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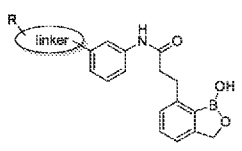
(54) Title: A NEW TYPE OF ANTITUMOR COMPOUNDS: DERIVATIVES OF 7-PROPANAMIDE SUBSTITUTED BENZOXABOROLE



(I)

(57) Abstract: The present disclosure relates to derivatives of 7-propanamide substituted benzoxaborole and their preparation and use. The structural general formula of the derivatives is (formula).The derivatives are used for the preparation of a medicament for the prevention and treatment of tumors. Compared with the prior art, the present derivatives inhibit the proliferation of tumor cells at the nanomolar level, the compounds have obvious inhibition to proliferation of tumor cells, especially tumor cell lines such as ovarian cancer SKOV3, breast cancer MDA-MB231, and colon cancer HCT116, but are not limited to the aforesaid tumor cell lines.

A new type of antitumor compounds: derivatives of 7-propanamide substituted benzoxaborole

TECHNICAL FIELD

The present disclosure relates to the research in the field of drug for inhibition of tumor cells, especially relates to the derivatives of 7-propanamide substituted benzoxaborole and their preparation and pharmaceutical use.

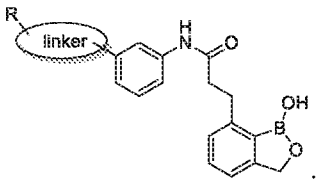
BACKGROUND OF THE DISCLOSURE

In recent ten years, the application of benzoxaboroles in the field of pharmaceutical chemistry has been rapidly developed, and it is expected to become a new type of anti-infective drug. An antifungal drug, 5-fluoroxaborole (tavaborole), has now been approved by the U.S. Food and Drug Administration (FDA) for treatment of onychomycosis in 2014; in addition, the phosphodiesterase-4 inhibitor crisaborole has been approved for marketing by the U.S. FDA in 2016 for the treatment of atopic dermatitis (http://www.fda.gov/).

Although benzoxaboroles are widely used in the antifungal, anti-bacterial, anti-parasitic, anti-viral and anti-inflammatory field (*Chem. Rev.* 2015, 115, 5224-5247; *Sci. China Chem.* 2013, 56, 1372-1381), few studies have been reported about their antitumor activity. It has been reported that benzoxaborole-chalcone hybrids have anti-tumor activity, but their half maximal inhibitor concentration (IC_{50}) for inhibiting the proliferation of tumor cells is micromolar (*Bioorg. Med. Chem.* 2016, 26, 5797-5801.). Recent research found that some derivatives of 7-propanamide substituted benzoxaborole showed better inhibition activity towards the tumor cells, among which the lowest IC_{50} value is around 20 nanomolar (CN107090000).

SUMMARY OF THE DISCLOSURE

The purpose of the present disclosure is to overcome the existing shortcomings of the prior art and to provide derivatives of 7-propanamide substituted benzoxaborole, which can inhibit the proliferation of tumor cells effectively with IC_{50} value around 2 nM.

The object of the present disclosure can be achieved by the following technical solutions: derivatives of 7-propanamide substituted benzoxaborole, wherein the structural general formula of the derivatives is 

.

In the general formula, linker is at the meta position of phenyl group and linker is one selected from carbonyl, carbinol, alkyoxy, amide or atom N and O, R is selected from phenyl or substituted phenyl, or a salt thereof.

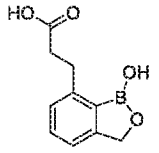
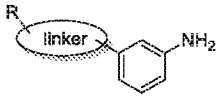
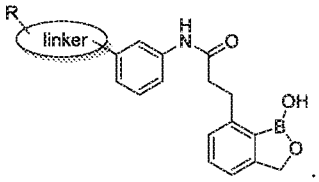
Preferably, the substituted phenyl is selected from one of hydrogen, halogen, C1-C10 alkyl, alkoxy, alkynyl, ethoxycarbonyl, nitro, amino, aminomethyl, methlmercapto, trifluoromethoxy, trifluoromethyl, cyano or acetyl.

Most preferably, in the general formula, the linker is amide and R is phenyl.

