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An expeditious approach to 1-(isoquinolin-1-yl)guanidines via a three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, with carbodiimide

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ABSTRACT

A small library of 1-(isoquinolin-1-yl)guanidine is constructed efficiently via a silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, with carbodiimide. The preliminary biological screens of these isoquinoline library members have been evaluated, which show promising results as PTP1B inhibitor and HCT-116 inhibitor.

1. Introduction

Library construction of small molecules has been recognized as an important step in drug development and drug discovery process, and intense interest has been directed toward the combinatorial synthesis of natural product-like compounds with privileged scaffolds using a diversity-oriented synthesis.[1] Among the skeletons, extensive studies have been toward the preparation of isoquinolines due to their immense biological importance.[2] Many methods including the Pomeranz–Fritsch,[3a,b] Bischler–Napieralski,[3c] Pictet–Spengler reactions,[3d] and metal-catalyzed reactions[4] have been developed. However, generally either harsh reaction conditions and/or tedious reaction procedures are required for these approaches, which limit their application for library synthesis. Recently, we developed an efficient route for the synthesis of 1-(isoquinolin-1-yl)ureas starting from 2-alkynylbenzaldoxime.[5] The 1-(isoquinolin-1-yl)urea, which possesses hydrogen bond donor/acceptor capabilities could be expected to confer interesting biological properties. Duo to the structural similarity of urea and guanidine, we conceived that 1-(isoquinolin-1-yl)guanidine would display the similar functions. Consequently, we started to consider for the library construction of diverse 1-(isoquinolin-1-yl)guanidines, which could be evaluated against various biological screens.

Multi-component reactions have been applied successfully for the formation of natural product-like compounds.[6] We also utilized this strategy for the preparation of a variety of *N*-heterocycles due to its high efficiency.[7] For instance, four-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, alcohol, and α,β-unsaturated aldehyde or ketone was demonstrated efficiently to generate the diverse *H*-pyrazolo[5,1-*a*]isoquinolines.[7a] Among the reaction process, *N*′-(2-alkynylbenzylidene)hydrazide, which was formed in situ from 2-alkynylbenzaldehyde and sulfonohydrazide was believed to be the active species. As mentioned above, 1-(isoquinolin-1-yl)ureas were generated via AgOTf-catalyzed reaction of 2-alkynylbenzaldoxime with carbodiimide.[5b] We envisioned that 1-(isoquinolin-1-yl)guanidine would be formed through a similar transformation starting from *N*′-(2-alkynylbenzylidene)hydrazide with carbodiimide. As shown in Scheme 1, we conceived that after condensation of 2-alkynylbenzaldehyde **1** with sulfonohydrazide, *N*′-(2-alkynylbenzylidene)hydrazide **A** would be generated, which then underwent intramolecular cyclization to afford the key intermediate isoquinolinium-2-yl amide **B** in the presence of silver triflate catalyst.[8] After the subsequent [3+2] cycloaddition reaction with carbodiimide **2** and further intramolecular rearrangement, the desired 1-(isoquinolin-1-yl)guanidine **3** would be produced. Thus, we started to explore the feasibility of this three-component reaction of 2-alkynylbenzaldehyde **1**, sulfonohydrazide, and carbodiimide **2** for rapid access to functionalized 1-(isoquinolin-1-yl)guanidines **3**.

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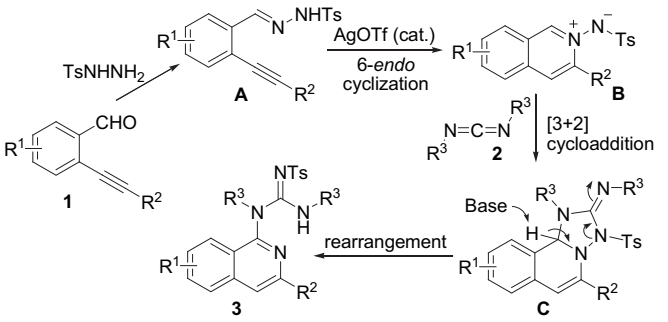
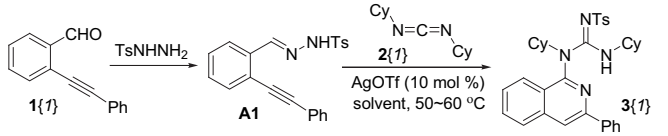


Scheme 1. Proposed synthetic route for formation of 1-(isoquinolin-1-yl)guanidines via a three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, and carbodiimide.

2. Results and discussion

During our initial studies, 2-alkynylbenzaldehyde **1**{1}, sulfonohydrazide, and *N*-((cyclohexylimino)methylene)-cyclohexanamine **2**{1} were selected as the substrates for reaction development. To simplify the optimization process, the reaction was performed in two steps. Thus, after condensation of 2-alkynylbenzaldehyde **1**{1} with sulfonohydrazide, reaction of *N*′-(2-alkynylbenzylidene)hydrazide **A1** and *N*-((cyclohexyl-imino) methylene)cyclohexanamine **2**{1} was investigated. Since silver triflate has been demonstrated as the most efficient catalyst for intramolecular cyclization of *N*′-(2-alkynylbenzylidene)-hydrazide,[8] this model reaction was performed in the presence of 10 mol % of silver triflate in different solvents at 50–60 °C (Table 1). As expected, the desired product **3**{1,1} was isolated in 91% yield when the reaction worked in dichloroethane (Table 1, entry 1). A good yield (81%) was observed as well when acetonitrile was used as a replacement (Table 1, entry 2). However, the yield was dramatically decreased when the reaction occurred in DMF, THF, or 1,4-dioxane (Table 1, entries 3–5). Additionally, a diminished reactivity was displayed when the catalytic amount of silver triflate was reduced or the reaction temperature was lower (data not shown in Table 1). With these results in hand, we re-examined the three-component reaction of 2-alkynylbenzaldehyde **1**{1}, sulfonohydrazide, and *N*-((cyclohexylimino)methylene)*cyclo*-hexanamine **2**{1} in a one-pot manner under the best conditions (Table 1, entry 1). We found that this reaction proceeded smoothly as well to furnish the corresponding product **3**{1,1} in 52% yield.

Table 1
Initial studies for reaction of 2-alkynylbenzaldehyde **1**{1}, sulfonohydrazide, and *N*-((cyclohexylimino)-methylene)cyclohexanamine **2**{1}



Entry	Solvent	Yield (%)[a]
1	DCE	91
2	MeCN	81
3	DMF	27
4	THF	70
5	1,4-Dioxane	26

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**.

Having identified the optimized conditions (10 mol % of silver triflate, $ClCH_2CH_2Cl$, 50–60 °C), we then explored the reaction scope of this three-component reaction. A series of 2-alkynylbenzaldehydes **1** and carbodiimides **2** were employed and the diversity reagents of 2-alkynylbenzaldehydes **1** and carbodiimide **2** are presented in Fig. 1 and Fig. 2. The corresponding results are shown in Table 2. We noticed that all reactions worked well to afford the expected 1-(isoquinolin-1-yl)guanidines in moderate to good yields. Not only aryl substituted carbodiimides but also alkyl substituted carbodiimides are good partners in this three-component reaction. Moreover, various substitutions attached on the triple bond or in the aromatic ring of 2-alkynylbenzaldehydes **1** do not affect the final outcome. Additionally, all products were obtained by a simple purification on silica gel. From the results, it seems that this solution-phase synthesis has the advantages with good substrate generality, mild conditions, and experimental ease. A wide variety of functionality could be readily accommodated and the diversity could be introduced easily.

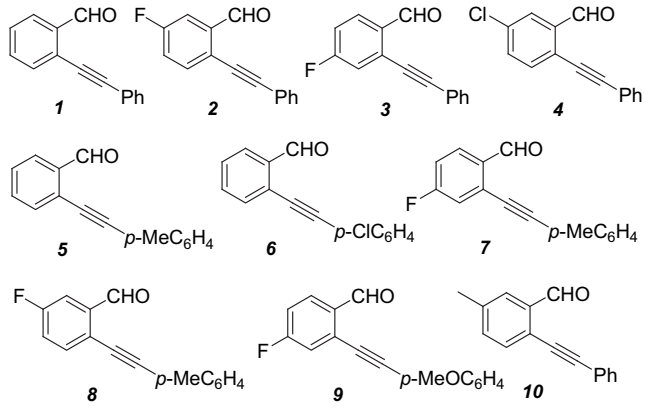


Fig. 1. Diversity reagents **1** {1–10}.

