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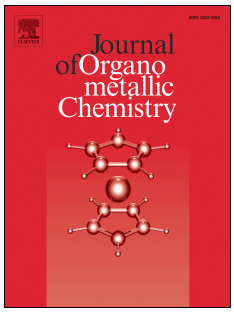

Synthesis and Evaluation of Functionalized Aminobenzoboroxoles as Potential *anti*-Cancer Agents

Pathi Suman, Bhawankumar P. Patel, Agasthya V. Kasibotla, Lucas N. Solano, Subash C. Jonnalagadda

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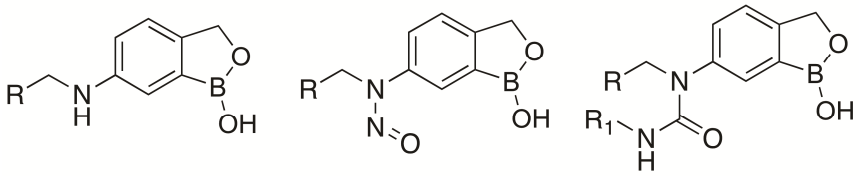

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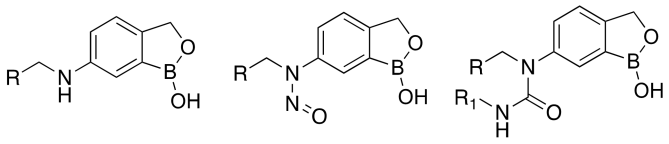

Synthesis and Evaluation of Functionalized Aminobenzoboroxoles as Potential *anti*-Cancer Agents

Pathi Suman,[a] Bhawankumar P. Patel,[a] Agasthya V. Kasibotla,[a] Lucas N. Solano,[a] Subash C. Jonnalagadda[a,b]*

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ABSTRACT
Several aminobenzoboroxole derivatives have been prepared starting from o-boronobenzaldehyde employing reductive amination protocol. The corresponding aminobenzoboroxole derivatives have been further functionalized as *N*-nitrosoaminobenzoboroxoles as well as *N*-benzoboroxolylureas. These derivatives have been evaluated for their anti-cancer activity on human pancreatic cancer MIAPaCa-2 and human breast cancer MDA-MB-231 cell lines.

Keywords

Benzoboroxoles; Aminobenzoboroxoles; *anti*-Cancer Agents; Reductive Amination; *N*-Nitrosoaminobenzoboroxoles; *N*-Benzoboroxolylureas.

Introduction

Benzoboroxoles (cyclic boronic acids) are highly valuable compounds because of their use in variety of disciplines such as organic, materials, and medicinal chemistry [1-3]. Benzoboroxoles have attracted significant attention because of their attractive therapeutic and biological profile and have been reviewed recently [2a-b]. Owing to our interest in boron chemistry, [4] we have been working on the functionalization of the oxaborole ring via a plethora of reaction pathways starting from o-boronobenzaldehyde **1** as our boron precursor (**Figure 1**) [5]. For example, reaction of **1** with activated olefins such as methyl acrylate, acrylonitrile, methyl vinyl ketone, acrolein and cyclohex-2-enone led to the formation of functionalized benzoboroxoles **2-3** under Baylis-Hillman [6] conditions (**Figure 1**, path a, b) [5a-b]. We were also able to synthesize the corresponding homologous benzoboroxole esters **4** via the reaction of Baylis-Hillman bromides with the aldehyde **1** under Barbier allylation conditions (**Figure 1**, path c) [5b]. Aldol addition on the boronoaldehyde **1** led to the formation of ketones and esters such as **5** and **6** (**Figure 1**, paths d-e) [5c]. Finally, reaction of aldehyde **1** with isonitriles furnished the benzoboroxole amides **7** under Passerini reaction [7] conditions (**Figure 1**, path f) [5d] While we have been routinely able to functionalize the oxaborole unit, much to our dismay, we found that these molecules did not exhibit any significant biological activity as *anti*-bacterial and *anti*-cancer agents [5]. Accordingly, we envisioned the preparation of aromatic ring-functionalized benzoboroxoles while leaving the benzylic carbon unbranched on the oxaborole ring so as to improve the biological efficacy. Herein, we provide an account of our synthetic and biological evaluation results.

