Transformation of Bromhexine, a Mucolytic Drug into Potential Pharmacologically Important Urea Derivatives

Muhammad Sharif
Chemistry Department, King Fahd University of Petroleum and Minerals, Dhahran 31261, Saudi Arabia.
msharif@kfupm.edu.sa

(Received on 3rd January 2020, accepted in revised form 20th May 2020)

Summary: A general synthesis for 1,3-diphenylurea and 1,3-diphenylthiourea derivatives of mucolytic agent bromhexine is described by reactions of different commercially available phenyl isocyanates and phenyl-isothiocyanates at room temperature without any additional catalyst and additive. Using commercially available electron donating and electron withdrawing phenyl isocyanates in the transformation of bromhexine into urea derivatives proceeded from moderate to high product yield (42-90%). Bromhexine resulting compounds add a general interest in the fields of Pharmaceuticals, diagnostics and materials.

Keywords: Metal-free coupling, Catalyst free coupling, Bromhexine, Phenyisocyanate, Phenyl-isothiocyanates, Mucolytic agent.

Introduction

Bromhexine is a well-known drug from the group of cough medicine. Commercially it is known under various names such as Bromex, Vasican or Paxir-asol. Usually these derivatives are used in bronchitis to clear mucus from the respiratory tract [1-3]. In some cases it is substituted by its metabolite ambroxol. Clinical research of Bromhexine showed a significantly enhanced production and transportation of mucus. Other studies show that such derivatives have shown anti-inflammatory properties and augment the production of pulmonic surfactant [5-6a-c]. In addition bromhexine and its metabolite ambroxol shows properties as an inhibitor of the human Glucocerobrosidase enzyme [7]. An indecorous Glucocerobrosidase enzyme leads to a sporadic genetic disease also known as Gaucher disease [7]. The most common form of Gaucher's disease is the incorrect folding of the enzyme in the mutant forms N370S and L444P. In general, urea analogues have been able to upsurge the activity of these mutant forms by stabilizing folded state and improve the intracellular transport [8]. Because of these substantial properties, it was decided to synthesize urea derivatives bromhexine for potential biological properties.

Urea or thiourea derivatives are often employed as useful anti-cancer drugs [9-11]. Due to their wide range of applications, these derivatives can be used against numerous categories of leukemia and against tumors. Urea- and thiourea-derivatives can be easily represented by a reaction of an amino group with isocyanates or thioisocyanates [13-17]. Despite the pharmacological significance of bromhexine derivatives and broad investigations of biological activities of bromhexine and ambroxol over decades, the synthetic chemistry of title compound and its catalytic conversions were barely explored [16, 17].

Based on our curiosity in synthetic organic chemistry [18-21], including syntheses of heterocycles and their wide range of pharmacological activities, we became interested in exploring the transformation of bromhexine into 1,3-diphenylurea and 1,3-diphenylthiourea compounds. In general, discerning coupling reactions should allow the synthesis of a multitude of pharmacologically interesting derivatives of bromhexine.

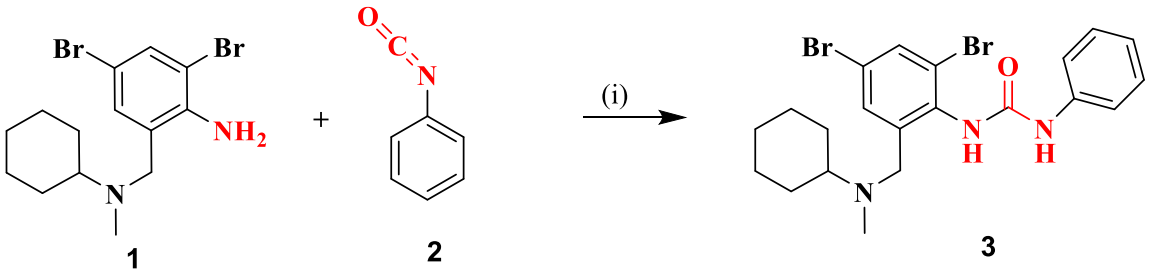
Experimental

General Methods: All reactions were performed under argon. Chemicals were commercially available and procured from Sigma Aldrich, Acros, Alfa Asar, and were used without any further purification. All the synthesized urea derivatives of bromhexine were characterized by using ^{1}H-NMR, ^{13}C-NMR, GCMS, HRMS, and IR spectroscopy. The ^{1}H-NMR spectroscopic data were recorded with Bruker AV 300 spectrometers. The ^{13}C-NMR spectra were recorded at Bruker AV 300 and AV 400 MHz. IR spectroscopic data were recorded on FTIR ALPHA with Platinum-ATR (Bruker). EI (70 eV) mass data were recorded with a MAT 95XP (Thermo ELECTRON-CORPORATION). GC was performed on an Agilent 6890 chromatograph using 30 m, HP5 column. HRMS was performed with a MAT 95XP (EI) and Agilent 6210 Time-of-Flight LC/MS (ESI). GCMS was recoded on an Agilent 5973 chromatograph mass

