, 13.2 mmol, 2.00 eq) were dissolved in acetonitrile (20 mL). Then, benzylbromide (860 µL, 7.24 mmol, 1.10 eq) was added and the reaction was stirred at reflux for 15 h. Completion of

the reaction was monitored via LC-MS. After cooling to rt, H_2O was added and extracted with CH_2Cl_2 (5x). The combined organic fractions were then washed with 2 M HCl (3x), brine (3x), dried over $MgSO_4$, filtered and evaporated. **22.1** was recrystallized (isohexane/EtOH 15:7) giving white crystals (723 mg, 35%), while **22.2** was purified by flash chromatography (isohexane:CH_2Cl_2 1:1) yielding as a white solid (1.02 g, 49%). **22.1**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.74 (ddd, *J* = 8.0, 1.3, 0.4 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.40 – 7.35 (m, 1H), 7.29 – 7.21 (m, 4H), 7.13 (ddd, *J* = 7.5, 1.8, 0.4 Hz, 1H), 7.04 – 6.98 (m, 2H), 5.46 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 153.7, 133.2, 133.1, 132.6, 131.9, 128.9, 128.9, 128.1, 127.7, 126.0, 123.2, 51.9. LC-MS (ESI-MS): m/z 314.88 $[M+H]^+$, 316.89 $[M+H]^+$. **22.2**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (ddd, *J* = 7.8, 1.8, 0.3 Hz, 1H), 7.72 (ddd, *J* = 8.1, 1.3, 0.3 Hz, 1H), 7.47 – 7.34 (m, 6H), 7.32 (ddd, *J* = 8.0, 7.4, 1.8 Hz, 1H), 5.85 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.4, 134.0, 133.2, 131.7, 131.2, 129.0, 129.0, 128.5, 128.4, 127.4, 122.1, 56.9. LC-MS (ESI-MS): m/z 314.88 $[M+H]^+$, 316.89 $[M+H]^+$.

1-Benzyl-5-(2-iodophenyl)-1*H*-tetrazole (22.3) and 2-benzyl-5-(2-iodophenyl)-2*H*-tetrazole (22.4). In a round bottom flask, **21.2** (1.30 g, 4.78 mmol, 1.00 qe) and K_2CO_3 (1.33 g, 9.62 mmol, 1.23 eq) were dissolved in acetonitrile (20 mL). Then, benzylbromide (624 µL, 5.25 mmol, 1.10 eq) was added and the reaction was stirred at reflux for 18 h. Completion of the reaction was monitored via LC-MS. After cooling to rt, H_2O was added and extracted with CH_2Cl_2 (5x). The combined organic fractions were then washed with 2 M HCl (3x), brine (3x), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (isohexane:EtOAc 50:1) yielded **22.3** (723 mg, 42%) and **22.4** (850 mg, 49%) both as white solids. **22.3**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.99 (ddd, *J* = 8.0, 1.2, 0.4 Hz, 1H), 7.40 (ddd, *J* = 7.6, 1.2 Hz, 1H), 7.30 – 7.22 (m, 4H), 7.05 (ddd, *J* = 7.6, 1.7, 0.4 Hz, 1H), 7.03 – 6.99 (m, 2H), 5.43 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 155.6, 139.6, 132.5, 131.4, 128.9, 128.9, 128.3, 128.2, 97.6, 51.9. LC-MS (ESI-MS): m/z 362.91 $[M+H]^+$. **22.4**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02 (ddd, *J* = 7.9, 1.2, 0.4 Hz, 1H), 7.73 (ddd, *J* = 7.8, 1.6, 0.4 Hz, 1H), 7.48 – 7.34 (m, 6H), 7.15 (ddd, *J* = 8.0, 7.4, 1.7 Hz, 1H), 5.85 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.7, 140.7, 133.2, 132.4, 131.2, 131.2, 129.0, 129.0, 128.5, 128.1, 95.7, 57.0. LC-MS (ESI-MS): m/z 362.91 $[M+H]^+$.

***N*-(2-(1-Benzyl-1*H*-tetrazol-5-yl)phenyl)-6-(trifluoromethyl)pyridin-2-amine (24.1).** Compound **24.1** was synthesized according to **GP1** using **22.1** (168 mg, 533 µmol, 1.00 eq), 6-(trifluoromethyl)pyridin-2-amine (**17.1**, 105 mg, 648 µmol, 1.22 eq), $Pd(OAc)_2$ (6.00 mg, 26.7 µmol, 0.05 eq), (±)-BINAP (27.0 mg, 43.4 µmol, 0.08 eq) and Cs_2CO_3 (245 mg, 752 µmol, 1.41 eq) in 5 mL dry toluene. The reaction was finished after 20 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/MTBE 3:1) yielded **24.1** as a yellowish oil (174 mg, 82%). R_f = 0.24 (isohexane/MTBE 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.57 (dd, *J* = 8.5, 1.0 Hz, 1H), 7.63 (ddd, *J* = 8.3, 7.4, 0.8 Hz, 1H), 7.55 (ddd, *J* = 8.5, 7.2, 1.5 Hz, 1H), 7.36 – 7.31 (m, 3H), 7.27 – 7.24 (m, 1H), 7.21 – 7.18 (m, 2H), 7.15 (d, *J* = 7.3 Hz, 1H), 7.08 (ddd, *J* = 7.6, 1.1 Hz, 1H), 6.86 (dd, *J* = 8.5, 0.9 Hz, 1H), 5.60 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 154.5, 152.9, 146.0 (q, *J* = 34.5 Hz), 139.6, 138.5, 133.7, 132.5, 129.2, 129.1, 128.8, 127.3, 121.9, 121.5 (q, *J* = 273.9 Hz), 121.1, 114.6, 112.1 (q, *J* = 3.1 Hz), 111.6, 51.8. LC-MS (ESI-MS): m/z 397.07 $[M+H]^+$.

***N*-(2-(2-Benzyl-2*H*-tetrazol-5-yl)phenyl)-2-(trifluoromethyl)pyridin-4-amine (24.2).** Compound **24.2** was synthesized according to **GP1** using **22.2** (148 mg, 470 µmol, 1.00 eq), 2-(trifluoromethyl)pyridin-4-amine (**17.2**, 92.0 mg, 568 µmol, 1.21 eq), $Pd(OAc)_2$ (7.00 mg, 31.2 µmol, 0.07 eq), (±)-BINAP (30.0 mg, 48.2 µmol, 0.10 eq) and Cs_2CO_3 (221 mg, 678 µmol, 1.44 eq) in 5 mL dry toluene. The reaction was finished after 28 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 5:1) yielded **24.2** as a pale yellow solid (136 mg, 73%). R_f = 0.23 (isohexane/EtOAc 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.15 (s, 1H), 8.40 (d, *J* = 5.7 Hz, 1H), 8.22 (ddd, *J* = 7.9, 1.6, 0.5 Hz, 1H), 7.57 (dd, *J* = 8.3, 1.1 Hz, 1H), 7.50 – 7.38 (m, 6H), 7.30 (d, *J* = 2.3 Hz, 1H), 7.20 (ddd, *J* = 7.9, 7.3, 1.2 Hz, 1H), 7.12 (dd, *J* = 5.7, 2.3 Hz, 1H), 5.84 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 164.2, 150.8, 150.6, 149.1 (q, *J* = 33.9 Hz), 138.1, 132.7, 131.1, 129.9, 129.3, 129.2, 128.6, 123.5, 121.5 (q, *J* = 274.4 Hz), 119.9, 116.8, 112.1, 107.8 (q, *J* = 3.0 Hz), 57.2. LC-MS (ESI-MS): m/z 397.11 $[M+H]^+$.

