Bulgarian Chemical Communications, Volume 46, Number 4 (pp. 724 – 730) 2014

Catalyst-free green synthesis of urea and thiourea derivatives of tetramethylguanidine (TMG) and evaluation of biological activity

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Received September 11, 2013; Revised April 18, 2014

An expeditious green approach was developed for the synthesis of urea and thiourea derivatives of 1,1,3,3-tetramethylguanidine in high yields under catalyst-free and solvent-free conditions. The procedure has many advantages, e.g., avoiding of harmful solvents, ease of work-up, short reaction time and high purity of the products with high yields. Various reaction parameters such as catalyst effect, solvent effect and temperature conditions were optimized. Antimicrobial activity of the title compounds was evaluated and the bio-screening data disclosed that compounds **3a**, **3e** and **3g**, **3j** exhibited promising antibacterial and antifungal activities, respectively.

Keywords: Green synthesis; Solvent and catalyst-free conditions; 1,1,3,3-Tetramethyl guanidine; Urea and thiourea derivatives; Antimicrobial activity.

INTRODUCTION

It is well known that guanidine derivatives are a promising class of biologically active molecules and exhibit a great number of biological activities such as antimicrobial [1], antifungal [2], anti-inflammatory, antimalarial [3,4], antitumor [5], analgesic [6]. They have also been used as extraction agents for periodate ions [7,8]. Further, the reaction of isocyanates and isothiocyanates with various amines affords urea and thiourea molecules. The literature survey revealed that these derivatives covered a wide range of biological activities like antibacterial, antifungal, antiviral, herbicidal, inhibiting NO production, anti-HIV, anticancer, HDL-elevating activities [9] and also could be used for elimination or detoxification of super antigens from body fluids and for the treatment of haemoglobinopathies in the cases of sickle-cell anemia [10]. The investigations on urea and thiourea derivatives revealed that the high molecular recognition of urea and thiourea derivatives is due to their strong hydrogen bonding property.

Over the last few decades, the intention of the organic chemists is to develop greener and more economically competitive processes [11] for the efficient synthesis of organic molecules, intermediates or biologically active compounds with potential application in the fields of pharmaceutical and agrochemical industries. In this connection solvent-free reactions have attained great interest not only from ecological point of view but for the afforded synthetic advantages in terms of reaction time, yield, selectivity and simple synthetic procedure [12,13]. The foremost advantages of solvent-free conditions are: reduced use of organic solvents, minimized formation of wastes and reactions occurring under mild conditions [14].

By considering the above facts and the prominence of urea and thiourea derivatives in regard of biology, we have shown significant interest to develop a new green methodology to prepare new urea and thiourea derivatives and evaluate their antimicrobial activity with good hope that the title compounds will exhibit enhanced biological activity.

EXPERIMENTAL PART

Chemicals and apparatus

All required chemicals were purchased from Sigma-Aldrich and Merck, and used without further purification. Melting points were determined in open capillaries in a Guna melting point apparatus and were uncorrected. Infrared (IR) spectra were obtained on a Nicolet 380 Fourier transform infrared (FT-IR) spectrophotometer using KBr optics. ^{1}H NMR and ^{13}C NMR were recorded with a Bruker instrument-400 MHz (400.13 MHz

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for ^{1}H NMR, 100.62 MHz for ^{13}C NMR) and tetramethylsilane was used as internal standard in $CDCl_3$. Chemical shifts (δ) are indicated in ppm and coupling (*J*) in Hz. Mass spectra were recorded on an ESI-MS mass spectrometer. Elemental analyses were carried out in FLASH EA 1112.

General Procedure

Tetramethylguanidine (**1**) (1.5 mmol, 0.18 mL) and 1-isothiocyanato-4-nitrobenzene (**2f**) (1mmol, 180 mg) were taken into a 50 mL flat-bottomed flask without solvent and catalyst. The reaction mixture was stirred for 90 min. at 60 ºC and the progress of the reaction was monitored by TLC using ethylacetate:*n*-hexane (2:3). After completion of the reaction, cold water (15 mL) was added to the reaction mixture and was stirred for 10 min. Then, the reaction mixture was filtered off to obtain the product, *N*-di(dimethylamino)methylene-*N′*-(4-nitrophenyl)thiourea (**3f**). The latter was washed with cold water, air-dried and recrystallized from methanol to get the pure compound. The same procedure was adopted for the synthesis of the other title compounds (Scheme 1).

