Supporting Information

Design, Synthesis and Biological Evaluation of Triazolo-pyrimidine Derivatives as Novel Inhibitors of Hepatitis B Virus Surface Antigen (HBsAg) Secretion

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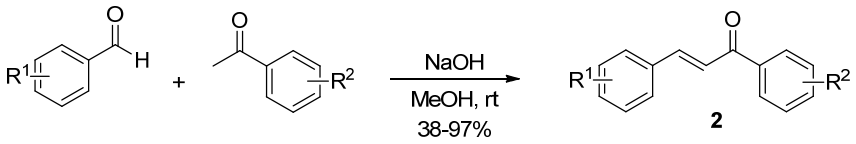
1. Synthesis of Compounds 1, 3 and 4

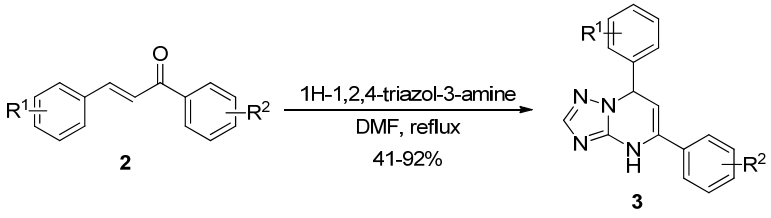
General information. ^{1}H NMR spectra were recorded on 500 MHz or 300 MHz INOVA VARIAN (75 MHz for ^{13}C NMR; 282 MHz for ^{19}F NMR) spectrometer. Chemical shifts values are given in ppm and referred as the internal standard to TMS (tetramethylsilane). The peak patterns are indicated as follows: s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet and dd, doublet of doublets. The coupling constants (*J*) are reported in Hertz (Hz). Melting points were determined with a national micromelting point apparatus without corrections. Mass Spectra were obtained on an Aligent LC-MS spectrometer (ES-API, Positive). Silica gel column chromatography was performed over silica gel 100-200 mesh, and the eluent was a mixture of ethyl acetate (EtOAc) and Hexanes. All the tested compounds possess a purity of at least 95% as determined by HPLC. Analytical HPLC was run on the Agilent 1100 HPLC instrument, equipped with Phenomenex® C12 column. Eluent system was: A (MeCN, 0.05%TFA) and C (H_2O, 0.05%TFA); flow rate = 1 mL/min; Method A: 60%A, 40%C, λ = 219 nm; Method B: 70%A, 30%C, λ = 254 nm; Method C: 80%A, 20%C, λ = 254 nm. Retention times (t_R) are given in minutes. Chiral resolution of compound **1a** was carried out on the Waters 2695 HPLC instrument, equipped with CHIRALPAK® AD-RH column. Eluent system was: 30%A (H_2O), 70%B (EtOH); flow rate = 0.5 mL/min; λ = 219 nm.

a. Preparation of 1,3-Diaryl-propenone 2



General Procedure A: To a stirred solution of substituted benzaldehyde (20 mmol) and acetophenone (20 mmol) in methanol (15 mL), was added dropwise a solution of sodium hydroxide (26 mmol) in methanol (15 mL). The resulting mixture was stirred at room temperature for 6 h, then filtered and washed with water to yield the crude product. Pure compound **2** was got by recrystallization from methanol or through silica gel column chromatography (EtOAc/Hexanes 2:98) as a light yellow solid in 38-97% yield.

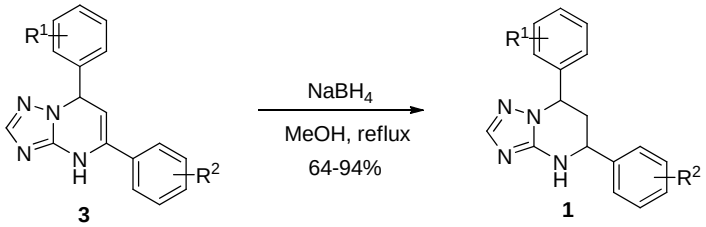
b. Preparation of 5,7-Diaryl-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine 3.



2 **3**

General Procedure B: A solution of **2** (5 mmol) and 3-amino-1,2,4-triazole (7.5 mmol) in DMF (5 mL) was refluxed for 2 h. The reaction mixture was cooled to room temperature, diluted with water (50 mL) and stirred sufficiently. The resulting mixture was filtered and washed with water to give the crude product, which was further purified either by recrystallization from EtOAc or through silica gel column chromatography (EtOAc/Hexanes 30:70) to afford **3** as a white solid in 41-92% yield.

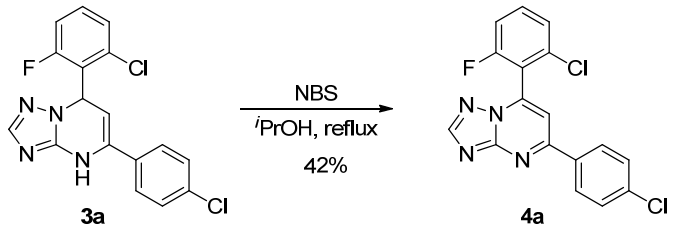
c. Synthesis of 5,7-Diaryl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine 1.



3 **1**

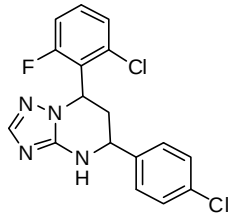
General Procedure C: A sample of sodium borohydride (10 mmol) was added to a suspension of **3** (1 mmol) in methanol (5 mL). The reaction mixture was refluxed for 30 min, then cooled to room temperature, diluted with water (50 mL) and stirred sufficiently. The resulting mixture was filtered and washed with water to give the crude product, which was further purified by recrystallization from a mixture of EtOAc and Hexanes to afford **1** as a white solid in 64-94% yield.

d. Synthesis of 7-(2-Chloro-6-fluorophenyl)-5-(4-chlorophenyl)-[1,2,4]triazolo [1, 5-a]pyrimidine 4a.



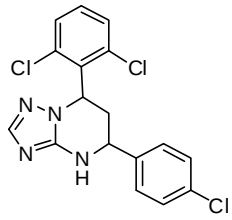
A sample of NBS (299 mg, 1.68 mmmol) was added to a solution of **3a** (101 mg, 0.28 mmol) in isopropanol (5 mL). The reaction mixture was refluxed for 36 h, then cooled to room temperature, treated with saturated $NaHCO_3$ solution (20 mL) and extracted with EtOAc (15 mL x 3). The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The given residue was purified through silica gel column chromatography (EtOAc/Hexanes 30:70) to afford a 42 mg white solid of **4a** in 42% yield.

7-(2-Chloro-6-fluorophenyl)-5-(4-chlorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1a).



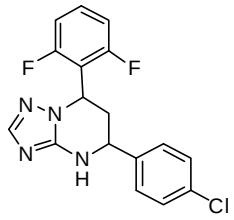
The product was obtained according to general procedure C, as a white solid. Yield: 89%. m.p. 227-228 ºC. R_f = 0.16 (EtOAc/Hexanes 33.3:66.7). MS: MH^+ = 363. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.54-7.15 (m, 8H, CH_{ar}), 5.98-5.94 (m, 1H, CH), 4.82-4.78 (m, 1H, CH), 2.47-2.13 (m, 2H, CH_2). HPLC: 99.8% (Method A, t_R= 3.67 min).

5-(4-Chlorophenyl)-7-(2,6-dichlorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1b).



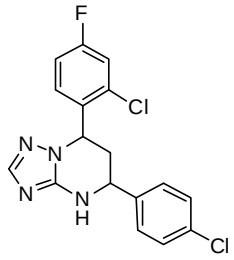
The product was obtained according to general procedure C, as a white solid. Yield: 88%. m.p. 246-247 ºC. R_f = 0.19 (EtOAc/Hexanes 75:25). MS: MH^+ = 379. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.55-7.35 (m, 8H, CH_{ar}), 6.17 (dd, J = 11.0, 6.5 Hz, 1H, CH), 4.81 (d, J = 10.0 Hz, 1H, CH), 2.42-2.30 (m, 2H, CH_2). HPLC: 98.2% (Method A, t_R = 4.10 min).

5-(4-Chlorophenyl)-7-(2,6-difluorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1c).



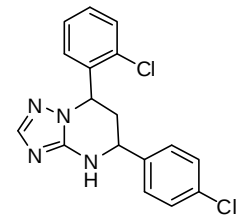
The product was obtained according to general procedure C, as a white solid. Yield: 84%. m.p. 245-246 ºC. R_f = 0.19 (EtOAc/Hexanes 75:25). MS: MH^+ = 347. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.52-7.11 (m, 8H, CH_{ar}), 5.80 (dd, J = 11.0, 4.5 Hz, 1H, CH), 4.79 (d, J = 11.0 Hz, 1H, CH), 2.46-2.18 (m, 2H, CH_2). HPLC: 98.9% (Method A, t_R = 3.35 min).

7-(2-Chloro-4-fluorophenyl)-5-(4-chlorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1d).



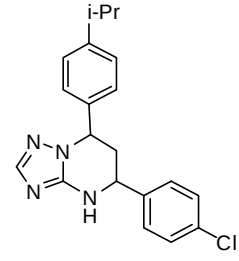
The product was obtained according to general procedure C, as a white solid. Yield: 94%. m.p. 224-225 ºC. R_f = 0.14 (EtOAc/Hexanes 75:25). MS: MH^+ = 363. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.58-7.17 (m, 8H, CH_{ar}), 5.73 (d, J = 3.5 Hz, 1H, CH), 4.78 (d, J = 10.5 Hz, 1H, CH), 2.44-2.18 (m, 2H, CH_2). HPLC: 96.8% (Method A, t_R = 4.12 min).

7-(2-Chlorophenyl)-5-(4-chlorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1e).



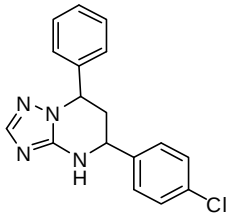
The product was obtained according to general procedure C, as a white solid. Yield: 68%. m.p. 202-204 ºC. R_f = 0.14 (EtOAc/Hexanes 75:25). MS: MH^+ = 345. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.56-7.27 (m, 9H, CH_{ar}), 7.08 (s, 1H, NH), 5.75 (s, 1H, CH), 4.78 (d, J = 10.5 Hz, 1H, CH), 2.46-2.16 (m, 2H, CH_2). HPLC: 98.8% (Method A, t_R = 3.63 min).

5-(4-Chlorophenyl)-7-(4-isopropylphenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1f).



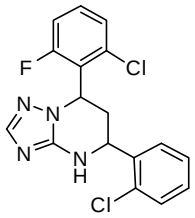
The product was obtained according to general procedure C, as a white solid. Yield: 75%. m.p. 194-195 ºC. R_f = 0.09 (EtOAc/Hexanes 75:25). MS: MH^+ = 353. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.47-7.44 (m, 3H, CH_{ar}), 7.41-7.38 (m, 2H, CH_{ar}), 7.18 (d, J = 8.0 Hz, 2H, CH_{ar}), 7.11 (d, J = 8.0 Hz, 2H, CH_{ar}), 5.34 (dd, J = 10.5, 5.0 Hz, 1H, CH), 4.70 (dd, J = 11.5, 2.5 Hz, 1H, CH), 2.90-2.82 (m, 1H, CH), 2.42-2.07 (m, 2H, CH_2), 1.18 (d, J = 7.0 Hz, 6H, CH_3). HPLC: 99.8% (Method A, t_R = 4.99 min).

5-(4-Chlorophenyl)-7-phenyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1g).



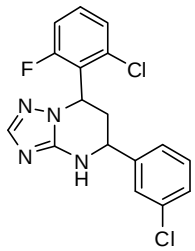
The product was obtained according to general procedure C, as a white solid. Yield: 77%. m.p. 210-212 ºC. R_f = 0.09 (EtOAc/Hexanes 75:25). MS: MH^+ = 311. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.48-7.46 (m, 3H, CH_{ar}), 7.42-7.39 (m, 2H, CH_{ar}), 7.35-7.26 (m, 3H, CH_{ar}), 7.22-7.20 (m, 2H, CH_{ar}), 5.40-5.37 (m, 1H, CH), 4.71 (dd, *J* = 11.0, 2.5 Hz, 1H, CH), 2.45-2.06 (m, 2H, CH_2). HPLC: 99.8% (Method A, t_R = 3.11 min).

7-(2-Chloro-6-fluorophenyl)-5-(2-chlorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1h).



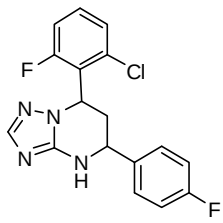
The product was obtained according to general procedure C, as a white solid. Yield: 90%. m.p. 271-272ºC. R_f = 0.17 (EtOAc/Hexanes 33.3:66.7). MS: MH^+ = 363. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.70-7.15 (m, 8H, CH_{ar}), 6.05-6.00 (m, 1H, CH), 5.16-5.13 (m, 1H, CH), 2.47-2.08 (m, 2H, CH_2). HPLC: 99.4% (Method A, t_R = 3.64 min).

7-(2-Chloro-6-fluorophenyl)-5-(3-chlorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1i).



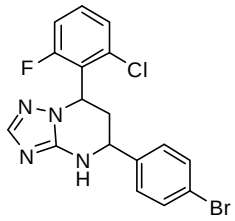
The product was obtained according to general procedure C, as a white solid. Yield: 80%. m.p. 262-263 ºC. R_f = 0.13 (EtOAc/Hexanes 33.3:66.7). MS: MH^+ = 363. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.56-7.17 (m, 8H, CH_{ar}), 5.94 (s, 1H, CH), 4.81 (s, 1H, CH), 2.48-2.15 (m, 2H, CH_2). HPLC: 99.7% (Method A, t_R = 3.16 min).

7-(2-Chloro-6-fluorophenyl)-5-(4-fluorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1j).



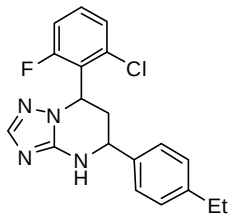
The product was obtained according to general procedure C, as a white solid. Yield: 68%. m.p. 240-241 ºC. R_f = 0.22 (EtOAc/Hexanes 75:25). MS: MH^+ = 347. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.52-7.15 (m, 8H, CH_{ar}), 5.98-5.93 (m, 1H, CH), 4.82-4.78 (m, 1H, CH), 2.48-2.14 (m, 2H, CH_2). HPLC: 98.4% (Method A, t_R = 3.86 min).

5-(4-Bromophenyl)-7-(2-chloro-6-fluorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1k).



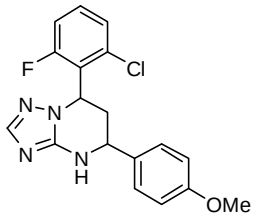
The product was obtained according to general procedure C, as a white solid. Yield: 64%. m.p. 246-247 ºC. R_f = 0.22 (EtOAc/Hexanes 75:25). MS: MH^+ = 409. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.58-7.15 (m, 8H, CH_{ar}), 5.97-5.95 (m, 1H, CH), 4.80-4.77 (m, 1H, CH), 2.43-2.15 (m, 2H, CH_2). HPLC: 99.5% (Method A, t_R = 4.09 min).

7-(2-Chloro-6-fluorophenyl)-5-(4-ethylphenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1l).



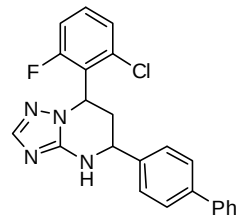
The product was obtained according to general procedure C, as a white solid. Yield: 90%. m.p. 230-231 ºC. R_f = 0.28 (EtOAc/Hexanes 75:25). MS: MH^+ = 357. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.44-7.15 (m, 8H, CH_{ar}), 5.97-5.93 (m, 1H, CH), 4.75-4.72 (m, 1H, CH), 2.60 (q, J = 7.5 Hz, 2H, CH_2), 2.47-2.15 (m, 2H, CH_2), 1.17 (t, J = 7.5 Hz, 3H, CH_3). HPLC: 99.8% (Method A, t_R = 3.67 min).

7-(2-Chloro-6-fluorophenyl)-5-(4-methoxyphenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1m).



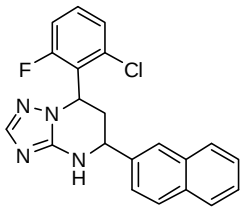
The product was obtained according to general procedure C, as a white solid. Yield: 86%. m.p. 221-222 ºC. R_f = 0.20 (EtOAc/Hexanes 75:25). MS: MH^+ = 359. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.41-6.93 (m, 8H, CH_{ar}), 5.96-5.92 (m, 1H, CH), 4.72 (d, J = 10.5 Hz, 1H, CH), 3.75 (s, 3H, OCH_3), 2.46-2.14 (m, 2H, CH_2). HPLC: 99.4% (Method A, t_R = 3.03 min).

5-([1,1'-Biphenyl]-4-yl)-7-(2-chloro-6-fluorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1n).



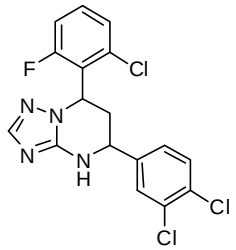
The product was obtained according to general procedure C, as a white solid. Yield: 84%. m.p. 213-215 ºC. R_f = 0.20 (EtOAc/Hexanes 75:25). MS: MH^+ = 405. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.69-7.16 (m, 13H, CH_{ar}), 6.01-5.97 (m, 1H, CH), 4.85-4.82 (m, 1H, CH), 2.47-2.21 (m, 2H, CH_2). HPLC: 99.0% (Method A, t_R = 4.92 min).

7-(2-Chloro-6-fluorophenyl)-5-(naphthalen-2-yl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1o).



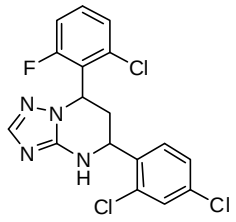
The product was obtained according to general procedure C, as a white solid. Yield: 72%. m.p. 224-225 ºC. R_f = 0.31 (EtOAc/Hexanes 75:25). MS: MH^+ = 379. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.01-7.16 (m, 11H, CH_{ar}), 6.05-6.00 (m, 1H, CH), 4.98-4.95 (m, 1H, CH), 2.61-2.27 (m, 2H, CH_2, overlapped with the peaks of DMSO). HPLC: 99.6% (Method A, t_R = 4.02 min).

7-(2-Chloro-6-fluorophenyl)-5-(3,4-dichlorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1p).



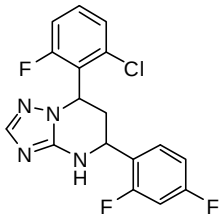
The product was obtained according to general procedure C, as a white solid. Yield: 77%. m.p. 252-254 ºC. R_f = 0.21 (EtOAc/Hexanes 75:25). MS: MH^+ = 397. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.72-7.15 (m, 7H, CH_{ar}), 5.97-5.92 (m, 1H, CH), 4.84-4.80 (m, 1H, CH), 2.47-2.14 (m, 2H, CH_2). HPLC: 99.7% (Method A, t_R = 4.56 min).

7-(2-Chloro-6-fluorophenyl)-5-(2,4-dichlorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1q).



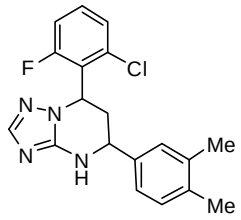
The product was obtained according to general procedure C, as a white solid. Yield: 88%. m.p. 267-269 ºC. R_f = 0.22 (EtOAc/Hexanes 33.3:66.7). MS: MH^+ = 397. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.70-7.15 (m, 7H, CH_{ar}), 6.05-6.00 (m, 1H, CH), 5.14-5.11 (m, 1H, CH), 2.49-2.09 (m, 2H, CH_2). HPLC: 98.7% (Method A, t_R = 4.96 min).

7-(2-Chloro-6-fluorophenyl)-5-(2,4-difluorophenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1r).



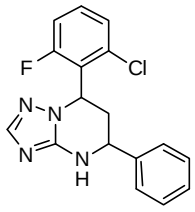
The product was obtained according to general procedure C, as a white solid. Yield: 92%. m.p. 225 ºC. R_f = 0.28 (EtOAc/Hexanes 75:25). MS: MH^+ = 365. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.65-7.12 (m, 7H, CH_{ar}), 6.04-5.99 (m, 1H, CH), 5.05 (d, J = 10.5 Hz, 1H, CH), 2.43-2.23 (m, 2H, CH_2). HPLC: 99.1% (Method A, t_R = 3.37 min).

7-(2-Chloro-6-fluorophenyl)-5-(3,4-dimethylphenyl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1s).



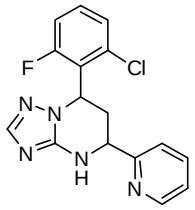
The product was obtained according to general procedure C, as a white solid. Yield: 88%. m.p. 223 ºC. R_f = 0.25 (EtOAc/Hexanes 75:25). MS: MH^+ = 357. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.41-7.12 (m, 7H, CH_{ar}), 5.97-5.92 (m, 1H, CH), 4.69 (d, J = 10.5 Hz, 1H, CH), 2.46-2.14 (m, 2H, CH_2, overlapped with the peaks of two CH_3), 2.23 (s, 3H, CH_3, overlapped with the peaks of CH_2), 2.20 (s, 3H, CH_3, overlapped with the peaks of CH_2). HPLC: 99.7% (Method A, t_R = 3.95 min).

7-(2-Chloro-6-fluorophenyl)-5-phenyl-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1t).



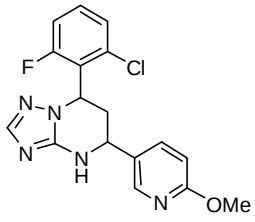
The product was obtained according to general procedure C, as a white solid. Yield: 82%. m.p. 270-271 ºC. R_f = 0.26 (EtOAc/Hexanes 75:25). MS: MH^+ = 329. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.50-7.15 (m, 9H, CH_{ar}), 5.99-5.94 (m, 1H, CH), 4.80-4.76 (m, 1H, CH), 2.48-2.16 (m, 2H, CH_2). HPLC: 99.5% (Method A, t_R = 3.05 min).

7-(2-Chloro-6-fluorophenyl)-5-(pyridin-2-yl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1u).



The product was obtained according to general procedure C, as a white solid. Yield: 65%. m.p. 232 ºC. R_f = 0.08 (EtOAc/Hexanes 90:10). MS: MH^+ = 330. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.56-8.54 (m, 1H, CH_{ar}), 7.87-7.83 (m, 1H, CH_{ar}), 7.60-7.13 (m, 6H, CH_{ar}), 6.05-5.99 (m, 1H, CH), 4.88-4.85 (m, 1H, CH), 2.60-2.23 (m, 2H, CH_2, overlapped with the peaks of DMSO). HPLC: 99.7% (Method A, t_R = 2.24 min).

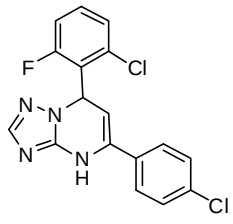
7-(2-Chloro-6-fluorophenyl)-5-(6-methoxypyridin-3-yl)-4,5,6,7-tetrahydro-[1,2,4]triazolo[1,5-a]pyrimidine (1v).



