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Design and Synthesis of New Boron-Based Benzo[c][1,2,5]oxadiazoles and Benzo[c][1,2,5]thiadiazoles as Potential Hypoxia Inhibitors

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Abstract: Benzo[c][1,2,5]oxadiazoles and benzo[c][1,2,5]thiadiazoles are recognized to possess potent pharmacological activities including anticancer potential. In continuation of our research endeavors in the development of boron-based heterocycles as potential therapeutic agents, herein we report the design and synthesis of new series of boron-based benzo[c][1,2,5]oxadiazoles and benzo[c][1,2,5]thiadiazoles as anticancer agents targeting tumor hypoxia. A series of seventeen compounds were synthesized in two steps in an efficient manner via substitution reactions followed by subsequent hydrolysis of aryltrifluoroboronate salts into corresponding boronic acid derivatives in the presence of silica. This is the first example to develop boron-based hypoxia agents. The synthesized hybrids were characterized by suitable spectroscopic techniques. The biological studies are currently underway.

Keywords: boron-based hetereocycles; benzo[c][1,2,5]oxadiazoles; benzo[c][1,2,5]thiadiazoles; hypoxia inhibitors

Citation: Das, S.; Shareef, M.A.; Das, B.C. Design and Synthesis of New Boron-Based Benzo[c][1,2,5]oxadiazoles and Benzo[c][1,2,5]thiadiazoles as Potential Hypoxia Inhibitors. *Inorganics* **2023**, *11*, 34. https://doi.org/10.3390/inorganics11010034

Academic Editor: Marina Yu. Stogniy

Received: 20 September 2022
Revised: 29 December 2022
Accepted: 30 December 2022
Published: 9 January 2023

1. Introduction

Hypoxia is an eminent hallmark of tumor cells that aids in metastasis of cancer by promoting angiogenesis, cancer cell division, and cell survival effectively [1,2]. Unfortunately, hypoxia inducing factor-1(HIF-1) is one of the many factors responsible for multi-drug resistance and resistance to radiation therapy [3]. Researchers were successful in identifying a number of pro-drugs targeting tumor hypoxia such as Tirapazamine, Banoxantrone (AQ4N) and (PR-104) (Figure 1). However, they are limited by low potency, poor pharmacokinetic profiles, and toxicity due to non-selectivity [4,5]. Although various strategies were discovered to combat hypoxic tumor cells, success was far from anticipation. Consequently, there is an intensifying necessity to develop novel new chemical entities and approaches targeting HIF-1 pathway [6].

Boron-based hetereocycles are being established as vital templates in the field of medicinal chemistry after the FDA approval of a number of boron-based drugs (e.g., Vaborbactam, Ixazomib, crisaborole, tavaborole and bortezomib) [7,8], (Figure 2). Literature survey reveals that boron-based heterocycles have tremendous potential in the search for newer pharmacological agents, as they elicit potent activity, can act as biososteres, and they display a wide array of pharmacological activities and appreciable pharmacokinetic profiles [9,10]. Additionally, more and more organo-boron compounds are inflowing toward clinical trials and the drug discovery pipeline, which suggests that they are proving to be extremely promising therapeutics. Undeniably, they could be effectively amalgamated with other promising medicinal moieties, which might result in potent molecular hybrids demonstrating novel bioactivities and possibly fewer side effects.

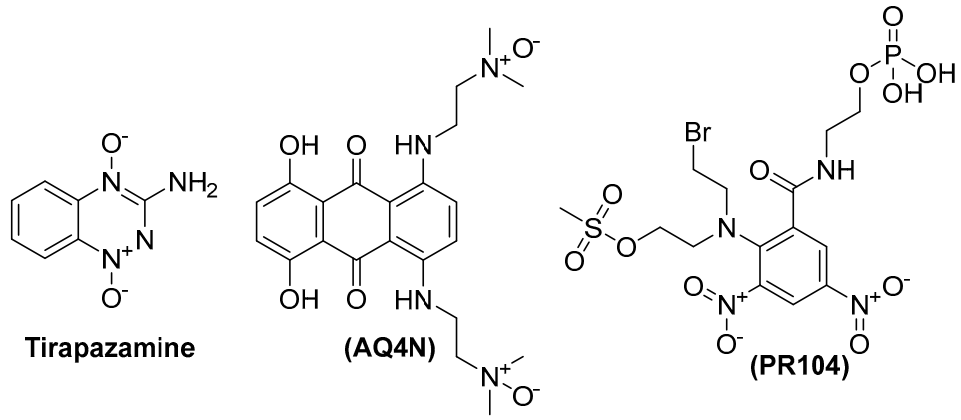


Figure 1. Hypoxia activated Prodrugs.

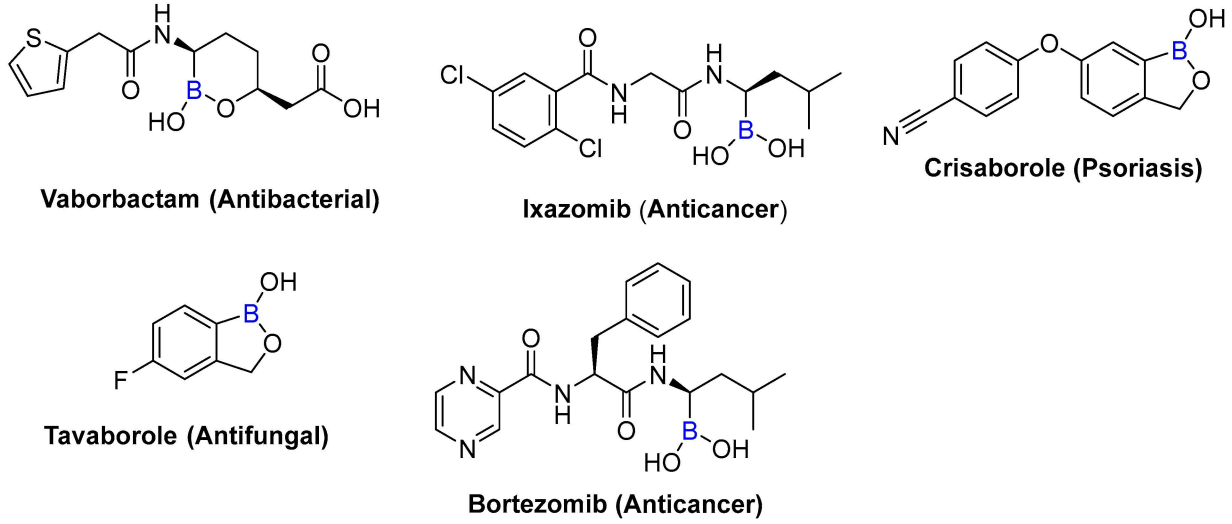


Figure 2. Boron-based compounds approved by the FDA for various therapeutic purposes.

