*Available online at* www.joac.info

ISSN: 2278-1862

**Journal of Applicable Chemistry**

**2014, 3 (6): 2573-2585**

(International Peer Reviewed Journal)

# Synthesis of Novel Potential DNA Cross Linking New Anti Neoplastic Alkylating Agents

**Sreedhar Maroju, P.Naveen Kumar, Ravichander Maroju, Ganapathy velupula, Abdul Haq and T.Ravi Prasad***

*Department of Chemistry, Rayalaseema University, Kurnool, Andhra Pradesh, **INDIA**

Email: raviprasad1947@gmail.com

Accepted on 16th November 2014

## ABSTRACT

*Twenty compounds of novel potential DNA cross linking new anti neoplastic alkylating agents (S)-5-((bis(2-chloroethyl)amino)methyl)-3-(3,4-substituted phenyl)oxazolidin-2-ones(**8a-t**) have been synthesized by the reaction of 5-(aminomethyl)-3-(3,4-substitutedphenyl)-oxazolidin-2-ones (**7a-t**) with1,2-dichloroethane inpresence of triethylamine in methylenedichloride under reflux.*

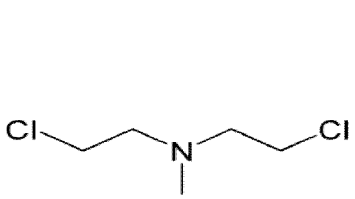
**Keywords:** Synthesis, DNA, Cross linking anti-neoplastics.

## INTRODUCTION

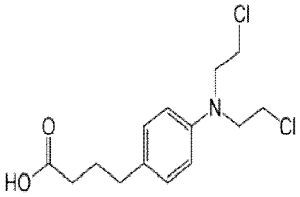
In view of sufficient scientific back ground, Cancer is a major human health problem worldwide and is the second leading cause of death in United States [1] Chemotherapy, the use of toxic drugs to kill cancer cells, is often used in combination with other therapies to destroy cancer cells and shrink the tumor. Alkylating agents are commonly used in cancer treatment. They work by binding to DNA [2] and interfering with normal DNA processing within the cancer cell, which prevents the cell from making the proteins it needs to grow and survive. After exposure to alkylation agents, the cancer cell becomes dysfunctional and dies.

There are a number of alkylation agents on the market that are targeted to treat a number of types of cancer.

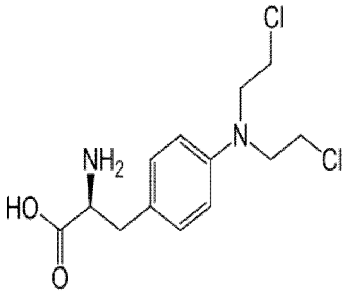
**Oxazolidin-2-ones:** Oxazolidinone derivatives showed very promising activities like monoamine oxidase A[3], cancer[4], HIV[5] and other interesting medicinal properties like aldose, reductase, inhibitors[6], metabotropic[7], and glutamate receptor antagonists[8]. These are new class of synthetic antibacterial agents active against multiple-resistant gram-positive pathogens, including methicillin-resistant Staphylococcus aureus (MRSA), penicillin-resistant streptococci, and vancomycin-resistant enterococci [9].There are number of oxazolidinones in the market some of them are as follows.



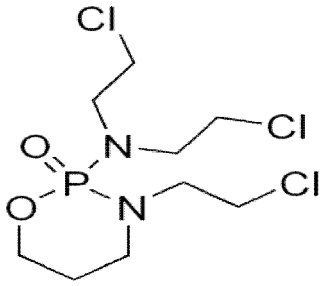
Mechlorethamine



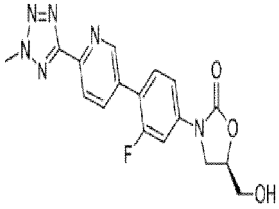
Chlorambucil



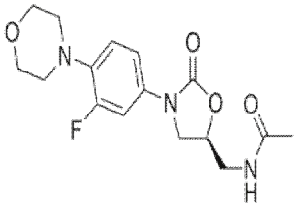
Melphalan



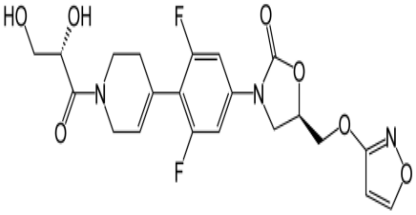
Trofosfamide



Torezolid



Linezolid

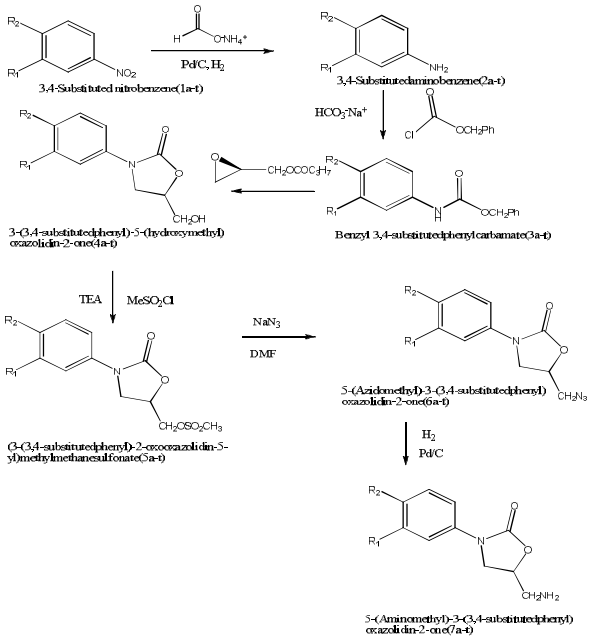


Posizolid

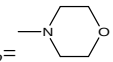
The biological importance and considerable therapeutic potential of alkylating agents and oxazolidine moieties generate considerable interest to us in designing the synthesis of novel potential DNA cross linking new anti neoplastic alkylating agents (S)-5-((bis(2-chloroethyl)amino)methyl)-3-(3,4-substituted phenyl)oxazolidin-2-ones and also study the anti neoplastic activity of these derivatives.

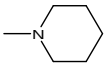
## MATERIALS AND METHODS

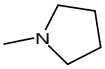
The synthesis of novel potential DNA cross linking new anti neoplastic alkylating agents (S)-5-((bis(2-chloroethyl)amino)methyl)-3-(3,4-substituted phenyl)oxazolidin-2-ones is divided in to two schemes, they are as follows.




