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SYNTHESIS AND ANTIDIABETIC EVALUATION OF SOME 2-SUBSTITUTED BENZOTHIAZOLE DERIVATIVES

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ABSTRACT: A series of 2-substituted benzothiazole derivatives (3a-3j) were synthesized using appropriate synthetic route. Synthesized derivatives were confirmed by IR, ^{1}HNMR and Mass spectrometry. All derivatives were screened for antidiabetic activity using alloxan induced method. Estimation of glucose, cholesterol and triglyceride levels were carried out. It was found that Compounds 3d exhibited significant antidiabetic activity. 3f, 3b and 3a possess a moderate antidiabetic activity.

KEYWORDS: Antidiabetic, Benzothiazole, Chloroacetanilide, Cholesterol, Glucose, Oral Hypoglycaemic, Triglyceride.

INTRUDUCTION: Benzothiazole is widely found in bio-organic and medicinal chemistry with application in drug discovery. [1] It has higher potency and significant biological activities. [2] After the Riluzole discovery as a Glutamate neurotransmission inhibitor, biologists started further exploitation of benzothiazole moiety. [3] Benzothiazole derivatives possess activities such as anti-tumour[4, 5], anti-microbial [6], anti-diabetic [7], anti-convulsant [8] anti-oxidant[9]; central muscle relaxants [10], antipsychotic and diuretic. [11] Research paper for docking study reflects that it has antidiabetic activity. [12] Diabetes mellitus means pancreas can't produce enough insulin so glucose in the blood can't be absorbed into the cells of the body. Symptoms are frequent urination, lethargy, excessive thirst and hunger. For treatment changes in diet, oral hypoglycaemic and in certain cases daily injection of insulin is needed. [13] Alloxan induced diabetes model appears to be the most reliable and reproducible method. [14] Diabetes is of major health concern for world hence there is a need to search for alternate molecules. Kumar et al.has reported synthesis and molecular docking studies of antidiabetic activity of 2-aminobenzothiazole derivatives. This paper reflects that bromo and chloro substitutions are favourable for antidiabetic activity. [12] Literature survey reflects that Benzothiazole possess antidiabetic property and further exploitation of benzothiazole mayoffer choice of antidiabeticdrug. This has made us to research antidiabetic potential of benzothiazole derivatives.

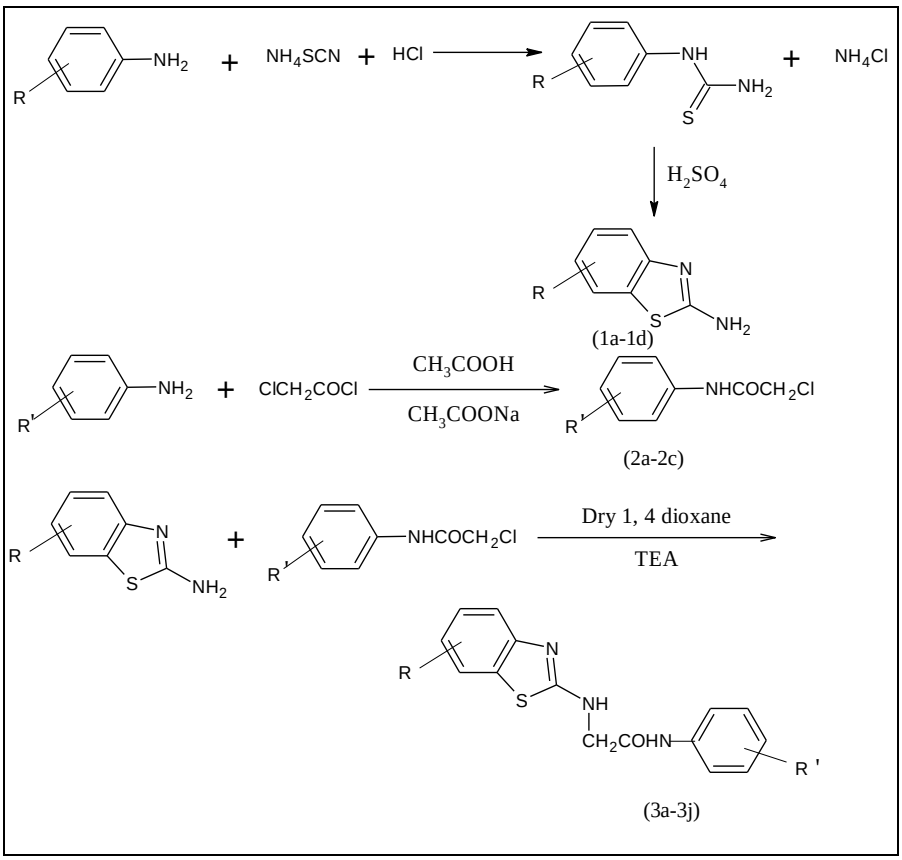
MATERIAL AND METHOD:

All chemicals were obtained from Merck Ltd., India and used without further purification. The reactions were carried out by conventional method. Melting points were determined in open capillary using melting point apparatus and are uncorrected. The purity of synthesized compounds was monitored by TLC using silica gel-G precoated plate. The structures of title (3a-3j) compounds were confirmed by IR, ^{1}H-NMR and Mass spectral analysis.

Procedurefor synthesis of 2-amino benzothiazole derivatives (1a-1d): Equimolarquantities of substituted anilines and ammonium thiocyanate were dissolved in ethanol containing conc. hydrochloric acid keep as it is for 30 minutes, to this conc. sulphuric acid was added and the reaction mixture was refluxed until the reaction completion was observed in TLC. The precipitate was washed with cold water to make it acid free, then it was dried and recrystallized. [2, 3]

Procedurefor synthesis of para substituted chloro acetanilide derivatives (2a-2c):
Substituted anilines (0.1 moles) were dissolved in glacial acetic acid and saturated solution of sodium acetate. To this chloroacetyl chloride (0.12 moles) was added drop wise with stirring. Reaction was monitored by TLC. After half an hour white precipitate was obtained, it was filtered, dried and recrystallized from alcohol.[9]

Procedure for synthesis of series of 2- substituted amino benzothiazole derivatives (3a-3j):
Equimolarquantities of substituted 2-amino benzothiazole and substituted chloroacetanilide were dissolved in dry 1,4-dioxane. To this triethyl amine was added, reaction mixture was refluxed for 2-4 hours till the reaction completion. Reaction was monitored by TLC. It was then cooled, poured onto crushed ice. Solid precipitate was filtered, dried and recrystallized from ethanol.



Synthesis of 2-substituted benzothiazole derivatives

(Where, R= 4-Br, 3-Cl, 4-NO_2, 3-NO_2 and R'= 4-Br, 4-Cl, 4-NO_2)

RESULT AND DISCUSSION: Physicochemical data, IR, ^{1}HNMR, Mass spectrometry, Antidiabetic activity readings for Glucose level, Cholesterol level, and Triglyceride level is given below.

Table 1: Physicochemical data of intermediate compounds;

Compound Code	R/R'	Molecular formula	Molecular weight	Melting point (°C)	% yield	Rf value
1a	6-Br	$C_7H_5N_2SBr$	229.09	201-203	87.1	0.58
1b	5-Cl	$C_7H_5N_2SCl$	184.65	186-188	82.5	0.52
1c	6-NO_2	$C_7H_5N_3SO_2$	195.19	123-124	89.5	0.54
1d	5-NO_2	$C_7H_5N_3SO_2$	195.19	145-148	78.7	0.50
2a	4-Br	$C_8H_7NOBrCl$	248.50	180-182	81.2	0.53
2b	4-Cl	$C_8H_7NOCl_2$	204.05	172-174	78.6	0.52
2c	4-NO_2	$C_8H_7N_2O_3Cl$	214.61	125-127	81.8	0.54

Table 2: Physicochemical data of title compounds (3a-3j):

Compound Code	R'	R	Molecular formula	Molecular weight	Melting point (°C)	% yield	Rf value
3a	6-Br	4-Br	$C_{15}H_{11}N_3OSBr$	441.02	165-166	50.01	0.68
3b	6-Br	4-NO_2	$C_{15}H_{11}N_4O_3SBr$	407.11	124-126	73.74	0.62
3c	6-NO_2	4-NO_2	$C_{15}H_{11}N_5O_5S$	373.22	099-101	70.57	0.60
3d	6-Br	4-Cl	$C_{15}H_{11}N_3SOBrCl$	396.63	150-152	82.55	0.72
3e	6-NO_2	4-Br	$C_{15}H_{11}N_4SO_3Br$	407.12	109-111	80.61	0.69
3f	5-Cl	4-Cl	$C_{15}H_{11}N_3SOCl_2$	352.21	152-155	82.56	0.63
3g	5-Cl	4-NO_2	$C_{15}H_{11}N_4SO_3Cl$	362.72	150-152	66.12	0.67
3h	5-NO_2	4-Cl	$C_{15}H_{11}N_4SO_3Cl$	362.72	155-157	65.00	0.66
3i	5-NO_2	4-Br	$C_{15}H_{11}N_4SO_3Br$	407.11	110-113	67.12	0.62
3j	5-NO_2	4-Cl	$C_{15}H_{11}N_5SO_5$	373.31	125-127	56.25	0.68