On the other hand, nitrobenzoxadiazoles (NBD) have engrossed significant interest in recent years, as they not only also exhibit photo-physical properties but are also endowed with therapeutic potential. In addition, NBD-based lipids are commonly documented as fluorescent probes in evaluating cellular metabolism in diverse models [11–13]. Moreover, nitrobenzoxadiazoles have been well explored by numerous researchers during the past decades for several biological activities, including anticancer, anti-viral [14] and antiparasitic activities [15]. They tend to exhibit anticancer potential by targeting dissimilar molecular mechanisms such as interference of EGFR phosphorylation, inhibition of glutathione transferase P1-1 (GSTP1-1) and by acting as nitrogen (II) oxide donors [16–21] (Figure 3).

The benzothiadiazole (BTD) motif has emerged as a key structural motif among the fused heterocycles in the field of organic and medicinal chemistry over the past decades. Compounds bearing this motif have been extensively valuable in the development of photovoltaic cells, solar cells, OLEDS, dyes and liquid crystals mainly due to their exclusive photo-luminescent properties [22]. Additionally, literature review suggests that benzothiadiazole derivatives exhibit antifungal, antibacterial and herbicidal activities [23,24]. Importantly, it is a core structural moiety of an existing drug, Tizanidine, an adrenergic agonist used as muscle relaxant [25] (Figure 3).

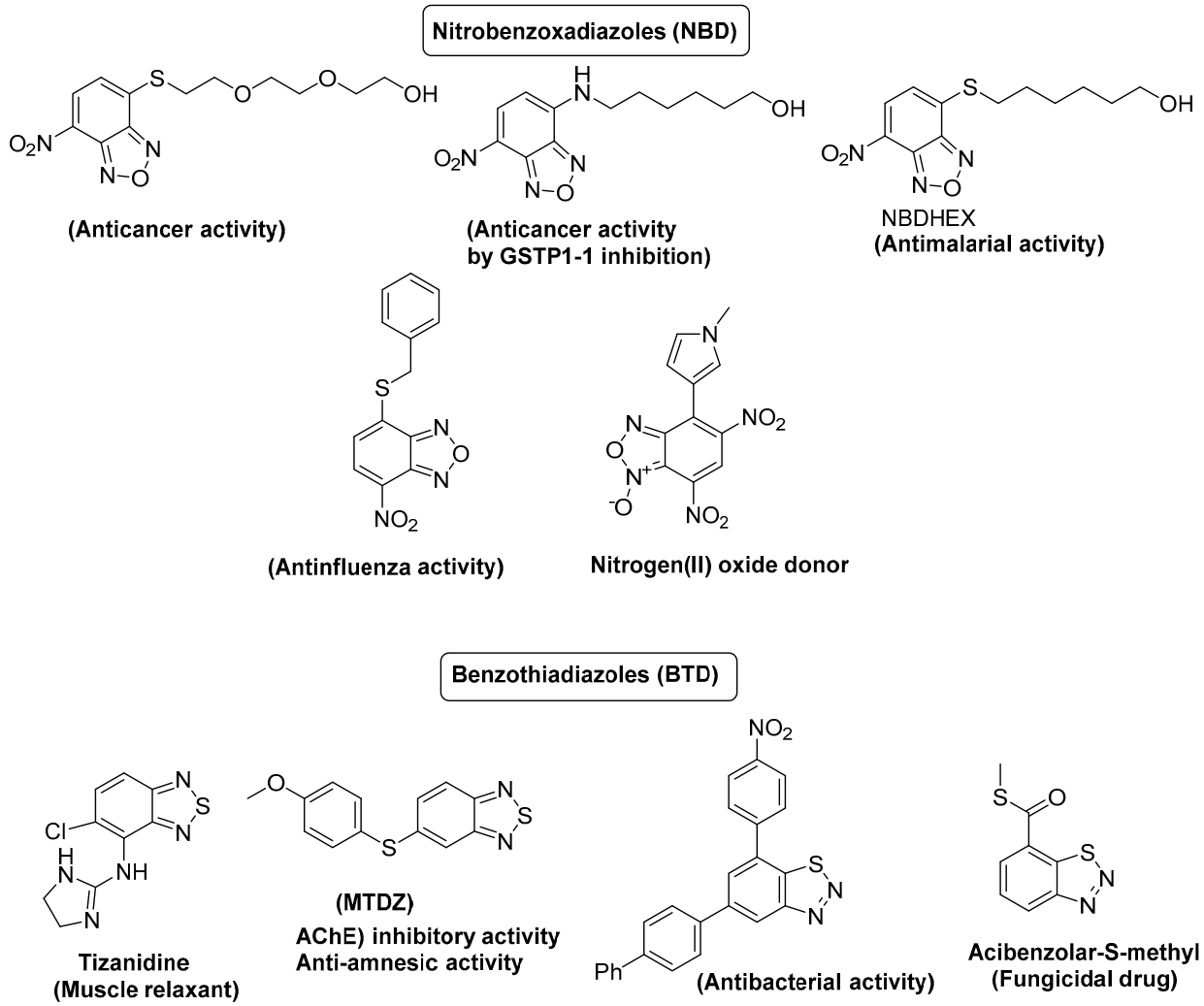


Figure 3. Structure of some nitrobenzoxadiazoles and benzothiadiazoles (BTD).

Moreover, Wang and co-workers prepared novel benzo[c][1,2,5]thiadiazole derivatives and screened them for their anticancer potential. The most active compound demonstrated SHP2 inhibitory activity. Further biological studies revealed that it inhibits protein tyrosine phosphatase 1B (PTP1B) and SHP2 [26]. Furthermore, benzo[c][1,2,5] thiadiazole was also explored for anti-cholinergic characteristics by many researchers, and the results revealed that 5-((4-methoxyphenyl)thio)benzo[c][1,2,5] thiadiazole (MTDZ) demonstrated acetylcholinesterase (AChE) inhibitory activity [27] while new arylsulfanyl-benzo-2,1,3-thiadiazoles display anti-amnesic activity and could be potential candidates in the treatment of neurodegenerative disorders such as Alzheimer's and dementia [28] (Figure 3).

Our research group has been dedicatedly working toward the development of new small-molecule boron-based heterocycles for the treatment of cancer and neurodegenerative disorders [29–31]. In this regard, we have recently reported on a borylated amidoxime reagent for the synthesis of boron-containing biologically important scaffolds such as oxadiazoles and quinazolinones in a single step [32]. More recently, we have unfolded a novel methodology for the preparation of borylated quinolines as homeodomain interacting protein kinase 2 (HIPK2) inhibitors [33].

In our initial efforts, we have reported 2H-benzo[b][1,4] oxazine hybrids targeting hypoxia downregulating hypoxia-induced genes (HIF-1a, P21and VEGF) suitably [4]. In view of the promising therapeutic potential of benzoxadiazoles and benzothiadiazoles and in continuation of our endeavor for the development of boron-based therapeutic agents, we

hypothesized to prepare boron-based benzoxadiazoles/benzothiadiazoles compounds by linking an ether and amine functionality, which could display promising anticancer activity (Figure 4).

