Imidazo[2,1-*b*]thiazole Carbamates and Acylureas as Potential Insect Control Agents

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Imidazo[2,1-*b*]thiazole carbamates and acylureas were prepared by reaction of 5-hydroxymethylimidazo-[2,1-*b*]thiazole and imidazo[2,1-*b*]thiazole-5-carboxyamide with arylisocyanates. The products formed depend from the substituent bonded at the 6 position of the imidazothiazole moiety, and from the reaction conditions.

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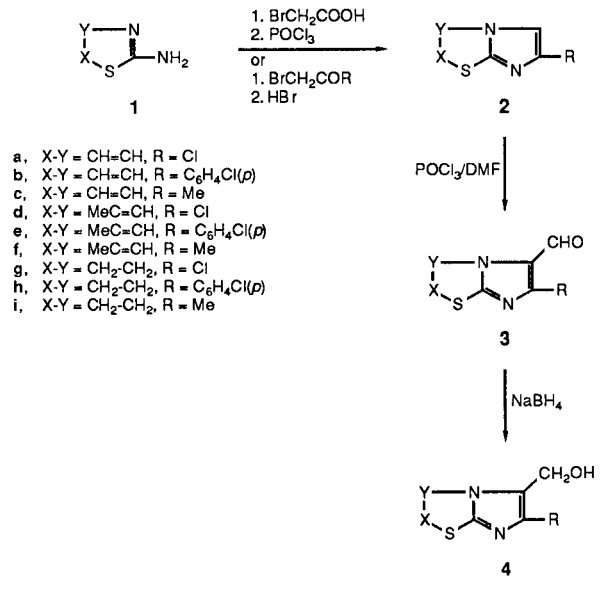
Bearing in mind three well-known classes of insecticides whose leader may be considered 2,3-dihydro-2,3-dimethyl-7-benzofuranyl methylcarbamate (carbofuran) [1,2], 3-(4-chlorophenyl)-1-(4-chlorophenylcarbamoyl)-2-pyrazoline (PH-6041) [3] and 1-(4-chlorophenyl)-3-(2,6-difluorobenzoyl)urea (diflubenzuron) [1-3] we planned the synthesis of carbamates and acylureas with an imidazo[2,1-*b*]thiazole moiety.

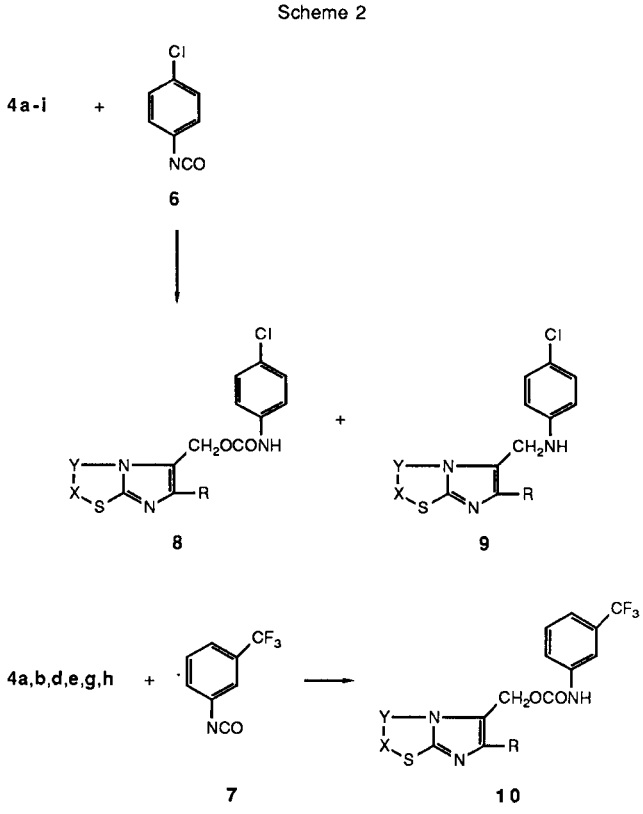
The synthesis of 2-methyl-6-chloroimidazo[2,1-*b*]thiazole (**2d**), 2-methyl-6-chloroimidazo[2,1-*b*]thiazole-5-carboxaldehyde (**3d**), 2-methyl-6-*p*-chlorophenylimidazo[2,1-*b*]thiazole-5-carboxaldehyde (**3e**), 5-hydroxymethyl-2-methyl-6-chloroimidazo[2,1-*b*]thiazole (**4d**), 5-hydroxymethyl-2-methyl-6-*p*-chlorophenylimidazo[2,1-*b*]thiazole (**4e**) and 5-hydroxymethyl-2,6-dimethylimidazo[2,1-*b*]thiazole (**4f**) (Scheme 1) is described in this paper (see Experimental); their structures were identified by comparing their spectroscopic data with those of the corresponding compounds reported in the literature and, in part, those obtained here.

