

SYNTHESIS AND *IN VIVO* DIURETIC ACTIVITY OF BIPHENYL
BENZOTHAZOLE-2-CARBOXAMIDE DERIVATIVES

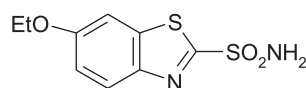
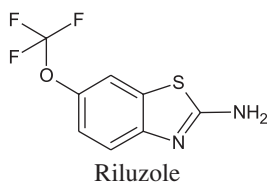
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Abstract: A series of N-[(substituted)1,3-benzothiazol-2-yl]-1,1'-biphenyl-4-carboxamides was synthesized by reaction between biphenyl acid chloride and 2-aminobenzothiazole. The synthesized compounds were screened *in vivo* for diuretic activity. Among the series, N-(1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (**II**) was found to be the most promising candidate.

Keywords: diuretic activity, biphenyl, benzothiazole, carboxamide

Diuretics are important class of drugs used in the treatment of edema, heart failure or in hepatic, renal or pulmonary disease. They are used, alone or in combination of antihypertensive agents, in the treatment of high blood pressure. So there exist urgent clinical requirements for novel, selective diuretics (high ceiling (loop)/potassium sparing/osmotic) devoid of many of the unpleasant side effects *viz.* hypokalemia, hyperuricemia etc. associated with current diuretic regimens. Benzothiazole derivatives are of particular interest within the realm of medicinal chemistry (1). They possess selective analgesic (2), antiinflammatory (3), antitumor (4), antitubercular (5), anticonvulsant (6), diuretic (7) and antimicrobial (8) properties etc. Biologist's attention was drawn to this series when the pharmacological profile of Riluzole was discovered. Thereafter, benzothiazole derivatives have been studied extensively and found to have diverse chemical reactivity and broad spectrum of biological activity. Ethoxzolamide, a benzothiazole derivative is a clinically effective diuretic carbonic anhydrase inhibitor. It is orally active but upset the acid-base balance and could only be given intermittently.



Ethoxzolamide

In pursuit of this goal it was proposed to carry out synthesis and diuretic screening of aforesaid heterocycle with appropriate substitution with improved efficacy and decreased toxicity.

EXPERIMENTAL

All chemicals were supplied by E. Merck (Darmstadt, Germany) and S.D. Fine Chemicals (India). Melting points were determined by open tube capillary method and are uncorrected. Purity of the compounds was checked by thin layer chromatography (TLC) on silica gel G plates 60 F₂₅₄ (0.2 mm), with the solvent system: toluene-ethyl formate-formic acid (5 : 4 : 1, v/v/v) and benzene-methanol (8 : 2, v/v). The spots were located under iodine vapors and UV light. The IR spectra were recorded (in KBr) on Bruker PCIR spectrophotometer, ¹H-NMR spectra on Bruker DPX 300 instrument, in DMSO-d₆ using TMS as an internal standard and mass spectra on MASPEC (MSW/9629) instrument.

Synthesis of biphenyl acid chloride

Biphenyl acid (0.02 mole) was suspended in benzene (25 mL), then heated with thionyl chloride

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(0.36 mole, 26 mL) for 6 h on an oil bath at 85°C to yield acid chloride.

IR (KBr, cm^{-1}): 1644 (C-H overtone, arom), 1558 (C=C str., phenyl), 1679 (C=O str.), 1602 (diphenyl); $^1\text{H NMR}$ (DMSO- d_6 , δ , ppm): 7.35-7.47 (m, 3H, H-2,6,4'), 7.64 (t, 4H, H-3',5',2',6'), 8.12 (d, 2H, H-3,5).

General procedure for the synthesis of substituted 2-aminobenzothiazole (Ia-j)

Desired substituted 2-aminobenzothiazoles (Ia-j) were synthesized by reported procedure (6).

General procedure for the synthesis of N-{substituted}1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide derivatives (II-XII)

To a mixture of substituted aminobenzothiazole (0.02 mol) and 20 mL of 10% NaOH solution in well-corked conical flask was added 2 mL of biphenyl acid chloride (0.5 mL at a time), with constant shaking and cooling in water. The mixture was shaken vigorously for 20 min until the odor of acid chloride had disappeared. The reaction mixture was kept alkaline. Then, the solid product was filtered off and washed with water and recrystallized from aqueous ethanol.

