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DESIGN AND SYNTHESIS OF SOME THIAZOLO[3,2-*a*] BENZIMIDAZOLE QUATERNARY SALTS OF POTENTIAL ANTIDIABETIC ACTIVITY[1]

A. A. El-Shorbagi, A. A. Hayallah, N. M. Omar and A. N. Ahmed

Department of Pharmaceutical Organic Chemistry, Faculty of Pharmacy, University of Assiut, Assiut-71526, Egypt

البحث المقدم يتضمن التخليق والدراسات الأقربازينية الأولية لبعض الأملاح الرباعية الجديدة (٥٢ مركب) لمشتقات ٣-أريل-٧،٦-ثنائى الميثيل للثيازولو بنزوثيازولات. تم تخليق هذه المركبات الرباعية عن طريق تفاعل مشتقات ٣-أريل-٧،٦-ثنائى ميثيل ثيازولو بنزوثيازولات (٥ مركبات منها مركبين فقط منشورين) مع مختلف هاليدات الألكيل (ميثيل وإيثيل وبروبيل وبيوتيل وبنزيل) وكلوريد البنزويل وكذلك مع مجموعة تم تحضيرها من مشتقات بروميد الفيناسيل. أما مشتقات ٣-أريل-٧،٦-ثنائى ميثيل ثيازولو بنزوثيازولات فقد تم تحضيرها عن طريق الحلقنة باستخدام بولى فوسفوريك للمشتقات ٦،٥-ثنائى ميثيل-٢-(فيناسيل ثيو) بنزوثيازولات (٥ مركبات منها مركبين فقط منشورين). المشتقات الأخيرة هى ناتج تفاعل البنزاميدازول مع المركبات المناسبة من مجموعة بروميد الفيناسيل المحضرة. أمكن دراسة العديد من هذه المركبات بيولوجيا لتأثيرها الخافض للسكر بالدم. وقد قيست هذه التأثيرات مقارنة بعقارى التولبيوتاميد والميتفورمين. سبعة مركبات من تلك التى قيست أعطت نتائج أعلى ضعفين إلى ثلاث أضعاف نتائج العقاقير القياسية.

The present work reports on the synthesis and preliminary pharmacological investigation of certain new 3-aryl-6,7-dimethyl-9-substituted thiazolo[3,2-a]benzimidazolium salts [(6a-e) - (15a-e), (16e) and (17e)]. These derivatives were synthesized by reacting the 3-aryl-6,7-dimethylthiazolo[3,2-a]benzimidazoles (5a-e) with the appropriate quaternizing agent. Compounds 5a-e were, in turn prepared by cycoldehydration of 5,6-dimethyl-2-(phenacylthio)benzimidazoles (4a-e) in polyphosphoric acid (PPA). The latter derivatives, (4a-e) were obtained by the reaction of 5,6-dimethylbenzimidazole-2-thione (2) with the appropriate phenacyl bromide (3a-e). The effects of the newly synthesized (5a-e) and the quaternary salts on blood glucose level (BGL) was carried out on mice. Tolbutamide and metformine were used as references. Some of the tested compounds have shown a pronounced hypoglycemic activity. The results do permit the assignment of compounds having N9-phenacyl entity as promising antidiabetic agents.

INTRODUCTION

Diabetes mellitus is commonly treated by diet regime, administration of insulin, oral hypoglycemic agents or a combination of these. Limitations of these treatments require the continuous search for new improved oral hypoglycemic agents.[2,3] Reports on the hypoglycemic activity of quaternary salts include: phenacylphosphoranes and phosphonium salts,[4] thiazolo[3,2-a]pyridinium salts, isoxazolylpyridinium salts and pyrazolylpyridinium salts.[5,6] From these, the lead compound; 1-methyl-3-phenacylimidazolium chloride (I) decreased BGL in mice that do not respond to sulfonylureas.[7] Probably, this effect is due to stabilization of hepatic glycogen *via* activation of glycogen synthase and inhibition of glycogen phosphorylase.[8]

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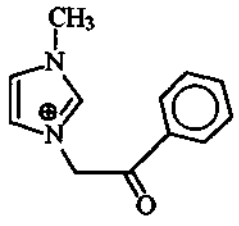

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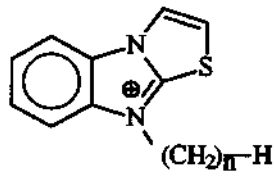

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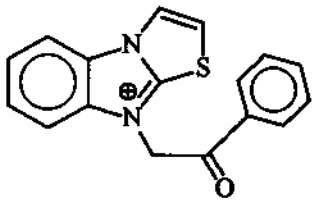

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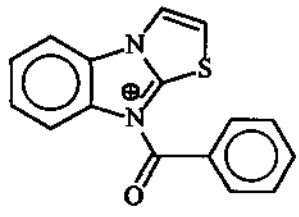
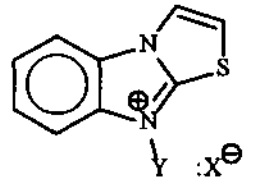


IV

Furthermore, several phenacylimidazolium halides were then synthesized and gave encouraging results as oral hypoglycemic agents.[9] In fact, survey of the literature revealed little information about quaternary salts of thiazolobenzimidazole ring system.[10-13] In view of these findings, it seemed reasonable to synthesize several new series of thiazolobenzimidazolium salts (**II, III and IV**), that incorporate the imidazole entity in a fused N-bridgehead system. A variety of different substituents were also introduced at C3, C6 and C7 in this ring system in order to affect the physicochemical properties of the compounds. Selection of the different quaternizing moieties is based on the following rationale:

1)- Simple alkyl groups of increasing carbon chain would investigate the effect of chain lengthening on biological response. 2)- p-Substituted phenacyl functions would evaluate the p-substituent effect. 3)- Benzyl moiety would explore the effect of introducing an aryl entity separated by one carbon from the quaternized nitrogen of the ring system. 4)- Benzoyl group, could evoke the most closer structural approach to the p-toluenesulfonyl entity of tolbutamide. The other substituents at C3, C6 and C7 of the ring system providing a wide range of physicochemical properties. The selection of such system enables the positive charge to be more stabilized through delocalization on the fused ring system (main contributors **V-VII**). Evaluation of the synthesized quaternary salts as potential oral hypoglycemic agents was also aimed at.



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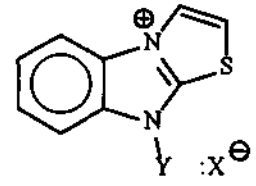

