Tele-substitution Reactions in the Synthesis of a Promising Class of Antimalarials

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Abstract

We have discovered and studied a *tele*-substitution reaction in a biologically important heterocyclic ring system. Conditions that favour the *tele*-substitution pathway were identified: the use of increased equivalents of the nucleophile or decreased equivalents of base, or the use of softer nucleophiles, less polar solvents and larger halogens on the electrophile. Using results from X-ray crystallography and isotope labelling experiments a mechanism for this unusual transformation is proposed. We focused on this triazolopyrazine as it is the core structure of the *in vivo* active anti-plasmodium compounds of Series 4 of the Open Source Malaria consortium.

1 Introduction

Nucleophilic substitution is a widely employed method for functionalising electron deficient aromatic systems. Most commonly, a halide or other leaving group is simply displaced by an incoming nucleophile, known as direct or *ipso*-substitution.[1] Under some circumstances however, a leaving group may be displaced from an aromatic system by a nucleophile entering at a different position on the ring, for example at the carbon adjacent to the leaving group (*cine*-substitution[2]) or even further away (*tele*-substitution,[3] Figure 1A). We report here our discovery, and mechanistic studies, of a *tele*-substitution reaction in a [1,2,4]triazolo[4,3-a]pyrazine system, which is at the core of a series of molecules with significant potential for the future treatment of malaria.[4]

The first example of a *tele*-substitution reaction was reported in 1930 (Figure 1B).[5] In this case, the reaction of 2-(chloromethyl)furan (**1**) with NaCN resulted in the attachment of the nitrile group not in place of the chlorine atom, but instead distant from the expected electrophilic site on the opposite side of the furan ring (**2**). Other examples of *tele*-substitution reactions have since been reported for a variety of aromatic systems ranging from simple pyrazine rings[6] (Figure 1C) to more complex triazolopyrazine ring systems[7,8] (Figures 1D and 1E), the latter of which are of particular relevance to the present work. Despite these and other reports,[9–12] *tele*-substitution reactions are not well understood; they remain hard to predict and appear to be strongly substrate dependent. Interestingly, many of the known examples of *tele*-substitution involve aza-aromatic ring systems which are common in medicinal chemistry

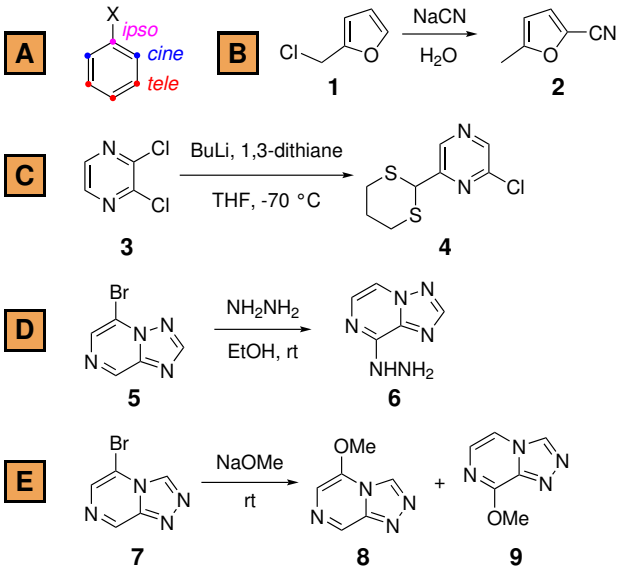


Figure 1: A) Possible positions for nucleophilic aromatic substitution of X. B) First reported case of a *tele*-substitution reaction in 1930. Further reports of *tele*-substitution in C) pyrazine, D) [1,2,4]triazolo[1,5-a]pyrazine and E) [1,2,4]triazolo[4,3-a]pyrazine ring systems.

and drug discovery campaigns. Given the isomeric nature of the *ipso*- and *tele*-substituted products, and the sometimes cursory level of characterisation in medicinal chemistry articles (where compound identity may be demonstrated using only a ^{1}H NMR spectrum and an LCMS trace) it is important, as we have discovered, to be aware of the possibility of this underappreciated reaction in order to avoid drawing conclusions from erroneous SAR data.

Here, we illustrate this with our studies on the *tele*-substitution reactions of the [1,2,4]triazolo[4,3-a]pyrazine (hereafter referred to as 'triazolopyrazine') heterocyclic system. These nitrogen-rich, electron-deficient heterocycles are important building blocks for the development of new medicines and have shown a wide variety of biological activities (Figure 2). We have an interest in this motif because it forms the core of Series 4 of the Open Source Malaria (OSM) consortium,[13] represented here by compound **10** which possesses *in vitro*[14] (IC_{50} = 38 nM) and *in vivo*[15] antimalarial activity. Compound **11** has been reported to have nanomolar potency as an inhibitor of the kidney urea transporter UT-A1.[16] Compound **12** was recently patented in 2016 as a renal outer medullary potassium channel (ROMK) inhibitor.[17] Sitagliptin (**13**) was approved by the FDA in 2006 as an antidiabetic drug (dipeptidyl peptidase (DPP)-IV inhibitor).[18] Compound **14** is a lead molecule (IC_{50} <100 nM), that acts as an inhibitor of bromodomain and extra-terminal motif (BET) proteins for cancer treatment.[19] Compound **15** is patented as an *N*-methyl-D-aspartate subtype 2B (NMDAR2B) receptor antagonist.[20]

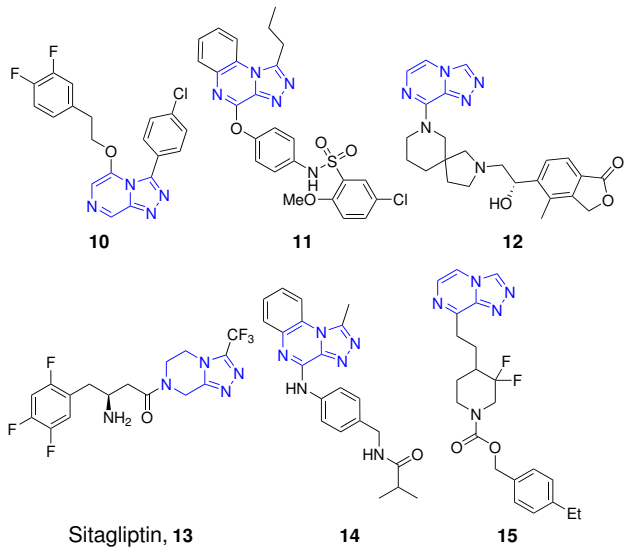


Figure 2: Examples of bioactive molecules that include a triazolopyrazine motif or close derivative. **10** is an example compound from OSM Series 4; **11** is an inhibitor of the UT-A1 transporter; **12** is a ROMK inhibitor; Sitagliptin (**13**) is an FDA approved antidiabetic drug; **14** is a BET inhibitor with potential in cancer treatment; **15** is an NMDAR2B receptor antagonist.

2 Results and discussion

The synthesis of members of OSM Series 4 relies on a routine S_NAr reaction involving the nucleophilic displacement of a chlorine atom from a triazolopyrazine core (e.g. **16**). When the synthesis of thioether analogue **17** was attempted using the standard conditions for this reaction (Figure 3A), in addition to this expected product, a compound with a significantly lower TLC retention factor was observed and isolated. This was later identified to be

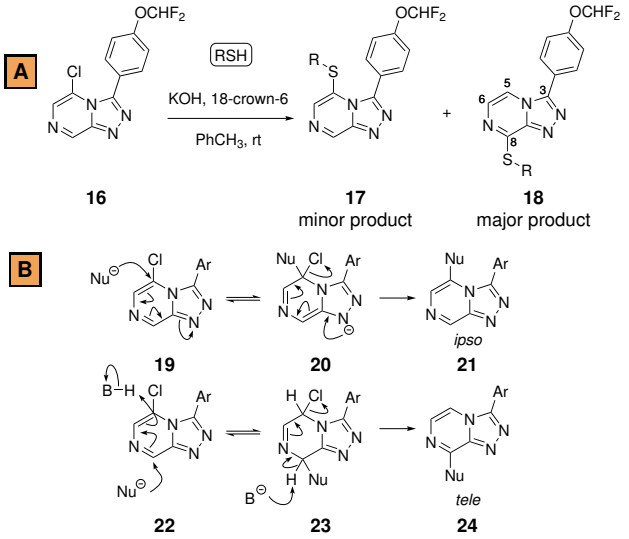


Figure 3: A) Reaction used to make an OSM Series 4 compound **17**, and its *tele*-substituted isomer **18**. B) Proposed mechanisms for *ipso*- and *tele*-substitution.[21] R = CH_2CH_2Ph.

the *tele*-substituted isomer **18**. Since the 8-isomer **18** is a main product that was formed in 83% yield and due to the similarity of the ^{1}H NMR spectra of these two isomers (Figure 4), the *tele*-substituted isomer **18** was initially misassigned as the desired product **17**. After the reaction had been repeated and examined more thoroughly compound **17** was successfully isolated as a minor product with 8% yield. The diagnostic spectroscopic difference between these isomers lies in the peaks arising from the hydrogen atoms at positions 5 and 8 on the triazolopyrazine ring; the correspondence between the NMR spectra and the structures was confirmed using X-ray crystallography (*vide infra*) and deuteration experiments. In a medicinal chemistry context, this spectroscopic similarity is a hazard for the understanding of structure activity relationships: the original evaluation of this synthetic product had concluded that **17** was inactive ($IC_{50} > 10$ μM) in a malaria parasite killing assay (*in vitro* against *P. falciparum* 3D7 strain), when in fact it was **18** that had been evaluated in its place. Compound **17** was later tested and found to have reasonable potency ($IC_{50} = 1.04$ μM).

According to the generally accepted *ipso*-substitution reaction mechanism, the first step is nucleophile attack on the carbon atom to which halogen is attached (**19**, Figure 3B). The resulting intermediate (**20**) expels chloride, leading to the *ipso*-substituted product (**21**). On the other hand, a plausible mechanism for the *tele*-substitution reaction could involve the initial attack of the nucleophile at the 8-position (**22**, Figure 3B), followed by loss of the 8-position proton as part of the elimination of the chloride (**23**). Since mechanistic studies on *tele*-substitution reactions are scarce in the literature, we sought better understanding of the process operating in this case.

To better define the scope of *tele*-substitution in this triazolopyrazine system, 8- and 6-halogenated variants of the triazolopyrazine core were synthesised from the corresponding dihalopyrazines following literature procedures[22] and subjected to the same reaction conditions as the original 5-chloro triazolopyrazine. The 8-halogenated cores (**25**-**27**, Figure 5A) reacted to give the expected *ipso*-substituted products only (**28**-**36**), while the 6-halogenated analogues (**37** and **38**, Figure 5B) resulted only in degradation of starting material without formation of any substituted product. While there is limited literature precedence, dihalopyrazines (e.g. **39**-**41**, Figure 5C) have been shown to give exclusively *ipso*-substituted products (**42**-**44** respectively). With these experiments showing that the *tele*-substitution reaction is observed only with the 5-halogenated cores (Figure 3A), the following mechanistic discussion will focus on that system.

Factors influencing *ipso*- vs. *tele*-substitution.

A) Influence of triazolopyrazine structure and nucleophile.[a] The nature of the nucleophile plays a crucial role in the outcome of the reaction (Table 1). When compared to reactions with alcohols, the use of more nucleophilic amines and thiols led to significantly more *tele*-substituted products (Entries 1-6, 12-17 and 21-26). This trend may explain why *tele*-substituted isomers were apparently not seen in the literature synthesis of related structures[23] in which the incoming nucleophile was restricted to alcohols.

[a]When the conditions employed with alcohols and thiols (KOH, 18-crown-6) were used with amine nucle-

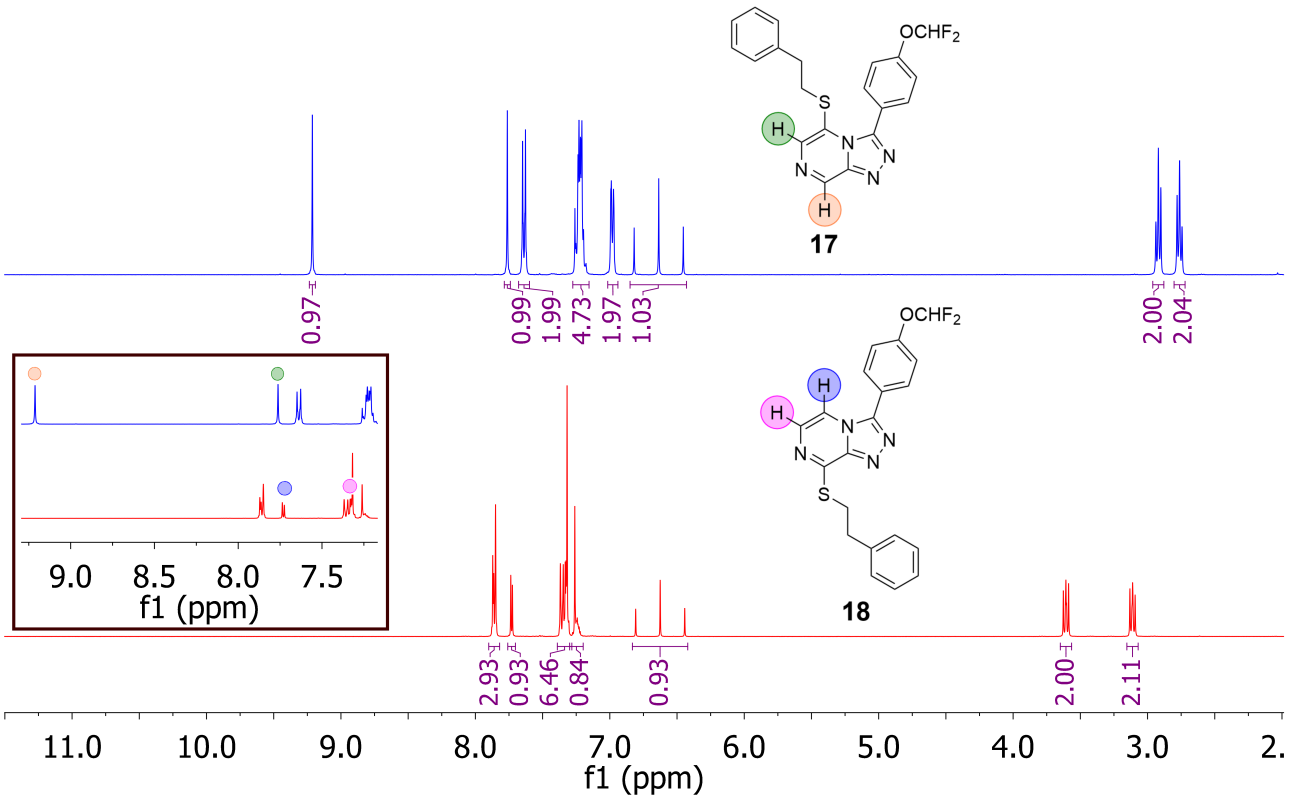


Figure 4: ^{1}H NMR spectra of **17** and **18** in $CDCl_3$. The hydrogen atoms on the pyrazine ring for the 5-substituted isomers (highlighted in green and orange in **17**) give rise to sharp singlets (δ∼7.5 and ∼9.0 ppm), while those in the 8-substituted isomers (highlighted in pink and blue in **18**) give well-defined doublets (δ∼7.2–7.7 ppm, J = 4.6 Hz).

