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# Synthesis of $\alpha\mbox{-Sulfoximino}$ Tetrazoles via Azido-Ugi Four-Component Reaction

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**Abstract** The sulfoximine-based tetrazoles have been synthesized via azido-Ugi four-component reactions of sulfoximines, isocyanides, alde-hydes, and TMS-azide in MeOH at 70 °C in the presence of InCl<sub>3</sub>. Replacement of sulfoximines with sulfonimidamides (SIA) has delivered the corresponding SIA-based tetrazole. Interestingly, SIA also acts as a surrogate amine to furnish the corresponding aminotetrazole as a by-product.

Key words sulfoximines, sulfonimidamides, Ugi reaction, tetrazoles, isocyanides

Tetrazoles are of great importance due to their distinctive chemical and biological properties.<sup>1</sup> This moiety has found applications in fields such as medicine,<sup>2</sup> biochemistry,<sup>3</sup> pharmacology,<sup>4</sup> materials,<sup>5</sup> coordination chemistry,<sup>6</sup> and organocatalysis<sup>7</sup> (Figure 1), as well as in synthetic chemistry.<sup>8</sup> Importantly, tetrazoles are well-established bioisosteres of carboxylic acids.<sup>9</sup>

Sulfoximines have recently received very good attention in synthetic, medicinal, and agrochemical areas.<sup>10</sup> Sulfoximine-containing bioactive molecules include Atuveciclib, BAY 1251152, and AZD6738.<sup>11</sup> Additionally, sulfoximines have been used as chiral auxiliaries and ligands in asymmetric synthesis, and as directing groups in *ortho*-C-H functionalization.<sup>12</sup> Considering the importance of tetrazoles, together with our recent interest in sulfoximines<sup>13</sup> and related chemistry,<sup>14</sup> we herein report that sulfoximine-



Figure 1 Representative tetrazole-bearing derivatives used in various fields

based tetrazoles, i.e.,  $\alpha$ -sulfoximino tetrazoles, have been prepared via four-component reaction of sulfoximines, iso-cyanides, aldehydes, and TMS-N<sub>3</sub>.

The classical four-component Ugi reaction utilizes carboxylic acids as one of the nucleophiles to synthesize the bis-amide.<sup>15</sup> Replacement of the carboxylic acid with an azide delivers the corresponding tetrazole in the Azido-Ugi tetrazole reaction (UT-4CR) (Scheme 1a). UT-4CRs have been widely employed to construct diverse tetrazole-based systems by altering the substituents in the substrate.<sup>16</sup> However, most of the previous reports on UT- 4CRs employ sp<sup>3</sup>-hybridized primary or secondary amines as amine component. Hence, despite being a very well-established field, the reaction behavior with sp<sup>2</sup> hybridized imine nucleophiles remains to be studied. In this context, we employed sulfoximines, which contain the sp<sup>2</sup>-hybridized imino group, as nucleophile in the UT-4CR to synthesize  $\alpha$ -sulfoximino tetrazoles (Scheme 1b).





Previously, Bolm et al. prepared *N*-(1*H*)-tetrazole sulfoximines via a  $ZnBr_{2-}$ catalyzed cycloaddition reaction (Scheme 2a).<sup>17</sup> Recently, the same research group prepared 2-sulfoximidoyl acetic acids via Petasis reaction (Scheme 2b).<sup>18</sup> Our  $\alpha$ -sulfoximino tetrazoles can be considered as tetrazole isosteres of 2-sulfoximidoyl acetic acid (Scheme 2b).



**Scheme 2** Previous routes to (a) sulfoximine derived tetrazoles, (b)  $\alpha$ -sulfoximidoyl acetic acids (this work: isosteric replacement of -COOH with tetrazole to access  $\alpha$ -sulfoximino tetrazole).

The starting NH-sulfoximines were prepared by following the reported protocol.<sup>19a</sup> We initiated the investigations with a four-component reaction of sulfoximine 1a, p-tolualdehyde (2a), t-butyl isocyanide (3a), and TMS-N<sub>3</sub> (4) under conditions that are summarized in Table 1. Initially, the reaction mixture was stirred in methanol at room temperature for 24 h, but the desired tetrazole **5a** was obtained only in 10% yield, along with unreacted sulfoximine and aldehyde (entry 1). To obtain a better outcome, the Lewis acid ZnCl<sub>2</sub> was added as mediator and a 40% yield of 5a was isolated (entry 2). Increased temperature gave a better yield of 5a (entries 3 and 4), and replacement of ZnCl<sub>2</sub> with InCl<sub>3</sub> resulted in a further improved yield at 70 °C (entry 6). Other Lewis acids such as Cu(OTf)<sub>2</sub>, CuBr, and Zn(OTf)<sub>2</sub> were not as effective as InCl<sub>3</sub> at 70 °C (entries 6–9). Other solvents, including EtOH, CH<sub>3</sub>CN, DCE, toluene, and DCM were investigated (entries 10-14), but MeOH was found to be the best solvent for the transformation. When we replaced the TMS-N<sub>3</sub> in the reaction with NaN3 we could isolate only 41% of 5a (entry 15). It should be noted that the Lewis acids were needed in 50 mol%; the use of lesser amounts (5/10/20/30/40 mol%) InCl<sub>3</sub> led to diminished product formation along with isolation of unreacted starting sulfoximine and aldehyde. A higher amount of InCl<sub>3</sub> (60%) did not give a better outcome.



Entry	Solvent	Lewis acid	Temp (°C)	Time (h)	Yield (%) <sup>♭</sup>	
1 <sup>c</sup>	MeOH	-	r.t.	24	10	
2 <sup>c</sup>	MeOH	ZnCl <sub>2</sub>	r.t.	15	40	
3	MeOH	$ZnCl_2$	45	12	46	
4	MeOH	$ZnCl_2$	70	12	50	
5	MeOH	$InCl_3$	45	12	55	
6	MeOH	$InCl_3$	70	12	61	
7	MeOH	Cu(OTf) <sub>2</sub>	70	12	20	
8	MeOH	CuBr	70	12	NR	
9	MeOH	$Zn(OTf)_2$	70	12	54	
10	EtOH	$InCl_3$	70	12	36	
11	CH₃CN	$InCl_3$	70	12	21	
12	DCE	$InCl_3$	70	12	NR	
13	Toluene	$InCl_3$	70	12	12	
14	DCM	$InCl_3$	70	12	26	
15 <sup>d</sup>	MeOH	$InCl_3$	45	12	41	

<sup>a</sup> General conditions for the one-pot four-component reaction: 1a (1.2

equiv), **2a** (1.2 equiv), **3a** (1.0 equiv), **4** (1.0 equiv), Lewis acid (0.5 equiv) in 1 mL solvent unless otherwise stated.

<sup>b</sup> Isolated yield.

<sup>c</sup> 1:1:1:1 ratio of all substrates.

<sup>d</sup> NaN<sub>3</sub> was used instead of TMSN<sub>3</sub>.

