# A novel and convenient synthesis of 3-amino-2*H*-1,2,4-triazoles from isoselenocyanates and hydrazine hydrate

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A novel and convenient one-pot synthesis of 3-amino-2*H*-1,2,4-triazoles from two molecules of isoselenocyanates and hydrazine hydrate *via* cyclodeselenisation was developed. Various 3-amino-2*H*-1,2,4-triazoles were obtained in moderate to good yields (33–45%, based on isoselenocyanates). The selenium powder and aromatic amine side products during the reaction could be recycled for efficient preparation of isoselenocyanates, which improved the atom economy. A plausible mechanism was proposed for the formation of the target products.

**Keywords:** isoselenocyanates, selenoureas, hydrazine hydrate, 3-amino-2*H*-1,2,4-triazoles

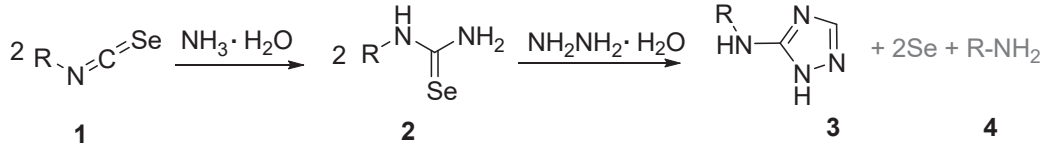
On account of their unique structures and reactivities, 3-amino-2*H*-1,2,4-triazoles are widely utilised as intermediates to prepare various biologically important compounds, such as hypoglycemic agents,[1] [1,2,4]triazolo[1,5-*a*]pyrimidine bioactive derivatives,[2] tumour inhibitors[3–6] and selective inhibitors of TYK2 and JAK1 over JAK2 and JAK3.[7] 1,2,4-Triazoles have an electron-rich bioisosteric ring that can mimic bioactive heterocyclic nuclei, such as imidazole,[8] pyrazole[9] and thiazole.[10,11] The wide-ranging applications of 3-amino-2*H*-1,2,4-triazoles have attracted considerable attention in synthesis. Although numerous procedures for the synthesis of 1,2,4-triazoles with various substituents have been reported, few studies have described the direct synthesis of 3-*N*-substituted-1,2,4-triazoles and 5-unsubstituted-1,2,4-triazoles. Over the past 50 years, the most widely used methods for the synthesis of 3-amino-2*H*-1,2,4-triazoles have involved the reaction of hydrazine hydrate with various cyanamides, such as *N*-cyanoethanimidothioates[12,13] and *N*-cyanoimidates,[14–16] and the reaction of amines with hydrazonitrile derivates, such as *N′*-cyanobenzohydrazides.[17,18] However, the substrates used in the above methods require cyanides, which are obtained from hypertoxic cyanogen chloride/bromide reacting with amines, imide or hydrazine salts.[19–21] To avoid using cyanides, Chorev *et al*.[22] described the preparation of 3-amino-1,2,4-triazoles from the reaction of 1,3-disubstituted-thioureas and acyl hydrazide with toxic $Hg(OAc)_2$ as a thiophilic reagent. On this basis, Guin *et al*.[23] have envisaged a strategy for the synthesis of 3-amino-1,2,4-triazoles from 1,3-disubstituted thioureas and formic hydrazide using hypotoxic molecular iodine as the desulfurising agent. Nevertheless, these methods suffer from environmental concerns as they directly or indirectly utilise hypertoxic or hypotoxic reagents, high reaction temperatures and tedious manipulative procedures, which impede the applicability of these methodologies.

Isoselenocyanates are widely employed in the synthesis of nitrogen-containing heterocycles due to their convenient preparation, low toxicity, relative stability and excellent reactivity.[24–26] We have been interested in the synthesis of 1,2,4-triazoles and consequently, we have developed unexpectedly a novel and convenient one-pot synthesis of 3-amino-2*H*-1,2,4-triazoles from two molecules of isoselenocyanates and hydrazine hydrate *via* cyclodeselenisation (Scheme 1). Without any harsh reagent, such as a deselenisation or cyclisation reagent, various 3-amino-2*H*-1,2,4-triazoles were constructed in moderate to good yields (33–45%, based on isoselenocyanates **1**). The selenium powder and aromatic amine byproducts during the reactions could be recycled to prepare the corresponding isoselenocyanates efficiently, which improved the atom economy.