The product was obtained according to general procedure C, as a white solid. Yield: 64%. m.p. 230-221 ºC. R_f = 0.14 (EtOAc/Hexanes 90:10). MS: MH^+ = 360. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.22 (d, J = 2.0 Hz, 1H, CH_{ar}), 7.79-7.77 (m, 1H, CH_{ar}), 7.48-7.16 (m, 4H, CH_{ar}), 6.86-6.82

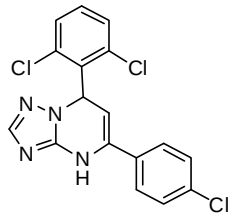
(m, 1H, CH_{ar}), 5.98-5.93 (m, 1H, CH), 4.79-4.75 (m, 1H, CH), 3.85 (s, 3H, OCH_3), 2.47-2.20 (m, 2H, CH_2). HPLC: 95.0% (Method A, t_R = 2.61 min).

7-(2-Chloro-6-fluorophenyl)-5-(4-chlorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3a).



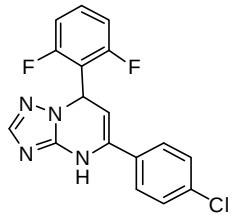
The product was obtained according to general procedure B, as a white solid. Yield: 78%. m.p. 213-215 ºC. R_f = 0.43 (EtOAc/Hexanes 50:50). MS: MH^+ = 361. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.16 (s, 1H, NH), 7.66-7.61 (m, 3H, CH_{ar}), 7.49-7.21 (m, 5H, CH_{ar}), 6.81-6.80 (m, 1H, CH=C), 5.19 (s, 1H, CH). HPLC: 99.5% (Method B, t_R = 5.75 min).

5-(4-Chlorophenyl)-7-(2,6-dichlorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3b).



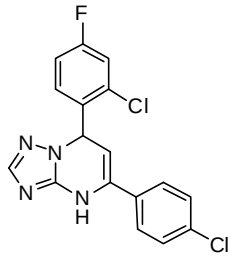
The product was obtained according to general procedure B, as a white solid. Yield: 91%. m.p. 235 ºC. R_f = 0.44 (EtOAc/Hexanes 50:50). MS: MH^+ = 377. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.20 (s, 1H, NH), 7.65-7.35 (m, 8H, CH_{ar}), 7.06 (d, J = 3.6 Hz, 1H, CH=C), 5.10 (dd, J = 3.3, 1.5 Hz, 1H, CH). HPLC: 99.9% (Method B, t_R = 6.64 min).

5-(4-Chlorophenyl)-7-(2,6-difluorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3c).



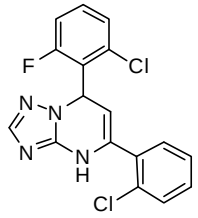
The product was obtained according to general procedure B, as a white solid. Yield: 83%. m.p. 223-224 ºC. R_f = 0.40 (EtOAc/Hexanes 50:50). MS: MH^+ = 345. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.13 (s, 1H, NH), 7.66-7.61 (m, 3H, CH_{ar}), 7.49-7.41 (m, 3H, CH_{ar}), 7.13-7.07 (m, 2H, CH_{ar}), 6.63 (d, J = 3.6 Hz, 1H, CH=C), 5.26-5.25 (m, 1H, CH); ^{19}F NMR (282 MHz, DMSO-d_6): δ -118.26. ^{13}C NMR (75 MHz, DMSO-d_6): δ 160.6 (dd, J_{C-F} = 247.9, 7.7 Hz, C), 150.5 (C), 150.4 (C), 135.9 (C), 134.3 (C), 133.5 (CH), 131.4 (t, J_{C-F} = 10.7 Hz, C), 129.2 (CH), 128.4 (CH), 117.2 (t, J_{C-F} = 15.2 Hz, C), 112.8 (d, J_{C-F} = 24.9 Hz, CH), 95.1 (CH), 50.8 (CH). HPLC: 98.8% (Method B, t_R = 4.96 min).

7-(2-Chloro-4-fluorophenyl)-5-(4-chlorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3d).



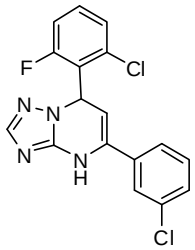
The product was obtained according to general procedure B, as a white solid. Yield: 83%. m.p. 250-251 ºC. R_f = 0.17 (EtOAc/Hexanes 50:50). MS: MH^+ = 361. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.18 (d, *J* = 1.5 Hz, 1H, NH), 7.69 (s, 1H, CH_{ar}), 7.64-7.61 (m, 2H, CH_{ar}), 7.49-7.46 (m, 3H, CH_{ar}), 7.25-7.22 (m, 2H, CH_{ar}), 6.57 (d, *J* = 3.6 Hz, 1H, CH=C), 5.17 (dd, *J* = 3.6, 1.5 Hz, 1H, CH). HPLC: 98.4% (Method B, t_R = 6.39 min).

7-(2-Chloro-6-fluorophenyl)-5-(2-chlorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3h).



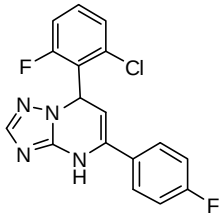
The product was obtained according to general procedure B, as a white solid. Yield: 77%. m.p. 192-193 ºC. R_f = 0.40 (EtOAc/Hexanes 50:50). MS: MH^+ = 361. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.12 (s, 1H, NH), 7.63 (s, 1H, CH_{ar}), 7.54-7.25 (m, 7H, CH_{ar}), 6.57 (d, *J* = 1.5 Hz, 1H, CH=C), 4.74 (s, 1H, CH). HPLC: 98.0% (Method B, t_R = 4.94 min).

7-(2-Chloro-6-fluorophenyl)-5-(3-chlorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3i).



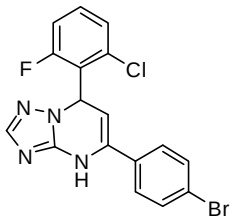
The product was obtained according to general procedure B, as a white solid. Yield: 88%. m.p. 246-248 ºC. R_f = 0.36 (EtOAc/Hexanes 50:50). MS: MH^+ = 361. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.15 (s, 1H, NH), 7.66-7.17 (m, 8H, CH_{ar}), 6. 78 (d, *J* = 2.1 Hz, 1H, CH=C), 5.26 (s, 1H, CH). HPLC: 97.5% (Method B, t_R = 5.85 min).

7-(2-Chloro-6-fluorophenyl)-5-(4-fluorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3j).



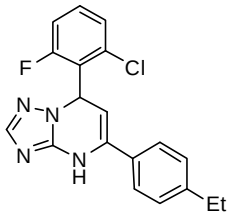
The product was obtained according to general procedure B, as a white solid. Yield: 57%. m.p. 203-204 ºC. R_f = 0.34 (EtOAc/Hexanes 50:50). MS: MH^+ = 345. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.13 (s, 1H, NH), 7.68-7.63 (m, 3H, CH_{ar}), 7.45-7.21 (m, 5H, CH_{ar}), 6.80-6.79 (m, 1H, CH=C), 5.12 (s, 1H, CH). HPLC: 96.4% (Method B, t_R = 4.62 min).

5-(4-Bromophenyl)-7-(2-chloro-6-fluorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3k).



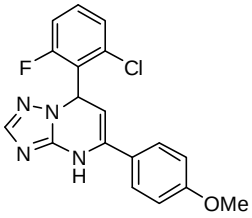
The product was obtained according to general procedure B, as a white solid. Yield: 73%. m.p. 242-243 ºC. R_f = 0.28 (EtOAc/Hexanes 50:50). MS: MH^+ = 407. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.16 (s, 1H, NH), 7.65-7.38 (m, 8H, CH_{ar}), 6.80 (d, J = 1.8 Hz, 1H, CH=C), 5.19 (s, 1H, CH). HPLC: 99.6% (Method B, t_R = 6.57 min).

7-(2-Chloro-6-fluorophenyl)-5-(4-ethylphenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3l).



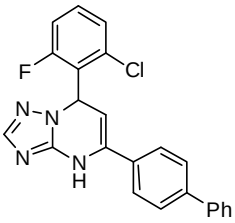
The product was obtained according to general procedure B, as a white solid. Yield: 76%. m.p. 220-221 ºC. R_f = 0.40 (EtOAc/Hexanes 50:50). MS: MH^+ = 355. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.15 (d, J = 0.9 Hz, 1H, NH), 7.64 (s, 1H, CH_{ar}), 7.53-7.23 (m, 7H, CH_{ar}), 6.80-6.79 (m, 1H, CH=C), 5.81 (s, 1H, CH), 2.63 (q, J = 1.8 Hz, 2H, CH_2), 1.18 (t, J = 7.5 Hz, 3H, CH_3). HPLC: 99.1% (Method B, t_R = 6.15 min).

7-(2-Chloro-6-fluorophenyl)-5-(4-methoxyphenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3m).



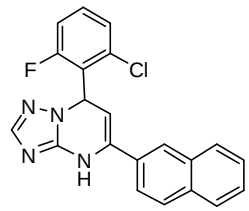
The product was obtained according to general procedure B, as a white solid. Yield: 76%. m.p. 217-218 ºC. R_f = 0.22 (EtOAc/Hexanes 50:50). MS: MH^+ = 357. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.02 (s, 1H, NH), 7.64-6.94 (m, 8H, CH_{ar}), 6.79-6.78 (m, 1H, CH=C), 5.03 (s, 1H, CH), 3.78 (s, 3H, OCH_3). HPLC: 99.1% (Method B, t_R = 4.32 min).

5-([1,1'-Biphenyl]-4-yl)-7-(2-chloro-6-fluorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3n).



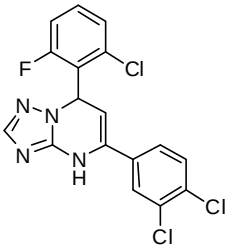
The product was obtained according to general procedure B, as a white solid. Yield: 81%. m.p. 267 ºC. R_f = 0.17 (EtOAc/Hexanes 50:50). MS: MH^+ = 403. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.17 (d, J = 1.2 Hz, 1H, NH), 7.72-7.66 (m, 7H, CH_{ar}), 7.50-7.38 (m, 6H, CH_{ar}), 6.83 (m, 1H, CH=C), 5.22 (s, 1H, CH). HPLC: 99.1% (Method B, t_R = 7.85 min).

7-(2-Chloro-6-fluorophenyl)-5-(naphthalen-2-yl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3o).



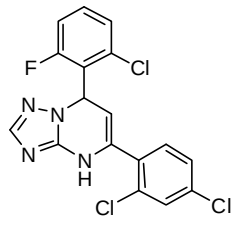
The product was obtained according to general procedure B, as a white solid. Yield: 92%. m.p. 237 ºC. R_f = 0.34 (EtOAc/Hexanes 50:50). MS: MH^+ = 377. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.25 (s, 1H, NH), 8.22 (s, 1H, CH_{ar}), 7.97-7.92 (m, 3H, CH_{ar}), 7.75-7.40 (m, 7H, CH_{ar}), 6.87 (d, *J* = 1.8 Hz, 1H, CH=C), 5.33 (s, 1H, CH). HPLC: 98.9% (Method B, t_R = 6.45 min).

7-(2-Chloro-6-fluorophenyl)-5-(3,4-dichlorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3p).



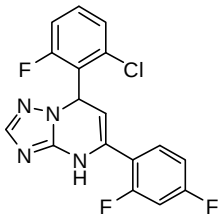
The product was obtained according to general procedure B, as a white solid. Yield: 57%. m.p. 246-247 ºC. R_f = 0.30 (EtOAc/Hexanes 50:50). MS: MH^+ = 395. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.20 (s, 1H, NH), 7.90 (d, *J* = 1.8 Hz, 1H, CH_{ar}), 7.69-7.19 (m, 6H, CH_{ar}), 6.82-6.80 (m, 1H, CH=C), 5.36 (s, 1H, CH). HPLC: 97.1% (Method B, t_R = 7.61 min).

7-(2-Chloro-6-fluorophenyl)-5-(2,4-dichlorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3q).



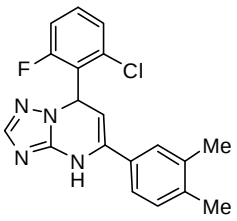
The product was obtained according to general procedure B, as a white solid. Yield: 52%. m.p. 209-211 ºC. R_f = 0.46 (EtOAc/Hexanes 50:50). MS: MH^+ = 395. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.14 (s, 1H, NH), 7.72-7.24 (m, 7H, CH_{ar}), 6.80 (d, *J* = 1.8 Hz, 1H, CH=C), 4.79 (s, 1H, CH). HPLC: 95.0% (Method B, t_R = 6.80 min).

7-(2-Chloro-6-fluorophenyl)-5-(2,4-difluorophenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3r).



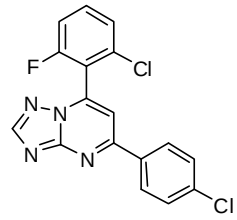
The product was obtained according to general procedure B, as a white solid. Yield: 66%. m.p. 186-188 ºC. R_f = 0.46 (EtOAc/Hexanes 50:50). MS: MH^+ = 363. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.15 (s, 1H, NH), 7.64-7.11 (m, 7H, CH_{ar}), 6.81-6.80 (m, 1H, CH=C), 4.91 (s, 1H, CH). HPLC: 96.3% (Method B, t_R = 4.65 min).

7-(2-Chloro-6-fluorophenyl)-5-(3,4-dimethylphenyl)-4,7-dihydro-[1,2,4]triazolo[1,5-a]pyrimidine (3s).



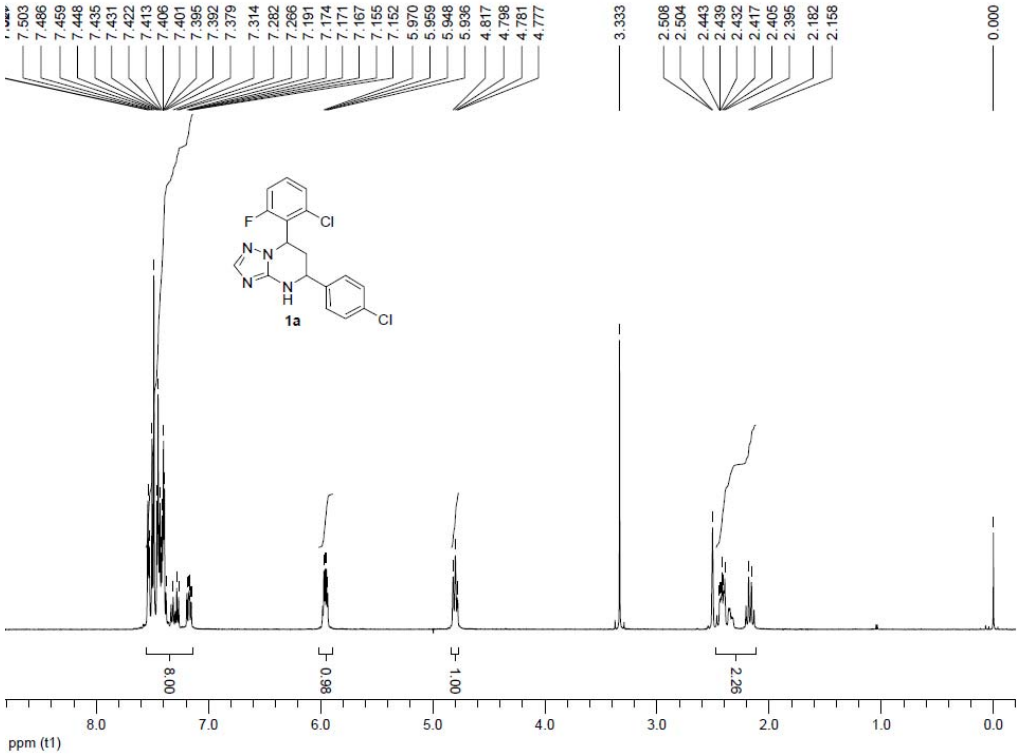
The product was obtained according to general procedure B, as a white solid. Yield: 70%. m.p. 217-218 ºC. R_f = 0.40 (EtOAc/Hexanes 50:50). MS: MH^+ = 355. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.00 (s, 1H, NH), 7.64 (s, 1H, CH_{ar}), 7.42-7.14 (m, 6H, CH_{ar}), 6.79-6.78 (m, 1H, CH=C), 5.07 (s, 1H, CH). HPLC: 99.6% (Method B, t_R = 6.37 min).

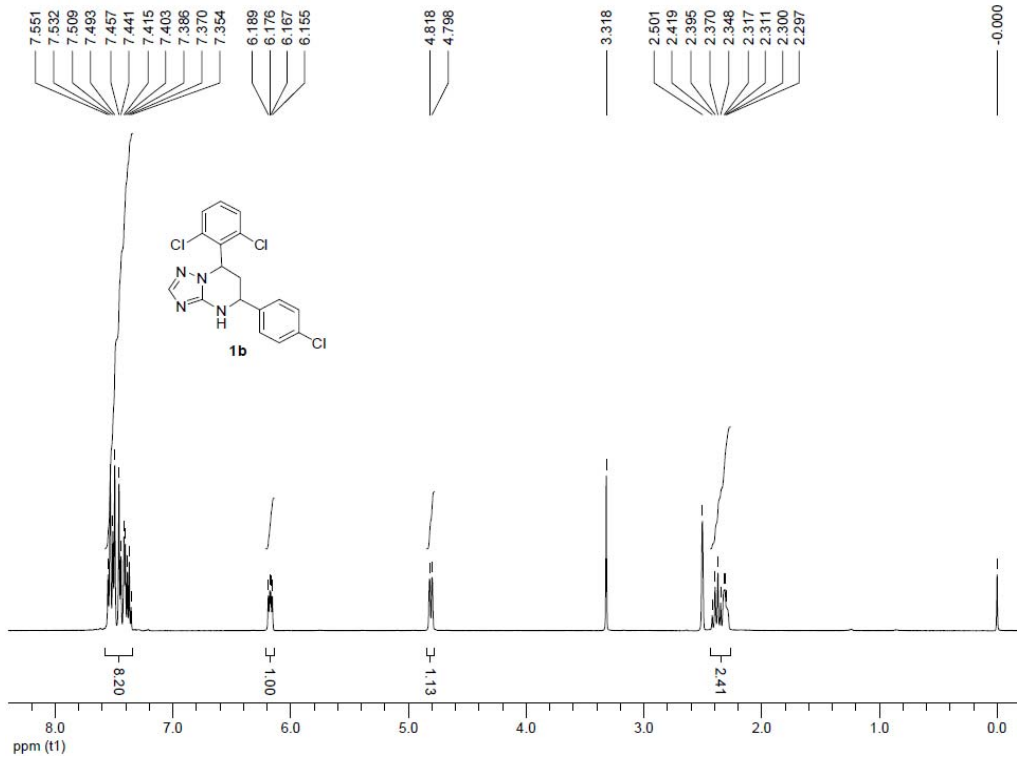
7-(2-Chloro-6-fluorophenyl)-5-(4-chlorophenyl)-[1,2,4]triazolo[1,5-a]pyrimidine (4a).

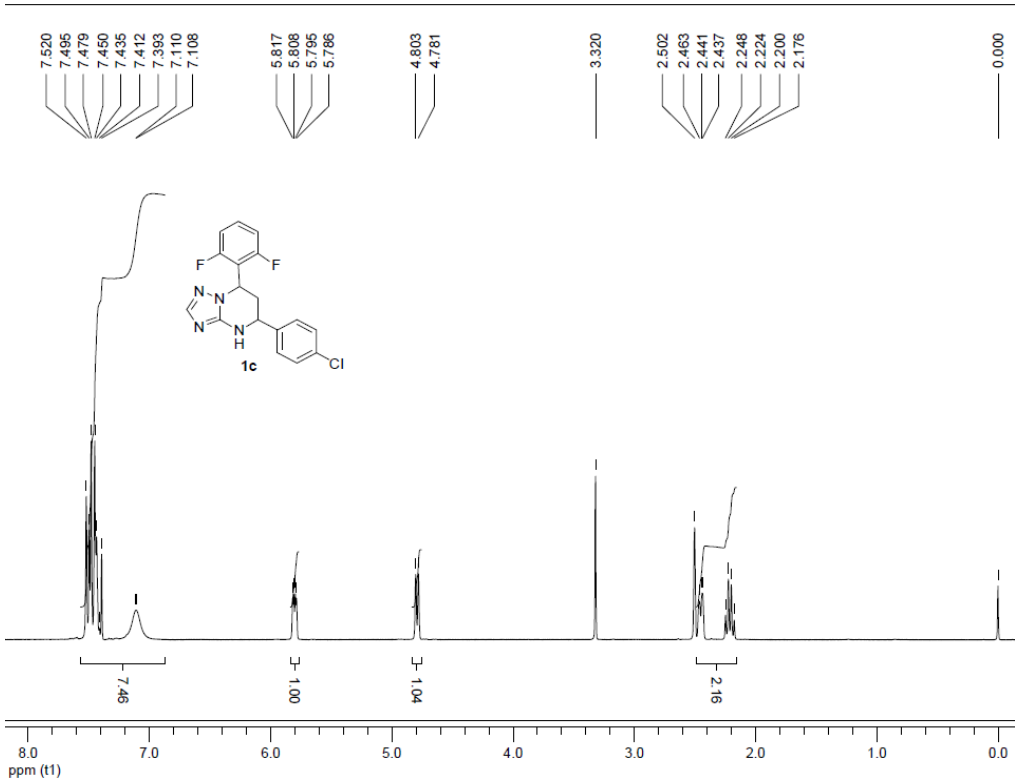


Yield: 42%. m.p. 238-239 ºC. R_f = 0.33 (EtOAc/Hexanes 30:70). MS: MH^+ = 359. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.48 (s, 1H, CH_{ar}), 8.15 (d, *J* = 7.5 Hz, 2H, CH_{ar}), 7.57-7.39 (m, 5H, CH_{ar}), 7.20-7.19 (m, 1H, CH_{ar}). HPLC: 97.9 % (Method C, t_R = 5.47 min).