With the optimal reaction condition in hand, next we explored the scope and limitations of the method for the synthesis of sulfoximine based tetrazoles **5**. Differently substituted sulfoximines, aldehydes, and isocyanides were utilized, and the results are shown in Scheme 3. Various aromatic aldehydes with electron-poor and electron-rich substitution patterns underwent successful reaction. It was noted that electron-deficient aryl aldehydes provided better outcomes than their electron-rich counterparts. Bulky triphenylamine aldehyde and heteroaromatic benzothiophene aldehyde also delivered **5n-p** in good yields. Several cyclic and acyclic isocyanides such as cyclohexyl, adamantyl, and *t*-butyl isocyanide furnished the desire products in moderate to good yields. Unfortunately, the primary alkyl isocyanide (*p*-toluenesulfonylmethyl isocyanide) and aro-

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Scheme 3 Substrate scope for preparing sulfoximine-based tetrazoles

matic isocyanide (4-methoxyphenyl isocyanide) both failed to produce the desired products **5s** and **5t**. The modifications of the *S*-aryl group (phenyl to substituted phenyl) and *S*-alkyl group (methyl to ethyl) of the *N*H-sulfoximines were well tolerated in the conversion.

In addition to S-aryl S-alkyl sulfoximines, diaryl/dialkyl symmetrical sulfoximines underwent reaction smoothly to produce the corresponding products **5q**–**r**. The electronic effects induced by S-aryl substituents appeared to have only a minor influence on product formation.

All the synthesized compounds were characterized by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy, and HRMS, and structures were unambiguously confirmed by single-crystal XRD analysis of two representative compounds (**5c** and **5e**; see the Supporting Information).

The successful utilization of *N*H-sulfoximines as nucleophiles in the UT-4CR, inspired us to apply sulfonimidamide (SIA) (**6**) (Scheme 4) to construct SIA derived tetrazoles via UT-4CR. SIAs, the mono-aza analogues of sulfonamides, with a stereogenic tetrahedral sulfur atom and sp<sup>2</sup> hybrid-



ized imino group (free -*N*H), are considered an important emerging scaffold due to their applications in asymmetric synthesis and the medicinal and agrochemical industries.<sup>20</sup>

Initially, SIA (**6a**) was treated with aldehyde **2a**, isocyanide **3a**, and TMS-N<sub>3</sub> (**4**) under the previously optimized reaction conditions (Table 1, entry 6), but the desired product **7a** was formed in only minor amounts, accompanied by the side-product, cyclic amine-based tetrazole **8a** as the major product. SIA **6** would appear to be acting as surrogate amine to yield **8**. A previous report from our group had already described the surrogate nature of SIA under specific conditions.<sup>14a</sup> Considering that the elevated reaction temperatures may result in S–N bond cleavage, the reaction was performed at lower temperature (Table 2, entry 3) and **7a** was obtained as the major product (52%) at 45 °C, along with 18% of by-product **8a**. Screening of other Lewis acids, such as ZnCl<sub>2</sub> and Zn(OTf)<sub>2</sub> showed that they were not as effective as InCl<sub>3</sub> (entries 4 and 5).

**Table 2** Optimization of the Synthesis of Sulfonimidamide DerivedTetrazoles<sup>a</sup>

Entry	Conditions					Yield (%) <sup>b</sup>	
	Solvent	Lewis acid	Temp (°C)	Time (h)	7a	8a	
1	MeOH	$InCl_3$	70	10	18	65	
2	MeOH	$InCl_3$	r.t	10	0	20	
3	MeOH	$InCl_3$	45	10	52	18	
4	MeOH	ZnCl <sub>2</sub>	45	10	30	40	
5	MeOH	ZnCl <sub>2</sub>	45	10	34	38	

<sup>a</sup> Conditions for the one-pot four-component reaction: **6a** (1.2 equiv), **2a** (1.2 equiv), **3a** (1.0 equiv), **4** (1.0 equiv), Lewis acid (0.5 equiv), in 1 mL solvent.

<sup>b</sup> Isolated yield.

Hence, by following the optimized condition (Table 2, entry 3), we scrutinized the scope and generality of the reaction with SIA (Scheme 5). Reaction of SIAs with various *S*aryl (-Ph, 4-MePh, 4-OMePh) and *S*-cyclic amines (pyrrolidine and piperidine) worked equally well to deliver the corresponding product **7**. Diverse substituted aromatic aldehydes, with electron-withdrawing and -donating substituents were employed successfully. The bulky triphenylamine benzaldehyde readily took part in the reaction to furnish **7e**. Different secondary and tertiary isocyanides were also well tolerated to deliver the desired products in moderate yield. However, our attempts to use a primary alkyl isocyanide (*p*-toluenesulfonyl methyl isocyanide) and an aromatic isocyanide (4-methoxyphenyl isocyanide) were unsuccessful (**7i**–**j**).

A probable mechanistic approach based on previous literature reports<sup>21</sup> and the current findings is portrayed in Scheme 6. In the presence of InCl<sub>3</sub>, sulfoximine 1 reacts with aldehyde 2 to generate 5Ia, which, on reaction with the isocyanide, yields intermediate nitrilium cation 5Ib. Subsequent cycloaddition of 5Ib with azide delivers the expected product 5 via 51c. SIA 6 follows a similar route to furnish the corresponding tetrazole 7. However, the surrogate nature of the SIA, which leads to 8, can be explained as in Scheme 7. In the presence of InCl<sub>3</sub>, the sp<sup>3</sup> amine of SIA attacks the aldehyde to generate intermediate 81a, which undergoes intramolecular rearrangement (transacylation) and C-O bond cleavage of 8Ib to produced iminium intermediate **8Ic** via elimination. Successive reaction of isocyanide with **8Ic** and further [3+2] cycloaddition of **8Id** with azide leads to the formation of 8.

In conclusion, we have demonstrated the azido-Ugi four-component reaction for the synthesis of  $\alpha$ -sulfoximino tetrazoles. A wide range of sulfoximines, aldehydes, and isocyanides have been assembled with TMS-azide in the presence of InCl<sub>3</sub> to form two new C–N bonds, one C–C bond, and one N–N bond in a single process. Use of SIAs instead of sulfoximines has delivered the corresponding SIA based tetrazoles. These compounds can be considered as sulfoximine/SIA-derived tetrazole isosteres of  $\alpha$ -amino acids. Notably, SIAs can also act as surrogate amines to produce the corresponding aminotetrazoles as by-products.



Scheme 5 Substrate scope for sulfonimidamide based tetrazoles







Scheme 7 Proposed mechanism for the formation of cyclic aminebased tetrazole 8

The starting sulfoximines/sulfonimidamides were synthesized by following reported methods.<sup>19</sup> The aldehydes, isocyanides, TMSN<sub>3</sub>, InCl<sub>3</sub>, and MeOH were purchased from various suppliers and used as received. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded with a Bruker spectrometer operating at 500 and 125 MHz, respectively, in CDCl<sub>3</sub> or CD<sub>6</sub>CO as solvents. Mass spectra were recorded with an Agilent QTOF G6545 XT spectrometer at 50,000 resolutions using ESI mode. Melting points are uncorrected.