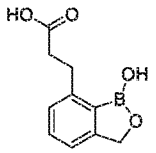
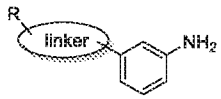
The above derivatives also include their isotopic compounds, racemates, optically active isomers, polymorphs or mixtures thereof, and pharmaceutically acceptable salts thereof, such as salts formed with metallic elements such as sodium, potassium, lithium, calcium, etc., or salts formed with organic

bases such as organic amines, pyridines, alkaloids and the like; or salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, hydrofluoric acid, nitric acid, sulfuric acid and phosphoric acid and the like, or salts formed with organic acids such as formic acid, acetic acid, sulfonic acid, tartaric acid and the like.

A preparation method of the derivatives of aforesaid 7-propanamide substituted benzoxaborole, wherein the preparation method is as followed:

Dissolve the  ,  and EDCI in dichloromethane or DMF and stir, solvent is removed by rotary evaporation at vacuum, to purify and obtain  .

In the aforesaid steps, linker is at the meta position of phenyl group and linker is one selected from carbonyl, carbinol, alkyoxy, amide or atom N and O, R is selected from phenyl or substituted phenyl.

Perferably, the molar ratio of  and  and EDCI is 1:(0.5-3):(1-3), stirring is performed at room temperature for a duration of 1-24h, and purification is performed by silica gel column chromatography.

Pharmaceutical use of the aforesaid derivative of 7-propanamide substituted benzoxaborole, the derivative is used for the preparation of a medicament for the prevention and treatment of tumors. Since the present derivatives inhibit the proliferation of tumor cells at the nanomolar level, therefore they can prevent and treat tumors, especially tumor cell lines such as ovarian cancer SKOV3, breast cancer MDA-MB231, and colon cancer HCT116, but are not limited to the aforesaid tumor cell lines.

Compared with the prior art, the beneficial effects of the present disclosure are represented in the following aspects:

(1) the compounds have good inhibition to proliferation of tumor cells with IC_{50} around 2 nM, and can effectively inhibit the proliferation of cells of common tumors exemplified by ovarian cancer, breast cancer, colon cancer.

(2) synthesis is simple, does not involve very complicated steps, synthesis cost is low.

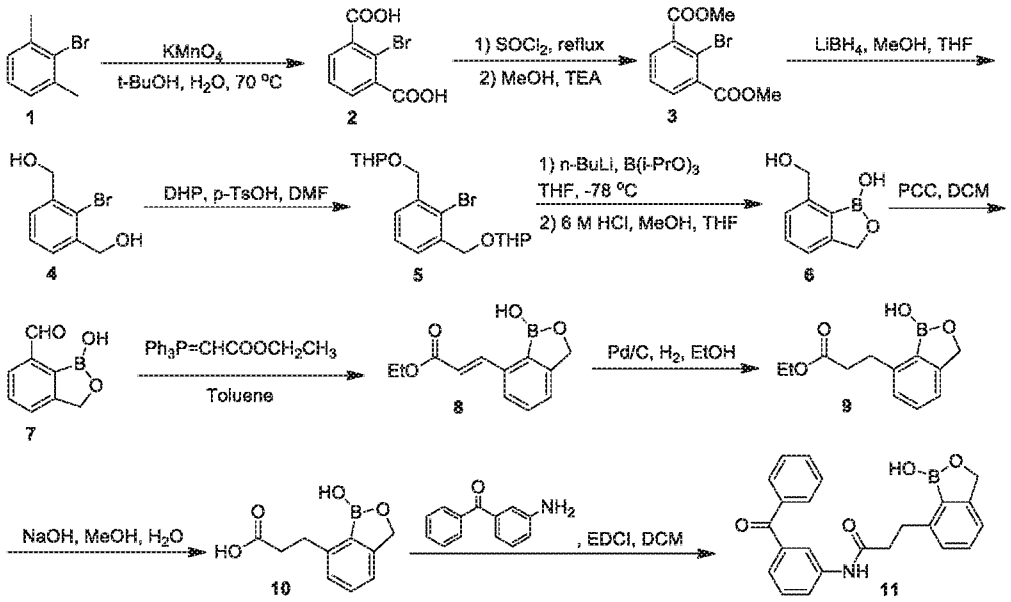
DETAILED DESCRIPTION

The embodiments of the present disclosure are described in detail below. The embodiments are implemented on the premise of the technical solutions of the present disclosure, and the detailed embodiments and specific operation procedures are provided. However, the protection scope of the present disclosure is not limited to the following embodiments.