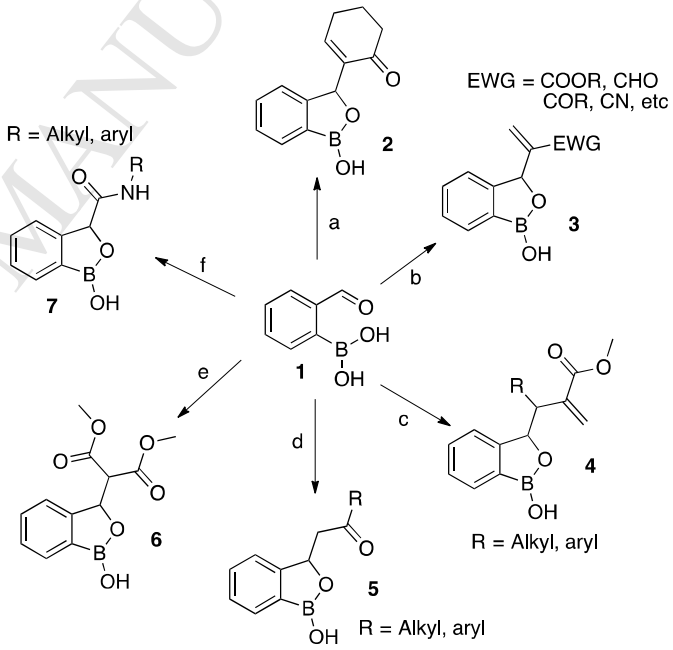
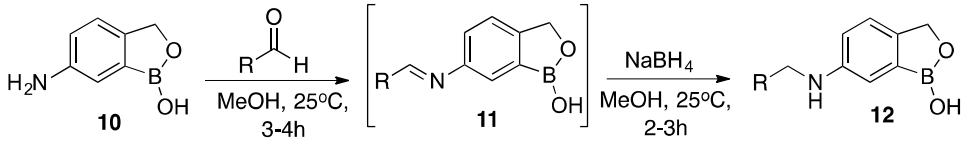


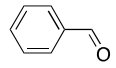
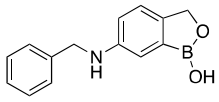
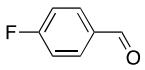
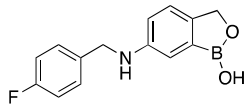
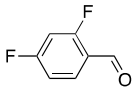
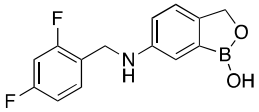
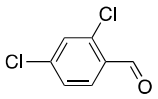
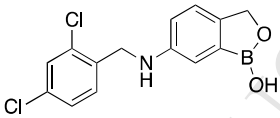
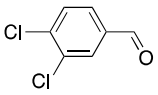
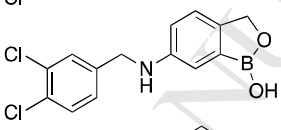
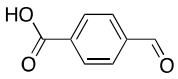
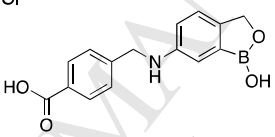
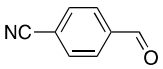
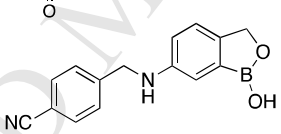
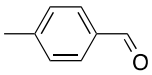
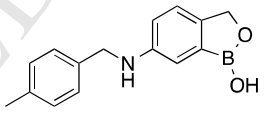
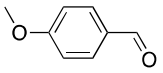
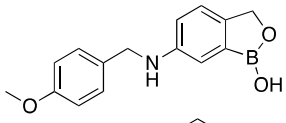
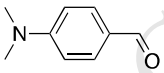
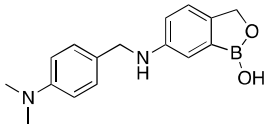
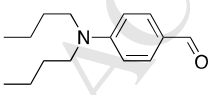
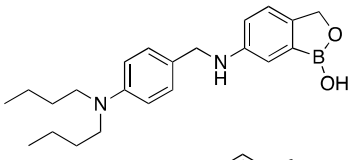
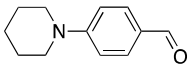
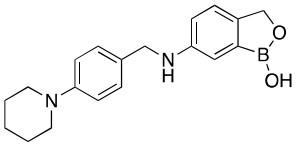
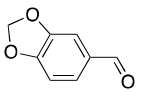
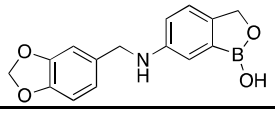
Figure 1: Functionalized Benzoboroxoles.

