SYNTHESIS OF NEW HETEROCYCLIC THIAZOLIDINONE AND AZETIDINONE COMPOUNDS AND THEIR ANTICANCER ACTIVITY

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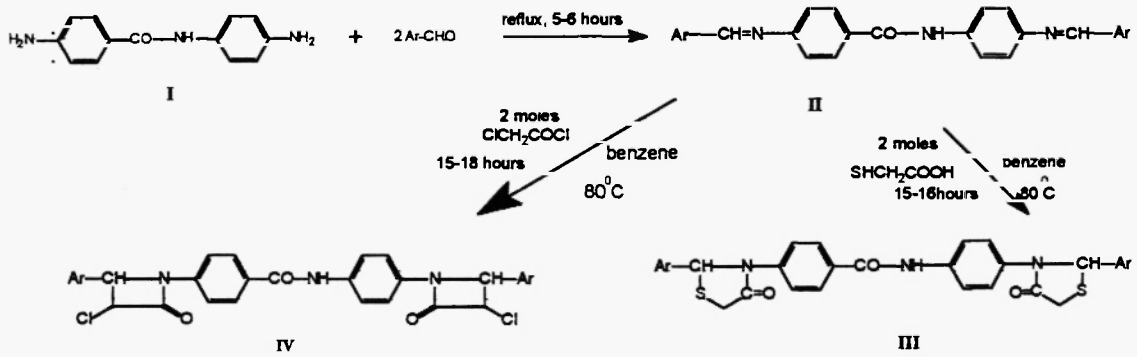
Abstract :- Thiazolidinones and azetidinones have been prepared by the reaction of various schiff bases with thioglycollic acid and chloroacetyl chloride respectively. The intermediate schiff bases were synthesised by the condensation of diaminobenzanilide with various aldehydes. The thiazolidinones and azetidinones were tested for their anticancer activity.

Introduction

Diaminobenzamlide was found to exhibit insecticidal property[1], growth inhibition of plants[2], tuberculostatic action[3] and herbicidal[4] property. Thiazolidinones are known to exhibit antitubercular, antibacterial[5,6], anticonvulsant[7,8], antifungal[9], antithyroid and amoebicidal[10] activities. Azetidinones(β-lactums) were tested as antibiotics, antidepressants, sedatives[11]. So an attempt was made to synthesize some thiazolidinones and azetidinones using diaminobenzanilide as the starting material and test them as anti-cancer drug. Diaminobenzanilide(I) was condensed with different aromatic aldehydes to yield di-imines (II) (schiff base).



I II IV III

The di-imines(schiff base,II) were further reacted with thioglycollic acid & chloroacetyl chloride to yield thiazolidinones(III) & azetidinones(IV) respectively.

The starting compound, diaminobenzanilide, shows IR absorption peak at 3400-3300 cm^{-1} and 3200-3100 cm^{-1}, 1560 cm^{-1} (C-N stretching and bending for amino group), 1700-1660 cm^{-1} (C=O stretching). The schiff bases of above starting compound shows IR absorption peak at 1587-1548 cm^{-1} (C=N stretching), 1660-1680 cm^{-1}(C=0 stretching). The thiazolidinone compounds were characterized by their IR absorption bands at 3330-3300 cm^{-1}(N-H stretching), 720-600 cm^{-1}(C-S stretching), 1750-1680 cm^{-1}(C=O stretching) and 1590-1560 cm^{-1}(C-N stretching). The azetidinone compounds were characterized by their IR absorption bands at 1730 -1680 cm^{-1} (C=O stretching), 1715 cm-1 and 730 cm^{-1}(C-Cl stretching and bending).

Experimental

All the melting points are taken in an open capillary and are uncorrected.The IR spectra was recorded with KBr pellets on Perkin-Elmer 783 Spectrophotometer.