Spectral Data

***N*-di(dimethylamino)methylene-*N′*-(4-nitrophenyl)urea (3a):** Yellow solid, Yield: 85.0 %, m.p. 308-311ºC. IR (KBr): ν= 3324 (NH), 1646 (-C=O), 1596 (-N=C), 1390, 1297 (OC-N-), 1044 (C-N)cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):δ= 8.29 (s, 1H, NH), 8.15 (d, 2H, J_{H-H} = 8.0 Hz, Ar-H), 7.79 (d, 2H, J_{H-H} = 8.0 Hz, Ar-H), 2.95 (s, 12H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 168.2, 164.5, 145.5, 143.1, 125.6, 118.9, 40.5. ESI-MS (m/z): 280 $(M+H)^+$. Anal. Calcd. for $C_{12}H_{17}N_5O_3$: C, 51.60; H, 6.14; N, 25.08%. Found: C, 51.54; H, 6.20; N, 24.90%.

***N*-di(dimethylamino)methylene-*N′*-(4-fluorophenyl)urea (3b):** Colourless solid, Yield: 82.5 %, m.p. 270-274ºC. IR (KBr): ν= 3285 (NH), 1606 (-C=O), 1556 (-N=C), 1392, 1293 (OC-N-), 1055 (C-N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):δ= 7.91 (s, 1H, NH), 7.19 (d, 2H, J_{H-H} = 7.9 Hz, Ar-H), 6.93 (d, 2H, J_{H-H} = 7.9 Hz, Ar-H), 3.03 (s, 12H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 169.3, 165.2, 161.0, 137.6, 128.9, 115.6, 41.7. ESI-MS (m/z): 253 $(M+H)^+$.

***N*-di(dimethylamino)methylene-*N′*-(2-fluoro-6-nitrophenyl)urea (3c):** Reddish brown solid, Yield: 76.0 %, m.p. 298-300ºC. IR (KBr): ν= 3335 (NH), 1637 (-C=O), 1590 (-N=C), 1390, 1305 (O=C-N-), 1039 (C-N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.18 (s, 1H, NH), 7.80-7.48 (m, 3H, Ar-H), 2.91 (s, 12H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 165.8, 164.5, 160.5, 146.0, 129.8, 123.4, 121.9, 120.9, 39.7. ESI-MS (m/z): 298 $(M+H)^+$.

***N*-di(dimethylamino)methylene-*N′*-(3,4-dichlorophenyl)urea (3d):** White solid, Yield: 85.5 %, m.p. 262-264ºC. IR (KBr): ν= 3280 (NH), 1631 (-C=O), 1577 (-N=C), 1392, 1298 (OC-N-), 1053 (C-N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.09 (m, 1H, NH), 6.98 (s, 1H, Ar-H), 6.84-6.77 (m, 2H, Ar-H), 2.91 (s, 12H, -CH_3). ^{13}CNMR (100 MHz, $CDCl_3$): δ= 165.7, 159.5, 140.4, 135.5, 133.2, 130.6, 125.3, 120.8, 39.7. ESI-MS (m/z): 303 $(M+H)^+$. Anal. Calcd. for $C_{12}H_{16}Cl_2N_4O$: C, 47.54; H, 5.32; N, 18.48%. Found: C, 47.69; H, 5.24; N, 18.55%.

***N*-di(dimethylamino)methylene-*N′*-(2,4-difluorophenyl)urea (3e):** Pale yellow solid, Yield: 88.0 %, m.p. 283-285ºC. IR (KBr): ν= 3196 (NH), 1627 (-C=O), 1570 (-N=C), 1393, 1303 (OC-N-), 1044 (C-N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 8.12 (s, 1H, NH), 7.34-7.02 (m, 3H, Ar-H), 2.97 (s, 12H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$):δ= 168.0, 165.7, 163.1, 159.3, 125.3, 115.8, 110.8, 103.3, 39.7. ESI-MS (m/z): 271 $(M+H)^+$. Anal. Calcd. for $C_{12}H_{16}F_2N_4O$: C, 53.33; H, 5.97; N, 20.73%. Found: C, 53.21; H, 6.06; N, 20.61%.

