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Microwave-assisted synthesis of 4-chloro-*N*-(naphthalen-1-ylmethyl)-5-(3-(piperazin-1-yl)phenoxy)thiophene-2-sulfonamide (B-355252): a new potentiator of nerve growth factor (NGF)-induced neurite outgrowth

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ABSTRACT

The synthesis of 4-chloro-*N*-(naphthalen-1-ylmethyl)-5-(3-(piperazin-1-yl)phenoxy)thiophene-2-sulfonamide (B-355252) using an MW-assisted nucleophilic aromatic substitution (S_NAr) reaction will be discussed. Utilization of this method allowed for the rapid generation of B-355252 heteroaryl ether core structure in the presence of cesium carbonate in dimethylformamide or tripotassium phosphate in *N*-methyl-2-pyrrolidone in 94% yield. Evaluation of B-355252 enhancement of nerve growth factor's ability to stimulate neurite outgrowths was determined using NS-1 cells.

1. Introduction

Nerve growth factor (NGF) is a member of a family of proteins called neurotrophins.[1] Other members of this family of proteins includes brain-derived neurotrophic factor (BDNF), neurotrophin (NT)-3, and NT-4/5. NGF is involved in the survival, development and function of neurons located in the central, and peripheral nervous system.[2] In the central nervous system, NGF is synthesized predominantly by neurons under physiological conditions[3] and has been shown to upregulate cholinergic function and to prevent degeneration of basal forebrain neurons.[4] The neuroprotective role displayed by NGF and the observations of reversing atrophy and age-related cognitive impairment made in animal models of neurodegeneration helped to establish the use of NGF as a potential treatment for a variety of neurological diseases like Alzheimer's disease (AD), Parkinson's disease (PD) and Amyotrophic lateral sclerosis (ALS).[5] Unfortunately, delivery of exogenous NGF failed to demonstrate efficacy in several human clinical trials.[6] The ineffectiveness of NGF as a treatment modality is hampered by the challenges of developing peptides as clinical candidates, which includes penetrating the blood–brain barrier, metabolic instability and ineffective protein delivery.[7] To overcome these hurdles, efforts have been focused on identifying small organic molecules as an alternative for enhancing neurite outgrowth by potentiating NGF-dependent activity in neuronal cells.

Over the years, a variety of small molecules have been reported to enhance neurite outgrowth by potentiating NGF dependent activity in neuronal cells.[8] Natural products like verbenachalcone (VC) and a host of other small molecules, such as the potent acetylcholinesterase (AChE) inhibitor donepezil, were reported to stimulate neurite outgrowth (Fig. 1).[9,10] A recent primary screen of our library collection[11] led us to the discovery of *N*-(naphthalen-1-ylmethyl)-5-(3-(piperazin-1-yl)phenoxy)thiophene-2-sulfonamide, B-355252 (Fig 1), which amplified neurite outgrowth in NS-1 cells in the presence of NGF. This finding launched the exploration into the

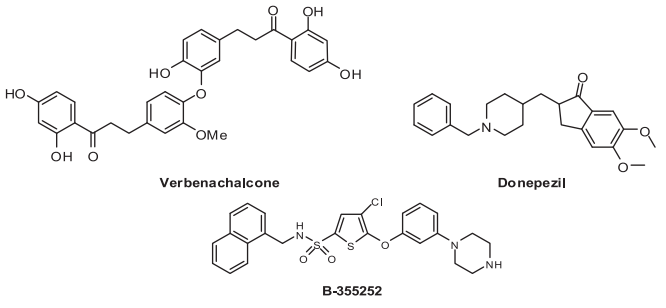

Fig. 1. Compounds that stimulate neurite outgrowth in neuronal cells.

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resynthesis of this new compound to confirm its structure and biological activity.

