Tele-substitution Reactions in the Synthesis of a Promising Class of 1,2,4-Triazolo[4,3-a]pyrazine-Based 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 crystallographic 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-substitution²) 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,⁴ which is at the core of a series of molecules with significant potential for the future treatment of malaria.⁵

The first example of a tele-substitution reaction was reported in 1930 (Figure 1B).⁶ 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 rings⁷ (Figure 1C) to more complex triazolopyrazine ring systems⁸,⁹ (Figures 1D and 1E), the latter being of particular relevance.
to the present work. Despite these and other reports, 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 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 under-appreciated 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, represented here by compound 10 which possesses in vitro (IC$ _{50}$ = 38 nM) and in vivo antimalarial activity. Compound 11 has been reported to have nanomolar potency as an inhibitor of the kidney urea transporter UT-A1. Compound 12 was recently patented in 2016 as a renal outer medullary potassium channel (ROMK) inhibitor. Sitagliptin (13) was approved by the FDA in 2006 as an antidiabetic drug (dipeptidyl peptidase (DPP)-IV inhibitor). 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. Compound 15 is patented as an N-methyl-D-aspartate subtype 2B (NMDAR2B) receptor antagonist.
2 Results and discussion

The synthesis of members of OSM Series 4 relies on a routine S\textsubscript{N}Ar 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 as the \textit{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 \textsuperscript{1}H NMR spectra of these two isomers (Figure 4), the \textit{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 diagnostically spectroscopic difference between these isomers lies in the peaks arising from the hy-
drogen atoms at positions 5 and 8 on the triazolopyrazine ring; the correspondence between the NMR spectra and the structures was confirmed using X-ray crystallographic (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, 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$^{23}$ 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.

![Diagram of reaction mechanism](image)

**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).

**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
Table 1: Influence of triazolopyrazine structure, leaving halogen X and nucleophile on the reaction outcome.

![Chemical structure]

| Entry | X    | R               | Nucleophile | 45 yield [%] | 46 yield [%] | 47 yield [%] | 48 yield [%] |
|-------|------|-----------------|-------------|--------------|--------------|--------------|--------------|
| 1     | Cl   | H               | 45a R₁OH   | 46a, 75      | ND           | -            | -            |
| 2     | Cl   | H               | 45a R₁SH   | 46b, 51      | ND           | -            | -            |
| 3     | Cl   | (4-OMe)Ph      | 45b R₁OH   | 46c, 69      | 47a, 3       | -            | -            |
| 4     | Cl   | (4-OMe)Ph      | 45b R₁SH   | 46d, 8       | 47b, 83      | -            | -            |
| 5     | Cl   | (4-OMe)Ph      | 45b R₁NH₂b | ND           | 47c, 89      | -            | -            |
| 6     | Cl   | (4-NO₂)Ph      | 45c R₁OH   | 46e, 77      | 34, 2        | -            | -            |
| 7     | Cl   | (2-OMe)Ph      | 45d R₁OH   | 46f, 58      | ND           | -            | -            |
| 8     | Cl   | (2-NO₂)Ph      | 45e R₁OH   | 46g, 65      | ND           | -            | -            |
| 9     | Cl   | (3,5-tBu)Ph    | 45f R₁OH   | 46h, 82      | 47d, 3       | -            | -            |
| 10    | Cl   | 9-anthracenyl  | 45g R₁OH   | 46i, 66      | 47e, 2       | -            | -            |
| 11    | Br   | H               | 45h R₁OH   | 46a, 66      | ND           | -            | -            |
| 12    | Br   | H               | 45h R₁SH   | 46b, 34      | 29, 17       | -            | -            |
| 13    | Br   | H               | 45h R₁NH₂b | ND           | 30, 72       | -            | -            |
| 14    | Br   | H               | 45i R₁OH   | 46c, 32      | 47a, 10      | 48a, 20      | -            |
| 15    | Br   | (4-OMe)Ph      | 45i R₁SH   | ND           | 47b, 93      | -            | -            |
| 16    | Br   | (4-OMe)Ph      | 45i R₁NH₂b | ND           | 47c, 66      | -            | -            |
| 17    | Br   | (4-NO₂)Ph      | 45j R₁OH   | 46e, 60      | ND           | 48b, 30      | -            |
| 18    | Br   | (2-OMe)Ph      | 45k R₁OH   | 46f, 26      | 47f, 9       | 48c, 49      | -            |
| 19    | Br   | (2-NO₂)Ph      | 45l R₁OH   | 46g, 76      | ND           | 48d, 12      | -            |
| 20    | Br   | (2-NO₂)Ph      | 45l R₁SH   | ND           | 29, 7        | -            | -            |
| 21    | I    | H               | 45m R₁OH   | 46a, 34      | ND           | -            | -            |
| 22    | I    | H               | 45m R₁SH   | 46b, 7       | 29, 7        | -            | -            |
| 23    | I    | H               | 45m R₁NH₂b | ND           | 30, 40       | -            | -            |
| 24    | I    | (4-OMe)Ph      | 45n R₁OH   | 46c, 23      | 47a, 54      | -            | -            |
| 25    | I    | (4-OMe)Ph      | 45n R₁SH   | ND           | 47b, 13      | -            | -            |
| 26    | I    | (4-OMe)Ph      | 45n R₁NH₂b | ND           | 47c, 58      | -            | -            |