***N*-di(dimethylamino)methylene-*N′*-(4-nitrophenyl)thiourea (3f):** Yellow solid, Yield: 95.0 %, m.p. 201-203ºC. IR (KBr): ν= 3180 (NH), 1590 (-N=C), 1388, 1322 (SC-N), 1133 (C=S), 1030 (C-N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):δ= 7.94 (s, 1H, NH), 7.62-7.33 (m, 4H, Ar-H), 3.01 (s, 12H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$):δ= 179.8, 165.2, 146.1, 145.4, 127.0, 126.4, 40.2. ESI-MS (m/z): 296 $(M+H)^+$. Anal. Calcd. for $C_{12}H_{17}N_5O_2S$: C, 48.80; H, 5.80; N, 23.71%. Found: C, 48.72; H, 5.89; N, 23.64%.

***N*-di(dimethylamino)methylene-*N′*-(4-fluorophenyl)thiourea (3g):** White solid, Yield: 86.5 %, m.p. 178-180ºC. IR (KBr): ν= 3183 (NH), 1570 (-N=C), 1390, 1294 (SC-N), 1148 (C=S), 1036 (C-N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.91 (s, 1H, NH), 7.44-7.40 (m, 2H, Ar-H), 6.98-6.93 (m, 2H, Ar-H), 3.01 (s, 12H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 180.5, 165.2, 164.3, 134.9, 133.2, 118.0, 39.9. ESI-MS (m/z): 269 $(M+H)^+$.

***N*-di(dimethylamino)methylene-*N′*-(4-chlorophenyl)thiourea (3h):** White solid, Yield: 91.0 %, m.p. 180-184 ºC. IR (KBr): ν= 3186 (NH), 1566 (-N=C), 1390, 1297 (SC-N), 1136 (C=S), 1034 (C-N) cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$):δ= 7.98 (s, 1H, NH), 7.44-7.42 (d, 2H, J_{H-H} = 8.8, Ar-H), 7.21-7.19 (d, 2H, J_{H-H} = 8.8, Ar-H), 3.02 (s, 12H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 180.1, 165.5, 137.4, 135.9, 133.3, 131.3, 40.6. ESI-

MS (m/z): 285 $(M+H)^+$. Anal. Calcd. for $C_{12}H_{17}ClN_5S$: C, 50.61; H, 6.02; N, 19.67%. Found: C, 50.69; H, 5.92; N, 19.59%.

***N*-di(dimethylamino)methylene-*N′*-phenylthiourea (3i):** White solid, Yield: 92.0 %, m.p. 204-207ºC. IR (KBr): ν= 3189 (NH), 1560 (-N=C), 1391, 1305 (SC-N), 1143 (C=S), 1033 (C-N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ= 7.91 (s, 1H, NH), 7.48-7.46 (d, 2H, J_{H-H} = 8.0, Ar-H), 7.28-7.24 (t, 2H, J_{H-H} = 8.0, Ar-H), 7.02-6.99 (t, 1H, J_{H-H} = 8.0, Ar-H), 3.02 (s, 12H, $-CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$):δ= 179.8, 160.2, 139.8, 131.2, 129.0, 127.5, 40.6. ESI-MS (m/z): 251 $(M+H)^+$.

***N*-di(dimethylamino)methylene-*N′*-[3-(trifluoromethyl)phenyl]thiourea (3j):** White solid, Yield: 93.5 %, m.p. 185-188ºC. IR (KBr): ν= 3184 (NH), 1547 (-N=C), 1394, 1326 (SC-N), 1108 (C=S), 1038 (C-N) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ= 8.03 (s, 1H, Ar-H), 7.96 (s, 1H, NH), 7.53-7.51 (d, 1H, J_{H-H} = 8.0, Ar-H), 7.37-7.34 (t, 1H, J_{H-H} = 8.0, Ar-H), 7.24-7.22 (d, 1H, J_{H-H} = 8.0, Ar-H), 3.04 (s, 12H, $-CH_3$). ^{13}C NMR (100 MHz, $CDCl_3$): δ= 178.7, 168.9, 156.0, 140.7, 129.0, 122.8, 118.8, 116.0, 110.8, 40.6. ESI-MS (m/z): 319 $(M+H)^+$. Anal. Calcd. for $C_{13}H_{17}F_3N_4S$: C, 49.04; H, 5.38; N, 17.60%. Found: C, 49.12; H, 5.30; N, 17.67%.