To assemble the heteroaryl ether core structure of B-355252, we recently developed a nucleophilic aromatic substitution (S_NAr) methodology, which involved reacting substituted phenols with *p*-methoxybenzyl (PMB) protected 4,5-chloro-*N*-(aryl/alkyl) thiophene-2-sulfonamides.[12] Under conventional heating, this method requires the use of a PMB protecting group for this reaction to proceed in 3–6 h. Although this reaction proceeds well using thermal heating, we want to develop a methodology, which could possibly eliminate the use of PMB protection and also develop a way to rapidly generate many diverse analogs of B-355252 by shortening the reaction times for synthesizing its heteroaryl ether core. One approach, which can be used accomplish this would be to heat the reaction using microwave (MW) irradiation. Due to its ability to increase reaction rates and to produce cleaner reactions in higher yields, microwave assisted synthesis is widely used to improve reaction conditions in organic synthesis.[13] Herein we report an MW-assisted S_NAr approach for the synthesis of B-355252 and evaluation of its enhancement of NGF activity on neurite outgrowths.

2. Results and discussion

To examine the use of MW irradiation toward synthesizing the heteroaryl ether core of B-355252, we first synthesized the S_NAr precursor, PMB protected 4,5-dichlorothiophene sulfonamide **4**, by reacting commercially available 4,5-dichlorothiophene-2-sulfonyl chloride **1** with 1-napthlymethyl amine **2** to generate 4,5-dichlorothiophene sulfonamide **3** in 91% yield. We then reacted **3** with NaH in DMF, *p*-methoxybenzyl bromide and a catalytic amount of TBAI to obtain compound **4** in 91% yield (Scheme 1).

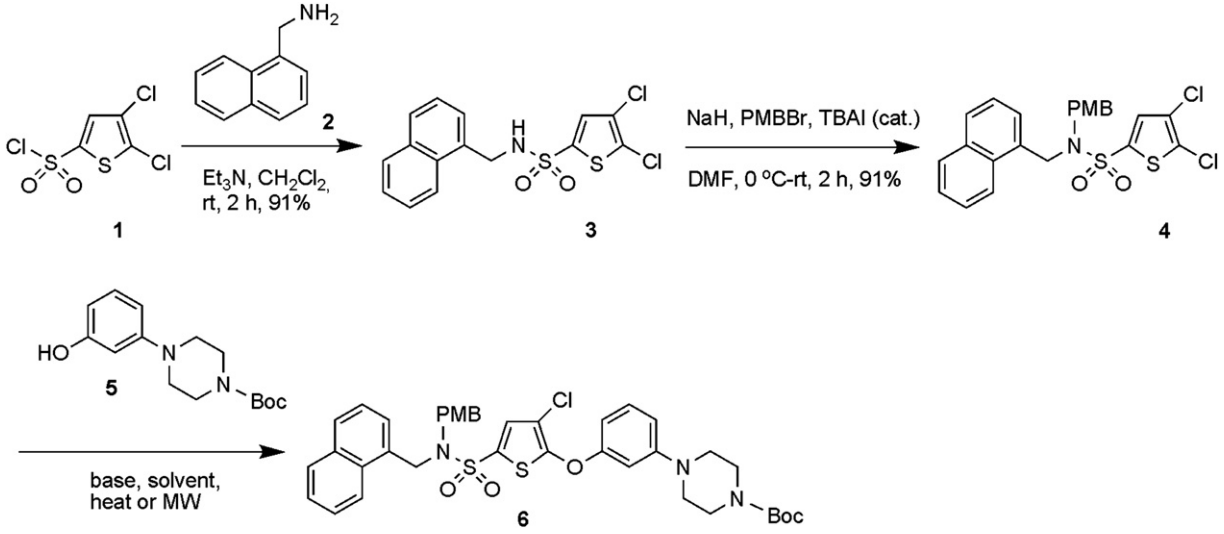
Table 1
Optimization of reaction conditions

Entry	Base[a]	Solvent	Temperature	*T* (min)	Yield[b] (%)
1	Cs_2CO_3	DMF	MW, 120 °C	25	94
2	Cs_2CO_3	DMF	80 °C	2.5 h	94
3	K_2CO_3	DMF	MW, 120 °C	25	50[c]
4	Na_2CO_3	DMF	MW, 120 °C	30	10[c]
5	K_3PO_4	DMF	MW, 120 °C	30	60[c]
6	Cs_2CO_3	DMF	MW, 150 °C	10	60[c]
7	Cs_2CO_3	DMF	MW, 200 °C	5	MP[d]
8	Cs_2CO_3	DMSO	MW, 150 °C	10	60[c]
9	Cs_2CO_3	DMA	MW, 200 °C	10	20[c]
10	K_3PO_4	NMP	MW, 120 °C	20	60[c]
11	K_3PO_4	NMP	MW, 140 °C	10	85[c]
12	K_3PO_4	NMP	MW, 160 °C	10	97
13	K_3PO_4	NMP	MW, 180 °C	6	91
14	K_3PO_4	NMP	MW, 200 °C	4	94
15	K_3PO_4	NMP	140 °C	40	97