The reaction of the 5-hydroxymethyl derivatives **4** bearing at the 6-position a chlorine atom or a *p*-chlorophenyl group, with *p*-chlorophenylisocyanate (**6**) in the presence of triethylamine in refluxing THF formed 6-chloroimidazo[2,1-*b*]thiazol-5-ylmethyl *p*-chlorophenylcarbamate (**8a**), 6-*p*-chlorophenylimidazo[2,1-*b*]thiazol-5-ylmethyl *p*-chlorophenylcarbamate (**8b**), 2-methyl-6-chloroimidazo-[2,1-*b*]thiazol-5-ylmethyl *p*-chlorophenylcarbamate (**8d**), 2-methyl-6-*p*-chlorophenylimidazo[2,1-*b*]thiazol-5-ylmethyl

Scheme 1



Scheme 2



p-chlorophenylcarbamate (**8e**), 2,3-dihydro-6-chloroimidazo[2,1-*b*]thiazol-5-ylmethyl *p*-chlorophenylcarbamate (**8g**) and 2,3-dihydro-6-*p*-chlorophenylimidazo[2,1-*b*]thiazol-5-ylmethyl *p*-chlorophenylcarbamate (**8h**) (Scheme 2). All these compounds gave the molecular ion peak in their mass spectrum. The multiplicity of the ir spectrum bands and the ^{1}H nmr spectroscopic data are in agreement with the assigned structures (see Experimental)

On the other hand compounds **4**, which are methyl substituted at the 6 position, when reacted under the above described conditions, led to *N*-(6-methylimidazo[2,1-*b*]thiazol-5-ylmethyl)-*N*-(*p*-chlorophenyl)amine (**9c**), *N*-(2,6-dimethylimidazo[2,1-*b*]thiazol-5-ylmethyl)-*N*-(*p*-chlorophenyl)amine (**9f**) and *N*-(2,3-dihydro-6-methylimidazo-[2,1-*b*]thiazol-5-ylmethyl)-*N*-(*p*-chlorophenyl)amine (**9i**) (Scheme 2), which were isolated together with *N,N'*-di-*p*-chlorophenylurea (**12**). Compounds **9c**, **9f** and **9i** were identified on the basis of their analytical and spectroscopic data. In particular all compounds gave the expected molecular ion peak in the mass spectrum. In the ir spectrum they show a NH group at 3250 cm^{-1} and two bands at 1600 and 1530 cm^{-1} but no bands at 1700 cm^{-1} significant for the -O-CO- group; the nmr spectra are in agreement with the assigned structures (see Experimental).

As to compound **12**, it is well known that aryl isocyanates [4] when treated with water or amines form *N,N'*-diarylureas, in other words compounds such as **12**. In fact, by treating *p*-chlorophenyl isocyanate with triethylamine in THF under reflux, compound **12** was obtained in good yield and it was identified by comparison with the product obtained from *p*-chlorophenyl isocyanate and *p*-chloroaniline (see Experimental) which, in turn, was identical to that prepared from urea and *p*-chloroaniline according to the literature [5]. The different behaviour of compounds **4**, 6 methyl-substituted, **4c**, **4f** and **4i** from those chlorine or *p*-chlorophenyl-substituted, could be envisaged in the different stability of compounds **8**: the 6-methyl-substituted imidazothiazole, could be more sensitive to the action of the high temperature and traces of water leading to the formation of compounds **9**. This assumption was verified throughout the transformation of compound **8b** into *N*-(6-*p*-chlorophenylimidazo[2,1-*b*]thiazol-5-ylmethyl)-*N*-(*p*-chlorophenyl)amine (**9b**) by refluxing it for 8 hours in THF in the presence of traces of water (see Experimental).

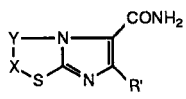
The fact that compound **9b** was obtained in 30% yield confirmed our supposition and suggested that compounds **8**, 6 methyl-substituted, could have been obtained from **4c**, **4f** and **4i** and *p*-chlorophenyl isocyanate (**6**) carrying out the reaction at room temperature.

An experiment carried out starting from **4i** and **6** in the presence of triethylamine gave compound **12** and another product whose ir spectrum showed a band at 1700 cm^{-1} which is typical of compounds **8**. All attempts to purify this compound either by chromatography on a silicagel column or by crystallization lead to the isolation of compound **9i** which was identified by comparing its spectroscopic data with other isolated carbamates. The crude product could be really the expected compound 2,3-dihydro-6-methylimidazo[2,1-*b*]thiazol-5-ylmethyl *p*-chlorophenylcarbamate (**8i**) that was transformed into **9i** during the purification.

