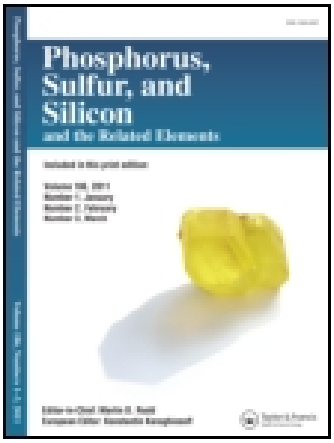

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A Facile, Sequential Multicomponent Approach to N-Aminoamidinothioureas—Versatile Synthons to Bioactive Heterocycles

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A FACILE, SEQUENTIAL MULTICOMPONENT APPROACH TO N-AMINOAMIDINOTHIOUREAS—VERSATILE SYNTHONS TO BIOACTIVE HETEROCYCLES

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A sequential, three-component approach for the rapid and convenient one-pot synthesis of N-aminoamidinothioureas is reported. The improved synthetic strategy involves the selective blocking of amino functionality in aminoguanidine by Schiff base formation with carbonyl compounds to generate corresponding N-(alkylidene/arylidene)aminoguanidines and their subsequent in situ condensation with isothiocyanate. The structural motif incorporates three points for diversity multiplication, making it a suitable candidate for combinatorial synthesis. The generality of the improved procedure was established by synthesizing a series of diverse compounds through solution phase parallel synthesis by varying the carbonyl and isothiocyanate components. The newly synthesized compounds were characterized by spectral methods. The developed synthetic procedure employs mild reaction conditions, and individual steps are carefully optimized for easy automation.

Keywords N-Aminoamidinothiourea; combinatorial synthesis; condensation; diversity; sequential multicomponent reaction

INTRODUCTION

Amidinothioureas are known to serve as precursors to bioactive heterocyclic compounds.[1] Our continuing endeavor in the direction of developing versatile synthons[2–4] to access bioactive heterocycles[5,6] has resulted in devising novel and improved syntheses of many interesting members of the thiourea family. A literature search indicated that synthesis of N-aminoamidinothioureas of the type **4**, also referred to as 1-arylthiocarbamoyl-3-[N-(alkylidene/arylideneamino) guanidine or N-(alkylidene/arylideneamino)-N′-(arylthiocarbamoyl)guanidine, has received only scarce mention, except for two older reports from Godfrey and Kurzer,[7,8] which employ extreme reaction conditions. With the growing interest in combinatorial design and evaluation of library members for different properties,[9] the synthetic routes to these molecules demand

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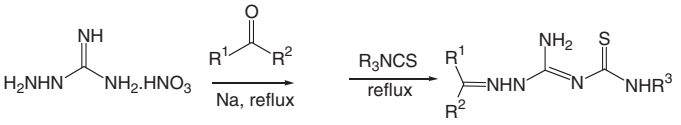


Scheme 1 Godfrey and Kurzer's method for the synthesis of N-(isopropylideamino)-N'-(phenylthiocarbamoyl)guanidine **4a**.

greater refinement. Thus it was felt useful to have an improved procedure to access the title compounds. Moreover, the elements of diversity incorporated by the core structure **4** appeared to be very attractive to fit into a combinatorial scenario based on parallel synthesis, which further facilitates high throughput screening (HTS) of the members for bioactivity.

The existing procedure available for the synthesis of N-aminoamidinothioureas involves refluxing a solution of metallic sodium in acetone and aminoguanidine sulfate to form N-(isopropylidene)aminoguanidine, which upon refluxing with isothiocyanate affords 1-arylthiocarbamoyl-3-[N-(isopropylidene)aminoguanidine]. This method is limited to the synthesis of isopropylidene derivatives only, thus limiting diversity multiplication, and so the synthetic scheme (Scheme 1) would require refinement before being applied in a parallel synthesis. A more general route following less drastic conditions and affording a diverse set of target molecules, preferably through a multicomponent approach,[10] was designed.