N-(1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (II)

IR (KBr, cm^{-1}): 1644 (C-H overtone, arom), 1604 (C = C str. phenyl), 3468 (N-H str.), 1714 (C=O str.), 1282 (C-N str.), 1599 (diphenyl), 1396 (benzothiazole); $^1\text{H NMR}$ (DMSO- d_6 , δ ppm): 7.32 (d, 1H, H-7), 7.42 (t, 2H, H-2',6'), 7.47 (d, 2H, H-6,5), 7.74 (s, 3H, H-3'',4'',5''), 7.84 (d, 2H, H-2'',6''), 7.99 (d, 1H, H-4), 8.21 (d, 2H, H-3',5'), 12.91 (s, 1H, -CONH-); MS (m/z): 330 (M^+).

N-(4-methyl-1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (III)

IR (KBr, cm^{-1}): 1727 (C-H overtone, arom), 1644 (C = C str. phenyl), 3577 (N-H str.), 1649 (C=O str.), 1306 (C-N str.), 3051 (C-H str. CH_3), 1606 (diphenyl), 1404 (benzothiazole) $^1\text{H NMR}$ (DMSO- d_6 , δ ppm): 2.45 (s, 3H, $-\text{CH}_3$), 6.88-6.97 (m, 4H, H-5,6,2',6'), 7.02-7.09 (m, 4H, H-2'',3'',5'',6''), 7.45 (s, 1H, H-7), 7.50 (s, 3H, H-4,3',5'), 8.68 (s, 1H, -CONH-); MS (m/z): 345 (M^+ +1).

N-(5-methyl-1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (IV)

IR (KBr, cm^{-1}): 1671 (C-H overtone, arom), 1548 (C = C str. phenyl), 3537 (N-H str.), 1644 (C=O str.), 1278 (C-N str.), 2965 (C-H str. $-\text{CH}_3$),

1604 (diphenyl), 1402 (benzothiazole); $^1\text{H NMR}$ (DMSO- d_6 , δ , ppm): 2.50 (s, 3H, $-\text{CH}_3$), 7.39-7.49 (m, 5H, H-6,2',6',3'',5''), 7.60-7.70 (m, 4H, H-7,2'',6'',4''), 8.09-8.19 (m, 3H, H-4,3',5'), 10.31 (s, 1H, -CONH-); MS (m/z): 345 (M^+ +1).

N-(6-methyl-1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (V)

IR (KBr, cm^{-1}): 1644 (C-H overtone, arom), 1592 (C = C str. phenyl), 3501 (N-H str.), 1696 (C=O str.), 1271 (C-N str.), 2897 (C-H str. $-\text{CH}_3$), 1567 (diphenyl), 1352 (benzothiazole); $^1\text{H NMR}$ (DMSO- d_6 , δ , ppm): 2.20 (s, 3H, $-\text{CH}_3$), 7.38 (t, 1H, H-5), 7.46 (t, 3H, H-2',6',7), 7.69 (d, 2H, H-3'',5''), 7.76 (d, 3H, H-2'',6'',4''), 7.98 (d, 3H, H-4,3',5'), 10.32 (s, 1H, -CONH-); MS (m/z): 345 (M^+ +1).

N-(4-methoxy-1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (VI)

IR (KBr, cm^{-1}): 1759 (C-H overtone, arom), 1599 (C = C str. phenyl), 3429 (N-H str.), 1698 (C=O str.), 1275 (C-N str.), 3062 (C-H str. $-\text{OCH}_3$), 1218 (C-O-C str.) 1549 (diphenyl), 1368 (benzothiazole); $^1\text{H NMR}$ (DMSO- d_6 , δ , ppm): 3.14 (s, 3H, $-\text{OCH}_3$), 7.26 (m, 3H, H-5,2',6'), 7.36 (m, 5H, H-6,7,3'',4'',5''), 7.44 (m, 2H, H-2'',6''), 7.54 (m, 2H, H-3',5'), 9.83 (s, 1H, -CONH-); MS (m/z): 361 (M^+ +1).

