Synthesis and Spectral studies of Nitrosourea derivatives of 3-Methyl– 5/7- Substituted –2- (3,4-dichloro) benzoyl-4H-1,4-Benzothiazines as Bifunctional Anticancer Agents.

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Abstract: The synthesis of of 3-methyl-5/7- substituted-4- (N-propyl-N-nitrosoamido)- 2- (3,4-dichloro benzoyl) -4H-1,4-Benzothiazines by the isocyanation and successive nitrosation of 3-methyl -5/7- substituted- 2- (3,4-dichlorobenzoyl) -4H-1,4-Benzothiazines has been reported. The synthesized compounds have been characterized by their elemental analyses and spectral characteristics.

Introduction:

Analogous to phenothiazines, benzothiazines possesss a wide spectrum of biological activities[1]. Their several derivatives are in clinical use[2-7]. They exhibit significant anticancer activities, which are assigned due to their interaction with DNA by complexation.

Nitrosourea derivatives constitute an important class of anticancer agents and its several derivatives like MNNG, CNU, MNU, GANU, and CDL-7 etc. are clinically significant. They interact with DNA via alkylation [8-9]. However their clinical use is limited because of cumulative and delayed side effects exerted by these compounds. Bone marrow toxicity being dose limiting, therefore it is worthwhile to develop a new series of nitrosoureas with minimum toxicity and side effects. 4H-1, 4- Benzothiazines are much less toxic and therefore it is anticipated that their nitrosourea derivatives will be potent anticancer agents with minimum toxicity, side effects etc.

In 3-methyl-5/7- substituted-4- (N-propyl-N-nitrosoamido)- 2- (3,4-dichloro benzoyl) -4H-1,4-Benzothiazines heterocyclic nitrogen with a side chain at 4-position constitutes N-nitrosourea linkage and possess both 1,4-benzothiazines nucleus and a nitrosourea moiety . They would show two fold interaction with DNA via complexation[10] as well as alkylation and will constitute bifunctional anticancer agents.

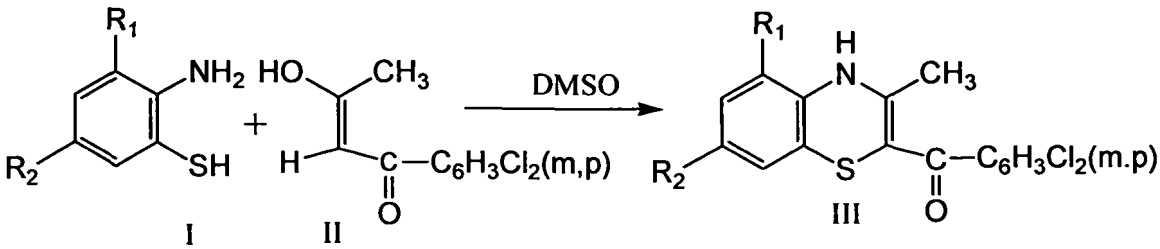
Experimental:

Melting points of the synthesized compounds were determined on an electric melting point apparatus and are uncorrected. IR spectra were recorded in KBr on SHIMADZU 8400S FT IR spectrophotometer. The ^{1}HNMR and ^{13}C NMR spectra were recorded on a model Bruker-DRX-300 NMR spectrometer at 300 MH_Z and 75 MH_Z respectively using $CDCl_3$ as a solvent and TMS as an internal standard. The Mass spectrum of the representative compound was recorded on JEOL-SX-102/DA-6000 mass spectrometer.

(i)Preparation of 3-methyl -5/7- substituted- 2- (3,4-dichlorobenzoyl) -4H-1,4-Benzothiazines(III a-g)

To the stirred suspension of 3,4-dichlorobenzoyl acetone II (10mmoles) in DMSO (5ml) was added 3-methyl/3-ethoxy/5-methyl/5-ethoxy/5-methoxy/5-chloro/3,5-dimethyl-2-amino benzenethiol I (10mmoles) and mixture was

refluxed for 30-40mins.The reaction mixture was concentrated and cooled down to room temperature. The solid separated out was filtered, washed with petroleum ether and crystallized from methanol (Scheme- 1).

