Supporting Information

Evaluation of Diarylureas for Activity Against *Plasmodium falciparum*: search for new pharmacophores

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General Consideration. All materials were obtained from commercial suppliers and used without further purification. Thin layer chromatography was performed using silica gel 60 F254 plate from EMD. Preparative RP-HPLC was carried out on an four-channel Biotage Parallel Flex system with xBridge Prep. C18 OBD 5 μm (19 × 50 mm), or an Dionex APS 4000 LC/MS Prep. System with Gemini C18 OBD 5 μm (30 × 50 mm). 1H NMR spectra were recorded on a Bruker 400 MHz, chemical shifts were expressed in ppm relative to TMS used as an internal standard. The identification and purity of each compound was estimated by chromatographic methods using an HPLC-MS (photodiode array, total ion count, and expected mass [m/z]) was obtained (Alliance HT, Micromass ZQ 4000 and RP-C18 Xterra column 5 μm, 6 mm × 50 mm [Waters]) or UPLC-MS (Acquity PDA detector, Acquity SQ detector and Acquity UPLC BEH-C18 column 1.7 μm, 2.1 × 50 mm [Waters]). Compounds prepared in our laboratory were over 90% purity. Novel compounds, which were not reported in literatures, were characterized by ^{1}H NMR and LCMS.

General Synthesis Procedure for diarylureas 4{x,y}. Diarylureas **4**{x,y} were synthesized according to the published procedure.[1] Aryl amines **1**{x} (0.2 M) and aryl isocyanates **2**{y} (0.2 M) were freshly prepared in anhydrous DMSO and stored over 4Å molecular sieves and used quickly afterwards. To a 96-well polypropylene deep well plate (1.8 mL), was added the aryl amines (0.26 mL, 0.2 M in DMSO, 0.052 mmol) followed by the appropriate isocyanate (0.2 mL, 0.2 M in DMSO, 0.04 mmol). The reaction block was covered with aluminum foil and shaken upright on the Lab-line Multi-purpose Rotator for 5 min. Release of gas was observed in the reaction. The crude reaction mixtures were transferred into a Thomason 96 well filter plate, containing a small amount of packed Celite 545, and filtered into a Waters 96 well collection plate. Approximately 500 μL of DMSO was added to each well to rinse the filter plate to make the final volume ~ 1 mL for purification on preparative RP-HPLC. Dionex APS 4000 LC/MS Prep. System with Gemini C18 OBD 5 μm (30 × 50 mm) was used for purification were with 4%THF/MeOH+0.1% formic acid as solvent B and H_2O+0.1% formic acid as solvent A. An alternative RP-HPLC was a four-channel Biotage Parallel Flex system with xBridge Prep. C18 OBD 5 μm (19 × 50 mm), eluting with MeOH+0.1% formic acid (solvent B) and H_2O+0.1% formic acid (solvent A).

Generation of aryl isocyanate. A solution of aryl amine (1.2 mmol) in DMSO (5.5 mL) was treated with 1,1′-carbonyldiimidazole (1.4 mmol). The mixture was stirred at room temperature for 2 h, and then used directly as a stock soluction (0.2 M in DMSO) for synthesis of diarylureas using the procedure described above.

1-(5-Chloro-2-methoxyphenyl)-3-(quinolin-5-yl)urea, 4{12,1}: ^{1}H NMR (400 MHz, DMSO) δ 9.40 (s, 1H), 8.94 (s, 1H), 8.29 (d, *J* = 2.6 Hz, 1H), 8.20 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.3 Hz, 1H), 7.65 (d, *J* = 8.2 Hz, 1H), 7.62 – 7.52 (m, 2H), 7.48 (t, *J* = 7.9 Hz, 1H), 7.06 (d, *J* = 8.8 Hz, 1H), 7.00 (dd, *J* = 8.7, 2.6 Hz, 1H), 3.93 (s, 3H).

1-(3-Chloro-4-methylphenyl)-3-(quinolin-5-yl)urea, 4{12,2}:^{1}H NMR (400 MHz, MeOD) δ 8.88 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.56 (d, *J* = 5.5 Hz, 1H), 7.90 (dd, *J* = 15.7, 8.0 Hz, 2H), 7.81 – 7.75 (m, 1H), 7.65 (d, *J* = 2.0 Hz, 1H), 7.60 (dd, *J* = 8.6, 4.3 Hz, 1H), 7.27 – 7.19 (m, 2H), 2.33 (s, 3H).

1-(3-Chloro-4-methoxyphenyl)-3-(quinolin-5-yl)urea, 4{12,3}: ^{1}H NMR (400 MHz, MeOD) δ 8.87 (d, *J* = 2.8 Hz, 1H), 8.55 (d, *J* = 8.5 Hz, 1H), 7.88 (dd, *J* = 12.0, 8.0 Hz, 2H), 7.79 – 7.72 (m, 1H), 7.59 (dd, *J* = 9.7, 3.4 Hz, 2H), 7.31 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.86 (s, 3H).

1-(4-Ethylphenyl)-3-(quinolin-5-yl)urea, 4{12,4}: ^{1}H NMR (400 MHz, MeOD) δ 8.86 (dd, *J* = 4.3, 1.5 Hz, 1H), 8.55 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.5 Hz, 1H), 7.81 – 7.71 (m, 1H), 7.58 (dd, *J* = 8.6, 4.3 Hz, 1H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.15 (d, *J* = 8.5 Hz, 2H), 2.70 – 2.40 (m, 2H), 1.22 (t, *J* = 7.6 Hz, 3H).

1-(3-Chlorophenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,7}: ^{1}H NMR (400 MHz, MeOD) δ 8.50 (s, 1H), 8.28 (d, *J* = 8.5 Hz, 1H), 7.98 – 7.89 (m, 2H), 7.78 – 7.71 (m, 2H), 7.34 (d, *J* = 8.3 Hz, 1H), 7.28 (t, *J* = 8.0 Hz, 1H), 7.07 (d, *J* = 7.8 Hz, 1H), 2.78 (s, 3H).

1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,12}: ^{1}H NMR (400 MHz, MeOD) δ 8.46 (s, 1H), 8.25 (m, 3H), 8.15 (d, *J* = 2.4 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.94 – 7.86 (m, 1H), 7.79 – 7.68 (m, 2H), 7.59 (d, *J* = 8.7 Hz, 1H), 2.79 (s, 3H).

1-(2-Methylquinolin-4-yl)-3-(m-tolyl)urea, 4{13,21}:^{1}H NMR (400 MHz, MeOD) δ 8.35 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.82 (t, *J* = 7.7 Hz, 1H), 7.70 – 7.61 (m, 1H), 7.37 – 7.29 (m, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 2.72 (s, 3H), 2.35 (s, 3H).

1-(2-(tert-Butyl)phenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,22}: ^{1}H NMR (400 MHz, MeOD) δ 8.36 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.93 (d, *J* = 8.5 Hz, 1H), 7.85 – 7.77 (m, 1H), 7.65 (t, *J* = 7.7 Hz, 1H), 7.60 (s, 1H), 7.33 (d, *J* = 9.0 Hz, 1H), 7.26 (t, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 2.71 (s, 3H), 1.34 (s, 9H).

1-(3-(tert-Butyl)phenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,23}: ^{1}H NMR (400 MHz, MeOD) δ 8.33 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.89 – 7.81 (m, 1H), 7.71 – 7.65 (m, 1H), 7.51 (d, *J* = 5.4 Hz, 1H), 7.33 (m, 1H), 7.28 (m, 2H), 2.71 (s, 3H), 1.47 (s, 9H).

1-(4-(tert-Butyl)phenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,24}: ^{1}H NMR (400 MHz, MeOD) δ 8.34 (s, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 7.7 Hz, 1H), 7.44 (m, 2H), 7.37 (m, 2H), 2.70 (s, 3H), 1.32 (s, 9H).

1-(2-Methylquinolin-4-yl)-3-(4-(trifluoromethyl)phenyl)urea, 4{13,27}: ^{1}H NMR (400 MHz, MeOD) δ 8.34 (s, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.81 (t, *J* = 7.7 Hz, 1H), 7.72 (m, 2H), 7.63 (m, 3H), 2.71 (s, 3H).

1-(2-Methylquinolin-4-yl)-3-(4-nitro-3-(trifluoromethyl)phenyl)urea, 4{13,28}: ^{1}H NMR (400 MHz, MeOD) δ 8.29 (s, 1H), 8.24 (d, *J* = 2.1 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 8.09 (d, *J* = 9.0 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.91 (dd, *J* = 8.9, 2.2 Hz, 1H), 7.80 – 7.75 (m, 1H), 7.64 (d, *J* = 8.2 Hz, 1H), 2.71 (s, 3H).

1-(2-Methylquinolin-4-yl)-3-(2-nitrophenyl)urea, 4{13,41}: ^{1}H NMR (400 MHz, MeOD) δ 7.81 (s, 1H), 7.53 (s, 1H), 7.34 (d, *J* = 8.5 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 2H), 7.00 (t, *J* = 7.7 Hz, 2H), 6.84 (t, *J* = 7.7 Hz, 1H), 6.77 (t, *J* = 8.2 Hz, 1H), 1.91 (s, 3H).

1-(2-Methylquinolin-4-yl)-3-(3-nitrophenyl)urea, 4{13,42}: ^{1}H NMR (400 MHz, MeOD) δ 8.63 (s, 1H), 8.34 (s, 1H), 8.16 (d, *J* = 8.5 Hz, 1H), 7.95 (m, 2H), 7.81 (m, 2H), 7.69 – 7.62 (m, 1H), 7.58 (t, *J* = 8.2 Hz, 1H), 2.73 (s, 3H).

1-(4-Hydroxyphenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,43}: ^{1}H NMR (400 MHz, MeOD) δ 8.44 (s, 1H), 8.31 (s, 1H), 8.25 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.90 (t, *J* = 7.7 Hz, 1H), 7.73 (t, *J* = 7.7 Hz, 1H), 7.35 (d, *J* = 8.7 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 2.77 (s, 3H).

1-(2-Aminophenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,44}: ^{1}H NMR (400 MHz, MeOD) δ 8.36 (d, *J* = 11.6 Hz, 1H), 8.21 (d, *J* = 8.4 Hz, 1H), 7.95 (d, *J* = 8.4 Hz, 1H), 7.83 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.66 (t, *J* = 7.7 Hz, 1H), 7.34 – 7.28 (m, 1H), 7.05 (dd, *J* = 11.0, 4.4 Hz, 1H), 6.89 (dd, *J* = 8.0, 1.1 Hz, 1H), 6.76 (ddd, *J* = 8.7, 7.7, 1.4 Hz, 1H), 2.71 (s, 3H).

1-(4-Aminophenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,45}: ^{1}H NMR (400 MHz, MeOD) δ 8.61 (s, 2H), 8.51 (s, 1H), 8.35 (d, *J* = 8.4 Hz, 1H), 8.15 (d, *J* = 8.6 Hz, 1H), 8.05 – 7.94 (m, 1H), 7.82 (dd, *J* = 15.4, 8.4 Hz, 2H), 7.74 (s, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 2.86 (s, 3H).

2-(3-(2-Methylquinolin-4-yl)ureido)benzamide, 4{13,49}: ^{1}H NMR (400 MHz, Acetone) δ 10.77 (s, 1H), 8.34 (d, *J* = 8.5 Hz, 1H), 8.18 (d, *J* = 8.5 Hz, 1H), 7.98 (s, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.54 (dd, *J* = 8.1, 7.1 Hz, 2H), 7.41 – 7.29 (m, 2H), 6.95 (t, *J* = 7.6 Hz, 1H), 3.18 (s, 3H).

3-(3-(2-Methylquinolin-4-yl)ureido)benzamide, 4{13,50}: ^{1}H NMR (400 MHz, MeOD) δ 8.42 (s, 1H), 8.23 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 1.5 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.87 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.81 – 7.75 (m, 1H), 7.70 (dd, *J* = 8.3, 7.1 Hz, 1H), 7.59 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 2.75 (s, 3H).

1-(1H-benzo[d]imidazol-6-yl)-3-(2-methylquinolin-4-yl)urea, 4{13,60}: ^{1}H NMR (400 MHz, MeOD) δ 8.41 (s, 2H), 8.37 (s, 1H), 8.19 (d, *J* = 8.4 Hz, 1H), 8.16 (s, 1H), 8.05 (s, 1H), 7.96 (d, *J* = 7.7 Hz, 1H), 7.82 (t, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.60 (d, *J* = 8.6 Hz, 1H), 7.27 (d, *J* = 8.6 Hz, 1H), 2.73 (s, 3H).

1-(5-Chloro-2-methoxyphenyl)-3-(1H-imidazol-2-yl)urea, 4{19,1}: ^{1}H NMR (400 MHz, MeOD) δ 8.30 – 8.26 (m, 1H), 7.02 – 6.94 (m, 2H), 6.78 (s, 2H), 3.94 (s, 3H).

1-(3-Chloro-4-methylphenyl)-3-(1H-imidazol-2-yl)urea, 4{19,2}: ^{1}H NMR (400 MHz, MeOD) δ 8.36 (s, 1H), 7.69 (s, 1H), 7.21 (dd, *J* = 11.6, 3.2 Hz, 2H), 6.83 (d, *J* = 26.0 Hz, 2H), 2.33 (s, 3H).

1-(3-Chloro-4-methoxyphenyl)-3-(1H-imidazol-2-yl)urea, 4{19,3}: ^{1}H NMR (400 MHz, MeOD) δ 8.31 (s, 1H), 7.66 (d, *J* = 2.6 Hz, 1H), 7.31 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.04 (d, *J* = 8.9 Hz, 1H), 6.88 (s, 2H), 3.88 (s, 3H).

1-(4-Ethylphenyl)-3-(1H-imidazol-2-yl)urea, 4{19,4}: ^{1}H NMR (400 MHz, MeOD) δ 8.49 (s, 1H), 7.53 – 7.28 (m, 2H), 7.16 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 16.2 Hz, 2H), 2.62 (q, *J* = 7.5 Hz, 2H), 1.23 (t, *J* = 7.6 Hz, 3H).

1-(3,4-Dichlorophenyl)-3-(1H-imidazol-2-yl)urea, 4{19,8}: ^{1}H NMR (400 MHz, MeOD) δ 8.26 (s, 1H), 7.89 (d, *J* = 2.3 Hz, 1H), 7.41 (dd, *J* = 16.2, 5.5 Hz, 2H), 6.90 (s, 2H).

1-(2,4-Dichlorophenyl)-3-(1H-imidazol-2-yl)urea, 4{19,9}: ^{1}H NMR (400 MHz, MeOD) δ 8.57 (s, 1H), 8.26 (d, *J* = 9.0 Hz, 1H), 7.52 – 7.27 (m, 2H), 6.79 (s, 2H).

Biological Assay.

Two *P. falciparum* strains were used in this study and were provided by the MR4 Unit of the American Type Culture Collection (ATCC, Manassas, VA). Those two strains were the chloroquine sensitive strain 3D7 and the chloroquine resistant strain K1.

Asynchronous parasites were maintained in culture based on the method of Trager [2]. Parasites were grown in presence of fresh group O-positive erythrocytes (Lifeblood Memphis, TN) in Petri dishes at a hematocrite of 4-6% in RPMI based media. It consisted of RPMI 1640 supplemented with 0.5% AlbuMAX II, 25 mM HEPES, 25 mM $NaHCO_3$ (pH 7.3), 100ug/mL hypoxanthine, and 5 ug/mL gentamycin. Cultures were incubated at 37C in a gas mixture of 90% N2, 5% O2, 5% CO2. For IC50 determinations, 20ul of RPMI 1640 with 5ug/ml gentamycin were dispensed per well in an assay plate (384-well mircoplate, clear bottom, tissue treated). 40nl of compound, previously serial diluted in a separate 384-well white polypropylene plate, were dispensed in the assay plate and then 20ul of a synchronized culture suspension (1% rings, 10% hematocrite) were added per well thus making a final hematocrite and parasitemia of 2% and 1% respectively. Assay plates were incubated for 72h and the parasitemia were determinated by a method previously described [3]: Briefly, 10ul of the following solution in RPMI (10X Sybr Green I, 0.5% v/v triton, 0.5 mg/ml saponin) were added per well, assay plates were shaken for 30s, incubated in the dark for 4h, then read with the Envision spectrophotomer at Ex/Em 485nm/535nm. IC50s were calculated with the Graphpad PRISM software.

Cytotoxicity assays

BJ, HEK293, Hep G2, and Raji cell lines were purchased from the American Type Culture Collection (ATCC, Manassas, VA) and were cultured according to recommendations. Cell culture media were purchased from ATCC. Cells were routinely tested for mycoplasma contamination using the MycoAlert Mycoplasma Detection Kit (Lonza). Exponentially growing cells were plated in Corning 384 well white custom assay plates, and incubated overnight at 37º C in a humidified, 5% CO_2 incubator. DMSO inhibitor stock solutions were added the following day to a top final concentration of 25 μM, 0.25% DMSO and then diluted 1/3 for a total of ten testing concentrations. Cytotoxicity was determined following a 72 hour incubation using Promega Cell Titer Glo Reagent according to the manufacturer's recommendation. Luminescence was measured on an Envision plate reader (Perkin Elmer).

PAMPA permeability assays

Parallel Artificial membrane Permeability Assay (PAMPA) was conducted by Biomek FX lab automation workstation (Beckman Coulter, Inc., Fullerton, CA) and PAMPA evolution 96 command software (pION Inc., Woburn, MA). The detailed method is described as following. 3 μL 10 μM test compound stock was mixed with 600 μL of SSB (system solution buffer, pH 7.4 or 4, pION Inc., Woburn, MA) to make diluted test compound. 150 μL of diluted test compound was transferred to a UV plate (pION Inc., Woburn, MA) and the UV spectrum was read as the reference plate. The membrane on pre-loaded PAMPA sandwich (pION Inc., Woburn, MA) was painted with 4 μL GIT lipid (pION Inc., Woburn, MA). The acceptor chamber was then filled with 200 μL ASB (acceptor solution buffer, pION Inc., Woburn, MA), and the donor chamber was filled with 180 μL diluted test compound. The PAMPA sandwich was assembled, placed on the Gut-box and stirred for 30 minutes. Aqueous Boundary Layer was set to 40 μm for stirring. The UV spectrum (250-500 nm) of the donor and the acceptor were read. The permeability coefficient was calculated using PAMPA evolution 96 command software (pION Inc., Woburn, MA) based on the AUC of the reference plate, the donor plate and the acceptor plate. All compounds were tested in triplicates.

Solubility assays

Solubility assay was carried out on Biomek FX lab automation workstation (Beckman Coulter, Inc., Fullerton, CA) using μSOL Evolution software (pION Inc., Woburn, MA). The detailed method is described as following. 10 μL of compound stock was added to 190 μL 1-propanol to make a reference stock plate. 5 μL from this reference stock plate was mixed with 70 μL 1-propanol and 75 μL phosphate buffered saline (PBS, pH 7.4 and 4) to make the reference plate, and the UV spectrum (250 nm – 500 nm) of the reference plate was read. 6 μL of 10 mM test compound stock was added to 600 μL PBS in a 96-well storage plate and mixed. The storage plate was sealed and incubated at room temperature for 18 hours. The suspension was then filtered through a 96-well filter plate (pION Inc., Woburn, MA). 75 μL filtrate was mixed with 75 μL 1-propanol to make the sample plate, and the UV spectrum of the sample plate was read. Calculation was carried out by μSOL Evolution software based on the AUC (area under curve) of UV spectrum of the sample plate and the reference plate. All compounds were tested in triplicates.

Kinase assays (KINOME*scan*™, Ambit Biosciences).

For most assays, kinase-tagged T7 phage strains were grown in parallel in 24-well blocks in an *E. coli* host derived from the BL21 strain. *E. coli* were grown to log-phase and infected with T7 phage from a frozen stock (multiplicity of infection = 0.4) and incubated with shaking at 32°C until lysis(90-150 minutes). The lysates were centrifuged (6,000 x g) and filtered (0.2μm) to remove cell debris. The remaining kinases were produced in HEK-293 cells and subsequently tagged with DNA for qPCR detection. Streptavidin-coated magnetic beads were treated with biotinylated small molecule ligands for

30 minutes at room temperature to generate affinity resins for kinase assays. The liganded beads were blocked with excess biotin and washed with blocking buffer (SeaBlock (Pierce), 1 % BSA, 0.05 % Tween 20, 1 mM DTT) to remove unbound ligand and to reduce non-specific phage binding. Binding reactions were assembled by combining kinases, liganded affinity beads, and test compounds in 1x binding buffer (20 % SeaBlock, 0.17x PBS, 0.05 % Tween 20, 6 mM DTT). Test compounds were prepared as 40x stocks in 100% DMSO and directly diluted into the assay. All reactions were performed in polypropylene 384-well plates in a final volume of 0.04 ml. The assay plates were incubated at room temperature with shaking for 1 hour and the affinity beads were washed with wash buffer (1x PBS, 0.05 % Tween 20). The beads were then re-suspended in elution buffer (1x PBS, 0.05 % Tween 20, 0.5 μm non-biotinylated affinity ligand) and incubated at room temperature with shaking for 30 minutes. The kinase concentration in the eluates was measured by qPCR.

Pharmacophore generation for compounds 4{13,1}, 4{13,39} and 4{13,58}.

All pharmacophore analysis were performed in Chemical Computing Group's Molecular Operating Environment (MOE). The pharmacophoric and structure features were generated based on one conformation of the most active molecules **4**{13,1}, **4**{13,39} and **4**{13,58}. Each compound was built using the Molecular Builder module. A systematic conformational search of all rotatable bonds were performed using default parameters and with the Energy Minimize Resulting Conformations option ON. For each compound, the conformer with the lowest energy was used for a pharmacophore query generation. Pharmacophore features of each compound were identified according to the PCH (Polarity-Charge-Hydrophobicity) pharmacophore scheme.