***N*-(2-(1-Benzyl-1*H*-tetrazol-5-yl)phenyl)-4-(trifluoromethyl)pyridin-2-amine (24.3).** Compound **24.3** was synthesized according to **GP1** using **22.1** (155 mg, 492 µmol, 1.00 eq), 4-(trifluoromethyl)pyridin-2-amine (**23.2**, 100 mg, 617 µmol, 1.25 eq), $Pd(OAc)_2$ (6.00 mg, 26.7

µmol, 0.05 eq), (±)-BINAP (27.0 mg, 43.4 µmol, 0.08 eq) and Cs_2CO_3 (232 mg, 712 µmol, 1.46 eq) in 5 mL dry toluene. The reaction was finished after 6 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 2:1) yielded **24.3** as an off-white solid (129 mg, 66%). R_f = 0.54 (isohexane/EtOAc 2:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.34 – 8.30 (m, 2H), 7.55 (ddd, *J* = 8.4, 7.4, 1.6 Hz, 1H), 7.34 – 7.30 (m, 3H), 7.28 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.20 – 7.16 (m, 2H), 7.11 (ddd, *J* = 7.6, 1.1 Hz, 1H), 6.96 (dd, *J* = 5.1, 0.9 Hz, 1H), 6.93 – 6.91 (m, 1H), 5.61 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 155.1, 152.7, 148.7, 140.2 (q, *J* = 33.9 Hz), 139.3, 133.7, 132.4, 129.5, 129.2, 128.8, 127.2, 122.6 (q, *J* = 273.3 Hz), 122.5, 121.5, 111.2 (q, *J* = 3.3 Hz), 107.3 (q, *J* = 4.0 Hz), 51.8. LC-MS (ESI-MS): m/z 397.12 $[M+H]^+$.

***N*-(2-(1-Benzyl-1*H*-tetrazol-5-yl)phenyl)-2-(trifluoromethyl)pyrimidin-4-amine (24.4).** Compound **24.4** was synthesized according to **GP1** using **22.3** (87.0 mg, 240 µmol, 1.00 eq), 2-(trifluoromethyl)pyrimidin-4-amine (**23.1**, 49.0 mg, 300 µmol, 1.25 eq), $Pd(OAc)_2$ (6.00 mg, 13.4 µmol, 0.06 eq), (±)-BINAP (14.0 mg, 22.5 µmol, 0.09 eq) and Cs_2CO_3 (110 mg, 338 µmol, 1.41 eq) in 3 mL dry toluene. The reaction was finished after 5 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 1:1) yielded **24.4** as a brownish solid (75.0 mg, 79%). R_f = 0.50 (isohexane/EtOAc 1:1). ^{1}H NMR (600 MHz, $CDCl_3$): δ 9.21 (s, 1H), 8.45 (d, *J* = 8.4 Hz, 1H), 8.40 (d, *J* = 5.9 Hz, 1H), 7.61 (ddd, *J* = 8.4, 7.4, 1.6 Hz, 1H), 7.35 – 7.30 (m, 4H), 7.22 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.19 – 7.15 (m, 2H), 6.72 (d, *J* = 5.9 Hz, 1H), 5.62 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 160.0, 156.7 – 155.9 (m), 156.4, 152.5, 137.4, 133.5, 132.5, 129.3, 129.2, 129.0, 127.2, 124.1, 123.3, 119.4 (q, *J* = 276.1 Hz), 113.6, 109.2, 51.9. LC-MS (ESI-MS): m/z 398.13 $[M+H]^+$.

***N*-(2-(2-Benzyl-2*H*-tetrazol-5-yl)phenyl)-4-(trifluoromethyl)pyrimidin-2-amine (24.5).** Compound **24.5** was synthesized according to **GP1** using **22.2** (151 mg, 479 µmol, 1.00 eq), 4-(trifluoromethyl)pyrimidin-2-amine (**17.4**, 102 mg, 625 µmol, 1.31 eq), $Pd(OAc)_2$ (7.00 mg, 31.2 µmol, 0.05 eq), (±)-BINAP (31.0 mg, 49.8 µmol, 0.08 eq) and Cs_2CO_3 (228 mg, 700 µmol, 1.46 eq) in 5 mL dry toluene. The reaction was finished after 2 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 5:1) yielded **24.5** as a light-yellow solid (161 mg, 85%). R_f = 0.54 (isohexane/EtOAc 2:1). ^{1}H

NMR (400 MHz, $CDCl_3$): δ 10.70 (s, 1H), 8.74 (dd, *J* = 8.6, 1.1 Hz, 1H), 8.68 (d, *J* = 4.9 Hz, 1H), 8.26 (ddd, *J* = 7.9, 1.7, 0.5 Hz, 1H), 7.54 – 7.46 (m, 2H), 7.44 – 7.34 (m, 3H), 7.16 (ddd, *J* = 7.9, 7.3, 1.2 Hz, 1H), 7.05 (d, *J* = 4.9 Hz, 1H), 5.86 (s, 2H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 164.5, 160.3, 160.2, 156.3 (q, *J* = 36.0 Hz), 137.7, 132.9, 131.2, 129.2, 129.1, 128.8, 128.7, 122.4, 120.5 (q, *J* = 275.2 Hz), 120.2, 114.5, 108.0 (q, *J* = 2.6 Hz), 57.1. LC-MS (ESI-MS): m/z 398.12 $[M+H]^+$.