The nature of the leaving halogen also influences the outcome, with *tele*-substitution favoured in the order I > Br > Cl (compare ratio in Entries 4, 15 and 24).

In cases where a larger substituent is in position 3 of the triazolopyrazine core (e.g. a (4-OMe)Ph group compared to a hydrogen atom), and the leaving halogen is either a Br or I atom, the distribution of *ipso*- to *tele*-substituted products is favoured towards the latter (compare Entries 12 and 15 or 21 and 24). Similar experiments in which the leaving halogen is a Cl atom show little to no change in distribution of products (compare Entries 1 and 4). Further investigation of the substituent at the 3-position led to the conclusion that bulkiness does not affect the reaction (i.e. substitution with (4-OMe)Ph is comparable to that of the larger (3,5-*t*Bu)Ph or 9-anthracene; Entries 4, 10 and 11 respectively).

Substrates with electron donating (EDG) and electron withdrawing (EWG) groups on the phenyl ring at the 3-position of the core were studied in order to evaluate the influence of electronic effects on the distribution of products. Experiments on bromo-triazolopyrazines showed that EDGs tend to promote the *tele*-substitution pathway of the reaction, while EWGs lead to *ipso*-products only (Entries 15 and 18-20). Interestingly, chloro-triazolopyrazines do not follow this pattern and show no dependence on the electronic effects from the substituent in the 3-position (Entries 4, 7, 8 and 9).

From the experiments summarised in Table 1, two gave surprising results. The reaction be-

ophiles, the reaction progress was comparatively slow so the base was replaced with silica, which gave better conversion; for convenience the rate was made comparable to those seen with the other nucleophiles by raising the reaction temperature, as the reaction at room temperature was not complete after 2 weeks.

Table 1: Influence of triazolopyrazine structure, leaving halogen X and nucleophile on the reaction outcome. Conditions: [a]KOH, 18-crown-6, toluene, room temperature; [b]silica, toluene, reflux. [c]Dehalogenation by-product **49** was isolated as well in 74% yield. [d]Dehalogenation by-product **49** was isolated in 11% yield along with ring opening product **50** in 17% yield (refer to Figure 6 for details). $R_1 = CH_2CH_2Ph$. ND: not determined.

45 **46** **47** **48**

Entry	X	R	**45**	Nucleophile	**46** yield [%]	**47** yield [%]	**48** yield [%]
1	Cl	H	**45a**	R_1OH	**46a**, 75	ND	-
2	Cl	H	**45a**	R_1SH	**46b**, 51	ND	-
3	Cl	H	**45a**	R_1NH_2[b]	ND	**30**, 65	-
4	Cl	(4-OMe)Ph	**45b**	R_1OH	**46c**, 70	**47a**, 3	-
5	Cl	(4-OMe)Ph	**45b**	R_1SH	**46d**, 8	**47b**, 83	-
6	Cl	(4-OMe)Ph	**45b**	R_1NH_2[b]	ND	**47c**, 89	-
7	Cl	(4-NO_2)Ph	**45c**	R_1OH	**46e**, 77	**34**, 2	-
8	Cl	(2-OMe)Ph	**45d**	R_1OH	**46f**, 58	ND	-
9	Cl	(2-NO_2)Ph	**45e**	R_1OH	**46g**, 65	ND	-
10	Cl	(3,5-*t*Bu)Ph	**45f**	R_1OH	**46h**, 82	**47d**, 3	-
11	Cl	9-anthracenyl	**45g**	R_1OH	**46i**, 66	**47e**, 2	-
12	Br	H	**45h**	R_1OH	**46a**, 66	ND	-
13	Br	H	**45h**	R_1SH	**46b**, 34	**29**, 17	-
14	Br	H	**45h**	R_1NH_2[b]	ND	**30**, 72	-
15	Br	(4-OMe)Ph	**45i**	R_1OH	**46c**, 32	**47a**, 10	**48a**, 20
16	Br	(4-OMe)Ph	**45i**	R_1SH	ND	**47b**, 93	-
17	Br	(4-OMe)Ph	**45i**	R_1NH_2[b]	ND	**47c**, 66	-
18	Br	(4-NO_2)Ph	**45j**	R_1OH	**46e**, 60	ND	**48b**, 30
19	Br	(2-OMe)Ph	**45k**	R_1OH	**46f**, 26	**47f**, 9	**48c**, 49
20	Br	(2-NO_2)Ph	**45l**	R_1OH	**46g**, 76	ND	**48d**, 12
21	I	H	**45m**	R_1OH	**46a**, 34	ND	-
22	I	H	**45m**	R_1SH	**46b**, 7	**29**, 7	-
23	I	H	**45m**	R_1NH_2[b]	ND	**30**, 40	-
24	I	(4-OMe)Ph	**45n**	R_1OH	**46c**, 23	**47a**, 53	-
25[c]	I	(4-OMe)Ph	**45n**	R_1SH	ND	**47b**, 13	-
26[d]	I	(4-OMe)Ph	**45n**	R_1NH_2[b]	ND	**47c**, 58	-

tween the iodo-triazolopyrazine core **45n** and the thiol nucleophile (Entry 25) in addition to the 8-substituted compound **47b**, isolated in 13% yield, gave dehalogenated product **49** in 74% yield. This product was not observed for any other reaction substrates bearing a chlorine or bromine atom. This type of the dehalogenation reaction has not previously been reported in the literature. The other unexpected product was isolated from the reaction between the iodo-triazolopyrazine core **45n** and the amine nucleophile (Entry 26). In addition to the isolation of the major *tele*-substituted isomer **47c** and dehalogenation product **49**, a minor by-product was obtained in 17% yield, the structure was determined by single crystal X-ray

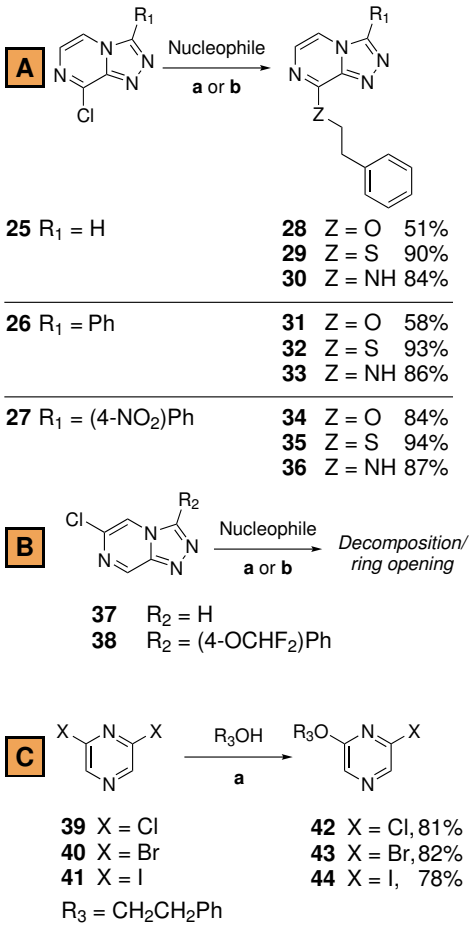


Figure 5: Reactions of halogenated triazolopyrazine isomers and pyrazines. A) 8-Isomer; B) 6-Isomer; C) Pyrazine; Conditions: [a]KOH, 18-crown-6, toluene, room temperature (reactions involve measuring small amounts of hygroscopic KOH, which can contribute to reproducibility challenges, thus experiments were performed in duplicate and are reported as average values); [b]silica, toluene, reflux (more details in Table 1).

diffraction to be based on a 5-(1H-imidazol-2-yl)-1H-1,2,4-triazole core instead of triazolopyrazine (**50**, Figure 6). It is possible that compound **50** could be formed *via* initial nucleophile attack at the 8-position of the pyrazine ring (**51**), followed by the pyrazine ring opening (**52**) and rearrangement (**53**) leading to **50**. While the analogous reaction utilising the chlorine-substituted triazolopyrazine (Entry 6) did not lead to this rearranged product, it was formed in trace amounts when the bromo-substituted triazolopyrazine was employed (Entry 17). This trend may either be due to a sub-optimal bond geometry (i.e. pseudo-equatorial I atom) arising from the larger halogen atom or from a better match of orbital energies for elimination (in the case of the chlorine leaving group).

B) Influence of solvent. With the reaction between **45i** and the alcohol nucleophile (Table 1, Entry 1) giving significant quantities of both isomers, this was used as the model reaction to investigate further the influence of solvent on the reaction outcome (Table 2). A screen of aprotic solvents clearly showed that solvents with higher dielectric constants lead to less *tele*-substitution and also lowers the overall yield of the reaction. Protic solvents are inherently unsuitable for this reaction as they can easily themselves react with the halogenated triazolopyrazine. This was demonstrated when water was used as the solvent, giving the product **48a** in 94% yield, by result of *tele*-substitution with H_2O.

C) Influence of excess alcohol and base. By using the same model reaction above, the effect of alcohol and base equivalents was investigated. It was found that the use of an excess of nucleophile resulted in a shift of the reaction outcome drastically towards the formation of the 8-isomer (**47a**, Figure 7A). These observations suggest that the use of a softer nucleophile (here one in which the anion is surrounded by a "solvent shell" of OH bonds arising from excess nucleophile) leads to greater formation of the 8-isomer. Similarly, when fewer equivalents of base were used, a higher proportion of *tele*-substitution was again observed (Figure 7B).

D) Influence of water and temperature. In order to evaluate the impact of the level of water present on *tele*-substitution, the reaction between **45a** (unsubstituted on the triazole ring) and piperidine was conducted in toluene with various levels of water, as well as in water itself (H_2O and D_2O). The isolated yields of the 5- (**55**) and 8-isomer (**56**) were identical for experiments in both wet and dry toluene (Table 3, Entries 1 and 3). At room temperature the reaction took 14 days to complete (Entry 2), but the outcome was comparable to that when heating under reflux conditions. When molecular sieves were included in the reaction mixture (using dried toluene) the ratio of products

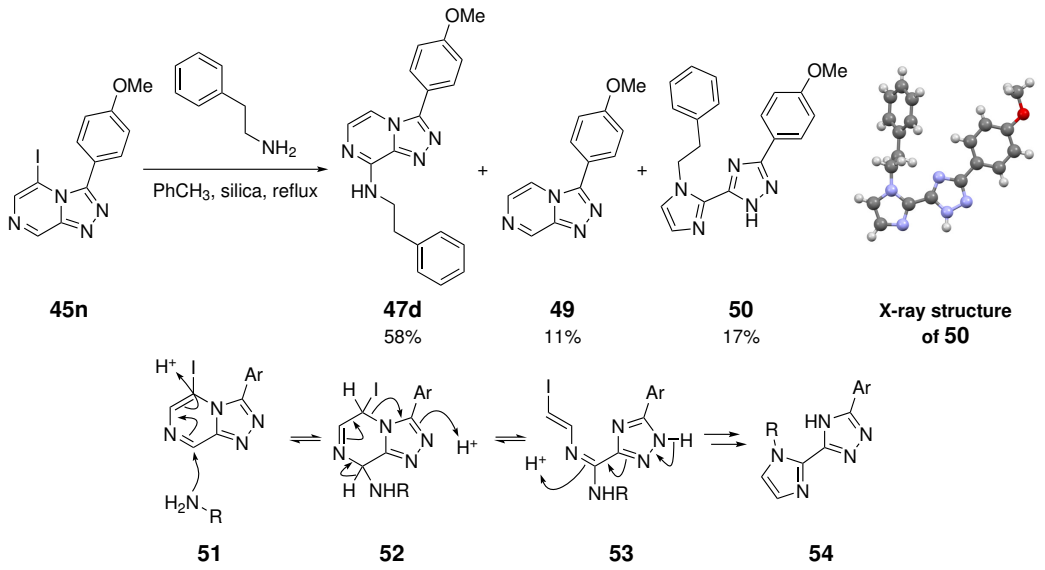


Figure 6: Unexpected product **50** of ring opening and rearrangement from the reaction of iodotriazolopyrazine and an amine nucleophlie, with an X-ray structure and proposed mechanism for this product (see SI for more details, Figure S2.

