Article

Photochemical permutation of thiazoles, isothiazoles and other azoles

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Thiazoles and isothiazoles are privileged motifs in drug and agrochemical discovery[1,2]. The synthesis of these derivatives is generally approached, designed and developed on a case-by-case basis. Sometimes, the lack of robust synthesis methods to a given target can pose considerable difficulties or even thwart the preparation of specific derivatives for further study[3,4]. Here we report a conceptually different approach in which photochemical irradiation can be used to alter the structure of thiazoles and isothiazoles in a selective and predictable manner. On photoexcitation, these derivatives populate their π,π^* singlet excited states that undergo a series of structural rearrangements, leading to an overall permutation of the cyclic system and its substituents. This means that once the initial heteroaromatic scaffold has been prepared, it can then function as an entry point to access other molecules by selective structural permutation. This approach operates under mild photochemical conditions that tolerate many chemically distinct functionalities. Preliminary findings also show the potential for extending this method to other azole systems, including benzo[*d*] isothiazole, indazole, pyrazole and isoxazole. This strategy establishes photochemical permutation as a powerful and convenient method for the preparation of complex and difficult-to-access derivatives from more available structural isomers.

Most medicinal chemistry campaigns rely on the screening of compound libraries that generally feature derivatives accessed using a set of robust chemical reactions[5,6]. Despite the many and continuous advancements in the way we construct molecules, synthetic chemistry is often the bottleneck step in the drug-development pipeline[7–10].

Amongst these libraries, electron-rich heteroaromatics are considered 'privileged scaffolds' due to their physicochemical properties that can often impact aspects like target recognition and pharmacokinetics. However, their occurrence in screening libraries is far from even, and it is greatly impacted by the availability of chemical methods for their preparation and/or functionalization. This can be aptly realized considering the fact that although thiazole is the fifth-most present aromatic in drugs, the isomeric isothiazole is not even in the top 100 (refs. 1,2). This imbalance in representation is a clear reflection of the many challenges that impact the development of synthesis strategies towards the incorporation of these motifs in drug-like molecules.

In general, the synthesis of these five-membered ring heterocycles primarily depends on the multistep preparation of appropriately functionalized precursors for condensation chemistry, which, however, is considerably more difficult in the case of isothiazoles[3,4] (Fig. 1a). Subsequent functionalization is generally achieved by fragment coupling through, for example, amidation, alkylation and cross-coupling reactivity (for example, Suzuki–Miyaura). However, this requires accessing derivatives with the correct disposition of functionality handles, something often difficult to achieve and/or restricted to specific positions. Furthermore, cross-coupling reactions are often highly sensitive to the substitution pattern of heteroaromatic compounds, with many systems lacking efficient methodologies for their use. A detailed analysis of cross-couplings developed for thiazole and isothiazole systems is provided in the Supplementary Information. Strategies based on transition-metal-catalysed C–H activation or radical intermediates have simplified these endeavours, but they still rely on either directing groups for vicinal functionalization or the targeting of the intrinsically more activated sites[2]. As an example, although it is easy to substitute a thiazole at C2, it is much more challenging to target either C4 or C5 (ref. 11). This means that complex derivatives necessitate tailored starting materials with the correct juxtaposition of substituents and/or functionalities for further elaboration, which often results in long or low-yielding synthetic sequences.

A further and intrinsic drawback in the current way of making molecules becomes evident when approaching the preparation of heterocycles featuring the same heteroatoms and substituents but with different patterns around the cyclic core. This is routinely pursued during the development of screening libraries as it enables an accurate understanding of exit vectors and their relevance to molecular interactions in the biological space[12]. Currently, this task requires the development of de novo individual synthesis approaches based on different starting materials and reactions to plan and optimize. In some cases, these 'altered states of substitution patterns' can pose such severe

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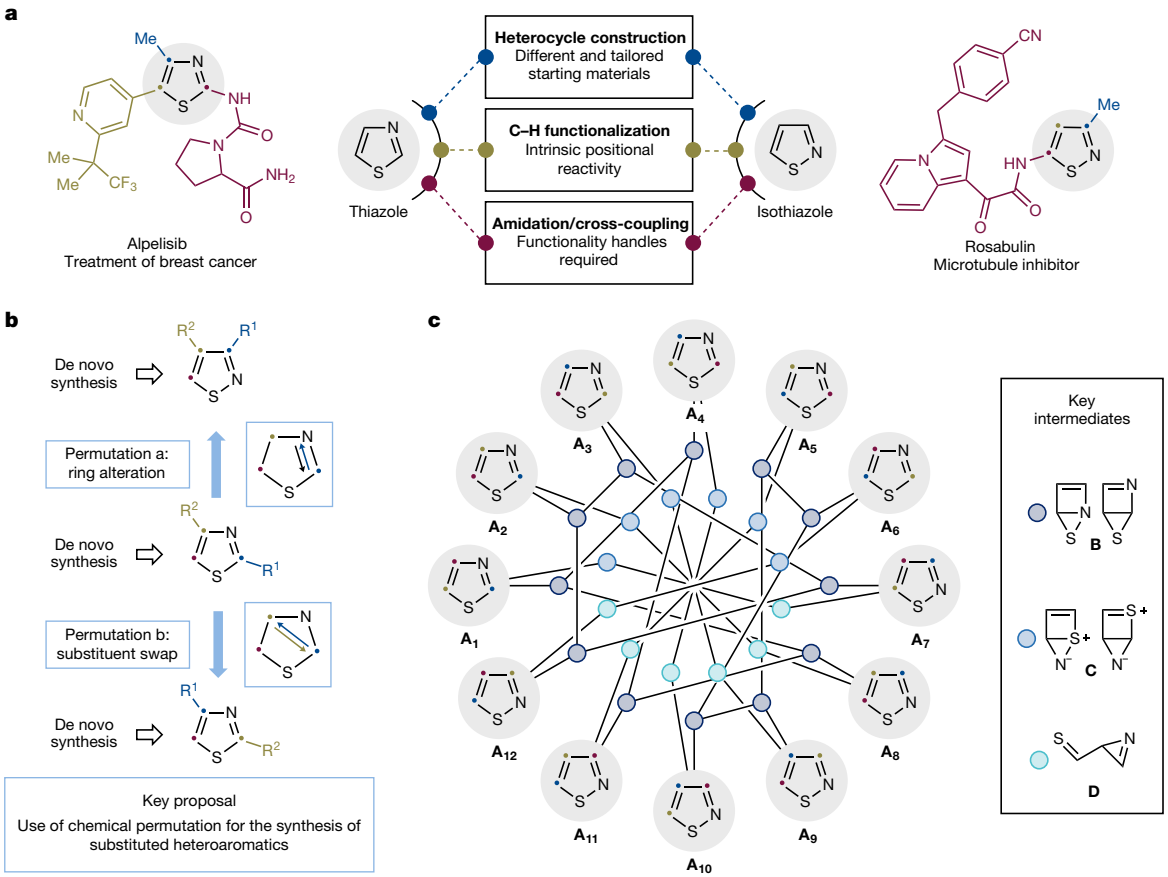

