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Synthesis And Anticancer Activities Of Benzimidazole-Oxadiazole Hybrids.

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ABSTRACT

Cancer is a large group of diseases that can start in almost any organ or tissue of the body. It is fundamentally uncontrollable growth of cells. Cancer is the secomd leading cause of death globally. It is exerting tremendous strain physicaly, emotionaly and financialy on individuals, families and countries. Hybrid formation is the process of combining two active moeties in to one to get the benefits of the two into one. The hybrid approach can be used to optimize certain biological properties like affinity and selectivity, but also to gain novel biological activities distinct from one of the components. In the present work, a total of eight benzimidazole-1,3,5-oxadiazole hybrid molecules were synthesized, characterized by spectral and elemental analysis. All the eight derivatives were screeened for in vitro anticancer activity on MCF-7 cell lines. The compound BO1 was found to be moderately active against tumour in the chosen cell lines. This was followed by the compound BO2 and all the other compounds were found to have negligible anti cancer activity in the chosen cell lines. Based on this work it can be concluded that compounds BO1 and BO2 should be considered as possible prototypes of benzimidazole- oxa diazole hybrids with medicinal potential.

Keywords: Cancer, Benzimidazole, 1,3,5-oxadiazole, Hybrid, MCF cell lines

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INTRODUCTION

Cancer is a large group of diseases that can start in almost any organ or tissue of the body when abnormal cells grow uncontrollably, go beyond their usual boundaries to invade adjoining parts of the body and spread to other organs.[1] The latter process is calledmeta stasizing and is a major cause of death from cancer. Although the causes of cancer are not completely understood, numerous factors are known to increase the disease'soccurrence, including many that are modifiable (e.g., tobacco use and excess body weight)and those that are not modifiable (e.g., inherited genetic mutations and immune conditions).[2,3]

Cancer is the second leading cause of death globally, accounting for an estimated 9.6 million deaths, or one in six deaths, in 2018.[4] Cancer causing infections, such as hepatitis and human papilloma virus (HPV), are responsible for up to 25% of cancer cases in low and middle-income countries.[5] Lung, prostate, colorectal, stomach and liver cancer are the most common types of cancer in men, while breast, colorectal, lung, cervical and thyroid are the common cancers in women.[6]

The cancer burden continues to grow globally, exerting tremendous physical, emotionaland financial strain on individuals, families, communities and health systems. The economic impact of cancer is significant and is increasing.[7] The total annual economic cost of cancer in 2010 was estimated at approximately US$ 1.16 trillion.[8] The cancer burden can be reduced through early detection of cancer and management of patients who develop cancer. Many cancers have a high chance of cure if diagnosed early and treated adequately.[9]

Some of the most common cancer types, such as breast cancer, cervical cancer, oral cancer,and colorectal cancer have high cure rates when detected early and treated according to best practices.

Hybrid molecules, obtained by the combination of two differently active fragments, are the most popular chemical entities to work upon for developing modified scaffolds with muchnimproved properties in the area of biology as well as medicinal chemistry[10] The hybrid approach can be used to optimize certain biological properties like affinity and selectivity, but also to gain novel biological activities distinct from one of the components Hybrid molecules are defined as chemical entities with two or more structural domains havingdifferent biological functions and dual activity, indicating that a hybrid molecule acts as two distinct pharmacophores. The hybrid approach can be used to optimize certain biological properties like affinity and selectivity, but also to gain novel biological activities distinct from one of the components.[11] The hybrid approach can be used to optimize certain biological properties like affinity and selectivity, but also to gain novel biological activities distinct from one of the components.[12]

Compounds holding a benzotriazole nucleus linked with another heterocyclic system are of broad significance by virtue of their divergent biological activities. The electron-rich benzotriazole ring can be employed to combine with other bioactive fragments to affordmore active compounds with remarkable physicochemical properties and pharmacological activities.[13]

Benzotriazole moiety attached to an 1,3,4-oxadiazole ring via a methylene bridge is reported to possess anticonvulsant[14], antibacterial[15-18], antifungal[19], anticancer,[20-21],antitubercular[22], antiviral activities [23] etc. Thus by combining these two heterocyclic nuclei, novel heterocycles which are more biologically active than individual nucleus containing compounds have been developed. Hence in the present study, we report our attempt to synthesize novel benzotriazole-oxatriazole hybrids and evaluation of their *in vitro* anticancer activity.