Table 1. LC/MS characterization of diarylureas **4**{x,y}

Compound	Formula	Molecular weight	Found Mass, [M+1]	retention time (min)	Purity, % (UV)	Analytic Method [a]
4{1,1}	C14H12Cl2N2O2	311.2	310.9	2.04	100	Method A
4{1,2}	C14H12Cl2N2O	295.2	294.9	2.00	100	Method A
4{1,3}	C14H12Cl2N2O2	311.2	311.0	1.78	99	Method A
4{1,4}	C15H15ClN2O	274.8	275.1	2.97	100	Method B
4{1,5}	C14H13ClN2O	260.7	261.1	1.77	90	Method A
4{1,8}	C13H9Cl3N2O	315.6	314.9	2.06	100	Method A
4{2,1}	C14H11Cl3N2O2	345.6	345.0	3.17	100	Method B
4{2,2}	C14H11Cl3N2O	329.6	329.0	3.06	100	Method B
4{2,3}	C14H11Cl3N2O2	345.6	345.0	3.07	100	Method B
4{2,4}	C15H14Cl2N2O	309.2	309.0	3.15	100	Method B
4{2,5}	C14H12Cl2N2O	295.2	295.0	3.10	100	Method B
4{2,6}	C13H9Cl3N2O	315.6	314.8	2.13	98	Method A
4{2,7}	C13H9Cl3N2O	315.6	314.9	2.13	100	Method A
4{3,1}	C14H12Cl2N2O2	311.2	311.0	3.04	100	Method B
4{3,2}	C14H12Cl2N2O	295.2	295.0	3.05	100	Method B
4{3,3}	C14H12Cl2N2O2	311.2	313.1	2.84	100	Method B
4{3,4}	C15H15ClN2O	274.8	275.1	2.97	100	Method B
4{3,5}	C14H13ClN2O	260.7	261.1	2.88	100	Method B
4{4,1}	C14H11Cl3N2O2	345.6	346.9	3.18	100	Method B
4{4,2}	C14H11Cl3N2O	329.6	330.9	3.20	100	Method B
4{4,3}	C14H11Cl3N2O2	345.6	345.0	1.97	99	Method A
4{4,4}	C15H14Cl2N2O	309.2	309.0	2.10	97	Method A
4{4,5}	C14H12Cl2N2O	295.2	295.0	1.97	97	Method A
4{4,6}	C13H9Cl3N2O	315.6	315.0	2.08	99	Method A
4{4,7}	C13H9Cl3N2O	315.6	314.9	2.08	98	Method A
4{5,2}	C14H12Cl2N2O	295.2	294.9	2.02	99	Method A
4{5,6}	C13H10Cl2N2O	281.1	280.8	1.91	100	Method A
4{6,1}	C14H12ClFN2O2	294.7	295.0	1.92	100	Method A
4{6,2}	C14H12ClFN2O	278.7	279.1	1.89	100	Method A
4{6,4}	C15H15FN2O	258.3	259.2	1.81	99	Method A
4{6,6}	C13H10ClFN2O	264.7	265.0	1.78	100	Method A
4{6,7}	C13H10ClFN2O	264.7	265.0	1.78	100	Method A
4{6,8}	C13H9Cl2FN2O	299.1	298.9	1.96	100	Method A
4{7,1}	C16H17ClN2O2	304.8	305.0	2.07	98	Method A
4{7,2}	C16H17ClN2O	288.8	289.1	2.04	99	Method A
4{7,3}	C16H17ClN2O2	304.8	305.0	1.82	99	Method A
4{7,5}	C16H18N2O	254.3	255.2	1.82	99	Method A

4{7,8}	C15H14Cl2N2O	309.2	309.1	2.10	100	Method A
4{8,1}	C18H15ClN2O2	326.8	327.1	3.16	100	Method B
4{8,2}	C18H15ClN2O	310.8	311.6	2.10	100	Method B
4{8,3}	C18H15ClN2O2	326.8	327.1	2.82	100	Method B
4{8,4}	C19H18N2O	290.4	291.2	2.71	100	Method B
4{9,1}	C18H15ClN2O2	326.8	327.1	2.24	100	Method B
4{9,2}	C18H15ClN2O	310.8	311.1	3.08	100	Method B
4{9,3}	C18H15ClN2O2	326.8	327.2	1.85	93	Method A
4{9,4}	C19H18N2O	290.4	291.3	3.00	100	Method B
4{9,5}	C18H16N2O	276.3	277.0	1.84	99	Method A
4{9,6}	C17H13ClN2O	296.8	296.9	1.95	86	Method A
4{9,7}	C17H13ClN2O	296.8	297.1	1.95	88	Method A
4{10,1}	C17H14ClN3O2	327.8	327.1	2.46	100	Method B
4{10,2}	C17H14ClN3O	311.8	312.1	1.52	100	Method C
4{10,3}	C17H14ClN3O2	327.8	328.1	2.36	100	Method B
4{10,4}	C18H17N3O	291.4	292.1	1.42	100	Method C
4{11,1}	C17H14ClN3O2	327.8	328.1	2.05	98	Method A
4{11,2}	C17H14ClN3O	311.8	312.1	3.10	88	Method B
4{11,3}	C17H14ClN3O2	327.8	328.0	1.81	95	Method A
4{11,4}	C18H17N3O	291.4	291.7	2.99	100	Method B
4{11,5}	C17H15N3O	277.3	278.1	1.81	96	Method A
4{11,6}	C16H12ClN3O	297.7	298.0	1.95	97	Method A
4{11,7}	C16H12ClN3O	297.7	298.1	1.96	99	Method A
4{11,8}	C16H11Cl2N3O	332.2	332.1	2.15	98	Method A
4{12,1}	C17H14ClN3O2	327.8	328.1	3.10	100	Method B
4{12,2}	C17H14ClN3O	311.8	312.1	1.59	100	Method B
4{12,3}	C17H14ClN3O2	327.8	328.0	1.71	100	Method B
4{12,4}	C18H17N3O	291.4	292.1	1.10	100	Method C
4{13,1}	C18H16ClN3O2	341.8	342.1	2.53	100	Method B
4{13,10}	C17H14ClN3O	311.8	312.2	2.36	100	Method B
4{13,11}	C17H13Cl2N3O	346.2	346.0	2.28	100	Method B
4{13,12}	C18H13ClF3N3O	379.8	382.2	6.08	100	Method D
4{13,13}	C17H14FN3O	295.3	296.1	2.21	100	Method B
4{13,14}	C17H14FN3O	295.3	296.1	2.99	100	Method B
4{13,15}	C17H14FN3O	295.3	296.2	2.18	100	Method B
4{13,16}	C17H13F2N3O	313.3	314.1	2.17	100	Method B
4{13,17}	C17H13F2N3O	313.3	314.1	2.25	100	Method B
4{13,18}	C17H13F2N3O	313.3	314.1	2.69	100	Method B
4{13,19}	C17H13F2N3O	313.3	314.1	2.41	100	Method B
4{13,2}	C18H16ClN3O	325.8	326.1	2.54	100	Method B
4{13,20}	C18H16FN3O2	325.3	326.2	2.13	100	Method B
4{13,21}	C18H17N3O	291.4	292.5	5.07	100	Method D
4{13,22}	C21H23N3O	333.4	335.3	6.00	92	Method D

4{13,23}	C21H23N3O	333.4	334.1	5.30	100	Method D
4{13,24}	C21H23N3O	333.4	335.4	6.03	100	Method D
4{13,25}	C18H14F3N3O	345.3	346.1	2.12	100	Method B
4{13,26}	C18H14F3N3O	345.3	346.2	5.67	100	Method D
4{13,27}	C18H14F3N3O	345.3	346.6	5.60	100	Method D
4{13,28}	C18H13F3N4O3	390.3	390.9	5.95	100	Method D
4{13,29}	C18H17N3O2	307.4	308.7	4.92	100	Method D
4{13,3}	C18H16ClN3O2	341.8	342.1	2.25	100	Method B
4{13,30}	C18H17N3O2	307.4	308.1	2.03	100	Method B
4{13,31}	C18H17N3O2	307.4	308.2	2.16	100	Method B
4{13,32}	C19H19N3O3	337.4	338.1	2.76	100	Method B
4{13,33}	C18H14F3N3O2	361.3	362.1	2.51	100	Method B
4{13,34}	C18H14F3N3O2	361.3	362.1	2.56	100	Method B
4{13,35}	C18H14F3N3O2	361.3	362.1	2.48	100	Method B
4{13,36}	C18H17N3OS	323.4	324.1	2.21	100	Method B
4{13,37}	C18H17N3OS	323.4	324.1	2.28	100	Method B
4{13,38}	C18H14F3N3OS	377.4	378.1	2.57	100	Method B
4{13,39}	C19H20N4O	320.4	321.0	4.48	100	Method D
4{13,4}	C19H19N3O	305.4	306.2	2.46	100	Method B
4{13,40}	C19H20N4O	320.4	321.0	3.92	95	Method D
4{13,41}	C17H14N4O3	322.3	323.2	5.03	95	Method D
4{13,42}	C17H14N4O3	322.3	322.8	5.08	100	Method D
4{13,43}	C17H15N3O2	293.3	294.2	4.03	100	Method D
4{13,44}	C17H16N4O	292.3	293.0	4.27	100	Method D
4{13,45}	C17H16N4O	292.3	293.0	4.95	100	Method D
4{13,46}	C19H17N3O2	319.4	320.2	2.00	100	Method B
4{13,47}	C19H17N3O3	335.4	336.1	2.19	100	Method B
4{13,48}	C19H17N3O3	335.4	336.1	2.16	100	Method B
4{13,49}	C18H16N4O2	320.4	320.9	4.72	100	Method D
4{13,5}	C18H17N3O	291.4	292.2	2.22	100	Method B
4{13,50}	C18H16N4O2	320.4	321.2	4.00	100	Method D
4{13,51}	C18H16N4O2	320.4	321.1	1.63	100	Method B
4{13,52}	C18H15N3O3	321.3	322.1	2.03	100	Method B
4{13,53}	C18H14FN3O3	339.3	340.1	3.03	100	Method B
4{13,54}	C18H15N3O4	337.3	338.1	1.84	100	Method B
4{13,55}	C16H14N4O	278.3	279.1	2.04	100	Method B
4{13,56}	C17H16N4O	292.3	293.2	0.45	100	Method C
4{13,57}	C20H16N4O	328.4	329.1	2.16	100	Method B
4{13,58}	C17H13N5OS	335.4	336.0	2.38	100	Method B
4{13,59}	C18H15N3O3	321.3	322.1	2.95	100	Method B
4{13,6}	C17H14ClN3O	311.8	312.0	5.08	100	Method D
4{13,60}	C18H15N5O	317.3	318.2	2.02	100	Method B
4{13,7}	C17H14ClN3O	311.8	312.2	2.35	100	Method B

4{13,8}	C17H13Cl2N3O	346.2	346.0	2.55	100	Method B
4{13,9}	C17H13Cl2N3O	346.2	346.1	5.80	100	Method D
4{14,1}	C13H12ClN3O2	277.7	278.1	2.25	100	Method B
4{14,2}	C13H12ClN3O	261.7	262.0	1.53	100	Method C
4{14,3}	C13H12ClN3O2	277.7	277.9	2.95	100	Method B
4{14,4}	C14H15N3O	241.3	242.1	1.67	100	Method C
4{15,1}	C13H12ClN3O2	277.7	278.1	2.58	100	Method B
4{15,2}	C13H12ClN3O	261.7	262.1	2.72	100	Method B
4{15,3}	C13H12ClN3O2	277.7	278.0	2.36	100	Method B
4{15,4}	C14H15N3O	241.3	242.1	2.05	100	Method C
4{16,1}	C13H12ClN3O2	277.7	278.1	2.25	100	Method B
4{16,2}	C13H12ClN3O	261.7	262.1	1.09	100	Method C
4{16,3}	C13H12ClN3O	261.7	261.9	1.10	100	Method A
4{16,3}	C13H12ClN3O2	277.7	278.0	0.84	100	Method C
4{16,4}	C14H15N3O	241.3	241.9	1.01	100	Method A
4{16,4}	C14H15N3O	241.3	242.1	1.01	100	Method C
4{16,5}	C13H13N3O	227.3	228.0	0.87	100	Method A
4{16,6}	C12H10ClN3O	247.7	247.7	0.95	100	Method A
4{16,7}	C12H10ClN3O	247.7	247.9	0.95	100	Method A
4{16,8}	C12H9Cl2N3O	282.1	281.7	1.16	100	Method A
4{17,1}	C14H14ClN3O2	291.7	292.1	2.54	100	Method B
4{17,2}	C14H14ClN3O2	291.7	292.0	1.54	100	Method A
4{17,3}	C14H14ClN3O	275.7	276.0	1.55	100	Method A
4{17,4}	C14H14ClN3O2	291.7	292.1	1.23	99	Method A
4{17,4}	C15H17N3O	255.3	256.2	1.59	100	Method C
4{17,7}	C13H12ClN3O	261.7	261.9	1.38	98	Method A
4{17,8}	C13H11Cl2N3O	296.2	296.0	1.70	96	Method A
4{18,1}	C15H13ClN4O2	316.7	317.0	2.46	100	Method B
4{18,2}	C15H13ClN4O	300.7	301.1	1.26	100	Method C
4{18,3}	C15H13ClN4O2	316.7	317.0	2.06	100	Method B
4{18,4}	C16H16N4O	280.3	281.1	1.10	100	Method C
4{19,1}	C11H11ClN4O2	266.7	267.1	2.00	100	Method B
4{19,2}	C11H11ClN4O	250.7	251.1	2.15	100	Method B
4{19,3}	C11H11ClN4O2	266.7	267.1	1.81	100	Method B
4{19,4}	C12H14N4O	230.3	231.1	2.04	100	Method B
4{19,5}	C11H12N4O	216.2	217.0	1.79	100	Method B
4{19,7}	C10H9ClN4O	236.7	237.0	1.93	100	Method B
4{19,8}	C10H8Cl2N4O	271.1	271.0	2.23	100	Method B
4{19,9}	C10H8Cl2N4O	271.1	271.1	2.06	100	Method B
4{20,1}	C11H10ClN3O2S	283.7	284.0	2.61	100	Method B
4{20,2}	C11H10ClN3OS	267.7	268.1	2.48	100	Method B
4{20,3}	C11H10ClN3O2S	283.7	284.0	2.03	100	Method B
4{20,4}	C12H13N3OS	247.3	248.1	1.61	100	Method C

[a] **Method A**: UPLC-MS (Acquity PDA detector, Acquity SQ detector and Acquity UPLC BEH-C18 column 1.7 μm, 2.1 × 50 mm [Waters]). Eluent solvent A: H_2O+0.1% formic acid, Eluent solvent B: Acetontrile. Gradient: 0-2.5 min, solvent B 10-95%; 2.5-2.9 min, solvent B 95%; 2.9-2.95 min, solvent B 95-10%. Flow rate: 0.6 mL/min.

Method B: UPLC-MS (Acquity PDA detector, Acquity SQ detector and Acquity UPLC BEH-C18 column 1.7 μm, 2.1 × 50 mm [Waters]). Eluent solvent A: H_2O+0.1% formic acid, Eluent solvent B: MeOH+0.1% formic acid. Gradient: 0-0.2 min, solvent B 0%; 0.2-2.8 min, solvent B 0-100%; 2.8-3.5 min, solvent B 100%; 3.5-3.7 min, solvent B 100-0%. Flow rate: 0.5 mL/min.

Method C: UPLC-MS (Acquity PDA detector, Acquity SQ detector and Acquity UPLC BEH-C18 column 1.7 μm, 2.1 × 50 mm [Waters]). Eluent solvent A: H_2O+0.1% formic acid, Eluent solvent B: MeOH+0.1% formic acid. Gradient: Gradient: 0-0.1 min, solvent B 20%; 0.1-1.3 min, solvent B 20-95%; 1.3-1.6 min, solvent B 95%; 1.6-1.8 min, solvent B 95-20%. Flow rate: 0.5 mL/min.

Method D: an HPLC-MS (photodiode array, total ion count, and expected mass [m/z]) was obtained (Alliance HT, Micromass ZQ 4000 and RP-C18 Xterra column 5 μm, 6 mm × 50 mm [Waters]). Eluent solvent A: H_2O+0.1% formic acid, Eluent solvent B: MeOH+0.1% formic acid. Gradient: 0-8 min, solvent B 5-100%; 8-9 min, solvent B 100%; 9-10 min solvent B 100-5%. Flow rate: 0.5 mL/min.

Table 2. Summary of diarylureas **4**{1-20, 1-9}.

Compound	EC_{50} (uM)[a]		PAMPA	uSol	Cytotoxicity LD_{50} (uM)[a]			
	3D7	K1	(Pe, 10^{-6}cm/s)	(uM)	BJ	HEK293	Hep G2	Raji
4{1,1}	>15	>15	0 ± 0	0.0 ± 0.0	>25	>25	>25	>25
4{1,2}	>15	>15	0 ± 0	0.1 ± 0.0	>25	>25	>25	>25
4{1,3}	>15	>15	20 ± 34	0.0 ± 0.0	>25	>25	>25	>25
4{1,4}	>15	>15	73 ± 126	0.3 ± 0.1	>25	>25	>25	>25
4{1,5}	>15	>15	16 ± 28	0.2 ± 0.0	>25	>25	>25	>25
4{1,8}	>15	>15	0 ± 0	0.0 ± 0.0	>25	>25	>25	>25
4{2,1}	>15	>15	0 ± 0	0.2 ± 0.0	>25	>25	>25	>25
4{2,2}	>15	>15	0 ± 0	0.1 ± 0.0	>25	>25	>25	>25
4{2,3}	>15	>15	364 ± 250	0.0 ± 0.0	>25	>25	>25	>25
4{2,4}	>15	>15	0 ± 0	0.3 ± 0.0	>25	>25	>25	>25
4{2,5}	>15	>15	29 ± 42	0.3 ± 0.2	>25	>25	>25	>25
4{2,6}	8.30 ± 0.82	>15	8 ± 15	0.0 ± 0.0	>25	>25	>25	>25
4{2,7}	10.34 ± 2.62	12.36 ± 0.58	0 ± 0	<0.33 ± 0.0	>25	24	22	23
4{3,1}	11.93 ± 1.08	12.23 ± 3.41	0 ± 0	0.1 ± 0.0	>25	>25	>25	>25
4{3,2}	7.45 ± 1.96	10.47 ± 3.71	0 ± 0	0.1 ± 0.1	>25	>25	>25	>25
4{3,3}	>15	>15	68 ± 66	<0.32 ± 0.0	>25	>25	>25	>25
4{3,4}	10.86 ± 3.59	7.69 ± 3.26	38 ± 33	0.3 ± 0.0	>25	>25	>25	3.26
4{3,5}	>15	>15	9 ± 16	0.2 ± 0.0	>25	>25	>25	>25
4{4,1}	10.93 ± 2.90	9.80 ± 5.21	0 ± 0	0.2 ± 0.0	>25	>25	>25	>25
4{4,2}	11.37 ± 2.11	10.72 ± 2.99	5 ± 6	0.0 ± 0.1	>25	>25	>25	>25
4{4,3}	>15	>15	0 ± 0	0.1 ± 0.0	>25	>25	>25	>25
4{4,4}	7.40 ± 2.44	12.58 ± 2.20	0 ± 0	0.1 ± 0.0	>25	>25	>25	>25
4{4,5}	12.86 ± 1.31	12.80 ± 1.44	0 ± 0	0.2 ± 0.0	>25	>25	>25	7
4{4,6}	5.86 ± 0.18	8.70 ± 4.89	0 ± 0	0.0 ± 0.0	>25	22	18	13
4{4,7}	10.19 ± 1.52	>15	0 ± 0	<0.32 ± 0.0	>25	26	26	16
4{5,2}	>15	>15	0 ± 0	0.1 ± 0.0	>25	>25	>25	>25
4{5,6}	5.99 ± 0.05	3.17	0 ± 0	0.5 ± 0.0	>25	>25	20	11
4{6,1}	9.43	9.14 ± 0.89	15 ± 26	0.0 ± 0.0	>25	>25	>25	14
4{6,2}	>15	>15	13 ± 23	0.2 ± 0.1	>25	>25	>25	>25
4{6,4}	>15	>15	11 ± 20	0.7 ± 0.0	>25	>25	>25	>25
4{6,6}	12.65 ± 0.65	13.40 ± 1.72	220 ± 112	1.0 ± 0.0	>25	>25	>25	15
4{6,7}	>15	>15	163 ± 64	0.7 ± 0.2	>25	>25	>25	>25
4{6,8}	>15	11.55 ± 3.34	9 ± 15	0.1 ± 0.2	>25	>25	>25	>25
4{7,1}	12.22 ± 1.13	13.12 ± 0.85	0 ± 0	0.1 ± 0.0	>25	>25	>25	>25
4{7,2}	>15	>15	53 ± 54	0.1 ± 0.1	>25	>25	>25	>25
4{7,3}	11.00 ± 0.39	12.52 ± 0.33	0 ± 0	0.0 ± 0.0	>25	>25	>25	14
4{7,5}	>15	>15	43 ± 51	0.2 ± 0.0	>25	>25	>25	>25
4{7,8}	>15	>15	17 ± 29	0.0 ± 0.0	>25	>25	>25	>25

4{8,1}	>15	>15	59 ± 103	0.1 ± 0.0	>25	>25	>25	>25
4{8,2}	>15	>15	0 ± 0	0.3 ± 0.0	>25	>25	>25	>25
4{8,3}	>15	>15	107 ± 151	0.1 ± 0.0	>25	>25	>25	>25
4{8,4}	>15	>15	300 ± 339	0.4 ± 0.1	>25	>25	>25	>25
4{9,1}	11.22 ± 2.30	12.27 ± 1.93	3 ± 4	0.1 ± 0.0	>25	>25	>25	>25
4{9,2}	>15	>15	0 ± 0	0.1 ± 0.1	>25	>25	>25	>25
4{9,3}	>15	>15	24 ± 41	0.0 ± 0.0	>25	>25	>25	>25
4{9,4}	>15	>15	0 ± 0	0.0 ± 0.0	>25	>25	>25	>25
4{9,5}	>15	>15	0 ± 0	0.2 ± 0.0	>25	>25	>25	>25
4{9,6}	10.05 ± 6.43	7.70 ± 4.53	0 ± 0	0.0 ± 0.0	>25	19	18	>25
4{9,7}	>15	9.97	2 ± 2	0.1 ± 0.0	>25	>25	>25	>25
4{10,1}	13.82 ± 0.48	14.19	103 ± 121	0.1 ± 0.1	>25	>25	>25	>25
4{10,2}	>15	>15	0 ± 0	0.1 ± 0.0	>25	>25	>25	>25
4{10,3}	>15	13.33	318 ± 107	<0.31 ± 0.0	>25	>25	>25	>25
4{10,4}	>15	>15	213 ± 217	0.1 ± 0.0	>25	>25	>25	17
4{11,1}	>15	>15	270 ± 81	0.0 ± 0.0	>25	>25	>25	>25
4{11,2}	>15	>15	309 ± 269	0.2 ± 0.1	>25	>25	>25	>25
4{11,3}	>15	>15	545 ± 256	0.1 ± 0.0	>25	>25	>25	>25
4{11,4}	>15	>15	701 ± 111	0.3 ± 0.2	>25	>25	>25	>25
4{11,5}	6.02 ± 1.95	11.01 ± 2.51	451 ± 31	0.7 ± 0.1	>25	>25	>25	>25
4{11,6}	>15	>15	197 ± 95	0.1 ± 0.0	>25	>25	>25	>25
4{11,7}	>15	12.62	670 ± 693	0.2 ± 0.1	>25	>25	>25	>25
4{11,8}	>15	>15	154 ± 135	0.2 ± 0.0	>25	>25	>25	>25
4{12,1}	>15	>15	12 ± 21	0.3 ± 0.1	>25	>25	>25	>25
4{12,2}	>15	>15	19 ± 23	0.3 ± 0.0	>25	>25	>25	>25
4{12,3}	>15	>15	139 ± 24	3.2 ± 0.2	>25	>25	>25	>25
4{12,4}	>15	>15	73 ± 65	1.7 ± 0.1	>25	>25	>25	>25
4{13,1}	0.05 ± 0.02	0.39 ± 0.13	337 ± 131	0.3 ± 0.1	>25	>25	>25	>25
4{13,2}	0.22 ± 0.09	1.57 ± 0.72	262 ± 161	0.3 ± 0.0	>25	>25	>25	>25
4{13,3}	1.22 ± 0.83	3.12 ± 0.12	336 ± 44	0.4 ± 0.0	23	26	>25	>25
4{13,4}	2.69 ±	6.71 ± 1.38	535 ± 34	3.3 ± 0.2	>25	16	17	>25
4{13,5}	4.38 ± 1.31	6.90 ± 2.17	669 ± 144	1.3 ± 0.1	>25	>25	>25	>25
4{13,7}	0.60 ± 0.55	>15	566 ± 170	0.8 ± 0.0	>25	21	19	18
4{13,8}	0.90 ± 0.36	2.05 ± 0.82	197 ± 56	0.3 ± 0.1	23	>25	17	10
4{13,9}	1.05 ± 0.36	4.24 ± 0.11	6 ± 6	0.1 ± 0.0	20	10	16	>25
4{14,1}	>15	>15	0 ± 0	0.2 ± 0.1	>25	>25	>25	>25
4{14,2}	>15	>15	0 ± 0	0.4 ± 0.1	>25	>25	>25	>25
4{14,3}	>15	>15	405 ± 158	2.0 ± 0.1	>25	>25	>25	>25
4{14,4}	>15	>15	193 ± 30	2.3 ± 0.2	>25	>25	>25	>25
4{15,1}	>15	>15	394 ± 102	2.3 ± 0.2	>25	>25	>25	>25
4{15,2}	>15	>15	1017 ± 200	22.2 ± 1.4	>25	>25	>25	>25
4{15,3}	>15	>15	396 ± 53	61.3 ± 1.6	>25	>25	>25	>25
4{15,4}	>15	>15	646 ± 43	62.1 ± 4.0	>25	>25	>25	>25
4{16,1}	8.87 ± 2.59	11.70 ± 3.00	314 ± 79	0.8 ± 0.1	>25	>25	>25	>25
4{16,2}	7.84 ± 5.84	15.48 ± 1.96	118 ± 24	3.8 ± 0.1	>25	>25	>25	>25
4{16,3}	>15	10.51 ± 2.94	78 ± 15	22.4 ± 6.0	>25	>25	>25	13
4{16,4}	>15	>15	722 ± 280	58.4 ± 3.5	>25	>25	>25	>25
4{16,6}	>15	>15	334 ± 67	55.1 ± 9.3	>25	>25	>25	>25
4{16,6}	8.07 ± 0.50	>15	273 ± 64	55.7 ± 3.5	>25	>25	>25	>25
4{16,7}	>15	>15	397 ± 41	48.7 ± 15.5	>25	>25	>25	>25
4{16,8}	3.38 ± 0.78	10.22	74 ± 37	0.4 ± 0.0	>25	>25	>25	>25

4{17,1}	>15	>15	51 ± 89	0.3 ± 0.1	>25	>25	>25	>25
4{17,3}	8.54 ± 2.83	10.58 ± 5.20	26 ± 33	0.7 ± 0.1	>25	>25	>25	>25
4{17,4}	>15	>15	236 ± 27	2.1 ± 0.0	>25	>25	>25	>25
4{17,4}	>15	>15	897 ± 221	4.1 ± 0.1	>25	>25	>25	>25
4{17,7}	>15	>15	525 ± 156	1.7 ± 0.2	>25	>25	>25	>25
4{17,8}	>15	>15	24 ± 42	1.2 ± 0.6	>25	>25	>25	>25
4{18,1}	11.23 ± 3.19	>15	242 ± 58	2.1 ± 0.1	>25	>25	>25	>25
4{18,2}	13.78 ± 0.20	12.13	185 ± 52	0.7 ± 0.0	>25	>25	>25	20
4{18,3}	13.26 ± 0.55	11.92	146 ± 19	1.2 ± 0.3	>25	>25	>25	>25
4{18,4}	13.46 ± 0.95	14.19 ± 2.06	60 ± 54	0.0 ± 0.0	>25	>25	>25	19
4{19,1}	>15	>15	465 ± 70	6.0 ± 0.2	>25	>25	>25	>25
4{19,2}	10.32 ± 1.87	>15	1565 ± 321	14.5 ± 1.1	>25	>25	>25	>25
4{19,3}	>15	>15	820 ± 111	42.4 ± 0.3	>25	>25	>25	>25
4{19,4}	>15	>15	1032 ± 63	27.6 ± 3.1	>25	>25	>25	>25
4{19,5}	>15	>15	588 ± 70	49.6 ± 1.8	>25	>25	>25	>25
4{19,7}	>15	>15	129 ± 167	<0.42 ± 0.0	>25	>25	>25	>25
4{19,8}	>15	>15	381 ± 84	51.2 ± 1.8	>25	>25	>25	>25
4{19,9}	>15	>15	401 ±	3.4 ± 0.2	>25	>25	>25	>25
4{20,1}	>15	>15	17 ± 30	0.5 ± 0.0	>25	>25	>25	>25
4{20,2}	>15	14.46	643 ± 280	2.4 ± 0.4	>25	>25	>25	>25
4{20,3}	>15	>15	544 ± 40	27.5 ± 3.0	>25	>25	>25	>25
4{20,4}	>15	>15	701 ± 165	0.2 ± 0.0	>25	>25	>25	>25

[a] Values are means of two independent experiments done in triplicate.

