SYNTHESIS OF SOME SCHIFF BASES,THIAZOLIDINONES AND AZETIDINONES DERIVED FROM 2,6-DIAMINOBENZO[1,2-d:4,5-d'] BISTHIAZOLE AND THEIR ANTICANCER ACTIVITIES

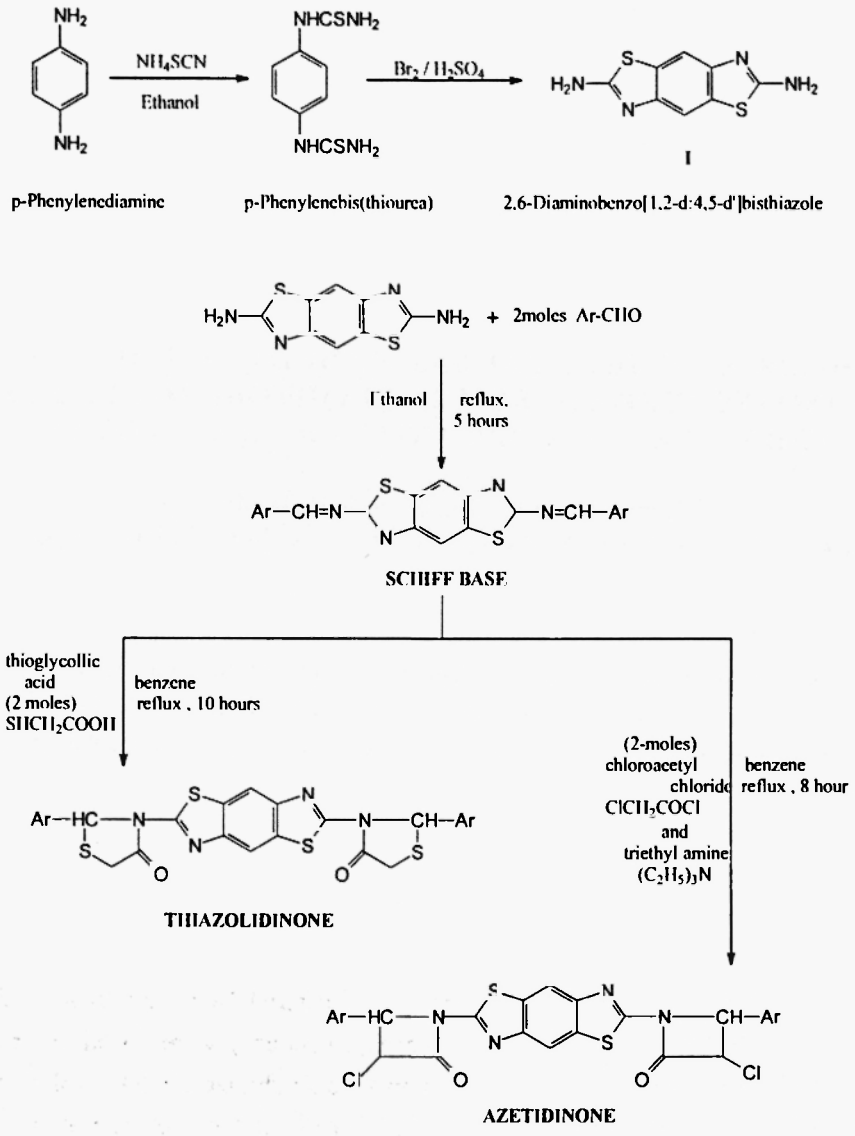
Sunil B Desai,P.B.Desai and K.R.Desai*
Department of Chemistry,South Gujarat University,Surat 395 007(India)

Abstract - New Thiazolidinones and Azetidinones were synthesized from Schiff Base derivatives which were prepared by the reaction of 2,6-Diaminobenzo[1,2-d:4,5-d'] bisthiazole and various aldehydes.The compounds were established on the basis of elemental analysis and spectral data.

Introduction

Thiazolidinones are known to exhibit antitubercular, antibacterial[1,2],anticonvulsant[3,4],antifungal[5], antithyroid and amoebicidal[6] activities. Azetidinones(β-Lactums) were tested as antibiotics, antidepressants and sedatives[7]. So an attempt was made to synthesize some thiazolidinones and azetidinones using 2,6-Diaminobenzo[1,2-d:4,5-d']bisthiazole as the starting material and test them as anti-cancer drugs.2,6-Diaminobenzo[1,2-d:4,5-d']bisthiazole was condensed with different aromatic aldehydes to yield di-amines(schiff bases).The diamines were further reacted with thioglycollic acid and chloroacetyl chloride to yield thiazolidinones and azetidinones respectively.