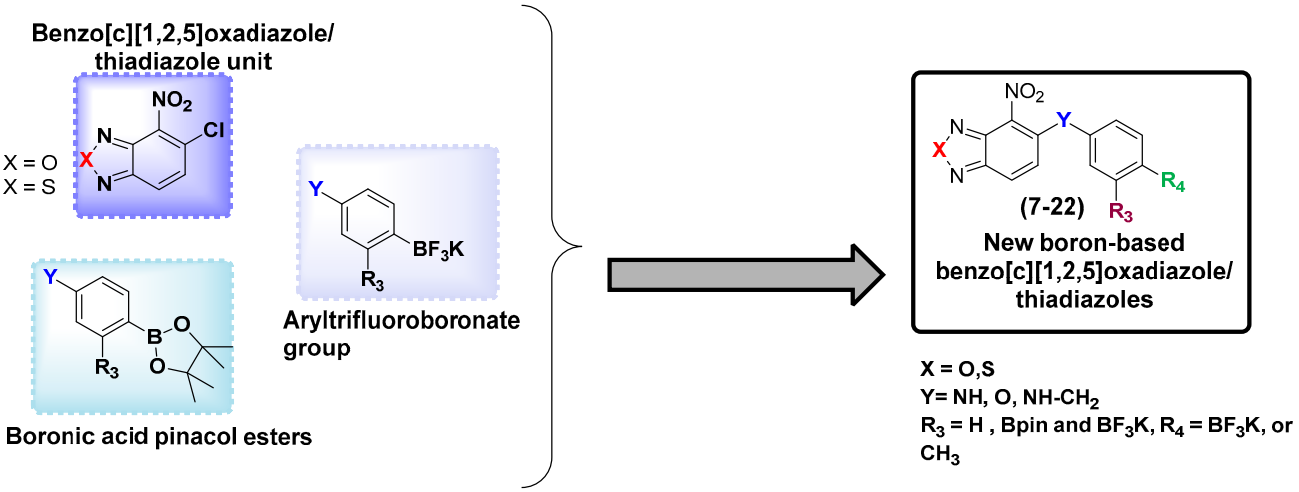


Figure 4. Design strategy.

2. Results and Discussion

The synthesis of boron-based benzo[c][1,2,5]oxadiazoles and benzo[c][1,2,5]thiadiazoles is depicted in Scheme 1. Initially, we prepared substituted amine linked and ether linked boronic acid pinacol ester derivatives (**7**–**14**) by base catalyzed substitution reaction. Further, the synthesized boronic acid pinacol esters (**7**–**14**) were converted to corresponding aryltrifluoroborate salts (**15**–**22**) in good to excellent yields.

First, we heated an equivalent quantity of 5-chloro-4-nitrobenzo[c][1,2,5]oxadiazole (**1**) and 5-chloro-4-nitrobenzo[c][1,2,5]thiadiazole (**2**) with 4-aminophenylboronic acid pinacol ester (**3**) in DMF at 90 °C for 3 h to obtain compounds (**7**) and (**8**), respectively.

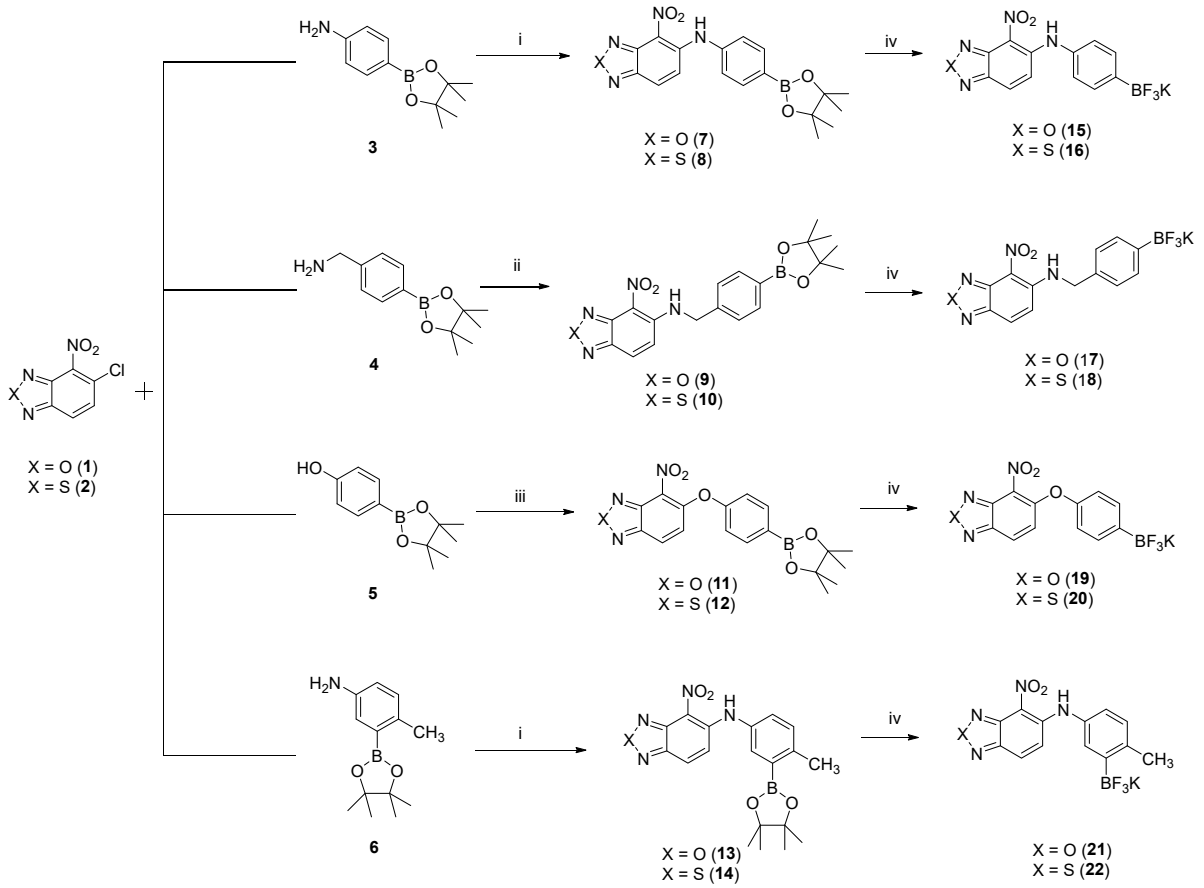
Next, derivatives (**9**) and (**10**) were synthesized by stirring substrates (**1**) and (**2**) with 4-(aminomethyl)phenylboronic acid pinacol ester (**4**) (1.0 equiv) in the presence of sodium tertiary butoxide (^{t}BuONa) (1.0–1.5 equiv) under nitrogen atmosphere in DMF at room temperature (25 °C) for 16 h.

Further, (**1**) and (**2**) were treated with 4-hydroxyphenylboronic acid pinacol ester (**5**) (1.0 equiv) in the presence of triethylamine (Et_3N) (1.0 equiv) under nitrogen atmosphere in acetonitrile at room temperature (25 °C) for 16 h to yield hybrids (**11** and **12**).