N-(6-methoxy-1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (VII)

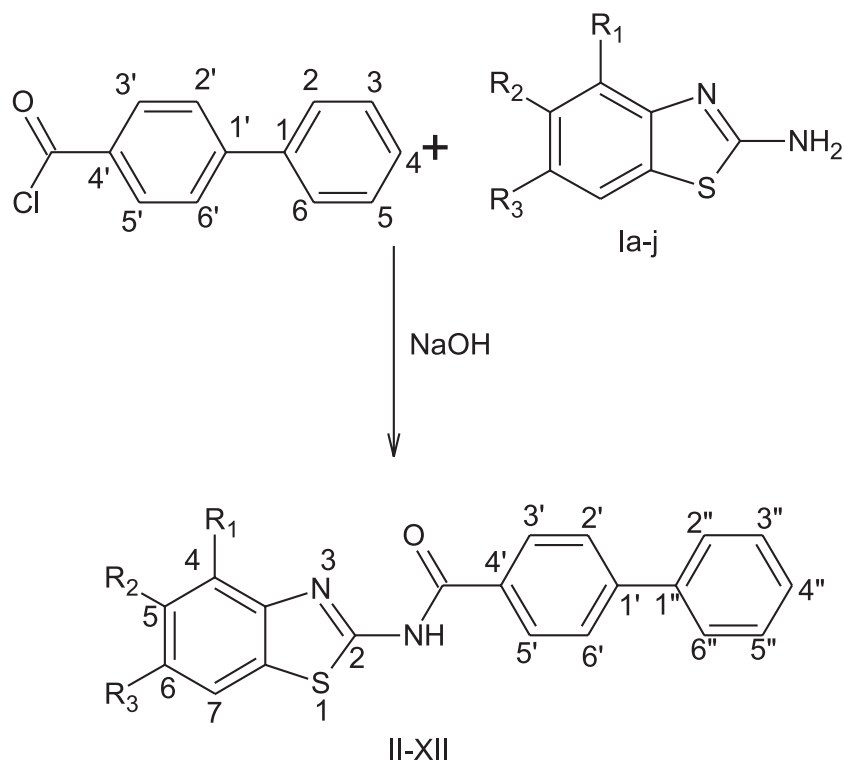
IR (KBr, cm^{-1}): 1601 (C-H overtone, arom), 1536 (C = C str. phenyl), 3510 (N-H str.), 1672 (C=O str.), 1264 (C-N str.), 1219 (C-O-C str.) 1563 (diphenyl), 1219 (benzothiazole); $^1\text{H NMR}$ (DMSO- d_6 , δ , ppm): 3.53 (s, 3H, $-\text{OCH}_3$), 7.42-7.53 (m, 4H, H-5,7,2',3'), 7.72-7.84 (m, 5H, H-2'',3'',4'',5'',6''), 8.03 (d, 3H, H-4,3',5'), 10.32 (s, 1H, -CONH-); MS (m/z): 361 (M^+ +1).

N-(5-chloro-1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (VIII)

IR (KBr, cm^{-1}): 3061 (C-H str. arom), 1500 (C = C str. phenyl), 3416 (N-H str.), 1677 (C=O str.), 1316 (C-N str.), 737 (C-Cl str.) 1487 (diphenyl), 1400 (benzothiazole); $^1\text{H NMR}$ (DMSO- d_6 , δ , ppm): 7.04 (d, 2H, H-2',6'), 7.35 (d, 2H, H-3'',5''), 7.65 (m, 3H, H-2'',6'',4''), 8.03 (m, 5H, H-4,6,7,3',5'), 8.58 (s, 1H, -CONH-); MS (m/z): 365 (M^+).

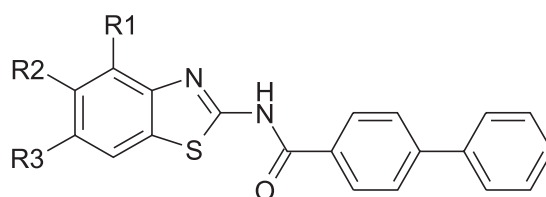
N-(6-chloro-1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (IX)

IR (KBr, cm^{-1}): 1671 (C-H overtone, arom.), 1593 (C = C str. phenyl), 3499 (N-H str.), 1649



