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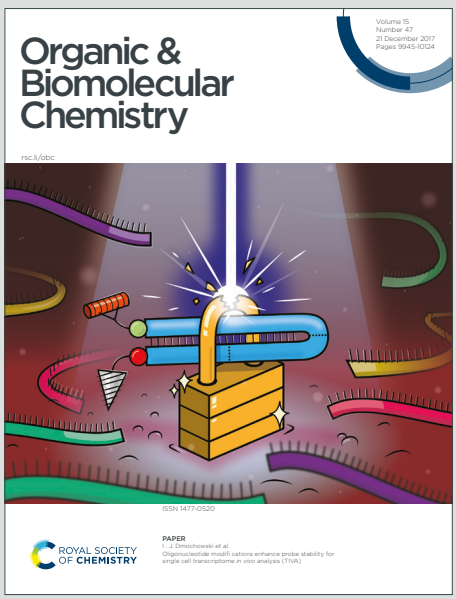

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ARTICLE

Efficient Synthesis of SCF_3-Substituted Tryptanthrins by a Radical Tandem Cyclization

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Jincheng Guo,[#a] Yanan Hao,[#a] Gang Li,[a] Ziwen Wang,*[ab] Yuxiu Liu,*[a] Yongqiang Li,[a] and Qingmin Wang*[a]

Herein, we report a new, efficient and atom-economical strategy for the synthesis of SCF_3-substituted tryptanthrin derivatives. These previously unreported derivatives were obtained by means of a radical tandem cyclization. The reaction was triggered by addition of SCF_3 radical to a carbon–carbon double bond and involved the formation of a C(sp^3)–SCF_3 bond, a C(sp^2)–C bond, and a C(sp^2)–N bond. This method has a mild condition and a wide range of substrates which is particularly useful for the preparation of substituted indolquinazoline derivatives that widely exists in many natural products, but are not easy to obtain in conventional approaches.

Introduction

The alkaloid tryptanthrin consists of a quinazoline ring fused to an indole moiety with carbonyl groups at the 6- and 12-positions (Figure 1). This compound can be isolated from *Polygonum tinctorium Lour*, *Strobilanthes cusia*, and *Isatis tinctoria*,[1] which are sources of blue dyes and were also used to treat cuts, infections, and hemorrhoids in ancient China. In addition, tryptanthrin has recently been found to have a broad spectrum of biological activities, including antitumor activity,[2] antifungal activity,[3] and antituberculotic activity.[4] Therefore, a large number of tryptanthrin derivatives, both naturally occurring and chemically synthesized, have been studied. These derivatives can be divided into two main types: one type containing various substituents on the two benzene rings[5] and a second type in which the C6 carbonyl group has been replaced by some other functional group[6] (Figure 1). It was found that the C6 substituted tryptamine showed better biological activity.

Tryptanthrin derivatives are generally prepared by reactions of substituted isatoic anhydrides and isatins[5c] (Figure 2a), but the necessary substituted isatoic anhydrides are not always easy to prepare. Another approach involves oxone-induced dimerization of indole-3-carbaldehydes[5b] (Figure 2b), but this method can be used only with indoles bearing a halogen atom at the 5-position of the aryl ring. In addition, Wang et al. reported a copper-catalyzed synthesis of tryptanthrins from substituted indoles[5e] (Figure 2c); however, the process is operationally complicated, and the yields are only moderate. Tryptanthrin analogues can also be synthesized via aldol reactions between tryptanthrin and various ketones[6a,7] (Figure 2d), and reactions of primary amines with the C6 carbonyl group of tryptanthrin afford Schiff base analogues[6b] (Figure 2e). Although significant achievements have been made for the synthesis of tryptanthrin derivatives, mild and efficient synthetic approaches for synthesis of C6 substituted tryptanthrin derivatives remain to be further developed.

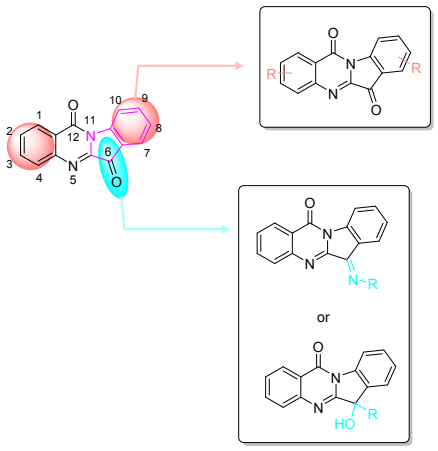

Figure 1. Structure of tryptanthrin and the two main types of derivatives.

Organofluorine chemistry has been garnering increasing attention because of its applications in drug development, pesticide chemistry, and materials technology.[8] In particular, various research groups have recently focused on the trifluoromethylthio group (CF_3S) owing to its electronic properties, high stability, and lipophilicity.[9] This functional group has been shown to improve the membrane permeability and bioavailability of molecules containing it.[10] Various trifluoromethylthiolation reagents have been reported, and the use of $AgSCF_3$ is a straightforward method for accomplishing trifluoromethylthiolation/cyclization reactions via radical,[11] anionic,[12] and cationic pathways.[13] Nevertheless, methods for direct

[a] State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, College of Chemistry, Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Nankai University Tianjin 300071 (China).E-mail: wangqm@nankai.edu.cn; E-mail: liuyuxiu@nankai.edu.cn
[b] Tianjin Key Laboratory of Structure and Performance for Functional Molecules, College of Chemistry, Tianjin Normal University, Tianjin 300387 (P. R. China). E-mail: hxxywzw@tjnu.edu.cn
# Guo and Hao contributed equally to this work.
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construction of common heterocyclic scaffolds while simultaneously incorporating a trifluoromethylthio group would be highly desirable.

N-Acyl cyanamide could be used as an effective radical acceptor for heterocycles synthesis.[14] Inspired by this and as the continuation of our efforts in heterocycles synthesis,[15] we synthesized a series of trifluoromethylthio-substituted tryptanthrin derivatives by means of a single-step protocol involving a direct trifluoromethylthiolation/cyclization cascade reaction (Figure 2f). This method is particularly useful for the preparation of substituted indolquinazoline derivatives which widely exists in many natural products, but are not easy to obtain in conventional approaches.