6-bromo-(p-bromoacetanilido)-2-aminobenzothiazole(3a):
Cream colour solid, IR (KBr) ν_{max} in cm^{-1}: 3265 (N-H), 2929 (C-H), 1670 (O=C-N), 1608 (Ar C=C), 1550(N-H), 1246(C-N),1134(Ar-Cl),1072(Ar-Br),701(C-S);^{1}HNMR(DMSO-d_6)δ:4.261(s,2H,-CH_2), 6.541-7.631 (m, 7H, Two aromatic systems), 10.464 (s, H, -NH); -NH Recognition spectra using D_2O as solvent is observed.

6-bromo-(4-nitroacetanilido)-2-aminobenzothiazole(3b):
Dark yellow colour solid, IR (KBr) ν_{max} in cm^{-1}: 3479 (N-H), 2951 (C-H), 1672 (O=C-N), 1631 (Ar C=C), 1600 (N-H),1481 (N=O), 1182 (C-N), 1072 (Ar-Br), 698 (C-S).

6-nitro-(4-nitroacetanilido)-2-aminobenzothiazole(3c):
Fresh yellow colour solid, IR (KBr) ν_{max} in cm^{-1}: 3480 (N-H), 2935 (C-H), 1684 (O=C-N), 1622 (Ar C=C), 1570, 1506 (2 N=O), 1336, 1301 (2N=O), 1255 (C-N), 690 (C-S).

6-bromo-(4-chloroacetanilido)-2-aminobenzothiazole(3d):

Cream colour solid, IR (KBr) ν_{max} in cm^{-1}: 3370 (N-H), 2953 (C-H), 1666 (O=C-N), 1614 (Ar C=C), 1554(N-H),1194(C-N),1097(Ar-Cl),1012(Ar-Br),717(C-S);^{1}HNMR(DMSO-d_6)δ:4.237(s,2H,-CH_2), 7.355-7.615 (m, 7H, Two aromatic systems), 10.404 (s, H, -NH).

6-nitro-(4-bromoacetanilido)-2-aminobenzothiazole (3e): Yellow colour solid, IR (KBr) νmax in cm^{-1}: 3480 (N-H), 2951 (C-H), 1672 (O=C-N), 1631 (Ar C=C), 1600(N-H),1481,1298(N=O),1182(C-N),1072(Ar-Br),698(C-S);^{1}HNMR(DMSO-d_6)δ:4.291(s, 2H, -CH_2), 7.211-8.262 (m, 7H, Two aromatic systems), 10.441 (s, H, -NH).

5-chloro-(4-chloroacetanilido)-2-aminobenzothiazole (3f):
Faint yellow colour solid, 3400(N-H),2953(C-H),1666(O=C-N),1612(ArC=C),1550(N-H),1194(C-N),1098 (Ar-Cl),1073(Ar-Br),717(C-S);^{1}HNMR(DMSO-d_6)δ:4.237(s,2H,-CH_2),7.355-7.615(m, 7H, Two aromatic systems), 10.404 (s, H, -NH).

5-chloro-(4-nitroacetanilido)-2-aminobenzothiazole(3g):
Fresh yellow colour solid, 3400 (N-H), 2941 (C-H), 1686 (O=C-N), 1622 (Ar C=C), 1572 (N-H), 1500,1341(N=O),1175 (C-N), 1113 (Ar-Cl), 689 (C-S) ; ^{1}H NMR (DMSO-d_6) δ: 4.349 (s, 2H,CH_2), 6.581-8.268 (m, 7H, Two aromatic systems), 10.917 (s, H, -NH); -NH Recognition spectra using D_2O as solvent is observed; MS m/z: 361.09 [M^+ ion peak], 315.09 [Base Peak (Ar-NO_2gives intense peak)].

5-nitro-(4-chloroacetanilido)-2-aminobenzothiazole(3h):
Greyish yellow colour solid, IR (KBr) ν_{max} in cm^{-1}: 3400 (N-H), 2960 (C-H), 1670 (O=C-N), 1489(N-H),1551,1339(N=O),1192(C-N),1096(Ar-Cl),733(C-S);^{1}HNMR(DMSO-d_6)δ:4.237(s,2H, -CH_2), 7.355-7.615 (m, 7H, Two aromatic systems), 10.404 (S, H, -NH); -NH Recognition spectra using D_2O as solvent is observed; MS m/z: 360.90 [M^+ ion peak], 315.15 [Base Peak: Ar-NO_2gives intense peak].