## Results and discussion

Phenyl selenourea **2a**,[27,28] which was obtained by phenyl isoselenocyanate reacting with aqueous ammonia at room temperature, was selected to optimise the reaction conditions to form 3-(phenylamino)-2*H*-1,2,4-triazole **3a**. First, we investigated the effects of different solvents, reaction temperatures and the amount of hydrazine hydrate. The results are summarised in Table 1. Among the solvents, MeOH proved to be optimal as 28% yield could be obtained, which may be due to the solubility, stability and reactivity of selenourea (Table 1, entries 1–5). The reaction proceeded best at 50 °C (Table 1, entries 6, 9 and 12). As both **2a** and **3a** might have low stability at 60 °C, the yield of **3a** declined at this temperature (Table 1, entries 11 and 12). Prolonged reaction times at 40 °C did not enhance the yield (Table 1, entries 6 and 7). A reaction time of 12 h gave the best yield (Table 1, entries 8–10). To further improve the yield of **3a**, the amount of hydrazine hydrate was investigated (Table 1, entries 9, 13 and 16). The yield was improved to 42% by increasing the amount of hydrazine hydrate to 2.0 equiv. (Table 1, entry 9). In addition, the recovery yields of Se powder and **4a** were up to 88% and 40%, respectively (Table 1, entry 14). Therefore, the optimal reaction conditions were established as using 2.0 equiv. of hydrazine hydrate, MeOH as solvent, a reaction temperature of 50 °C and about 12 h reaction time.

With the optimised conditions, we set out to explore the substrate scope. In a one-pot procedure, various aromatic selenoureas **2** were obtained by isoselenocyanates **1** reacting with aqueous ammonia in $CH_2Cl_2$ and then further reacting with hydrazine hydrate to form the corresponding triazoles




**Scheme 1** Preparation of 3-amino-2*H*-1,2,4-triazoles from isoselenocyanates and hydrazine hydrate.

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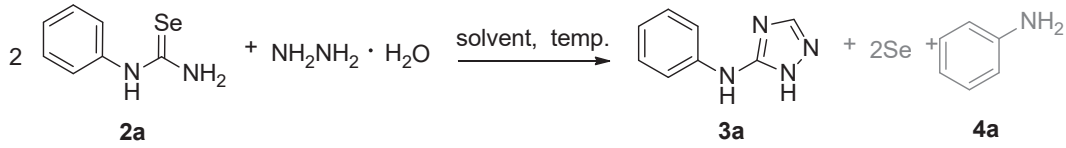
**Table 1** Optimisation of reaction conditions for the conversion of selenoureas to 3-amino-2*H*-1,2,4-triazoles




**2a** **3a** **4a**

| Entry | Solvent | Aqueous $NH_2NH_2$ (50%, equiv.) | Temperature (°C) | Time (h)[a] | Yield (**3a**, %)[b] |
|---|---|---|---|---|---|
| 1 | $H_2O$ | 1.5 | 25 | 20 | <5 |
| 2 | $CH_2Cl_2$ | 1.5 | 25 | 20 | 10 |
| 3 | DMF | 1.5 | 25 | 20 | 15 |
| 4 | EtOH | 1.5 | 25 | 16 | 20 |
| 5 | MeOH | 1.5 | 25 | 16 | 28 |
| 6 | MeOH | 1.5 | 40 | 12 | 30 |
| 7 | MeOH | 1.5 | 40 | 24 | 28 |
| 8 | MeOH | 1.5 | 50 | 8 | 35 |
| 9 | MeOH | 1.5 | 50 | 12 | 38 |
| 10 | MeOH | 1.5 | 50 | 16 | 36 |
| 11 | MeOH | 1.5 | 60 | 8 | 26 |
| 12 | MeOH | 1.5 | 60 | 12 | 25 |
| 13 | MeOH | 1.0 | 50 | 12 | 29 |
| 14 | MeOH | 2.0 | 50 | 12 | 42, 95[c], 40[d] |
| 15 | MeOH | 2.5 | 50 | 12 | 40 |
| 16 | MeOH | 3.0 | 50 | 12 | 41 |

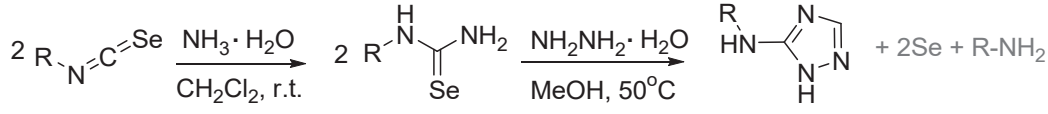
[a]Monitored by TLC.