**Scheme 1**

7a: $R_1$=-F, $R_2$= 

7b: $R_1$=F, R2= 

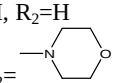
7c: $R_1$=F, $R_2$= 

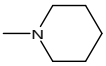
7d: $R_1$=F, $R_2$=-$NO_2$

7e: $R_1$=F, $R_2$=-$CH_3$

7f: $R_1$=H, $R_2$=H

7g: $R_1$= -$CH_3$, $R_2$=H

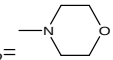
7h: $R_1$=-$CH_3$, $R_2$= 

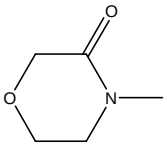
7i: $R_1$=- $CH_3$, $R_2$= 

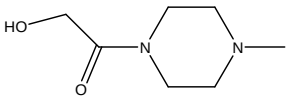
7j: $R_1$=H, $R_2$=-Cl

7k:$R_1$=H, $R_2$=-$OCH_3$,

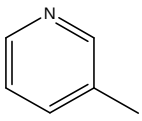
7l: $R_1$=F, $R_2$=F

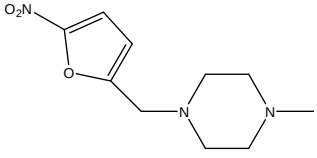
7m: $R_1$=Br, $R_2$= 

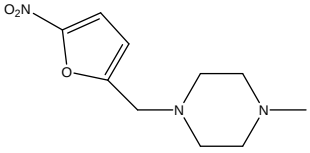
7n: $R_1$=F, $R_2$= 

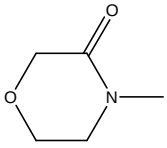
7o: $R_1$=F, $R_2$= 

7p: $R_1$=Br, $R_2$=Br

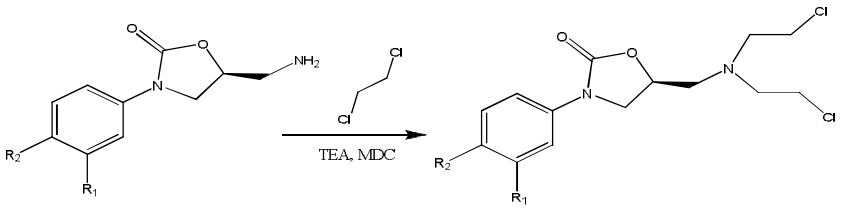
7q: $R_1$=H, $R_2$= 

7r: $R_1$=H, $R_2$= 

7s: $R_1$=F, $R_2$= 

7t: $R_1$=H, $R_2$= 

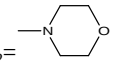
On hydrogenation of 3,4-substituted nitrobenzenes(**1a-t**) with ammonium formate in presence of Pd/C yields 3,4-substituted aminobenzenes(**2a-t**), which on reaction reaction with benzylchloroformate in presence of sodium bicarbonate to give benzyl 3,4-subtitutedphenylcarbamate(**3a-t**). The compound(**3a-t**) on reaction with ((R)-oxiran-2-yl)methylbutyrate to yields 3-(3,4-substitutedphenyl)-5-(hydroxymethyl)oxazolidin-2-ones(**4a-t**). The compounds(**4a-t)** were converted in to (3-(3,4-substituted phenyl)-2-oxazolidin-5yl)methylmethanesulfonate(**5a-t**) by reacting with methanesulfonyl chloride in presence of triethyl amine. The compounds (**5a-t**) undergoes substitution with sodium azide yields 5-(azidomethyl)-3-(3,4-substituted phenyl)-oxazolidin-2-ones(**6a-t**), which were undergoes hydrogenation in presence of palladium on carbon yields 5-(aminomethyl)-3-(3,4-substitutedphenyl)-oxazolidin-2-ones(**7a-t**).

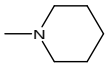


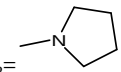

(S)-5-(Aminomethyl)-3-(3,4-substituted phenyl)oxazolidin-2-one(**7a-t**)

(S)-5-((Bis(2chloroethyl)amino) methyl)-3-(substituted phenyl) oxazolidin-2-one(**8a-t**)

**Scheme-II**

8a: $R_1$=-F, $R_2$= 

8b: $R_1$=F, R2= 

8c: $R_1$=F, $R_2$= 

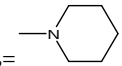
8d: $R_1$=F, R2=-$NO_2$

8e: $R_1$=F, $R_2$=-$CH_3$

8f: $R_1$=H, R2=H

8g: $R_1$= -$CH_3$, R2=H

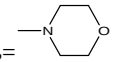
8h: $R_1$=-$CH_3$, $R_2$= 

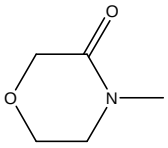
8i: $R_1$=- $CH_3$, $R_2$= 

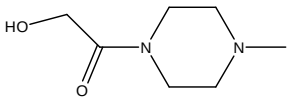
8j: $R_1$=H, $R_2$=-Cl

8k:$R_1$=H, $R_2$=-$OCH_3$,

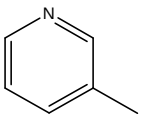
8l: $R_1$=F, $R_2$=F

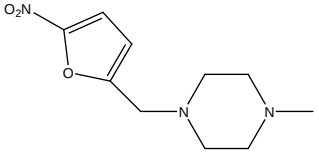
8m: $R_1$=Br, $R_2$= 

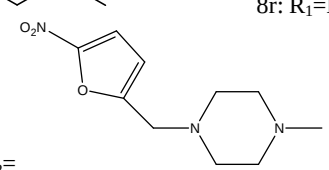
8n: $R_1$=F, $R_2$= 

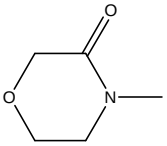
8o: $R_1$=F, $R_2$= 

8p: $R_1$=Br, $R_2$=Br

8q: $R_1$=H, $R_2$= 

8r: $R_1$=H, $R_2$= 

8s: $R_1$=F, $R_2$= 

8t: $R_1$=H, $R_2$= 

The reaction of (S)-(aminomethyl)-3-(substituted phenyl)oxazolidin-2-one(**1a-t)** with 2m.eq. of 1,2-dichloroethane in methylenedichloride in presence of triethylamine at 25-30$^{o}$C to yield (S)-5-((bis(2-chloroethyl)amino)methyl)-3-(substituted phenyl)oxazolidin-2-ones(**8a-t**)

**Experimental Procedure:** All the melting points are uncorrected. The purity was checked by thin layer chromatography with silica gel 60 GF254 E.Merck precoated plates (0.25 mm) was visualized using UV. 0.1 for flash chromatography on silica gel (particle size 100-200 mesh) and characterized by spectral studies. The IR spectra were recorded on shimadzu FTIR model 8010 spectrophotometer and are given in $cm^{-1}$ in KBr. The $^{1}$HNMR & $^{13}$CNMRspectra were recorded on Bruker AM-400 NMR spectrometers in deuterated chloroform and deuterated DMSO. The chemical shifts are reported in δ (ppm) relative to tetramethylsilane as internal standard. Mass spectra analyses performed with an Agilent 6400 Series equipped with an electrospray ionization source (capillary voltage at 4000V, nebulizing gas temperature at 300 °C, nebulizing gas flow at 12 L $min^{-1}$).