* KOH, 18-crown-6, toluene, room temperature.  
* Silica, toluene, reflux.  
* Dehalogenation by-product 49 was isolated as well in 74% yield.  
* Dehalogenation by-product 49 was isolated in 11% yield along with ring opening product 50 in 17% yield (refer to Figure 6 for details).  

\( R₁ = \text{CH}_2\text{CH}_2\text{Ph} \).  
ND: not determined.

seen in the literature synthesis of related structures\(^{24}\) in which the incoming nucleophile was restricted to alcohols.

The nature of the leaving halogen also influences the outcome, with *tele*-substitution favoured in the order I > Br > Cl (compare 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.

\(^{24}\) When the conditions employed with alcohols and thiols (KOH, 18-crown-6) were used with amine nucleophiles, the reaction progress was comparatively slow so the base was replaced with silica, which gave better
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-tBu)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 between 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 47d and dehalogenation product 49, a minor by-product was obtained in 17% yield, the structure of which was determined by single crystal X-ray diffraction (see SI) to be based on a 5-(1H-imidazol-2-yl)-1H-1,2,4-triazole core instead of the expected triazolopyrazine structure (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 lower 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 H₂O.

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 (H₂O and D₂O). 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, for X-ray single crystal structure of 45a and 56 see the SI). 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 changed, though it is possible that this could arise from catalytic activity at the zeolite surface itself (Entry 4).²⁵,²⁶ Performing the reaction in H₂O (Entry 5) gave a comparable result to that in wet toluene. This is counter to the example where the alcohol nucleophile 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 performed to gain insight into the reaction mechanism. This reaction was carried out in D₂O giving two compounds, 57 and 58 (Figure 8A). The examination of products with ¹H NMR and ²H NMR spectroscopy showed incorporation of one D
Table 2: A) Reaction used to study the influence of solvent; B) Product isolated when H2O 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 = CH2CH2Ph.

| 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             |

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,27,28 but not for the triazolopyrazine system investigated here. In order to prove that deuteration occurs at the 3-position as a parallel reaction to the main substitution, compounds 45a, 55 and 56 were heated under reflux in D2O without piperidine to give corresponding mono-deuterated products 59, 57 and 60 respectively (Figure 8B). The deuterium exchange at the 3-position could be explained by the relatively high acidity of the hydrogen in C-H bond on the triazole, though pKa values have not been reported, a prediction model estimates pKa of similar structures to be around 29, compared to > 35 for the C-H bond of pyrazine.29 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 solvent and not from the substrate (see the proposed mechanism for 19 in Figure 3B). Deuteration position assignment was based on 1H NMR spectra comparison of non-deuterated compounds 55 and 56 with deuterated 57 and 60, as well as 2D NMR data for 55 and 56.