2. NMR Spectra of Compounds 1, 3 and 4



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7.110
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5.808
5.795
5.786
4.803
4.781
3.320
2.502
2.463
2.441
2.437
2.248
2.224
2.200
2.176
0.000
F
F
N
N
N
H
Cl
1c
7.46
1.00
1.04
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7.0
6.0
5.0
4.0
3.0
2.0
1.0
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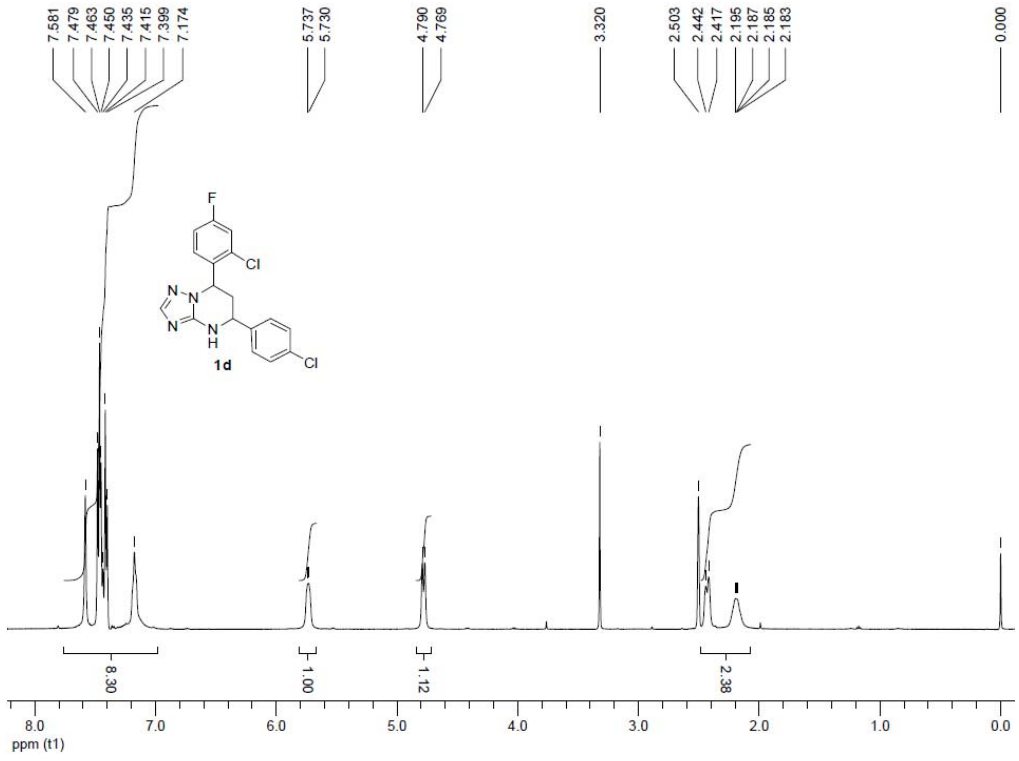
ppm (t1)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7.399
7.174
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5.730
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3.320
2.503
2.442
2.417
2.195
2.187
2.185
2.183
0.000
F
Cl
N
N
N
H
Cl
1d
8.30
1.00
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6.0
5.0
4.0
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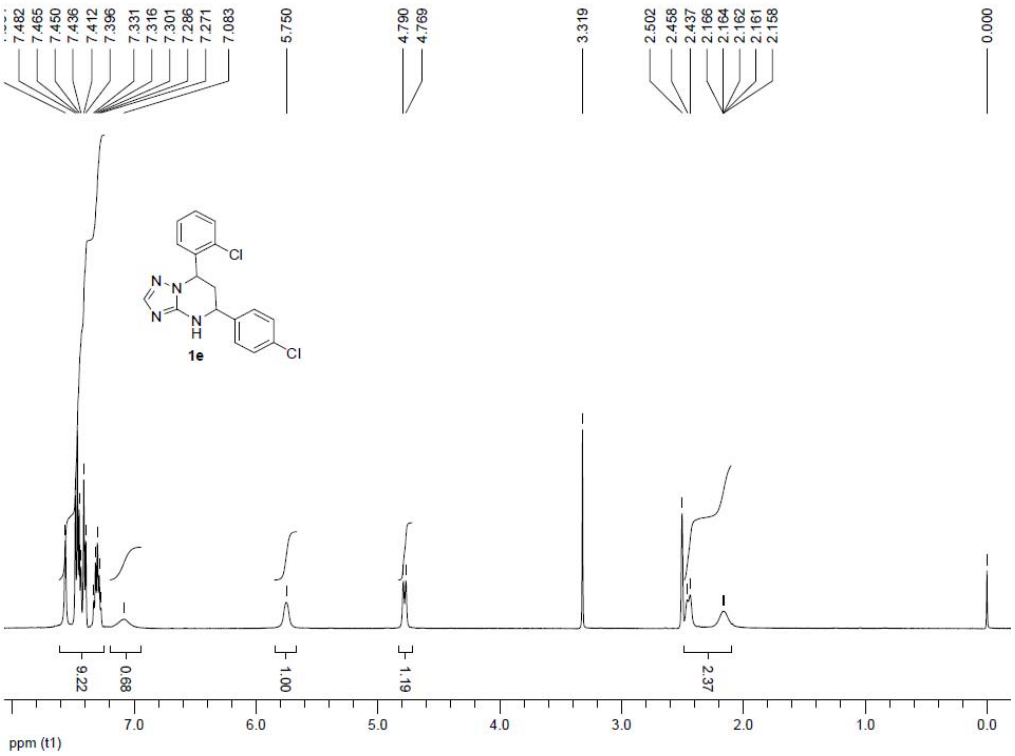
0.0
ppm (t1)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7.316
7.301
7.286
7.271
7.083
5.750
4.790
4.769
3.319
2.502
2.458
2.437
2.166
2.164
2.162
2.161
2.158
0.000
Cl
N
N
N
H
Cl
1e
9.22
0.88
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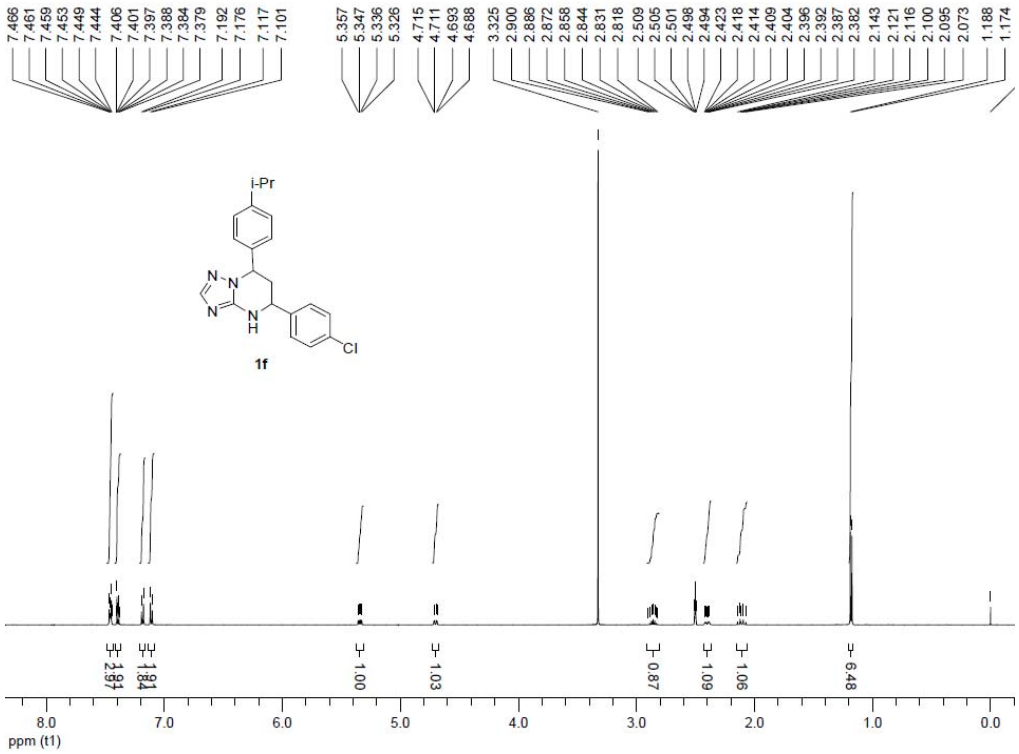
0.0
ppm (t1)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7.406
7.401
7.397
7.388
7.384
7.379
7.192
7.176
7.117
7.101
5.357
5.347
5.336
5.326
4.715
4.711
4.693
4.688
3.325
2.900
2.886
2.872
2.858
2.844
2.831
2.818
2.509
2.505
2.501
2.498
2.494
2.423
2.418
2.414
2.409
2.404
2.396
2.392
2.387
2.382
2.143
2.121
2.116
2.100
2.095
2.073
1.188
1.174
i-Pr
N
N
N
H
Cl
1f
2.97
1.91
1.84
1.00
1.03
0.87
1.09
1.06
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6.0
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4.0
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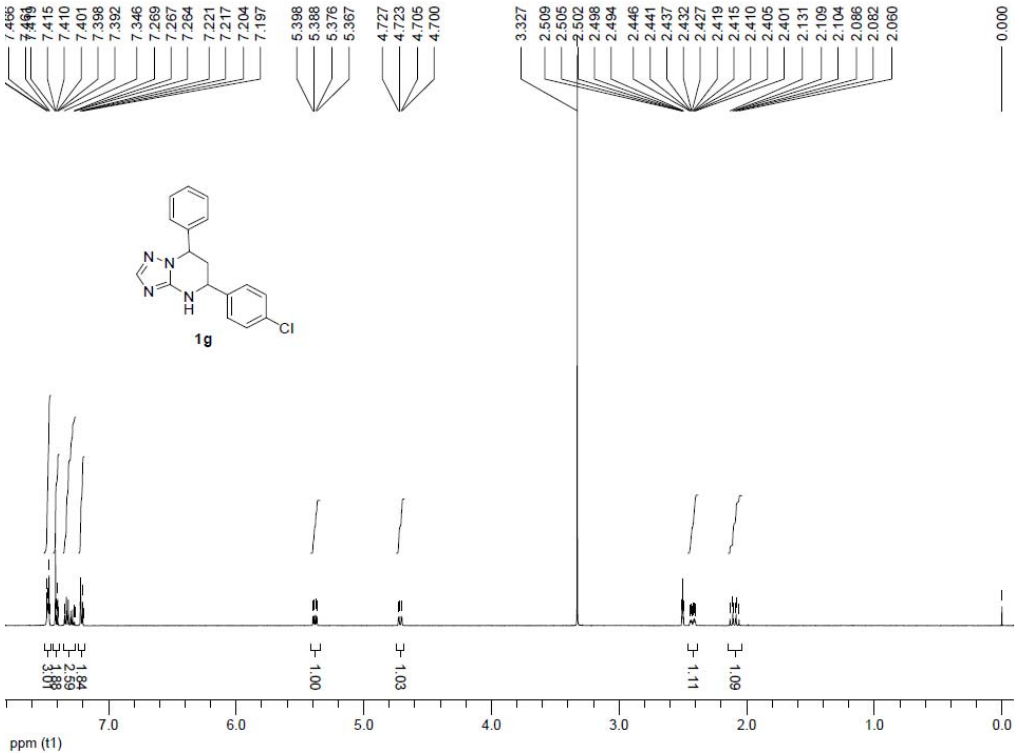
ppm (t1)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7.410
7.401
7.398
7.392
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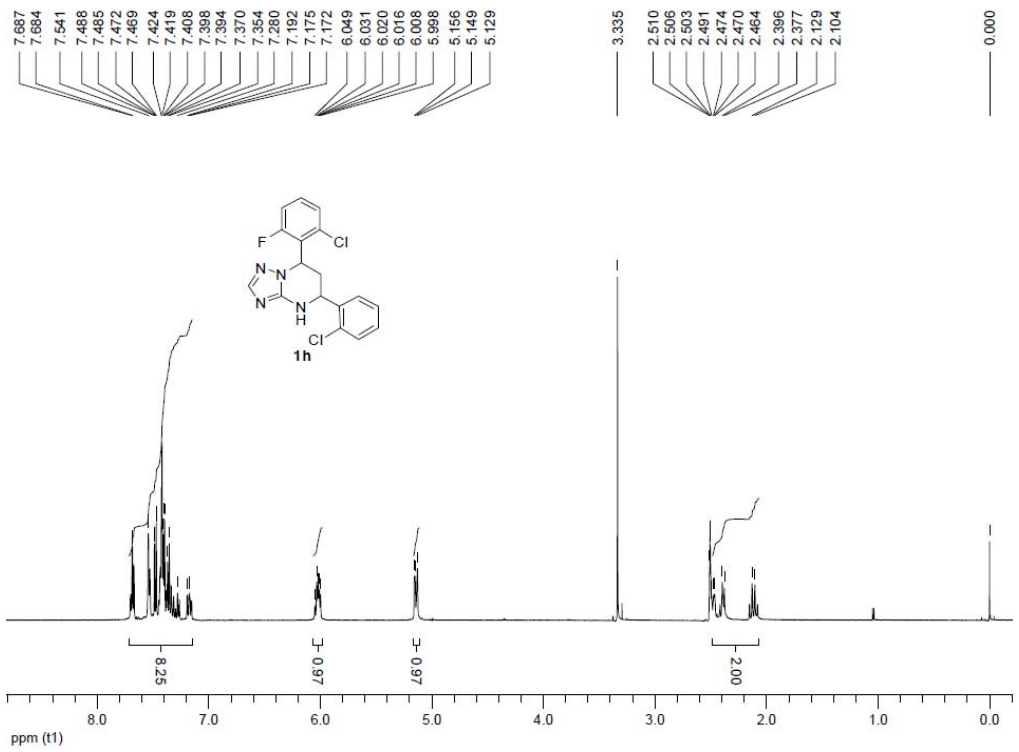
7.269
7.267
7.264
7.221
7.217
7.204
7.197
5.398
5.388
5.376
5.367
4.727
4.723
4.705
4.700
3.327
2.509
2.505
2.502
2.498
2.494
2.446
2.441
2.437
2.432
2.427
2.419
2.415
2.410
2.405
2.401
2.131
2.109
2.104
2.088
2.082
2.060
0.000
1g
1.00
1.03
1.11
1.09
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)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7.424
7.419
7.408
7.398
7.394
7.370
7.354
7.280
7.192
7.175
7.172
6.049
6.031
6.020
6.016
6.008
5.998
5.156
5.149
5.129
3.335
2.510
2.506
2.503
2.491
2.474
2.470
2.464
2.396
2.377
2.129
2.104
0.000
1h
8.25
0.97
0.97
2.00
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6.0
5.0
4.0
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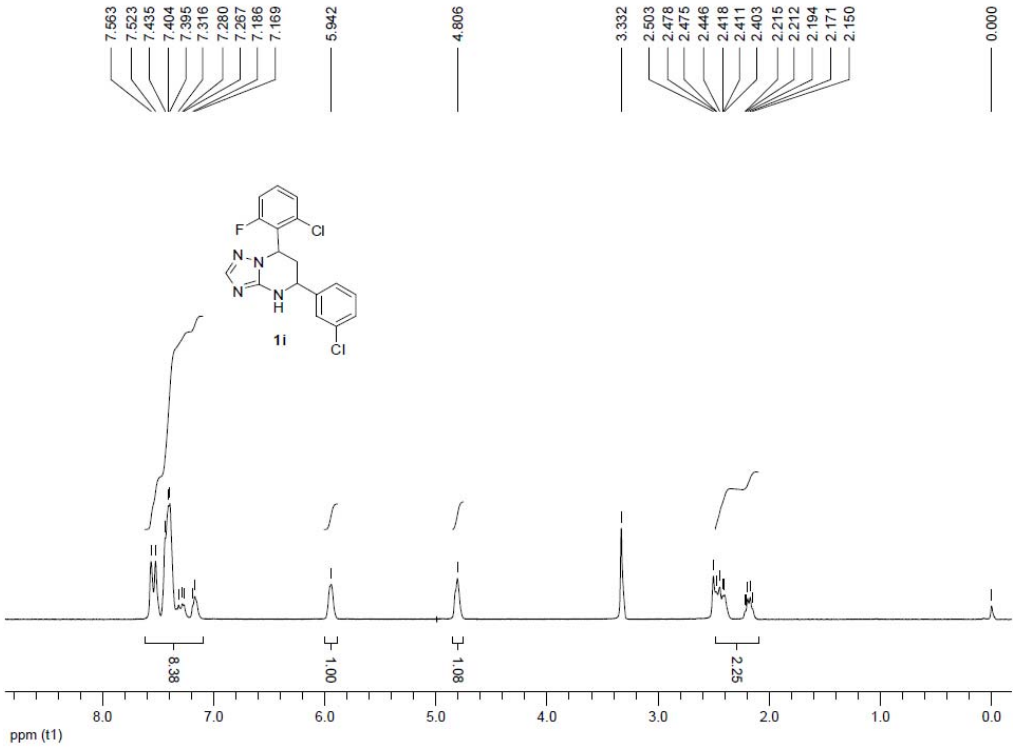
2.0
1.0
0.0
ppm (t1)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7.404
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7.280
7.267
7.186
7.169
5.942
4.806
3.332
2.503
2.478
2.475
2.446
2.418
2.411
2.403
2.215
2.212
2.194
2.171
2.150
0.000
F
Cl
N
N
N
H
Cl
1i
8.38
1.00
1.08
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7.0
6.0
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4.0
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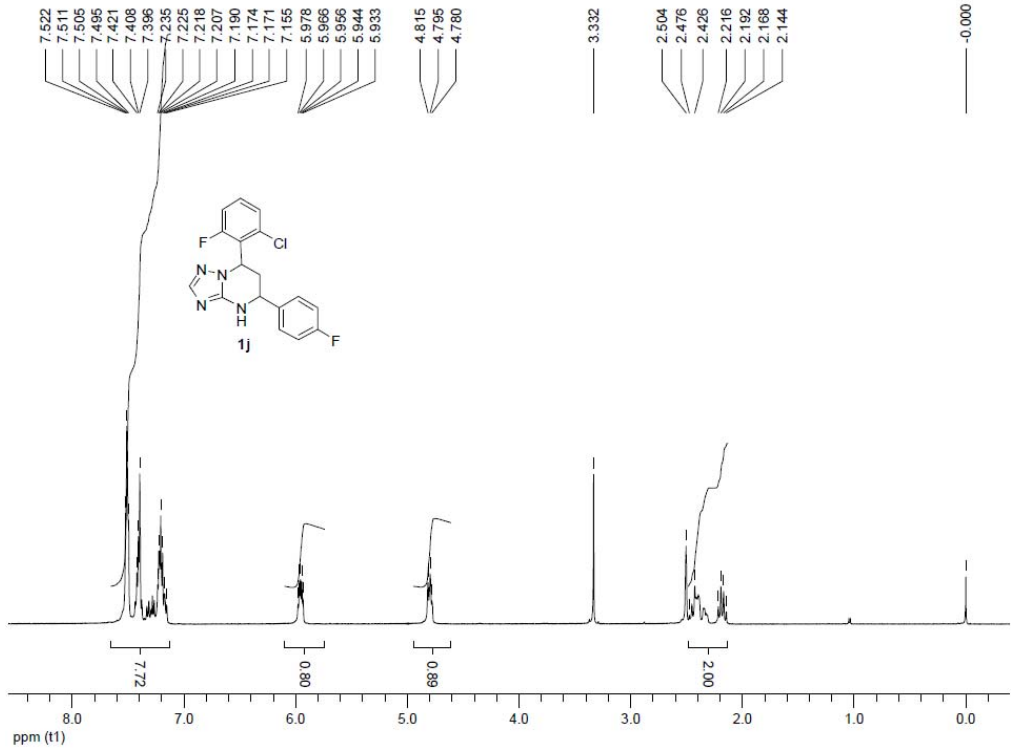
2.0
1.0
0.0
ppm (t1)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7.408
7.396
7.235
7.225
7.218
7.207
7.190
7.174
7.171
7.155
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5.966
5.956
5.944
5.933
4.815
4.795
4.780
3.332
2.504
2.476
2.426
2.216
2.192
2.168
2.144
-0.000
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Cl
N
N
N
H
F
1j
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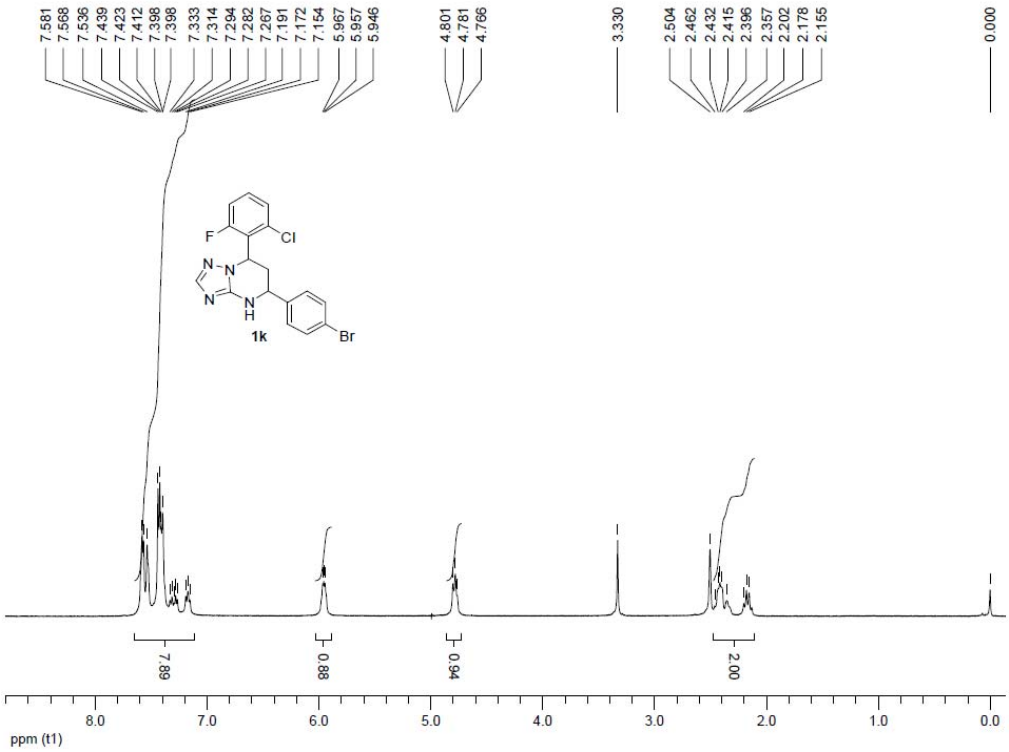
ppm (t1)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7.398
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7.267