**General procedure for preparation of 3,4-disubstituted aniline.(2a-t):** To a solution of 135.7mmol of 3,4-disubstituted nitrobenzene (1a-u) in 80mL of tetrahydrofuran and320mL of methanol (320 mL) was added 540.2mmol of ammonium formate. The flask was alternately evacuated and filled with nitrogen and cooled to 0 °C; then 10%palladium on carbon was added (0.9-1.25g), and the system was again evacuated and filled with nitrogen. After stirring for 2h, the reaction mixture was filtered through a plug of diatomaceous earth, which was then washed with tetrahydrofuran (30mL) and ethyl acetate (60mL). The volume of the solution was reduced to 300mL; then water (250mL) and ethyl acetate (300mL) were added and the phases separated, and the aqueous portion was extracted with ethyl acetate (1X200 mL, 2X100mL). The combined organic portions were washed with saturated sodium chloride (150mL), dried (MgSO4),and evaporated to give 29-32g of crude **2a-t** as a yellow solid which was immediately taken on "as is" in the next reaction.

**General procedure for Preparation of N-Carbobenzoxy-3, 4-disubstitutedaniline (3a-t):** To a solution of **2a-u** (135.7mmol) in acetone (500mL) and water (250mL) at 0 °C were added 2.5meq of sodium bicarbonate and then 1.06 meq of benzyl chloroformate over 6-10 min *via* syringe. The mixture was stirred overnight and then poured onto 500mL of ice and1.2 L of water and the solid filtered and washed thoroughly with water (3X250mL) to give (90-93%) of **3a-t** as a cream-colored solid, which was recrystallized from acetone and water to give 31-33 g (66-70%)

**General procedure for preparation of (*R*)-[*N*-3-(3, 4-disubstitutedphenyl)-2-oxo-5-oxazolidinyl] methanol (4a-t):** To a solution of 123.0mmol of **3a-u** in tetrahydrofuran (500mL) under nitrogen at-78 °C was added *n*-butyl lithium (1.6 M in hexane,1m.eq) over 20 min *via* syringe. The solution was stirred at -78 °C for 35 min; then a tetrahydrofuran solution (25mL) of (*R*)-glycidyl butyrate (1.02m.eq) was added in a drop wise fashion *via* addition funnel, over 30 min. After stirring at -78 °C for 1 h, the bath was removed and the reaction mixture was stirred at room temperature over night. The reaction was then quenched with 20mL of saturated ammonium chloride, ethyl acetate (300mL), saturated ammonium chloride (400mL), and water (300mL) were added, the phases were separated, and the aqueous portion was extracted with ethyl acetate (3X300mL). The combined organic portions were washed with saturated sodium chloride, dried (MgSO4), and evaporated to give 4a-u (55-65 g) as a yellow solid; this was recrystallized from ethyl acetate and hexanes to give 28-32g (78-85%)

**General procedure for preparation of (*R*)-[*N*-3-(3, 4-disubstitutedphenyl)-2-oxo-5 oxazolidinyl] methyl Methanesulfonate(5a-t) :** To a solution of 101.9mmol of **4a-u** and 28.0mL (200.9mmol) of triethylamine in 600mL of methylene chloride at 0 °C was added 11.0mL (0.8m.eq) of methanesulfonyl chloride over15 min. After 20 min, the mixture was filtered, and the white solid was washed with water (3X100mL) and dried in a vacuum oven to give 25-28 g of **5a-u** as a white solid. The layers of the filtrate were separated, and the aqueous portion was extracted with methylene chloride (3X100mL). The

combined organic portions were dried (MgSO4) and evaporated to give a tan solid (12-15 g). Each lot was recrystallized from acetonitrile and water to give a total of 32-35 g of **5a-t** as an off-white solid. The mesylate was used "as is" in the next reaction.

**General procedure for preparation of (*R*)-[*N*-3-(3,4-disubstitutedphenyl)-2-oxo-5-oxazolidinylazide (6a-t):** A mixture of 53.06 mmol of **5a-u** and 5.5m.eq of sodium azide in 400mL of dimethylformamide was heated at 75 °C for 16 h, at which time, after cooling, water (750mL) and ethyl acetate (300mL) were added. The phases were separated, and the aqueous portion was extracted with ethyl acetate (3X200mL).The combined organic portions were dried (MgSO4) and evaporated to give 16-20gm g of **6a-u**, which was not purified

**General procedure for preparation of (S)-5-(aminomethyl)-3-(3,4-disubstitutedphenyl)-oxazolidin-2-one (7a-t):** To a solution of 49.16mmol of azide **6a-u** in 300mL of ethyl acetate was added 0.180 -0.330g of 10% palladium on carbon, and the system was alternately evacuated and filled with nitrogen; then hydrogen was introduced *via* a balloon system, with three cycles of evacuation and filling from the balloon. The mixture was stirred overnight, and then additional 0.238 g of palladium black and hydrogen were added; after 6 h, 0.436-0.540 g of 10%palladium on carbon was added with more hydrogen and left to stir overnight. The reaction mixture was then evacuated and flushed with nitrogen and filtered the catalyst. the reaction mixture was concentrated under reduced pressure and the resulting solid was purified in ethyl acetate(100ml) yield:80-85%

**7a) 5-(aminomethyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.05(m,1H);2.3(m,1H);2.5(m,1H);2.75(m,1H);3.15(m,4H);3.4(m,1H);3.65-3.7(m,5H);
5.1(NH2);6.35(d,1H); 6.8(d,1H);7.05(d,1H).
$^{13}$CNMR: 155.5,153,133,130,128,116,111,87,66.5,53.5,48,44,
CHN; Cal: 56.94,6.14,14.23 Found: 57.00; 6.29; 14.02;
FTIR: 3397, 3027, 2953, 2827, 1738, 1627, 1237, 1049,
Mass: 296.1(M+1)

