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Synthesis of Aryl Urea Derivatives from Aryl Amines and Aryl Isocyanates

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The present study describes the synthesis of novel diaryl urea derivatives derived from aryl amine and aryl isocyanates. The synthesized compounds are analogs of sorafenib [4-[4-[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]phenoxy]-N-methylpyridine-2-carboxamide] having potential antiproliferative activity.

Key Words: Sorafenib, Kinase inhibitor, Triphosgene, Aryl isocyanates, Diaryl ureas.

INTRODUCTION

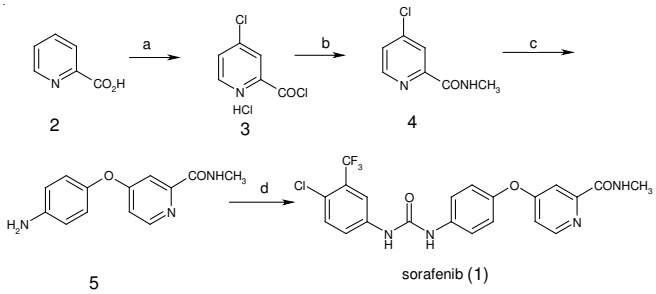
Protein kinases are overactive in many of the molecular pathway that cause cells to become cancerous. These pathways include Raf kinase, platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) receptor 2 and kinases and C-kit the receptor for stem cell factor. A growing number of drugs target these key pathways.

Sorafenib (**1**) is a small molecular inhibitor of several tyrosine protein kinases[1]. Sorafenib is unique in targeting the Raf/Mek/Erk pathway (MAP kinase path way). Sorafenib inhibits VEGFR and PDGFRB signalling pathways and reduces angiogenesis in human tumor xenografts[2,3]. Sorafenib could also interact with TSH-signalling pathways. Indeed, the TSH signal transduction cascade has been reported to involve the RAF path way, a target of sorafenib[4,5].

These observations and our continued interest in the synthesis of aryl urea derivatives as sorafenib analogs has prompted us to prepare various aryl urea derivatives and investigate their biological activities.

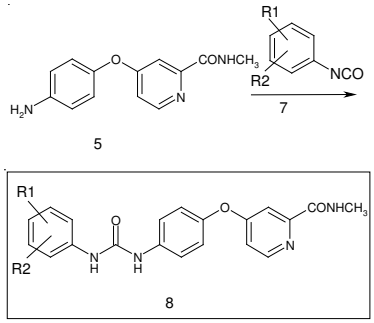
Sorafenib is a novel diaryl urea derivative that is currently used in the market as an anti neoplastic agent in a variety of tumor types. Sorafenib was first reported in 1999[6] and approved by U.S. FDA in December 2005, which is marketed under the brand name Nexavar®. The synthetic path way of sorafenib (**1**) is depicted in **Scheme-I**.

In the contemporary literature on these functionalized aryl ureas, phenoxy pyridyl moiety in the final active compounds has been modified by introducing different kinds of substituents and chloro-trifluoromethyl phenyl moiety remains same. In present strategy we designed different types of aryl urea derivatives by replacing chloro and CF_3 groups with various other functional variants and synthesized new analogs. The synthetic scheme for novel analogues of sorafenib is shown in **Scheme-II**.



Reagents & conditions: (a) $SOCl_2$, DMF, 72 ºC, 16 h; (b) CH_3NH_2, 3 ºC, 5 h; (c) 4-Aminophenol, pot.*t*-butoxide, K_2CO_3, DMF; (d) 4-Cl-3-CF_3-phenyl isocyanate, CH_2Cl_2, 0 ºC, 22 h

Scheme-I



Scheme-II

The key intermediate isocyanates (**7**) have been prepared from the reaction of triphosgene and appropriate amine.