*To whom all correspondence should be addressed.

selective detector. All of the reactions were executed in pressure tubes. All reported yields refer to isolated yields.

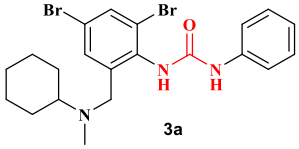
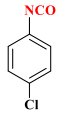
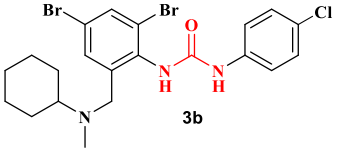
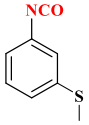
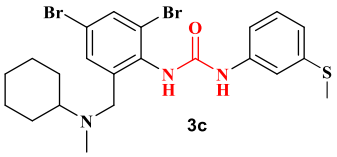
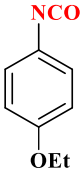
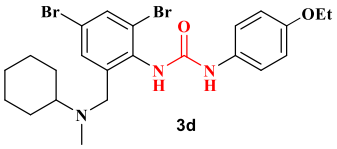
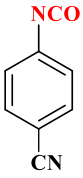
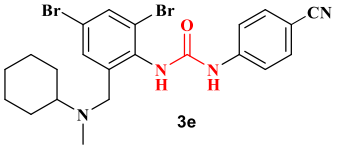
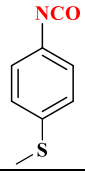
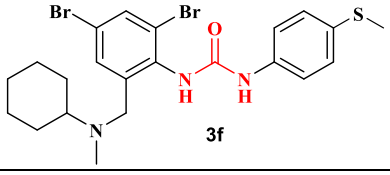
*General Procedure***:** After the pressure tube was filled with argon, bromhexine **(**2.0 mmol), phenylisocyanat **1** (2.0 mmol) and tetrahydrofuran (5.0 ml) were added, the mixture was stirred at room temperature for 4 hours. The mixture was diluted with hexane. The precipitates were filtered and washed with hexane/ethyl acetate 95:5 and dried.

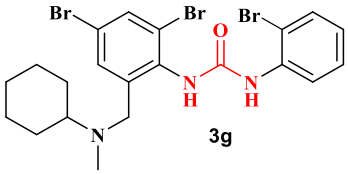
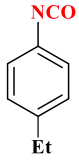
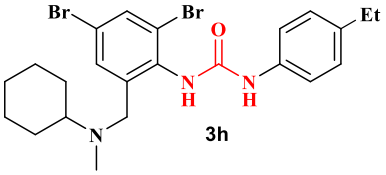
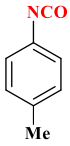
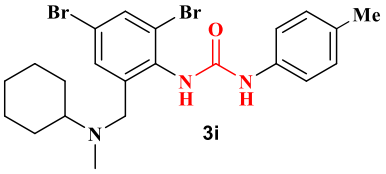
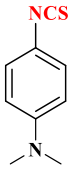
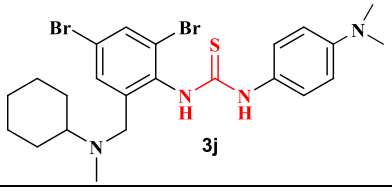


Reagents and conditions: bromhexine (1 mmol), phenylisocyanate (1.1 mmol), RT, 4 h; General procedure.

Scheme-1: Synthesis of urea-type derivatives from bromhexine, phenyl isocyanates and phenyl isothiocyante.

