SUPPORTING INFORMATION

FOR

Asymmetric imidazole-4,5-dicarboxamides derivatives as SARS-CoV-2 main protease inhibitors: Design, Synthesis and Biological Evaluation

Phuong Nguyen Hoai Huynh[1], Phatcharin Khamplong[2], Minh-Hoang Phan[1], Thanh-Phuc Nguyen[1], Phuong Ngoc Lan Vu[1], Quang-Vinh Tang[1], Phumin Chamsodsai[3], Supaphorn Seetaha[3], Truong Lam Tuong[1], Thien Y Vu[4], Duc-Duy Vo[5,6,7], Kiattawee Choowongkomon[2,3*], Cam-Van T. Vo[1*]

[1]Department of Medicinal Chemistry, Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh city, Vietnam

[2]Department of Biochemistry, Faculty of Science, Kasetsart University, Bangkok, 10900 Thailand

[3]Genetic Engineering Interdisciplinary Program, Graduate School, Kasetsart University, Bangkok, 10900 Thailand;

[4]Faculty of Pharmacy, Ton Duc Thang University, Ho Chi Minh City, Vietnam

[5]Department of Cell and Molecular Biology, Biomedical Centre, Uppsala University, Husargatan 3, 75237 Uppsala, Sweden

[6]Department of Chemistry, Biomedical Centre, Uppsala University, Husargatan 3, 75237 Uppsala, Sweden

[7]School of Applied Chemistry, Tra Vinh University, 126 Nguyen Thien Thanh Street, Ward 5, Tra Vinh City, Viet Nam

Corresponding authors: vocamvan@ump.edu.vn; kiattawee.c@ku.th

1. Chemical synthesis

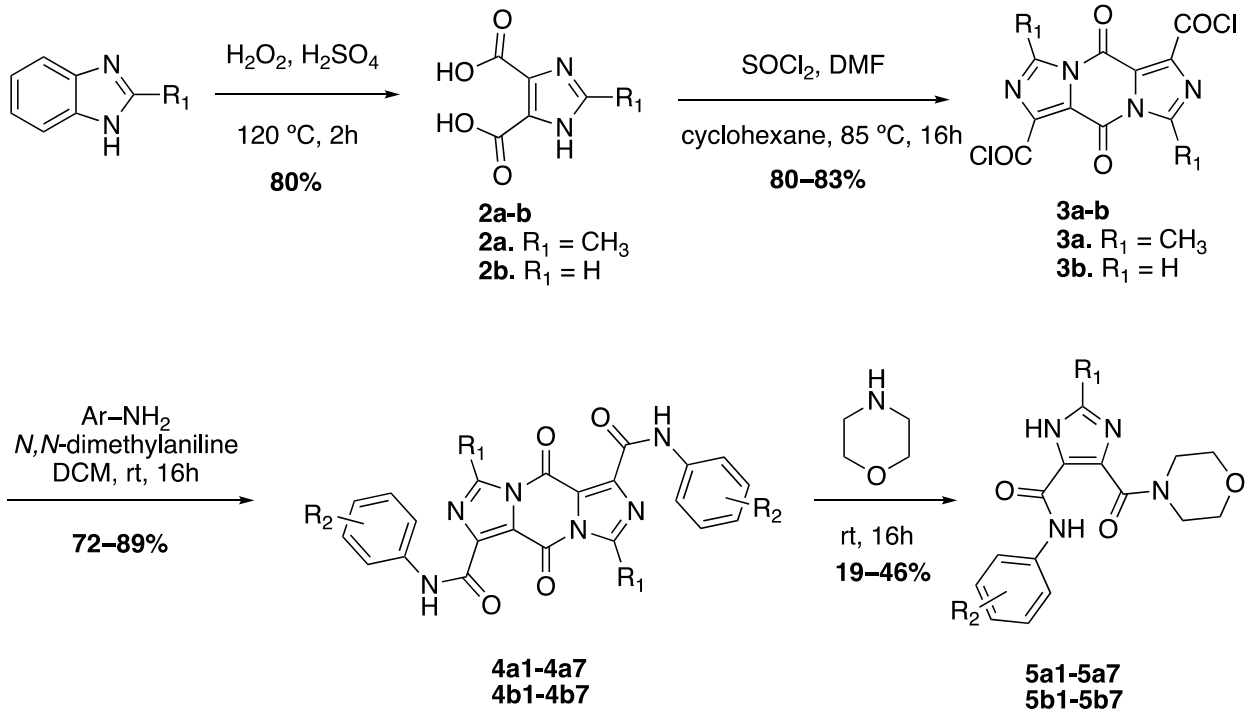
General chemistry information. Room temperature is considered 27−30 °C. Reaction conditions are described in detail in the sections below. All commercial reagents and solvents from suppliers were used without further purification.