Fig. 1 | Synthetic strategies for thiazole and isothiazole preparation versus a permutation concept. a, Standard workflow for the preparation of thiazoles and isothiazoles. **b**, Chemical permutation can alter the structures of thiazoles and isothiazoles, but would require directionality. **c**, Duodecimal system ($\mathbf{A_1}$–$\mathbf{A_{12}}$) arising from the permutation of a generic thiazole ($\mathbf{A_1}$) with three different substituents.

chemical and reactivity challenges that the corresponding heterocycle may practically not be accessible.

Here we introduce an alternative tactic for the preparation of thiazole and isothiazole derivatives in which photochemical irradiation is used to 'alter' the heterocycle structure. This blueprint provides a new logic in which chemical permutation enables the use of a fully functionalized heteroaromatic as a direct precursor for a different structural isomer. This offers the synthetic advantage that easy-to-make derivatives can be converted into synthetically challenging ones as well as doubling or even tripling the number of accessible analogues for screening libraries from a single derivative without the need for de novo synthesis.

In approaching the development of an alternative strategy for thiazole or isothiazole synthesis, we considered the synthetic benefits obtained using an easy-to-access material and then convert it into either a different heteroaromatic system (path a; for example, from thiazole to isothiazole) or to keep the heterocyclic skeleton 'fixed' and move the substituents around the ring (path b; for example, from C2-substituted thiazole to C4-substituted thiazole; Fig. 1b).

In a geometrical sense, both transformations (paths a and b) would represent specific examples of permutation pathways. Considering the pentagonal shape with two heteroatoms and up to three different substituents, a generic fully substituted thiazole $\mathbf{A_1}$ can lead to a duodecimal system ($\mathbf{A_1}$–$\mathbf{A_{12}}$) ($P'_5 = (5-1)!/2 = 12$) (Fig. 1c). To be synthetically useful, permutating the structure of $\mathbf{A_1}$ into one of any other group elements ($\mathbf{A_2}$–$\mathbf{A_{12}}$) requires (1) the identification of suitable chemical pathways and (2) the provision of directionality to these processes to avoid the formation of product mixtures. A potential way to approach this challenge would be to use photoexcitation to temporarily disrupt the heterocycle aromaticity and access high-energy intermediates from which structural alterations can take place. Previous studies on the photochemistry of thiazoles or isothiazoles proposed the formation of either Dewar intermediates (valence bond tautomers) (for example, **B** and **C**) through excited-state 4π electrocyclization followed by 'S-atom walk' or thioketone–azirine species (for example, **D**) and then cyclization as plausible processes for chemical permutation[13–22]. This, however, creates an intricate network of high-energy intermediates, all interconnected by potentially reversible pathways—a scenario from which it is difficult to understand how to achieve directional selectivity. Indeed, these pioneering studies, which were run using high-energy mercury lamps, revealed the photochemistry of thiazoles and isothiazoles to generally result in complex mixtures of products often obtained with low chemical yields[13,23]. As a result, any type of permutation tactic has been overlooked by the synthetic and medicinal chemistry communities despite its potential in the preparation and diversification of high-value molecules.

We postulated that under photochemical conditions, there could be two ways to achieve directional selectivity across the permutation group. The first option would require the various thiazoles or isothiazoles to absorb in different ranges of the electromagnetic spectrum such that irradiation at specific wavelengths could target the photoexcitation of some derivatives over others. Alternatively, because different reaction conditions (for example, solvent, additives and so on) might impact the intrinsic photophysical properties of specific molecules, photostability could be exploited to accumulate one derivative over others. As the absorbance of different thiazoles or isothiazoles falls in the same region (Supplementary Information), we decided to evaluate the feasibility of the second approach.

To begin, we focused on permutating monosubstituted thiazoles or isothiazoles and started by preparing and evaluating the behaviour