7.191
7.172
7.154
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5.957
5.946
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4.781
4.766
3.330
2.504
2.462
2.432
2.415
2.396
2.357
2.202
2.178
2.155
0.000
F
Cl
N
N
N
H
1k
Br
7.89
0.88
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5.0
4.0
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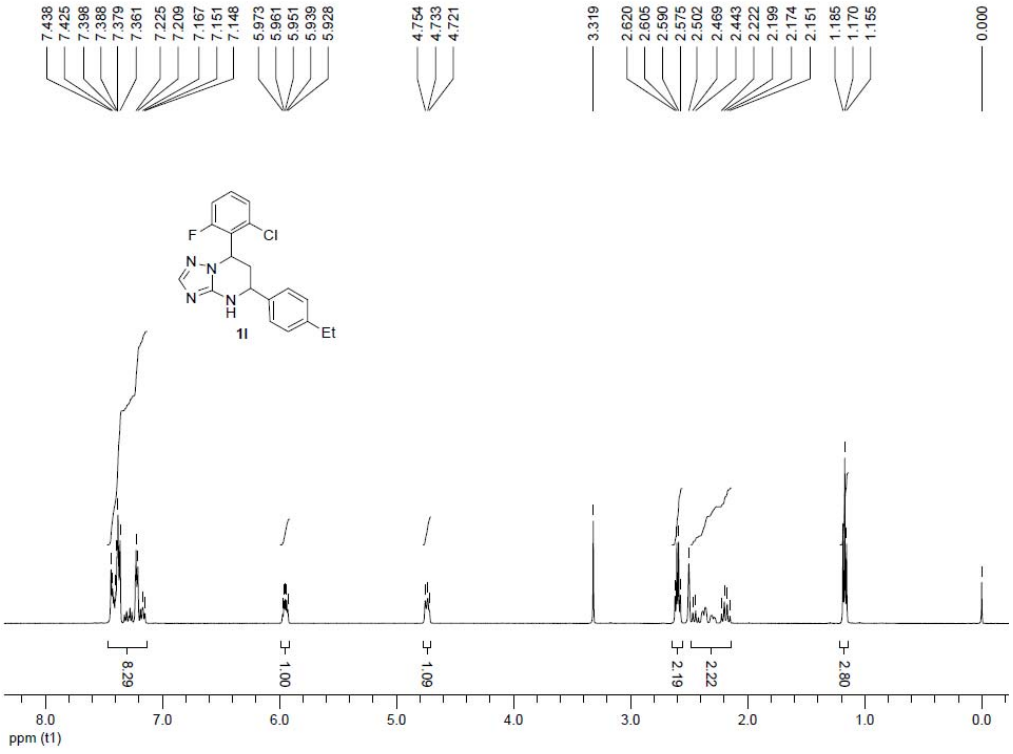
ppm (t1)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7.151
7.148
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5.961
5.951
5.939
5.928
4.754
4.733
4.721
3.319
2.620
2.605
2.590
2.575
2.502
2.469
2.443
2.222
2.199
2.174
2.151
1.185
1.170
1.155
0.000
F
Cl
N
N
N
H
1l
Et
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1.00
1.09
2.19
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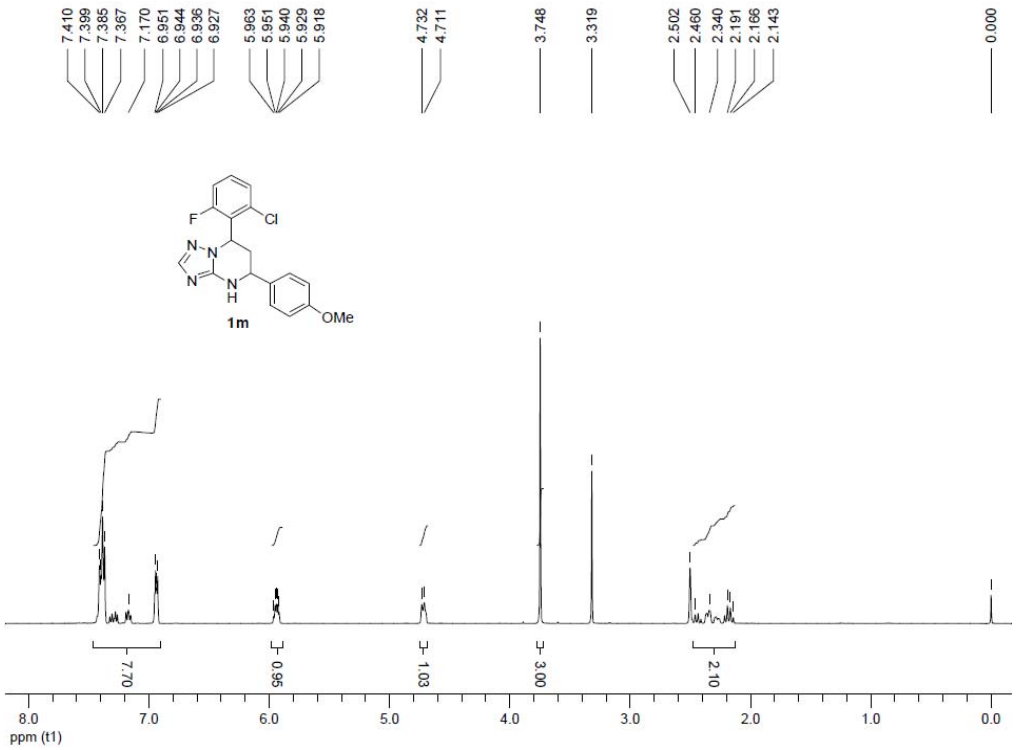
ppm (t1)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6.936
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5.940
5.929
5.918
4.732
4.711
3.748
3.319
2.502
2.460
2.340
2.191
2.166
2.143
0.000
F
Cl
N
N
N
H
OMe
1m
7.70
0.95
1.03
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6.0
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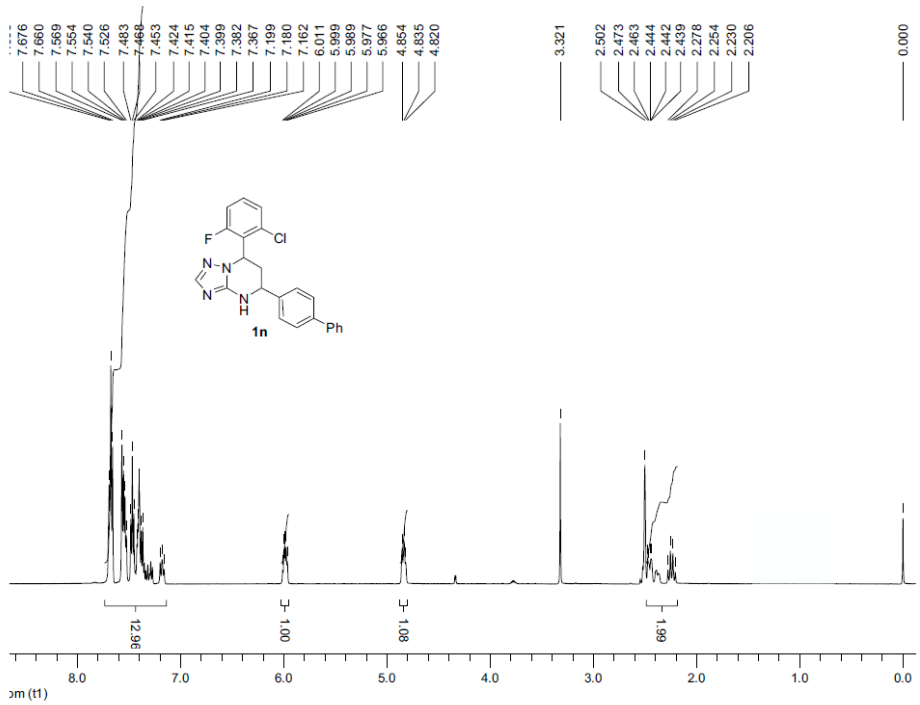
ppm (t1)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7.367
7.199
7.180
7.162
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5.977
5.966
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4.820
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2.444
2.442
2.439
2.278
2.254
2.230
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Cl
N
N
N
H
Ph
1n
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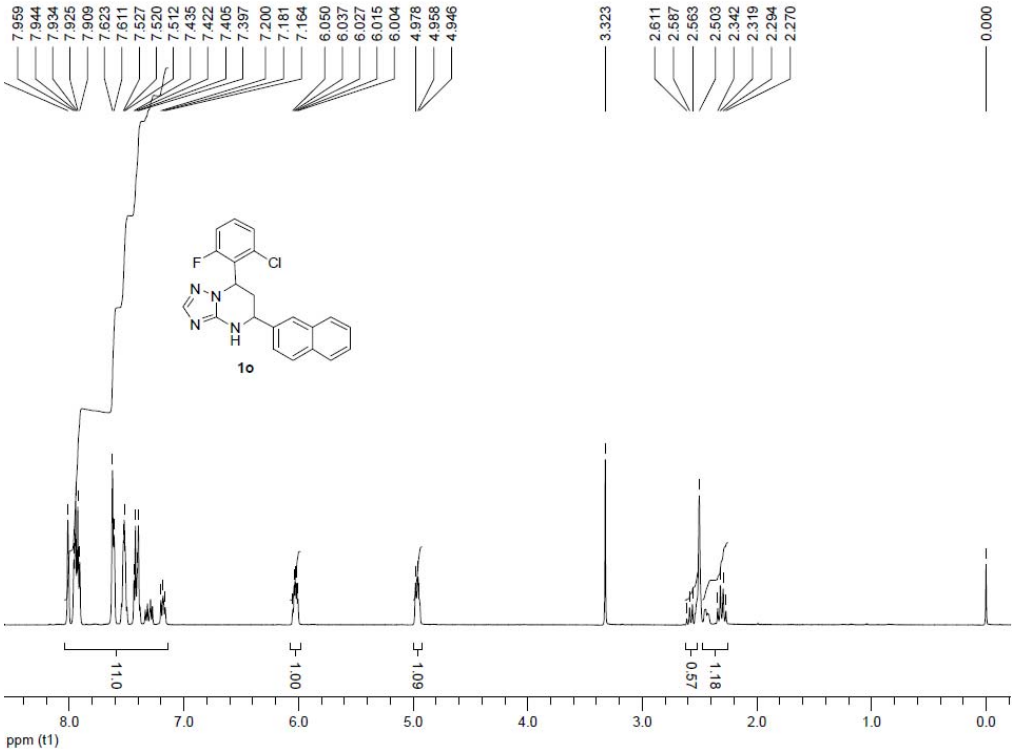
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7.512
7.435
7.422
7.405
7.397
7.200
7.181
7.164
6.050
6.037
6.027
6.015
6.004
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4.958
4.946
3.323
2.611
2.587
2.563
2.503
2.342
2.319
2.294
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Cl
N
N
N
H
1o
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1.00
1.09
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2.0
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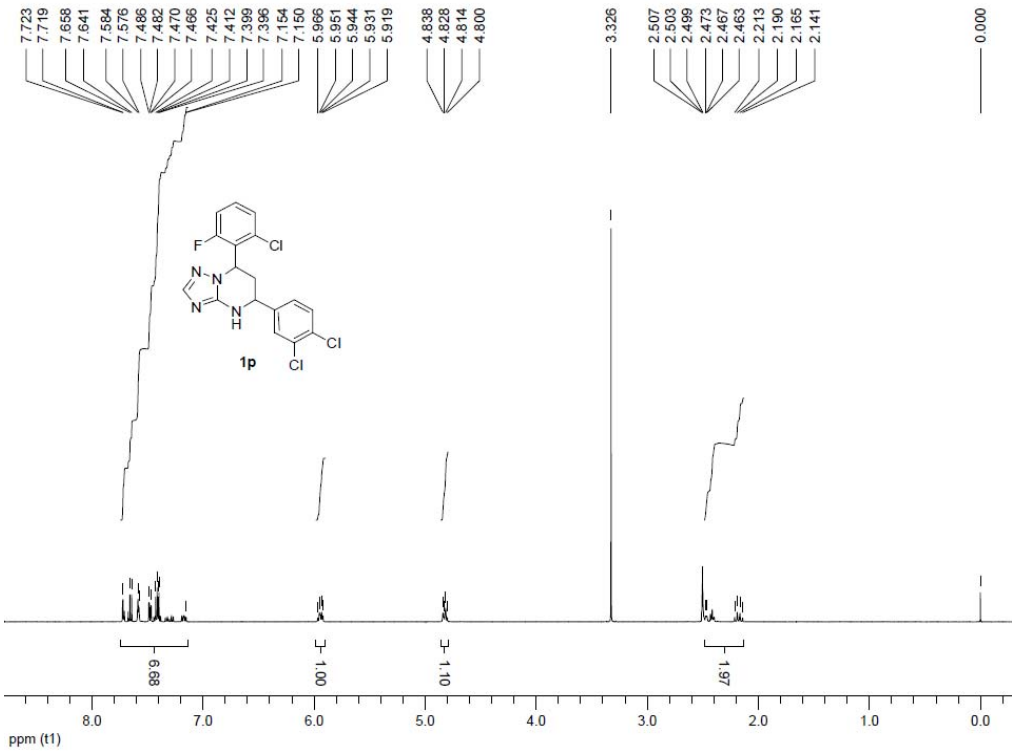
ppm (t1)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7.412
7.399
7.396
7.154
7.150
5.966
5.951
5.944
5.931
5.919
4.838
4.828
4.814
4.800
3.326
2.507
2.503
2.499
2.473
2.467
2.463
2.213
2.190
2.165
2.141
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N
N
N
H
Cl
Cl
1p
6.88
1.00
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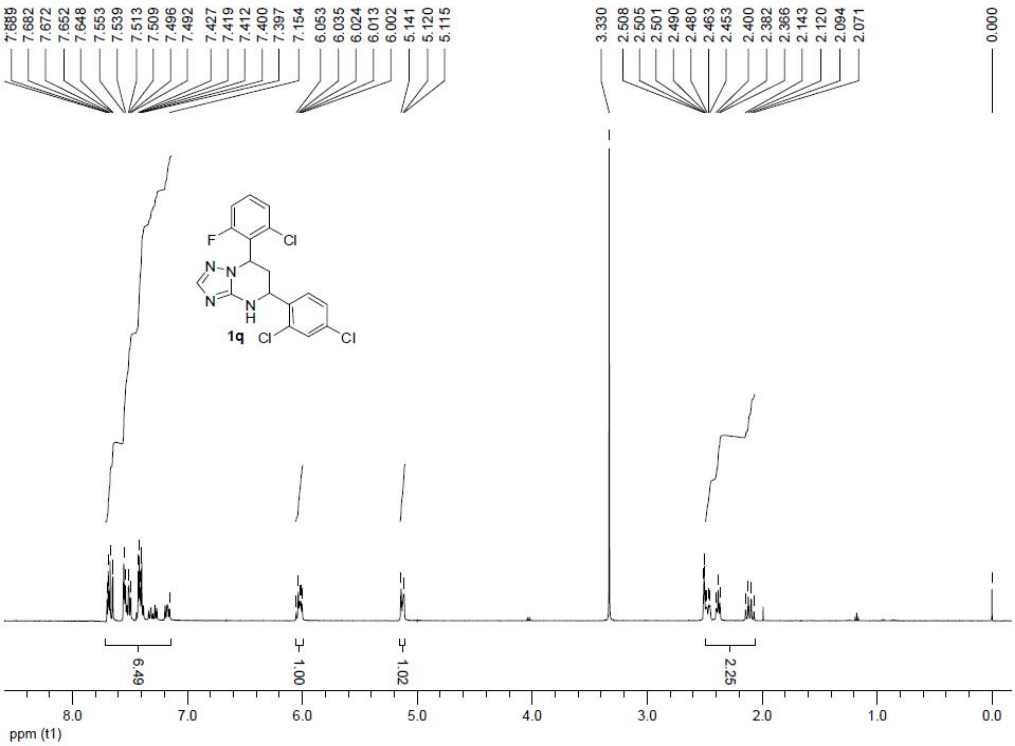
ppm (t1)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7.419
7.412
7.400
7.397
7.154
6.053
6.035
6.024
6.013
6.002
5.141
5.120
5.115
3.330
2.508
2.505
2.501
2.490
2.480
2.463
2.453
2.400
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2.366
2.143
2.120
2.094
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0.000
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Cl
N
N
N
H
Cl
Cl
1q
6.49
1.00
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7.0
6.0
5.0
4.0
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2.0
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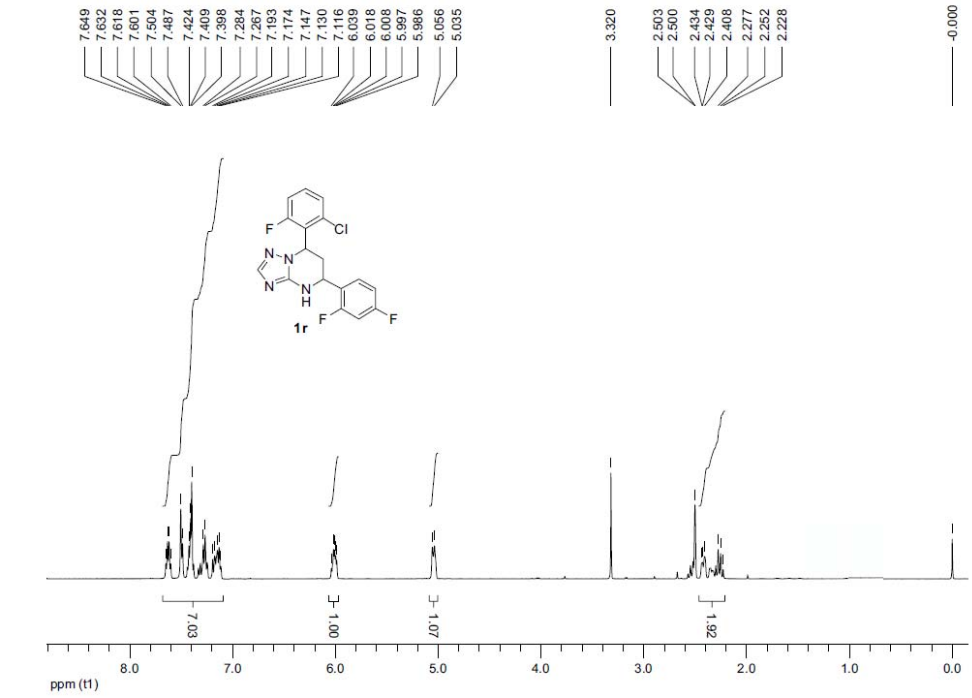
ppm (t1)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7.147
7.130
7.116
6.039
6.018
6.008
5.997
5.986
5.056
5.035
3.320
2.503
2.500
2.434
2.429
2.408
2.277
2.252
2.228
-0.000
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Cl
N
N
N
H
F
F
1r
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1.00
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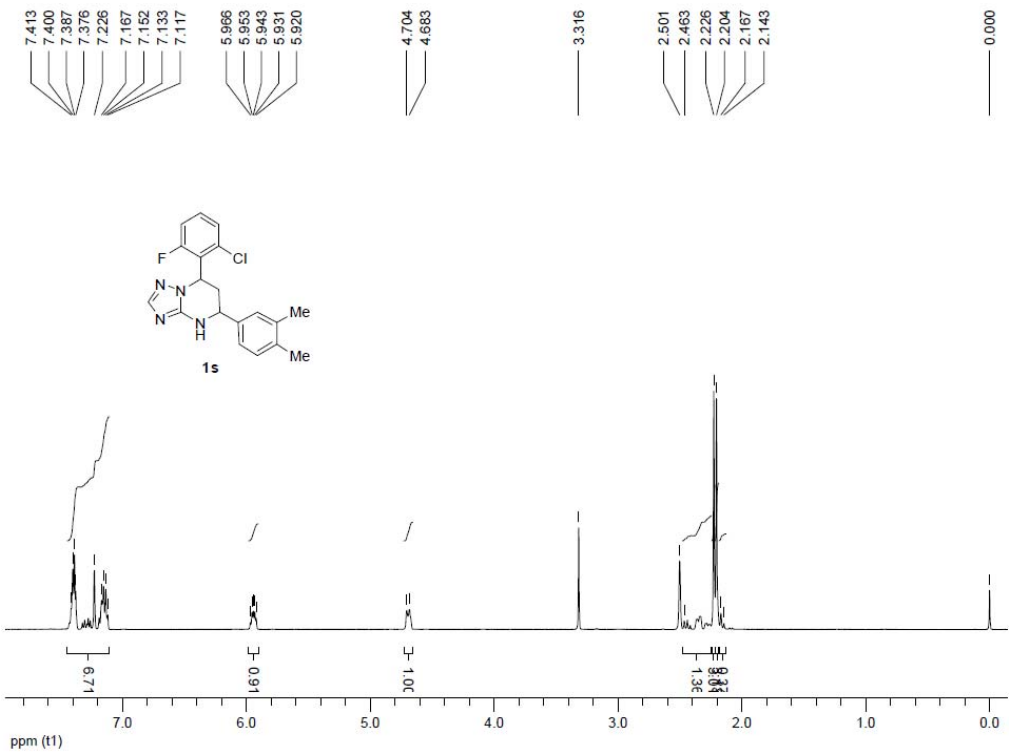
ppm (t1)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5.920
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4.683