5-Hydroxymethyl-6-chloroimidazo[2,1-*b*]thiazole (**4a**), 5-hydroxymethyl-6-*p*-chlorophenylimidazo[2,1-*b*]thiazoles **4b**, **4d**, and **4e**, 2,3-dihydro-5-hydroxymethyl-6-chloroimidazo[2,1-*b*]thiazole (**4g**) and 2,3-dihydro-5-hydroxymethyl-6-methylimidazo[2,1-*b*]thiazole (**4h**) were also reacted with *m*-trifluoromethylphenyl isocyanate (**7**) in THF at room temperature in the presence of triethylamine. In this case *m*-trifluoromethylphenylcarbamates **10a**, **10b**, **10d**, **10e**, **10g** and **10h** were isolated in about 60% yield (Scheme 2). Compounds **10** were identified on the basis of their spectroscopic data in comparison with those of compounds **8**.

N-(6-Chloroimidazo[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11a**), *N*-(6-phenylimidazo[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11b**), *N*-(6-methylimidazo-[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11c**) *N*-(2,3-dihydro-6-chloroimidazo[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11d**), *N*-(2,3-dihydro-6-phenylimidazo[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11e**), and *N*-(2,3-dihydro-6-methylimidazo[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11f**), were obtained from the corresponding imidazo[2,1-*b*]thiazole-5-carboxyamides **5a-f** with *p*-chlorophenyl isocyanate (**6**) in THF under reflux (Scheme 3). These compounds also were identified by their analytical and spectroscopic data in the same way described above for compounds **8**, **9** and **10**.

Scheme 3



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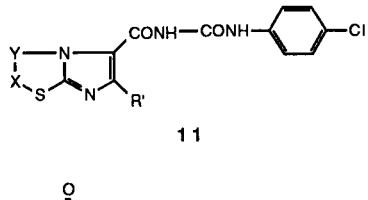
+ 6

a: X-Y = CH=CH, R' = Cl
b: X-Y = CH=CH, R' = Ph
c: X-Y = CH=CH, R' = Me
d: X-Y = CH_2-CH_2, R' = Cl
e: X-Y = CH_2-CH_2, R' = Ph
f: X-Y = CH_2-CH_2, R' = Me



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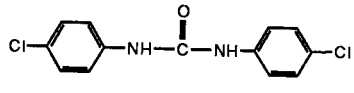

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Compounds **8-11** were devoid of insecticidal activity. Some of them provided a significant rate of control of *Meloidogyne incognita* in the soil-incorporated nematicide assay, however this level of activity was considered insufficient to pursue further tests.

EXPERIMENTAL

Melting points were detected by an Electrothermal apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer spectrophotometer for nujol mulls. The ^{1}H nmr spectra were recorded on a Varian EM390 using TMS as an internal standard. Mass spectra were recorded on a Varian 112S spectometer.

Compounds **2a** [6], **2b** [7], **2c** [8], **2e** [9], **2f** [9], **2g** [6], **2h** [10], **2i** [11], **3a** [6], **3b** [12], **3c** [13], **3f** [14], **3g** [11], **3h** [12], **3i** [11], **4a** [15], **4b** [12], **4c** [15], **4g** [15], **4h** [12], **4i** [15] and **5a-f** [16] were prepared as described in the literature.

2-Methyl-6-chloroimidazo[2,1-*b*]thiazole (**2d**).

2-Amino-5-methylthiazole (4.6 g, 40 mmoles) and bromoacetic acid (5.6 g, 40 mmoles) in 55 ml of ethanol were refluxed for 7 hours. After cooling the precipitate was collected and treated without further purification with phosphoryl chloride (30 ml) under reflux for 2 hours. The solution was then evaporated to dryness under vacuum and the residue poured into ice. The obtained solution was basified with 20% aqueous ammonia. The precipitate was filtered under vacuum and dried to the air, mp 114-116° from petroleum ether, yield 35%; ir: ν max 1345, 1245, 1115, 950 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.40 (3H, d, CH$_3$, J = 1.5 Hz), 7.70 (1H, q, H-3, J = 1.5 Hz), 7.82 (1H, s, H-5).

Anal. Calcd. for $C_6H_5ClN_2S$: C, 41.74; H, 2.92; N, 16.23. Found: C, 41.85; H, 2.91; N, 16.19.

2-Methyl-6-chloroimidazo[2,1-*b*]thiazole-5-carboxaldehyde (**3d**).

The solution of 2-methyl-6-chloroimidazo[2,1-*b*]thiazole (**2d**) (30 mmoles) in 100 ml of chloroform cooled at 5-10° was added dropwise and with stirring to the Vilsmeier reagent prepared with cooling from 0.1 mole of phosphorylchloride and 0.1 mole of DMF in 10 ml of chloroform. The solution was kept at room temperature for 3 hours and then refluxed for 4 hours. The solvent was evaporated and the obtained oil poured into ice. The precipitate of **3d** was filtered off, dried and purified from ethanol, yield 60%, mp 170-172°; ir: ν max 1650, 1295, 1260, 885 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.53 (3H, d, CH$_3$, J = 1.5 Hz), 8.25 (1H, q, H-3, J = 1.5 Hz), 8.82 (1H, s, CHO).