MATERIALS AND METHODS

All the chemicals and reagents used in the present work were of analytical grade and obtained from Sisco research laboratories, Chemco, Isochem laboratories, Loba chemie, Nice chemicals & Himedia laboratories.

NMR spectra of the synthesized compounds were recorded in DMSO on Bruker AvanceIII FT NMR spectrometer at 400 MHz in Chemical shifts were reported in δ scale (ppm) with reference to Tetra Methyl Silane(TMS) as the internal standard.Mass spectral analysis were carried out by EI ionization mode on a JEOL

JMS600H EI mass spectrometer. The peaks were recorded as m/z values.Elemental analysis of the synthesized compounds were carried out on ELEMENTAR Vario EL III CHNS analyser.

Step 1- Synthesis of Ethyl (1H-benzotriazol-1-yl)acetate

Benzotriazole (1.19 g) was dissolved in dry acetone (60 ml) and then anhydrous potassium carbonate (3g) and ethyl chloro acetate (1.07 ml) was added. The contentsof the flask were mixed magnetically at 45°C, and then refluxed for 6 hours. The resulting hot solution after filtration was poured into a beaker containing crushed ice.
The separated solid was filtered and then recrystallized from ethanol. (M.P: 58-60°C) Yield:65%.

Step 2: Synthesis of 2-(1H-benzotriazol-1-yl)acetohydrazide

To a solution of ethylbenzotriazol-1-yl) acetate (4.1 g) in ethanol, 85% hydrazine hydrate (3.9ml) was added. The solution was then refluxed for 3 hours and poured intocold water. The separated solid product was filtered and recrystallized from ethanol.(M.P: 118-120°C) Yield 55%.

Step 3: Synthesis of 2-substituted-5-benzotriazomethyl-1,3,4-oxadiazole

2-(1H-benzotriazol-1-yl)acetohydrazide (0.01 mole, 1.91 g) was refluxed witharomatic acid (0.01mole) for 6 hours in the presence of phosphorous oxy chloride (10ml). The hot mixture was poured into ice-cold water and basified with 20% sodium bicarbonate solution. The solid mass was filtered, washed with water and recrystallizedfrom ethanol.

Synthesis of BO1(1-({5-[(naphthalen-1-yl)methyl]-1,3,4-oxadiazol-2-yl}methyl)-1H-benzotriazole)

2-(1H-benzotriazol-1-yl)acetohydrazide (0.01 mole, 1.91 g) was refluxed with 1-naphthyl acetic acid (0.01mole, 1.86 g) for 6 hours in the presence of phosphorous oxychloride (10 ml). The hot mixture was poured into ice-cold water and basified with 20%sodium bi carbonate solution. The solid mass was filtered, washed with water andrecrystallized from ethanol.

IR: (KBR cm^{-1}) 3020 cm-1(Aromatic C-H stretching), 2830 cm-1(CH2- stretching),2360 cm-1(N=N), 1610 cm-1(C=N), 1400,1480 cm-1(Aromaticregion), 1125 cm-1(C-O-C of Oxadiazole ring)

^{1}HNMR(DMSO): 7.023-7.547 - multiplet, aromatic proton(7 H)5.553- singlet, -CH2 (2 H)4.80- singlet, -OCH2 (2 H)

^{13} C NMR(DMSO) 169.589 - Carbon atoms of oxadiazole ring (2 C)114.930-152.360 - Aromatic carbon atoms (12 C) 65.249 - OCH2 (1 C) 49.443 - CH2 (1 C)

CHNS : Cal C- 51.08%, H-2.95%,Cl-18.85%,N-18.62%,O-8.51% Found: C- 51.12%, H-2.79%,Cl-18.87%,N-18.64%,O-8.57%

MS: 341.12 (M+)

Synthesis of BO2 (2-{5-[(1H-benzotriazol-1-yl)methyl]-1,3,4-oxadiazol-2-yl}phenyl acetate)

2-(1H-benzotriazol-1-yl)acetohydrazide (0.01 mole, 1.91 g) was refluxed with Acetylsalicylic acid (0.01mole, 1.80 g) for 6 hours in the presence of phosphorous oxychloride (10 ml). The hot mixture was poured into ice-cold water and basified with 20%sodium bi carbonate solution. The solid mass was filtered, washed with water andrecrystallized from ethanol.

