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A facile metal-free one-pot synthesis of 3-aminoisoquinolines by intramolecular transannulation of 1-sulfonyl-4-(2-aminomethylphenyl)-1,2,3-triazoles†

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A metal-free one-pot intramolecular transannulation of 1-sulfonyl-4-(2-aminomethylphenyl)-1,2,3-triazoles has been developed, which enables the facile synthesis of the various 3-aminoisoquinolines as well as relevant scaffolds from readily available starting materials.

Introduction

Isoquinoline represents an important class of heterocyclic skeleton, which is widely distributed in diverse natural products, and some are found to have promising biological performance and medicinal importance.^{1–3} The unique structure of 3-aminoisoquinolines is well-explored to be commonly used as the unit for synthesizing biologically active representatives, such as compounds **1–3** (Fig. 1a).^{4–6} In view of the wide application of 3-aminoisoquinolines in medicinal chemistry, a large array of synthetic methods had been developed for the construction of 3-aminoisoquinolines and their structurally similar analogues.

In general, synthetic approaches towards 3-aminoisoquinolines were historically reported, including the direct amination of 3-haloisoquinoline with sodium amide, aqueous ammonia or cyclic amine.^{7–9} In order to prove the acceptable reaction efficiency of the above mentioned transformations, some harsh reaction conditions are commonly required, such as high reaction temperature or pressure. Otherwise, the cyclocondensation of 2-cyanomethyl benzoaldehydes or 2-acylphenylacetonitriles with amines has been served as an accessible option for obtaining the 3-aminoisoquinolines, which highly depends on the intrinsic nature of nitrogen substrates used.^{10,11} For instance, ammonia or primary amines could smoothly afford 3-aminoisoquinolines with good yields whereas the

secondary amines were converted slowly, and failed to proceed to the formation of desired product with satisfying results in the most cases. In addition, some alternative procedures have also been reported. These methods include the cyclization of arylmethylazapropenylum perchlorates,¹² Cu(i)-catalyzed cyclocondensation of *o*-iodobenzylamine and acetonitriles¹³ and the palladium catalyzed α -arylation reaction of *tert*-butyl cyanoacetate, followed by *in situ* trapping with an electrophile, and aromatization with ammonium chloride.¹⁴ However, these methods are revealed to suffer from difficult access to starting material, the necessity of transition metal catalysts, the limited scope of applicability or low yield. The synthetically practical and operationally convenient method for preparing the 3-aminoisoquinoline is still necessary.

N-Sulfonyl ketenimine, which is readily *in situ* generated from ring-opening of *N*-sulfonyl 1,2,3-triazole, has been evolved into a useful synthetic intermediate in recent years for the synthesis of numerous complex organic compounds, particularly the biologically interesting heterocycles (Fig. 1b).¹⁵ As a highly active intermediate, *N*-sulfonyl ketenimine can readily undergo nucleophilic additions to give their corresponding products.¹⁶ For example, Li's group developed a method for synthesis of naphthalenes by intramolecular transannulation of 1-sulfonyl-4-(2-alkenylphenyl)-1,2,3-triazoles (Fig. 1c).¹⁷ Inspired by this work, we envisaged the *N*-sulfonyl ketenimine could pave the way of advancing to the aforementioned heterocycles. As a result, we report herein a metal-free intramolecular transannulation of 1-sulfonyl-4-(2-aminomethylphenyl)-1,2,3-triazoles, a reaction enabling the efficient synthesis of 3-aminoisoquinolines (Fig. 1d).

