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SYNTHESIS, CHARACTERIZATION AND EVALUATION OF NOVEL CARBAZOLE BORONIC ACID DERIVATIVES IN THE TREATMENT OF BREAST CANCER

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Keywords:

Boronic acid, Carbazole, MCF-7, Cancer, Molecular hybridization

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ABSTRACT: The present study aimed to synthesize Carbazole boronic acid derivatives and determine their efficacy in treating breast cancer using the MCF-7 cell line. Nine different derivatives (C1-C12) of boronic acid were prepared i.e. 9-ethyl-(9H-carbazol-3-yl)-boronic acid (C1); (9-benzyl-9H-carbazol-3-yl)-boronic acid (C2); [9-(4-fluorobenzyl)-9H-carbazol-3-yl]-boronic acid (C3); [9-(sec-butyl)-9H-carbazol-3-yl]-boronic acid (C4); (9-pentyl-9H-carbazol-3-yl)-boronic acid (C5); (9-octyl-9H-carbazol-3-yl)-boronic acid (C6); (9-cyclopentyl-9H-carbazol-3-yl)-boronic acid (C7); [9-(4-chlorobenzyl)-9H-carbazol-3-yl)-boronic acid (C8); and [9-(2,4-dichlorobenzyl)-9H-carbazol-3-yl)-boronic acid (C9). Results showed that C3, C7, C8 and C9 exhibited more than 90% inhibition of cancer cell growth in MCF-7 breast cancer cell line. The percentage yield of these compounds was 20%, 26%, 24% and 24%, respectively. However, other compounds have also shown good anticancer properties compared to the control group. Thus, these compounds have shown potential in *in-vitro* studies and can be used as an anticancer drugs after pre-clinical and clinical studies.

INTRODUCTION: Cancer is the world's second-leading cause of mortality after heart disease [1]. More than 9.6 million cancer-related fatalities were recorded in 2018, according to GLOBOCAN, the world's largest study of cancer incidence, mortality, and prevalence [2-3]. Metastasis to secondary tissues is the primary cause of death in breast cancer patients. Before it has spread, patients diagnosed with breast cancer early have a better chance of recovery [4]. Therapeutic approaches that prevent cancer cells from adhering to one another make sense to prevent cancer cells from migrating. Carbazole structure has been a common pattern in many physiologically active chemicals [5].

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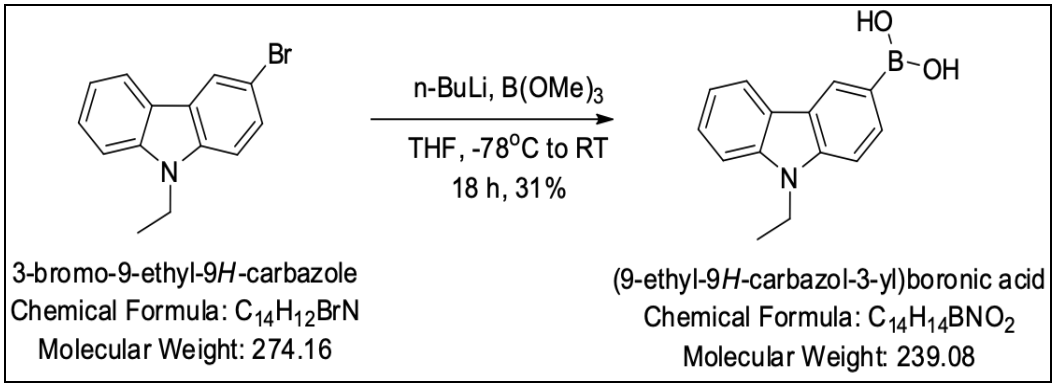
Both the tricyclic molecular skeleton and several fused carbazoles, such as the tetracyclic (with five-, six- and seven-member ring), pentacyclic (with six and seven-membered ring) and lastly heptacyclic fused carbazoles are included in the name "carbazole" [6]. A wide range of species, including bacteria, fungi, plants and animals have been shown to contain carbazoles, which have played an essential role in all currently available anticancer medications. It's most common to find carbazole alkaloids in the genera *Glycosmis*, *Clausena*, *Murraya*, and *Micromelum*, all of which belong to the Rutaceae family [7].

It isn't just bacteria, algae, and fungi that contribute to the abundance of nitrate (e.g., Aspergillus species). In 1872, Graebe and Glazer discovered the parent chemical 9H-carbazole from coal tar [8]. There have since been a plethora of carbazole derivatives produced, which are well known for their pharmacological properties, such as their ability to combat oxidative stress and inflammation