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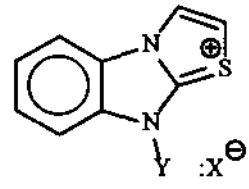
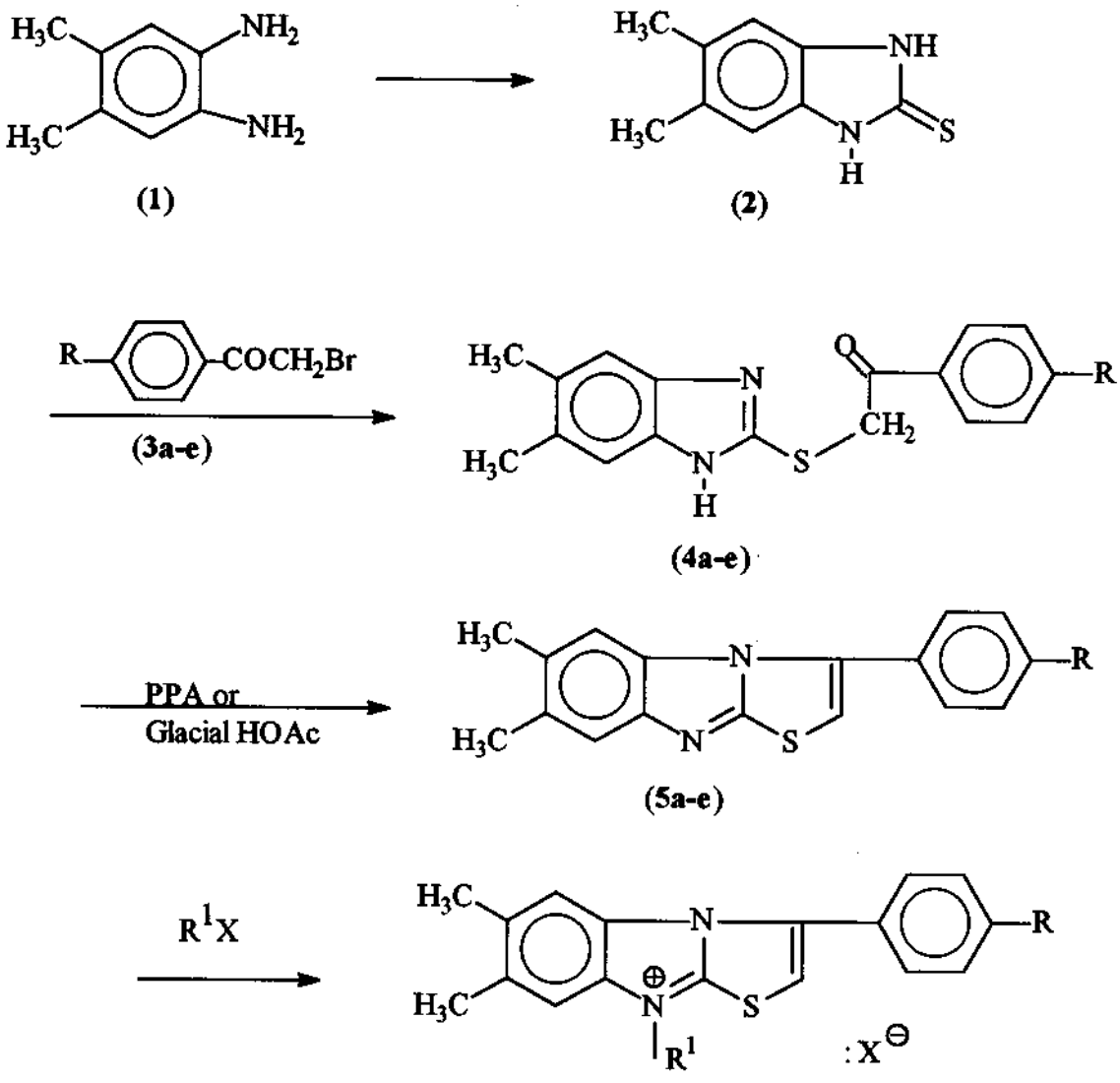


VII

Chemistry

The general synthetic route to obtain the designed 3-aryl-6,7-dimethylthiazolo[3,2-a]benzimidazoles, their quaternary salts and the intermediates used in their preparation is presented in Scheme 1. 5,6-Dimethyl-benzimidazole-2 thione, was synthesized from 4,5-dimethyl-*o*-phenylenediamine[14] and then subjected to the interaction with the prepared phenacyl bromides, **3a-e**[15-18] in the presence of potassium hydroxide to give the required 5,6-dimethyl-2-(phenacylthio)benzimidazoles **4a-e**. Structural elucidation of the newly synthesized derivatives within this series was confirmed by elemental and spectral data. The IR spectra of this series are mostly characterized by the presence of a strong carbonyl absorption at 1700-1705 cm^{-1}. In the ^1H-NMR spectra of **4a-e**, the appearance of the two methyls at C5 and C6 as a singlet of 6 protons, the two hydrogens at C4 and C7 as a singlet of two protons, in addition to the presence of an NH is a strong support for an S-alkylation reaction rather than N-alkylation one. 3-Aryl-6,7-dimethyl thiazolo[3,2-a]benzimidazoles (**5a-e**) were synthesized by cycoldehydration of **4a-e** in PPA.



Scheme 1 : a: (R=H), **b:** (R=Br), **c:** (R=Cl), **d:** (R=CH_3O), **e:** (R=CH_3)
R^1X = CH_3, C_2H_5, C_3H_7, C_4H_9, **3a-f (f:** (R=NO_2), $C_6H_5CH_2Cl$, C_6H_5COCl

In the ^{1}H-NMR of **5a-e** (Table 1), the proton at C5 of the ring system appeared upfield than expected due to the shielding effect of the C3 aryl substituent on this proton. Guided by MNDO/3 optimization program,[19] the aryl substituents at C3 deviate from the plane of thiazolobenzimidazole by a dihedral angles 48-51°. Another characteristic feature of this series is the appearance of the methyls at C6 and C7 as two separate singlets. The downfield one was attributed to the C7 since it is present at the para position to the less negative (bridgehead) nitrogen in the ring system. On the other hand, the utilization of PPA in cyclodehydration of **4a-e** was found unfavorable for **4d** due to the demethylation of the para methoxy group to afford exclusively the demethylated **5d**. The required **5d** was then obtained in glacial acetic acid. In this work, the use of chloroform was very successful, rather than hydric solvents,[20] due to the ease of separation of the quaternary salts which readily precipitated during the reaction or by cooling. Thus, 3-Aryl-6,7-dimethyl-9-substituted thiazolo[3,2-a] benzimidazolium salts (**6a-e, 7a-e, 8a-e, 9a-e, 10a-e, 11a-e, 12a-e, 13a-e, 14a-e, 15a-e, 16a and 17a**) were synthesized by refluxing **5a-e** in chloroform containing drops of acetonitrile with the appropriate quaternizing agent. Structures of the prepared compounds were verified on the basis of elemental analyses and spectroscopic methods (experimental).

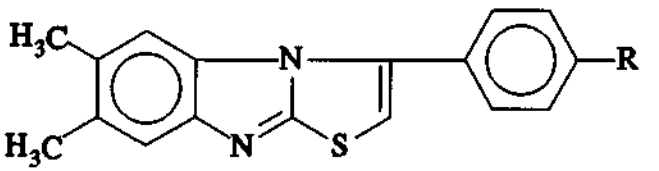
Pharmacological investigations

The testing of new chemical entities for potential antidiabetic activity was conducted by using Glucostix strips method,[21,22] which was adopted for the determination of BGL in mice using digital glucometer, type 11 (AMES Division, Miles Lab., Inc.). Three groups each of 4 female mice (18-20 g) were starved for 12 h. Elevation of BGL was induced by i.p. injection of 2 g/kg of 50% aqueous solution of glucose.[23] In the first group the tested compounds were administered by i.p. injection of equimolar doses (1.954 X 10^{-2} mmol/kg) in distilled water as a vehicle. In the second group tolbutamide (40 mg/kg, 14.81 X 10^{-2} mmol/kg) and metformine (10 mg/kg, 7.75 X 10^{-2} mmol/kg) were evaluated as reference drugs. The third group was taken as a control test. Levels of BGL (mg/100 ml) were determined at different time intervals (Table 2). Blood samples (one drop taken by using a standard hematocrit tube) were collected from the inner corner of the eye of each animal after the specified time and allowed to interact with a dry Glucostix strip (Bayer Diagnostics, GmbH, Germany) at room temperature. The strip is directly mounted into the glucometer and the BGL is automatically registered by the instrument. The degree of variability in results was expressed in terms of mean ± standard error (SE). The percentage reduction (or increase) of BGL compared to the control was determined for each compound. The significance of the difference between samples data was determined using student t-test. The difference was regarded as significant when $P < 0.05$ and as highly significant when $P < 0.01$.[24]

EXPERIMENTAL

Precoated silica gel 60 F-254 plates (Merck) were used for thin layer chromatography; spots were detected by ultraviolet light and/or staining with iodine vapor. Melting points were determined on an electrothermal melting point apparatus [Fa. Stuart Scientific, England], and were uncorrected. ^{1}H-NMR Spectra were determined on an EM-60 Varian spectrometer in $CDCl_3$ or DMSO-d_6, using TMS as internal standard and the chemical shifts were given in δ ppm. IR spectra were recorded (KBr discs) on a Shimadzu-408 spectrophotometer. Elemental analyses (C, H, N) were performed at the Department of Chemistry, Faculty of Science, Assiut University. Compound **2** was prepared according to a conventional procedure[14] starting from the commercially available o-phenylenediamine **1**. Phenacyl bromides **3a-f** were synthesized by utilizing reported methods.[15-18]

Table 1: NMR-Data (δ values, $CDCl_3$) of 3-aryl-6,7-dimethylthiazolo[3,2-a]benzimidazoles.