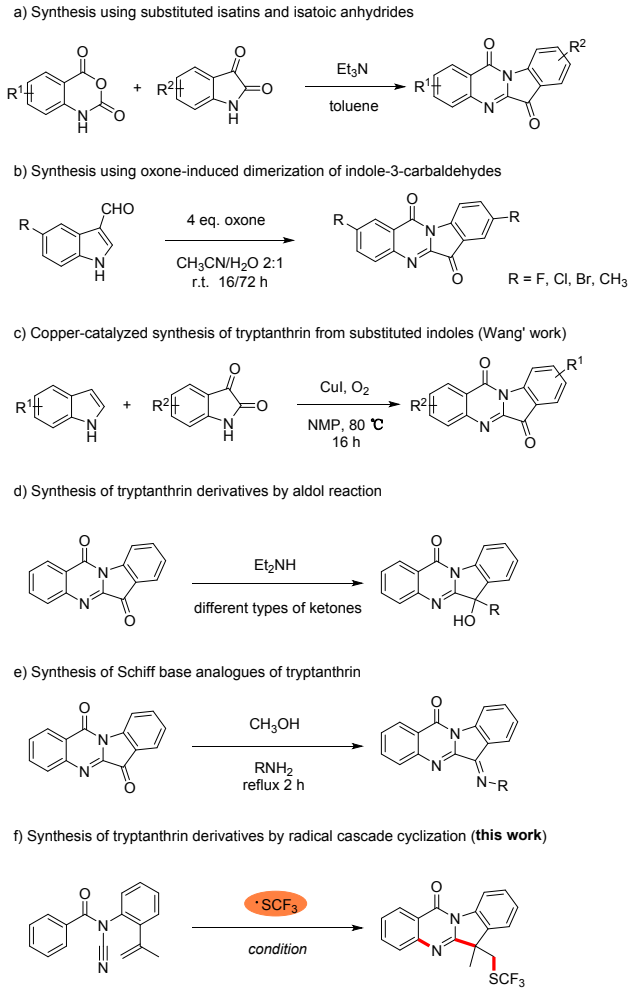
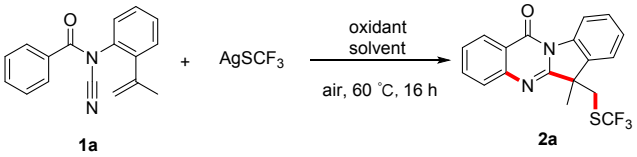


Figure 2. Previously reported strategies for the synthesis of tryptanthrin derivatives and our new approach to the synthesis of trifluoromethylthio-substituted tryptanthrins.

Results and discussion

We set out to obtain trifluoromethylthio-substituted tryptanthrin **2a** from *N*-acylcyanamide **1a** (0.2 mmol) by reaction with $AgSCF_3$ (1.2 equiv) and $K_2S_2O_8$ (2.0 equiv) in DMSO under air at 60 °C for 16 h; and we were pleased to find that these conditions did in fact afford 2a, in a yield of 92% as indicated by ^1H NMR spectroscopy (Table 1, entry 1). Subsequently, we evaluated the effects of decreasing the amount of oxidant (entries 2 and 3) and changing the oxidant to benzoyl peroxide, iodobenzene diacetate, ceric sulfate, or a peroxosulphate (entries 4–8); these experiments revealed that 1.5 equiv of $K_2S_2O_8$ was optimal. Screening of various solvents—other polar organic solvents (acetonitrile, DMF, acetone), a chlorinated solvent (DCE), ethers (THF, dioxane), and toluene (entries 9–15)—showed no improvement relative to DMSO.

Table 1. Optimization of the reaction conditions.[a]



1a **2a**

entry	*oxidant (equiv)*	*solvent*	*yield (%)*[b]
1	$K_2S_2O_8$ (2.0)	DMSO	92
2	$K_2S_2O_8$ (1.5)	DMSO	95 (86[c])
3	$K_2S_2O_8$ (1.0)	DMSO	84
4	benzoyl peroxide (1.5)	DMSO	NR
5	$PhI(OAc)_2$ (1.5)	DMSO	trace
6	$Ce(SO_4)_2$ (1.5)	DMSO	trace
7	$(NH_4)_2S_2O_8$ (1.5)	DMSO	79
8	$Na_2S_2O_8$ (1.5)	DMSO	81
9	$K_2S_2O_8$ (1.5)	CH_3CN	66
10	$K_2S_2O_8$ (1.5)	DMF	17
11	$K_2S_2O_8$ (1.5)	DCE	NR
12	$K_2S_2O_8$ (1.5)	THF	NR
13	$K_2S_2O_8$ (1.5)	dioxane	NR
14	$K_2S_2O_8$ (1.5)	toluene	NR
15	$K_2S_2O_8$ (1.5)	acetone	NR

[a] Reaction conditions: 1a (0.2 mmol), $AgSCF_3$ (0.24 mmol, 1.2 equiv), oxidant (1.0–2.0 equiv), 2 mL solvent, at 60 °C under air for 16 h. [b] Determined by ^1H NMR spectroscopy with CH_2Br_2 as an internal standard. [c] Isolated yield. NR = no reaction.