IR(KBR cm^{-1}): 3020 cm-1 (Aromatic C-H stretching), 2850 cm-1(CH2- stretching),2350 cm-1(N=N), 1740 cm-1(C=O stretching), 1610 cm-1(C=N),1450, 1275 cm-1(Aromatic region), 1125 cm-1(C-O-C of Oxadiazole

^{1}HNMR(DMSO): 7.03-7.487 - multiplet, aromatic proton(7 H)5.234- singlet, -CH2 (2 H)

4.83- singlet, -OCH2 (2 H)
^{13} C NMR(DMSO) 168.232 - Carbon atoms of oxadiazole ring (2 C)114.930-152.360 - Aromatic carbon atoms (12 C) 65.224 - OCH2 (1 C)48.245 - CH2 (1 C)

CHNS : Cal : C(61.43%) H(3.78%) N(23.88%) O(10.91%)Found: C(61.33%) H(3.73%) N(23.65%) O(10.85%)
MS:293.09: (M+)

Synthesis of BO3 (1-({5-[(2,4-dichlorophenoxy)methyl]-1,3,4-oxadiazol-2-yl}methyl)-1H-benzotriazole)

2-(1H-benzotriazol-1-yl)acetohydrazide (0.01 mole, 1.91 g) was refluxed with 2,4-dichlorophenoxy acetic acid (0.01mole, 2.2 g) for 6 hours in the presence ofphosphorous oxy chloride (10 ml). The hot mixture was poured into ice-cold water andbasified with 20% sodium bi carbonate solution. The solid mass was filtered, washed with water and recrystallized from ethanol.

IR(KBR cm^{-1}): 3050 cm-1(Aromatic C-H stretching), 2850 cm-1(CH2- stretching),2475 cm-1(N=N), 1600 cm-1(C=N), 1480, 1240 cm-1(Aromaticregion), 1125 cm-1(C-O-C of Oxadiazole ring), 640 cm-1(C-Cl)

^{1}HNMR(DMSO: 6.923-7.437 - multiplet, aromatic proton(7 H)5.554- singlet, -CH2 (2 H)4.80- singlet, -OCH2 (2 H)

^{13} C NMR(DMSO): 170.287 - Carbon atoms of oxadiazole ring (2 C)116.030-151.260 - Aromatic carbon atoms (12 C)65.249 - OCH2 (1 C)49.443 - CH2 (1 C)

CHNS Analysis: Cal :C(70.37%) H(4.43%) N(20.52%) O(4.69%)Found: C(70.25%) H(4.32%) N(20.49%) O(4.78%)

MS: 375.02(M+) 376.03(M+1), 377.05(M+2).

Synthesis of BO4 (4-{5-[(1H-benzotriazol-1-yl)methyl]-1,3,4-oxadiazol-2-yl} phenol)

2-(1H-benzotriazol-1-yl)acetohydrazide (0.01 mole, 1.91 g) was refluxed with phydroxy benzoic acid (0.01mole, 1.38 g) for 6 hours in the presence of phosphorousoxy chloride (10 ml). The hot mixture was poured into ice-cold water and basified with20% sodium bi carbonate solution. The solid mass was filtered, washed with water andrecrystallized from ethanol.

IR(KBR cm^{-1}): 3580 cm-1 (OH stretch), 3080 cm-1(Aromatic C-H stretching), 2850cm-1(CH2- stretching), 2350 cm-1(N=N), 1510 cm-1(C=N), 1280,1200 cm-1(Aromatic region), 1050 cm-1(C-O-C of Oxadiazole ring)

^{1}HNMR (DMSO): 7.024-7.547 - multiplet, aromatic proton(7 H)5.443- singlet, -CH2 (2 H)4.83- singlet, -OCH2 (2 H)

^{13} C NMR (DMSO) 159.287 - Carbon atoms of oxadiazole ring (2 C)117.930-158.260 - Aromatic carbon atoms (12 C)66.228 - OCH2 (1 C)49.443 - CH2 (1 C)