Anal. Calcd. for $C_7H_5ClN_2OS$: C, 41.90; H, 2.51; N, 13.96. Found: C, 41.82; H, 2.48; N, 14.00.

2-Methyl-6-*p*-chlorophenylimidazo[2,1-*b*]thiazole-5-carboxaldehyde (**3e**).

Compound **3e** was prepared in the same way as **3d** above starting from 2-methyl-6-*p*-chlorophenylimidazo[2,1-*b*]thiazole (**2e**), yield 60%, mp 198-200° from ethanol; ir: ν max 1645, 1325, 850, 830 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.60 (3H, d, CH$_3$, J = 1.5 Hz), 7.90 (2H, d, arom, J = 9 Hz), 8.25 (2H, d, arom, J = 9 Hz), 8.60 (1H, q, H-3, J = 1.5 Hz), 10.33 (1H, s, CHO).

Anal. Calcd. for $C_{13}H_9ClN_2OS$: C, 56.42; H, 3.28; N, 10.12. Found: C, 56.33; H, 3.21; N, 10.15.

2-Methyl-5-hydroxymethyl-6-chloroimidazo[2,1-*b*]thiazole (**4d**).

Sodium borohydride (7 g, 185 mmoles) was added to a solution of **3d** (3.6 g, 18 mmoles) in small portions during 1 hour with stirring at room temperature. After 3 hours the reaction solution was refluxed for 4 hours and then evaporated to dryness. The residue was poured into ice and the products extracted with chloroform. The organic layer was separated, dried over sodium sulfate and evaporated to dryness. Compound **4d** was obtained in 60% yield by crystallization of the residue from ethanol, mp 158-160°; ir: ν max 3200, 1225, 1000, 760 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.47 (3H, d, CH$_3$, J = 1.5 Hz), 4.75 (2H, d, C*H*$_2$-OH, J = 5.5 Hz, s after deuterium oxide exchange), 5.50 (1H, t, OH, J = 5.5 Hz), 7.96 (1H, q, H-3, J = 1.5 Hz).

Anal. Calcd. for $C_7H_7ClN_2OS$: C, 41.48; H, 3.48; N, 13.82. Found: C, 41.32; H, 3.46; N, 13.85.

2-Methyl-5-hydroxymethyl-6-(*p*-chlorophenyl)imidazo[2,1-*b*]thiazole (**4e**).

Compound **4e** was obtained starting from **3e** as above and precipitated when the residue was poured into ice, then it was separated by filtration under vacuum, mp 208-210° from ethanol; ir: ν max 3100, 990, 825, 765 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.48 (3H, d, CH$_3$, J = 1.5 Hz), 4.90 (2H, d, C*H*$_2$-OH, J = 5.5 Hz, s after deuterium oxide exchange), 5.61 (1H, t, OH, J = 5.5 Hz), 7.75 (2H, d, arom, J = 9.0 Hz), 8.0 (1H, q, H-3, J = 1.5 Hz), 8.05 (2H, d, arom, J = 9.0 Hz).

Anal. Calcd. for $C_{13}H_{11}ClN_2OS$: C, 56.00; H, 3.98; N, 10.05. Found: C, 55.97; H, 3.99; N, 10.07.

2,6-Dimethyl-5-hydroxymethylimidazo[2,1-*b*]thiazole (**4f**).

Compound **4f** was obtained in the same way described for **4d** starting from 2,6-dimethylimidazo[2,1-*b*]thiazole-5-carboxaldehyde (**3f**), mp 148-150° from ethanol, yield 55%; ir: ν max 3170, 1220, 1010, 790 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.26 (3H, s, CH$_3$ at C-6), 2.47 (3H, d, CH$_3$ at C-2, J = 1.5 Hz), 4.75 (2H, d, C*H*$_2$OH, s after deuterium oxide exchange), 5.29 (1H, t, OH, J = 5.5 Hz), 7.83 (1H, q, H-3, J = 1.5 Hz).

Anal. Calcd. for $C_8H_{10}N_2OS$: C, 52.72; H, 5.53; N, 15.37. Found: C, 52.70; H, 5.55; N, 15.38.

General Procedure for the Reaction of the Hydroxymethyl Derivatives **4a**, **4b**, **4d**, **4e**, **4g**, and **4h** with *p*-Chlorophenyl Isocyanate (**6**). Synthesis of Compounds **8**.