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,30 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
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. aReaction time 14 days. bProducts 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<sup>a</sup> | 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<sub>2</sub>O                 | -                 | 21                     | 57                     | 78              |
| 6<sup>b</sup> | D<sub>2</sub>O             | -                 | 24                     | 59                     | 83              |

Figure 8: A) Reaction between simplified chloro-substituted core 45a and piperidine, performed in D<sub>2</sub>O 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. <sup>a</sup>D<sub>2</sub>O, heating at reflux.

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 possibility 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 (for a graphical summary see Figure 10). Computational studies to rationalise and predict substitutions of these kinds are non-trivial (in part because of the possibility of direct vs stepwise substitution) but are ongoing and will be reported in due course.

Figure 10: Summary of ipso- and tele-substitution reactions observed with 5-halo-1,2,4-triazolo[4,3-a]pyrazines. Increased levels of tele-substitution observed (i) when X = I > Br > Cl, and (ii) when NuH = RNH₂ > RSH > ROH.

5 Experimental

5.1 General Procedures

General Procedure A. Preparation of halogen-hydrazinylpyrazines
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 H₂O (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 Na₂SO₄ and evaporated under reduced pressure to give the desired compound, which was used in the subsequent reaction without further purification (for reaction schemes of general procedures see SI, Figure S1).

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. 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 H₂O (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 H₂O (30 mL × 3) followed by Et₂O (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 using a gradient of 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. 9 136–139 °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). \(^1^3\)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.\(^9\)\(^,\)\(^35\)

**2-Chloro-5-hydrazinylpyrazine** (**S5**). Compound was prepared following literature procedures.\(^37\) 2,5-Dichloropyrazine (2.00 g, 13.4 mmol, 1.0 equiv.) was added to H\(_2\)O (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\(_2\)O (25 mL × 3), then dried in vacuo to give **S5** as a yellow solid (1.62 g, 11.2 mmol, 83%). mp 168–170 °C.

**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), 7.97 (d, \(J = 2.8\) Hz, 2H), 7.41 (t, \(J = 73.6\) Hz, 1H), 7.36 (d, \(J = 8.2\) Hz, 2H). \(^1^3\)C{\(^1\)H} 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\(_8\)ClF\(_2\)N\(_3\)O \(297.0349\); found 297.0346.

**3-(4-(Difluoromethoxy)phenyl)-5-(phenethylthio)-1,2,4-triazolo[4,3-a]pyrazine** (**17**). 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. \(^{36}\) 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). \(^1^3\)C{\(^1\)H} 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.\(^23\)\(^,\)\(^36\)

**2-Chloro-5-hydrazinylpyrazine** (**S4**). General Procedure A was applied using 2,6-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. \(^{36}\) 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). \(^1^3\)C{\(^1\)H} 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.\(^23\)\(^,\)\(^36\)
eral 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\(_3\)): \(\delta\) 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\[^{1}\]H NMR (101 MHz, CDCl\(_3\)): \(\delta\) 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 \(C_{20}H_{17}F_{2}N_4\)OS 399.1086; found 399.1080.

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 18 as an off-white solid (113 mg, 0.284 mmol, 83%). mp 156–158 °C. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta\) 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\[^{1}\]H NMR (126 MHz, DMSO-\(d_6\)): \(\delta\) 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-\(d_6\)): \(\delta\) -82.8. HRMS (ESI/FTICR) \(m/z\): [M + H]\(^+\) calcd for \(C_{29}H_{21}F_2N_4O_3S\) 399.1086; found 399.1083.