<Preparation of compounds >

Embodiment 1

The preparation of N-(3-benzoylphenyl)-3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanamide (**11**) was as follows:



(1) 2,6-dimethyl bromobenzene (30.0 g, 162.2 mmol) was dissolved in a mixed solvent of tert-butanol (200 mL) and water (200 mL), followed by potassium permanganate (128.0 g, 810.0 mmol) batchwise. After refluxing at 70 °C overnight, while the reaction fluid was still hot, it was filtered through diatomite, and the filter cake was washed with water (50 mL × 3). The filtrates were combined and concentrated in vacuum to 300 mL and adjusted to pH 3 with concentrated hydrochloric acid to give a precipitate which was filtered to give 2-bromo-1,3-phthalic acid (**2**) (28.0 g, 70.5%) as white solid compound. ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.57 (br, 2H), 7.70 (d, J = 7.6 Hz, 2H), 7.52 (t, J = 7.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 167.8, 136.7, 130.7, 127.8, 116.2 ppm.

(2) 2-bromo-1,3-phthalic acid (**2**) (17.9 g, 73.1 mmol) was dissolved in thionyl chloride (100 mL) and heated to reflux for 6 h before spinning in vacuum. A mixed solution of methanol (80 mL) and triethylamine (40 mL) was added dropwise to the residue at 0 °C for 0.5 h. After stirring for 2 h at room temperature, the solution is concentrated in vacuum. The residue was dissolved in ethyl acetate and washed with 0.5 M aqueous hydrochloric acid and saturated sodium bicarbonate, respectively. The organic phase was dried over anhydrous sodium sulfate and spinned in vacuum to obtain 2-bromo-1,3-phthalic acid dimethyl ester (**3**) (19.9 g, 99.7%) as yellow oil compound. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.80 (d, J = 7.6 Hz, 2H), 7.59 (t, J = 7.6 Hz, 1H), 3.88 (s, 6H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 135.3, 132.2, 127.1, 119.0, 52.7 ppm.

(3) 2-bromo-1,3-phthalic acid dimethyl ester (**3**) (16.6 g, 60.8 mmol) was dissolved in a mixed solvent of dry tetrahydrofuran (150 mL) and methanol (3 mL), at 0 °C, lithium borohydride (3.3 g, 151.5 mmol) was added batchwise. After overnight reaction at room temperature, the reaction was quenched with water (150 mL). The reaction fluid was extracted with ethyl acetate (150 mL × 3), dried over anhydrous sodium sulfate and spinned in vacuum to obtain 2,6-dihydroxymethylbromobenzene (**4**)

(13.2 g, 100%) as white solid compound. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.44-7.39 (m, 3H), 5.39 (t, J = 5.6 Hz, 2H), 4.52 (d, J = 5.6 Hz, 4H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 140.8, 126.9, 126.1, 120.2, 62.7 ppm.

(4) 2,6-dihydroxymethylbromobenzene (**4**) (10.7 g, 49.3 mmol) and 3,4-dihydropyran (16.6 g, 197.2 mmol) were dissolved in DMF (120 mL), and p-toluenesulfonic acid monohydrate (469.3 mg, 2.5 mmol) was added. After stirring overnight at room temperature, the reaction was quenched with saturated sodium bicarbonate. The reaction fluid was extracted with ethyl acetate. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and dried in vacuum to obtain compound **5** (19.0 g, 100%) as colorless semi-solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, J = 7.6 Hz, 2H), 7.33 (t, J = 7.6 Hz, 1H), 4.85 (d, J = 13.4 Hz, 2H), 4.78 (t, J = 3.4 Hz, 2H), 4.61 (d, J = 13.4 Hz, 2H), 3.96-3.90 (m, 2H), 3.60-3.54 (m, 2H), 1.94-1.54 (m, 12H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 127.8, 127.1, 98.3, 68.8, 62.1, 30.5, 25.4, 19.3 ppm.