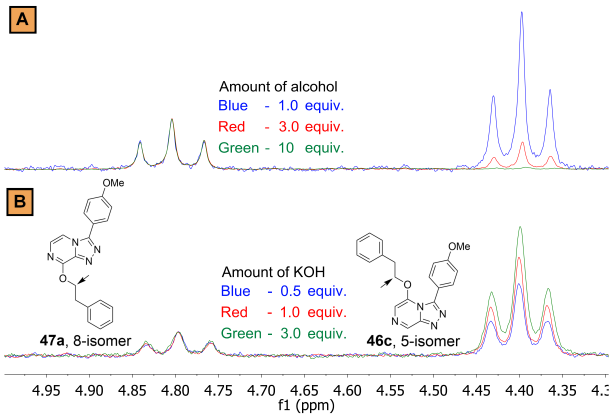
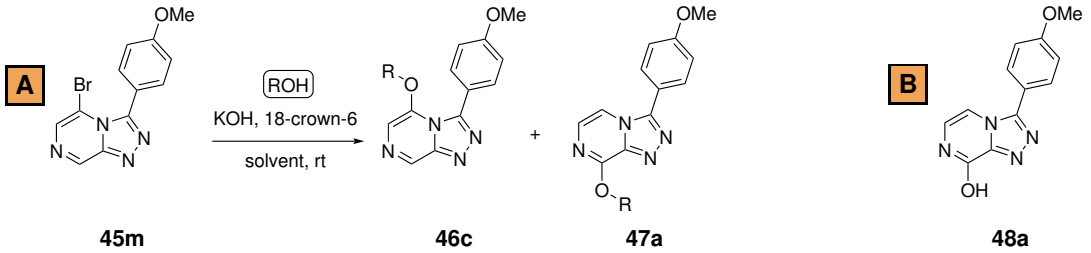


Figure 7: Crude ^{1}H NMR comparison of the reaction outcome depending on A) amount of alcohol; B) amount of base. Structures of isomers placed next to corresponding signals from CH_2 groups which are indicated by arrow.

changed, though it is possible that this could arise from catalytic activity at the zeolite surface itself (Entry 4).[24,25] Performing the reaction in H_2O (Entry 5) gave a comparable result to that in wet toluene. This is counter to the example where the alcohol nucelophile was out-competed by the solvent water to give the *tele*-substitution product (*vide supra*). It could be concluded that the presence of water in the solvent and the reaction temperature do not alter the distribution of products in the studied reaction.

E) Isotope labeling experiments. Following the observation that no hydroxy-substituted product was identified in the reaction between the halogenated triazolopyrazine core **45a** and an amine nucleophile in the presence of water, deuteration experiments were peformed to gain insight into the reaction mechanism. This reaction was carried out in D_2O giving two compounds, **57** and **58** (Figure 8A). The examination of products with ^{1}H NMR and ^{2}H NMR spectroscopy showed incorporation of one D atom in **57** and two in **58**. Both molecules underwent deuterium exchange of the triazole H atom. The deuteration of triazole rings has been reported in a handful of cases,[26,27] but not for the triazolopyrazine system investigated here. In order to prove that deuteration at the 3-position occurs as a parallel reaction to the main substitution, compounds **45a**, **55** and **56** were heated under reflux in D_2O without piperidine to give corresponding monodeuterated products **59**, **57** and **60** respectively (Figure 8B). The second D atom in **58** was at the 5-position, thus confirming that the proton which takes the place of the leaving group in the *tele*-substitution reaction comes from the

Table 2: A) Reaction used to study the influence of solvent; B) Product isolated when H_2O was employed as a solvent. Results of the reaction in different solvents (reactions performed in duplicate). All solvents were dried over molecular sieves (3 Å) for 48 h before application. All reactions proceed to complete consumption of bromo-triazolopyrazine as indicated by TLC. Total yield reported is the sum of both isomers. Product **48a** typically observed to form in ∼15% yield but was not isolated in these reactions. R = CH_2CH_2Ph.



45m **46c** **47a** **48a**

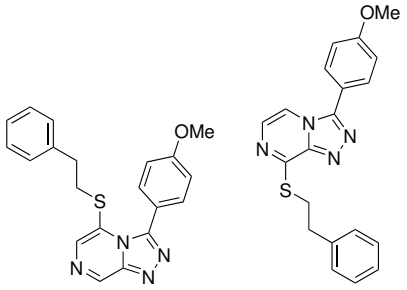
Entry	Solvent	**46c** (5-isomer) yield [%]	**47a** (8-isomer) yield [%]	Total yield [%]	Dielectric constant
1	Cyclohexane	35	24	58	2.02
2	Toluene	31	8	40	2.38
3	Dioxane	20	9	29	2.25
4	THF	19	3	22	7.58
5	Acetonitrile	43	3	45	37.5
6	DMF	25	2	27	36.7

solvent and not from the substrate (see the proposed mechanism for **19** in Figure 3B).

Importantly, the amine products **55** and **56** were found to be not interconvertible when each product separately was subjected to the reaction conditions for 3 days, as no conversion of one isomer into another could be detected by TLC. Thus the ratios of products observed in these telesubstitution reactions arise from a kinetic difference rather than one that has a thermodynamic origin.

3 Biological activity

As mentioned above, 5-substituted triazolopyrazines (e.g. **17**) showed antiplasmodium activity, while an 8-substituted isomer (**18**) proved to be inactive. Based on the structural similarity of these triazolopyrazines to kinase inhibitors,[28] we evaluated several compounds in the preliminary KINOMEscan® assay (at 1 µM concentration). The results revealed complementary activity of *ipso*- and *tele*-isomers, for example **47b** has higher potency against serine/threonine-protein kinase 3 (STK3) compared to **46d** (Figure 9, see SI for full screening results). Thus the occurrence of this *tele*-substitution reaction allows the generation of two biologically active compounds with complentary activities from a single reaction.



46d
STK3 Control = 81%
moderate affinity

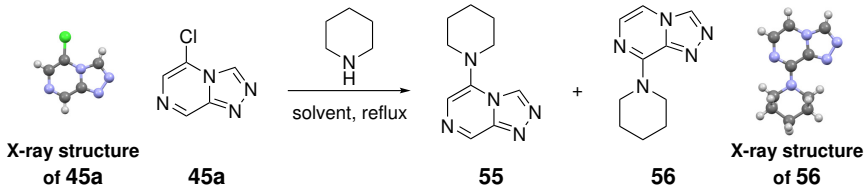
47b
STK3 Control = 42%
low affinity

Figure 9: Compounds evaluated in KINOMEscan® assay.

4 Conclusion

Tele-substitution reactions are simple to achieve in the triazolopyrazine ring system, and it is important to be aware of the possi-

Table 3: Results of the reaction with wet and dry solvent. 3Å molecular sieves were used to dry the toluene. Water levels were measured with a Karl-Fischer titration apparatus immediately before the experiment. [a]Reaction time 14 days. [b]Products were partially deuterated (Figure 8).



Entry	Solvent	Water level (ppm)	**55** (5-isomer) yield [%]	**56** (8-isomer) yield [%]	Total yield [%]
1	Toluene commercial	136	16	71	87
2[a]	Toluene commercial at rt	136	7	86	93
3	Toluene dry	6	16	71	87
4	Toluene dry with sieves in rxn	6	36	40	76
5	H_2O	-	21	57	78
6[b]	D_2O	-	24	59	83

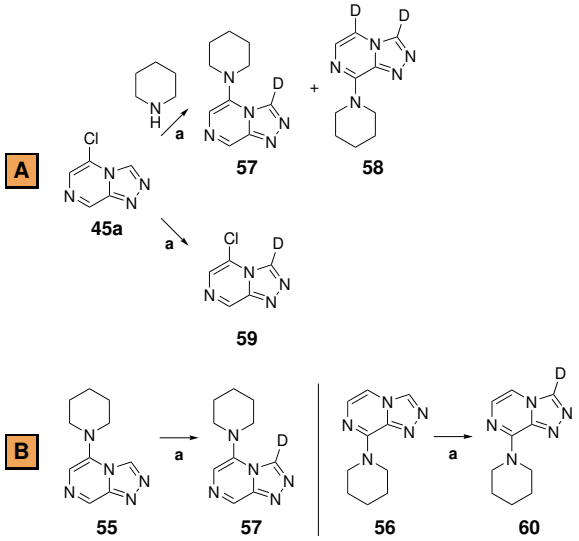


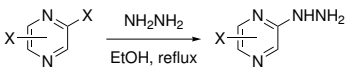
Figure 8: A) Reaction between simplified chloro-substituted core **45a** and piperidine, performed in D_2O as the solvent; B) Verification that H/D exchange on the triazole, but not the pyrazine, is a parallel reaction to the main substitution reaction. [a]D_2O, heating at reflux.

bility of such isomers forming, given the wide biological relevance of many of these structures. The *tele*-substitution reaction occurs only in 5-halogenated triazolopyrazine cores, while 8- or 6-halogenated cores tend to give *ipso*-substitution or degradation respectively. The *tele*-substitution pathway of the reaction is also made more likely by the use of stronger nucleophiles, triazolopyrazines with bulkier halogens and the use of less polar solvents. As concluded from the isotope labeling experiments, the hydrogen atom that takes the place of the halogen derives from solvent and not from substrate. The product ratios arise from a kinetic difference in the reactions rather than a thermodynamic difference in product energies, where, broadly, a combination of hard nucleophile and hard electrophile promotes *ipso*-substitution while a softer combination promotes *tele*-substitution.

5 Experimental

5.1 General Procedures

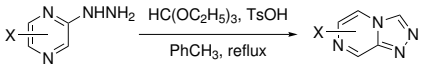
General Procedure A. Preparation of halogenhydrazinylpyrazines



Mono or dihalogenopyrazine (70 mmol, 1 equiv.) was dissolved in ethanol (100 mL), then hydrazine monohydrate was added (140 mmol, 2 equiv.) and the mixture was heated at reflux overnight. The solvent was removed under reduced pressure. Equal amounts of EtOAc (100 mL) and H_2O (100 mL) were added, the EtOAc

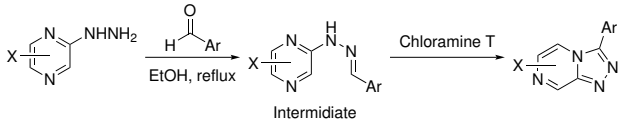
layer was separated and the aqueous layer was washed with EtOAc (30 mL × 3). The combined organic phases were washed with brine (30 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give the desired compound, which was used in the subsequent reaction without further purification.

General Procedure B. Preparation of halogeno-[1,2,4]triazolo[4,3-a]pyrazine



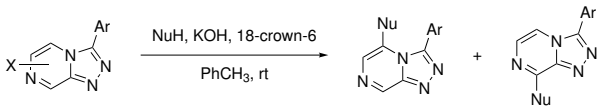
To a suspension of halogen-hydrazinylpyrazine (70.0 mmol, 1.0 equiv.) in toluene (200 mL) triethyl orthoformate or trimethyl orthoformate (140 mmol, 2.0 equiv.) was added followed by *p*-toluenesulfonic acid monohydrate (14.0 mmol, 0.2 equiv.). The mixture was heated at reflux for 5 h. The solvent was removed under reduced pressure and the residue purified by flash column chromatography (FCC) on silica using a gradient of EtOAc (20% to 100%) in hexanes to give the desired product.

General Procedure C. Preparation of halogeno-3-aryl-[1,2,4]triazolo[4,3-a]pyrazine



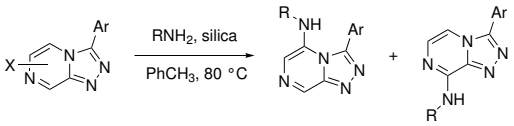
Adopted from the literature procedures.[22] To a stirred suspension of halogeno-hydrazinylpyrazine (7.0 mmol, 1.0 equiv.) in ethanol (100 mL) was added aldehyde (7.7 mmol, 1.1 equiv.) and the mixture heated at reflux overnight. After the full consumption of starting material as indicated by TLC, the reaction was cooled in an ice bath and chloramine T trihydrate (9.1 mmol, 1.3 equiv.) was added portionwise while stirring over 1 h. After consumption of the intermediate was confirmed by TLC, cold H_2O (100 mL) was added to the reaction mixture. The solution was stirred for 10 min, then filtered through a sintered glass filter (P3 porosity) and washed with H_2O (30 mL × 3) followed by Et_2O (30 mL). The solid was dried *in vacuo* to give desired product that was used without further purification.

General Procedure D. Coupling of alcohol or thiol with halogen-heterocycle



To a suspension of halogen-heterocycle (0.40 mmol, 1 equiv.) in toluene (10 mL) was added 18-crown-6 (0.032 mmol, 0.08 equiv.) and alcohol or thiol (0.40 mmol, 1 equiv.) followed by KOH (1.20 mmol, 3.0 equiv.). The reaction mixture stirred for 2-24 h at room temperature. Upon completion as indicated by TLC, the reaction mixture was directly subjected to the purification by FCC on silica and flushed at the beginning with hexanes (in order to wash out toluene from the column) followed by a gradient of EtOAc (30% to 100%) in hexanes (unless specified in the compound preparation) to give the desired product.

