Solid-Phase Synthesis of N,N-Disubstituted *S,N′*-Diarylisothioureas: Facile Exchange Reactions of Isocyanates

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Reactions of resin-bound 1,1-disubstituted-2-arylisothioureas **4aa′**,**ab′**−**ec′** with aryl isocyanates, diversely substituted at the para and/or meta positions, and with *o*-fluoro- and 2,4-difluorophenyl isocyanate followed by appropriate cleavage led to the formation of N,N-disubstituted *S,N′*-diarylisothioureas **9**{*1*−*70*} in good yields and high purities.

Recently we disclosed an efficient procedure for the preparation of resin-bound N,N-disubstituted *S*-arylisothioureas of the general type **4**.[1] To access an increased diversity of isothioureas **4**, we introduced a protocol for the preparation of the corresponding *N*-acyl derivatives **5**[1] (Scheme 1).

The present paper documents a further modification of the imino group of *S*-arylisothiourea resins **4** by reactions with aryl isocyanates. In analogy to the similar reactions in solution phase (Scheme 2),[2] we expected to obtain *N′*,*S*-diarylisothioureas of type **9** and/or iminoureas **10** (Scheme 3). Apparently, reactions of imino derivatives on solid support with isocyanates have previously not been investigated systematically. Resins containing BocNH(C═NH)Ph and TeocNH−CHBnCOOH groups were reported to react with isocyanates by exclusive acylation at the BocNH or TeocNH groups, with the imino groups remaining unchanged.[3]

Results and Discussion

We investigated the reactivity of resin-bound isothioureas and extended their utility in providing combinatorial libraries by reacting resin **4aa′** (R^1 = Bn, R^2 = 4-Me−C_6H_4) with 40 aryl isocyanates. The products cleaved from these resins (TFA, 20% in DCM, room temp, 0.5 h) were all analyzed by LC−MS (Scheme 3, Table 1).

The 28 isocyanates diversely substituted at the meta and/or para positions, *o*-fluoro and 2,4-difluoro isocyanates each gave *N′*-arylisothioureas **9**{*1*−*28*} in 90−99% yield. By contrast, ortho-substituted isocyanates with substituents other than fluorine and also 1-naphthyl isocyanate gave mixtures of iminoureas **10**{*29*−*40*} (up to 50%), *N′*-arylisothioureas **9**{*29*−*40*} (up to 30%), and unreacted starting isothiourea (Table 1).

To confirm the formation of compounds of type **9** in the reactions of resins **4** with isocyanates, we isolated and fully characterized derivative **9**{*1*} (R^1 = Bn, R^2 = 4-Me−Ph, R^3 = Ph) starting from 1 g of resin **4aa′**. Cleaved material was washed with 10% Na_2CO_3 solution, concentrated, and purified on column. The spectral and microanalytical data of compound **9**{*1*} correspond to its assigned structure.

A trial library of thirty ($5_{R^1} \times 2_{R^2} \times 3_{R^3}$ = 30) *S,N′*-diarylisothioureas **9**{*41*−*70*} was prepared by sequential treatment of each of the five resins **3a**−**e** [R^1 = Bn (**3a**); R^1 = 4-MeO−$C_6H_4CH_2$ (**3b**); R^1 = Ph$(CH_2)_2$ (**3c**); R^1 = 4-MeO−$C_6H_4CH_2CH_2$ (**3d**); R^1 = cyclohexyl (**3e**)] with each of two thiols R^2SH (R^2 = Ph and 4-Cl−C_6H_4) and each of three isocyanates R^3NCO (R^3 = Ph, 4-MeO−C_6H_4, 4-Cl−C_6H_4) followed by cleavage with TFA. All 30 compounds **9**{*41*−*70*} were obtained in 92−100% yields with 85−100% purities (Table 2) and were characterized by ^{1}H NMR and LC−MS analyses. No products of type **10** were detected.

Comparison of these results with preparation of *N′*,*O*(*S*)-diaryl derivatives in solution phase (39−54% yields)[2,4] shows that a much better selectivity is obtained on the solid support. The lower than 50% yield of *O,N′*-diphenylisourea Et_2NC-(OPh)═NPh obtained in solution[4] was explained by the formation of triuret $Et_2NC(OPh)$═N−C(═O)−NH−C-(═O)−NHPh in a secondary sequence of reactions of the starting diphenylisourea $Et_2N(OPh)$═NH with HNCO formed and then with unreacted phenyl isocyanate. The large excesses of isocyanates (10 equiv) used for the reactions on solid support prevent similar secondary reactions of resins **4aa′**,**ab′**−**ec′**.