3.316
2.501
2.463
2.226
2.204
2.167
2.143
0.000
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N
N
N
H
Me
Me
1s
6.71
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5.0
4.0
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2.0
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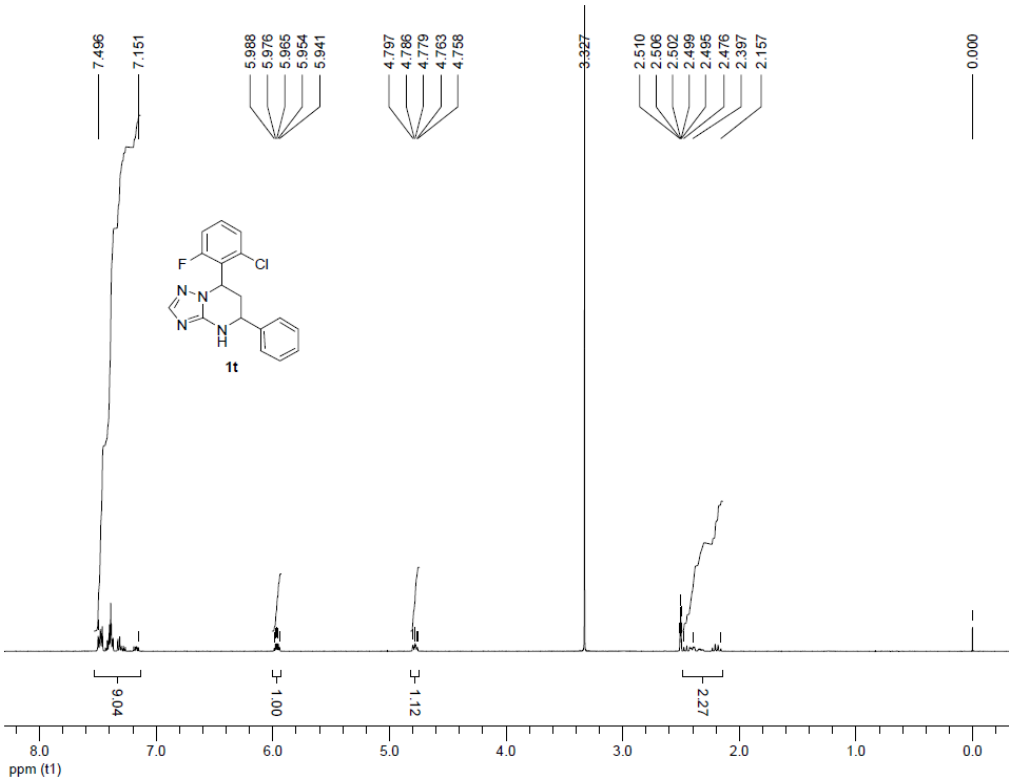
ppm (t1)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3.327
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2.506
2.502
2.499
2.495
2.476
2.397
2.157
0.000
F
Cl
N
N
N
H
1t
9.04
1.00
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6.0
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4.0
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2.0
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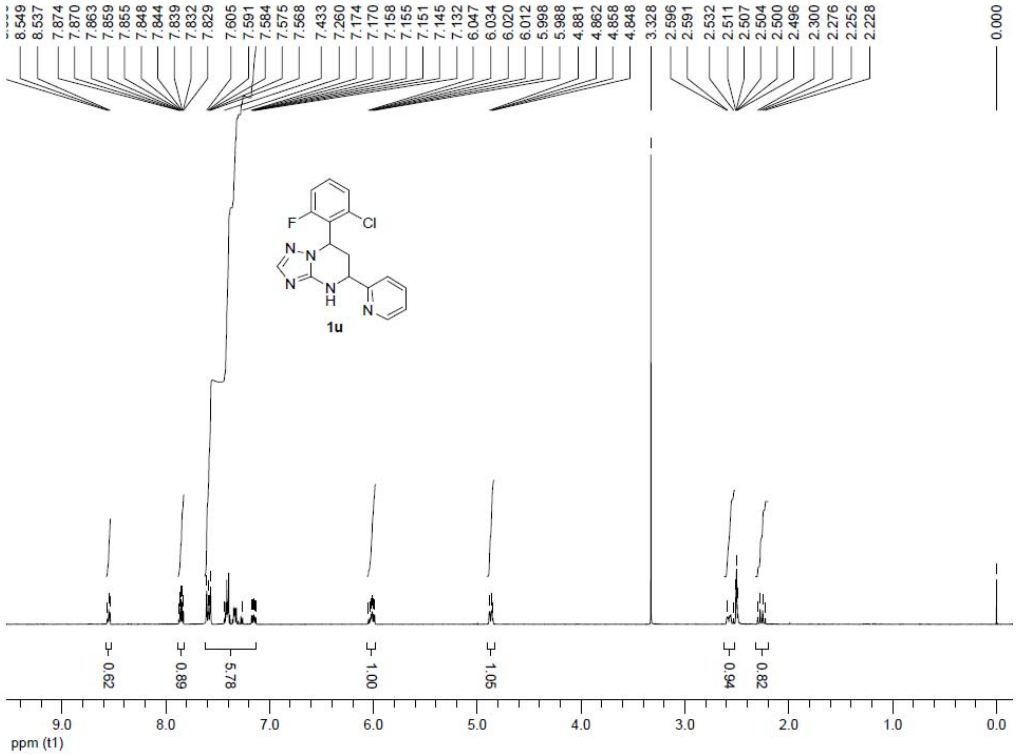
0.0
ppm (t1)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7.844
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7.605
7.591
7.584
7.575
7.568
7.433
7.260
7.174
7.170
7.158
7.155
7.151
7.145
7.132
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6.020
6.012
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Cl
N
N
N
N
H
N
1u
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0.82
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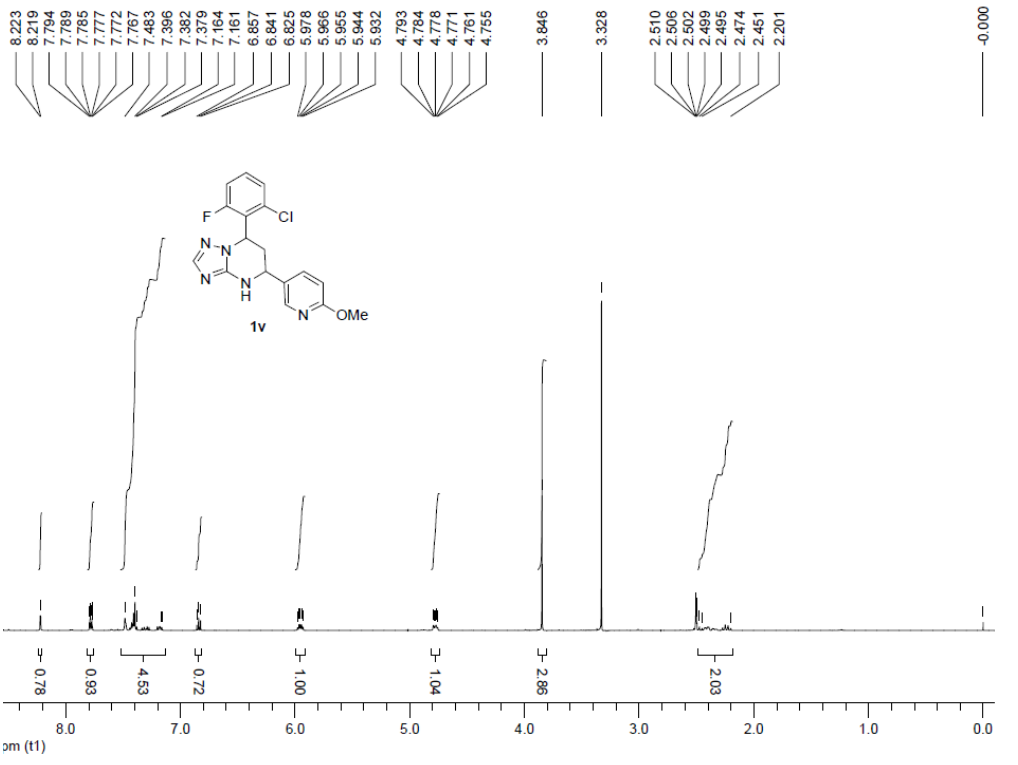
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7.767
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7.164
7.161
6.857
6.841
6.825
5.978
5.966
5.955
5.944
5.932
4.793
4.784
4.778
4.771
4.761
4.755
3.846
3.328
2.510
2.506
2.502
2.499
2.495
2.474
2.451
2.201
-0.000
F
Cl
N
N
N
N
H
N
OMe
1v
0.78
0.83
4.53
0.72
1.00
1.04
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2.0
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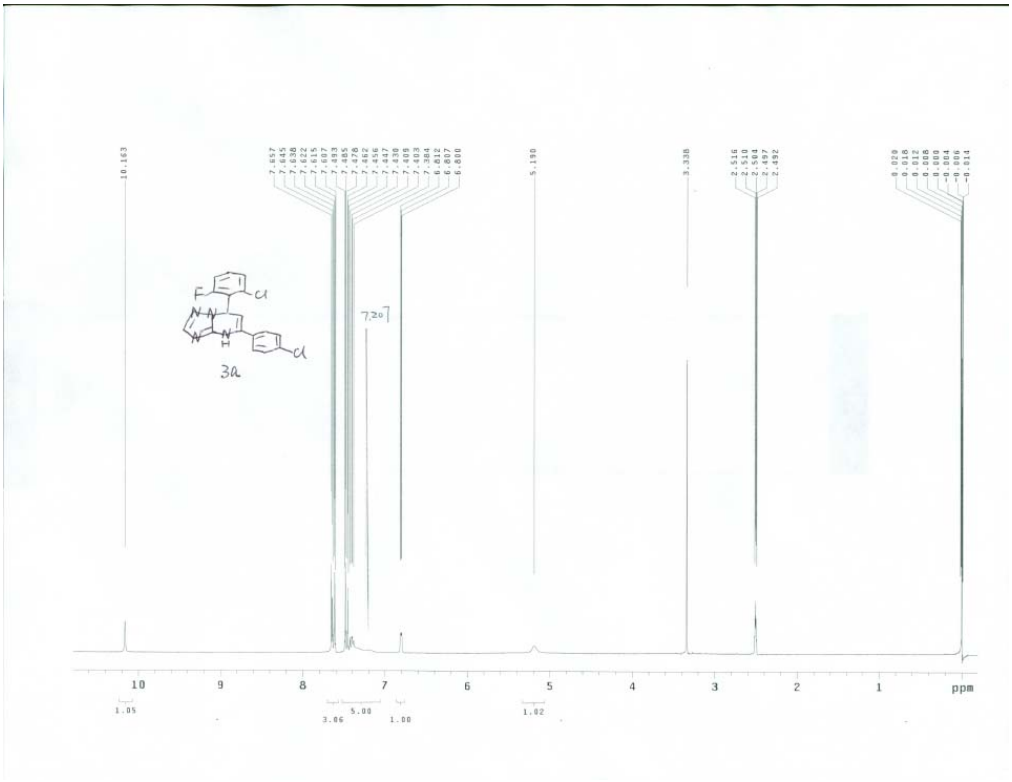
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7.622
7.615
7.607
7.493
7.485
7.476
7.462
7.456
7.447
7.430
7.408
7.400
7.384
6.812
6.807
6.800
5.190
3.338
2.516
2.510
2.504
2.497
2.492
0.039
0.016
0.012
0.006
0.000
-0.004
-0.009
-0.014
F
Cl
Cl
7.20
3a
10
9
8
7
6
5
4
3
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ppm
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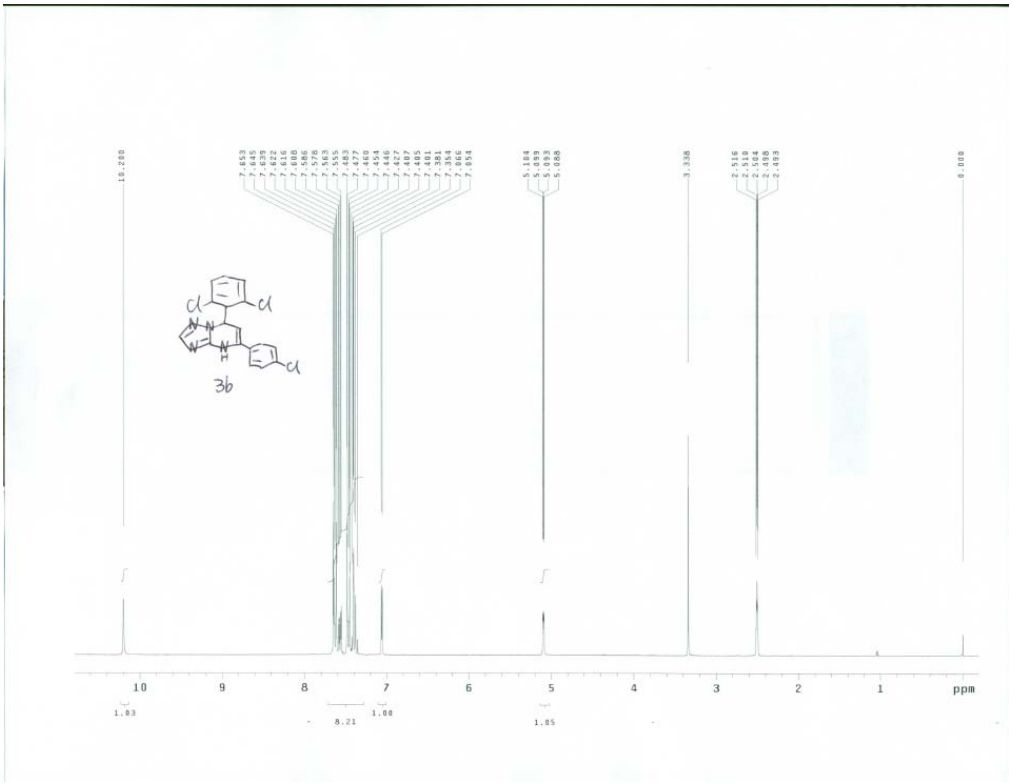
3.06
5.00
1.00
1.02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7.616
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7.606
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7.477
7.460
7.454
7.444
7.427
7.407
7.405
7.401
7.381
7.354
7.346
7.654
5.104
5.099
5.093
5.088
3.338
2.516
2.510
2.504
2.497
2.493
0.000
Cl
Cl
Cl
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8
7
6
5
4
3
2
1
ppm
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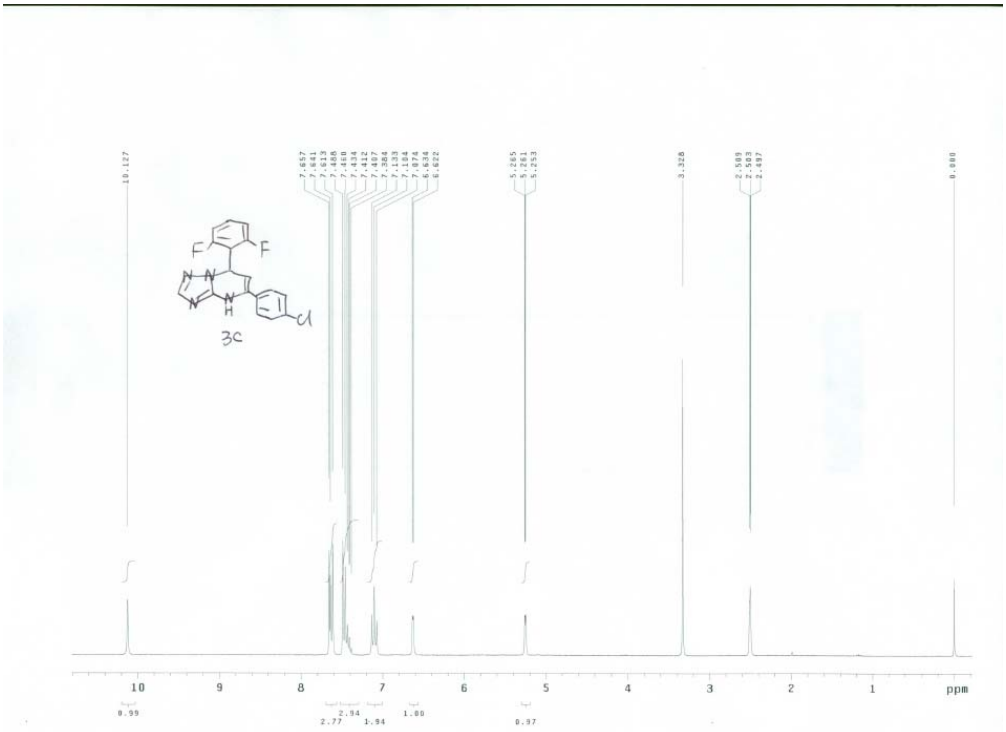
8.21
1.00
1.05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7.468
7.434
7.412
7.407
7.387
7.133
7.104
7.074
6.844
6.822
5.265
5.261
5.253
3.328
2.509
2.503
2.497
0.000
F
F
N
N
N
H
Cl
3c
10
9
8
7
6
5
4
3
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ppm
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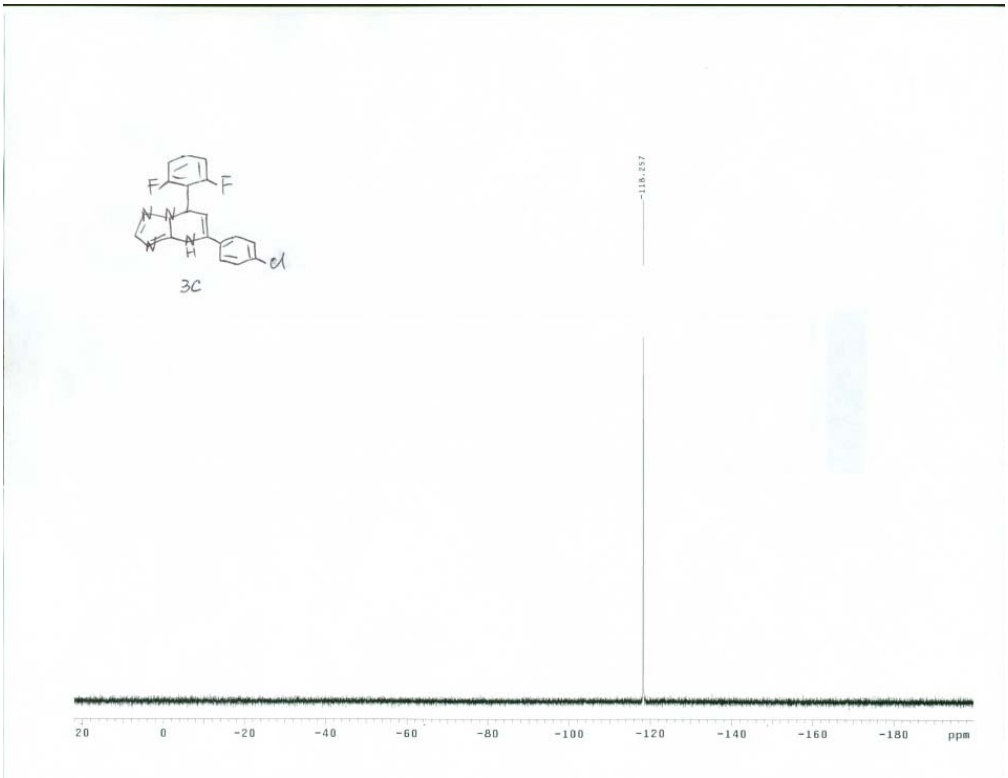
2.77
1.94
1.88
0.97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N
N
N
H
Cl
3c
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-20
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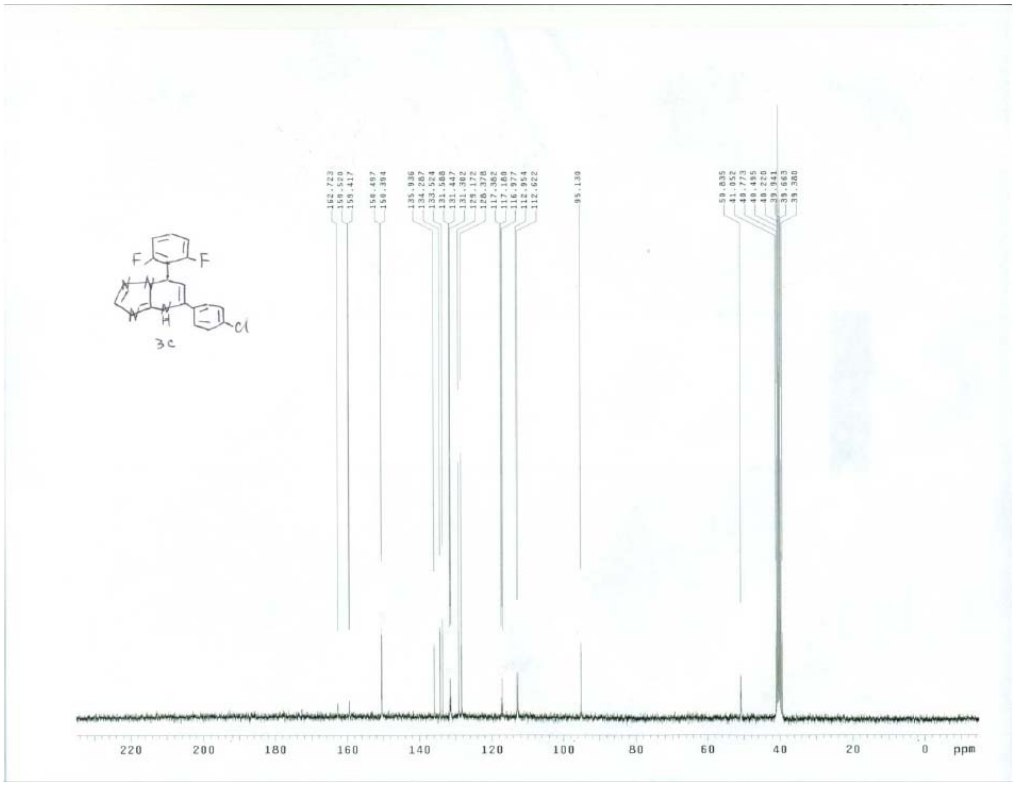
-60
-80
-100
-120
-140
-160
-180
ppm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F
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150.394
135.936
134.267
132.524
131.568
131.447
131.302
131.172
126.378
117.382
117.060
116.977
112.954
112.622
95.130
59.835
41.952
40.573
40.495
40.220
39.841
39.665
39.380
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200
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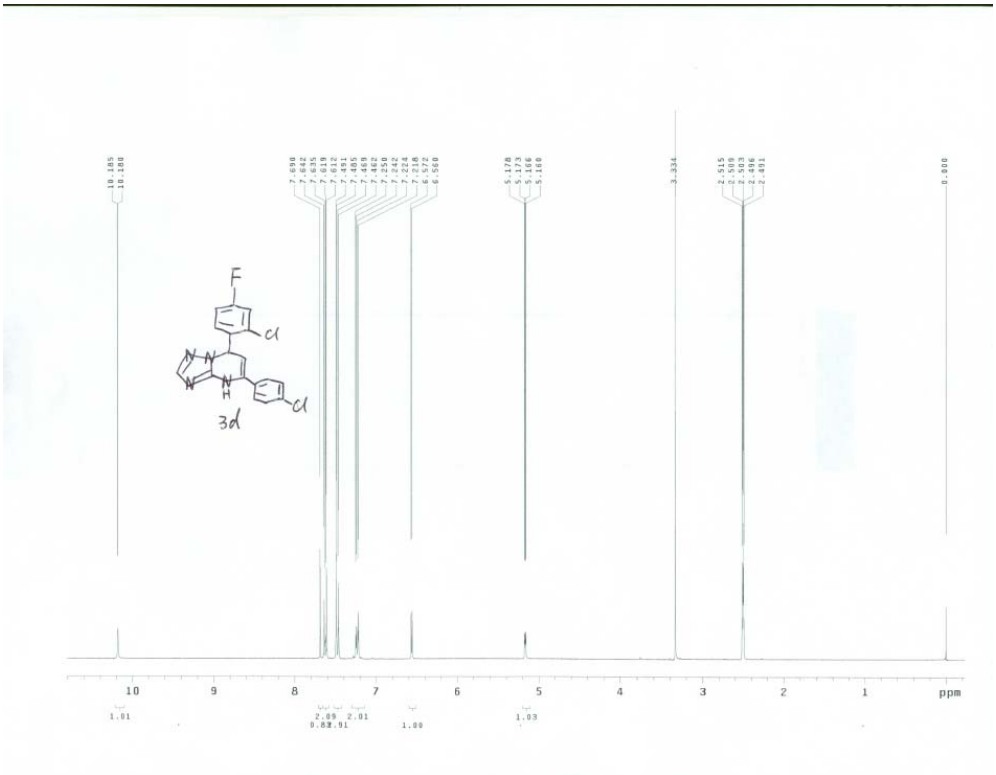