[b]Isolated yield based on **2a**.

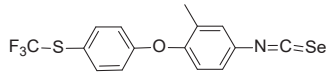
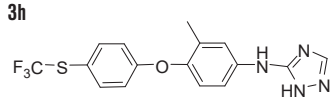
[c]Recovery yield of Se powder based on **2a**.

[d]Recovery yield of **4a** based on **2a**.

**Table 2** One-pot synthesis of 3-amino-2*H*-1,2,4-triazoles from isoselenocyanates and hydrazine hydrate




**1** **2** **3** **4**

| Entry | Reactant | R | Product[a] | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **1a** | $C_6H_5$ | **3a** | 40,3[4]c |
| 2 | **1b** | 2-$CH_3C_6H_4$ | **3b** | 37 |
| 3 | **1c** | 3-$CH_3C_6H_4$ | **3c** | 41 |
| 4 | **1d** | 4-$CH_3C_6H_4$ | **3d** | 45,38[c] |
| 5 | **1e** | 3-$BrC_6H_4$ | **3e** | 36 |
| 6 | **1f** | 4-$FC_6H_4$ | **3f** | 39 |
| 7 | **1g** | α-Naphthyl | **3g** | 33 |
| 8 | **1h** |  | **3h**  | 36 |



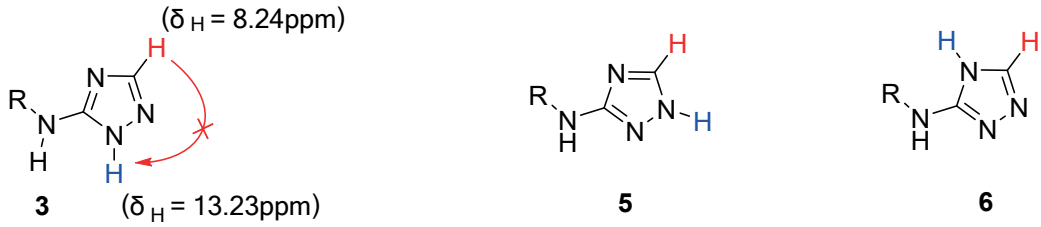
[a]Confirmed by IR, $^1$H and $^{13}$C NMR, MS-ESI, HRMS-ESI.

[b]Isolated yield based on isoselenocyanates **1**.

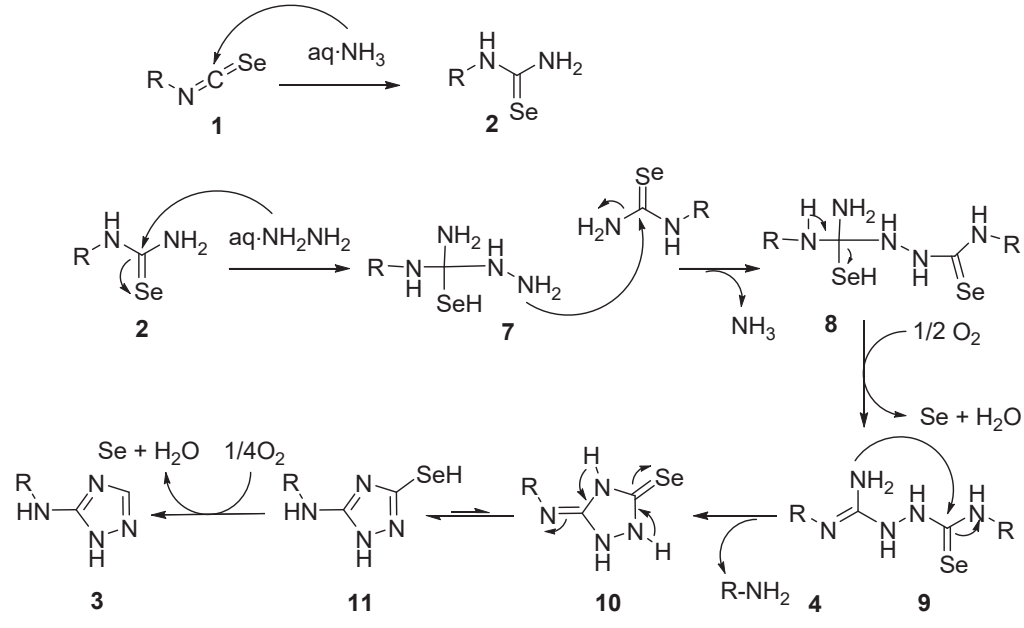
[c]Using isoselenocyanates produced from recycled byproducts.