Table

Entry	Isocyanates	Isolated product	% Yield
1		 3a	80
2		 3b	42
3		 3c	56
4		 3d	66
5		 3e	59
6		 3f	90

7		 **3g**	63
8		 **3h**	57
9		 **3i**	37
10		 **3j**	72

Spectral Characterizations

1-(2,4-dibromo-6-((cyclohexyl(methyl)amino)methyl)phenyl)-3-phenylurea **(3a):** ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 0.92 - 1.32 ppm (m, 6H), 1.54 (d, *J* = 11.5 Hz, 1H), 1.70 (d, *J* = 7.9 Hz, 2H), 1.79 (d, *J* = 9.0 Hz, 2H), 2.08 (s, 3H), 2.35 (s, 1H), 6.95 (t, *J* = 7.3 Hz, 1H), 7.22 - 7.31 (m, 2H), 7.45 (d, *J* = 7.7 Hz, 2H), 7.62 (d, *J* = 2.3 Hz, 1H), 7.79 (d, *J* = 2.3 Hz, 1H), 8.30 (br. s., 1H), 9.16 (br. s., 1H). ^{13}C-NMR (DMSO-d_6, 75 MHz): δ = 25.5 ($2CH_2$), 25.8 (CH_2), 28.0 ($2CH_2$), 37.5 (CH_3), 54.1 (CH_2), 62.1 (CH), 118.1 (2CH), 118.7 (C), 121.8 (CH), 123.7 (C), 128.7 (2CH), 131.0 (CH), 132.8 (CH), 135.6 (C), 139.9 (C), 141.2 (C), 152.3 (CO) ppm. IR (ATR): ν = 3057(w), 2968(w), 2917(m), 2852(m), 1680(s), 1597(m), 1559(w), 1489(s), 1449(s), 1435(s), 1393(m), 1378(m), 1362(m), 1342(m), 1321(m), 1310(m), 1298(m), 1238(m), 1214(m), 1183(w), 1149(m), 1125(m), 1117(m), 1077(w), 1046(m), 1030(w), 1016(w), 982(w), 964(m), 911(m), 890(m), 857(m), 789(m), 746(s), 728(m), 691(s), 670(m), 659(m), 643(m), 625(m), 606(m), 562(m), 546(m), 540(m), 515(s), 491(m), 473(w) cm^{-1}.

1-(4-chlorophenyl)-3-(2,4-dibromo-6-((cyclohexyl(methyl)amino)-methyl)phenylurea **(3b):** ^{1}H-NMR (DMSO-d_6 ,300 MHz): δ = 1.13 - 1.25 (m, 5H), 1.55 (d, *J* = 11.7 Hz, 1H), 1.70 (d, *J* = 8.1 Hz, 2H), 1.79 (d, *J* = 9.2 Hz, 2H), 1.99 (s, 1H), 2.09 (s, 3H), 2.36 (br. s., 1H), 3.55 (br. s., 2H), 7.33 (d, *J* = 4.3 Hz, 2H), 7.46 (d, *J* = 3.0 Hz, 2H), 7.61 (d, *J* = 2.3 Hz, 1H), 7.80 (d, *J* = 2.1 Hz, 1H), 8.37 (s, 1H), 9.31 (s, 1H) ppm. ^{13}C-NMR (DMSO-d_6, 75 MHz): δ = 25.4 ($2CH_2$), 25.7 (CH_2), 28.0 ($2CH_2$), 37.5 (CH_3), 54.1 (CH_2), 62.1 (CH), 118.8 (C), 119.6 (CH), 119.8 (2 CH), 123.7 (C), 128.6 (2CH), 131.1 (CH), 132.8 (CH), 144.5 (C), 135.4 (C), 138.9 (C), 141.1 (C) 152.23 (CO) ppm. MS (ESI-TOF): M = $C_{21}H_{24}Br_2ClN_3O$, m/z = 526.99747 ($[M]^+$), 528.00474 ($[M+H]^+$), 530.00268 ($[M+H]^+$), 532.00064 ($[M+H]^+$). MS (EI, 70 eV): M = $C_{21}H_{24}Br_2ClN_3O$, m/z = 376 (30.8), 359 (27.4), 305 (54.1), 293 (85.5), 264 (60.7), 153 (100), 127 (34.0), 112 (54.2), 90 (19.8), 70 (98.3), 63 (18.2), 44 (18.7). IR (ATR): ν = 3368 (w), 3231(w), 2974 (w), 2948 (w), 2926 (m), 2851 (w), 1684 (w), 1653 (m), 1591 (m), 1560 (m), 1533 (s), 1491 (s), 1466 (m), 1444 (s), 1397 (m), 1359 (s), 1301 (m), 1276 (m), 1253 (m), 1224 (s), 1210 (s), 1185 (s), 1174 (m), 1153 (m), 1115 (m), 1094 (s), 1060 (m), 1050 (m), 1012 (m), 993 (w), 965 (m), 908 (m), 898 (m), 863 (m), 836 (m), 816 (m), 794 (s), 755 (m), 734 (w), 699 (m), 693 (m), 651 (m), 626 (m), 571 (m), 553 (m), 540 (m), 500 (s), 446 (m), 423 (m), 409 (m) cm^{-1}.