Compd. No.	R	C2-H	C5-H	C8-H	C6-Me	C7-Me	C3-aryl	Other	dihedral angle C2-C3-C1`-C2`
5a	H	6.50	6.97	7.50	2.30	2.40	7.65 (br.s., 5H)	-	49.64
5b	Br	6.55	6.97	7.53	2.25	2.36	7.50 (d, 2H), 7.75 (d, 2H)	-	49.30
5c	Cl	6.53	6.97	7.50	2.25	2.36	7.55 (br.s., 4H)	-	49.30
5d	OMe	6.40	6.97	7.50	2.25	2.33	7.05 (d, 2H), 7.55 (d, 2H)	3.90 (OMe)	48.78
5e	Me	6.43	7.00	7.50	2.25	2.40	7.30 (d, 2H), 7.50 (d, 2H)	2.50 (Me)	50.01

Table 2: Effect of 3-aryl-6,7-dimethylthiazolo[3,2-a]benzimidazoles and their quaternary salts on BGL of mice.

Compd. No.	BGL (mg/100 ml at time intervals min.) ± SE			Change (%) at 120
	0	60	120	
5a	69.00±3.43	129.00±3.48	69.00±2.65	2.37
5c	53.00±2.70	126.50±3.77	67.00±3.08*	-0.59
5e	60.00±2.40	130.00±3.54	68.00±2.48	0.89
6a	44.30±2.52	132.00±1.44*	84.30±2.78**	25.07
6c	59.75±2.56	86.25±1.44*	67.25±1.40	-0.22
6e	70.75±2.90	101.50±2.50**	78.75±1.10**	16.84
7a	68.50±2.25	107.00±4.60**	78.00±2.16*	15.73
7c	62.25±2.00	88.00±2.50**	66.00±2.55	-2.08
7e	59.50±2.50	90.00±2.48**	68.75±2.30	2.00
9a	70.25±3.60	86.50±4.70**	59.50±2.90*	-11.72
10a	63.00±1.47	115.00±1.58**	51.00±1.68**	-24.33
10c	59.00±2.68	73.75±2.17**	52.00±2.08**	-22.84
10e	62.25±2.40	74.25±2.52**	44.50±1.66**	-33.98
12a	45.40±0.50	87.20±0.58**	42.20±1.02**	-37.39
12c	50.75±1.89	106.25±2.69**	46.25±1.70**	-31.38
12e	69.25±0.63	92.00±1.50**	60.00±1.90	-10.98
14a	59.00±1.63	121.75±2.06**	47.50±1.70**	-29.53
14c	54.50±2.10	83.50±2.84**	52.25±2.72**	-22.47
14e	65.75±2.46	70.00±1.08**	60.25±1.10**	-10.61
16e	85.50±1.90	85.00±2.70*	56.50±1.70**	-16.17
17e	80.50±1.80	99.50±2.10	62.00±1.80*	-8.00
tolbutamide	59.00±1.47	120.50±1.94*	59.00±1.23**	-12.46
metformine	41.40±0.68	119.20±1.02*	58.60±0.68**	-13.06
control	52.20±1.02	127.80±0.58	67.40±0.68	

*, Significant; **, Highly significant

General procedure for synthesis of 2-(p-(un)substituted phenacylthio)-5,6 dimethyl-bezimidazoles; 4a-e

To a solution of **2** (0.017 mol) in NaOH (1%, 70 ml), was added portionwise with stirring a solution of the appropriate **3a-e** (0.017 mol) in ethanol (10 ml). The reaction mixture was then stirred at ambient temperature for 3 h. After cooling, the precipitated residue was collected, washed with water and crystallized from ethanol. Derivatives **4a** and **4b** were obtained as reported.[25]

2-(p-chlorophenacylthio)-5,6-dimethyl-bezimidazole 4c. Yield 67%, m.p 131-132° (EtOH), NMR ($CDCl_3$): δ 2.30 (s, 6H, 6,7-dimethyl), 5.00 (s, 2H, CH_2), 7.20 (s, 2H, C4-H and C7-H), 7.60 (d, 2H, C3-H and C5-H of C3-C_6H_4), 8.10 (d, 2H, C2-H and C6-H of C3-C_6H_4), 12.17 (hump, 1H, NH). Anal ($C_{17}H_{15}ClN_2OS$) C, H, N.

2-(p-methoxyphenacylthio)-5,6-dimethyl-bezimidazole 4d. Yield 66%, m.p 155-156° (EtOH), NMR ($CDCl_3$): δ 2.33 (s, 6H, 6,7-dimethyl), 3.95 (s, 3H, OCH_3), 4.95 (s, 2H, CH_2), 7.10 (d, 2H, C3-H and C5-H of C3-C_6H_4), 7.20 (s, 2H, C4-H and C7-H), 8.10 (d, 2H, C2-H and C6-H of C3-C_6H_4), 12.20 (hump, 1H, NH). Anal ($C_{18}H_{18}N_2O_2S$) C, H, N.

2-(p-methylphenacylthio)-5,6-dimethyl-bezimidazole 4e. Yield 62%, m.p 118-120° (EtOH), NMR ($CDCl_3$): δ 2.35 (s, 6H, 6,7-dimethyl), 2.45 (s, 3H, p-CH_3), 4.98 (s, 2H, CH_2), 7.20 (s, 2H, C4-H and C7-H), 7.35 (d, 2H, C3-H and C5-H of C3-C_6H_4), 8.00 (d, 2H, C2-H and C6-H of C3-C_6H_4), 12.00 (hump, 1H, NH). Anal ($C_{18}H_{18}N_2OS$) C, H, N.

General procedure for synthesis of 3-(p-(un)substituted phenyl)-6,7-dimethyl thiazolo[3,2-a]benzimidazoles; 5a-e

To a stirred freshly prepared PPA formed from phosphorus pentoxide (8 g) and phosphoric acid (6 ml) was added the appropriate **4a-c or 4e** (0.005 mol). The reaction mixture was heated at 140-150° for 6h, cooled, poured into ice water and neutralized with saturated solution of sodium carbonate. The precipitated solid was filtered and crystallized from ethanol. Derivatives **5a** and **5b** were obtained as reported.[25]

3-(p-chlorophenyl)-6,7-dimethylthiazolo[3,2-a]-benzimidazole 5c. Yield 64%, m.p 275-277° (EtOH). NMR (Table 1). Anal ($C_{17}H_{13}ClN_2S$) C, H, N.

6,7-dimethyl-3-(p-tolyl)thiazolo[3,2-a]-benzimidazole 5e. Yield 63%, m.p 214-216° (EtOH). NMR (Table 1). Anal ($C_{18}H_{16}N_2S$) C, H, N.

3-(p-methoxyphenyl)-6,7-dimethylthiazolo-[3,2-a]benzimidazole 5d. A solution of **4d** (3.3 g, 0.01 mol) in glacial acetic acid (25 ml) was heated under reflux for about 72h (tlc monitored), and the reaction mixture was then poured into water. The precipitated solid was filtered, washed with water and crystallized from ethanol.

5d: Yield 58%, m.p 165-166° (EtOH). NMR (Table 1). Anal ($C_{18}H_{16}N_2OS$) C, H, N.

General procedure for the synthesis of quaternary salts [(6a-e) - (15a-e), (16e) and (17e)]

To a solution of the concerned **5a-e** (0.002 mol) in chloroform (15 ml) containing acetonitrile (3 drops) was added the appropriate alkyl halide, **3a-f**, benzyl chloride or benzoyl chloride (0.002 mol) portionwise with stirring for 1h at room temperature. The reaction mixture was then refluxed for a suitable time as monitored by tlc. The product, separated on cooling and/or addition of ether, was crystallized from the appropriate solvent (solvent of crystallization and reaction time).

6,7,9-trimethyl-3-phenylthiazolo[3,2-a]-benzimidazolium iodide 6a. as reported.[12]

3-(p-bromophenyl)-6,7,9-trimethylthiazolo-[3,2-a]benzimidazolium iodide 6b. Yield 70%, m.p 282-284° (chloroform, 8 h). NMR (DMSO-$_6$): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, C7- C$\underline{H}_3$ overlap. DMSO), 4,15 (s, 3H, N9-C$\underline{H}_3$), 7.03 (s, 1H, C5-H), 7,70-7.9 (m, 6H, C2-H, C8-H and C3-C_6H_4). Anal ($C_{18}H_{16}BrIN_2S$) C, H, N.

3-(p-chlorophenyl)-6,7,9-trimethylthiazolo-[3,2-a]benzimidazolium iodide 6c. Yield 68%, m.p 280-283° (chloroform, 10 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, C7-C$\underline{H}_3$ overlap. DMSO), 4,17 (s, 3H, N9-C$\underline{H}_3$), 7.05 (s, 1H, C5-H), 7,80 (br. s, 6H, C2-H and C3-C_6H_5), 7.90 (s, 1H, C8-H). Anal ($C_{18}H_{16}ClIN_2S$) C, H, N.