EXPERIMENTAL

Reagent-grade chemicals and solvents were purchased from commercial sources and used without further purification. The pyridylamide (**5**) was synthesized by a known procedure[6]. The ^{1}H NMR and ^{13}C NMR spectra were recorded on Brucker 400-MHz spectrometer. The chemical shifts were reported in δ parts per million (ppm) relative to TMS. The IR spectra were recorded in liquid state as KBr cell and solid state as KBr dispersion using Perkin-Elmer FT-IR spectrometer. The mass spectra were recorded on Waters Quattro Micro LC/MS/MS. Melting points were determined using Mettler Toledo melting point apparatus and are uncorrected. All preparations were carried out under moisture-free conditions.

General procedure for the preparation of isocyanates (7): To a stirred solution of the amine (**6**, 0.01 mol) in dichloromethane (50 mL) was added triphosgene (0.005 mol) in lots at 15-20 ºC. The condenser was provided with cold water circulation during addition of triphosgene and carbon (1.0 g) was added to the reaction mass. The reaction mass was maintained at room temperature for 2 h, raised to reflux and maintained for 5-6 h. Aliquots were followed by IR for confirmation of isocyanate formation by observing the peak at 2275-2250 cm^{-1} and absence of characteristic peak of primary amine at *ca.* 3200 cm^{-1}. After completion of the reaction by IR, the reaction mass was cooled and filtered then concentrated under reduced pressure. Finally, the residual mass was distilled with toluene (3 × 10 mL) under vacuum to remove the traces of triphosgene. The resulting crude isocyanate was dissolved in acetone and taken to next step.

Yields and purity of the synthesized isocyanates (**7**) are given in Table-1.

TABLE-1
ARYL ISOCYANATES (**7**)

Compd. No.	R1	R2	Yield (%)	Purity (%) HPLC*
7a	4-Br	H	85	95
7b	2-Cl	H	87	93
7c	2-Cl	6-Me	91	97
7d	4-Cl-2-CF_3	5-NO_2	68	89
7e	4-F	H	92	91
7f	4-F	2-NO_2	86	93
7g	3-CF_3	H	94	92
7h	2-Me	3-Me	93	97
7i	2-Me	4-Me	92	98
7j	2-Me	5-Me	91	97
7k	2-Me	6-Me	95	99
7l	3-Me	4-Me	94	94
7m	3-Me	5-Me	90	92
7n	3-NO_2	H	88	88
7o	4-NO_2	H	79	96

*Purity of the isocyanates are determined by converting the unstable isocyanates to stable carbamates by quenching in methanol. Purity of the isolated carbamates is determined by HPLC.

Spectral data of aryl isocyanates

4-Bromophenyl isocyanate (7a): m.f. C_7H_4NOBr; IR (KBr, cm^{-1}): 2273, 1575, 1520, 1457, 1049, 736; ^{1}H NMR (400 MHz, $CDCl_3$): 7.28 (d, 2H), 7.80 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 121.1, 125.4, 128.3, 132.9, 133.3, Mass: [198, M$^+$].

2-Chlorophenyl isocyanate (7b): m.f. C_7H_4NOCl; IR (KBr, cm^{-1}): 2262, 1591, 1517, 1450, 1053, 751; ^{1}H NMR (400 MHz, $CDCl_3$): 7.31 (s, 1H), 77.35 (d, 2H), 7.53 (bs, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 121.5, 124.1, 127.2, 127.9, 130.0, 130.9, Mass: [152.4, (M-1)].

2-Chloro-6-methyl phenyl isocyanate (7c): m.f. C_8H_6NOCl; IR (KBr, cm^{-1}): 2270, 1601, 1519, 1470, 1047, 764; ^{1}H NMR (400 MHz, $CDCl_3$): 2.23 (s, 3H), 7.24 (d, 1H), 7.52 (bs, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 21.1, 126.2, 127.3, 127.8, 128.2, 130.4, 134.2, 134.7, Mass: [168, (M+1)].

4-Chloro-2-trifluoromethyl-5-nitro phenyl isocyanate (7d): m.f. $C_8H_2N_2O_3ClF_3$; IR (KBr, cm^{-1}): 2274, 1625, 1527, 1369, 1345, 1304, 1263,1152, 909, 827, 761; ^{1}H NMR (400 MHz, $CDCl_3$): 7.72 (s, 1H), 8.17 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 121.5, 122.6, 127.1, 127.8, 132.7, 152.1; Mass: [265, (M-1)].