**7b) 5-(aminomethyl)-3-(3-fluoro-4-(piperidin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:1.5(m,1H);1.6(m,2H);2.05(m,1H);2.3(m,1H);2.35(m,1H);2.5(m,1H)2.75(m,1M)3.1(m,4H);3.4(m,
1H)3.65(m,1H)5.1(NH2);6.35(d,1H)7.05(d,1H)
$^{13}$CNMR;155.5,153,133,130,128,116,111,87,54.4,48,44,25.5,24.5.
CHN;Cal: 61.42,6.87,14.32. Found: 61.30; 6.9; 14.41
FTIR: 3395, 3025, 2950, 2829, 1740, 1630, 1234, 1050
Mass: 294.1(M+1)

**7c) 5-(aminomethyl)-3-(3-fluoro-4-(pyrrolidin-1-yl)phenyl)oxazolidin-2-one:**
$^{1}$HNMR:1.9(m,4H);2.75(m,1H)3.0to3.1(m,3H)3.35(m,1H)3.45(m,4H);6.7(d,1H);6.9(d,1H);7.55(d,1H)
$^{13}$CNMR :NMR:155.5,153,133,130,128,116,111,87,54.5,48,44,25.5.
CHN: C-60.2; H-6.5; N-15.04 Found: 60.10; 6.55; 15.09
FTIR: 3405, 3030, 2955, 2830, 1743, 1627, 1235, 1045.
Mass: 280.1(M+1)

**7d) 5-(aminomethyl)-3-(3-fluoro-4-nitrophenyl)oxazolidin-2-one**
$^{1}$HNMR: 2.75(m,1H); 3.0(m,1H), 3.1(m,1H),3.35(m,1H),4.8(m,1H),
5.1NH2),7.15(d,1H),8.0(d,1H),8.2(d,1H)
$^{13}$CNMR: 155.5,153,147,132.5,126.5,125.5,87,48,44.
CHN: 47.06,3.95,16.47 Found: 47.10; 4.0; 16.38
FTIR: 3390, 3023, 2951, 2834, 1749, 1630, 1543, 1328, 1230, 1052.
Mass: 256.0(M+1)

**7e) 5-(aminomethyl)-3-(3-fluoro-4-methylphenyl)oxazolidin-2-one**
$^{1}$HNMR:2.35(s,3H);2.75(m,1H);3.0(m,1H);3.1(m,1H);3.35(m.1H);4.8(m,1H)5.1(NH2);7.1(d,1H);7.2(d,1H);7.65(d,1H).
$^{13}$CNMR; 160,153,137.5,131,129,115,110,87,48,44,14.5.
CHN: 58.92,5.84,12.49; Found: 58.81; 5.9; 12.54
FTIR: 3400, 2960, 2829, 1741, 1631, 1450, 1238, 1049.
Mass: 225.1(M+1)

**7f) 5-(aminomethyl)-3-phenyloxazolidin-2-one**
$^{1}$HNMR:2.75(m,1H);3.0(m,1H);3.1(m,1H);3.35(m,1H);4.8(m,1H)5.1(NH2);7.2(d,1H);7.45(dd,sH);7.8(dd,2H).
$^{13}$CNMR;153,139,129,128,127.5,87,48,44.
CHN: Cal: 62.49; 6.29; 14.57. Found: 62.35; 6.37; 14.6
FTIR: 3402, 2951, 2828, 1740, 1629, 1452, 1238, 1044.
Mass: 193.0(M+1)

**7g) 5-(aminomethyl)-3-m-tolyloxazolidin-2-one**
$^{1}$HNMR:2.35(s,3H);2.75(m,1H);3.0(m,1H);3.1(m,1h);3.35(m,1H);4.8(m,1H);5.1(NH2);7.0(d,1H);7.3(d,1H);7.6(d,1H);7.75(d,1H)
$^{13}$CNMR:153,139,129,124.5,121.5,87,48,44,21.5
CHN:64.06; 6.84; 13.58 Found: 63.94; 6.9; 13.64
FTIR: 3398, 2953, 2827, 1738, 1627, 1450, 1240, 1045
Mass: 207.1(M+1)

**7h) 5-(aminomethyl)-3-(3-methyl-4-morpholinophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.1(s,3H);2.75(m,1h);3.1(m,1H)3.2(t,4H);3.35(m,1H);3.65(t,4H);4.8(m,1H)5.1(NH2);;6.6(d,1H);6.95(d,1H);7.55(d,1H)
$^{13}$CNMR;153,146.5,129.5,128.5,127,122,87,66.5,53.5,48,44,18.
CHN; 61.84; 7.27; 14.42. Found: 61.71; 7.35; 14.47
FTIR:3406, 258, 2824, 1734, 1625, 1450, 1237, 1045.
Mass: 291.1(M+1)

**7i) 5-(aminomethyl)-3-(3-methyl-4-(piperidin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR: 1.55(m,4H);1.6(m,2H),2.1(s,3H);2.75(m,1H),3.0(m,1H0;3.1(m,5H);3.5-4.0(m,5H);5.1(NH2);6.6(d,1H);6.95(d,1H);7.55(d,1H)
$^{13}$CNMR;153,146.5,129.5,128.5,127,122,114.5,87,55,48,44,25,24.5.
CHN; 66.41; 8.01; 14.52 Found 66.50; 8.1; 14.34.
FTIR: 3409, 2948, 2820, 1730, 1625, 1445, 1230, 1049
Mass: 289.1(M+1)

**7j) 5-(aminomethyl)-3-(4-chlorophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.75(m,1H);3.0(m,1H);3.1(m,1H);3.35(m,1H)4.8(m,1H)5.1(NH2);7.47(dd,2H);7.9(ss,2H)
$^{13}$CNMR;153,137,133.5,129,125.5,87,48,44.
CHN;52.99; 4.89; 12.36 Found: 52.85; 4.98;12.41
FTIR:3405, 2958, 2825, 1742, 1628, 1230, 1040.
Mass: 228.0(M+1)

**7k) 5-(aminomethyl)-3-(4-methoxyphenyl)oxazolidin-2-one**
1HNMR:2.75(m,1H);3.0(m,1H);3.1(m,1H);3.35(m,1H);3.85(s,3H);4.8(m,1H);5.1(NH2);7.0(dd,2H);7.95(dd,2H)
$^{13}$CNMR; 159, 153, 131.5,122.5,114.5,87,56,48,44