3-(p-methoxyphenyl)-6,7,9-trimethylthiazolo-[3,2-a]benzimidazolium iodide 6d. Yield 64%, m.p 268-270° (EtOH, 12 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.47 (s, C7- C$\underline{H}_3$ overlap. DMSO), 3.95 (s, 3H, OC$\underline{H}_3$), 4.17 (s, 3H, N9-C$\underline{H}_3$), 7.05 (s, 1H, C5-H), 7.20 (d, 2H, C3-H and C5-H of C3-C_6H_4OMe), 7.70 (m, 3H, C2-H and C2-H and C6-H of C3-C_6H_4OMe), 7.80 (s, 1H, C8-H). Anal ($C_{19}H_{19}IN_2OS$) C, H, N.

6,7,9-trimethyl-3-(p-tolyl)thiazolo[3,2-a]-benzimidazolium iodide 6e. Yield 67%, m.p 251-253° (EtOH, 10 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.50 (s, C7- C$\underline{H}_3$ overlap. DMSO), 2.62 (s, 3H, p-C$\underline{H}_3$), 4.20 (s, 3H, N9-C$\underline{H}_3$), 7.03 (s, 1H, C5-H), 7.46 (d, 2H, C3-H and C5-H of C3-C_6H_4OMe), 7.70 (s, 1H, C2-H), 7.74 (d, 2H, C2-H and C6-H of C3-C_6H_4Me), 7.93 (s, 1H, C8-H). Anal ($C_{19}H_{19}IN_2S$) C, H, N.

9-ethyl-6,7-dimethyl-3-phenylthiazolo[3,2-a]-benzimidazolium iodide 7a. Yield 64%, m.p 282-284° (chloroform, 12 h). NMR (DMSO-d_6): δ 1.50 (t, 3H, N9-$CH_2C\underline{H}_3$), 2.23 (s, 3H, C6-C$\underline{H}_3$), 2.40 (s, 3H, C7-C$\underline{H}_3$), 4.60 (q, 2H, N9-C$\underline{H}_2CH_3$), 6.93 (s, 1H, C5-H), 7.70 (s, 6H, C2-H and C_6H_5), 7.95 (s, 1H, C8-H). Anal ($C_{19}H_{19}IN_2S$) C, H, N.

3-(p-bromophenyl)-9-ethyl-6,7-dimethyl-thiazolo[3,2-a]benzimidazolium iodide 7b. Yield 67%, m.p 284-286° (EtOH, 12 h). NMR (DMSO-d_6): δ 1.55 (t, 3H, N9-$CH_2C\underline{H}_3$), 2.27 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, 3H, C7-C$\underline{H}_3$ overlap. DMSO), 4.65 (q, 2H, N9-C$\underline{H}_2CH_3$), 7.05 (s, 1H, C5-H), 7.70-8.25 (m, 6H, C2-H, C8-H and C3-C_6H_4). Anal ($C_{19}H_{18}BrIN_2S$) C, H, N.

3-(p-chlorophenyl)-9-ethyl-6,7-dimethyl-thiazolo[3,2-a]benzimidazolium iodide 7c. Yield 65%, m.p 284-285° (EtOH, 12 h). NMR (DMSO-d_6): δ 1.55 (t, 3H, N9-$CH_2C\underline{H}_3$), 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.47 (s, 3H, C7-C$\underline{H}_3$ overlap. DMSO), 4.65 (q, 2H, N9-C$\underline{H}_2CH_3$), 7.05 (s, 1H, C5-H), 7.80 (br. s, 5H, C2-H and C3-C_6H_4), 7.93 (s, 1H, C8-H). Anal ($C_{19}H_{18}ClIN_2S$) C, H, N.

9-ethyl-3-(p-methoxyphenyl)-6,7-dimethyl-thiazolo[3,2-a]benzimidazolium bromide 7d. Yield 63%, m.p 272-274° (chloroform, 15 h). NMR (DMSO-d_6): δ 1.57 (t, 3H, N9-$CH_2C\underline{H}_3$), 2.33 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, 3H, C7-C$\underline{H}_3$ overlap. DMSO), 3.95 (s, 3H, OC$\underline{H}_3$), 4.70 (q, 2H, N9-C$\underline{H}_2CH_3$), 7.05 (s, 1H, C5-H), 7.20 (d, 2H, C3-H and C5-H of C3-C_6H_4OMe), 7.70 (m, 3H, C2-H and C2-H and C6-H of C3-C_6H_4OMe), 7.93 (s, 1H, C8-H). Anal ($C_{20}H_{21}IN_2OS$) C, H, N.

9-ethyl-6,7-dimethyl-3-(p-tolyl)thiazolo[3,2-a]-benzimidazolium iodide 7e. Yield 65%, m.p 260-261° (EtOH 15 h). NMR (DMSO-d_6): δ 0.97 (t, 3H, N9-$CH_2C\underline{H}_3$), 2.33 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, 3H, C7-C$\underline{H}_3$ overlap. DMSO), 2.60 (s, 3H, p-C$\underline{H}_3$), 4.70 (q, 2H, N9-C$\underline{H}_2CH_3$), 7.05 (s, 1H, C5-H), 7.50 (d, 2H, C3-H and C5-H of C3-C_6H_4Me), 7.70 (s, 1H, C2-H), 7.73 (d, 2H, C2-H and C6-H of C3-C_6H_4Me), 7.99 (s, 1H, C8-H). Anal ($C_{20}H_{21}IN_2S$) C, H, N.

6,7-dimethyl-3-phenyl-9-propylthiazolo[3,2-a]-benzimidazolium bromide 8a. Yield 60%, m.p 264-266° (EtOH/ether, 24 h). NMR (DMSO-d_6): δ 1.00 (t, 3H, N9-$CH_2CH_2C\underline{H}_3$), 1.65-2.23 (m, 5H, N9-$CH_2C\underline{H}_2CH_3$, C6-C$\underline{H}_3$), 2.40 (s, 3H, C7-C$\underline{H}_3$), 4.60 (t, 2H, N9-C$\underline{H}_2CH_2CH_3$), 6.95 (s, 1H, C5-H), 7.75 (s, 6H, C2-H and C_6H_5), 7.93 (s, 1H, C8-H). Anal ($C_{20}H_{21}BrN_2S$) C, H, N.

3-(p-bromophenyl)-6,7-dimethyl-9-propyl-thiazolo[3,2-a]benzimidazolium bromide 8b. Yield 62%, m.p 288-289° (EtOH, 24 h). NMR (DMSO-d_6): δ 1.00 (t, 3H, N9-$CH_2CH_2C\underline{H}_3$), 1.95 (m, 2H, N9-$CH_2C\underline{H}_2CH_3$), 2.30 (s, 3H,

C6-C$\underline{H}_3$), 2.50 (s, C7-C$\underline{H}_3$ overlap. DMSO), 4.65 (t, 2H, N9-C$\underline{H}_2$CH$_2$CH$_3$), 7.06 (s, 1H, C5-H), 7.75 (br. s, 5H, C2-H and C_6H_4), 8.05 (s, 1H, C8-H). Anal ($C_{20}H_{20}Br_2N_2S$) C, H, N.

3-(p-chlorophenyl)-6,7-dimethyl-9-propylthiazolo[3,2-a]benzimidazolium bromide 8c. Yield 53%, m.p 281-282° (EtOH/ether, 24 h). NMR (DMSO-d_6): δ 1.03 (t, 3H, N9-CH$_2$CH$_2$C$\underline{H}_3$), 2,00 (m, 2H, N9-CH$_2$C$\underline{H}_2$CH$_3$), 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, C7-C$\underline{H}_3$ overlap. DMSO), 4.60 (t, 2H, N9-C$\underline{H}_2$CH$_2$CH$_3$), 7.05 (s, 1H, C5-H), 7.80 (br. s, 5H, C2-H and C_6H_4), 7.97 (s, 1H, C8-H). Anal ($C_{20}H_{20}BrClN_2S$) C, H, N.