Compound **4** (5 mmoles) and *p*-chlorophenyl isocyanate (**6**), (5 mmoles), in 80 ml of THF were refluxed for 8 hours in the presence of triethylamine (0.3 ml). The reaction solution was then evaporated to dryness and the residue crystallized from ethanol; compounds **8** were obtained in 60-70% yields.

6-Chloroimidazo[2,1-*b*]thiazol-5-ylmethyl *p*-Chlorophenylcarbamate (**8a**).

This compound had mp 155-156°; ir: ν max 3250, 1725, 1605, 1215 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 5.62 (2H, s, CH$_2$), 7.63 (2H, d, arom, J = 9.0 Hz), 7.78 (1H, d, H-2, J = 4.5 Hz), 7.85 (2H, d, arom, J = 9.0 Hz), 8.45 (1H, d, H-3, J = 4.5 Hz), 10.45 (1H, s, NH).

Anal. Calcd. for $C_{13}H_9Cl_2N_3O_2S$: C, 45.62; H, 2.65; N, 12.28. Found: C, 45.58; H, 2.66; N, 12.24.

6-*p*-Chlorophenylimidazo[2,1-*b*]thiazol-5-ylmethyl *p*-Chlorophenylcarbamate (**8b**).

This compound had mp 129-131°; ir: ν max 3630, 1710, 1540, 1225 cm^1; ^{1}H nmr (DMSO-d$_6$): δ 5.71 (2H, s, CH$_2$), 7.70 (1H, d, H-2, J = 4.5 Hz), 7.88 (8H, m, arom) 8.45 (1H, d, H-3, J = 4.5 Hz), 10.45 (1H, s, NH).

Anal. Calcd. for $C_{19}H_{13}Cl_2N_3O_2S$: C, 54.55; H, 3.13; N, 10.04. Found: C, 54.57; H, 3.15; N, 10.07.

2-Methyl-6-chloroimidazo[2,1-*b*]thiazol-5-ylmethyl *p*-Chlorophenylcarbamate (**8d**).

This compound had mp 153-155°; ir: ν max 3240, 1725, 1540, 1210 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 2.52 (3H, d, CH$_3$, J = 1.5 Hz), 5.53 (2H, s, CH$_2$), 7.62 (2H, d, arom, J = 9.0 Hz), 7.82 (2H, d, arom, J = 9.0 Hz), 8.20 (1H, 9, H-3, J = 1.5 Hz), 10.40 (1H, s, NH).

Anal. Calcd. for $C_{14}H_{11}Cl_2N_3O_2S$: C, 47.20; H, 3.11; N, 11.79. Found: C, 47.15; H, 3.08; N, 11.81.

2-Methyl-6-*p*-chlorophenylimidazo[2,1-*b*]thiazol-5-ylmethyl *p*-Chlorophenylcarbamate (**8e**).

This compound had mp 170-172°; ir: ν max 3620, 1715, 1220, 1035 cm^{-1}; ^{1}H nmr (DMSO-d$_6$): δ 5.58 (3H, d, CH$_3$, J = 1.5 Hz), 5.70 (2H, s, CH$_2$), 7.90 (8H, m, arom) 8.20 (1H, q, H-3, J = 1.5 Hz), 10.40 (1H, s, NH).

Anal. Calcd. for $C_{20}H_{15}Cl_2N_3O_2S$: C, 55.56; H, 3.50; N, 9.72. Found: C, 55.58; H, 3.52; N, 9.69.

2,3-Dihydro-6-chloroimidazo[2,1-*b*]thiazol-5-ylmethyl *p*-Chlorophenylcarbamate (**8g**).

This compound had mp 140-141°; ir: ν max 3220, 1720, 1220, 1020 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.04 (2H, m, CH_2 of C-2), 4.48 (2H, m, CH_2 of C-3), 5.20 (2H, s, CH_2), 7.60 (2H, d, arom, J = 9.0 Hz), 7.80 (2H, d, arom, J = 9.0 Hz), 10.40 (1H, s, NH).

Anal. Calcd. for $C_{13}H_{11}Cl_2N_3O_2S$: C, 45.36; H, 3.22; N, 12.20. Found: C, 45.40; H, 3.21; N, 12.17.

2,3-Dihydro-6-*p*-chlorophenylimidazo[2,1-*b*]thiazol-5-ylmethyl *p*-Chlorophenylcarbamate (**8h**).

Compound **8h** had mp 179-180°; ir ν max 3160, 1720, 1215, 1035 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.10 (2H, m, CH_2 of C-2), 4.50 (2H, m, CH_2 of C-3), 5.45 (2H, s, CH_2), 7.85 (8H, m, arom), 10.40 (1H, s, NH).

Anal. Calcd. for $C_{19}H_{15}Cl_2N_3O_2S$: C, 54.29; H, 3.59; N, 9.99. Found: C, 54.36; H, 3.60; N, 9.97.