[a] Amount of base used, Cs_2CO_3, K_2CO_3, and Na_2CO_3: 1.5 equiv; K_3PO_4: 3 equiv
[b] Isolated yields.
[c] Conversion based on LC/MS.
[d] Multiple products.

reaction temperature above 120 °C in DMF, DMSO or DMA only gave reduced yields and multiple products (Table 1, entries 5–8).

We then switched to using the base and solvent combination of K_3PO_4 in NMP. Initial heating at 120 °C for 20 min gave only a 60% conversion to **6** (Table 1, entry 10) but as the temperature was increased, the reaction times decreased and the yield of **6** increased (Table 1, entries 11–14). The best results were obtained when the reaction was heated to 200 °C for 4 min to produce **6** in a yield of 94% (Table 1, entry 14). In addition, we also observed that K_3PO_4 in NMP substantially reduced the reaction time when heated ther-

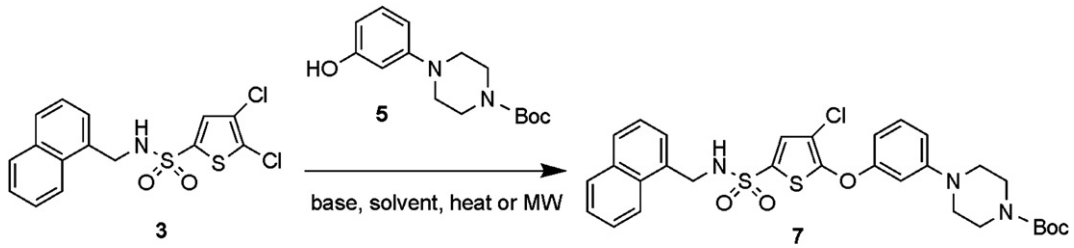


Scheme 1.

With **4** now in hand, we began investigating the optimal conditions to use in our MW assisted S_NAr reaction using a variety of reaction conditions (Table 1). When we initiated our search using Cs_2CO_3 in DMF as the base and solvent, we observed nucleophilic displacement of the C-5 chlorine of **4** with *N*-Boc protected 3-(piperazin-1-yl)phenol **5** to produce *N*,*N*′-diprotected 5-(3-(piperazin-1-yl)phenoxy)thiophene-2-sulfonamide **6** in an excellent yield of 94% after only 25 min with MW heating (Table 1, entry 1). When compared to thermal heating, this reaction required 2.5 h to produce **6** in the same yield (Table 1, entry 2). The use of other bases, such as K_2CO_3, Na_2CO_3, and K_3PO_4 in DMF resulted in lower yields of **6** (Table 1, entries 3–4 and 9). Attempts to elevate the mally. Under these conditions, **6** was generated in an excellent yield of 97% at 140 °C after heating for only 40 min (Table 1, entry 15). This enhancement of reaction times using both MW and thermal heating reveals the versatility of this base and solvent system in our S_NAr reactions.

We next turned our attention toward determining whether MW irradiation can be used to overcome the need for using a PMB protecting group in our S_NAr reaction (Scheme 2).

Using both Cs_2CO_3 in DMF and K_3PO_4 in NMP, we microwave irradiated unprotected 4,5-dichlorothiophene sulfonamide **3** in the presence of phenol **5** (Table 2). We found that we were only able to achieve 3–6% conversion to compound **7** after 30 min when we



Scheme 2.