***N*-(2-(1*H*-Tetrazol-5-yl)phenyl)-6-(trifluoromethyl)pyridin-2-amine (25.1).** Compound **25.1** was synthesized according to a modified **GP3** using **24.1** (49.0 mg, 124 µmol, 1.00 eq) and palladium on carbon (10 wt%, 20.0 mg, 187 µmol, 1.5 eq) in EtOH (4.5 mL). The reaction was finished after 20 h. Completion of the reaction was monitored via TLC and LC-MS. After filtration and evaporation of solvent, saturated $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3x), acidified with 2 M HCl to pH 2. The formed precipitate was filtered and purified by flash chromatography (CH_2Cl_2/MeOH 25:1 + 0.1% HCOOH) yielding **25.1** as a white solid (21.0 mg, 55%). R_f = 0.22 (CH_2Cl_2/MeOH 25:1 + 0.1% HCOOH). RP-HPLC: > 99.9% (t_R = 19.5 min, system A), > 99.9% (t_R = 17.6 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.13 (s, 1H), 8.35 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.90 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.86 (ddd, *J* = 8.3, 7.4, 0.8 Hz, 1H), 7.58 (ddd, *J* = 8.6, 7.3, 1.6 Hz, 1H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.26 – 7.19 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 155.5, 144.6 (q, *J* = 33.5 Hz), 139.8, 139.2, 132.2, 129.7, 122.9, 122.0 (q, *J* = 273.9 Hz), 121.2, 115.9, 113.7 112.2 (q, *J* = 3.2 Hz). LC-MS (ESI-MS): m/z 307.01 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{13}H_{10}F_3N_6$: 307.0914, found: 307.0914.

***N*-(2-(1*H*-Tetrazol-5-yl)phenyl)-2-(trifluoromethyl)pyridin-4-amine (25.2).** Compound **25.2** was synthesized according to **GP3** using **24.2** (69.0 mg, 174 µmol) and palladium on carbon (10 wt%, 22.0 mg, 207 µmol, 1.19 eq) in a mixture of EtOH (4 mL) and CH_2Cl_2 (1 mL). The reaction was finished after 3 days. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH) yielded **25.2** as a white powder (15.0 mg, 31%). R_f = 0.23 (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH). RP-HPLC: > 99.9% (t_R = 17.3 min, system A), 99% (t_R = 15.3 min, system B). ^{1}H NMR (400 MHz, DMSO-d_6): δ 9.26 (s, 1H), 8.31 (d, *J* = 5.7 Hz, 1H), 7.94 – 7.90 (m, 1H), 7.67 – 7.59 (m, 2H), 7.41

(ddd, *J* = 7.8, 6.5, 2.0 Hz, 1H), 7.21 (d, *J* = 1.9 Hz, 1H), 7.02 (dd, *J* = 5.7, 2.3 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 151.7, 150.4, 147.1 (q, *J* = 32.8 Hz), 137.6, 132.0, 130.4, 125.0, 123.6, 121.7 (q, *J* = 274.2 Hz), 118.0, 111.1, 106.3 (q, *J* = 3.2 Hz). LC-MS (ESI-MS): m/z 307.06 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{13}H_{10}F_3N_6$: 307.0914, found: 307.0915.

***N*-(2-(1*H*-Tetrazol-5-yl)phenyl)-4-(trifluoromethyl)pyridin-2-amine (25.3).** Compound **25.3** was synthesized according to a modified **GP3** using **24.3** (56.0 mg, 141 µmol, 1.00 eq) and palladium on carbon (10 wt%, 12.0 mg, 113 µmol, 0.8 eq) in a mixture of EtOH (2 mL) and CH_2Cl_2 (0.2 mL). The reaction was finished after 5 days. Completion of the reaction was monitored via TLC and LC-MS. After filtration and evaporation of solvent, saturated $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3x), acidified with 0.5 M HCl to pH 3-4. The formed precipitate was filtered and the remaining aqueous solution was extracted with EtOAc (3x) and evaporated. Precipitate and extracts were combined and purified by flash chromatography (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH) yielding **25.3** as an off-white solid (19.0 mg, 44%). R_f = 0.18 (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH). RP-HPLC: > 99.9% (t_R = 19.4 min, system A), > 99.9% (t_R = 17.2 min, system B). ^{1}H NMR (400 MHz, CD_3CN): δ 10.09 (s, 1H), 8.54 (ddd, *J* = 8.5, 1.2, 0.5 Hz, 1H), 8.40 (ddd, *J* = 5.3, 0.7 Hz, 1H), 7.87 (ddd, *J* = 7.9, 1.6, 0.5 Hz, 1H), 7.56 (ddd, *J* = 8.5, 7.3, 1.6 Hz, 1H), 7.23 – 7.18 (m, 2H), 7.07 (ddd, *J* = 5.3, 1.5, 0.7 Hz, 1H). ^{13}C NMR (101 MHz, CD_3CN): δ 156.9, 155.7, 150.4, 140.6, 140.2 (q, *J* = 33.5 Hz), 133.1, 129.8, 124.2 (q, *J* = 272.1 Hz), 123.2, 121.6, 111.9 (q, *J* = 3.4 Hz), 108.6 (q, *J* = 4.1 Hz). LC-MS (ESI-MS): m/z 307.04 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{13}H_{10}F_3N_6$: 307.0914, found: 307.0913.

***N*-(2-(1*H*-Tetrazol-5-yl)phenyl)-2-(trifluoromethyl)pyrimidin-4-amine (25.4).** Compound **25.4** was synthesized according to **GP3** using **24.4** (47.0 mg, 118 µmol, 1.00 eq) and palladium on carbon (10 wt%, 31.0 mg, 291 µmol, 2.47 eq) in a mixture of EtOH (2 mL) and CH_2Cl_2 (1 mL). The reaction was finished after 2 days. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH) yielded **25.4** as white powder (22.0 mg, 61%). R_f = 0.08 (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH). RP-HPLC: 96% (t_R = 15.7 min, system A), 95% (t_R = 17.6 min, system B). ^{1}H NMR (600 MHz, DMSO-d_6): δ 10.22 (s, 1H), 8.42 (d, *J* = 6.0 Hz, 1H), 7.91 (d, *J* = 8.1 Hz, 1H), 7.88 (dd, *J* = 7.8,

1.6 Hz, 1H), 7.64 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H), 7.42 (ddd, *J* = 7.6, 1.2 Hz, 1H), 6.98 (d, *J* = 6.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 161.3, 156.5, 155.0 (q, *J* = 34.9 Hz), 136.7, 132.1, 130.4, 125.9, 125.2, 119.9 (q, *J* = 275.8 Hz), 118.5, 109.6. LC-MS (ESI-MS): m/z 308.07 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{12}H_9F_3N_7$: 308.0866, found: 308.0863.