Results and discussion

Using **1a** as a model substrate, we commenced our investigation by treating it in 1,2-DCE at 80 °C in a sealed tube (Scheme 1). After 36 h, two main products were obtained, which were

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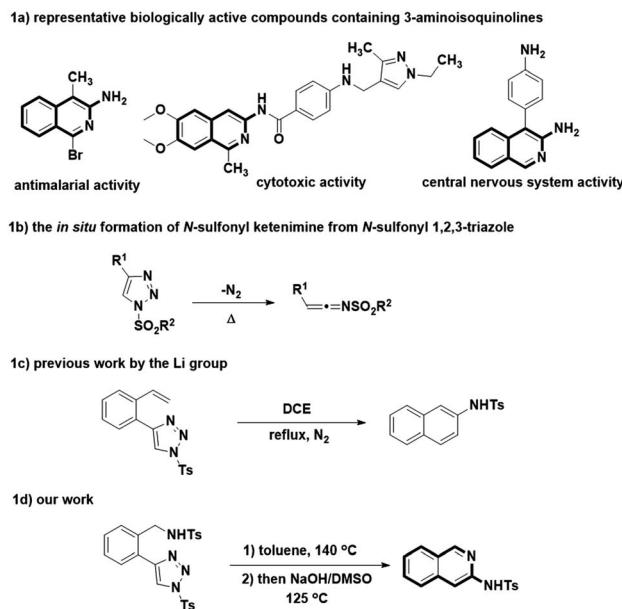
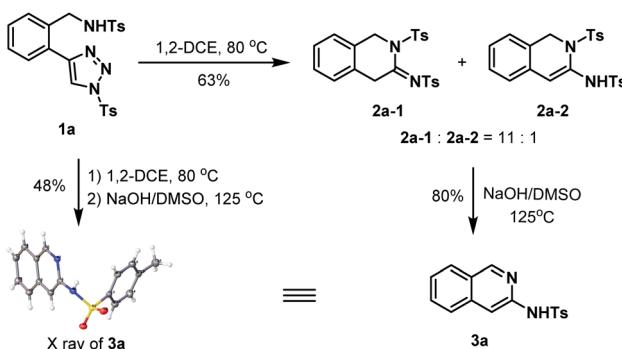


Fig. 1 Background and our work.

further identified as the 1,2-dihydroisoquinolin-3(4*H*)-imine **2a-1**, and its regioisomer 1,2-dihydroisoquinoline **2a-2** generated from the enamine-iminium isomerization. The overall isolated yield of **2a-1** and **2a-2** was 63% and the molar ratio **2a-1** : **2a-2** = 11 : 1. Of note, the two isomers were observed as an inseparable mixture that each of them was unable to be respectively obtained by simply using the silica gel column chromatography. In order to unambiguously characterize the presumed structures of the two isomers, the mixture was subject to the treatment of NaOH/DMSO solution that prompting the formation of 3-aminoisoquinoline **3a** (80%) as an aromatized product.¹⁸ The structure of **3a** was unambiguously confirmed by the X-ray crystallographic study.¹⁹ Furthermore, we found that the tandem annulation and aromatization could be smoothly achieved in an operationally simple one-pot manner, which allowed for the access of **3a** directly from **1a** with comparable efficiency.

To improve the efficiency of the above mentioned transformation, we performed an extensive condition screening

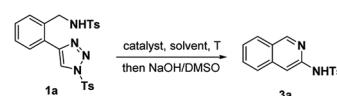


Scheme 1 Initial result of intramolecular annulation of 1-sulfonyl-4-(2-aminomethylphenyl)-1,2,3-triazoles.

(Table 1). First of all, we discovered that the better reactivity could be secured by gradually increasing the reaction temperature from 80 to 140 °C (entries 2–4). A good yield (73%) of **3a** was obtained with raising the reaction temperature to 140 °C. Gratifyingly, simply replacing the reaction solvent with non-polar toluene can provide the best result (81%) instead of the rest (THF, CHCl₃, CH₃CN and EtOAc). In sharp contrast, the lower reaction temperature actually led to inferior results that advance to the desired product **3a** with only moderate yield (entries 5 and 6). In addition, the Rh catalyst were also examined, but negative impact on the reaction outcome was observed.