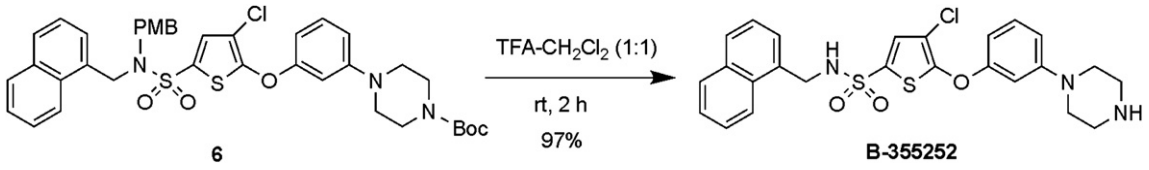
Table 2
Attempted reaction conditions

Entry	Base (equiv)	Conditions	Yield (%)[a]
1	Cs_2CO_3 (1.5)	DMF, MW, 120 °C, 30 min	3
2	Cs_2CO_3 (1.5)	DMF, MW, 140 °C, 30 min	3
3	Cs_2CO_3 (1.5)	DMF, MW, 160 °C, 30 min	6
4	K_3PO_4 (3)	NMP, MW, 160 °C, 20 min	12[b]
5	K_3PO_4 (3)	NMP, MW, 180 °C, 20 min	14[b]
6	K_3PO_4 (3)	NMP, MW, 200 °C, 20 min	16[b]
7	K_3PO_4 (3)	NMP, 140 °C, 40 h	26[b]

[a] Based on LC/MS analysis.
[b] In addition to unreacted **3**, several minor products (LC/MS) also present.

used Cs_2CO_3 in DMF (Table 2, entries 1–3). MW irradiation for longer than 30 min resulted in compound decomposition. When we attempted to use K_3PO_4 in NMP, the conversion to compound **7** was slightly improved but multiple products were detected by LC/MS (Table 2, entries 4–6). When we heated the reaction thermally, we saw a 26% conversion to product **7** (Table 2, entry 7). Previous attempts using a variety different bases and solvents resulted in no product formation.[12a] Although using K_3PO_4 in NMP gave product **7**, the reaction was not clean and required heating for 40 h. To complete our synthesis, both PMB and Boc protecting groups of compound **6** were simultaneously removed using TFA in DCM (1:1) to give us B-355252 in 97% yield (Scheme 3).

With B-355252 in hand, we commenced assessing the compounds enhancement of NGF-primed neurite outgrowth (NOG) in a Neuroscreen-1 (NS-1) cell line.[14] We used verbenachalcone (VC) as a positive control compound for biological activity potentiation of NGF in NS-1 cells. The ratio of neutite bearing cells to total cells was detected using a Beckton Dickinson (BD) Pathway 855 High-Content automated imaging platform and Cellomics NOG kit. The data was analyzed with a BD AttoVision neurite outgrowth software version 1.6 (BD Biosciences, Franklin Lakes, NJ). In the presence of 2 ng/mL NGF, VC shows a dose-dependent enhancement of NGF's effects with a peak enhancement at 15 μM when compared to NGF treatment alone (Fig. 2, panel A). This result is consistent with what was observed by Li et al. using PC-12 cells.[9a] We next examined B-355252 at various concentrations in the presence of 1 ng/mL NGF. This lower NGF concentration was used to better observe the neurite outgrowth and elongation effects of B-355252. As shown (Fig. 2, panel B), co-treatment of NS-1 with 1 ng/mL NGF and B-355252 was accompanied by a marked dose-dependent increase neutite bearing cells, with a peak enhancement of approximately 2-fold observed in the



Scheme 3.