***N*-(2-(1*H*-Tetrazol-5-yl)phenyl)-4-(trifluoromethyl)pyrimidin-2-amine (25.5).** Compound **25.5** was synthesized according to a modified **GP3** using **24.3** (63.0 mg, 159 µmol, 1.00 eq) and palladium on carbon (10 wt%, 19.0 mg, 179 µmol, 1.13 eq) in a mixture of EtOH (3 mL) and CH_2Cl_2 (3 mL). The reaction was finished after 4 days. Completion of the reaction was monitored via TLC and LC-MS. After filtration and evaporation of solvent, saturated $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2 (3x), acidified with 2 M HCl to pH 3-4. The resulting suspension was extracted with EtOAc (2x), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH) yielded **25.5** as a white powder (15.0 mg, 31%). R_f = 0.27 (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH). RP-HPLC: > 99.9% (t_R = 19.1 min, system A), > 99.9% (t_R = 17.1 min, system B). ^{1}H NMR (400 MHz, CD_3CN): δ 11.01 (s, 1H), 8.82 – 8.77 (m, 2H), 7.90 (ddd, *J* = 7.9, 1.6, 0.5 Hz, 1H), 7.65 – 7.59 (m, 1H), 7.30 – 7.21 (m, 2H). ^{13}C NMR (101 MHz, CD_3CN): δ 162.5, 161.2, 156.5 (q, *J* = 35.6 Hz), 155.9, 139.4, 133.2, 129.6, 123.7, 121.8 (q, *J* = 274.0 Hz), 121.4, 112.3, 109.8 (q, *J* = 2.8 Hz). LC-MS (ESI-MS): m/z 308.05 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{12}H_9F_3N_7$: 308.0866, found: 308.0867.

***N*-(2-(2-Benzyl-2*H*-tetrazol-5-yl)phenyl)-4-methyl-6-(trifluoromethyl)pyrimidin-2-amine (27.1).** Compound **27.1** was synthesized according to **GP1** using **22.2** (154 mg, 489 µmol, 1.00 eq), 4-methyl-6-(trifluoromethyl)pyrimidin-2-amine (**26.1**, 109 mg, 615 µmol, 1.20 eq), $Pd(OAc)_2$ (7.00 mg, 31.2 µmol, 0.05 eq), (±)-BINAP (28.0 mg, 45.0 µmol, 0.08 eq) and Cs_2CO_3 (226 mg, 694 µmol, 1.40 eq) in 5 mL dry toluene. The reaction was finished after 16 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 7:1) yielded **27.1** as an off-white solid (163 mg, 81%). R_f = 0.39 (isohexane/EtOAc 7:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.61 (s, 1H), 8.81 (dd, *J* = 8.5, 1.1 Hz, 1H), 8.25 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.54 – 7.47 (m, 3H), 7.44 – 7.34 (m, 3H), 7.13 (ddd, *J* = 7.9, 7.3, 1.2 Hz, 1H), 6.94 (s, 1H), 5.87 (s, 2H), 2.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$):

δ 170.9, 164.6, 160.1, 155.9 (q, *J* = 35.4 Hz), 138.0, 132.9, 131.2, 129.2, 129.1, 128.8, 128.8, 125.2 – 116.2 (m), 122.1, 120.0, 114.1, 107.8 (q, *J* = 2.8 Hz), 57.1, 24.6. LC-MS (ESI-MS): m/z 412.15 $[M+H]^+$.

***N*-(2-(1-Benzyl-1*H*-tetrazol-5-yl)phenyl)-4-(*tert*-butyl)-6-(trifluoromethyl)pyrimidin-2-amine (27.2).** Compound **27.2** was synthesized according to **GP1** using **22.3** (146 mg, 403 µmol, 1.00 eq), 4-(*tert*-butyl)-6-(trifluoromethyl)pyrimidin-2-amine (**26.2**, 106 mg, 484 µmol, 1.20 eq), $Pd(OAc)_2$ (7.00 mg, 31.2 µmol, 0.08 eq), (±)-BINAP (27.0 mg, 43.4 µmol, 0.10 eq) and Cs_2CO_3 (189 mg, 580 µmol, 1.44 eq) in 5 mL dry toluene. The reaction was finished after 14 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 5:1) yielded **27.2** as an orange slurry (154 mg, 84%). R_f = 0.41 (isohexane/EtOAc 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (s, 1H), 8.62 – 8.58 (m, 1H), 7.57 (ddd, *J* = 8.6, 7.3, 1.7, 0.5 Hz, 1H), 7.33 – 7.27 (m, 3H), 7.24 – 7.16 (m, 3H), 7.12 (ddd, *J* = 7.8, 7.3, 1.1 Hz, 1H), 7.07 (s, 1H), 5.56 (d, *J* = 0.8 Hz, 2H), 1.34 (s, 9H). ^{13}C NMR (151 MHz, $CDCl_3$): δ 182.2, 159.2, 157.4 – 155.1 (m), 152.7, 138.6, 133.7, 132.2, 129.2, 129.1, 128.7, 127.3, 126.8 – 114.5 (m), 122.4, 121.7, 112.3, 104.4 (q, *J* = 2.6 Hz), 51.6, 38.2, 29.2. LC-MS (ESI-MS): m/z 454.14 $[M+H]^+$.

***N*-(2-(1*H*-Tetrazol-5-yl)phenyl)-4-methyl-6-(trifluoromethyl)pyrimidin-2-amine (28.1).** Compound **28.1** was synthesized according to **GP3** using **27.1** (65.0 mg, 158 µmol,1 .00 eq) and palladium on carbon (10 wt%, 22.0 mg, 207 µmol, 1.31 eq) in a mixture of EtOH (4 mL) and CH_2Cl_2 (1 mL). The reaction was finished after 6 days. Completion of the reaction was monitored via TLC via LC-MS. Purification by flash chromatography (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH) yielded **28.1** as a white powder (30.0 mg, 59%). R_f = 0.15 (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH). RP-HPLC: > 99.9% (t_R = 10.8 min, system A), > 99.9% (t_R = 17.6 min, system B). ^{1}H NMR (400 MHz, CD_3CN): δ 10.93 (s, 1H), 8.86 (dd, *J* = 8.6, 0.8 Hz, 1H), 7.88 (ddd, *J* = 7.9, 1.6, 0.5 Hz, 1H), 7.60 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.25 (ddd, *J* = 7.9, 7.3, 1.2 Hz, 1H), 7.16 (s, 1H), 2.54 (s, 3H). ^{13}C NMR (101 MHz, $CDCN_3$): δ 173.3, 161.0, 156.8 – 155.3 (m), 139.7, 133.2, 129.5, 123.4, 121.4, 120.6, 112.0, 109.6 (q, *J* = 2.9 Hz), 24.8. LC-MS (ESI-MS): m/z 322.06 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{13}H_{11}F_3N_7$: 322.1023, found: 322.1018.