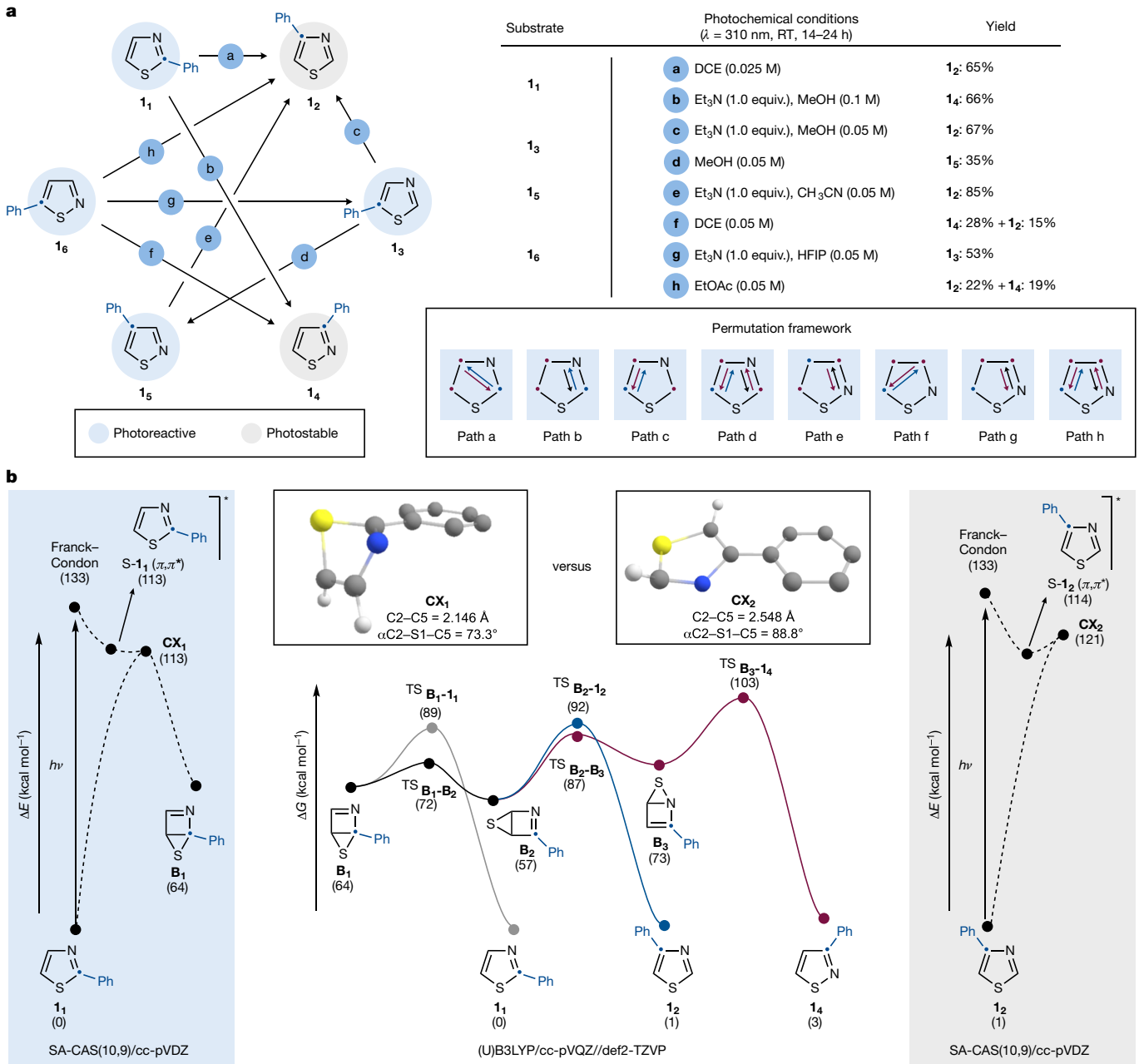

Fig. 2 | Permutation chemistry of Ph-substituted thiazoles and isothiazoles. **a**, Permutation chemistry on Ph-substituted thiazoles and isothiazoles. **b**, Computational studies (gas phase) on the conversion of $\mathbf{1}_1$ into $\mathbf{1}_2$ and $\mathbf{1}_4$. The numbers in brackets under each species are the Gibbs free energies in kcal mol^{-1}. RT, room temperature; TS, transition state.

of six Ph-containing derivatives $\mathbf{1}_1$–$\mathbf{1}_6$ (Fig. 2a). From this initial study of photochemical stability, we identified C4-Ph-thiazole $\mathbf{1}_2$ and C3-Ph-isothiazole $\mathbf{1}_4$ to be largely stable under room-temperature irradiation (λ = 310 nm, 16 h) in several solvents. Hence, we set out to develop synthesis conditions to convert the other derivatives into either $\mathbf{1}_2$ and/or $\mathbf{1}_4$. Fortunately, the irradiation of 2-Ph-thiazole $\mathbf{1}_1$ in dichloroethane (DCE) as the solvent led to its selective conversion into C4-Ph-thiazole $\mathbf{1}_2$ with a good chemical yield (path a). To our surprise, changing the reaction media from DCE to MeOH completely shifted the selectivity of the process, giving access to C3-isothiazole $\mathbf{1}_4$ as the major product also with a good chemical yield (path b). Furthermore, because additives are often impacting the performance of photochemical reactions, we conducted a screening of various species with different characteristics and identified the stoichiometric addition of Et_3N to further increase the yield of the process. In a permutation framework, $\mathbf{1}_1 \rightarrow \mathbf{1}_2$ seemingly features the Ph group 'moving' across the thiazole core, while $\mathbf{1}_1 \rightarrow \mathbf{1}_4$ can be visualized as a 'swap' between the vicinal C2 and the N atom. The retrosynthetic opportunity offered by these processes might be realized considering that thiazole C4–H arylation requires the protection of the intrinsically more activated C2 site, whereas C3-aryl-isothiazoles need de novo construction from linear precursors. This can now be obviated by straightforward C2–H arylation followed by selective structural permutation.

5-Ph-thiazole $\mathbf{1}_3$ was also permutated in two different directions, providing either $\mathbf{1}_2$ (path c) or $\mathbf{1}_5$ (path d) with high and moderate yields, respectively. Remarkably, both reactions were run in MeOH and the different outcomes were obtained depending on the presence of Et_3N. Furthermore, in the $\mathbf{1}_3 \rightarrow \mathbf{1}_5$ case, the reaction had to be monitored and stopped after 14 h to avoid further reactivity of $\mathbf{1}_5$, which eventually converts into $\mathbf{1}_2$. Indeed, $\mathbf{1}_5 \rightarrow \mathbf{1}_2$ (path e) could be easily achieved with a

high yield using CH_3CN as the solvent and Et_3N as the additive. Overall, $\mathbf{1_3}$→$\mathbf{1_2}$ and $\mathbf{1_5}$→$\mathbf{1_2}$ can be represented as a '1,2-swap' between C4 and C5 and between C3 and the N atom, respectively, whereas $\mathbf{1_3}$→$\mathbf{1_5}$ necessarily features a double permutation movement of C4 with C5 and C2 with the N atom. Finally, 5-Ph-isothiazole $\mathbf{1_6}$ represents an interesting substrate as it was permutated in three different directions, providing $\mathbf{1_2}$ (path h; 1,2-swap between C4 and C5 and between C3 and the N atom), $\mathbf{1_4}$ (path f; swap between C3 and C5) and, unexpectedly, $\mathbf{1_3}$ (path g; swap between C3 and the N atom) with moderate to good yields. In the latter case, $\mathbf{1_3}$ is photoreactive in MeOH or DCE, but we discovered that it displayed some photostability in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP), which enabled the $\mathbf{1_6}$→$\mathbf{1_3}$ permutation.

Fortunately, electronic effects had a minimum impact on the directionality of the transformations, as demonstrated by subjecting *p*-OMe and *p*-CF_3 derivatives of $\mathbf{1_1}$–$\mathbf{1_6}$ to analogous reaction conditions (Supplementary Information).