**3** in MeOH at 50 °C. The results are summarised in Table 2. A variety of 3-amino-2*H*-1,2,4-triazoles were constructed in moderate to good yields ranging from 33 to 45% (based on isoselenocyanates **1**).The nature of the R group affected the reaction yields to some extent. Compounds substituted with an electron donating group (Table 2, entries 2–4) showed higher yields than compounds substituted with an electron withdrawing group (Table 2, entries 3 and 5). When substituents were attached to the *ortho* position of the phenyl isoselenocyanate (Table 2, entries 1–4), the reaction yields decreased slightly due to steric effects. Naphthyl- and macroradical-substituted isoselenocyanates also provided the desired product in moderate yield — 33% and 36%, respectively (Table 2, entries 7 and 8). Furthermore, 3-amino-2*H*-1,2,4-triazoles were still obtained in satisfactory yields using isoselenocyanates produced from the recycled byproducts (Table 2, entries 1 and 4).

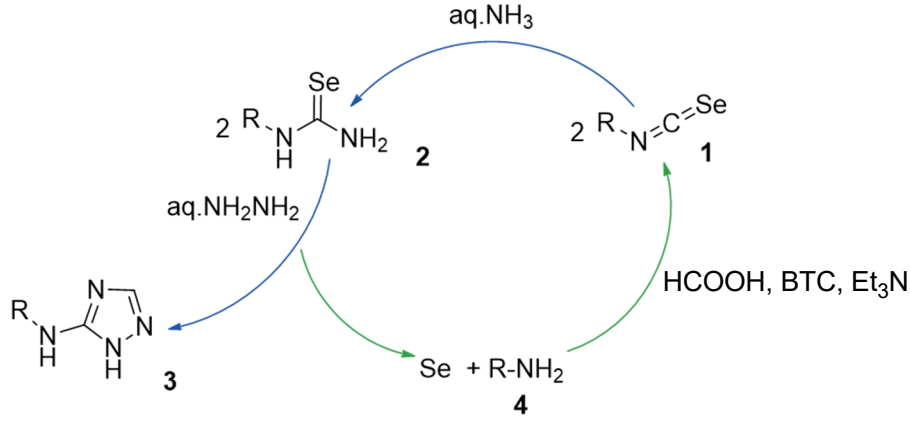
According to the $^1$H NMR spectra of **3a**, we could confirm that the C–H signal of triazole appeared as a singlet at around δ 8.25 ppm. Furthermore, according to the $^1$H–$^1$H COSY spectra of **3a**, the C–H signal of triazole was not correlative to N–H. Therefore, the triazoles could be assigned as 3-amino-2*H*-1,2,4-triazoles **3**, not 1*H* isomers **5** or **6** (Scheme 2).




**Scheme 2**




**Scheme 3** Plausible mechanism proposed for the formation of **3**.




**Scheme 4** Recovery and recycling of selenium powder and aromatic amines **4**.

A plausible mechanism is proposed for the formation of 3-amino-2*H*-1,2,4-triazoles **3** in Scheme 3. First, selenourea **2** is generated from isoselenocyanate **1** and aqueous ammonia rapidly and efficiently, and then reacts with hydrazine hydrate to form intermediates **7**. Subsequently, intermediate **7** attacks another selenourea **2** to form intermediate **8** *via* sloughing ammonia. Intermediate **8** is converted to intermediate **9** *via* deselenisation with the aid of oxygen. Afterwards, the intramolecular cyclisation of **9** produces the intermediate **10** and the byproduct aromatic amine **4**. Finally, intermediate **10** tended to transform to the resonance forms 1,2,4-triazoles **11**, which converted to the target products 3-amino-2*H*-1,2,4-triazoles **3** *via* deselenisation with the aid of oxygen. To prove these processes, the reactions were carried out in a nitrogen-protected vessel — no desired product or selenium powder were detected, which meant that oxygen was significant to the reaction. Further discussion can be found in our previous paper.[29]