5-nitro-(4-bromoacetanilido)-2-aminobenzothiazole(3i):
Yellow colour solid,IR (KBr) ν_{max} in cm^{-1}: 3400 (N-H), 2901 (C-H), 1686 (O=C-N), 1624 (Ar C=C), 1487 (N-H),1543, 1337 (N=O) 1200 (C-N), 1072 (Ar-Br), 690 (C-S).

5-nitro-(4-nitroacetanilido)-2-aminobenzothiazole(3j)
Yellow colour solid, IRincm^{-1}[KBr]ν_{max}:3490(N-H),2961(C-H),1686(O=C-N),1624(ArC=C),1597(N-H),1572,1506(N=O),1337,1296(N=O),1175(C-N),689(C-S);^{1}HNMR(DMSO-d_6)δ: 4.323 (s,2H, CH_2), 6.573-8.262 (m, 7H, Two aromatic systems),10.93 (S, H, -NH); -NH Recognition spectra using D_2O as solvent is observed.

Oral acute toxicity study:
Oral acute toxicity study was carried out to determine the lethal dose of the test compounds. Groups of animals of non-pregnant female albino wistar were dosed in a stepwise procedure using the fixed doses of 5, 50, 300 and 2000 mg/kg. This procedure continues until the dose causing evident toxicity or no more than one death is identified. The suspension of test compounds in sodium CMC was administered orally. The first test group received a dose of 5 mg/kg. The animals were observed for 24 hr. Similarly other groups of animals were administered the test compounds at a dose of 50, 300 and 2000 mg/kg and observations were made on subsequent day after 24 h. of administration of dose for mortality. The lethal dose of compound 3a was found 1000mg/kg. Hence the $1/10^{th}$ of the lethal dose i.e. 100mg/kg was selected as dose of test compound for the study.

Antidiabetic activity: All the title compounds synthesized during the present work were

subjected to alloxan induced antidiabetic activity. The readings for blood glucose, cholesterol and triglycerides were taken because Diabetes mellitus is a metabolic disorder. Following are the requirements for activity.[17, 18]

Standard drug: Pioglitazone (10 mg/kg body weight in 0.5% CMC solution) bulk drug.

Test compounds: The test compounds (100 mg/kg body weights in 0.5% CMC solution).

Other Necessities: Alloxan monohydrate, Glucometer (ACCU-CHEK Active-Roche), Disposable syringe (1ml tuberculin syringe), feeding needles (for oral dose), Clinical analyser.

Animals used: Albino wistar female rats of weight range 150-200gm.

Procedure used for induction of experimental diabetes by Alloxan is as follows:
The acclimatized animals Albino wistar rats were kept for fasting for 18 hour with water ad libitum and then alloxan monohydrate (120mg/kg i.p.) in normal saline was administered. After 1 hour of alloxan administration the animals had givenad libitum, 5% dextrose solution which was administered via feeding bottle for a day to overcome the early hypoglycemic phase. Hyperglycemia was confirmed after 72 hours for this blood was collected by tail tipping method and 0day readings for Glucose, Cholesterol and Triglycerides were taken. Then treatment of test compounds and standard was started daily for 12days. Experimental Design is as follows.

Experimental design: Animals were divided into 13 groups and 6 animals in each group. Group1: Normal control group, Nondiabetic rats**;** Group2: Diabetic animals without any treatment; Group3: Diabetic animals receive Pioglitazone hydrochloride (10mg/Kg b.w. p.o. resp. for 12 days continuously**;** Group4-13: Diabetic animals will receive compounds 3a-3j in a single dose of 100mg/Kg b.w. p.o. resp. for 12 days continuously.

Parameter Estimation: Blood was withdrawn from the tail vein each time by tail tipping method. At the end of 0, 3, 6, 9, 12 days glucose was estimated and at the end of 0, 6, 12 days along with glucose Cholesterol, Triglycerides were also estimated. The above protocol was approved by animal ethics committee.