#### Sulfoximine Synthesis; General Procedure

To a stirred solution of diaryl (or alkylaryl) sulfide (1 mmol) in MeOH (5 mL),  $NH_4CO_2NH_2$  (1.5 equiv) and  $Phl(OAc)_2$  (2.3 equiv) were added, and the solution was stirred at r.t. for 3–4 h. After the disappearance of the sulfide (checked by TLC), the solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (25–40% EtOAc/hexane).

For the gram-scale reaction, sulfide (20 mmol) and MeOH (100 mL) were used.



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# One-Pot Tandem Synthesis of Tetrazole Based Sulfoximine/Sulfonimidamide (5/7); General Procedure

**Precautions:** We have not experienced any problems with the use of TMSN<sub>3</sub> under the reaction conditions employed and working on small scale. However, essential precautions should be taken on scaling up this chemistry.

A solution of sulfoximine (30 mg 1.2 equiv), aldehyde (1.2 equiv), isocyanide (1.0 equiv), and  $InCl_3$  (0.5 equiv) in MeOH (1 mL) in a 20 mL sealed tube was stirred at 70 °C under argon atmosphere. After 15 min, TMS-azide (1.0 equiv) was added to the reaction mixture and the reaction was stirred for the stipulated period. Upon completion of reaction (confirmed by TLC), the reaction mixture was poured in water and extracted with EtOAc (2 × 10 mL). The organic layers were washed with sat. aq. NaHCO<sub>3</sub>, water, brine and dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>. After filtration, the solvent was evaporated under reduced pressure, and the resulting crude product was purified by silica gel column chromatography with 20–30% of EtOAc in hexane as the eluent.

For sulfonimidamides, the reaction was stirred at 45 °C.

All the synthesized compounds (except **5q/5r**) have more than one (generally two) stereogenic centers. Hence, mixtures of diastereomers could be expected to form. However, we isolated only single diastereomer for **5a–m**, **5p**, **5q**, and **7**. Another diastereomer was formed in trace amounts for **5a–m**, **5p**, **5q**, and **7**. For compounds **5n–o**, two diastereomers were isolated in almost equal amounts.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(*p*-tolyl)methyl) *S*-Methyl *S*-4-Bromophenyl Sulfoximine (5a)

Colorless viscous liquid; 61% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.25 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.63 (d, *J* = 8.5 Hz, 2 H), 7.57 (d, *J* = 8.5 Hz, 2 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 7.10 (d, *J* = 8.0 Hz, 2 H), 6.01 (s, 1 H), 3.08 (s, 3 H), 2.29 (s, 3 H), 1.41 (s, 9 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 156.2, 139.9, 138.9, 137.7, 137.4, 132.7, 130.2, 129.4, 127.5, 61.7, 52.3, 45.6, 29.9, 21.1.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>25</sub>BrN<sub>5</sub>OS: 462.0958; found: 462.0960.

# *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(phenyl)methyl) *S*-Methyl *S*-*p*-Tolyl Sulfoximine (5b)

Yellowish viscous liquid; 60% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.26 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.65 (d, *J* = 7.0 Hz, 1 H), 7.57 (d, *J* = 8.5 Hz, 2 H), 7.32 (d, *J* = 7.5 Hz, 1 H), 7.27–7.24 (m, 2 H), 7.19 (d, *J* = 8.0 Hz, 2 H), 7.05 (t, *J* = 8.0 Hz, 1 H), 6.01 (s, 1 H), 3.06 (s, 3 H), 2.34 (s, 3 H), 1.36 (s, 9 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 156.3, 144.5, 140.8, 137.5, 136.5, 130.1, 128.7, 127.5, 123.6, 61.7, 52.6, 45.6, 29.9, 21.6.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>26</sub>N<sub>5</sub>OS: 384.1853; found: 384.1857.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl) *S*-Methyl *S*-4-Bromophenyl Sulfoximine (5c)

White solid; mp 114–116 °C; 65% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.35 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.58 (br s, 4 H), 7.28–7.27 (m, 4 H), 6.00 (s, 1 H), 3.12 (s, 3 H), 1.42 (s, 9 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.8, 139.9, 139.1, 138.5, 133.8, 132.8, 130.1, 128.9, 128.9, 61.9, 52.0, 45.6, 29.8.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>22</sub>BrClN<sub>5</sub>OS: 482.0411; found: 482.0418.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(*p*-tolyl)methyl) *S*-Methyl *S*-4-Chlorophenyl Sulfoximine (5d)

Yellowish viscous liquid; 57% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.21 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz,  $CDCl_3$ ):  $\delta$  = 7.71 (d, J = 8.5 Hz, 2 H), 7.41 (d, J = 8.5 Hz, 2 H), 7.24 (d, J = 8.0 Hz, 2 H), 7.11 (d, J = 8.0 Hz, 2 H), 6.01 (s, 1 H), 3.08 (s, 3 H), 2.29 (s, 3 H), 1.41 (s, 9 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 156.3, 139.9, 138.4, 137.7, 137.5, 130.1, 129.7, 129.5, 127.5, 61.7, 52.4, 45.7, 29.9, 21.1.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>25</sub>ClN<sub>5</sub>OS: 418.1463; found: 418.1472.

#### *N*-((1-Cyclohexyl-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl) *S*-Methyl *S*-4-Bromophenyl Sulfoximine (5e)

White solid; mp 117–118 °C; 68% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.45 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz,  $CDCI_3$ ):  $\delta$  = 7.67 (d, J = 8.5 Hz, 2 H), 7.57 (d, J = 8.5 Hz, 2 H), 7.38 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.5 Hz, 2 H), 5.91 (s, 1 H), 4.51–4.46 (m, 1 H), 3.18 (s, 3 H), 2.25–2.24 (m, 2 H), 1.96–1.93 (m, 2 H), 1.81–1.76 (m, 2 H), 1.49–1.46 (m, 2 H), 1.32–1.30 (m, 2 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl\_3):  $\delta$  = 155.2, 140.6, 138.1, 137.2, 133.9, 133.1, 130.1, 128.8, 128.0, 58.3, 51.5, 45.5, 33.2, 25.5, 24.9.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>24</sub>BrClN<sub>5</sub>OS: 508.0568; found: 508.0571.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl) *S*-Ethyl *S*-Phenyl Sulfoximine (5f)