The starting compound,2,6-Diaminobenzo[1,2-d:4,5-d']bisthiazole, 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). 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 melting points were taken in an open capillary and are uncorrected. the IR Spectra were recorded with KBr pellets on Perkin-Elmer 783 Specrophotometer.

Preparation of 2,6-Diaminobenzo[1,2-d:4,5-d']bisthiazole[8,9]

(0.25 mol,56.5 g) p-phenylenebis(thiourea) was added to 98% H_2SO_4 in a flat-bottomed flask at 40-50°C.To it (0.30 mol,16.0 ml) Bromine was added dropwise at 80-85°C over 2 hours with continuous stirring.After the addition was complete,the mixture was stirred and refluxed for 8 hours.The mixture pH was adjusted to 10 with 28% NaOH forming 98.1% crude product and was recrystallized from water/ethanol to give 70% recrystallized product. M.P.- 320°C

Preparation of Schiff Bases[10]

2,6-Diaminobenzo[1,2-d:4,5-d']bisthiazole (0.025 mol,5.55 g) was taken in alcohol. Benzaldehyde (0.05 mol,5.3 g) was added. The mixture was then refluxed with occasional stirring for 5 hours. After 5 hours the alcohol was distilled off to get the product. The schiff base was recrystallized from alcohol. Other substituted Schiff Bases were prepared in a similar manner (**Table - 1**).

Preparation of Thiazolidinones[11]

The above synthesized schiff's base (0.0075 mol,3.0 g) in benzene was taken in Dean-Stark apparatus. To it thioglycollic acid (0.015 mol,1.38 g) was added slowly. Then it was refluxed for 10-12 hours. During the course of the reaction the water was removed continuously. The product was filtered from benzene and recrystallized from alcohol. Other substituted thiazolidinones were prepared in a similar manner (**Table - 2**).

Preparation of Azetidinones[12]

The above synthesized schiff's base (0.0075 mol,3.0 g) in benzene was taken in a 500 ml flat bottomed flask. To it chloroacetyl chloride(0.015 mol,1.68 g) and triethyl amine(0.015 mol,1.5 g) in benzene were added slowly. The mixture was then refluxed for 8-10 hours. The product was filtered, dried and washed with water to remove triethyl aminehydrochloride and was recrystallized from alcohol. Other substituted azetidinones were prepared in a similar manner (**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

TABLE - 1

SR. NO.	COMP. NO	SUBSTITUENT Ar-	MOLECULAR FORMULA	MOLECULAR WEIGHT	YIELD %	MELTING POINT °C	ELEMENTAL ANALYSIS					
							% C		% H		% N	
							FOUND	REQD.	FOUND	REQD.	FOUND	REQD.
1	1	C_6H_5-	$C_{22}H_{14}N_4S_2$	398.50	80	>300	66.28	66.31	3.50	3.54	14.09	14.06
2	2	(4-OCH_3), C_6H_4-	$C_{24}H_{18}N_4O_2S_2$	458.55	84	>300	62.82	62.86	3.91	3.96	12.19	12.22
3	3	(2-OH), C_6H_4-	$C_{22}H_{14}N_4O_2S_2$	430.50	78	>300	61.35	61.38	3.24	3.28	12.98	13.01
4	4	C_6H_5CH=CH-	$C_{26}H_{18}N_4S_2$	450.57	70	>300	69.27	69.31	4.01	4.03	13.39	12.43
5	5	C_4H_3S-	$C_{18}H_{10}N_4S_4$	410.54	72	>300	52.62	52.66	2.41	2.46	13.62	13.65
6	6	3,4,5-$(OCH_3)_3$, C_6H_2-	$C_{28}H_{26}N_4O_6S_2$	578.65	69	>300	58.14	58.12	4.56	4.53	9.72	9.68
7	7	(2-NO_2), C_6H_4-	$C_{22}H_{12}N_6O_4S_2$	488.49	71	>300	54.05	54.09	2.45	2.48	17.17	17.20
8	8	(2-Cl), C_6H_4-	$C_{22}H_{12}N_4S_2Cl_2$	467.39	67	>300	56.51	56.54	2.54	2.59	11.95	11.99
9	9	(4-OH, 3-OC_2H_5),C_6H_3-	$C_{26}H_{22}N_4O_4S_2$	518.60	75	>300	60.25	60.22	4.24	4.28	10.77	10.81
10	10	4-N,N-$(CH_3)_2$ C_6H_4-	$C_{26}H_{24}N_6S_2$	484.64	76	>300	64.41	64.44	4.96	4.99	17.30	17.34
11	11	(3-OC_6H_5), C_6H_4-	$C_{34}H_{22}N_4O_2S_2$	582.69	72	>300	70.05	70.08	3.77	3.81	9.60	9.62
12	12	(2-OCH_3), C_6H_4-	$C_{24}H_{18}N_4O_2S_2$	458.55	74	>300	62.83	62.86	3.94	3.96	12.19	12.22