CHN; 59.45; 6.35; 12.6 Found: 59.34; 6.43; 12.63
FTIR: 3395, 2946, 2825, 1740, 1624, 1230, 1044, 1010.
Mass: 223.1(M+1)

**7l) 5-(aminomethyl)-3-(3,4-difluorophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.75(m,1H);3.0(m,1H);3.1(m,1H);3.2(m,4H);3.35(m,1H);;4.8(m,1H);5.1(NH2);7.6(d,1H);7.55(d, 1H);7.75(d,1H).
$^{13}$CNMR :153,147,145,136.5,119,115,112,87,48,44.
CHN; 52.63; 4.42; 16.65. Found: 52.50; 4.5; 16.7
FTIR: 3402, 2958, 2820, 1736, 1630, 1235, 1040
Mass: 229.0(M+1)

**7m) 5-(aminomethyl)-3-(3-bromo-4-morpholinophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.759m,1H);3.0(m,1H);3.1(m,1H);3.2(m,4H)3.35(m,1H);3.65(t,4H);4.8(m,1H);5.1(NH2);6.65(d, 1H);7.05(d,1H);7.7(d,1H);
$^{13}$CNMR;153,147,131.5,131,121.5,116.5,115.5,87,66.5,52.5,48,44.
CHN; 47.20, 5.09,11.8. Found: 47.00; 5.2; 11.89
FTIR: 3398, 2958, 2828, 1742, 1627, 1237, 1050, 1045
Mass: 357.0(M+2); 358.0(M+4).

**7n) 4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)morpholin-3-one**
$^{1}$HNMR**;**2.759m,1H);3.0(m,1H);3.35(m,1H);3.5(t,2H);3.55(t,2H);4.3(s,2H);4.8(m,1H);5.1(NH2);7.15(d,1 H);7.3(d,1H);7.9(d,1H)
$^{13}$CNMR;164.5,153,139,137,130.5,124,123,121,87,73.5,66,54.5,48,44
CHN; 45.42; 4.36; 11.35 Found: 45.23; 4.40; 11.5
FTIR: 3400, 2950, 2827, 1738, 1627, 1237, 1050, 1044,
Mass: 310.1(M+1)

**7o) 5-(aminomethyl)-3-(3-fluoro-4-(4-(2-hydroxyacetyl)piperazin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:2.75(m,1H);3.0(m,1H);3.1(m,1H);3.35(m,5H);3.55(t,4H);3.65((OH);4.4(s,2H);4.8(,.1H)6.7(d,1H) ;6.9(d,1H);7.55(d,1H)
$^{13}$CNMR;166.5,155.5,153,133,130,128,116,111,87,59.5,53.5,48,46.5,44
CHN 54.54; 6.01; 15.90 Found: 54.35; 6.10; 16.0
FTIR: 3401, 3350, 2958, 2823, 1740, 1680, 1627, 1237, 1045.
Mass: 353.1(M+1)

**7p) 5-(aminomethyl)-3-(3,4-dibromophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.75(m,1H);3.0(m,1H);3.1(m,1H);3.35(m,1H);4.8(m,1H)5.1(NH2);7.45(d,1H);7.65(d,1H);7.75(d, 1H);
$^{13}$CNMR;153,140.5,135.5,134,126,123,120,87,48,44.
CHN: 34.32; 2.88; 8.00. Found: 34.08; 2.97; 8.15
FTIR: 3405, 2958, 2821, 1731, 1620, 1233, 1040.
Mass: 349.9(M+2); 351.9(M+4).

**7q)** 5-(aminomethyl)-3-(4-(pyridin-3-yl)phenyl)oxazolidin-2-one
$^{1}$HNMR :2.75(m,1H);3.0(m,1H);3.1(m,1H);3.35(m,1H);4.8(m,1H);5.1(NH2);7
55(t,1H);7.5(d,2H);7.85(d,2H);8.7(d,1H);8.4(d,1H);9.2(s,1H).
$^{13}$CNMR;153,149,148,139,134,133,132,127.5,124,122,87,48,44.
CHN; 66.90; 5.61; 15.60. Found: 66.78; 5.73; 15.60
FTIR: 3390, 2948, 2831, 1748, 1629, 1235, 1045
Mass: 270.1(M+1)

**7r) 5-(aminomethyl)-3-(4-(4-((5-nitrofuran-2-yl)methyl)piperazin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:2.6(t,4H);2.75(m,1H);3.0(m,1H);3.1(m,1H);3.2(t.2H);3.5(m,1H);3.75(s.2H);4.8(m,1H);5.1(NH2);5.5(s,2H);6.0(d,1H);6.15(d,1H);6.9(d,2H);7.1(d,2H)
$^{13}$CNMR;15314.85,147,145,132.5,128.5,113,107.5,87,76.5,57,52,51.5,48,44.
CHN; 57.82; 6.07; 16.86. Found: 57.68; 6.15; 16.92
FTIR: 3395, 2958, 2834, 1742, 1630, 1540, 1335, 1238, 1050.
Mass: 402.1(M+1).

**7s)5-(aminomethyl)-3-(3-fluoro-4-(4-((5-nitrofuran-2-yl)methyl)piperazin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:2.62(t,4H);2.75(m,1H);3.0(m,1H);3.1(m,1H);3.35(m,1H);3.45(t,4H);3.75(m,1H);4.8(m,1H);5.1(NH2);5.5(s,2H);6.0(d,1H);6.15(d,1H);6.7(d,1H);6.9(d,1H)7.55(d,1H)
$^{13}$CNMR;155.5,153,148.5,147,133,130,128,116,111,107,87,76.5,57,52,51.5,48,44
CHN; 55.42; 5.58; 16.16. Found: 55.23; 5.69; 16.26
FTIR: 3402, 2950, 2836, 1743, 1627, 1549, 1328, 1237, 1049.
Mass: 420.1(M+1)

**7t) 4-(4-(5-(aminomethyl)-2-oxooxazolidin-3-yl)phenyl)morpholin-3-one**
$^{1}$HNMR:2.75(m,1H);3.0(m,1H);3.1(m,1H)3.35(m,1H);3.5(t,2H);3.55(t,2H);4.3(s,2H);4.8(m,1H);5.1(NH2);6.75(d,2H);7.35(d,2H)
$^{13}$CNMR;164.5,153,135,134.5,131.5,87,73.5,66,48,44.
CHN; 57.70; 5.9; 14.40.Found: 57.58; 6.08; 14.36
FTIR: 3410, 2950, 2835, 1743, 1682, 1634, 1245, 1040.
Mass: 292.1(M+1)

**General procedure for preparation of S)-5-((bis(2-chloroethyl)amino)methyl)-3-(substituted phenyl) oxazolidin-2-ones(8a-t):** To a solution of 50 mmol of **7a-t** in 150 mL of dichloromethane(MDC) was added 2.5 m.eq of 1,2-dichloroethane and 4 m. eq of triethyl amine at 5-10$^{o}$C. Raise the temperature to 25-30$^{o}$C and stir the mixture for 25-36hrs. After completion of reaction water is added to the mixture and stir for three minutes. Separate the organic layer and dried over sodium sulfate. Concetrate MDC completely under vacuum. Add isopropyl alcohol to the residue and stir for 3-5 hrs. Filter the solid and wash it with isopropyl alcohol. The yield of the product (8a-t) is 65-73%.