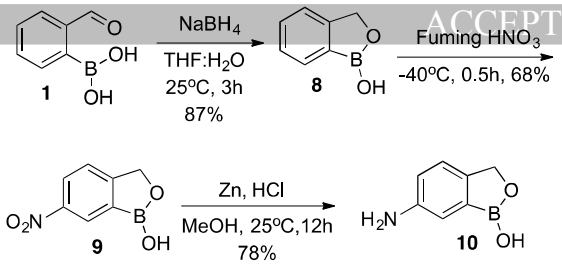
Results and Discussion

We began our efforts with the synthesis of the precursor aminobenzoboroxole **10**. The reaction of commercially available *o*-boronobenzaldehyde **1** with sodium borohydride in THF and water provided benzoboroxole **8** in 87% yield. Nitration of benzoboroxole with fuming nitric acid resulted in the formation of 6-nitrobenzoboroxole **9** [8]. Reduction of **9** with Zinc and hydrochloric acid furnished the aminobenzoboroxole **10** in 78% yield (**Scheme 1**). None of these three reactions involved chromatographic purification and the compounds could be readily obtained by simple acid-base manipulations.

Table 1: Preparation of Functionalized Benzoboroxoles via Reductive Amination of Aldehydes with Aminobenzoboroxole.



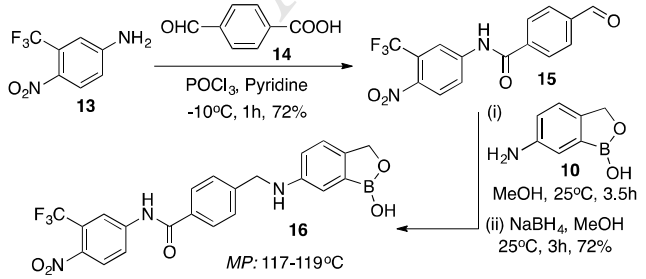
No.	*RCHO*	*Product*	*Yield*	*M.P.*
1		**12a** 	82%	123-125°C
2		**12b** 	79%	135-137°C
3		**12c** 	81%	136-138 °C
4		**12d** 	80%	106-108°C
5		**12e** 	78%	128-130°C
6		**12f** 	85%	221-223°C
7		**12g** 	82%	141-143°C
8		**12h** 	71%	148-150°C
9		**12i** 	76%	122-124°C
10		**12j** 	74%	122-124°C
11		**12k** 	78%	94-96°C
12		**12l** 	73%	65-67°C
13		**12m** 	77%	136-138°C



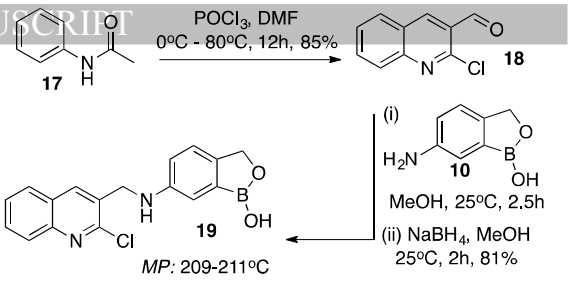
Scheme 1: Preparation of Aminobenzoboroxole.