TLC and column chromatography: Thin-layer chromatography (TLC) was perform using TLC Silica gel 60 GF_{254} precoated aluminium plates and the developed plates were visualized using Vilber Lourmat UV lamp. Normal phase flash column chromatography was run using silica gel 40 – 63 microns. The desired fractions from column chromatography (confirmed by TLC) were collected and concentrated under vaccuum to afford the product.

NMR: All NMR data were collected at ambient temperature. All NMR solvents were purchased from Cambridge Isotoped. NMR spectra were processed with MestReNova software. ^{1}H-NMR spectra were obtained on Bruker 400, 500 or 600 MHz spectrometers. Proton chemical shifts were reported in ppm. Proton data were reported as chemical shifts, multiplicity (singlet (s), triplet (t), multiplet (m), …), coupling constants [Hz] and integration. ^{13}C-NMR spectra were obtained on Bruker 100, 125, 150 MHz spectrometer. Carbon chemical shifts were reported in ppm.

Infrared Spectroscopy: Infrared spectra were recorded on FTIR 8201 PC Shimadzu spectrometer, and select νmax were reported in cm^{-1}.

Mass Spectrometry: Mass spectrometry was conducted by Shimadzu LCMS 8040, using ESI. The HRMS was conducted by Water Xevo G2-XS Qtof.

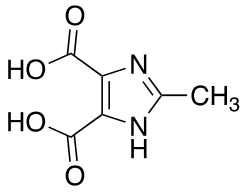


5a1: $R_1 = CH_3$, R_2 = 2,5–diCl
5a2: $R_1 = CH_3$, R_2 = 4–Cl
5a3: $R_1 = CH_3$, R_2 = 2–Cl
5a4: $R_1 = CH_3$, R_2 = 2–NO_2, 4–MeO
5a5: $R_1 = CH_3$, R_2 = 2,4,5–triCl
5a6: $R_1 = CH_3$, R_2 = 3,4–diCl
5a7: $R_1 = CH_3$, R_2 = H

5b1: R_1 = H, R_2 = 2,5–diCl
5b2: R_1 = H, R_2 = 4–Cl
5b3: R_1 = H, R_2 = 2–Cl
5b4: R_1 = H, R_2 = 2–NO_2, 4–MeO
5b5: R_1 = H, R_2 = 2,4,5–triCl
5b6: R_1 = H, R_2 = 3,4–diCl
5b7: R_1 = H, R_2 = H

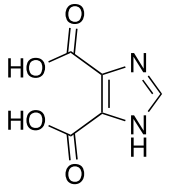
Scheme S1. Synthesis of asymmetric imidazole-4,5-dicarboxamide derivatives

Analytical Characterization Data

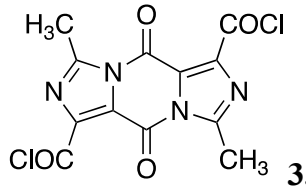


2-Methyl-imidazole-4,5-dicarboxylic acid (2a). Obtained as pale yellow solid; **Yield** 6.76 g, 80%; **M.p.** 255-256 ºC; **IR** (cm^{-1}): 3531, 1379; **^{1}H-NMR** (400 MHz, DMSO-d_6) δ (ppm): 2.49 (s, 3H); **^{13}C-NMR** (100 MHz, DMSO-d_6) δ (ppm): 159.80, 146.28, 128.34, 11.68, **MS-ESI:** $C_6H_6N_2O_4$ *m/z* $[M-H]^-$ 169.02 (Calcd.), 168.75 (found). This compound has been reported.[1]

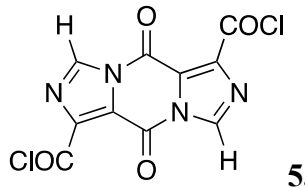
[1] M. A. Brusina, D. N. Nikolaev, S. M. Ramsh and L. B. Piotrovskii, *Russian Journal of Organic Chemistry,* 2016, **52**(10), 1528–1530.