3-(p-methoxyphenyl)-6,7-dimethyl-9-propylthiazolo[3,2-a]benzimidazolium bromide 8d. Yield 61%, m.p 259-261° (EtOH/ether 24 h). NMR (DMSO-d_6): δ 1.02 (t, 3H, N9-CH$_2$CH$_2$C$\underline{H}_3$), 2,00 (m, 2H, N9-CH$_2$C$\underline{H}_2$CH$_3$), 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, C7-C$\underline{H}_3$ overlap. DMSO), 3.95 (s, 3H, OC$\underline{H}_3$), 4.63 (t, 2H, N9-C$\underline{H}_2$CH$_2$CH$_3$), 7.05 (s, 1H, C5-H), 7.20 (d, 2H, C3-H and C5-H of C3-C_6H_4OMe), 7.72 (m, 3H, C2-H and C2-H and C6-H of C3-C_6H_4OMe), 7.90 (s, 1H, C8-H). Anal ($C_{21}H_{23}BrN_2OS$) C, H, N.

6,7-dimethyl-9-propyl-3-(p-tolyl)thiazolo-[3,2-a]benzimidazolium bromide 8e. Yield 60%, m.p 269-270° (EtOH/ether 24 h). NMR (DMSO-d_6): δ 1.02 (t, 3H, N9-CH$_2$CH$_2$C$\underline{H}_3$), 2,00 (m, 2H, N9-CH$_2$C$\underline{H}_2$CH$_3$), 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, C7-C$\underline{H}_3$ overlap. DMSO), 2.53 (s, 3H, p-C$\underline{H}_3$), 4.60 (t, 2H, N9-C$\underline{H}_2$CH$_2$CH$_3$), 7.05 (s, 1H, C5-H), 7.55 (d, 2H, C3-H and C5-H of C3-C_6H_4Me), 7.55 (d, 2H, C2-H and C6-H of C3-C_6H_4Me), 7.69 (s, 1H, C2-H), 7.94 (s, 1H, C8-H). Anal ($C_{21}H_{23}BrN_2S$) C, H, N.

9-butyl-6,7-dimethyl-3-phenylthiazolo[3,2-a]-benzimidazolium bromide 9a. Yield 60%, m.p 255-257° (EtOH/ether, 36 h). NMR (DMSO-d_6): δ 1.00 (t, 3H, N9-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$), 1.50 (m, 2H, N9-CH$_2$CH$_2$C$\underline{H}_2$CH$_3$), 2.20 (m, 2H, N9-CH$_2$C$\underline{H}_2$CH$_2$CH$_3$), 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, 3H, overlap with DMSO for C7-C$\underline{H}_3$), 4.60 (t, 2H, N9-C$\underline{H}_2$CH$_2$CH$_2$CH$_3$), 6.96 (s, 1H, C5-H), 7.75 (s, 6H, C2-H and C_6H_5), 7.90 (s, 1H, C8-H). Anal ($C_{21}H_{23}BrN_2S$) C, H, N.

3-(p-bromophenyl)-9-butyl-6,7-dimethylthiazolo[3,2-a]benzimidazolium bromide 9b. Yield 64%, m.p 263-266° (EtOH/ether, 36 h). NMR (DMSO-d_6): δ 1.00 (t, 3H, N9-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$), 1.50 (m, 2H, N9-CH$_2$CH$_2$C$\underline{H}_2$CH$_3$), 2.00 (m, 2H, N9-CH$_2$C$\underline{H}_2$CH$_2$CH$_3$), 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, 3H, overlap with DMSO for C7-C$\underline{H}_3$), 4.65 (t, 2H, N9-C$\underline{H}_2$CH$_2$CH$_2$CH$_3$), 7.05 (s, 1H, C5-H), 7.80 (br. s, 5H, C2-H and C_6H_4), 8.00 (s, 1H, C8-H). Anal ($C_{21}H_{22}Br_2N_2S$) C, H, N.

9-butyl-3-(p-chlorophenyl)-6,7-dimethylthiazolo[3,2-a]benzimidazolium bromide 9c. Yield 50%, m.p 278-279° (EtOH/ether, 36 h). NMR (DMSO-d_6): δ 1.00 (t, 3H, N9-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$), 1.50 (m, 2H, N9-CH$_2$CH$_2$C$\underline{H}_2$CH$_3$), 2.00 (m, 2H, N9-CH$_2$C$\underline{H}_2$CH$_2$CH$_3$), 2.33 (s, 3H, C6-C$\underline{H}_3$), 2.50 (s, 3H, overlap with DMSO for C7-C$\underline{H}_3$), 4.65 (t, 2H, N9-C$\underline{H}_2$CH$_2$CH$_2$CH$_3$), 7.10 (s, 1H, C5-H), 7.75 (s, 6H, C2-H and C_6H_4), 7.90 (s, 1H, C8-H). Anal ($C_{21}H_{22}BrClN_2S$) C, H, N.

9-butyl-3-(p-methoxyphenyl)-6,7-dimethylthiazolo[3,2-a]benzimidazolium bromide 9d. Yield 61%, m.p 258-260° (chloroform, 36 h). NMR (DMSO-d_6): δ 1.00 (t, 3H, N9-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$), 1.50 (m, 2H, N9-CH$_2$CH$_2$C$\underline{H}_2$CH$_3$), 2.00 (m, 2H, N9-CH$_2$C$\underline{H}_2$CH$_2$CH$_3$), 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, 3H, overlap with DMSO for C7-C$\underline{H}_3$), 3.96 (s, 3H, OC$\underline{H}_3$), 4.65 (t, 2H, N9-C$\underline{H}_2$CH$_2$CH$_2$CH$_3$), 7.05 (s, 1H, C5-H), 7.23 (d, 2H, C3-H and C5-H of C3-C_6H_4OMe), 7.70 (m, 3H, C2-H and C2-H and C6-H of C3-C_6H_4OMe), 7.93 (s, 1H, C8-H). Anal ($C_{22}H_{25}BrN_2OS$) C, H, N.

9-butyl-6,7-dimethyl-3-(p-tolyl)thiazolo[3,2-a]-benzimidazolium bromide 9e. Yield 54%, m.p 258-259° (EtOH/ether 36 h). NMR (DMSO-d_6): δ 1.00 (t, 3H, N9-CH$_2$CH$_2$CH$_2$C$\underline{H}_3$), 1.50 (m, 2H, N9-CH$_2$CH$_2$C$\underline{H}_2$CH$_3$), 2.00 (m, 2H, N9-CH$_2$C$\underline{H}_2$CH$_2$CH$_3$), 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.45 (s, 3H, overlap with DMSO for C7-C$\underline{H}_3$), 2.56 (s, 3H, p-C$\underline{H}_3$), 4.60 (t, 2H, N9-

$C\underline{H}_2CH_2CH_2CH_3$), 7.05 (s, 1H, C5-H), 7.40 (d, 2H, C3-H and C5-H of C3-$C_6\underline{H}_4$Me), 7.60 (m, 3H, C2-H and C2-H and C6-H of C3-$C_6\underline{H}_4$Me), 7.88 (s, 1H, C8-H). Anal ($C_{22}H_{25}BrN_2S$) C, H, N.

6,7-dimethyl-9-phenacyl-3-phenylthiazolo-[3,2-a]benzimidazolium bromide 10a. Yield 90%, m.p 287-289° (EtOH, 7 h). NMR (DMSO-d_6): δ 2.27 (s, 3H, C6-C$\underline{H}_3$), 2.39 (s, 3H, C7-C$\underline{H}_3$), 6.65 (s, 2H, phenacyl C$\underline{H}_2$), 7.05 (s, 1H, C5-H), 7.60-7.85 (m, 9H, C3-$C_6\underline{H}_5$, C2-H and phenacyl C3-H, C4-H and C5-H), 8.00 (s, 1H, C8-H), 8.26 (m, 2H, phenacyl C2-H and C6-H). Anal ($C_{25}H_{21}BrN_2OS$) C, H, N.

3-(p-bromophenyl)-6,7-dimethyl-9-phenacyl-thiazolo[3,2-a]benzimidazolium bromide 10b. Yield 81%, m.p 285-287° (chloroform, 7 h). Anal ($C_{25}H_{20}Br_2N_2OS$) C, H, N.

3-(p-chlorophenyl)-6,7-dimethyl-9-phenacyl-thiazolo[3,2-a]benzimidazolium bromide 10c. Yield 80%, m.p 289-291° (EtOH, 7 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.40 (s, 3H, C7-C$\underline{H}_3$), 6.55 (s, 2H, phenacyl C$\underline{H}_2$), 7.05 (s, 1H, C5-H), 7.60-8.25 (m, 11H, C3-$C_6\underline{H}_4$, C2-H, C8-H, phenacyl $C_6\underline{H}_5$). Anal ($C_{25}H_{20}BrClN_2OS$) C, H, N.