4-Fluorophenyl isocyanate (7e): m.f. C_7H_4NOF; IR (KBr, cm^{-1}): 3404, 2280, 1735, 1522, 1231, 1151, 1094, 1014, 834; ^{1}H NMR (400 MHz, $CDCl_3$): 7.21-7.45 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): 117.2, 126.8, 127.9, 130.2, 160.5; Mass: [137, M$^+$].

4-Fluoro-2-nitro-phenyl isocyanate (7f): m.f. $C_7H_3N_2O_3F$; IR (KBr, cm^{-1}): 3472, 3356, 3096, 2267, 1730, 1543, 1342, 1132, 944, 879, 814, 731, 565; ^{1}H NMR (400 MHz, $CDCl_3$): 7.42-7.58 (m, 2H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 113.1, 122.6, 123.2, 127.9, 28.1, 148.7, 160.4; Mass: [183, (M+1)].

3-Trifluoro methyl phenyl isocyanate (7g): m.f. $C_8H_4F_3NO$; IR (KBr, cm^{-1}): 2270, 1617, 1596, 1325, 1179, 1134, 1067, 944, 820, 696, 525; ^{1}H NMR (400 MHz, $CDCl_3$): 7.274-7.295 (m, 1H), 7.35 (bs, 1H), 7.46 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 121.6, 122.02, 122.48, 124.7, 128.03, 130.16, 132.2, 134.28; Mass: [186, (M-1)].

2,3-Dimethylphenyl isocyanate (7h): m.f. C_9H_9NO; IR (KBr, cm^{-1}): 2272, 1499, 1086, 864, 776, 566; ^{1}H NMR (400 MHz, $CDCl_3$): 2.28 (s, 3H), 2.42 (s, 3H), 6.86-7.2 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 18.6, 22.7, 121.2, 126.6, 127.5, 127.8, 131.1, 131.6,138.0; Mass: [147, M$^+$].

2,4-Dimethylphenyl isocyanate (7i): m.f. C_9H_9NO; IR (KBr, cm^{-1}): 2922, 2273, 1617, 1518, 1079, 810, 559; ^{1}H NMR (400 MHz, $CDCl_3$): 2.34 (d, 6H), 6.95 (d, 1H), 7.12 (bs, 1H), 7.21 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 18.1, 21.4, 125.1, 127.2, 127.6, 127.9, 128.8, 131.9, 132.4; Mass: [147, M$^+$].

2,5-Dimethylphenyl isocyanate (7j): m.f. C_9H_9NO; IR (KBr, cm^{-1}): 2922, 2273, 1617, 1518, 1079, 810, 559; ^{1}H NMR (400 MHz, $CDCl_3$): 2.27 (d, 6H), 6.89 (t, 2H), 7.05 (d, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 17.57, 20.47, 125.39, 126.45, 128.09, 128.90, 129.47, 131.93, 136.62; Mass: [147, M$^+$].

2,6-Dimethylphenyl isocyanate (7k): m.f. C_9H_9NO; IR (KBr, cm^{-1}): 2919, 2275, 1609, 1510, 845, 571; ^{1}H NMR (400 MHz, $CDCl_3$): 2.29 (d, 6H), 7.13 (d, 2H), 7.5 (t, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 18.3, 126.1, 127.9, 130.7, 131.4, 134.2; Mass: [147, M$^+$].

3,4-Dimethylphenyl isocyanate (7l): m.f. C_9H_9NO; IR (KBr, cm^{-1}): 2918, 2269, 1607, 899, 839, 567; ^{1}H NMR (400 MHz, $CDCl_3$): 2.43 (d, 6H), 6.72 (d, 2H), 7.4 (bd, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 19.1, 122.3, 126.2, 127.6, 129.0, 131.8, 134.6, 134.9; Mass: [147, M$^+$].