(5) The compound **5** (26.8 g, 69.6 mmol) was dissolved in dry tetrahydrofuran (300 mL) and n-butyllithium (2.5 mL in hexane, 33 mL) was added dropwise at -78°C for 0.5 h. After stirring for 1 h at -78 °C, triisopropyl borate (15.7 g, 83.5 mmol) was added dropwise. The reaction temperature was then slowly raised to room temperature and stirred overnight. The reaction fluid was quenched with a mixed solution of 6 M hydrochloric acid (100 mL) and methanol (100 mL). After stirring at room temperature for another 6 h, the reaction fluid was subjected to rotary evaporation at vacuum to remove the tetrahydrofuran and methanol. The remaining reaction fluid was extracted with ethyl acetate, dried over anhydrous sodium sulfate and spinned in vacuum to obtain crude product **6** (11.9 g) as gray solid. The crude product was used directly in the next step without further purification.

(6) Crude product **6** (11.9 g, 72.5 mmol), PCC (23.5 g, 109.0 mmol) and diatomite (12.0 g) were suspended in dichloromethane (150 mL), and stirred overnight at room temperature, and filtered through diatomite. The filtrate was extracted with 1 M aqueous sodium hydroxide solution (150 mL). The aqueous phase was then adjusted to pH 3 with concentrated hydrochloric acid and extracted with ethyl acetate (150 mL × 3). The organic phases were combined, washed with saturated brine, dried over anhydrous sodium sulfate and spinned in vacuum to obtain 7-formyl benzoxaborole (**7**) (6.3 g, 53.8%) as yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.40 (s, 1H), 9.20 (s, 1H), 7.87 (d, J = 7.4 Hz, 1H), 7.76 (d, J = 7.4 Hz, 1H), 7.70 (t, J = 7.4 Hz, 1H), 5.13 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 193.5, 155.0, 138.6, 131.2, 127.3, 126.0, 70.3 ppm.

(7) 7-formyl benzoxaborole (**7**) (1.68 g, 10.4 mmol) and ethyl (triphenylphosphoranylidene) acetate (4.34 g, 12.4 mmol) were dissolved in toluene (150 mL). After stirring at room temperature overnight, solvent was removed by rotary evaporation at vacuum. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to obtain compound **8** (1.6 g, 66.7%) as white solid.^{1}H NMR (400 MHz, DMSO-d_6): δ 9.33 (s, 1H), 8.10 (d, J = 16.2 Hz, 1H), 7.81 (d, J = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.44 (d, J = 7.6 Hz, 1H), 6.80 (d, J = 16.2 Hz, 1H), 5.02 (s, 2H), 4.19 (q, J = 7.0 Hz, 2H), 1.26 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 166.3, 154.5, 143.0, 137.2, 131.1, 125.0, 123.0, 119.1, 69.6, 59.9, 14.1 ppm.

(8) The compound **8** (1.3 g, 5.6 mmol) and 10% Pd/C (592 mg) were dissolved in ethanol (120 mL). The reaction fluid was stirred at room temperature overnight in a hydrogen atmosphere and filtered. The solvent was removed from the filtrate by rotary evaporation at vacuum. The crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate = 2/1) to obtain compound **9** (1.2 g, 93.2%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 8.98 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.13 (d, J = 7.5 Hz, 1H), 4.96 (s, 2H), 4.02 (q, J = 7.0 Hz, 2H),

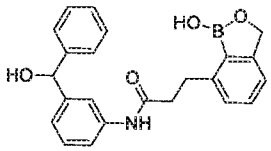
3.30 (t, J = 7.8 Hz, 2H), 2.26 (t, J = 7.8 Hz, 2H), 1.14 (t, J = 7.0 Hz, 3H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 172.2, 154.1, 144.6, 130.8, 126.7, 119.1, 69.7, 59.6, 35.4, 29.2, 14.0 ppm.

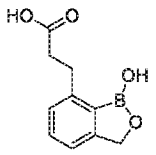
(9) The compound **9** (1.51 g, 6.45 mmol) was dissolved in methanol (66 mL) and an additional 1 M NaOH (33 mL) was added. After stirring at room temperature overnight, the reaction fluid was adjusted to pH 3 with concentrated hydrochloric acid. 3-(1-hydroxy-1,3-dihydro-benzo[c]benzoxaborol -7-yl) propionic acid (**10**) (1.23 g, 92.9%) as white solid compound is obtained from filtration. ^{1}H NMR (400 MHz, DMSO-d_6): δ 12.04 (s, 1H), 8.96 (s, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.20 (d, J = 7.5 Hz, 1H), 7.14 (d, J = 7.5 Hz, 1H), 4.96 (s, 2H), 2.99 (t, J = 7.8 Hz, 2H), 2.54 (t, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.8, 154.1, 145.0, 130.8, 126.6, 119.0, 69.7, 35.5, 29.2 ppm; HRMS (ESI): $[M + H]^+$ $C_{10}H_{12}BO_4$calcd 207.0829, found 207.0827; mp: 159-162 °C; HPLC: purity 99.1%, retention time 3.5 min.