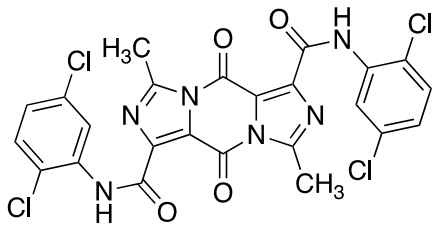
Imidazole-4,5-dicarboxylic acid (**2b**)**:** Obtained as pale yellow solid; **Yield** 6.25 g, 80%; **M.p.** 264-266 ^{o}C; **IR** (cm^{-1}): 3172, 1382; **^{1}H-NMR** (600 MHz, DMSO-d_6) δ (ppm): 9.11 (s, 1H, H2); **^{13}C-NMR** (150 MHz, DMSO-d_6) δ (ppm): 159.26, 135.47, 128.63; **MS-ESI:** $C_5H_4N_2O_4$ *m/z* [M-H]$^{-}$ 155.01 (Calcd.), 155.16 (found). This compound has been reported.[1]



3,8-Dimethyl-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarbonyl dichloride (3a). Obtained as pale brown solid; **Yield** 1.82 g, 83%; **M.p.** > 300 ^{o}C; **IR** (cm^{-1}): 1757, 1344, 758. This compound has been reported.[2]



5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarbonyl dichloride (**3b)** Obtained as pale brown solid; **Yield** 1.62 g, 80%; **IR** (cm^{-1}): 1597, 1381, 759. This compound has been reported.[3]

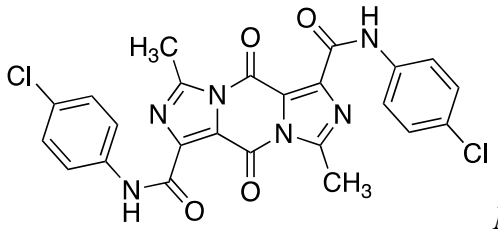


***N*^{1},*N*^{6}-bis(2,5-dichlorophenyl)-3,8-dimethyl-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxamide (4a1)** Obtained as yellow solid; **Yield** 0.95 g, 80%; **M.p.** 254-256 ^{o}C (decomposed); **IR** (cm^{-1}): 3080, 1674, 1236.

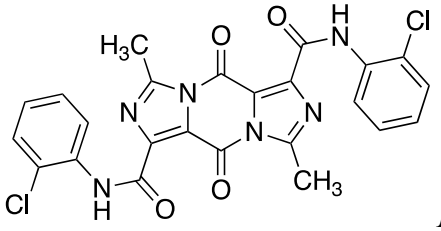
---

[2] T.-V. Phan, P. N. H. Huynh, T.-P. Nguyen, T.-T. Vu, M.-T. Le, B. G. D. Nguyen, P. Truong and K.-M. Thai, *New Journal of Chemistry*, 2023, **47**, 20718-20722.

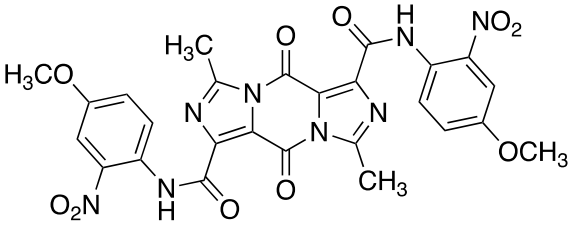
[3] A. V. Wiznycia, P. W Baures, *Journal of Organic Chemistry*, 2002, **67**(20), 7151-7154.



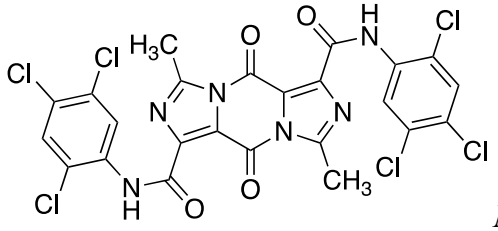
***N*^{1},*N*^{6}-bis(4-chlorophenyl)-3,8-dimethyl-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxamide (4a2)** Obtained as yellow solid; **Yield** 0.78 g, 75%; **M.p.** 251-253 ^{o}C (decomposed); **IR** (cm^{-1}): 3262, 1674, 1298.