Having the optimal conditions in hands, we then turned to evaluate the substrate scope generality of the above reaction (Table 2). First of all, the substituent variants on the phenyl ring were examined. It was shown that all of them could undergo the desired reactions to provide the corresponding products **3b–k** in moderate to excellent yields. 5-Br, 5-Cl and 4-Cl substituted phenyl triazoles delivered **1b–d** with satisfactory yield (78–85%), as well as **3e** and **3f** gave the acceptable results (65% and 63%) when 4-F and 5-F substituted phenyl triazoles were used.

The arene substitution pattern indicates that the bromo and chloro substituents are superior to fluoro substituent. The 5- and 4-functionalized substrates result in comparable reactivity, afford their corresponding products with moderate to good yield. For substrate **1g** with trifluoromethyl group, the reaction gave the desired product **3g** in moderate yield. The reaction could also be applied to substrates with electron-donating groups (**1h–k**). As shown, mono-substituted phenyl triazoles with electron-donating groups (**1h**, **1i**) could proceed smoothly to furnish the desired products **3h** and **3i** in 72% and 74%

Table 1 Condition optimization of intramolecular annulation of 1-sulfonyl-4-(2-aminomethylphenyl)-1,2,3-triazoles^a

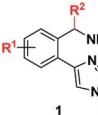
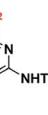
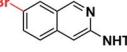
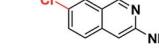
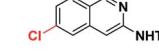
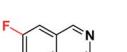
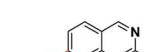
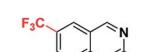
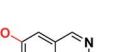
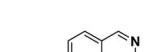
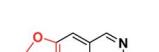
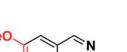
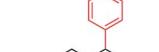
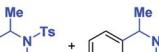
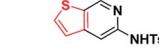
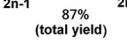
Entry	Cat.	Solvent	T [°C]	Yield ^b
1		1,2-DCE	80	48%
2		1,2-DCE	100	56%
3		1,2-DCE	120	65%
4		1,2-DCE	140	73%
5		PhMe	100	59%
6		PhMe	120	71%
7		PhMe	140	81%
8		THF	140	77%
9		CHCl ₃	140	62%
10		CH ₃ CN	140	73%
11		EtOAc	140	77%
12	Rh ₂ (Oct) ₄	PhMe	140	45%
13	Rh ₂ (esp) ₂	PhMe	140	39%

^a Reaction conditions: **1a** (0.1 mmol), catalyst (2.0 μ mol), and solvent (1.0 mL) in a sealed tube, then NaOH (1.0 mmol) and DMSO (1.0 mL).

^b Refers to isolated yield. 1,2-DCE = dichloroethane, Oct = octanoate, esp = $\alpha,\alpha,\alpha,\alpha$ -tetramethyl-1,3-benzenedipropionic acid.



Table 2 Scope of intramolecular annulation of 1-sulfonyl-4-(2-aminomethylphenyl)-1,2,3-triazoles^{a,b}

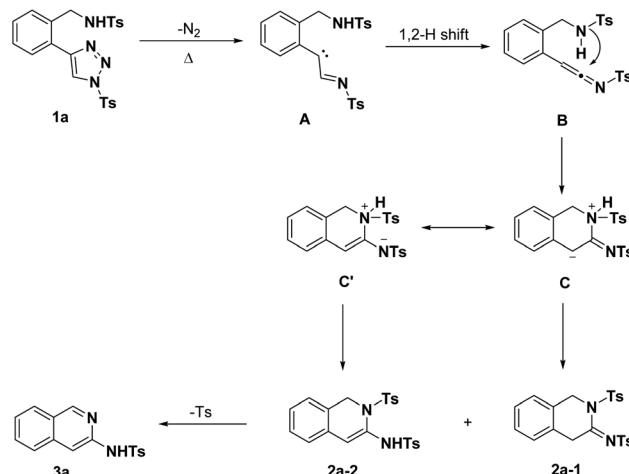
	1) toluene, 140 °C 2) then NaOH/DMSO 125 °C	
	3b 82%	
	3c 78%	
	3d 85%	
	3e 65%	
	3f 63%	
	3g 50%	
	3h 74%	
	3i 72%	
	3j 56%	
	3k 55%	
	3l 81%	
	2m-1	
	2m-2	
	79% (total yield)	
	2n-1	
	2n-2	
	87% (total yield)	
	3o 91%	
	3p 55%	