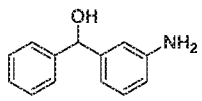
(10) 3-(1-hydroxy-1,3-dihydro-benzo [c]benzoxaborol-7-yl) propionic acid (**10**) (200 mg, 0.97 mmol), (3-aminophenyl)(phenyl)methanone (230 mg, 1.17 mmol) and EDCI (372 mg, 1.1 mmol) were dissolved in dry dichloromethane (20 ml). After stirring at room temperature overnight, the solvent was removed from the filtrate by rotary evaporation at vacuum. The crude product was purified by silica gel chromatography (dichloromethane/methanol=150/1) to obtain compound **11** (110.8 mg, 29.63%) as white solid. The final test result was: ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.12 (s, 1H), 9.06 (s, 1H), 8.00 (s, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.73 (d, J = 7.2 Hz, 2H), 7.68 (t, J = 7.4 Hz, 1H), 7.57 (t, J = 7.7 Hz, 2H), 7.48 (t, J = 7.9 Hz, 1H), 7.38 (d, J = 7.7 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.6 Hz, 1H), 7.15 (d, J = 7.4 Hz, 1H), 4.96 (s, 2H), 3.09 (t, J = 7.7 Hz, 2H), 2.67 (t, J = 7.7 Hz, 2H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6): δ 196.23, 171.51, 154.67, 145.76, 139.78, 137.87, 137.46, 133.19, 131.33, 130.05, 129.53, 129.05, 127.16, 124.70, 123.47, 120.49, 119.56, 70.21, 56.54, 38.66, 29.87, 18.95 ppm; HRMS (ESI): $[M + H]^+$ $C_{23}H_{20}BNO_4$ calcd 386.1564, found 386.1568; mp: 127-130 °C; HPLC: purity 96.1%, retention time 17.2 min.

Embodiment 2

N-(3-(hydroxy(phenyl)methyl)phenyl)-3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl) propanamide (**12**)



was prepared by using the synthesis method similar to Embodiment 1, in which steps (1) to step (9) are the same, except that in step (10), the molar ratio of 

and 

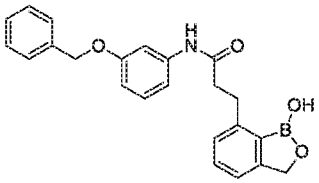
and EDCI is 1:3:2, stirring is performed at temperature of 20 °C for a duration of 24 h, and purification is performed by silica gel column chromatography.

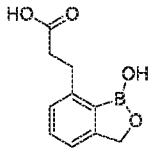
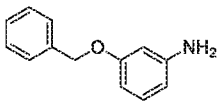
The final test result was: ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.83 (s, 1H), 9.04 (s, 1H), 7.53 (s, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.38 – 7.32 (m, 3H), 7.29 (t, J = 7.7 Hz, 2H), 7.23 – 7.17 (m, 3H), 7.15 (d, J = 7.4 Hz, 1H), 7.03 (d, J = 7.7 Hz, 1H), 5.90 (s, 1H), 5.63 (d, J = 3.8 Hz, 1H), 4.96 (s, 2H), 3.07 (t, J = 7.7 Hz, 2H), 2.61 (t, J = 7.7 Hz, 2H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.05, 154.65, 146.70, 145.98, 145.92, 139.50, 131.32, 128.80, 128.55, 127.21, 127.11, 126.68, 121.49, 119.52, 118.04,

117.39, 74.69, 70.20, 38.61, 29.92 ppm; HRMS (ESI): $[M + H - H_2O]^+$ $C_{23}H_{22}BNO_4$ calcd 370.1614, found 370.1615; mp:165-168 °C; HPLC: purity 95.3%, retention time 10.2 min.