1-(2,4-dibromo-6-((cyclohexyl-(methyl)amino)methyl)phenyl)-3-(3-(-methylthio)phenylurea **(3c):** ^{1}H-NMR (DMSO-d_6 ,300 MHz): δ = 0.92 - 1.29 (m, 5H), 1.54 (d, *J* = 10.9 Hz, 1H), 1.71 (br. s., 2H), 1.77 (br. s., 2H), 2.09 (s, 3H), 2.35 (br. s., 1H), 2.43 (s, 3H), 3.54 (br. s., 2H),

6.84 (d, *J* = 7.3 Hz, 1H), 7.07 - 7.27 (m, 2H), 7.45 (br. s., 1H), 7.61 (br. s., 1H), 7.78 (br. s., 1H), 8.31 (br. s., 1H), 9.17 (br. s., 1H), ppm. ^{13}C-NMR (DMSO-d_6, 75 MHz): δ = 14.6 (CH_3), 25.4 ($2CH_2$), 25.8 (CH_2), 28.0 ($2CH_2$), 37.5 (CH_3), 54.1 (CH_2), 62.1 (CH), 114.7 (CH), 115.2 (CH), 118.8 (C), 119.2 (CH), 123.7 (C), 129.2 (CH), 131.0 (CH), 132.8 (CH), 135.5 (C), 138.5 (C), 140.4 (C), 141.2 (C), 152.3 (CO) ppm. MS (ESI-TOF): M = $C_{22}H_{27}Br_2N_3OS$, m/z = 539.02416 ($[M]^+$), 540.03157 ($[M+H]^+$), 542.02979 ($[M+H]^+$), 544.02761 ($[M+H]^+$). IR (ATR): ν = 3369 (w), 2968 (w), 2928 (m), 2853 (w), 1604 (s), 1580 (s), 1560 (s), 1474 (s), 1437 (m), 1391 (m), 1358 (w), 1346 (w), 1318 (s), 1303 (m), 1232 (w), 1219 (w), 1166 (w), 1148 (m), 1122 (m), 1104 (m), 1083 (m), 1045 (m), 1026 (m), 967 (m), 950 (w), 918 (w), 901 (m), 889 (m), 856 (s), 839 (m), 807 (m), 778 (s), 728 (m), 713 (m), 683 (m), 669 (m), 643 (m), 620 (m), 571 (w), 564 (w), 553 (w), 541 (m), 515 (w), 441 (m), 428 (w) cm^{-1}.

1-(2,4-dibromo-6-((cyclohexyl-(methyl)amino)methyl)phenyl)-3-(4-ethoxy)phenylurea **(3d):** ^{1}H-NMR (DMSO-d_6, 300MHz): δ = 1.00 - 1.24 (m, 5H), 1.26 - 1.37 (t, *J* = 6.8, 6.8 Hz, 3H), 1.55 (d, *J* = 10.2 Hz, 1H), 1.63 - 1.84 (m, 4H), 2.09 (s, 3H), 2.35 (br. s., 1H), 3.50 - 3.65 (s, 2H), 3.96 (q, *J* = 7.1 Hz, 2H), 6.84 (d, *J* = 7.5 Hz, 2H), 7.32 (d, *J* = 7.2 Hz, 2H), 7.61 (s, 1H), 7.78 (s, 1H), 8.20 - 8.36 (m, 1H), 8.97 (br. s., 1H) ppm. IR (ATR): ν = 3337 (w), 3285 (w), 2977 (w), 2944 (w), 2928 (m), 2873 (w), 2855 (w), 2783 (w), 1694 (w), 1654 (s), 1617 (w), 1601 (w), 1560 (m), 1539 (s), 1513 (m), 1498 (m), 1481 (m), 1445 (m), 1414 (w), 1388 (w), 1380 (w), 1363 (w), 1315 (w), 1302 (w), 1275 (w), 1245 (s), 1226 (s), 1209 (m), 1184 (w), 1172 (m), 1153 (m), 1110 (m), 1082 (w), 1055 (m), 1043 (m), 1030 (w), 1011 (w), 991 (w), 965 (m), 927 (w), 909 (m), 896 (m), 864 (m), 842 (w), 823 (m), 808 (m), 798 (m), 780 (w), 755 (w), 714 (w), 696 (m), 656 (m), 632 (m), 580 (m), 568 (m), 554 (m), 539 (m), 519 (m), 475 (w), 425 (w), 405 (w) cm^{-1}.