After synthesizing 6-aminobenzoboroxole **10**, we attempted the reductive amination of benzaldehyde with **10** (**Entry 1, Table 1**) in methanol at room temperature, and after stirring for 3 hours, complete conversion of amine to imine **11** was observed. Sodium borohydride was then added to the reaction mixture at room temperature and stirred for 2 hours to effect reduction of the imine. Our initial efforts of isolating the product proved difficult and the standard work up with ethyl acetate and water after evaporation of ethanol did not furnish the product N-benzylaminobenzoboroxole **12a**. The product was finally obtained after acidification with dilute HCl to pH 1 and work up with ethyl acetate, *albeit* in low yields (~30%). The isolation step was finally optimized and aminobenzoboroxole **12a** was obtained in 82% yield after careful neutralization of the aqueous solution to a neutral pH, at which point, the product started precipitating out of the solution. The solid was then filtered and dried over vacuum to obtain analytically pure product **12a**. We were then able to extend this protocol for the reaction of 6-aminobenzoboroxole with a variety of aldehydes substituted with electron-withdrawing (**Entries 2-7, Table 1**) as well as electron-donating (**Entries 8-13, Table 1**) groups. All of these aldehydes readily reacted with **10** at room temperature and complete formation of the imine was observed in all these cases within 3-4 hours. The imines **11b-m** were then subjected to $NaBH_4$ reduction to afford the products **12b-m** in 72-85% overall yields (**Entries 2-13, Table 1**). As expected, imine formation was observed to be relatively faster with electron withdrawing group substituted aldehydes and slightly better yields of the product were observed in these cases (**Entries 2-7, Table 1**).

Using the reductive amination strategy, an aminobenzoboroxole-flutamide hybrid congener **16** was synthesized as shown in **Scheme 2**. Briefly, 4-nitro-3-triflormethylaniline **13** was treated with *p*-formylbenzoic acid **14** in the presence of $POCl_3$ to obtain the aldehyde **15** in 72% yield. The aldehyde **15** was then subjected to reductive amination with aminobenzoboroxole **10** under standard conditions in a one-pot procedure as described above to obtain the hybrid congener **16** (**Scheme 2**). A chloroquinoline-aminobenzoboroxole conjugate **19** was also synthesized in a similar manner starting from acetanilide **17** in two steps using Vilsmeier-Haack formylation [9] followed by reductive amination (**Scheme 3**).