8-Chloro-1,2,4|triazolo|4,3-a|pyrazine (25). General Procedure B was applied using 16 (2.71 g, 18.8 mmol) to give 25 as a yellow solid (0.870 g, 5.63 mmol, 30%). mp 192–195 °C (lit. \(^{30}\) mp 193–195 °C). \(^1\)H NMR (200 MHz, CDCl\(_3\)): \(\delta\) 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 \(C_{11}H_7ClN_3\) 253.0251; found 253.0252. The spectroscopic data and melting point were in agreement with those in the literature. \(^{40}\)

8-Chloro-3-(4-nitrophenyl)-1,2,4|triazolo|4,3-a|pyrazine (27). General Procedure C was applied using 19 (0.655 g, 4.53 mmol, 1.0 equiv.) 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%). mp 231–234 °C (decomp.) (lit. \(^{23}\) mp 201–204 °C). \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta\) 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\[^{1}\]H NMR (126 MHz, DMSO-\(d_6\)): \(\delta\) 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 \(C_{11}H_7ClN_3\) 298.0102; found 298.0103. The spectroscopic data were in agreement with the literature, but the melting point was significantly higher. \(^{23}\)

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. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta\) 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\[^{1}\]H NMR (126 MHz, DMSO-\(d_6\)): \(\delta\) 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 \(C_{13}H_{12}N_4\)O\(_4\) 263.0903; found 263.0900.

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. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta\) 9.38 (d, \(J = 0.8\) Hz, 1H), 8.33 (dd, \(J = 4.6, 0.8\) Hz, 1H), 7.79
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-phenylethyl-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-phenylethyl-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-d6): 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). 13C{1H} NMR (126 MHz, DMSO-d6): 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 C13H12N3Na 279.0675; found 279.0671.

8-Phenethoxy-3-phenyl-[1,2,4]triazolo[4,3-a]pyrazin-8-amine (31). General Procedure D was applied using 26 (115 mg, 0.499 mmol, 1.0 equiv.) and 2-phenylethyl-1-ol (244 mg, 1.95 mmol, 2.0 equiv.) to give 31 as a white solid (91.0 mg, 0.288 mmol, 58%). mp 145–147 °C. 1H NMR (500 MHz, DMSO-d6): 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). 13C{1H} NMR (126 MHz, DMSO-d6): 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 C19H16N4O4Na 339.1216; found 339.1217.

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-phenylethylene-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. 1H NMR (500 MHz, DMSO-d6): 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). 13C{1H} NMR (126 MHz, DMSO-d6): 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 + Na]+ calcd for C19H17N4SNa 333.1168; found 333.1164.

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-phenylethyl-1-amine (161 mg, 1.33 mmol, 3.0 equiv.) to give 33 (120 mg, 0.381 mmol, 86%). mp 206–209 °C. 1H NMR (500 MHz, DMSO-d6): 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). 13C{1H} NMR (126 MHz, DMSO-d6): 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 C19H18N5 316.1557; found 316.1553.

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-phenylethyl-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.). 1H NMR (500 MHz, DMSO-d6): 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). 13C{1H} NMR (126 MHz, DMSO-d6): 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 C19H16N5O3 362.1248; found 362.1246.

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-phenylethan-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.). 1H NMR (500 MHz, DMSO-d6): 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). 13C{1H} NMR (126 MHz, DMSO-d6): 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 C13H16N2O2S 378.1020; found 378.1018.

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.). 1H NMR (500 MHz, DMSO-d6): 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). 13C{1H} NMR (126 MHz, DMSO-d6): 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 C19H17N2O2 361.1408; found 361.1404.

2-Chloro-3-(4-difluoromethoxy)phenyl]-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.). 1H NMR (500 MHz, DMSO-d6): 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). 13C{1H} NMR (126 MHz, DMSO-d6): δ 143.9, 143.0, 137.3, 133.4, 116.3. HRMS (ESI/FTICR) m/z: [M + H]+ calcd for C12H12ClF2N4 155.0119; found 155.0118.

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. 1H NMR (500 MHz, DMSO-d6): 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 = 7.35 Hz, 1H). 13C{1H} NMR (126 MHz, DMSO-d6): 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. 19F NMR (471 MHz, DMSO-d6): δ -82.8. HRMS (ESI/FTICR) m/z: [M + Na]+ calcd for C12H7ClF2N4ONa 319.0169; found 319.0169.