Table3: Effect of title compounds (3a-3j) on blood glucose level data:

Drug	Blood glucose level mg/dl (Mean±SEM)				
	O day	3 day	6 day	9 day	12 day
Control	107.7±2.1	108.5±1.8	107.5±2.9	108.6±2.1	108.8±1.3
Diabetic Control	363.0±2.5	361.2±2.8	361.7±2.4	361.3±2.3	360.1±1.4
Standard	361.1±3.9	215.7±2.4**	151.1±3.2**	122.3±4.3**	101.2±2.2**
3a	357.0±2.6	235.2±3.2**	155.3±4.9**	132.4±4.7**	119.3±3.6**
3b	354.7±2.8	230.2±2.5**	154.7±3.8**	128.1±2.5**	115.4±2.1**
3c	353.0±2.2	277.4±3.9**	204.3±4.3**	160.6±2.4**	135.3±3.6**
3d	363.3±3.5	225.2±1.7**	150.4±3.5**	119.9±2.1**	102.8±1.8**
3e	382.8±4.4	272.1±2.6**	208.3±5.3**	170.5±4.1**	142.7±4.3**
3f	366.8±2.3	220.2±2.9**	152.8±3.2**	126.3±3.1**	110.5±2.3**
3g	368.8±3.2	240.3±2.1**	157.5±2.1**	139.5±2.1**	121.3±3.4**

3h	349.7±2.5	284.3±5.1**	210.1±3.3**	180.6±2.9**	145.2±4.5**
3i	350.7±4.9	275.5±4.9**	236.8±4.3**	190.8±3.7**	152.8±5.1**
3j	357.7±4.5	274.3±3.8**	239.6±5.3**	198.6±4.3**	155.0±6.9**

The values are expressed as mean ± SEM. n=6 animals in each group, Statistical significant test for comparison was done by ANOVA, followed by Dunnett's t-test. The blood glucose values of groups are compared with diabetic control animals, values ***p<0.001, **p<0.01, *p<0.05

Table 4: Effect of title compounds (3a-3j) on blood cholesterol level data:

Drug	Cholesterol level mg/dl (Mean±SEM)		
	O day	6 day	12 day
Control	139.3±6.1	138.4±5.3	139.5±6.7
Diabetic control	346.3±6.1	347.3±5.4	346.4±5.9
Standard	348.5±6.4	189.4±5.1**	131.3±2.5**
3a	346.4±3.3	198.3±2.9**	134.5±2.5**
3b	342.2±5.5	193.5±3.3**	133.4±3.1**
3c	341.8±6.8	262.2±4.9**	156.6±2.4**
3d	349.9±5.5	190.8±1.6**	132.6±3.9**
3e	351.6±3.8	131.4±3.2**	139.7±2.5**
3f	349.5±1.0	192.4±4.3**	131.6±5.3**
3g	348.4±4.5	216.5±1.1**	160.8±2.5**
3h	352.3±3.3	201.9±2.5**	162.2±4.4**
3i	354.3±2.3	234.1±3.5**	133.4±6.4**
3j	355.9±2.8	239.2±2.2**	131.3±2.8**

The values are expressed as mean ± SEM. n=6 animals in each group, Statistical significant test for comparison was done by ANOVA, followed by Dunnett's t-test. The blood glucose values of groups are compared with diabetic control animals, values ***p<0.001, **p<0.01, *p<0.05.

Table 5: Effect of title compounds (3a-3j) on blood Triglyceride level data:

Drug	Triglyceride level mg/dl (Mean±SEM)		
	O day	6 day	12 day
Control	120.4±9.8	121.5±8.8	120.3±9.6
Diabetic control	251.5±7.5	252.4±6.8	251.7±7.1
Standard	249.4±8.4	188.5±7.1**	121.5±6.5**
3a	248.5±7.5	222.5±8.0**	130.2±7.5**
3b	246.9±8.4	190.4±7.2**	126.2±3.8**
3c	248.8±7.8	206.3±6.8**	115.2±7.6**
3d	246.6±8.5	191.7±6.7**	124.3±6.9**

3e	254.4±9.8	204.5±5.9**	125.4±8.6**
3f	248.4±7.0	192.9±7.5**	120.5±7.4**
3g	251.6±6.5	205.4±6.1**	147.5±3.5**
3h	253.2±5.3	212.5±7.5**	142.4±5.4**
3i	257.3±6.3	219.6±8.5**	139.6±6.4**
3j	254.4±5.8	221.8±9.0**	140.8±7.8**

The values are expressed as mean ± SEM. n=6 animals in each group, Statistical significant test for comparison was done by ANOVA, followed by Dunnett's t-test. The blood glucose values of groups are compared with diabetic control animals, values ***p<0.001, **p<0.01, *p<0.05

CONCLUSION: Benzothiazole is important scaffold showing antidiabetic activity. As per present study bromo and chloro substitutions are favourable for antidiabetic activity. Particularly Benzothiazole core has antidiabetic potential.Further structural modifications may lead to a discovery of a drug candidate.

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