^a Reaction conditions: 1 (0.1 mmol), toluene (1.0 mL) in a sealed tube, then NaOH (1.0 mmol), DMSO (1.0 mL). ^b Refers to isolated yield.

yields. Comparably, substrates with double electron-donating groups led to relatively lower yields (3j, 3k), most likely due to the stronger electronic effect causing the decomposition of partial substrate under the current reaction conditions.

In addition to the substituent on the phenyl ring, substitution effect on the benzylic position has also been evaluated. 2l bearing Ph group (R^2) at the benzylic position underwent the reactions smoothly to afford the desired product 3l in 81% yield. For the alkyl substituted substrates 1m and 1n, the corresponding annulation products were obtained in 79 and 87% total yields, respectively. However, it failed to undergo aromatization to give the corresponding 3-aminoisoquinolines under NaOH condition, presumably due to electron-donating effect of alkyl group. Finally, it was found that the benzene ring unit of the substrates could be replaced by some other aromatic rings, such as naphthalene and thiophene, as shown by the cases of 3o and 3p.

Based on the above results and the previously reported literature, the presumable mechanistic hypothesis of the transannulation using substrate 1a as a model is rationally illustrated in Scheme 2. Substrate 1a undergoes a ring-opening denitrogenative process upon heating to afford carbene intermediate A, which was followed by a 1,2-H migration to give



Scheme 2 Proposed mechanism of intramolecular annulation of 1-sulfonyl-4-(2-aminomethylphenyl)-1,2,3-triazoles.

ketenimine intermediate B. Through the intramolecular nucleophilic addition, zwitterionic intermediate C and its resonance intermediates C' were generated, which could convert to 2a-1 and 2a-2 *via* intramolecular proton transfer. Finally, base-mediated elimination/aromatization of sulfinate results in 3-aminoisoquinoline 3a.

Conclusions

In summary, we have developed an efficient method for the construction of 3-aminoisoquinolines through a metal-free one-pot intramolecular transannulation of 1-sulfonyl-4-(2-aminomethyl phenyl)-1,2,3-triazoles. This method would provide an alternative to the current toolbox for the synthesis of 3-aminoisoquinolines, and further applications of the method to the syntheses of bioactive molecules are in progress.

Experimental

General information

NMR spectra were recorded on Bruker AV III 600 NMR spectrometer and Bruker AV 400 instrument. Solvent signal was used as reference for ^1H NMR (CDCl_3 , 7.26 ppm; DMSO-d_6 , 2.50 ppm) and ^{13}C NMR (CDCl_3 , 77.16 ppm; DMSO-d_6 , 39.52 ppm). The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, td = triple doublet, m = multiplet. Infrared (IR) spectra were recorded on a FTIR-8400S spectrometer. High-resolution mass spectra (HRMS) were recorded on a Waters SYNAPT G2 HDMS.

Reactions were monitored by Thin Layer Chromatography on plates (GF_{254}) supplied by Yantai Chemicals (China). If not specially mentioned, flash column chromatography uses silica gel (200–300 mesh) supplied by Tsingtao Haiyang Chemicals (China). Solvent purification was conducted according to Purification of Laboratory Chemicals (D. D. Perrin, W. L. Armarego and D. R. Perrin, Pergamon Press, Oxford, 1980).