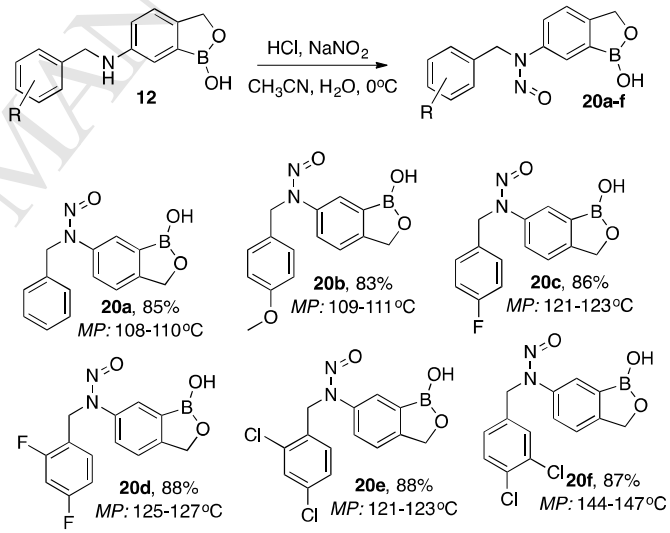


Scheme 2: Preparation of Aminobenzoboroxole-Flutamide Hybrid



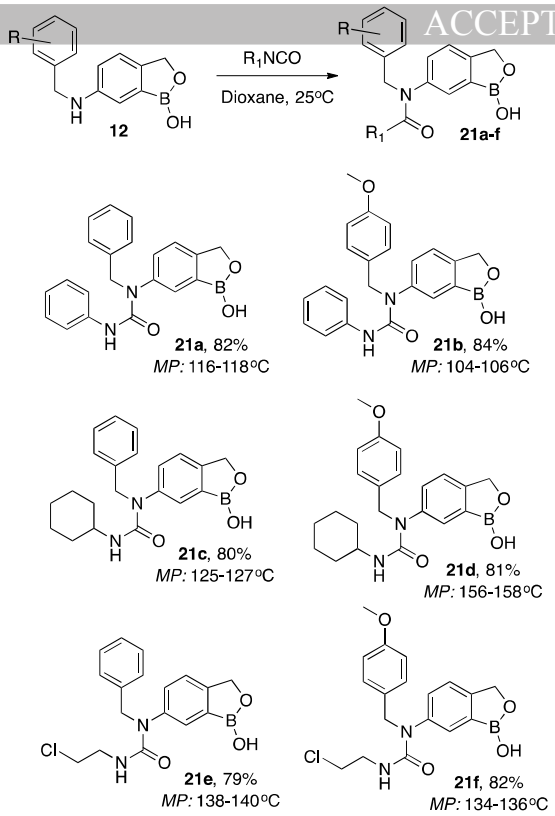
Scheme 3: Preparation of Chloroquinoline-Aminobenzoboroxole Conjugate

Nitrosoamines and nitrosoureas are of particular interest for the treatment of various types of cancers and compounds such as Lomustine and Carmustine are prescribed as alkylating agents in chemotherapy [10]. To demonstrate the robustness of the benzoboroxole moiety, some of the representative secondary amines **12** mentioned above (**Table 1**), were then subjected to nitrosation. All of the compounds readily reacted with sodium nitrite and HCl in acetonitrile/water solvent system and the corresponding *N*-nitrosoaminobenzoboroxoles **20a-f** precipitated out of the reaction within 1-2 hours. The products were obtained in high yields and were characterized by standard analytical techniques (**Scheme 4**).



Scheme 4: Preparation of *N*-Nitrosoaminobenzoboroxoles

Further, *N*-substituted aminobenzoboroxoles **12a** and **12i** were reacted with phenyl, cyclohexyl, and 2-chloroethyl isocyanates in dioxane to furnish the urea derivatives **21a-f** in 79-84% yields (**Scheme 5**). The pure products were obtained upon the removal of solvent and addition of cold water. The products were filtered, dried, and characterized by IR, NMR, and mass spectrometry. In the case of cyclohexyl isocyanate and 2-chloroethyl isocyanate, the products had to be further triturated with hexane under sonication to remove traces of unreacted starting material or other byproducts. Our efforts towards the nitrosation of chloroethylureas **21e** and **21f** did not materialize and a complex mixture of products was observed.



Scheme 5: Preparation of Aminobenzoboroxole-Based Urea Derivatives.

After synthesizing the functionalized aminobenzoboroxoles, these molecules were evaluated for their general cytotoxicity against breast cancer cell lines (MDA-MB-231) and pancreatic cancer cell lines (MIAPaCa-2). While most of the compounds tested were not found to exhibit any significant cytotoxicity at 12.5 and 50 µM concentration, couple of derivatives **19** and **21b** showed activity against MIAPaCa-2 cell lines at 12.5 µM concentration (**Table 2).**

The IC_{50} values for the two most active derivatives **19** and **21b** were found to be 11.5 µM and 11.9 µM respectively in human breast cancer cell lines MDA-MB-231. Similarly, the IC_{50} values for these compounds were determined to be 8.3 µM and 2.7 µM respectively in human pancreatic cancer cell lines MIAPaCa-2 (**Figure 2**).