and inhibit the growth of bacteria, fungi, and tumours [9]. Aromatic heterocyclic organic compounds include carbazole. DNA damage is the primary mechanism by which this agent operates. These occurrences inhibit the production of new DNA or RNA. Carbazole derivatives and similar chemicals have been investigated extensively in the past [10]. Anticancer drug designation has been granted to three variants in various nations. Boronic acid is derived from boric acid by replacing one of the three hydroxyl groups. According to popular belief, the boronic acid functional group is rather nontoxic. In the discovery and synthesis of pharmacological drugs, the Suzuki coupling is popular, among others [11]. Many routinely used boronic acids and derivatives are Ames-positive chemical mutagens. The oxidation of boronic acid by ambient oxygen is assumed to be the mechanism for mutagen city, resulting in the production of organic radicals [12]. Up to 90 percent of cancer-related deaths can be blamed on chemotherapy, despite a vast list of viable medications. There are several reasons for this, but resistance to the treatment is a major one. Multiple processes, such as genetic mutations and/or epigenetic alterations, preserved but increased drug efflux and other cellular and molecular pathways contribute to resistance to pharmaceutical treatments [13]. Researchers are developing medications that can affect more than one target at once to solve this problem. If an individual combines two or more pharmacophores from distinct bioactive substances, you can create an enhanced hybrid molecule with better affinity and efficacy than the original medications [14]. Molecules with altered selectivity profiles, diverse and/or numerous mechanisms of action, and reduce unwanted side effects may also be the consequence of this approach. Numerous research groups are developing and testing new chemical entities based on drug design to find new and potent anticancer medications. In the current investigation, different carbazole boronic acid derivative compounds were produced and tested for anticancer efficacy against the MCF-7 breast cancer cell line.

MATERIAL AND METHODS

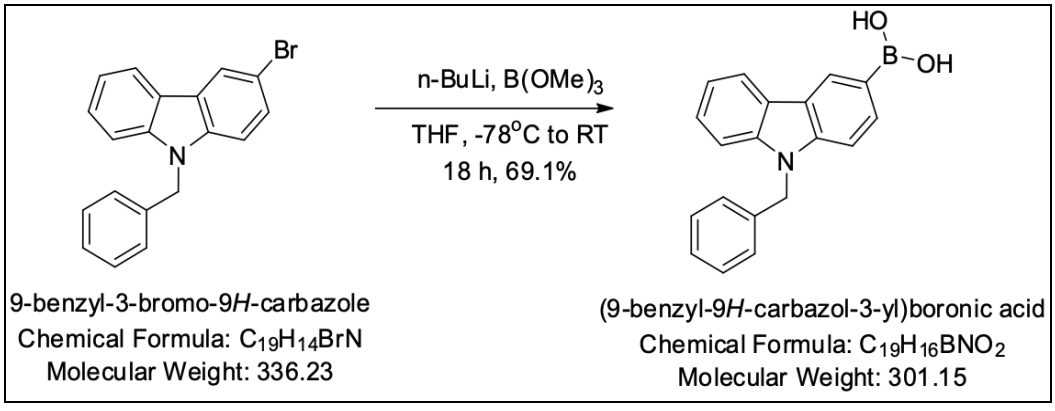
Synthesis of Compound-1:



3-bromo-9-ethyl-9*H*-carbazole
Chemical Formula: $C_{14}H_{12}BrN$
Molecular Weight: 274.16

(9-ethyl-9*H*-carbazol-3-yl)boronic acid
Chemical Formula: $C_{14}H_{14}BNO_2$
Molecular Weight: 239.08

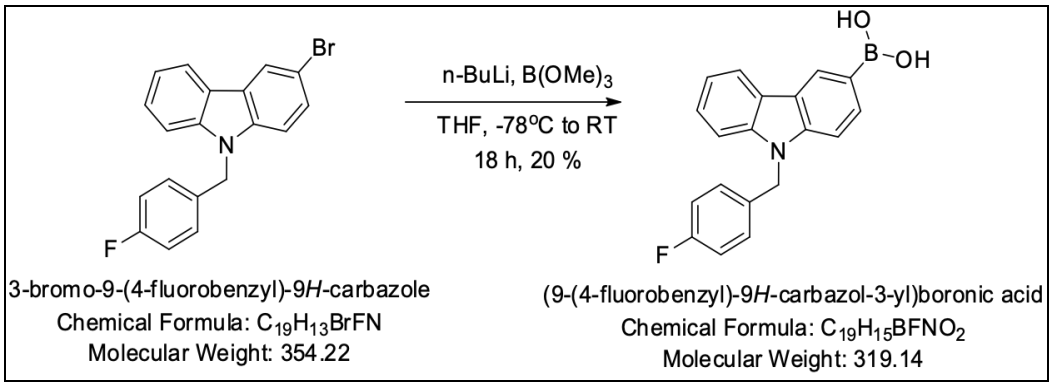
Synthesis of Compound-2:



9-benzyl-3-bromo-9*H*-carbazole
Chemical Formula: $C_{19}H_{14}BrN$
Molecular Weight: 336.23

(9-benzyl-9*H*-carbazol-3-yl)boronic acid
Chemical Formula: $C_{19}H_{16}BNO_2$
Molecular Weight: 301.15