CHNS Analysis Cal :C(60.89%) H(3.91%) N(20.89%) O(14.31%) Found: C(60.37%) H(3.35%) N(20.65%) O(14.28%)

MS:335.10 (M+)

Synthesis of BO5 (1-({5-[2-phenylethenyl]-1,3,4-oxadiazol-2-yl}methyl)-1Hbenzotriazole)

2-(1H-benzotriazol-1-yl)acetohydrazide (0.01 mole, 1.91 g) was refluxed with Cinnamic acid (0.01mole, 1.48 g) for 6 hours in the presence of phosphorous oxychloride (10 ml). The hot mixture was poured into ice-cold water and basified with 20%sodium bi carbonate solution. The solid mass was filtered, washed with water and recrystallized from ethanol.

IR(KBR cm^{-1}):3150 cm-1(Aromatic C-H stretching), 2850 cm-1(CH2- stretching),2350 cm-1(N=N), 1650 cm-1(C=C stretch), 1640 cm-1(C=N), 1480,1240 cm-1(Aromatic region), 1050 cm-1(C-O-C of Oxadiazole ring)

^{1}HNMR(DMSO): 7.113-7.146 - multiplet, aromatic proton(7 H)5.452- singlet, -CH2 (2 H)4.81- singlet, -OCH2 (2 H)

^{13} C NMR (DMSO) 169.249 - Carbon atoms of oxadiazole ring (2 C)

115.530-150.260 - Aromatic carbon atoms (12 C)66.141 - OCH2 (1 C)48.843 - CH2 (1 C)

CHNS Analysis: Cal: C(67.32%) H(4.32%) N(23.09%) O(5.27%)

Found: C(67.28%) H(4.26%) N(23.25%) O(5.13%)

MS: (M+)

Synthesis of BO6 ({5-[(1H-benzotriazol-1-yl)methyl]-1,3,4-oxadiazol-2-yl}(phenyl)methanol)

2-(1H-benzotriazol-1-yl)acetohydrazide (0.01 mole, 1.91 g) was refluxed withmandelic acid (0.01mole, 1.52 g) for 6 hours in the presence of phosphorous oxychloride (10 ml). The hot mixture was poured into ice-cold water and basified with 20% sodium bi carbonate solution. The solid mass was filtered, washed with water and recrystallized from ethanol.

IR (KBR cm^{-1}) 3500 cm-1(OH stretch), 3180 cm-1(Aromatic C-H stretching), 2850cm-1(CH2- stretching), 1580 cm-1(C=N), 1500, 1240 cm-1(Aromaticregion), 1150 cm-1(C-O-C of Oxadiazole ring)

,**^{1}HNMR (DMSO)**: 7.026-7.527 - multiplet, aromatic proton(7 H)5.357- singlet, -CH2 (2 H)4.78- singlet, -OCH2 (2 H)

^{13} C NMR (DMSO) 170.328 - Carbon atoms of oxadiazole ring (2 C)115.930-151.860 - Aromatic carbon atoms (12 C)66.151 - OCH2 (1 C) 50.141 - CH2 (1 C)

CHNS : Cal C(65.44%) H(4.27%) N(25.44%) O(4.84%)Found: C(65.42%) H(4.28%) N(25.25%) O(4.67%)

MS: M+: 330.12 (M+)

Synthesis of BO7 (2-{5-[(1H-benzotriazol-1-yl) methyl]-1,3,4-oxadiazol-2-yl}phenol)

2-(1H-benzotriazol-1-yl)acetohydrazide (0.01 mole, 1.91 g) was refluxed with salicylic acid (0.01mole, 1.38 g) for 6 hours in the presence of phosphorous oxychloride (10 ml). The hot mixture was poured into ice-cold water and basified with 20%sodium bi carbonate solution. The solid mass was filtered, washed with water and recrystallized from ethanol.