Embodiment 3

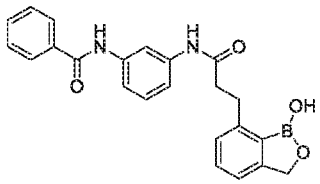
N-(3-(benzyloxy)phenyl)-3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanamide (**13**)

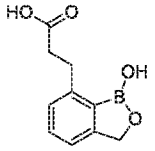
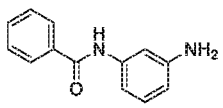


was prepared by using the synthesis method similar to Embodiment 1, in which steps (1) to step (9) are the same, except that in step (10), the molar ratio of  and  and EDCI is 1:3:2, stirring is performed at temperature of 20 °C for a duration of 24 h, and purification is performed by silica gel column chromatography. The final result was: ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.87 (s, 1H), 9.04 (s, 1H), 7.51 – 7.30 (m, 7H), 7.26 – 7.15 (m, 3H), 7.12 (d, J = 8.0 Hz, 1H), 6.69 (dd, J = 8.1, 1.7 Hz, 1H), 5.08 (s, 2H), 5.00 (s, 2H), 3.11 (t, J = 7.8 Hz, 2H), 2.66 (t, J = 7.8 Hz, 2H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.12, 159.04, 154.66, 145.96, 140.94, 137.55, 131.31, 129.92, 128.90, 128.27, 128.11, 127.16, 119.50, 112.05, 109.62, 106.25, 70.24, 69.54, 38.77, 29.92 ppm; HRMS (ESI): $[M + Na]^+$ $C_{23}H_{22}BNO_4$ calcd 410.1540, found 410.1532; mp: 158-161 °C; HPLC: purity 98.5%, retention time 8.6 min.

Embodiment 4

N-(3-(3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)propanamido)phenyl)benzamide (**14**)

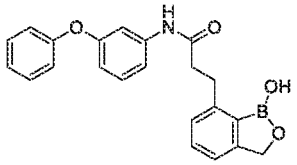


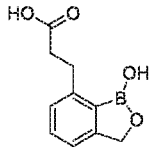
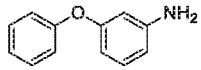
was prepared by using the synthesis method similar to Embodiment 1, in which steps (1) to step (9) are the same, except that in step (10), the molar ratio of  and  and EDCI is 1:3:2, stirring is performed at temperature of 20 °C for a duration of 24 h, and purification is performed by silica gel column chromatography. The final result was: ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.27 (s, 1H), 9.92 (s, 1H), 9.06 (s, 1H), 8.12 (s, 1H), 7.97 – 7.92 (m, 2H), 7.58 (t, J = 7.8 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.40 (d, J = 7.8 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 8.3 Hz, 1H), 7.25 (t, J = 8.1 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.18 (d, J = 7.4 Hz, 1H), 4.97 (s, 2H), 3.11 (t, J = 7.7 Hz, 2H), 2.67 (t, J = 7.7 Hz, 2H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ 171.15, 166.07, 154.66, 145.96, 139.87, 139.79, 135.70, 135.36, 132.04, 131.33, 129.15, 128.84, 128.13, 127.15, 119.52, 115.87,

115.20, 112.02, 70.21, 38.63, 29.95 ppm; HRMS (ESI): $[M + Na]^+$ $C_{23}H_{21}BN_2O_4$ calcd 423.1492, found 423.1491; mp: 130-133 °C; HPLC: purity 95.1%, retention time 7.6 min.

Embodiment 5

3-(1-hydroxy-1,3-dihydrobenzo[c][1,2]oxaborol-7-yl)-N-(3-phenoxyphenyl)propanamide (**15**)



was prepared by using the synthesis method similar to Embodiment 1, in which steps (1) to step (9) are the same, except that in step (10), the molar ratio of  and  and EDCI is 1:3:2, stirring is performed at temperature of 20 °C for a duration of 24 h, and purification is performed by silica gel column chromatography. The final result was: ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.95 (s, 1H), 8.97 (s, 1H), 7.43 – 7.23 (m, 6H), 7.20 (d, J = 7.6 Hz, 1H), 7.17 – 7.09 (m, 2H), 7.04 – 6.96 (m, 2H), 6.69 – 6.62 (m, 1H), 4.95 (s, 2H), 3.05 (t, J = 7.7 Hz, 2H), 2.61 (t, J = 7.7 Hz, 2H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.19, 157.47, 156.93, 154.66, 145.89, 141.27, 131.29, 130.51, 130.47, 127.12, 124.00, 119.50, 119.31, 114.32, 113.46, 109.39, 70.22, 38.70, 29.85ppm ; HRMS (ESI): $[M + H]^+$ $C_{22}H_{20}BNO_4$ calcd 374.1564, found 374.1565; mp: 165-168 °C; HPLC: purity 97.3%, retention time 13.6 min.