***N*-(2-(1*H*-Tetrazol-5-yl)phenyl)-4-(*tert*-butyl)-6-(trifluoromethyl)pyrimidin-2-amine (28.2).** Compound **28.2** was synthesized according to **GP3** using **27.2** (64.0 mg, 141 µmol, 1.00 eq) and palladium on carbon (10 wt%, 71.0 mg, 667 µmol, 4.73 eq) in a mixture of EtOH (4 mL) and CH_2Cl_2 (1 mL). The reaction was finished after 5 days. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH) followed by preparative (flow: 30% acetonitrile in 0.3% aqueous formic acid for 3 min, 30% to 95% in 17 min, 95% for 1 min, 95% to 30% in 1 min, 30% for 1 min, t_R = 16.01 min) yielded **28.2** as white powder (23.0 mg, 45%). R_f = 0.33 (CH_2Cl_2/MeOH 40:1 + 0.1% HCOOH). RP-HPLC: 99% (t_R = 15.7 min, system A), > 99.9% (t_R = 17.6 min, system B). ^{1}H NMR (600 MHz, CD_3CN): δ 10.91 (s, 1H), 8.88 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.89 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.61 (ddd, *J* = 8.8, 7.4, 1.5 Hz, 1H), 7.30 (s, 1H), 7.26 – 7.23 (m, 1H), 1.38 (s, 9H). ^{13}C NMR (151 MHz, CD_3CN): δ 183.7, 160.7, 156.9 (q, *J* = 34.9 Hz), 156.1 – 155.6 (m), 139.8, 133.2, 129.5, 123.3, 122.1 (q, *J* = 274.4 Hz), 121.5, 112.0, 105.9 (q, *J* = 2.8 Hz), 39.2, 29.5. LC-MS (ESI-MS): m/z 364.20 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{16}H_{17}F_3N_7$: 364.1492, found: 364.1489.

4-(Benzyloxy)-6-(trifluoromethyl)pyrimidin-2-amine (30). In a flame-dried microwave tube, 60% NaH on mineral oil (50.0 mg, 1.25 mmol, 1.22 eq) was suspended in dry DMF (3 mL). Then, benzyl alcohol (120 µL, 1.17 mmol, 1.13 eq) was added and the mixture was stirred at rt. After H_2 formation has ceased, 4-chloro-6-(trifluoromethyl)pyrimidin-2-amine (**29**, 203 mg, 1.03 mmol, 1.00 eq) was added under constant argon flow, the tube was sealed with a crimp cap with a rubber septum and stirred at 90°C for 2 h. Completion of the reaction was monitored via LC-MS. After cooling to rt, the mixture was quenched with H_2O, acidified with 2 M HCl and extracted with EtOAc (3x). The combined organic fractions were washed with brine (3x), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (isohexane/EtOAc 5:1) yielded **30** as a white solid (184 mg, 67%) of a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44 – 7.32 (m, 5H), 6.45 (s, 1H), 5.42 (s, 2H), 5.37 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.0, 163.1, 156.9 (q, *J* = 35.0 Hz), 135.7, 128.6, 128.4, 128.2, 120.6 (q, *J* = 274.6 Hz), 95.6 (q, *J* = 3.3 Hz), 68.4.

***N*-(2-(1-Benzyl-1*H*-tetrazol-5-yl)phenyl)-4-(benzyloxy)-6-(trifluoromethyl)pyrimidin-2-amine (31).** Compound **31** was synthesized according to **GP1** using **22.3** (197 mg, 544 µmol, 1.00 eq), **30** (162 mg, 602 µmol, 1.11 eq), $Pd(OAc)_2$ (8.00 mg, 22.2 µmol, 0.04 eq), XantPhos (29.0 mg, 50.1 µmol, 0.09 eq) and Cs_2CO_3 (258 mg, 792 µmol, 1.46 eq) in 5 mL dry toluene. The reaction was finished after 3 h. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (isohexane/EtOAc 5:1) yielded a not fully pure product, which was taken to the next step without further purification. R_f = 0.25 (isohexane/EtOAc 4:1). LC-MS (ESI-MS): m/z 504.25 $[M+H]^+$.

2-((2-(1*H*-Tetrazol-5-yl)phenyl)amino)-6-(trifluoromethyl)pyrimidin-4-ol (32). Compound **32** was synthesized according to **GP3** using crude **31** and palladium on carbon (10 wt%, 55.0 mg, 517 µmol) in a mixture of EtOH (4 mL) and CH_2Cl_2 (1 mL). The reaction was finished after 3 days. Completion of the reaction was monitored via TLC and LC-MS. Purification by flash chromatography (CH_2Cl_2/MeOH 20:1 + 0.1% HCOOH) yielded **32** as a white solid (59.0 mg, 34% over 2 steps). R_f = 0.21 (CH_2Cl_2/MeOH 20:1 + 0.1% HCOOH). RP-HPLC: 98% (t_R = 18.3 min, system A), 99.9% (t_R = 15.2 min, system B). ^{1}H NMR (400 MHz, CD_3OD): δ 8.44 (d, *J* = 8.4 Hz, 1H), 7.91 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.59 (ddd, *J* = 8.5, 7.4, 1.6 Hz, 1H), 7.33 (ddd, *J* = 7.9, 7.4, 1.2 Hz, 1H), 6.29 (s, 1H). ^{13}C NMR (151 MHz, CD_3OD): δ 156.7, 155.8 (q, *J* = 34.3, 32.9 Hz), 137.9, 132.8, 129.6, 125.5, 124.6, 122.15 (q, *J* = 274.1 Hz),115.7, 104.2 – 103.1 (m). LC-MS (ESI-MS): m/z 324.10 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{12}H_9F_3N_7O$: 324.0815, found: 324.0812.

***N*-(2-(1*H*-Tetrazol-5-yl)phenyl)-4-chloro-6-(trifluoromethyl)pyrimidin-2-amine (33).** In a microwave tube, **32** (55.0 mg, 170 µmol, 1.00 eq) was suspended in $POCl_3$ (0.4 mL, 4.41 mmol, 25.9 eq). The tube was sealed with a crimp cap with rubber septum and stirred at 60°C for 2 h. Completion of the reaction was monitored via TLC and LC-MS. After cooling to 0°C in an ice bath, the mixture was quenched with H_2O and extracted with EtOAc (3x). The combined organic fractions were washed with brine (3x), dried over $MgSO_4$, filtered and evaporated. Purification flash chromatography (CH_2Cl_2/ACN 20:1 + 0.1% HCOOH) yielded **33** as an off-white solid (48.0 mg, 83%). R_f = 0.26 (CH_2Cl_2/ACN 20:1). RP-HPLC: > 99.9% (t_R = 20.4 min, system A), 99% (t_R = 18.3 min, system B). ^{1}H NMR (400 MHz, CD_3CN): δ 11.03 (s, 1H), 8.65

(dd, *J* = 8.5, 1.1 Hz, 1H), 7.92 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.67 – 7.61 (m, 1H), 7.35 – 7.30 (m, 2H). ^{13}C NMR (101 MHz, CD_3CN): δ 164.3, 160.9, 158.0 (q, *J* = 36.1 Hz), 156.1, 138.5, 133.1, 129.7, 124.5, 124.3 – 118.7 (m), 121.9, 113.4, 110.1 (q, *J* = 2.5 Hz). LC-MS (ESI-MS): m/z 342.02 $[M+H]^+$.