The title compounds could be accessed from aminoguanidine, carbonyl compound, and isothiocyanate. The multisite reactivity of the reagents suggested the possibility of formation of different products if a multicomponent route is adopted. Thus, to access the desired compounds, it was decided to employ a sequential multicomponent route (SMCR).[11] A SMCR is a sensible modification of a multicomponent reaction (MCR) in which the functional groups in a reactant are selectively made to react with different reagents in a sequence to generate a specific compound. Such reactions are usually carried out through one-pot tandem procedures without any intermediate or product isolation.

Studies in our laboratories have made useful contributions to the chemistry of sulfur-containing compounds. For accessing thioureas and related compounds, simple routes and mild reaction conditions were developed. Amidinothioureas were accessed by reacting guanidine salts with isothiocyanates in dimethyl formamide containing powdered KOH.[4] It was decided to test the applicability of a similar strategy in the present case.

RESULTS AND DISCUSSION

The sequence of reactions in the planned route may give a product that can exist in two tautomeric forms—either the azo form or the hydrazino form (Chart 1). The present study may shed light into the actual structure of the products.

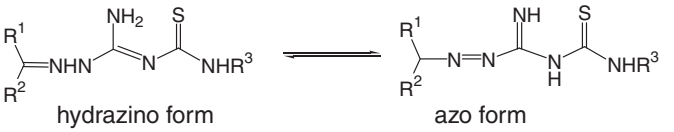
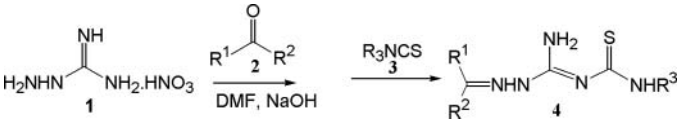


Chart 1 Tautomers possible for compound **4**.



Scheme 2 Synthesis of N-(aminoamidino)thioureas **4a–l** through SMCR approach.

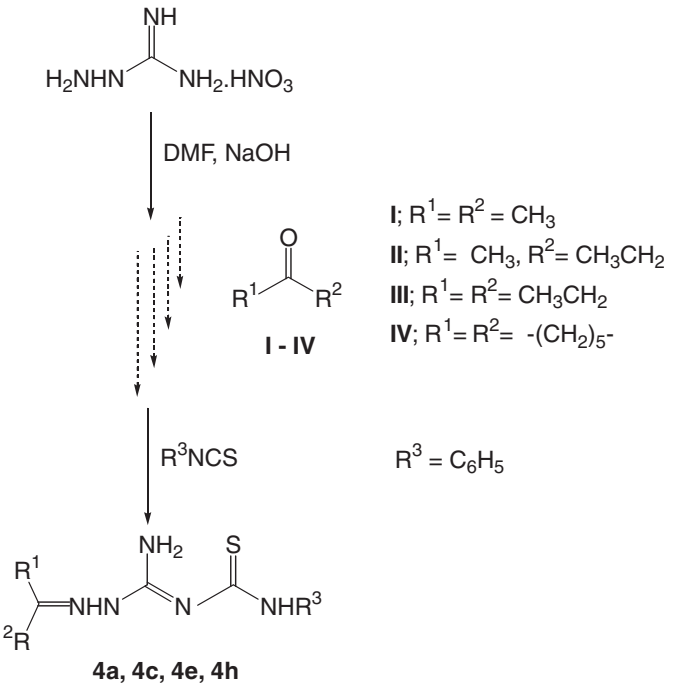
Aminoguanidine **1** was reacted with a particular carbonyl compound **2** in DMF containing NaOH. The corresponding hydrazone derivatives formed were reacted subsequently with isothiocyanates **3** to afford the title compounds **4** in good yield as the sole major product (Scheme 2). The synthesis required stirring of the reaction mixture for 2 h at room temperature. This was indeed an excellent modification of the existing literature procedure. The variables incorporated by the core structure are summarized in Table I.