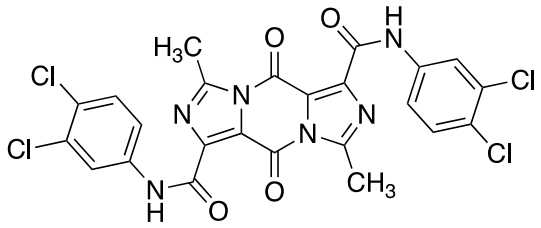
***N*^{1},*N*^{6}-bis(2-chlorophenyl)-3,8-dimethyl-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxamide (4a3)** Obtained as yellow solid; **Yield** 0.91 g, 87%; **M.p.** 244-246 ^{o}C (decomposed), **IR** (cm^{-1}): 3334, 1693, 1276. This compound has been reported.[2]



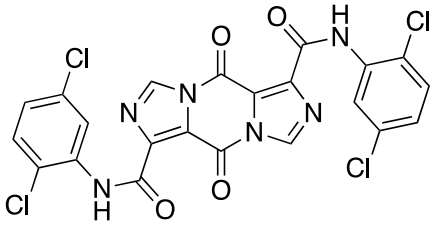
***N*^{1},*N*^{6}-bis(4-methoxy-2-nitro-phenyl)-3,8-dimethyl-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazin-1,6-dicarboxamide (4a4)** Obtained as yellow solid; **Yield** 1.08 g, 89%; **M.p.** 255-256 ^{o}C (decomposed); **IR** (cm^{-1}): 3279, 1694, 1261.



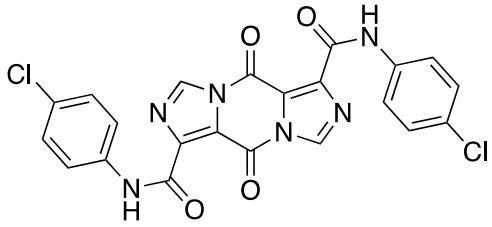
***N*^{1},*N*^{6}-bis(2,4,5-trichlorophenyl)-3,8-dimethyl-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxamide (4a5).** Obtained as yellow solid; **Yield** 0.96 g, 73%; **M.p.** 255-256 ^{o}C; **IR** (cm^{-1}): 3265, 1687, 1250. This compound has been reported.[2]



***N*¹,*N*⁶-bis(3,4-dichlorophenyl)-3,8-dimethyl-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxamide (4a6).** Obtained as yellow solid; **Yield** 1.03 g, 87%; **M.p.** 244-245 °C, **IR** (cm^{-1}): 3251, 1674, 1286. This compound has been reported.[2]

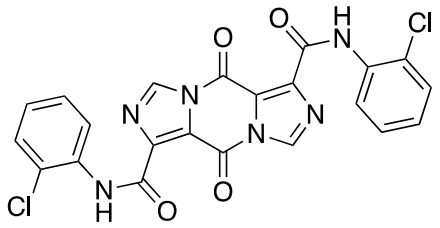


***N*¹,*N*⁶-bis(2,5-dichlorophenyl)-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxamide (4b1)** Obtained as yellow solid, **Yield** 0.95 g, 84%; **M.p.** 258-260 °C; **IR** (cm^{-1}): 3323, 1693, 1240.