***N*-(2-(1*H*-Tetrazol-5-yl)phenyl)-4-iodo-6-(trifluoromethyl)pyrimidin-2-amine (34).** In a microwave tube, **33** (13.0 mg, 38.1 µmol, 1.00 eq) and NaI (27.0 mg, 180 µmolm 4.73 eq) were suspended in 57% aqueous HI (0.5 mL). The tube was sealed with a crimp cap with rubber septum and stirred at rt for 3 h. Completion of the reaction was monitored via LC-MS. After the reaction was finished, solid $Na_2S_2O_5$ was added and the mixture was extracted with EtOAc (3x). The combined organic fractions were washed with brine (3x), dried over $MgSO_4$, filtered and evaporated. Purification by preparative HPLC (gradient of 30% to 95% ACN in H_2O with 0.3% HCOOH) yielded **34** as an off-white solid (12.0 mg, 73%). RP-HPLC: 99% (t_R = 20.6 min, system A), 99% (t_R = 17.6 min, system B). ^{1}H NMR (600 MHz, CD_3CN): δ 11.02 (s, 1H), 8.66 (dd, *J* = 8.5, 1.1 Hz, 1H), 7.95 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.70 (s, 1H), 7.65 (ddd, *J* = 8.7, 7.3, 1.6 Hz, 1H), 7.33 (ddd, *J* = 8.1, 7.4, 1.1 Hz, 1H). ^{13}C NMR (151 MHz, CD_3CN): δ 159.7, 155.4 (q, *J* = 36.2 Hz), 138.6, 133.2, 132.4, 129.7, 124.4, 123.7 – 117.9 (m), 121.7, 120.6 (q, *J* = 2.9 Hz), 113.1. LC-MS (ESI-MS): m/z 434.25 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{12}H_8F_3IN_7$: 433.9832, found: 433.9833.

2-((2-(1*H*-Tetrazol-5-yl)phenyl)amino)-6-(trifluoromethyl)pyrimidine-4-carbonitrile (35). In a microwave tube, **34** (13.0 mg, 38.1 µmol, 1.00 eq) was dissolved in dry DMF (0.4 mL). The solution was purged with argon, $Pd(PPh_3)_4$ (3.00 mg, 2.60 µmol, 0.14 eq) and $Zn(CN)_2$ (7.00 mg, 59.6 µmol, 3.23 eq) were added and the tube was sealed with a crimp cap with rubber septum and stirred at 80°C for 4 h. Completion of the reaction was monitored via LC-MS. Purification by preparative HPLC ((flow: 30% acetonitrile in 0.3% aqueous formic acid for 3 min, 30% to 95% in 17 min, 95% for 1 min, 95% to 30% in 1 min, 30% for 1 min, t_R = 12.35 min) yielded **35** as an off-white solid (4.00 mg, 65%). %). RP-HPLC: > 99.9% (t_R = 19.2 min, system A), > 99.9% (t_R = 17.4 min, system B). ^{1}H NMR (400 MHz, CD_3CN): δ 11.23 (s, 1H), 8.62 (dd, *J* = 8.5, 0.7 Hz, 1H), 7.99 (ddd, *J* = 7.9, 1.6, 0.4 Hz, 1H), 7.71 – 7.64 (m, 2H), 7.37 (ddd, *J* = 7.9, 7.4, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, CD_3CN): 161.1, 160.0 – 158.1 (m), 156.0,

145.2, 138.1, 133.2, 129.8, 125.4 – 116.7 (m), 125.0, 122.1, 116.1, 113.7, 112.8 (q, *J* = 2.5 Hz). LC-MS (ESI-MS): m/z 333.06 $[M+H]^+$. HR-MS (ESI-MS): m/z $[M+H]^+$ calculated for $C_{13}H_8F_3N_8$: 333.0819, found: 333.0815.

4-Chloro-2-(methylthio)-6-(trifluoromethyl)pyrimidine (37).[40] In a microwave tube equipped with a stirring bar, 2-(methylthio)-6-(trifluoromethyl)pyrimidin-4(3*H*)-one (**36**, 772 mg, 3.67 mmol, 1.00 eq) was suspended in $POCl_3$ (2 mL 21.5 mmol, 5.86 eq). The tube was purged with argon, sealed with a crimp cap with a rubber septum and stirred at 100°C. After 1h, the mixture was poured onto an ice bath and while stirring the pH was adjusted to 8 using 6 M NaOH solution. The mixture was extracted with CH_2Cl_2 (3x), the combined organic fractions were washed with brine (3x), dried over $MgSO_4$, filtered and evaporated. This yielded **37** as a clear liquid (614 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 (s, 1H), 2.61 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.6, 162.8, 156.7 (q, *J* = 36.9 Hz), 119.7 (q, *J* = 275.7 Hz), 112.4 (q, *J* = 2.9 Hz), 14.5. LC-MS (APPI): m/z 228.9811 $[M+H]^+$

2-(Methylthio)-4-(trifluoromethyl)-6-((triisopropylsilyl)ethynyl)pyrimidine (38). In a microwave tube equipped with a stirring bar, **37** (208 mg, 910 µmol, 1.00 eq), $PdCl_2(PPh3)_2$ (54.0 mg, 76.9 µmol, 0.08 eq) were dissolved in dry ACN (4 mL). Then, NEt_3 (888 µL, 6.37 mmol, 7.00 eq) and TIPS-acetylene (816 µL, 3.64 mmol, 4.00 eq) were added under continuous argon flow. The tube was sealed with a crimp cap with a rubber septum and stirred at 80°C. Completion of the reaction was monitored via TLC and LC-MS. After 90 minutes, the mixture was cooled to rt, diluted with EtOAc, washed with 2 M HCl (3x), brine (3x), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (isohexane/CH_2Cl_2 5:1) yielded **38** as an off-white solid (268 mg, 79%). R_f = 0.36 (isohexane/CH_2Cl_2 5:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (s, 1H), 2.59 (s, 3H), 1.19 – 1.10 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 174.8, 155.8 (q, *J* = 36.5 Hz), 152.7, 120.3 (q, *J* = 275.5 Hz), 114.4 (q, *J* = 2.7 Hz), 103.0, 100.9, 18.7, 14.5, 11.3. LC-MS (ESI-MS): m/z 375.10 $[M+H]^+$.