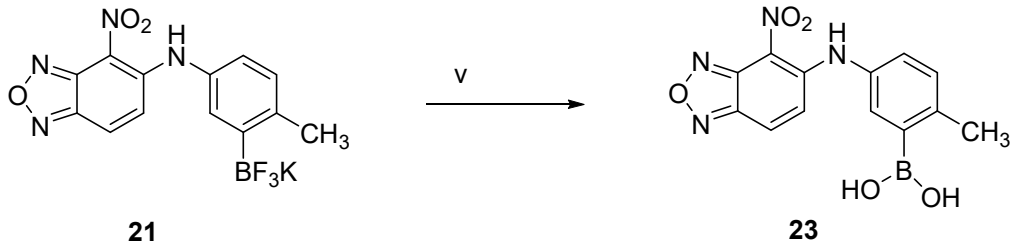
Similarly, compounds (**13**) and (**14**) were synthesized by heating substrates (**1**) and (**2**) with 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (**6**) (1.0 equiv) in DMF at 90 °C for 3 h.

Aryltrifluoroborate salts are considered significant structural units in organic and medicinal chemistry. With substituted boronic acid pinacol esters in hand, we therefore turned our attention toward converting them to their respective aryltrifluoroborate salts. The synthesis of aryltrifluoroborates (**15**–**22**) was accomplished by the treatment of boronic acid pinacol ester derivatives (**7**–**14**) with (3M) KHF_2 in MeOH at room temperature (25 °C) for 2 h in good yield to excellent yields (75%) (Scheme 1).

Our next focus was to obtain a boronic acid derivative from trifluoroborate salt, as they are found in most boron-based drugs in the market. In this regard, the trifluoroborate salt derivative (**21**) was then transformed into compound (**23**) in 64% yield using silica gel in ethyl acetate/water at room temperature (25 °C) for 1–2 h (Scheme 2). The structures of all the synthesized compounds are represented in (Figure 4). The synthesized compounds were characterized by modern spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR and mass spectrometry.



Scheme 1. General synthetic scheme of boron-based compounds. Reagents and conditions: (i) DMF, 90 °C, 3 h; (ii) ^{t}BuONa, DMF, room temperature (25 °C), 16 h; (iii) Et_3N, ACN, room temperature (25 °C), 16 h (iv) KHF_2 (3M), MeOH, room temperature (25 °C), 2 h.



Scheme 2. Synthesis of boronic acid derivative (**23**). Reagents and conditions: (v) SiO_2, EtOAc, H_2O 1–2 h, room temperature (25 °C) 64%.

The ^{1}H NMR spectrum of compounds (**7**) and (**8**) displayed characteristic singlet –NH-peak at δ 11.75 and 11.22, respectively. In addition, characteristic boronic acid pinacol ester singlet –CH_3-peak for 12 protons was observed at δ 1.38 and 1.37, respectively. In addition, ^{13}C NMR spectrum of compounds (**7**) and (**8**) displayed characteristic boronic acid pinacol ester peak in the range of δ 84.00 and δ 24.90, respectively. The ^{1}H NMR spectrum of compounds (**9**) and (**10**) displayed characteristic singlet –NH-peak at δ 10.77 and 10.36, respectively. In addition, characteristic –CH_2-singlet-protons were observed at δ 4.87 and δ 4.84, respectively. Moreover, the charachteristic boronic acid pinacol ester singlet –CH_3-peak for 12 protons at δ 1.34. In addition, ^{13}C NMR spectrum of compounds (**9**) and (**10**) displayed characteristic boronic acid pinacol ester peak at δ 84.00 and 24.90, respectively. Moreover, the charachteristic –CH_2–carbons for both the compounds were observed at δ 24.87.

The ^{1}H NMR spectrum of compounds (**11**) and (**12**) displayed boronic acid pinacol ester singlet –CH_3-peak for 12 protons at δ 1.36 and 1.35, respectively. In addition, ^{13}C NMR spectrum of compounds (**11**) and (**12**) displayed characteristic boronic acid pinacol ester peak at δ 84 and 24, respectively.

Similarly, ^{1}H NMR spectrum of compounds (**13**) and (**14**) displayed characteristic singlet –NH-peak at δ 11.69 and 11.23, respectively. In addition, singlet signal for characteristic methyl protons were observed at δ 2.61 and 2.60, respectively. Moreover, boronic acid pinacol ester singlet –CH_3-peak for 12 protons was observed at δ 1.35. In addition, ^{13}C NMR spectrum of compounds (**13**) and (**14**) displayed characteristic boronic acid pinacol ester carbons and methyl carbons were observed the range of δ 84.0, δ 24.0, and 21.8, respectively.

Moreover, the ^{1}H NMR and ^{13}C NMR of compounds revealed that the precursor boronic acid pinacol ester protons and carbons disappeared indicating the formation of trifluoroborate salt derivatives (**15**–**22**). Additionally, the presence of fluorine in compounds (**16**), (**20**), and (**21**) was confirmed by ^{19}F NMR in the range of δ 138–139. The ^{1}H NMR spectrum of compound (**23**) was confirmed as it displayed characteristic singlet boronic acid –OH-peak at δ 8.20.

The compounds (Figure 5) are being evaluated for their anticancer potential, and the biological evaluation is underway.