A preliminary understanding of the permutation directionality has been obtained using computational studies on the $\mathbf{1_1}$→$\mathbf{1_2}$ versus $\mathbf{1_1}$→$\mathbf{1_4}$ conversion (Fig. 2b). On irradiation, $\mathbf{1_1}$ populates its singlet excited state that has a π,π^* configuration[22,24]. From there, S_1/S_0 conical intersection (S_1, first excited singlet state; S_0, singlet ground state) was determined to be barrierless, leading to the Dewar intermediate $\mathbf{B_1}$. This species can revert to $\mathbf{1_1}$, but the S-atom walk to $\mathbf{B_2}$ was determined to have a lower barrier. This valence bond tautomer is thermodynamically more stable and can provide $\mathbf{1_2}$ by electrocyclic ring opening. We rationalized the observed $\mathbf{1_2}$ photostability based on the fact that its photoexcitation should be followed by thermal relaxation rather than $\mathbf{B_2}$ formation. Indeed, its corresponding S_1/S_0 conical intersection point is geometrically fairly different from the one identified for $\mathbf{1_1}$ and similar to ground-state $\mathbf{1_2}$. We propose this to be the key aspect that ultimately controls the permutation directionality for this example. We also considered further S-atom walk from $\mathbf{B_2}$ as this could lead to $\mathbf{B_3}$ that would eventually form $\mathbf{1_4}$. Our analysis supports the formation of $\mathbf{1_2}$ through $\mathbf{B_2}$ to be thermodynamically feasible. However, as the $\mathbf{B_2}$→$\mathbf{B_3}$ conversion also has an accessible barrier, we propose that solvent effects can sufficiently perturb the system, thereby leading to the formation of $\mathbf{1_4}$ under specific conditions.

To continue understanding the reactivity implications of this permutation approach, we sought to benchmark it across the full duodecimal group of thiazole or isothiazole derivatives featuring Ph, Me and H substituents ($\mathbf{2_1}$–$\mathbf{2_{12}}$) (Fig. 3a). In this case, all the heteroaromatic positions are differentiated such that each permutation pathway discussed above for the $\mathbf{1_1}$–$\mathbf{1_6}$ can potentially lead to a bifurcation and, therefore, to two isomeric products.

The first issue we encountered in approaching this study was the actual assembly of the duodecimal library despite the 'structural simplicity' of its components. Indeed, although methods are available for the synthesis of thiazoles $\mathbf{2_1}$–$\mathbf{2_6}$ and isothiazoles $\mathbf{2_{10}}$–$\mathbf{2_{12}}$, there is still limited capacity for the preparation of substrates matching the substitution pattern of isothiazoles $\mathbf{2_7}$, $\mathbf{2_8}$ and $\mathbf{2_9}$ (Supplementary Information provides a discussion of previous synthesis approaches for these derivatives). Fortunately, the permutation chemistry developed here proved to be useful and, as discussed below, it was used to access these derivatives. With $\mathbf{2_1}$–$\mathbf{2_{12}}$ in hand, we first evaluated their photostability and then subjected them to all the previously developed reaction conditions. In line with the results discussed above, the C4-Ph-thiazoles $\mathbf{2_3}$ and $\mathbf{2_4}$ and the C3-Ph-isothiazoles $\mathbf{2_7}$ and $\mathbf{2_8}$ pairs matched the photostability displayed by $\mathbf{1_2}$ and $\mathbf{1_4}$. Interestingly, although isothiazole $\mathbf{1_5}$ could be accumulated on careful reaction monitoring, the C3-Me derivative $\mathbf{2_9}$ was photostable.

The permutation network developed across the duodecimal library is pictorially depicted in Fig. 3a. In general, the substrates followed the reactivity trend identified across the six Ph-substituted derivatives $\mathbf{1_1}$–$\mathbf{1_6}$. Hence, C2-Ph-thiazoles $\mathbf{2_1}$ and $\mathbf{2_2}$ were converted into either $\mathbf{2_8}$ (path a) or $\mathbf{2_3}$ (path b) and either $\mathbf{2_4}$ (path d) or $\mathbf{2_7}$ (path c), respectively, with moderate yields. It is interesting that although the permutation of $\mathbf{2_2}$ required the addition of Et_3N, we fortunately identified *N*,*N*′-dimethylthiourea (DMT) to be beneficial to improve the yields for the reaction on $\mathbf{2_1}$. C5-Ph-thiazole $\mathbf{2_5}$ selectively led to the formation of isothiazoles $\mathbf{2_9}$ (path f) or $\mathbf{2_{10}}$ (path e) on irradiation in MeOH, remarkably depending solely on the presence of Et_3N. Isomer $\mathbf{2_6}$ could only be converted into $\mathbf{2_9}$ (path g) and this permutation occurred with a high yield. Finally, C4-Ph-isothiazole $\mathbf{2_{10}}$ led to thiazole $\mathbf{2_4}$ (path h), whereas both C5-isothiazoles $\mathbf{2_{11}}$ and $\mathbf{2_{12}}$ were selectively converted into either $\mathbf{2_3}$ (path j) or $\mathbf{2_8}$ (path i) and either $\mathbf{2_9}$ (path k) or $\mathbf{2_7}$ (path l).

The impact of an electron-withdrawing ester functionality was evaluated next (Fig. 3b). In this case, it was not possible to assemble the full duodecimal library of Ph- and ester-disubstituted derivatives due to the lack of synthesis methods. However, isothiazole $\mathbf{3_7}$ was conveniently accessed using the permutation chemistry and further demonstrated to be photostable along with thiazole $\mathbf{3_3}$. Thus, out of the six possible thiazole derivatives, we identified $\mathbf{3_1}$, $\mathbf{3_2}$ and $\mathbf{3_4}$ to be reactive (Supplementary Information provides more information). Hence, $\mathbf{3_1}$ underwent permutation to thiazole $\mathbf{3_3}$, whereas both $\mathbf{3_2}$ and $\mathbf{3_4}$ converged towards isothiazole $\mathbf{3_7}$ with good yields. The reactivity of $\mathbf{3_4}$ is noteworthy because C4-Ph thiazoles ($\mathbf{1_2}$, $\mathbf{2_3}$ and $\mathbf{2_4}$) were previously identified as photostable, something that can be clearly modulated by the introduction of an ester functionality at C5. Furthermore, standard synthesis approaches to substrates matching the substitution pattern of $\mathbf{3_7}$ require condensation chemistry in the presence of toxic and corrosive (chlorocarbonyl)sulfenyl chloride.

Overall, the evaluation of these three classes of substrates ($\mathbf{1_1}$–$\mathbf{1_6}$, $\mathbf{2_1}$–$\mathbf{2_{12}}$ and $\mathbf{3_1}$–$\mathbf{3_7}$) gave us some experimental guidelines to explore the permutation scope in terms of both reaction conditions to use and possible structural outcomes.