3,5-Dimethylphenyl isocyanate (7m): m.f. C_9H_9NO; IR (KBr, cm^{-1}): 2921, 2266, 1609, 900, 843, 682, 551; ^1H NMR (400 MHz, $CDCl_3$): 2.41 (d, 6H), 7.21 (d, 2H), 7.29 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 22.1, 121.6, 127.9, 128.2, 134.5, 140.2; Mass: [147, M^+].

3-Nitrophenyl isocyanate (7n): m.f. $C_7H_4N_2O_3$; IR (KBr, cm^{-1}): 2269, 1594, 1515, 1340, 847, 753; ^1H NMR (400 MHz, $CDCl_3$): 7.41 (d, 1H), 7.71-7.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 121.0, 121.6, 127.9, 131.7, 132.3, 134.9, 150.2; Mass: [164, M^+].

4-Nitrophenyl isocyanate (7o): m.f. $C_7H_4N_2O_3$; IR (KBr, cm^{-1}): 2262, 1596, 1518, 1344, 855, 749. ^1H NMR (400 MHz, $CDCl_3$): 7.24 (d, 2H), 8.22 (d, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 125.3, 126.8, 128.2, 140.3, 145.3; Mass: [164, M^+].

General procedure for the preparation of diaryl urea derivative (8): To a stirred solution of the pyridyl amide (**5**, 0.01 mol) in acetone (50 mL) was added isocyanate (**7**, 0.01 mol) in acetone (10 mL) keeping the temperature below 40 ºC. The reaction mass was maintained at room temperature for 3-4 h followed by monitoring by TLC. After completion of reaction the product was filtered from the reaction mass, washed with acetone (5 mL) and dried at 60-65 ºC for 2 h.

The physical properties, yields and purities of the prepared diaryl ureas (**8**) are furnished in Table-2.

Spectral data of diaryl urea derivatives

4-[4-[[[4-Bromophenyl]amino]carbonyl]amino]-phenoxy]-N-methylpyridine-2-carboxamide (8a): m.f. $C_{20}H_{17}N_4O_3Br$; IR (KBr, cm^{-1}): 3391, 3256, 1677, 1654, 1593, 1545, 1538, 1504, 1487, 1463, 1406, 1391, 1296, 1222, 1199, 1073, 993, 928, 828, 785, 766, 556, 505; ^1H NMR (400 MHz, DMSO-d_6): 8.907 (s, 2H), 8.792 (d, 1H), 8.507 (d, 1H), 7.583 (d, 2H), 7.46 (s, 4H), 7.386 (d, 1H), 7.181 (d, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 26.04, 108.72, 113.31, 113.96, 120.11, 120.18, 121.47, 131.53, 137.42, 139.12, 147.56, 150.29, 152.40, 152.47,1638, 166.04; Mass: [443.4, (M+2)].

4-[4-[[[2-Chlorophenyl]amino]carbonyl]amino]-phenoxy]-N-methylpyridine-2-carboxamide (8b): m.f. $C_{20}H_{17}N_4O_3Cl$; IR (KBr, cm^{-1}): 3296, 1687, 1646, 1591, 1560, 1530, 1505, 1471, 1441, 1407, 1297, 1222, 922, 847, 739; ^1H NMR (400 MHz, DMSO-d_6): 8.549 (s, 1H), 8.423 (d, 1H), 8.263-8.287 (dd, 2H), 7.686 (s, 1H), 7.637 (d, 1H), 7.451 (d, 2H), 7.246-7.316 (m, 3H), 7.068- 7.089 (q, 1H), 6.99 (d, 3H). 3.055 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) : 26.40, 109.09, 114.71, 121.14, 121.62, 122.84, 123.35, 127.44, 128.98, 135.60, 136.90, 148.30, 149.73, 151.40, 152.86, 165.16, 166.81; Mass: [397.5, (M+1)].