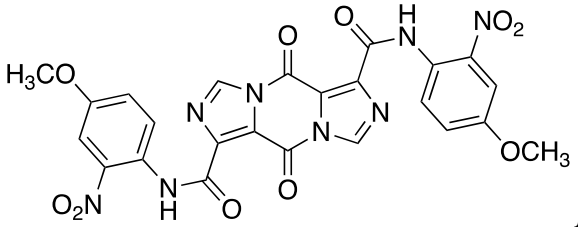


***N*¹,*N*⁶-bis(4-chlorophenyl)-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxamide (4b2)** Obtained as red solid; **Yield** 0.83 g, 84%,; **M.p.** 251-253 °C (decomposed); **IR** (cm^{-1}): 3256, 1678, 1253. This compound has been reported.[4]

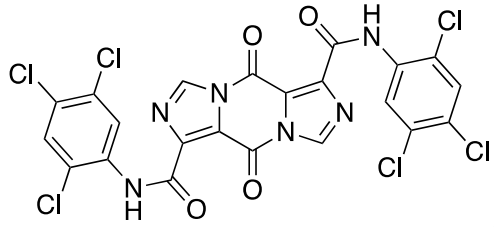
[4] E. M. Perchellet, J.-P. Perchellet and P. W. Baures, *Journal of medicinal chemistry*, 2005, **48**, 5955-5965.



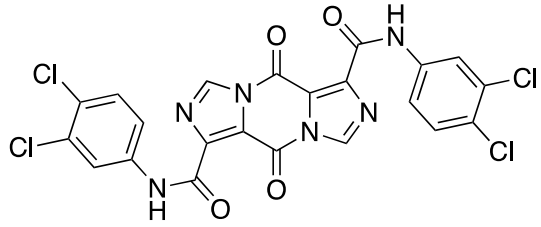
***N*^{1},*N*^{6}-bis(2-chlorophenyl)-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxamide (4b3)** Obtained as yellow solid; **Yield** 0.72 g, 73%; **M.p.** 259-257 ^oC (decomposed); **IR** (cm^{-1}): 3343, 1693, 1240.



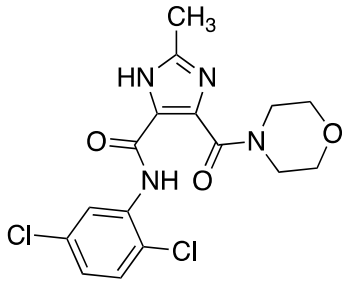
***N*^{1},*N*^{6}-bis(4-methoxy-2-nitrophenyl)-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxamide (4b4)** Obtained as yellow solid; **Yield** 0.83 g, 72%; **M.p.** 255-256 ^oC (decomposed); **IR** (cm^{-1}): 3265, 1688, 1252.



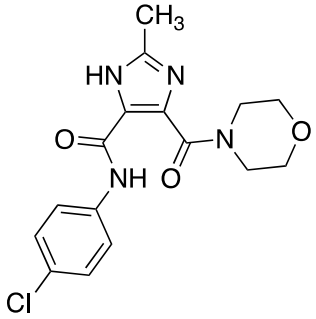
***N*^{1},*N*^{6}-bis(2,4,5-trichlorophenyl)-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxamide (4b5)** Obtained as yellow solid; **Yield** 0.95 g, 75%; **M.p.** 255-257 ^oC (decomposed); **IR** (cm^{-1}): 3219, 1674, 1242.



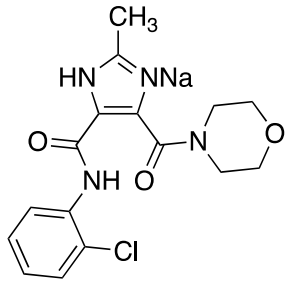
***N*^{1},*N*^{6}-bis(3,4-dichlorophenyl)-5,10-dioxo-5*H*,10*H*-diimidazo[1,5-*a*:1',5'-*d*]pyrazine-1,6-dicarboxamide (4b6)** Obtained as orange solid; **Yield** 0.95 g, 84%; **M.p.** 256-257 ^oC (decomposed); **IR** (cm^{-1}): 3302, 1686, 1254. This compound has been reported.[4]