Preparation of Schiff bases[12]
Diaminobenzanilide(0.02 mol,4.54 g) was taken in benzene in a Dean-Stark apparatus and to it benzaldehyde(0.04 mol, 4.24 g) was added over a period of 15 minutes.Then the mixture was refluxed for 5 hours.During the course of the reaction the water was removed continuously.The benzene was then distilled off to get the product.The Schiff's base was recrystallised in benzene. Other sustituted Schiff bases were prepared in a similar manner.The analytical data for various substituted schiff bases are given in Table-1

Preparation of Thiazolidinone[13]
The schiff's base (0.0075 mol,3.0 g) in benzene was taken in Dean-Stark apparatus.To it thioglycollic acid(0.015 mol,1.37 g) in benzene was added slowly.Then it was refluxed for 15-16 hours.During the course of the reaction the water was removed continuously.The benzene was distilled off to get the product. Other substituted thiazolidinones were prepared in similar manner.The analytical data for different substituted thiazolidinones are given in Table-2

Preparation of Azetidinone[14]
The schiff's base (0.0075 mol,3.0 g) in benzene was taken in a 50 ml flat bottomed flask.To it chloroacetyl chloride (0.015 mol,1.68 g) and triethyl amine (0.015 mol,1.50 g) in benzene were added slowly.It was then refluxed for 15-16 hours.The triethylamine hydrochloride was removed and the benzene was distilled off to get the product.Other substituted azetidinones were prepared in a similar manner.The analytical data for different substituted azetidinones are given in Table-3.

Report on the anti-cancer activity.

Experimental
The compounds were also screened for their anti-cancer activity by measuring their effect on percentage growth(PG) of more than two different cell lines for variety of cancer.They have been tested at 5 different concentration of the compound ($-4\log_{10}$ to $-8\log_{10}$).The optical density of SRB derived colour by the cell lines was measured at 0 time ($Mean_{zero}$) after 48 hours in presence of drug($Mean_{test}$) and in absence of drug after 48 hours($Mean_{control}$).The PG was calculated from it using the following formula-

If $Mean_{test} - Mean_{zero} > 0$ then,

$$PG = \frac{100 \times (Mean_{test} - Mean_{zero})}{(Mean_{control} - Mean_{zero})}$$

But if $(Mean_{test} - Mean_{zero}) < 0$ then,

$$PG = \frac{100 \times (Mean_{test} - Mean_{zero})}{Mean_{zero}}$$

The effects were interpreted from dose response curves created by plotting PG's (-100 to +100) against $\log_{10}$ molar concentration (-4 to -8).The response parameter GI50,TGI and LC50 are interpolated values representing the concentrations at which the PG is +50. , 0 and -50.

Results and Discussion

The invitro effect of compound number-16, 4,4'-bis[2"-oxo-5"-(3'",4'",5'"-trimethoxyphenyl)thiazolidine] -benzanilide drug at different concentrations expressed as percentage growth (PG).From it three response parameters G150, TGI (Test Growth Index) and LC50(Lethal Concentration showing -50 PG) are interpolated.The compounds for which it was not possible to determine their response parameters were tested at highest concentration.Only in some of the cell lines the compounds were found to be effective at - 4 log10M concentration.Similarly from the invitro effect for compound number-12,20 and 15 shows that compound-12 is most effective among the three of them showing nearly -25PG.

The dose of the effective compounds were determined from the Dose Response Curves. All 56 cell lines tested for different panel,i.e, organ cancer were effective at -4Log10M concentration while higher concentrations(i.e. -5,-6,-7 and -8Log10M) were comparitively less effective.It was found that out of 56 cell lines only 5 viz.HOP-92 of lung cancer,UACC-62 of Melanoma and NCI/ADR-RES,MDA-N and MDA-MB-435 of Breast Cancer were effective as their TGI is -4.10,-4.12,-4.15,-4.19 and -4.21 respectively.The compound is most effective for MDA MB-435 cell line of Breast Cancer.