General Procedure for the Reaction of the Hydroxymethyl Derivatives **4c**, **4f** and **4i** with *p*-Chlorophenyl Isocyanate (**6**). Synthesis of Compound **9**.

Compound **4** (5 mmoles) and *p*-chlorophenyl isocyanate (**6**) (5 mmoles) were refluxed in 80 ml of THF for 4 hours. The reaction solution was evaporated to dryness and the residue chromatographed on silicagel column from benzene/acetone 9:1. The first eluate was compound **12** which was identified with an authentic sample (see below). Compounds **9** were isolated in 30-40% yield from the second eluate and crystallized from ethanol.

N-(6-Methylimidazo[2,1-*b*]thiazol-5-ylmethyl)-*N*-(*p*-chlorophenyl)amine (**9c**).

This compound had mp 163-164°; ir: ν max 3260, 1600, 1490, 1305, cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.35 (3H, s, CH_3), 4.54 (2H, d, CH_2, J = 6.0 Hz), 6.50 (1H, t, NH, J = 6.0 Hz), 6.90 (2H, d, arom, J = 9.0 Hz), 7.40 (2H, d, arom, J = 9.0 Hz), 7.45 (1H, d, H-2, J = 4.5 Hz), 8.15 (1H, d, H-3, J = 4.5 Hz).

Anal. Calcd. for $C_{13}H_{12}ClN_3S$: C, 56.21; H, 4.36; N, 15.12. Found: C, 56.24; H, 4.37; N, 15.08.

N-(2,6-Dimethylimidazo[2,1-*b*]thiazol-5-ylmethyl)-*N*-(*p*-chlorophenyl)-amine (**9f**).

This compound had mp 187-189°; ir: ν max 3250, 1595, 1520, 1315 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.30 (3H, s, CH_3 at C-6), 2.41 (3H, d, CH_3 at C-2, J = 1.5 Hz), 2.45 (2H, d, CH_2, J = 5.5 Hz), 6.40 (1H, t, NH, J = 5.5 Hz), 6.85 (2H, d, arom, J = 9.0 Hz), 7.38 (2H, d, arom, J = 9.0 Hz), 7.90 (1H, q, H-3, J = 1.5 Hz).

Anal. Calcd. for $C_{14}H_{14}ClN_3S$: C, 57.62; H, 4.83: N, 14.40. Found: C, 57.61; H, 4.85; N, 14.37.

N-(2,3-Dihydro-6-methylimidazo[2,1-*b*]thiazol-5-ylmethyl)-*N*-(*p*-chlorophenyl)amine (**9i**).

This compound had mp 184-186°; ir: ν max 3240, 1595, 1325, 1295 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.15 (3H, s, CH_3), 3.91 (2H, m, CH_2 of C-2), 4.19 (2H, m, CH_2 of C-3), 4.25 (2H, d, CH_2, J = 5.5 Hz), 6.25 (1H, t, NH, J = 5.5 Hz), 6.88 (2H, d, arom, J = 9.0 Hz), 7.35 (2H, d, arom, J = 9.0 Hz).

Anal. Calcd. for $C_{13}H_{14}ClN_3S$: C, 55.80; H, 5.04; N, 15.02. Found: C, 55.78; H, 5.05; N, 15.01.

General Procedure for the Reaction of the Hydroxymethyl Derivatvies **4a**, **4b**, **4d**, **4e**, **4g** and **4h** with *m*-Trifluoromethylphenyl Isocyanate (**7**). Synthesis of Compounds **10**.

Compounds **4** (5 mmoles) and *m*-trifluoromethylphenyl isocyanate (**7**) (5 mmoles) in 80 ml of THF were stirred at room temperature in the presence of 0.3 ml of triethylamine. After 1 hour the reaction solution was evaporated under vacuum and the residue was crystallized from ethanol. Compounds **10** were isolated in 55-65% yields.

6-Chloroimidazo[2,1-*b*]thiazol-5-ylmethyl *m*-Trifluoromethylphenylcarbamate (**10a**).

This compound had mp 131-132°: ir: ν max 3240, 1720, 1330, 1215 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.43 (2H, s, CH_2), 7.50 (1H, d, H-2, J = 4.5 Hz), 7.65 (4H, m, arom), 8.15 (1H, d, H-3, J = 4.5 Hz), 10.22 (1H, s, NH).

Anal. Calcd. for $C_{14}H_9ClF_3N_3O_2S$: C, 44.74: H, 2.41; N, 11.18. Found: C, 44.63; H, 2.40; N, 11.20.

6-*p*-Chlorophenylimidazo[2,1-*b*]thiazol-5-ylmethyl *m*-Trifluoromethylphenylcarbamate (**10b**).

This compound had mp 132-134°; ir: ν max 3510, 1710, 1330, 1215 cm^{-1}; ^1H nmr (DMSO-d_6): δ 5.56 (2H, s, CH_2), 7.45 (1H, d, H-2, J = 4.5), 7.65 (8H, m, arom), 8.20 (1H, d, H-3, J = 4.5 Hz), 10.30 (1H, s, NH).