140
120
100
80
60
40
20
0
ppm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Cl
Cl
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7.618
7.612
7.491
7.485
7.469
7.462
7.259
7.232
7.224
7.216
6.572
6.568
5.178
5.173
5.166
5.160
3.334
2.515
2.509
2.503
2.496
2.491
0.000
10
9
8
7
6
5
4
3
2
1
ppm
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2.01
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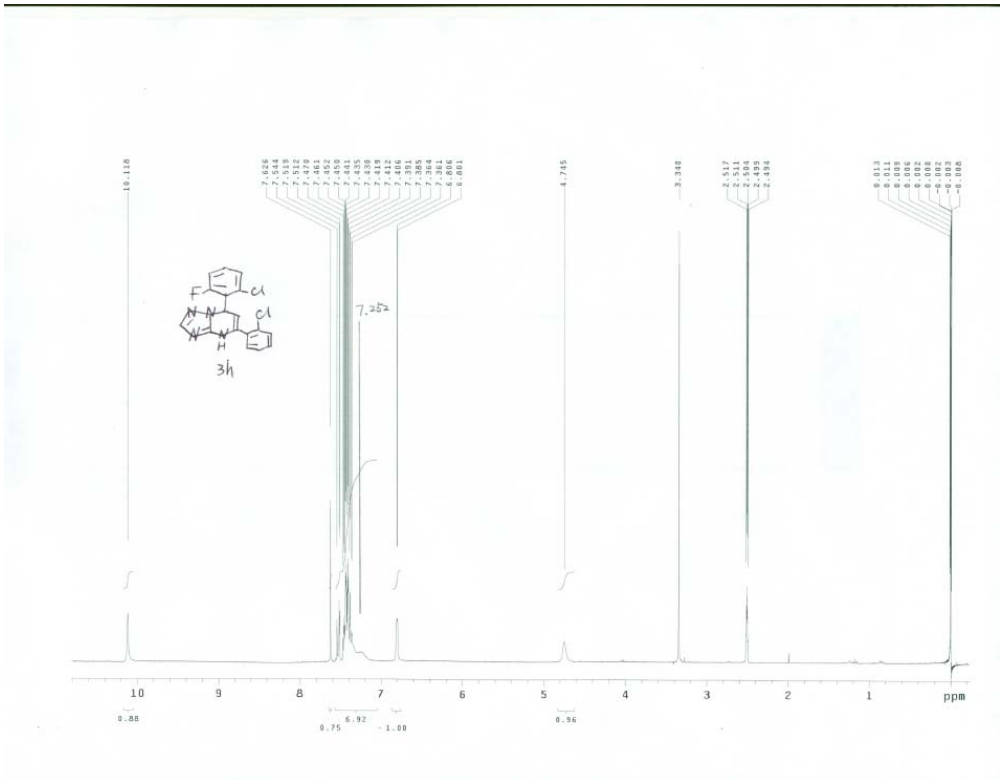
0.91
1.00
1.03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7.419
7.412
7.406
7.391
7.385
7.364
7.361
6.806
6.801
4.745
3.340
2.517
2.511
2.504
2.499
2.494
0.013
0.011
0.008
0.006
0.005
0.003
0.000
-0.002
-0.003
-0.005
7.252
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10
9
8
7
6
5
4
3
2
1
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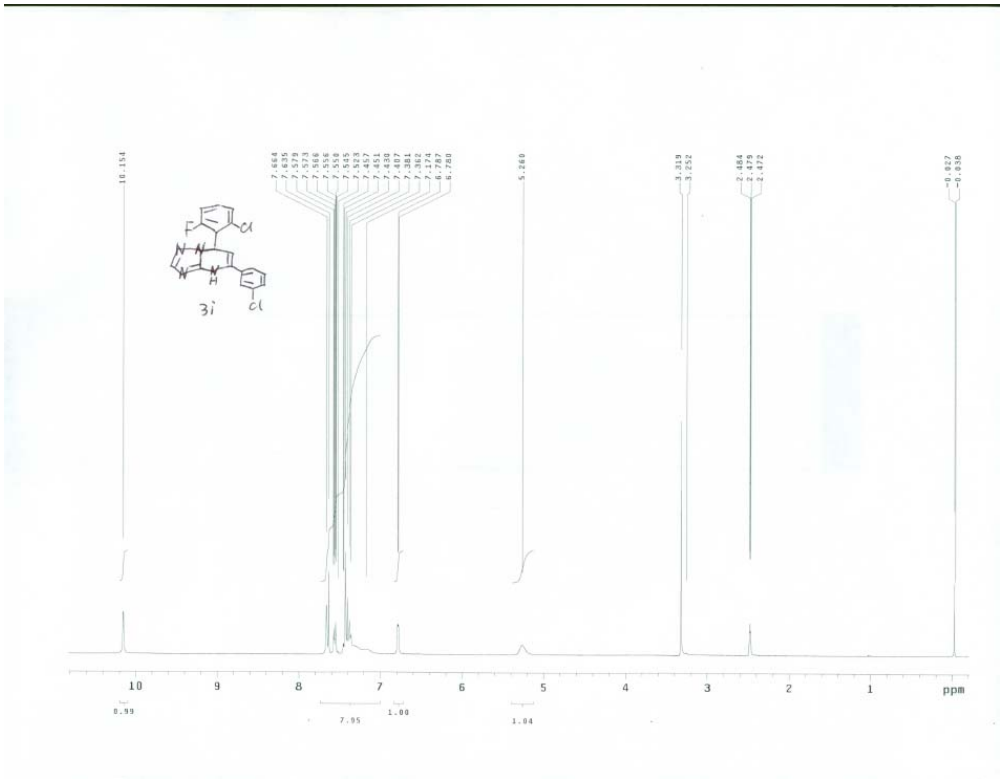
0.75
1.00
0.96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7.556
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7.532
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7.451
7.438
7.407
7.381
7.362
7.223
6.787
6.780
5.260
3.339
3.252
2.484
2.478
2.472
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9
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7
6
5
4
3
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ppm
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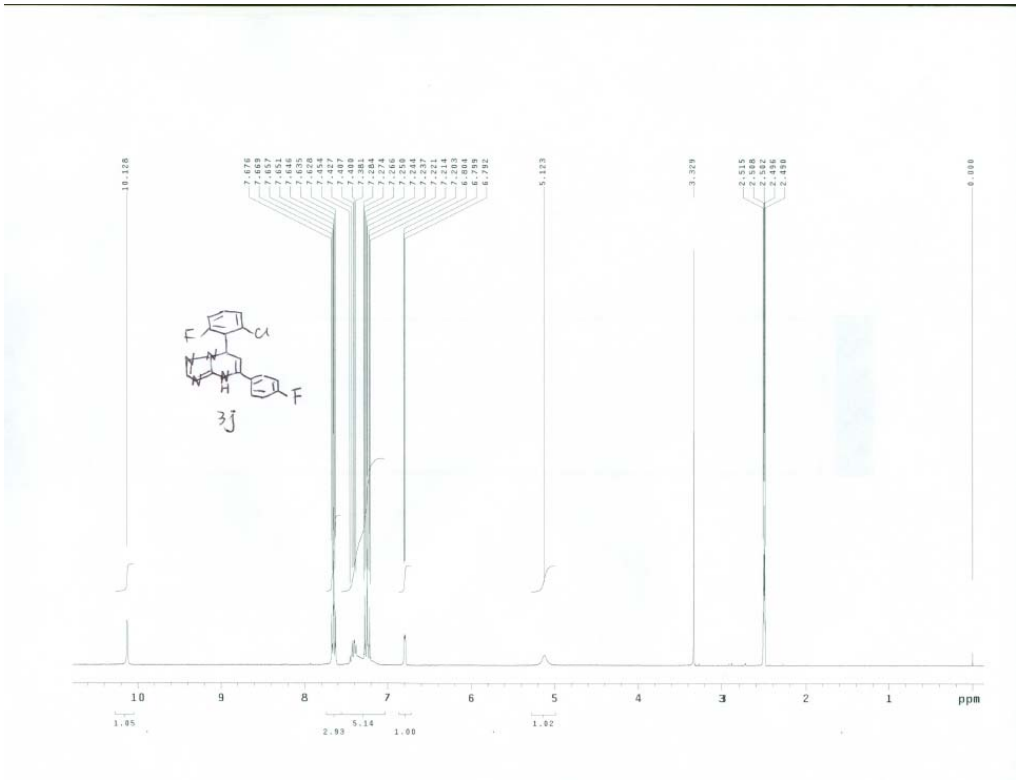
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7.635
7.628
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7.427
7.407
7.400
7.381
7.264
7.274
7.266
7.250
7.244
7.237
7.221
7.214
7.203
6.804
6.798
6.792
5.123
3.329
2.515
2.508
2.502
2.496
2.490
0.000
F
Cl
N
N
N
H
F
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7
6
5
4
3
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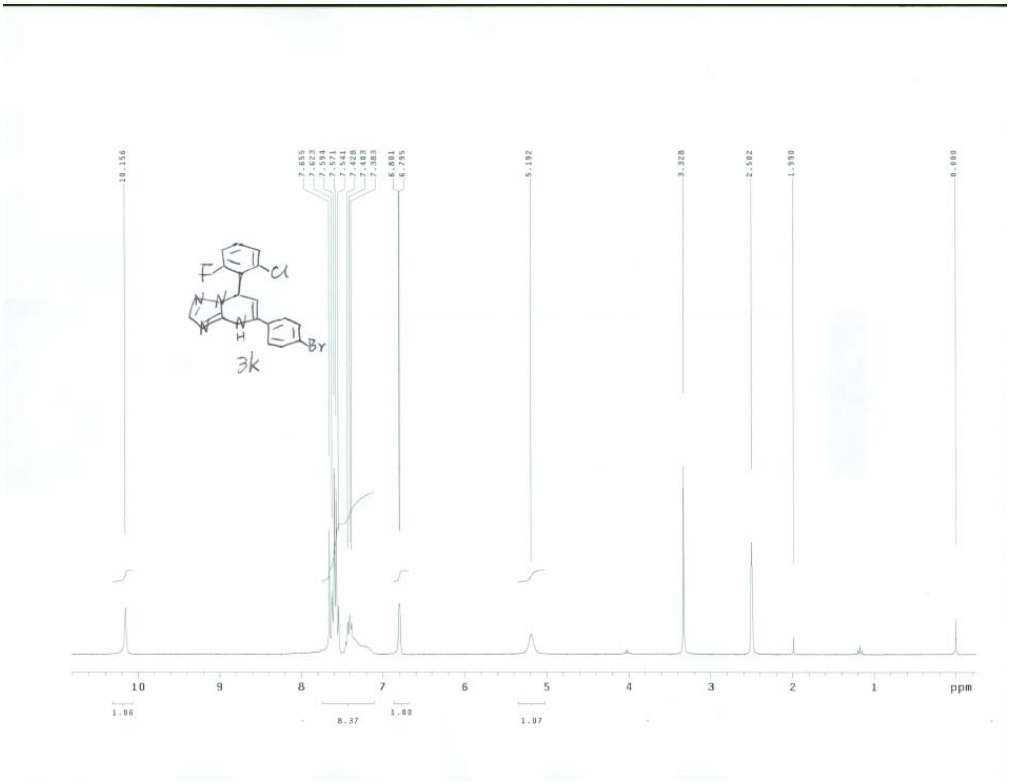
1.02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7.403
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5.192
3.328
2.582
1.990
0.000
F
Cl
N
N
N
H
Br
3k
10
9
8
7
6
5
4
3
2
1
ppm
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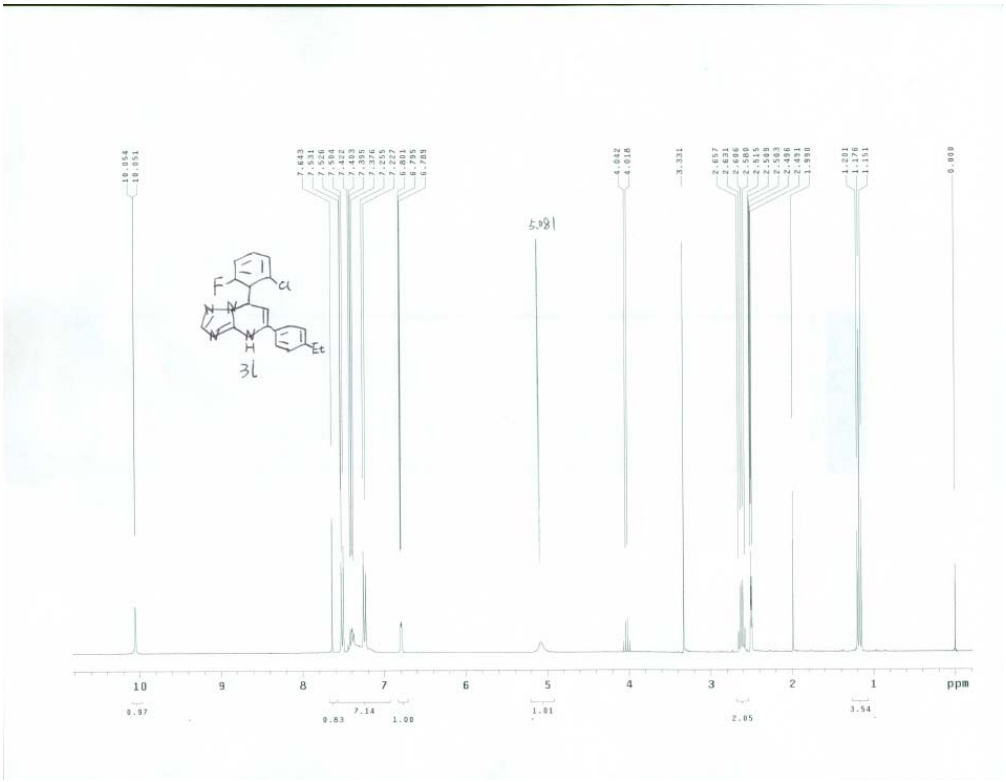
1.80
1.07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7.386
7.255
7.227
6.801
6.795
6.789
5.081
4.602
4.618
3.331
2.657
2.631
2.606
2.580
2.515
2.489
2.463
2.496
2.491
1.998
1.201
1.176
1.151
0.000
3l
10
9
8
7
6
5
4
3
2
1
ppm
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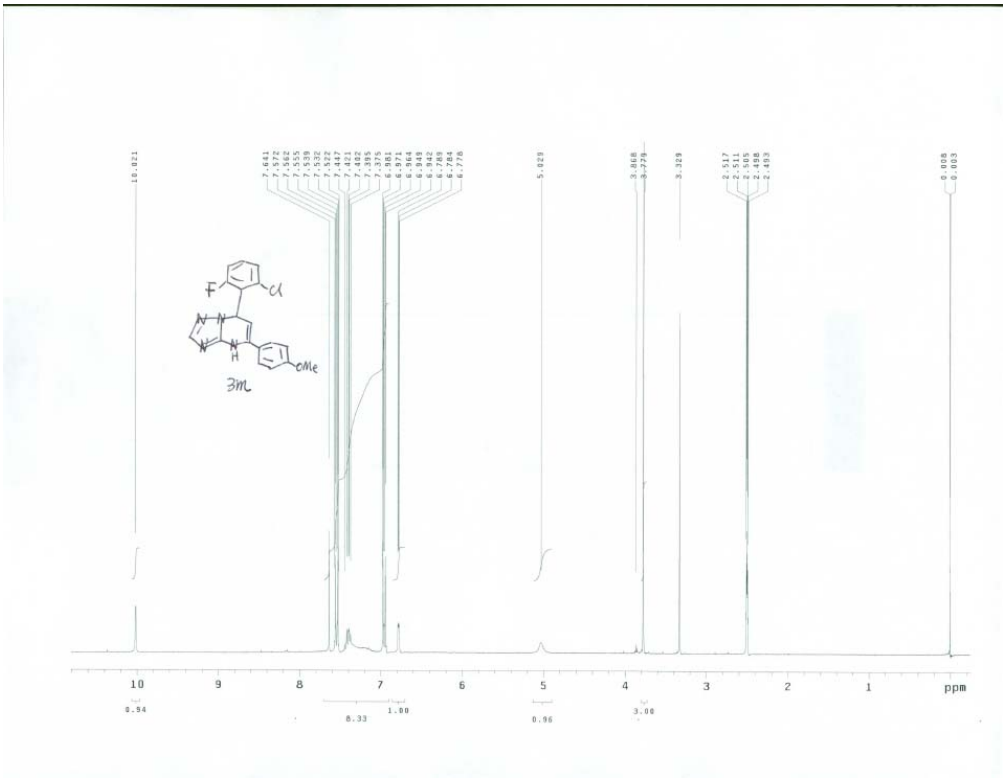
1.01
2.05
3.54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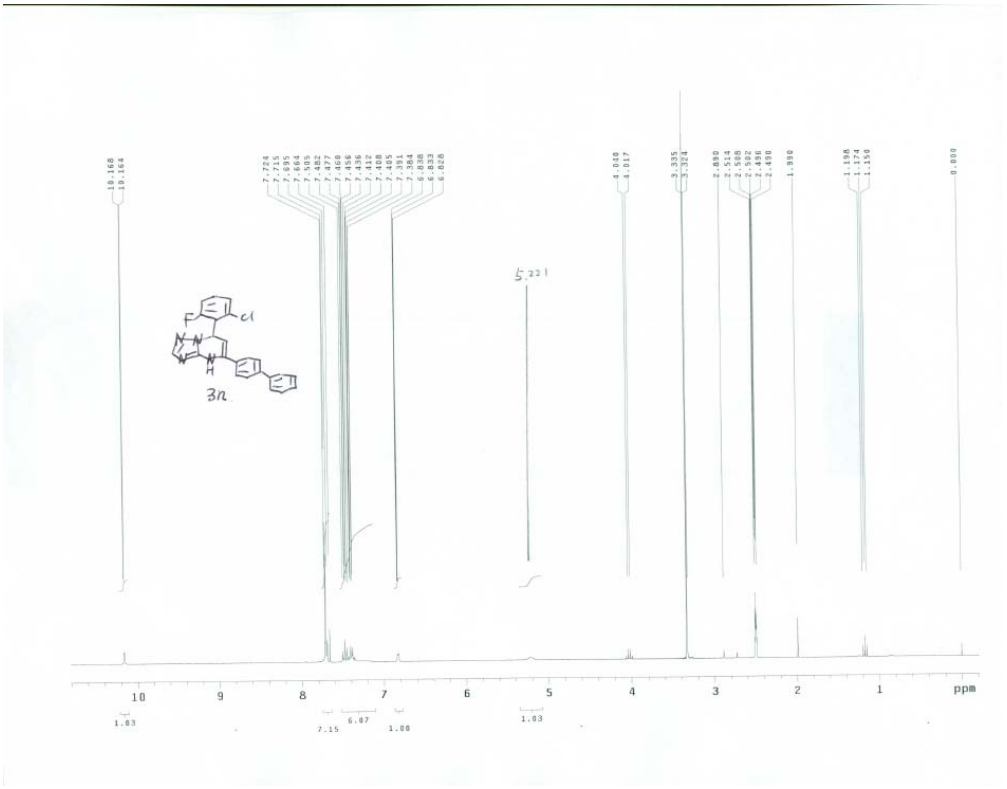
7.532
7.522
7.447
7.421
7.402
7.395
7.375
6.971
6.964
6.948
6.642
6.640
6.780
6.784
6.776
5.029
3.868
3.779
3.329
2.517
2.511
2.505
2.498
2.493
0.008
0.003
3m
10
9
8
7
6
5
4
3
2
1
ppm
0.94
6.33
1.00
0.96
3.00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7.684
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7.482
7.477
7.460
7.456
7.436
7.412
7.408
7.405
7.381
7.364
6.838
6.833
6.808
5.221
4.010
4.017
3.335
3.324
2.890
2.514
2.506
2.502
2.496
2.490
1.990
1.198
1.174
1.159
0.000
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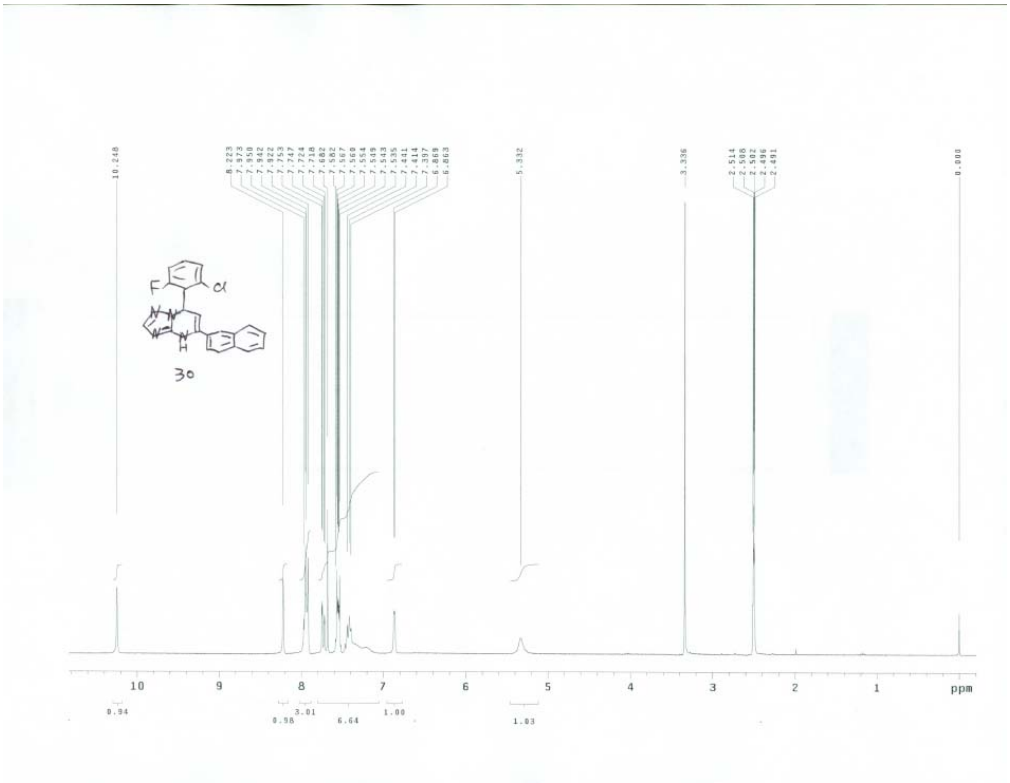
10
9
8
7
6
5
4
3
2
1
ppm
1.03
7.15
6.87
1.00
1.03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7.682
7.672
7.567
7.560
7.554
7.548
7.543
7.535
7.411
7.404
7.397
6.809
6.803
5.332
3.336
2.514
2.506
2.502
2.496
2.491
0.000
3o
10
9
8
7
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5
4
3
2
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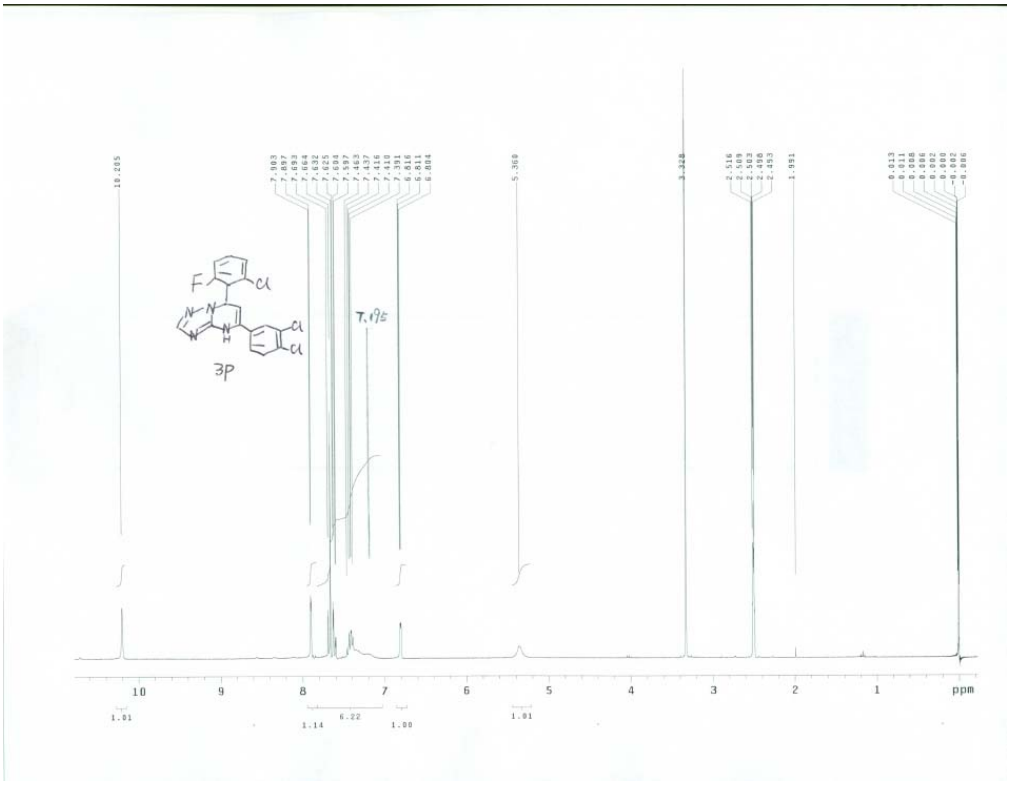
1.00
1.03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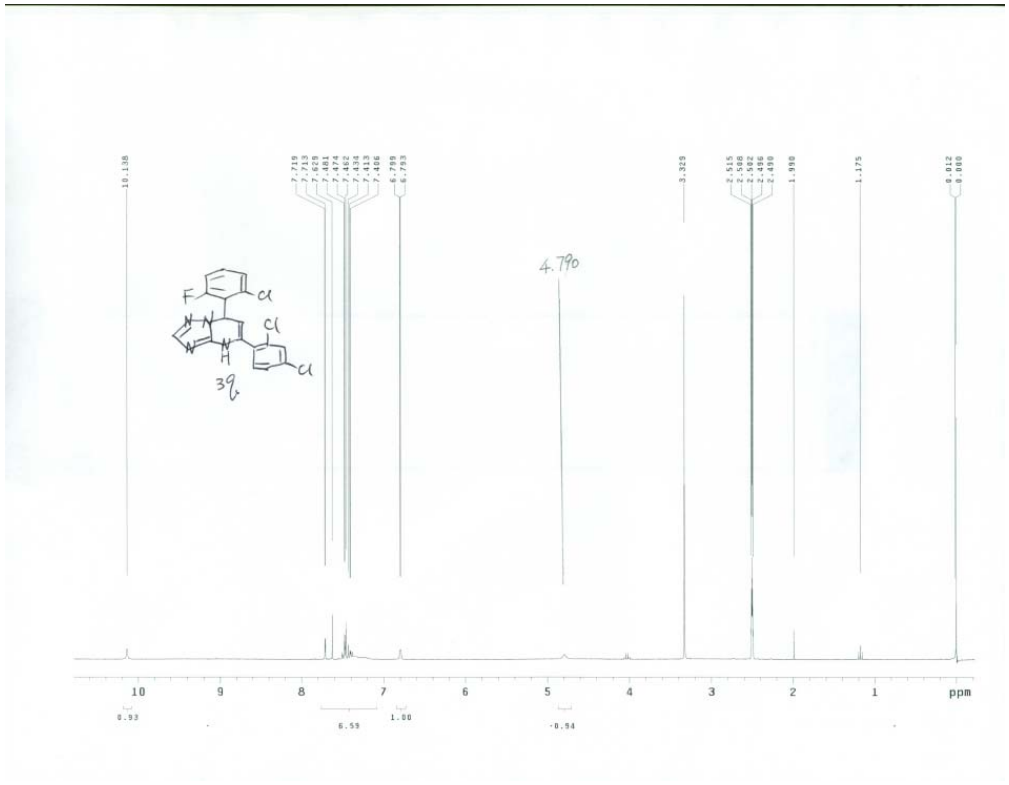
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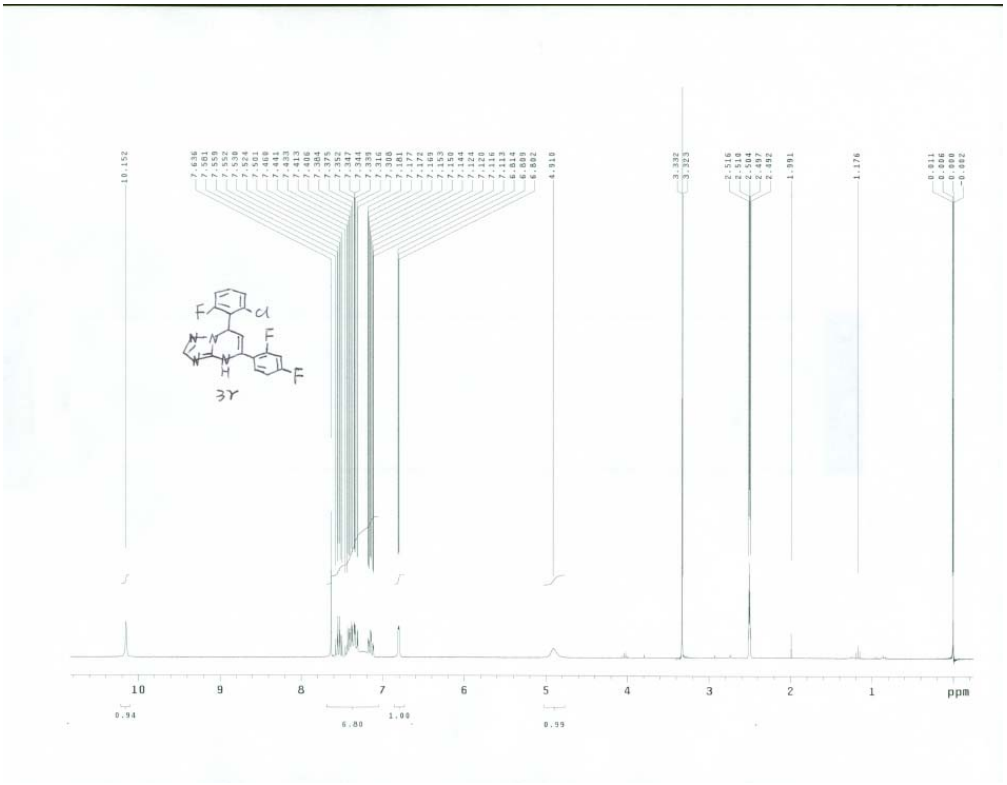
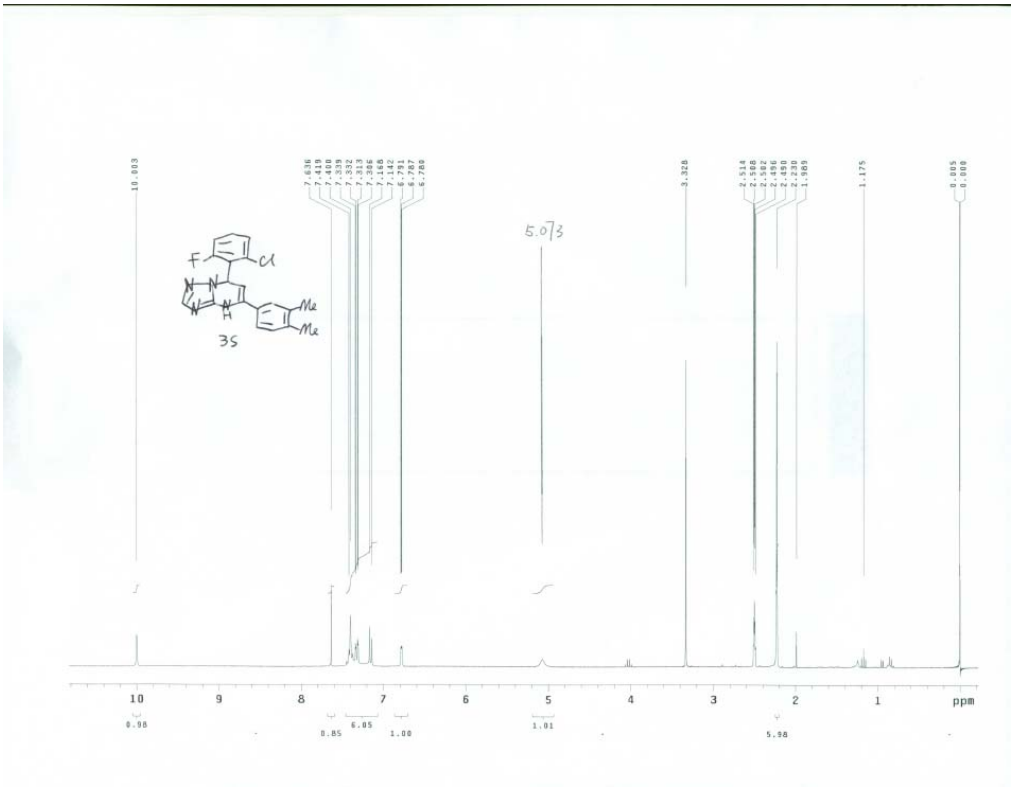