For selecting a potential drug for a particular cell line or for a particular cancer, mean graphs have been obtained for all the three interpolated values G150,TGI and LC50 for compound 16.12,20 and 15 respectively..Similarly mean graphs were also obtained for compound-12 , 4,4'-bis[2"-oxo-5"-(2'"-hydroxyphenyl)thiazolidine]benzanilide ,compound-20, 4,4'-bis[2"-oxo-5"((4'"-N,N-dimethyl) phenyl) thiazolidine]benzanilide and compound-15, 4,4'-bis[2"-oxo-5"-(thiophenyl)thiazolidine]benzanilide ,against all 56 cell lines.Among them compound-12, 4,4'-bis[2"-oxo-5"-(2'"-hydroxyphenyl) thiazolidine]- benzanilide , is effective on most of the cell lines at >-4log10M concentration ..It was found that out of 56 cell lines tested only five were showing its effectiveness on the cell lines viz. HOP-92 for Lung Cancer, SNB-75 of CNS cancer ,M-14 ,UACC-62 for Melanoma and SK-OV-3 for Ovarian Cancer having TGI -4.06,-4.08,-4.21 and -4.21 respectively . It was found that this compound shows >- 4.0 TGI only in case of four cell lines.Among four of them M-14 and SK-OV-3 were affected by M1

Compound-20, 4,4'-bis[2"-oxo-5"((4'"-N,N-dimethyl)phenyl)thiazolidine]benzanilide, is totally ineffective showing TGI - 4.0. Similarly compound-15, 4,4'-bis[2"-oxo-5"-(thiophenyl)thiazolidine]benzanilide, is effective only on one cell line i.e. NCI-H23 for Lung Cancer having TGI -4.02.The rest of the 55 cell lines show TGI - 4.0 at -4log10M. concentration.

Finally we can conclude that all compounds were effective on lung cancer except compound-20,but on different cell lines.Two of them, compound-16 and 12 are effective on UACC-62 cell line for Melonoma.It was specifically found that compound -16 is effective on 3 different cell lines for Breast Cancer.The compound-12 is also effective on Ovarian Cancer cell line SK-OV-3.Among the four compound-12 is most effective on Melonoma Cancer M-14 cell lines and SK-OV-3 for Ovarian Cancer showing - 4.21 log10M and compound-12 on Breast Cancer cell line MDA-MB-435 showing nearly similar TGI.The latter anti-cancer agent also shows its effectiveness,but slightly less,on MDA-N,another cell line for Breast Cancer as the logTGI for it is - 4.19.None of the four compound is showing -50PG.

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Table-1 THE ANALYTICAL DATA OF THE SCHIFF'S BASE

Compound Number	Substituent Ar-	Molecular Formulae	Molecular Weight(gms)	Melting Point °C	% Yield	Elemental Analysis, %Theoritical (Practical)		
						C	H	N
1	C_6H_5-	$C_{27}H_{21}N_1O$	403	192	91	80.39(80.41)	5.21(5.24)	10.42(10.44)
2	4-OCH_3,C_6H_4-	$C_{29}H_{25}N_3O_3$	463	176	88	69.97(69.95)	5.39(5.36)	9.07(9.09)
3	2-OH,C_6H_4-	$C_{27}H_{21}N_3O_3$	435	210	95	74.48(74.44)	4.82(4.84)	9.65(9.67)
4	C_6H_5-CH=CH-	$C_{31}H_{25}N_3O$	455	188	93	81.75(81.77)	5.49(5.47)	9.23(9.21)
5	C_4H_3S-	$C_{23}H_{17}N_3OS_2$	415	132	89	66.50(66.51)	4.09(4.11)	10.12(10.14)
6	3,4,5-$(OCH_3)_3C_6H_2$-	$C_{33}H_{33}N_3O_7$	583	183	95	67.92(67.94)	5.66(5.65)	7.20(7.22)
7	2-NO_2,C_6H_4-	$C_{27}H_{19}N5O_5$	493	175	75	65.72(65.75)	3.85(3.86)	14.19(14.18)
8	4-Cl,C_6H_4-	$C_{27}H_{19}N_3OCl_2$	472	141	82	68.64(68.66)	4.02(4.05)	8.89(8.87)
9	3-OC_2H_5,4-OH,C_6H_3-	$C_{31}H_{29}N_3O_5$	523	164	78	71.12(71.13)	5.54(5.57)	8.03(8.05)
10	N,N-$(CH_3)_2$,C_6H_4-	$C_{29}H_{25}N_5O$	459	180	93	75.81(75.83)	5.54(5.53)	15.25(15.22)