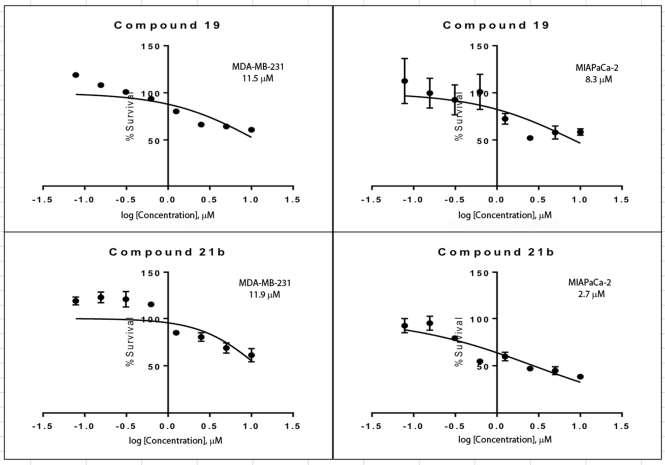


Figure 2: *In Vitro* (IC_{50}) Data for Aminobenzoboroxoles **19** and **21b** on human breast cancer MDA-MB-231 and human pancreatic cancer MIAPaCa-2 cell lines.

Table 2: %Cell viability of the synthesized compounds on human pancreatic cancer (MIAPaCa-2) and human breast cancer (MDA-MB-231) cell lines.

	MIAPaCa-2		**MDA-MB-231**	
	50µM	12.5µM	50µM	12.5µM
12a	34.5	76.6	80.2	73.7
12b	73.6	87.2	91.7	84.0
12c	63.9	90.9	90.0	80.2
12d	65.8	86.4	75.7	75.2
12e	62.6	95.3	68.7	69.2
12f	80.6	71.3	123.6	100.1
12g	47.0	80.8	109.2	77.7
12h	45.9	57.2	82.8	84.1
12i	37.9	51.8	90.0	90.2
12j	78.4	72.1	71.1	97.6
12k	58.2	89.1	102.6	106.5
12l	49.5	92.0	90.7	93.9
12m	69.0	88.9	101.7	88.5
16	77.7	85.8	49.5	112.0
19	***28.6***	***28.2***	***44.8***	***44.3***
20a	51.5	83.5	115.3	120.7
20b	61.0	83.0	123.2	118.7
20c	62.8	77.7	107.9	128.3
20d	70.5	70.3	125.6	121.7
20e	69.5	95.7	106.1	133.7
20f	59.9	84.8	146.0	121.5
21a	*30.0*	*49.6*	47.0	115.9
21b	***17.5***	***22.4***	***53.9***	***63.0***
21c	39.4	64.8	127.6	80.9
21d	25.1	45.5	60.8	96.3
21e	61.8	103.9	100.9	134.8
21f	60.4	74.9	63.2	95.8
Control	100.0	100.0	100.0	100.0

Conclusions

In conclusion, we have demonstrated the applicability of aminobenzoboroxoles towards reductive amination of aldehydes. Further, the resulting benzoboroxoles have also been transformed into *N*-benzoboroxolylureas as well as *N*-nitrosoaminobenzoboroxoles. The preliminary biological evaluation of these molecules has shown some promise and we have been able to identify few leads for future development as *anti*-cancer agents.

Experimental

Procedure for the preparation of 6-aminobenzoboroxole 10: 6-Nitrobenzoboroxole **9** (400 mg, 2.23 mmol) was stirred in methanol (15 mL) under sonication until a white turbid solution was obtained. The solution was cooled to 0°C and conc. HCl (2.5 mL) was added. After stirring the reaction mixture for 20 min, Zinc powder (1.62 g, 25.0 mmol) was added in three portions at 0-5°C. The reaction mixture was stirred overnight at room temperature and was filtered through a celite pad. The filtrate was concentrated *in vacuo*, and the crude mixture was stirred in ethyl acetate (20 mL) for 10 min to dissolve the bright red residue. The resulting solution was neutralized with 1 M aq. K_2CO_3 and extracted with ethyl acetate (2 x 10 mL). The combined organic extract was washed with brine (1 x 10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to obtain pure 6-aminobenzoboroxole **10** as a pale yellow powder (260 mg, 78%). The spectral information matched very well with literature data.