Anal. Calcd. for $C_{20}H_{13}ClF_3N_3O_2S$: C, 53.16; H, 2.90; N, 9.30. Found: C, 52.99; H, 2.89; N, 9.28.

2-Methyl-6-chloroimidazo[2,1-*b*]thiazol-5-ylmethyl *m*-Trifluoromethylphenylcarbamate (**10d**).

This compound had mp 156-157°; ir: ν max 3245, 1735, 1330, 1210 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.45 (3H, d, CH_3, J = 1.5 Hz), 5.38 (2H, s, CH_2), 7.65 (4H, m, arom), 7.90 (1H, q, H-3, J = 1.5 Hz), 10.21 (1H, s, NH).

Anal. Calcd. for $C_{15}H_{11}ClF_3N_3O_2S$: C, 46.22; H, 2.84; N, 10.78. Found: C, 46.28; H, 2.85; N, 10.74.

2-Methyl-6-*p*-chlorophenylimidazo[2,1-*b*]thiazol-5-ylmethyl *m*-Trifluoromethylphenylcarbamate (**10e**).

This compound had mp 152-153°; ir: ν max 3505, 1710, 1330, 1220 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.46 (3H, d, CH_3, J = 1.5 Hz), 5.52 (2H, s, CH_2), 7.68 (8H, m, arom), 7.92 (1H, q, H-3, J = 1.5 Hz), 10.27 (1H, s, NH).

Anal. Calcd. for $C_{21}H_{15}ClF_3N_3O_2S$: C, 54.14; H, 3.24; N, 9.02. Found: C, 54.20; H, 3.22; N, 9.06.

2,3-Dihydro-6-chloroimidazo[2,1-*b*]thiazol-5-ylmethyl *m*-Trifluoromethylphenylcarbamate (**10g**).

This compound had mp 150-151°; ir: ν max 3240, 1720, 1210, 1125 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.07 (2H, m, CH_2 of C-2), 4.48 (2H, m, CH_2 of C-3), 5.35 (2H, s, CH_2), 7.95 (4H, m, arom), 10.58 (1H, s, NH).

Anal. Calcd. for $C_{14}H_{11}ClF_3N_3O_2S$: C, 44.51; H, 2.93; N, 11.12. Found: C, 44.48; H, 2.91; N, 11.08.

2,3-Dihydro-6-*p*-chlorophenylimidazo[2,1-*b*]thiazol-5-ylmethyl *m*-Trifluoromethylphenylcarbamate (**10h**).

This compound had mp 146-148°; ir: ν max 3520, 1715, 1335, 1215 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.95 (2H, m, CH_2 of C-2), 4.35 (2H, m, CH_2 of C-3), 5.30 (2H, s, CH_2), 7.62 (8H, m, arom), 10.25 (1H, s, NH).

Anal. Calcd. for $C_{20}H_{15}ClF_3N_3O_2S$: C, 52.92; H, 3.33; N, 9.26. Found: C, 52.88; H, 3.36; N, 9.29.

General Procedure for the Reaction of the Carbamides **5a-f** with *p*-Chlorophenyl Isocyanate (**6**). Synthesis of Compounds **11**.

Compound **5** (14 mmoles) and *p*-chlorophenyl isocyanate (**6**) (16 mmoles) in 250 ml of xylene were refluxed for 8-48 hours. The reactions were stopped when the reagents disappeared in the tlc test. The reaction solution was then evaporated to dryness under vacuum. Compounds **11** were isolated in 45-55% yield by crystallizing the residue from ethanol.

N-(6-Chloroimidazo[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11a**).

This compound had mp 217-218°; ir: ν max 3360, 3100, 1725, 1655 cm^{-1}; ^1H nmr (DMSO-d_6): 7.43 (2H, d, arom, J = 9.0 Hz), 7.65 (2H, d, arom, J = 9.0 Hz), 7.70 (1H, d, H-2, J = 4.5 Hz), 8.28 (1H, d, H-3, J = 4.5 Hz), 9.87 (1H, s, CONH-Ar), 10.42 (1H, s, CONH-CO).

Anal. Calcd. for $C_{13}H_8Cl_2N_4O_2S$: C, 43.95; H, 2.27; N, 15.77. Found: C, 43.80; H, 2.25; N, 15.76.

N-(6-Phenylimidazo[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11b**).

This compound had mp 210-211°; ir: ν max 3330, 3120, 1720, 1650 cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.50 (1H, d, H-2, J = 4.5 Hz), 7.60 (9H, m, arom), 8.20 (1H, d, H-3, J = 4.5 Hz), 10.02 (1H, s, CONH-Ar), 10.54 (1H, s, CONH-CO).