With the optimized conditions in hand (Table 1, entry 2), we explored the generality of the protocol by carrying out reactions of various substrates 1. We began by evaluating the effects of substituents on the phenyl ring attached to the carbonyl group (Scheme 1). Substrates with an electron-withdrawing group (**1b–1e**) or an electron-donating group (**1f–1h**, **1k**) in the *para* position afforded the corresponding products in 70–86% yields. Comparison of the yields of methyl-substituted products **2f**, **2i**, and **2j** indicated that the position of the methyl group had little effect; however, when the methyl substituent was in the *meta* position of the phenyl ring, there were two sites at which the ring could undergo attack by the imine radical generated during the reaction, so two regioisomers, **2i-1** and

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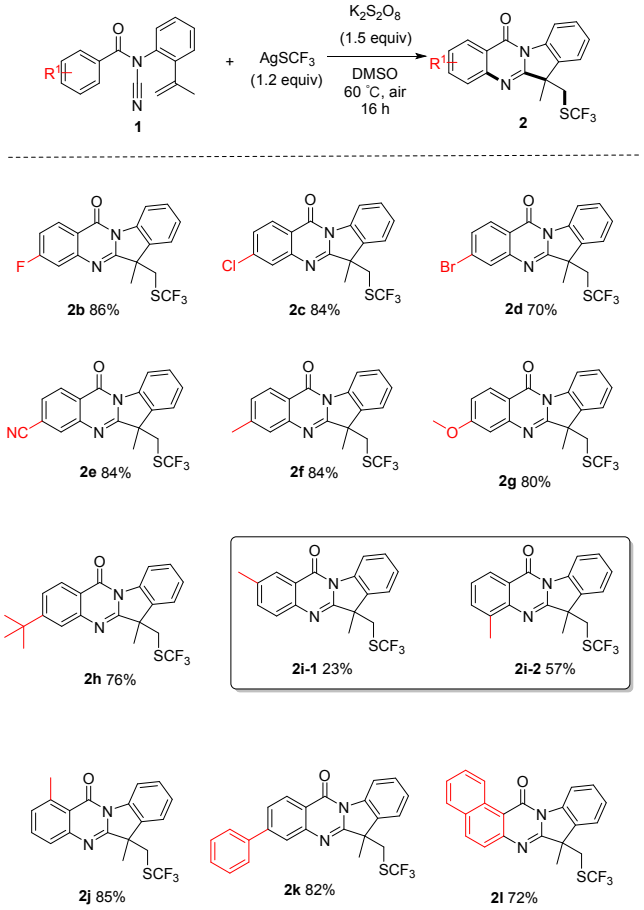
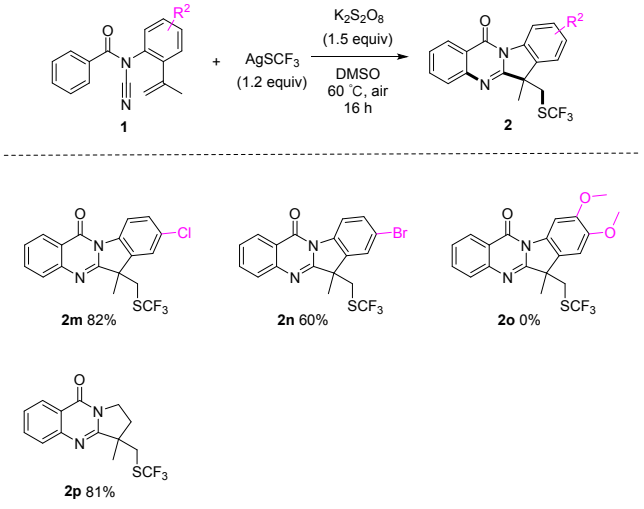
2i-2, were obtained in a 1:2.5 ratio. Replacing the phenyl group with naphthyl group also gave the desired product (**2l**) in good yield (72%).



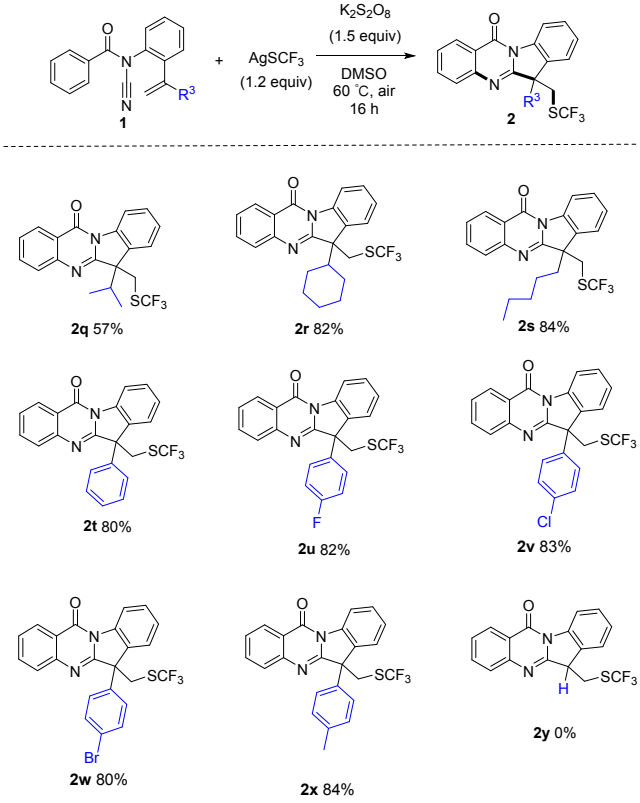
Scheme 1. Synthesis of trifluoromethylthio-substituted tryptanthrins **2b**–**2l**. Unless otherwise noted, all reactions were performed with **1** (0.2 mmol, 1 equiv), $AgSCF_3$ (1.2 equiv), and $K_2S_2O_8$ (1.5 equiv) in DMSO (2 mL) at 60 °C under air for 16 h. Isolated yields are given.



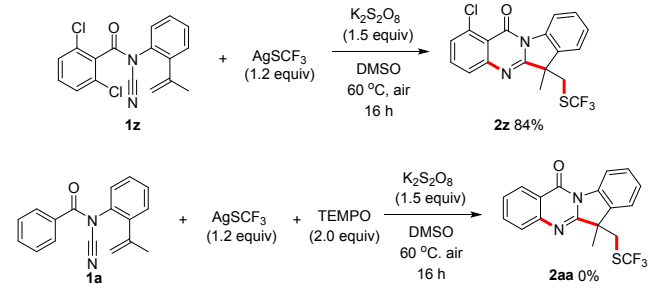
Scheme 2. Synthesis of trifluoromethylthio-substituted tryptanthrins **2m**–**2p**. The reaction conditions are described in Scheme 1.

Next, we explored the effects of substituents on the phenyl ring attached to the amide nitrogen (Scheme 2). Electron-withdrawing groups had a negligible effect on the yields (**2m**, **2n**), but a substrate with two electron-donating methoxy groups did not afford the corresponding product (**2o**). Furthermore, when the 2-phenylpropene moiety of the substrate was replaced with an alkyl chain bearing a terminal olefin, **2p** was obtained in 81% yield.