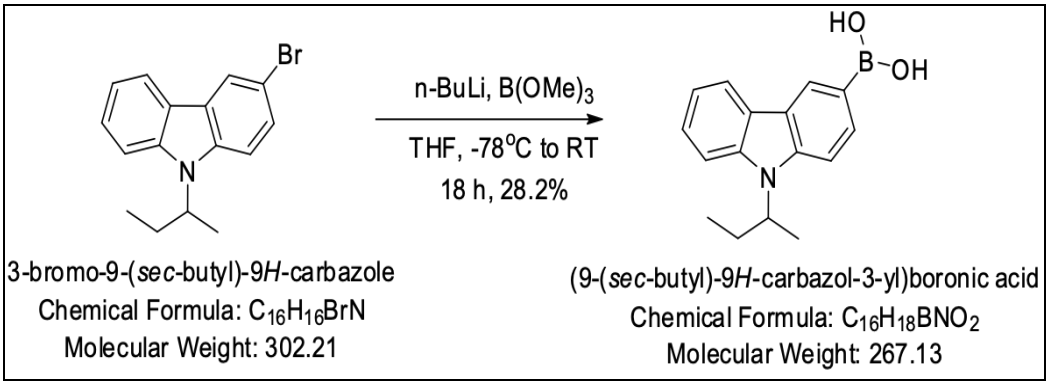
Synthesis of Compound-3:



3-bromo-9-(4-fluorobenzyl)-9*H*-carbazole
Chemical Formula: $C_{19}H_{13}BrFN$
Molecular Weight: 354.22

(9-(4-fluorobenzyl)-9*H*-carbazol-3-yl)boronic acid
Chemical Formula: $C_{19}H_{15}BFNO_2$
Molecular Weight: 319.14

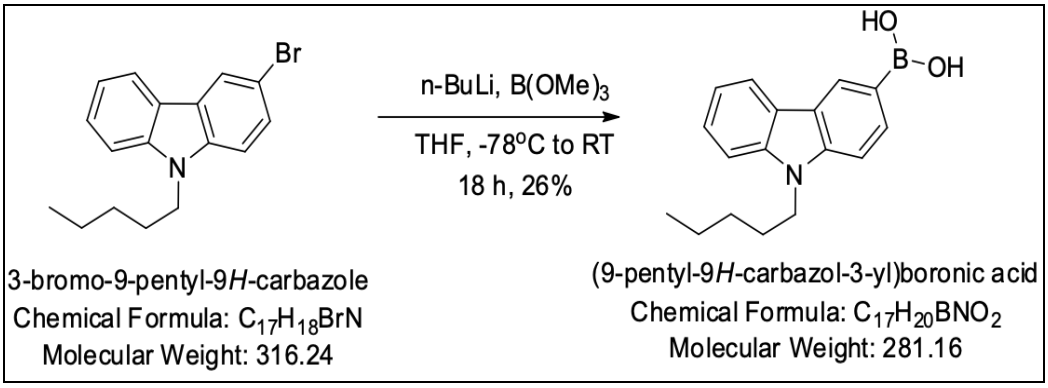
Synthesis of Compound-4:



3-bromo-9-(*sec*-butyl)-9*H*-carbazole
Chemical Formula: $C_{16}H_{16}BrN$
Molecular Weight: 302.21

(9-(*sec*-butyl)-9*H*-carbazol-3-yl)boronic acid
Chemical Formula: $C_{16}H_{18}BNO_2$
Molecular Weight: 267.13

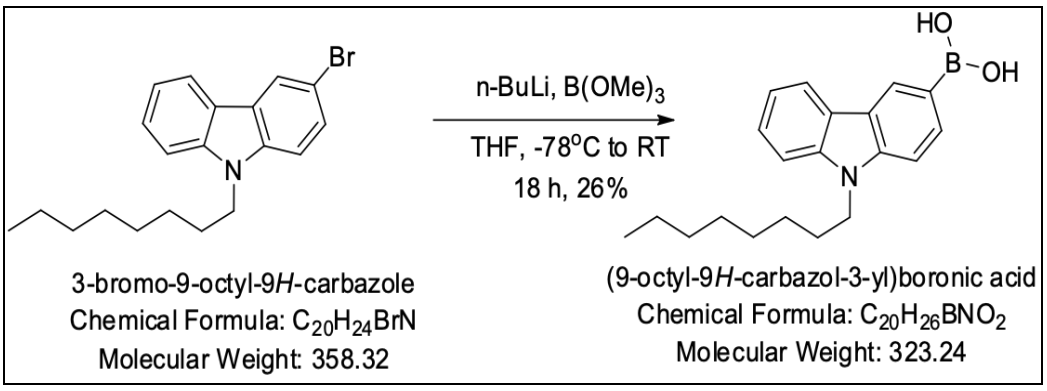
Synthesis of Compound-5:



3-bromo-9-pentyl-9*H*-carbazole
Chemical Formula: $C_{17}H_{18}BrN$
Molecular Weight: 316.24

(9-pentyl-9*H*-carbazol-3-yl)boronic acid
Chemical Formula: $C_{17}H_{20}BNO_2$
Molecular Weight: 281.16