Scope evaluation continued testing the reactivity of CF_3-containing $\mathbf{4_1}$ that was permutated to give either $\mathbf{4_2}$ or $\mathbf{4_3}$ with good yields. It is interesting to note that although 2-aryl-5-CF_3-thiazoles are relatively easy to prepare, $\mathbf{4_2}$ has been previously made in five steps[25,26], and there are currently no methods to access the isomeric 3-aryl-4-CF_3-isothiazoles (for example, $\mathbf{4_3}$), something that can be streamlined with this approach. Moreover, the permutation reactivity is not restricted to carbon-based substituents, as demonstrated by $\mathbf{5_1}$ featuring a C4-NHBoc functionality that was selectively converted into $\mathbf{5_2}$ with a good yield. Furthermore, in agreement with our previous results, a series of C4-Me-C5-aryl-thiazoles ($\mathbf{6_1}$–$\mathbf{9_1}$) provided access to the corresponding C3-Me-C4-aryl isothiazoles. These examples demonstrate the tolerance of chemically different functionalities like stereocentres with a free amine group ($\mathbf{6_2}$), phenol and nitrile ($\mathbf{7_2}$) groups, and pyrazole ($\mathbf{8_2}$) and isoxazole ($\mathbf{9_2}$) heteroaromatics. As for limitations, we were unable to use substrates with halogen atoms directly attached to the heteroaromatic scaffold. In the case of Br-functionalized materials, we typically observed C–Br bond homolysis, whereas Cl-substituted derivatives were generally photostable.

The possibility to move three substituents across the heterocyclic unit was attempted next using $\mathbf{10_1}$ and $\mathbf{11_1}$ that feature two Ph groups at C4 and C5. In these cases, it was interesting to note how the electronic nature of the C2 substituent controlled the permutation directionality. Thus, the C2-Me derivative $\mathbf{10_1}$ led to isothiazole $\mathbf{10_2}$, whereas the C2-NH_2 substrate $\mathbf{11_1}$ provided $\mathbf{11_2}$ with good yields. It is interesting to note that $\mathbf{10_1}$→$\mathbf{10_2}$ matches the $\mathbf{2_6}$→$\mathbf{2_9}$ permutation discussed above, whereas $\mathbf{11_1}$→$\mathbf{11_2}$ constitutes a different manifold.

The application of permutation chemistry to substrates containing three different groups was studied using thiazoles $\mathbf{12_1}$–$\mathbf{17_1}$, all featuring an aromatic group at C2, a methyl group at C4 and an electron-withdrawing ester or nitrile functionality at C5. In these cases, we observed an interesting permutation dichotomy based on the electronics of the C2-aryl group. Specifically, all the substrates could be selectively converted into the corresponding thiazoles $\mathbf{12_2}$–$\mathbf{17_2}$ in which the aryl and Me groups seemingly swap positions across the heteroaromatic. Furthermore, the derivatives containing an electron-rich aromatic group ($\mathbf{12_1}$–$\mathbf{15_1}$) could be converted into isothiazoles $\mathbf{12_3}$–$\mathbf{15_3}$, an outcome that, overall, is in line with that observed for both $\mathbf{2_1}$ and $\mathbf{3_2}$.

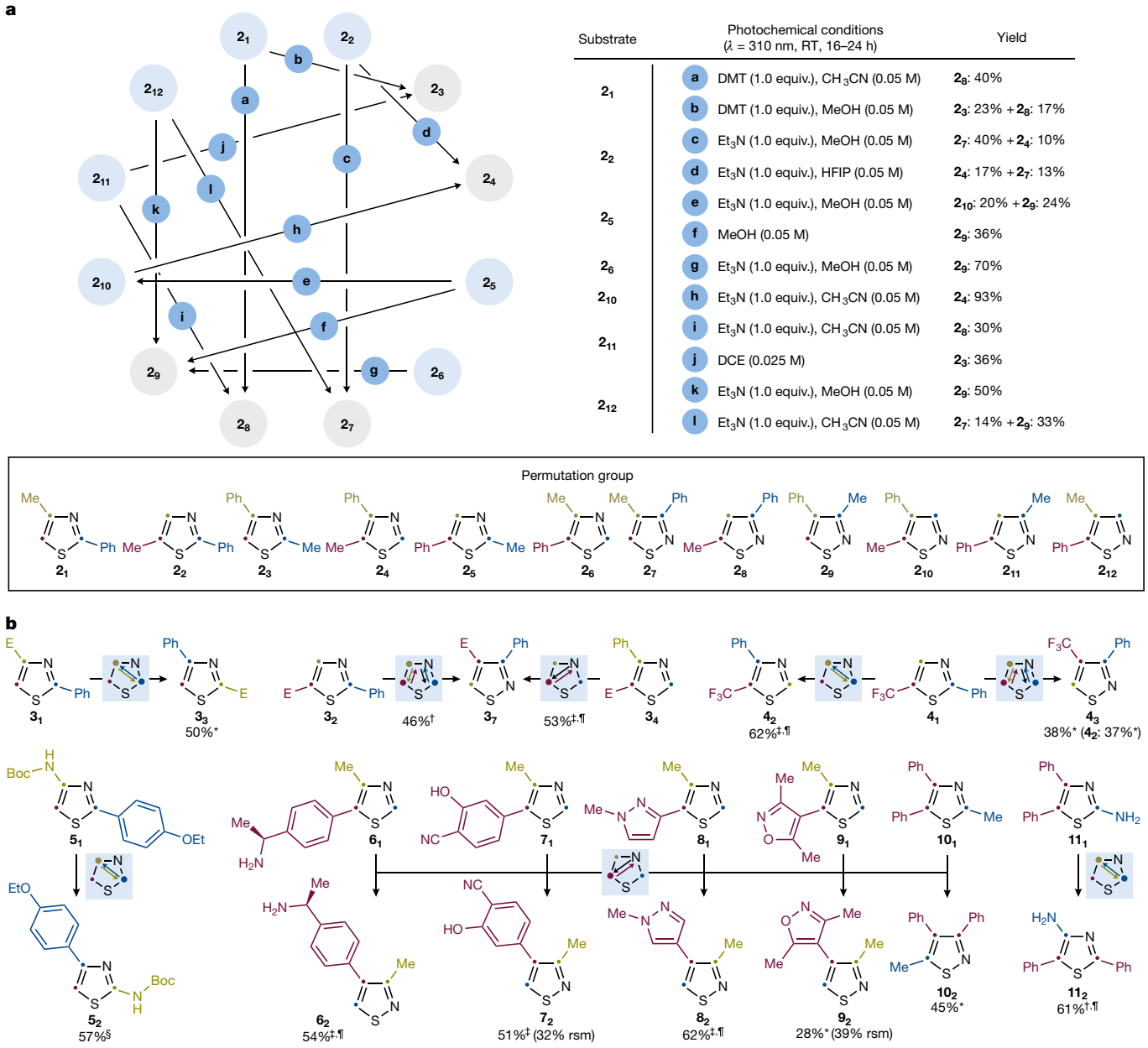

Fig. 3 | Permutation of disubstituted thiazoles and isothiazoles. a, Permutation chemistry on Ph- and Me-disubstituted thiazoles and isothiazoles. **b**, Substrate scope on disubstituted thiazoles. All the reactions were irradiated (λ = 310 nm) at room temperature (RT). Solvent: *DCE; †HFIP; ‡MeOH; §1,4-dioxane. Additives: ¶Et_3N (1.0 equiv.). E = CO_2Me. rsm, recovered starting material.