General Procedure E. Coupling of amine with halogen-heterocycle



To a suspension of halogen-heterocycle (0.40 mmol, 1.0 equiv.) in toluene (10 mL) was added amine (1.20 mmol, 3.0 equiv.) followed by silica (0.5 g). The reaction was heated at 80 °C overnight. Upon completion of the reaction as indicated by TLC, the solvent was evaporated *in vacuo* and the mixture purified by FCC on silica using a gradient of EtOAc EtOAc (30% to 100%) in hexanes (unless specified in the compound preparation) to give the desired product.

5.2 Synthesis

2-Chloro-6-hydrazinylpyrazine (**S1**). General Procedure A was applied using 2,6-dichloropyrazine (35.0 g, 235 mmol) to give **S1** as a yellow solid (29.2 g, 202 mmol, 86%). mp 137–139 °C (lit.[8] 136–139 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.42 (s, 1H), 8.05 (s, 1H), 7.70 (s, 1H), 4.37 (s, 2H). ^{13}C{^{1}H} NMR (50 MHz, DMSO-d_6): δ 157.1, 145.7, 129.0, 128.6.

The spectroscopic data and melting point were in agreement with those in the literature.[8,29]

2-Bromo-6-hydrazinylpyrazine (**S2**). General Procedure A was applied using 2,6-dibromopyrazine (8.09 g, 34.0 mmol) to give **S2** as an orange solid (5.45 g, 28.9 mmol, 85%). mp 142–144 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.16 (s, 1H), 7.98 (s, 1H), 6.28 (s, 1H), 3.72 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$): δ 156.8, 138.1, 135.4, 129.2. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ calcd for $C_4H_6{}^{79}BrN_4$ 188.97704; found 188.97728.

2-Iodo-6-hydrazinylpyrazine (**S3**). General Procedure A was applied using **41** (8.37 g, 25.2 mmol) to give **S3** as a yellow solid (4.87 g, 20.7 mmol, 82%). mp 154–156 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.31 (s, 1H), 8.05 (s, 1H), 7.91 (s, 1H), 4.33 (s, 2H). $^{13}C\{^1H\}$ NMR (75 MHz, DMSO-d_6): δ 157.8, 137.8, 128.9, 115.9. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ calcd for $C_4H_6IN_4$ 236.96317; found 236.96297.

2-Chloro-3-hydrazinylpyrazine (**S4**). General Procedure A was applied using 2,3-dichloropyrazine (10.2 g, 68.3 mmol) to give **S4** as a yellow solid (6.61 g, 45.7 mmol, 67%). mp 156–158 °C (lit.[30] mp 154 °C). ^{1}H NMR (200 MHz, DMSO-d_6): δ 8.23 (s, 1H), 8.04 (d, J = 2.7 Hz, 1H), 7.55 (d, J = 2.8 Hz, 1H), 4.34 (s, 2H). $^{13}C\{^1H\}$ NMR (50 MHz, DMSO-d_6): δ 152.6, 140.6, 132.6, 130.0. The spectroscopic data and melting point were in agreement with those in the literature.[22,30]

2-Chloro-5-hydrazinylpyrazine (**S5**). Compound was prepared following literature procedures.[31] 2,5-Dichloropyrazine (2.00 g, 13.4 mmol, 1.0 equiv.) was added to H_2O (12.5 mL) followed by 28% aq. ammonia solution (2.63 mL, 38.9 mmol, 2.9 equiv.) and hydrazine monohydrate (1.57 mL, 1.61 g, 32.2 mmol, 2.4 equiv.). The mixture was heated at reflux overnight, then cooled in an ice bath for 15 min, filtered through a sintered funnel and washed with cold H_2O (25 mL × 3), then dried *in vacuo* to give **S5** as a pale yellow solid (1.62 g, 11.2 mmol, 83%). mp 168–170 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.14 (s, 1H), 8.02 (d, J = 1.4 Hz, 1H), 7.93 (d, J = 1.4 Hz, 1H), 4.32 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 156.6, 140.3, 133.9, 129.5. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ calcd for $C_4H_6ClN_4$ 145.02755; found 145.02749. The spectroscopic data were in agreement with those in the literature.[32]

5-Chloro-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**16**). General Procedure C was applied using **S1** (1.51 g, 10.4 mmol, 1.0 equiv.) and 4-(difluoromethoxy)benzaldehyde (1.98 g, 11.5 mmol, 1.1 equiv.) to give **16** as a brown solid (2.26 g, 7.62 mmol, 73%). mp 124–126 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.47 (s, 1H), 8.08 (s, 1H), 7.79 (d, J = 8.2 Hz, 2H), 7.41 (t, J = 73.6 Hz, 1H), 7.36 (d, J = 8.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 153.3 – 152.1 (m), 147.0, 146.7, 142.7, 133.3, 129.2, 124.0, 121.8, 117.4, 116.2 (t, J = 258.0 Hz) ($OCHF_2$). HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ calcd for $C_{12}H_8ClF_2N_4O$ 297.03492; found 297.03460.

3-(4-(Difluoromethoxy)phenyl)-5-(phenethylthio)-[1,2,4]triazolo[4,3-a]pyrazine (**17**). General Procedure D was applied using **16** (101 mg, 0.341 mmol, 1.0 equiv.) and 2-phenylethane-1-thiol (47.1 mg, 0.341 mmol, 1.0 equiv.). Fractions corresponding to the second peak were evaporated to give **17** as a yellow solid (11.0 mg, 0.0276 mmol, 8%). mp 78–83 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.21 (s, 1H), 7.76 (s, 1H), 7.68 – 7.60 (m, 2H), 7.28 – 7.15 (m, 5H), 7.02 – 6.94 (m, 2H), 6.64 (t, J = 73.1 Hz, 1H), 2.92 (t, J = 7.5 Hz, 2H), 2.76 (t, J = 7.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$): δ 153.10 (t, J = 2.8 Hz), 147.6, 146.4, 142.3, 138.3, 133.5, 131.3, 128.8, 128.6, 128.4, 127.1, 124.1, 118.3, 115.65 (t, J = 261.3 Hz), 35.8, 34.6. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{17}F_2N_4OS$ 399.10856; found 399.10801.

3-(4-(Difluoromethoxy)phenyl)-8-(phenethylthio)-[1,2,4]triazolo[4,3-a]-pyrazine (**18**). Isolated from the same reaction as for **17**. Fractions corresponding to the first peak were evaporated to give to give **18** as an off-white solid (113 mg, 0.284 mmol, 83%). mp 156–158 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.32 (d, J = 4.8 Hz, 1H), 8.04 – 7.96 (m, 2H), 7.83 (d, J = 4.8 Hz, 1H), 7.58 – 7.39 (m, 5H), 7.37 – 7.29 (m, 4H), 7.30 – 7.20 (m, 1H), 3.59 (dd, J = 8.4, 6.7 Hz, 2H), 3.05 (dd, J = 8.4, 6.7

Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 153.0, 152.4 (t, J = 3.3 Hz), 146.9, 143.8, 139.9, 130.2, 129.5, 128.6, 128.4, 126.4, 122.5, 119.2, 116.1 (t, J = 258.5 Hz), 113.2, 34.4, 29.4. ^{19}F NMR (471 MHz, DMSO-d_6): δ -82.8. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{20}H_{17}F_2N_4OS$ 399.10856; found 399.10827.

8-Chloro-[1,2,4]triazolo[4,3-a]pyrazine (**25**). General Procedure B was applied using **S4** (2.71 g, 18.8 mmol) to give **25** as a yellow solid (0.870 g, 5.63 mmol, 30%). mp 203–206 °C (lit.[30] mp 205 °C). ^1H NMR (200 MHz, $CDCl_3$): δ 9.00 (s, 1H), 8.05 (d, J = 4.7 Hz, 1H), 7.74 (d, J = 4.7 Hz, 1H). HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_5H_3ClN_4Na$ 176.99384; found 176.99367. The spectroscopic data and melting point were in agreement with those in the literature.[30,33]

8-Chloro-3-phenyl-[1,2,4]triazolo[4,3-a]pyrazine (**26**). General Procedure C was applied using **S4** (0.768 g, 5.31 mmol, 1.0 equiv.) and benzaldehyde (0.620 g, 5.84 mmol, 1.1 equiv.) to give **26** as a white solid (0.976 g, 4.23 mmol, 80%). mp 192–195 °C (lit.[34] mp 193–195 °C). ^1H NMR (200 MHz, $CDCl_3$): δ 8.16 (d, J = 4.8 Hz, 1H), 7.92 – 7.78 (m, 2H), 7.72 (d, J = 4.8 Hz, 1H), 7.64 (q, J = 3.1 Hz, 3H). HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{11}H_7ClN_4Na$ 253.02514; found 253.02522. The spectroscopic data and melting point were in agreement with those in the literature.[34]

8-Chloro-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**27**). General Procedure C was applied using **S4** (0.655 g, 4.53 mmol, 1.0 equiv.) and 4-nitrobenzaldehyde (0.754 g, 4.99 mmol, 1.1 equiv.) to give **27** as a yellow solid (1.15 g, 4.16 mmol, 92%). m.p. 231–234 °C (decomp.) (lit.[22] mp 201–204 °C). ^1H NMR (500 MHz, DMSO-d_6): δ 8.77 (d, J = 4.8 Hz, 1H), 8.47 (d, J = 8.6 Hz, 2H), 8.26 (d, J = 8.6 Hz, 2H), 7.89 (d, J = 4.8 Hz, 1H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 148.9, 147.6, 144.6, 142.5, 132.0, 130.1, 129.6, 124.8, 118.4. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{11}H_7ClN_5O_2$ 298.01022; found 298.01025. The spectroscopic data were in agreement with the literature, but the melting point was significantly higher.[22]

8-Phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine (**28**). General Procedure D was applied using **25** (104 mg, 0.673 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (82.2 mg, 0.673 mmol, 1.0 equiv.) to give **28** as an off-white solid (83.0 mg, 0.345 mmol, 51%). mp 161–162 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 9.36 (s, 1H), 8.19 (d, J = 4.7 Hz, 1H), 7.42 (d, J = 4.7 Hz, 1H), 7.38 – 7.27 (m, 4H), 7.26 – 7.19 (m, 1H), 4.72 (t, J = 6.9 Hz, 2H), 3.16 (t, J = 6.9 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 152.6, 138.7, 138.4, 137.9, 128.9, 128.4, 126.6, 126.4, 113.2, 113.2, 67.2, 34.2. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{13}H_{12}N_4ONa$ 263.09033; found 263.08997.

8-(Phenethylthio)-[1,2,4]triazolo[4,3-a]pyrazine (**29**). General Procedure D was applied using **25** (104 mg, 0.673 mmol, 1.0 equiv.) and 2-phenylethane-1-thiol (93.0 mg, 0.673 mmol, 1.0 equiv.) to give **29** as an off-white solid (154 mg, 0.602 mmol, 90%). mp 148–150 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 9.38 (d, J = 0.8 Hz, 1H), 8.33 (dd, J = 4.6, 0.8 Hz, 1H), 7.79 (dd, J = 4.7, 0.8 Hz, 1H), 7.31 (d, J = 4.4 Hz, 4H), 7.23 (h, J = 4.0 Hz, 1H), 3.59 – 3.53 (m, 2H), 3.06 – 3.00 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 152.2, 142.7, 139.9, 138.1, 128.7, 128.6, 128.4, 126.4, 114.3, 34.4, 29.4. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{13}H_{12}N_4SNa$ 279.06749; found 279.06714.

N-Phenethyl-[1,2,4]triazolo[4,3-a]pyrazin-8-amine (**30**). Preparation 1: General Procedure E was applied using **25** (104 mg, 0.654 mmol) and 2-phenylethan-1-amine (244 mg, 2.01 mmol, 3.0 equiv.) to give **30** as an off-white solid (135 mg, 0.564 mmol, 84%). Preparation 2: General Procedure E was applied using **45a** (100 mg, 0.649 mmol, 1.0 equiv.) and 2-phenylethan-1-amine (235 mg, 1.95 mmol, 3.0 equiv.) to give **30** as an off-white solid (102 mg, 0.424 mmol, 65%). mp 191–193 °C (decomp.). ^1H NMR (500 MHz, DMSO-d_6): δ 9.19 (s, 1H), 8.16 (t, J = 5.8 Hz, 1H), 7.74 (d, J = 4.7 Hz, 1H), 7.32 – 7.23 (m, 5H), 7.23 – 7.15 (m, 1H), 3.71 (q, J = 6.9 Hz, 2H), 2.99 – 2.92 (m, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 147.4, 139.5, 138.6, 138.1, 129.1, 128.6, 128.3, 126.0, 107.2, 41.6, 34.5. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{13}H_{14}N_5$ 240.12437; found 240.12406.

8-Phenethoxy-3-phenyl-[1,2,4]triazolo[4,3-a]pyrazine (**31**). General Procedure D was applied using **26** (115 mg, 0.499 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (60.9 mg, 0.499 mmol, 1.0 equiv.) to give **31** as a white solid (91.0 mg, 0.288 mmol, 58%). mp 145–147 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.19 (d, J = 4.9 Hz, 1H), 7.94 – 7.88 (m, 2H), 7.68 – 7.59 (m, 3H), 7.47 (d, J = 4.9 Hz, 1H), 7.41 – 7.29 (m, 4H), 7.24 (t, J = 7.3 Hz, 1H), 4.76 (t, J = 6.8 Hz, 2H), 3.19 (t, J = 6.9 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 153.2, 148.0, 139.7, 138.0, 130.5, 129.3, 129.0, 128.4, 128.1, 127.4, 126.4, 125.9, 112.1, 67.4, 34.2. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{19}H_{16}N_4ONa$ 339.12163; found 339.12165.