Scheme 1

Table 1. Physical data of biphenylbenzothiazole-2-carboxamide derivatives



Compound	R ₁	R ₂	R ₃	Mol. wt.	Mol. formula	M.p. (°C)	R _f	Yield
II	H	H	H	330	C ₂₀ H ₁₄ N ₂ OS	200-202	0.9	80%
III	CH ₃	H	H	344	C ₂₁ H ₁₆ N ₂ OS	206-208	0.7	60%
IV	H	CH ₃	H	344	C ₂₁ H ₁₆ N ₂ OS	120-122	0.6	80%
V	H	H	CH ₃	344	C ₂₁ H ₁₆ N ₂ OS	140-142	0.8	50%
VI	OCH ₃	H	H	360	C ₂₁ H ₁₆ N ₂ O ₂ S	70-72	0.7	60%
VII	H	H	OCH ₃	360	C ₂₁ H ₁₆ N ₂ O ₂ S	80-82	0.8	60%
VIII	H	Cl	H	365	C ₂₀ H ₁₃ ClN ₂ OS	76-78	0.6	80%
IX	H	H	Cl	365	C ₂₀ H ₁₃ ClN ₂ OS	180-182	0.7	70%
X	H	H	F	348	C ₂₀ H ₁₃ FN ₂ OS	120-122	0.8	60%
XI	H	Cl	F	383	C ₂₀ H ₁₂ ClFN ₂ OS	80-82	0.5	70%
XII	H	H	Br	409	C ₂₀ H ₁₃ BrN ₂ OS	150-152	0.8	80%

Table 2.: Diuretic activity of biphenylbenzothiazole-2-carboxamide derivatives

TREATMENT	DOSE (mg/kg body wt.)	TOTAL URINARY OUTPUT (mL)	NORMAL SALINE INTAKE (mL)	URINARY EXCRETION (%)	DIURESIS		
					DIURETIC ACTION	DIURETIC ACTIVITY	Lipschitz value
II	45	16.08 ± 0.650 **	4.91 ± 0.416	327.49	2.8	1.75	2.03
III	45	4.4 ± 0.351	5.33 ± 0.247	82.55	0.7	0.43	0.55
IV	45	5.83 ± 0.926	4.83 ± 0.511	120.70	1.0	0.62	0.73
V	45	4.43 ± 0.578	4.66 ± 0.166	95.06	0.8	0.5	0.56
VI	45	4.31 ± 0.541	4.83 ± 0.401	89.23	0.7	0.43	0.54
VII	45	4.58 ± 0.419	4.85 ± 0.390	94.44	0.8	0.5	0.57
VIII	45	7.86 ± 0.616	4.73 ± 0.256	166.17	1.4	0.87	0.99
IX	45	8.25 ± 0.311 *	4.60 ± 0.588	179.34	1.5	0.93	1.04
X	45	8.28 ± 0.806 *	5.00 ± 0.387	165.60	1.4	0.87	1.04
XI	45	5.16 ± 0.459	5.05 ± 0.2754	102.17	0.8	0.5	0.65
XII	45	8.28 ± 0.864 *	4.96 ± 0.339	166.93	1.4	0.87	1.04
CONT	—	5.75 ± 0.359	4.98 ± 0.329	115.46	1.0	0.62	—
UREA	1000	7.9 ± 0.517	5.66 ± 0.278	139.57	1.2	0.75	1.0
ACET	45	8.9 ± 0.535 **	4.76 ± 0.633	186.97	1.6	1.0	1.12

Each value represents the mean ± S.E.M. (n = 6). * p < 0.05, ** p < 0.01 (Dunnett's multiple comparison test)
CONT= control, ACET= Acetazolamide

$$\text{Urinary excretion} = \frac{\text{Total urinary output}}{\text{Total liquid intake}} \times 100$$

$$\text{Diuretic action} = \frac{\text{Urinary excretion of treated group}}{\text{Urinary excretion of control group}}$$

$$\text{Diuretic activity} = \frac{\text{Diuretic action of treated group}}{\text{Diuretic action of standard group}}$$

(C=O str.), 1293 (C-N str.), 739 (C-Cl str.) 1599 (diphenyl), 1392 (benzothiazole); ¹H NMR (DMSO-d₆, δ, ppm): 7.29-7.35 (m, 2H, H-2',6'), 7.41 (t, 2H, H-3'',5''), 7.59 (d, 2H, H-2'',6''), 7.62 (s, 1H, H-4''), 7.67 (d, 2H, H-5,7), 7.77 (s, 1H, H-4), 8.19 (d, 2H, H-3',5'), 12.57 (s, 1H, -CONH-); MS (m/z): 365 (M⁺).