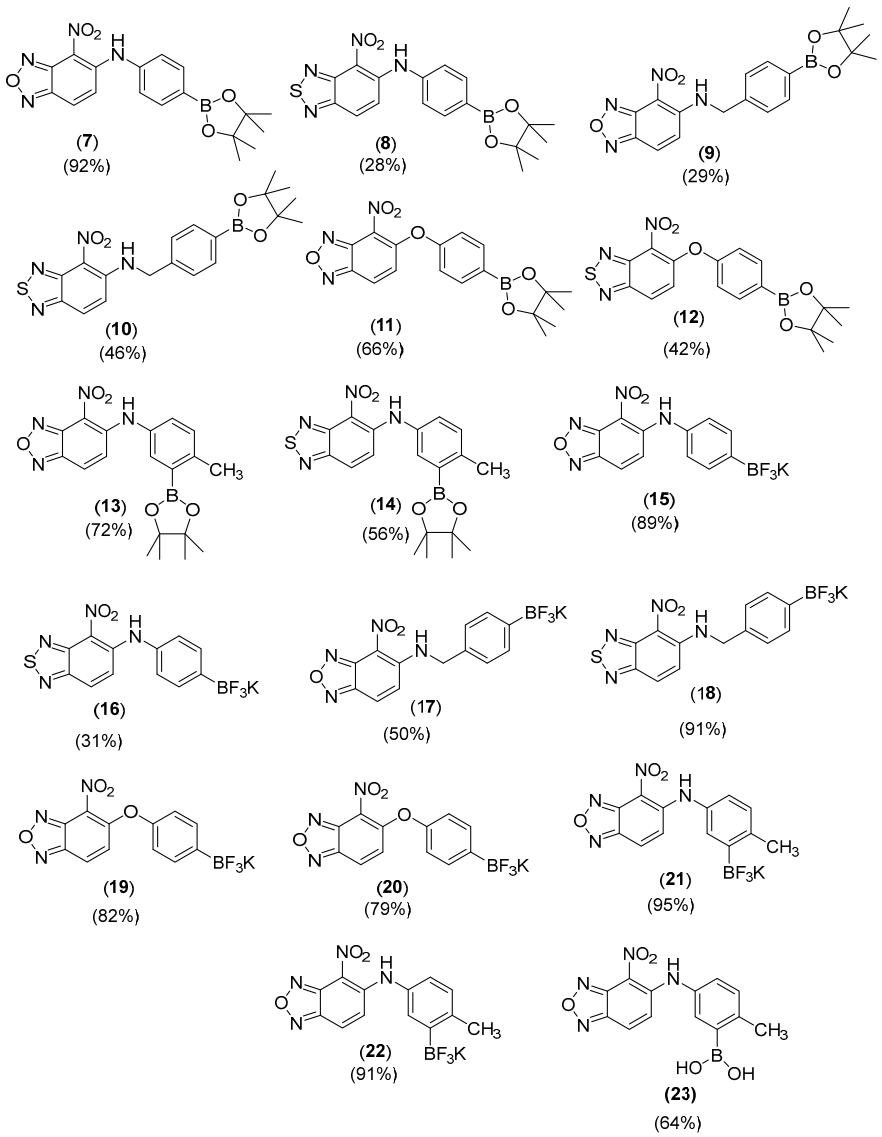


Figure 5. Structures and yields of boron-based derivatives synthesized in the present work.

3. Materials and Methods

Compounds used as starting materials and reagents were obtained from SIGMA-Aldrich, ACROS ORGANICS, FISHER SCIENTIFICS or other chemical companies, and utilized without further purification. Thin-layer chromatography (TLC) and column chromatography (CC) were performed with Kieselgel 60 F_{254} (Merck) and silica gel (Kieselgel 60, 230–400 mesh, Merck), respectively. Since all the compounds prepared contain aromatic ring, they were visualized and detected on TLC plates with UV light (short-wave, long-wave or both). NMR spectra were recorded on a BRUKER AVANCE NEO NANOBAY-USA (400 MHz for ^{1}H NMR, 62.5 MHz for ^{13}C NMR and 376.5 MHz for ^{19}F NMR), and chemical shifts were calibrated to TMS (tetramethylsilane). All ^{19}F NMR chemical shifts were referenced to external CF_3CO_2H (0.0 ppm). Chemical shifts (δ) were recorded in ppm and coupling constants (*J*) in hertz (Hz). Signal patterns are indicated as s, singlet; d, doublet; dd, doublet of doublets; t, triplet; m, multiplet and bs, broad singlet. All compounds analytical data's are presented in Supplementary Information Figure S1. Spectra of the products (**7**–**23**).

General procedure for the synthesis of boronic ester derivatives (**7**–**14**).

*3.1. General Method for the Synthesis of (**7**), (**8**), (**13**) and (**14**)*

Compound (**1**) or (**2**) (1.00 equiv) and (**3**) (1.00 equiv) were dissolved in DMF and stirred at room temperature for a few minutes. Later, the resulting mixture was heated at 90 °C and stirred under N_2 for 3 h, and the progress was monitored by TLC until the reaction was complete. After the reaction was completed, the reaction mixture was poured into 10 mL of ice cold water and extracted with EtOAc (30 mL), washed with H_2O (10 mL × 3), satd. NaCl (5 mL) was dried over Na_2SO_4 and filtered. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum. Further purification was performed by column chromatography using ethyl acetate and n-hexane to obtain yellow solids.

3.1.1. 4-Nitro-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[c][1,2,5] oxadiazol-5-amine (**7**)

Compound (**7**) was prepared according to the general procedure described in Section 3.1 by using compound (**1**) (0.100 g, 0.501 mmol, 1.00 equiv) and (**3**) (0.109 g, 0.501 mmol, 1.00 equiv) in DMF (1 mL) a yellow solid (0.176 g, 0.46 mmol, 91.9%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 11.75 (s, 1H, –NH–), 7.97 (d, *J* = 7.80 Hz, 2H, phenyl H-3, H-5), 7.86 (d, *J* = 9.87 Hz, 1H, benzoxadiazole H-7), 7.35 (d, *J* = 10.5 Hz, 1H, benzoxadiazole H-6), 7.33 (d, *J* = 8.35 Hz, 2H, phenyl H-2, H-6), 1.38 (s, 12H, 4 × –CH_3–); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 148.13, 146.38, 144.82, 138.21, 136.76, 125.01, 124.90, 124.62, 84.35, 24.90. MS calcd. for $C_{18}H_{19}BN_4O_5H$– 382.1830, found 381.1159

3.1.2. 4-Nitro-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)benzo[c][1,2,5] thiadiazol-5-amine (**8**)

Compound (**8**) was prepared according to the general procedure described in Section 3.1 by taking compound (**2**) (0.100 g, 0.46 mmol, 1.00 equiv) and (**3**) (0.101 g, 0.46 mmol, 1.00 equiv) in DMF (2 mL) to obtain compound (**8**) as yellow solid (0.051 g, 0.128 mmol, 27.83%).

^{1}H NMR (400 MHz, $CDCl_3$) *δ* 11.22 (s, 1H, –NH–), 7.95 (d, *J* = 8.33 Hz, 2H, phenyl H-3, H-5), 7.92 (d, *J* = 7.89 Hz, 1H, benzothiadiazole, H-7), 7.53 (d, *J* = 9.79 Hz, 1H, benzothiadiazole H-6), 7.34 (d, *J* = 8.07 Hz, 2H, phenyl H-2, H-6), 1.37 (s, 12H, 4 × –CH_3–); ^{13}C NMR (62.5 MHz, $CDCl_3$) *δ* 150.29, 149.48, 147.26, 139.46, 136.63, 128.55, 124.52, 121.96, 84.20, 24.88. MS calcd for $C_{18}H_{19}BN_4O_4SH$– 397.2440, found 397.0921

*3.2. General Method for the Synthesis of (**9**) and (**10**)*

Initially, Compound (**4**) (1.50 equiv) and sodium tertiary butoxide (^{t}BuONa) (1.00 or 1.50 equiv) were dissolved in DMF and stirred at room temperature (25 °C) for 1 h. After that, compound (**1**) or (**2**) (1.00 equiv) was added slowly at room temperature under N_2

atmosphere, and the resultant mixture was stirred at 25 °C for 16 h. After the reaction was completed, the reaction mixture was poured into 10 mL of ice cold water and extracted with EtOAc (30 mL), washed with H_2O (10 mL × 3), satd. NaCl (5 mL), dried over Na_2SO_4 and filtered. The combined organic layer was dried over Na_2SO_4, filtered and concentrated in vacuum. Further purification was performed by column chromatography using ethyl acetate and n-hexane to obtain yellow solids.