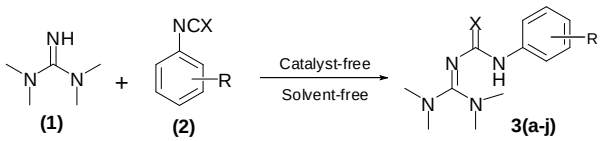
Biological assays

Antibacterial activity: All synthesized compounds were screened for their antibacterial activity against Gram positive bacteria, *Bacillus subtilis* (MTCC-441), *Staphylococcus aureus* (MTCC-737) and Gram negative bacteria, *Escherichia coli* (MTCC-443), *Pseudomonas aeruginosa* (MTCC-741) using a disk diffusion method [15,16]. 2 mg of the title compounds and the standard drug were dissolved in 10 mL of dimethylsulphoxide (DMSO) and further diluted to a concentration of 100 µg/mL of the tested samples. The sterile nutrient agar medium 15 mL was taken in a set of petri plates and the bacterial culture was uniformly spread with sterile inocula onto the surface of the medium. The sterile disks (6 mm diameter) previously soaked in 100 µg/mL test solutions were placed on petri plates and incubated for 24 h at 37±1ºC. The zone of inhibition around the disc was measured. Ampicillin was used as a positive control and DMSO was used as a negative control. For each treatment, triplicate experiments were carried out and the average zone of inhibition was calculated in mm (Table 3).

Antifungal activity: Antifungal activity of the synthesized compounds was screened against *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans* and *Mucor indicus* by the poisoned plate technique [17]. 2 mg of the synthesized and of the standard compounds were dissolved in 10 mL of dimethylsulphoxide (DMSO) and their concentration was adjusted to 200 µg/mL by dilution before mixing with potato dextrose agar (PDA, 90 mL). The fungi were incubated in PDA at 25±1 ºC for 5 days for new mycelium, 45 mm of mycelia disc was cut from the culture medium with a sterilized cork borer, inoculated in the center of the PDA plate and incubated for another 5 days at 25±1ºC. Nystatin was used as a positive control while a disk poured in DMSO was used as a negative control. Triplicate experiments were carried out for each treatment and results were expressed in mm (Table 4). The inhibiting activity of the title compounds was calculated by the formula I=C-T/C, where I indicates the rate of inhibition, C indicates the diameter of fungi growth in the control and T indicates the diameter of fungi growth in treatment.

RESULTS AND DISCUSSIONS

As a result of our continuing research on the development of new methodologies for the synthesis of useful scaffolds [18], herein, we developed a green approach for the synthesis of urea and thiourea derivatives of tetramethylguanidine, as depicted in Scheme 1.



X = S, O

Compd	X	R	Compd	X	R
3a	O	4-NO_2	**3f**	S	4-NO_2
3b	O	4-F	**3g**	S	4-F
3c	O	2-NO_2, 6-F	**3h**	S	4-Cl
3d	O	3,4-Cl_2	**3i**	S	H
3e	O	2,4-F_2	**3j**	S	3-CF_3

Scheme 1. Solvent- and catalyst-free synthesis of urea and thiourea derivatives of tetramethylguanidine.

Initially, the experimental conditions were optimized by taking tetramethylguanidine (**1**) and 1-isothiocyanato-4-nitrobenzene (**2f**) as models for the production of the title compound **3f**. The model reaction was primarily carried out in the presence of different base catalysts, Et_3N, dimethylpiperazine and catalyst-free conditions in THF solvent (Table 1 entries 1-3). No significant yield difference was observed both in the presence of base catalyst and under catalyst-free conditions in THF solvent. Hence, the catalyst-free condition

was preferred. The model reaction was performed in different organic solvents like THF, chloroform, dichloromethane, acetonitrile as well as under solvent-free conditions (Table 1, entries 4-7) without catalyst. Interestingly, it was found that simple mixing of 4-nitrophenylisothiocyanate and 1,1,3,3-tetramethyl guanidine without solvent afforded high-purity *N*-di(dimethylamino) methylene-*N*'-(4-nitrophenyl) thiourea (**3f**) in high yield with a simple work-up procedure (filtration and recrystallization) as compared with the reactions in presence of solvents. Later, the optimized solvent-free conditions were tested at different temperatures 40ºC, 50ºC and 60ºC (Table 1, entries 7-10) and revealed that the reaction was effective at 60 ºC.