4-[4-[[[2-Chloro-6-methyl]phenyl]amino]carbonyl]-amino]phenoxy]-N-methylpyridine-2-carboxamide (8c): m.f. $C_{21}H_{19}N_4O_3Cl$; IR (KBr, cm^{-1}): 3264, 3244, 1642, 1593, 1505, 1469, 1409, 1239.5, 1203.5, 928.5,773, 667.2; ^1H NMR (400 MHz, DMSO-d_6): 9.087 (s, 1H), 8.027 (s, 1H), 7.59 (d, 2H), 7.381 (d, 1H), 7.356 (s, 1H), 7.137-7.263 (m, 5H), 2.788 (d, 3H), 2.279 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 18.74, 26.22, 108.91, 114.15, 119.90, 120.00, 121.67, 127.05, 127.59, 129.32, 132.12, 134.02, 138.03, 138.85, 147.54, 150.60, 152.52, 153.09, 164.17, 166.28; Mass: [411.16, (M+1)].

4-[4-[[[4-Chloro-2-[trifluoromethyl]-5-nitrophenyl]-amino]carbonyl]amino]phenoxy]-N-methylpyridine-2-carboxamide (8d): m.f. $C_{21}H_{15}N_5O_5ClF_3$; IR (KBr, cm^{-1}): 3371, 3303, 3077, 1714, 1654, 1558, 1489, 1448, 1411, 1302, 1175, 1148, 1033, 922, 907, 836, 735, 714, 672, 610, 510, 459; ^1H NMR (400 MHz, DMSO-d_6): 9.933 (1, 1H), 9.276 (s, 1H), 8.661 (bs, 1H), 8.443 (d, 1H), 8.288 (s, 1H), 8.236 (d, 1H), 7.607 (d, 1H), 7.465-7.487 (d, 2H), 7.101-7.121 (q, 1H), 7.059 (s, 1H), 7.037 (s, 1H), 3.526 (bs, 1H), 3.041 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 25.97, 108.77, 114.01, 120.65, 121.52, 121.81, 121.87, 122.10,123.24, 128.06, 130.53, 130.84, 131.15, 131.46, 134.12, 136.52, 139.10, 148.31, 150.36, 151.62, 152.46, 163.76, 165.85; Mass [510.4, M].

4-[4-[[[4-Fluorophenyl]amino]carbonyl]amino]-phenoxy]-N-methylpyridine-2-carboxamide (8e): m.f. $C_{20}H_{17}N_4O_3F$; IR (KBr, cm^{-1}): 3395,3328, 3270, 1672, 1600, 1557, 1504, 1466, 1410, 1298, 1228, 1202, 931, 860, 835, 600, 556, 511; ^1H NMR (400 MHz, DMSO-d_6): 8.839 (s, 1H), 8.77 (bs, 2H), 8.503 (d, 1H), 7.574 (d, 2H), 7.458-7.481 (q, 2H), 7.377 (d, 1H), 7.131-7.17 (m, 5H), 2.784 (d, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 26.01, 108.70, 113.96, 115.18, 115.40, 120.02, 120.09, 121.45, 135.98, 137.59, 147.46, 150.31, 152.40, 152.70, 156.22, 158.58, 163.81, 166.06; Mass [381.5, M+1].

TABLE-2
ARYL UREA DERIVATIVES (**8**)

Compd. No.	R1	R2	Melting point (ºC)			Yield (%)	Purity by HPLC (%)
			Base	HCl salt	Tosylate salt		
8a	4-Br	H	229.6	192.6	145.2	94	97.5
8b	2-Cl	H	213.8	150.0	146.5	97	99.2
8c	2-Cl	6-Me	184.6	153.9	Salt not formed	87	99.5
8d	4-Cl-2-CF_3	5-NO_2	208.4	213.8	216.2	91	99.6
8e	4-F	H	221.5	233.7	141.0	93	93.4
8f	4-F	2-NO_2	226.6	209.3	215.5	96	97.8
8g	3-CF_3	H	187.6	179.9	212.5	82	99.1
8h	2-Me	3-Me	194.1	162.9	185.6	97	99.3
8i	2-Me	4-Me	181.5	216.2	177.6	98	94.3
8j	2-Me	5-Me	186.4	154.9	193.8	94	98.7
8k	2-Me	6-Me	220.7	197.5	Salt not formed	96	99.5
8l	3-Me	4-Me	190.9	199.6	Salt not formed	95	95.6
8m	3-Me	5-Me	212.1	178.4	220.9	96	98.3
8n	3-NO_2	H	199.6	194.7	218.3	86	92.5
8o	4-NO_2	H	242.2	248.3	233.5	91	96.0