Finally, we investigated the effects of the R^3 substituent on the carbon–carbon double bond (Scheme 3). When the substituent was an isopropyl group, the yield of **2q** was only 57%; but products with a long-chain alkyl group (**2s**), a cycloalkyl group (**2r**), or an aryl group (**2t**–**2x**) could be obtained in 80–84% yields. However, when R^3 was a hydrogen atom, none of the desired product (**2y**) was detected; the double bond of **1y** may have oxidized or polymerized.



Scheme 3. Synthesis of trifluoromethylthio-substituted tryptanthrins **2q**–**2x**. The reaction conditions are described in Scheme 1.

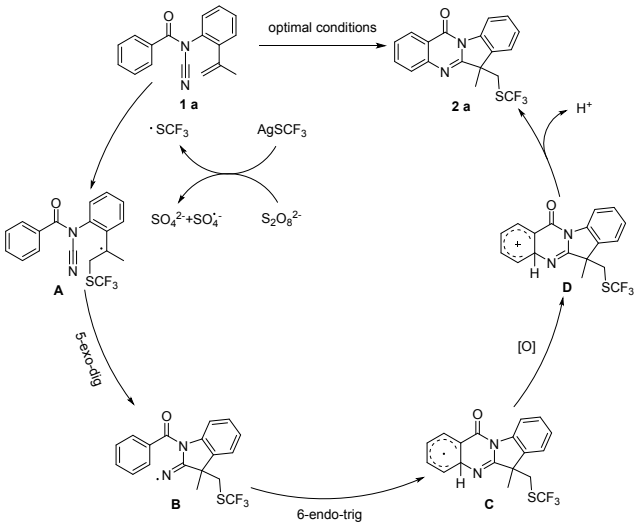


Scheme 4. Mechanistic experiments.

Two control experiments were conducted to probe the reaction mechanism (Scheme 4). When an *N*-acylcyanamide with a chlorine atom at each of the two *ortho* positions of the phenyl ring attached to the carbonyl carbon was subjected to the standard conditions, a

product **2z** generated by the loss of one of the chlorine atoms was obtained in 84% yield, a result that rules out a mechanism involving cyclization of an imine cation. Specifically, the addition of the radical scavenger TEMPO completely inhibited the reaction. We recovered **1a** with 96% yield. The corresponding product **2aa** and the directing trapping product between TEMPO and SCF3 radical were not observed based on ^{1}H NMR and HRMS.

On the basis of the above-described experiments and relevant literature precedents, a plausible mechanism is depicted in Scheme 5. First, oxidation of $AgSCF_3$ by $K_2S_2O_8$ gives the SCF_3 radical, which adds to the carbon–carbon double bond of substrate **1a** to give benzyl radical intermediate **A**. Intermediate **A** undergoes subsequent 5-*exo-dig* cyclization to generate imine radical intermediate **B**, and then 6-*endo-tig* cyclization affords phenyl radical intermediate **C**. Finally, oxidation of **C** produces cationic intermediate **D**, which undergoes deprotonation to generate **2a**.



Scheme 5. Proposed reaction mechanism.

Experimental

General Experimental Details. Reagents were purchased from commercial sources and were used as received. ^{1}H and ^{13}C Nuclear Magnetic Resonance (NMR) spectra were recorded on Bruker Avance 400 Ultrashield NMR spectrometers. Chemical shifts (δ) were given in parts per million (ppm) and were measured downfield from internal tetramethylsilane. High-resolution mass spectrometry (HRMS) data were obtained on an FTICR-MS instrument (Ionspec 7.0 T). The melting points were determined on an X-4 microscope melting point apparatus and are uncorrected. Conversion was monitored by thin layer chromatography (TLC). Flash column chromatography was performed over silica gel (100-200 mesh). The preparation of substrates **1** can be seen in Supporting Information.

General procedures for the condition optimization.

To a 25 mL over-dried shrek tube was added **1a** (52.4 mg, 0.2 mmol, 1.0 equiv), $AgSCF_3$ (50.4 mg, 0.24 mmol, 1.2 equiv), corresponding oxidant (1.0–2.0 equiv) and 2.0 mL corresponding solvent. The reaction mixture was stirred rapidly at 60 °C for 16 h. The mixture was diluted with brine (40 mL), and extracted with EA (40 mL × 3). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was directly used to determine yield by ^{1}H NMR spectroscopy with CH_2Br_2 as an internal standard.

General procedures for the synthesis of 2a–2x.

To a 25 mL over-dried shrek tube was added **1** (0.2 mmol, 1.0 equiv) $AgSCF_3$ (0.24 mmol, 1.2 equiv), $K_2S_2O_8$ (0.3 mmol, 1.5 equiv) and 2.0 mL DMSO. The reaction mixture was stirred rapidly at 60 °C for 16 h. The mixture was diluted with brine (40 mL), and extracted with EA (40 mL × 3). The combined organic extracts were washed with brine (40 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by flash chromatography on silica gel using the PE/EA system to afford the desired products **2a–2x**.

6-Methyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2a**). White solid, 86% yield, mp: 97-98 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 8.0 Hz, 1H), 8.43 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 3.7 Hz, 2H), 7.57 – 7.45 (m, 3H), 7.37 (t, *J* = 7.5 Hz, 1H), 3.61 (q, *J* = 12.9 Hz, 2H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.2, 159.8, 147.3, 139.3, 134.5, 133.1, 130.4 (q, *J* = 307.8 Hz), 129.6, 127.5, 127.2, 126.9, 126.8, 123.0, 121.6, 117.4, 48.7, 38.60 (q, *J* = 2.0 Hz), 25.1. HRMS (ESI) calcd for $C_{18}H_{14}F_3N_2OS$ $[M+H]^+$ 363.0773, found 363.0776.