To compare the reactivity of *S*-aryl- and *S*-alkylisothioureas on solid support, we prepared *S*-benzylisothiourea resins **11a**,**b** and reacted them with phenyl isocyanate (Scheme 4). In contrast to the results discussed above with *S*-aryl-substituted resins **4aa′**,**ab′**−**ec′**, exclusive formation of iminoureas **12a**,**b** was observed; this is in full agreement with similar results obtained in solution phase.[2] Obviously, the difference in the reactivity of resins **4aa′**,**ab′**−**ec′** and **11a**,**b** is explained by the relatively strong electron-

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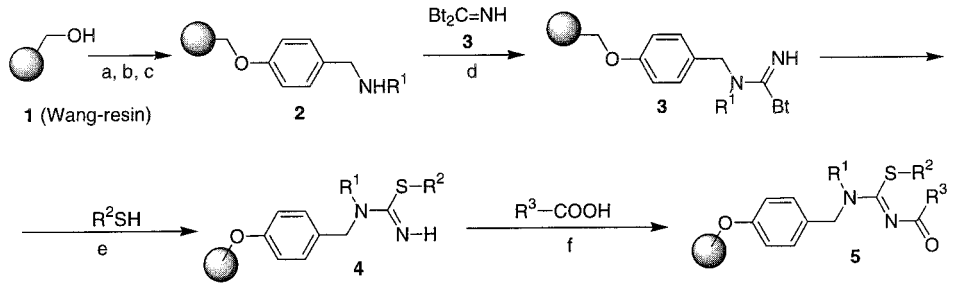
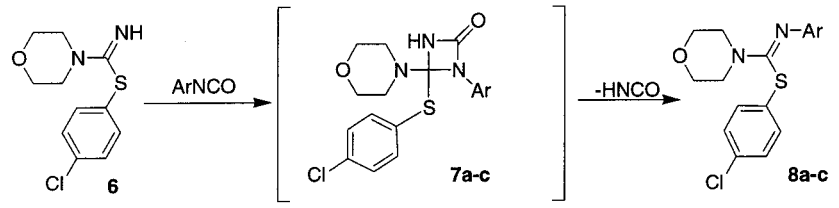
Scheme 1[a]



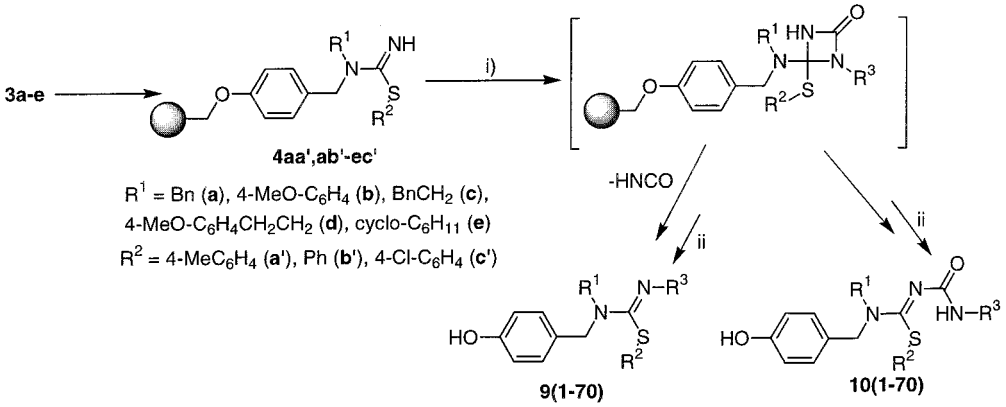
[a] Reagents and conditions: (a) Ph_3PBr_2, DCM, room temp; (b) 4-HO−C_6H_4CHO, *t*-BuOK, DMA, 80 °C, 4 h, 40 °C, 15 h; (c) R^1NH_2, $NaBH(OAc)_3$, DCE, room temp, 12−24 h; (d) THF, 7 h, room temp; (e) THF, room temp, 12−14 h; (f) DIC, HOBt, DIEA, room temp, 24 h.

Scheme 2



Ar = Ph (**a**), 4-Me-C_6H_4 (**b**), 4-Cl-C_6H_4 (**c**)

Scheme 3[a]



R^1 = Bn (**a**), 4-MeO-C_6H_4 (**b**), $BnCH_2$ (**c**), 4-MeO-$C_6H_4CH_2CH_2$ (**d**), cyclo-C_6H_{11} (**e**)

R^2 = 4-MeC_6H_4 (**a'**), Ph (**b'**), 4-Cl-C_6H_4 (**c'**)

[a] (i) R^3NCO (10 equiv, 0.25 mmol/mL), THF, 24 h, room temp; (ii) 20% TFA in DCM, room temp, 0.5 h.

withdrawing properties of arylthio substituents R^2 in resins **4aa′**,**ab′**−**ec′** as compared to the benzylthio group in resins **11a**,**b**.

Conclusions

Reactions of resin-bound 1,1-disubstituted 2-arylisothioureas **4aa′**,**ab′**−**ec′** with phenyl isocyanates diversely substituted at the para and/or meta positions and with *o*-fluoro- and 2,4-difluorophenyl isocyanates, followed by appropriate cleavage, lead to the formation of N,N-disubstituted *S*,*N*′-diarylisoureas **9**{*1*−*70*} in good yields and high purities.

Experimental Section

General Methods. ^{1}H NMR spectra were recorded on a 300 MHz NMR spectrometer using acetone-d_6 as solvent with tetramethylsilane as internal standard. Tetrahydrofuran (THF) was distilled under nitrogen immediately before use from sodium/benzophenone. All other reagents and solvents were obtained from commercial sources and were used without purification.