Table-2 THE ANALYTICAL DATA OF THE THIAZOLIDINONES

Compound Number	Substituent Ar-	Molecular Formulae	Molecular Weight(gms)	Melting Point °C	% Yield	Elemental Analysis, %Theoritical (Practical)		
						C	H	N
11	C_6H_5-	$C_{31}H_{25}N_1O_3S_2$	551	118	74	67.51(67.48)	4.53(4.50)	7.62(7.65)
12	4-OCH_3,C_6H_4-	$C_{33}H_{29}N_3O_5S_2$	611	141	78	64.81(64.76)	4.74(4.69)	6.87(6.80)
13	2-OH,C_6H_4-	$C_{31}H_{25}N_3O_5S_2$	583	159	85	63.80(63.84)	4.28(4.33)	7.20(7.22)
14	C_6H_5-CH=CH-	$C_{33}H_{29}N_3O_3S_2$	603	123	69	69.65(69.62)	4.80(4.83)	6.97(6.99)
15	C_4H_3S-	$C_{27}H_{21}N_3O_3S_4$	563	89	71	57.54(57.55)	3.73(3.76)	7.46(7.44)
16	3,4,5-$(OCH_3)_3C_6H_2$-	$C_{37}H_{37}N_3O_9S_2$	731	112	85	60.73(60.75)	5.06(5.04)	5.74(5.70)
17	2-NO_2,C_6H_4-	$C_{31}H_{23}N_5O_7S_2$	641	131	73	58.03(58.07)	3.58(3.57)	10.72(10.68)
18	4-Cl,C_6H_4-	$C_{31}H_{23}N_3O_3Cl_2S_2$	620	127	82	60.00(60.02)	3.70(3.73)	6.77(6.73)
19	3-OC_2H_5,4-OH,C_6H_3-	$C_{35}H_{33}N_3O_7S_2$	671	114	78	62.59(62.57)	4.91(4.92)	6.25(6.27)
20	N,N-$(CH_3)_2$,C_6H_4-	$C_{33}H_{29}N_5O_3S_2$	607	105	63	65.23(65.20)	4.77(4.74)	11.53(11.55)

Table-3 THE ANALYTICAL DATA OF THE AZETIDINONES

Compound Number	Substitucnt Ar-	Molccular Formulac	Molccular Weight(gms)	Mclting Point °C	% Yield	Elcmcntal Analysis, %Thcoritical (Practical)		
						C	H	N
21	C_6H_5-	$C_{31}H_{23}N_3O_3Cl_2$	556	>250	92	66.90(66.87	4.13(4.11)	7.55 (7.51)
22	4-OCH_3,C_6H_4	$C_{33}H_{27}N_3O_5Cl_2$	616	>250	78	64.28(64.26)	4.38(4.34)	6.81(6.79)
23	2-OH,C_6H_4-	$C_{31}H_{23}N_3O_5Cl_2$	588	>250	89	63.26(63.28)	3.91(3.94)	7.14(7.18)
24	C_6H_5-CH=CH-	$C_{33}H_{27}N_3O_3Cl_2$	608	>250	95	69.07(69.05)	4.40(4.43)	6.90(6.88)
25	C_4H_3S-	$C_{27}H_{19}N_3O_3S_2Cl_2$	568	>250	86	57.04(57.06)	3.34(3.37)	7.39(7.41)
26	3,4,5-$(OCH_3)_3$,C_6H_2-	$C_{37}H_{35}N_3O_9Cl_2$	736	>250	91	60.32(60.29)	4.75(4.73)	5.70(5.71)
27	2-NO_2,C_6H_4-	$C_{31}H_{21}N_5O_7Cl_2$	646	>250	78	57.58(57.55)	3.25(3.27)	10.83(10.86)
28	4-Cl,C_6H_4-	$C_{31}H_{21}N_3O_3Cl_4$	625	>250	92	59.52(59.49)	3.36(3.33)	6.72(6.71)
29	3-OC_2H_5,4-OH,C_6H_3	$C_{35}H_{31}N_3O_7Cl_2$	676	>250	84	61.58(61.56)	5.42(5.39)	6.15(6.11)
30	N,N-$(CH_3)_2$,C_6H_4-	$C_{33}H_{27}N_5O_3Cl_2$	612	>250	87	64.70(64.73)	4.41(4.44)	11.43(11.45)

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