2-(Methylsulfonyl)-4-(trifluoromethyl)-6-((triisopropylsilyl)ethynyl)pyrimidine (39). In a microwave tube equipped with a stirring bar, **38** (116 mg, 309 µmol, 1.00 eq) and *m*-CPBA (214 mg, 1.24 mmol, 4.07 eq) were dissolved in dry CH_2Cl_2 (3 mL). The tube was sealed with a crimp cap with a rubber septum and stirred at rt. Completion of the reaction was monitored

via LC-MS. After 15h, the mixture was diluted with CH_2Cl_2, washed with sat. Na_2SO_4 (3x), sat. $NaHCO_3$ (3x), brine (3x), dried over $MgSO_4$, filtered, and evaporated. Purification by flash chromatography (isohexane/EtOAc 10:1) yielded **39** as an off-white solid (99.0 mg, 79%) of an off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 3.43 (s, 3H), 1.18 – 1.11 (m, 21H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 167.0, 157.1 (q, J = 38.2 Hz), 154.9, 124.4 – 115.5 (m), 121.9 (q, J = 2.6 Hz), 107.3, 101.8, 39.2, 18.7, 11.2. LC-MS (ESI-MS): m/z 407.27 $[M+H]^+$.

5-(2-Nitrophenyl)-1H-tetrazole (41).[41] In a microwave tube equipped with a stirring bar, 2-nitrobenzonitrile (**40**, 1.02 g, 6.89 µmol, 1.00 eq), TBAF * 3 H_2O (400 mg, 1.27 µmol, 0.18 eq) and $TMSN_3$ (4.00 mL, 30.4 mmol, 2.21 eq) were stirred at 85°C for 17 h. Completion of the reaction was monitored via LC-MS. The reaction was then cooled to rt, diluted with EtOAc, washed with 2 M HCl (3x), H_2O (3x), dried over $MgSO_4$, filtered and evaporated. The residue was then recrystallized from toluene/EtOH (25:1) twice to yield **41** as white needles (625 mg, 47%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.21 – 8.17 (m, 1H), 7.96 – 7.90 (m, 2H), 7.90 – 7.85 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 148.56, 134.03, 132.74, 131.91, 125.23, 119.66. LC-MS (ESI-MS): m/z 191.82 $[M+H]^+$.

2-(1H-Tetrazol-5-yl)aniline (42).[42] In a flame-dried Schlenk flask, compound **41** (194 mg, 1.01 µmol, 1.00 eq) was dissolved in EtOH (4 mL). After evacuating and backfilling with argon, palladium on carbon (10 wt%, 86.0 mg, 808 µmol, 800 eq) was added, evacuated and backfilled with argon three times, purged with H_2 and stirred at rt for 1 h. Completion of the reaction was monitored via LC-MS. The mixture was filtered through a syringe filter which yielded **42** as a white solid (154 mg, 94%) which could be taken to the next step without further purification. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.71 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.22 (ddd, *J* = 8.5, 7.1, 1.5 Hz, 1H), 6.88 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.67 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6): δ 147.9, 132.2, 128.5, 116.8, 116.0, 105.0. LC-MS (ESI-MS): m/z 161.83 $[M+H]^+$.

N-(2-(1H-Tetrazol-5-yl)phenyl)-4-(trifluoromethyl)-6-((triisopropylsilyl)ethynyl)pyrimidin-2-amine (43). In a microwave tube equipped with a stirring bar, **39** (38.0 mg, 93.5 µmol, 1.00 eq) was dissolved in 2,2,2-trifluoroethanol (0.9 mL). Then, TFA (40.0 µL, 768 µmol, 8.21 eq) and **42** (21.0 mg, 130 µmol, 1.39 eq) were added and

the mixture was purged with argon. The tube was sealed with a crimp cap with a rubber septum and stirred for 540min at 140°C under microwave irradiation. Completion of the reaction was monitored via LC-MS. After cooling, the mixture was diluted with EtOAc, washed with H_2O (3x), sat. $NaHCO_3$ (3x), the combined aqueous fractions were acidified with 2 M HCl to pH = 1 and extracted with EtOAc (3x). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (CH_2Cl_2/MeOH 40:1 → CH_2Cl_2/MeOH 40:1 + 0,05% HCOOH) yielded **43** as an impure product which was taken to the next step without further purification. LC-MS (ESI-MS): m/z 489.74 $[M+H]^+$.

N-(2-(1H-Tetrazol-5-yl)phenyl)-4-ethynyl-6-(trifluoromethyl)pyrimidin-2-amine (44).[19] In a microwave tube equipped with stirring bar, crude **43** was dissolved in dry THF (1.5 mL). Then, AcOH (10.0 µL, 175 µmol) and 1M TBAF in THF (94.0 µL, 94.0 µmol, 1.00 eq) were added. The tube was sealed with a crimp cap with rubber septum and stirred at rt for 1 h. Completion of the reaction was monitored via LC-MS. The mixture was evaporated and taken up in EtOAc, washed with 2 M HCl (3x), brine (3x), dried over $MgSO_4$, filtered and evaporated. Purification by flash chromatography (CH_2Cl_2/MeOH 40:1 to CH_2Cl_2/MeOH 40:1 + 0,05% HCOOH) yielded an impure product which was further purified by preparative HPLC (flow: 30% acetonitrile in 0.1% aqueous formic acid for 3 min, 30% to 95% in 17 min, 95% for 1 min, 95% to 30% in 1 min, 30% for 1 min, t_R = 12.37 min) yielding **44** as a yellowish solid (11.0 mg, 36% over two steps). RP-HPLC: 98% (t_R = 19.9 min, system A), > 99% (t_R = 17.7 min, system B). ^{1}H NMR (400 MHz, CD_3CN): δ 11.00 (s, 1H), 8.71 (d, *J* = 8.5 Hz, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.62 (dd, *J* = 8.0 Hz, 1H), 7.34 (s, 1H), 7.29 (dd, *J* = 7.6 Hz, 1H), 3.89 (s, 1H). ^{13}C NMR (101 MHz, CD_3CN): δ 161.04, 158.43 – 156.40 (m), 153.98, 138.92, 133.14, 129.58, 125.68 – 117.12 (m), 124.00, 121.58, 112.33 (q, *J* = 2.6 Hz), 84.29, 81.05. LC-MS (ESI-MS): m/z 332.03 $[M+H]^+$.