4-[4-[[[4-Fluoro-2-nitrophenyl]amino]carbonyl]-amino]phenoxy]-N-methylpyridine-2-carboxamide (8f): m.f. $C_{20}H_{16}N_5O_5F$; IR (KBr, cm^{-1}): 3330, 3092, 1709, 1660, 1557, 1500, 1453, 1409, 1340, 1296, 1186, 1133, 942, 922, 850; ^1H NMR (400 MHz, DMSO-d_6): 9.959 (s, 1H), 9.537 (s, 1H), 8.803 (d, 1H), 8.51 (d, 1H), 8.256-8.293 (q, 1H), 7.980-8.01 (q, 1H), 7.599-7.699 (m, 3H), 7.386 (d, 1H); 7.152-7.209 (m, 3H), 2.789 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 26.9, 109.03, 111.96, 112.23, 114.25, 120.69, 121.76, 122.56, 122.78, 125.18, 131.55, 137.19, 138.3, 148.2, 150.68, 152.3, 157.3, 164.14, 164.21, 164.21, 166.17; Mass [426.2, M+1].

4-[4-[[[3-(Trifluoromethyl)phenyl]amino]carbonyl]-amino]phenoxy]-N-methylpyridine-2-carboxamide (8g): m.f. $C_{20}H_{17}N_4O_3F_3$; IR (KBr, cm^{-1}): 3358, 3090, 1708, 1654, 1568, 1541, 1505, 1465, 1407, 1338, 1300, 1228, 1195, 1170, 1126, 1096, 1072, 993, 926, 879, 846, 786, 702, 661, 564, 510, 487; ^1H NMR (400 MHz, DMSO-d_6): 8.462 (d, 1H), 8.366 (d, 1H), 8.33 (s, 1H), 8.108 (s, 1H), 7.701 (s, 1H) 7.654 (d, 1H), 7.559 (d, 1H), 7.362 (d, 3H), 7.244 (s, 1H), 7.155-7.175 (q, 1H), 6.984 (d, 2H), 3.0515 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 25.66, 109.41, 113.42, 114.64, 118.13, 120.18, 120.90, 121.11, 122.31, 125.01, 128.87, 130.36, 130.68, 136.55, 139.76, 148.00, 149.27, 152.52, 164.16, 166.11; Mass [431.6, (M+1)].

4-[4-[[[2,3-Dimethyl phenyl]amino]carbonyl]amino]-phenoxy]-N-methylpyridine-2-carboxamide (8h): m.f. $C_{22}H_{22}N_4O_3$; IR (KBr, cm^{-1}): 3412, 3284, 1681, 1643, 1604, 1567, 1534, 1506, 1466, 1406, 1295, 1230, 1200, 1099, 925, 856, 686, 593, 546, 509; ^1H NMR (400 MHz, DMSO-d_6): 9.108 (s, 1H), 8.768-8.791 (q, 1H), 8.503 (d, 1H), 8.01 (s, 1H), 7.524-7.598 (dd, 3H), 7.389 (d, 1H), 7.133-7.164 (m, 3H), 7.019-7.058 (t, 1H), 6.908 (d, 1H), 2.789 (d, 3H), 2.26 (s, 3H), 2.148 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 13.64, 20.33, 26.01, 108.72, 113.93, 119.64, 120.55, 121.45, 125.02, 125.24, 127.67, 136.59, 136.90, 137.97, 147.19, 150.21, 152.29, 152.98, 163.72, 166.17; Mass [391.6, (M+1)].

