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

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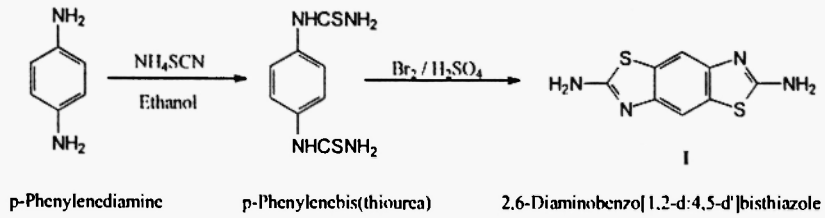
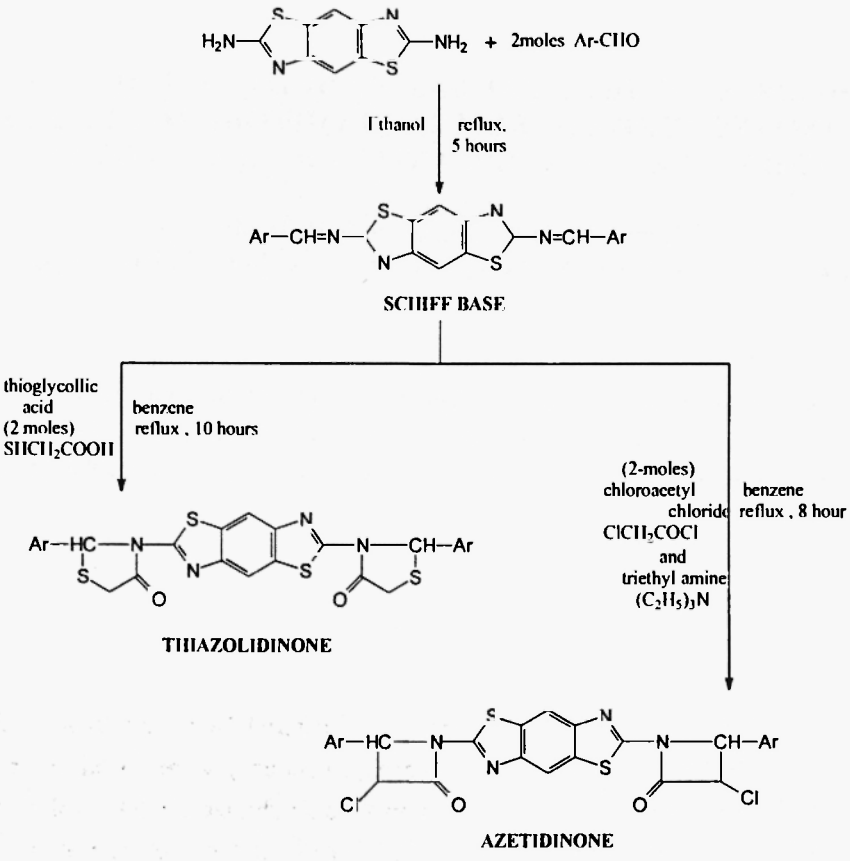
Abstract - New Thiazolidinones and Azetidinones were synthesized from Schiff Base derivatives which were prepared by the reaction of 2,6-Diaminobenzo[1,2-d:4,5-d'] bisthiazole and various aldehydes.The compounds were established on the basis of elemental analysis and spectral data.

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-	$C_{26}H_{18}N_4O_2S_4$	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-	$C_{33}H_{26}N_4O_6S_4$	666.80	66	>300	54.01	54.05	3.88	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 -	$C_{18}H_{14}N_6O_6S_2Cl_2$	641.46	67	>300	48 66	48 69	2.16	2.20	13 07	13.10
32	32	(2-Cl), C_6H_4 -	$C_{26}H_{14}N_4S_2Cl_4O_2$	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-	$C_{38}H_{24}N_4O_4S_2Cl_2$	735 68	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.

Acknowledgement

The authors are thankful to The South Gujarat University for providing the research facilities.They are also thankful to Dr. V.L.Narayanan, National Cancer Institute, Maryland, USA for screening the compounds for their anti-cancer activities.

References

1. K.J.Mehta,A.C.Chavda and A.R.Parikh, ***J.Ind.Chem.Soc.***,56(2),173-4(1979).
2. K.Deasi and A.J.Baxi, ***J.Ind.Chem.Soc.***69,212(1992).
3. C.Dwivedi,T.K.Gupta and S.C.Parmar, ***J.Med.Chem.***,15,553(1972).
4. S.P.Singh,B.Ali,T.K.Auyong,S.S.Parmar and B.DE Boer, ***J.Pharm.Sci.***,65,391(1976).
5. N.C.Misra and K.K.Patnaik, ***Ind.J.Appl.Chem.***34,148(1971).
6. K.A.Thaker,B.R.Parekh and N.C.Desai, ***J.Ind.Chem.Soc.***,LXIV,491(1987).
7. P.G.Summer, ***Chem.Rev.***, 76,113(1976).
8 K.M.Sprague and A.H.Land , ***Heterocyclic Compounds***, vol. **5**, p 484.
9. H.Farbwerke , ***Chem. Abstr.***, **101**, 23461u (1984)
10. K. Von Auwers and H.Stuhlmann , ***Ber.***, 59, 1043 (1926).
11. F.C. Brown, ***Chem. Revs.***, 61, 463 (1961).
12. J.M.Vanderveen,S. Bari,I. Krishnan,M.S. Manhas and A.K.Bose, ***J.Org.Chem.***, 54, 5758 (1989).

Received on August 8, 2000