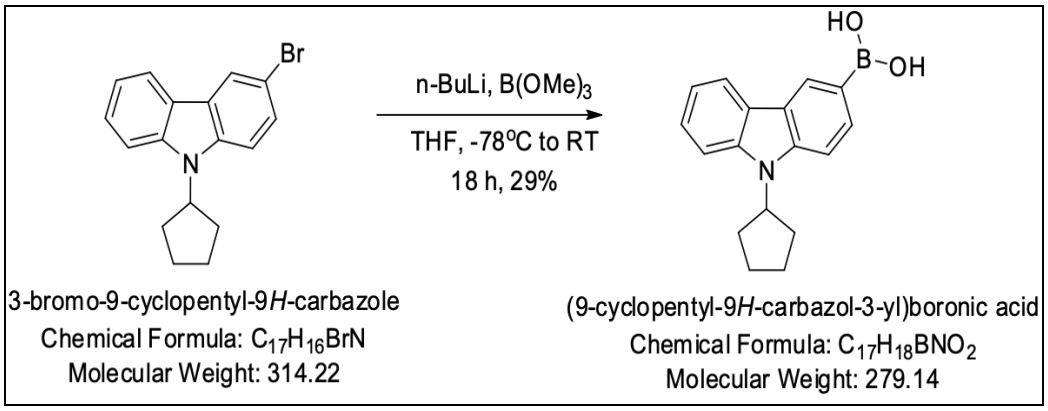
Synthesis of Compound-6:



3-bromo-9-octyl-9*H*-carbazole
Chemical Formula: $C_{20}H_{24}BrN$
Molecular Weight: 358.32

(9-octyl-9*H*-carbazol-3-yl)boronic acid
Chemical Formula: $C_{20}H_{26}BNO_2$
Molecular Weight: 323.24

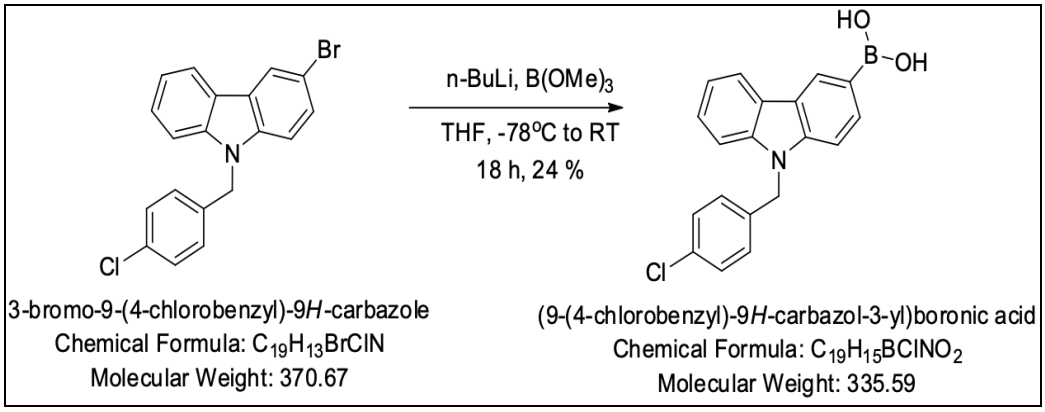
Synthesis of Compound-7:



3-bromo-9-cyclopentyl-9*H*-carbazole
Chemical Formula: $C_{17}H_{16}BrN$
Molecular Weight: 314.22

(9-cyclopentyl-9*H*-carbazol-3-yl)boronic acid
Chemical Formula: $C_{17}H_{18}BNO_2$
Molecular Weight: 279.14

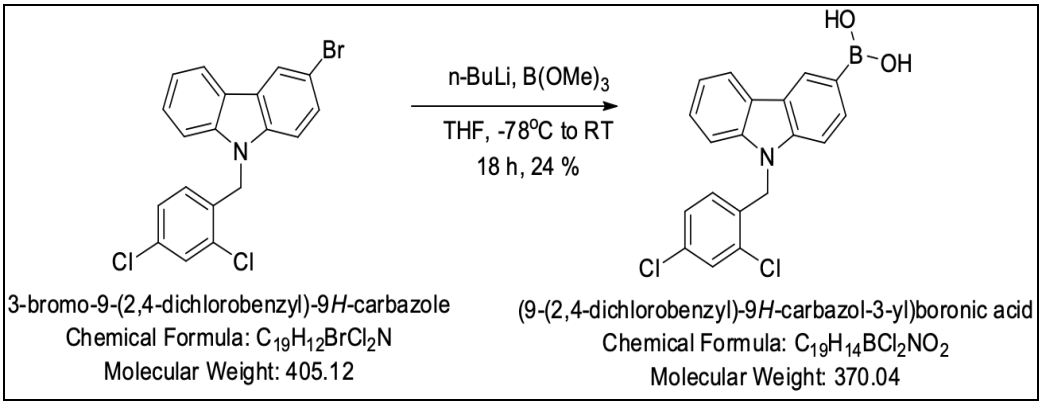
Synthesis of Compound-8:



3-bromo-9-(4-chlorobenzyl)-9*H*-carbazole
Chemical Formula: $C_{19}H_{13}BrClN$
Molecular Weight: 370.67

(9-(4-chlorobenzyl)-9*H*-carbazol-3-yl)boronic acid
Chemical Formula: $C_{19}H_{15}BClNO_2$
Molecular Weight: 335.59

Synthesis of Compound-9:



3-bromo-9-(2,4-dichlorobenzyl)-9*H*-carbazole
Chemical Formula: $C_{19}H_{12}BrCl_2N$
Molecular Weight: 405.12

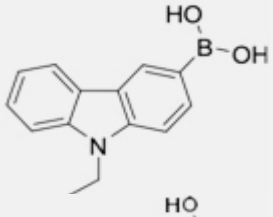
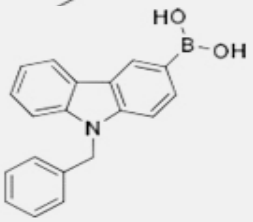
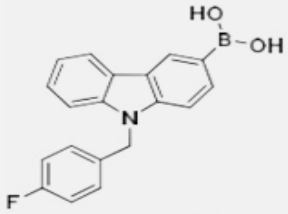
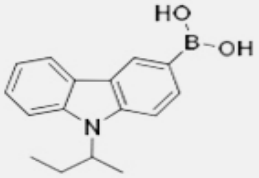
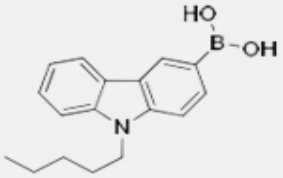
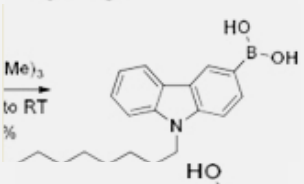
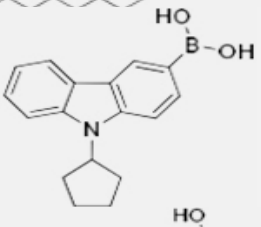
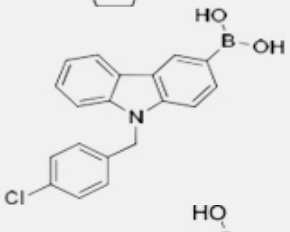
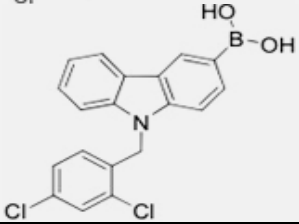
(9-(2,4-dichlorobenzyl)-9*H*-carbazol-3-yl)boronic acid
Chemical Formula: $C_{19}H_{14}BCl_2NO_2$
Molecular Weight: 370.04

Procedure: Nine substances were synthesized using the same method. Starting compound (1.23 g, 3.65 mmol) was mixed in dry THF (18.25 ml, 5ml/mmol), then n-Butyl Lithium (1.6 M in Hexane, 3.42 ml) was added dropwise at -78°C. 30 minutes of constant stirring, then 5 minutes at -45°C.

Trimethyl borate (0.61 ml) is introduced at -78°C. Slowly bringing the temperature to RT took 16 hours. Saturated aqueous Ammonium chloride solution (1 ml) was added, diluted with Ethylacetate (100 ml), and rinsed with water (25 ml) and brine (25 ml).

Volatiles were evaporated after drying the organic layer over anhydrous Na_2SO_4. The crude was refined on a silica gel column in Ethylacetate: hexane to get 760 mg (69.1%) product **Table 1.**

TABLE 1: SYNTHESIS OF NOVEL CARBAZOLE BORONIC ACID DERIVATIVE COMPOUNDS

Compounds	IUPAC name	Yield (%)	Molecular formula	Structure
C1	9-ethyl-(9H-carbazol-3-yl)-boronic acid	31	$C_{14}H_{14}BNO_2$	
C2	(9-benzyl-9H-carbazol-3-yl)-boronic acid	69.1	$C_{19}H_{16}BNO_2$	
C3	[9-(4-fluorobenzyl)-9H-carbazol-3-yl]-boronic acid	20	$C_{19}H_{15}BFNO_2$	
C4	[9-(sec-butyl)-9H-carbazol-3-yl]-boronic acid	28.2	$C_{16}H_{18}BNO_2$	
C5	(9-pentyl-9H-carbazol-3-yl)-boronic acid	26	$C_{16}H_{18}BNO_2$	
C6	(9-octyl-9H-carbazol-3-yl)-boronic acid	26	$C_{20}H_{26}BNO_2$	
C7	(9-cyclopentyl-9H-carbazol-3-yl)-boronic acid	26	$C_{17}H_{18}BNO_2$	
C8	[9-(4-chlorobenzyl)-9H-carbazol-3-yl)-boronic acid	24	$C_{19}H_{15}BClNO_2$	
C9	[9-(2,4-dichlorobenzyl)-9H-carbazol-3-yl)-boronic acid	24	$C_{19}H_{14}BCl_2NO_2$	

***In-vitro* Anticancer Activity:**

Cell lines and Culture Medium: The obtained cells were grown in DMEM supplemented with 10% inactivated FBS, 100 IU/ml penicillin, and 100µg/ml streptomycin at 37°C until confluent. Cell dissociation solution was employed (0.2 percent trypsin, 0.02 percent EDTA, 0.05 percent glucose in PBS). Centrifuging verifies cell viability. After 24 hours at 37°C, 5% CO_2, 50,000 cells/well were planted in 96-well plates.