The isolated products were purified by simple crystallization from aqueous ethanol. The structures of all the new compounds were confirmed on the basis of analytical data and spectral studies of the compounds. For example, IR spectra of **4a** showed NH stretching at 3300 and 3200 cm^{-1}. An aryl CH bending band at 735 cm^{-1} indicated the presence of a phenyl group. The presence of C=N groups was suggested by a band at 1620 cm^{-1}. The ^1H NMR spectrum displayed two singlets at 2.02 and 2.07 δ integrating for three protons each, which suggested the presence of two methyl groups in the compound. These signals strongly indicated that the compound existed in the hydrazino form instead of the azo tautomeric form. A broad band at 6.43 δ was assigned to NH_2 protons. The triplet-triplet-doublet pattern in the aryl region suggested a C_6H_5NH group in the compound. Two more broad signals at 7.90 and 12.95 δ were assigned to C=NNH and NH-aryl protons, respectively. These data confirmed the formation of product **4a**. A similar spectral study was carried out for establishing the structures of the other products (see the Experimental section).

The efficiency of the newly developed synthetic sequence prompted us to explore its validity in a parallel library synthesis. Since we had two elements for diversity multiplication—the carbonyl compound and the isothiocyanate—two different approaches for combinatorial library synthesis were laid out. In the first approach, different carbonyl

Table I Different elements of diversity incorporated in N-aminoamidinothioureas **4a–l**

Compound no.	Carbonyl component		Isothiocyanate component
4	R^1	R^2	R^3
a	CH_3	CH_3	C_6H_5
b	CH_3	CH_3	4-$CH_3OC_6H_4$
c	CH_3	CH_3CH_2	C_6H_5
d	CH_3	CH_3CH_2	4-$CH_3CH_2OC_6H_4$
e	CH_3CH_2	CH_3CH_2	C_6H_5
f	CH_3CH_2	CH_3CH_2	4-$CH_3CH_2OC_6H_4$
g	CH_3CH_2	CH_3CH_2	4-ClC_6H_4
h	$-(CH_2)_5-$		C_6H_5
i	$-(CH_2)_5-$		4- ClC_6H_4
j	C_6H_5	H	C_6H_5
k	C_6H_5	H	4-$CH_3C_6H_4$
l	C_6H_5	H	4-$CH_3OC_6H_4$



Scheme 3 Structural diversity possible by varying carbonyl compounds.

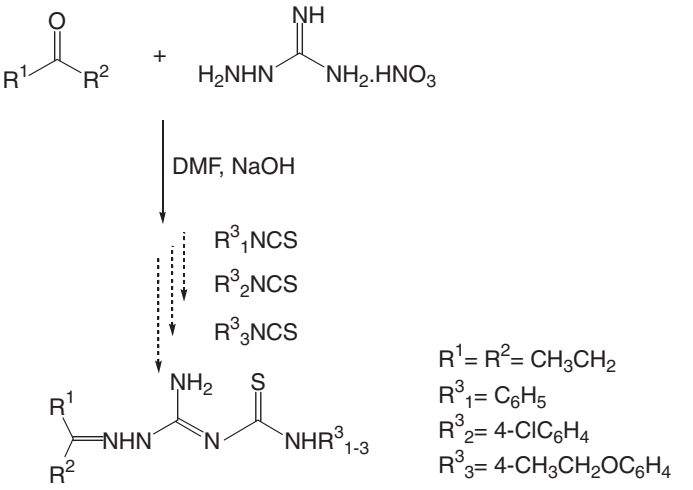
compounds were used to demonstrate the synthesis of a small library (Scheme 3) by keeping the isothiocyanate component the same. Equimolar quantities of aminoguanidine nitrate and NaOH were stirred in DMF, to which a mixture of four carbonyl compounds (0.25 molar equivalent each) was added. A particular isothiocyanate was added in quantities slightly less than one molar equivalent after the completion of the hydrazone formation reaction. The reaction mixture upon workup afforded a solid product.

The formation of the expected products in the library was sufficiently established through HPLC analysis of the crude product. For mixed melting point analysis, already prepared and characterized compounds were used as standards. This was sufficient enough to establish our objective to create a library that could be further extended by the use of various carbonyl compounds commercially available in large numbers. In the second approach, different isothiocyanates were employed for generating chemical diversity (Scheme 4).