General Procedure for the Preparation of Isothioureas 9{*1*−*70*}. Resins **4aa′**,**ab′**−**ec′** (loading, 1.3 mmol/g)[1] were treated with THF solution of appropriate isocyanate (10 equiv, concentration of 0.25 mmol/mL) at room temperature. After 24 h, solutions were removed and the resins were washed and dried. The washing procedure is as follows (∼5 mL of a solvent was used for each 100 mg of a resin): THF × 4, DCM × 2, THF × 2, DCM × 2, THF × 2, DCM × 4, MeOH × 2, DCM × 2, MeOH × 2, DCM × 2, MeOH × 4. After being washed, the resin was dried in a vacuum for 15 h and was cleaved with a 20% solution of TFA in DCM for 30 min at room temperature.

Isothioureas **9**{*1*−*40*} were prepared in a microplate (20 mg of resin **4aa′** in each well), and compounds **9**{*41*−*70*} were prepared in polypropylene tea bags (200 mg of resins **4aa′**,**ab′**−**ec′** in each tea bag).

1-Benzyl-1-(4-hydroxybenzyl)-3-phenyl-2-*p*-tolylisothiourea 9{*1*}. Resin **4aa′** (1 g, five tea bags) was reacted with phenyl isocyanate following the procedure given above. Cleaved material was treated with 10% aqueous Na_2CO_3 and

Table 1. Composition of the Cleaved Materials Obtained in the Reactions of Isothiourea Resin **4aa′** (R^1 = Bn, R^2 = 4-Me−C_6H_4) with Isocyanates R^3NCO (Scheme 2)

		composition[a] (%)		
entry	R^3	**9**	**10**	**4**
{*1*}	Ph	99+	<1	<1
{*2*}	4-F−C_6H_4	99+	<1	N/d
{*3*}	3-F−C_6H_4	99+	<1	N/d
{*4*}	2-F−C_6H_4	99+	N/d	N/d
{*5*}	2,4-F−C_6H_3	99+	N/d	<1
{*6*}	4-F, 3-Cl−C_6H_3	99+	N/d	N/d
{*7*}	4-F, 3-NO_2−C_6H_3	99+	N/d	N/d
{*8*}	4-Cl−C_6H_4	99+	N/d	<1
{*9*}	3-Cl−C_6H_4	99+	N/d	<1
{*10*}	3-Cl, 4-Me-C_6H_3	99+	N/d	<1
{*11*}	3,4-Cl−C_6H_3	99+	N/d	N/d
{*12*}	3,5-Cl−C_6H_3	99+	N/d	<1
{*13*}	4-Cl, 3-NO_2−C_6H_3	99+	N/d	N/d
{*14*}	4-Br−C_6H_4	99+	<1	<1
{*15*}	4-CF_3−C_6H_4	99+	N/d	<1
{*16*}	3-CF_3−C_6H_4	99+	N/d	<1
{*17*}	4-CN−C_6H_4	99+	N/d	N/d
{*18*}	4-Me−C_6H_4	95	<1	<1
{*19*}	3-Me−C_6H_4	98	<1	N/d
{*20*}	3,5-Me−C_6H_4	95	N/d	N/d
{*21*}	4-Et−C_6H_4	98	<1	<1
{*22*}	3-Et−C_6H_4	95	<1	1
{*23*}	4-*i*-Pr−C_6H_4	98	1	<1
{*24*}	4-*n*-Bu−C_6H_4	98	<1	<1
{*25*}	4-MeO−C_6H_4	90	4	2
{*26*}	4-EtO−C_6H_4	95	<1	2
{*27*}	3-NO_2−C_6H_4	99+	<1	N/d
{*28*}	3-MeO−C_6H_4	99+	N/d	<1
{*29*}	2-Cl−C_6H_4	14	1	15
{*30*}	2,3-Cl−C_6H_4	1	1	5
{*31*}	2,4-Cl−C_6H_3	30	5	15
{*32*}	2,5-Cl−C_6H_3	5	1	4
{*33*}	2,6-Cl−C_6H_3	1	1	18
{*34*}	2,6-F−C_6H_3	10	10	20
{*35*}	2-Me−C_6H_4	5	30	15
{*36*}	2,4-Me−C_6H_3	N/d	50	20
{*37*}	2-CF_3−C_6H_4	5	5	40
{*38*}	2-NO_2−C_6H_4	N/d	<1	10
{*39*}	2-Ph−C_6H_4	N/d	5	35
{*40*}	1-$C_{10}H_7$	10	10	40

[a] N/d, not detected.