(**8a**): **5-((bis(2-chloroethyl)amino)methyl)-3-(3-fluoro-4-morpholinophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.45(m,1H);2.65(t,4H);2.70(m,1H);3.05(m,1H);3.15(t,4H);3.30(m,1H);3.5(t,4H);3.65(t,4H);4.80(m,1H);6.75(dd,1H);6.9(d,1H);7.55(d,1H).
$^{13}$CNMR:153,136,133,130,128,116,111,82.5,66.5,58.5,54.5,53.5,49,42.5.
CHN: Cal: 51.44,5.76,10.00.Found: 51.64; 5.66; 10.1
FTIR: 3027, 2958, 2825, 1740, 1630, 1240, 1050.
Mass: 420.1(M+1), 421.1(M+2)

(**8b**): **5-((bis(2-chloroethyl)amino)methyl)-3-(3-fluoro-4-(piperidin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:1.5to1.6(m,6H);2.45(m,1H);2.65(t,4H);2.70(m,1H);3.05to3.35(m,5H);3.5(t,4H);4.80(m,1H);6.75(dd,1H);6.9(d,1H);7.55(d,1H).
$^{13}$C NMR:153,136,133,130,128,116,111,82.5,59,55,49,42.5,25.5,24.5.
CHN: Cal: 54.55,6.26,10.04. Found: 54.65; 6.16; 10.1
FTIR: 3028, 2954, 2826, 1738, 1625, 1238, 1047.
Mass: 418.1(M+1); 419.1(M+2)

(**8c**) **5-((bis(2-chloroethyl)amino)methyl)-3-(3-fluoro-4-(pyrrolidin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:1.90(t,4H);2.45(m,1H);2.65(t,4H);2.75(m,1H);3.05(m,1H);3.30(m,1H);3.44-3.5(m,8H);4.80(m,1H);6.7(dd,1H);6.9(d,1H);7.55(d,1H).
$^{13}$C NMR:153,136,133,130,128,116,111,82.5,54.5,49,42.5,25.5.
CHN; Calc: 53.5, 6.0, 10.39. Found: 53.6, 6.05; 10.24
FTIR: 3025, 2955, 2820, 1732, 1629, 1240, 1042.
Mass: 404.1(M+1); 405.1(M+2)

(**8d): 5-((bis(2-chloroethyl)amino)methyl)-3-(3-fluoro-4-nitrophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.5(m,1H);2.65(t,4H);2.75(m,1H)3.1(m,1H)3.35(m,1H);3.5(t,4H);4.8 (m,1H);7.15(d,1H);8.0(d,1H);8.22(dd,1H).
$^{13}$C NMR:153,147,136,133,127,126,111,83,59,54.5,49,42.5.
CHN: Calc: 44.23; 4.24; 11.05; . Found44.32; 4.27; 10.93
FTIR: 3035, 2960, 2823, 1735, 1622, 1541, 1322, 1234, 1055.
Mass: 380.0(M+1); 381.0(M+2)

(**8e): 5-((bis(2-chloroethyl)amino)methyl)-3-(3-fluoro-4-methylphenyl)oxazolidin-2-one**
$^{1}$HNMR:2.35(s,3H);2.45(m,1H);2.6(t,4H);2.7(m,1H);3.05(m,1H);3.30(m,1H);3.45 (t,4H);4.85(m,1H);7.10(d,1H);7.20(dd,1H)7.63(d,1H).
$^{13}$C NMR:160,153,138,131,129,115,110,83,59,55,49,42.5,14.5.
CHN: Cal: 51.59; 5.48; 8.02; Found: 51.65; 5.38; 8.06
FTIR: 3021, 2958, 2818, 1734, 1627, 1450, 1233, 1042.
Mass: 349.0(M+1):350.0(M+2).

(**8f**): **5-((bis(2-chloroethyl)amino)methyl)-3-phenyloxazolidin-2-one**
$^{1}$HNMR:2.45(m,1H);2.65(t,4H);2.75(m,1H);3.1(m,1H);3.35(m,1H);3.5(t,4H);4.80(m,1H) 7.2(t,1H);7.45(t,1H);7.8(t,2H)
$^{13}$C NMR: 153,140,129,128,127.5, 83,59,49,43.
CHN: Cal: 53.01; 5.72; 8.83 Found: 52.89; 5.8; 8.87.
FTIR: 3030, 2951, 2821, 1743, 1624, 1238, 1047.
Mass: 317.0(M+1):318.0(M+2)

(**8g**): **5-((bis(2-chloroethyl)amino)methyl)-3-m-tolyloxazolidin-2-one**
$^{1}$HNMR:2.35(s,3H);2.5(m,1H);2.65(t,4H);2.75(m,1H);3.1(m,1H);3.35(m,1H);3.5(t,4H) 4.8(m,1H);6.7(d,1H);7.3(dd,1H);7.6(dd,1H)7.7(dd,1H).
$^{13}$C NMR: 153, 139, 129, 124, 121, 83, 59,55,49,43.
CHN: Cal: 54.39; 6.09; 8.46. Found: 54.25; 6.15; 8.54
FTIR: 3033, 2959, 2823, 1738, 1624, 1452, 1237, 1044.
Mass: 331.0(M+1);332.0(M+2)

(**8h): morpholinophenyl)oxazolidin-2-one5-((bis(2-chloroethyl)amino)methyl)-3-(3-methyl-4-**
$^{1}$HNMR:2.1(s,3H);2.5(m,1H);2.65(t,4H);2.7(m,1H);3.1(m,1H);3.2(t,4H);3.35(m,1H); 3.5 (t,4H);3.65(t,4H);4.8(m,1H);6.6(d,1H);6.9(d,1H);7.5(d,1H)
$^{13}$C NMR:153,147,130,128.5,127,122,114.5,83,66.5,59,54,49,42.5,18.
CHN Cal: 54.81; 6.54; 10.09. Found: 54.70; 6.6; 10.14
FTIR: 3035, 2956, 2824, 1732, 1623, 1455, 1240, 1045
Mass: 415.1(M+1):416.1(M+2)

(**8i**): **5-((bis(2-chloroethyl)amino)methyl)-3-(3-methyl-4-(piperidin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:1.5(m,4H);1.6(m,1H);2.1(s,3H);2.5(m,1H);2.65(t,4H);2.7(m,1H);3.1(m,5H);3.3 (m,1H);3.5(t,4H);4.8(m,1H);6.6(d,1H);6.9(d,1H);7.55(d,1H).