With the intention of making the library synthesis more attractive, we next decided to resort to a split-pool approach,[12] which would incorporate both the variations in a single reaction scheme. Thus work on elaborating the library synthesis, its screening (preliminary screening of the members has given promising results), and application of the newly developed precursors in heterocycle synthesis is being pursued, and the results will be published summarily.

EXPERIMENTAL

All chemicals employed were of commercial grade. Melting points are uncorrected and were determined by open capillary method. TLC was performed using silica gel-G (E. Merck, India) coated on glass plates or commercial plastic plates from Kodak. The



Scheme 4 Structural diversity possible by varying isothiocyanates.

spots were visualized in iodine vapor or under UV light. IR spectra were obtained from a Nicolet 400 D FT-IR spectrophotometer using KBr pellets. ^{1}H NMR spectra were recorded on a Jeol DRX 300 MHz spectrometer in $CDCl_3$ using TMS as the internal standard. Mass spectrum was recorded on a Jeol D-300 spectrometer by electron impact technique, and elemental analysis was carried out using an Elementar Vario EL III CHN analyzer.

Synthesis of 1-Aryl-3-[N-(alkyl/arylidene)aminoguanidines] (4a–l)

To a well-stirred suspension of aminoguanidine nitrate (1.37g, 0.01 mol) and sodium hydroxide (400 mg, 0.01 mol) in DMF (5 mL), the appropriate carbonyl compound (0.01 mol) was added, and the mixture was stirred for 1 h. This was followed by the addition of isothiocyanates (0.009 mol), and stirring was continued for another 50 min. The reaction mixture was worked up to afford the title compounds, which were purified by crystallization from and ethanol/water 2:1 mixture.

N-(Isopropylideneamino)-N′-(phenylthiocarbamoyl)guanidine (4a)

Off-white shining crystals. Yield 70%. Mp 167–168°C (d.). Lit.[7] Mp 167–169°C (d.). IR (KBr) υ cm^{-1}: 3300, 3200 (NH), 2840 (C—H aliphatic), 1620 (C=N), 1550, 1400 (CH aromatic) 1300, 1230, 1185 (C—N), 1100 (C=S), 830,735 (aromatic). ^{1}H NMR: 300 MHz, ($CDCl_3$): δ 2.02 (s, 3H, CH_3), 2.07 (s, 3H, CH_3), 6.43 (br, 2NH), 7.10 (t, 1ArylH, J = 6.9 Hz), 7.31 (t, 2 ArylH, J = 9 Hz), 7.47 (d, 2 ArylH, J = 9 Hz), 7.90 (br, 1NH), 12.95 (br, 1NH). Anal. calcd. for $C_{11}H_{15}N_5S$ (249.33): C, 52.99; H, 6.06; N, 28.09%. Found: C, 52.77; H, 6.23; N, 28.30%.

N-(Isopropylideneamino)-N′-(p-methoxylphenylthiocarbamoyl) guanidine (4b)

Off-white shining crystals. Yield 62%. Mp 161–163°C. IR (KBr) υ cm^{-1}: 3400, 3235 (NH), 2832 (C—H aliphatic), 1648, 1629 (C=N), 1528, 1438, 1426 (CH aromatic), 1297,

1177 (C—N), 1110, 1034 (C=S), 823, 668, 572 (aromatic). ^{1}H NMR: 300 MHz, ($CDCl_3$): δ 2.01 (s, 3H, CH_3), 2.06 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 6.35 (br, 2NH), 6.81–6.84 (m, 2ArylH), 7.30–7.32 (m, 2 ArylH), 7.75 (br, 1NH), 12.39 (br, 1NH). Anal. calcd. for: $C_{12}H_{17}N_5OS$ (279.36): C, 51.58; H, 6.13; N, 25.07%. Found C, 51.45; H, 6.04; N, 25.02%.