After reaction completion, the precipitated selenium powder was easily obtained by filtering, washed with $CH_2Cl_2$ and reused for the preparation of isoselenocyanates. The filtrate was concentrated under vacuum, and then the residue was dissolved in ethyl acetate and precipitated by adding petroleum ether. Most aromatic amines **4** were found in petroleum ether and obtained easily by filtering and concentrating under vacuum. Afterwards, selenium powder and aromatic amines **4** could be recycled to prepare the corresponding isoselenocyanates efficiently by reacting with HCOOH and bis(trichloromethyl) carbonate under base,[27] which improved the atom economy (Scheme 4 and Table 2, entries 1 and 4).

## Conclusion

A novel and convenient one-pot synthesis of 3-amino-2*H*-1,2,4-triazoles was developed starting from two molecules of isoselenocyanates and hydrazine hydrate *via* cyclodeselenisation in moderate to good yields. The procedure obviates using any harsh reagent, such as a deselenisation or cyclisation reagent. Luckily, both selenium powder and aromatic amines **4** are byproducts during the reactions that could be easily recovered and reused to achieve the economic and ecofriendly synthesis of 3-amino-2*H*-1,2,4-triazoles.

## Experimental

Infrared spectra were determined on a Nicolet Avatar-370 spectrometer in KBr (ν in $cm^{-1}$). Melting points were measured on a Büchi B-540 capillary melting point apparatus and uncorrected. Mass spectra (ESI-MS) were determined on a Thermo Finnigan LCQ-Advantage. High-resolution mass spectra (ESI-HRMS) were determined on an Agilent 6210 TOF instrument. $^1$H NMR and $^{13}$C NMR spectra were recorded on Varian Mercury Plus-400 spectrometer (400 and 100 MHz), δ in parts per million, *J* in Hertz, using TMS as internal standard.

*Synthesis of 3-amino-*2H*-1,2,4-triazoles* **3a**–**h** (**3a** *selected as example); general procedure*

Phenyl isoselenocyanate **1a** (0.364 g, 2 mmol) and aqueous ammonia (25%, 0.336 g, 2.4 mmol) were added to $CH_2Cl_2$ (3 mL) with magnetic stirring for 30 min at room temperature. Phenyl selenourea **1a** was confirmed by TLC. The reaction mixture was concentrated under vacuum to remove $CH_2Cl_2$, then hydrazine hydrate (50%, 0.400 g, 4 mmol) and MeOH (10 mL) were added and stirred for about 12 h at 50 °C. Selenium powder precipitated out gradually. After reaction completion, selenium powder was filtered off and washed with $CH_2Cl_2$ (20 mL). The recovery rate of selenium powder was about 90% (0.143 g, based on **1a**). The filtrate was concentrated under vacuum, and the residue was dissolved in ethyl acetate (7 mL) and precipitated by adding petroleum ether (5 mL). Most of phenylamine **4a** was found in petroleum ether and obtained easily by filtering and concentrating under vacuum with 38% recovery yield (0.071 g, based on **1a**). The residue was purified through column chromatography on silica gel ($CH_2Cl_2$/MeOH = 8:1–4:1) to give the pure product 3-(phenylamino)-2*H*-1,2,4-triazole **3a**.

*3-(Phenylamino)-*2H*-1,2,4-triazole* (Table 2, **3a**): Light brown solid; yield 0.128 g (40%, based on **1a**); m.p. 175–176 °C (lit.[12] 175–178 °C); IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3146, 2913, 1609, 1573, 1558, 1500, 1458, 1241, 977, 748; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 13.23 (s, 1H, NH), 9.07 (s, 1H, NH), 8.26 (s, 1H, N=CH), 7.53–7.51 (m, 2H, ArH), 7.19–7.18 (m, 2H, ArH), 6.74 (s, 1H, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 160.0, 142.0, 141.7, 1128.5, 118.8, 115.4.