$^{13}$C NMR: 153, 147, 129.5, 128.5,127, 122, 114.5, 83, 59, 54.5, 53, 42.5, 25.5, 24.5.
CHN: Cal: 57.97; 7.05; 10.14. Found: 58.06; 7.1; 10.00
FTIR: 3031, 2953, 2821, 1735, 1630, 1450, 1239, 1038.
Mass: 413.1(M+1):414.1(M+2).

(**8j**): **5-((bis(2-chloroethyl)amino)methyl)-3-(4-chlorophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.5(m,1H);2.65(t,4H);2.7(m,1H);3.1(m,1H);3.35(m,1H);3.5(t,4H);4.8(m,1H);7.5 (dd,2H);7.9(dd,2H).
$^{13}$C NMR: 153,137,133,129,125.5, 82.5, 59, 54.5, 49, 42.5.
CHN; Cal: 49.27; 5.24; 7.66 Found: 49.36; 5.30; 7.51.
FTIR: 3029, 2954, 2821, 1743, 1629, 1233, 1038.
Mass: 352.0(M+2):354.0(M+4).

(**8k**): **5-((bis(2-chloroethyl)amino)methyl)-3-(4-methoxyphenyl)oxazolidin-2-one**
$^{1}$HNMR:2.5(m,1H);2.65(t,4H);2.7(m,1H);3.1(m,1H);3.35(m,1H);3.5(t,4H);4.8(m,1H);7.0(dd,1H);7.9(dd,2H).
$^{13}$C NMR: 159,153,131.5, 122.5, 114.5, 82.5, 59, 56, 54.5, 49, 42.5
CHN; Cal: 53.19; 6.14; 7.75 Found: 53.1; 6.2; 7.78
FTIR: 3034, 2948, 2819, 1728, 1618, 1228, 1034.
Mass: 347.0(M+1):348.0(M+2)

(**8l**): **5-((bis(2-chloroethyl)amino)methyl)-3-(3,4-difluorophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.5(m,1H);2.65(t,4H);2.7(m,1H);3.1(m,1H);3.35(m,1H);3.5(t,4H);4.8(m,1H);7.6 (d,2H)7.7(dd,1H).
$^{13}$C NMR153,147,145,136.5,119,115,112,82.5,59,54.4,42.5
CHN: Cal: 47.61; 4.57; 7.93; Found: 47.5; 4.6; 8.01
FTIR: 3026, 2945, 2815, 1724, 1617, 1231, 1038.
Mass: 353.0(M+1);354.0(M+2).

(**8m**): **5-((bis(2-chloroethyl)amino)methyl)-3-(3-bromo-4-morpholinophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.5(m,1H);2.65(t,4H);2.7(m,1H);3.1(m,1H);3.2(t,4H);3.35(m,1H);3.5(t,4H);3.65(t,4H);4.8(m,1H);6.6(d,1H);7.0(d,1H);7.7(d,1H)
$^{13}$C NMR:153,147,131.5,131,122,116.5,115.5,82.5,66.5,59,54.5,52.5,42.5.
CHN; Cal: 44.93; 5.03; 8.73 Found: 45.00; 5.1; 8.59.
FTIR: 3024, 2951, 2824, 1734, 1630, 1231, 1050, 1044.
Mass: 481.0(M+2); 483.0(M+4)

(**8n**): **4-(4-(5-((bis(2-chloroethyl)amino)methyl)-2-oxooxazolidin-3-yl)-2-fluorophenyl)morpholin-3-one**
$^{1}$HNMR:2.5(m,1H);2.65(t,4H);2.7(m,1H)3.1(m,1H);3.2(t,2H);3.3(m,1H);3.5(t,4H);3.65 (t,4H);4.8(m,1H);6.6(d,1H);7.0(dd,1H);7.7(d,1H).
$^{13}$C NMR:164.5,153,139,137,130.5,124,123,121,82.5,73.5,66,58.5,54.5,42.5
CHN: Cal: 43.66; 4.48; 8.49. Found: 43.70; 4.5; 8.43
FTIR: 3028, 2952, 2834, 1745, 1633, 1245, 1059, 1038.
Mass: 434.1(M+1); 435.0(M+2).

(**8o**): **5-((bis(2-chloroethyl)amino)methyl)-3-(3-fluoro-4-(4-(2-hydroxyacetyl)piperazin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:2.5(m,1H);2.65(t,4H);2.7(m,1H);3.1(m,1H);3.3(m,1H);3.4(t,4H);3.5(t,4H);3.6 (t,4H)3.65(s,1H)4.4(s,2H)4.8(m,1H);6.7(d,1H);6.9(d,1H);7.6(d,1H).
$^{13}$C NMR:166.5,153,155.5,133,130,128,116,82.5,60,58.5,54.5,53.5,46.5,42.5

CHN: Cal: 50.32; 5.70; 11.74; Found: 50.20; 5.75; 11.81
FTIR: 3350, 3028, 2956, 2824, 1741, 1680, 1627, 1235, 1042.
Mass: 477.1(M+1); 478.1(M+2)

(**8p**): **5-((bis(2-chloroethyl)amino)methyl)-3-(3,4-dibromophenyl)oxazolidin-2-one**
$^{1}$HNMR:2.5(m,1H);2.65(t,4H);2.7(m,1H);3.1(m,1H);3.3(m,1H);3.5(t,4H);4.8(m,1H);7.5 (dd,1H)7.75(d,1H);8.7(d,1H).
$^{13}$C NMR:135,140.5,135.5,134,126,120,82.5,59,54.5,49,42.5.
CHN; Cal: 35.40; 3.40; 5.90; Found: 35.45; 3.31; 5.94
FTIR: 3030, 2958, 2826, 1736, 1629, 1240, 1040.
Mass: 473.8(M+2); 475.8(M+4).