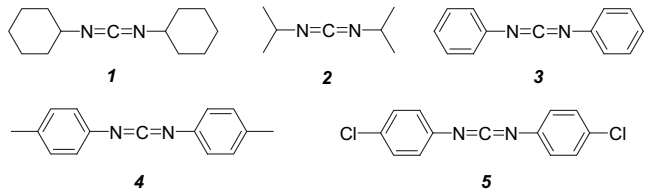


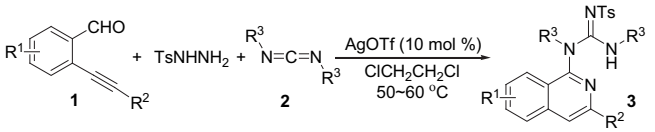
Fig. 2. Carbodiimide reagents **2** {1–5}.

After successful generation of this 1-(isoquinolin-1-yl)guanidine library, the preliminary biological results from this library have proven quite interesting. Although no active compounds were found for the Aurora A assay. Compound **3**{5,2} shows interesting result as HCT-116 inhibitor (IC_{50} 17.378 μg/mL). In the meantime, these compounds were screened in a PTP1B assay, and the active hits are displayed in Table 3. Protein tyrosine phosphatase 1 B (PTP1B) is a novel target for diabetes and obesity because it plays an important role in the negative regulation of insulin signaling pathway. Therefore, the sensitivity of insulin signaling could be improved by inhibition of PTP1B's activity.[9] As shown in Table 3, it is found that the results are promising. Among the compounds, **3** {9,2} is the most effective one (IC_{50} 6.38 μg/mL).

3. Conclusions

In conclusion, a small library of 1-(isoquinolin-1-yl)guanidines has been rapidly constructed utilizing an AgOTf-catalyzed three-component reaction of 2-alkynylbenzaldehyde, sulfonohydrazide, with carbodiimide. The method readily accommodates a wide variety of functionality and the diversity could be introduced by using the easily available building blocks. The preliminary biological screens of these isoquinoline library members have been evaluated,

Table 2
Silver triflate-catalyzed three-component reaction of 2-alkynylbenzaldehyde **1**, sulfonohydrazide, with carbodiimide **2**



Entry	Substrate **1**	Carbodiimide **2**	Product	Yield (%)[a]
1	**1**{1}	**2**{1}	**3**{1,1}	52
2	**1**{2}	**2**{1}	**3**{2,1}	54
3	**1**{3}	**2**{1}	**3**{3,1}	51
4	**1**{4}	**2**{1}	**3**{4,1}	70
5	**1**{5}	**2**{1}	**3**{5,1}	45
6	**1**{6}	**2**{1}	**3**{6,1}	37
7	**1**{7}	**2**{1}	**3**{7,1}	32
8	**1**{8}	**2**{1}	**3**{8,1}	43
9	**1**{9}	**2**{1}	**3**{9,1}	30
10	**1**{10}	**2**{1}	**3**{10,1}	30
11	**1**{1}	**2**{2}	**3**{1,2}	67
12	**1**{2}	**2**{2}	**3**{2,2}	65
13	**1**{3}	**2**{2}	**3**{3,2}	51
14	**1**{4}	**2**{2}	**3**{4,2}	66
15	**1**{5}	**2**{2}	**3**{5,2}	57
16	**1**{6}	**2**{2}	**3**{6,2}	51
17	**1**{7}	**2**{2}	**3**{7,2}	58
18	**1**{8}	**2**{2}	**3**{8,2}	52
19	**1**{9}	**2**{2}	**3**{9,2}	52
20	**1**{10}	**2**{2}	**3**{10,2}	40
21	**1**{1}	**2**{3}	**3**{1,3}	61
22	**1**{4}	**2**{3}	**3**{4,3}	80
23	**1**{5}	**2**{3}	**3**{5,3}	65
24	**1**{6}	**2**{3}	**3**{6,3}	77
25	**1**{8}	**2**{3}	**3**{8,3}	82
26	**1**{10}	**2**{3}	**3**{10,3}	84
27	**1**{1}	**2**{4}	**3**{1,4}	88
28	**1**{4}	**2**{4}	**3**{4,4}	73
29	**1**{5}	**2**{4}	**3**{5,4}	85
30	**1**{6}	**2**{4}	**3**{6,4}	76
31	**1**{8}	**2**{4}	**3**{8,4}	66
32	**1**{10}	**2**{4}	**3**{10,4}	83
33	**1**{1}	**2**{5}	**3**{1,5}	88
34	**1**{6}	**2**{5}	**3**{6,5}	56
35	**1**{8}	**2**{5}	**3**{8,5}	60
36	**1**{10}	**2**{5}	**3**{10,5}	88

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**.

Table 3
Biological screening results for 1-(isoquinolin-1-yl)guanidines (PTP1B activity assay)

Compound	Concentration	Result type	Result unit	Result
3{4,2}	20 μg/mL	%Inhibition	Percent	58.12
3{4,2}		IC_{50}	μg/mL	10.24
3{7,2}	20 μg/mL	%Inhibition	Percent	70.65
3{7,2}		IC_{50}	μg/mL	12.33
3{8,2}	20 μg/mL	%Inhibition	Percent	57.26
3{8,2}		IC_{50}	μg/mL	18.54
3{9,2}	20 μg/mL	%Inhibition	Percent	85.93
3{9,2}		IC_{50}	μg/mL	6.38
3{4,3}	20 μg/mL	%Inhibition	Percent	89.46
3{4,3}		IC_{50}	μg/mL	8.94

which show promising results as PTP1B inhibitor and HCT-116 inhibitor.

4. Experimental section

4.1. General

General procedure for AgOTf-catalyzed three-component reaction of 2-alkynylbenzaldehyde **1**, sulfonohydrazide, with carbodiimide **2**. Silver triflate (0.02 mmol, 10 mol %) was added to a solution of 2-alkynylbenzaldehyde **1** (0.2 mmol), sulfonohydrazide (0.2 mmol), and carbodiimide compound **2** (0.4 mmol, 2.0 equiv) in DCE (2.0 mL). The solution was stirred at 50–60 °C for overnight. After completion of reaction as indicated by TLC, the reaction was quenched by addition of saturated aqueous NH_4Cl (5.0 mL), and the mixture was extracted with EtOAc (4.0 mL×3). The combined organic layer was dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel to provide the desired product **3**.

*4.1.1. 1,3-Dicyclohexyl-1-(3-phenylisoquinolin-1-yl)-2-tosylguanidine (**3**{1,1}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.55–0.60 (m, 2H), 0.64–0.71 (m, 2H), 0.80–0.87 (m, 1H), 0.91–0.99 (m, 1H), 1.20–1.33 (m, 7H), 1.53–1.64 (m, 7H), 2.00–2.01 (m, 1H), 2.43 (s, 3H), 4.90–4.96 (m, 1H), 7.00 (d, *J*=7.0 Hz, 1H), 7.30 (d, *J*=8.0 Hz, 2H), 7.43 (t, *J*=8.0 Hz, 1H), 7.49 (d, *J*=8.0 Hz, 1H), 7.51 (d, *J*=7.0 Hz, 1H), 7.57 (t, *J*=8.5 Hz, 1H), 7.69 (t, *J*=7.5 Hz, 1H), 7.88–7.90 (m, 3H), 8.08 (t, *J*=9.0 Hz, 2H), 8.13 (d, *J*=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 24.3, 24.8, 25.3, 25.8, 32.9, 33.8, 53.2, 60.3, 115.7, 124.8, 124.9, 126.3, 126.4, 127.4, 128.2, 128.8, 129.0, 130.9, 137.3, 138.7, 141.0, 141.9, 149.0, 152.1, 157.5; HRMS (ESI) calcd for $C_{35}H_{40}N_4O_2S$: 581.2950 ($M+H^+$), found: 599.2940.