3-(p-methoxyphenyl)-6,7-dimethyl-9-phenacyl-thiazolo[3,2-a]benzimidazolium bromide 10d. Yield 74%, m.p 268-270° (chloroform, 7 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.40 (s, 3H, C7-C$\underline{H}_3$), 3.95 (s, 3H, OC$\underline{H}_3$), 6.57 (s, 2H, phenacyl C$\underline{H}_2$), 7.10 (s, 1H, C5-H), 7.33-7.85 (m, 6H, C3-H, C4-H and C5-H of ph$C_6\underline{H}_5$, C3-H and C5-H of C3-C_6H_4OM and C2-H), 7.95 (s, 1H, C8-H), 8.20 (m, 2H, C2-H and C6-H of C3-C_6H_4OMe). Anal ($C_{26}H_{23}BrN_2O_2S$) C, H, N.

6,7-dimethyl-9-phenacyl-3-(p-tolyl)thiazolo-[3,2-a]benzimidazolium bromide 10e. Yield 64%, m.p 275-276° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.29 (s, 3H, C6-C$\underline{H}_3$), 2.46 (s, 3H, C7-C$\underline{H}_3$), 2.53 (s, 3H, p-C$\underline{H}_3$), 6.60 (s, 2H, phenacyl C$\underline{H}_2$), 7.10 (s, 1H, C5-H), 7.50-7.73 (m, 8H, C3-H, C4-H and C5-H of phenacyl $C_6\underline{H}_5$, C3-$C_6\underline{H}_4$Me and C2-H), 7.95 (s, 1H, C8-H), 8.20 (m, 2H, C2-H and C6-H of phenacyl). Anal ($C_{26}H_{23}BrN_2OS$) C, H, N.

9-(p-bromophenacyl)-6,7-dimethyl-3-phenyl-thiazolo[3,2-a]benzimidazolium bromide 11a. Yield 90%, m.p 265-266° (EtOH, 6 h). NMR (DMSO-d_6): δ 2.27 (s, 3H, C6-C$\underline{H}_3$), 2.37 (s, 3H, C7-C$\underline{H}_3$), 6.70 (s, 2H, phenacyl C$\underline{H}_2$), 7.03 (s, 1H, C5-H), 7.80 (br. s, 6H, C3-$C_6\underline{H}_5$, C2-H), 7.95 (m, 3H, phenacyl C3-H, C4-H and C5-H), 8.00 (s, 1H, C8-H), 8.25 (m, 2H, phenacyl C2-H and C6-H). Anal ($C_{25}H_{20}Br_2N_2OS$) C, H, N.

9-(p-bromophenacyl)-3-(p-bromophenyl)-6,7-dimethylthiazolo[3,2-a]benzimidazolium bromide 11b. Yield 84%, m.p 280-282° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.33 (s, 3H, C6-C$\underline{H}_3$), 2.40 (s, 3H, C7-C$\underline{H}_3$), 6.55 (s, 2H, phenacyl C$\underline{H}_2$), 7.10 (s, 1H, C5-H), 7.78-7.97 (m, 9H, C3-$C_6\underline{H}_4$, C2-H, and phenacyl $C_6\underline{H}_4$), 8.07 (s, 1H, C8-H). Anal ($C_{25}H_{19}Br_3N_2OS$) C, H, N.

9-(p-bromophenacyl)-3-(p-chlorophenyl)-6,7-imethylthiazolo[3,2-a]benzimidazolium bromide 11c. Yield 82%, m.p 282-284° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.35 (s, 3H, C6-C$\underline{H}_3$), 2.43 (s, 3H, C7-C$\underline{H}_3$), 6.57 (s, 2H, phenacyl C$\underline{H}_2$), 7.10 (s, 1H, C5-H), 7.75-8.20 (m, 10, C3-$C_6\underline{H}_4$, C2-H, C8-H, phenacyl $C_6\underline{H}_4$). Anal ($C_{25}H_{19}Br_2ClN_2OS$) C, H, N.

9-(p-bromophenyl)-3-(p-methoxyphenyl)-6,7-dimethylthiazolo[3,2-a]benzimidazolium bromide 11d. Yield 70%, m.p 263-265° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.43 (s, 3H, C7-C$\underline{H}_3$), 3.95 (s, 3H, OC$\underline{H}_3$), 6.55 (s, 2H, phenacyl C$\underline{H}_2$), 7.10 (s, 1H, C5-H), 7.25 (d, 2H, C3-H and C5-H of C3-C_6H_4OMe), 7.63 (s, 1H, C2-H), 7.65-7.80 (m, 4H, C2-H and C6-H of C3-$C_6\underline{H}_4$, and C3-H and C5-H of phenacyl $C_6\underline{H}_4$), 8.00 (m, 3H, C2-H and C6-H of C3-C_6H_4OMe and C8-H). Anal ($C_{26}H_{22}Br_2N_2O_2S$) C, H, N.

9-(p-bromophenacyl)-6,7-dimethyl-3-(p-tolyl)-thiazolo[3,2-a]benzimidazolium bromide 11e. Yield 75%, m.p 274-275° (chloroform, 5 h). Anal ($C_{26}H_{22}Br_2N_2OS$) C, H, N.

9-(p-chlorophenacyl)-6,7-dimethyl-3-phenyl-thiazolo[3,2-a]benzimidazolium bromide 12a. Yield 93%, m.p 279-281° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.27 (s, 3H, C6-C$\underline{H}_3$), 2.37 (s, 3H, C7-C$\underline{H}_3$), 6.60 (s, 2H, phenacyl C$\underline{H}_2$), 6.98 (s, 1H, C5-H), 7.70-7.80 (m, 8H, C3-C$_6\underline{H}_5$, C2-H and phenacyl C3-H and C5-H), 7.97 (s, 1H, C8-H), 8.20 (m, 2H, phenacyl C2-H and C6-H). Anal ($C_{25}H_{20}BrClN_2OS$) C, H, N.

3-(p-bromophenyl)-9-(p-chlorophenacyl)-6,7-dimethylthiazolo[3,2-a]benzimidazolium bromide 12b. Yield 85%, m.p 281-282° (chloroform, 6 h). Anal ($C_{25}H_{19}Br_2ClN_2OS$) C, H, N.

9-(p-chlorophenacyl)-3-(p-chlorophenyl)-6,7-dimethylthiazolo[3,2-a]benzimidazolium iodide 12c. Yield 80%, m.p 280-281° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.33 (s, 3H, C6-C$\underline{H}_3$), 2.43 (s, 3H, C7-C$\underline{H}_3$), 6.60 (s, 2H, phenacyl C$\underline{H}_2$), 7.05 (s, 1H, C5-H), 7.60-7.80 (m, 7H, C3-C$_6\underline{H}_4$, C2-H and phenacyl C3-H and C5-H), 7.97 (s, 1H, C8-H), 8.25 (d, 2H, phenacyl C2-H and C6-H). Anal ($C_{25}H_{19}BrCl_2N_2OS$) C, H, N.

9-(p-chlorophenyl)-3-(p-methoxyphenyl)-6,7-dimethylthiazolo[3,2-a]benzimidazolium bromide 12d. Yield 70%, m.p 263-264° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.29 (s, 3H, C6-C$\underline{H}_3$), 2.40 (s, 3H, C7-C$\underline{H}_3$), 3.95 (s, 3H, OC$\underline{H}_3$), 6.57 (s, 2H, phenacyl C$\underline{H}_2$), 7.06-7.90 (m, 11H, C2-H, C5-H, C8-H, C3-C$_6\underline{H}_4$, phenacyl C_6H_4). Anal ($C_{26}H_{22}BrClN_2O_2S$) C, H, N.

9-(p-chlorophenacyl)-6,7-dimethyl-3-(p-tolyl)-thiazolo[3,2-a]benzimidazolium bromide 12e. Yield 74%, m.p 272-273° (EtOH 6 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.40 (s, 3H, C7-C$\underline{H}_3$), 2.60 (s, 3H, p-C$\underline{H}_3$), 6.60 (s, 2H, phenacyl C$\underline{H}_2$), 7.10 (s, 1H, C5-H), 7.50 (d, 2H, C3-H and C5-H of C3-C$_6\underline{H}_4$), 7.65-7.80 (m, 5H, C2-H and C2-H, C6-H of C3-C$_6\underline{H}_4$ and phenacyl C3-H, C5-H), 7.97 (s, 1H, C8-H), 8.25 (d, 2H, phenacyl C2-H, C6-H). Anal ($C_{26}H_{22}BrClN_2OS$) C, H, N.