2,6-Diiodopyrazine (41). Compounds was prepared following literature procedures.11 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 Et2O (200 mL). The solution was washed with H2O (100 mL × 2), sat. aq. NaHCO3 (50 mL), sat. aq. Na2SO3 (50 mL), brine (30 mL), dried (Na2SO4), filtered and concentrated under reduced pressure to give 41 as a white solid (9.91 g, 29.9 mmol, 88%). mp 90–92 °C. 1H NMR (300 MHz, CDCl3): δ 8.74 (s, 2H). 13C{1H} NMR (75 MHz, CDCl3): δ 151.2, 116.8. The spectroscopic data were in agreement with those in the literature.41

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%). 1H NMR (500 MHz, CDCl3): 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$_3$): $\delta$ 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$_2$ONa 257.0452; found 257.0451.

2-Bromo-6-phenethoxyypyrazine (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$_3$): $\delta$ 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$_3$): $\delta$ 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$_{11}$Br$_2$ONa 300.9947; found 300.9947.

2-Iodo-6-phenethoxyppyrazine (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$_3$): $\delta$ 8.38 (s, 1H), 8.11 (s, 1H), 7.37 – 7.21 (m, 5H), 4.54 (t, $J$ = 7.0 Hz, 2H). $^{13}$C$^{1}$H NMR (126 MHz, CDCl$_3$): $\delta$ 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$_{11}$BrONa 348.9808; found 348.9807.

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. 9 167 – 172 °C). $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 9.27 (s, 1H), 9.04 (s, 1H), 7.93 (s, 1H). $^{13}$C$^{1}$H NMR (126 MHz, CDCl$_3$): $\delta$ 145.8, 141.9, 134.7, 128.3, 121.3. The spectroscopic data and melting point were in agreement with those in the literature. 9 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$_3$): $\delta$ 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$_6$): $\delta$ 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$_4$O 261.0538; found 261.0535.

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$_6$): $\delta$ 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$_6$): $\delta$ 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$_7$ClN$_3$O$_2$ 276.0282; found 276.0274.

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$_6$): $\delta$ 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$_6$): $\delta$ 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$_3$O 261.0538; found 261.0539.

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.
the literature, but the melting point was significantly different.  

5-Bromo-3-(4-methoxyphenyl)-[1,2,4]triazolo[4,3-a]pyrazine (45f). 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. 1H NMR (500 MHz, DMSO-\(d_6\)): \(\delta\) 9.44 (s, 1H), 8.10 (s, 1H), 7.66 – 7.57 (m, 2H), 7.13 – 7.06 (m, 2H), 3.86 (s, 3H). 13C\{\text{\textsuperscript{1}H}\} NMR (126 MHz, DMSO-\(d_6\)): \(\delta\) 150.2, 149.6, 148.8, 143.0, 133.9, 133.2, 121.8, 110.8. HRMS (ESI/FTICR) m/z: [M + H]\(^+\) calcd for C\(_{12}\)H\(_{10}\)BrN\(_2\)O \(305.0033\); found \(305.0030\).

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.). \(\text{\textsuperscript{1}H}\) NMR (500 MHz, DMSO-d\(_6\)): \(\delta\) 9.54 (s, 1H), 8.41 (d, \(J = 8.0 \text{ Hz}, 2\text{H}\)), 8.20 (s, 1H), 8.04 (d, \(J = 8.2 \text{ Hz}, 2\text{H}\)). 13C\{\text{\textsuperscript{1}H}\} NMR (126 MHz, DMSO-d\(_6\)): \(\delta\) 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\(_7\)BrN\(_3\)O \(319.9778\); found 319.9781.

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. \(\text{\textsuperscript{1}H}\) NMR (500 MHz, CDCl\(_3\)): \(\delta\) 9.34 (s, 1H), 7.95 (s, 1H), 7.58 (dd, \(J = 8.4, 7.5, 1.7 \text{ Hz}, 1\text{H}\)), 7.54 (dd, \(J = 7.5, 1.7 \text{ Hz}, 1\text{H}\)), 7.11 (td, \(J = 7.5, 1.0 \text{ Hz}, 1\text{H}\)), 6.97 (dd, \(J = 8.4, 1.0 \text{ Hz}, 1\text{H}\)), 3.73 (s, 3H). 13C\{\text{\textsuperscript{1}H}\} NMR (126 MHz, CDCl\(_3\)): \(\delta\) 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\(_{10}\)BrN\(_2\)O \(305.0033\); found 305.0036.