4-[4-[[[2,4-Dimethyl phenyl]amino]carbonyl]amino]-phenoxy]-N-methylpyridine-2-carboxamide (8i): m.f. $C_{22}H_{22}N_4O_3$; IR (KBr, cm^{-1}): 3288, 1686, 1646, 1601, 1557, 1505, 1467, 1297, 1197, 928, 829, 784, 691, 545, 510; ^1H NMR (400 MHz, DMSO-d_6): 9.133 (s, 1H), 8.77-8.8 (q, 1H), 8.505 (d, 1H), 7.915 (s, 1H), 7.572-7.657 (dd, 3H), 7.394 (d, 1H), 7.15 (d, 3H), 6.998 (s, 1H), 6.948-6.969 (d, 1H), 2.791 (d, 3H), 2.224 (d, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): 17.84, 20.33, 26.02, 108.81, 113.95, 119.63, 121.44, 121.67, 126.59, 128.07, 130.73, 131.81, 134.67, 137.96, 147.19, 150.13, 152.17, 152.86, 163.65, 166.25; Mass [391, (M+1)].

4-[4-[[[2,5-Dimethyl phenyl]amino]carbonyl]amino]-phenoxy]-N-methylpyridine-2-carboxamide (8j): m.f. $C_{22}H_{22}N_4O_3$; IR (KBr, cm^{-1}): 3298, 1640, 1555, 1537, 1505, 1406, 1288, 1227, 1196, 996, 922, 833, 799, 668, 563; ^1H NMR (400 MHz, DMSO-d_6): 9.158 (s, 1H), 8.784 (d, 1H), 8.506 (d, 1H), 7.905 (s, 1H), 7.676 (s, 1H), 7.591 (d, 2H), 7.386 (d, 1H), 7.144-7.171 (d, 3H), 7.048 (d, 1H), 6.778 (d, 1H), 2.791 (d, 3H), 2.23 (d, 6H); ^{13}C NMR (100 MHz, DMSO-d_6):17.44, 20.89, 25.98, 30.61, 108.73, 113.93, 119.71, 121.42, 121.86, 123.48, 124.61, 129.98, 135.10, 137.09, 137.82, 147.36, 150.30, 152.45, 152.72, 163.84, 166.06; Mass [391, M+1].

4-[4-[[[2,6-Dimethylphenyl]amino]carbonyl]amino]-phenoxy]-N-methylpyridine-2-carboxamide (8k): m.f. $C_{22}H_{22}N_4O_3$; IR (KBr, cm^{-1}): 3310, 2918,1673, 1641, 1590, 1557, 1503, 1468, 1405, 1295, 1259, 1227, 1199, 1147, 921, 831, 768, 701, 563, 482; ^1H NMR (400 MHz, DMSO-d_6): 8.931 (s, 1H), 8.792 (d, 1H), 8.49 (d, 1H), 7.774 (s, 1H), 7.584 (d, 2H), 7.373 (d, 1H), 7.122-7.144 (m, 3H), 7.074 (s, 3H), 2.785 (d, 3H), 2.224 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): 18.43, 26.21, 108.87, 114.14, 119.88, 121.62, 126.32, 127.97, 135.35, 135.86, 138.37, 147.31, 150.59, 152.51, 153.47, 164.18, 166.32; Mass [391, (M+1)].

4-[4-[[[3,4-Dimethylphenyl]amino]carbonyl]amino]-phenoxy]-N-methylpyridine-2-carboxamide (8l): m.f. $C_{22}H_{22}N_4O_3$; IR (KBr, cm^{-1}): 3317, 1673, 1642. 1591, 1556, 1503, 1405, 1295, 1227, 1199, 921, 768; ^1H NMR (400 MHz, DMSO-d_6): 8.807 (bs, 2H), 8.556 (s, 1H), 8.507 (d, 1H), 7.578 (d, 2H), 7.386 (d, 1H), 7.247 (bs, 1H), 7.139-7.201 (m, 4H), 7.035 (d, 1H) 2.791 (d, 3H), 2.176 (d, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): 18.96, 19.92, 26.22, 109.07, 114.29, 116.24, 120.01, 120.25, 121.76, 130.02, 130.12, 136.79, 137.35, 147.70, 150.69, 152.49, 152.89, 164.26, 166.41; Mass [391, (M+1)].