Table 3. Summary of 4-aminoquinaldine-derived diaryl ureas **4**{13, 1-60}

Compound	R2 (B ring)	EC_{50}/uM[a]		Permeability (Pe, 10-6cm/s)	Solubility (uM)	Cytotoxicity LD_{50} (uM)[a]			
		3D7	K1			BJ	HEK 293	HepG 2	Raji
4{13,1}	3-Cl-6-OMe-phenyl	0.053 ± 0.02	0.39 ± 0.13	337 ± 131	0.3 ± 0.1	>25	>25	>25	>25
4{13,2}	3-Cl-4-Me-phenyl	0.22 ± 0.09	1.57 ± 0.72	262 ± 161	0.3 ± 0.0	>25	>25	>25	>25
4{13,3}	3-Cl-4-OMe-phenyl	1.22 ± 0.83	3.12 ± 0.12	336 ± 44	0.4 ± 0.0	23	26	>25	>25
4{13,4}	4-Et-phenyl	2.69	6.71 ± 1.38	535 ± 34	3.3 ± 0.2	>25	16	17	>25
4{13,5}	4-Me-phenyl	4.38 ± 1.31	6.90 ± 2.17	669 ± 144	1.3 ± 0.1	>25	>25	>25	>25
4{13,7}	3-Cl-phenyl	0.60 ± 0.55	>15	566 ± 170	0.8 ± 0.0	>25	21	19	18
4{13,8}	3,4-Cl_2 phenyl	0.90 ± 0.36	2.05 ± 0.82	197 ± 56	0.3 ± 0.1	23	>25	17	10
4{13,9}	2,4-Cl_2 phenyl	1.05 ± 0.36	4.24 ± 0.11	6 ± 6	0.1 ± 0.0	20	10	16	>25
4{13,10}	4-Cl-phenyl	2.76 ± 1.81	6.80 ± 0.54	537 ± 53	1.4 ± 0.1	>25	>25	>25	>25
4{13,11}	3,5-Cl_2-phenyl	2.07	6.17	0 ± 0	0.8 ± 0.1	>25	>25	>25	>25
4{13,12}	4-Cl-3-CF_3-phenyl	0.47 ± 0.49	2.76 ± 0.91	63 ± 20	1.3 ± 0.1	25	>25	>25	>25
4{13,13}	2-F-phenyl	1.89 ± 1.42	0.69	817 ± 75	3.8 ± 0.2	>25	>25	>25	>25
4{13,14}	3-F-phenyl	2.43 ± 2.57	>15	0 ± 1	0.1 ± 0.0	>25	>25	>25	>25
4{13,15}	4-F-phenyl	2.19 ± 1.74	4.72 ± 0.09	801 ± 166	3.7 ± 0.0	>25	>25	>25	>25
4{13,16}	2,4-F_2-phenyl	0.94 ± 0.21	4.95 ± 1.59	640 ± 121	3.0 ± 0.2	20	10	17	>25
4{13,17}	2,5-F_2-phenyl	0.69 ± 0.17	1.64 ± 0.03	541 ± 120	0.5 ± 0.2	7	12	>25	>25
4{13,18}	3,4-F_2-phenyl	1.30 ± 0.93	3.66 ± 1.84	478 ± 237	0.5 ± 0.3	>25	>25	21	>25
4{13,19}	3,5-F2-phenyl	3.37 ± 1.46	1.89	0 ± 0	0.3 ± 0.0	>25	>25	>25	>25
4{13,20}	3-F-4-OMe-phenyl	2.37 ± 1.58	4.62 ± 1.49	50 ± 24	2.7 ± 0.2	26	>25	>25	>25
4{13,21}	3-Me-phenyl	2.15 ± 0.04	10.05 ± 1.15	4 ± 3	0.3 ± 0.0	>25	>25	>25	>25
4{13,22}	2-tBu-phenyl	1.54 ± 0.21	3.00 ± 0.57	27 ± 25	0.1 ± 0.0	22	>25	>25	>25
4{13,23}	3-tBu-phenyl	>15	>15	555 ± 40	34.7 ± 0.0	>25	>25	>25	>25
4{13,24}	4-tBu-phenyl	2.03 ± 0.02	3.34 ± 0.37	142 ±	6.2 ± 0.0	20	>25	17	>25
4{13,25}	2-CF_3-phenyl	>15	>15	945 ± 54	3.8 ± 0.3	>25	>25	>25	>25
4{13,26}	3-CF_3-phenyl	0.32	>15	0 ± 0	0.1 ± 0.0	>25	16	21	10
4{13,27}	4-CF_3-phenyl	1.49 ± 0.76	2.61 ± 0.64	2 ± 2	0.1 ± 0.0	>25	25	23	23
4{13,28}	3-CF_3-4-NO_2-phenyl	1.97	>15	45 ± 39	0.0 ± 0.0	>25	>25	>25	>25
4{13,29}	2-OMe-phenyl	2.05 ± 1.01	6.90 ± 1.16	0 ± 0	0.1 ± 0.0	>25	>25	>25	>25
4{13,30}	3-OMe-phenyl	2.01 ± 1.17	4.74 ± 1.50	818 ± 125	1.2 ± 0.1	27	>25	>25	>25
4{13,31}	4-OMe-phenyl	5.38 ± 1.76	6.84 ± 0.16	787 ± 61	19.8 ± 0.9	>25	>25	>25	>25
4{13,32}	3,4-$(OMe)_2$-phenyl	5.67 ± 0.61	7.04 ± 0.80	552 ± 46	4.1 ± 0.3	>25	>25	>25	>25
4{13,33}	2-OCF_3-phenyl	3.41 ± 2.37	5.00 ± 1.73	1107 ± 227	4.6 ± 0.3	>25	>25	>25	>25
4{13,34}	3-OCF_3-phenyl	1.04 ± 1.00	2.75 ± 0.83	464 ± 73	0.6 ± 0.0	25	22	13	9
4{13,35}	4-OCF_3-phenyl	2.63 ± 1.19	4.85 ± 0.95	531 ± 98	0.3 ± 0.0	25	14	15	10
4{13,36}	2-SMe-phenyl	6.10 ± 1.06	7.31 ± 1.03	1259 ± 266	21.0 ± 1.1	>25	>25	>25	>25
4{13,37}	4-SMe-phenyl	3.13 ± 1.77	6.98 ± 0.65	473 ± 47	1.3 ± 0.1	>25	24	16	>25
4{13,38}	4-SCF_3-phenyl	2.86 ± 2.76	4.33 ± 1.90	206 ± 50	0.2 ± 0.0	>25	13	20	10
4{13,39}	3-NMe_2-phenyl	0.031 ± 0.02	0.11 ± 0.09	0 ± 0	0.0 ± 0.0	>25	>25	>25	>25
4{13,40}	4-NMe_2-phenyl	5.61 ± 0.39	7.80 ± 2.47	2 ± 2	0.0 ± 0.0	>25	>25	>25	>25
4{13,41}	2-NO_2-phenyl	1.81 ± 2.24	6.59	204 ± 55	0.2 ± 0.0	>25	>25	>25	>25
4{13,42}	3-NO_2-phenyl	2.54 ± 1.80	>15	42 ± 38	0.0 ± 0.0	>25	>25	>25	>25
4{13,43}	4-OH-phenyl	>15	>15	3 ± 6	0.1 ± 0.0	>25	>25	>25	>25
4{13,44}	2-NH_2-phenyl	>15	>15	300 ± 168	51.8 ± 3.4	>25	>25	>25	>25
4{13,45}	4-NH_2-phenyl	10.16	8.78	530 ± 27	18.5 ± 0.6	>25	>25	>25	>25
4{13,46}	4-COMe-phenyl	4.42 ± 0.12	6.77 ± 0.66	473 ± 93	3.8 ± 1.6	22	>25	19	>25

4{13,47}	3-COOMe-phenyl	>15	8.17 ± 1.35	746 ± 231	0.6 ± 0.0	21	26	23	26
4{13,48}	4-COOMe-phenyl	7.18 ± 1.27	6.16 ± 0.18	448 ± 46	1.2 ± 0.0	21	15	20	17
4{13,49}	2-$CONH_2$-phenyl	>15	>15	0 ± 0	0.2 ± 0.0	>25	>25	>25	>25
4{13,50}	3-$CONH_2$-phenyl	13.13 ± 0.54	>15	2 ± 3	0.1 ± 0.0	>25	>25	>25	>25
4{13,51}	4-$CONH_2$-phenyl	10.73 ± 1.66	5.48 ± 1.82	0 ± 0	0.9 ± 0.0	>25	>25	>25	>25
4{13,52}	4-COOH-phenyl	>15	>15	0 ± 0	9.3 ± 1.9	>25	>25	>25	>25
4{13,53}	2-COOH-4-F-phenyl	>15	>15	5 ± 1	44.3 ± 3.0	>25	>25	>25	>25
4{13,54}	3-OH-4-COOH-phenyl	>15	>15	0 ± 0	26.6 ± 1.7	>25	>25	>25	>25
4{13,55}	pyridin-3-yl	3.42 ± 1.08	6.20 ± 4.28	63 ± 6	0.0 ± 0.9	>25	>25	>25	>25
4{13,56}	3-Me-pyridin-2-yl	>15	>15	369 ± 49	1.3 ± 0.0	>25	>25	>25	>25
4{13,57}	quinolin-3-yl	2.95 ± 1.54	6.021 ± 3.04	46 ± 1	0.4 ± 0.0	>25	>25	>25	>25
4{13,58}	benzisothiadiazol-4-yl	0.016 ± 0.01	0.08	155 ± 36	0.3 ± 0.0	>25	>25	>25	>25
4{13,59}	benzodioxol-5-yl	5.08 ± 3.53	10.10 ± 2.35	266 ± 124	1.6 ± 0.1	>25	>25	>25	>25
4{13,60}	benzimidazol-5-yl	1.09 ± 0.27	1.70 ± 0.31	2 ± 3	7.3 ± 0.0	>25	>25	>25	>25

[a] Values are means of two independent experiments done in triplicate.

Table 4. Inhibition summary of diarylurea **4**{13, 34}in competition kinase binding assay.

Ambit Gene Symbol	Entrez Gene Symbol	%ctrl[a]
AAK1	AAK1	100
ABL1	ABL1	100
ABL1(E255K)	ABL1	100
ABL1(F317I)	ABL1	100
ABL1(F317L)	ABL1	100
ABL1(H396P)	ABL1	100
ABL1(M351T)	ABL1	100
ABL1(Q252H)	ABL1	100
ABL1(T315I)	ABL1	100
ABL1(Y253F)	ABL1	100
ABL2	ABL2	100
ACVR1	ACVR1	100
ACVR1B	ACVR1B	100
ACVR2A	ACVR2A	100
ACVR2B	ACVR2B	100
ACVRL1	ACVRL1	100
ADCK3	CABC1	100
ADCK4	ADCK4	100
AKT1	AKT1	100
AKT2	AKT2	100
AKT3	AKT3	100
ALK	ALK	99
AMPK-alpha1	PRKAA1	100
AMPK-alpha2	PRKAA2	100
ANKK1	ANKK1	100
ARK5	NUAK1	100
ASK1	MAP3K5	100
ASK2	MAP3K6	100
AURKA	AURKA	100
AURKB	AURKB	92
AURKC	AURKC	88
AXL	AXL	100
BIKE	BMP2K	100
BLK	BLK	99
BMPR1A	BMPR1A	100
BMPR1B	BMPR1B	97
BMPR2	BMPR2	100
BMX	BMX	100
BRAF	BRAF	99
BRAF(V600E)	BRAF	100
BRK	PTK6	100
BRSK1	BRSK1	100
BRSK2	BRSK2	100
BTK	BTK	100
CAMK1	CAMK1	100
CAMK1D	CAMK1D	100
CAMK1G	CAMK1G	100
CAMK2A	CAMK2A	100

Ambit Gene Symbol	Entrez Gene Symbol	%ctrl[a]
MAP3K1	MAP3K1	100
MAP3K15	MAP3K15	100
MAP3K2	MAP3K2	100
MAP3K3	MAP3K3	100
MAP3K4	MAP3K4	100
MAP4K2	MAP4K2	100
MAP4K3	MAP4K3	100
MAP4K4	MAP4K4	99
MAP4K5	MAP4K5	100
MAPKAPK2	MAPKAPK2	96
MAPKAPK5	MAPKAPK5	100
MARK1	MARK1	100
MARK2	MARK2	100
MARK3	MARK3	100
MARK4	MARK4	100
MAST1	MAST1	96
MEK1	MAP2K1	100
MEK2	MAP2K2	100
MEK3	MAP2K3	100
MEK4	MAP2K4	100
MEK6	MAP2K6	98
MELK	MELK	94
MERTK	MERTK	100
MET	MET	100
MET(M1250T)	MET	100
MET(Y1235D)	MET	86
MINK	MINK1	100
MKNK1	MKNK1	100
MKNK2	MKNK2	100
MLCK	MLCK	99
MLK1	MAP3K9	100
MLK2	MAP3K10	100
MLK3	MAP3K11	100
MRCKA	CDC42BPA	100
MRCKB	CDC42BPB	100
MST1	STK4	100
MST1R	MST1R	90
MST2	STK3	100
MST3	STK24	100
MST4	MST4	100
MUSK	MUSK	98
MYLK	MYLK	100
MYLK2	MYLK2	100
MYO3A	MYO3A	100
MYO3B	MYO3B	95
NDR1	STK38	100
NDR2	STK38L	100
NEK1	NEK1	100

CAMK2B	CAMK2B	100
CAMK2D	CAMK2D	100
CAMK2G	CAMK2G	100
CAMK4	CAMK4	100
CAMKK1	CAMKK1	100
CAMKK2	CAMKK2	100
CDC2L1	CDC2L1	86
CDC2L2	CDC2L2	91
CDK11	CDC2L6	100
CDK2	CDK2	100
CDK3	CDK3	95
CDK5	CDK5	100
CDK7	CDK7	100
CDK8	CDK8	100
CDK9	CDK9	98
CDKL2	CDKL2	87
CDKL3	CDKL3	100
CDKL5	CDKL5	69
CHEK1	CHEK1	100
CHEK2	CHEK2	100
CIT	CIT	82
CLK1	CLK1	93
CLK2	CLK2	100
CLK3	CLK3	91
CLK4	CLK4	98
CSF1R	CSF1R	100
CSK	CSK	100
CSNK1A1L	CSNK1A1L	100
CSNK1D	CSNK1D	96
CSNK1E	CSNK1E	100
CSNK1G1	CSNK1G1	100
CSNK1G2	CSNK1G2	100
CSNK1G3	CSNK1G3	98
CSNK2A1	CSNK2A1	100
CSNK2A2	CSNK2A2	100
CTK	MATK	100
DAPK1	DAPK1	100
DAPK2	DAPK2	100
DAPK3	DAPK3	100
DCAMKL1	DCLK1	100
DCAMKL2	DCLK2	93
DCAMKL3	DCLK3	100
DDR1	DDR1	0.3
DDR2	DDR2	84
DLK	MAP3K12	96
DMPK	DMPK	100
DMPK2	CDC42BPG	100
DRAK1	STK17A	73
DRAK2	STK17B	85
DYRK1A	DYRK1A	100
DYRK1B	DYRK1B	99
DYRK2	DYRK2	100
EGFR	EGFR	100

NEK2	NEK2	100
NEK5	NEK5	99
NEK6	NEK6	100
NEK7	NEK7	100
NEK9	NEK9	100
NIM1	MGC42105	100
NLK	NLK	100
OSR1	OXSR1	100
p38-alpha	MAPK14	100
p38-beta	MAPK11	100
p38-delta	MAPK13	79
p38-gamma	MAPK12	100
PAK1	PAK1	100
PAK2	PAK2	100
PAK3	PAK3	100
PAK4	PAK4	100
PAK6	PAK6	100
PAK7	PAK7	100
PCTK1	PCTK1	100
PCTK2	PCTK2	96
PCTK3	PCTK3	99
PDGFRA	PDGFRA	97
PDGFRB	PDGFRB	71
PDPK1	PDPK1	100
PFTAIRE2	PFTK2	100
PFTK1	PFTK1	79
PHKG1	PHKG1	92
PHKG2	PHKG2	100
PIK3C2B	PIK3C2B	100
PIK3C2G	PIK3C2G	100
PIK3CA	PIK3CA	100
PIK3CA(C420R)	PIK3CA	100
PIK3CA(E542K)	PIK3CA	100
PIK3CA(E545A)	PIK3CA	99
PIK3CA(E545K)	PIK3CA	100
PIK3CA(H1047L)	PIK3CA	100
PIK3CA(H1047Y)	PIK3CA	100
PIK3CA(M1043I)	PIK3CA	100
PIK3CA(Q546K)	PIK3CA	100
PIK3CB	PIK3CB	79
PIK3CD	PIK3CD	97
PIK3CG	PIK3CG	100
PIK4CB	PI4KB	91
PIM1	PIM1	100
PIM2	PIM2	100
PIM3	PIM3	100
PIP5K1A	PIP5K1A	100
PIP5K2B	PIP4K2B	78
PKAC-alpha	PRKACA	100
PKAC-beta	PRKACB	100
PKMYT1	PKMYT1	100
PKN1	PKN1	100
PKN2	PKN2	100

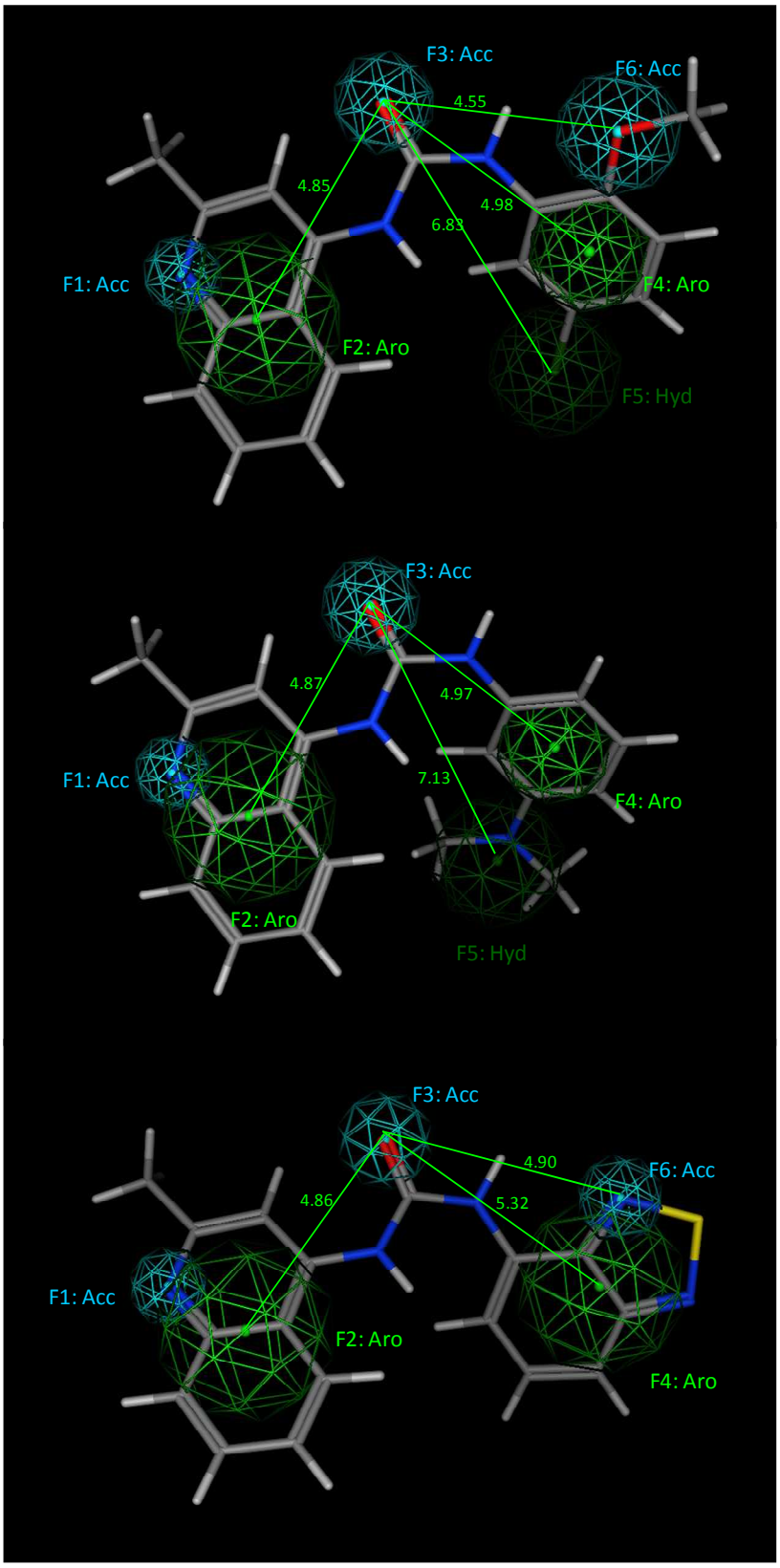
EGFR(E746-A750del)	EGFR	93	PLK1	PLK1	100
EGFR(G719C)	EGFR	89	PLK2	PLK2	100
EGFR(G719S)	EGFR	99	PLK3	PLK3	100
EGFR(L747-E749del, A750P)	EGFR	100	PLK4	PLK4	88
EGFR(L747-S752del, P753S)	EGFR	100	PRKCD	PRKCD	100
EGFR(L747-T751del,Sins)	EGFR	95	PRKCE	PRKCE	100
EGFR(L858R)	EGFR	100	PRKCH	PRKCH	100
EGFR(L858R,T790M)	EGFR	100	PRKCQ	PRKCQ	100
EGFR(L861Q)	EGFR	100	PRKD1	PRKD1	100
EGFR(S752-I759del)	EGFR	84	PRKD2	PRKD2	100
EPHA1	EPHA1	100	PRKD3	PRKD3	100
EPHA2	EPHA2	100	PRKG1	PRKG1	94
EPHA3	EPHA3	100	PRKG2	PRKG2	100
EPHA4	EPHA4	100	PRKR	EIF2AK2	100
EPHA5	EPHA5	100	PRKX	PRKX	97
EPHA6	EPHA6	38	PRP4	PRPF4B	100
EPHA7	EPHA7	79	PYK2	PTK2B	100
EPHA8	EPHA8	99	QSK	KIAA0999	100
EPHB1	EPHB1	100	RAF1	RAF1	100
EPHB2	EPHB2	94	RET	RET	100
EPHB3	EPHB3	88	RET(M918T)	RET	100
EPHB4	EPHB4	85	RET(V804L)	RET	100
EPHB6	EPHB6	100	RET(V804M)	RET	95
ERBB2	ERBB2	100	RIOK1	RIOK1	98
ERBB3	ERBB3	100	RIOK2	RIOK2	100
ERBB4	ERBB4	100	RIOK3	RIOK3	100
ERK1	MAPK3	100	RIPK1	RIPK1	100
ERK2	MAPK1	100	RIPK2	RIPK2	96
ERK3	MAPK6	100	RIPK4	RIPK4	81
ERK4	MAPK4	98	ROCK1	ROCK1	100
ERK5	MAPk7	92	ROCK2	ROCK2	100
ERK8	MAPK15	100	ROS1	ROS1	100
ERN1	ERN1	100	RPS6KA1(Kin.Dom.1-N-terminal)	RPS6KA1	90
FAK	PTK2	99	RPS6KA1(Kin.Dom.2-C-terminal)	RPS6KA1	100
FER	FER	100	RPS6KA2(Kin.Dom.1-N-terminal)	RPS6KA2	100
FES	FES	100	RPS6KA2(Kin.Dom.2-C-terminal)	RPS6KA2	100
FGFR1	FGFR1	100	RPS6KA3(Kin.Dom.1-N-terminal)	RPS6KA3	100
FGFR2	FGFR2	100	RPS6KA4(Kin.Dom.1-N-terminal)	RPS6KA4	100
FGFR3	FGFR3	100	RPS6KA4(Kin.Dom.2-C-terminal)	RPS6KA4	98
FGFR3(G697C)	FGFR3	100	RPS6KA5(Kin.Dom.1-N-terminal)	RPS6KA5	100
FGFR4	FGFR4	100	RPS6KA5(Kin.Dom.2-C-terminal)	RPS6KA5	100
FGR	FGR	100	RPS6KA6(Kin.Dom.1-N-terminal)	RPS6KA6	98
FLT1	FLT1	100	RPS6KA6(Kin.Dom.2-C-terminal)	RPS6KA6	100
FLT3	FLT3	92	SBK1	SBK1	100
FLT3(D835H)	FLT3	91	SgK085	LOC340156	95
FLT3(D835Y)	FLT3	84	SgK110	SgK110	98
FLT3(ITD)	FLT3	100	SIK	SNF1LK	98
FLT3(K663Q)	FLT3	80	SIK2	SNF1LK2	100
FLT3(N841I)	FLT3	86	SLK	SLK	100
FLT4	FLT4	100	SNARK	NUAK2	100
FRK	FRK	97	SRC	SRC	100
FYN	FYN	100	SRMS	SRMS	94
GAK	GAK	100	SRPK1	SRPK1	100