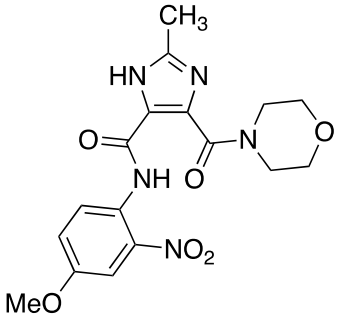
***N*-(2,5-dichlorophenyl)-2-methyl-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide** (**5a1**) Obtained as white solid; **Yield** 0.35 g, 46%; **M.p.** 227-229 ^{o}C; **IR** (cm^{-1}): 3238, 1653, 1288; **^{1}H-NMR** (500 MHz, $CDCl_3$ with 0.05% v/v TMS) δ (ppm): 12.48 (s, 1H), 11.48 (s, 1H), 8.28 (d, 1H, ^{4}J = 2.5 Hz), 7.35 (d, 1H, J = 9.0 Hz), 7.09 (dd, 1H, ^{3}J = 9.0 Hz, ^{4}J = 2.5 Hz), 4.28 (t, J = 5.0 Hz), 3.84-3.78 (m, 4H), 3.76 (t, J = 5.0 Hz), 2.44 (s, 3H); **^{13}C-NMR** (125 MHz, $CDCl_3$ with 0.05% v/v TMS) δ (ppm): 163.84, 158.07, 145.40, 135.99, 134.87, 132.57, 130.44, 129.38, 125.52, 124.12, 124.03, 67.29, 66.93, 48.34, 43.57, 14.06. NMR data matched with the literature.[2]



***N*-(4-chlorophenyl)-2-methyl-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide** (**5a2**) Obtained as white solid; **Yield** 0.19 g, 27%; **M.p.** 279-281 ^{o}C ; **IR** (cm^{-1}): 3203, 1654, 1263; **^{1}H-NMR** (500 MHz, $CDCl_3$ with 0.05% v/v TMS) δ (ppm): 12.79 (s, 1H), 11.38 (s, 1H), 7.70 (d, 1H, J = 9 Hz), 7.31 (d, 1H, J = 9.0 Hz), 4.32 (t, 2H, J = 5.0 Hz, CH_2-N), 3.84-3.80 (m, 4H, CH_2-O), 3.76 (t, 2H, J = 5.0 Hz, CH_2-N), 2.43 (s, 3H, CH_3); **^{13}C-NMR** (125 MHz, $CDCl_3$ with 0.05% v/v TMS) δ (ppm): 164.36, 157.30 144.65, 136.80, 133.81, 130.55, 129.37, 128.96, 121.60, 67.27, 66.87, 48.54, 43.72, 14.11; **HRMS-ESI**: $C_{15}H_{15}ClN_4O_3$ *m/z* $[M+H]^+$ 349.1067 (Calcd.), 349.1082 (found).



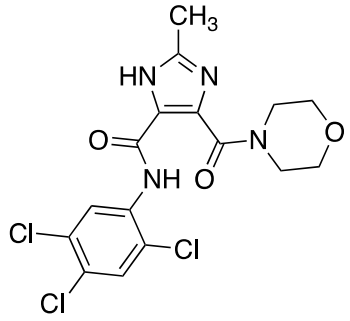
***N*-(2-chlorophenyl)-2-methyl-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide (5a3).** Obtained as white solid; **Yield** 0.17 g, 24%; **M.p.** 223-225 °C, **IR** (cm^{-1}): 3242, 1653, 1285; **^{1}H-NMR** (500 MHz, $CDCl_3$ with 0.05% v/v TMS) δ (ppm): 12.26 (s, 1H), 11.50 (s, 1H), 8.12 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.5 Hz), 7.44 (dd, 1H, ^3J = 8.0 Hz, ^4J = 1.5 Hz), 7.27 (td, 1H, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 7.12 (td, ^3J = 7.5 Hz, ^4J = 1.5 Hz), 4.26 (t, 2H, J = 5.0 Hz), 3.84-3.78 (m, 4H), 3.75 (t, 2H, J = 5.0 Hz), 2.36 (s, 3H); **^{13}C-NMR** (125 MHz, DMSO-d_6) δ (ppm): 163.69, 160.32, 159.50, 157.10, 145.52, 144.96, 134.91, 134.60, 133.95, 130.83, 129.58, 129.27, 128.78, 127.87, 127.49, 127.03, 125.63, 124.81, 124.31, 124.04, 122.82, 122.43, 66.48, 66.16, 66.07, 65.82, 47.80, 46.90, 42.96, 41.93, 13.50. NMR data matched with the literature.[2]