*4.1.2. 1,3-Dicyclohexyl-1-(7-fluoro-3-phenylisoquinolin-1-yl)-2-tosylguanidine (**3**{2,1}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.57–0.62 (m, 2H), 0.68–0.75 (m, 2H), 0.80–0.87 (m, 1H), 0.91–0.96 (m, 1H), 2.06–2.07 (m, 1H), 2.43 (s, 3H), 4.91 (t, *J*=10.5 Hz, 1H), 7.00 (d, *J*=6.5 Hz, 1H), 7.30 (d, *J*=7.5 Hz, 2H), 7.44 (d, *J*=7.5 Hz, 1H), 7.49–7.52 (m, 3H), 7.71 (dd, *J*=2.0, 9.0 Hz, 1H), 7.89–7.94 (m, 3H), 8.09 (s, 1H), 8.11 (d, *J*=7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 24.3, 24.8, 25.3, 25.8, 30.0, 53.4, 60.4, 108.3 (d, $^2J_{CF}$=21.5 Hz), 115.4, 121.8 (d, $^2J_{CF}$=25.6 Hz), 126.2, 126.4, 128.8, 128.9, 129.0, 130.1 (d, $^3J_{CF}$=9.3 Hz), 135.8, 137.9, 141.0, 142.0, 148.8, 151.6, 151.7, 157.4, 161.4 (d, J_{CF}=250.0 Hz); HRMS (ESI) calcd for $C_{35}H_{39}FN_4O_2S$: 599.2856 ($M+H^+$), found: 599.2834.

*4.1.3. 1,3-Dicyclohexyl-1-(6-fluoro-3-phenylisoquinolin-1-yl)-2-tosylguanidine (**3**{3,1}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.55–0.62 (m, 2H), 0.66–0.74 (m, 2H), 0.80–0.87 (m, 1H), 0.91–0.99 (m, 1H), 1.22–1.35 (m, 7H), 1.53–1.65 (m, 7H), 2.02–2.04 (m, 1H), 2.43 (s, 3H), 4.88–4.94 (m, 1H), 7.03 (d, *J*=6.5 Hz, 1H), 7.29–7.31 (m, 3H), 7.45 (d, *J*=7.5 Hz, 1H), 7.49–7.52 (m, 3H), 7.89 (d, *J*=8.5 Hz, 2H), 8.03 (s, 1H), 8.11–8.13 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 24.3, 24.8, 25.3, 25.8, 33.0, 53.3, 60.5, 110.6 (d, $^2J_{CF}$=20.6 Hz), 115.7 (d, $^3J_{CF}$=5.0 Hz), 118.6 (d, $^2J_{CF}$=25.5 Hz), 122.0, 126.3, 126.5, 128.1 (d, $^3J_{CF}$=9.8 Hz),128.9, 129.0, 129.2, 137.9, 140.3, 140.4, 140.9, 142.0, 150.2, 152.2, 157.6, 163.5 (d, J_{CF}=253.9 Hz); HRMS (ESI) calcd for $C_{35}H_{39}FN_4O_2S$: 621.2675 ($M+Na^+$), found: 621.2641.

*4.1.4. 1-(7-Chloro-3-phenylisoquinolin-1-yl)-1,3-dicyclohexyl-2-tosylguanidine (**3**{4,1}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.55–0.62 (m, 2H), 0.70–0.77 (m, 2H), 0.83–0.88 (m, 1H), 0.93–0.98 (m, 1H), 1.22–1.36 (m, 7H), 1.53–1.65 (m, 7H), 2.04–2.06 (m, 1H), 2.43 (s, 3H), 4.92 (m, 1H), 6.98 (s, 1H), 3.30 (d, *J*=7.5 Hz, 2H), 7.44 (t, *J*=7.5 Hz, 1H), 7.51 (t, *J*=7.5 Hz, 2H), 7.62 (d, *J*=9.0 Hz, 1H), 7.85 (d, *J*=9.0 Hz, 1H), 7.90 (d, *J*=7.5 Hz, 2H), 8.06 (d, *J*=7.0 Hz, 2H), 8.11 (d, *J*=7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 17.5, 21.4, 24.3, 24.7, 25.3, 25.8, 33.0, 33.8, 53.4, 60.4, 115.4, 123.4, 125.5, 126.2, 126.4, 128.4, 128.9, 129.0, 129.1, 132.2, 134.1, 137.0, 137.8, 141.0, 141.9, 149.5, 151.3, 157.4. HRMS (ESI) calcd for $C_{35}H_{39}ClN_4O_2S$: 615.2560 ($M+H^+$), found: 615.2557.

*4.1.5. 1,3-Dicyclohexyl-1-(3-p-tolylisoquinolin-1-yl)-2-tosylguanidine (**3**{5,1}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.55–0.60 (m, 2H), 0.64–0.70 (m, 2H), 0.80–0.86 (m, 1H), 0.90–0.98 (m, 1H), 1.20–1.32 (m, 7H), 1.52–1.61 (m, 7H), 2.01–2.02 (m, 1H), 2.43 (s,

3H), 4.87–4.97 (m, 1H), 7.03 (d, *J*=6.5 Hz, 1H), 6.99 (d, *J*=6.0 Hz), 7.29–7.31 (m, 4H), 7.55 (t, *J*=7.5 Hz, 1H), 7.67 (t, *J*=7.5 Hz, 1H), 7.86 (d, *J*=8.5 Hz, 1H), 7.89 (d, *J*=8.0 Hz, 2H), 8.02–8.07 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.4, 24.3, 24.8, 25.3, 25.8, 33.8, 53.2, 60.3, 115.2, 124.7, 126.2, 126.3, 127.3, 128.0, 128.9, 129.0, 129.6, 130.8, 135.5, 138.7, 138.9, 141.0, 141.9, 149.1, 152.0, 157.5. HRMS (ESI) calcd for $C_{36}H_{42}N_4O_2S$: 595.3107 ($M+H^+$), found: 595.3099.

*4.1.6. 1-(3-(4-Chlorophenyl)isoquinolin-1-yl)-1,3-dicyclohexyl-2-tosylguanidine (**3**{6,1}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.50–0.58 (m, 2H), 0.64–0.71 (m, 2H), 0.78–0.85 (m, 1H), 0.91–0.98 (m, 1H), 1.21–1.33 (m, 7H), 1.54–1.64 (m, 7H), 1.97–1.98 (m, 1H), 2.45 (s, 3H), 4.90–4.95 (m, 1H), 7.01 (d, *J*=7.5 Hz, 1H), 7.30 (d, *J*=7.5 Hz, 2H), 7.46 (d, *J*=9.0 Hz, 2H), 7.58 (t, *J*=7.5 Hz, 1H), 7.70 (t, *J*=8.0 Hz, 1H), 7.88–7.90 (m, 3H), 8.05–8.09 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 24.4, 24.8, 25.3, 25.9, 33.0, 33.9, 53.3, 60.4, 115.7, 124.8, 125.0, 126.3, 127.4, 127.7, 128.5, 129.0, 131.1, 135.0, 136.7, 138.6, 141.0, 142.0, 147.8, 152.3, 157.5; HRMS (ESI) calcd for $C_{35}H_{39}ClN_4O_2S$: 615.2560 ($M+H^+$), found: 615.2549.