Representative procedure for the reductive amination of aldehydes: To a stirred solution of 6-aminobenzoboroxole **10** (200 mg, 1.34 mmol) in 5 mL of methanol was added *p*-anisaldehyde (163 µL, 1.34 mmol) at room temperature and stirred for 3 hours. Upon complete consumption of the reactants (TLC), sodium borohydride (76 mg, 2.01 mmol) was added in portions and stirred for 2 hours. After completion of the reaction as indicated by TLC, methanol was removed *in vacuo* and the residue was dissolved in water (5 mL). The solution was neutralized to pH 7 with 10% HCl to effect precipitation. The resulting solid was filtered, washed with water, and dried under vaccum to afford 6-*N*-(p-methoxybenzyl)aminobenzoboroxole **12i** (274 mg, 76%) as pale cream color solid. Anal. Calc. C; 66.95, H; 5.99, N; 5.20. Found C; 66.85, H; 6.05, N; 5.40. M.P = 122-124°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 8.88 (s, 1H), 7.25 (d, J = 8.8 Hz, 2H), 7.04 (d, J = 8.4 Hz, 1H), 7.08 (d, J = 8.4 Hz, 1H), 6.85 (d, J = 8.8 Hz, 2H), 6.83 (s, 1H), 6.72 (dd, J = 2.4, 8.4 Hz, 1H), 6.11 (t, J = 6.0 Hz, 1H), 4.78 (s, 2H), 4.17 (d, J = 6.0 Hz, 2H), 3.69 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 158.7, 148.5, 142.1, 132.7, 129.0, 122.1, 117.3, 114.4, 113.0, 70.2, 55.7, 46.8; IR (neat): 3298, 2983, 1526, 1437, 1238, 1172, 769 cm^{-1}; ESI-MS: *m/z*, 283 $[M\text{-}H+CH_3]^+$.

Procedure for the preparation of aldehyde 15: $POCl_3$ (136 µL, 1.46 mmol) was added to a solution of 4-formylbenzoic acid **14** (200 mg, 1.33 mmol) and 4-nitro-3-(trifluoromethyl)aniline **13** (247 mg, 1.20 mmol) in pyridine (5 mL) at -10°C dropwise and the reaction was stirred 1 hour at the same temperature. Upon completion (TLC), the reaction was quenched with cold water and extracted with ethyl acetate (2 x 10 mL). The combined organic extracts were washed with sat. aq. $NaHCO_3$ solution (1 x 10 mL), brine (1 x 10 mL), and dried over anhydrous Na_2SO_4. The ethyl acetate was concentrated *in vacuo* and the crude product was purified by silica gel column chromatography (ethyl acetate/hexane, 2:8) to yield aldehyde **15** (292 mg, 72%) as pale yellow solid. M.P: 185-187°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 11.12 (s, 1H), 10.10 (s, 1H), 8.43 (s, 1H), 8.31 (d, J = 8.8 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H), 8.14 (d, J = 8.4 Hz, 2H), 8.05 (d, J = 8.4 Hz, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 193.5, 166.2, 155.0, 144.3, 142.5, 139.2, 139.1, 130.3, 130.2, 129.3, 128.2, 124.1, 119.2; IR (neat): 3483, 3370, 2956, 1720, 1680, 1524, 1331, 1139, 1042, 749 cm^{-1}; ESI-MS: *m/z*, 339 $[M+H]^+$.