General procedure for the preparation of 3-aminoisoquinolines

A 10 mL pressure tube, fitted with a rubber septum, was charged with triazole (0.1 mmol, 1.0 eq.). The reaction vessel was added freshly distilled toluene (1.0 mL) and then was sealed with a Teflon screwcap and placed in an oil bath preheated to 140 °C. Upon complete consumption of the substrate (monitored by TLC), the solvent was removed and DMSO (1.0 mL) with an aqueous solution of sodium hydroxide (30% w/w, 133 mg, 1.0 mmol) was added. The mixture was heated to around 125 °C, and then stirred at this temperature for 2 h. The reaction was monitored by TLC. After the reaction was complete, the mixture was allowed to cool to room temperature and diluted with water (10 mL). The aqueous solution was then extracted with ethyl acetate (3 × 15 mL) and the combined extracts were dried with anhydrous Na₂SO₄. The solvent was evaporated *in vacuo* and the residue was purified by a silica gel flash column chromatography (eluent: petroleum ether/EtOAc) to give the corresponding products.

N-(Isoquinolin-3-yl)-4-methylbenzenesulfonamide (3a).

Yield: 81%; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.03 (s, 1H), 9.01 (s, 1H), 7.97 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.81 (d, *J* = 8.3 Hz, 2H), 7.67 (dd, *J* = 8.4 Hz, 8.3 Hz, 1H), 7.51 (s, 1H), 7.49 (dd, *J* = 8.4 Hz, 8.2 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 2.30 (s, 3H); ¹³C NMR (150 MHz, DMSO-*d*₆) δ 152.2, 147.1, 143.8, 137.8, 137.5, 131.5, 130.0, 128.0, 127.4, 126.5, 126.3, 125.9, 106.1, 21.4; IR ν_{max} (film): 3326, 2920, 1596, 1352, 1162, 1090, 986 cm⁻¹; HRMS *m/z* calcd for C₁₆H₁₅N₂O₂S [M + H]⁺: 299.0854; found: 299.0858.

N-(7-Bromoisoquinolin-3-yl)-4-methylbenzenesulfonamide (3b).

Yield: 82%; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.13 (s, 1H), 8.99 (s, 1H), 8.26 (s, 1H), 7.86 (d, *J* = 8.9 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.79–7.75 (m, 1H), 7.52 (s, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 2.30 (s, 3H); ¹³C NMR (150 MHz, DMSO-*d*₆) δ 150.9, 147.1, 143.4, 137.2, 135.7, 134.0, 129.6, 129.6, 128.4, 127.0, 126.3, 118.2, 105.4, 20.9; IR ν_{max} (film): 3056, 2847, 1585, 1560, 1513, 1341, 1155, 1091, 936 cm⁻¹; HRMS *m/z* calcd for C₁₆H₁₄BrN₂O₂S [M + H]⁺: 376.9959; found: 376.9965.

N-(7-Chloroisoquinolin-3-yl)-4-methylbenzenesulfonamide (3c).

Yield: 78%; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.12 (s, 1H), 9.00 (s, 1H), 8.10 (d, *J* = 2.0 Hz, 1H), 7.93 (d, *J* = 8.9 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 2H), 7.67 (dd, *J* = 8.9 Hz, 2.0 Hz, 1H), 7.54 (s, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 2.30 (s, 3H); ¹³C NMR (150 MHz, DMSO-*d*₆) δ 151.0, 147.2, 143.4, 137.3, 135.6, 131.6, 129.8, 129.6, 128.4, 127.0, 126.2, 125.8, 105.4, 20.9; IR ν_{max} (film): 3056, 2870, 2848, 1625, 1515, 1341, 1155, 940, 811, cm⁻¹; HRMS *m/z* calcd for C₁₆H₁₄ClN₂O₂S [M + H]⁺: 333.0465; found: 333.0464.

N-(6-Chloroisoquinolin-3-yl)-4-methylbenzenesulfonamide (3d).

Yield: 85%; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.14 (s, 1H), 9.03 (s, 1H), 8.05 (d, *J* = 1.6 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.50 (s, 1H), 7.48 (dd, *J* = 8.8 Hz, 1.6 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 2.30 (s, 3H); ¹³C NMR (150 MHz, DMSO-*d*₆) δ 151.8, 147.6, 143.4, 138.0, 137.2, 136.0, 129.9, 129.6, 127.0, 126.4, 124.8, 123.7, 104.4, 20.9; IR ν_{max} (film): 3057, 2846, 2753, 1627, 1516, 1418, 1344, 1156, 1092, 946 cm⁻¹; HRMS *m/z* calcd for C₁₆H₁₄ClN₂O₂S [M + H]⁺: 333.0465; found: 333.0468.