Procedure: Following trypsinization, the monolayer cell count was lowered to 5x105 cells/ml in an appropriate medium with 10% FBS. 100 l of the diluted cell suspension (50,000 cells/well) was put into each well of the 96-well microtiter plate. It was then washed with media, the supernatant was flung off, and 100 l of different doses of test medicines were introduced to the monolayer in microtiter plates after 24 h, when a monolayer had formed. At 37°C, the plates were kept in a 5 percent CO_2 environment for 24 hours. It was necessary to remove the test solutions from the wells and fill each one with 100 microliters of MTT (5 mg/ 10 ml of MTT in PBS). Incubation was placed for four hours at 37°C in a CO_2 environment of 5 percent. Excess supernatant was removed from the plates and 100l of DMSO was added to dissolve the generated formazan. A microplate reader set to a 590 nm wavelength measured the absorbance. A formula was used to quantify the percentage of cell growth inhibition. The concentration of test medication needed to inhibit cell growth by 50% (IC50) values were derived from the dose-response curves for each cell type [15]. Using the following formula, a percentage of inhibition was determined:

(OD of Control – OD of the sample) / OD of Control) x 100 = percent inhibition.

Following trypsinization, the monolayer cell count was reduced to $5x10^5$ cells/ml in 10% FBS. 100 microliters of diluted cell suspension (50,000/well) was added to each 96-well microtiter plate. The monolayer was rinsed with medium, the supernatant was discarded, and 100 microliters of test medications were added after 24 h. At 37°C for 24 hours, the plates were in 5% CO2. After removing the test solutions from the wells, 100 microliters of MTT (5 mg/ 10 ml in PBS) were added to each. At 37°C and 5% CO2, the sample was incubated for four hours. The supernatant was withdrawn from the plates, and 100 microliters of DMSO was added to dissolve the formazan. A 590 nm microplate reader recorded absorbance. A formula was used to determine the concentration of the test drug needed to inhibit cell growth by 50% (IC50) for each cell type [16]. Percentage of inhibition determined using the formula: (OD of control-OD of the sample)/OD of control x 100 = percent inhibition

RESULT:

The Different Compounds Synthesized (C1-C9) were as follows:

9-ethyl-(9*H*-carbazol-3-yl)-boronic Acid (C1): [1] H NMR (400 MHz, $CDCl_3$): δ 9.13 (s, 1H), 8.50 (d, J = 7.2 Hz, 1H), 8.38 (d, J = 7.6 Hz, 1H), 7.61-7.26 (m, 4H), 4.47 (q, J = 7.2 Hz, 2H), 1.53 (t, J = 7.2 Hz, 3H); MS (ESI) m/z: calculated, $C_{14}H_{14}BNO_2$, 239.08 $[M]^+$; found, 240.2 $[M+H]^+$.

(9-benzyl-9*H*-carbazol-3-yl)-boronic acid (C2): [1] H NMR (400 MHz, DMSO-d_6): δ 8.62 (s, 1H), 8.13 (d, J = 7.6 Hz, 1H), 7.96 (s, 1H), 7.67-7.16 (m, 9H), 5.67 (s, 2H); MS (ESI) m/z: calculated, $C_{19}H_{16}BNO_2$, 301.15 $[M]^+$; found, 300.05 $[M-1]^-$.

[9-(4-fluorobenzyl)-9*H*-carbazol-3-yl]-boronic acid (C3): [1] H NMR (400 MHz, DMSO-d_6): δ 12.68 (s, 1H), 8.82 (s, 1H), 8.31 (d, J = 7.6 Hz, 1H), 8.05 (dd, J = 8.4&1.6 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.50 (t, J = 7.2 Hz, 1H), 7.28-7.09 (m, 5H), 5.72 (s, 2H); MS (ESI) m/z: calculated, $C_{19}H_{15}BFNO_2$, 319.14 $[M]^+$; found, 319.22 $[M]^+$, 325.2.

[9-(sec-butyl)-9*H*-carbazol-3-yl]-boronic acid (C4): [1] H NMR (400 MHz, DMSO-D6): δ 8.41 (s, 1H), 8.22 (d, J = 7.6 Hz, 1H), 7.72-7.39 (m, 4H), 7.20 (t, J = 7.2 Hz, 1H), 4.86-4.80 (m, 1H), 2.23-2.16 (m, 1H), 1.99-1.92 (m, 1H), 1.60 (d, J = 7.2 Hz, 3H), 0.64 (t, J = 7.6 Hz, 3H); MS (ESI) m/z: calculated, $C_{16}H_{18}BNO_2$, 267.13 $[M]^+$; found, 265.8 $[M-1]^-$.