3-Fluoro-6-methyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2b**). White solid, 86% yield, mp: 106-107 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.0 Hz, 1H), 8.45 – 8.39 (m, 1H), 7.53 – 7.35 (m, 4H), 7.30 – 7.21 (m, 1H), 3.60 (q, *J* = 12.9 Hz, 2H), 1.75 (s, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (d, *J* = 254.8 Hz), 162.6, 159.1, 149.5 (d, *J* = 13.1 Hz), 139.2, 133.0, 130.3 (q, *J* = 306.7 Hz), 129.7, 129.6 (d, *J* = 10.7 Hz), 126.9, 123.0, 118.2, 117.4, 115.8 (d, *J* = 23.3 Hz), 113.1 (d, *J* = 22.2 Hz), 48.9, 38.5 (q, *J* = 2.0 Hz), 25.0. HRMS (ESI) calcd for $C_{18}H_{14}F_4N_2OS$ $[M+H]^+$ 381.0679, found 381.0675.

3-Chloro-6-methyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2c**). White solid, 84% yield, mp: 140-141 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (t, *J* = 6.6 Hz, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 7.79 (d, *J* = 1.9 Hz, 1H), 7.55 – 7.44 (m, 3H), 7.43 – 7.36 (m, 1H), 3.60 (q, *J* = 12.9 Hz, 2H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 159.3, 148.2, 139.1, 133.0, 130.5, 130.3, 130.2 (q, *J* = 306.7 Hz), 129.7, 129.2, 128.3, 127.0, 123.0, 120.4, 117.4, 48.9, 38.5(q, *J* = 2.0 Hz), 25.0. HRMS (ESI) calcd for $C_{18}H_{13}ClF_3N_2OS$ $[M+H]^+$ 397.0384, found 397.0384.

3-Bromo-6-methyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2d**). White solid, 70% yield, mp: 159-161 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.1 Hz, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 1.8 Hz, 1H), 7.65 (dd, *J* = 8.5, 1.9 Hz, 1H), 7.56 – 7.44 (m, 2H), 7.39 (t, *J* = 7.5 Hz, 1H), 3.59 (q, *J* = 12.9 Hz, 2H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 159.3, 148.2, 139.1, 133.0, 130.5, 130.3, 130.2 (q, *J* = 306.7 Hz), 129.7, 129.2, 128.3, 127.0, 123.0, 120.4, 117.4, 48.9, 38.5(q, *J* = 2.0 Hz), 25.0. HRMS (ESI) calcd for $C_{18}H_{13}BrF_3N_2OS$ $[M+H]^+$ 440.9879, found 440.9872.

6-Methyl-12-oxo-6-(((trifluoromethyl)thio)methyl)-6,12-dihydroindolo[2,1-b]quinazoline-3-carbonitrile (**2e**). White solid, 84% yield, mp: 127-128 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 8.0 Hz, 1H), 8.52 (d, *J* = 8.2 Hz, 1H), 8.11 (d, *J* = 0.9 Hz, 1H), 7.78 – 7.70

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(m, 1H), 7.60 – 7.38 (m, 3H), 3.62 (q, *J* = 13.1 Hz, 2H), 1.76 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 163.2, 158.5, 147.2, 138.8, 133.0, 132.2, 130.2 (q, *J* = 306.7 Hz), 129.9, 129.0, 128.2, 127.4, 124.6, 123.1, 117.8, 117.6, 117.5, 49.2, 38.4 (q, *J* = 1.8 Hz), 25.0. HRMS (ESI) calcd for $C_{19}H_{13}F_3N_3OS$ $[M+H]^+$ 388.0726, found 388.0719.

3,6-Dimethyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2f**). White solid, 84% yield, mp: 131-132 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.62 (d, *J* = 8.1 Hz, 1H), 8.31 (d, *J* = 8.1 Hz, 1H), 7.59 (s, 1H), 7.52 – 7.44 (m, 2H), 7.40 – 7.35 (m, 2H), 3.59 (q, *J* = 12.8 Hz, 2H), 2.54 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 161.2, 159.9, 147.4, 145.6, 139.4, 133.1, 129.6, 128.7, 127.4, 126.8, 126.6, 123.0, 119.1, 117.3, 48.6, 38.62 (q, *J* = 1.6 Hz), 25.1, 21.9. HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2OS$ $[M+H]^+$ 377.0930, found 377.0932.

3-Methoxy-6-methyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2g**). White solid, 82% yield, mp: 137-138 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.62 (d, *J* = 8.0 Hz, 1H), 8.32 (d, *J* = 8.8 Hz, 1H), 7.58 – 7.43 (m, 2H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.20 (d, *J* = 2.3 Hz, 1H), 7.12 (dd, *J* = 8.8, 2.4 Hz, 1H), 3.97 (s, 3H), 3.61 (q, *J* = 12.9 Hz, 2H), 1.77 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 164.8, 162.0, 159.5, 149.6, 139.5, 130.4 (q, *J* = 306.8 Hz), 133.0, 129.6, 128.4, 126.5, 122.9, 117.3, 117.0, 114.9, 108.5, 55.8, 48.6, 38.6 (q, *J* = 1.2 Hz), 25.0. HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2O_2S$ $[M+H]^+$ 393.0879, found 393.0881.

3-(Tert-butyl)-6-methyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2h**). White solid, 86% yield, mp: 140-141 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.62 (d, *J* = 8.0 Hz, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 7.78 (s, 1H), 7.61 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.43 (m, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 3.60 (q, *J* = 12.8 Hz, 2H), 1.75 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 161.2, 159.8, 158.7, 147.3, 139.4, 133.1, 130.4 (q, *J* = 306.8 Hz), 129.6, 126.6, 126.5, 125.3, 123.8, 123.0, 119.0, 117.3, 48.6, 38.6(q, *J* = 1.6 Hz), 35.5, 31.1, 25.1. HRMS (ESI) calcd for $C_{22}H_{22}F_3N_2OS$ $[M+H]^+$ 419.1399, found 419.1401.