Anal. Calcd. for $C_{19}H_{13}ClN_4O_2S$: C, 57.50; H, 3.30; N, 14.12. Found: C, 57.42; H, 3.29; N, 14.07.

N-(6-Methylimidazo[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11c**).

This compound had mp 211-213°; ir: ν max 3300, 3110, 1710, 1645 cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.60 (3H, s, CH_3), 7.42 (2H, d, arom, J = 9.0 Hz), 7.48 (1H, d, H-2, J = 4.5 Hz), 7.67 (2H, d, arom, J = 9.0 Hz), 8.12 (1H, d, H-3, J = 4.5 Hz) 10.28 (1H, s, CONH-Ar), 10.65 (1H, s, CONH-CO).

Anal. Calcd. for $C_{14}H_{11}ClN_4O_2S$: C, 50.22; H, 3.31; N, 16.74. Found: C, 50.15; H, 3.33; N, 16.76.

N-(2,3-Dihydro-6-chloroimidazo[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11d**).

This compound had mp 224-225°: ν max 3395, 3230, 1715, 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.0 (2H, m, CH_2 of C-2), 4.50 (2H, m, CH_2 of C-3), 7.45 (2H, d, arom, J = 9.0 Hz), 7.67 (2H, d, arom, J = 9.0 Hz), 10.0 (1H, s, CONH-Ar), 10.41 (1H, s, CONH-CO).

Anal. Calcd. for $C_{13}H_{10}Cl_2N_4O_2S$: C, 43.70; H, 2.82; N, 15.68. Found: C, 43.74; H, 2.79; N, 15.62.

N-(2,3-Dihydro-6-phenylimidazo[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11e**).

This compound had mp 210-212°; ir: ν max 3340, 3280, 1710, 1660 cm^{-1}; ^1H nmr (DMSO-d_6): δ 4.0 (2H, m, CH_2 of C-2), 4.45 (2H, m, CH_2 of C-3), 7.58 (9H, m, arom), 10.35 (1H, s, CONH-Ar), 10.57 (1H, s, CONH-CO).

Anal. Calcd. for $C_{19}H_{15}ClN_4O_2S$: C, 57.21; H, 3.79; N, 14.05. Found: C, 57.17; H, 3.80; N, 14.08.

N-(2,3-Dihydro-6-methylimidazo[2,1-*b*]thiazol-5-acyl)-*N'*-(*p*-chlorophenyl)urea (**11f**).

This compound had mp 206-208°; ir: ν max 3220, 3120, 1715, 1650 cm^{-1}; ^1H nmr (DMSO-d_6): δ 3.95 (2H, m, CH_2 of C-2), 4.37 (2H, m, CH_2 of C-3), 7.41 (2H, d, arom, J = 9.0 Hz), 7.65 (2H, d, arom, J = 9.0 Hz), 10.30 (1H, s, CONH-Ar), 10.65 (1H, s, CONH-CO).

Anal. Calcd. for $C_{14}H_{13}ClN_4O_2S$: C, 49.92; H, 3.89; N, 16.63. Found: C, 49.94; H, 3.88; N, 16.66.

Decarboxylation of 6-*p*-Chlorophenylimidazo[2,1-*b*]thiazole-5-ylmethyl-*p*-chlorophenylcarbamate (**8b**).

Compound **8b** (3 g) was refluxed for 8 hours in 80 ml of THF and 0.5 ml of water. The solution was then evaporated to dryness and the residue chromatographed on a silicagel column using petroleum ether/acetone in 8:2 ratio. From the second eluate 1.4 g of *N*-(6-*p*-chlorophenylimidazo-[2,1-*b*]thiazol-5-ylmethyl)-*N'*-(*p*-chlorophenyl)urea (**9b**) was isolated; mp 160-162° from ethanol; ir: ν max 3280, 1600, 1540 cm^{-1}; ^1H nmr (DMSO-d_6): 4.55 (2H, d, CH_2, J = 5.5 Hz), 6.35 (1H, t, NH, J = 5.5 Hz), 6.83 (4H, pseudo, -9 A_2B_2 arom), 7.6 (2H, pseudo-q, AB arom), 7.62 (4H, pseudo-q, A_2B_2 arom).

Anal. Calcd. for $C_{18}H_{13}Cl_2N_3S$: C, 57.76; H, 3.50; N, 11.23. Found: C, 57.64; H, 3.48; N, 11.26.

N,N'-Di-*p*-chlorophenylurea (**12**).

p-Chloroaniline (166 mg) and *p*-chlorophenyl isocyanate (200 mg) were reacted at room temperature for 1 hour in 50 ml of THF. The solution evaporated to dryness gave a residue that separated 230 mg of compound **12** by treatment with 10 ml of ethyl acetate, mp 308-310° from ethanol.

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