IR(KBR cm^{-1}): 3450 cm-1(OH stretch), 3150 cm-1(Aromatic C-H stretching), 2810cm-1(CH2- stretching), 1550 cm-1(C=N), 1480, 1250 cm-1(Aromaticregion), 1160 cm-1(C-O-C of Oxadiazole ring)

^{1}HNMR (DMSO): 7.126-7.348 - multiplet, aromatic proton(7 H)5.254- singlet, -CH2 (2 H), 4.73- singlet, -OCH2 (2 H)

^{13} C NMR (DMSO) 169.589 - Carbon atoms of oxadiazole ring (2 C)112.839-152.370 - Aromatic carbon atoms (12 C)65.238 - OCH2 (1 C)49.543 - CH2 (1 C)

CHNS : Cal C(62.53%) H(4.26%) N(22.79%) O(10.41%) Found: C(62.45%) H(4.35%) N(22.35%) O(10.47%)

MS:307.10 (M+)

Synthesis of BO8 (1-({5-[(1H-indol-3-yl)methyl]-1,3,4-oxadiazol-2-yl}methyl)-1H-benzotriazole

2-(1H-benzotriazol-1-yl) acetohydrazide (0.01 mole, 1.91 g) was refluxed with Indole-3-acetic acid (0.01mole, 1.75 g) for 6 hours in the presence of phosphorous oxy chloride(10 ml). The hot mixture was

poured into ice-cold water and basified with 20% sodiumbi carbonate solution. The solid mass was filtered, washed with water and recrystallizedfrom ethanol.

IR(KBR cm^{-1}): 3350 cm-1(NH stretch), 3080 cm-1(Aromatic C-H stretching), 2825cm-1(CH2- stretching), 2350 cm-1(N=N), 1480 cm-1(C=N), 1500,1240 cm-1(Aromatic region), 1010 cm-1(C-O-C of Oxadiazole ring)

^{1}HNMR(DMSO): 7.012-8.108- multiplet, aromatic proton (9 H)5.703, 5.730- singlet, -CH2 (4 H)5.635,5.648- doublet, -NH- (1 H)

^{13}NMR(DMSO):169.249- Carbon atoms of oxadiazole ring(2 C)115.226-134.464 – Aromatic carbon atoms(14 C)59.433, 45.263- 2 CH2(2 C)

CHNS : Cal: C(61.43%) H(3.78%) N(23.88%) O(10.91%) Found: C(61.45%) H(3.26%) N(23.81%) O(10.67%)
MS:293.09(M+)

Anticancer Activity

All the synthesized compounds were screened for *in vitro* anticancer activity by MTT assay**.** MCF-7 cell line was used for *in vitro* cytotoxicity testing. [24]

RESULTS AND DISCUSSION

The synthesized compounds were characterized by IR, ^{1}H NMR, ^{13}CNMR, mass spectra and elemental analysis. The spectral values were in accordance to the strucutre of the synthesized compounds. The IR spectra of all the synthesized compounds contained a peak ranging from 2347-2360 cm-1 which is indicative of strechting vibrations between the two nitrogen atoms of benzimidazole ring. The ^{1}HNMR spectra of all compounds possessed peaks indicative of aromatic protons and -NH protons.Peaks at 169 and 170 of ^{13}CNMR spectra is indicative of the carbon atoms of the oxadiazole ring. The mass spectra of all the synthesized compounds produced M+ ion peak at the m/z value. For compounds like BO3, which had chlorine atoms in their strucuture M+2 and M+4 peaks were also observed in their mass spectras. All the synthesized compounds were tested for *in vitro* anticancer activity by MTT assay. Among the synthesized compounds, BO1 exhibited moderate anticancer activity. All the other compounds exhibited negligible anticancer activity. The experimental details of anticancer activites of all compounds are presented in table number 2.

CONCLUSION

Among the compounds synthesized BO1 exhibited moderate *in vitro* anticancer activity. All the other compounds exhibited negligible anticancer activity. The reason for moderate anticancer activity of BO1 can be attributed to the presence of 2,4-dichloro phenyl group attached to benzo triazole oxadiazole hybrid stucture through an oxy methylene bridge.Hence it can be concluded that phenyl rings possessing highly electron withdrawing groups when attached to benzotriazole-oxadiazole structure may act as scaffolds for anticancer activity. Hence detailed molecular level studies may be carried out to identify the potential binding sites in the receptor. Ultimately an effective anticancer lead may be presented to the scientific community in their fight against cancer.