$CHCl_3$, and the organic layer was dried over $MgSO_4$, concentrated, and purified on column to give 0.4 g (70%) of compound **9**{*1*} as off-white microcrystals, mp 132−133 °C. ^{1}H NMR δ 2.28 (s, 3H), 4.56 (s, 2H), 4.65 (s, 2H), 6.71−6.75 (m, 4H), 6.60 (br s, 1H), 6.96−7.05 (m, 5H), 7.03−7.08 (m, 2H), 7.09−7.17 (m, 2H), 7.19−7.21 (m, 2H), 7.27−7.34 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.1, 51.9, 52.1, 115.5, 122.2, 122.4, 127.3, 128.1, 128.3, 128.4, 128.6, 129.1, 129.5, 129.0, 131.9, 137.4, 137.6, 149.8, 155.4, 155.7; calcd for $C_{28}H_{26}N_2OS$, 438; LC−MS 439.1, [MH^+]; retention time 4.66 min. Anal. Calcd for $C_{28}H_{26}N_2OS$, C, 76.68; H, 5.98; N, 6.39. Found: C, 76.18; H, 6.17; N, 6.34.

1-Benzyl-1-(4-hydroxybenzyl)-2,3-diphenylisothiourea 9{*41*}**.** Oil; ^{1}H NMR δ 5.13 (s, 2H), 5.18 (s, 2H), 6.85−6.92 (m, 4H), 7.12−7.44 (m, 15H); calcd for $C_{27}H_{24}N_2OS$, 424; LC−MS 425.1, [MH^+]; retention time 3.54 min.

1-Benzyl-1-(4-hydroxybenzyl)-3-(4-methoxyphenyl)-2-phenylisothiourea 9{*42*}**.** Oil; ^{1}H NMR δ 3.74 (s, 3H), 5.16 (s, 2H), 5.21 (s, 2H), 6.69 (d, 2H, J = 8.9 Hz), 6.80 (d, 2H, J = 8.9 Hz), 6.92 (d, 2H, J = 8.5 Hz), 7.13−7.16 (m, 2H), 7.23−7.43 (m, 10H), 9.18 (br s, 1H); calcd for $C_{28}H_{26}N_2O_2S$, 454; LC−MS 455.2, [MH^+]; retention time 3.47 min.

Table 2. Yields and Purities of Isothioureas **9**{*41*−*70*}

9	R^1	R^2	R^3	purity (%)	yield (%)
{*41*}	Bn	Ph	Ph	95	100[a]
{*42*}	Bn	Ph	MeO	90	100[a]
{*43*}	Bn	Ph	Cl	90	100[a]
{*44*}	Bn	Cl	Ph	85	100[a]
{*45*}	Bn	Cl	MeO	95	100[a]
{*46*}	Bn	Cl	Cl	85	100[a]
{*47*}	4-MeO−$C_6H_4CH_2$	Ph	Ph	100	100[a]
{*48*}	4-MeO−$C_6H_4CH_2$	Ph	MeO	95	100[a]
{*49*}	4-MeO−$C_6H_4CH_2$	Ph	Cl	99	100[a]
{*50*}	4-MeO−$C_6H_4CH_2$	Cl	Ph	99	100[a]
{*51*}	4-MeO−$C_6H_4CH_2$	Cl	MeO	95	100[a]
{*52*}	4-MeO−$C_6H_4CH_2$	Cl	Cl	95	100[a]
{*53*}	$PhCH_2CH_2$	Ph	Ph	90	100[a]
{*54*}	$PhCH_2CH_2$	Ph	MeO	95	100[a]
{*55*}	$PhCH_2CH_2$	Ph	Cl	95	95
{*56*}	$PhCH_2CH_2$	Cl	Ph	95	100[a]
{*57*}	$PhCH_2CH_2$	Cl	MeO	95	97
{*58*}	$PhCH_2CH_2$	Cl	Cl	90	92
{*59*}	4-MeO−$C_6H_4CH_2CH_2$	Ph	Ph	100	100[a]
{*60*}	4-MeO−$C_6H_4CH_2CH_2$	Ph	MeO	100	100[a]
{*61*}	4-MeO−$C_6H_4CH_2CH_2$	Ph	Cl	100	100
{*62*}	4-MeO−$C_6H_4CH_2CH_2$	Cl	Ph	100	100[a]
{*63*}	4-MeO−$C_6H_4CH_2CH_2$	Cl	MeO	100	97
{*64*}	4-MeO−$C_6H_4CH_2CH_2$	Cl	Cl	95	98
{*65*}	*cyclo*-C_6H_{11}	Ph	Ph	100	100[a]
{*66*}	*cyclo*-C_6H_{11}	Ph	MeO	100	100[a]
{*67*}	*cyclo*-C_6H_{11}	Ph	Cl	99	100[a]
{*68*}	*cyclo*-C_6H_{11}	Cl	Ph	99	100[a]
{*69*}	*cyclo*-C_6H_{11}	Cl	MeO	95	100[a]
{*70*}	*cyclo*-C_6H_{11}	Cl	Cl	90	100[a]

[a] Found values were slightly higher than 100% because of the remains of TFA.

1-Benzyl-3-(4-chlorophenyl)-1-(4-hydroxybenzyl)-2-phenylisothiourea 9{*43*}**.** Oil; ^{1}H NMR δ 5.04 (s, 2H), 5.10 (s, 2H), 6.82 (d, 2H, J = 8.6 Hz), 6.89 (d, 2H, J = 8.5 Hz), 7.12 (d, 2H, J = 8.6 Hz), 7.16−7.72 (m, 12H); calcd for $C_{27}H_{23}ClN_2OS$, 458; LC−MS 459.1, [MH^+]; retention time 3.86 min.