N-(7-Fluoroisoquinolin-3-yl)-4-methylbenzenesulfonamide (3e). Yield: 65%; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.02 (s, 1H), 9.00 (s, 1H), 7.99 (dd, *J* = 9.0 Hz, 5.3 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 2H), 7.78 (d, *J* = 9.0 Hz, 1H), 7.64–7.59 (m, 1H), 7.58 (s, 1H), 7.33 (d, *J* = 8.2 Hz, 2H), 2.30 (s, 3H); ¹³C NMR (150 MHz, DMSO-*d*₆) δ 159.2 (d, *J* = 244.8 Hz), 151.0 (d, *J* = 5.0 Hz), 146.5 (d, *J* = 1.8 Hz), 143.3, 137.3, 134.4, 129.6, 129.2 (d, *J* = 8.2 Hz), 127.0, 125.8 (d, *J* = 8.8 Hz), 121.6 (d, *J* = 25.9 Hz), 110.4 (d, *J* = 21.0 Hz), 106.0, 20.9; IR ν_{max} (film): 3057, 2849, 1596, 1521, 1354, 1341, 1209, 1154, 1091, 955 cm⁻¹; HRMS *m/z* calcd for C₁₆H₁₄FN₂O₂S [M + H]⁺: 317.0760; found: 317.0762.

N-(6-Fluoroisoquinolin-3-yl)-4-methylbenzenesulfonamide (3f).

Yield: 63%; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.11 (s, 1H), 9.01 (s, 1H), 8.07 (dd, *J* = 8.9 Hz, 5.8 Hz, 1H), 7.83 (d, *J* = 8.3 Hz, 2H), 7.70 (dd, *J* = 10.2 Hz, 2.2 Hz, 1H), 7.52 (s, 1H), 7.37 (td, *J* = 8.9 Hz, 2.2 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 2H), 2.30 (s, 3H); ¹³C NMR (150 MHz, DMSO-*d*₆) δ 163.1 (d, *J* = 249.9 Hz), 151.6, 147.5, 143.4, 138.7 (d, *J* = 11.4 Hz), 137.3, 131.3 (d, *J* = 10.6 Hz), 129.6, 127.0, 122.8, 116.2 (d, *J* = 26.1 Hz), 109.3 (d, *J* = 21.6 Hz), 104.9 (d, *J* = 5.3 Hz), 20.9; IR ν_{max} (film): 3356, 3260, 3066, 1635, 1436, 1345, 1161, 1092, 968 cm⁻¹; HRMS *m/z* calcd for C₁₆H₁₄FN₂O₂S [M + H]⁺: 317.0760; found: 317.0756.

4-Methyl-N-(7-(trifluoromethyl)isoquinolin-3-yl)benzenesulfonamide (3g).

Yield: 50%; ¹H NMR (600 MHz, DMSO-*d*₆) δ 11.31 (s, 1H), 9.21 (s, 1H), 8.48 (s, 1H), 8.09 (d, *J* = 8.8 Hz, 1H), 7.88 (d, *J* = 8.8 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 2H), 7.59 (s, 1H), 7.35 (d, *J* = 8.3 Hz, 2H), 2.31 (s, 3H); ¹³C NMR (150 MHz, DMSO-*d*₆) δ 153.2, 148.7, 143.5, 138.7, 137.1, 129.6, 127.8, 127.1, 126.1 (q, *J* = 4.6 Hz), 126.0 (q, *J* = 4.4 Hz), 125.6 (q, *J* = 32.1 Hz), 124.0 (q, *J* = 272.2 Hz), 123.9, 104.7, 21.0; IR ν_{max} (film): 3063, 2865, 1641, 1605, 1485, 1309, 1178, 1123, 1064, 945 cm⁻¹; HRMS *m/z* calcd for C₁₇H₁₄F₃N₂O₂S [M + H]⁺: 367.0728; found: 367.0731.