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. 1H NMR (200 MHz, CDCl3): 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). 13C{1H} NMR (126 MHz, DMSO-d6): 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]+ calcld for C11H9BrN3O2 319.9778; found 319.9780.

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.). 1H NMR (500 MHz, DMSO-d6): δ 9.54 (s, 1H), 9.36 (s, 1H), 8.24 (s, 1H). 13C{1H} NMR (126 MHz, DMSO-d6): δ 144.4, 142.2, 140.2, 137.7, 83.9. HRMS (ESI/FTICR) m/z: [M + H]+ calcld for C5H4BrN4 246.9475; found 246.9475.

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.). 1H NMR (500 MHz, DMSO-d6): 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). 13C{1H} NMR (126 MHz, DMSO-d6): δ 161.6, 149.5, 142.2, 143.9, 140.6, 134.4, 119.4, 113.6, 84.1, 55.8. HRMS (ESI/FTICR) m/z: [M + H]+ calcld for C12H11NO4 352.9894; found 352.9891.

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.). 1H NMR (500 MHz, DMSO-d6): 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). 13C{1H} NMR (126 MHz, DMSO-d6): 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]+ calcld for C13H9BrN4O4 421.1084; found 421.1081.

5-(Phenethylthio)-[1,2,4]triazolo[4,3-a]pyra-
2.93 (t, m/z 122.6, 109.3, 70.9, 33.5. HRMS (ESI/FTICR) 137.1, 134.9, 134.1, 131.9, 128.4, 128.1, 126.3, 119.9, 117.4, 110.9, 108.8, 71.4, 55.3, 34.1. HRMS (ESI/FTICR) m/z: [M + H]^+ calcld for C_{20}H_{19}N_{4}O_{3} 347.1503; found 347.1504.

3-(2-Nitrophenyl)-5-phenethoxy-[1,2,4]triazolo[4,3-a]pyrazine (46e). 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 46e 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 45f (128 mg, 0.400 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (48.8 mg, 0.400 mmol, 1.0 equiv.) to give 46f as a yellow solid (first run: 56.5 mg, 0.181 mmol, 68%, second run: 85.6 mg, 0.237 mmol, 60%). m.p. 168–170 °C. 1H NMR (500 MHz, DMSO-d6): δ 8.19 – 8.22 (m, 1H), 7.79 – 7.93 (m, 1H), 7.70 (s, 1H), 7.66 (d, J = 6.4 Hz, 1H), 7.58 (d, J = 7.5, 1.6 Hz, 1H), 7.67 (s, 1H), 7.19 – 7.11 (m, 2H), 6.83 – 6.76 (m, 2H), 4.38 (t, J = 6.5 Hz, 2H), 2.68 (t, J = 6.4 Hz, 2H). 13C{¹H} NMR (126 MHz, DMSO-d6): 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, 55.3, 34.1. HRMS (ESI/FTICR) m/z: [M + H]^+ calcld for C_{20}H_{19}N_{4}O_{3} 347.1503; found 347.1504.

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.). Fraction corresponding to the second peak were combined and evaporated to give 46g as a yellow solid (first run: 78.6 mg, 0.227 mmol, 72%, second run: 111 mg, 0.307 mmol, 77%, average yield is 76%). m.p. 178–181 °C (decomp.). 1H NMR (500 MHz, DMSO-d6): δ 8.19 (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). 13C{¹H} NMR (126 MHz, DMSO-d6): 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, 55.3, 34.1. HRMS (ESI/FTICR) m/z: [M + H]^+ calcld for C_{20}H_{19}N_{4}O_{3} 347.1503; found 347.1504.
(126 MHz, DMSO-\(d_6\)) \(\delta\) 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]\(^+\) \(\text{calcld for C}_{22}\text{H}_{23}\text{NO}_{11}\) 451.2468; found 451.2471.