4-[4-[[[3,5-Dimethyl phenyl]amino]carbonyl]amino]-phenoxy]-N-methylpyridine-2-carboxamide (8m): m.f. $C_{22}H_{22}N_4O_3$; IR (KBr, cm^{-1}): 3300, 1651, 1551, 1504, 1467, 1296, 1234, 1205, 922, 834, 686, 562; ^1H NMR (400 MHz, DMSO-d_6): 8.78 (s, 2H), 8.496-8.55 (s, d; 2H), 7.57 (d, 2H), 7.38 (d, 1H), 7.08-7.16 (m, 5H), 6.62 (s, 1H), 2.78 (d, 3H), 2.23 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6): 21.13, 26.00, 108.66, 113.96, 116.01, 119.85, 121.44, 123.53, 137.66, 137.73, 139.45, 147.35, 150.33, 152.41, 152.52, 163.78, 166.06; Mass [391, (M+1)].

4-[4-[[[3-Nitrophenyl]amino]carbonyl]amino]-phenoxy]-N-methylpyridine-2-carboxamide (8n): m.f. $C_{20}H_{17}N_5O_5$; IR (KBr, cm^{-1}): 3361, 1720, 1654, 1600, 1560, 1504, 1405, 1347, 1299, 1233, 1193, 1163, 931, 880, 833, 735, 672, 567, 511, 483; ^1H NMR (400 MHz, DMSO-d_6): 9.414 (s, 1H), 9.13 (s, 1H), 8.83 (d, 1H), 8.58 (s, 1H), 8.52 (d, 1H), 7.84 (d, 1H), 7.74 (d, 1H), 7.58-7.63 (t, 3H), 7.41 (s, 1H), 7.17-7.21 (d, 3H), 2.796 (d, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 26.24, 109.29, 112.43, 114.36, 116.73, 120.74, 121.74, 124.58, 130.36, 137.26, 141.08, 148.10, 148.40, 150.37, 152.04, 152.69, 163.93, 166.61; Mass [408, (M+1)].

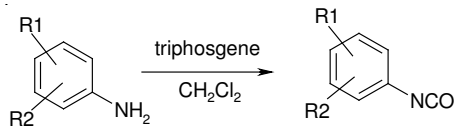
4-[4-[[[4-Nitrophenyl]amino]carbonyl]amino]-phenoxy]-N-methylpyridine-2-carboxamide (8o): m.f. $C_{20}H_{17}N_5O_5$; IR (KBr, cm^{-1}): 3391, 3335, 3247, 1682, 1654, 1552, 1531, 1495, 1415, 1335, 1197, 1115, 857, 753; ^1H NMR (400 MHz, DMSO-d_6): 9.51 (s, 1H), 9.09 (s, 1H), 8.78 (d, 1H), 8.51 (d, 1H), 8.21 (d, 2H), 7.71 (d, 2H), 7.61 (d, 2H), 7.39 (d, 1H), 7.15-7.21 (m, 3H), 2.79 (d, 3H); ^{13}C NMR (100 MHz, DMSO-d_6): 26.04, 108.68, 114.05, 117.53, 120.50, 121.57, 125.19, 136.91, 141.04, 146.37, 147.96, 150.39, 152.05, 152.44, 163.81, 165.97, Mass [408, (M+1)].

RESULTS AND DISCUSSION

A series of aryl ureas have been synthesized as novel analogues of sorafenib and characterized. The novel analogues of sorafenib of present work consist of urea derivatives having

functional variants in the aryl fragment other than the phenoxy pyridyl moiety.

The key intermediate isocyanates (**7**) are prepared from the reaction of triphosgene and appropriate amine in methylene chloride at reflux temperature (**Scheme-III**). Purity of isocyanates are estimated by HPLC *via* preparation of methyl carbamates due to the inherent instability of isocyanates.



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Scheme-III

The novel analogues of sorafenib are designated as (**8a-8o**) and the synthetic scheme for the preparation of these compounds is depicted in **Scheme-II**. The process consists of coupling of amine (**5**) and isocyanate (**7**) in acetone medium at room temperature to afford the required product in good yield and purity.

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