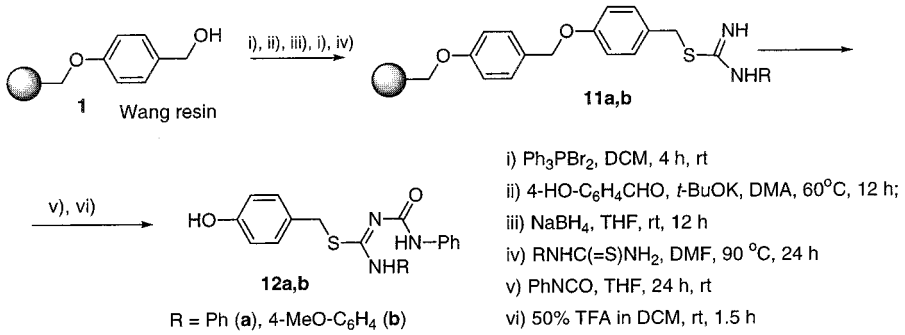
1-Benzyl-2-(4-chlorophenyl)-1-(4-hydroxybenzyl)-3-phenylisothiourea 9{*44*}**.** Oil; ^{1}H NMR δ 5.10 (s, 2H), 5.15 (s, 2H), 6.84−6.91 (m, 4H), 7.13−7.42 (m 14H); calcd for $C_{27}H_{23}ClN_2OS$, 458; LC−MS 459.2, [MH^+]; retention time 3.72 min.

1-Benzyl-2-(4-chlorophenyl)-1-(4-hydroxybenzyl)-3-(4-methoxyphenyl)isothiourea 9{*45*}**.** Oil; ^{1}H NMR δ 3.75 (s, 3H), 5.15 (s, 2H), 5.20 (s, 2H), 6.69−6.72 (m, 2H), 6.78−6.81 (m, 2H), 6.91 (d, 2H, J = 8.5 Hz), 7.15−7.18 (m, 2H), 7.25−7.31 (m, 4H), 7.43 (s, 5H); calcd for $C_{28}H_{25}ClN_2O_2S$, 488; LC−MS 489.1, [MH^+]; retention time 3.60 min.

1-Benzyl-2,3-bis(4-chlorophenyl)-1-(4-hydroxybenzyl)-isothiourea 9{*46*}**.** Oil; ^{1}H NMR δ 4.99 (s, 2H), 5.04 (s, 2H), 6.80 (d, 2H, J = 8.6 Hz), 6.89 (d, 2H, J = 8.5 Hz), 7.12−7.40 (m, 13H); calcd for $C_{27}H_{22}Cl_2N_2OS$, 492; LC−MS 493.2, [MH^+]; retention time 4.20 min.

1-(4-Hydroxybenzyl)-1-(4-methoxybenzyl)-2,3-diphenylisothiourea 9{*47*}**.** Semisolid; ^{1}H NMR δ 3.81 (s, 3H), 5.10 (s, 2H), 5.13 (s, 2H), 6.86−6.92 (m, 4H), 6.96−6.99 (m, 2H), 7.13−7.35 (m, 12H); calcd for $C_{28}H_{26}N_2O_2S$, 454; LC−MS 455.2, [MH^+]; retention time 3.49 min.

Scheme 4



1-(4-Hydroxybenzyl)-1-(4-methoxybenzyl)-3-(4-methoxyphenyl)-2-phenylisothiourea 9{*48*}. Oil; ^{1}H NMR δ 3.74 (s, 3H), 3.82 (s, 3H), 5.11 (s, 2H), 5.13 (s, 2H), 6.69 (d, 2H, J = 8.9 Hz), 6.81 (d, 2H, J = 8.9 Hz), 6.92 (d, 2H, J = 8.4 Hz), 6.99 (d, 2H, J = 8.6 Hz), 7.17−7.29 (m, 6H), 7.34−7.38 (m, 3H); calcd for $C_{29}H_{28}N_2O_3S$, 484; LC−MS 485.3, [MH$^+$]; retention time 3.44 min.

3-(4-Chlorophenyl)-1-(4-hydroxybenzyl)-1-(4-methoxybenzyl)-2-phenylisothiourea 9{*49*}. Oil; ^{1}H NMR δ 3.81 (s, 3H), 5.01 (s, 2H), 5.03 (s, 2H), 6.82 (d, 2H, J = 8.6 Hz), 6.89 (d, 2H, J = 8.3 Hz), 6.97 (d, 2H, J = 8.4 Hz), 7.13 (d, 2H, J = 8.6 Hz), 7.17−7.35 (m, 9H); calcd for $C_{28}H_{25}ClN_2O_2S$, 488; LC−MS 489.3, [MH$^+$]; retention time 3.75 min.

2-(4-Chlorophenyl)-1-(4-hydroxybenzyl)-1-(4-methoxybenzyl)-3-phenylisothiourea 9{*50*}. Oil; ^{1}H NMR δ 3.81 (s, 3H), 5.06 (s, 2H), 5.09 (s, 2H), 6.85−6.91 (m, 4H), 6.98 (d, 2H, J = 8.6 Hz), 7.14−7.17 (m, 5H), 7.22−7.29 (m, 4H), 7.36 (d, 2H, J = 8.6 Hz); calcd for $C_{28}H_{25}ClN_2O_2S$, 488; LC−MS 489.4, [MH$^+$]; retention time 3.66 min.