3.2.1. 4-Nitro-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzo[c][1,2,5] oxadiazol-5-amine (**9**)

Compound (**9**) was prepared according to the general procedure described in Section 3.2 with compound (**1**) (0.100 g, 0.501 mmol, 1.00 equiv), (**4**) (0.202 g, 0.751 mmol, 1.50 equiv), and ^{t}BuONa (0.072 g, 0.75 mmol, 1.50 equiv) in DMF (1 mL) to obtain yellow solid (0.057 g, 0.14 mmol, 28.7%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.77 (s, 1H, –NH–), 7.90 (dd, J = 9.84, 0.81 Hz, 1H, benzoxadiazole H-7), 7.85 (d, J = 8.16 Hz, 2H, phenyl H-3, H-5), 7.34 (d, J = 8.22 Hz, 2H, phenyl H-2, H-6), 7.25 (d, J = 9.38 Hz, 1H, benzoxadiazole H-6), 4.87 (d, J = 6.08 Hz, 2H, –CH_2–), 1.34 (s, 12H, 4 × –CH_3–);^{13}C NMR (62.5 MHz, $CDCl_3$) δ 150.07, 145.89, 144.85, 138.15, 135.86, 126.03, 125.34, 123.32, 84.09, 48.00, 24.87. MS calcd for $C_{19}H_{21}BN_4O_5Na^+$ 419.2100, found 419.1670.

3.2.2. 4-Nitro-N-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzyl)benzo[c][1,2,5] thiadiazol-5-amine (**10**)

Compound (**10**) was prepared according to the general procedure described in Section 3.2 with compound (**2**) (0.107 g, 0.50 mmol, 1.00 equiv), (**4**) (0.202 g, 0.75 mmol, 1.50 equiv), and ^{t}BuONa (0.072 g, 0.75 mmol, 1.50 equiv) in DMF (2 mL) to obtain yellow solid (0.095 g, 0.23 mmol, 46.37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H, –NH–), 7.93 (d, J = 9.79 Hz, 1H, benzothiadiazole H-7), 7.83 (d, J = 7.83 Hz, 2H, phenyl H-3, H-5), 7.36 (d, J = 7.67 Hz, 2H, phenyl H-2, H-6), 7.30 (d, J = 9.80 Hz, 1H, benzothiadiazole H-6), 4.84 (d, J = 6.00 Hz, 2H, –CH_2–), 1.34 (s, 12H, 4 × –CH_3–); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 149.78, 149.70, 149.56, 138.94, 135.72, 129.27, 126.07, 120.23, 84.02, 47.89, 24.87. HRMS calcd for $C_{19}H_{21}BN_4O_4SH^+$ 413.2710, found 413.2773.

*3.3. General Method for the Synthesis of (***11***) and (***12***)*

To a stirred solution of compound (**5**) (1.00 equiv) in acetonitrile, was added Et_3N (0.90 equiv). After stirring for 30 min, compound (**1**) was added slowly at 25 °C, and the resultant mixture was stirred at 25 °C for 16 h. After the reaction was completed, the reaction mixture was extracted with EtOAc (30 mL), washed with H_2O (10 mL × 3), satd. NaCl (5 mL), dried over Na_2SO_4 and filtered. The organic layer collected was concentrated to obtain red viscous compounds. Further purification was performed by column chromatography using ethyl acetate and n-hexane to obtain yellow solids.

3.3.1. 4-Nitro-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)benzo[c][1,2,5] oxadiazole (**11**)

Compound (**11**) was prepared according to the general procedure described in Section 3.3 with compound (**1**) (0.150 g, 0.75 mmol, 1.00 equiv), (**5**) (0.165 g, 0.75 mmol, 1.00 equiv) and Et_3N (0.068 g, 0.67 mmol, 0.90 equiv) in ACN (3 mL) to obtain compound (**11**) as yellow solid (0.190 g, 0.495 mmol, 66.1%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, J = 9.71 Hz, 1H, benzoxadiazole H-7), 7.92 (d, J = 8.31 Hz, 2H, phenyl H-3, H-5), 7.18 (d, J = 9.75 Hz, 1H, benzoxadiazole H-6), 7.13 (d, J = 8.33 Hz, 2H, phenyl H-2, H-6), 1.36 (s, 12H, 4 × –CH_3–); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.24, 153.60, 146.93, 144.06, 137.35, 126.21, 122.78, 119.12, 84.21, 24.86. MS calcd for $C_{18}H_{18}BN_3O_6Na^+$ 406.1670, found 406.1500.

3.3.2. 4-Nitro-5-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)benzo[c][1,2,5] thiadiazole (**12**)

Compound (**12**) was prepared according to the general procedure described in Section 3.3 with compound (**2**) (0.107 g, 0.50 mmol, 1.00 equiv), (**5**) (0.110 g, 0.50 mmol, 1.00 equiv) and Et_3N (0.068 g, 0.67 mmol, 0.90 equiv) in Acetonitrile (3 mL) to obtain compound (**12**) as yellow solid (0.083 g, 0.208 mmol, 41.68%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 9.60 Hz, 1H, benzothiadiazole H-7), 7.88 (d, J = 8.59 Hz, 2H, phenyl H-3, H-5), 7.33 (d, J = 9.62 Hz, 1H, benzothiadiazole H-6), 7.12 (d, J = 8.60 Hz, 2H, phenyl H-2, H-6), 1.35 (s, 12H, 4 × –CH_3–); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.54, 151.48, 150.52, 147.38, 137.12, 125.10, 123.03, 118.70, 84.06, 24.86. MS calcd for $C_{18}H_{18}BN_3O_5SH^+$ 400.2280, found 400.3127.

3.3.3. N-(4-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-nitrobenzo[c][1,2,5] oxadiazol-5-amine (**13**)

Compound (**13**) was prepared according to the general procedure described in Section 3.1 by using compound (**1**) (0.100 g, 0.50 mmol, 1.00 equiv), (**6**) (0.116 g, 0.50 mmol, 1.00 equiv) in DMF (2 mL) to obtain compound (**13**) as yellow solid (0.143 g, 0.36 mmol, 72.18%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.69 (s, 1H, –NH–), 7.83 (dd, J = 9.88, 0.83 Hz, 1H, benzoxadiazole H-7), 7.68 (d, J = 2.45 Hz, 1H, phenyl H-2), 7.33 (d, J = 8.10 Hz, 1H, phenyl H-5), 7.29 (d, J = 9.87 Hz, 1H, benzoxadiazole H-6), 7.25 (dd, J = 8.11, 2.48 Hz, 1H, phenyl H-6), 2.61 (s, 3H, 4-CH_3), 1.35 (s, 12H, 4 × –CH_3–); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 148.88, 146.34, 145.95, 144.89, 133.16, 132.51, 131.64, 128.17, 125.07, 124.43, 84.10, 24.88, 21.88. MS calcd for $C_{19}H_{21}BN_4O_5Na^+$ 419.2100, found 419.1691.