(9-pentyl-9*H*-carbazol-3-yl)-boronic acid (C5): [1] H NMR (400 MHz, $CDCl_3$): δ 8.14 (s, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.55 (d, J = 7.6Hz, 2H), 7.27 (d, J = 7.6 Hz, 1H + $CDCl_3$), 7.18-7.12 (m, 2H), 4.24 (t, J = 7.2 Hz, 2H), 1.85-1.81 (m, 2H), 1.36-1.25 (m,

4H), 0.88-0.85 (m, 3H); MS (ESI) m/z: calculated, $C_{16}H_{18}BNO_2$, 267.13 $[M]^+$; found, 265.8 $[M-1]^-$.

(**9-octyl-9*H*-carbazol-3-yl)-boronic acid (C6):** ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (s, 1H), 7.98 (d, J = 7.6 Hz, 1H), 7.62-7.68 (m, 2H), 7.33-7.12 (m,3H), 4.23 (t, J = 7.2 Hz, 2H), 1.83-1.78 (m, 2H), 1.30-1.22 (m, 10 H), 0.856 (t, J = 6.4 Hz, 3H); MS (ESI) m/z: calculated, $C_{20}H_{26}BNO_2$, 323.24 $[M]^+$; found, 322.0 $[M-1]^-$.

(**9-cyclopentyl-9*H*-carbazol-3-yl)-boronic acid (C7):** ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.78-7.46 (m, 5H), 7.22 (m, 1H), 5.31-5.27 (m, 1H), 2.16-2.03 (m, 6H), 1.80-1.78 (m, 2H); MS (ESI) m/z: calculated, $C_{17}H_{18}BNO_2$, 279.14 $[M]^+$; found, 280.0 $[M+H]^+$.

[**9-(4-chlorobenzyl)-9*H*-carbazol-3-yl)-boronic acid (C8):** ^{1}H NMR (400 MHz, DMSO-d6): δ 8.24 (s, 1H), 7.68-7.42 (m, 6H), 7.38 (d, J = 7.6 Hz, 2H), 7.16 (d, J = 7.6 Hz, 2H), 5.66 (s, 2H); MS (ESI) m/z: calculated, $C_{19}H_{15}BClNO_2$, 335.59 $[M]^+$; found, 334 $[M-1]^-$.

[**9-(2,4-dichlorobenzyl)-9*H*-carbazol-3-yl)-boronic acid (C9):** ^{1}H NMR (400 MHz, DMSO-d6): δ 8.58 (s, 1H), 7.62-7.45 (m, 4H), 7.25-7.08 (m, 5H), 5.78 (s, 2H); MS (ESI) m/z: calculated, $C_{19}H_{14}BCl_2NO_2$, 370.04 $[M]^+$; found, 371.7 $[M+1]^+$.

Effect of Synthesized Compounds MCF-7 Breast Cancer Cell Line: Table 2 shows the effect of carbazole boronic acid derivative compound on MCF-7 breast cancer cell line. All the synthesized compounds effectively inhibited cancerous cell growth compared to the control group. The percentage inhibition of C1-C9 was 87.25%, 89.77%, 93.46%, 81.74%, 74.65%, 85.18%, 90.50%, 93.04%, and 92.38%, respectively.

However, compounds C3, C7, C8 and C9 exhibited more than 90% inhibition of cancer cell growth in MCF-7 breast cancer cell line as compared to the control group, which was more than the standard drug doxorubicin.

Fig. 1 shows the IC_{50} values of different synthesized compounds. IC_{50} values of C1-C9 was 75.88, 20.46, 18.84, 40.52, 54.03, 70.97, 21.61, 13.77 and 15.99 µg/mL, respectively. However, IC_{50} of doxorubicin was 28.09 µg/mL.

TABLE 2: ANTICANCER ACTIVITY OF CARBAZOLE BORONIC ACID DERIVATIVES ON MCF-7 BREAST CANCER CELL LINE

Groups/Compounds	Concentration (µg/mL)	OD at 590 nm	Inhibition (%)
Control	0	0.958	0
	10	0.836	12.75
	20	0.705	26.42
Doxorubicin	40	0.570	40.45
(Reference compound)	80	0.454	52.62
	160	0.264	72.47
	320	0.105	89.02
	10	0.859	10.29
	20	0.787	17.86
C1	40	0.620	35.25
	80	0.427	55.40
	160	0.289	69.83
	320	0.122	87.25
C2	10	0.717	25.15
	20	0.526	45.08
	40	0.385	59.81
	80	0.267	72.14
	160	0.167	82.58
	320	0.098	89.77
C3	10	0.577	39.77
	20	0.476	50.27
	40	0.269	71.91
	80	0.165	82.73
	160	0.105	89.05
	320	0.063	93.46