White solid; mp 120–122 °C; 62% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.25 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz,  $CDCl_3$ ):  $\delta$  = 7.67 (dd, *J* = 8.0, 1.0 Hz, 2 H), 7.56 (t, *J* = 7.5 Hz, 1 H), 7.44 (t, *J* = 8.0 Hz, 2 H), 7.29–7.26 (m, 4 H), 6.06 (s, 1 H), 3.34–3.19 (m, 2 H), 1.41 (s, 9 H), 1.26 (t, *J* = 8.0 Hz, 3 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl\_3):  $\delta$  = 156.1, 139.9, 139.7, 137.7, 133.5, 129.5, 129.4, 128.9, 128.7, 61.8, 51.8, 51.4, 30.0, 7.1.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>25</sub>ClN<sub>5</sub>OS: 418.1463; found: 418.1473.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl) *S*-Ethyl *S*-4-Methoxyphenyl Sulfoximine (5g)

White solid; mp 129–130 °C; 67% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.21 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.56 (d, J = 9.0 Hz, 2 H), 7.31–7.25 (m, 4 H), 6.90 (d, J = 9.0 Hz, 2 H), 6.09 (s, 1 H), 3.84 (s, 3 H), 3.29–3.17 (m, 2 H), 1.45 (s, 9 H), 1.25 (t, J = 7.5 Hz, 3 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 163.6, 156.1, 139.8, 133.3, 131.4, 128.7, 128.5, 128.3, 114.6, 61.8, 55.6, 51.7, 51.6, 29.9, 7.1.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>21</sub>H<sub>27</sub>ClN<sub>5</sub>O<sub>2</sub>S: 448.1568; found: 448.1578.

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#### *N*-((1-Adamantyl-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl) *S*-Ethyl *S*-Phenyl Sulfoximine (5h)

White solid; mp 132–134 °C; 66% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.25 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz,  $CDCl_3$ ):  $\delta$  = 7.66 (d, *J* = 8.5 Hz, 2 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 7.44 (t, *J* = 7.5 Hz, 2 H), 7.31–7.26 (m, 4 H), 6.08 (s, 1 H), 3.33–3.21 (m, 2 H), 2.07–2.01 (m, 6 H), 1.94–1.92 (m, 3 H), 1.67–1.64 (m, 3 H), 1.60–1.57 (m, 3 H), 1.27 (t, *J* = 7.5 Hz, 3 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 156.1, 140.0, 137.9, 133.5, 133.4, 129.4, 129.3, 128.9, 128.7, 62.9, 51.9, 51.4, 42.1, 35.6, 29.6, 7.1.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>26</sub>H<sub>31</sub>ClN<sub>5</sub>OS: 496.1932; found: 496.1935.

#### *N*-((1-Adamantyl-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl) *S*-Methyl *S*-4-Methoxyphenyl Sulfoximine (5i)

White solid; mp 179–181 °C; 70% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.24 (30% EtOAc in hexane).

 $^1\text{H}$  NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.63 (d, J = 9.0 Hz, 2 H), 7.29 (q, J = 8.5 Hz, 4 H), 6.91 (d, J = 9.0 Hz, 2 H), 6.04 (s, 1 H), 3.84 (s, 3 H), 3.14 (s, 3 H), 2.08–2.04 (m, 6 H), 1.98–1.96 (m, 3 H), 1.68–1.65 (m, 3 H), 1.61–1.59 (m, 3 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 163.7, 156.1, 139.8, 133.5, 130.8, 130.5, 128.9, 128.7, 114.7, 63.0, 55.8, 52.2, 46.0, 42.0, 35.6, 29.6.

HRMS (ESI-TOF):  $m/z \ [M + H]^+$  calcd for  $C_{26}H_{30}ClN_5NaO_2S$ : 534.1701; found: 534.1711.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(2-bromophenyl)methyl) *S*-Methyl *S*-4-Bromophenyl Sulfoximine (5j)

White solid; mp 125–127 °C; 57% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.25 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.75 (dd, *J* = 8.0, 1.5 Hz, 1 H), 7.69 (d, *J* = 8.5 Hz, 2 H), 7.53 (d, *J* = 8.5 Hz, 2 H), 7.50 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.27 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.10 (td, *J* = 7.5, 1.5 Hz, 1 H), 6.39 (s, 1 H), 2.94 (s, 3 H), 1.46 (s, 9 H).

 $^{13}\text{C}$  NMR (126 MHz, CDCl\_3):  $\delta$  = 155.6, 139.2, 133.3, 132.5, 131.1, 129.9, 129.8, 128.6, 128.2, 125.2, 123.2, 61.7, 51.6, 46.0, 29.8.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>22</sub>Br<sub>2</sub>N<sub>5</sub>OS: 525.9901; found: 525.9912.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(3-bromophenyl)methyl) *S*-Methyl *S*-4-Bromophenyl Sulfoximine (5k)

Colorless viscous liquid; 62% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.25 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.67 (d, *J* = 2.0 Hz, 1 H), 7.53 (brs, 4 H), 7.34–7.32 (m, 1 H), 7.17–7.16 (m, 1 H), 7.11 (t, *J* = 8.0 Hz, 1 H), 5.96 (s, 1 H), 3.07 (s, 3 H), 1.38 (s, 9 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.6, 142.8, 139.9, 138.5, 132.8, 131.1, 130.6, 130.2, 130.1, 126.1, 122.9, 62.0, 52.0, 45.7, 29.9.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>19</sub>H<sub>22</sub>Br<sub>2</sub>N<sub>5</sub>OS: 525.9906; found: 525.9889.

#### *N*-((1-Cyclohexyl-1H-tetrazol-5-yl)(3-bromophenyl)methyl) *S*-Ethyl *S*-4-Methoxyphenyl Sulfoximine (51)

Colorless viscous liquid; 68% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.21 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.65 (s, 1 H), 7.47 (d, *J* = 9.0 Hz, 2 H), 7.30 (dt, *J* = 7.5, 1.5, 0.5 Hz, 1 H), 7.23 (dt, *J* = 7.5, 1.5, 0.5 Hz, 1 H), 7.09 (t, *J* = 8.0 Hz, 1 H), 6.91 (d, *J* = 9.0 Hz, 2 H), 5.91 (s, 1 H), 4.49–4.46 (m, 1 H), 3.80 (s, 3 H), 3.22–3.16 (m, 2 H), 2.21–2.18 (m, 1 H), 2.01–1.98 (m, 1 H), 1.94–1.92 (m, 1 H), 1.87–1.84 (m, 1 H), 1.78–1.71 (m, 1 H), 1.55–1.53 (m, 1 H), 1.31–1.26 (m, 1 H), 1.23 (t, *J* = 7.5 Hz, 3 H), 1.18–1.14 (m, 1 H), 1.01–0.98 (d, *J* = 13.1 Hz, 1 H), 0.90–0.88 (d, *J* = 12.4 Hz, 1 H).

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 $^{13}\text{C}$  NMR (125 MHz, CDCl\_3):  $\delta$  = 163.9, 155.4, 142.5, 140.5, 131.4, 130.7, 129.9, 126.8, 125.3, 122.7, 114.9, 58.8, 58.1, 55.7, 51.2, 33.1, 25.5, 24.8, 7.5.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>29</sub>BrN<sub>5</sub>O<sub>2</sub>S: 518.1220; found: 518.1229.