<Inhibition Tests>

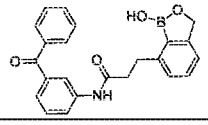
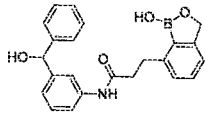
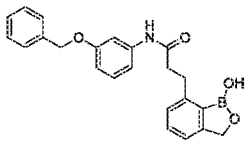
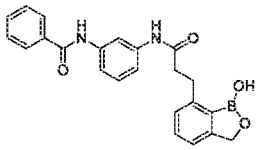
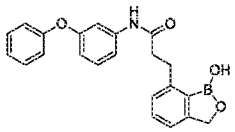
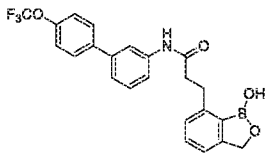
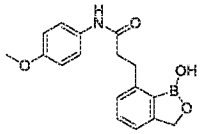
The above preparations were tested for cell proliferation inhibition, the specific steps are as follows:

(1) Cell culture. All tumor cell lines (MDA-MB231, SKOV3 and HCT116) were purchased from ATCC (American Type Culture Collection). Tumor cell lines were cultured in DMEM complete medium (high glucose DMEM medium supplemented with 10% fetal bovine serum, 100 units/mL of penicillin, 100 mg/mL of streptomycin). Cells were cultured in a CO_2 cell incubator at 37 °C. When cells have been passaged no less than three times after thawing, reaching a confluence of 80% and in good condition, they can be used for activity test.

(2) Specific operation. Compounds were tested for their inhibition to cell growth using methyl thiazolyl tetrazolium (MTT) method. Briefly, the cells were seeded in 96-well plates and incubated with different concentrations of compound for 72 h. Then 20 μL MTT (5 mg / mL) was added to each well and the plate was incubated for 4 h. The supernatant was aspirated and 150 μL of DMSO was added to each well, the plate was shaked for 20 min. The optical density values (ODs) of the wells at 550 nm was read by Microplate readings (Thermo Varioskan Flash). Triplicate wells are provided for each compound at each concentration.

(3) The inhibitory rate of proliferation of cell line of a medicament was calculated by the following formula: inhibition rate of cell proliferation = $(OD_{negative\ control}–OD_{test})$ / $(OD_{negative\ control}–OD_{blank})$ × 100%. Dose response curves were plotted with inhibition rate of cell proliferation by different concentrations of the same sample, and analyzed by GraphPad Prism 5 software, to determine the half maximal inhibitory concentration IC_{50} of the sample.

Table 1 IC_{50} of inhibition of cell proliferation by some compounds

NO.	Structure	IC_{50} (μM)		
		SKOV3	MDA-MB231	HCT116
11		0.5179	0.2134	0.4325
12		0.0448	0.2498	0.1256
13		0.0926	0.4659	0.3266
14		0.0022	0.0113	0.0084
15		0.2210	0.8580	0.8391
I		0.5586	0.6384	0.7320
II		0.9021	0.8511	1.67
III	Doxorubicin	0.1348	0.1177	0.0266

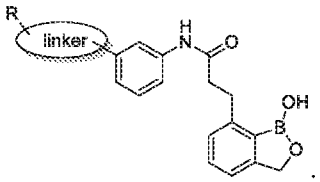
It can be seen from Table 1 that some compounds provided in the present disclosure have good inhibition of cell proliferation. Compound **11-15** show better activity compared with compound **I**, which is one negative control, especially in the inhibition of SKOV3 proliferation. This result proves that the linker as defined in the present disclosure in the formula does contribute to the anticancer activity of 7-propanamide substituted benzoxaborole-derived compound, probably because of certain interactions with amino acid residue around. It's worth noting that compound **14** achieves an extraordinary inhibition effect on all 3 cell lines with IC_{50} around 2 nM.