1-(4-cyanophenyl)-3-(2,4-dibromo-6-((cyclohexyl(methyl)amino)methyl)phenyl)urea **(3e):** ^{1}H-NMR (DMSO-d_6, 300MHz): δ = 1.01 - 1.27 ppm (m, 5H) 1.35 (q, *J* = 10.4 Hz, 2H), 1.56 (d, *J* = 11.7 Hz, 1H), 1.63 - 1.81 (m, 2H), 2.41 (s, 3H), 2.86 (br. s., 1H), 3.76 (d, *J* = 12.6 Hz, 1H), 3.88 (d, *J* = 13.0 Hz, 1H), 4.03 (q, *J* = 7.2 Hz, 1H), 7.63 - 7.70 (m, 3H), 7.84 (d, *J* = 2.1 Hz, 1H), 7.93 (d, *J* = 8.7 Hz, 2H), 9.74 (br. s., 1H). MS (EI, 70 eV): m/z = 376 (38.2), 333 (13.8), 307 (39.6), 293 (84.7), 264 (76.5), 160 (100), 126 (21.1), 118 (17.2), 112 (70.6), 102 (77.7), 84 (26.6), 75 (21.7), 70 (88.8), 66 (26.4), 55 (13.3), 51 (11.2) 44 (16.3), 42 (13.6). IR (ATR): ν = 3428 (w), 2946(w), 2854 (w), 2389 (w), 2216 (m), 1725 (w), 1607 (m), 1578 (w), 1555 (s), 1504 (s), 1472 (s), 1447 (m), 1403 (m), 1367 (w), 1311 (s), 1272 (m), 1237 (w), 1199 (w), 1172 (m), 1159 (w), 1108 (s), 1092 (m), 1053 (m), 998 (w), 961 (m), 920 (m), 897 (m), 880 (w), 862 (w), 854 (w), 839 (m), 814 (m), 785 (w), 773 (m), 680 (w), 634 (w), 618 (w), 595 (w), 568 (m), 544 (s), 528 (w), 506 (w), 480 (m), 432 (w) cm^{-1}.

1-(2,4-dibromo-6-((cyclohexyl(methyl)amino)methyl)phenyl)-3-(4-(-methylthio)phenyl)thiourea **(3f):**

^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.06 - 1.13 (m, 1H), 1.13 - 1.24 (m, 4H), 1.55 (d, *J* = 10.7 Hz, 1H), 1.66 - 1.76 (m, 4H), 2.12 (s, 3H), 2.38 (br. s., 1H), 2.45 (s, 3H), 3.55 (d, *J* = 4.3 Hz, 2H), 7.25 (d, *J* = 5.8 Hz, 2H), 7.44 (d, *J* = 9.6 Hz, 2H), 7.62 (d, *J* = 2.1 Hz, 1H), 7.80 (d, *J* = 2.3 Hz, 1H), 9.74 (s, 1H), 9.88 (br. s., 1H), ppm ^{13}C-NMR (DMSO-d_6, 75 MHz): δ = 15.3 (CH_3), 25.4 (2 CH_2), 25.7 (CH_2), 28.0 (2 CH_2), 37.2 (CH_3), 54.0 (CH_2), 62.3 (CH), 115.8 (C), 118.8 (C), 124.5 (CH), 124.7 (CH), 126.4 (CH), 126.7 (CH), 131.1 (CH), 133.0 (CH), 133.6 (C), 136.5 (C), 136.7 (C) ppm. MS (ESI-TOF): M = $C_{22}H_{27}Br_2N_3S_2$, m/z = 555.00132 ($[M]^+$), 556.00863 ($[M+H]^+$), 558.0069 ($[M+H]^+$), 560.00467 ($[M+H]^+$). IR (ATR): ν = 3182 (w), 3143 (w), 3076 (w), 2986(w), 2919 (w), 2853 (w), 1579 (m), 1523 (s), 1486 (s), 1454 (m), 1435 (m), 1395 (m), 1360 (m), 1321 (m), 1305 (s), 1279 (m), 1255 (m), 1230 (m), 1221 (m), 1205 (m), 1181 (m), 1155 (m), 1120 (m), 1093 (m), 1042 (w), 1032 (w), 1013 (w), 973 (w), 956 (w), 941 (w), 909 (w), 889 (w), 857 (m), 840 (w), 820 (m), 798 (m), 787 (m), 754 (w), 699 (m), 655 (m), 607 (m), 574 (m), 548 (m), 535 (m), 512 (s), 492 (m), 466 (m), 451 (m) cm^{-1}.