#### *N*-((1-Cyclohexyl-1*H*-tetrazol-5-yl)(4-bromophenyl)methyl) *S*-Ethyl *S*-2-Thiophenyl Sulfoximine (5m)

Brownish viscous liquid; 67% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.30 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz,  $CDCI_3$ ):  $\delta$  = 7.69 (d, J = 6.5 Hz, 1 H), 7.42 (d, J = 8.5 Hz, 2 H), 7.32 (d, J = 3.5 Hz, 1 H), 7.29 (d, J = 8.5 Hz, 2 H), 7.12–7.10 (m, 1 H), 6.11 (s, 1 H), 4.50–4.47 (m, 1 H), 3.38–3.36 (m, 2 H), 2.26–2.23 (m, 2 H), 1.95–1.92 (m, 3 H), 1.81–1.76 (m, 2 H), 1.73–1.71 (m, 1 H), 1.48–1.45 (m, 2 H), 1.37 (t, J = 7.0 Hz, 3 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.2, 140.7, 138.9, 137.5, 135.3, 131.6, 128.5, 128.3, 121.8, 58.9, 53.3, 51.1, 33.2, 25.5, 24.9, 7.9.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>20</sub>H<sub>25</sub>BrN<sub>5</sub>OS<sub>2</sub>: 494.0678; found: 494.0671.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(*N*,*N*-diphenylaniline)methyl) *S*-methyl *S*-4-Methoxyphenyl Sulfoximine (5n)

Obtained as a diastereomeric mixture. Total yield 72%.

Diastereomer 1

White solid; mp 170–172 °C. TLC (SiO<sub>2</sub>):  $R_f$  0.24 (40% EtOAc in hexane).

IR (KBr): 3059, 3038, 2937, 2835, 1735, 1587, 1508, 1487, 1405, 1375, 1317, 1259, 1215, 1154, 1078, 1025, 981, 800, 697  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (500 MHz,  $CDCl_3$ ):  $\delta$  = 7.66 (d, *J* = 9.0 Hz, 2 H), 7.22 (t, *J* = 8.0 Hz, 6 H), 7.04 (dd, *J* = 7.5 Hz, 4 H), 7.00–6.98 (m, 4 H), 6.89 (d, *J* = 9.0 Hz, 2 H), 6.02 (s, 1 H), 3.83 (s, 3 H), 3.12 (s, 3 H), 1.46 (s, 9 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl\_3):  $\delta$  = 163.5, 156.5, 147.6, 147.1, 134.6, 130.8, 130.7, 129.2, 128.4, 124.3, 123.5, 122.9, 114.5, 61.6, 55.7, 51.9, 45.9, 29.9.

HRMS (ESI-TOF):  $m/z \ [M + Na]^+$  calcd for  $C_{32}H_{34}N_6NaO_2S$ : 589.2356; found: 589.2356.

Diastereomer 2

White solid; mp 172–173 °C.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.71 (d, *J* = 9.0 Hz, 2 H), 7.23–7.17 (m, 6 H), 7.01–6.99 (m, 2 H), 6.97–6.95 (m, 4 H), 6.92 (d, *J* = 9.0 Hz, 2 H), 6.83 (d, *J* = 8.5 Hz, 2 H), 6.02 (s, 1 H), 3.87 (s, 3 H), 3.10 (s, 3 H), 1.68 (s, 9 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 163.1, 157.0, 147.5, 147.1, 133.2, 130.3, 129.2, 128.9, 125.4, 124.3, 123.1, 122.9, 114.3, 61.5, 55.6, 52.5, 46.3, 30.1.

HRMS (ESI-TOF):  $m/z [M + Na]^+$  calcd for  $C_{32}H_{34}N_6NaO_2S$ : 589.2356; found: 589.2357.

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#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(*N*,*N*-diphenylaniline)methyl)*S*-Methyl *S*-Phenyl Sulfoximine (50)

Obtained as a diastereomeric mixture. Total yield 70%.

Diastereomer 1

White solid; mp 169–170 °C. TLC (SiO<sub>2</sub>):  $R_f$  0.26 (40% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.76 (d, *J* = 7.5 Hz, 2 H), 7.54 (t, *J* = 7.5 Hz, 1 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.24–7.20 (m, 6 H), 7.04 (d, *J* = 7.5 Hz, 4 H), 7.00–6.97 (m, 4 H), 6.01 (s, 1 H), 3.14 (s, 3 H), 1.43 (s, 9 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 156.4, 147.7, 147.3, 139.9, 134.5, 133.4, 129.5, 129.3, 128.6, 128.5, 124.5, 123.6, 123.0, 61.6, 52.0, 45.6, 30.0.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>31</sub>H<sub>32</sub>N<sub>6</sub>NaOS: 559.2251; found: 559.2257.

#### Diastereomer 2

White solid; mp 167–168 °C.

<sup>1</sup>H NMR (500 MHz,  $CDCl_3$ ):  $\delta$  = 7.79 (d, J = 7.5 Hz, 2 H), 7.57 (t, J = 7.5 Hz, 1 H), 7.45 (t, J = 8.0 Hz, 2 H), 7.23–7.19 (m, 4 H), 7.17 (d, J = 8.5 Hz, 2 H), 7.00 (t, J = 7.5 Hz, 2 H), 6.95 (d, J = 7.5 Hz, 4 H), 6.80 (d, J = 8.5 Hz, 2 H), 6.04 (s, 1 H), 3.13 (s, 3 H), 1.68 (s, 9 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 157.0, 147.6, 140.2, 132.9, 129.7, 129.3, 129.2, 129.1, 128.3, 127.2, 124.4, 123.3, 123.0, 61.7, 52.7, 46.1, 30.3.

HRMS (ESI-TOF): m/z [M + Na]<sup>+</sup> calcd for C<sub>31</sub>H<sub>32</sub>N<sub>6</sub>NaOS: 559.2251; found: 559.2259.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(benzo[*b*]thiophen-3-yl)methyl) *S*-Ethyl *S*-4-Methoxyphenyl Sulfoximine (5p)

Brown viscous liquid; 58% yield. TLC (SiO<sub>2</sub>):  $R_f 0.18$  (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 8.18 (d, *J* = 8.0 Hz, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 9.0 Hz, 2 H), 7.43–7.34 (m, 2 H), 7.20 (s, 1 H), 6.87 (d, *J* = 9.0 Hz, 2 H), 6.46 (s, 1 H), 3.83 (s, 3 H), 3.29–3.22 (m, 1 H), 3.18–3.13 (m, 1 H), 1.34 (s, 9 H), 1.20 (t, *J* = 7.5 Hz, 3 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 163.4, 156.1, 140.9, 137.2, 134.9, 131.4, 129.0, 125.7, 124.5, 124.3, 122.7, 122.3, 114.3, 61.2, 55.6, 51.7, 46.4, 29.6, 6.8.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>28</sub>N<sub>5</sub>O<sub>2</sub>S<sub>2</sub>: 470.1679; found: 470.1689.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(4-bromophenyl)methyl) *S*-Diisopropyl Sulfoximine (5q)

Off-white solid; mp 87–88 °C; 44% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.20 (30% EtOAc in hexane).