N-(6-fluoro-1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (X)

IR (KBr, cm⁻¹): 1782 (C-H overtone, arom), 1530 (C = C str. phenyl), 3554 (N-H str.), 1674 (C=O str.), 1256 (C-N str.), 1003 (C-F str.) 1601 (diphenyl), 1397 (benzothiazole); ¹H NMR (DMSO-d₆, δ, ppm): 7.11-7.26 (m, 2H, H-2',6'), 7.42-7.50 (m, 4H, H-4,3'',5'',4''), 7.72-7.81 (m, 4H, H-5,7,2'',6''), 7.95-8.01 (m, 2H, H-3',5'), 11.65 (s, 1H, -CONH-); MS (m/z): 349 (M⁺+1).

N-(5-chloro-6-fluoro-1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (XI)

IR (KBr, cm⁻¹): 3056 (C-H str. arom), 1482 (C = C str. phenyl), 3493 (N-H str.), 1679 (C=O str.), 1293 (C-N str.), 732 (C-Cl str.), 1003 (C-F str.), 1595 (diphenyl), 1401 (benzothiazole); ¹H NMR (DMSO-d₆, δ, ppm): 7.32-7.48 (m, 3H, H-2',6',4''), 7.69-7.79 (m, 4H, H-2'',3'',5'',6''), 7.97-8.01 (m, 2H, H-3',5'), 8.79 (s, 2H, H-4,7), 12.95 (broad peak, 1H, -CONH-); MS (m/z): 384 (M⁺+1).

N-(6-bromo-1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (XII)

IR (KBr, cm⁻¹): 3051 (C-H str. arom), 1551 (C = C str. phenyl), 3578 (N-H str.), 1667 (C=O str.), 1307 (C-N str.), 521 (C-Br str.) 1600 (diphenyl), 1389 (benzothiazole); ¹H NMR (DMSO-d₆, δ, ppm): 7.41-7.51 (m, 3H, H-2',6',4''), 7.61 (d, 1H,

Table 3. Effects of biphenylbenzothiazole-2-carboxamide derivatives on electrolyte excretion

TREATMENT	DOSE (mg/kg body wt.)	ELECTROLYTE CONCENTRATION (mEqL ⁻¹)		
		Na ⁺	K ⁺	Na ⁺ / K ⁺
II	45	4.81 ± 0.574 **	2.117 ± 0.248 **	2.27
III	45	2.40 ± 0.404	0.80 ± 0.139	3.00
IV	45	2.30 ± 0.405	0.933 ± 0.154	2.46
V	45	2.20 ± 0.428	1.10 ± 0.115	2.00
VI	45	1.80 ± 0.089	0.683 ± 0.149	2.63
VII	45	2.40 ± 0.150	0.550 ± 0.131	4.36
VIII	45	2.70 ± 0.307	0.70 ± 0.131	3.85
IX	45	2.90 ± 0.273	1.083 ± 0.140	2.67
X	45	3.20 ± 0.429 *	0.916 ± 0.113	3.49
XI	45	2.30 ± 0.253	0.583 ± 0.104	3.94
XII	45	3.50 ± 0.307 **	1.80 ± 0.115 **	1.94
CONT	—	1.58 ± 0.278	0.633 ± 0.117	2.49
UREA	1000	2.96 ± 0.255 *	0.90 ± 0.121	3.28
ACET	45	3.40 ± 0.194 **	1.417 ± 0.174 **	2.39

Each value represents the mean ± S.E.M. (n = 6). * p < 0.05, ** p < 0.01 (Dunnett's multiple comparison test). CONT = control, ACET = Acetazolamide

H-5), 7.72-7.80 (m, 4H, H-2',3'',5'',6''), 7.87 (d, 2H, H-3',5'), 8.01 (d, 1H, H-7), 8.23 (d, 1H, H-4), 13.03 (broad peak, 1H, CONH-); MS (m/z): 410 (M⁺+1).