(**8q**): **5-((bis(2-chloroethyl)amino)methyl)-3-(4-(pyridin-3-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:2.5(m,1H);2.65(t,4H)2.7(m,1H)3.1(m,1H);3.3(m,1H);3.5(t,4H);4.8(m,1H)7.55 (t,1H):7.75(t,2H);7.85(t,1H);8.4(d,1H);8.7(d,1H);9.25(s,1H).
$^{13}$C NMR153,149,148,134,132,127.5,124,122,82.5,59,54.5,49,42.5
CHN: Cal: 57.88; 5.37; 10.66 Fond: 57.65; 5.40; 10.86
FTIR: 3029, 2951, 2824, 1745, 1632, 1247, 1052.
Mass: 394.0(M+1); 395.1(M+2).

(**8r**): **5-((bis(2-chloroethyl)amino)methyl)-3-(4-(4-((5-nitrofuran-3-yl)methyl)piperazin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:2.5(m,1H0;2.6-2.65(m,8H);2.7(m,1H);3.1(m,1H);3.3(m,1H);3.45-3.5(m,8H);3.75(s,2H);4.8(m,1H);6.6(d,1H);6.8(d,1H);7.0(d,1H)7.5(d,1H);7.7(s,1H).
$^{13}$CNMR:153,152.5,150,145,132.5,128.5,113,111,82.5,59,58.5,56,54.5,52,51.5,49.0,42.5
CHN; Cal: 54.86; 5.76; 10.66. Found: 54.75; 5.8; 10.73,
FTIR: 3035, 2943, 2834, 1729, 1634, 1549, 1331, 1244, 1058.
Mass: 526.1(M+1); 527.1(M+2)

(**8s**): **5-((bis(2-chloroethyl)amino)methyl)-3-(3-fluoro-4-(4-((5-nitrofuran-3-yl)methyl)piperazin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:2.5(m,1H);2.6-2.65(m,8H);2.7(m,1H);3.1(m,1H);3.3(m,1H);3.45-3.5(m,8H);3.75(s,2H);4.8(m,1H);6.7(dd,1H);6.8(d,1H);6.9(d,1H);7.5(m,2H).
$^{13}$CNMR:155,153,152.5,150,133,130,128,116,111,109.5,82.5,58.5,56,54.5,52,51.5,49,42.5
CHN: Cal: 53.05; 5.38; 10.31; Found: 53.1; 5.4; 10.24.
FTIR: 3035, 2953, 2821, 1742, 1684, 1624, 1233, 1049.
Mass: 544.1(M+1)545.1(M+2).

(**8t**):**5-((bis(2-chloroethyl)amino)methyl)-3-(4-(2-oxopiperidin-1-yl)phenyl)oxazolidin-2-one**
$^{1}$HNMR:2.5(m,1H);2.65(t,4H);2.7(m.1H);3.1(m,1H);3.3(m,1H);3.5-3.55(m,8H);4.3(s,2H);4.8(m,1H);6.75(d,2H);7.35(d,2H).
$^{13}$C NMR:164.5,163,153,136.5,127,123.5,110,82.5,73.5,66,59,54.5,49,42.5
CHN: Cal: 51.93; 5.57; 10.09 Found: 52.00; 5.43; 10.16
FTIR: 3039, 2958, 2827, 1738, 1680, 1627, 1237, 1049.
Mass: 416.1(M+1); 417.1(M+2)

## APPLICATIONS

An alkylating antineoplastic agent is an alkylating agent used in cancer treatment that attaches an alkyl group ($C_nH_{2n+1}$) to DNA. The alkyl group is attached to the guanine base of DNA, at the number 7 nitrogen atom of the purine ring. Since cancer cells, in general, proliferate faster and with less error-

correcting than healthy cells, cancer cells are more sensitive to DNA damage such as being alkylated. Alkylating agents are used to treat several cancers. Some alkylating agents are active under conditions present in cells; and the same mechanism that makes them toxic allows them to be used as anti-cancer drugs. They stop tumor growth by cross linking guanine nucleobases in DNA double-helix strands, directly attacking DNA. This makes the strands unable to uncoil and separate. As this is necessary in DNA replication, the cells can no longer divide.

## CONCLUSIONS

We have prepared twenty pure novel antineoplastic DNA cross coupling compounds and these are characterized by 1HNMR, $^{13}$CNMR, CHN analysis, FTIR and Mass spectroscopic techniques. All these found to be in accordance with the required data.

## ACKNOWLEDGEMENTS

I am thankful to New Age Life Sciences for providing me an opportunity to do my research work and also sponsoring research fund. I also grateful to my research colleagues.

## REFERENCES

[1] Louis.J, Lombardo, Francis.Y, Lee, Ping Chen and Derek Norris etal, *J.Med.Chem.* **2004**, 47; 6658-6661.
[2] "antineop", Archived from the original on 7 March 2009. Retrieved 2009-01-24.
[3] T. Z. E. Jones, P. Fleming, C. J. Eyermann, M. B. Gravestock and R. R. Ramsay, "Orientation of oxazolidinones in the active site of monoamine oxidase," *Biochemical Pharmacology*, **2005**, 70(3), 407–416.
[4] M. Rami, R. Macherla et al., Patent number **2008**, 7879892.
[5] M. G. Madariaga and S. Swindells, "Oxazolidinones and human immunode ciency virus," *Antimicrobial Agents and Chemotherapy*, vol. **2007**, 51(3), 1130.
[6] S. Rapposelli, F. Da Settimo, M. Digiacomo et al., "Synthesis and biological evaluation of 2-oxo-2, 3-dihydro-3H-spiro [chromene-4,5-[1,3]oxazolidin]-3-yl]acetic acid derivatives as aldose reductase inhibitors," *Archiv der Pharmazie*, **2011**, 344(6), 372–385.
[7] E. J. Brnardic, M. E. Fraley, and R. M. Garbaccio Bioorg, "3-Aryl-5-phenoxymethyl-1, 3-oxazolidin-2-ones as positive allosteric modulators of mGluR2 for the treatment of schizophrenia: hit-to-lead efforts," *Bioorganic & Medicinal Chemistry Letters*, **2010**, 20(10), 3129–3133.
[8] S. Welsch-Kunze and K. Kuschinsky, "On the possible involvement of glutamate receptors in conditioning of behavioural effects of apomorphine," *Psychopharmacology*, **1990**, 101(3), 421–428.
[9] J. Vara Prasad, "New oxazolidinones," *Current Opinion in Microbiology*, **2007**, 10(5), 454–460.