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 first 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. \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta\) 10.31 (s, 1H), 8.99 (s, 1H), 8.31 (d, \(J = 8.5\) Hz, 2H), 7.61 (d, \(J = 8.3\) Hz, 2H), 7.55 – 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, \(J = 6.6\) Hz, 2H), 1.57 (t, \(J = 6.2\) Hz, 2H).

\(^{13}\)C\{\(^1\)H\} NMR (126 MHz, DMSO-\(d_6\)): \(\delta\) 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]\(^+\) \(\text{calcld for C}_{27}\text{H}_{21}\text{N}_{10}\text{O}_{12}\) 417.1710; found 417.1713.

3-(4-Methoxyphenyl)-5-phenethoxy-[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-phenylethanol-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-phenylethanol-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.

\(^{13}\)C\{\(^1\)H\} NMR (126 MHz, DMSO-\(d_6\)): \(\delta\) 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]\(^+\) \(\text{calcld for C}_{20}\text{H}_{10}\text{N}_{11}\text{O}_2\) 347.1503; found 347.1499.

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-phenylethanol-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-phenylethanol-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.

Frations corresponding to the first peak were evaporated to give 47b as a yellow solid (first run: 13.0 mg, 0.0118 mmol, 3%). Preparation 2: General Procedure D was applied using 45n (132 mg, 0.375 mmol, 1.0 equiv.) and 2-phenylethan-1-ol (48.8 mg, 0.399 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 3: 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-\(d_6\)): \(\delta\) 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).
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$_5$O 346.1662; found 346.1657.

3-[3,5-Di-tert-butylphenyloxy]-8-phenethoxy-triazolo/[1,2,4]triazolo/[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$_4$O$_3$ 451.2468; found 451.2471.

3-[Anthracen-9-yl]-8-phenethoxy-triazolo/[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$_4$O$_3$ 417.1710; found 417.1709.

3-(2-Methoxyphenyl)-8-phenethoxy-triazolo/[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$_4$O$_2$Na 369.1322; found 369.1326.

3-[4-Methoxyphenyl]-8-phenethoxy-triazolo-[1,2,4]-pyrazin-8-ol (48a). General Procedure D was applied (with following modification: H$_2$O was used as a solvent) using 45i (107 mg, 0.341 mmol) and 2-phenylethanol-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$_4$O$_2$Na 265.0696; found 265.0696.

3-[4-Nitrophenyl]-8-phenethoxy-triazolo-[1,2,4]-pyrazin-8-ol (48b). General Procedure D was applied using 45j (128 mg, 0.400 mmol, 1.0 equiv.) and 2-phenylethanol-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-
Preparation 2: General Procedure D was applied using 45n (108 mg, 0.307 mmol, 1.0 equiv.) and 2-phenylethyl-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-\(d_6\)): \(\delta\) 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-\(d_6\)) : \(\delta\) 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\(_4\)O\(_2\)Na 249.0747; found 249.0747.

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\(_3\)OD): \(\delta\) 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\(_3\)OD): \(\delta\) 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\(_{38}\)H\(_{20}\)N\(_4\)O\(_2\) 346.1662; found 346.1656. 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-\(d_6\)): \(\delta\) 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\(_5\) 204.1244; found 204.1243.

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\(_3\)CN): 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\(_3\)CN): 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\(_5\) 204.1244; found 204.1241. 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\(_2\)O (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 to give 57 as a white solid (197 mg, 1.27 mmol, 86%). mp 181–183 °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 \( \mu \)mol) was dissolved in D\(_2\)O (5 mL) and heated at reflux for 72 h. Solvent was evaporated to give 60 as an orange solid (10 mg, 49 \( \mu \)mol, 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.

Supporting Information Available

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.1c00271. 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 format for all compounds described in the article with reference codes to the laboratory notebook. (XLS)

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Graphical TOC Entry

Unusual tele-substitution in bioactive compounds

\[ \text{NuH} = \text{ROH, RSH, RNH}_2 \]
\[ \text{X} = \text{Cl, Br, I} \]
\[ \text{Y} = \text{EWG, EDG} \]