2-(4-Chlorophenyl)-1-(4-hydroxybenzyl)-1-(4-methoxybenzyl)-3-(4-methoxyphenyl)isothiourea 9{*51*}. Oil; ^{1}H NMR δ 3.76 (s, 3H), 3.82 (s, 3H), 5.13 (s, 2H), 5.15 (s, 2H), 6.72 (d, 2H, J = 8.9 Hz), 6.82 (d, 2H, J = 8.9 Hz), 6.89−6.93 (m, 2H), 6.99 (d, 2H, J = 8.6 Hz), 7.17−7.20 (m, 2H), 7.26−7.30 (m, 4H), 7.38 (d, 2H, J = 8.5 Hz); calcd for $C_{29}H_{27}ClN_2O_3S$, 518; LC−MS 519.3, [MH$^+$]; retention time 3.57 min.

2,3-Bis(4-chlorophenyl)-1-(4-hydroxybenzyl)-1-(4-methoxybenzyl)isothiourea 9{*52*}. Oil; ^{1}H NMR δ 3.81 (s, 3H), 4.98 (s, 2H), 5.01 (s, 2H), 6.83 (d, 2H, J = 8.6 Hz), 6.89 (d, 2H, J = 8.7 Hz), 6.97 (d, 2H, J = 8.8 Hz), 7.13−7.20 (m, 4H), 7.25 (d, 4H, J = 7.6 Hz), 7.34 (d, 2H, J = 8.6 Hz); calcd for $C_{28}H_{24}C_2lN_2O_2S$, 522; LC−MS 523.4, [MH$^+$]; retention time 4.09 min.

1-(4-Hydroxybenzyl)-1-phenethyl-2,3-diphenylisothiourea 9(53). Oil; ^{1}H NMR δ 3.20 (t, 2H, J = 7.3 Hz), 4.30 (t, 2H, J = 7.3 Hz), 5.26 (s, 2H), 6.77−6.87 (m, 2H), 6.91−7.03 (m, 4H), 7.10−7.43 (m, 13H), 9.41 (br s, 1H); calcd for $C_{28}H_{26}N_2OS$, 438; LC−MS 439.1, [MH$^+$]; retention time 3.47 min.

1-(4-Hydroxybenzyl)-3-(4-methoxyphenyl)-1-phenethyl-2-phenylisothiourea 9{*54*}. Oil; ^{1}H NMR δ 3.20 (t, 2H, J = 7.3 Hz), 3.75 (s, 3H), 4.29 (t, 2H, J = 7.5 Hz), 5.25 (s, 2H), 6.68 (d, 2H, J = 9.1 Hz), 6.74 (d, J = 9.1 Hz), 6.95 (d, 2H, J = 8.5 Hz), 7.20 (d, 2H, J = 7.5 Hz), 7.20−7.43 (m, 10H), 9.37 (s, 1H); calcd for $C_{29}H_{28}N_2O_2S$, 468; LC−MS 469.1, [MH$^+$]; retention time 3.46 min.

3-(4-Chlorophenyl)-1-(4-hydroxybenzyl)-1-phenethyl-2-phenylisothiourea 9{*55*}. Oil; ^{1}H NMR δ 3.17 (t, 2H, J = 7.1 Hz), 4.27 (t, 2H, J = 7.1 Hz), 5.23 (s, 2H), 6.80 (d, 2H, J = 8.6 Hz), 6.94 (d, 2H, J = 8.5 Hz), 7.02 (d, 2H, J = 7.5 Hz), 7.12 (d, 2H, J = 8.7 Hz), 7.20 (t, 2H, J = 7.6 Hz), 7.27−7.41 (m, 8H); calcd for $C_{28}H_{25}ClN_2OS$, 472; LC−MS 473.1, [MH$^+$]; retention time 3.66 min.

2-(4-Chlorophenyl)-1-(4-hydroxybenzyl)-1-phenethyl-3-phenylisothiourea 9{*56*}. Oil; ^{1}H NMR δ 3.21 (t, 2H, J = 7.3 Hz), 4.33 (t, 2H, J = 7.3 Hz), 5.28 (s, 2H), 6.83−6.86 (m, 2H), 6.93−6.97 (m, 4H), 7.16−7.41 (m, 12H); calcd for $C_{28}H_{25}ClN_2OS$, 472; LC−MS 473.1, [MH$^+$]; retention time 3.63 min.

2-(4-Chlorophenyl)-1-(4-hydroxybenzyl)-3-(4-methoxyphenyl)-1-phenethylisothiourea 9{*57*}. Oil; ^{1}H NMR δ 3.20 (t, 2H, J = 7.3 Hz), 3.76 (s, 3H), 4.31 (t, 2H, J = 7.3 Hz), 5.26 (s, 2H), 6.68−6.76 (m, 4H), 6.95 (t, 4H, J = 8.6 Hz), 7.24 (d, 2H, J = 8.4 Hz), 7.30−7.50 (m, 7H); calcd for $C_{29}H_{27}ClN_2O_2S$, 502; LC−MS 503.2, [MH$^+$]; retention time 3.70 min.