3r
ppm


3s
5.073
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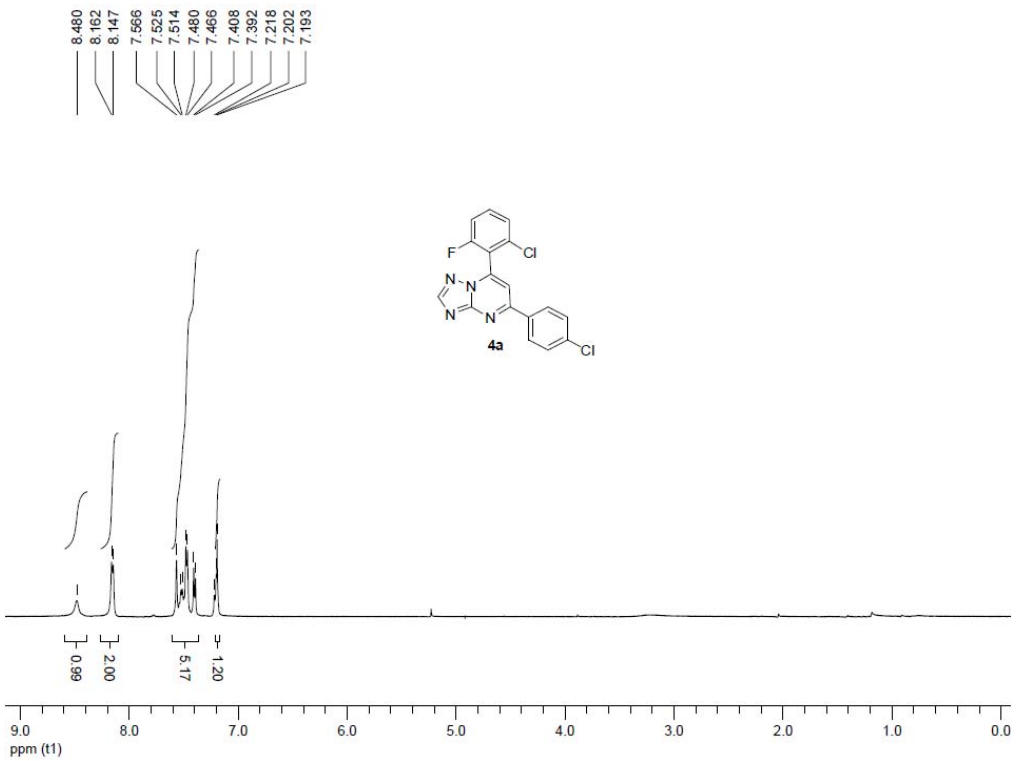


3. X-ray Structure and Data of 1a

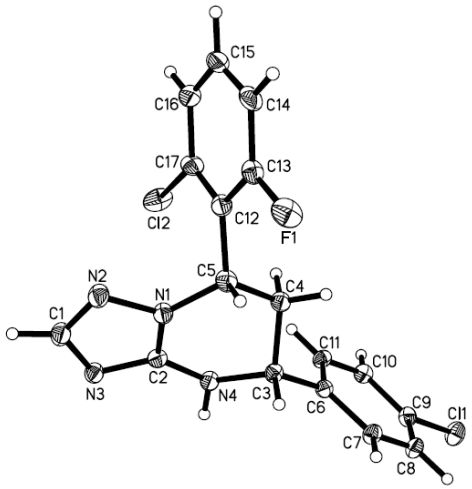


Table 1. Crystal data and structure refinement for 10mxu1h.

Identification code	10mxu1h
Empirical formula	C18 H17 Cl2 F N4 O
Formula weight	395.26
Temperature	100(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, P 21/c
Unit cell dimensions	a = 8.1141(6) A alpha = 90 deg. b = 10.4273(8) A beta = 108.576O(10) deg. c = 22.6565(17) A gamma = 90 deg.
Volume	1817.1(2) A^3
Z, Calculated density	4, 1.445 Mg/m^3
Absorption coefficient	0.382 mm^-1
F(000)	816
Crystal size	0.54 x 0.45 x 0.20 mm
Theta range for data collection	1.90 to 28.34 deg.
Limiting indices	-10<=h<=10, -13<=k<=13, -30<=l<=30
Reflections collected / unique	34527 / 4515 [R(int) = 0.0331]
Completeness to theta = 28.34	99.7 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9275 and 0.82O2
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4515 / 50 / 269
Goodness-of-fit on F^2	1.156
Final R indices [I>2sigma(I)]	R1 = 0.0492, wR2 = 0.1046
R indices (all data)	R1 = 0.0576, wR2 = 0.1084
Largest diff. peak and hole	0.577 and -0.472 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for 10mxu1h.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Cl(1)	2710(1)	745(1)	-292(1)	35(1)
N(1)	-994(2)	5997(2)	1954(1)	24(1)
N(2)	-1867(2)	6939(2)	2167(1)	30(1)
N(3)	-3460(2)	6257(2)	1195(1)	25(1)
N(4)	-1389(2)	4707(2)	1066(1)	23(1)
C(1)	-3305(3)	7044(2)	1694(1)	30(1)
C(2)	-1958(3)	5612(2)	1383(1)	22(1)
C(3)	41(3)	3891(2)	1437(1)	21(1)
C(4)	1442(3)	4759(2)	1860(1)	24(1)
C(5)	764(3)	5573(2)	2300(1)	27(1)
C(6)	742(3)	3103(2)	1011(1)	20(1)
C(7)	859(3)	1774(2)	1072(1)	25(1)
C(8)	1468(3)	1040(2)	674(1)	26(1)
C(9)	1966(3)	1652(2)	217(1)	25(1)
C(10)	1897(3)	2974(2)	151(1)	24(1)
C(11)	1283(3)	3695(2)	550(1)	23(1)
Cl(2)	917(4)	8043(2)	1548(1)	40(1)
F(1)	2886(4)	5346(3)	3523(2)	40(1)
C(12)	1972(6)	6619(4)	2616(2)	27(1)
C(13)	3028(5)	6453(4)	3226(2)	27(1)
C(14)	4185(5)	7375(4)	3548(2)	37(1)
C(15)	4318(6)	8494(5)	3239(3)	38(1)
C(16)	3327(5)	8684(4)	2628(2)	34(1)
C(17)	2162(6)	7741(5)	2324(2)	28(1)
Cl(2')	3583(3)	5626(2)	3558(1)	40(1)
F(1')	827(19)	7820(10)	1493(6)	40(1)
C(12')	1923(11)	6765(7)	2475(4)	27(1)
C(13')	3272(9)	6913(7)	3056(3)	27(1)
C(14')	4334(11)	7990(9)	3256(5)	37(1)
C(15')	4135(10)	9013(8)	2860(4)	38(1)
C(16')	2923(9)	8988(7)	2265(4)	34(1)
C(17')	1897(13)	7871(10)	2087(3)	28(1)
O(1)	3596(2)	6312(2)	108(1)	41(1)
C(18)	3062(4)	7498(3)	262(2)	59(1)

Table 3. Bond lengths [A] and angles [deg] for 10mxu1h.

Cl(1)-C(9)	1.741(2)
N(1)-C(2)	1.343(2)
N(1)-N(2)	1.385(2)
N(1)-C(5)	1.460(3)
N(2)-C(1)	1.314(3)
N(3)-C(2)	1.337(3)
N(3)-C(1)	1.371(3)
N(4)-C(2)	1.353(3)
N(4)-C(3)	1.469(2)
N(4)-H(4N)	0.87(3)
C(1)-H(1)	0.9500
C(3)-C(6)	1.511(3)
C(3)-C(4)	1.528(3)
C(3)-H(3)	1.0000
C(4)-C(5)	1.538(3)
C(4)-H(4A)	0.9900
C(4)-H(4B)	0.9900
C(5)-C(12)	1.488(4)
C(5)-C(12')	1.532(5)
C(5)-H(5)	1.0001
C(6)-C(7)	1.393(3)
C(6)-C(11)	1.398(3)
C(7)-C(8)	1.387(3)
C(7)-H(7)	0.9500
C(8)-C(9)	1.382(3)
C(8)-H(8)	0.9500
C(9)-C(10)	1.385(3)
C(10)-C(11)	1.385(3)
C(10)-H(10)	0.9500
C(11)-H(11)	0.9500
Cl(2)-C(17)	1.755(5)
F(1)-C(13)	1.359(5)
C(12)-C(17)	1.376(6)
C(12)-C(13)	1.385(5)
C(13)-C(14)	1.379(5)
C(14)-C(15)	1.382(7)
C(14)-H(14)	0.9500
C(15)-C(16)	1.377(7)
C(15)-H(15)	0.9500
C(16)-C(17)	1.385(6)
C(16)-H(16)	0.9500
Cl(2')-C(13')	1.727(7)
F(1')-C(17')	1.350(14)
C(12')-C(13')	1.427(10)
C(12')-C(17')	1.446(12)
C(13')-C(14')	1.400(12)
C(14')-C(15')	1.371(14)
C(14')-H(14')	0.9500
C(15')-C(16')	1.393(10)
C(15')-H(15')	0.9500
C(16')-C(17')	1.413(12)
C(16')-H(16')	0.9500
O(1)-C(18)	1.391(3)
O(1)-H(10)	0.87(3)
C(18)-H(18A)	0.9800
C(18)-H(18B)	0.9800
C(18)-H(18C)	0.9800

C(2)-N(1)-N(2)	110.03(17)
C(2)-N(1)-C(5)	126.59(17)
N(2)-N(1)-C(5)	123.26(16)
C(1)-N(2)-N(1)	101.21(17)
C(2)-N(3)-C(1)	101.76(17)
C(2)-N(4)-C(3)	116.16(16)
C(2)-N(4)-H(4N)	118(2)
C(3)-N(4)-H(4N)	117.3(19)
N(2)-C(1)-N(3)	116.61(19)
N(2)-C(1)-H(1)	121.7
N(3)-C(1)-H(1)	121.7
N(3)-C(2)-N(1)	110.39(17)
N(3)-C(2)-N(4)	127.75(18)
N(1)-C(2)-N(4)	121.85(18)
N(4)-C(3)-C(6)	109.82(15)
N(4)-C(3)-C(4)	108.08(16)
C(6)-C(3)-C(4)	111.51(16)
N(4)-C(3)-H(3)	109.1
C(6)-C(3)-H(3)	109.1
C(4)-C(3)-H(3)	109.1
C(3)-C(4)-C(5)	112.64(17)
C(3)-C(4)-H(4A)	109.1
C(5)-C(4)-H(4A)	109.1
C(3)-C(4)-H(4B)	109.1
C(5)-C(4)-H(4B)	109.1
H(4A)-C(4)-H(4B)	107.8
N(1)-C(5)-C(12)	114.7(3)
N(1)-C(5)-C(12')	107.9(4)
N(1)-C(5)-C(4)	108.01(16)
C(12)-C(5)-C(4)	113.5(3)
C(12')-C(5)-C(4)	107.4(4)
N(1)-C(5)-H(5)	106.8
C(12)-C(5)-H(5)	106.5
C(12')-C(5)-H(5)	119.4
C(4)-C(5)-H(5)	106.9
C(7)-C(6)-C(11)	119.00(19)
C(17')-C(16')-H(16')	121.3
F(1')-C(17')-C(16')	116.7(9)
F(1')-C(17')-C(12')	117.1(9)
C(16')-C(17')-C(12')	126.2(7)
C(18)-O(1)-H(10)	106(2)
O(1)-C(18)-H(18A)	109.5
O(1)-C(18)-H(18B)	109.5
H(18A)-C(18)-H(18B)	109.5
O(1)-C(18)-H(18C)	109.5
H(18A)-C(18)-H(18C)	109.5
H(18B)-C(18)-H(18C)	109.5

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for 10mxu1h.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
Cl(1)	45(1)	32(1)	34(1)	-3(1)	20(1)	7(1)
N(1)	24(1)	27(1)	20(1)	-4(1)	5(1)	2(1)
N(2)	30(1)	31(1)	27(1)	-8(1)	6(1)	4(1)
N(3)	24(1)	25(1)	23(1)	-1(1)	3(1)	3(1)
N(4)	24(1)	24(1)	17(1)	-2(1)	2(1)	2(1)
C(1)	29(1)	29(1)	30(1)	-5(1)	6(1)	5(1)
C(2)	23(1)	22(1)	19(1)	1(1)	5(1)	-1(1)
C(3)	23(1)	21(1)	19(1)	2(1)	5(1)	2(1)
C(4)	24(1)	27(1)	20(1)	-2(1)	2(1)	1(1)
C(5)	26(1)	32(1)	19(1)	-3(1)	2(1)	2(1)
C(6)	21(1)	21(1)	18(1)	2(1)	3(1)	1(1)
C(7)	29(1)	22(1)	24(1)	5(1)	9(1)	1(1)
C(8)	30(1)	20(1)	29(1)	4(1)	9(1)	4(1)
C(9)	26(1)	27(1)	22(1)	-1(1)	7(1)	1(1)
C(10)	27(1)	27(1)	19(1)	4(1)	7(1)	0(1)
C(11)	28(1)	20(1)	21(1)	3(1)	5(1)	0(1)
Cl(2)	57(1)	30(1)	28(1)	9(1)	8(1)	-7(1)
F(1)	39(1)	51(1)	24(1)	10(1)	1(1)	-1(1)
C(12)	25(1)	30(1)	23(1)	-6(1)	5(1)	3(1)
C(13)	26(2)	33(2)	21(2)	-1(1)	6(1)	4(2)
C(14)	24(2)	48(2)	30(2)	-14(2)	-3(1)	6(2)
C(15)	22(2)	40(2)	49(2)	-19(2)	9(2)	-2(2)
C(16)	29(2)	29(2)	46(2)	-5(2)	14(2)	-2(1)
C(17)	26(2)	35(2)	19(2)	-8(2)	3(2)	-2(1)
Cl(2')	39(1)	51(1)	24(1)	10(1)	1(1)	-1(1)
F(1')	57(1)	30(1)	28(1)	9(1)	8(1)	-7(1)
C(12')	25(1)	30(1)	23(1)	-6(1)	5(1)	3(1)
C(13')	26(2)	33(2)	21(2)	-1(1)	6(1)	4(2)
C(14')	24(2)	48(2)	30(2)	-14(2)	-3(1)	6(2)
C(15')	22(2)	40(2)	49(2)	-19(2)	9(2)	-2(2)
C(16')	29(2)	29(2)	46(2)	-5(2)	14(2)	-2(1)
C(17')	26(2)	35(2)	19(2)	-8(2)	3(2)	-2(1)
O(1)	34(1)	37(1)	36(1)	-11(1)	-9(1)	10(1)
C(18)	45(1)	40(1)	71(2)	-14(1)	-8(1)	7(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic
displacement parameters (A^2 x 10^3) for 10mxu1h.

	x	y	z	U(eq)
H(4N)	-2140(40)	4360(30)	738(14)	46(8)
H(1)	-4194	7634	1698	36
H(3)	-404	3303	1700	26
H(4A)	1889	5336	1599	29
H(4B)	2421	4223	2111	29
H(5)	660	4988	2636	32
H(7)	518	1365	1389	30
H(8)	1541	134	715	32
H(10)	2263	3378	-161	29
H(11)	1228	4602	511	28
H(14)	4871	7245	3970	44
H(15)	5105	9142	3452	45
H(16)	3440	9450	2417	41
H(14')	5175	8011	3659	44
H(15')	4837	9754	2993	45
H(16')	2790	9694	1989	41
H(1O)	4590(40)	6150(30)	391(14)	47(8)
H(18A)	2298	7911	-115	88
H(18B)	4081	8041	448	88
H(18C)	2429	7378	561	88

4. Effect of 1a and 3c on Complete Blood Count and Serum Chemistry

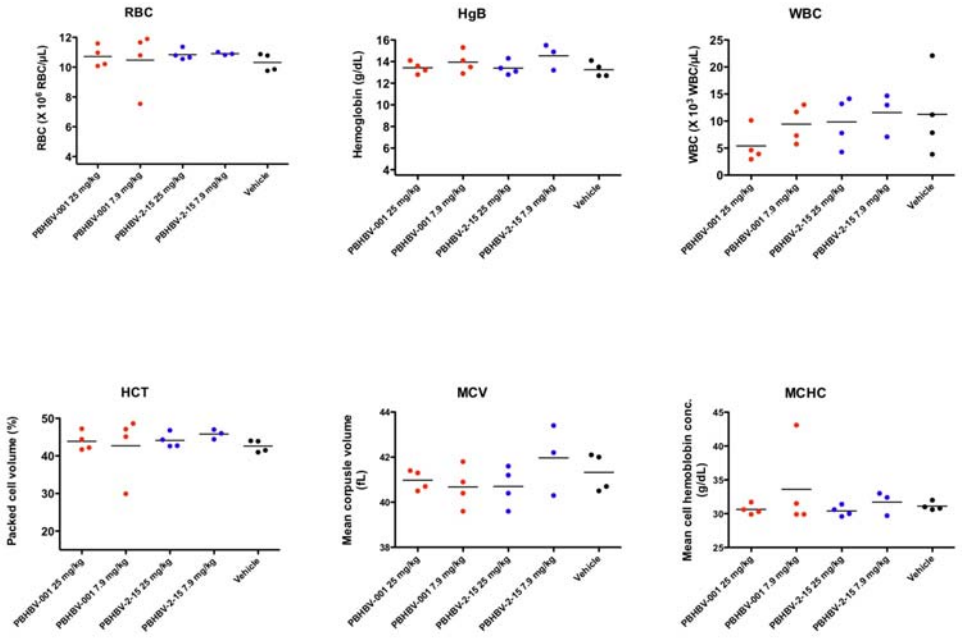


Figure 1. Effect of **PBHBV-001** (**1a**) and **PBHBV-2-15** (**3c**) Administered i.v. on RBC, HgB, WBC, HCT, MCV, and MCHC in C57BL/6 Mice (24 hours).