8-(Phenethylthio)-3-phenyl-[1,2,4]triazolo-[4,3-a]pyrazine (**32**). General Procedure D was applied using **26** (107 mg, 0.464 mmol) and 2-phenylethane-1-thiol (65.1 mg, 0.464 mmol, 1.0 equiv.) to give **32** as an off-white solid (145 mg, 0.440 mmol, 94%). mp 154–156 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.33 (d, J = 4.8 Hz, 1H), 7.97 – 7.88 (m, 2H), 7.83 (d, J = 4.8 Hz, 1H), 7.69 – 7.59 (m, 3H), 7.33 (d, J = 5.0 Hz, 4H), 7.24 (ddd, J = 8.8, 5.3, 3.5 Hz, 1H), 3.63 – 3.56 (m, 2H), 3.09 – 3.02 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 153.0, 147.6, 143.8, 140.0, 130.5, 129.5, 129.3, 128.6, 128.4, 128.2, 126.4, 125.7, 113.2, 34.4, 29.4. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{19}H_{17}N_4S$ 333.11684; found 333.11641.

N-Phenethyl-3-phenyl-[1,2,4]triazolo[4,3-a]pyrazin-8-amine (**33**). General Procedure E was applied using **26** (102 mg, 0.442 mmol) and 2-phenylethan-1-amine (161 mg, 1.33 mmol, 3.0 equiv.) to give **33** (120 mg, 0.381 mmol, 86%). mp 206–209 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.27 (t, J = 5.7 Hz, 1H), 7.92 – 7.86 (m, 2H), 7.75 (d, J = 4.8 Hz, 1H), 7.67 – 7.57 (m, 3H), 7.36 (d, J = 4.8 Hz, 1H), 7.34 – 7.25 (m, 4H), 7.25 – 7.17 (m, 1H), 3.79 – 3.71 (m, 2H), 3.02 – 2.95 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 147.9, 147.7, 139.6, 139.5, 130.2, 130.2, 129.3, 128.7, 128.3, 128.0, 126.3, 126.1, 106.0, 41.6, 34.5. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{19}H_{18}N_5$ 316.15567; found 316.15526.

3-(4-Nitrophenyl)-8-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine (**34**). Preparation 1: General Procedure D was applied using **27** (113 mg, 0.410 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (50.1 mg, 0.410 mmol, 1.0 equiv.) to give **34** as a yellow solid (125 mg, 0.346 mmol, 84%). Preparation 2: isolated from the same reaction as for **46e** preparation 1: fractions correspond to the first peak were evaporated to give **34** as a yellow solid (2.05 mg, 5.51 μmol, 2%). mp 238–240 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.45 (d, J = 8.3 Hz, 2H), 8.32 (d, J = 4.9 Hz, 1H), 8.24 (d, J = 8.4 Hz, 2H), 7.56 (d, J = 4.9 Hz, 1H), 7.38 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.24 (t, J = 7.2 Hz, 1H), 4.79 (t, J = 6.8 Hz, 2H), 3.20 (t, J = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 153.2, 148.2, 146.5, 140.1, 137.9, 132.0, 129.4, 128.9, 128.4, 127.9, 126.4, 124.3, 112.4, 67.5, 34.2. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{19}H_{16}N_5O_3$ 362.12477; found 362.12462.

3-(4-Nitrophenyl)-8-(phenethylthio)-[1,2,4]-triazolo[4,3-a]pyrazine (**35**). Preparation 1: General Procedure D was applied using **27** (107 mg, 0.390 mmol) and 2-phenylethane-1-thiol (65.7 mg, 0.390 mmol, 1.0 equiv.) to give **35** as a yellow solid (103 mg, 0.273 mmol, 70%). Preparation 2: Isolated from the same reaction as for **46j**. Fractions corresponding to the first peak were evaporated to give **35** as a yellow solid (66.2 mg, 0.175 mmol, 44%). mp 236–238 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.46 (dd, J = 6.9, 2.0 Hz, 3H), 8.28 – 8.22 (m, 2H), 7.92 (d, J = 4.8 Hz, 1H), 7.37 – 7.30 (m, 4H), 7.29 – 7.21 (m, 1H), 3.61 (dd, J = 8.4, 6.7 Hz, 2H), 3.07 (dd, J = 8.4, 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 153.1, 148.3, 146.2, 144.2, 139.9, 131.8, 130.0, 129.5, 128.6, 128.4, 126.4, 124.3, 113.5, 34.4, 29.5. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{19}H_{16}N_5O_2S$ 378.10192; found 378.10180.

3-(4-Nitrophenyl)-N-phenethyl-[1,2,4]triazolo[4,3-a]pyrazin-8-amine (**36**). Preparation 1: General Procedure E was applied using **27** (112 mg, 0.406 mmol, 1.0 equiv.) and 2-phenylethan-1-amine (148 mg, 1.22 mmol, 3.0 equiv.) to give **36** (127 mg, 0.352 mmol, 87%). Preparation 2: General Procedure E was applied using **45c** (103 mg, 0.374 mmol,

1.0 equiv.) and 2-phenylethan-1-amine (136 mg, 1.12 mmol, 3.0 equiv.) to give **36** as a yellow solid (133 mg, 0.369 mmol, 99%). mp 236–238 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.47 – 8.41 (m, 2H), 8.38 (t, J = 5.8 Hz, 1H), 8.29 – 8.20 (m, 2H), 7.88 (d, J = 4.8 Hz, 1H), 7.45 (d, J = 4.8 Hz, 1H), 7.30 (h, J = 5.9 Hz, 4H), 7.21 (tt, J = 5.9, 2.1 Hz, 1H), 3.76 (q, J = 6.8 Hz, 2H), 3.02 – 2.96 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 148.0, 147.9, 146.1, 139.9, 139.5, 132.4, 130.8, 129.1, 128.7, 128.3, 126.1, 124.3, 106.2, 41.6, 34.4. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{19}H_{17}N_6O_2$ 361.14075; found 361.14041.

6-Chloro-[1,2,4]triazolo[4,3-a]pyrazine (**37**). General Procedure B was applied using **S5** (1.53 g, 10.6 mmol) to give **37** as an orange solid (0.800 g, 5.18 mmol, 49%). mp 215–217 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.41 (d, J = 0.7 Hz, 1H), 9.36 (dd, J = 1.5, 0.7 Hz, 1H), 8.90 (d, J = 1.5 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 143.9, 143.0, 137.3, 133.4, 116.3. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_5H_4ClN_4$ 155.01190; found 155.01178.

6-Chloro-3-(4-(difluoromethoxy)phenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**38**). General Procedure C was applied using **S5** (1.33 g, 9.23 mmol, 1.0 equiv.) and 4-(difluoromethoxy)benzaldehyde (1.22 mL, 1.59 g, 9.23 mmol, 1.1 equiv.) to give **27** as a pale brown solid (1.75 g, 5.89 mmol, 64%). mp 159–161 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.41 (s, 1H), 8.85 (s, 1H), 8.05 (d, J = 8.6 Hz, 2H), 7.43 (d, J = 8.4 Hz, 2H), 7.41 (t, J = 73.5 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 152.5 (t, J = 3.3 Hz), 146.2, 145.2, 143.4, 134.6, 130.3, 122.1, 119.2, 116.1 (t, J = 258.6 Hz), 115.2. ^{19}F NMR (471 MHz, DMSO-d_6): δ -82.8. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{12}H_7ClF_2N_4ONa$ 319.01687; found 319.01690.

2,6-Diiodopyrazine (**41**). Compounds was prepared following literature procedures.[35] Hydroiodic acid (50% solution, 25 mL, 5.0 equiv.) was added to 2,6-dichloropyrazine (5.07 g, 34.0 mmol, 1.0 equiv.) and NaI (6.63 g, 44.2 mmol, 1.3 equiv.) in a sealed tube and heated at 100 °C for 3 h. The reaction was cooled to room temperature and diluted with Et_2O (200 mL). The solution was washed with H_2O (100 mL × 2), sat. aq. $NaHCO_3$ (50 mL), sat. aq. $Na_2S_2O_3$ (50 mL), brine (30 mL), dried (Na_2SO_4), filtered and concentrated under reduced pressure to give **41** as a white solid (9.91 g, 29.9 mmol, 88%). mp 90–92 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.74 (s, 2H). ^{13}C{^{1}H} NMR (75 MHz, $CDCl_3$): δ 151.2, 116.8. The spectroscopic data were in agreement with those in the literature.[35]

2-Chloro-6-phenethoxypyrazine (**42**). General Procedure D was applied using 2,6-dichloropyrazine (107 mg, 0.718 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (87.8 mg, 0.718 mmol, 1.0 equiv.). The reaction mixture was purified by FCC on silica using a gradient of EtOAc (0% to 6%) in hexanes to give **42** as a colourless oil (137 mg, 0.582 mmol, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.13 (s, 1H), 8.11 (s, 1H), 7.36 – 7.20 (m, 5H), 4.56 (t, J = 7.0 Hz, 2H), 3.11 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.3, 145.5, 137.8, 135.3, 133.3, 129.1, 128.7, 126.8, 67.8, 35.2. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{12}H_{11}ClN_2ONa$ 257.04521; found 257.04508.

2-Bromo-6-phenethoxypyrazine (**43**). General Procedure D was applied using 2,6-dibromopyrazine (127 mg, 0.534 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (65.2 mg, 0.534 mmol, 1.0 equiv.). The reaction mixture was purified by FCC on silica using a gradient of EtOAc (0% to 6%) in hexanes to give **43** as a colourless oil (122 mg, 0.436 mmol, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (s, 1H), 8.12 (s, 1H), 7.35 – 7.20 (m, 5H), 4.55 (t, J = 7.0 Hz, 2H), 3.09 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.4, 138.3, 137.8, 136.5, 133.5, 129.1, 128.7, 126.8, 68.0, 35.2. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{12}H_{11}{}^{79}BrN_2ONa$ 300.99470; found 300.99465.

2-Iodo-6-phenethoxypyrazine (**44**). General Procedure D was applied using **41** (108 mg, 0.325 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (39.8 mg, 0.325 mmol, 1.0 equiv.). The reaction mixture was purified by FCC on silica using a gradient of EtOAc (0% to 6%) in hexanes

to give **44** as a colourless oil (83.0 mg, 0.254 mmol, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.11 (s, 1H), 7.37 – 7.21 (m, 5H), 4.54 (t, J = 7.0 Hz, 2H), 3.09 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.5, 144.2, 137.8, 133.7, 129.1, 128.7, 126.8, 112.7, 68.0, 35.2. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{12}H_{11}IN_2ONa$ 348.98083; found 348.98065.

5-Chloro-[1,2,4]triazolo[4,3-a]pyrazine (**45a**). General Procedure B was applied using **S1** (25.4 g, 176 mmol) to give **45a** as a yellow solid (12.3 g, 79.8 mmol, 45%). mp 169–171 °C (lit.[8] 167–172 °C). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.27 (s, 1H), 9.04 (s, 1H), 7.93 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.8, 141.9, 134.7, 128.3, 121.3. The spectroscopic data and melting point were in agreement with those in the literature.[8] X-ray single crystal data can be found in the supporting information.

5-Chloro-3-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**45b**). General Procedure C was applied using **S1** (1.01 g, 6.97 mmol, 1.0 equiv.) and 4-methoxybenzaldehyde (1.04 g, 7.66 mmol, 1.1 equiv.) to give **45b** as an off-white solid (1.34 g, 5.16 mmol, 74%). mp 145–147 °C (decomp.). ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.31 (s, 1H), 7.84 (s, 1H), 7.63 – 7.47 (m, 2H), 7.11 – 6.95 (m, 2H), 3.91 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 160.8, 147.4, 146.9, 142.7, 132.8, 129.1, 121.8, 119.1, 113.1, 55.3. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{12}H_{10}ClN_4O$ 261.05377; found 261.05348.

5-Chloro-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**45c**). General Procedure C was applied using **S1** (1.06 g, 7.33 mmol, 1.0 equiv.) and 4-nitrobenzaldehyde (1.21 g, 8.07 mmol, 1.1 equiv.) to give **45c** as an off-white solid (1.91 g, 6.93 mmol, 95%). mp 238–240 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.53 (s, 1H), 8.41 (d, J = 8.8 Hz, 2H), 8.15 (s, 1H), 8.05 (d, J = 8.7 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 148.6, 147.2, 145.8, 142.7, 133.7, 132.9, 129.4, 122.7, 121.9. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{11}H_7ClN_5O_2$ 276.02828; found 276.02784.

5-Chloro-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**45d**). General Procedure C was applied using **S1** (400 mg, 2.77 mmol, 1.0 equiv.) and 2-methoxybenzaldehyde (414 mg, 3.04 mmol, 1.1 equiv.) to give **45d** as an off-white solid (430 mg, 1.65 mmol, 60%); **m.p.** 142–145 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.47 (s, 1H), 8.08 (s, 1H), 7.63 (ddd, J = 8.3, 7.5, 1.7 Hz, 1H), 7.54 (dd, J = 7.5, 1.7 Hz, 1H), 7.20 (dd, J = 8.5, 1.0 Hz, 1H), 7.13 (td, J = 7.5, 1.0 Hz, 1H), 3.73 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ 158.4, 146.9, 144.7, 142.8, 132.7, 132.0, 129.0, 121.8, 120.1, 116.3, 111.0, 55.4; HRMS (ESI/FTICR+) m/z: $[M + H]^+$ calcd for $C_{12}H_{10}ClN_4O$ 261.05377; found 261.05389.