9-(p-methoxyphenacyl)-6,7-dimethyl-3-phenyl-thiazolo[3,2-a]benzimidazolium bromide 13a. Yield 77%, m.p 267-268° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.25 (s, 3H, C6-C$\underline{H}_3$), 2.39 (s, 3H, C7-C$\underline{H}_3$), 4.00 (s, 3H, para methoxy), 6.65 (s, 2H, phenacyl C$\underline{H}_2$), 7.05 (s, 1H, C5-H), 7.25 (d, 2H, phenacyl C3-H and C5-H), 7.85 (br. s, 6H, C2-H and C3-C$_6\underline{H}_5$), 8.05 (s, 1H, C8-H), 8.25 (d, 2H, phenacyl C2-H and C6-H). Anal ($C_{26}H_{23}BrN_2O_2S$) C, H, N.

3-(p-bromophenyl)-9-(p-methoxyphenacyl)-6,7-dimethylthiazolo[3,2-a]benzimidazolium bromide 13b. Yield 70%, m.p 284-285° (chloroform, 6 h). Anal ($C_{26}H_{22}Br_2N_2O_2S$) C, H, N.

3-(p-chlorophenyl)-9-(p-methoxyphenacyl)-6,7-dimethylthiazolo[3,2-a]-benzimidazolium bromide 13c. Yield 70%, m.p 279-281° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.40 (s, 3H, C7-C$\underline{H}_3$), 3.95 (s, 3H, para methoxy), 6.50 (s, 2H, phenacyl C$\underline{H}_2$), 7.15 (m, 3H, C5-H, phenacyl C3-H and C5-H), 7.75 (br. s, 5H, C2-H and C3-C$_6\underline{H}_4$), 7.90 (s, 1H, C8-H), 8.15 (d, 2H, phenacyl C2-H and C6-H). Anal ($C_{26}H_{22}BrClN_2O_2S$) C, H, N.

9-(p-methoxyphenacyl)-3-(p-methoxyphenyl)-6,7-dimethylthiazolo[3,2-a]benz-imidazolium bromide 13d. Yield 60%, m.p 260-262° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.43 (s, 3H, C7-C$\underline{H}_3$), 3.95 (s, 6H, 2 of OC$\underline{H}_3$) 6.57 (s, 2H, phenacyl C$\underline{H}_2$), 7.10-7.40 (m, 5H, C5-H, phenacyl C3-H and C5-H and C3-H and C5-H of C3-C_6H_4OMe), 7.80 (m, 3H, C2-H and C2-H and C6-H of C3-C_6H_4OMe), 7.95 (s, 1H, C8-H), 8.20 (d, 2H, phenacyl C2-H and C6-H). Anal ($C_{27}H_{25}BrN_2O_3S$) C, H, N.

9-(p-methoxyphenacyl)-6,7-dimethyl-3-(p-tolyl) thiazolo[3,2-a]benzimidazolium bromide 13e. Yield 64%, m.p 269-270° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.40 (s, 3H, C7-C$\underline{H}_3$), 2.57 (s, 3H, p- C$\underline{H}_3$), 3.95 (s,

3H, OC<u>H</u>$_3$) 6.57 (s, 2H, phenacyl C<u>H</u>$_2$), 7.20 (m, 3H, C5-H, phenacyl C3-H and C5-H), 7.50 (d, 2H, C3-H and C5-H of C3-C$_6$H$_4$Me), 7.75 (m, 3H, C2-H and C2-H, C6-H of C3-C$_6$H$_4$Me), 7.95 (s, 1H, C8-H), 8.20 (d, 2H, phenacyl C2-H and C6-H). Anal ($C_{27}H_{25}BrN_2O_2S$) C, H, N.

6,7-dimethyl-9-(p-methylphenacyl)-3-phenylthiazolo[3,2-a]benzimidazolium bromide 14a. Yield 70%, m.p 271-272° (EtOH/ether, 8 h). NMR (DMSO-d$_6$): δ 2.30 (s, 3H, C6-C<u>H</u>$_3$), 2.43 (s, 3H, C7-C<u>H</u>$_3$), 2.55 (s, 3H, para methyl overlap DMSO), 6.67 (s, 2H, phenacyl C<u>H</u>$_2$), 7.06 (s, 1H, C5-H), 7.70 (d, 2H, phenacyl C3-H and C5-H), 7.80 (s, 1H, C2-H), 7.90 (s, 5H, C3-C$_6$<u>H</u>$_5$), 8.05 (s, 1H, C8-H), 8.20 (d, 2H, phenacyl C2-H and C6-H). Anal ($C_{26}H_{23}BrN_2OS$) C, H, N.

3-(p-bromophenyl)-6,7-dimethyl-9-(p-methylphenacyl)thiazolo[3,2-a]benzimidazolium bromide 14b. Yield 76%, m.p 290-292° (EtOH/ether, 8 h). NMR (DMSO-d$_6$): δ 2.30 (s, 3H, C6-C<u>H</u>$_3$), 2.39 (s, 3H, C7-C<u>H</u>$_3$), 2.50 (s, 3H, para methyl overlap DMSO), 6.50 (s, 2H, phenacyl C<u>H</u>$_2$), 7.10 (s, 1H, C5-H), 7.45 (d, 2H, phenacyl C3-H and C5-H), 7.80 (br. s, 5H, C2-H, C3-C$_6$<u>H</u>$_4$), 8.10 (s, 1H, C8-H), 8.15 (d, 2H, phenacyl C2-H and C6-H).Anal ($C_{26}H_{22}Br_2N_2OS$) C, H, N.

3-(p-chlorophenyl)-6,7-dimethyl-9-(p-methylphenacyl)thiazolo[3,2-a]benzimidazolium bromide 14c. Yield 70%, m.p 286-288° (chloroform, 8 h). NMR (DMSO-d$_6$): δ 2.30 (s, 3H, C6-C<u>H</u>$_3$), 2.36 (s, 3H, C7-C<u>H</u>$_3$), 2.50 (s, 3H, para methyl overlap DMSO), 6.56 (s, 2H, phenacyl C<u>H</u>$_2$), 7.10 (s, 1H, C5-H), 7.45 (d, 2H, phenacyl C3-H and C5-H), 7.83 (br. s, 5H, C2-H, C3-C$_6$<u>H</u>$_4$), 7.90 (s, 1H, C8-H), 8.10 (d, 2H, phenacyl C2-H and C6-H). Anal ($C_{26}H_{22}BrClN_2OS$) C, H, N.

3-(p-methoxyphenyl)-6,7-dimethyl-9-(p-methylphenacyl)thiazolo[3,2-a]benzimidazolium bromide 14d. Yield 65%, m.p 271-272° (EtOH, 8 h). NMR (DMSO-d$_6$): δ 2.30 (s, 3H, C6-C<u>H</u>$_3$), 2.40 (s, 3H, C7-C<u>H</u>$_3$), 2.50 (s, 3H, para methyl overlap DMSO), 3.95 (s, 3H, OC<u>H</u>$_3$), 6.55 (s, 2H, phenacyl C<u>H</u>$_2$), 7.10 (s, 1H, C5-H), 7.25 (d, 2H, C3-H and C5-H of C3-C$_6$H$_4$OMe), 7.45 (d, 2H, phenacyl C3-H and C5-H), 7.65 (s, 1H, C2-H), 7.75 (d, 2H, C2-H and C2-H and C6-H of C3-C$_6$H$_4$OMe), 7.90 (s, 1H, C8-H), 8.10 (d, 2H, phenacyl C2-H and C6-H). Anal ($C_{27}H_{25}BrN_2O_2S$) C, H, N.