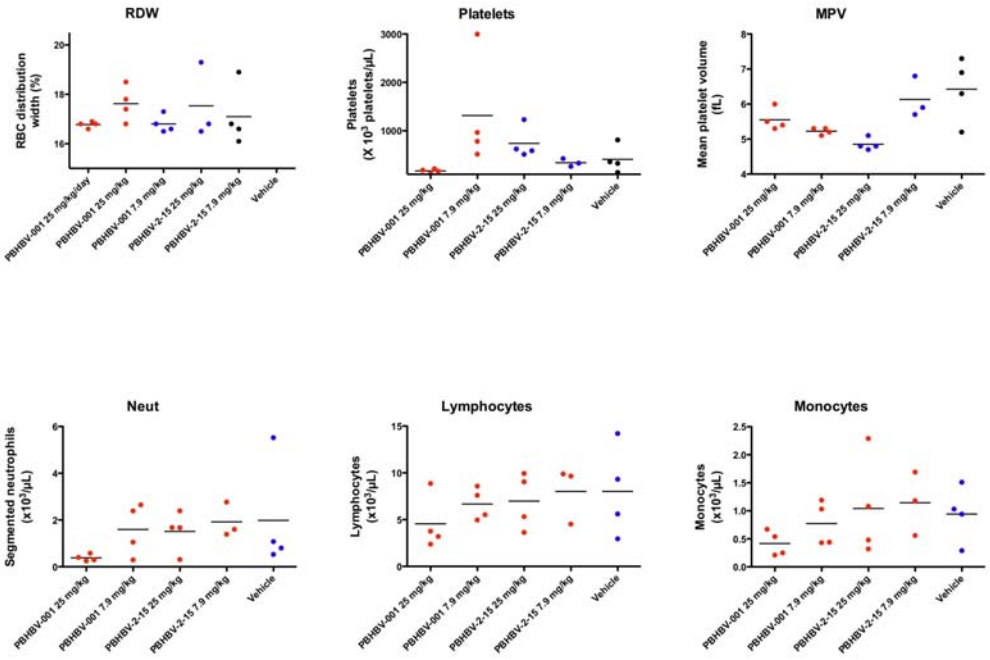


Figure 2. Effect of **PBHBV-001** (**1a**) and **PBHBV-2-15** (**3c**) Administered i.v. on RDW, Platelets, MPV, Neut, Lymphocytes, and Monocytes in C57BL/6 Mice (24 hours).

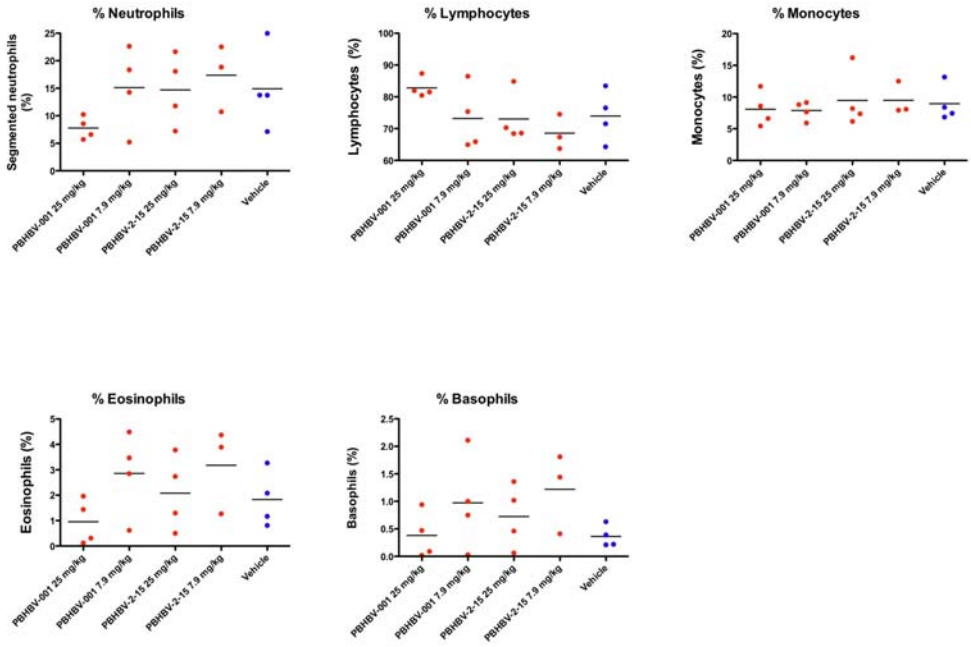


Figure 3. Effect of **PBHBV-001** (**1a**) and **PBHBV-2-15** (**3c**) Administered i.v. on % Neutrophils, % Lymphocytes, % Monocytes, % Eosinophils, and % Basophils in C57BL/6 Mice (24 hours).

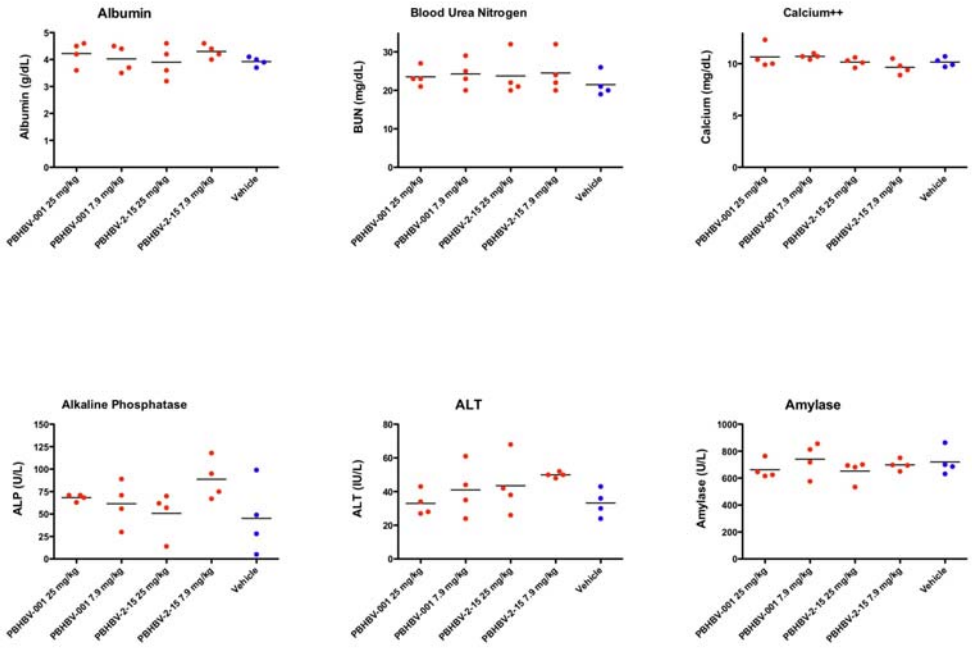


Figure 4. Effect of **PBHBV-001** (**1a**) and **PBHBV-2-15** (**3c**) Administered i.v. on Albumin, BUN, Calcium, Alk Phos, ALT, and Amylase in C57BL/6 Mice (24 hours).

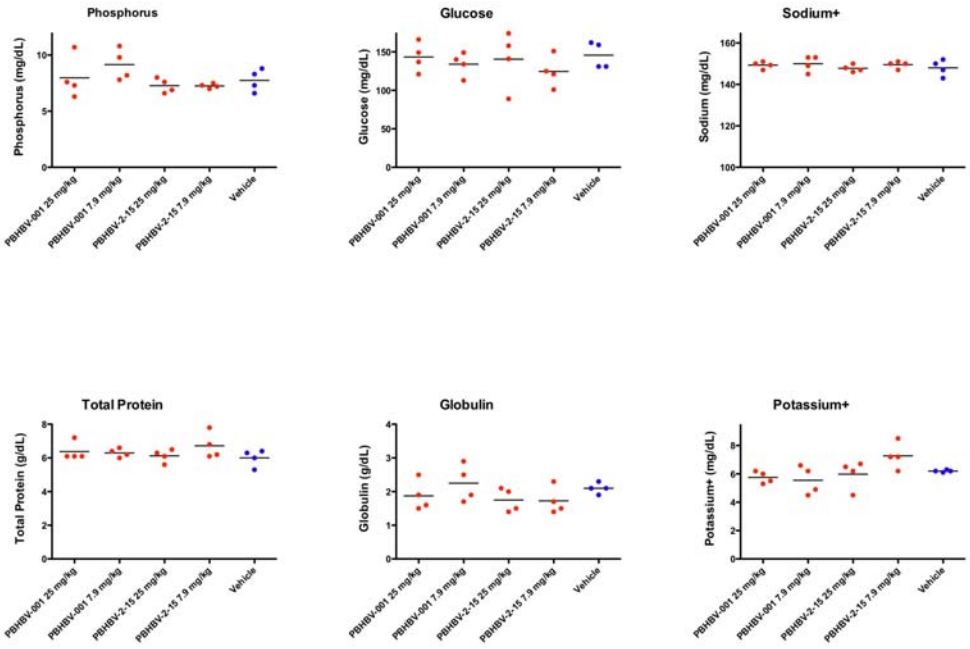


Figure 5. Effect of **PBHBV-001** (**1a**) and **PBHBV-2-15** (**3c**) Administered i.v. on Phosphorus, Glucose, Sodium, Total Protein, Globulin, and Potassium^{+} in C57BL/6 Mice (24 hours).

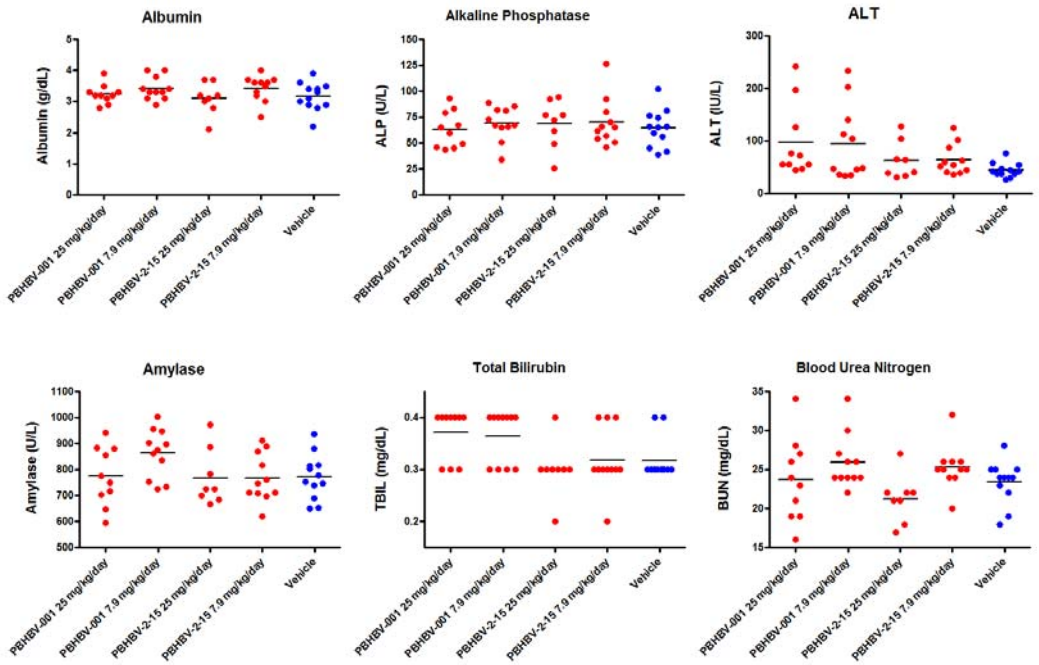


Figure 6. Effect of **PBHBV-001** (**1a**) and **PBHBV-2-15** (**3c**) Administered Orally on Albumin, Alkaline Phosphatase, ALT, Amylase, Total Bilirubin and Blood Urea Nitrogen in HBV-transgenic Mice (14 days).

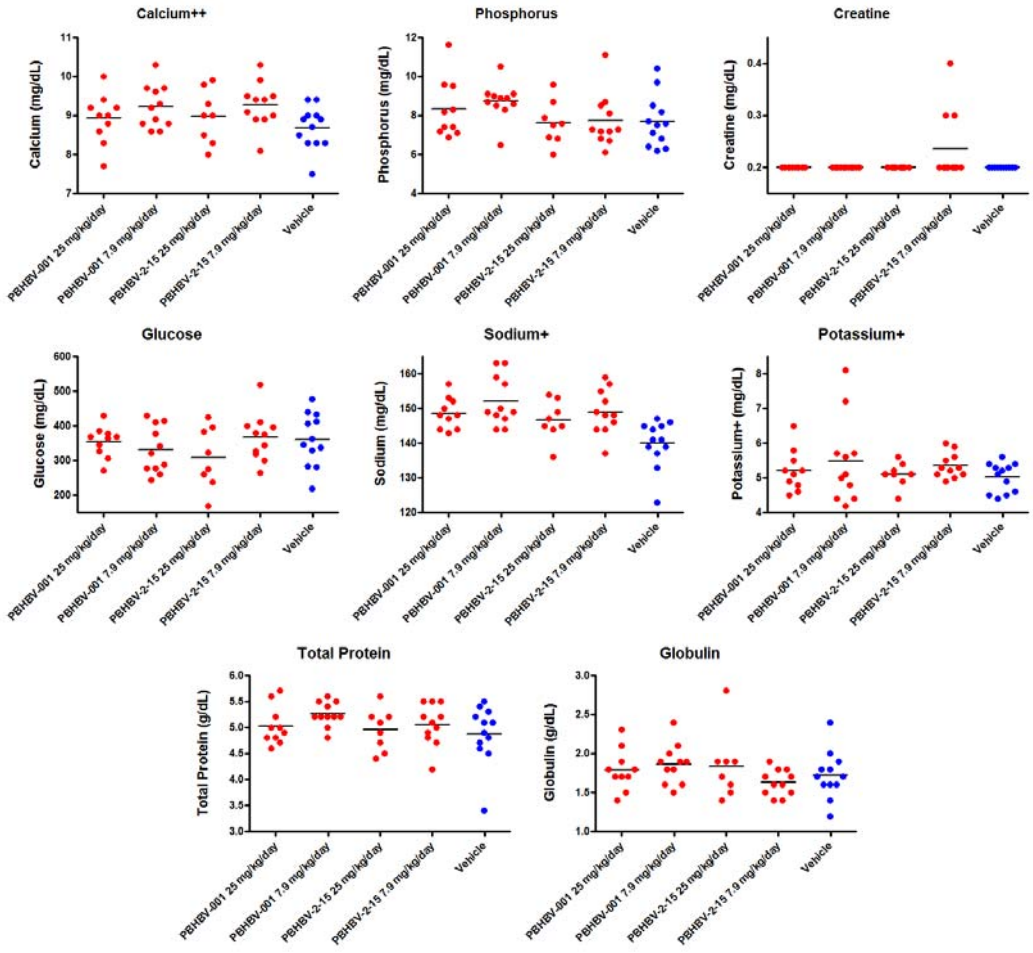


Figure 7. Effect of **PBHBV-001** (**1a**) and **PBHBV-2-15** (**3c**) Administered Orally on Calcium++, Phosphorus, Creatine, Glucose, Sodium+, Potassium+, Total Protein, Globulin, and in HBV-transgenic Mice (14 days).

5. Effect of 1a and 3c on Mice's Weight

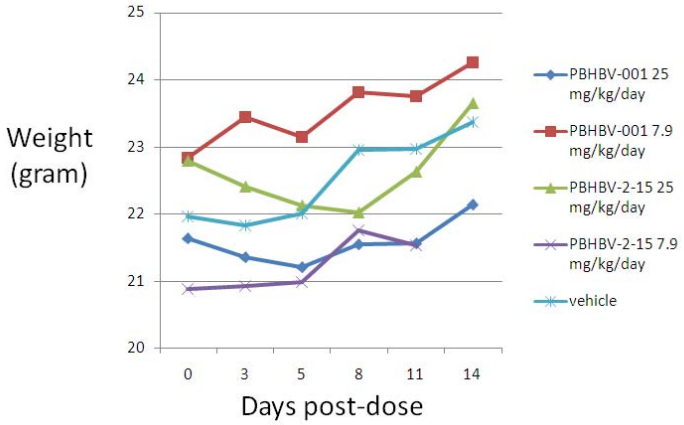
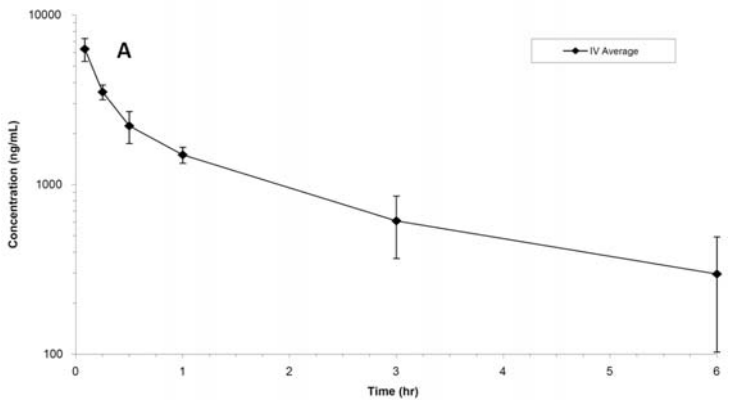


Figure 8. Effect of **PBHBV-001** (**1a**) and **PBHBV-2-15** (**3c**) Administered Orally on Mice's Weight (14 days).

6. Pharmacokinetics and Bioavailability of 1a and 3c



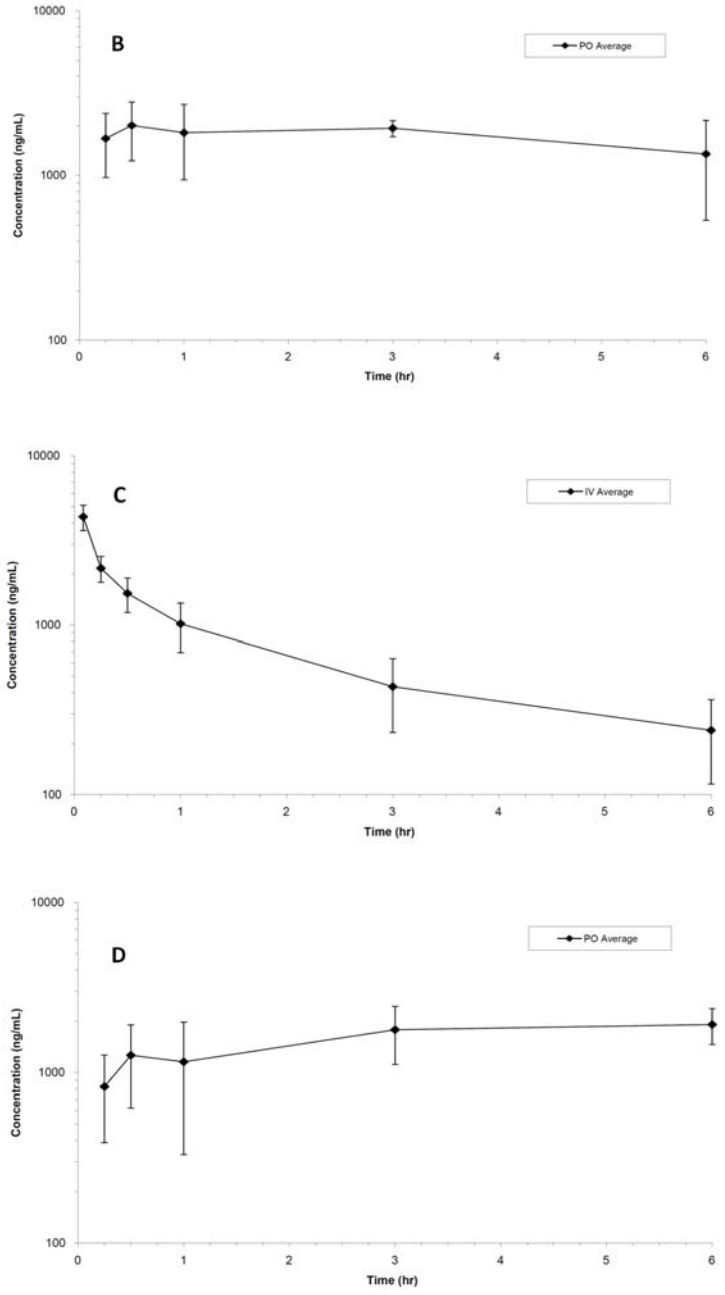


Figure 9. Pharmacokinetics and Bioavailability of Derivative Compounds: A. Intravenous PK Profile of **PBHBV-001** (**1a**); B. Oral PK Profile of **PBHBV-001** (**1a**); C. Intravenous PK Profile of **PBHBV-2-15** (**3c**); D. Oral PK Profile of **PBHBV-2-15** (**3c**). The Average Values from Three Animals are Depicted. Error Bars Represent Standard Deviation.