N-(Isobutylideneamino)-N′-(phenylthiocarbamoyl)guanidine (4c)

Off-white shining crystals. Yield 56%. Mp 153–154°C (d.). Lit.[7] Mp 153–155°C (d.). IR (KBr) υ cm^{-1}: 3395, 3295 (NH), 3180 (C—H aromatic), 2830 (C—H aliphatic), 1615 (C=N), 1520, 1480, 1390 (CH aromatic), 1300, 1235, 1180 (C—N), 1115, 1012 (C=S), 740, 685 (aromatic). Anal. calcd. for: $C_{12}H_{17}N_5S$ (263.36): C, 54.73; H, 6.51; N, 26.59. Found: C, 54.94; H, 6.71; N, 26.79:

N-(p-Ethoxyphenylthiocarbamoyl)-N′-(isobutylideneamino)guanidine (4d)

Off-white shining crystals. Yield 55%. Mp. 147–148°C (d.). IR (KBr) υ cm^{-1}: 3263 (NH), 2987, 2940, 2802 (C—H aliphatic), 1650 (C=N), 1445, 1400 (CH aromatic), 1297, 1231, 1179 (C—N), 1113, 1049 (C=S), 827, 733 (aromatic). ^{1}H NMR: 300 MHz, ($CDCl_3$): δ 1.12 (t, J = 7.4 Hz, 3H, CH_3), 1.40 (t, J = 7 Hz, 3H, CH_3), 2.02 (s, 3H, CH_3), 2.34 (q, J = 7.4 Hz, 2H, CH_2), 4.01 (q, J = 7 Hz, 2H, OCH_2), 6.41 (br, 2NH), 6.83 (d, 2ArylH, J = 6 Hz), 7.32 (d, 2ArylH, J = 6 Hz), 7.79 (br, 1NH) 12.22 (br, 1NH). EIMS: m/z (%): 307(M^+, 14), 273(9), 236(5), 180(13), 179(83), 171(14), 152(13), 151(100), 150(16), 137(46), 128(32), 119(10), 109(17), 108(24), 99(16). Anal. calcd. for: $C_{14}H_{21}N_5OS$ (307.41): C, 54.70; H, 6.89; N, 22.78%. Found: C, 54.89; H, 7.03; N, 22.54%.

N-(Isopentylideneamino)-N′-(phenylthiocarbamoyl)guanidine (4e)

Off-white shining crystals. Yield 58%. Mp 155–156°C. IR (KBr) υ cm^{-1}: 3567, 3311, 3221 (NH), 2972 (C—H aliphatic), 1718, 1617 (C=N), 1534, 1450 (CH aromatic), 1122 (C—N), 1076 (C=S), 832, 743, 690 (aromatic). ^{1}H NMR: 300 MHz, ($CDCl_3$): δ 1.11–1.22 (m, 6H, $2CH_3$), 2.32–2.42 (m, 4H, $2CH_2$), 6.03–6.45 (br, 2NH), 7.08–7.10 (m, 1ArylH), 7.29–7.31 (m, 2ArylH), 7.45 (d, 2ArylH, J = 7.4 Hz), 7.86 (br, 1NH), 12.75 (br, 1NH). EIMS: m/z (%): 243(11), 185(10), 142(22), 135(99), 113(16), 93(22), 91(10), 77(100), 60(15), 59(45), 45(73). Anal. calcd. for: $C_{13}H_{19}N_5S$ (277.38): C, 56.28; H, 6.90; N, 25.25%. Found: C, 56.01; H, 7.14; N, 25.44%.