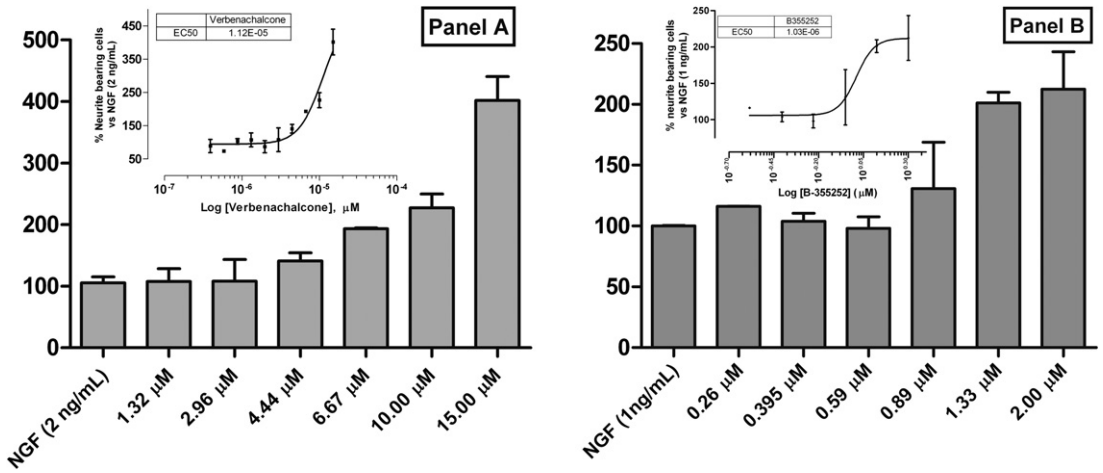


Fig. 2. Resynthesized B-355252 potentiates NGF dependent neurite outgrowth and elongation in a neuronal cell model. Panel A shows the response of control VC assay in 2 ng/mL NGF while panel B represents the dose dependent activity of B-355252 for NOG in the presence of 1 ng/mL NGF. Each data point was acquired in triplicate from two separate experiments.

presence of 1.33 μM B-355252 when compared to NGF treatment alone. B-322525 was devoid of neurite promoting properties in the NS-1 neuronal cell model in the absence of NGF (data not shown). From the generated dose response curve (Fig. 1, panel B), B-355252 was determined to display an EC_{50} of ~1.0 μM. The EC_{50} of resynthesized B-355252 is essentially the same as the value obtained from the original hit compound in our initial primary screen and this confirmed our compounds structure and activity.

3. Conclusions

The synthesis of B-355252, *N*-(naphthalen-1-ylmethyl)-5-(3-(piperazin-1-yl)phenoxy)thiophene-2-sulfonamide, was successfully completed using an MW assisted S_NAr reaction. The generation of the heteroaryl ether core structure of B-355252 was optimal in the presence of Cs_2CO_3 in DMF or K_3PO_4 in NMP. Addition of *N*-Boc protected phenol **5** to give *N*,*N*′-diprotected compound **6** occurs more rapidly and in higher yields when 4,5-dichlorothiophene sulfonamide **4** is PMB protected compared to low product **7** conversion and by-product formation without this protection. These results stress the importance of having a PMB protecting group present in this reaction. Resynthesized B-355252 enhancement of NGF's effects on neurite outgrowths was demonstrated in an NS-1 cell line thus confirming its biological activity. The synthesis of the heteroaryl ether core using our MW assisted S_NAr methodology should allow for the very rapid generation of many diverse analogs of B-355252 to be used in future structure–activity relationship (SAR) studies.

4. Experimental

4.1. General experimental procedures

All solvents and reagents were obtained from commercial sources and used without further purification unless otherwise stated. All reactions were performed in oven-dried glassware (either in RB flasks or 10 mL microwave tubes equipped with a cap) under an atmosphere of nitrogen and the progress of reactions was monitored by thin-layer chromatography and LC/MS. All microwave irradiations were performed using a CEM Explorer 24 sample microwave reactor. Analytical thin-layer chromatography was performed on precoated 250 μm layer thickness silica gel 60 F_{254} plates (EMD Chemicals Inc.). Visualization was performed by ultraviolet light and/or by staining with phosphomolybdic acid (PMA) or *p*-anisaldehyde. All the silica gel column chromatography purifications were carried out by using Combiflash® R_f (Teledyne Isco) either with EtOAc/hexane or MeOH/CH_2Cl_2 mixtures as the eluants. Melting points were measured on a MEL-TEMP® capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a Varian VNMRS-500 (500 MHz) spectrometer. Chemical shifts (δ) for proton are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to it (TMS 0.0 ppm). Coupling constants (J) are reported in hertz. Multiplicities are reported using the following abbreviations: br=broad; s=singlet; d=doublet; t=triplet; q=quartet; m=multiplet. Chemical shifts (δ) for carbon are reported in parts per million (ppm) downfield from tetramethylsilane and are referenced to residual solvent peaks: carbon ($CDCl_3$ 77.0 ppm). HRMS data were recorded on an Agilent Technologies 6210 LC-TOF.