TABLE - 2

SR NO.	COMP. NO	SUBSTITUENT Ar-	MOLECULAR FORMULA	MOLECULAR WEIGHT	YIELD %	MELTING POINT °C	ELEMENTAL ANALYSIS					
							% C		% H		% N	
							FOUND	REDD.	FOUND	REOD.	FOUND	REDD
13	13	C_6H_5-	$C_{26}H_{18}N_4O_2S_4$	546.69	71	>300	57.09	57.12	3.29	3.32	10.21	10.25
14	14	(4-OCH_3), C_6H_4-	$C_{28}H_{22}N_4O_4S_4$	606.74	74	>300	55.40	55.43	3.61	3.65	9.18	9.23
15	15	(2-OH) ,C_6H_4-	$C_{26}H_{18}N_4O_4S_4$	578.69	72	>300	53.92	53.96	3.10	3.14	9.64	9.68
16	16	C_6H_5CH=CH-	$C_{30}H_{22}N_4O_2S_4$	598.77	67	>300	60.15	60.18	3.66	3.70	9.33	9.36
17	17	C_4H_3S-	$C_{22}H_{14}N_4O_2S_6$	558.74	69	>300	47.25	47.29	2.49	2.53	10.01	10.03
18	18	3,4,5-(OCH_3)$_3$, C_6H_2-	$C_{32}H_{30}N_4O_6S_4$	726.85	70	>300	52.85	52.88	4.12	4.16	7.67	7.70
19	19	(2-NO_2), C_6H_4-	$C_{26}H_{16}N_6O_6S_4$	636.69	68	>300	49.02	49.05	2.51	2.53	13.18	13.20
20	20	(2-Cl), C_6H_4-	$C_{26}H_{16}N_4S_4Cl_2O_2$	615.58	65	>300	50.70	50.73	2.60	2.62	9.07	9.10
21	21	(4-OH, 3-OC_2H_5),C_6H_3-	$C_{32}H_{26}N_4O_6S_4$	666.80	66	>300	54.01	54.05	3.68	3.93	8.37	8.40
22	22	4-N,N-(CH_3)$_2$ C_6H_4-	$C_{30}H_{28}N_6O_2S_4$	632.83	67	>300	56.92	56.94	4.43	4.46	13.25	13.28
23	23	(3-OC_6H_5), C_6H_4-	$C_{38}H_{26}N_4O_4S_4$	730.89	69	>300	62.41	62.45	3.55	3.59	7.64	7.67
24	24	(2-OCH_3), C_6H_4-	$C_{28}H_{22}N_4O_4S_4$	606.74	66	>300	55.41	55.43	3.62	3.65	9.20	9.23