N-(7-Methoxyisoquinolin-3-yl)-4-methylbenzenesulfonamide (3h).

Yield: 74%; ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.80 (s, 1H), 8.88 (s, 1H), 7.80 (d, *J* = 9.1 Hz, 1H), 7.77 (d, *J* = 8.3 Hz, 2H), 7.49 (s, 1H), 7.37 (d, *J* = 2.5 Hz, 1H), 7.34 (dd, *J* = 9.1 Hz, 2.5 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 2H), 3.85 (s, 3H), 2.30 (s, 3H); ¹³C NMR (150 MHz, DMSO-*d*₆) δ 157.0, 149.9, 145.1, 143.1, 137.4, 132.7, 129.5, 127.7, 126.9, 126.7, 124.1, 106.8, 104.9, 55.4, 20.99; IR ν_{max} (film): 3064, 2870, 1601, 1577, 1517, 1419, 1342, 1154, 1090, 981 cm⁻¹; HRMS *m/z* calcd for C₁₇H₁₇N₂O₃S [M + H]⁺: 329.0960; found: 329.0954.

4-Methyl-N-(6-methyliisoquinolin-3-yl)benzenesulfonamide (3i).

Yield: 72%; ¹H NMR (600 MHz, DMSO-*d*₆) δ 10.94 (s, 1H), 8.92 (s, 1H), 7.86 (d, *J* = 8.4 Hz, 1H), 7.80 (d, *J* = 8.3 Hz, 2H), 7.61 (s, 1H), 7.40 (s, 1H), 7.34–7.30 (m, 3H), 2.44 (s, 3H), 2.30 (s, 3H); ¹³C NMR (150 MHz, DMSO-*d*₆) δ 151.1, 146.8, 143.2, 141.2, 137.4, 129.5, 128.1, 127.4, 127.0, 124.7, 124.0, 105.1, 21.6, 20.9; IR ν_{max} (film): 3058, 2849, 1634, 1595, 1520, 1343, 1155, 1092, 983 cm⁻¹; HRMS *m/z* calcd for C₁₇H₁₇N₂O₂S [M + H]⁺: 313.1011; found: 313.1015.

N-[1,3]Dioxolo[4,5-*g*]isoquinolin-7-yl)-4-methylbenzenesulfonamide (3j).

Yield: 56%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.83 (s, 1H), 8.67 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 2H), 7.39 (s, 1H), 7.34–7.28 (m, 3H), 7.27 (s, 1H), 6.15 (s, 2H), 2.30 (s, 3H); ¹³C NMR (100 MHz, DMSO-*d*₆) δ 151.4, 148.7, 147.2, 146.1, 143.1, 137.5, 136.0, 129.5,



127.0, 122.6, 106.5, 102.5, 101.9, 101.8, 21.0; IR ν_{max} (film): 3329, 2919, 2848, 1604, 1451, 1341, 1229, 1150, 1039 cm^{-1} ; HRMS m/z calcd for $\text{C}_{17}\text{H}_{15}\text{N}_2\text{O}_4\text{S}$ [$\text{M} + \text{H}$]⁺: 343.0753; found: 343.0759.

N-(6,7-Dimethoxyisoquinolin-3-yl)-4-methylbenzenesulfonamide (3k). Yield: 55%; ^1H NMR (400 MHz, DMSO- d_6) δ 10.82 (s, 1H), 8.71 (s, 1H), 7.77 (d, $J = 8.3$ Hz, 2H), 7.41 (s, 1H), 7.34–7.28 (m, 3H), 7.26 (s, 1H), 3.89 (s, 3H), 3.84 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (100 MHz, DMSO- d_6) δ 153.4, 149.1, 148.3, 145.6, 143.0, 137.7, 134.2, 129.5, 126.9, 121.5, 105.7, 105.3, 104.5, 55.8, 55.6, 21.0; IR ν_{max} (film): 3060, 2848, 1597, 1507, 1423, 1337, 1244, 1161, 1091, 990 cm^{-1} ; HRMS m/z calcd for $\text{C}_{18}\text{H}_{19}\text{N}_2\text{O}_4\text{S}$ [$\text{M} + \text{H}$]⁺: 359.1066; found: 359.1068.