IR (KBr): 3343, 2997, 2981, 2879, 2136, 1907, 1673, 1586, 1511, 1484, 1460, 1393, 1314, 1297, 1261, 1251, 1147, 1127, 1042, 1009, 950, 829, 783, 665 cm<sup>-1</sup>.

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.42 (d, *J* = 8.5 Hz, 2 H), 7.26 (d, *J* = 8.5 Hz, 2 H), 6.32 (s, 1 H), 3.35–3.31 (m, 2 H), 1.62 (s, 9 H), 1.30 (d, 7.0 Hz, 3 H), 1.28 (d, *J* = 6.5 Hz, 3 H), 1.21 (d, 7.0 Hz, 3 H), 1.18 (d, 7.0 Hz, 3 H), 1.21 (d, 7.0 Hz, 3 H), 1.18 (d, 7.0 Hz, 3 H), 1.21 (d, 7.

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 156.9, 141.3, 131.5, 129.1, 121.4, 61.9, 52.7, 51.8, 51.0, 30.1, 16.1, 15.7, 15.5, 15.4.

HRMS (ESI-TOF): *m*/*z* [M + Na]<sup>+</sup> calcd for C<sub>18</sub>H<sub>28</sub>BrN<sub>5</sub>NaOS: 442.1271; found: 442.1273.

#### *N*-((1-Cyclohexyl-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl) Di-*S*-4-methoxyphenyl Sulfoximine (5r)

Yellowish viscous liquid; 47% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.28 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz,  $CDCl_3$ ):  $\delta$  = 7.87 (d, J = 9.0 Hz, 2 H), 7.62 (d, J = 9.0 Hz, 2 H), 7.53 (d, J = 9.0 Hz, 2 H), 7.38 (d, J = 8.5 Hz, 2 H), 6.95 (d, J = 6.5 Hz, 2 H), 6.85 (d, J = 9.0 Hz, 2 H), 4.60 (s, 1 H), 4.30-4.27 (m, 1 H), 3.83 (s, 3 H), 3.81 (s, 3 H), 1.98-1.95 (m, 2 H), 1.83-1.79 (m, 1 H), 1.60-1.56 (m, 3 H), 1.34-1.31 (m, 2 H), 1.19 (br s, 2 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 171.5, 163.3, 163.2, 133.0, 132.2, 130.6, 130.4, 128.7, 128.4, 127.0, 114.9, 114.7, 114.6, 61.8, 58.9, 55.8, 48.0, 33.1, 25.7, 24.8.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>28</sub>H<sub>31</sub>ClN<sub>5</sub>O<sub>3</sub>S: 552.1831; found: 552.1840.

# *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(*p*-tolyl)methyl) *S*-Pyrrolidyl *S*-Phenyl Sulfonimidamide (7a)

Yellowish solid; mp 110–112 °C; 52% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.45 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.97 (d, J = 7.5 Hz, 2 H), 7.57–7.54 (m, 1 H), 7.51–7.48 (m, 2 H), 7.45 (d, J = 7.5 Hz, 2 H), 7.14 (d, J = 7.5 Hz, 2 H), 6.53 (s, 1 H), 3.09–3.07 (m, 2 H), 2.96–2.94 (m, 2 H), 2.33 (s, 3 H), 1.72 (brs, 4 H), 1.59 (s, 9 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 157.1, 137.9, 137.2, 136.7, 132.4, 129.1, 128.9, 127.8, 127.4, 61.9, 51.1, 48.4, 30.2, 25.2, 21.2.

HRMS (ESI-TOF):  $m/z \,[M + H]^+$  calcd for  $C_{23}H_{31}N_6OS$ : 439.2275; found: 439.2281.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl) *S*-Pyrrolidyl *S*-Phenyl Sulfonimidamide (7b)

Off-white solid; mp 107–108 °C; 56% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.45 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.94 (d, J = 8.0 Hz, 2 H), 7.54–7.51 (m, 5 H), 7.31 (d, J = 8.0 Hz, 2 H), 6.52 (s, 1 H), 3.09–3.08 (m, 2 H), 2.95–2.93 (m, 2 H), 1.72 (brs, 4 H), 1.59 (s, 9 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 156.6, 139.5, 136.5, 133.5, 132.6, 129.1, 128.9, 128.7, 127.8, 62.2, 50.9, 48.5, 30.2, 25.2.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>22</sub>H<sub>28</sub>ClN<sub>6</sub>OS: 459.1728; found: 459.1733.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(4-bromophenyl)methyl) *S*-Pyrrolidyl *S*-*p*-Tolyl Sulfonimidamide (7c)

White solid; mp 89–91 °C; 59% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.44 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz,  $CDCI_3$ ):  $\delta$  = 7.80 (d, J = 8.0 Hz, 2 H), 7.45 (brs, 4 H), 7.29 (d, J = 8.0 Hz, 2 H), 6.48 (s, 1 H), 3.08–3.06 (m, 2 H), 2.93–2.91 (m, 2 H), 2.41 (s, 3 H), 1.71 (brs, 4 H), 1.58 (s, 9 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 156.6, 143.4, 140.2, 133.5, 131.5, 129.6, 129.2, 127.8, 121.5, 62.2, 51.0, 48.4, 30.2, 25.2, 21.5.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>23</sub>H<sub>30</sub>BrN<sub>6</sub>OS: 517.1380; found: 517.1385.

#### *N*-((1-Adamantyl-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl) *S*-Pyrrolidyl *S*-4-Methoxyphenyl Sulfonimidamide (7d)

White solid; mp 83–95 °C; 61% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.42 (30% EtOAc in hexane).

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IR (KBr): 3357, 3259, 3085, 2960, 2839, 2581, 2037, 1898, 1727, 1590, 1494, 1390, 1325, 1261, 1154, 1098, 1059, 1017, 892, 833, 753, 677  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (500 MHz,  $CDCI_3$ ):  $\delta$  = 7.87 (d, J = 9.0 Hz, 2 H), 7.50 (d, J = 8.0 Hz, 2 H), 7.31 (d, J = 8.5 Hz, 2 H), 6.97 (d, J = 9.0 Hz, 2 H), 6.50 (s, 1 H), 3.86 (s, 3 H), 3.09–3.07 (m, 2 H), 2.96–2.94 (m, 2 H), 2.31–2.28 (m, 3 H), 2.21–2.19 (m, 4 H), 2.11 (br s, 4 H), 1.64–1.61 (m, 8 H).

<sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 162.8, 156.6, 139.8, 133.2, 129.9, 128.8, 128.4, 128.3, 114.0, 63.0, 55.5, 51.2, 48.3, 41.9, 35.6, 29.6, 25.1.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>29</sub>H<sub>36</sub>ClN<sub>6</sub>O<sub>2</sub>S: 567.2303; found: 567.2307.