3.3.4. N-(4-Methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-4-nitrobenzo[c][1,2,5] thiadiazol-5-amine (**14**)

Compound (**14**) was prepared according to the general procedure described in Section 3.1 by using compound (**2**) (0.100 g, 0.46 mmol, 1.00 equiv), (**6**) (0.108 g, 0.46 mmol, 1.00 equiv) in DMF (2 mL) to obtain compound (**14**) as yellow solid (0.107 g, 0.26 mmol, 56.52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 11.23 (s, 1H, –NH–), 7.89 (dd, J = 9.82, 0.65 Hz, 1H, benzothiadiazole H-7), 7.69 (d, J = 2.30 Hz, 1H, phenyl H-2), 7.42 (d, J = 9.82 Hz, 1H, benzothiadiazole H-6), 7.31 (d, J = 8.07 Hz, 1H, phenyl H-5), 7.26 (dd, J = 7.87, 2.38 Hz, 1H, phenyl H-6), 2.60 (s, 3H, 4-CH_3), 1.35 (s, 12H, 4 × –CH_3–); ^{13}C NMR (62.5 MHz, $CDCl_3$) 150.14, 149.63, 148.41, 145.06, 133.58, 133.12, 133.10, 131.49, 128.49, 128.13, 122.08, 83.98, 24.87, 21.85. MS calcd for $C_{19}H_{21}BN_4O_54H^+$ 413.2710, found 413.2669.

*3.4. General Method for Preparation of Trifluoroborate Salts (***15**–**22***)*

Compound (**7**–**14**) (1.00 equiv) was added to methanol. After stirring for a few minutes, 3M aqueous KHF_2 (4.50 equiv) was added slowly. The reaction mixture was stirred at room temperature (25 °C) for 2 h. After the completion of the reaction, solvent was evaporated to obtain yellow residue. The crude product was dissolved in acetone and filtered. The filtrate collected was concentrated to obtain yellow solid, which was further recrystallized in acetone and ether to give pure compounds (**15**–**22**).

3.4.1. Potassium Trifluoro (4-((4-Nitrobenzo[c][1,2,5] oxadiazol-5-yl)amino)phenyl) Borate (**15**)

Compound (**15**) was prepared according to the general procedure described in Section 3.4 using KHF_2 (0.091 g, 1.17 mmol, 4.50 equiv) in MeOH (15 mL) to obtain compound (**15**) as yellow solid (0.084 g, 0.23 mmol, 88.9%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.80 (s, 1H, –NH–), 8.07 (d, J = 9.95 Hz, 1H, benzoxadiazole, H-7), 7.48 (d, J = 8.15 Hz, 2H, phenyl H-2, H-6), 7.28 (d, J = 9.95 Hz, 1H, benzoxadiazole, H-6), 7.16 (d, J = 7.64 Hz, 2H, phenyl H-3, H-5); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 149.14, 146.47, 145.07, 132.43, 132.41, 126.79, 124.13, 123.97, 112.27; ^{19}F NMR (282 MHz, DMSO-d_6) δ -139.41.

3.4.2. Potassium Trifluoro (4-((4-Nitrobenzo[c][1,2,5] thiadiazol-5-yl)amino)phenyl) Borate (**16**)

Compound (**16**) was prepared according to the general procedure described in Section 3.4 compound **8** (0.065 g, 0.163 mmol, 1.00 equiv) and KHF_2 (0.057 g, 0.734 mmol, 4.50 equiv) in MeOH (10 mL) to obtain compound (**16**) as yellow solid (0.0193 g, 0.051 mmol, 31.31%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.12 (s, 1H, –NH–), 8.03 (d, J = 9.87 Hz, 1H, benzothiadiazole H-7), 7.46 (d, J = 8.01 Hz, 2H, phenyl H-2, H-6), 7.43 (d, J = 9.90 Hz, 1H, benzothiadiazole H-6), 7.16 (d, J = 7.79 Hz, 2H, phenyl H-3, H-5); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 149.80, 149.27, 147.84, 134.25, 132.48, 128.14, 123.82, 123.22, 119.97; ^{19}F NMR (376.5 MHz, DMSO-d_6) δ -139.22.

3.4.3. Potassium Trifluoro (4-(((4-Nitrobenzo[c][1,2,5] oxadiazol-5-yl)amino)methyl)phenyl) Borate (**17**)

Compound (**17**) was prepared according to the general procedure described in Section 3.4 with compound (**9**) (0.03 g, 0.075 mmol, 1.00 equiv) and KHF_2 (0.026 g, 0.34 mmol, 4.50 equiv) in MeOH (10 mL) to obtain compound (**17**) as yellow solid (0.014 g, 0.037 mmol, 49.6%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, 1H, –NH–), 8.19 (d, J = 10.00 Hz, 1H, benzoxadiazole, H-7), 7.63 (d, J = 10.00 Hz, 1H, benzoxadiazole H-6), 7.31 (d, J = 7.60 Hz, 2H, phenyl H-2, H-6), 7.12 (d, J = 7.60 Hz, 2H, phenyl H-3, H-5), 4.90 (d, J = 6.00 Hz, 2H, –CH_2–); MS calcd for $C_{13}H_9BF3_KN_4O_3Na^+$ 399.1435, found 399.0680.

3.4.4. Potassium Trifluoro (4-(((4-Nitrobenzo[c][1,2,5] thiadiazol-5-yl)amino)methyl)phenyl) Borate (**18**)

Compound (**18**) was prepared according to the general procedure described in Section 3.4 with compound (**10**) (0.05 g, 0.12 mmol, 1.00 equiv) and KHF_2 (0.042 g, 0.54 mmol, 4.50 equiv) in MeOH (10 mL) to obtain compound (**18**) as yellow solid (0.043 g, 0.109 mmol, 91.3%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H, –NH–), 8.11 (d, J = 10.00 Hz, 1H, benzothiadiazole, H-7), 7.63 (d, J = 10.00 Hz, 1H, benzothiadiazole H-6), 7.31 (d, J = 7.60 Hz, 2H, phenyl H-2, H-6), 7.12 (d, J = 7.60 Hz, 2H, phenyl H-3, H-5), 4.84 (d, J = 5.60 Hz, 2H, –CH_2–);^{13}C NMR (62.5 MHz, DMSO-d_6) δ 149.65, 149.39, 149.25, 133.56, 131.68, 128.71, 124.96, 124.92, 122.18, 119.10, 46.93.

3.4.5. Potassium Trifluoro (4-((4-Nitrobenzo[c][1,2,5] oxadiazol-5-yl)oxy)phenyl) Borate (**19**)

Compound (**19**) was prepared according to the general procedure described in Section 3.4 with compound (**11**) (0.150 g, 0.391 mmol, 1.00 equiv) and KHF_2 (0.137 g, 1.76 mmol, 4.50 equiv) in MeOH (20 mL) to obtain compound (**19**) as yellow solid (0.116 g, 0.319 mmol, 81.7%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.35 (d, J = 9.79 Hz, 1H, benzoxadiazole, H-7), 7.45 (d, J = 8.36 Hz, 2H, phenyl H-2, H-6), 7.28 (d, J = 9.79 Hz, 1H, benzoxadiazole, H-6), 7.03 (d, J = 8.23 Hz, 2H, phenyl H-3, H-5);^{13}C NMR (62.5 MHz, DMSO-d_6) δ 156.19, 151.49, 147.03, 144.39, 133.23, 126.89, 126.83, 123.95, 123.93, 117.92.