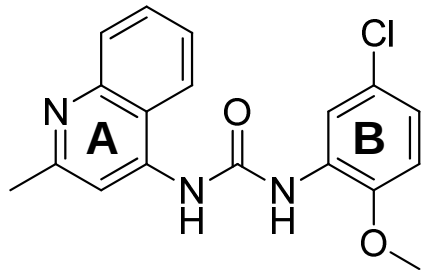
GCN2(Kin.Dom.2,S808G)	EIF2AK4	100	SRPK2	SRPK2	93
GRK1	GRK1	100	SRPK3	SRPK3	87
GRK4	GRK4	85	STK16	STK16	100
GRK7	GRK7	100	STK33	STK33	92
GSK3A	GSK3A	100	STK35	STK35	100
GSK3B	GSK3B	100	STK36	STK36	100
HCK	HCK	100	STK39	STK39	84
HIPK1	HIPK1	100	SYK	SYK	100
HIPK2	HIPK2	100	TAK1	MAP3K7	100
HIPK3	HIPK3	100	TAO1	TAOK2	100
HIPK4	HIPK4	100	TAOK1	TAOK1	100
HPK1	MAP4K1	100	TAOK3	TAOK3	100
HUNK	HUNK	100	TBK1	TBK1	100
ICK	ICK	95	TEC	TEC	97
IGF1R	IGF1R	98	TESK1	TESK1	100
IKK-alpha	CHUK	100	TGFBR1	TGFBR1	100
IKK-beta	IKBKB	81	TGFBR2	TGFBR2	100
IKK-epsilon	IKBKE	100	TIE1	TIE1	100
INSR	INSR	99	TIE2	TEK	100
INSRR	INSRR	100	TLK1	TLK1	100
IRAK1	IRAK1	47	TLK2	TLK2	100
IRAK3	IRAK3	100	TNIK	TNIK	100
ITK	ITK	100	TNK1	TNK1	100
JAK1(JH1domain-catalytic)	JAK1	100	TNK2	TNK2	100
JAK1(JH2domain-pseudokinase)	JAK1	94	TNNI3K	TNNI3K	100
JAK2(JH1domain-catalytic)	JAK2	100	TRKA	NTRK1	100
JAK3(JH1domain-catalytic)	JAK3	100	TRKB	NTRK2	100
JNK1	MAPK8	87	TRKC	NTRK3	100
JNK2	MAPK9	100	TSSK1B	TSSK1B	100
JNK3	MAPK10	100	TTK	TTK	92
KIT	KIT	88	TXK	TXK	100
KIT(D816V)	KIT	100	TYK2(JH1domain-catalytic)	TYK2	97
KIT(L576P)	KIT	96	TYK2(JH2domain-pseudokinase)	TYK2	100
KIT(V559D)	KIT	87	TYRO3	TYRO3	91
KIT(V559D,T670I)	KIT	96	ULK1	ULK1	100
KIT(V559D,V654A)	KIT	98	ULK2	ULK2	100
LATS1	LATS1	86	ULK3	ULK3	100
LATS2	LATS2	100	VEGFR2	KDR	100
LCK	LCK	100	WEE1	WEE1	100
LIMK1	LIMK1	100	WEE2	WEE1B	100
LIMK2	LIMK2	100	YANK2	STK32B	100
LKB1	STK11	100	YANK3	STK32C	100
LOK	STK10	94	YES	YES1	100
LTK	LTK	100	YSK1	STK25	100
LYN	LYN	100	YSK4	YSK4	84
LZK	MAP3K13	100	ZAK	ZAK	100
MAK	MAK	62	ZAP70	ZAP70	100

[a] The compound was screened at 10 μM, and results for screen binding interactions were reported as "% ctrl", where lower numbers indicated stronger hits.

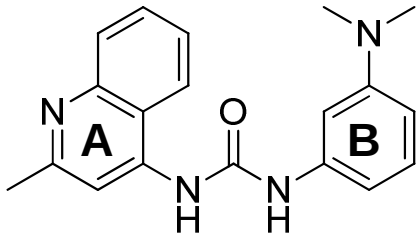
% Ctrl = 100 x (test compound signal - positive control signal)/(negative control signal – positive control signal)

Figure 1. Pharmacophore mapping of **4**{13, 1}, **4**{13, 39} and **4**{13, 58}. Pharmacophore features are color coded with green for aromatic feature (Aro), cyan for hydrogen-bond acceptor feature (Acc), and dark green for hydrophobic feature (Hyd).

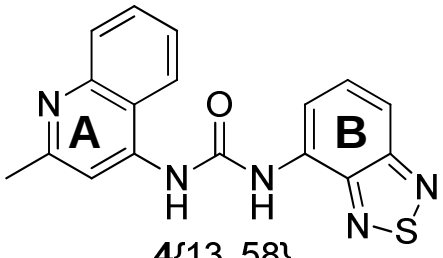




4{13, 1}

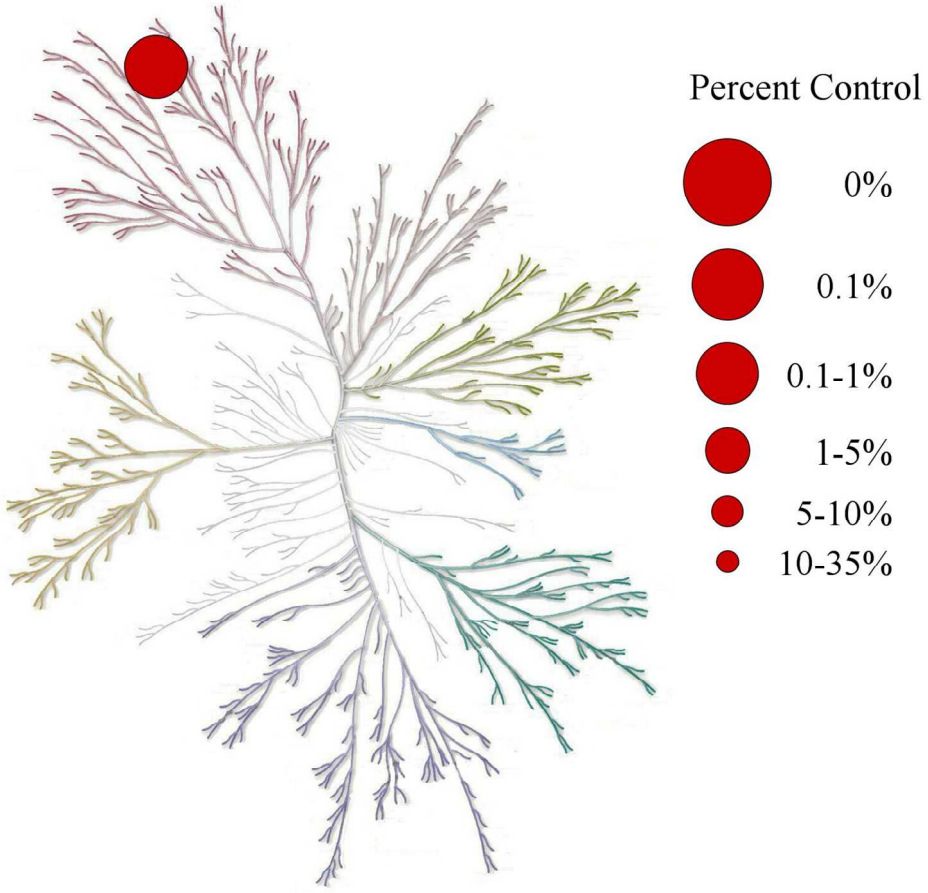


4{13, 39}



4{13, 58}

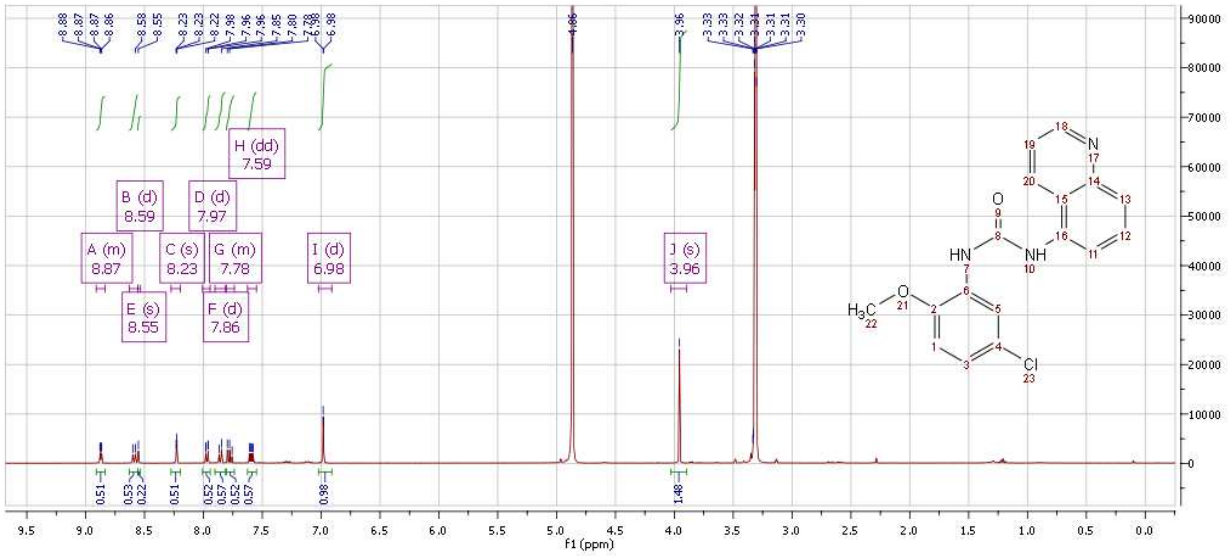
Figure 2. Treespot™ interaction maps for **4**{13, 34} in human kinases. Kinases found to bind are marked with red circles, where larger circles indicate higher-affinity binding. Mutant and lipid kinases are not presented.



References

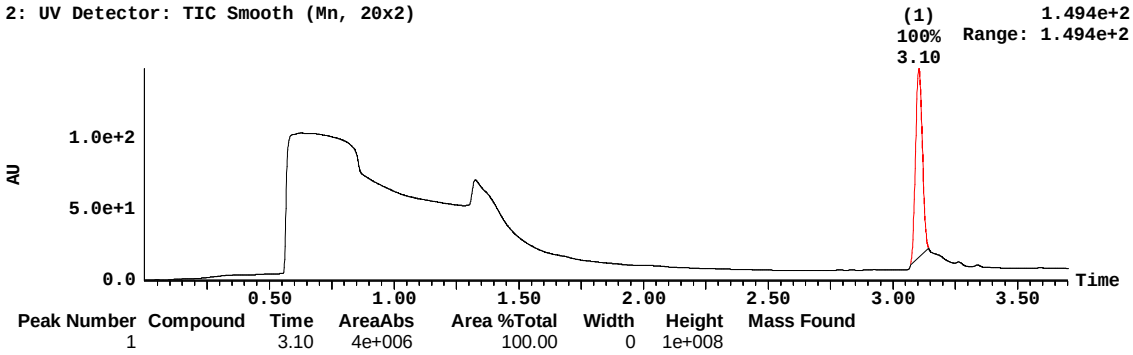
1. Anderson, M. O.; Yu, H.; Penaranda, C.; Maddux, B. A.; Goldfine, I. D.; Youngren, J. F.; Guy, R. K., *J. Comb. Chem.* **2006,** *8*, 784-790.
2. Trager, W.; Jensen, J. B., *Science* **1976,** *193* (4254), 673-5.
3. Smilkstein, M.; Sriwilaijaroen, N.; Kelly, J. X.; Wilairat, P.; Riscoe, M., *Antimicrob Agents Chemother* **2004,** *48* (5), 1803-6.

1-(5-Chloro-2-methoxyphenyl)-3-(naphthalen-1-yl)urea, **4**{12,1}



Sample Report:

Sample 8 Vial 2:E,12 ID File MLUA261_A2_LCMS_pure Date 20-Jan-2008 Time 02:28:56 Description



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
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Peak ID	Compound	Time	Mass Found
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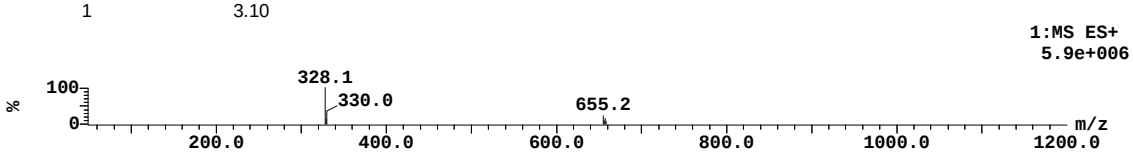
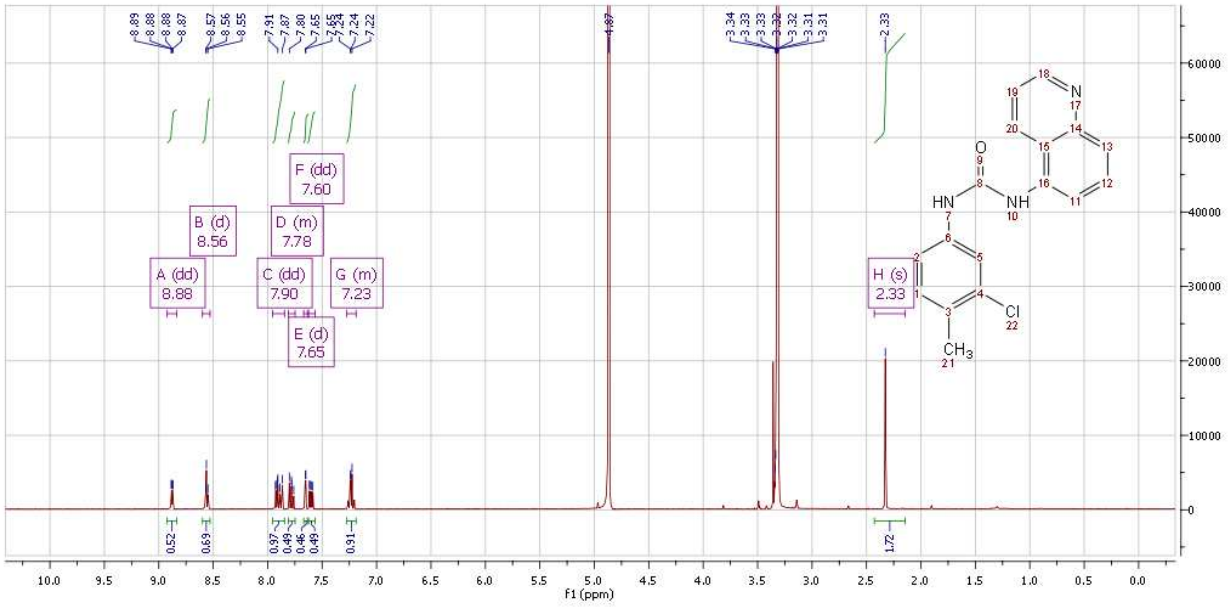
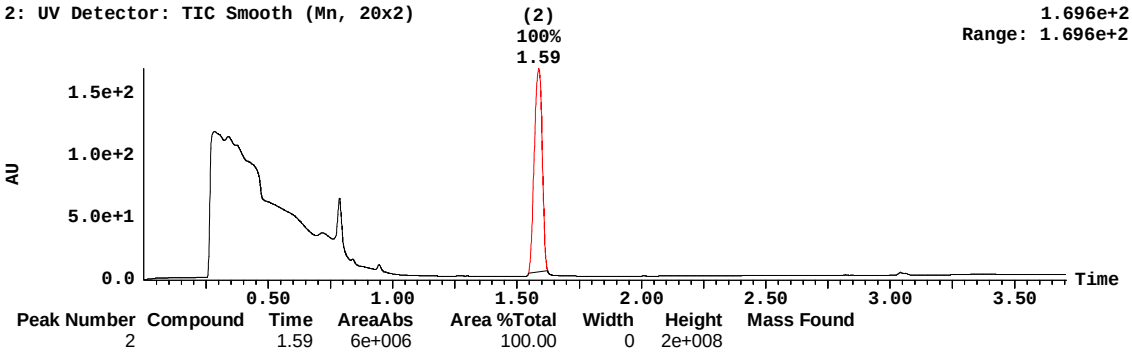


1-(3-Chloro-4-methylphenyl)-3-(quinolin-5-yl)urea, 4{12,2}





Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
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Sample Report (continued):

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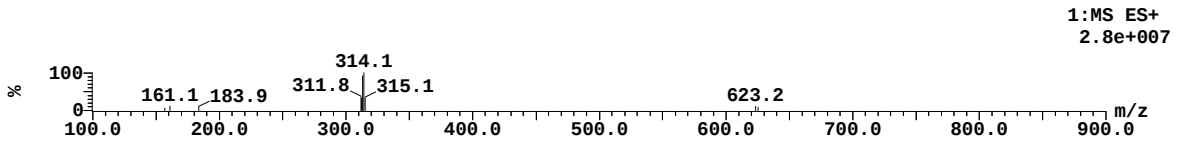
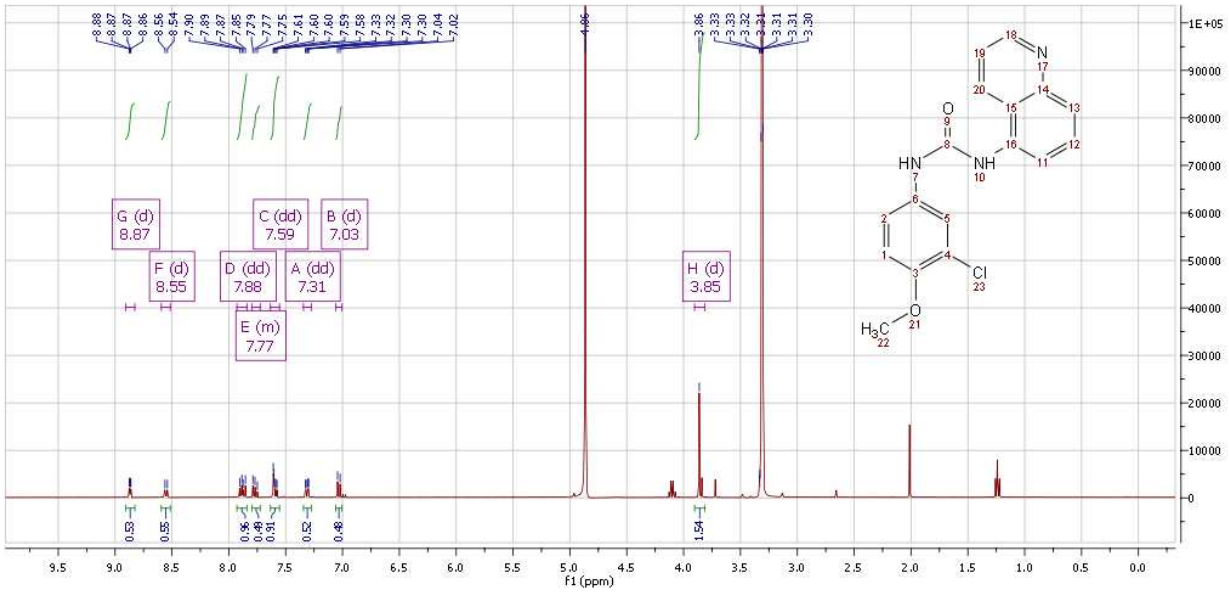
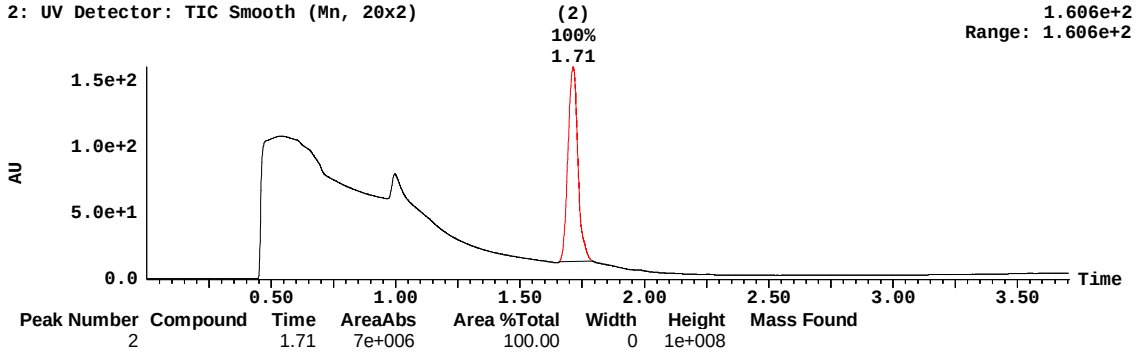


1-(3-Chloro-4-methoxyphenyl)-3-(quinolin-5-yl)urea, 4{12,3}:





Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
2		1.71	7e+006	100.00	0	1e+008	

Sample Report (continued):