#### *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(*N*,*N*-diphenylaniline)methyl)*S*-Pyrrolidyl *S*-*p*-Tolyl Sulfonimidamide (7e)

Yellow solid; mp 189–191 °C; 58% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.45 (30% EtOAc in hexane).

IR (KBr): 3033, 2972, 2849, 1588, 1504, 1485, 1402, 1317, 1272, 1254, 1194, 1006, 789, 754, 699  $\rm cm^{-1}.$ 

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 7.82 (d, *J* = 8.0 Hz, 2 H), 7.45 (d, *J* = 8.5 Hz, 2 H), 7.27 (d, *J* = 8.0 Hz, 2 H), 7.24–7.21 (m, 4 H), 7.05–7.04 (m, 5 H), 7.02–6.98 (m, 3 H), 6.48 (s, 1 H), 3.10–3.06 (m, 2 H), 2.98–2.93 (m, 2 H), 2.41 (s, 3 H), 1.65 (s, 9 H), 1.63–1.61 (m, 4 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 157.1, 147.8, 147.2, 143.1, 135.0, 133.8, 129.5, 129.3, 128.6, 127.9, 124.4, 123.6, 123.0, 61.9, 51.1, 48.4, 30.3, 25.2, 21.5.

HRMS (ESI-TOF): m/z [M + Na]<sup>+</sup> calcd for C<sub>35</sub>H<sub>39</sub>N<sub>7</sub>NaOS: 628.2829; found: 628.2825.

# *N*-((1-Cyclohexyl-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl) *S*-Piperidyl *S*-*p*-Tolyl Sulfonimidamide (7f)

Yellowish solid; mp 112–113 °C; 55% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.44 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  = 7.74 (d, J = 8.0 Hz, 2 H), 7.55 (d, J = 8.5 Hz, 2 H), 7.35–7.32 (m, 4 H), 6.23 (s, 1 H), 4.72–4.67 (m, 1 H), 2.90–2.85 (m, 2 H), 2.80–2.76 (m, 2 H), 2.44 (s, 3 H), 1.99–1.97 (m, 1 H), 1.93–1.87 (m, 1 H), 1.76–1.74 (m, 1 H), 1.68–1.66 (m, 5 H), 1.49–1.47 (m, 2 H), 1.42–1.39 (m, 2 H), 1.33–1.25 (m, 3 H), 1.18–1.16 (m, 1 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.7, 143.4, 138.7, 133.7, 132.7, 129.7, 128.8, 128.4, 127.7, 58.0, 49.8, 47.7, 32.4, 25.5, 25.3, 25.0, 23.6, 21.6.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>26</sub>H<sub>34</sub>ClN<sub>6</sub>OS: 513.2198; found: 513.2193.

## *N*-((1-(*tert*-Butyl)-1*H*-tetrazol-5-yl)(4-chlorophenyl)methyl) *S*-Piperidyl-*S*-4-Methoxyphenyl Sulfonimidamide (7g)

Yellowish viscous liquid; 57% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.42 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, acetone- $d_6$ ): δ = 7.84 (d, J = 9.0 Hz, 2 H), 7.69 (d, J = 8.5 Hz, 2 H), 7.39 (d, J = 8.5 Hz, 2 H), 7.09 (d, J = 9.0 Hz, 2 H), 6.45 (s, 1 H), 3.87 (s, 3 H), 2.78–2.77 (m, 4 H), 1.67 (s, 9 H), 1.43–1.39 (m, 4 H), 1.33–1.31 (m, 2 H).

<sup>13</sup>C NMR (125 MHz, Acetone): δ = 163.9, 157.6, 141.6, 133.6, 130.7, 130.2, 129.2, 128.1, 114.9, 62.5, 56.1, 51.3, 48.3, 25.9, 24.2.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>24</sub>H<sub>32</sub>ClN<sub>6</sub>O<sub>2</sub>S: 503.1990; found: 503.2001.

#### *N*-((1-Cyclohexyl-1*H*-tetrazol-5-yl)(2-bromophenyl)methyl) *S*-Piperidyl *S*-4-Bromophenyl Sulfonimidamide (7h)

Yellowish viscous liquid; 45% yield. TLC (SiO<sub>2</sub>):  $R_f$  0.44 (30% EtOAc in hexane).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 8.11 (dd, J = 8.0, 1.5 Hz, 1 H), 7.74 (d, J = 8.5 Hz, 2 H), 7.64 (d, J = 8.5 Hz, 2 H), 7.54 (dd, J = 8.0, 1.0 Hz, 1 H), 7.45 (t, J = 7.5 Hz, 1 H), 7.22–7.18 (m, 1 H), 6.52 (s, 1 H), 4.79–4.73 (m, 1 H), 2.82–2.79 (m, 2 H), 2.67–2.62 (m, 2 H), 1.99–1.88 (m, 5 H), 1.81–1.78 (m, 1 H), 1.71–1.69 (m, 1 H), 1.37–1.32 (m, 3 H), 1.29–1.25 (m, 3 H), 1.21–1.18 (m, 3 H).

 $^{13}\text{C}$  NMR (125 MHz, CDCl<sub>3</sub>):  $\delta$  = 155.0, 139.5, 134.5, 132.7, 132.2, 131.3, 129.7, 129.2, 128.1, 127.7, 122.8, 57.8, 48.8, 48.0, 33.1, 32.8, 25.6, 25.4, 25.2, 23.5.

HRMS (ESI-TOF): m/z [M + H]<sup>+</sup> calcd for C<sub>25</sub>H<sub>31</sub>Br<sub>2</sub>N<sub>6</sub>OS: 621.0641; found: 621.0644.

### **Conflict of Interest**

The authors declare no conflict of interest.

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### **Supporting Information**

Supporting information for this article is available online at https://doi.org/10.1055/a-1981-9151.

### References

- (a) Butler, R. N. In Comprehensive Heterocyclic Chemistry, Vol. 4; Katritzky, A. R.; Ress, C. W.; Scriven, E. F. V., Ed.; Pergamon: Oxford, **1996**, 621–678. (b) Lesnikovich, A. I.; Levchik, S. V.; Balabanovich, A. I.; Ivashkevich, O. A.; Gaponik, P. N. Thermochim. Acta **1992**, 200, 427. (c) Koldobskii, G. I.; Ostrovskii, V. A. Russ. Chem. Rev. **1994**, 63, 797.
- (2) Wei, C.-X.; Bian, M.; Gong, G.-H. Molecules 2015, 20, 5528.
- (3) Ostrovskii, V.; Trifonov, R.; Popova, E. Russ. Chem. Bull. 2012, 61, 768.
- (4) (a) Myznikov, L. V.; Hrabalek, A.; Koldobskii, G. I. *Chem. Heterocycl. Compd.* 2007, 43, 1. (b) Rodrigues, T.; Reker, D.; Welin, M.; Caldera, M.; Brunner, C.; Gabernet, G.; Schneider, P.; Walse, B.; Schneider, G. *Angew. Chem. Int. Ed.* 2015, 54, 15079. (c) Wan, Z.-K.; Follows, B.; Kirincich, S.; Wilson, D.; Binnun, E.; Xu, W.; Joseph-, Mc. Carthy D.; Wu, J.; Smith, M.; Zhang, Y.-L. *Bioorg. Med. Chem. Lett.* 2007, *17*, 2913.
- (5) (a) Lv, F.; Liu, Y.; Zou, J.; Zhang, D.; Yao, Z. Dyes Pigm. 2006, 68, 211. (b) Song, W.; Wang, Y.; Qu, J.; Madden, M. M.; Lin, Q. Angew. Chem. Int. Ed. 2008, 47, 2832.
- (6) Gao, H.; Shreeve, J. M. Chem. Rev. 2011, 111, 7377.