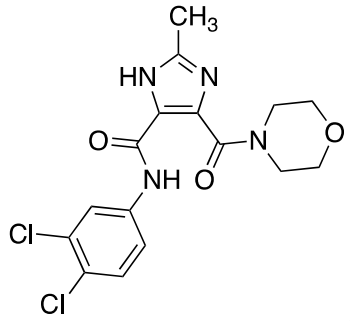
***N*-(4-methoxy-2-nitrophenyl)-2-methyl-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide** (**5a4**) Obtained as yellow solid; **Yield** 0.15 g, 19%; **M.p.** 282-284 °C; **IR** (cm^{-1}): 3219, 1664, 1255; **^{1}H-NMR** (500 MHz, DMSO-d_6) δ (ppm): 13.13 (s, 0.4H), 12.96 (s, 0.6H), 12.31 (s, 0.4H), 11.12 (s, 0.6H), 8.42 (d, 0.6H, J = 9.0 Hz), 7,65 (d, 0.4H, J = 9.0 Hz), 7.63 (d, 0.6H, J = 3.0 Hz), 7.54 (d, 0.4H, J = 3.0 Hz), 7.41 (dd, 0.6H, ^3J = 9.0 Hz, ^4J = 5.0 Hz), 7.35 (dd, 0.4H, ^3J = 9.0 Hz, ^4J = 5.0 Hz), 4.15 (t, 0.7H, J = 5.0 Hz), 4.04 (m, 0.8H), 3.86 (m, 3H), 3.70 (s, 1.3H), 3.67-3.64 (m, 3.2H), 3.54 (t, 1.2H, J = 5.0 Hz), 3.31 (s, 0.8H), 2.37-2.33 (m, 3H); **^{13}C-NMR** (150 MHz, DMSO-d_6) δ (ppm): 160.56, 160.30, 159.94, 159.72, 156.33, 154.70, 145.50, 144.84, 138.80, 138.48, 134.16, 130.80, 128.27, 127.58, 127.35, 126.82, 124.29, 123.21, 122.21, 120.28, 109.10, 108.83, 66.43, 66.06, 66.01, 65.77, 59.67, 55.90, 47.85,

46.80, 43.04, 41.86, 13.5; **HRMS-ESI:** $C_{17}H_{19}N_5O_6$ *m/z* $[M+H]^+$ 390.1335 (Calcd.), 390.1388 (found).

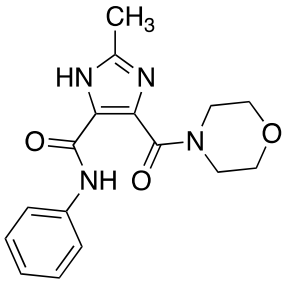
There were two conformers of this compound: intrahydrogen bonding conformer and non-intrahydrogen bonding conformer.[4]



***N*-(2,4,5-trichlorophenyl)-2-methyl-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide (5a5).** Obtained as white solid; **Yield** 0.32 g, 38%; **M.p.** 261-263 °C, **IR** (cm^{-1}): 3342, 1645, 1288; **^{1}H-NMR** (500 MHz, $CDCl_3$ with 0.05% v/v TMS) δ (ppm): 12.61 (s, 1H), 11.12 (s, 1H), 8.50 (s, 1H), 7.55 (s, 1H), 4.33 (t, 2H, *J* = 5.0 Hz), 3.84 (m, 4H), 3.79 (t, 2H, *J* = 5.0 Hz), 2.48 (s, 3H); **^{13}C-NMR** (150 MHz, DMSO-d_6) δ (ppm): 163.42, 157.26, 145.87, 135.24, 134.32, 130.54, 129.83, 128.45, 126.24, 123.67, 123.89, 66.40, 66.10, 47.75, 42.99, 13.51. NMR data matched with the literature.[2]