4-Methyl-N-(1-phenylisoquinolin-3-yl)benzenesulfonamide (3l). Yield: 81%; ^1H NMR (400 MHz, CDCl_3) δ 7.95 (d, $J = 8.5$ Hz, 1H), 7.84–7.78 (m, 3H), 7.77 (s, 1H), 7.68 (s, 1H), 7.63 (ddd, $J = 8.3$ Hz, 6.8 Hz, 1.0 Hz, 1H), 7.54–7.49 (m, 2H), 7.48–7.42 (m, 3H), 7.38 (ddd, $J = 8.5$ Hz, 6.8 Hz, 1.1 Hz, 1H), 7.20 (d, $J = 8.1$ Hz, 2H), 2.32 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 160.5, 144.6, 144.1, 139.0, 138.4, 136.5, 130.7, 129.9, 129.8, 129.0, 128.5, 127.6, 127.5, 127.0, 126.1, 124.5, 105.9, 21.6; IR ν_{max} (film): 3061, 2921, 1733, 1622, 1592, 1558, 1339, 1154, 1089, 952 cm^{-1} ; HRMS m/z calcd for $\text{C}_{22}\text{H}_{19}\text{N}_2\text{O}_2\text{S}$ [$\text{M} + \text{H}$]⁺: 375.1167; found: 375.1168.

N-(Benzo[f]isoquinolin-2-yl)-4-methylbenzenesulfonamide (3o). Yield: 91%; ^1H NMR (600 MHz, DMSO- d_6) δ 11.22 (s, 1H), 8.97 (s, 1H), 8.59–8.54 (m, 1H), 8.24 (s, 1H), 8.03–7.99 (m, 1H), 7.88 (d, $J = 8.3$ Hz, 2H), 7.83–7.76 (m, 4H), 7.34 (d, $J = 8.3$ Hz, 2H), 2.29 (s, 3H); ^{13}C NMR (150 MHz, DMSO- d_6) δ 150.5, 148.8, 143.3, 137.5, 136.2, 133.4, 129.6, 129.3, 128.8, 127.5, 127.4, 127.1, 126.5, 124.5, 123.2, 123.1, 102.5, 20.9; IR ν_{max} (film): 3071, 2838, 1595, 1499, 1345, 1156, 963 cm^{-1} ; HRMS m/z calcd for $\text{C}_{20}\text{H}_{17}\text{N}_2\text{O}_2\text{S}$ [$\text{M} + \text{H}$]⁺: 349.1011; found: 349.1014.

4-Methyl-N-(thieno[2,3-c]pyridin-5-yl)benzenesulfonamide (3p). Yield: 55%; ^1H NMR (600 MHz, DMSO- d_6) δ 10.94 (s, 1H), 8.86 (s, 1H), 8.07 (d, $J = 5.3$ Hz, 1H), 7.78 (d, $J = 8.3$ Hz, 2H), 7.59 (d, $J = 0.8$ Hz, 1H), 7.47 (d, $J = 5.3$ Hz, 1H), 7.32 (d, $J = 8.3$ Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (150 MHz, DMSO- d_6) δ 147.1, 143.1, 137.5, 135.2, 131.3, 129.5, 126.9, 123.1, 105.5, 20.9; IR ν_{max} (film): 2869, 2848, 1596, 1490, 1437, 1406, 1341, 1302, 1152, 1091, 977 cm^{-1} ; HRMS m/z calcd for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_2\text{S}_2$ [$\text{M} + \text{H}$]⁺: 305.0418; found: 305.0426.

Conflicts of interest

There are no conflicts to declare.

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