*4.1.7. 1,3-Dicyclohexyl-1-(6-fluoro-3-p-tolylisoquinolin-1-yl)-2-tosylguanidine (**3**{7,1}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.55–0.62 (m, 2H), 0.66–0.73 (m, 2H), 0.79–0.88 (m, 1H), 0.90–0.98 (m, 1H), 1.22–1.35 (m, 7H), 1.53–1.64 (m, 7H), 2.00–2.02 (m, 1H), 2.42 (s, 3H), 2.43 (s, 3H), 4.87–4.93 (m, 1H), 7.01 (d, *J*=7.01 Hz, 1H), 7.28–7.32 (m, 5H), 7.45 (dd, *J*=2.5, 9.5 Hz, 1H), 7.88 (d, *J*=8.0 Hz, 2H), 7.98 (s, 1H), 8.01 (d, *J*=8.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.4, 24.3, 24.8, 25.3, 25.9, 33.0, 53.3, 60.5, 110.5 (d, $^2J_{CF}$=20.8 Hz), 114.6 (d, $^3J_{CF}$=5 Hz), 118.4 (d, $^2J_{CF}$=24.4 Hz), 121.9, 126.3, 126.5, 128.1 (d, $^3J_{CF}$=10 Hz), 128.3, 129.1, 129.6, 135.2, 139.3, 140.4, 140.9, 142.0, 150.3, 152.1, 157.6, 163.5 (d, J_{CF}=252.8 Hz); HRMS (ESI) calcd for $C_{36}H_{41}FN_4O_2S$: 613.3013 ($M+H^+$), found: 613.3008.

*4.1.8. 1,3-Dicyclohexyl-1-(7-fluoro-3-p-tolylisoquinolin-1-yl)-2-tosylguanidine (**3**{8,1}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.55–0.62 (m, 2H), 0.67–0.75 (m, 2H), 0.79–0.88 (m, 1H), 0.89–0.97 (m, 1H), 1.22–1.35 (m, 7H), 1.52–1.64 (m, 7H), 2.02–2.04 (m, 1H), 2.42 (s, 3H), 2.43 (s, 3H), 4.88–4.92 (m, 1H), 6.99 (d, *J*=5.0 Hz, 1H), 7.29–7.32 (m, 4H), 7.46 (td, *J*=2.0, 8.0 Hz, 1H), 7.69 (dd, *J*=2, 9.5 Hz, 1H), 7.88–7.90 (m, 3H), 8.01 (d, *J*=8.5 Hz, 2H), 8.04 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.4, 24.3, 24.8, 25.3, 25.8, 33.0, 53.4, 60.4, 108.3, (d, $^2J_{CF}$=22.1 Hz), 114.9, 121.8 (d, $^2J_{CF}$=25.9 Hz), 125.7 (d, $^3J_{CF}$=8.9 Hz), 126.3, 129.1, 129.6, 129.9, 130.0 (d, $^3J_{CF}$=7.6 Hz), 135.2, 135.8, 139.1, 141.0, 142.0, 148.9, 151.5, 151.6, 157.4, 161.3 (d, J_{CF}=249.5 Hz); HRMS (ESI) calcd for $C_{36}H_{41}FN_4O_2S$: 613.3013 ($M+H^+$), found: 613.3008.

*4.1.9. 1,3-Dicyclohexyl-1-(6-fluoro-3-(4-methoxyphenyl)isoquinolin-1-yl)-2-tosylguanidine (**3**{9,1}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.55–0.62 (m, 2H), 0.66–0.73 (m, 2H), 0.80–0.88 (m, 1H), 0.91–0.98 (m, 1H), 1.22–1.35 (m, 7H), 1.53–1.65 (m, 7H), 2.01–2.04 (m, 1H), 2.43 (s, 3H), 3.88 (s, 3H), 4.86–4.92 (m, 1H), 7.02–7.03 (m, 3H), 7.28–7.31 (m, 3H), 7.44 (dd, *J*=2.5, 8.5 Hz, 1H), 7.88 (d, *J*=7.5 Hz, 2H), 7.92 (s, 1H), 8.04–8.09 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 24.3, 24.9, 25.3, 25.9, 33.0, 42.6, 53.3, 55.4, 60.4, 110.4 (d, $^2J_{CF}$=22.0 Hz), 113.8, 113.9, 114.0, 114.3, 118.2 (d, $^2J_{CF}$=25.8 Hz), 121.7, 126.3, 127.9, 128.1 (d, $^3J_{CF}$=10.0 Hz), 129.1, 130.5, 140.4, 140.9, 150.1, 152.1, 157.6, 161.6 (d, J_{CF}=232 Hz); HRMS (ESI) calcd for $C_{36}H_{41}FN_4O_3S$: 629.2962 ($M+H^+$), found: 629.2960.

*4.1.10. 1,3-Dicyclohexyl-1-(7-methyl-3-phenylisoquinolin-1-yl)-2-tosylguanidine (**3**{10,1}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.52–0.59 (m, 2H), 0.64–0.72 (m, 2H), 0.78–090 (m, 1H), 0.91–0.99 (m, 1H), 1.20–1.34 (m, 7H), 1.52–1.68 (m, 7H), 2.00–2.01 (m, 1H), 2.43 (s, 3H), 2.54 (s, 3H), 4.91–4.97 (m, 1H), 6.95 (d, *J*=4.5 Hz, 1H), 7.29 (d, *J*=7.5 Hz, 2H), 7.41 (t, *J*=7.0 Hz, 1H), 7.47–7.53 (m, 3H), 7.78 (d, *J*=8.5 Hz, 1H), 7.82 (s, 1H), 7.89 (d, *J*=8.5 Hz, 2H), 8.04 (s, 1H), 8.11 (d, *J*=7.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 22.2, 24.4, 24.9, 25.3, 25.6, 25.9, 33.1, 33.9, 53.3, 60.2, 115.7, 123.3, 125.2, 126.3, 126.4, 127.3, 128.7, 128.8, 129.0, 133.3, 137.0, 138.4, 138.7, 141.2, 141.9, 148.2, 151.3, 157.4; HRMS (ESI) calcd for $C_{36}H_{42}N_4O_2S$: 595.3107 ($M+H^+$), found: 595.3086.

*4.1.11. 1,3-Diisopropyl-1-(3-phenylisoquinolin-1-yl)-2-tosylguanidine (**3**{1,2}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.53 (s, 6H), 1.23 (s, 6H), 2.37–2.40 (m, 1H), 2.13 (s, 3H), 5.34–5.40 (m, 1H), 6.90 (d, *J*=7.0 Hz, 1H), 7.30 (d, *J*=8.0 Hz, 2H), 7.42 (t, *J*=7.5 Hz, 1H), 7.50 (t, *J*=7.5 Hz, 2H), 7.57 (t, *J*=8.0 Hz, 1H), 7.69 (t, *J*=7.5 Hz, 1H), 7.89–7.92 (m, 3H), 8.04 (d, *J*=8.5 Hz, 1H), 8.08 (s, 1H), 8.14 (d, *J*=7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.3, 22.8, 46.1, 52.6, 115.8, 124.5, 124.6, 126.4, 126.5, 127.5, 128.2, 128.8, 128.9, 129.0, 130.9, 138.2, 138.8, 140.8, 142.0, 149.0, 152.0, 157.8; HRMS (ESI) calcd for $C_{29}H_{32}N_4O_2S$: 501.2324 ($M+H^+$), found: 501.2331.

*4.1.12. 1-(7-Fluoro-3-phenylisoquinolin-1-yl)-1,3-diisopropyl-2-tosylguanidine (**3**{2,2}).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.58 (d, *J*=6.2 Hz, 6H), 1.22 (d, *J*=6.6 Hz, 6H), 2.43 (s, 3H), 2.45–2.47 (m, 1H), 5.31–5.34 (m, 1H), 6.89 (d, *J*=7.68 Hz, 1H), 7.30 (d, *J*=8.0 Hz, 2H), 7.41–7.52 (m, 4H), 7.66 (dd, *J*=2.2, 9.1 Hz, 1H), 7.89–7.93 (m, 3H), 8.08 (s, 1H), 8.11–8.13 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 22.8, 46.3, 52.8, 108.2 (d, $^2J_{CF}$=22.9 Hz), 115.6, 121.8 (d, $^2J_{CF}$=25.6 Hz), 125.5 (d, $^3J_{CF}$=7.8 Hz), 126.4, 128.9, 129.0, 129.1, 130.2 (d, $^3J_{CF}$=8.9 Hz), 135.9, 137.9, 140.8, 142.1, 148.4, 151.5, 151.6, 157.7, 161.4 (d, J_{CF}=249.8 Hz); HRMS (ESI) calcd for $C_{29}H_{31}FN_4O_2S$: 519.2230 ($M+H^+$), found: 519.2226.