6,7-dimethyl-9-(p-methylphenacyl)-3-(p-tolyl)thiazolo[3,2-a]benzimidazolium bromide 14e. Yield 60%, m.p 273-274° (EtOH/ether 7 h). NMR (DMSO-d$_6$): δ 2.30 (s, 3H, C6-C<u>H</u>$_3$), 2.43 (s, 3H, C7-C<u>H</u>$_3$), 2.50 (s, 6H, two p-<u>H</u>$_3$ overlap DMSO), 6.55 (s, 2H, phenacyl C<u>H</u>$_2$), 7.10 (s, 1H, C5-H), 7.45 (d, 4H, C3-H and C5-H of C3-C$_6$H$_4$Me and phenacyl C3-H and C5-H), 7.75 (m, 3H, C2-H and C2-H, C6-H of C3-C$_6$H$_4$Me), 7.93 (s, 1H, C8-H), 8.10 (d, 2H, phenacyl C2-H and C6-H). Anal ($C_{27}H_{25}BrN_2OS$) C, H, N.

6,7-dimethyl-9-(p-nitrophenacyl)-3-phenylthiazolo[3,2-a]benzimidazolium bromide 15a. Yield 90%, m.p 272-274° (chloroform, 5 h). NMR (DMSO-d$_6$): δ 2.27 (s, 3H, C6-C<u>H</u>$_3$), 2.40 (s, 3H, C7-C<u>H</u>$_3$), 6.99 (s, 1H, C5-H), 7.47 (s, 2H, phenacyl C<u>H</u>$_2$), 7.67 (s, 1H, C2-H), 7.80 (m, 7H, C5-H, C3-C$_6$<u>H</u>$_5$, C8-H), 8.40 (m, 4H, phenacyl C$_6$H$_4$). Anal ($C_{25}H_{20}BrN_3O_3S$) C, H, N.

3-(p-bromophenyl)-6,7-dimethyl-9-(p-nitrophenacyl)thiazolo[3,2-a]benzimidazolium bromide 15b. Yield 92%, m.p 280-281° (EtOH, 5 h). Anal ($C_{25}H_{19}Br_2N_3O_3S$) C, H, N.

3-(p-chlorophenyl)-6,7-dimethyl-9-(p-nitrophenacyl)thiazolo[3,2-a]benzimidazolium bromide 15c. Yield 87%, m.p 287-289° (chloroform, 6 h). NMR (DMSO-d$_6$): δ 2.33 (s, 3H, C6-C<u>H</u>$_3$), 2.40 (s, 3H, C7-C<u>H</u>$_3$), 6.65 (s, 2H, phenacyl C<u>H</u>$_2$), 7.05(s, 1H, C5-H), 7.85 (br. s, 5H, C2-H, C3-C$_6$<u>H</u>$_4$), 8.00 (s, 1H, C8-H), 8.47 (m, 4H, phenacyl C$_6$H$_4$). Anal ($C_{25}H_{19}BrClN_3O_3S$) C, H, N.

3-(p-methoxyphenyl)-6,7-dimethyl-9-(p-nitrophenacyl)thiazolo[3,2-a]benzimidazolium bromide 15d. Yield 72%, m.p 275-276° (chloroform, 6 h). NMR (DMSO-d_6): δ Anal ($C_{26}H_{22}BrN_3O_4S$) C, H, N.

6,7-dimethyl-9-(p-nitrophenacyl)-3-(p-tolyl)-thiazolo[3,2-a]benzimidazolium bromide 15e. Yield 70%, m.p 263-265° (chloroform, 6 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.43 (s, 3H, C7-C$\underline{H}_3$), 2.57 (s, 3H, p-C$\underline{H}_3$), 6.70 (s, 2H, phenacyl C$\underline{H}_2$), 7.10 (s, 1H, C5-H), 7.50 (d, 2H, C3-H and C5-H of C3-C$_6\underline{H}_4$), 7.70 (s, 1H, C2-H), 7.73 (d, 2H, C2-H and C6-H of C3-C_6H_4Me), 7.99 (s, 1H, C8-H), 8.49 (m, 4H, phenacyl C_6H_4). Anal ($C_{26}H_{22}BrN_3O_3S$) C, H, N.

9-benzyl-6,7-dimethyl-3-(p-tolyl)thiazolo-[3,2-a]benzimidazolium bromide 16e. Yield 69%, m.p 270-271° (EtOH/ether 24 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.43 (s, 3H, C7-C$\underline{H}_3$), 2.53 (s, 3H, p-C$\underline{H}_3$), 5.85 (s, 2H, benzyl C$\underline{H}_2$), 7.03 (s, 1H, C5-H), 7.35-7.70 (m, 10H, C3-C$_6\underline{H}_4$, C2-H, and benzyl C_6H_5), 7.99 (s, 1H, C8-H). Anal ($C_{25}H_{23}BrN_2S$) C, H, N.

9-benzoyl-6,7-dimethyl-3-(p-tolyl)thiazolo-[3,2-a]benzimidazolium bromide 17e. Yield 53%, m.p 260-262° (EtOH/ether 30 h). NMR (DMSO-d_6): δ 2.30 (s, 3H, C6-C$\underline{H}_3$), 2.41 (s, 3H, C7-C$\underline{H}_3$), 2.57 (s, 3H, p-C$\underline{H}_3$), 7.10 (s, 1H, C5-H), 7.50-7.80 (m, 8H, C3-C$_6\underline{H}_4$, C3-H, C4-H, C5-H of benzoyl and C2-H), 7.90 (s, 1H, C8-H), 8.00 (m, 2H, C2-H and C6-H of benzoyl). Anal ($C_{25}H_{21}ClN_2OS$) C, H, N.

RESULTS AND DISCUSSION

Blood glucose level (BGL). Structure-activity relationship

The compounds tested have demonstrated good effects as antidiabetics. Several SAR generalizations can be made from the data contained in Table 2.

1. The parent thiazolo[3,2-a]benzimidazoles (**5a-e**) did not show any decrease in BGL.
2. On comparing the blood glucose reduction for compounds that are quaternized at N9 by alkyl groups, only that quaternized by butyl group (**9a**), was found to be active (11.72% reduction). Alkyl chains shorter than butyl (compds. **6a,c,e, 7a,c,e**) did not provide convenient activity.
3. N9 Benzyl substitution (**16e**) revealed a good activity of about (16.17% reduction) in BGL. When compared with the N9 butyl, it appeared more active.
4. N9 Benzoyl substitution (**17e**) revealed weaker activity (8% reduction) than the N9 benzyl and N9 butyl derivatives.
5. Effect of N9 phenacyl substitution: All of the tested compounds in this series were more active than, or equally active with, the references. Their effects range from good to very good. Generally, they were more active than those having N9 benzyl, N9 benzoyl or N9 alkyl substituents.
   Within the limited number of para substituents of the tested derivatives, it was difficult to make a concrete conclusion as their effects on BGL. However, the N9 (p-chlorophenacyl) substituent afforded two of the most active derivatives (**12a**, 37.39% reduction, **12c**, 31.38% reduction).
   On the other hand, combination of the N9 phenacyl substituent and C3 p-tolyl resulted in the third most active derivative (**10e**, 33.98% reduction).
6. Effect of the C3 phenyl substitution: In presence of the C3 phenyl substituent, the N9 (p-chlorophenacyl) derivative was more active than the N9 -(p-methylphenacyl) derivative which in turn was more active than the N9-phenacyl compound. On changing the C3-phenyl by C3-(p-chlorophenyl), the N9-(p-chlorophenacyl) derivative was still more active than the N9-(p-methylphenacyl) and N9-phenacyl compounds, which were equally active. On the other hand, on replacing the C3-phenyl substituent by a C3-p-tolyl function, the N9-phenacyl compound became more active than both N9-(p-methylphenacyl) and N9-(p-chlorophenacyl) compounds which were equally active.
7. Out of the tested compounds, eight derivatives (**10a,c,e, 12a,c, 14a,c, 16e**) were considered more potent than references, the most active one is compound (**12a**) (37.39% reduction). This

compound conserves N9-(p-chlorophenacyl) and C3-phenyl functions and appeared three times more potent than the reference drugs used, in their cited doses.

Conclusion

The obtained data suggest that a positively charged fused imidazole (i.e. thiazolobenzimidazolium skeleton) and an N9 substituent of suitable bulkiness are two essential requirements for this series of compounds to reveal BGL reduction. Proper substitution at C3 also adds to this activity.

In this context, compounds having N9 phenacyl substituent can be advocated as promising hypoglycemic agents. Detailed pharmacological studies are needed so as to assign the exact mechanism of activity of this new class of hypoglycemic bridgehead heterocyclic quaternary salts. Mention, also have to be paid for derivatives (**6a,e and 7a**) that significantly increased BGL rather than decreasing it.

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