After optimization of the reaction conditions, the generality of the reaction conditions was checked by altering the substituted phenyl isocyanates and isothiocyanates to get the title compounds **3**(**a-j**) (Table 2). This method gave high yields of desired products in a short time with high purity using simple work-up instead of using tedious time taking column chromatography. The results revealed that isocyanates or isothiocyanates with electron withdrawing groups afforded good yields of the products as compared to those with electron donating groups. Isothiocyanates were more efficient than isocyanates to afford high yields of the products.

The structures of the title compounds **3**(**a-j**) were characterized using IR, ^{1}H NMR, ^{13}C NMR, mass spectral studies and elemental analysis. IR spectra gave absorption bands in the regions of 3180-3335 cm^{-1}, 1606-1646 cm^{-1}, 1596-1547 cm^{-1} and 1108-1148 cm^{-1} stretching which confirmed the presence of –NH, -C=O, -C=N and –C=S functionalities in the title compounds. In the ^{1}H NMR spectra, a singlet\multiplet at 8.29-7.91 ppm was assigned to NH proton in urea and thiourea derivatives and a singlet signal in the region of 2.91-3.04 ppm was ascribed to methyl groups attached to nitrogen atoms in the synthesized compounds. All phenyl protons showed signals as multiplets/triplets/doublets/singlets based on structures in the region of 6.77-7.80 ppm. The chemical shifts of carbon in the ^{13}C NMR spectra, the molecular ions in the mass spectra and the elemental analytical data gave further evidence for structural elucidation of the title compounds **3**(**a-j**).

BIOLOGY

The antibacterial and antifungal activities of the newly synthesized compounds **3**(**a-j**) were screened using disc diffusion method and poisoned plate technique, respectively. Primarily, both activities were tested at 100 µg/mL concentration of the test samples. The experiments revealed that most of the compounds exhibited potent antibacterial activity at 100 µg/mL concentration and only a few compounds exhibited moderate antifungal activity. Hence, antifungal activity of the test samples was screened at 200 µg/mL concentration. The biological data revealed that thiourea derivatives show better activity than urea derivatives against fungi whereas urea compounds showed promising activity towards bacteria. Among the screened compounds, the thiourea based analogues **3g** and **3j** exhibited good activity towards fungi which might be due to the presence of the highly liphophilic fluoro and trifluoromethyl groups, respectively (Table 3). The compounds **3a** and **3e** showed good antibacterial activity which could be related to the presence of nitro and difluoro groups on the benzene ring (Table 4).

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Table-1 Optimization of the reaction conditions for the synthesis of urea and thiourea derivatives 3(a-j)[a].

Entry	Solvent	Catalyst	Time (h)	Yield (%)
1	THF	Et_3N (1 equiv)	3	86.5
2	THF	DMP (1 equiv)	2.5	88.3
3	THF	No catalyst	4	86.1
4	$CHCl_3$	No catalyst	6	73.2
5	DCM	No catalyst	6	78.6
6	CAN	No catalyst	7	60.9
7	Neat[b]	No catalyst	1.5	95.7
8	Neat[c]	No catalyst	4	89.3
9	Neat[d]	No catalyst	5	83.6
10	Neat[e]	No catalyst	7	79.4

[a]Tetramethylguanidine (1) and 1-isothiocyanato-4-nitrobenzene (2f) were selected as substances to carry out the model reaction; [b]The model reaction was monitored by keeping the temperature at 60ºC; [c]The model reaction was monitored by keeping the temperature at 50ºC; [d]The model reaction was monitored by preserving the temperature at 40ºC; [e]The model reaction was monitored by keeping the ambient temperature conditions.

Table 2 Physical data of the newly synthesized urea and thiourea derivatives **3(a-j)**.