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- (7) (a) Shmatova, O. I.; Nenajdenko, V. G. J. Org. Chem. 2013, 78, 9214. (b) Torii, H.; Nakadai, M.; Ishihara, K.; Saito, S.; Yamamoto, H. Angew. Chem. Int. Ed. 2004, 43, 1983. (c) Hartikka, A.; Arvidsson, P. I. Eur. J. Org. Chem. 2005, 4287.
- (8) (a) Gutmann, B.; Glasnov, T.; Razzaq, T.; Goessler, W.; Roberge, D. M.; Kappe, C. O. *Beilstein J. Org. Chem.* 2011, *7*, 503. (b) Frija, L. M. T.; Ismael, A.; Cristiano, M. L. S. *Molecules* 2010, *15*, 3757.
- (9) Lassalas, P.; Gay, B.; Lasfargeas, C.; James, M. J.; Tran, V.; Vijayendran, K. G.; Brunden, K. R.; Kozlowski, M. C.; Thomas, C. J.; Smith, A. B. III.; Huryn, D. M.; Ballatore, C. *J. Med. Chem.* **2016**, 59, 3183.
- (10) (a) Shultz, Z. P.; Scattolin, T.; Wojtas, L.; Lopchuk, J. M. Nat. Synth. 2022, 1, 170. (b) Lucking, U. Angew. Chem. Int. Ed. 2013, 52, 9399. (c) Sirvent, J.; Lücking, U. ChemMedChem 2017, 12, 487.
- (11) Boulard, E.; Zibulski, V.; Oertel, L.; Lienau, P.; Schäfer, M.; Ganzer, U.; Lücking, U. *Chem. Eur. J.* **2020**, *26*, 4378.
- (12) (a) Craig, D.; Grellepois, F.; White, A. J. P. J. Org. Chem. 2005, 70, 6827. (b) Shen, X.; Zhang, W.; Ni, C.; Gu, Y.; Hu, J. J. Am. Chem. Soc. 2012, 134, 16999. (c) Worch, C.; Mayer, A. C.; Bolm, C.; Toru, T.; Bolm, C. Organosulfur Chemistry in Asymmetric Synthesis; Wiley-VCH: Weinheim, 2008, 209. (d) Moessner, C.; Bolm, C. Angew. Chem. Int. Ed. 2005, 44, 7564. (e) Hosseinian, A.; Fekri, L. Z.; Monfared, A.; Vessally, E.; Nikpassand, M. J. Sulfur Chem. 2018, 39, 674. (f) Ghosh, P.; Ganguly, B.; Das, S. Asian J. Org. Chem. 2020, 9, 2035.
- (13) (a) Natarajan, K.; Jesin, C. P. I.; Mercy, A. A. H.; Nandi, G. C. Org. Biomol. Chem. 2021, 19, 7061. (b) Priya, V. R. P.; Jesin, C. P. I.; Nandi, G. C. Synlett. 2022, in press; DOI: 10.1055/a-1921-0875.

(c) Natarajan, K.; Sharma, S.; Jesin, C. P. I.; Kataria, R.; Nandi, G. C. Org. *Biomol. Chem.* **2022**, *20*, 7036. (d) Priya, V. R. P.; Natarajan, K.; Nandi, G. C. *Tetrahedron* **2022**, *111*, 132711.

Paper

- (14) (a) Jesin, C. P. I.; Nandi, G. C. Chem. Eur. J. 2019, 25, 743. (b) Jesin,
  C. P. I.; Ravindra, S.; Nandi, G. C. Tetrahedron 2019, 75, 130622.
  (c) Nandi, G. C. Eur. J. Org. Chem. 2017, 6633. (d) Nandi, G. C.;
  Raju, C. Org. Biomol. Chem. 2017, 15, 2234. (e) Jesin, C. P. I.;
  Nandi, G. C. Adv. Synth. Catal. 2018, 360, 2465. (f) Ravindra, S.;
  Rohith, J.; Jesin, C. P. I.; Kataria, R.; Nandi, G. C. ChemistrySelect
  2019, 4, 14004. (g) Ravindra, S.; Nayak, A.; Jesin, C. P. I.; Nandi, G.
  C. Adv. Synth. Catal. 2022, 364, 1144.
- (15) Ugi, I. Angew. Chem. 1959, 71, 386.
- (16) Neochoritis, C. G.; Zhao, T.; Domling, A. *Chem. Rev.* **2019**, *119*, 1970.
- (17) Mancheño, O. G.; Bolm, C. Org. Lett. 2007, 9, 2951.
- (18) Hommelsheim, R.; Ponce, H. M. N.; Truong, K.-N.; Rissanen, K.; Bolm, C. Org. Lett. **2021**, 23, 3415.
- (19) (a) Xie, Y.; Zhou, B.; Zhou, S.; Zhou, S.; Wei, W.; Liu, J.; Zhan, Y.; Cheng, D.; Li, Y.; Wang, B.; Xue, X.; Li, Z. *ChemistrySelect* **2017**, *2*, 1620. (b) Izzo, F.; Schafer, M.; Stockman, R.; Lucking, U. *Chem. Eur. J.* **2017**, *23*, 15189.
- (20) (a) Worch, C.; Bolm, C. Synlett 2009, 2425. (b) Steurer, M.; Bolm, C. J. Org. Chem. 2010, 75, 3301. (c) Nandi, G. C.; Arvidsson, P. I. Adv. Synth. Catal. 2018, 360, 2976. (d) Chinthakindi, P. K.; Naicker, T.; Thota, N.; Govender, T.; Kruger, H. G.; Arvidsson, P. I. Angew. Chem. Int. Ed. 2017, 56, 4100. (e) Boulard, E.; Zibulski, V.; Oertel, L.; Lienau, P.; Schäfer, M.; Ganzer, U.; Lücking, U. Chem. Eur. J. 2020, 26, 4378.
- (21) (a) Shmatova, O. I.; Nenajdenko, V. G. J. Org. Chem. 2013, 78, 9214. (b) Patil, P.; Zhang, J.; Kurpiewska, K.; Kalinowska-Tłuścik, J.; Dömling, A. Synthesis 2016, 48, 1122.