C4	10	0.878	8.37
	20	0.699	27.01
	40	0.586	38.79
	80	0.401	58.12
	160	0.279	70.86
	320	0.175	81.74
C5	10	0.895	6.58
	20	0.788	17.75
	40	0.678	29.20
	80	0.453	52.77
	160	0.310	67.61
	320	0.243	74.65
C6	10	0.855	10.75
	20	0.715	25.37
	40	0.604	36.95
	80	0.456	52.40
	160	0.213	77.79
	320	0.142	85.18
C7	10	0.725	24.32
	20	0.547	42.92
	40	0.384	59.95
	80	0.254	73.52
	160	0.141	85.27
	320	0.091	90.50
C8	10	0.546	43.04
	20	0.377	60.63
	40	0.272	71.64
	80	0.131	86.37
	160	0.071	92.64
	320	0.067	93.04
C9	10	0.654	31.75
	20	0.414	56.82
	40	0.376	60.79
	80	0.205	78.65
	160	0.174	81.86
	320	0.0073	92.38

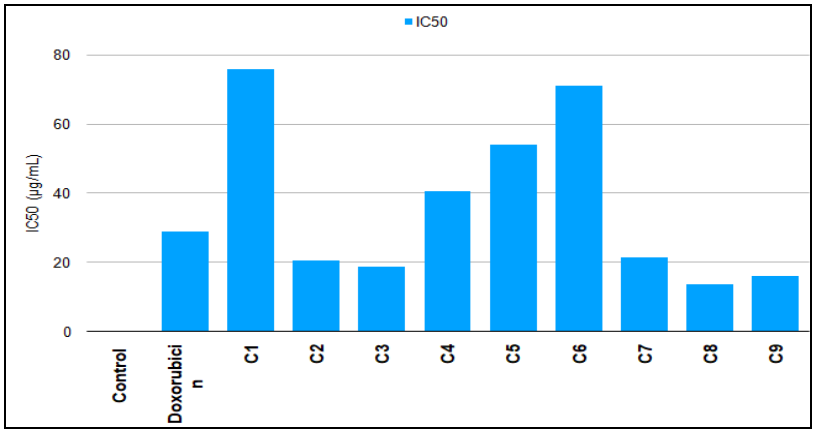


FIG. 1: INHIBITOR CONCENTRATION OF DIFFERENT SYNTHESIZED COMPOUNDS ON MCF-7 BREAST CANCER CELL LINE

DISCUSSION: The most common disease in women is breast cancer, which affects about one in every eight women who are diagnosed. In light of its widespread impact, this disease is a significant public health issue that necessitates extra attention in determining its prognosis and appropriate treatment. These cell lines can be employed in a wide range of laboratory experiments, including cancer research, which is vital for achieving this goal. For four decades, many research facilities have promoted the MCF-7 breast cancer cell line. Boronic acids can bind biologically relevant 1,2-

and 1,3-diols, such as saccharides and peptidoglycans, to form hydrogels with dynamic covalent or responsive behaviour. Despite various boronic acid designs, structure–reactivity connections governing diol binding affinity must be better understood. This study used boronic acid to manufacture fifteen carbazole derivative compounds in molecular hybrids. The carbazole group can generate either an aromatic amine (2-position) or an amide (3-position). A more compact ortho-substituted connection is projected to yield molecules with enhanced activity in both possibilities [17] Vlaar and colleagues (2018). Nine newly synthesised carbazole boronic acid compounds (C1-C9) were created and tested on MCF-7 breast cancer cell lines in this work. Ultimately, it was found that all of the compounds generated were effective at slowing down the growth of cancer cells.

The cancer cells were found to be sensitive to the growth-inhibitory action of several chemicals (C3, C7, C8 and C9). According to previous studies, HER2/Neu (ErbB-2, which is overexpressed in 15–20 percent of breast cancer) is frequently overexpressed in this cell line. Test compounds' growth rates over these three cell lines are shown in **Table 2**. The findings of Liu *et al.,* 2021, were in conformity with our analysis. To examine the anticancer properties of pyranocarbazole derivatives, they used MCF-7 breast cancer cell lines. The researchers found IC50 values of 1.77 and 4.32 μM for compounds 3 and 7i containing N-methyl piperazine when tested against MCF-7 cell lines. Inhibiting the growth of breast cancer cells is achieved by the novel carbazole boronic acid derivatives. In the future, these compounds could be used to treat breast cancer.

CONCLUSION: Carbazole-boronic acid analogues have been developed and produced as potential anticancer agents. Analogs with different substituents at the C-9 position of the core scaffold can be generated quickly and easily using a simple and efficient synthesis approach established. Using the MCF-7 breast cancer cell line panel, the representative analogues were found to have highly selective inhibitory effects on cancer cell proliferation. This new class of molecularly targeted chemotherapeutic medicines has intriguing beginning points in the compounds 3, 7, 8, and 9. Studies on the drug's mechanism of action (MOA) are now being conducted to identify its cellular targets. Compounds 3, 7, 8 and 9 in particular, were shown to have qualities for further development as possible clinical trial candidates for treating malignancies.

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