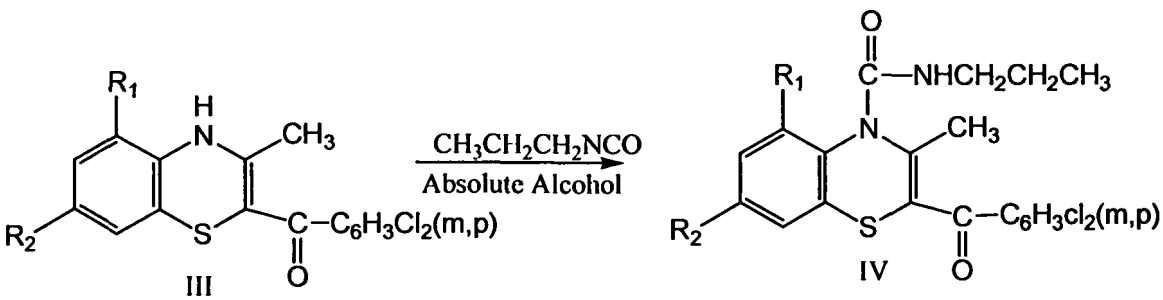


R_1 / R_2 = CH_3/H, OC_2H_5/H, H/CH_3, H/OC_2H_5, H/OCH_3, H/Cl, CH_3/CH_3

Scheme-1

(ii) Preparation of 3-methyl -5/7- substituted- 2- (3,4-dichlorobenzoyl) –4-(N-propyl amido) - 1,4-benzothiazines (IVa-g)

A mixture of 3-methyl -5/7- substituted- 2- (3,4-dichlorobenzoyl) -4H-1,4-Benzothiazines III (10mmoles),10 ml of absolute alcohol and propyl isocyanate (10mmoles) was refluxed on hot plate for 2 hrs .Then the solvent was removed under vacuum rotatory evaporator The product 3-methyl-5/7-substituted-2-(3,4-dichlorobenzoyl)–4-(N-propyl amido)-1,4-benzothiazines was crystallised from ethanol (Scheme 2).



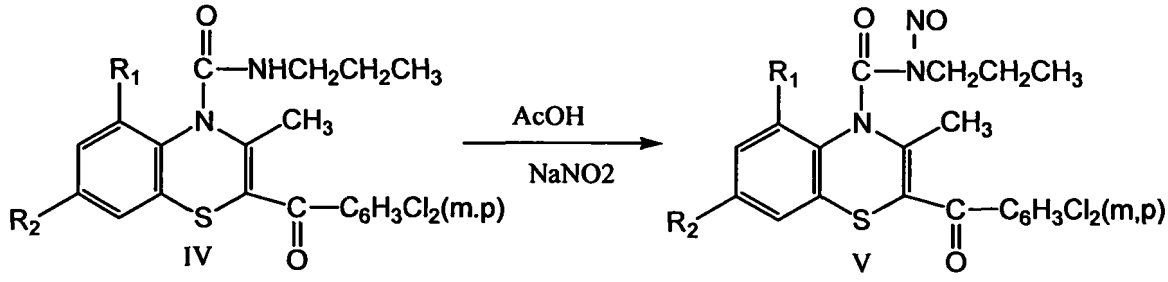
R_1 / R_2 = CH_3/H, OC_2H_5/H, H/CH_3, H/OC_2H_5, H/OCH_3, H/Cl, CH_3/CH_3

Scheme -2

(iii) Preparation of 3-methyl-5/7- substituted-4- (N-propyl-N-nitrosoamido)- 2- (3,4-dichloro benzoyl) -4H-1,4-Benzothiazines (Va-g)

3-Methyl-5/7-substituted-2-(3,4-dichlorobenzoyl)–4-(N-propylamido)-1,4-benzothiazines IV (3mmoles) was dissolved in 50 ml of acetic acid, sodium nitrite (5mmoles) was added portion wise with strirring. The mixture was strirred for 30mins at room temperature and for one hour at 50^0 C . Acetic acid was evaporated under reduced pressure in vacuum rotatory evaporator. The residue was treated with water. The resulting precipitate of 3-methyl-5/7-substituted-4- (N-propyl-N-nitrosoamido)- 2- (3,4-dichloro benzoyl) -4H-1,4-Benzothiazines was collected and crystallized from methanol.