2,6-Dimethyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2i-1**). White solid, 23% yield, mp: 88-99 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.63 (d, *J* = 8.0 Hz, 1H), 8.22 (s, 1H), 7.68 (d, *J* = 8.2 Hz, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.55 – 7.43 (m, 2H), 7.37 (t, *J* = 7.4 Hz, 1H), 3.59 (q, *J* = 12.8 Hz, 2H), 2.53 (s, 3H), 1.74 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.3, 159.9, 145.3, 139.4, 137.4, 135.8, 133.2, 130.4 (q, *J* = 306.6 Hz), 129.6, 127.3, 126.6, 126.4, 123.0, 121.3, 117.4, 48.5, 38.7 (q, *J* = 1.5 Hz), 25.0, 21.3. HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2OS$ $[M+H]^+$ 377.0930, found 377.0930.

4,6-Dimethyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2i-2**). White solid, 57% yield, mp: 129-130 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.63 (d, *J* = 8.0 Hz, 1H), 8.27 (d, *J* = 7.9 Hz, 1H), 7.64 (d, *J* = 7.2 Hz, 1H), 7.54 – 7.32 (m, 4H), 3.59 (dd, *J* = 29.4, 12.8 Hz, 2H), 2.68 (s, 3H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.2, 159.7, 145.8, 139.4, 136.2, 135.1, 133.4, 130.5 (q, *J* = 306.6 Hz), 129.6, 126.6, 124.5, 123.0, 121.5, 117.4, 48.6, 38.6 (q, *J* = 1.5 Hz), 25.3, 17.4. HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2OS$ $[M+H]^+$ 377.0930, found 377.0928.

1,6-Dimethyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2j**). White solid, 85% yield, mp: 114-115 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.62 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 4.4 Hz, 2H), 7.51 – 7.43 (m, 2H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 4.3 Hz, 1H), 3.58 (q, *J* = 12.8 Hz, 2H), 2.98 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.8, 160.7, 148.9, 141.7, 139.6, 133.6, 133.2, 130.0, 129.5, 126.5, 125.8, 122.0, 120.0, 117.4, 48.4, 38.5 (q, *J* = 2.0 Hz), 25.0, 23.4. HRMS (ESI) calcd for $C_{19}H_{16}F_3N_2OS$ $[M+H]^+$ 377.0930, found 377.0935.

6-Methyl-3-phenyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2k**). White solid, 82% yield, mp: 122-123 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.67 (d, *J* = 8.0 Hz, 1H), 8.50 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 1.5 Hz, 1H), 7.82 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.77 (d, *J* = 7.3 Hz, 2H), 7.57 – 7.39 (m, 6H), 3.65 (dd, *J* = 28.2, 12.9 Hz, 2H), 1.80 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 161.6, 159.7, 147.7, 147.4, 139.5, 139.4, 133.1, 130.4 (d, *J* = 306.6 Hz), 129.7, 129.1, 128.6, 127.5, 127.5, 126.7, 126.2, 125.6, 123.0, 120.3, 117.4, 48.7, 38.6 (q, *J* = 1.6 Hz), 25.1. HRMS (ESI) calcd for $C_{24}H_{18}F_3N_2OS$ $[M+H]^+$ 439.1086, found 439.1089.

8-Methyl-8-(((trifluoromethyl)thio)methyl)benzo[f]indolo[2,1-b]quinazolin-14(8*H*)-one (**2l**). White solid, 72% yield, mp: 111-112 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 10.06 (d, *J* = 8.6 Hz, 1H), 8.79 (d, *J* = 8.0 Hz, 1H), 8.15 (d, *J* = 8.8 Hz, 1H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.83 – 7.73 (m, 2H), 7.63 (t, *J* = 7.4 Hz, 1H), 7.58 – 7.44 (m, 2H), 7.38 (t, *J* = 7.4 Hz, 1H), 3.63 (q, *J* = 12.9 Hz, 2H), 1.78 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.5, 149.6, 139.8, 135.9, 133.6, 132.2, 131.3, 130.4 (q, *J* = 306.6 Hz), 129.7, 128.8, 128.4, 127.2, 126.9, 126.8, 126.2, 123.0, 118.0, 115.0 48.8, 38.4 (q, *J* = 1.6 Hz), 24.8. HRMS (ESI) calcd for $C_{22}H_{16}F_3N_2OS$ $[M+H]^+$ 413.0930, found 413.0930.

8-Chloro-6-methyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2m**). White solid, 82% yield, mp: 188-189 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.44 (dd, *J* = 38.2, 7.2 Hz, 2H), 7.92 – 7.39 (m, 5H), 3.58 (dd, *J* = 33.7, 12.8 Hz, 2H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.4, 159.6, 147.2, 138.3, 135.3, 134.6, 132.7, 130.2 (q, *J* = 307.1 Hz), 127.6, 127.4, 126.9, 126.4, 121.4, 119.9, 118.8, 48.8, 38.4 (q, *J* = 1.6 Hz), 24.9. HRMS (ESI) calcd for $C_{18}H_{13}ClF_3N_2OS$ $[M+H]^+$ 397.0384, found 397.0382.

8-Bromo-6-methyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2n**). White solid, 80% yield, mp: 175-176 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.55 (d, *J* = 8.5 Hz, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 7.84 – 7.74 (m, 2H), 7.59 – 7.52 (m, 1H), 7.50 – 7.42 (m, 2H), 3.59 (q, *J* = 13.1 Hz, 2H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.6, 159.6, 147.2, 137.8, 135.0, 134.6, 132.3, 130.2 (q, *J* = 306.8 Hz),129.7, 127.6, 127.4, 126.9, 123.5, 121.4, 118.4, 48.8, 38.4(q, *J* = 1.6 Hz), 24.9. HRMS (ESI) calcd for $C_{18}H_{13}BrF_3N_2OS$ $[M+H]^+$ 440.9879, found 440.9870.

3-Methyl-3-(((trifluoromethyl)thio)methyl)-2,3-dihydropyrrolo[2,1-b]quinazolin-9(1*H*)-one (**2p**). White solid, 81% yield, mp: 44-45 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.31 (d, *J* = 8.0 Hz, 1H), 7.80 – 7.69 (m, 2H), 7.49 (t, *J* = 7.4 Hz, 1H), 4.35 – 4.25 (m, 1H), 4.14 – 4.03 (m, 1H), 3.40 (dd, *J* = 40.1, 13.4 Hz, 2H), 2.49 – 2.39 (m, 1H), 2.20 – 2.12 (m, 1H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 161.8, 160.8, 149.0, 134.28, 130.7 (q, *J* = 306.0 Hz), 127.2, 126.6, 126.4, 120.9, 47.1, 43.2, 37.6 (q, *J* = 1.6 Hz), 31.7, 24.0. HRMS (ESI) calcd for $C_{14}H_{14}F_3N_2OS$ $[M+H]^+$ 315.0773, found 315.0775.