1-(2-bromophenyl)-3-(2,4-dibromo-6-((cyclohexyl(methyl)amino)met-hyl)phenyl)urea **(3g):** ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.0 - 1.24 (m, 5H), 1.54 (d, *J*=11.5 Hz, 1H), 1.65 - 1.85 (m, 4H), 2.09 (s, 3H), 2.36 (br. s., 1H), 3.54 (br. s., 2H), 6.97 (td, *J* = 7.7, 1.5 Hz, 1H), 7.32 (td, *J* = 7.8, 1.3 Hz, 1H), 7.61 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.64 (d, *J* = 1.3 Hz, 1H), 7.81 (d, *J* = 1.3 Hz, 1H), 7.96 (dd, *J* = 8.3, 1.3 Hz, 1H), 8.43 (br. s., 1H), 8.83 (br. s., 1H) ppm. ^{13}C-NMR (DMSO-d_6, 75 MHz): δ = 25.5 ($2CH_2$), 25.8 (CH_2), 28.1 (2 CH_2), 37.5 (CH_3), 53.8 (CH_2), 62.2 (CH), 113.6 (C), 119.4 (C), 122.7 (CH), 124.1 (C) 124.3 (CH), 128.1 (CH), 131.1 (CH), 132.5 (CH), 132.7 (CH), 134.9 (C), 137.2 (C), 142.3 (C), 152.4 (CO) ppm. MS (ESI-TOF): M = $C_{21}H_{24}Br_3N_3O$, m/z = 570.94695 ($[M]^+$), 571.95435 ($[M+H]^+$), 573.95309 ($[M+H]^+$), 575.95127 ($[M+H]^+$), 577.94902 ($[M+H]^+$). MS (EI, 70 eV): M = $C_{21}H_{24}Br_3N_3O$, m/z

= 376 (24.8), 307 (24.7), 305 (59.6), 303 (26.9), 295 (43.0), 293 (100.0), 291 (47.9), 266 (26.5), 264 (64.5), 262 (27.9), 199 (91.6), 197 (94.0), 153 (100), 112 (52.2), 90 (39.0), 70 (96.5), 66 (21.0). IR (ATR): ν = 3207 (w), 3077 (w), 2941 (w), 2923 (w), 2854 (w), 1681(s), 1586 (m), 1483 (m), 1455 (m), 1432 (m), 1393 (m), 1378 (m), 1347 (w), 1318 (s), 1294 (m), 1244 (w), 1227 (w), 1184 (w), 1154 (m), 1124 (w), 1081 (w), 1051 (w), 1029 (m), 986 (w), 965 (w), 943 (w), 912 (w), 889 (w), 861 (m), 843 (w), 775 (m), 749 (s), 707 (m), 658 (w), 628 (w), 614 (m), 563 (w), 548 (w), 527 (w), 513 (w), 473 (w), 443 (w), 425 (w) cm^{-1}.