*4.1.13. 1-(6-Fluoro-3-phenylisoquinolin-1-yl)-1,3-diisopropyl-2-tosylguanidine (**3**{3,2}).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (d, *J*=6.2 Hz, 6H), 1.23 (d, *J*=6.2 Hz, 6H), 2.38–2.42 (m, 1H), 2.43 (s, 3H), 5.33–5.36 (m, 1H), 6.92 (d, *J*=7.7 Hz, 1H), 7.30–7.35 (m, 3H), 7.42–7.46 (m, 1H), 7.48–7.52 (m, 3H), 7.90 (d, *J*=8.1 Hz, 2H), 8.02 (s, 1H), 8.08 (dd, *J*=5.5, 9.5 Hz, 1H), 8.12 (d, *J*=6.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 22.8, 46.2, 52.8, 110.7 (d, $^2J_{CF}$=21.1 Hz), 115.2, 115.3, 118.6 (d, $^2J_{CF}$=25.5 Hz), 121.7, 126.4, 126.6, 128.0 (d, $^3J_{CF}$=9.8 Hz), 128.9, 129.1, 129.2, 137.9, 140.5 (d, $^3J_{CF}$=9.8 Hz), 140.7, 142.1, 150.2, 152.1, 157.9, 163.5 (d, J_{CF}=252.8 Hz); HRMS (ESI) calcd for $C_{29}H_{31}FN_4O_2S$: 519.2230 ($M+H^+$), found: 519.2220.

*4.1.14. 1-(7-Chloro-3-phenylisoquinolin-1-yl)-1,3-diisopropyl-2-tosylguanidine (**3**{4,2}).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.60 (d, *J*=6.2 Hz, 6H), 1.23 (d, *J*=7.0 Hz, 6H), 2.43 (s, 3H), 2.48–2.50 (m, 1H), 5.30–5.34 (m, 1H), 6.85 (d, *J*=7.7 Hz, 1H), 7.30 (d, *J*=8.0 Hz, 2H), 7.42–7.46 (m, 1H), 7.49–7.52 (m, 2H), 7.63 (dd, *J*=1.84, 8.8 Hz, 1H), 7.85 (d, *J*=8.8 Hz, 1H), 7.9 (d, *J*=8.4 Hz, 2H), 8.00 (d, 1H), 8.05 (d, 1H), 8.11–8.13 (m. 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 21.5, 22.9, 46.4, 52.9, 115.5, 123.4, 125.2, 126.4, 126.5, 128.9, 129.1, 129.2, 132.2, 134.2, 137.1, 137.8, 140.9, 142.1, 149.5, 151.2, 157.8; HRMS (ESI) calcd for $C_{29}H_{31}ClN_4O_2S$: 557.1754 ($M+Na^+$), found: 557.1749.

*4.1.15. 1,3-Diisopropyl-1-(3-p-tolylisoquinolin-1-yl)-2-tosylguanidine (**3**{5,2}).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.53 (d, *J*=5.12 Hz, 6H), 1.22 (d, *J*=4.8 Hz, 6H), 2.37–2.39 (m, 1H), 2.42 (s, 3H), 2.43 (s, 3H), 5.34–5.38 (m, 1H), 6.88 (d, *J*=7.68 Hz, 1H), 7.30 (d, *J*=8.1 Hz, 4H), 7.54–7.57 (m, 1H), 7.66–7.70 (m, 1H), 7.87 (d, *J*=8.0 Hz, 1H), 7.90 (d, *J*=8.1 Hz, 2H), 8.01–8.04 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 21.4, 22.8, 115.3, 124.4, 124.6, 126.3, 126.4, 127.4, 128.0, 129.1, 129.6, 130.9, 135.5, 138.8, 139.0, 140.8, 142.0, 149.0, 151.8, 157.8; HRMS (ESI) calcd for $C_{30}H_{34}N_4O_2S$: 537.2300 ($M+Na^+$), found: 537.2306.

*4.1.16. 1-(3-(4-Chlorophenyl)isoquinolin-1-yl)-1,3-diisopropyl-2-tosylguanidine(**3**{6,2}).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.54 (d, *J*=5.8 Hz, 6H), 1.22 (d, *J*=6.2 Hz, 6H), 2.37–2.38 (m, 1H), 2.43 (s, 3H), 5.33–5.37

(m, 1H), 6.91 (d, *J*=7.72 Hz, 1H), 7.31 (d, *J*=8.0 Hz, 2H), 7.46 (d, *J*=8.44 Hz, 2H), 7.59 (t, *J*=7.7 Hz, 1H), 7.71 (t, *J*=7.4 Hz, 1H), 7.88–7.91 (m, 3H), 8.03–8.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4, 22.8, 46.1, 52.7, 115.8, 124.6, 124.7126.4, 127.5, 127.7, 128.5, 129.0, 129.1, 131.1, 135.0, 136.7, 138.7, 140.7, 142.1, 147.8, 152.1, 157.8; HRMS (ESI) calcd for $C_{29}H_{31}ClN_4O_2S$: 535.1934 ($M+H^+$), found: 535.1922.

*4.1.17. 1-(6-Fluoro-3-p-tolylisoquinolin-1-yl)-1,3-diisopropyl-2-tosylguanidine (**3**{7,2}).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.56 (d, *J*=5.8 Hz, 6H), 1.22 (d, *J*=6.2 Hz, 6H), 2.39–2.40 (m, 1H), 2.42 (s, 3H), 2.43 (s, 3H), 6.90 (d, *J*=7.7 Hz, 1H), 7.28–7.32 (m, 5H), 7.47 (dd, *J*=2.6, 9.2 Hz 1H), 7.89 (d, *J*=8.0 Hz, 2H), 7.97 (s, 1H), 8.01 (d, *J*=8.1 Hz, 2H), 8.06 (dd, *J*=5.5, 9.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.4, 22.8, 46.2, 52.8, 110.6 (d, $^2J_{CF}$=20.8 Hz), 114.7, 114.8, 118.4 (d, $^2J_{CF}$=13.3 Hz), 121.6, 126.4 (d, $^3J_{CF}$=9.9 Hz), 127.9, 128.0, 129.1, 129.6, 135.1, 139.4, 140.6, 140.8, 142.1, 150.3, 152.0, 157.9, 163.4 (d, J_{CF}=252.5 Hz); HRMS (ESI) calcd for $C_{30}H_{33}FN_4O_2S$: 533.2387 ($M+H^+$), found: 533.2377.

*4.1.18. 1-(7-Fluoro-3-p-tolylisoquinolin-1-yl)-1,3-diisopropyl-2-tosylguanidine (**3**{8,2}).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (d, *J*=6.2 Hz, 6H), 1.21 (d, *J*=6.6 Hz, 6H), 2.42 (s, 3H), 2.43 (s, 3H), 2.45–2.49 (m, 1H), 5.30–5.33 (m, 1H), 6.88 (d, *J*=7.7 Hz, 1H), 7.27 (s, 1H), 7.30 (d, *J*=8.1 Hz, 3H), 7.47 (dt, *J*=2.6, 8.6 Hz, 1H), 7.64 (dd, *J*=2.2, 9.2 Hz, 1H), 7.88–7.91 (m, 3H), 8.00–8.03 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.4, 22.9, 46.3, 52.7, 108.2 (d, $^2J_{CF}$=21.6 Hz), 115.1, 121.8 (d, $^2J_{CF}$=26.6 Hz), 125.3 (d, $^3J_{CF}$=9.0 Hz), 126.3, 126.4, 129.1, 129.6, 130.1 (d, $^3J_{CF}$=9.1 Hz), 135.2, 135.9, 139.1, 140.9, 142.1, 148.9, 151.5, 157.7, 161.4 (d, J_{CF}=249.8 Hz); HRMS (ESI) calcd for $C_{30}H_{33}FN_4O_2S$: 533.2387 ($M+H^+$), found: 533.2380.