5-Chloro-3-(2-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**45e**). General Procedure C was applied using **S1** (1.04 g, 7.20 mmol, 1.0 equiv.) and 2-nitrobenzaldehyde (1.20 g, 7.92 mmol, 1.1 equiv.) to give **45e** as a grey solid (1.74 g, 6.29 mmol, 87%). mp 224–228 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.57 (s, 1H), 8.44 (dd, J = 7.9, 1.6 Hz, 1H), 8.17 (s, 1H), 8.06 – 7.95 (m, 2H), 7.93 (dd, J = 7.1, 2.0 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 148.0, 146.8, 143.8, 143.0, 134.5, 134.3, 132.9, 129.2, 125.0, 122.4, 121.4. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{11}H_6ClN_5O_2Na$ 298.01022; found 298.01092.

5-Chloro-3-(3,5-di-tert-butylphenyl)-[1,2,4]-triazolo[4,3-a]pyrazine (**45f**). General Procedure C was applied using **S1** (1.05 g, 7.26 mmol, 1.0 equiv.) and 3,5-di-*tert*-butylbenzaldehyde (1.74 g, 7.99 mmol, 1.1 equiv.) to give **45f** as a grey solid (1.68 g, 4.90 mmol, 67%). mp 133–135 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.46 (s, 1H), 8.06 (s, 1H), 7.61 (t, J = 1.8 Hz, 1H), 7.56 (d, J = 1.8 Hz, 2H), 1.34 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 149.6, 148.1, 147.0, 142.7, 129.2, 126.3, 125.8, 123.6, 121.8, 34.6, 31.1. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{19}H_{24}ClN_4$ 343.16840; found 343.16865.

3-(Anthracen-9-yl)-5-chloro-[1,2,4]triazolo[4,3-a]pyrazine (**45g**). General Procedure C was applied using **S1** (1.08 g, 7.47 mmol, 1.0 equiv.) and anthracene-9-carbaldehyde (1.69 g, 8.22 mmol, 1.1 equiv.) to give **45g** as a bright

yellow solid (1.62 g, 4.90 mmol, 66%). mp 218–221 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.64 (s, 1H), 8.96 (s, 1H), 8.24 (d, J = 8.4 Hz, 2H), 8.02 (s, 1H), 7.58 (ddd, J = 8.2, 6.6, 1.1 Hz, 2H), 7.49 (ddd, J = 8.8, 6.5, 1.2 Hz, 2H), 7.34 (dd, J = 8.7, 1.1 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 147.8, 144.0, 143.4, 132.4, 130.6, 130.3, 129.2, 128.6, 127.5, 125.8, 125.5, 121.1, 120.5. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{19}H_{12}ClN_4$ 331.07450; found 331.07449.

5-Bromo-[1,2,4]triazolo[4,3-a]pyrazine (**45h**). General Procedure B was applied using **S2** (2.35 g, 12.4 mmol) to give **45h** as an orange solid (1.75 g, 8.81 mmol, 71%). mp 167–170 °C (decomp.) (lit.[8] 214–217 °C). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.62 (s, 1H), 9.43 (s, 1H), 8.20 (s, 1H). ^{13}C{^{1}H} NMR (75 MHz, DMSO-d_6): δ 145.3, 142.0, 137.5, 131.0, 109.9. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_5H_3{}^{79}BrN_4Na$ 220.94333; found 220.94309. The spectroscopic data were in agreement with the literature, but the melting point was significantly different.[8]

5-Bromo-3-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**45i**). General Procedure C was applied using **S2** (1.03 g, 5.46 mmol, 1.0 equiv.) and 4-methoxybenzaldehyde (0.818 g, 6.01 mmol, 1.1 equiv.) to give **45i** as a pale brown solid (1.00 g, 3.27 mmol, 60%). mp 156–157 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.44 (s, 1H), 8.10 (s, 1H), 7.66 – 7.57 (m, 2H), 7.13 – 7.06 (m, 2H), 3.86 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 160.8, 148.1, 146.6, 143.0, 133.1, 132.7, 119.1, 113.1, 110.2, 55.3. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{12}H_{10}{}^{79}BrN_4O$ 305.00325; found 305.00303.

5-Bromo-3-(4-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**45j**). General Procedure C was applied using **S2** (0.65 g, 3.4 mmol, 1.0 equiv.) and 4-nitrobenzaldehyde (0.57 g, 3.8 mmol, 1.1 equiv.) to give **45j** as a yellow solid (0.93 g, 2.9 mmol, 85%). mp 200–205 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.54 (s, 1H), 8.41 (d, J = 8.0 Hz, 2H), 8.20 (s, 1H), 8.04 (d, J = 8.2 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 148.7, 146.9, 146.4, 143.0, 133.9, 133.2, 133.0, 122.6, 110.4. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{11}H_7{}^{79}BrN_5O_2$ 319.97776; found 319.97811.

5-Bromo-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**45k**). General Procedure C was applied using **S2** (0.66 g, 3.5 mmol, 1.0 equiv.) and 2-methoxybenzaldehyde (0.52 g, 3.8 mmol, 1.1 equiv.) to give **45k** as a white solid (0.75 g, 2.5 mmol, 71%). mp 137–139 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.34 (s, 1H), 7.95 (s, 1H), 7.58 (ddd, J = 8.4, 7.5, 1.7 Hz, 1H), 7.54 (dd, J = 7.5, 1.7 Hz, 1H), 7.11 (td, J = 7.5, 1.0 Hz, 1H), 6.97 (dd, J = 8.4, 1.0 Hz, 1H), 3.73 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 159.2, 147.1, 146.6, 143.4, 133.1, 133.0, 132.5, 120.5, 116.3, 110.5, 110.1, 55.4. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{12}H_{10}{}^{79}BrN_4O$ 305.00325; found 305.00359.

5-Bromo-3-(2-nitrophenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**45l**). General Procedure C was applied using **S2** (0.62 g, 3.3 mmol, 1.0 equiv.) and 2-nitrobenzaldehyde (0.54 g, 3.6 mmol, 1.1 equiv.) to give **45l** as a yellow solid (0.84 g, 2.6 mmol, 81%). mp 210–213 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 9.41 (s, 1H), 8.50 – 8.36 (m, 1H), 8.00 (s, 1H), 7.94 – 7.80 (m, 2H), 7.72 (d, J = 6.6 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 148.1, 146.4, 144.6, 143.2, 134.6, 134.2, 132.9, 132.7, 124.9, 122.6, 109.9. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{11}H_7{}^{79}BrN_5O_2$ 319.97776; found 319.97803.

5-Iodo-[1,2,4]triazolo[4,3-a]pyrazine (**45m**). General Procedure B was applied using **S3** (1.54 g, 6.52 mmol, 1.0 equiv.) to give **45m** as a brown solid (1.08 g, 4.39 mmol, 67%, contains 0.5% DCM). mp 180–185 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.54 (s, 1H), 9.36 (s, 1H), 8.24 (s, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 144.4, 142.2, 140.2, 137.7, 83.9. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_5H_4IN_4$ 246.94752; found 246.94745.

5-Iodo-3-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrazine (**45n**). General Procedure C was applied using **S3** (1.47 g, 6.21 mmol) and 4-methoxybenzaldehyde (0.930 g, 6.83 mmol, 1.1 equiv.) to give **45n** as an off-white solid (1.55 g, 4.39 mmol, 71%). mp 229–230 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.40 (s, 1H), 8.22 (s, 1H), 7.60 – 7.54 (m, 2H), 7.15 – 7.09 (m, 2H), 3.86 (s, 3H). ^{13}C{^{1}H} NMR

(126 MHz, DMSO-d_6): δ 161.6, 149.5, 146.2, 143.9, 140.6, 134.4, 119.4, 113.6, 84.1, 55.8. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{10}IN_4O$ 352.98938; found 352.98910.

5-Phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine (**46a**). General Procedure D was applied using **45a** (107 mg, 0.692 mmol) and 2-phenylethanol (84.5 mg, 0.692 mmol, 1.0 equiv.). The reaction mixture was purified by FCC on silica using a gradient of EtOAc (20 to 100%) in hexanes to give **46a** as an off-white solid (125 mg, 0.520 mmol, 75%). mp 143–146 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.38 (d, J = 0.7 Hz, 1H), 9.02 (t, J = 0.7 Hz, 1H), 7.63 (s, 1H), 7.43 – 7.37 (m, 2H), 7.35 – 7.28 (m, 2H), 7.26 – 7.19 (m, 1H), 4.63 (t, J = 6.7 Hz, 2H), 3.19 (t, J = 6.7 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 145.8, 142.4, 137.3, 134.4, 133.0, 129.2, 128.4, 126.5, 108.3, 71.3, 34.4. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{13}N_4O$ 241.10839; found 241.10813.

5-(Phenethylthio)-[1,2,4]triazolo[4,3-a]pyrazine (**46b**). General Procedure D was applied using **45a** (105 mg, 0.681 mmol, 1.0 equiv.) and 2-phenylethane-1-thiol (94.2 mg, 0.681 mmol, 1.0 equiv.) to give **46b** as an off-white solid (88.6 mg, 0.346 mmol, 51%). mp 108–110 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.55 (d, J = 0.8 Hz, 1H), 9.33 (s, 1H), 8.03 (s, 1H), 7.27 – 7.20 (m, 4H), 7.20 – 7.12 (m, 1H), 3.48 (dd, J = 7.9, 7.0 Hz, 2H), 2.95 (t, J = 7.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 144.6, 141.5, 139.0, 136.1, 131.5, 128.6, 128.2, 126.4, 126.1, 34.8, 33.5. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{13}N_4S$ 257.08554; found 257.08534.

3-(4-Methoxyphenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine (**46c**). Preparation 1: General Procedure D was applied using **45b** (103 mg, 0.395 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (48.3 mg, 0.395 mmol, 1.0 equiv.) to give **46c** as a yellow solid (95.1 mg, 0.275 mmol, 69%). Preparation 2: General Procedure D was applied using **45i** (122 mg, 0.400 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (48.9 mg, 0.400 mmol, 1.0 equiv.). Fractions corresponding to the second peak were evaporated to give **46c** (first run: 45.4 mg, 0.127 mmol, 33%, second run: 43.0 mg, 0.124 mmol, 31%, average yield is 32%). mp 162–163 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.00 (s, 1H), 7.67 – 7.60 (m, 2H), 7.55 (s, 1H), 7.22 – 7.12 (m, 3H), 7.07 – 7.01 (m, 2H), 6.96 – 6.88 (m, 2H), 4.48 (t, J = 6.4 Hz, 2H), 3.83 (s, 3H), 2.89 (t, J = 6.4 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 160.4, 147.3, 146.3, 143.9, 137.4, 135.0, 132.2, 128.7, 128.2, 126.3, 120.0, 113.0, 108.6, 71.2, 55.3, 33.9. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{19}N_4O_2$ 347.15025; found 347.14983.

3-(4-Methoxyphenyl)-5-(phenethylthio)[1,2,4]-triazolo[4,3-a]pyrazine (**46d**). General Procedure D was applied using **45b** (100 mg, 0.384 mmol, 1.0 equiv.) and 2-phenylethane-1-thiol (53.0 mg, 0.384 mmol, 1.0 equiv.). The reaction mixture was purified by FCC on silica using a gradient of MeOH (0% to 10%) in DCM, fractions corresponding to the second peak were evaporated to give **46d** as a yellow solid (11.3 mg, 0.0312 mmol, 8%). mp 202–205 °C. ^{1}H NMR (500 MHz, CD_3CN): δ 9.12 (s, 1H), 7.78 (s, 1H), 7.59 – 7.51 (m, 2H), 7.27 – 7.19 (m, 2H), 7.21 – 7.14 (m, 1H), 7.09 – 6.99 (m, 4H), 3.89 (s, 3H), 2.94 (t, J = 7.3 Hz, 2H), 2.72 (t, J = 7.3 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, CD_3CN): δ 162.5, 149.2, 147.5, 142.8, 140.2, 134.1, 132.3, 129.59, 129.56, 129.4, 127.5, 120.7, 113.9, 56.2, 36.3, 35.1. HRMS (ESI/FTICR) *m/z*: $[M + H]^+$ calcd for $C_{20}H_{19}N_4OS$ 363.12741; found 363.12700.

3-(4-Nitrophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine (**46e**). Preparation 1: General Procedure D was applied using **45c** (104 mg, 0.377 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (46.1 mg, 0.377 mmol, 1.0 equiv.). Fraction corresponding to the second peak were evaporated to give **46e** as a yellow solid (105 mg, 0.290 mmol, 77%). Preparation 2: General Procedure D was applied using **45j** (128 mg, 0.400 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (48.8 mg, 0.400 mmol, 1.0 equiv.) to give **46e** (first run: 85.6 mg, 0.237 mmol, 59%, second run: 87.8 mg, 0.243 mmol, 61%, average yield is 60%). m.p.168–170 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.11 (s, 1H), 8.29 – 8.22 (m, 2H), 7.99 – 7.93 (m, 2H), 7.70 (s, 1H), 7.15 (dd, J = 5.0, 1.9 Hz, 3H), 6.95 (dd, J = 6.6, 2.9 Hz, 2H), 4.58 (t,

J = 6.4 Hz, 2H), 2.93 (t, J = 6.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 147.9, 147.6, 144.6, 143.8, 137.1, 134.9, 134.1, 131.9, 128.4, 128.1, 126.3, 122.6, 109.3, 70.9, 33.5. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{19}H_{16}N_5O_3$ 362.12477; found 362.12448.