1-(2,4-dibromo-6-((cyclohexyl(methyl)amino)methyl)phenyl)-3-(4-ethylphenyl)urea **(3h):** ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.01 - 1.28 (m, 8H), 1.55 (d, *J* = 11.1 Hz, 1H), 1.70 (d, *J* = 8.9 Hz, 2H), 1.78 (d, *J* = 8.3 Hz, 2H), 2.09 (s, 3H), 2.29 - 2.39 (m, 1H), 2.6 (m, 2H), 3.54 (s, 2H), 7.09 (d, *J* = 8.5 Hz, 2H), 7.34 (d, *J* = 8.5 Hz, 2H), 7.61 (d, *J* = 2.1 Hz, 1H), 7.78 (d, *J* = 2.2 Hz, 1H), 8.25 (s, 1H), 9.05 (s, 1H) ppm. ^{13}C-NMR (DMSO-d_6, 75 MHz): δ = 15.9 (CH_3), 25.5 ($2CH_2$), 25.8 (CH_2), 27.5 (CH_2), 28.0 (CH_2), 37.5 (CH_3), 54.2 (CH_2), 62.1 (CH), 118.4 (2CH), 118.6 (C), 123.6 (C), 127.9 (2CH), 131.0 (CH), 132.8 (CH),135.7 (C), 137.2 (C),137.5 (C), 141.1 (C), 152.4 (CO) ppm. MS (ESI-TOF): M = $C_{23}H_{29}Br_2N_3O$, m/z = 521.06774 ($[M]^+$), 522.07518 ($[M+H]^+$), 524.07365 ($[M+H]^+$), 526.07166 ($[M+H]^+$). MS (EI, 70 eV): M = $C_{23}H_{29}Br_3N_3O$, m/z = 405 (20.6), 404 (20.6), 403(48.3), 402 (34.7), 401 (21.9), 376 (24.5), 361 (68.2), 359 (94.6), 357 (66.6), 307 (27.6), 305 (69.1), 303 (35.0), 295 (51.0), 293 (89.6), 292 (26.3), 291 (61.8), 290 (49.1), 288 (23.0), 266 (33.0), 264 (73.8), 262 (34.5), 147 (59.7), 132 (100.0), 126 (20.0), 121 (38.2), 112 (75.5), 106 (77.6), 77 (23.6), 70 (88.7), 42 (22.5). IR (ATR): ν = 3195 (w), 3061 (w), 2966 (m), 2929 (m), 2856 (w), 2776 (w), 1897 (w), 1677 (s), 1611 (w), 1584 (w), 1557 (w), 1514 (m), 1473 (s), 1456 (s), 1394 (m), 1359 (m), 1331(m), 1310 (m), 1293 (m), 1237 (w), 1214 (w), 1183 (w), 1148 (m), 1124 (m), 1113 (m), 1068 (w), 1048 (m), 1036 (w), 1010 (w), 985 (w), 968 (w), 958 (w), 942 (w), 911 (w), 889 (m), 861 (m), 834 (m), 827 (m), 801 (m), 789 (s), 751 (m), 727 (m), 686 (w), 658 (w), 644 (m), 612 (s), 585 (m), 563 (w), 544 (m), 534 (m), 523 (w), 511 (w), 471 (w), 427 (w), 410 (m) cm^{-1}.

1-(2,4-dibromo-6-((cyclohexyl(methyl)amino)methyl)phenyl)-3-(p-tolyl)thiourea **(3i):** ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.04 - 1.20 (m, 5H), 1.55 (d, *J* = 10.7 Hz, 1H), 1.69 - 1.78 (m, 4H), 2.09 (s, 3H), 2.28 (s, 3H), 2.34 (m, H), 3.53 (br. d, *J* = 9.2 Hz, 2H), 7.15 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.7 Hz, 2H), 7.61 (d, *J* = 2.1 Hz, 1H), 7.79 (d, *J* = 1.5 Hz, 1H), 9.25 (br. s., 1H), 9.87 (br. s., 1H) ppm. MS (ESI-TOF): M = $C_{22}H_{27}Br_2N_3S$, m/z = 523.02924 ($[M]^+$), 524.04062 ($[M+H]^+$), 526.03532 ($[M+H]^+$), 528.03295 ($[M+H]^+$). IR (ATR): ν = 3154 (w), 2925 (m), 2850 (m), 2791 (w), 2111 (w), 1589 (w), 1528 (s), 1510 (s), 1477 (s), 1449 (s), 1395 (m), 1344 (m), 1313 (s), 1295 (m), 1251 (m), 1219 (m), 1198 (s), 1148 (s), 1113 (m), 1091 (w), 1023 (m), 966 (w), 943 (w), 910 (m), 890 (w),858 (m), 835 (w), 816 (m), 785 (s), 748 (m), 706 (m), 665 (m), 642 (m), 602 (m), 579 (m), 564 (m), 551 (m), 518 (m), 500 (s), 453 (w), 419 (w) cm^{-1}.