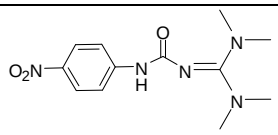
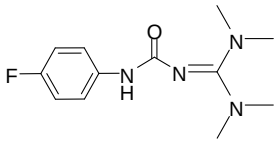
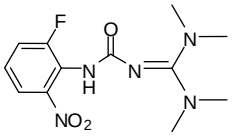
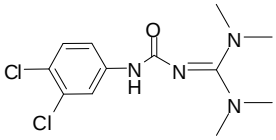
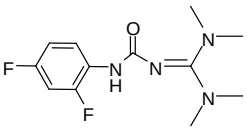
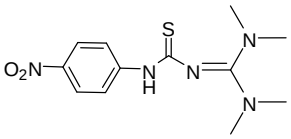
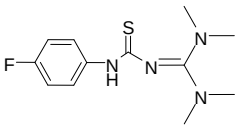
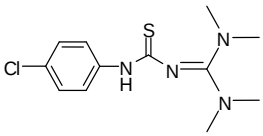
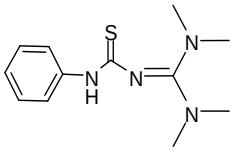
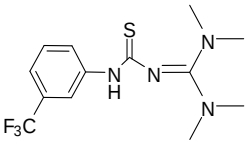
Compd.	Product	Time (h)	Yield (%)	Melting point (°C)
3a		4.0	85.0	308-310
3b		3.5	82.5	270-272
3c		6.0	76.0	298-300
3d		5.5	85.5	262-264
3e		4.5	88.0	283-285
3f		1.5	95.0	201-203
3g		1.5	86.5	178-180
3h		2.5	91.0	180-182
3i		2.0	92.0	204-206
3j		1.5	93.5	185-188

Table 3 Antibacterial Activity of the synthesized compounds **3(a-j)**

Compd.	Zone of inhibition (mm) at 100 μg/ mL			
	Bacillus subtilis (MTCC-441)	*Staphylococcus aureus* (MTCC-737)	*Escherichia coli* (MTCC-443)	*Pseudomonas aeruginosa* (MTCC-741)
3a	15.0 ± 0.56	12.2 ± 0.42	13.2 ± 0.45	11.4 ± 0.27
3b	10.2 ± 0.45	8.2 ± 0.33	7.5 ± 0.28	9.6 ± 0.35
3c	8.4 ± 0.21	7.6 ± 0.27	8.4 ± 0.26	8.6 ± 0.35
3d	8.6 ± 0.32	8.0 ± 0.35	8.2 ± 0.41	7.2 ± 0.24
3e	12.6 ± 0.49	11.6 ± 0.29	11.2 ± 0.33	10.8 ± 0.41
3f	N.A	N.A	N.A	N.A
3g	8.2 ± 0.12	9.1 ± 0.19	8.6 ± 0.16	8.4 ± 0.22
3h	11.5 ± 0.66	10.6 ± 0.36	10.2 ± 0.42	10.4 ± 0.25
3i	N.A	N.A	N.A	N.A
3j	N.A	N.A	N.A	N.A
Ampicillin	21	19	20	18
DMSO	N.A	N.A	N.A	N.A

(N.A: No activity)

Table 4 Antifungal activity of the synthesized compounds **3(a-j)**

Compd.	Zone of inhibition (mm) at 200 μg/ mL			
	Aspergillus niger	*Aspergillus flavus*	*Candida albicans*	*Mucorindicus*
3a	8.8 ± 0.25	14.4 ± 0.33	6.6 ± 0.45	8.8 ± 0.51
3b	4.4 ± 0.65	4.4 ± 0.52	4.4 ± 0.44	8.1 ± 0.47
3c	16.6 ± 0.42	14.4 ± 0.38	N.A	2.2 ± 0.52
3d	13.0 ± 0.78	12.0 ± 0.59	8.8 ± 0.47	8.8 ± 0.39
3e	11.1 ± 0.22	17.0 ± 0.39	15.6 ± 0.43	11.1 ± 0.47
3f	14.6 ± 0.56	17.7 ± 0.47	16.6 ± 0.40	6.6 ± 0.29
3g	14.4 ± 0.80	15.5 ± 0.67	13.3 ± 0.58	12.4 ± 0.61
3h	10.3 ± 0.37	4.4 ± 0.30	6.6 ± 0.25	N.A
3i	8.8 ± 0.22	6.6 ± 0.29	6.6 ± 0.34	N.A
3j	15.5 ± 0.71	15.5 ± 0.41	16.6 ± 0.49	13.3 ± 0.41
Nystatin	20	23	21	18
DMSO	N.A	N.A	N.A	N.A

(N.A: No activity)

CONCLUSION

In conclusion, we have developed a new green methodology for the synthesis of urea and thiourea derivatives in high yields under solvent-free and catalyst-free conditions. The reaction conditions like catalyst, solvent and temperature effects were optimized. The urea and thiourea derivatives of tetramethylguanidine were obtained in high yields with high purity by a simple work-up procedure like filtration and recrystallization without tedious and time taking techniques like column chromatography. The antimicrobial activity screening revealed that the urea derivatives (**3a**, **3e**) showed promising activity against bacteria while the thiourea derivatives (**3g**, **3j**) exhibited potent activity against fungi.