*4.1.19. 1-(6-Fluoro-3-(4-methoxyphenyl)isoquinolin-1-yl)-1,3-diisopropyl-2-tosylguanidine (**3**{9,2}).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.57 (d, *J*=6.2 Hz, 6H), 1.22 (d, *J*=6.2 Hz, 6H), 2.40–2.41 (m, 1H), 2.43 (s, 3H), 3.88 (s, 3H), 5.31–5.35 (m, 1H), 6.90 (d, *J*=7.7 Hz, 1H), 7.02 (d, *J*=9.1 Hz, 2H), 7.28–7.36 (m, 3H), 7.45 (dd, *J*=9.2 Hz, 1H), 7.88–7.92 (m, 3H), 8.02–8.02 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 22.8, 46.3, 52.7, 55.4, 110.5 (d, $^2J_{CF}$=21.8 Hz), 114.0, 114.1, 114.3, 118.2 (d, $^2J_{CF}$=25.5 Hz), 121.3, 126.4, 127.9 (d, $^3J_{CF}$=10.5 Hz), 129.1, 130.5, 140.5, 140.6, 140.7, 142.1, 150.5, 151.9, 157.8, 160.7, 163.5 (d, J_{CF}=252.8 Hz); HRMS (ESI) calcd for $C_{30}H_{33}FN_4O_3S$: 549.2366 ($M+H^+$), found: 549.2348.

*4.1.20. 1,3-Diisopropyl-1-(7-methyl-3-phenylisoquinolin-1-yl)-2-tosylguanidine (**3**{10,2}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.55 (s, 6H), 1.21 (s, 6H), 2.43 (s, 3H), 2.44–2.46 (m, 1H), 2.54 (s, 3H), 5.34–5.40 (m, 1H), 7.30 (d, *J*=7.5 Hz, 2H), 7.41 (t, *J*=7.5 Hz, 1H), 7.57–7.53 (m, 3H), 7.79 (d, *J*=9.0 Hz, 2H), 7.91 (d, *J*=8.5 Hz, 2H), 8.03 (s, 1H), 8.12 (d, *J*=7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 22.1, 22.8, 46.2, 52.2, 115.8, 123.1, 124.9, 126.4, 127.4, 128.7, 128.8, 129.1, 133.3, 137.1, 138.4, 138.6, 141.0, 141.9, 148.2, 151.2, 157.7; HRMS (ESI) calcd for $C_{30}H_{34}N_4O_2S$: 515.2481 ($M+H^+$), found: 515.2465.

*4.1.21. 1,3-Diphenyl-1-(3-phenylisoquinolin-1-yl)-2-tosylguanidine (**3**{1,3}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.34 (s, 1H), 6.70 (t, *J*=7.0 Hz, 1H), 6.79–6.85 (m, 6H), 6.98 (t, *J*=7.5 Hz, 1H), 7.04–7.08 (m, 4H), 7.21–7.24 (m, 1H), 7.42–7.49 (m, 4H), 7.61 (d, *J*=9.0 Hz, 1H), 7.66 (d, *J*=8.0 Hz, 2H), 7.70 (d, *J*=8.0 Hz, 1H), 7.87 (s, 1H), 8.00 (d, *J*=7.0 Hz, 2H), 9.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 115.9, 123.3, 124.8, 125.0, 125.1, 125.6, 125.8, 126.4, 126.6, 127.1, 127.2, 128.3, 128.7, 128.8, 129.1, 130.2, 136.4, 138.2, 139.2, 142.4, 142.6, 149.1, 152.8, 157.5; HRMS (ESI) calcd for $C_{35}H_{28}N_4O_2S$: 569.2011 ($M+H^+$), found: 669.2024.

*4.1.22. 1-(7-Chloro-3-phenylisoquinolin-1-yl)-1,3-diphenyl-2-tosylguanidine (**3**{4,3}).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.73–6.74 (m, 3H), 6.83 (s, 3H), 7.01 (d, *J*=7.3 Hz, 3H), 7.07 (t, *J*=7.7 Hz, 4H), 7.38 (dd, *J*=2.2, 8.8 Hz, 1H), 7.46–7.49 (m, 4H), 7.62 (s, 1H), 7.64–7.67 (m, 2H), 7.86 (s, 1H), 8.01 (d, *J*=6.7 Hz, 2H), 9.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 115.5, 119.2, 123.8, 124.0, 124.8, 125.0, 125.9, 126.0, 126.4, 126.6, 128.4, 128.6, 128.7, 128.8, 129.2, 131.2, 132.7, 136.3, 137.5, 137.7, 138.8, 142.1, 142.6, 149.6, 152.0, 157.6; HRMS (ESI) calcd for $C_{35}H_{27}ClN_4O_2S$: 603.1621 ($M+H^+$), found: 603.1598.

*4.1.23. 1,3-Diphenyl-1-(3-p-tolylisoquinolin-1-yl)-2-tosylguanidine (**3**{5,3}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.33 (s, 3H), 2.43 (s, 3H), 6.68 (t, *J*=7.0 Hz, 1H), 6.77–6.83 (t, 6H), 6.97 (t, *J*=7.0 Hz, 1H), 7.04 (d, *J*=7.5 Hz, 2H), 7.07 (d, *J*=8.0 Hz, 2H), 7.19 (t, *J*=7.5 Hz, 1H), 7.27 (d, *J*=8.0 Hz, 2H), 7.44 (t, *J*=7.0 Hz, 1H), 7.57 (d, *J*=8.0 Hz, 1H), 7.65–7.67 (m, 3H), 7.82 (s, 1H), 7.90 (d, *J*=8.5 Hz, 2H), 9.37 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.4, 115.4, 123.1, 124.7, 124.9, 125.0, 125.5, 125.7, 126.4, 126.5, 126.9, 127.1, 128.3, 128.7, 129.1, 129.4, 130.1, 135.4, 136.3, 138.6, 139.1, 139.2, 142.3, 142.6, 149.1, 152.7, 157.5; HRMS (ESI) calcd for $C_{36}H_{30}N_4O_2S$: 583.2168($M+H^+$), found: 583.2168.

*4.1.24. 1-(3-(4-Chlorophenyl)isoquinolin-1-yl)-1,3-diphenyl-2-tosylguanidine (**3**{6,3}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 6.71 (q, *J*=4.5, 8.5 Hz, 1H), 6.80–6.83 (m, 6H), 6.99 (d, *J*=7.0 Hz, 1H), 7.04 (d, *J*=8.0 Hz, 2H), 7.08 (d, *J*=7.5 Hz, 2H), 7.22 (d, *J*=7.0 Hz, 2H), 7.40 (d, *J*=8.0 Hz, 2H), 7.47 (t, *J*=7.0 Hz, 1H), 7.59 (d, *J*=9.0 Hz, 1H), 7.64 (d, *J*=8.5 Hz, 2H), 7.69 (d, *J*=8.5 Hz, 1H), 7.83 (s, 1H), 7.90 (d, *J*=8.5 Hz, 2H), 9.39 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 115.8, 123.3, 124.7, 124.9, 125.0, 125.7, 125.8, 126.0, 126.4, 127.2, 127.4, 127.8, 128.3, 128.7, 128.8, 129.1, 130.3, 134.6, 136.3, 136.6, 139.1, 142.4, 147.8, 152.9, 157.3; HRMS (ESI) calcd for $C_{35}H_{27}ClN_4O_2S$: 603.1621 ($M+H^+$), found: 603.1636.