Functional evaluation. Determination of ligand-induced TAS2R14 activation was performed employing an IP_1 accumulation assay (HTFR IP-One Gq Kit PerkinElmer, Rodgau, Germany) according to the manufacturer's protocol and as previously described.[7, 43] In brief, HEK 293T (gift from the Chair of Physiology, FAU Erlangen-Nürnberg) cells were maintained in DMEM-F12 (Invitrogen) supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 100 U/mL penicillin and 100 µg/mL streptomycin and split every 3 to four days. Cells were regularly

confirmed to be free of mycoplasma contamination using the MycoAlert Plus detection kit (Lonza). Cells were grown to a confluence of 50-80% and transiently transfected with 2 µg of a plasmid (pcDNA3.1) encoding N-terminally modified TAS2R14 (N-terminal addition of a cleavable HA-signal peptide, followed by a FLAG-tag and the first 45 amino acids of the rat somatostatin receptor 3[7, 21]) and 1 µg of a plasmid encoding the chimeric $G\alpha_{qi5}$ protein ($G\alpha_q$ protein with the last five amino acids at the C-terminus replaced by the corresponding sequence of $G\alpha_i$, gift from The J. David Gladstone Institutes, San Francisco, CA)[20] employing Mirus TransIT-293 (Peqlab) in a 1:3 DNA to reagent ratio. Cells were incubated in complete growth medium for 24 h at 37 °C and 5% CO_2, before 10,000 cells/well were transferred into 384 well microplates (Greiner) and incubated for 24 h. On the day of the experiment, cells were incubated with serial dilutions of the test compounds in assay buffer (Cisbio) for 150 min at 37°C. Accumulation of the second messenger was stopped by adding detection reagents (IP1-d2 conjugate and Anti-IP1cryptate TB conjugate, Cisbio). After 60 min, time-resolved FRET was measured with a Clariostar plate reader equipped with the respective filters. FRET-ratios were calculated as the ratio of emission intensity of the FRET acceptor (665/10 nm) divided by the FRET donor intensity (620/10 nm). Raw FRET-ratios were normalized to buffer conditions (0%) and the maximum effect of flufenamic acid (100%) and the obtained responses were analyzed using the equation for sigmoid concentration-response curves (four-parameter) implemented in GraphPad Prism 9.3 for Windows (GraphPad Software, La Jolla, USA) to derive the maximum effect (E_{max}, relative to flufenamic acid) and the ligand potency (EC_{50}). Per compound, three to ten independent experiments were performed, with each concentration in duplicate.

Computational studies. The TAS2R14 model was generated through I-TASSER and prepared with the Protein Preparation tool from Schrödinger Suite 2021.1 (Schrödinger Release 2021-1: Maestro, Schrödinger, LLC). The definition of the binding site region was performed with SiteMap, and used as input for Glide docking grid generation. A list of known TAS2R14 active ligands was retrieved from BitterDB[44] and merged with the new active ligands here identified. The molecules were then prepared with LigPrep and docked to the receptor

with the Glide XP algorithm. Schrödinger's Induced Fit Docking was applied to the complexes in order to generate 1,100 conformations for the receptor, differing in sidechain orientations within the binding pocket. The Cross Docking tool was employed to generate the Glide docking grid for each conformation, with the coordinates of the docking grid identified through the centroid of the docked ligand.

A set of decoys, compounds not supposed to bind the receptor, was retrieved from DUD-E using as input the complete list of TAS2R14 agonists.[45] The decoys and the compounds from Tables 1 and 2 were prepared with LigPrep and docked to each of the conformations using the Virtual Screening Workflow tool, which helps to automatize the docking of a set of ligands to a pool of receptors. The ability of each conformation to discriminate actives from decoys was evaluated by means of the Enrichment Factor (EF) 1%, calculated with the Enrichment Calculator tool within Schrödinger. The conformation showing higher EF1% was selected and used for the docking analysis.

An additional homology model of TAS2R14 was generated based on the newly released CryoEM structure of the bitter taste receptor TAS2R46 (sequence identity circa 45%). The structure was generated with Swiss-Model, prepared for docking through the Protein Preparation tool and through generation of a docking grid by means of SiteMap.[46] Docking was performed with Glide.

PAINS screening. All target compounds were transformed into SMILES using ChemDraw 21.0.0 (PerkinElmer) and subsequently screened for pan-assay interference and aggregation lability employing the ZINC15 database.[47] The results of the screenings showed no properties of PAINS or aggregators[33] (**Supplementary Table 1**).

Receptor screening. To investigate receptor specificity, we measured radioligand competition with flufenamic acid, **16.1**, **28.1**, and **35** for 24 pharmacologically relevant non-bitter taste GPCRs (**Supplementary Fig. S1**). Thus, we measured the ability of the test compounds and flufenamic acid to compete with a radioligand for binding to the respective receptors with membranes from cells either transiently or stably overexpressing the appropriate receptors as previously described.[43, 48] For each receptor subtype experimental conditions including

radioligand and total protein concentrations are listed in Table S2. Data were analyzed in GraphPad Prism 9.1 (GraphPad Software, USA) calculating the fraction of remaining radioligand bound for each of the test ligand concentrations (1, 10, 30 µM) in comparison to the total (100%, buffer) and non-specific binding of the radioligand (0%) determined in the presence of a high concentration of a known competitor for the respective receptor. Per compound and receptor, two experiments were performed with each concentration in triplicates. For ligands showing a substantial amount of radioligand displacement at 10 µM concentration, complete concentration-response curves were obtained and analyzed using the algorithms for one-site binding competition implemented in GraphPad Prism 9.1 to determine an IC_{50} which was subsequently transformed into an affinity constant (K_i) employing the equation of Cheng and Prusoff.[49]

ASSOCIATED CONTENT

Supporting Information. Supplementary Figure S1-S2, Supplementary Tables S1-S2, Supplementary Text, ^{1}H NMR and ^{13}C NMR spectra and HPLC traces of the target compounds are provided.

AUTHOR INFORMATION

Corresponding author. *Email: peter.gmeiner@fau.de; masha.niv@mail.huji.ac.il

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ABBREVIATIONS

ACN, acetonitrile; Asn, asparagine; (±)-BINAP, ([1,1′-binaphthalene]-2,2′-diyl)bis(diphenylphosphane); Bn, benzyl; COPD, chronic obstructive pulmonary

disease; DAD, diode-array detection; DBU, 2,3,4,6,7,8,9,10-Octahydropyrimido[1,2-a]azepine; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; FLAG-tag, DYKDDDDK-tag; flufenamic acid, 2-{[3-(trifluoromethyl)phenyl]amino}benzoic acid; Gln, glutamine; HASM, human airway smooth muscles; HA, Human influenza hemagglutinin; HPLC, high-performance liquid chromatography; IP_1, inositol monophosphate; mCPBA, 3-Chlorobenzene-1-carboperoxoic acid; MS, mass spectrometry; NMR, nuclear magnetic resonance; PAINS, pan assay interfering structural motifs; Phe, phenylalanine; R_f, retardation factor; RP, reverse phase; hTAS1R, human taste receptor 1; hTAS2R14, human bitter taste receptor 2 member 14; TBAF, tetrabutylammonium fluoride; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TIPS, triisopropylsilyl; TMs, transmembrane helices; TMS, trimetylsilyl/ tetramethylsilane; Trp, tryptophane; XantPhos, (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane); XPhos, dicyclohexyl[2′,4′,6′-tris(propan-2-yl)[1,1′-biphenyl]-2-yl]phosphane.

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