Acknowledgment: *The author, SK. Thaslim Basha expresses thanks to UGC for financial support through UGC-JRF.*

REFERENCES

1. S. M. Aldhaheri**,** *Talanta.* **46**, 1613(1998).
2. C. Li, M. R. Lewis, A. B. Gilbert, M. D. Noel, D. H. Scoville, G. W. Albrann, P. B. Savage, *Antimicrob. Agents Ch.* **43**, 1347 (1999).
3. W. M. Golebiewski, M. Cholewinskai, *Polish Journal of Applied Chemistry*, **47**, 137 (2003).
4. G. H. Jana, S. Jain, S. K. Arora, N. Sinha, *Bioorg. Med. Chem.Lett.* **15**, 3592 (2005).
5. M. Calas, M. Ouattara, G. Piquet, Z. Ziora, Y. Bordat, M. L. Ancelin, R. Escale, H. Viral, *J. Med.Chem.* **50**, 6307 (2007).
6. Z. Brzozowski, F. Saczewski, J. Slawinski, *Eur. J. Med. Chem.* **42**, 1218 (2007).
7. R. N. Gacche, D. S. Gond, N. A. Dhole, B. S. Dawane, *J. Enzyme Inhib. Med. Chem.* **21**, 152 (2006).
8. E. Bramm, L. Binderup, E. Arrigoni-Martelli, *Agents Actions* **11**,402 (1981).
9. L. D. Santos, L. A. Lima, V. Cechinel-Filho, R. Correa, F. D. C. Buzzi, R. J. Nunes, *Bioorg. Med. Chem.* **16**, 8526 (2008).

10. S. A. Khan, N. Singh, K. Saleem, *Euro. J. Med. Chem.* **43**, 2272 (2008).
11. A. Corma, A. Garcia,*Chem. Rev.* **103,** 4307 (2003).
12. K. Tanaka, F. Toda, *Chem. Rev.* **100**, 1025 (2000).
13. R. S. Varma, *Green Chem.* **1**, 43 (1999).
14. A. Zare, A. Hasaninejad, M. Shekouhy, A. R. Moosayi, *Org. Prep. Proced. Int.* **40**, 457 (2008).
15. R. Cruickshank, J. P. Duguid, B. P. Marion, R. H. A. Swain Medicinal Microbiology, 12thed.; Churchill Livingstone: London, **2**, 196 (1975).
16. A. H. Collins, Microbiology Methods, 2nd ed.; Butterworth: London, 1976.
17. S. Q. Song, L. G. Zhou, D. Li, D. Tang, J. Q. Li, W. B. Jiang, *Nat. Prod. Res. Dev.* **16**, 157 (2004).
18. (a) D. SubbaRao, D. Srinivasulu, D. Rajasekhar, C. NagaRaju, *Chin. Chem. Lett*. **24**, 759 (2013); (b) D. SubbaRao, SK. ThaslimBasha, C. NagaRaju, *Der Pharmacia Lettre*, **5(3)**, 341 (2013).

ЗЕЛЕНИ, БЕЗКАТАЛИТИЧНИ ТЕХНОЛОГИИ ЗА СИНТЕЗ НА ПРОИЗВОДНИ НА КАРБАМИДА И ТИОКАРБАМИДА С ТЕТРАМЕТИЛГВАНИДИН (TMG) И ОЦЕНЯВАНЕ НА БИОЛОГИЧНАТА ИМ АКТИВНОСТ

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Постъпила на 11 септември, 2013 г.; Коригирана 18 април, 2014 г.

(Резюме)

Разработен е бърз зелен метод за синтезата на производни на карбамида и тиокарбамида с 1,1,3,3-тетраметилгванидин с високи добиви в отсъствие на катализатор и разтворител. Процесът има много предимства, напр. избягване на вредни разтворители, лесни и кратки операции, висока чистота с висок добив. Оптимизирани са работните условия по различни параметри. Оценена е антимикробната активност на получените съединения и е установено, че съединенията **3a**, **3e** и **3g**, **3j** проявяват обещаващи анти-бактериални и фунгицидни свойства