(Scheme 3)



R_1 / R_2 = CH_3/H, OC_2H_5/H, H/CH_3, H/OC_2H_5, H/OCH_3, H/Cl, CH_3/CH_3

Scheme-3

Table 1: Physical data of 3-methyl-5/7- substituted-4- (N-propyl-N-nitrosoamido)- 2- (3,4-dichloro benzoyl) -4H-1,4-Benzothiazines

Compound	Molecular formula	M.P °C	Yield %	% C (Found) (Calc.)	H (Found) (Calc.)	N (Found) (Calc.)
A	$C_{21}H_{19}Cl_2N_3O_3S$	178	60	(54.32) (54.10)	(4.12) (4.02)	(9.05) (9.00)
B	$C_{22}H_{21}Cl_2N_3O_4S$	viscous	62	(53.45) (53.24)	(4.28) (4.03)	(8.50) (8.46)
C	$C_{21}H_{19}Cl_2N_3O_3S$	152	61	(54.32) (61.42)	(4.12) (5.45)	(9.05) (9.65)
D	$C_{22}H_{21}Cl_2N_3O_4S$	viscous	50	(53.45) (53.29)	(4.28) (4.08)	(8.50) (8.42)
E	$C_{21}H_{19}Cl_2N_3O_4S$	viscous	63	(52.51) (52.45)	(3.99) (3.89)	(8.75) (8.65)
F	$C_{20}H_{16}Cl_3N_3O_3S$	166	61	(49.55) (49.45)	(3.33) (3.22)	(8.67) (8.42)
G	$C_{22}H_{21}Cl_2N_3O_3S$	170	63	(55.23) (55.13)	(4.22) (4.12)	(8.78) (8.65)

Table 2: Infra red spectral data of 3-methyl-5/7- substituted-4- (N-propyl-N-nitrosoamido)- 2- (3,4-dichloro benzoyl) -4H-1,4-Benzothiazines

Compound	Molecular formula	C=O (cm^{-1})	C-Cl (cm^{-1})
A	$C_{21}H_{19}Cl_2N_3O_3S$	1585, 1645	-
B	$C_{22}H_{21}Cl_2N_3O_4S$	1605, 1665	-
C	$C_{21}H_{19}Cl_2N_3O_3S$	1615, 1750	-
D	$C_{22}H_{21}Cl_2N_3O_4S$	1610, 1695	-
E	$C_{21}H_{19}Cl_2N_3O_4S$	1605, 1685	-
F	$C_{20}H_{16}Cl_3N_3O_3S$	1615, 1650	790
G	$C_{22}H_{21}Cl_2N_3O_3S$	1610, 1640	-

Table 3: NMR Spectral data of 3-methyl-5/7- substituted-4- (N-propyl-N-nitrosoamido)- 2- (3,4-dichloro benzoyl) -4H-1,4-Benzothiazines

S.No	Molecular formula	Solvent	δ(ppm)	Hydrogen	Multiplicity	Assignment
A	$C_{21}H_{19}Cl_2N_3O_3S$	$CDCl_3$	6.72-7.79	6	Multiplet	Aromatic protons
			1.66	3	Singlet	CH_3 protons at C_3
			2.25	3	Singlet	CH_3 protons at C_5
			0.90 –0.98	3	Triplet	CH_3 protons at C'_1 of propyl group
			1.35-1.42	2	Multiplet	CH_2 protons at C'_2 of propyl group
			2.7--3.05	2	Triplet	CH_2 protons at C'_3 of propyl group
B	$C_{22}H_{21}Cl_2N_3O_4S$	$CDCl_3$	6.63-7.68	6	Multiplet	Aromatic protons
			3.4 - 4.1	2	Quartet	CH_2 protons of C_2H_5
			1.30-1.4	3	Triplet	CH_3 protons of C_2H_5
			1.73	3	Singlet	CH_3 protons at C'_3
			3.4-3.61	2	Triplet	CH_2 protons at C'_1 of propyl group
			1.48-1.55	2	Multiplet	H_2 protons at C'_2 of propyl group
			0.96-1.10	3	Triplet	CH_3 protons at C'_3 of propyl group
C	$C_{21}H_{19}Cl_2N_3O_3S$	$CDCl_3$	6.82-7.36	6	Multiplet	Aromatic protons
			1.60	3	Singlet	CH_3 protons at C_3
			2.25	3	Singlet	CH_3 protons at C_7
			0.91-1.0	3	Triplet	CH_3 protons at C'1 of propyl group
			1.35-1.48	2	Multiplet	CH_2 protons at C'_2 of propyl group
			2.5-2.8	2	Triplet	CH_3 protons at C'3 of propyl group
D	$C_{22}H_{21}Cl_2N_3O_4S$	$CDCl_3$	6.53-7.77	6	Multiplet	Aromatic protons
			3.86-4.10	2	Quartet	CH_2 protons of C_2H_5
			1.20-1.25	3	Triplet	CH_3 protons of C_2H_5