2,3-Bis(4-chlorophenyl)-1-(4-hydroxybenzyl)-1-phenethylisothiourea 9(58). Oil; ^{1}H NMR δ 3.16 (t, 2H, J = 7.3 Hz), 4.24 (t, 2H, J = 7.3 Hz), 5.20 (s, 2H), 6.82 (d, 2H, J = 8.6 Hz), 6.93 (d, 2H, J = 8.4 Hz), 7.01 (d, 2H, J = 8.3 Hz), 7.15 (d, 2H, J = 8.5 Hz), 7.22 (d, 2H, J = 8.5 Hz), 7.26−7.39 (m, 7H); calcd for $C_{28}H_{24}Cl_2N_2OS$, 506; LC−MS 507.2, [MH$^+$]; retention time 4.02 min.

1-(4-Hydroxybenzyl)-1-[2-(4-methoxyphenyl)ethyl]-2,3-diphenylisothiourea 9{*59*}. Oil; ^{1}H NMR δ 3.13 (t, 2H, J = 7.1 Hz), 3.82 (s, 3H), 4.26 (t, 2H, J = 7.2 Hz), 5.25 (s, 2H), 6.80−6.83 (m, 2H), 6.92−6.98 (m, 6H), 7.12−7.19 (m, 5H), 7.27−7.31 (m, 3H), 7.39 (d, 2H, J = 8.4 Hz); calcd for $C_{29}H_{28}N_2O_2S$, 468; LC−MS 469.2, [MH$^+$]; retention time 3.50 min.

1-(4-Hydroxybenzyl)-3-(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]-2-phenylisothiourea 9{*60*}. Oil; ^{1}H NMR δ 3.13 (t, 2H, J = 7.1 Hz), 3.74 (s, 3H), 3.80 (s, 3H), 4.24 (t, 2H, J = 7.0 Hz), 5.23 (s, 2H), 6.62−6.76 (m, 4H), 6.90−7.00 (m, 6H), 7.18−7.39 (m, 7H), 8.91 (br s, 1H); calcd for $C_{30}H_{30}N_2O_3S$, 498; LC−MS 499.1, [MH$^+$]; retention time 3.49 min.

3-(4-Chlorophenyl)-1-(4-hydroxybenzyl)-1-[2-(4-methoxyphenyl)ethyl]-2-phenylisothiourea 9{*61*}. Oil; ^{1}H NMR δ 3.07 (t, 2H, J = 7.1 Hz), 3.78 (s, 3H), 4.17 (t, 2H, J = 7.1

Hz), 5.16 (s, 2H), 6.77 (d, 2H, J = 8.6 Hz), 6.91 (d, 4H, J = 8.2 Hz), 6.99 (d, 2H, J = 7.6 Hz), 7.99 (d, 2H, J = 8.6 Hz), 7.15−7.20 (m, 2H), 7.23−7.28 (m, 3H), 7.33−7.36 (m, 2H); calcd for $C_{29}H_{27}ClN_2O_2S$, 502; LC−MS 503.2, [MH^+]; retention time 3.66 min.

2-(4-Chlorophenyl)-1-(4-hydroxybenzyl)-1-[2-(4-methoxyphenyl)ethyl]-3-phenylisothiourea 9(62). Oil; ^{1}H NMR δ 3.13 (t, 2H, J = 7.0 Hz), 3.80 (s, 3H), 4.27 (t, 2H, J = 7.0 Hz), 5.25 (s, 2H), 6.2−6.85 (m, 2H), 6.91−6.97 (m, 6H), 7.15−7.19 (m, 5H), 7.29 (d, 2H, J = 8.5 Hz), 7.39 (d, 2H, J = 8.5 Hz); calcd for $C_{29}H_{27}ClN_2O_2S$, 502; LC−MS 503.2, [MH^+]; retention time 3.64 min.

2-(4-Chlorophenyl)-1-(4-hydroxybenzyl)-3-(4-methoxyphenyl)-1-[2-(4-methoxyphenyl)ethyl]isothiourea 9(63). Oil; ^{1}H NMR δ 3.12 (t, 2H, J = 7.0 Hz), 3.76 (s, 3H), 3.81 (s, 3H), 4.25 (t, 2H, J = 7.0 Hz), 5.23 (s, 2H), 6.66−6.77 (m, 4H), 6.92−6.99 (m, 6H), 7.22 (d, 2H, J = 8.3 Hz), 7.29 (d, 2H, J = 8.3 Hz), 7.38 (d, 2H, J = 8.2 Hz); calcd for $C_{30}H_{29}ClN_2O_3S$, 532; LC−MS 533.3, [MH^+]; retention time 3.67 min.