This provides a valuable synthetic complementary as previous approaches towards this class of derivatives are generally challenging and often low yielding (**13**$_3$, four steps; **14**$_3$, five steps)[27–29]. Conversely, **16**$_1$ and **17**$_1$ that contain electron-poor aromatics gave isothiazoles **16**$_3$ and **17**$_3$ in which all three substituents and the N atom seem to have changed their original position through an unprecedented permutation mode.

This chemistry is not limited to isolated heteroaromatics and has been extended to bicyclic thiazoles, enabling access to corresponding bicyclic isothiazoles, for which there are currently few synthesis methods (Fig. 4b). Specifically, cyclohexane- and cycloheptane-annellated thiazoles (**18**$_1$ and **19**$_1$) were selectively converted into the corresponding isothiazoles (**18**$_2$ and **19**$_2$). By placing substituents at the C6 position of the saturated ring, such as OMe (**20**$_1$) and *gem*-difluoro (**21**$_1$), we were able to confirm that the permutation occurred through a double 1,2-swap between C2 and the N atom, as well as between C3 and C4. This rearrangement not only changes the heteroaromatic core (thiazole to isothiazole) but also shifts the substituents from the C6 to the C7 position in the product (**20**$_2$ and **21**$_2$).

The chemistry was also applied to systems featuring annellated heterocyclic rings, such as pyran (**22**$_1$) and *N*-Boc-piperidine (**23**$_1$), in which the permutation again occurred selectively, yielding isothiazoles (**22**$_2$ and **23**$_2$) that form heterocyclic frameworks for which no other synthesis methods exist.

So far, this permutation chemistry has been applied to interconverted thiazole and isothiazole cores. We believe that this concept has the potential to be extended to the broader azole family. Preliminary results supporting this are shown in Fig. 4c. For example, we successfully applied this reactivity to benzo[*d*]isothiazole (**24**$_1$), in which a structural rearrangement occurred with a high yield, producing the corresponding benzothiazole (**24**$_2$) in the presence of a tertiary amine and quaternary ammonium functionalities. Here a selective 1,2-swap between C2 and the N atom took place.

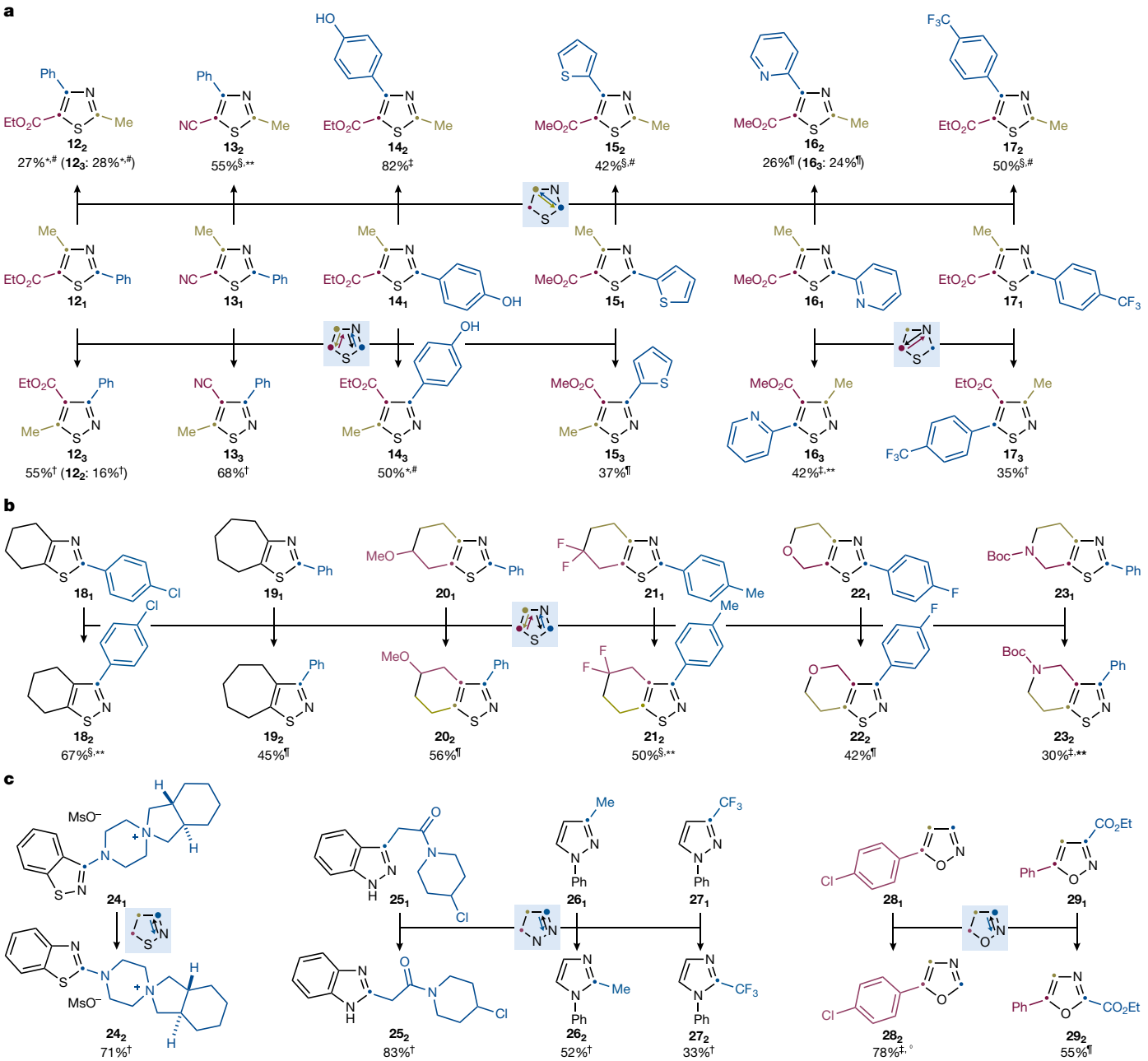

Fig. 4 | Permutation chemistry of trisubstituted thiazoles, bicylic thiazoles and other azoles. a, Substrate scope using trisubstituted thiazoles. **b**, Application of the permutation reactivity for the conversion of bicylic thiazoles into bicyclic isothiazoles. **c**, Permutation reactivity on other azoles. All the reactions were irradiated (λ = 310 nm; except for $\mathbf{26_1}$, $\mathbf{27_1}$ and $\mathbf{29_1}$, where λ = 254 nm) at room temperature. Solvent: *EtOH; †HFIP; ‡MeOH; §CH_3CN; ¶DCE. Additives: #*N*,*N*′-dimethylthiourea (1.0 equiv.); **Et_3N (1.0 equiv.); °2,6-lutidine (0.2 equiv.).