3-(2-Methoxyphenyl)-5-phenethoxy-[1,2,4]-triazolo[4,3-a]pyrazine (**46f**). General Procedure D was applied using **45k** (122 mg, 0.400 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (48.8 mg, 0.400 mmol, 1.0 equiv.). Fractions corresponding to the second peak were combined and evaporated to give **46f** as a yellow solid (first run: 36.1 mg, 0.104 mmol, 26%, second run: 34.2 mg, 0.100 mmol, 25%, average yield is 26%). mp 147–150 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 9.02 (s, 1H), 7.62 (ddd, J = 8.3, 7.5, 1.8 Hz, 1H), 7.53 (s, 1H), 7.50 (dd, J = 7.5, 1.8 Hz, 1H), 7.22 (dd, J = 8.4, 1.0 Hz, 1H), 7.20 – 7.10 (m, 4H), 6.79 – 6.73 (m, 2H), 4.37 (s, 2H), 3.72 (s, 3H), 2.65 (s, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 158.2, 147.1, 143.9, 143.2, 137.2, 135.1, 132.0, 131.4, 128.8, 128.2, 126.3, 119.9, 117.4, 110.9, 108.8, 71.4, 55.4, 34.1. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{20}H_{19}N_4O_2$ 347.15025; found 347.15041.

3-(2-Nitrophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine (**46g**). Preparation 1: General Procedure D was applied using **45e** (110 mg, 0.399 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (48.8 mg, 0.399 mmol, 1.0 equiv.). The reaction mixture was purified by FCC on silica using a gradient of EtOAc (30% to 100%) in hexanes, then MeOH (0% to 5%) in EtOAc to give **46g** as a yellow solid (first run: 123 mg, 0.341 mmol, 86%, second run: 113 mg, 0.313 mmol, 79%, average yield is 83%). Preparation 2: General Procedure D was applied using **45l** (128 mg, 0.400 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (48.8 mg, 0.400 mmol, 1.0 equiv.) to give **46g** (first run: 108 mg, 0.299 mmol, 75%, second run: 111 mg, 0.307 mmol, 77%, average yield is 76%). mp 178–181 °C (decomp.). ^1H NMR (500 MHz, DMSO-d_6): δ 9.13 (s, 1H), 8.37 (dd, J = 8.1, 1.4 Hz, 1H), 7.96 (td, J = 7.5, 1.4 Hz, 1H), 7.90 (td, J = 7.8, 1.6 Hz, 1H), 7.85 (dd, J = 7.5, 1.6 Hz, 1H), 7.63 (s, 1H), 7.18 – 7.11 (m, 3H), 6.83 – 6.76 (m, 2H), 4.38 (t, J = 6.5 Hz, 2H), 2.68 (t, J = 6.4 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 147.7, 147.0, 143.1, 142.5, 136.7, 135.3, 134.0, 133.8, 131.9, 128.4, 128.2, 126.4, 124.7, 123.1, 109.1, 71.2, 33.6. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{19}H_{16}N_5O_3$ 362.12477; found 362.12469.

3-(3,5-Di-tert-butylphenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine (**46h**). General Procedure D was applied using **45f** (137 mg, 0.400 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (48.8 mg, 0.400 mmol, 1.0 equiv.). Fractions corresponding to the second peak were combined and evaporated to give **46h** as a yellow solid (first run: 139 mg, 0.325 mmol, 81%, second run: 140 mg, 0.326 mmol, 82%, average yield is 82%). mp 175–177 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 9.01 (s, 1H), 7.65 (t, J = 1.9 Hz, 1H), 7.57 (d, J = 1.8 Hz, 2H), 7.54 (s, 1H), 7.16 – 7.01 (m, 3H), 6.75 – 6.68 (m, 2H), 4.43 (t, J = 6.3 Hz, 2H), 2.76 (t, J = 6.2 Hz, 2H), 1.37 (s, 18H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 149.6, 147.2, 147.0, 143.9, 137.4, 135.0, 128.6, 128.1, 127.4, 126.3, 124.7, 123.7, 108.8, 71.4, 34.7, 34.1, 31.3. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{27}H_{32}N_4ONa$ 451.24683; found 451.24708.

3-(Anthracen-9-yl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine (**46i**). General Procedure D was applied using **45g** (132 mg, 0.399 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (48.8 mg, 0.399 mmol, 1.0 equiv.). Fractions corresponding to the second peak were combined and evaporated to give **46i** as a yellow solid (first run: 110 mg, 0.264 mmol, 66%, second run: 107 mg, 0.258 mmol, 65%, average yield is 66%). mp 207–211 °C. ^1H NMR (500 MHz, DMSO-d_6): δ 9.22 (s, 1H), 8.95 (s, 1H), 8.27 (d, J = 8.5 Hz, 2H), 7.62 (ddd, J = 8.3, 6.6, 1.1 Hz, 2H), 7.56 – 7.47 (m, 3H), 7.39 (dd, J = 8.7, 1.1 Hz, 2H), 6.96 – 6.89 (m, 1H), 6.78 – 6.70 (m, 2H), 6.08 – 6.03 (m, 2H), 3.94 (t, J = 6.2 Hz, 2H), 1.57 (t, J = 6.2 Hz, 2H). $^{13}C\{^1H\}$ NMR (126 MHz, DMSO-d_6): δ 147.7, 143.6, 142.4, 136.7, 135.7, 131.8, 130.5, 129.8, 128.5, 128.2, 127.7, 127.1, 126.0, 125.6, 125.5, 121.8, 109.2, 71.4, 33.3. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{27}H_{21}N_4O$ 417.17099; found 417.17134.

3-(4-Methoxyphenyl)-8-phenethoxy-[1,2,4]-triazolo[4,3-a]pyrazine (**47a**). Preparation 1: General Procedure D was applied using **45n** (132 mg, 0.375 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (45.8 mg, 0.375 mmol, 1.0 equiv.). Fraction corresponding to the first peak were evaporated to give **47a** as an off-white solid (70.0 mg, 0.202 mmol, 54%). Preparation 2: isolated from the same reaction as for **46c** preparation 2. Fractions corresponding to the first peak were evaporated to give **47a** (first run: 13.0 mg, 0.0375 mmol, 9%, second run: 15.5 mg, 0.0447 mmol, 11%, average yield is 10%). mp 208–211 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.17 – 8.12 (m, 1H), 7.88 – 7.81 (m, 2H), 7.47 – 7.42 (m, 1H), 7.40 – 7.29 (m, 4H), 7.27 – 7.23 (m, 1H), 7.22 – 7.15 (m, 2H), 4.76 (t, J = 6.8 Hz, 2H), 3.87 (s, 2H), 3.18 (t, J = 6.9 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 160.8, 153.2, 147.9, 139.5, 138.0, 129.7, 128.9, 128.4, 127.2, 126.4, 118.1, 114.8, 112.1, 67.3, 55.4, 34.2. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{20}H_{19}N_4O_2$ 347.15025; found 347.14994.

3-(4-Methoxyphenyl)-8-(phenethylthio)[1,2,4]-triazolo[4,3-a]pyrazine (**47b**). Preparation 1: General Procedure D was applied using **45i** (110 mg, 0.360 mmol) and 2-phenylethane-1-thiol (50.0 mg, 0.360 mmol, 1.0 equiv.) to give **47b** as a yellow solid (122 mg, 0.337 mmol, 93%). Preparation 2: General Procedure D was applied using **45n** (108 mg, 0.307 mmol, 1.0 equiv.) and 2-phenylethane-1-thiol (43.0 mg, 0.307 mmol, 1.0 equiv.) to give **47b** (14.0 mg, 0.0390 mmol, 13%). Preparation 3: isolated from the same reaction as for **46d**. Fractions corresponding to the first peak were evaporated to give **47b** (116 mg, 0.319 mmol, 83%). mp 192–194 °C. ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85 (d, J = 4.8 Hz, 1H), 7.77 (d, J = 8.7 Hz, 2H), 7.69 (d, J = 4.8 Hz, 1H), 7.32 (d, J = 4.3 Hz, 4H), 7.11 (d, J = 8.8 Hz, 2H), 3.91 (s, 3H), 3.69 – 3.52 (m, 2H), 3.20 – 3.02 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 160.9, 152.9, 147.6, 143.7, 140.0, 129.8, 129.3, 128.6, 128.4, 126.4, 117.9, 114.8, 113.2, 55.5, 34.5, 29.4. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{20}H_{19}N_4OS$ 363.12741; found 363.12676.

3-(4-Methoxyphenyl)-N-phenethyl-[1,2,4]-triazolo[4,3-a]pyrazin-8-amine (**47c**). Preparation 1: General Procedure E was applied using **45b** (106 mg, 0.407 mmol, 1.0 equiv.) and 2-phenylethan-1-amine (148 mg, 1.22 mmol, 3.0 equiv.) to give **47c** as a yellow solid (126 mg, 0.365 mmol, 90%). Preparation 2: General Procedure E was applied using **45i** (101 mg, 0.331 mmol, 1.0 equiv.) and 2-phenylethan-1-amine (120 mg, 0.993 mmol, 3.0 equiv.) to give **47c** (75.0 mg, 0.217 mmol, 66%). Preparation 3: General Procedure E was applied using **45n** (341 mg, 0.968 mmol) and 2-phenylethan-1-amine (350 mg, 2.91 mmol, 3.0 equiv.) to give **47c** (195 mg, 0.564 mmol, 58%). mp 193–196 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.23 (t, J = 5.8 Hz, 1H), 7.86 – 7.80 (m, 2H), 7.69 (d, J = 4.8 Hz, 1H), 7.34 (d, J = 4.9 Hz, 1H), 7.32 – 7.25 (m, 4H), 7.21 (dd, J = 6.8, 2.1 Hz, 1H), 7.19 – 7.15 (m, 2H), 3.86 (s, 3H), 3.74 (q, J = 6.9 Hz, 2H), 2.98 (t, J = 7.5 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 160.6, 147.9, 147.6, 139.5, 139.4, 129.9, 129.5, 128.7, 128.3, 126.0, 118.5, 114.7, 105.9, 55.4, 41.6, 34.5. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{20}H_{20}N_5O$ 346.16624; found 346.16572.

3-(3,5-Di-tert-butylphenyl)-8-phenethoxy-[1,2,4]tria-zolo[4,3-a]pyrazine (**47d**). Isolated from the same reaction as for **46h**. Fractions corresponding to the first peak were combined and evaporated to give **47d** as a yellow sticky solid (first run: 5.0 mg, 11.6 μmol, 3%, second run: 5.00 mg, 11.6 μmol, 3%, average yield is 3%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.76 (d, J = 4.8 Hz, 1H), 7.65 – 7.60 (m, 3H), 7.39 – 7.27 (m, 5H), 7.24 (t, J = 7.2 Hz, 1H), 4.81 (t, J = 7.5 Hz, 2H), 3.28 (t, J = 7.5 Hz, 2H), 1.39 (s, 18H). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 154.4, 152.3, 149.8, 140.5, 137.7, 129.3, 128.7, 128.0, 126.8, 125.4, 125.1, 122.8, 110.8, 68.3, 35.3, 35.2, 31.5. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{27}H_{32}N_4ONa$ 451.24683; found 451.24714.

3-(Anthracen-9-yl)-8-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine (**47e**). Isolated from the same reaction as for **46i**. Fractions corresponding to the first peak were combined and

evaporated to give **47e** as a yellow solid (first run: 2.50 mg, 6.00 μmol, 2%, second run: 3.00 mg, 7.20 μmol, 2%, average yield is 2%). mp 175–180 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.00 (s, 1H), 8.28 (d, J = 8.5 Hz, 2H), 7.74 – 7.68 (m, 1H), 7.61 (ddd, J = 8.3, 6.6, 1.1 Hz, 2H), 7.51 (ddd, J = 8.9, 6.6, 1.3 Hz, 2H), 7.47 – 7.42 (m, 2H), 7.41 – 7.34 (m, 4H), 7.32 (d, J = 4.8 Hz, 1H), 7.30 – 7.23 (m, 2H), 4.83 (t, J = 6.8 Hz, 2H), 3.25 (t, J = 6.8 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 153.4, 145.4, 141.8, 141.4, 140.0, 138.1, 131.0, 130.83, 130.79, 129.3, 129.0, 128.9, 128.4, 127.8, 127.5, 126.5, 125.9, 125.6, 124.6, 118.1, 111.8, 67.5, 34.4. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{27}H_{21}N_4O$ 417.17099; found 417.17089.

3-(2-Methoxyphenyl)-8-phenethoxy-[1,2,4]-triazolo[4,3-a]pyrazine (**47f**). Isolated from the same reaction as for **46f**. Fractions corresponding to the first peak were combined and evaporated to give **47f** as a white solid (first run: 13.1 mg, 37.8 μmol, 9%, second run: 12.2 mg, 35.2 μmol, 9%, average yield is 9%). mp 124–128 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.71 (d, J = 4.8 Hz, 1H), 7.65 (ddd, J = 8.5, 7.4, 1.8 Hz, 1H), 7.59 (dd, J = 7.5, 1.8 Hz, 1H), 7.42 (d, J = 4.9 Hz, 1H), 7.40 – 7.37 (m, 2H), 7.36 – 7.28 (m, 3H), 7.27 – 7.20 (m, 1H), 7.18 (td, J = 7.4, 0.9 Hz, 1H), 4.76 (t, J = 6.9 Hz, 2H), 3.82 (s, 3H), 3.19 (t, J = 6.9 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 156.9, 152.9, 146.7, 139.4, 138.0, 132.7, 131.9, 128.9, 128.4, 126.5, 126.4, 120.9, 114.2, 113.3, 112.1, 67.3, 55.6, 34.2. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{20}H_{18}N_4O_2Na$ 369.13220; found 369.13255.