*3-[(2-Methylphenyl)amino]-*2H*-1,2,4-triazole* (Table 2, **3b**): White solid; yield 0.129 g (37%); m.p. 168–169 °C; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3101, 3056, 1621, 1584, 1549, 1462, 1209, 1046, 958, 746; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 13.14 (s, 1H, NH), 8.22 (s, 1H, NH), 7.81–7.79 (m, 1H, ArH), 7.89 (s, 1H, N=CH), 7.10–7.01 (m, 2H, ArH), 6.73–6.70 (m, 1H, ArH), 2.23 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 158.4, 141.9, 141.6, 131.3, 128.5, 126.5, 123.7, 115.4, 17.6; MS (ESI) *m*/*z* (%): 175.1 ([M + H]$^+$, 100%). HRMS (ESI) calcd for $C_9H_{11}N_4$ [M + H]$^+$: 175.0983; found: 175.0989.

*3-[(3-Methylphenyl)amino]-*2H*-1,2,4-triazole* (Table 2, **3c**): Light brown solid; yield 0.143 g (41%); m.p. 131–133 °C; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3041, 2920, 1600, 1540, 1463, 1250, 1040, 979, 866, 778; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 13.20 (s, 1H, NH), 8.99 (s, 1H, NH), 8.25 (s, 1H, N=CH), 7.35–7.30 (m, 2H, ArH), 7.08–7.04 (m, 1H, ArH), 6.58 (s, 1H, ArH), 2.24 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 160.1, 141.9, 141.7, 137.4, 128.3, 119.5, 115.9, 112.7, 21.5; MS (ESI) *m*/*z* (%) 173.1 ([M − H]$^-$, 100%). HRMS (ESI) calcd for $C_9H_9N_4$ [M − H]$^-$: 173.0827; found: 173.0832.

*3-[(4-Methylphenyl)amino]-*2H*-1,2,4-triazole* (Table 2, **3d**): Yellow solid; yield 0.157 g (45%); m.p. 197–199 °C (lit.[12] 196–198 °C); IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3118, 2917, 1598, 1553, 1514, 1450, 1250, 1048, 979, 821, 794; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 13.08 (s, 1H, NH), 8.86 (s, 1H, NH), 8.18 (s, 1H, N=CH), 7.37 (d, *J* = 8 Hz, 2H, ArH), 6.94 (d, *J* = 8 Hz, 2H, ArH), 2.19 (s, 3H, $CH_3$).

*3-[(3-Bromophenyl)amino]-*2H*-1,2,4-triazole* (Table 2, **3e**): Light yellow solid; yield 0.171 g (36%); m.p. 180–182 °C; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3129, 2935, 1618, 1593, 1556, 1469, 1298, 1249, 1074, 981, 775, 751; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 13.33 (s, 1H, NH), 9.38 (s, 1H, NH), 8.32 (s,1H, N=CH), 7.89–7.88 (m, 1H, ArH), 7.45–7.42 (m, 1H, ArH), 7.16–7.12 (m, 1H, ArH), 6.93–6.91 (m, 1H, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 159.6, 143.6, 142.0, 130.3, 121.7, 121.0, 117.4, 114.4; MS (ESI) *m*/*z* (%): 239.0 ([M($C_8H_7{}^{79}BrN_4$) + H]$^+$, 100%), 241.0 ([M($C_8H_7{}^{81}BrN_4$) + H]$^+$, 97%). HRMS (ESI) calcd for $C_8H_8{}^{79}BrN_4$ [M + H]$^+$: 238.9932; found: 238.9940. HRMS (ESI) calcd for $C_8H_8{}^{81}BrN_4$ [M + H]$^+$: 240.9912; found: 240.9920.