A similar permutation process was achieved with indazole ($\mathbf{25_1}$), which was converted into benzimidazole ($\mathbf{25_2}$), with the amide-containing alkyl substituent migrating from C3 (ref. 30). Moreover, we extended this chemistry to the pyrazole-to-imidazole permutation, as shown by the conversion of the N-Ph derivatives ($\mathbf{26_1}$ and $\mathbf{27_1}$)[30,31]. On irradiation in HFIP (λ = 254 nm), the C3-Me and C3-CF_3 groups cleanly migrated to C2 in the products ($\mathbf{26_2}$ and $\mathbf{27_2}$).

Furthermore, we successfully demonstrated similar reactivity in an isoxazole-to-oxazole permutation[32,33]. In this case, the process tolerated a C5 *p*-Cl-Ph substituent ($\mathbf{28_1}$→$\mathbf{28_2}$) and was compatible with a disubstituted derivative ($\mathbf{29_1}$→$\mathbf{29_2}$).

These preliminary results highlight the potential of permutation reactivity across a broader range of valuable heteroaromatic systems. However, it is important to note that specific aspects of the permutation mechanism and reactivity guidelines may differ from one heterocycle class to another. Therefore, the details discussed above for the thiazole or isothiazole permutation may not be fully applicable to other systems, and dedicated studies will be necessary.

Finally, Fig. 5a–k depicts ten representative examples in which this photochemical permutation logic was reliably used to permutate the structure of biologically active materials. This has enabled direct access to other complex and bioactive materials and tapping into unexplored areas of chemical space without extensive de novo synthesis efforts.

The indole natural product camalexin ($\mathbf{30_1}$) is found in many crucifers and has an interesting anti-prostate cancer property (Fig. 5a). This C2-arylated thiazole was selectively converted into either the corresponding C4 isomer ($\mathbf{30_2}$) or the C3-isothiazole derivative ($\mathbf{30_3}$) with moderate yields.

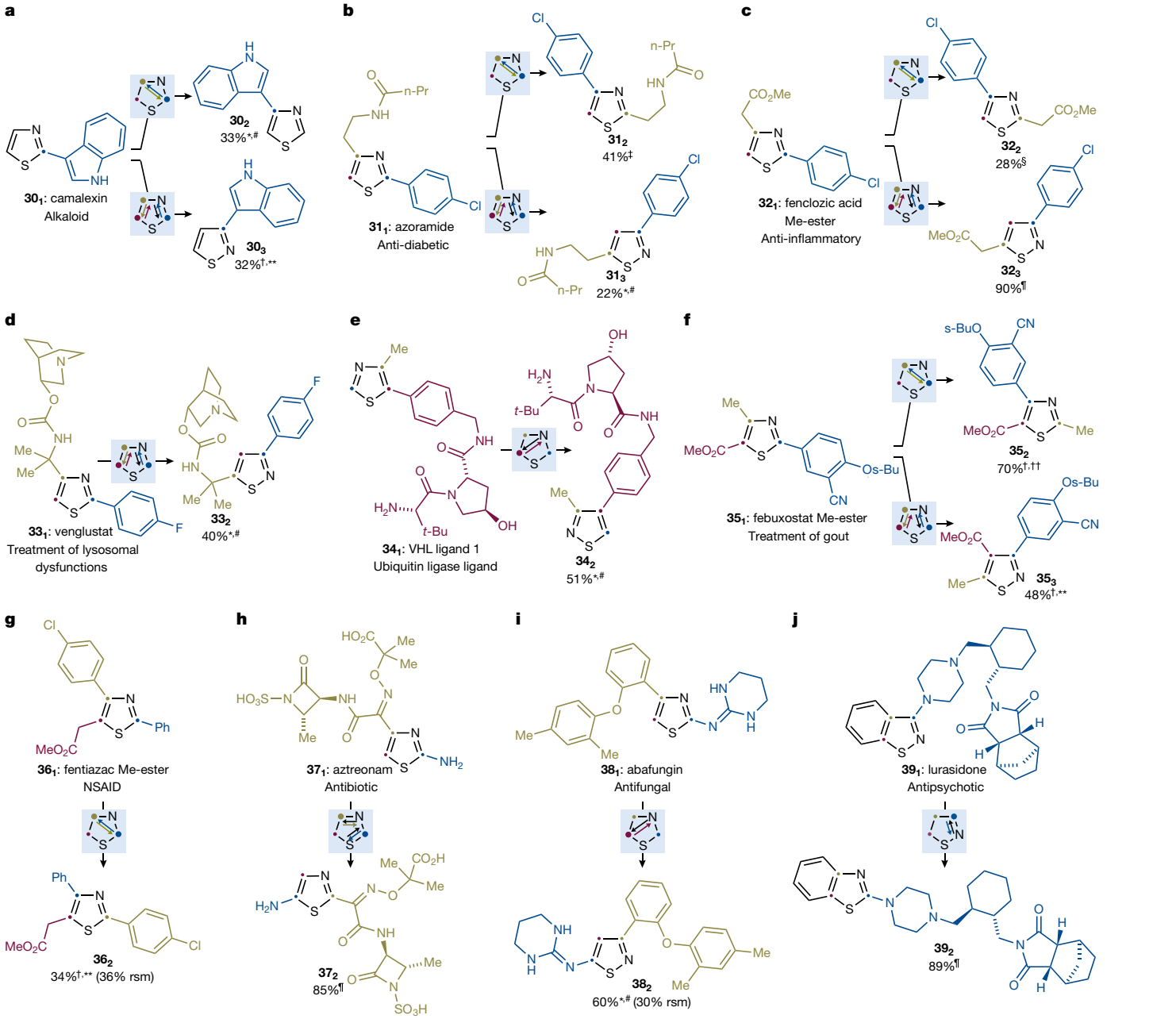

Fig. 5 | Permutation of bioactive molecules. All the reactions were irradiated (λ = 310 nm) at room temperature. Solvent: *CH_3CN; †MeOH; ‡1,4-dioxane; §DCE; ¶HFIP. Additives: #Et_3N (1.0 equiv.); **BzOH (1.0 equiv.); ††*N*,*N*-dimethylthiourea (1.0 equiv.). rsm, recovered starting material.