*4.1.25. 1-(7-Fluoro-3-p-tolylisoquinolin-1-yl)-1,3-diphenyl-2-tosylguanidine (**3**{8,3}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 2.45 (s, 3H), 6.71–6.74 (m, 1H), 6.81–8.83 (m, 6H), 7.00 (d, *J*=7.5 Hz, 1H), 7.05–7.09 (m, 5H), 7.22 (td, *J*=2.5, 8.5 Hz, 1H), 7.29 (d, *J*=8.5 Hz, 2H), 7.66–7.69 (m, 3H), 7.84 (s, 1H), 7.91 (d, *J*=8.5 Hz, 2H), 9.36 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.4, 108.6, 108.7 (d, $^2J_{CF}$=23.0 Hz), 115.1, 119.2, 120.9 (d, $^2J_{CF}$=25.6 Hz), 124.8, 125.0, 125.8, 125.9, 126.4, 126.5, 128.4, 128.6, 129.0, 129.2, 129.5, 129.7, 129.8, 135.1, 136.3, 138.9 (d, $^3J_{CF}$=8.8 Hz), 142.0, 142.5, 148.9, 152.2 (d, $^3J_{CF}$=5.8 Hz), 157.6, 160.2 (d, J_{CF}=247.5 Hz); HRMS (ESI) calcd for $C_{36}H_{29}FN_4O_2S$: 623.1893($M+Na^+$), found: 623.1874.

*4.1.26. 1-(7-Methyl-3-phenylisoquinolin-1-yl)-1,3-diphenyl-2-tosylguanidine (**3**{10,3}).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.29 (s, 3H), 2.31 (s, 3H), 6.73 (t, *J*=6.5 Hz, 1H), 6.81–6.86 (m, 6H), 6.96 (d, *J*=7.5 Hz, 1H), 7.02–7.06 (m, 4H), 7.31 (d, *J*=8.5 Hz, 1H), 7.34 (d, *J*=7.0 Hz, 1H), 7.40–7.42 (m, 2H), 7.61 (d, *J*=8.5 Hz, 1H), 7.64 (d, *J*=8.5 Hz, 2H), 7.85 (s, 1H), 7.97 (d, *J*=6.5 Hz, 2H), 9.34 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 21.9, 115.9, 119.0, 122.1, 123.6, 123.8, 124.7, 124.8, 125.2, 125.8, 126.4, 126.5, 127.0, 128.3, 128.5, 128.6, 128.7, 129.1, 132.5, 136.4, 137.4, 137.6, 138.3, 139.1, 142.4, 148.3, 152.2, 157.5; HRMS (ESI) calcd for $C_{36}H_{30}N_4O_2S$: 583.2168 ($M+H^+$), found: 583.2168.

*4.1.27. 1-(3-Phenylisoquinolin-1-yl)-1,3-dip-tolyl-2-tosylguanidine (**3**{1,4}).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.89 (s, 3H), 2.20 (s, 3H), 2.37 (s, 3H), 6.55 (q, *J*=8.4 Hz, 4H), 6.72 (d, *J*=8.1 Hz, 2H), 6.88 (d, *J*=8.1 Hz, 2H), 7.10–7.14 (m, 3H), 7.20–7.24 (m, 1H), 7.40–7.48 (m, 3H), 7.58 (d, *J*=8.4 Hz, 1H), 7.67 (d, *J*=8.4 Hz, 1H), 7.70 (d, *J*=8.4 Hz, 2H), 7.83 (s, 1H), 8.00 (d, *J*=7.0 Hz, 2H), 9.23 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.3, 20.7, 21.3, 115.6, 123.3, 124.9, 125.0, 125.9, 126.4, 126.5, 126.9, 127.0, 128.5, 128.7, 129.0, 129.1, 129.3, 129.9, 133.7, 135.3, 135.6, 138.1, 139.0, 139.2, 140.1, 142.2, 150.0, 152.7, 157.9;

HRMS (ESI) calcd for $C_{37}H_{32}N_4O_2S$: 597.2324 ($M+H^+$), found: 597.2312.

*4.1.28. 1-(7-Chloro-3-phenylisoquinolin-1-yl)-1,3-diphenyl-2-tosylguanidine (**3**{4,4}).* ^1H NMR (500 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.22 (s, 3H), 2.39 (s, 3H), 6.58 (s, 4H), 6.71 (d, J=8.0 Hz, 2H), 6.90 (d, J=8.5 Hz, 2H), 7.14 (d, J=8.5 Hz, 2H), 7.38 (dd, J=2.0, 7.0 Hz, 1H), 7.44–7.46 (m, 2H), 7.50 (t, J=7.0 Hz, 2H), 7.61 (d, J=8.0 Hz, 1H), 7.70 (d, J=8.0 Hz, 2H), 7.84 (s, 1H), 8.04 (d, J=7.5 Hz, 2H), 9.22 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.5, 20.8, 21.5, 115.4, 123.9, 124.3, 124.9, 125.4, 126.5, 126.7, 128.7, 128.8, 128.9, 129.0, 129.1, 129.2, 129.6, 131.0, 132.4, 133.8, 135.8, 136.0, 137.5, 137.8, 139.7, 142.5, 149.6, 152.1, 158.2; HRMS (ESI) calcd for $C_{37}H_{31}ClN_4O_2S$: 631.1934 ($M+H^+$), found: 631.1900.

*4.1.29. 1,3-Dip-tolyl-1-(3-p-tolylisoquinolin-1-yl)-2-tosylguanidine (**3**{5,4}).* ^1H NMR (500 MHz, $CDCl_3$) δ 1.90 (s, 3H), 2.20 (s, 3H), 2.31 (s, 1H), 2.37 (s, 3H), 2.43 (s, 3H), 6.55 (m, 4H), 6.71 (d, J=8.5 Hz, 2H), 6.87 (d, J=8.0 Hz, 2H), 7.11–7.14 (m, 3H), 7.18 (t, J=7.5 Hz, 1H), 7.27 (d, J=8.0 Hz, 2H), 7.44 (t, J=8.5 Hz, 1H), 7.55 (d, J=8.5 Hz, 1H), 7.64 (d, J=8.5 Hz, 1H), 7.71 (d, J=8.0 Hz, 2H), 7.80 (s, 1H), 7.90 (d, J=8.0 Hz, 2H), 9.22 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 20.8, 21.4, 21.8, 115.2, 123.2, 125.0, 125.1, 126.0, 126.4, 126.5, 126.7, 127.0, 128.9, 129.0, 129.1, 129.2, 129.4, 129.9, 133.8, 135.4, 135.5, 135.6, 138.6, 139.2, 140.2, 142.3, 149.2, 152.7, 158.0; HRMS (ESI) calcd for $C_{38}H_{34}N_4O_2S$: 611.2481 ($M+H^+$), found: 611.2487.

*4.1.30. 1-(3-(4-Chlorophenyl)isoquinolin-1-yl)-1,3-dip-tolyl-2-tosylguanidine (**3**{6,4}).* ^1H NMR (500 MHz, $CDCl_3$) δ 1.91 (s, 3H), 2.21 (s, 3H), 2.39 (s, 3H), 6.55 (s, 4H), 6.70 (d, J=8.0 Hz, 2H), 6.88 (d, J=8.0 Hz, 2H), 7.13 (d, J=8.5 Hz, 2H), 7.25 (d, J=8 Hz, 1H), 7.41 (d, J=7.5 Hz, 2H), 7.48 (t, J=8.0 Hz, 1H), 7.60 (d, J=8.5 Hz, 1H), 7.67–7.69 (m, 4H), 7.81 (s, 1H), 7.91 (d, J=8.5 Hz, 2H), 9.24 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 20.8, 21.5, 115.6, 123.4, 124.9, 125.0, 125.2, 126.0, 126.5, 127.1, 127.2, 127.8, 128.8, 128.9, 129.1, 129.4, 130.2, 133.7, 134.6, 135.5, 135.8, 136.7, 139.1, 140.1, 142.4, 147.8, 153.0, 157.9; HRMS (ESI) calcd for $C_{37}H_{31}ClN_4O_2S$: 631.1934 ($M+H^+$), found: 631.1910.