*4.1.1. 4,5-Dichloro-N-(naphthalen-1-ylmethyl)thiophene-2-sulfonamide (**3**).* To a solution of 4,5-dichlorothiophene-2-sulfonyl chloride (**1**) (1.000 g, 4.002 mmol) in anhydrous CH_2Cl_2 (20 mL) was added 1-naphthylmethylamine (**2**) (0.630 g, 4.007 mmol) followed by Et_3N (0.84 mL, 6.027 mmol) and stirred at room temperature for 2 h. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (100 mL), washed with brine, dried (Na_2SO_4), and concentrated under vacuo. The residue was purified by recrystallization from CH_2Cl_2/hexane to afford **3** (1.350 g, 91%) as a white crystalline product; mp:136–138 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 4.66 (d, 2H, J=4.0 Hz), 4.98 (br s, 1H), 7.21 (s, 1H), 7.34–7.40 (m, 2H), 7.49–7.56 (m, 2H), 7.79–7.83 (m, 1H), 7.85 (d, 1H, J=2.5 Hz), 7.90 (d, 1H, J=3.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 45.8, 122.9, 124.6, 125.1, 126.2, 126.9, 127.4, 128.9, 129.5, 130.4, 131.0, 131.1, 133.8, 137.2; HRMS (ESI) m/z calcd for $C_{15}H_{11}Cl_2NO_2S_2Na$ $[M+Na]^+$ 393.9500, obsd: 393.9503.

*4.1.2. 4,5-Dichloro-N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)thiophene-2-sulfonamide (**4**).* Sodium hydride (0.081 g, 3.375 mmol) was slowly added in portions to a solution of **3** (1.250 g, 3.358 mmol) in anhydrous DMF (10 mL) at 0 °C and stirred for 15 min. Then, 4-methoxybenzyl bromide (PMBBr) (0.675 g, 3.357 mmol) and a catalytic amount of TBAI (0.030 g, 0.081 mmol) were added and stirred at room temperature for 2 h. After the completion of the reaction, it was quenched by slow addition of water (5 mL) and extracted with EtOAc (100 mL), washed with water and brine, dried (Na_2SO_4), and concentrated under vacuo. The residue purified by flash silica gel column chromatography (Combiflash® R_f) using EtOAc/hexane (1:9) as eluant to afford **4** (1.500 g, 91%) as a white solid; mp: 63–65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 3.71 (s, 3H), 4.28 (s, 2H), 4.83 (s, 2H), 6.61 (d, 2H, J=8.5 Hz), 6.90 (d, 2H, J=8.5 Hz), 7.10 (s, 1H), 7.32–7.38 (m, 2H), 7.46–7.50 (m, 2H), 7.76 (d, 1H, J=7.0 Hz), 7.78–7.82 (m, 1H), 8.02–8.05 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 50.2, 51.1, 55.2, 113.6, 123.4, 124.7, 124.9, 126.0, 126.5, 127.0, 127.7, 128.6, 129.2, 129.4, 129.7, 130.0, 130.7, 130.9, 131.6, 133.7, 136.9, 159.1; HRMS (ESI) m/z calcd for $C_{23}H_{19}Cl_2NO_3S_2Na$ $[M+Na]^+$ 514.0076, obsd: 514. 0078.

*4.1.3. tert-Butyl 4-(3-(3-chloro-5-(N-(4-methoxybenzyl)-N-(naphthalen-1-ylmethyl)sulfamoyl)thiophen-2-yloxy)phenyl)piperazine-1-carboxylate (**6**).* A mixture of **4** (0.050 g, 0.101 mmol), *tert*-butyl 4-(3-hydroxyphenyl)piperazine-1-carboxylate (**5**) (0.034 g, 0.122 mmol), and Cs_2CO_3 (0.050 g, 0.152 mmol) in anhydrous DMF (1 mL) was taken in a 10 mL microwave tube, and the tube sealed with a pressure cap. The tube was submitted to microwave irradiation for 25 min at 120 °C. The solvent was evaporated under vacuo and the residue purified by flash silica gel column chromatography (Combiflash® R_f) using EtOAc/hexane (1:4) to afford **6** as a white solid (0.070 g, 94%); mp: 116–118 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 1.48 (s, 9H), 3.16 (t, 4H, J=5.0 Hz), 3.57 (t, 4H, J=5.0 Hz), 3.71 (s, 3H), 4.27 (s, 2H), 4.82 (s, 2H), 6.52 (dd, 1H, J=2.5, 8.5 Hz), 6.58–6.62 (m, 2H), 6.65 (t, 1H, J=2.5 Hz), 6.75 (dd, 1H, J=2.5, 8.5 Hz), 6.86–6.90 (m, 2H), 7.20 (s, 1H), 7.25 (t, 1H, J=8.0 Hz), 7.31–7.37 (m, 2H), 7.45–7.50 (m, 2H), 7.75 (d, 1H, J=8.0 Hz), 7.79–7.82 (m, 1H), 8.03–8.06 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 28.4, 48.7, 49.9, 50.9, 55.2, 80.0, 105.6, 108.2, 111.8, 112.9, 113.5, 123.5, 124.9, 125.9, 126.5, 127.2, 127.5, 127.9, 128.6, 129.1, 129.7, 130.2, 130.5 (2), 131.7, 133.7, 152.9, 154.6, 158.3, 159.0; HRMS (ESI) m/z calcd for $C_{38}H_{41}ClN_3O_6S_2$ $[M+H]^+$ 734.2120, obsd: 734.2117.