3.4.6. Potassium Trifluoro (4-((4-Nitrobenzo[c][1,2,5] thiadiazol-5-yl)oxy)phenyl) Borate (**20**)

Compound (**20**) was prepared according to the general procedure described in Section 3.4 with compound (**12**) (0.040 g, 0.100 mmol, 1.00 equiv) and KHF_2 (0.035 g, 0.45 mmol, 4.50 equiv) in MeOH (8 mL) to obtain compound (**20**) as yellow solid (0.03 g, 0.079 mmol, 79.12%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 8.28 (d, J = 10.00 Hz, 1H, benzothiadiazole, H-7), 7.42 (d, J = 9.60 Hz, 1H, benzothiadiazole H-6), 7.41 (d, J = 5.20 Hz, 2H, phenyl H-2, H-6), 6.97 (d, J = 8.00 Hz, 2H, phenyl H-3, H-5);^{13}C NMR (62.5 MHz, DMSO-d_6) δ 152.40, 151.10, 150.68, 146.57, 133.09, 125.68, 122.57, 117.45; ^{19}F NMR (376.5 MHz, DMSO-d_6) δ -139.07.

3.4.7. Potassium Trifluoro (2-Methyl-5-((4-nitrobenzo[c][1,2,5] oxadiazol-5-yl)amino)phenyl) Borate (**21**)

Compound (**21**) was prepared according to the general procedure described in Section 3.4 compound (**13**) (0.050 g, 0.126 mmol, 1.00 equiv) and KHF_2 (0.044 g, 0.56 mmol, 4.50 equiv) in MeOH (12 mL) to obtain compound (**21**) as yellow solid (0.045 g, 0.119 mmol, 94.9%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.78 (s, 1H, –NH–), 8.11 (d, J = 9.96 Hz, 1H, benzoxadiazole H-7), 7.28 (d, J = 2.44 Hz, 1H, phenyl H-6), 7.25 (d, J = 10.12 Hz, benzoxadiazole H-6), 7.08 (d, J = 7.87 Hz, 1H, phenyl H-3), 7.00 (dd, J = 7.79, 2.41 Hz, 1H, phenyl H-4), 2.37 (s, 3H, –CH_3–); ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 149.18, 146.46, 145.08, 141.27, 129.38, 128.98, 126.62, 124.00, 122.76, 21.10; ^{19}F NMR (376.5 MHz, DMSO-d_6) δ -138.29.

3.4.8. Potassium Trifluoro (2-Methyl-5-((4-nitrobenzo[c][1,2,5] thiadiazol-5-yl)amino)phenyl) Borate (**22**)

Compound (**22**) was prepared according to the general procedure described in Section 3.4 with compound (**14**) (0.050 g, 0.121 mmol, 1.00 equiv) and KHF_2 (0.042 g, 0.54 mmol, 4.50 equiv) in MeOH (15 mL) to obtain compound (**22**) as yellow solid (0.043 g, 0.109 mmol, 90.6%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.15 (s, 1H, –NH–), 8.05 (d, J = 9.89 Hz, 1H, benzothiadiazole H-7), 7.39 (d, J = 9.89 Hz, 1H, benzothiadiazole H-6), 7.28 (d, J = 2.41 Hz, 1H, phenyl H-6), 7.08 (d, J = 7.92 Hz, 1H, phenyl H-3), 7.00 (dd, J = 7.88, 2.43 Hz, 1H, phenyl H-4), 2.37 (s, 3H, –CH_3–);^{13}C NMR (62.5 MHz, DMSO-d_6) δ 149.80, 149.36, 148.13, 140.54, 132.75, 129.42, 128.82, 128.17, 123.18, 122.53, 119.76, 21.08.

3.4.9. (2-Methyl-5-((4-nitrobenzo[c][1,2,5]oxadiazol-5-yl)amino)phenyl)boronic acid (**23**)

To an RBF were added compound (**21**) (0.020 g, 0.053 mmol, 1.00 equiv) and SiO_2 (0.0032 g, 0.053 mmol, 1.00 equiv). After that, solvent mixture of EtOAc: H_2O (0.5:0.5 mL) was added, and reaction mixture was stirred at room temperature (25 °C) for 1–2 h. After the completion of the reaction, H_2O (5 mL) was added and extracted with EtOAc (15 mL × 2). Organic phase was collected dried over Na_2SO_4, filtered and concentrated to obtain compound (**23**) as yellow solid (10.6 mg, 0.033 mmol, 63.68%).

^{1}H NMR (400 MHz, DMSO-d_6) δ 11.77 (s, 1H, –NH–), 8.20 (s, 2H, –OH × 2), 8.13 (d, J = 9.89 Hz, 1H, benzoxadiazole H-7), 7.40 (s, 1H, phenyl H-6), 7.31 (s, 2H, phenyl H-3, H-4), 7.27 (d, J = 9.93, 1H, benzoxadiazole H-6), 2.47 (s, 3H, –CH_3–);^{13}C NMR (62.5 MHz, DMSO-d_6) δ 148.91, 146.48, 145.00, 141.46, 133.06, 130.77, 130.47, 126.59, 126.54, 124.19, 21.65.

4. Conclusions

In conclusion, we have designed new series of benzo[c][1,2,5]oxadiazoles/thiadiazoles and boronic acid pinacol esters by molecular hybridization via amine and ether linkage. A series of seventeen compounds were synthesized in two steps in good yields. Initially, substituted boronic acid pinacol esters were prepared in an efficient manner via substitution reaction. In the next step, they were converted to aryltrifluoroboronate salts. In addition, one of the aryltrifluoroboronate salts was converted to the corresponding boronic acid derivative in the presence of silica. The synthesized compounds were characterized by modern spectroscopic techniques such as ^{1}H NMR, ^{13}C NMR and mass spectrometry. These are the first boron-based compounds that were evaluated for their anticancer potential, and the biological evaluation is underway.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/inorganics11010034/s1. Spectral Data of Products **7**–**23**.

Author Contributions: S.D. synthesized and analyzed the compounds and edited the paper. B.C.D. conceived the idea, designed the molecules, synthesized the molecules, wrote the paper, edited the paper, performed data analysis, and coordinated with all authors. M.A.S. synthesized the compounds, analyzed the compounds, and wrote and edited the paper. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by National Institutes of Health grant number R01AI132614-01A1, R21 AA027374-01, 1R01NS109423-01A1.

Data Availability Statement: Not applicable.

Acknowledgments: B.D. acknowledges the NIH for support: R01AI132614-01A1, R21 AA027374-01, 1R01NS109423-01A1.

Conflicts of Interest: The authors declare no conflict of interest.

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