6-Isopropyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2q**). White solid, 85% yield, mp: 96-97 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.68 (d, *J* = 8.0 Hz, 1H), 8.47 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 3.1 Hz, 2H), 7.63 – 7.51 (m, 2H), 7.47 (d, *J* = 7.2 Hz,

1H), 7.40 (t, *J* = 7.4 Hz, 1H), 3.76 (q, *J* = 12.3 Hz, 2H), 2.58 (dt, *J* = 13.6, 6.8 Hz, 1H), 1.03 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.5, 159.8, 147.2, 140.5, 134.4, 130.6, 130.4 (q, *J* = 306.3 Hz), 129.6, 127.7, 127.1, 126.9, 126.4, 123.8, 121.5, 117.2, 56.0, 37.5, 36.2 (q, *J* = 1.5 Hz), 17.3. HRMS (ESI) calcd for $C_{20}H_{18}F_3N_2OS$ $[M+H]^+$ 391.1086, found 391.1085.

6-Cyclohexyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2r**). White solid, 82% yield, mp: 145-146 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.68 (d, *J* = 8.0 Hz, 1H), 8.47 (d, *J* = 7.9 Hz, 1H), 7.91 – 7.78 (m, 2H), 7.63 – 7.51 (m, 2H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 3.84 – 3.68 (m, 2H), 2.24 (t, *J* = 11.8 Hz, 1H), 1.79 (t, *J* = 12.0 Hz, 2H), 1.63 (s, 2H), 1.43 (d, *J* = 12.3 Hz, 1H), 1.30 – 1.14 (m, 3H), 1.08 – 0.94 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.8, 159.8, 147.2, 140.5, 134.4, 131.0, 130.5 (q, *J* = 306.7 Hz), 129.5, 127.7, 127.1, 126.9, 126.4, 123.9, 121.4, 117.1, 56.2, 47.4, 35.9 (q, *J* = 1.1 Hz), 27.2, 26.4, 26.1, 25.9. HRMS (ESI) calcd for $C_{23}H_{22}F_3N_2OS$ $[M+H]^+$ 431.1339, found 431.1394.

6-Pentyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2s**). White solid, 80% yield, mp: 57-58 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.64 (d, *J* = 8.0 Hz, 1H), 8.44 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 3.7 Hz, 2H), 7.62 – 7.47 (m, 2H), 7.45 – 7.32 (m, 2H), 3.61 (dd, *J* = 32.1, 12.7 Hz, 2H), 2.37 – 2.20 (m, 1H), 2.13 – 1.97 (m, 1H), 1.12 (s, 4H), 0.94 – 0.76 (m, 2H), 0.77 – 0.67 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.5, 159.8, 147.3, 140.2, 134.4, 131.6, 130.4 (q, *J* = 306.6 Hz), 129.6, 127.6, 127.1, 126.9, 126.7, 123.1, 121.5, 117.3, 53.1, 39.0, 38.2(q, *J* = 1.6 Hz), 31.6, 29.7, 23.8, 22.1, 13.8. HRMS (ESI) calcd for $C_{22}H_{22}F_3N_2OS$ $[M+H]^+$ 419.1399, found 419.1398.

6-Phenyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2t**). White solid, 81% yield, mp: 41-43 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.71 (d, *J* = 8.1 Hz, 1H), 8.41 (d, *J* = 7.7 Hz, 1H), 7.79 – 7.73 (m, 2H), 7.61 – 7.48 (m, 3H), 7.47 – 7.40 (m, 3H), 7.37 – 7.27 (m, 3H), 4.12 (dd, *J* = 40.4, 12.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 160.0, 159.9, 147.3, 140.2, 139.0, 134.5, 131.9, 131.5, 130.1, 129.0, 128.4, 127.9, 127.3, 127.0, 126.9, 126.8, 125.2, 121.5, 117.6, 56.1, 38.2 (q, *J* = 1.6 Hz). HRMS (ESI) calcd for $C_{23}H_{16}F_3N_2OS$ $[M+H]^+$ 425.0930, found 425.0934.

6-(4-Fluorophenyl)-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2u**). White solid, 82% yield, mp: 91-92 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.76 – 8.67 (m, 1H), 8.42 (d, *J* = 7.7 Hz, 1H), 7.82 – 7.73 (m, 2H), 7.63 – 7.58 (m, 1H), 7.57 – 7.52 (m, 1H), 7.50 (d, *J* = 6.5 Hz, 1H), 7.47 – 7.44 (m, 1H), 7.44 – 7.38 (m, 2H), 7.35 – 7.28 (m, 2H), 4.07 (dd, *J* = 31.4, 12.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 163.8, 161.3, 159.8 (d, *J* = 2.6 Hz), 147.2, 140.2, 134.5, 131.1, 130.3, 129.1, 129.0 (d, *J* = 8.2 Hz), 128.5, 127.8, 127.4, 126.9, 126.8, 125.2, 121.5, 117.7, 115.9 (d, *J* = 21.6 Hz), 55.5, 38.5 (q, *J* = 1.3 Hz). HRMS (ESI) calcd for $C_{23}H_{15}F_4N_2OS$ $[M+H]^+$ 443.0836, found 443.0840.

6-(4-Chlorophenyl)-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2v**). White solid, 83% yield, mp: 183-184 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.71 (d, *J* = 8.1 Hz, 1H), 8.41 (d, *J* = 7.7 Hz, 1H), 7.79 – 7.75 (m, 2H), 7.62 – 7.56 (m, 1H), 7.56 – 7.51 (m, 1H), 7.51 – 7.47 (m, 1H), 7.47 – 7.43 (m, 1H), 7.43 – 7.38 (m, 2H), 7.34 – 7.28 (m, 2H), 4.07 (dd, *J* = 31.4, 12.5 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.8, 159.5, 147.1, 140.2, 137.4, 134.6, 134.5, 130.9, 130.3, 129.1, 128.5, 127.8, 127.4, 127.2 (q, *J* = 306.9 Hz), 126.9, 126.8, 125.1, 121.4, 117.7, 55.6, 38.3 (q, *J* = 1.3 Hz). HRMS (ESI) calcd for $C_{23}H_{15}ClF_3N_2OS$ $[M+H]^+$ 459.0540, found 459.0536.