4.1.4. 4-Chloro-N-(naphthalen-1-ylmethyl)-5-(3-(piperazin-1-yl)phenoxy)thiophene-2-sulfonamide (B-355252). To a solution **6** (0.140 g, 0.191 mmol) in anhydrous CH_2Cl_2 (1 mL) was added TFA (1 mL) and stirred at room temperature for 2 h. The solvent mixture was removed under vacuo and the residue was re-dissolved in CH_2Cl_2 (25 mL), washed with aqueous satd $NaHCO_3$ followed by brine, dried (Na_2SO_4), and concentrated under vacuo. The crude product was purified by flash silica gel column chromatography (Combiflash® R_f) using MeOH/CH_2Cl_2 (1:9) to afford B-355252 as a white solid (0.095 g, 97%); mp: 142–144 °C; ^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm) 2.81 (t, 4H, J=5.0 Hz), 3.09 (t, 4H, J=5.0 Hz), 4.56 (s, 2H), 6.43 (dd, 1H, J=2.0, 8.0 Hz), 6.75 (t, 1H, J=2.5 Hz), 6.83 (dd,

1H, J=2.5, 8.0 Hz), 7.26 (t, 1H, J=8.0 Hz), 7.43–7.48 (m, 3H), 7.54–7.58 (m, 2H), 7.87 (dd, 1H, J=1.5, 7.5 Hz), 7.93–7.96 (m, 1H), 8.06–8.09 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ (ppm) 44.5, 45.3, 48.6, 104.3, 106.7, 109.5, 112.1, 123.5, 125.2, 125.8, 126.2, 126.8, 128.3, 128.5, 129.0, 129.6, 130.5, 130.8, 132.2, 133.2, 153.3, 157.5, 157.8; HRMS (ESI) m/z calcd for $C_{25}H_{25}ClN_3O_3S_2$ $[M+H]^+$ 514.1020, obsd: 514.1028.

4.2. Neurite outgrowth assay

The enhancement of NGF-primed neurite outgrowth (NOG) by resynthesized B-355252 was assessed in the Neuroscreen-1 (NS-1) cell line, a clonal outgrowth of the rat pheochromocytoma PC12 neuronal cell model, using the Beckton Dickinson (BD) Pathway 855 High-Content automated imaging platform and Cellomics NOG kit (Cellomics, Inc., Pittsburg, PA). NS-1 cells were plated at 1×10^3 cells/well in a 96-well imaging plate. Following overnight incubation at 37 °C in a humidified cell culture incubator, the wells were co-treated with NGF (1 ng/mL) and various concentrations of B-355252 in treatment media (RPMI-1640 supplemented with 1% FBS, 2% horse serum, and 4 mM glutamine). The neurite bearing cells as a percentage of total cells were detected and captured on the BD bioimager after 48 h of compound treatment by staining the cells with fluorescent labeled antibody neurite outgrowth reagent kit (Cellomics, Pittsburg, PA) according to the manufacturer's protocol. The image was analyzed with BD AttoVision neurite outgrowth software version 1.6 (BD Biosciences, Franklin Lakes, NJ). Cells with neurite processes equal to or greater than twice the diameter of the cell body were counted as positive. Verbenachalcone (VC) was used as a positive control compound for potentiation of NGF induced NOG in NS-1 cells.

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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.2010.09.028.

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