Peak ID	Compound	Time	Mass Found
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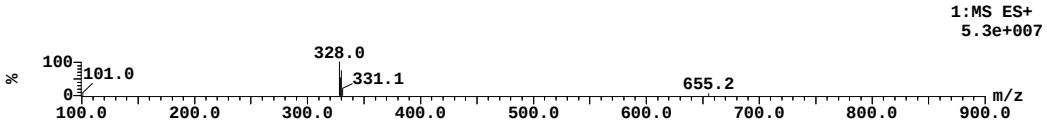
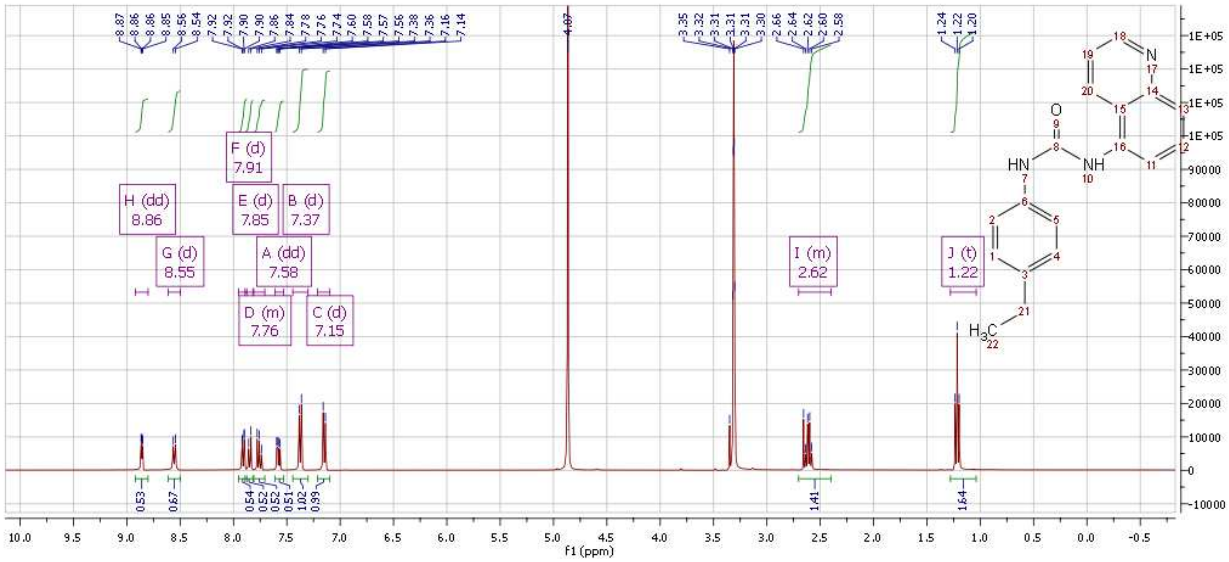
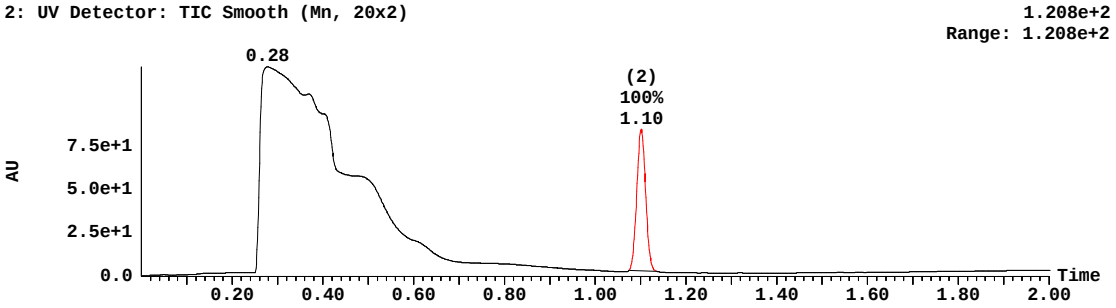


1-(4-Ethylphenyl)-3-(quinolin-5-yl)urea, 4{12,4}:





Peak ID	Compound	Time	Mass Found
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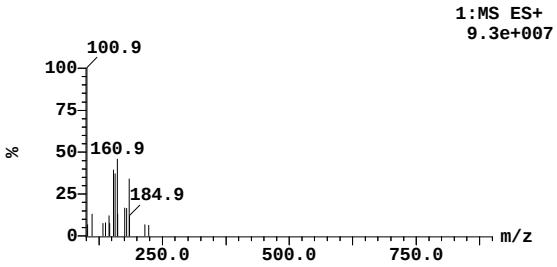
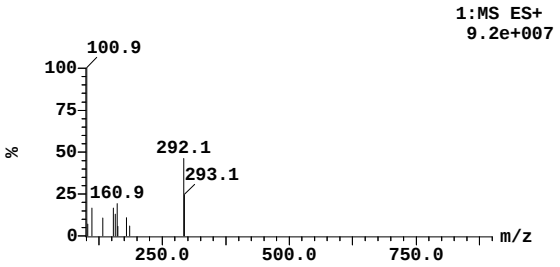
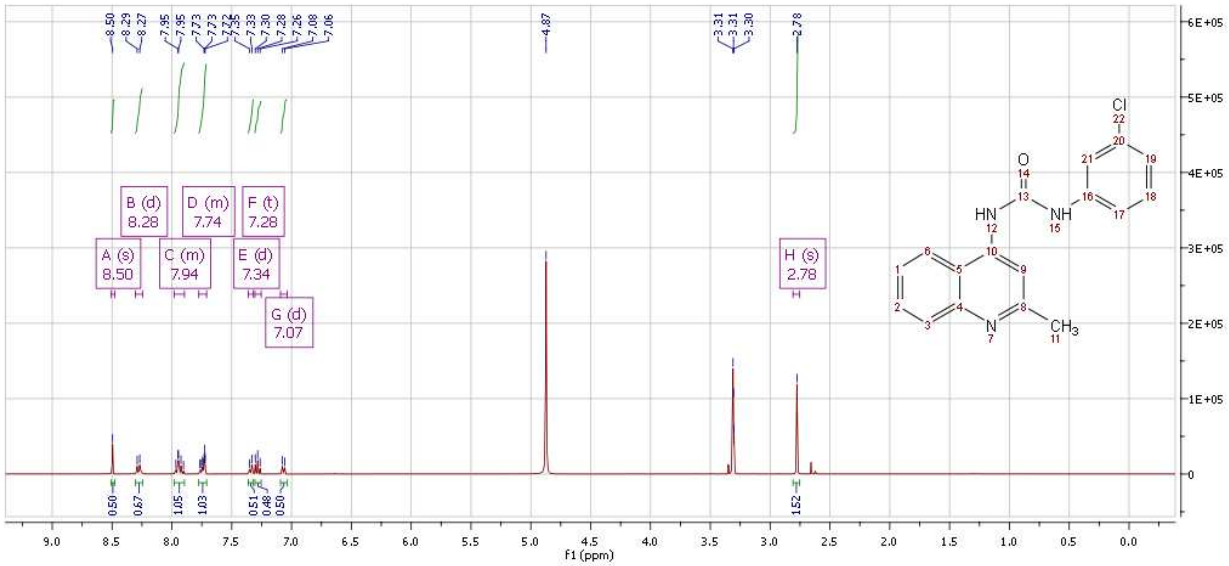
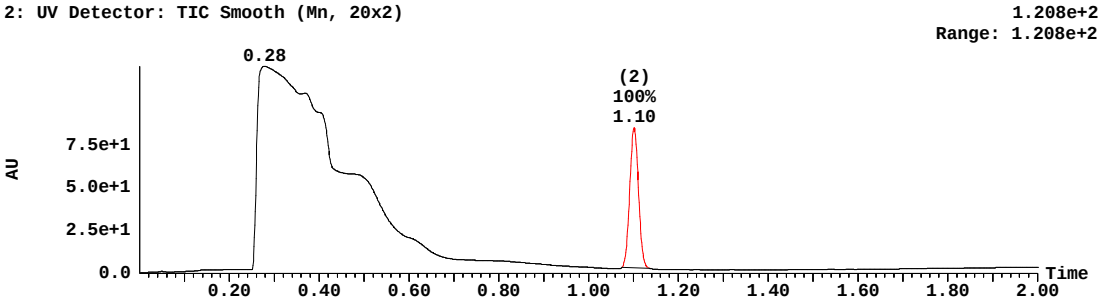


Peak ID	Compound	Time	Mass Found
2		1.10	

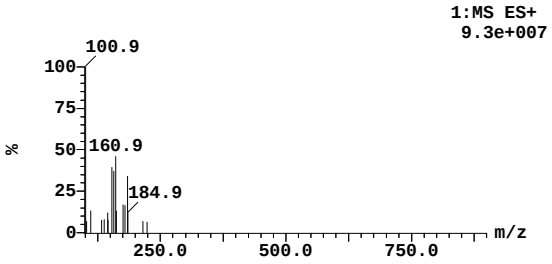


1-(3-Chlorophenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,7}:

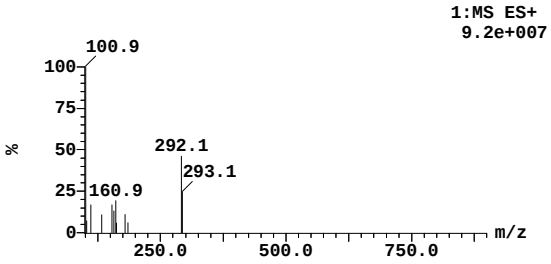




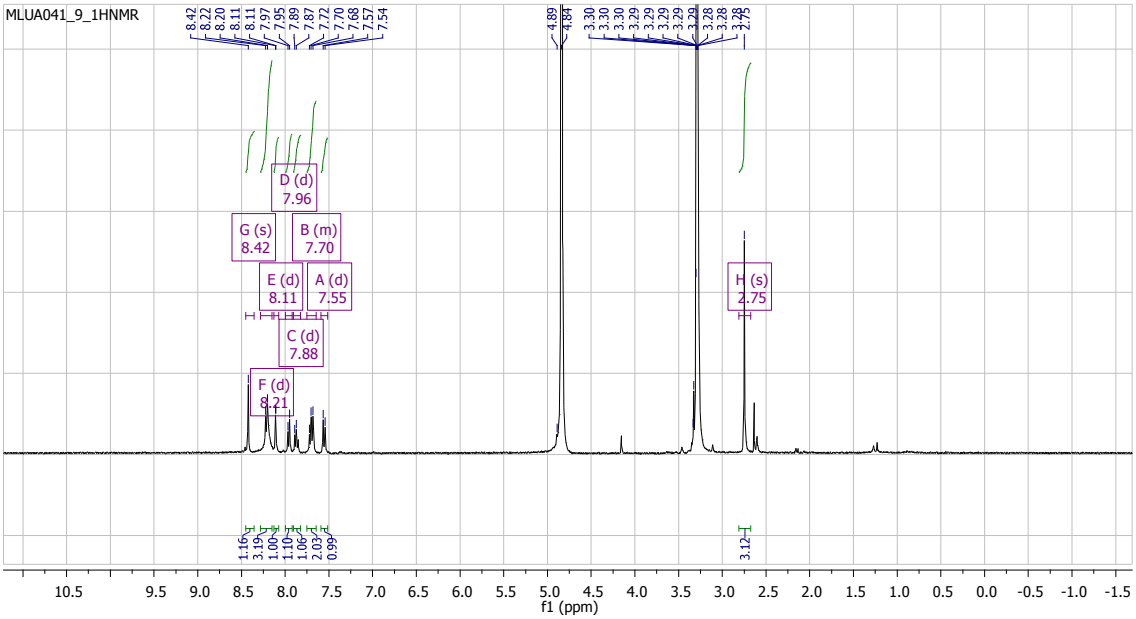
Peak ID	Compound	Time	Mass Found
1		0.78	



Peak ID	Compound	Time	Mass Found
2		1.10	

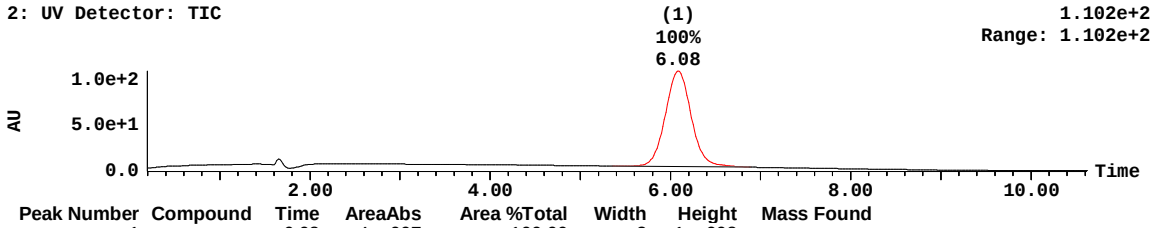


1-(4-Chloro-3-(trifluoromethyl)phenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,12}:



Sample Report:

Sample 3 Vial 3:12,F ID MLUA041_9_LCMS_PURE Date 23-Feb-2007 Time 15:56:40 Description



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
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Peak ID	Compound	Time	Mass Found
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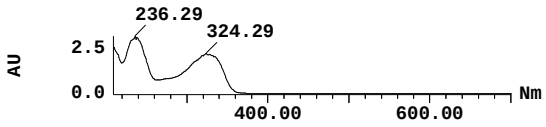
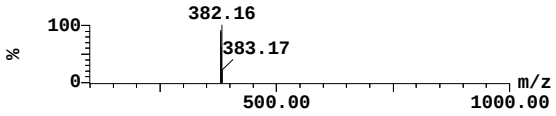
1:(Time: 6.08)

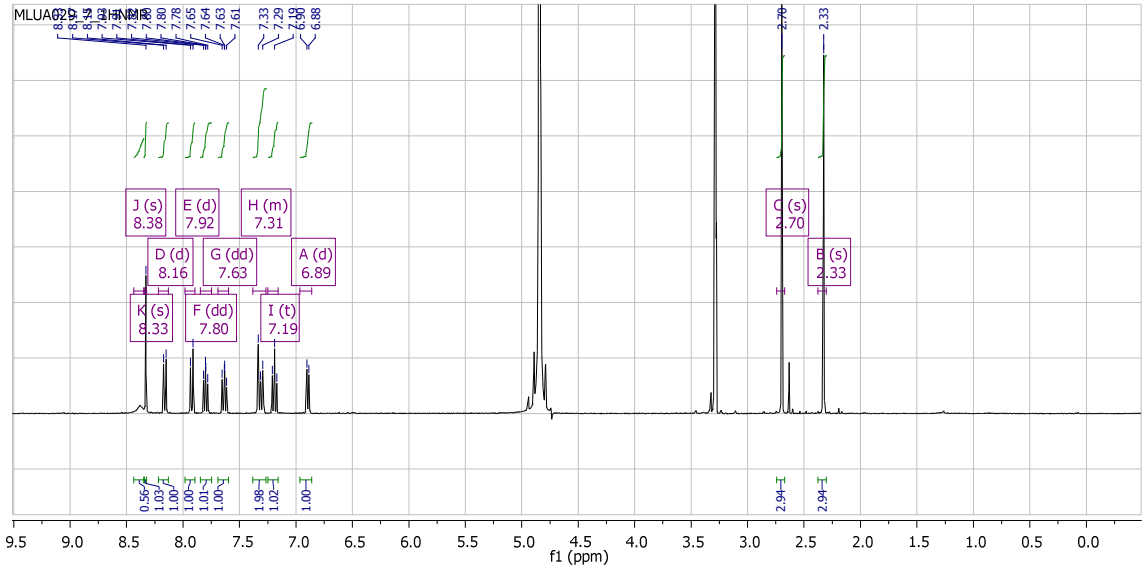


Peak ID	Compound	Time	Mass Found
1		6.08	

3.119 AU 1:(Time: 6.08) 7.4e+007

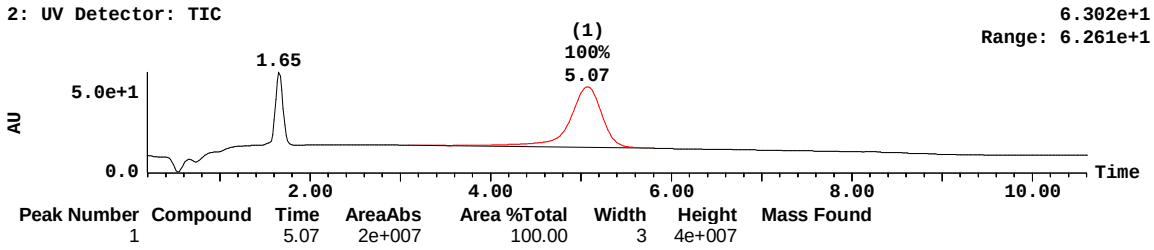


1-(2-Methylquinolin-4-yl)-3-(m-tolyl)urea, 4{13,21}:



Sample Report:

Sample 5 Vial 4:8,G ID File MLUA029_7_LCMS_pure Date 12-Feb-2007 Time 09:32:55 Description



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
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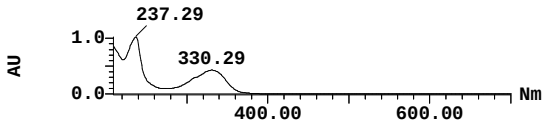
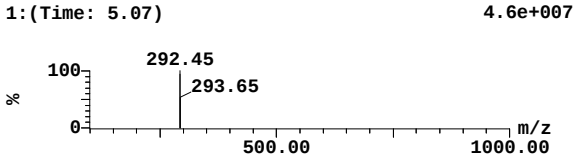
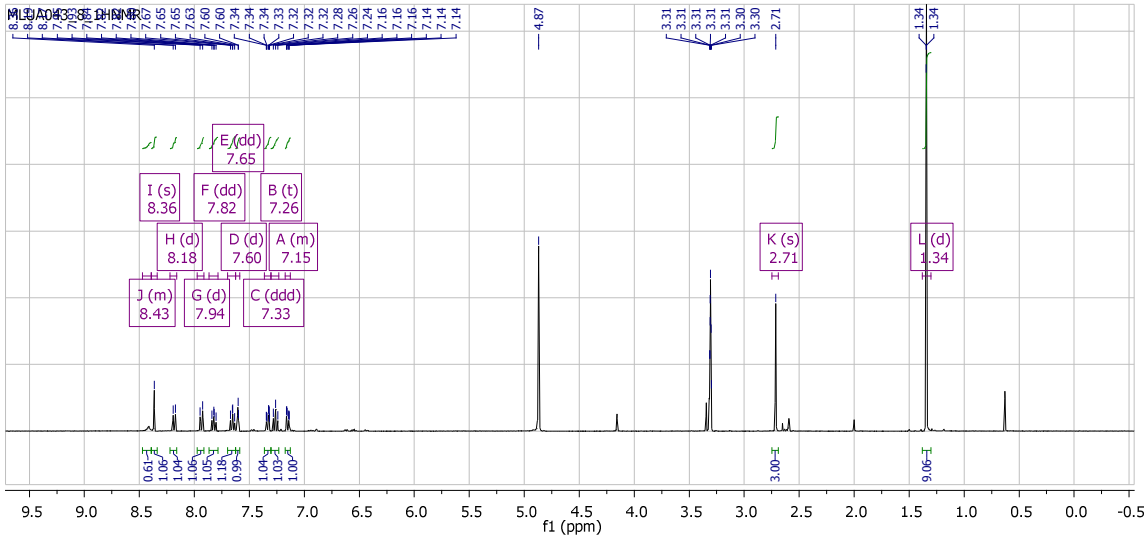
Peak ID	Compound	Time	Mass Found
1		5.07	



Peak ID	Compound	Time	Mass Found
1		5.07	

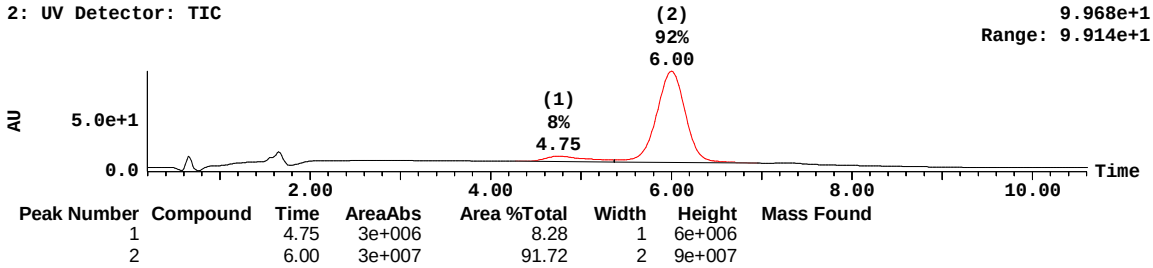


1-(2-(tert-Butyl)phenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,22}:



Sample Report:

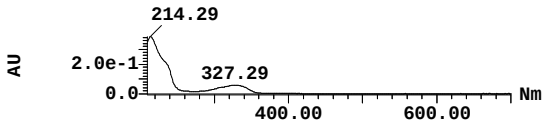
Sample 10 Vial 3:1,C ID File MLUA043_8_LCMS_PURE Date 23-Feb-2007 Time 17:46:31 Description



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.75	3e+006	8.28	1	6e+006	
2		6.00	3e+007	91.72	2	9e+007	

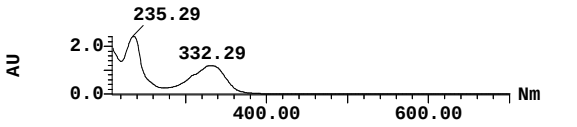
Peak ID	Compound	Time	Mass Found
1		4.75	

1:(Time: 4.75) 3.855e-1 AU



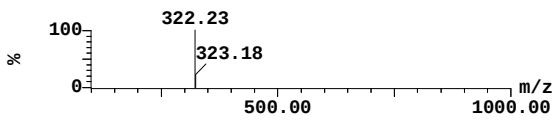
Peak ID	Compound	Time	Mass Found
2		6.00	

2:(Time: 6.00) 2.406 AU



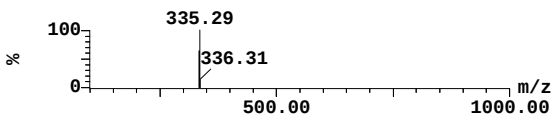
Peak ID	Compound	Time	Mass Found
1		4.75	

1:(Time: 4.75) 1.7e+007

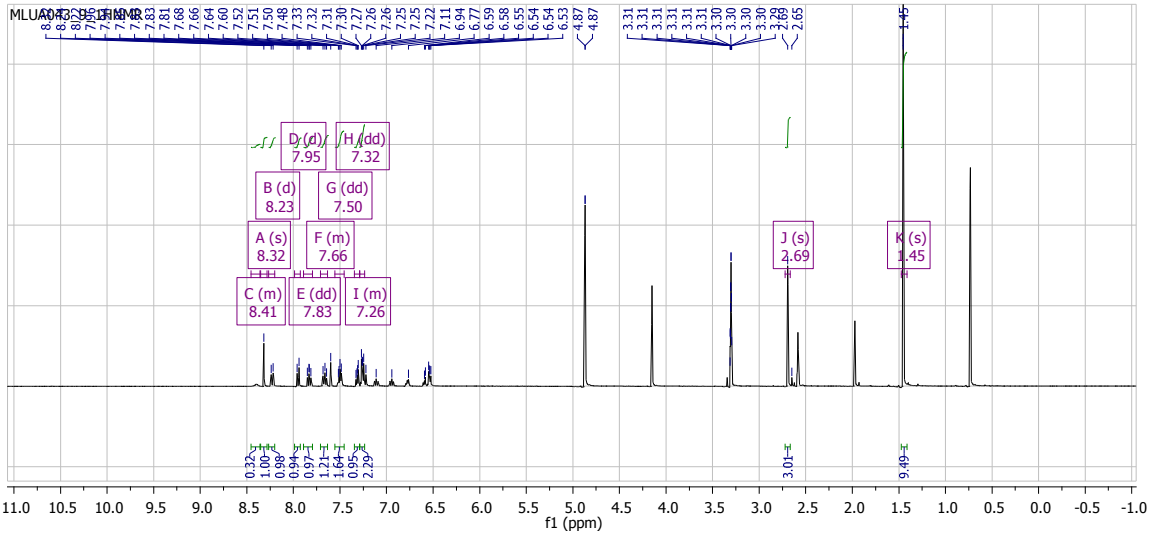


Peak ID	Compound	Time	Mass Found
2		6.00	

2:(Time: 6.00) 5.9e+007

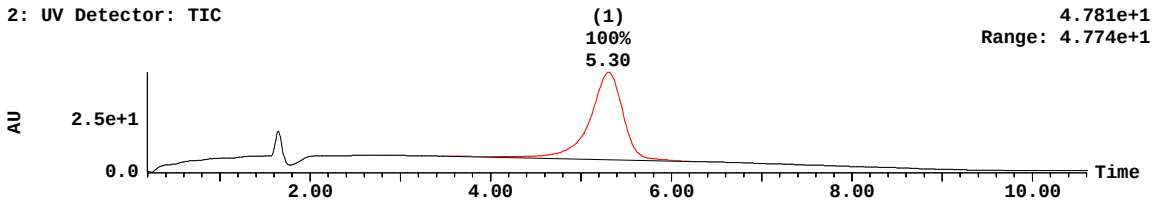


1-(3-(tert-Butyl)phenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,23}:



Sample Report:

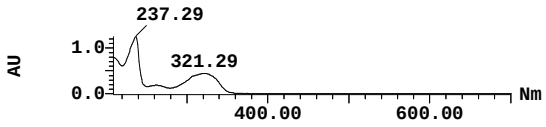
Sample 6 Vial 3:12,H ID File MLUA043_9_LCMS_PURE Date 23-Feb-2007 Time 16:44:30 Description



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		5.30	2e+007	100.00	3	4e+007	

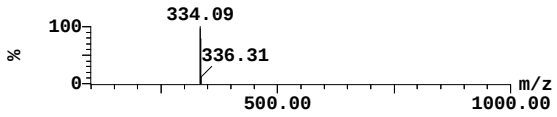
Peak ID	Compound	Time	Mass Found
1		5.30	

1:(Time: 5.30)

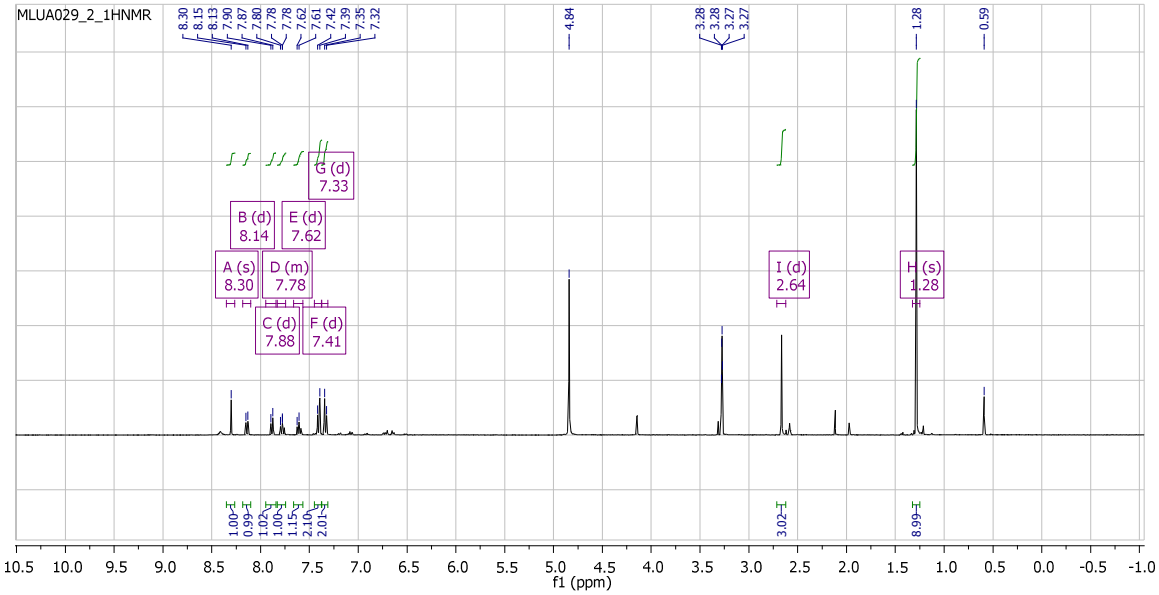


Peak ID	Compound	Time	Mass Found
1		5.30	

1.247 AU 1:(Time: 5.30) 3.1e+007

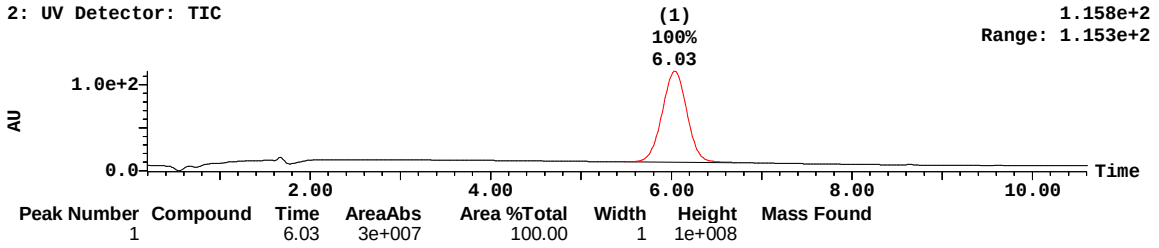


1-(4-(tert-Butyl)phenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,24}:



Sample Report:

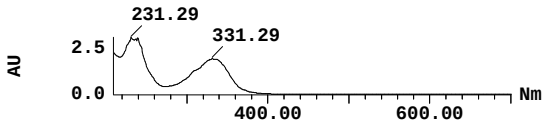
Sample 4 Vial 4:12,F ID File MLUA029_2_LCMS_PURE2 Date 16-Feb-2007 Time 18:45:47 Description

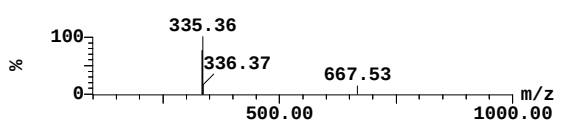


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		6.03	3e+007	100.00	1	1e+008	

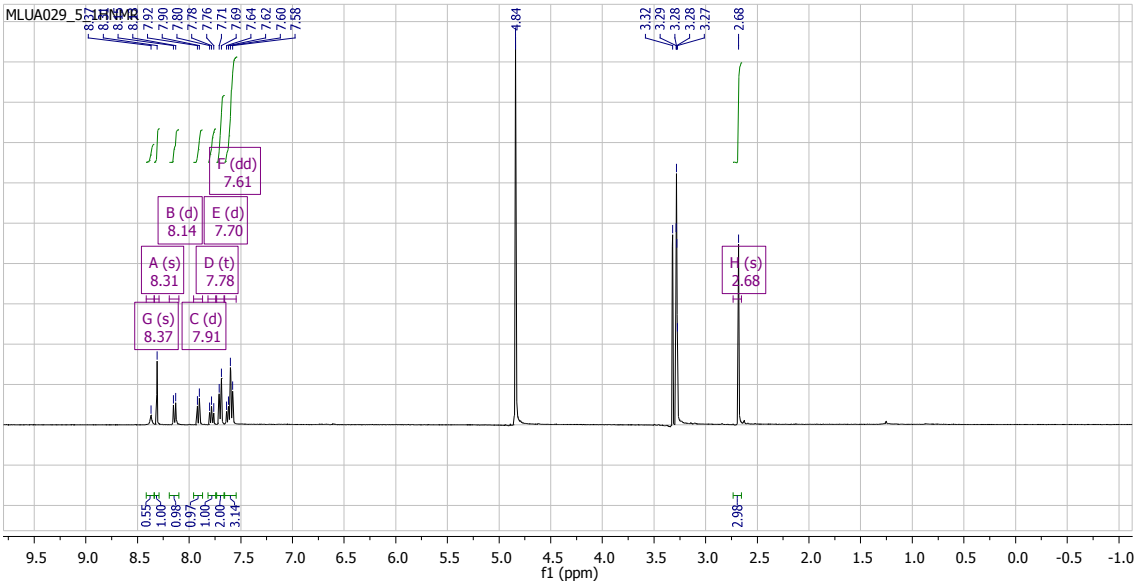
Peak ID	Compound	Time	Mass Found
1		6.03	

Peak ID	Compound	Time	Mass Found
1		6.03	



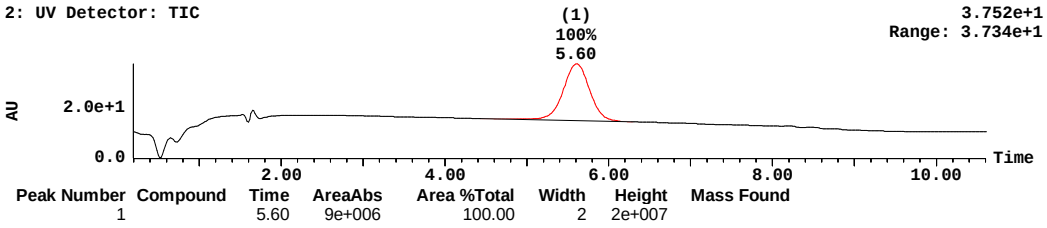


1-(2-Methylquinolin-4-yl)-3-(4-(trifluoromethyl)phenyl)urea, 4{13,27}:



Sample Report:

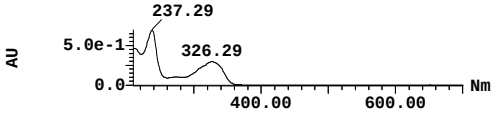
Sample 3 Vial 4:8,E ID File MLUA029_5_LCMS_pure Date 12-Feb-2007 Time 09:10:10 Description



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		5.60	9e+006	100.00	2	2e+007	

Peak ID	Compound	Time	Mass Found
1		5.60	

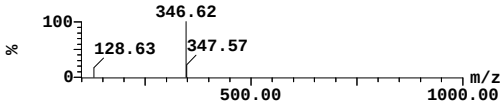
1:(Time: 5.60)



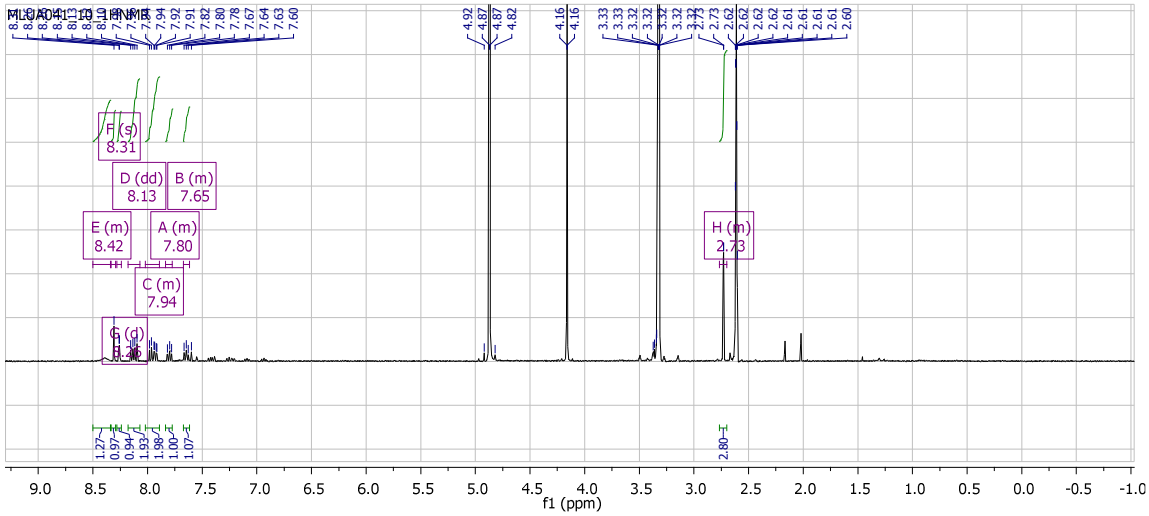
Peak ID	Compound	Time	Mass Found
1		5.60	

6.958e-1 AU 1:(Time: 5.60)

4.8e+007

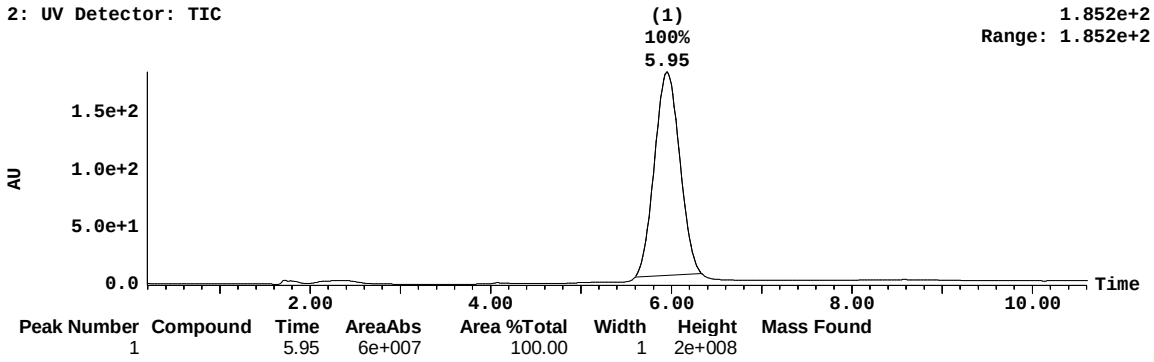


1-(2-Methylquinolin-4-yl)-3-(4-nitro-3-(trifluoromethyl)phenyl)urea, 4{13,28}:



Sample Report:

Sample 5 Vial 3:8,B ID File MLUA041_10_pure Date 28-Feb-2007 Time 17:43:34 Description

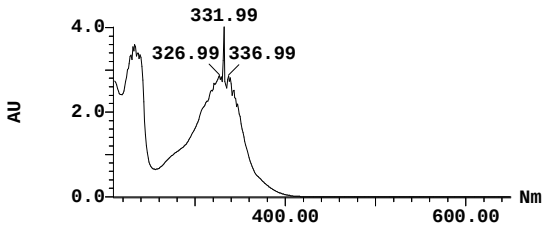


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		5.95	6e+007	100.00	1	2e+008	

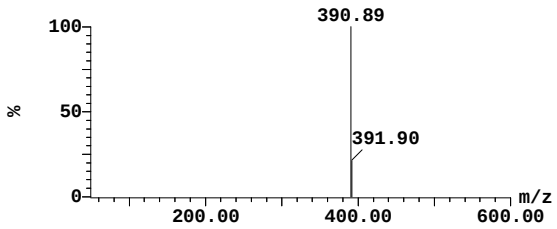
Peak ID	Compound	Time	Mass Found
1		5.95	

Peak ID	Compound	Time	Mass Found
1		5.95	

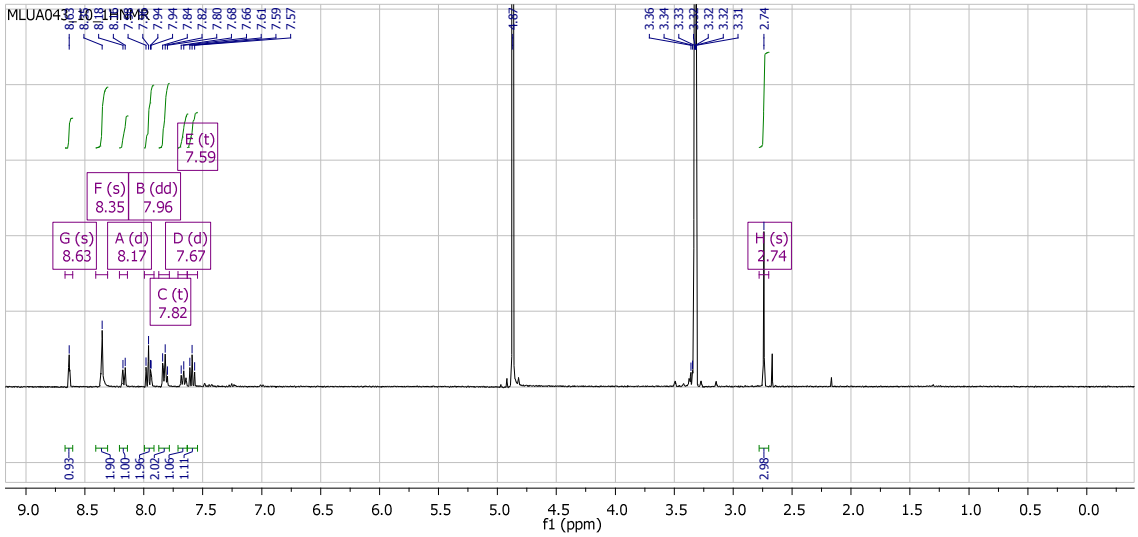
1:(Time: 5.95)



4.013 AU 1:(Time: 5.95) 9.4e+006

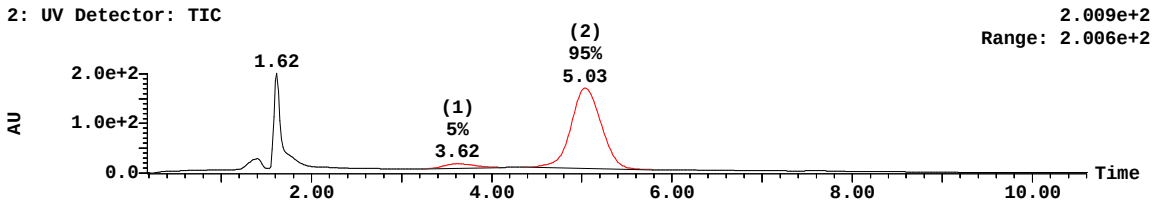


1-(2-Methylquinolin-4-yl)-3-(2-nitrophenyl)urea, **4**{13,41}:



Sample Report:

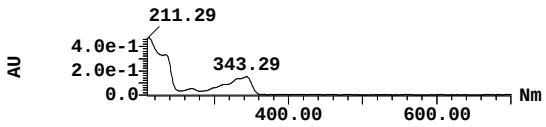
Sample 13 Vial 2:6,F ID File MLUA043_10_LCMS_crude Date 26-Feb-2007 Time 09:44:55 Description



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		3.62	3e+006	5.21	1	9e+006	
2		5.03	6e+007	94.79	1	2e+008	

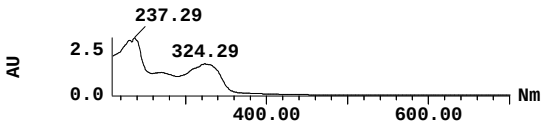
Peak ID	Compound	Time	Mass Found
1		3.62	

1:(Time: 3.62) 4.715e-1 AU



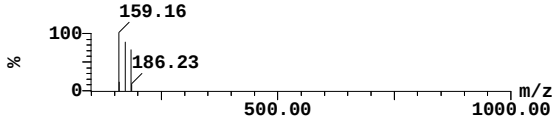
Peak ID	Compound	Time	Mass Found
2		5.03	

2:(Time: 5.03) 3.154 AU



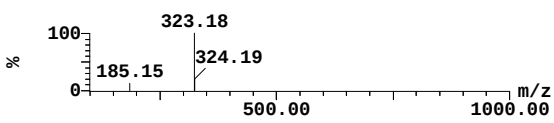
Peak ID	Compound	Time	Mass Found
1		3.62	

1:(Time: 3.62) 2.0e+006

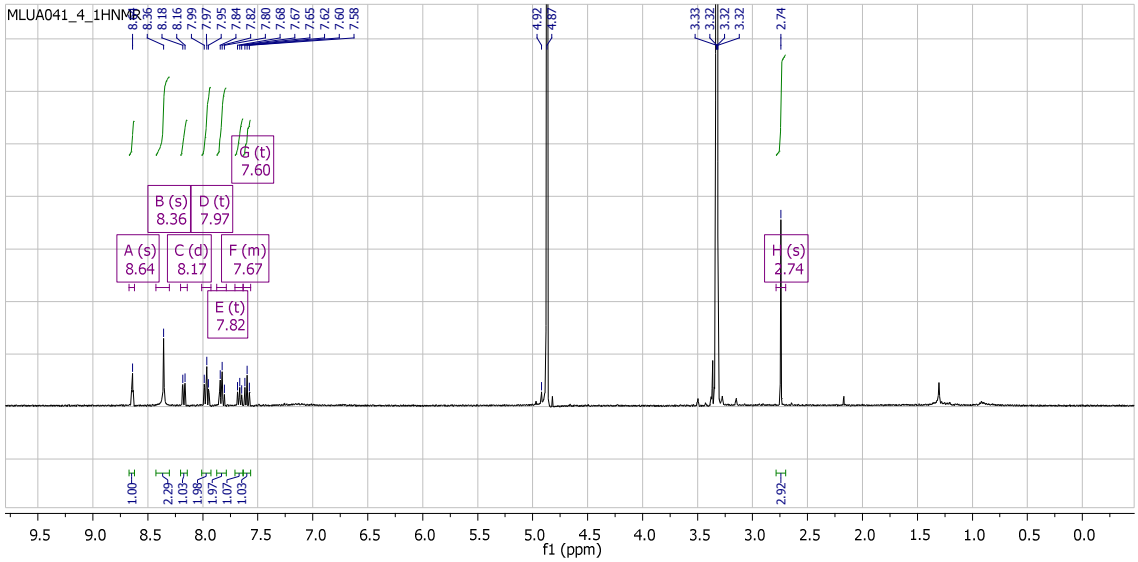


Peak ID	Compound	Time	Mass Found
2		5.03	

2:(Time: 5.03) 6.4e+007

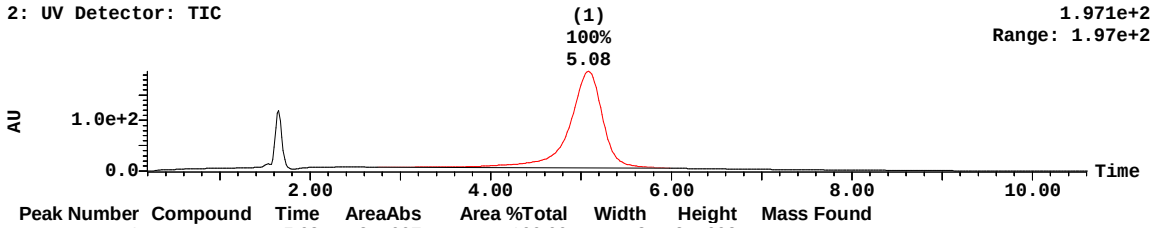


1-(2-Methylquinolin-4-yl)-3-(3-nitrophenyl)urea, **4**{13,42}:



Sample Report:

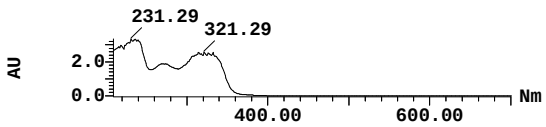
Sample 13 Vial 4:9,H ID File MLUA041_4_LCMS_pure Date 05-Mar-2007 Time 10:52:08 Description



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		5.08	8e+007	100.00	3	2e+008	

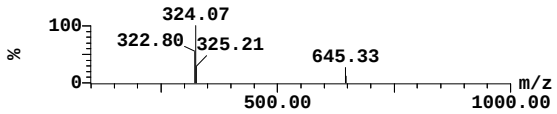
Peak ID	Compound	Time	Mass Found
1		5.08	

1:(Time: 5.08)

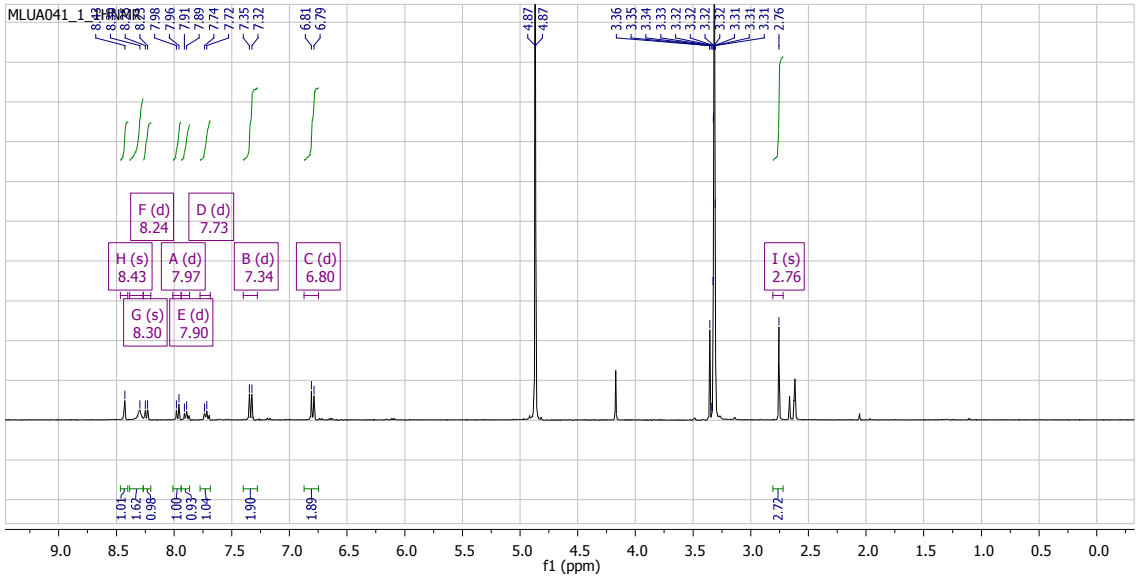


Peak ID	Compound	Time	Mass Found
1		5.08	

3.357 AU 1:(Time: 5.08) 3.7e+007

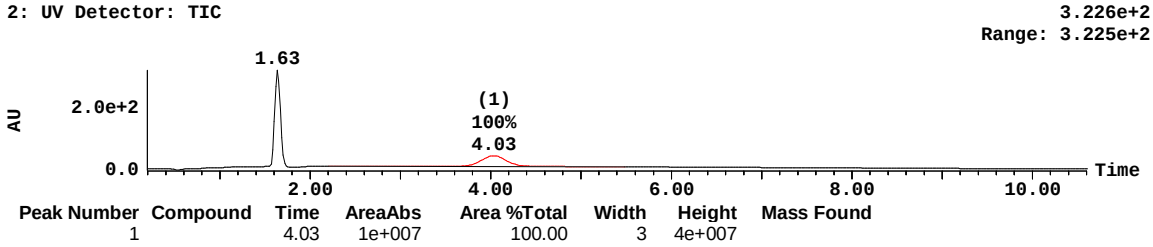


1-(4-Hydroxyphenyl)-3-(2-methylquinolin-4-yl)urea, **4**{13,43}:



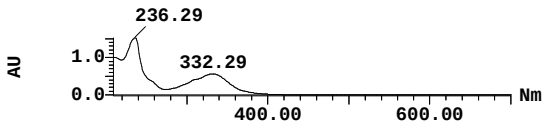
Sample Report:

Sample 4 Vial 3:12,E ID File MLUA041_1_LCMS_PURE Date 23-Feb-2007 Time 15:45:15 Description

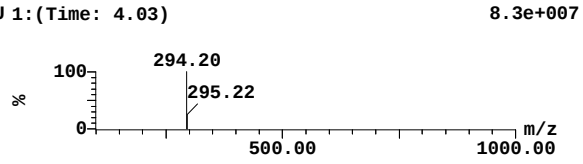


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.03	1e+007	100.00	3	4e+007	

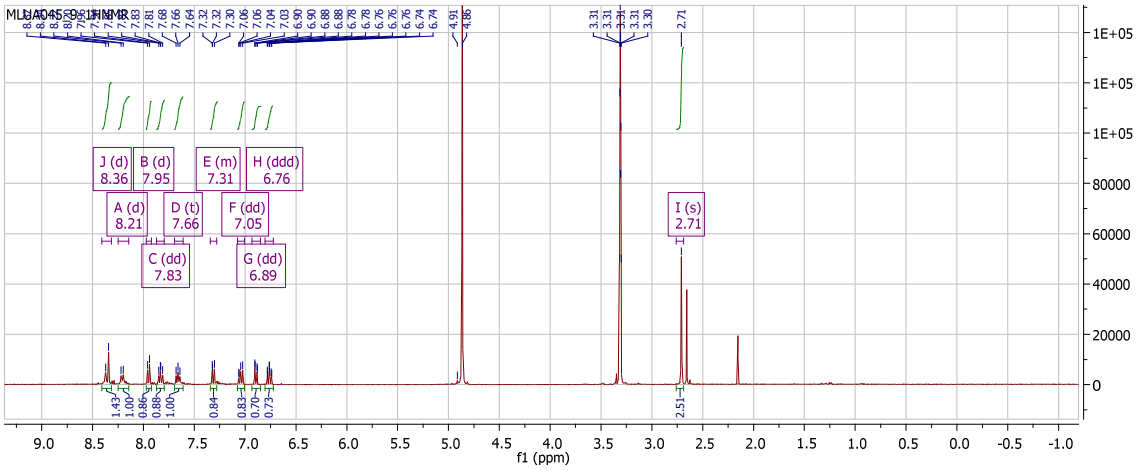
Peak ID	Compound	Time	Mass Found
1		4.03	



Peak ID	Compound	Time	Mass Found
1		4.03	

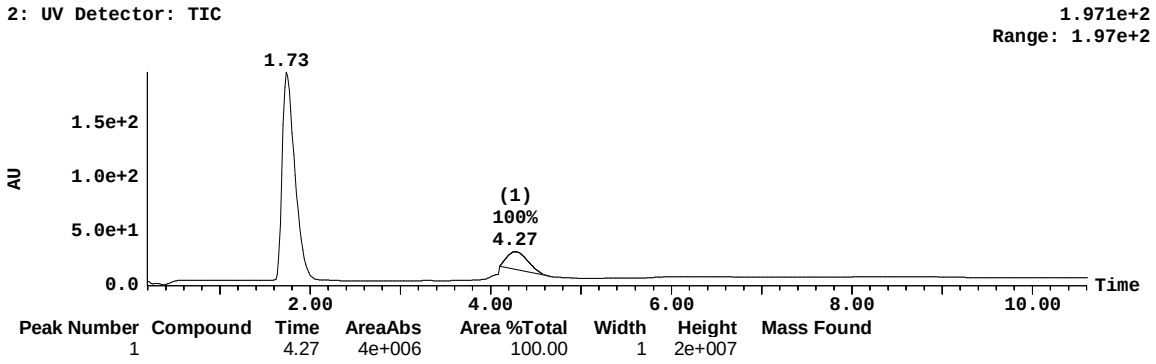


1-(2-Aminophenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,44}:



Sample Report:

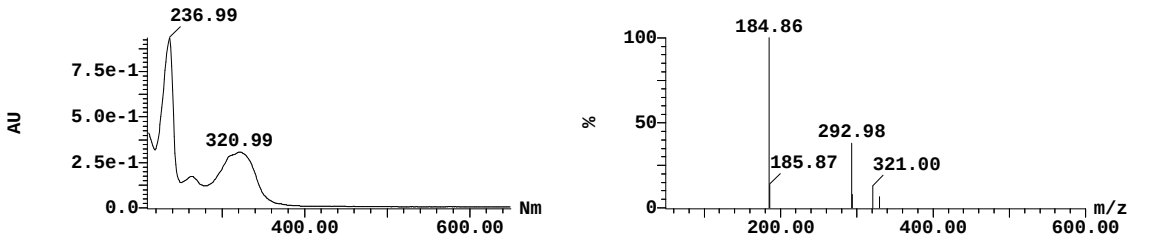
Sample 9 Vial 2:4,G ID File MLUA045_9_pure Date 28-Feb-2007 Time 17:31:22 Description



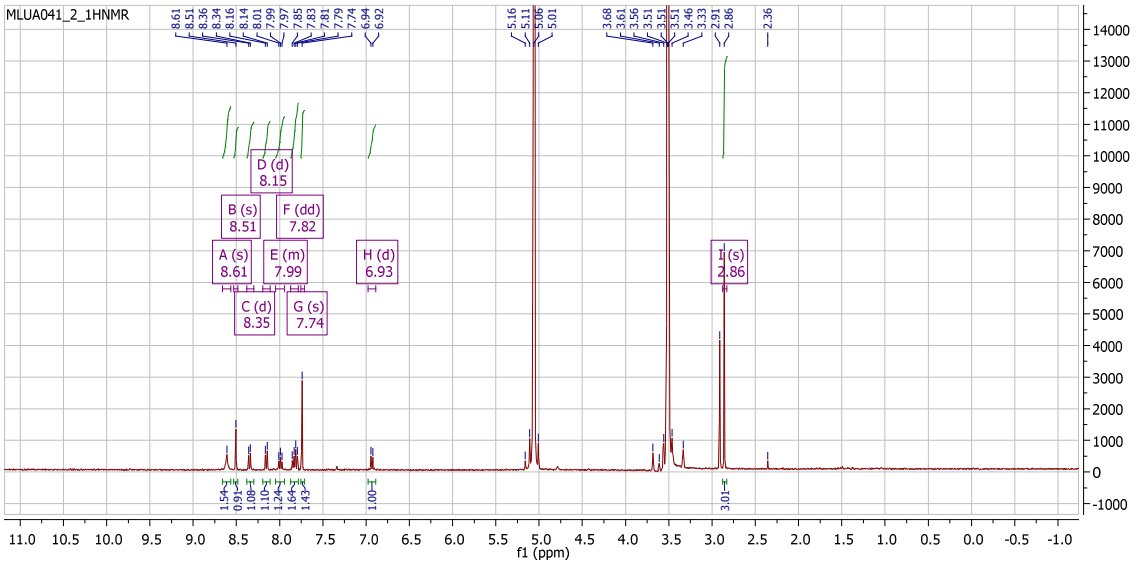
Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.27	4e+006	100.00	1	2e+007	

Peak ID	Compound	Time	Mass Found
1		4.27	

Peak ID	Compound	Time	Mass Found
1		4.27	

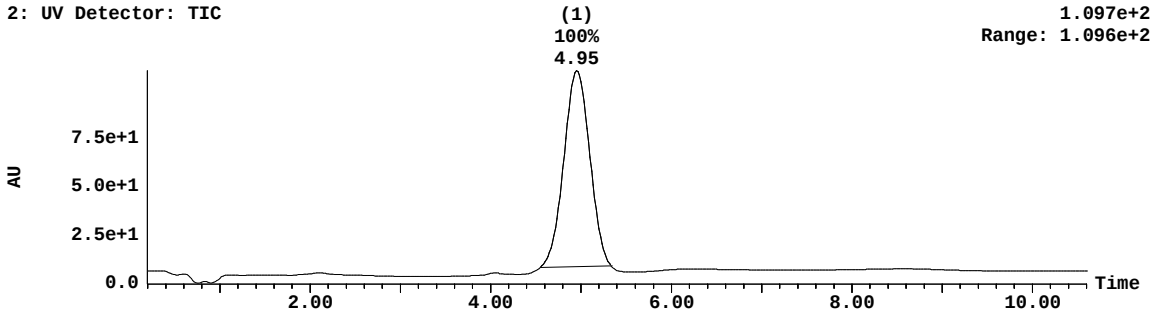


1-(4-Aminophenyl)-3-(2-methylquinolin-4-yl)urea, 4{13,45}:



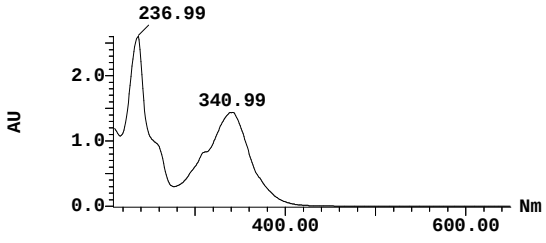
Sample Report:

Sample 13 Vial 4:3,A ID File MLUA0041_2_LCMS_pure Date 27-Feb-2007 Time 19:50:08 Description

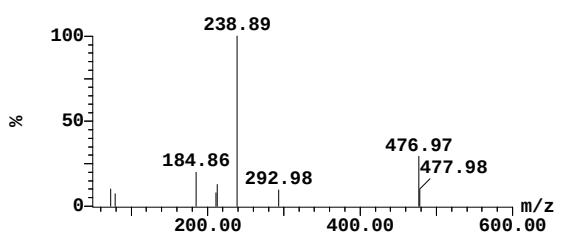


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.95	3e+007	100.00	1	1e+008	

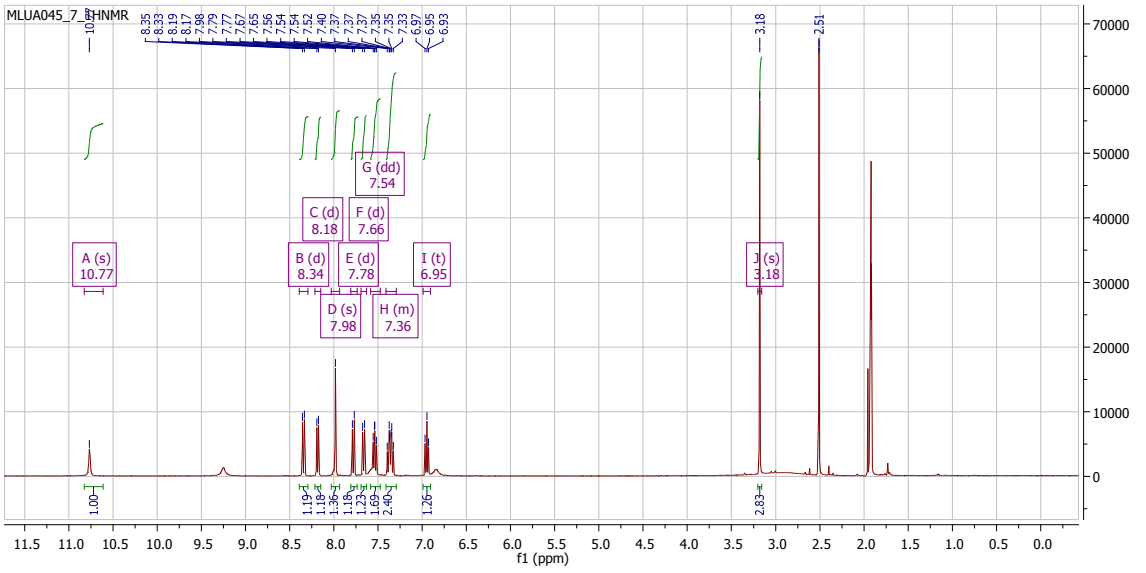
Peak ID	Compound	Time	Mass Found
1		4.95	



Peak ID	Compound	Time	Mass Found
1		4.95	

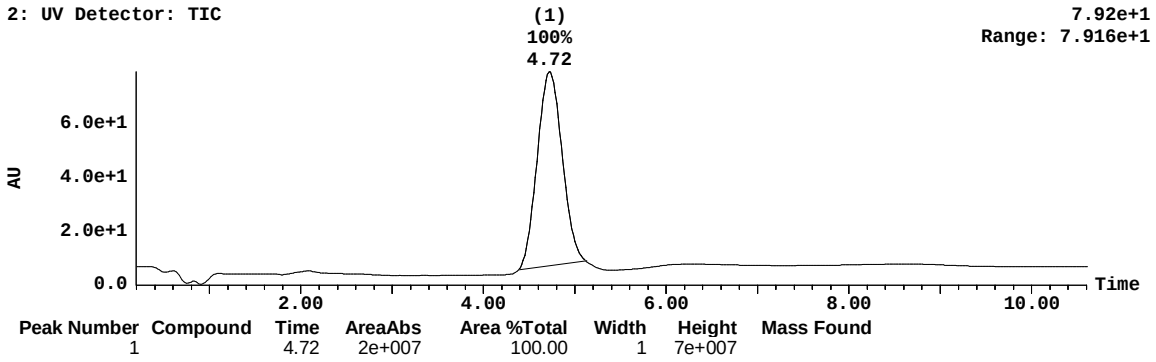


2-(3-(2-Methylquinolin-4-yl)ureido)benzamide, **4**{13,49}:



Sample Report:

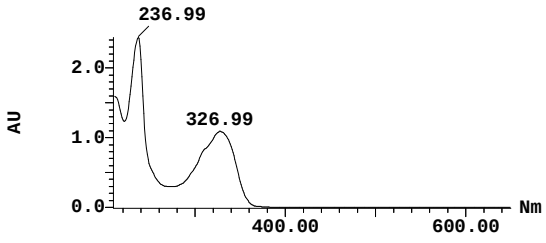
Sample 12 Vial 3:10,C ID File MLUA0045_7_LCMS_pure Date 27-Feb-2007 Time 00:40:59 Description



Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.72	2e+007	100.00	1	7e+007	

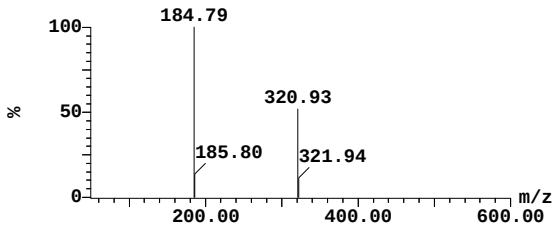
Peak ID	Compound	Time	Mass Found
1		4.72	

1:(Time: 4.72)

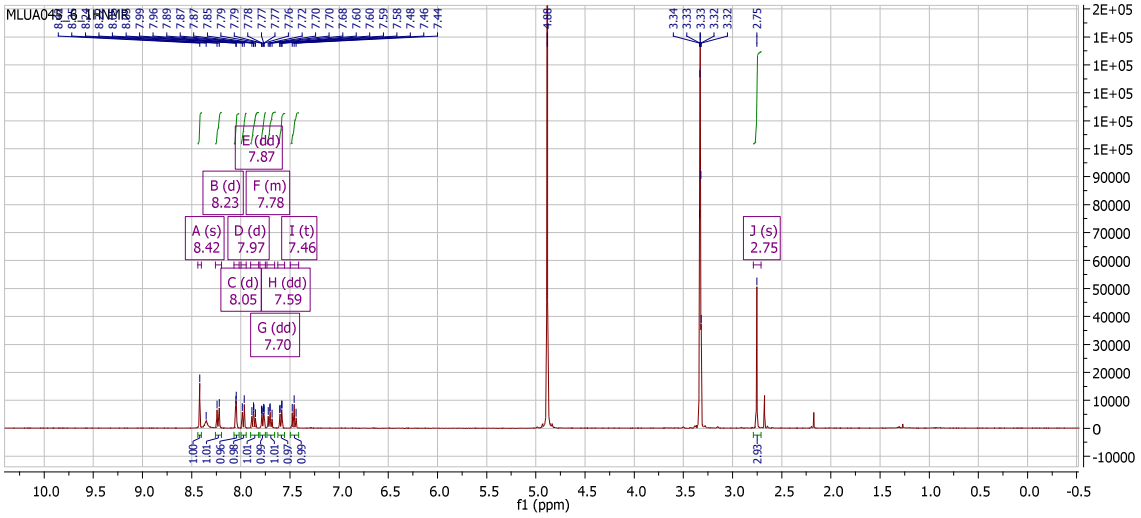


Peak ID	Compound	Time	Mass Found
1		4.72	

2.438 AU 1:(Time: 4.72) 6.7e+006

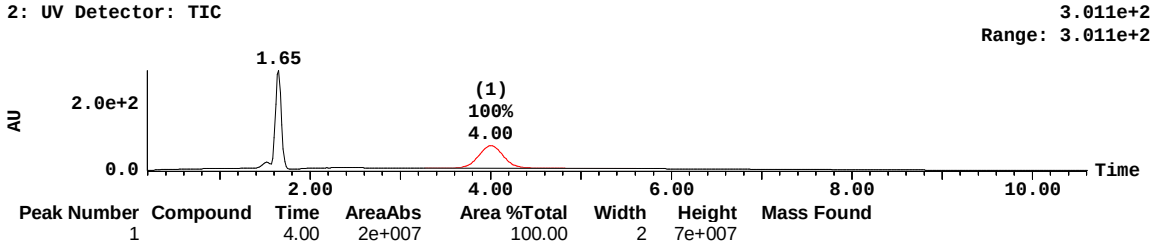


3-(3-(2-Methylquinolin-4-yl)ureido)benzamide, **4**{13,50}:



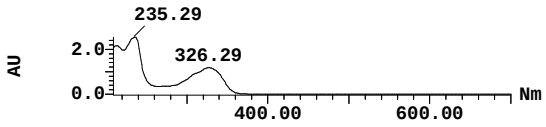
Sample Report:

Sample 12 Vial 4:9,F ID File MLUA045_6_LCMS_pure Date 05-Mar-2007 Time 10:11:39 Description

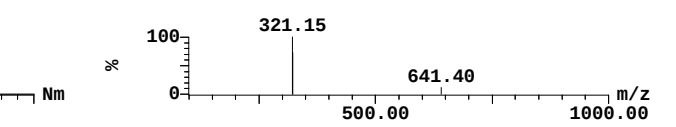


Peak Number	Compound	Time	AreaAbs	Area %Total	Width	Height	Mass Found
1		4.00	2e+007	100.00	2	7e+007	

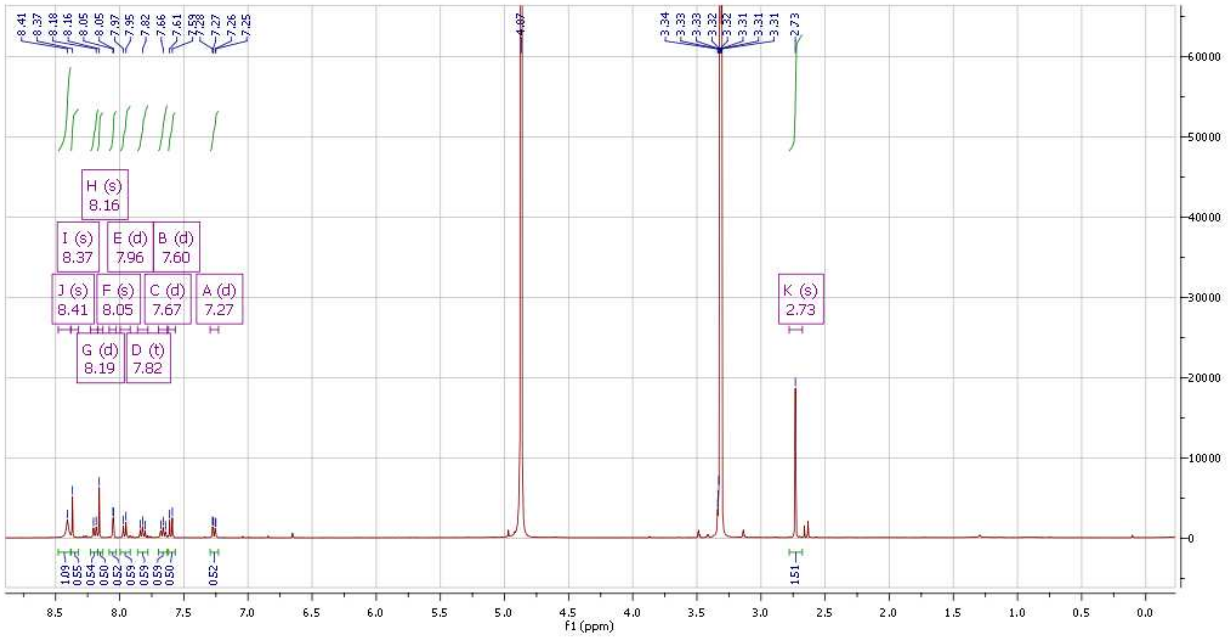
Peak ID	Compound	Time	Mass Found
1		4.00	

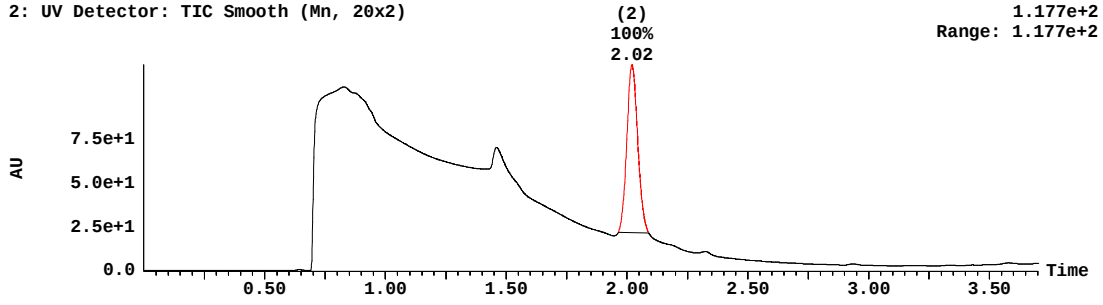


Peak ID	Compound	Time	Mass Found
1		4.00	

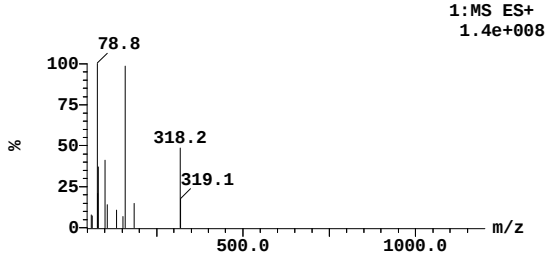


1-(1H-benzo[d]imidazol-6-yl)-3-(2-methylquinolin-4-yl)urea, 4{13,60}:

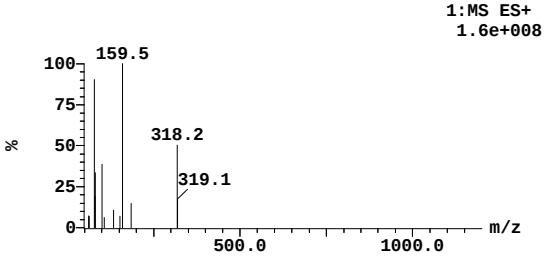




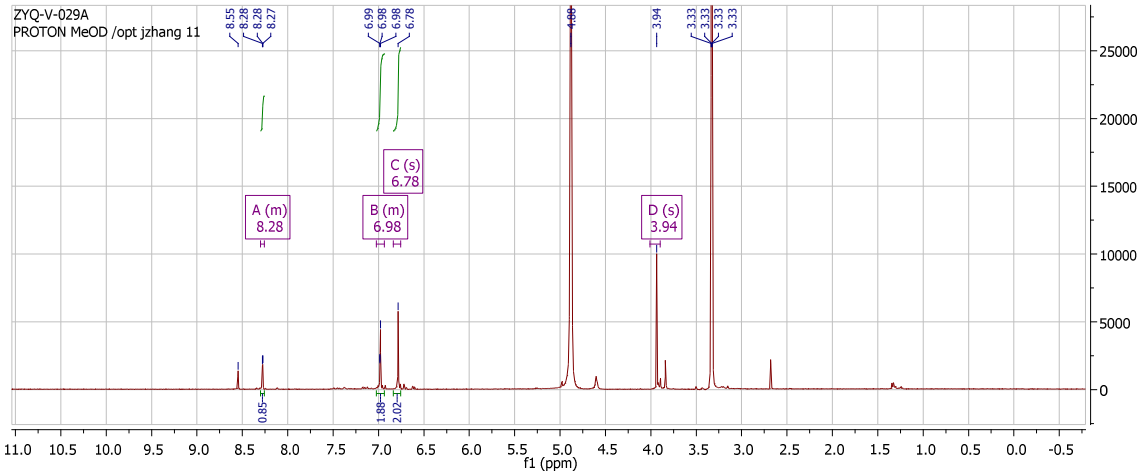
Peak ID	Compound	Time	Mass Found
3		2.11	



Peak ID	Compound	Time	Mass Found
4		2.15	

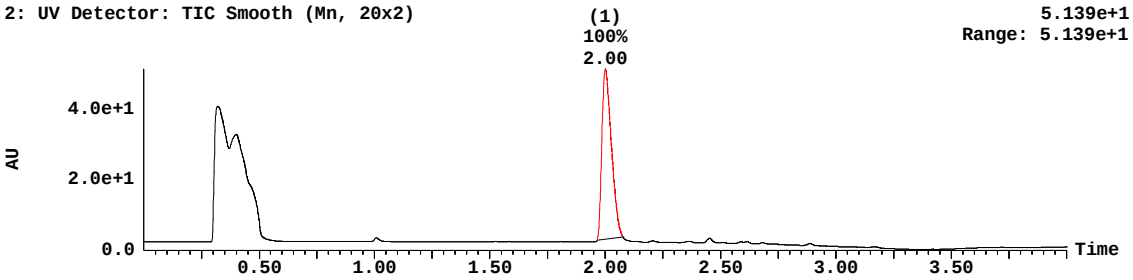


1-(5-Chloro-2-methoxyphenyl)-3-(1H-imidazol-2-yl)urea, 4{19,1}:

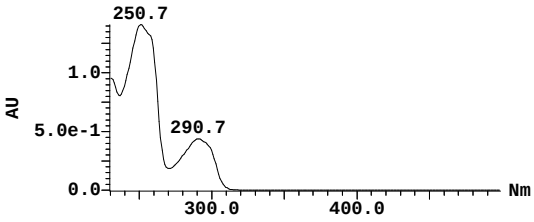


Sample Report:

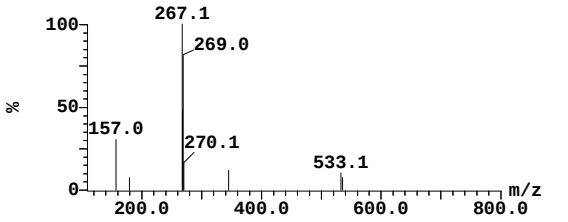
Sample 33 File MLUC013_A2_pure



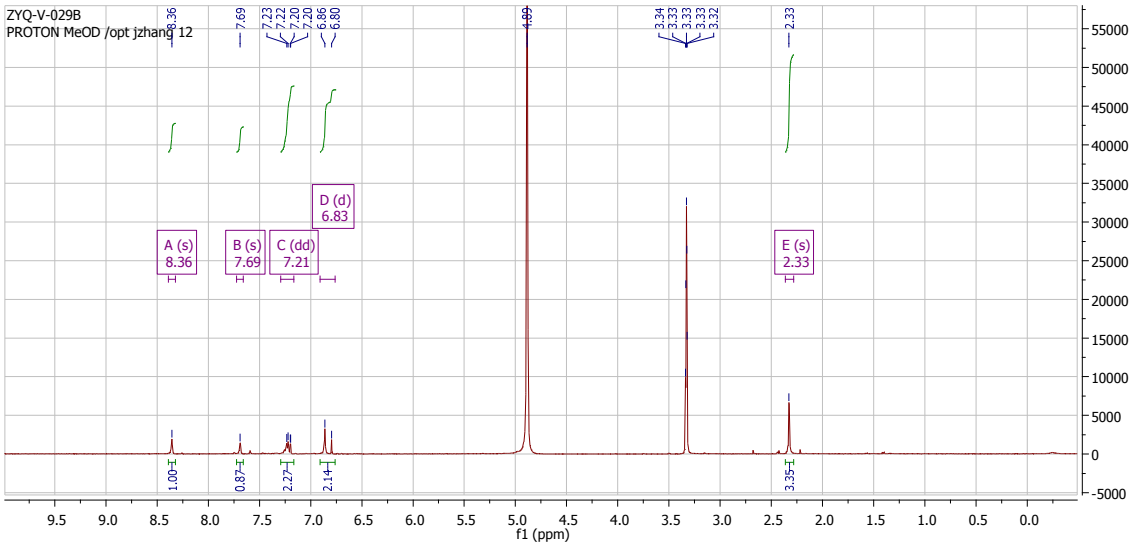
Peak ID	Compound	Time	Mass Found
1		2.00	



Peak ID	Compound	Time	Mass Found
1		2.00	

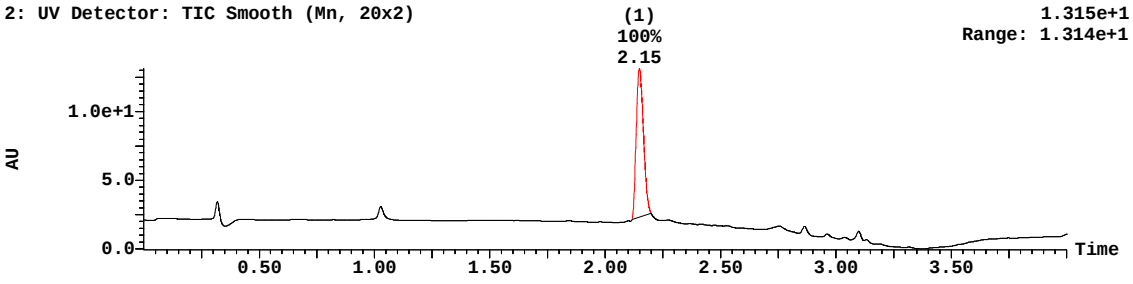


1-(3-Chloro-4-methylphenyl)-3-(1H-imidazol-2-yl)urea, 4{19,2}:

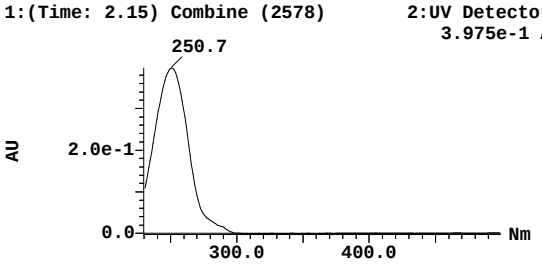


Sample Report:

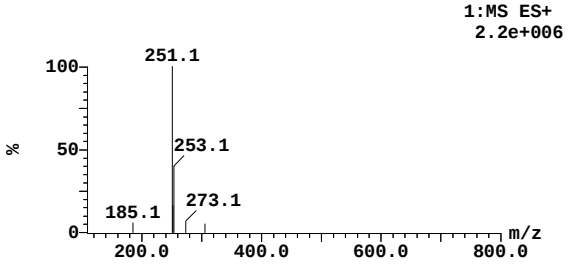
Sample 9 File MLUC005_C2_pure



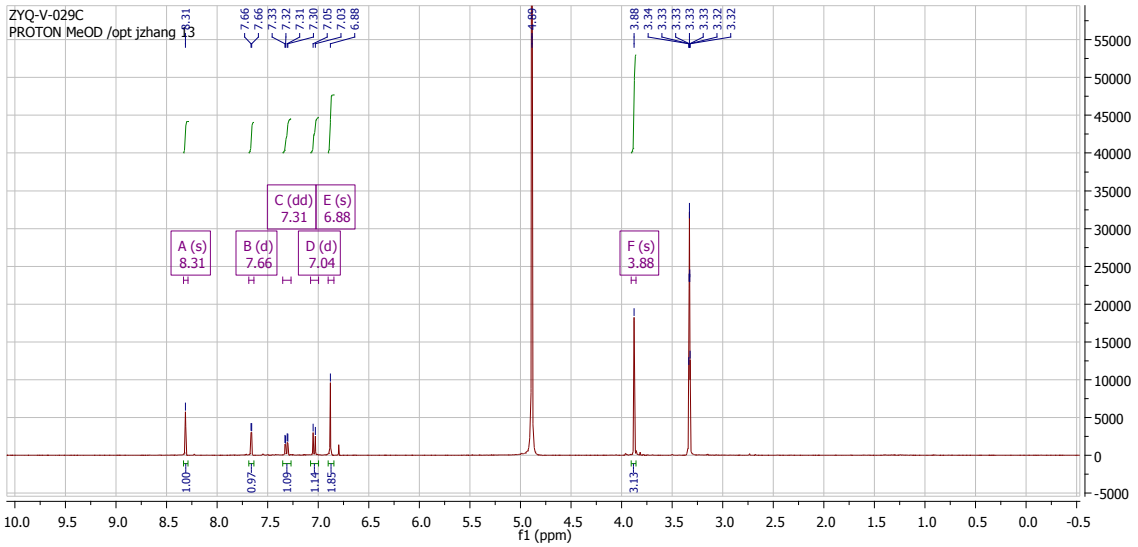
Peak ID	Compound	Time	Mass Found
1		2.15	



Peak ID	Compound	Time	Mass Found
1		2.15	

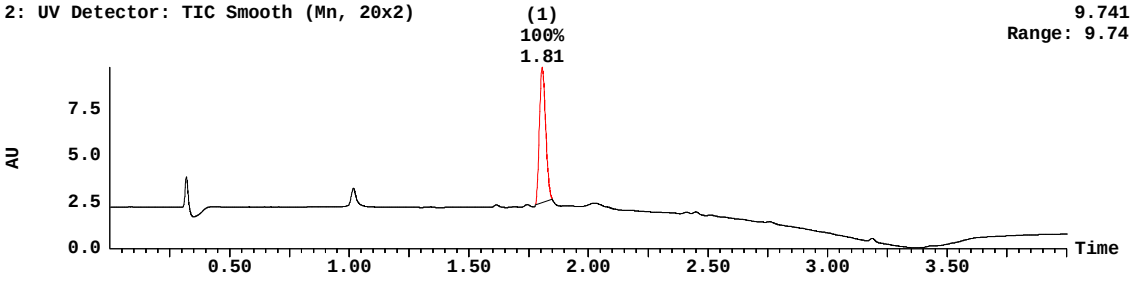


1-(3-Chloro-4-methoxyphenyl)-3-(1H-imidazol-2-yl)urea, 4{19,3}:

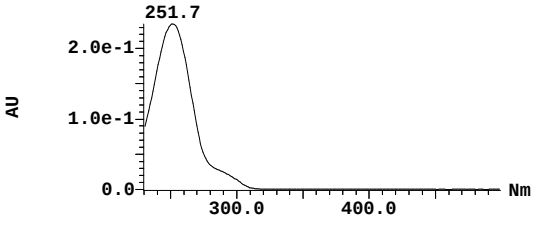


Sample Report:

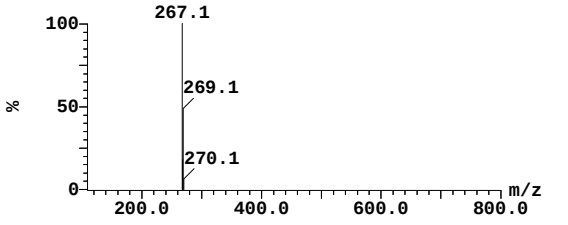
Sample 35 File MLUC013_B2_pure



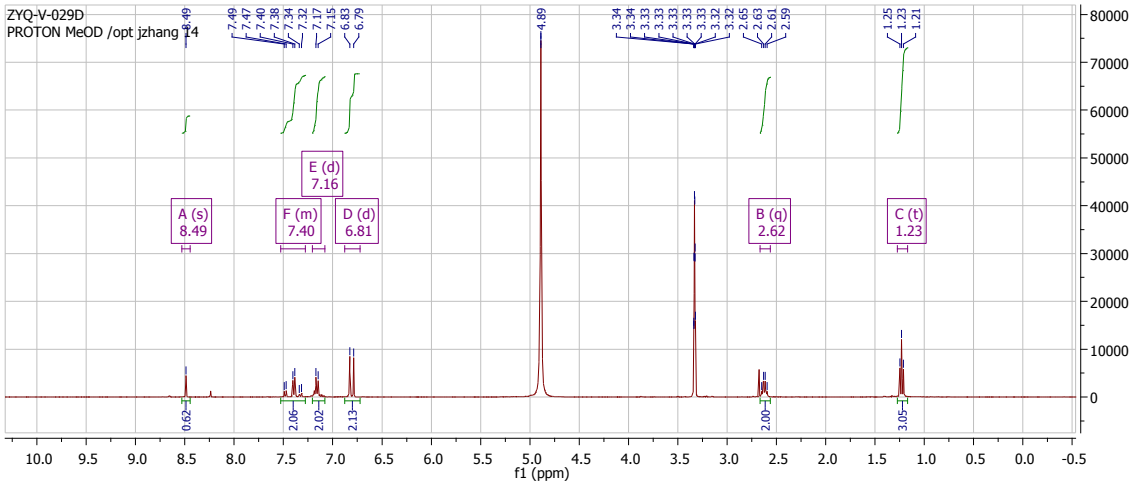
Peak ID	Compound	Time	Mass Found
1		1.81	



Peak ID	Compound	Time	Mass Found
1		1.81	

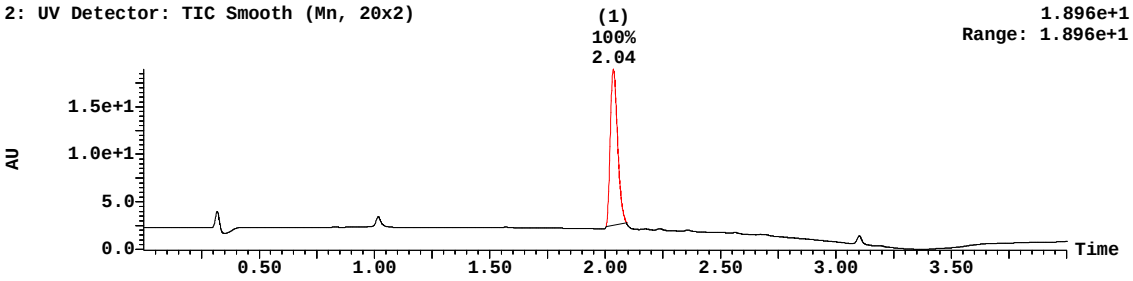


1-(4-Ethylphenyl)-3-(1H-imidazol-2-yl)urea, 4{19,4}:

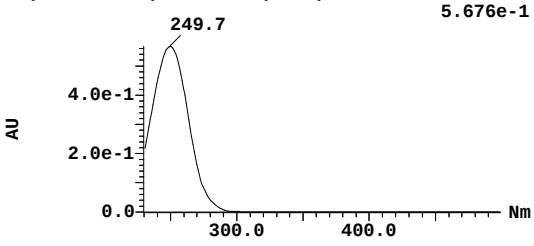


Sample Report:

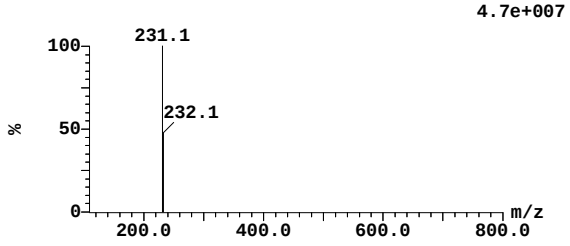
Sample 21 File MLUC005_F2_pure



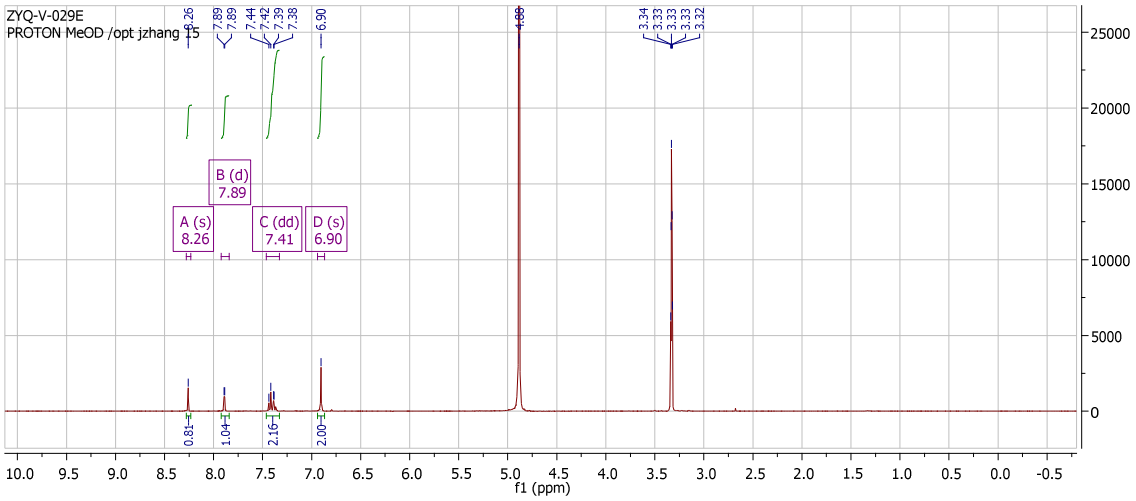
Peak ID	Compound	Time	Mass Found
1		2.04	



Peak ID	Compound	Time	Mass Found
1		2.04	

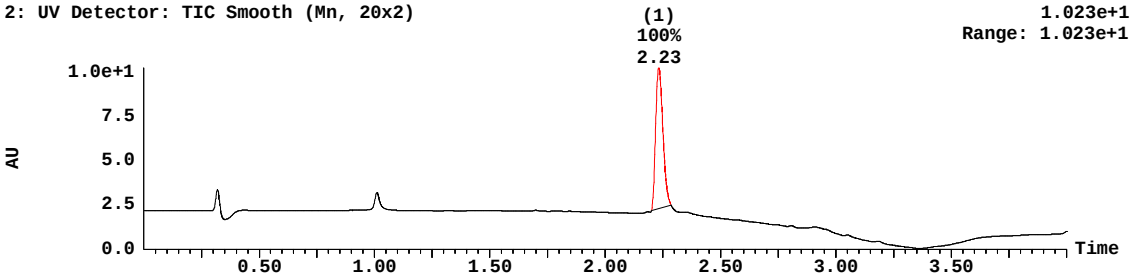


1-(3,4-Dichlorophenyl)-3-(1H-imidazol-2-yl)urea, 4{19,8}:

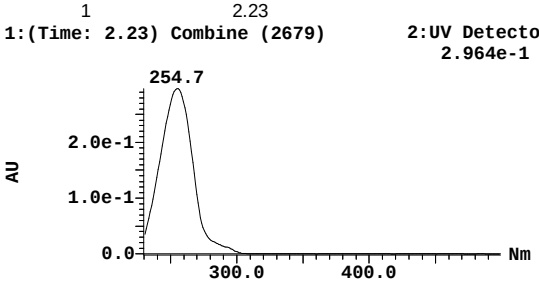


Sample Report:

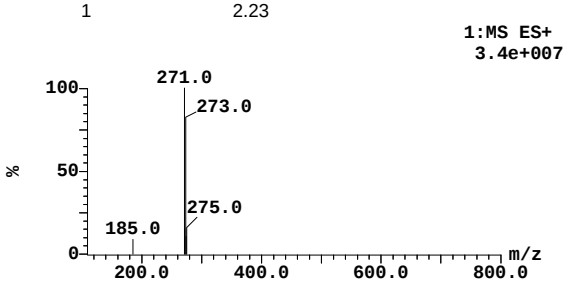
Sample 26 File MLUC005_G2_pure



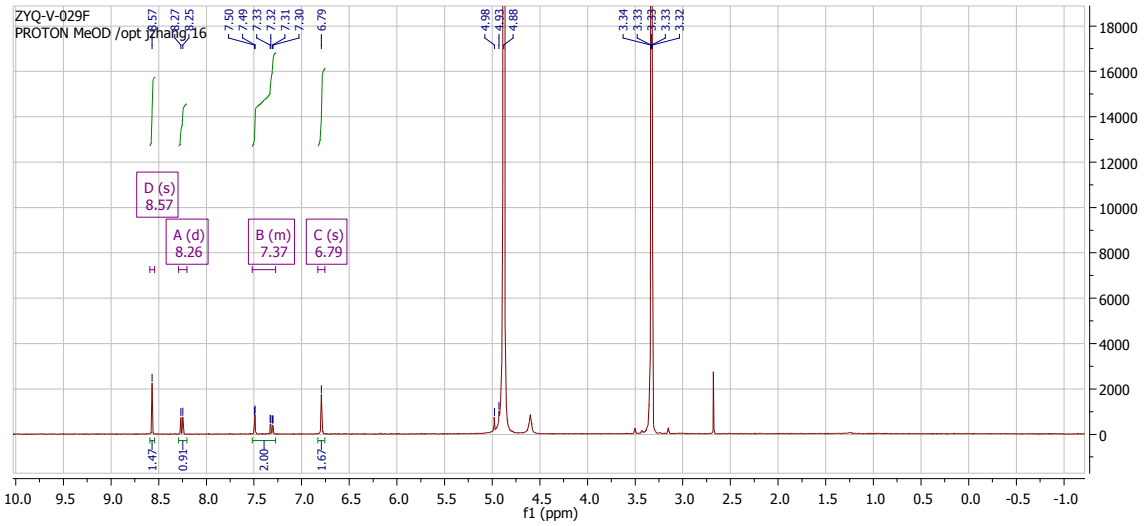
Peak ID	Compound	Time	Mass Found
1		2.23	



Peak ID	Compound	Time	Mass Found
1		2.23	

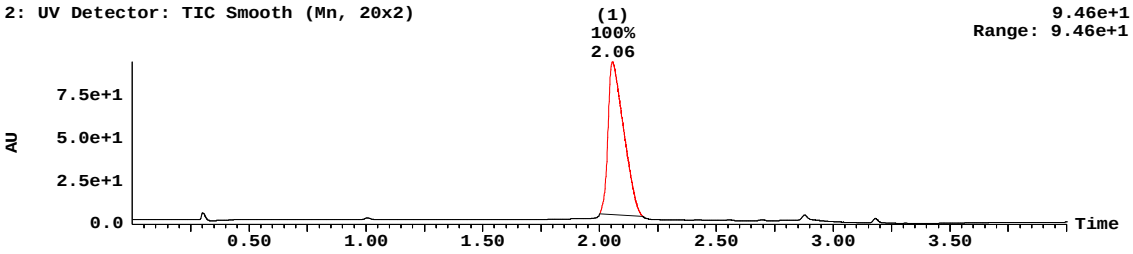


1-(2,4-Dichlorophenyl)-3-(1H-imidazol-2-yl)urea, 4{19,9}:

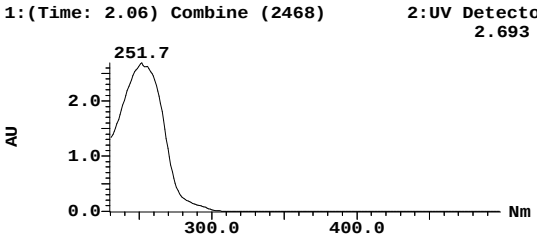


Sample Report:

Sample 16 File MLUC005_E2_pure



Peak ID	Compound	Time	Mass Found
1		2.06	



Peak ID	Compound	Time	Mass Found
1		2.06