1-(2,4-dibromo-6-((cyclohexyl(methyl)amino)methyl)phenyl)-3-(4-(dimethylamino)phenyl)thiourea **(3j):** ^{1}H-NMR (DMSO-d_6, 300 MHz): δ = 1.05 - 1.23 (m, 5H), 1.55 (d, *J*=10.5 Hz, 1H), 1.63 - 1.78 (m, 4H), 2.05 (s, 3H), 2.25 - 2.34 (m, 1H), 2.88 (s, 6H), 3.50 (br. s., 2H), 6.72 (d, *J*=9.2 Hz, 2H), 7.20 (d, *J*=8.9 Hz, 2H), 7.59 (d, *J*=2.3 Hz, 1H), 7.77 (d, *J*=2.3 Hz, 1H), 8.91 (br. s., 1H), 9.73 (br. s., 1H) ppm. ^{13}C-NMR (DMSO-d_6, 75 MHz): δ = 25.4 (CH_2), 25.8 (CH_2), 28.0 ($2CH_2$), 37.2 (CH_3), 40.9 ($2CH_3$), 54.2 (CH_2), 62.0 (CH), 112.5 (2CH), 119.7 (C), 125.2 (C), 125.7 (2 CH), 130.7 (CH), 132.7 (CH), 137.2, 142.5 (C), 144.3 (C), 148.5 (C), 179.7 (CS) ppm. MS (ESI-TOF): M = $C_{23}H_{30}Br_2N_4S$, m/z = 552.05579 ($[M]^+$), 553.06119 ($[M+H]^+$), 555.06127 ($[M+H]^+$), 557.05996 ($[M+H]^+$). IR (ATR): ν = 3131 (w), 2924 (m), 2849 (m), 5071 (w), 1734 (w), 1613 (w), 1571 (w), 1522 (s), 1471 (s), 1449 (m), 1396 (m), 1343 (m), 1318 (m), 1305 (m), 1254 (m), 1213 (m), 1178 (m), 1158 (m), 1145 (m), 1124 (m), 1064 (m), 1035 (m), 1026 (m), 965 (w), 949 (w), 910 (m), 851 (m), 816 (m), 789 (s), 782 (m), 753 (m), 728 (w), 691 (m), 666 (m), 631 (w), 591 (m), 562 (m), 552 (m), 519 (m), 496 (m), 452 (m), 422 (w) cm^{-1}.

Results and Discussions

Chemistry

In order to screen the suitable reaction conditions at the beginning of our study, the reaction of Bromhexine (as free base) with phenylisocyanate was performed. The phenyl isocyanate was used slightly in excess (10% more). This excess of the phenyl isocyanate, worsened the yields of the product **3a**. The model reaction the equivalent ratio of bromhexine and phenyl isocyanate furnished the best yields. It was observed that the desired product **3a** precipitates during stirring. The reaction proceeded without any additional catalyst or additive. The reaction time and temperature was optimized and

80% yield was obtained at room temperature in 4 hours.

Once the best model reaction conditions were obtained, the optimized reaction conditions were applied to explore the substrate scope to test the generality and limitations of the reaction. Several electron-rich and electron-poor phenylisocyanates and phenylthioisocyanates were applied for the transformation of bromhexine to its derivatives (Table 1, entries 1-10). The best yield 90% was obtained when (4-isocyanatophenyl)(methyl)sulfane coupled with bromhexine to give product **3f** (Table 1, entry 6), whereas 4-isothiocyanato-*N*,*N*-dimethylaniline afforded 72% isolated yields of **3j** at the screened reaction conditions (table 1, entry 10). It was noted that the electron withdrawing substituted phenylisocanate afforded the lower yileds 42% of **3b** (Table 1, entry 2). Interstingly, in the case of *para* -CN substituted phenylisocyanates the moderate 59% yield of **3e** was obtained (Table 1, entry 2), whereas *para*-OEt substituted phenylisocyanates furnished 66% yieled of product **3d** (Table 1, entry 4). Several other substituted phenylisocyanate were applied in this transformation and moderate to good yields were obtained in general 37-90% (Table 1, entries 1–10).

Conclusion

In conclusion, a catalyst free and at room temperature transformation of commercially available bromhexine with various phenylisocyanates and phenylthisocycantes to urea and thiothiourea derivatives of bromhexine are smoothly carried out. Various potential pharmaceutically important derivatives have been efficiently synthesized from moderate to good yields. All the synthesized products have been submitted for biological activities and the potential results will be discussed in full length manuscript in due course of time. The structures of all the synthesized products were characterized by ^{1}H & ^{13}C-NMR, GCMS, HRMS and ESI experiments etc.

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