TABLE - 3

SR. NO.	COMP. NO	SUBSTITUENT Ar-	MOLECULAR FORMULA	MOLECULAR WEIGHT	YIELD %	MELTING POINT °C	ELEMENTAL ANALYSIS					
							% C		% H		% N	
							FOUND	REQD.	FOUND	REQD.	FOUND	REQD.
25	25	C_6H_5-	$C_{26}H_{16}N_4O_2S_2Cl_2$	551.46	62	>300	56 61	56 63	2 89	2.92	10 13	10.16
26	26	(4-OCH_3), C_6H_4-	$C_{28}H_{20}N_4O_4S_2Cl_2$	611.51	65	>300	54 97	55 00	3 26	3.30	9.12	9 16
27	27	(2-OH), C_6H_4-	$C_{26}H_{16}N_4O_4S_2Cl_2$	583.46	68	>300	53 49	53 52	2.73	2.76	9 58	9.60
28	28	C_6H_5CH=CH-	$C_{30}H_{20}N_4O_2S_2Cl_2$	603 54	64	>300	59 66	59.70	3.31	3.34	9.24	9 28
29	29	C_4H_3S-	$C_{22}H_{12}N_4O_2S_4Cl_2$	563 51	65	>300	46 86	46.89	2.12	2.15	9.90	9 94
30	30	3,4,5-(OCH_3)$_3$, C_6H_2-	$C_{32}H_{28}N_4O_8S_2Cl_2$	731.62	68	>300	52.50	52.53	3.82	3.86	7.63	7.66
31	31	(2-NO_2), C_6H_4-	$C_{28}H_{14}N_6O_6S_2Cl_2$	641.46	67	>300	48 66	48.69	2.16	2.20	13 07	13.10
32	32	(2-Cl), C_6H_4-	$C_{28}H_{14}N_4S_2Cl_4O_2$	620.35	64	>300	50.31	50.34	2.23	2.27	9.00	9.03
33	33	(4-OH, 3-OC_2H_5),C_6H_3-	$C_{30}H_{24}N_4O_6S_2Cl_2$	671.57	64	>300	53 62	53.66	3.57	3.60	8 31	8 34
34	34	4-N,N-(CH_3)$_2$ C_6H_4-	$C_{30}H_{26}N_6O_2S_2Cl_2$	637.60	68	>300	56 48	56.51	4.07	4.11	13 15	13.18
35	35	(3-OC_6H_5), C_6H_4-	$C_{38}H_{21}N_4O_4S_2Cl_2$	735 66	63	>300	62.08	62.04	3.34	3.29	7.58	7.62
36	36	(2-OCH_3), C_6H_4-	$C_{28}H_{20}N_4O_4S_2Cl_2$	611.51	67	>300	54.97	55.01	3.25	3.30	9.14	9.16

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 $Mean_{time} - Mean_{zero} > 0$ 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 G150,TGI and LC50 are interpolated values representing the concentrations at which the PG is +50 , 0 and -50.Ten different compounds were tested in vitro for their anti cancer activity against 57 different cell lines for different panels-organ cancers such as Lung Cancer , Colon Cancer , CNS Cancer , Ovarian Cancer , Renal Cancer , Prostrate Cancer , Breast Cancer , Melanoma and Leukemia.

Results and Discussion

Among the Ten different Compounds tested , five of them showing zero percent growth were found effective on different cell lines of different panels viz. Lung Cancer , Colon Cancer , CNS Cancer , Melanoma and Leukemia. The cell lines found to be effective are SR and MOLT-4 (Leukemia), NCI-H460 and NCI-H226 (Lung Cancer), COLO-205 (Colon Cancer), SF-539 (CNS Cancer) and SK-MEL-28 and UACC-257 (Melanoma). Only three compounds-1, 6 and 21 were effective on different cell lines for Breast Cancer. The only effective compound for Prostrate Cancer is compound-22, on DU-145 cell line. On the COLO-250 cell line for Colon Cancer , five compounds viz. Compound-3, 4, 13, 16 and 17 were showing >-5.0 TGI and the most effective is compound-17 showing -5.0 TGI. It was also found that eight out of the ten compounds were showing >-4.0 LC50, that is, -50 PG. The most effective one is compound-4 showing -4.18 LC50.

Finally we can conclude that, among the Schiff Bases, compounds-3, 4 and 9 were effective on Leukemia Cancer, compounds-3 and 4 on Colon Cancer , compounds-6 and 9 on CNS Cancer and Melanoma Cancer and compounds-3 and 6 on Breast Cancer. None of them were effective on Lung Cancer, Ovarian Cancer, Renal Cancer and Prostrate Cancer. Compound-4 is the most effective, among the Schiff Bases, against Leukemia.

We can also conclude that, among the Thiazolidinones, compounds-15, 16, 17, 21 and 22 are effective on Lung Cancer. Whereas only compound-22 is effective against Prostrate Cancer and compound-21 against Breast Cancer. Compounds-13, 16 and 17 are effective on Colon Cancer

and CNS Cancer. Compunds-16, 21 and 22 are effective against Melanoma. Compound -17 is the most effective among the thiazolidinones against Colon Cancer.

The Azetidinones were comparitively ineffective and inactive.

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