Biological activity

Forty-two healthy adult albino rats weighing 180–200 g were used. Each group comprised six animals (n = 6). They were housed in standard environmental conditions (temperature: 25-30°C). The rats were fed with standard diet (Altromin® pellets) and water *ad libitum*. Fifteen hours prior to the experiment food and water were withdrawn. Diuretic activity was measured by collecting total excreted urine (0-5 h) of rat kept in metabolic cage. The cages together with the funnel and measuring cylinder used in the studies were coated with liquid paraffin before each experiment to facilitate the collection of urine with a minimum loss. Each animal was placed in metabolic cage provided with a wire mesh at the bottom and a funnel to collect the urine. Stainless steel sieves were placed in the funnel to retain feces and to allow the urine to pass. Rats were placed in metabolic cages individually as soon as the treatments started. The urine sample was collected for a total period of 5 h (urine collected for initial 20 min was discarded). The test compounds were applied orally at a dose of 45 mg/kg body weights in

5 mL of 0.9% NaCl solution. Control group received 5 mL of 0.9% NaCl solution per kg body weight. The test compounds were compared with two standard diuretics: urea (1 g/kg body weight in 5 mL of 0.9% NaCl solution) and acetazolamide (45 mg/kg body weight in 5 mL of 0.9% NaCl solution). Animal was reused after two-week washout period for remaining test compounds (9).

RESULTS AND DISCUSSION

Chemistry

N-{(substituted)1,3-benzothiazol-2-yl}-1,1'-biphenyl-4-carboxamide derivatives (**II-XII**) described in this study are shown in Table 1 and the reaction sequence for their preparation is outlined in Scheme 1. The required benzothiazoles (**Ia-j**) were prepared by reacting substituted aniline and ammonium thiocyanate in the presence of aqueous hydrochloric acid. Substituted phenylthiourea so formed was cyclized by bromine solution in chloroform. The reaction between biphenyl acid chloride and substituted benzothiazoles in NaOH solution afforded respective benzothiazole carboxamide **II-XII** in 50-80% yield after recrystallization from aqueous ethanol. The purity of the compounds was checked by TLC and elemental analyses. Both analytical and spectral data (¹H-NMR, IR) of all the

synthesized compounds were in full agreement with the proposed structures.

Diuretic activity

The *in vivo* diuretic activity of the synthesized compounds is summarized in Tables 2 and 3. Compounds **II**, **VIII**, **IX**, **X** and **XII** showed good cumulative urine output, among them urinary output of *N*-(1,3-benzothiazol-2-yl)-1,1'-biphenyl-4-carboxamide (**II**) was highly significant 16.08 ± 0.650 ($p < 0.01$), i.e. increased by $> 300\%$ with respect to control. Urinary excretions of compounds **VIII**, **IX**, **X** and **XII** were in between urea (139.57%) and standard acetazolamide (186.97%). Diuretic action of **II** was 2.8 as compared to 1.2 and 1.6 for urea and acetazolamide, respectively. Diuretic activity of compound **II** was found to be 1.75 (1.75 times more potent than acetazolamide), while **VIII**, **IX**, **X** and **XII** were calculated as 0.87, 0.93, 0.87 and 0.87, respectively (Table 2).

The Lipschitz value (the ratio T/U , in which T is the response of the test compound, and U , that of urea treatment, indices of 1.0 and higher are regarded as a positive effect in terms of diuretic activity) shows that **II** is 2 times as potent as urea, as far as urinary output is concerned, and compounds **IX**, **X** and **XII** were nearly equipotent to urea (Table 2).

Compounds **II** and **XII** showed a significant increase in the Na^+ excretion ($p < 0.01$), i.e. 4.81 ± 0.574 and 3.50 ± 0.307 , respectively, which was greater than for standards, i.e. urea (2.96 ± 0.255) and acetazolamide (3.40 ± 0.194). The Na^+ excretion of compound **X** was also significant as compared to urea ($p < 0.05$), i.e. 3.20 ± 0.429 and 2.96 ± 0.255 , respectively (Table 3).

Compounds **II** and **XII** were also found to possess significant kaliuretic property ($p < 0.01$), i.e. 2.11 ± 0.248 and 1.80 ± 0.115 , respectively, with regards to the Na^+/K^+ ratio and it was observed that **XII** is a stronger kaliuretic (1.94) (Table 3).

CONCLUSION

To obtain a non-mercurial diuretic we designed and synthesized a series of biphenylbenzothiazole-2-carboxamide derivatives and evaluated their diuretic potential. The preliminary *in vivo* diuretic studies suggested the following structure activity relationships (SAR):

Compound **II**, a prototype of the series, possesses a strong aquaretic activity when given orally in a single dose.

Substitution at position 6 of benzothiazole ring system with electron withdrawing group (Cl, F, Br) significantly increases urinary excretion.

Compounds with electron releasing group such as $-\text{CH}_3$ or $-\text{OCH}_3$ substitution at any position of benzothiazole ring reduced diuresis.

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