Representative procedure for the preparation of *N*-nitrosoaminobenzoboroxoles 20a-f*:* 6-*N*-(p-methoxybenzyl) aminobenzoboroxole **12i** (100 mg, 0.37 mmol) was dissolved in a 1:2 mixture of acetonitrile and water (3 mL) and the reaction mixture was cooled to 0°C. HCl (155µL, 12M solution, 1.86 mmol) was added dropwise and the mixture was stirred for 30 min at 0°C. $NaNO_2$ (0.2 mL, 2M solution, 0.4 mmol) was added dropwise and the reaction was stirred for 1.5 hours, during this time, *N*-nitrosoamine gradually started precipitating out as a pale yellow solid. After completion of the reaction (TLC), the solid was filtered, washed with distilled water, and dried under vaccum to obtain 6-*N*-nitroso-*N*-(p-methoxybenzyl)amino-benzoboroxole **20b** (92 mg, 83%). Anal. Calc. C; 60.44, H; 5.07, N; 9.40. Found C; 60.73, H; 4.98, N; 9.57. M.P: 109-111°C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.30 (s, 1H), 7.87 (d, J = 1.6 Hz, 1H), 7.72 (dd, J = 2.0, 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 1H), 6.99 (d, J = 8.4 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 5.26 (s, 2H), 5.00 (s, 2H), 3.67 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 159.2, 153.7, 140.8, 129.3, 127.0, 123.7, 123.3, 122.7, 114.8, 70.4, 55.7, 46.7; IR (neat): 2928, 1453, 1404, 1179, 1124, 787 cm^{-1}; ESI-MS: *m/z*, 312 $[M\text{-}H+CH_3]^+$.

Represenative procedure for the synthesis of *N*-benzoboroxolyl ureas (21a-f)*:* 2-Chloroethyl isocyanate (31 µL, 0.37 mmol) was added to the solution of 6-*N*-(p-methoxybenzyl)aminobenzoboroxole **12i** (100 mg, 0.37 mmol) in dioxane (3 mL) and the reaction was stirred overnight at room temperature. After completion of the reaction (TLC), the solvent was removed *in vacuo* and the residue was diluted with deionized water. The resulting solid was filtered, washed with water, and dried under vaccum. The crude solid was triturated with hexane under sonication to obtain the pure urea derivative **21f** (113 mg, 82%) as colourless solid. Anal. Calc. C; 57.71, H; 5.38, N; 7.48. Found C; 57.63, H; 5.50, N; 7.29. M.P: 134-136 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 9.18 (s, 1H), 7.42 (s, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.17 (dd, J = 1.6, 8.4 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 6.80 (d, J = 8.8 Hz, 2H), 5.92 (t, J = 5.6 Hz, 1H), 4.93 (s, 2H), 4.71 (s, 2H), 3.68 (s, 3H), 3.53 (t, J = 6.4 Hz, 2H), 3.28-3.30 (m, 2H); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 158.8, 157.4, 152.9, 141.2, 131.4, 130.7(2C), 129.6 (2C), 123.2, 114.3 (2C), 70.5, 55.6, 52.6, 44.1, 42.9; IR (neat): 3244, 2932, 1640, 1594, 1301, 1178, 736 cm^{-1}; ESI-MS: *m/z*, 388 $[M\text{-}H+CH_3]^+$.

Cell Viability Assay: Human pancreatic cancer MIAPaCa-2 cells were purchased from ATCC and were maintained in D-MEM supplemented with 10% FBS, 2.5% horse serum, and 1% Penicillin Streptomycin in a humidified atmosphere of 5% CO_2 at 37°C. Human breast cancer MDA-MB-231 cells were purchased from ATCC and were maintained in D-MEM supplemented with 10% FBS and 1% Penicillin Streptomycin in a humidified atmosphere of 5% CO_2 at 37°C. Cells were seeded in 96 well plates at a density of 5 x 10^4 cells/mL, incubated for 18-24 hours, then exposed to benzoboroxoles **1-21** at 50µM and 12.5µM concentrations in duplicate for 72 hours. DMSO was added as a negative control. To determine the cell viability, MTT (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide) was dissolved in PBS solution (5mg/mL) and 10µL was added to each well and incubated. After 4 hours, 100µL of SDS (sodium dodecyl sulfate) solution (1g in 10 mL of 0.01 N HCl) was added to solubilize formazan precipitate and incubated for an additional 4 hours. The absorbance of each well was then measured using a microplate reader at 570 nm. The absorbance of control wells was defined as 100% viability and all of the tested compounds were expressed as percentage relative to the control.

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Highlights

1. We have prepared functionalized benzoboroxoles via reductive amination protocol.
2. We have also prepared N-nitrosoaminobenzoboroxoles and benzoboroxolylureas.
3. These benzoboroxoles have been further evaluated as potential anti-cancer agents.