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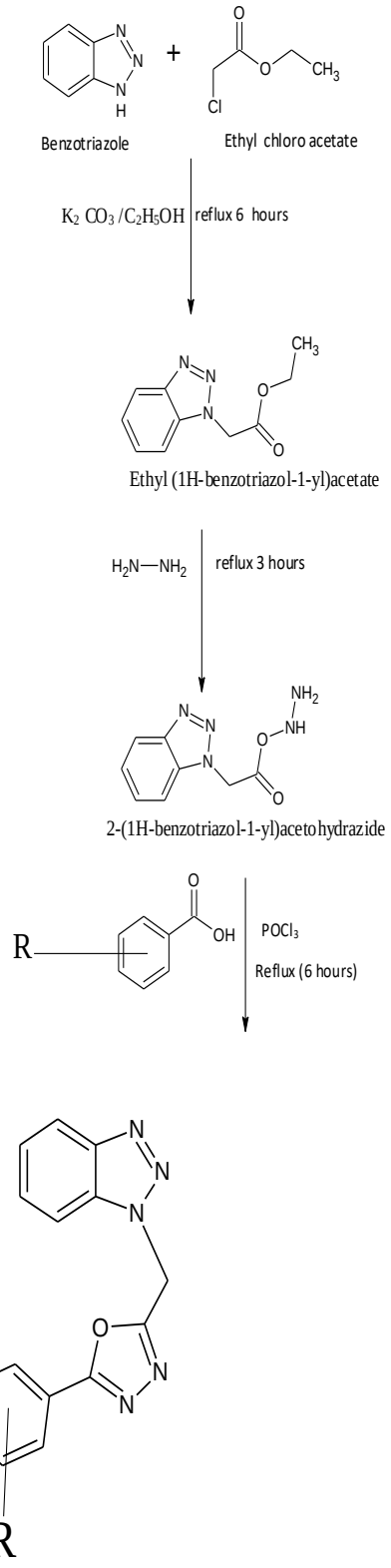

2-(substituted)-5-(benzotriazomethyl)-1,3,4-oxadiazole

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Table 1: Physical data of the synthesized derivatives

Compound code	Molecular formula	Colour & physical nature	Rf value (solvent system = Benzene : Methanol = 8:2)	M.P(°C)	Yield (%)
BO1	C20H15N5O	White powder	0.68	155-158	53
BO2	C17H13N5O3	Buff-yellow powder	0.65	117-120	55
BO3	C16H11Cl2N5O2	Off-white powder	0.72	115-118	62
BO4	C15H11N5O2	Buff yellow powder	0.69	116-119	48
BO5	C17H13N5O	Creamy-white powder	0.66	163-166	53
BO6	C16H13N5O2	Yellow powder	0.65	108-111	58
BO7	C15H11N5O2	Brown-yellow powder	0.49	110-113	64
BO8	C18H14N6O	Brown powder	0.67	195-198	55

Table Number:2 Anticancer activity of synthesized compounds

Sample Code	Sample Concentration	% viability	% cytotoxicity	IC50
BO1	50	86.84	13.16	110.12
	100	50.45	49.55	
	150	40.60	59.40	
	200	32.20	67.80	
	250	20.20	79.80	
BO2	50	81.45	18.55	146.15
	100	45.67	54.33	
	150	39.18	60.82	
	200	28.67	71.33	
	250	18.45	81.55	
BO3	50	87.98	12-02	150.37
	100	56.80	43.2	
	150	45.50	54.5	
	200	34.40	65.6	
	250	18.90	81.1	
BO4	50	85.65	14.34	160.35
	100	52.35	47.65	
	150	42.35	57.65	
	200	32.75	67.75	
	250	19.56	80.44	
BO5	50	75.25	24.75	163.23
	100	50.55	49.45	
	150	42.45	57.45	
	200	30.75	69.25	
	250	18.85	81.15	
BO6	50	83.45	16.55	167.24
	100	51.65	48.35	
	150	40.55	59.45	
	200	32.35	67.65	
	250	17.35	82.65	
BO7	50	80.15	19.85	175.65
	100	52.35	47.65	

	150	39.70	60.30	
	200	27.45	72.55	
	250	17.65	82.35	
BO8	50	88.80	11.20	178.45
	100	49.45	50.55	
	150	40.15	59.85	
	200	28.35	71.65	
	250	18.45	81.55	

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Conflict Of Interest

The authors declare no conflict of interest.

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