The anti-diabetic agent azoramide **31**$_1$ and the anti-inflammatory drug fenclozic acid **32**$_1$ feature a thiazole ring with a C2-aromatic unit and a C4-carbonyl-containing alkyl chain (Fig. 5b,c). These derivatives were selectively converted into either thiazoles **31**$_2$ and **32**$_2$ in which the aromatic and alkyl chain have been 'swapped around' or isothiazoles **31**$_3$ and **32**$_3$ in which all the heterocyclic positions have been swapped. It is interesting to note that **31**$_2$ and **32**$_2$ have been recently developed as potential antibacterial (**31**$_2$)[34] or anticancer (**32**$_2$)[35] agents, two biological profiles rather different from the one displayed by the parent drug. Furthermore, the preparation of **31**$_2$ required four steps involving condensation and multistep functionalization, something that can be obviated by this method.

Venglustat **33**$_1$ is an investigational agent currently evaluated for the treatment of lysosomal dysfunctions like Fabry's and Gaucher's diseases (Fig. 5d). In this case, we have been able to selectively permutate its structure into the C3-Ar, C5-alkyl isothiazole **33**$_2$ and demonstrate tolerance of basic tertiary amine and carbamate functionalities and, most notably, the movement of a quaternary centre. Interestingly, **33**$_2$ has been prepared as part of a drug discovery campaign towards innovative glucosylceramide synthase inhibitors and its synthesis required eight steps based on the de novo assembly of the isothiazole core and extensive functional group interconversion[36].

The von Hippel–Lindau (VHL) ligand 1 **34**$_1$ is broadly used for the preparation of proteolysis-targeting chimera (PROTAC) technologies owing to its strong ability to act as a ubiquitin ligase ligand (Fig. 5e). This species features a C4-Me- and C5-aryl-disubstituted thiazole and was converted into the corresponding C3–C4 isothiazole **34**$_2$ with a good yield. In this case, the permutation chemistry tolerated the complex peptidic backbone featuring both free alcohol and amino functionalities.

Febuxostat **35**$_1$ and fentiazac **36**$_1$ are two trisubstituted thiazoles currently used for the treatment of gout and inflammatory processes, respectively (Fig. 5f,g). **35**$_1$ matches the general C2-aryl, C4-alkyl and

C5-ester functionalization patterns that we have discussed above (for example, $\mathbf{12}_1$). Thus, irradiation in MeOH in the presence of DMT switched the position of the aryl and Me group across the thiazole core ($\mathbf{35}_2$). Conversely, the use of MeOH and not BzOH as the additive caused a full structural change to isothiazole $\mathbf{35}_3$ in which ester and Me as well as Ar and N atom have been swapped around. Although we do not yet have a mechanistic explanation regarding the role of DMT versus BzOH in controlling the permutation direction, we believe these results to be noteworthy as the further screening of solvents or additive combinations might provide additional and unexpected synthetic opportunities. Furthermore, a simplified analogue of $\mathbf{35}_3$ in which C3-Ar = Ph has been recently prepared during the development of calpain modulators required four steps with de novo isothiazole synthesis from the corresponding 2-benzylidenemalononitriline, something difficult to translate for the preparation of more complex derivatives like $\mathbf{35}_3$ (ref. 37).

Fentiazac $\mathbf{36}_1$ represents an interesting target for this methodology as it contains two different aromatic substituents that can potentially affect the permutation in opposite ways (Fig. 5g). Indeed, our previous results generally showed that although C2-Ar thiazoles can be permutated, C4-substituted derivatives are photostable. Interestingly, the irradiation of $\mathbf{36}_1$ in MeOH in the presence of BzOH provided a 1:1 mixture of $\mathbf{36}_1$ and $\mathbf{36}_2$ in which the two aromatic groups have been swapped across the thiazole core. We propose that this type of permutation reactivity might represent something analogous to a photostationary equilibrium.

Aztreonam $\mathbf{37}_1$ and abafungin $\mathbf{38}_1$ are current antibiotic and antifungal medicines and they feature substitution patterns different from the ones we have evaluated until now. In particular, the thiazole core of $\mathbf{37}_1$ does not contain any aromatic substituents but a C2-free amino group and a complex and potentially labile C4-oxime (Fig. 5h). Fortunately, on irradiation in HFIP, we have been able to selectively permutate its structure to $\mathbf{37}_2$, thereby 'moving' the oxime unit from C4 to C2 of the thiazole core. We believe these results to be remarkable as they suggest that the permutation chemistry can be expanded to other types of functionalized thiazole or isothiazole beyond arylated ones, thereby opening additional synthesis options.

The reactivity of $\mathbf{38}_1$ is also noteworthy as the C4-aryl group could potentially render it photostable in analogy to the previously discussed $\mathbf{1}_2$, $\mathbf{2}_3$ and $\mathbf{2}_4$ (Fig. 5j). However, the C2-guanidine substituent might provide sufficient electronic perturbation; indeed, we successfully developed conditions for its selective conversion into the isothiazole $\mathbf{38}_2$.

Finally, the antipsychotic drug lurasidone $\mathbf{39}_1$ showcases the application of permutation chemistry to complex benzothiazole derivatives (Fig. 5k). This species contains two basic tertiary amine functionalities as well as a diamide group, and was selectively converted into the corresponding benzothiazole $\mathbf{39}_2$ with a high yield.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41586-024-08342-8.

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Data availability

All data are available in the Article or its Supplementary Information and can also be obtained from the corresponding authors upon request.

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Author contributions D.L., A.R. and B.R. designed the project. B.R., M.A., G.L., C.S.B., T.d.S. and Y.X. performed all the synthesis experiments. D.B.Y. performed all the computational studies. B.R., M.A., G.L., D.B.Y., C.S.B., T.d.S., Y.X., M.B., V.D., M.M., J.L., A.R. and D.L. discussed the results and wrote the manuscript.

Competing interests M.B., V.D. and M.M. are employees of Sanofi and might have shares and/or stock options in the company. The other authors declare no competing interests.

Additional information

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