N-(p-Ethoxyphenylthiocarbamoyl)-N′-(isopentylideneamino)guanidine (4f)

Off-white shining crystals. Yield 58%. Mp 145–146°C. IR (KBr) υ cm^{-1}: 3568, 3230 (NH), 2977, 2928 (C—H aliphatic), 2799, 1870, 1774, 1734, 1718 (C=N), 1528, 1479 (CH aromatic), 1253 (C—N), 1122 (C=S), 828, 696 (aromatic). ^{1}H NMR: 300 MHz, ($CDCl_3$): δ 1.11–1.21 (m, 6H, $2CH_3$), 1.41 (t, J = 7Hz, 3H, CH_3), 2.06–2.41 (m, 4H, $2CH_2$), 4.01 (q, J = 7Hz, 2H, OCH_2), 6.41 (br, 2NH), 6.81 (d, 2ArylH, J = 6 Hz), 7.29 (d, 2ArylH, J = 8 Hz), 7.72 (br, 1NH), 12.68 (br, 1NH). EIMS: m/z (%): 178(64), 152(12), 151(100), 150(14), 142(16), 137(18), 134(10), 122(18), 113(14), 108(15), 65(26), 63(12), 59(14),

58(55), 56(32), 45(26), 44(70). Anal. calcd. for: $C_{15}H_{23}N_5OS$ (321.44): C, 56.05; H, 7.21; N, 21.79%. Found: C, 56.35; H, 7.34; N, 21.67%.

N-(p-Chlorophenylthiocarbamoyl)-N′-(isopentylideneamino)guanidine (4g)

Off-white shining crystals. Yield 60%. Mp 132–133°C. IR (KBr) υ cm^{-1}: 3566, 3219 (NH), 2973 (C—H aliphatic), 1716, 1616 (C=N), 1539, 1488 (CH aromatic), 1283 (C—N), 1122, 1021 (C=S), 820, 659 (aromatic). ^{1}H NMR: 300 MHz, ($CDCl_3$): δ 1.12–1.22 (m, 6H, $2CH_3$), 2.33–2.42 (m, 4H, $2CH_2$), 6.00–6.48 (br, 2NH), 7.24 (d, 2ArylH, J = 9 Hz), 7.41 (d, 2ArylH, J = 8.4 Hz), 7.80 (br, 1NH), 12.73 (br, 1NH). EIMS: m/z (%): 279(5), 277(11), 172(9), 171(36), 169(100), 142(18), 127(15), 113(24), 111(39), 75(27), 58(46). Anal. calcd. for: $C_{13}H_{18}ClN_5S$ (311.83): C, 50.07; H, 5.82; N, 22.46%. Found: C, 49.91; H, 5.95; N, 22.2%.

N-(Cyclohexylideneamino)-N′-(phenylthiocarbamoyl)guanidine (4h)

Off-white shining crystals. Yield 69%. Mp 160–162°C. IR (KBr) υ cm^{-1}: 3350, 3160 (NH), 3090, 2990, 2850, 2750 (C—H aliphatic), 1620 (C=N), 1550, 1400 (CH aromatic), 1300, 1230 (C—N), 1180, 1000 (C=S), 735, 680 (aromatic). ^{1}H NMR: 300 MHz, ($CDCl_3$): δ 1.62–1.77 (m, 6H, cyclohexyl), 2.33–2.46 (m, 4H, cyclohexyl), 6.29–6.47 (br, 2 NH), 7.09 (t, 1 ArylH, J = 6 Hz), 7.30 (t, 2 ArylH, J = 6 Hz), 7.47 (d, 2ArylH, J = 9 Hz), 7.87(br, 1NH), 12.50(br, 1NH). EIMS: m/z (%): 289(M^+, 10), 256(17), 255(27), 197(39), 196(10), 192(29), 154(36), 135(100), 119(10), 111(26), 102(10), 98(18), 96(31), 93(31), 86(14), 77(80). Anal. calcd. for: $C_{14}H_{19}N_5S$ (289.39): C, 58.10; H, 6.62; N, 24.20%. Found: C, 58.32; H, 6.47; N, 23.96%.