3-(4-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]-pyrazin-8-ol (**48a**). General Procedure D was applied (with following modification: H_2O was used as a solvent) using **45i** (107 mg, 0.341 mmol) and 2-phenylethan-1-ol (41.7 mg, 0.341 mmol, 1.0 equiv.). The reaction mixture was purified by FCC on silica using a gradient of MeOH (0% to 20%) in EtOAc to give **48a** as a pale brown solid (80.0 mg, 0.330 mmol, 94%). mp 312–316 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.42 (s, 1H), 7.81 – 7.74 (m, 2H), 7.39 (d, J = 5.7 Hz, 1H), 7.21 – 7.14 (m, 2H), 6.89 (d, J = 5.8 Hz, 1H), 3.86 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 160.9, 153.0, 149.2, 145.0, 129.9, 118.4, 117.9, 114.8, 103.8, 55.4. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{12}H_{10}N_4O_2Na$ 265.06960; found 265.06955.

3-(4-Nitrophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-8-ol (**48b**). General Procedure D was applied using **45j** (128 mg, 0.400 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (48.8 mg, 0.400 mmol, 1.0 equiv.). The reaction mixture was purified by FCC on silica using a gradient of EtOAc (30% to 100%) in hexanes, then MeOH (0% to 20%) in EtOAc, fractions corresponding to the third peak were combined and evaporated to give **48b** as a yellow solid (first run: 28.8 mg, 0.112 mmol, 28%, second run: 31.9 mg, 0.124 mmol, 31%, average yield is 30%). mp 207–210 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.48 – 8.36 (m, 2H), 8.20 – 8.14 (m, 2H), 7.41 (d, J = 4.7 Hz, 1H), 7.10 (d, J = 4.7 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 159.9, 147.4, 146.3, 144.6, 133.7, 132.7, 128.3, 124.3, 99.8. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{11}H_7N_5O_3Na$ 280.04411; found 280.04439.

3-(2-Methoxyphenyl)-[1,2,4]triazolo[4,3-a]-pyrazin-8-ol (**48c**). Isolated from the same reaction as for **46f**. Fractions corresponding to the third peak were combined and evaporated to give **48c** as a yellow solid (first run: 47.6 mg, 0.197 mmol, 49%, second run: 46.3 mg, 0.191 mmol, 48%, average yield is 49%). mp 116–119 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.45 (s, 1H), 7.65 (ddd, J = 8.9, 7.4, 1.8 Hz, 1H), 7.56 (dd, J = 7.5, 1.7 Hz, 1H), 7.29 (dd, J = 8.5, 0.9 Hz, 1H), 7.17 (td, J = 7.5, 1.0 Hz, 1H), 7.00 (d, J = 5.7 Hz, 1H), 6.86 (d, J = 5.8 Hz, 1H), 3.83 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 156.9, 152.9, 147.9, 144.9, 132.8, 131.9, 120.9, 117.7, 114.2, 112.1, 104.8, 55.7. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{12}H_{10}N_4O_2Na$ 265.06960; found 265.06995.

3-(2-Nitrophenyl)-[1,2,4]triazolo[4,3-a]pyrazin-8-ol (**48d**). Isolated from the same reaction as for **46g** preparation 2. Fractions corresponding to the third peak were combined and evaporated to give **48d** as an orange solid (first run: 11.4 mg, 44.3 μmol, 11%, second run: 13.8

mg, 53.7 μmol, 13%, average yield is 12%). mp 124–127 °C (decomp.). ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.65 (s, 1H), 8.37 (dd, J = 8.1, 1.3 Hz, 1H), 8.02 (td, J = 7.5, 1.4 Hz, 1H), 7.97 (td, J = 7.8, 1.6 Hz, 1H), 7.87 (dd, J = 7.5, 1.6 Hz, 1H), 7.20 (d, J = 5.6 Hz, 1H), 6.93 (d, J = 5.7 Hz, 1H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 152.7, 148.1, 146.2, 144.9, 134.6, 133.1, 132.7, 125.4, 119.9, 118.9, 103.7. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{11}H_7N_5O_3Na$ 280.04411; found 280.04426.

3-(4-Methoxyphenyl)-[1,2,4]-triazolo[4,3-a]pyrazine (**49**). Preparation 1: General Procedure E was applied using **45n** (341 mg, 0.968 mmol, 1.0 equiv.) and 2-phenylethan-1-amine (352 mg, 2.91 mmol, 3.0 equiv.). Fractions corresponding to the second peak were re-purified by RP-FCC on C18 using a gradient of MeOH (5% to 80%) in H_2O. Fractions corresponding to the first peak were combined and evaporated to give **49** as a white solid (24.0 mg, 0.106 mmol, 11%). Preparation 2: General Procedure D was applied using **45n** (108 mg, 0.307 mmol, 1.0 equiv.) and 2-phenylethane-1-thiol (43.0 mg, 0.307 mmol, 1.0 equiv.). The reaction mixture was purified by FCC on silica using a gradient of MeOH (0% to 10%) in DCM, fractions corresponding to the second peak were evaporated to give **49** as a yellow solid (51.0 mg, 0.225 mmol, 74%). mp 202–205 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.45 (d, J = 1.6 Hz, 1H), 8.57 (dd, J = 4.9, 1.6 Hz, 1H), 7.94 (d, J = 4.9 Hz, 1H), 7.93 – 7.87 (m, 2H), 7.23 – 7.16 (m, 2H), 3.87 (s, 3H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 160.9, 146.5, 145.5, 144.1, 129.8, 129.7, 117.8, 116.9, 114.8, 55.4. HRMS (ESI/FTICR) m/z: $[M + Na]^+$ calcd for $C_{12}H_{10}N_4ONa$ 249.07468; found 249.07465.

3-(4-Methoxyphenyl)-5-(1-phenethyl-1H-imidazol-2-yl)-4H-1,2,4-triazole (**50**). Isolated from the same reaction as for **49** preparation 1. Fractions corresponding to the second peak, after RP-FCC were combined and evaporated to give **50** as a white solid (57.0 mg, 0.165 mmol, 17%). mp 143–146 °C. ^{1}H NMR (500 MHz, CD_3OD): δ 8.00 (d, J = 8.8 Hz, 2H), 7.29 – 7.17 (m, 2H), 7.19 – 7.12 (m, 4H), 7.07 (d, J = 8.8 Hz, 2H), 7.05 (s, 1H), 4.78 (t, J = 7.4 Hz, 2H), 3.87 (s, 3H), 3.12 (t, J = 7.3 Hz, 2H). ^{13}C{^{1}H} NMR (126 MHz, CD_3OD): δ 162.9, 139.3, 129.9, 129.5, 129.1, 127.7, 124.0, 115.4, 55.9, 50.0, 38.6. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{20}H_{20}N_5O$ 346.16624; found 346.16560. X-ray single crystal data can be found in the supporting information.

5-(Piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyrazine (**55**). General Procedure E was applied using **45a** (101 mg, 0.652 mmol, 1.0 equiv.) in toluene (10 mL) and piperidine (167 mg, 1.96 mmol, 3.0 equiv.) and heated at reflux for 72 h. The reaction mixture was purified by FCC on silica using a gradient of EtOAc (50% to 100%) in hexanes, then MeOH (0% to 5%) in EtOAc. Fractions corresponding to the second peak were evaporated to give **55** as an orange crystalline solid (20.7 mg, 0.102 mmol, 16%). mp 158–161 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.39 (d, J = 0.8 Hz, 1H), 9.05 (d, J = 0.7 Hz, 1H), 7.48 (s, 1H), 3.23 – 3.05 (m, 4H), 1.76 (p, J = 5.8 Hz, 4H), 1.67 – 1.58 (m, 2H). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 145.6, 138.4, 135.7, 134.5, 116.4, 50.2, 25.0, 23.6. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{10}H_{14}N_5$ 204.12437; found 204.12426.

8-(Piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyrazine (**56**). Isolated from the same reaction as for **55**. Fractions corresponding to the first peak were evaporated to give **56** as an orange crystalline solid (93.4 mg, 0.460 mmol, 71%). mp 181–183 °C. ^{1}H NMR (500 MHz, CD_3CN): δ 8.82 (s, 1H), 7.56 (d, J = 4.5 Hz, 1H), 7.26 (d, J = 4.6 Hz, 1H), 4.25 (t, J = 5.4 Hz, 4H), 1.78 – 1.70 (m, 2H), 1.66 (dd, J = 7.6, 3.9 Hz, 4H). ^{13}C{^{1}H} NMR (126 MHz, CD_3CN): δ 148.8, 141.5, 138.3, 129.9, 108.3, 48.1, 26.9, 25.5. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{10}H_{14}N_5$ 204.12437; found 204.12412. X-ray single crystal data can be found in the supporting information.

5-(Piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyrazine-3-d (**57**). General Procedure E was applied using **45a** (101 mg, 0.652 mmol, 1.0 equiv.) and piperidine (167 mg, 1.96 mmol, 3.0 equiv.) in D_2O (5 mL). The reaction mixture was heated at reflux for 72 h and purified by FCC on silica using a gradient of EtOAc (50% to 100%) in hexanes then MeOH (0% to 5%) in EtOAc. Fractions corresponding to the

second peak were evaporated to give **57** as an orange crystalline solid (31.1 mg, 0.153 mmol, 23%). mp 158–161 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.05 (s, 1H), 7.48 (s, 1H), 3.19 – 3.13 (m, 4H), 1.75 (p, J = 5.7 Hz, 4H), 1.66 – 1.58 (m, 2H). ^{2}H NMR (77 MHz, DMSO-d_6): δ 9.44 (s, 1D). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6): δ 145.6, 138.3, 135.7, 134.7 – 133.9 (m), 116.3, 50.2, 25.0, 23.6. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{10}H_{13}DN_5$ 205.13065; found 205.13038.

8-(Piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyrazine-3,5-d$_2$ (**58**). Isolated from the same reaction as for **57**. Fractions corresponding to the first peak were evaporated to give **58** as an orange crystalline solid (78.7 mg, 0.387 mmol, 59%). mp 181–183 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.31 (s, 1H), 4.21 (t, J = 5.5 Hz, 4H), 1.68 (tt, J = 6.4, 2.4 Hz, 2H), 1.61 (tq, J = 8.4, 5.3, 4.2 Hz, 4H). ^{2}H NMR (77 MHz, DMSO-d_6): δ 9.28 (s, 1D), 7.88 (s, 1D). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6 δ 147.1, 139.6, 137.86 – 137.14 (m), 128.6, 107.41 (t, J = 29.3 Hz), 46.6, 25.7, 24.2. HRMS (ESI/FTICR) m/z: $[M + H]^+$ calcd for $C_{10}H_{12}D_2N_5$ 206.13693; found 206.13662.

5-Chloro-[1,2,4]triazolo[4,3-a]pyrazine-3-d (**59**). Compound **45a** (227 mg, 1.47 mmol) was stirred in D_2O (5 mL) at 80 °C for 2 days. The solvent was evaporated and the reaction mixture was purified by FCC on silica using a gradient of EtOAc (20 to 100%) in hexanes to give **59** as a white solid (197 mg, 1.27 mmol, 86%). mp 170–173 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.30 (s, 1H), 7.95 (s, 1H). ^{2}H NMR (77 MHz, $CDCl_3$): δ 9.10 (s, 1D). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 145.9, 142.0, 134.96 – 134.04 (m), 128.4, 121.3. LRMS (ESI/IT) m/z: $[M + H]^+$ 156.0.

8-(Piperidin-1-yl)-[1,2,4]triazolo[4,3-a]pyrazine-3-d (**60**). **56** (10 mg, 49 μmol) was dissolved in D_2O (5 mL) and heated at reflux for 72 h. Solvent was evaporated to give **60** as an orange solid (10 mg, 49 μmol, 100%). mp 181–183 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, J = 4.5 Hz, 1H), 7.31 (d, J = 4.5 Hz, 1H), 4.30 (s, 4H), 1.72 (d, J = 7.5 Hz, 6H). ^{2}H NMR (77 MHz, $CDCl_3$): δ 8.75 (s, 1D). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$): δ 148.1, 140.7, 137.1 – 136.1 (m), 130.0, 106.0, 47.6, 26.4, 24.9. LRMS (ESI/IT) m/z: $[M + Na]^+$ 227.1.

Acknowledgement We thank Mark Coster for suggestions on the mechanism of the tele-substitution reaction; Chris Swain, Chase Smith and other members of the OSM consortium for their valuable discussion on GitHub; Peter Turner for the help with X-ray crystallography; Irene Hallyburton for conducting *in vitro* antiplasmodial activity assay and the Structural Genomics Consortium at The University of North Carolina at Chapel Hill (SGC-UNC) for facilitating the KINOMEscan® assay. Also we thank the Australian Research Council and the Medicines for Malaria Venture for support (LP150101226).

Supporting Information Available

The Supporting Information is available free of charge on the ACS Publications website at DOI:

The following files are available free of charge.

- ORTEP diagrams for the X-ray structures and crystal data; experimental details for biological activity evaluations and copies of ^{1}H and ^{13}C{^{1}H} NMR spectra of novel compounds. (PDF)
- The archive of laboratory notebook with all experiments described in the article and raw NMR data for all novel compounds. (ZIP)
- The KINOMEscan® assay report on the biological activity of compounds **46d** and **47b**. (XLS)
- X-ray crystal data of **45a, 50, 56**. (CIF)
- The structural information in strings formant for all compounds described in the article with reference codes to the laboratory notebook. (XLS)

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