*3-[(4-Fluorophenyl)amino]-*2H*-1,2,4-triazole* (Table 2, **3f**): Light brown solid; yield 0.139 g (39%); m.p. 197–198 °C; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3285, 2920, 1573, 1540, 1507, 1232, 1211, 980, 836; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 13.23 (s, 1H, NH), 9.10 (s, 1H, NH), 8.26 (s, 1H, N=CH), 7.55–7.52 (m, 2H, ArH), 7.05–7.01 (m, 2H, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 160.1, 155.4 ($^1J_{CF}$ = 232 Hz), 141.8, 138.6, 116.5, 114.7; MS (ESI) *m*/*z* (%): 179.3 ([M + H]$^+$, 100%). HRMS (ESI) calcd for $C_8H_8FN_4$ [M + H]$^+$: 179.0732; found: 179.0727.

*3-[(α-Naphthyl)amino]-*2H*-1,2,4-triazole* (Table 2, **3g**): Golden yellow solid; yield 0.138 g (33%); m.p. 200–202 °C; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3210, 3173, 1675, 1634, 1584, 1529, 1479, 1402, 1344, 1258; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 13.34 (s, 1H, NH), 8.93 (s, 1H, NH), 8.38–8.35 (m, 1H, ArH), 8.02 (s,1H, N=CH), 7.84 (s, 1H, ArH), 7.47–7.39 (m, 5H, ArH); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 160.5, 142.0, 137.5, 133.7, 127.8, 125.8, 125.7, 125.5, 124.6, 121.9, 119.7, 111.7; MS (ESI) *m*/*z* (%): 211.4 ([M + H]$^+$, 100%). HRMS (ESI) calcd for $C_{12}H_{11}N_4$ [M + H]$^+$: 211.0984; found: 211.0982.

*3-({3-Methyl-4-[4-(trifluoromethylthio)phenoxy]phenyl}amino)-*2H*-1,2,4-triazole* (Table 2, **3h**): Golden yellow solid; yield 0.243 g (36%); m.p. 202–203 °C; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 3290, 2928, 1619, 1554, 1487, 1241, 1151, 1122, 1087, 835; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 13.24 (s, 1H, NH), 9.14 (s, 1H, NH), 8.27 (s, 1H, N=CH), 7.64–7.62 (m, 2H, ArH), 7.52 (s, 1H, ArH), 7.44–7.42 (m, 1H, ArH), 6.95–6.91 (m, 3H, ArH), 2.05 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 160.9, 144.2, 142.0, 138.2, 130.9, 129.8 ($^1J_{CF}$ = 305 Hz), 129.7, 127.8, 121.4, 118.1, 116.5, 114.7, 114.2, 16.0; MS (ESI) *m*/*z* (%): 367.2 ([M + H]$^+$, 100%). HRMS (ESI) calcd for $C_{16}H_{14}F_3N_4OS$ [M + H]$^+$: 367.0840; found: 367.0845.

*Synthesis of {3-Methyl-4-[4-(trifluoromethylthio)phenoxy]phenyl} isoselenocyanate* (Table 2, **1h**)

Compound **1h** was prepared[25] from {3-methyl-4-[4-(trifluoromethylthio)phenoxy]phenyl}amine (from Guobang Pharmaceutical Co. Ltd of Zhejiang province), HCOOH and selenium powder to give: Oil; IR (KBr) ($\nu_{max}$ $cm^{-1}$): 2922, 2108, 1601, 1589, 1487, 1280, 1258, 1233, 1207, 1120, 1808, 1010, 854, 830, 751; $^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.59 (d, *J* = 8.4 Hz, 2H, ArH), 7.22 (d, *J* = 2.4 Hz, 1H, ArH), 7.12 (dd, $J_1$ = 1.2 Hz, $J_2$ = 8.8 Hz, 1H, ArH), 6.91–6.88 (m, 3H, ArH), 2.22 (s, 3H, $CH_3$); $^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 153.5, 148.5, 138.2, 134.9, 132.8 ($^1J_{CF}$ = 305 Hz), 131.6, 131.2, 121.8, 121.5, 117.8, 116.9, 116.3, 16.4; MS (ESI) *m*/*z* (%): 390 ([M + H]$^+$, 100). HRMS (ESI) calcd for $C_{15}H_{11}F_3NOS^{80}Se$ (M + H)$^+$: 389.9679; found: 389.9683.

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## Electronic Supplementary Information

The ESI is available through:
http://ingentaconnect.com/content/stl/jcr/2018/00000042/00000005/art00007

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