N-(p-Chlorophenylthiocarbamoyl)-N′-(cyclohexylideneamino) guanidine (4i)

Off-white shining crystals. Yield 70%. Mp 166–168°C (d.). IR (KBr) υ cm^{-1}: 3309, 3235 (NH), 2928 (C—H aliphatic), 1645 (C=N), 1569, 1523, 1488, 1391 (CH aromatic), 1284 (C—N), 1180, 1086 (C=S), 828, 730, 649 (aromatic). ^{1}H NMR: 300 MHz, ($CDCl_3$): δ 1.68–1.75 (m, 6H, cyclohexyl), 2.33–2.46 (m, 4H, cyclohexyl), 6.20–6.46 (br, 2NH), 7.22 (m, 2ArylH), 7.40 (d, 2ArylH, J = 6 Hz), 7.82 (br, 1NH), 12.64 (br, 1NH). EIMS: m/z (%): 289(6), 287(14), 274(16), 231(35), 210(15), 208(46), 195(12), 153 (50), 151(16), 137(20), 128(18), 126(66), 115(79), 111(10), 110(64), 96(7), 95(28), 82(19), 81(22), 43(100). Anal. calcd. for: $C_{14}H_{18}ClN_5S$ (323.84): C, 59.99; H, 5.61; N, 21.63%. Found: C, 51.66; H, 5.44; N, 21.82%.

N-(Benzylideneamino)-N′-(phenylthiocarbamoyl)guanidine (4j)

Pale green shining crystals. Yield 43%. Mp 169–170°C (d.). Lit.[7] Mp. 168–170°C (d.). IR (KBr) υ cm^{-1}: 3425, 3398 (NH), 3041 (C—H aromatic), 1619 (C=N), 1591, 1560, 1464 (CH aromatic), 1310 (C—N), 1095 (C=S), 807, 748, 686 (aromatic). Anal. calcd. for: $C_{15}H_{15}N_5S$ (297.37): C, 60.58; H, 5.08; N, 23.55%. Found: C, 60.83; H, 5.26; N, 23.75%.

N-(Benzylideneamino)-N′-(p-methylphenylthiocarbamoyl)guanidine (4k)

Pale green shining crystals. Yield 50%. Mp 156–158°C. IR (KBr) υ cm^{-1}: 3400 (NH), 3080 (C—H aromatic), 1610, 1600 (C=N), 1580, 1550, 1500, 1435 (CH aromatic), 1090 (C=S), 805, 750, 680 (aromatic). ^{1}H NMR: 300 MHz, ($CDCl_3$): δ 2.33 (s, 3H, CH_3), 6.6 (br, 1NH), 7.43 (m, 3 ArylH), 7.65 (m, 2 ArylH), 7.93 (br, 2 NH), 8.51 (br, 1NH). EIMS: m/z (%):195(9), 162(35), 161(20), 150(14), 149(100), 148(42), 119(15), 117(12), 106(12), 92(13), 91(97), 90(34), 89(30), 85(25), 77(20). Anal. calcd. for: $C_{16}H_{17}N_5S$ (311.40): C, 61.71; H, 5.50; N, 22.49%. Found: C, 61.52; H, 5.63; N, 22.30%.

N-(Benzylideneamino)-N′-(p-methoxyphenylthiocarbamoyl)guanidine (4l)

Pale green shining crystals. Yield 45%. Mp 165–66°C. IR (KBr) υ cm^{-1}: 3427, 3225 (NH), 2830, 1720, 1621 (C=N), 1534, 1509 (CH aromatic), 1110, 1099 (C=S), 835, 800, 751, 690 (aromatic). ^{1}H NMR: 300 MHz, ($CDCl_3$): δ 3.80 (s, 3H, OCH_3), 6.56 (br, 1NH), 6.85–6.87 (m, 2 ArylH), 7.38–7.46 (m, 4 ArylH), 7.60–7.68 (m, 3ArylH), 7.89–8.01 (br, 1H, CH = N + 2 NH), 8.54 (br, 1NH). EIMS: m/z (%): 293(17), 292(53), 277(18), 250(17), 249(36), 210(27), 205(21), 195(30), 189(45), 166(7), 163(19), 162(46), 160(20), 119(10), 104(30), 91(100), 90(30), 77(40). Anal. calcd. for: $C_{16}H_{17}N_5OS$ (327.40): C, 58.69; H, 5.23; N, 21.39%. Found: C, 58.42; H, 5.48; N, 21.27%.

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