2,3-Bis(4-chlorophenyl)-1-(4-hydroxybenzyl)-1-[2-(4-methoxyphenyl)ethyl]isothiourea 9(64). Oil; ^{1}H NMR δ 3.07 (t, 2H, J = 7.3 Hz), 3.79 (s, 3H), 4.16 (t, 2H, 7.3 Hz), 5.14 (s, 2H), 6.80 (d, 2H, J = 8.7 Hz), 6.91 (d, 4H, J = 8.2 Hz), 7.10 (d, 2H, J = 8.4 Hz), 7.14 (d, 2H, J = 8.7 Hz), 7.19−7.27 (m, 4H), 7.36 (d, 2H, J = 8.5 Hz); calcd for $C_{29}H_{26}Cl_2N_2O_2S$, 536; LC−MS 537.2, [MH^+]; retention time 3.90 min.

1-Cyclohexyl-1-(4-hydroxybenzyl)-2,3-diphenylisothiourea 9{65}. Semisolid; ^{1}H NMR δ 1.17−2.00 (m, 10H), 4.81 (s, 1H), 5.16 (s, 2H), 6.81 (br s, 2H), 6.91 (d, 2H, J = 8.3 Hz), 7.12−7.29 (m, 9H), 7.33−7.38 (m, 1H), 9.45 (s, 1H); calcd for $C_{26}H_{28}N_2OS$, 416; LC−MS 417.2, [MH^+]; retention time 3.52 min.

1-Cyclohexyl-1-(4-hydroxybenzyl)-3-(4-methoxyphenyl)-2-phenylisothiourea 9{*66*}. Semisolid; ^{1}H NMR δ 1.17−2.00 (m, 10H), 3.74 (s, 3H), 4.70−4.80 (m, 1H), 5.12 (s, 2H), 6.70 (s, 4H), 6.92 (d, 2H, J = 8.3 Hz), 7.17−7.32 (m, 6H), 7.36−7.41 (m, 1H), 9.54 (br s, 1H); calcd for $C_{27}H_{30}N_2O_2S$, 446; LC−MS 447.1, [MH^+]; retention time 3.53 min.

3-(4-Chlorophenyl)-1-cyclohexyl-1-(4-hydroxybenzyl)-2-phenylisothiourea 9{*67*}. Semisolid; ^{1}H NMR δ 1.12−2.03 (m, 10H), 4.72−4.83 (m, 1H), 5.13 (s, 2H), 6.78 (d, 2H, J = 8.3 Hz), 6.89 (d, 2H, J = 8.5 Hz), 7.13 (d, 2H, J = 8.6 Hz), 7.17−7.28 (m, 6H), 7.34−7.38 (m, 1H); calcd for $C_{26}H_{27}ClN_2OS$, 450; LC−MS 451.2, [MH^+]; retention time 3.75 min.

2-(4-Chlorophenyl)-1-cyclohexyl-1-(4-hydroxybenzyl)-3-phenylisothiourea 9{*68*}. Semisolid; ^{1}H NMR δ 1.1−2.01 (m, 10H), 4.63−4.72 (m, 1H), 5.01 (s, 2H), 6.73 (d, 2H, J = 6.7 Hz), 6.87 (d, 2H, J = 8.5 Hz), 7.10−7.16 (m, 5H), 7.23−7.27 (m, 4H); calcd for $C_{26}H_{27}ClN_2OS$, 450; LC−MS 451.2, [MH^+]; retention time 3.72 min.

2-(4-Chlorophenyl)-1-cyclohexyl-1-(4-hydroxybenzyl)-3-(4-methoxyphenyl)isothiourea 9{*69*}. Semisolid; ^{1}H NMR δ 1.10−1.90 (m, 10H), 3.74 (s, 3H), 4.50−4.57 (m, 1H), 4.90 (s, 2H), 6.64−6.74 (m, 4H), 6.85 (d, 2H, J = 8.4 Hz), 7.17 (t, 4H, J = 8.7 Hz), 7.31 (d, 2H, J = 8.5 Hz); calcd for $C_{27}H_{29}ClN_2O_2S$, 480; LC−MS 481.3, [MH^+]; retention time 3.63 min.

2,3-Bis(4-chlorophenyl)-1-cyclohexyl-1-(4-hydroxybenzyl)isothiourea 9{*70*}. Semisolid; ^{1}H NMR δ 1.10−2.01 (m, 10H), 4.73−4.81 (m, 1H), 5.13 (s, 2H), 6.80 (d, 2H, J = 8.4 Hz), 6.89 (d, 2H, J = 8.5 Hz), 7.10−7.22 (m, 4H), 7.24−7.29 (m, 4H); calcd for $C_{26}H_{26}Cl_2N_2OS$, 484; LC−MS 485.2, [MH^+]; retention time 3.94 min.

2-(4-Hydroxybenzyl)-1-phenyl-3-phenylacetylisothiourea 12a. Calcd for $C_{22}H_{20}N_2O_2S$, 377; LC−MS 377.9, [MH^+]; retention time 4.51 min; content 80%.

2-(4-Hydroxybenzyl)-1-(4-methoxyphenyl)-3-phenylacetylisothiourea 12b. Calcd for $C_{23}H_{22}N_2O_3S$, 406; LC−MS 407.9, [MH^+]; retention time 4.51 min; content 90%.

References and Notes

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