			1.67	3	Singlet	CH_3 protons at C_3
			2.4 - 3.1	2	Triplet	CH_2 protons at C'_1 of propyl group
			1.34-1.38	2	Multiplet	CH_2 protons at C'_2 of propyl group
			0.86-0.9	3	Triplet	CH_3 protons at C'_3 of propyl group
E	$C_{21}H_{19}Cl_2N_3O_4S$	$CDCl_3$	6.54 -7.77	6	Multiplet	Aromatic protons
			3.73	3	Singlet	CH_3 protons of OCH3
			1.71	3	Singlet	CH_3 protons at C_3
			3.1-3.3	2	Triplet	CH_2 protons at C'_1 of propyl group
			1.54-1.65	2	Multiplet	CH_2 protons at C'_2 of propyl group
			0.90-0.96	3	Triplet	CH_3 protons at C'_3 of propyl group
F	$C_{20}H_{16}Cl_3N_3O_3S$	$CDCl_3$	7.03-7.87	6	Multiplet	Aromatic protons
			1.66	3	Singlet	CH_3 protons at C_3
			3.5-4.0	2	Triplet	CH_2 protons at C'_1 of propyl group
			1.60-1.70	2	Multiplet	CH_2 protons at C'_2 of propyl group
			0.95-0.99	3	Triplet	CH_3 protons at C'_3 of propyl group
G	$C_{22}H_{21}Cl_2N_3O_3S$	$CDCl_3$	6.63-7.62	5	Multiplet	Aromatic protons
			1.65	3	Singlet	CH_3 protons of C_3
			2.35	6	Singlet	CH_3 protons at C_5&C_7
			2.9--3.25	2	Triplet	CH_3 protons at C'1 of propyl group
			1.53-1.58	2	Multiplet	CH_2 protons at C'_2 of propyl group
			0.85-0.9	3	Triplet	CH_2 protons at C'3 of propyl group

Results and Discussion:

The synthesis of 3-methyl-5/7- substituted-4- (N-propyl-N-nitrosoamido)- 2- (3,4-dichloro benzoyl) -4H-1,4-benzothiazines is based on the synthesis of substituted 3-methyl -5/7- substituted- 2- (3,4-dichlorobenzoyl) -4H-1,4-Benzothiazines reported elsewhere[1]. 4H-1,4-Benzothiazines are analogs of phenothiazines and like phenothiazines they bear a fold along nitrogen and sulphur axis which is considered responsible to impart them biological activities. So it was considered worthwhile to incorporate the activities of benzothiazines and nitrosoureas into one molecule i.e nitrosourea derivatives of 3-methyl -5/7- substituted- 2- (3,4-dichlorobenzoyl) -4H-1,4-Benzothiazines. 4H-1,4-Benzothiazines are key compounds to synthesize the above mentioned compounds. Here the 4H-1,4-benzothiazines were allowed to undergo isocyanation at 4-position, thereby giving 3-methyl -5/7- substituted- 2- (3,4-dichlorobenzoyl) –4-(N-propyl amido) - 1,4-benzothiazines. These were then let to undergo nitrosation with sodium nitrite in acetic acid.

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