*4.1.31. 1-(7-Fluoro-3-p-tolylisoquinolin-1-yl)-1,3-dip-tolyl-2-tosylguanidine (**3**{8,4}).* ^1H NMR (500 MHz, $CDCl_3$) δ 1.93 (s, 3H), 2.21 (s, 3H), 2.38 (s, 3H), 2.44 (s, 3H), 6.56–6.60 (m, 4H), 6.70 (d, J=8.5 Hz, 2H), 6.88 (d, J=8.5 Hz, 2H), 7.06 (d, J=10.0 Hz, 1H), 7.13 (d, J=7.5 Hz, 2H), 7.20 (td, J=2.0, 8.0 Hz, 1H), 7.29 (d, J=8.0 Hz, 2H), 7.65 (dd, J=5.5, 9.0 Hz, 1H), 7.70 (d, J=7.5 Hz, 2H), 7.81 (s, 1H), 9.3 (d, J=8.0 Hz, 2H), 9.24 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 20.8, 21.2, 21.4, 108.9 (d, $^2J_{CF}$=22.9 Hz), 114.9, 120.6 (d, $^2J_{CF}$=26.0 Hz), 124.9, 125.2, 126.4, 126.5, 128.8, 129.1, 129.5 (d, $^3J_{CF}$=8.3 Hz), 133.8, 135.2, 135.6, 135.8, 136.3, 138.8, 139.2, 139.7, 142.4, 148.9, 152.2 (d, $^3J_{CF}$=5.9 Hz), 158.1, 160.1 (d, J_{CF}=247.8 Hz); HRMS (ESI) calcd for $C_{38}H_{37}FN_4O_2S$: 629.2387 ($M+H^+$), found: 629.2366.

*4.1.32. 1-(7-Methyl-3-phenylisoquinolin-1-yl)-1,3-dip-tolyl-2-tosylguanidine (**3**{10,4}).* ^1H NMR (500 MHz, $CDCl_3$) δ 1.94 (s, 3H), 2.22 (s, 3H), 2.39 (s, 3H), 6.56–6.60 (m, 4H), 6.70 (d, J=8.5 Hz, 2H), 6.90 (d, J=8.0 Hz, 2H), 7.38 (dd, J=2.0, 8.0 Hz, 1H), 7.43–7.46 (m, 2H), 7.48–7.51 (m, 2H), 7.61 (d, J=8.0 Hz, 1H), 7.70 (d, J=8.0 Hz, 2H), 7.84 (s, 1H), 8.04 (d, J=7.5 Hz, 2H), 9.22 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 20.4, 20.8, 21.4, 21.9, 15.7, 23.7, 123.8, 124.9, 125.0, 126.0, 126.4, 126.5, 126.9, 128.4, 128.7, 129.0, 129.1, 129.2, 129.3, 132.3, 133.9, 135.3, 135.7, 137.1, 137.5, 138.3, 139.4, 140.0, 142.2, 148.3, 152.2, 158.0; HRMS (ESI) calcd for $C_{38}H_{34}N_4O_2S$: 611.2481 ($M+H^+$), found: 611.2494.

*4.1.33. 1,3-Bis(4-chlorophenyl)-1-(3-phenylisoquinolin-1-yl)-2-tosylguanidine (**3**{1,5}).* ^1H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 6.71 (d, J=9.0 Hz, 2H), 6.75–6.79 (m, 4H), 7.07 (d, J=9.0 Hz, 2H), 7.11 (d, J=7.5 Hz, 2H), 7.24–7.30 (m, 2H), 7.48 (t, J=8.0 Hz, 2H), 7.53 (t, J=8.0 Hz, 2H), 7.65 (d, J=8.0 Hz, 2H), 7.74 (d, J=8.0 Hz, 2H), 7.91 (s, 1H), 7.97 (d, J=6.5 Hz, 2H), 9.30 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 116.2, 123.0, 124.6, 126.0, 126.1, 126.3, 126.5, 127.4, 127.5, 128.5, 128.7, 128.8, 129.0, 129.2, 129.5, 130.5, 131.4, 131.7, 134.8, 137.9, 138.8, 139.2, 141.0, 142.7, 149.3, 152.2, 157.1; HRMS (ESI) calcd for $C_{35}H_{26}Cl_2N_4O_2S$: 637.1232 ($M+H^+$), found: 637.1227.

*4.1.34. 1,3-Bis(4-chlorophenyl)-1-(3-(4-chlorophenyl)isoquinolin-1-yl)-2-tosylguanidine (**3**{6,5}).* ^1H NMR (500 MHz, $CDCl_3$) δ 2.35 (s, 3H), 6.71 (q, J=8.0 Hz, 1H), 6.80–6.83 (m, 5H), 7.05 (d, J=8.0 Hz, 1H), 7.08 (d, J=7.5 Hz, 2H), 7.22 (t, J=7.0 Hz, 2H), 7.41 (d, J=8.0 Hz, 2H), 7.47 (t, J=8.0 Hz, 1H), 7.59 (d, J=9.0 Hz, 1H), 7.64 (d, J=8.5 Hz, 2H), 7.69 (d, J=8.5 Hz, 1H), 7.83 (s, 1H), 7.91 (d, J=8.5 Hz, 2H), 9.39 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.5, 116.1, 123.1, 124.7, 126.0, 126.1, 126.4, 127.5, 127.8, 128.6, 128.9, 129.1, 1129.2, 130.7, 131.5, 131.9, 134.8, 135.0, 136.4, 138.8, 139.2, 141.0, 142.9, 148.1, 152.4, 157.1; HRMS (ESI) calcd for $C_{35}H_{25}Cl_3N_4O_2S$: 671.0842 ($M+H^+$), found: 671.0813.

*4.1.35. 1,3-Bis(4-chlorophenyl)-1-(7-fluoro-3-tolylisoquinolin-1-yl)-2-tosylguanidine (**3**{8,5}).* ^1H NMR (500 MHz, $CDCl_3$) δ 2.36 (s, 3H), 2.45 (s, 3H), 6.73–6.81 (m, 6H), 7.04 (d, J=9.0 Hz, 1H), 7.08 (d, J=9.0 Hz, 2H), 7.11 (d, J=7.5 Hz, 2H), 7.27–7.31 (m, 3H), 7.64 (d, J=8.0 Hz, 2H), 7.73 (dd, J=5.5, 9.5 Hz, 1H), 7.87–7.88 (m, 3H), 9.31 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.2, 21.5, 108.3 (d, $^2J_{CF}$=22.9 Hz), 115.4, 121.1 (d, $^2J_{CF}$=25.6 Hz), 123.7, 123.8, 126.0, 126.3, 126.4, 128.6, 129.2, 129.6, 130.0, 130.1, 131.6, 131.9, 134.8, 136.4, 138.7, 139.1, 140.5, 142.8, 149.1, 151.7 (d, $^3J_{CF}$=5.9 Hz), 157.2, 160.4 (d, J_{CF}=248.9 Hz); HRMS (ESI) calcd for $C_{36}H_{27}Cl_2FN_4O_2S$: 669.1294 ($M+H^+$), found: 669.1280.

*4.1.36. 1,3-Bis(4-chlorophenyl)-1-(7-methyl-3-phenylisoquinolin-1-yl)-2-tosylguanidine (**3**{10,5}).* ^1H NMR (500 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.33 (s, 3H), 6.73 (d, J=8.0 Hz, 2H), 6.78–6.79 (m, 3H), 7.07 (t, J=9.0 Hz, 4H), 7.32 (s, 1H), 7.37 (d, J=8.5 Hz, 1H), 7.42 (d, J=7.5 Hz, 1H), 7.46 (m, J=7.5 Hz, 2H), 7.63–7.66 (m, 3H), 7.88 (s, 2H), 7.94 (d, J=7.5 Hz, 2H), 9.28 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.4, 22.0, 116.2, 123.3, 123.4, 125.9, 126.2, 126.3, 126.4, 127.2, 128.4, 128.7, 129.0, 129.2, 129.5, 131.2, 131.7, 132.8, 134.9, 137.6, 137.8, 138.0, 138.9, 141.0, 142.6, 148.5, 151.6, 157.2; HRMS (ESI) calcd for $C_{36}H_{28}Cl_2N_4O_2S$: 651.1388 ($M+H^+$), found: 651.1384.

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Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.06.056. These data include MOL files and InChIKeys of the most important compounds described in this article.

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