However, a linker within the defined scope might not achieve similar desirable inhibition effect.

For example, compound **II**, a potent antiprotozoal agent (US 2011/0207701 A1), which has a substituent at para position of phenyl group, has s relatively weak anticancer activity, thus serves as another negative control. The superior inhibition effect of Compound **11-15** draws our attention to the specific meta position of linker on the phenyl group, instead of para position.

Besides, as a comparison to Compound **III**, doxorubicin, which is a well-known medicine used in clinical chemotherapy, Compound **11-15** show comparable or even better effects in the experiment.

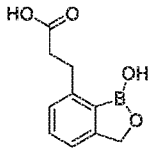
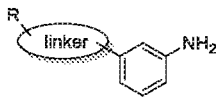
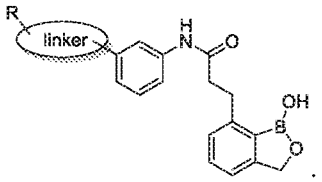
WHAT IS CLAIMED IS

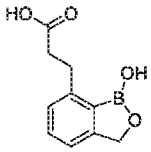
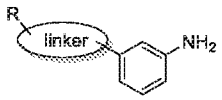
1. A derivative of 7-propanamide substituted benzoxaborole, wherein the structural general formula of the derivatives is  .

wherein, In the general formula, linker is at the meta position of phenyl group and linker is one selected from carbonyl, carbinol, alkyoxy, amide or atom N and O, R is selected from phenyl or substituted phenyl, or a salt thereof.

2. The derivative of 7-propanamide substituted benzoxaborole according to claim 1, the substituted phenyl is selected from one of hydrogen, halogen, C1-C10 alkyl, alkoxy, alkynyl, ethoxycarbonyl, nitro, amino, aminomethyl, methlmercapto, trifluoromethoxy, trifluoromethyl, cyano or acetyl.

3. A preparation method of the derivative of aforesaid 7-propanamide substituted benzoxaborole, wherein the preparation method is as followed:

dissolve the  and  and EDCI in dichloromethane or DMF and stir, solvent is removed by rotary evaporation at vacuum, to purify and obtain  .

4. The preparation method of the derivative of 7-propanamide substituted benzoxaborole according to claim 4, the molar ratio of  and  and EDCI is 1:(0.5-3):(1-3), stirring is performed at room temperature for a duration of 1-24h, and purification is performed by silica gel column chromatography.

5. Pharmaceutical use of the derivative of 7-propanamide substituted benzoxaborole according to any one of claims 1 to 3, wherein the derivative is used for the preparation of a medicament for the prevention and treatment of tumors.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CN2019/079004

A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/69(2006.01)i; A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K; A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CNABS(CN),DWPI,SIPOABS, CNTXT, EPTXT,USTXT,WOTXT,CNKI(CN),Chinese Pharmaceutical Abstract (CN), CHEMICAL ABSTRACTS(US), EMBASE, Baidu scholar, ISI-WEB OF SCIENCE,STN:structure search, propanamide, benzoxaborol?, tumor, tumour, cancer, neoplasms

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 107090000 A (HANGHAI JIAO TONG UNIVERSIT) 25 August 2017 (2017-08-25) Claims 1, 10, description pages 3-11, examples 1, 7, 9	1-5
X	WO 2011022337 A1 (ANACOR PHARMACEUTICALS INCet al.) 24 February 2011 (2011-02-24) Claims 1-20, description pages 84-85	1-4

☐ Further documents are listed in the continuation of Box C. ☑ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
06 December 2019	**26 December 2019**
Name and mailing address of the ISA/CN **National Intellectual Property Administration, PRC** **6, Xitucheng Rd., Jimen Bridge, Haidian District, Beijing 100088** **China** Facsimile No. **(86-10)62019451**	Authorized officer **XIU,Wen** Telephone No. **(86-10)62411076**

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/CN2019/079004

Patent document cited in search report	Publication date (day/month/year)	Patent family member(s)	Publication date (day/month/year)
CN 107090000 A	25 August 2017	CN 107090000 B	12 July 2019
WO 2011022337 A1	24 February 2011	MX 2012002031 A	04 July 2012
		IL 218163 D0	31 July 2012
		US 2011207701 A1	25 August 2011