6-(4-Bromophenyl)-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2w**). White solid, 80% yield, mp: 160-161 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.71 (d, *J* = 8.1 Hz, 1H), 8.41 (d, *J* = 7.9 Hz, 1H), 7.85 – 7.71 (m, 2H), 7.59 (t, *J* = 7.7 Hz, 1H), 7.57 – 7.51 (m, 1H), 7.50 – 7.39 (m, 4H), 7.34 (d, *J* = 8.6 Hz, 2H), 4.06 (dd, *J* = 30.7, 12.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.8, 159.4, 147.1, 140.2, 137.9, 134.6, 132.1, 130.9, 130.4, 128.8, 127.8, 127.5, 126.9, 126.9, 125.1, 122.8, 121.4, 117.7, 100.0, 55.6, 38.2 (q, *J* = 1.5 Hz). HRMS (ESI) calcd for $C_{23}H_{15}BrF_3N_2OS$ $[M+H]^+$ 503.0335, found 503.0335.

6-(*p*-Tolyl)-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (**2x**). White solid, 84% yield, mp: 126-127 °C, ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 8.71 (d, *J* = 8.0 Hz, 1H), 8.40 (d, *J* = 7.8 Hz, 1H), 7.78 – 7.70 (m, 2H), 7.59 – 7.46 (m, 3H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.32 (d, *J* = 8.2 Hz, 2H), 7.14 (d, *J* = 8.1 Hz, 2H), 4.10 (q, *J* = 12.4 Hz, 2H), 2.30 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 159.9, 147.3, 140.2, 138.4, 136.1, 134.4, 131.8, 130.4 (d, *J* = 306.9 Hz), 130.0, 129.7, 127.9, 127.2, 126.9, 126.8, 126.7, 125.2, 121.5, 117.5, 55.8, 38.2 (q, *J* = 1.5 Hz), 21.0. HRMS (ESI) calcd for $C_{24}H_{18}F_3N_2OS$ $[M+H]^+$ 439.1086, found 439.1085.

Verify experiment (Scheme 4), preparation of 1-chloro-6-methyl-6-(((trifluoromethyl)thio)methyl)indolo[2,1-b]quinazolin-12(6*H*)-one (2z).

To a 25 mL over-dried shrek tube was added 1z (83.4 mg, 0.2 mmol, 1.0 equiv), $AgSCF_3$ (50.4 mg, 0.24 mmol, 1.2 equiv), $K_2S_2O_8$ (81 mg, 0.3 mmol, 1.5 equiv) and 2.0 mL DMSO. The reaction mixture was stirred rapidly at 60 °C for 16 h. Compound **2z** was isolated in 84% yield, white solid, mp: 69-71 °C. ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.66 (d, *J* = 7.7 Hz, 1H), 7.54 – 7.40 (m, 3H), 7.36 (d, *J* = 7.1 Hz, 1H), 6.68 (d, *J* = 7.0 Hz, 2H), 3.56 (s, 2H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 181.4, 179.0, 167.7, 146.5, 146.4, 136.1, 134.0, 130.4, 130.3 (q, *J* = 348.1 Hz) , 130.1 127.0, 124.4, 113.5, 45.1, 37.2 (q, *J* = 2.1 Hz), 24.5. HRMS (ESI) calcd for $C_{18}H_{13}ClF_3N_2OS$ $[M+H]^+$ 397.0348, found 397.0380.

TEMPO were used as radical scavenger (Scheme 4).

To a 25 mL over-dried shrek tube was added 1a (52.4 mg, 0.2 mmol, 1.0 equiv), $AgSCF_3$ (50.4 mg, 0.24 mmol, 1.2 equiv), TEMPO (62.5 mg, 0.4 mmol, 2.0 equiv), $K_2S_2O_8$ (0.3 mmol, 1.5 equiv) and 2.0 mL DMSO. The reaction mixture was stirred rapidly at 60 °C for 16 h. We recovered **1a** with 96% yield. The corresponding product **2aa** and the directing trapping product between TEMPO and SCF_3 radical were not observed based on ^{1}H NMR and HRMS.

Conclusions

In short, we used *N*-acylcyanamides as starting materials for the synthesis of previously unreported trifluoromethylthio-substituted tryptanthrin derivatives by means of a radical trifluoromethylthiolation/cyclization cascade. This transformation, which involves the formation of a C(sp^3)–SCF_3 bond, a C(sp^2)–C bond, and a C(sp^2)–N bond, proceeds smoothly in moderate to excellent yields and represents a new strategy for synthesis of tryptanthrin derivatives.

Conflicts of interest

There are no conflicts to declare.

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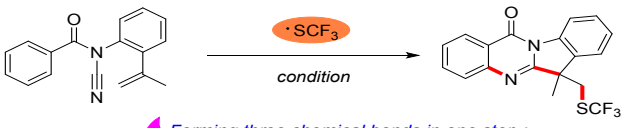
ARTICLE

Graphical Abstract



- *Forming three chemical bonds in one step ;*
- *24 substrates, 57%~86% isolated yield;*
- *Mild condition, cheap catalyst*
- *atom-economical strategy*

An efficient strategy for synthesis of SCF_3-substituted tryptanthrin derivatives was developed with $AgSCF_3/K_2S_2O_8$-promoted radical trifluoromethylthiolation/cyclization cascade reaction as key step.

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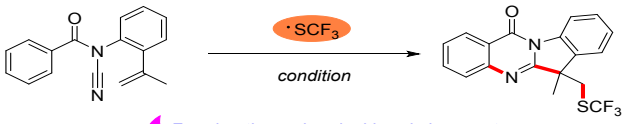

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