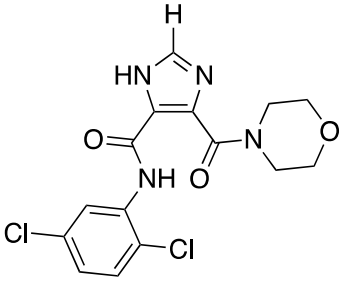


***N*-(3,4-dichlorophenyl)-2-methyl-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide (5a6).** Obtained as white solid; **Yield** 0.24 g, 31%; **M.p.** 261-263 °C, **IR** (cm^{-1}): 3257, 1678, 1269; **^{1}H-NMR** (600 MHz, DMSO-d_6) δ (ppm): 13.09 (s, 1H), 12.85 (s, 0.7H), 10.26 (s, 0.3H), 8.07 (s, 1H), 7.61-7.50 (m, 2H), 4.18-3.63 (m, 8H), 2.35 (s, 3H); **^{13}C-NMR** (150 MHz, DMSO-d_6) 164.03, 160.61, 160.54, 156.83, 145.50, 144.64, 139.05, 138.47, 133.65, 131.33, 131.27, 131.02, 130.72, 130.34, 129.30, 127.42, 125.19, 124.64, 121.22, 120.39, 120.05, 119.39, 66.40, 66.10, 65.96, 65.93, 48.05, 42.26, 13.54, 13.45. NMR data matched with the literature.[2]



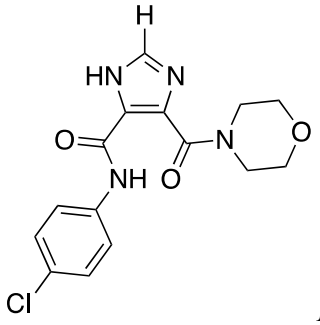
***N*-(phenyl)-2-methyl-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide (5a7).** Obtained as white solid; **Yield** 0.12 g, 19%; **M.p.** 265-267 ^{o}C, **IR** (cm^{-1}): 3260, 1665, 1296; **^{1}H-NMR** (600 MHz, DMSO-d_6 with 0.03% v/v TMS) δ (ppm): 13.07 (s, 0.8H), 12.82 (s, 0.2H), 12.47 (s, 0.8H), 9.81 (s, 0.2H), 7.79 (s, 0.4H), 7.63 (d, 7.61-7.50 (m, 2H), 4.18-3.63 (m, 8H), 2.35 (s, 3H); **^{13}C-NMR** (600 MHz, DMSO-d_6 with 0.03% v/v TMS) 164.03, 160.61, 160.54, 156.83, 145.50, 144.64, 139.05, 138.47, 133.65, 131.33, 131.27, 131.02, 130.72, 130.34, 129.30, 127.42, 125.19, 124.64, 121.22, 120.39, 120.05, 119.39, 66.40, 66.10, 65.96, 65.93, 48.05, 42.26, 13.54, 13.45; **HRMS-ESI:** $C_{16}H_{18}N_4O_3$ *m/z* $[M+H]^+$ 315.1452 (Calcd.), 315.1460 (found).

There were two conformers of this compound: intrahydrogen bonding conformer and non-intrahydrogen bonding conformer.[4]



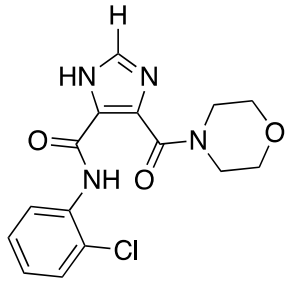
***N*-(2,5-dichlorophenyl)-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide (5b1**) Obtained as white solid; **Yield** 0.15 g, 20%; **M.p.** 223-225 ^{o}C; **IR** (cm^{-1}): 3177, 1670, 1282; **^{1}H-NMR** (600 MHz, DMSO-d_6) δ (ppm): 13.48 (s, 1H), 12.28 (s, 0.6H), 9.78 (s, 0.4H), 8.36 (s, 1H), 7.95 (s, 1H), 7.57 (d, 1H, J = 8.4 Hz), 7.24 (dd, ^{3}J = 8.4 Hz, ^{4}J = 2.4 Hz), 4.11-3.67 (m, 8H); **^{13}C-NMR** (125 MHz, DMSO-d_6 with 0.03% v/v TMS) δ (ppm): 162.42, 156.95, 149.97, 141.41, 136.95, 136.47, 135.90, 131.80, 130.76, 124.78, 121.98, 66.25, 65.96, 47.38, 42.49; **HRMS-ESI:** $C_{15}H_{14}Cl_2N_4O_3$ *m/z* $[M+H]^+$ 369.0521 (Calcd.), 369.0560 (found).

There were two conformers of this compound: intrahydrogen bonding conformer and non-intrahydrogen bonding conformer.[4]



***N*-(4-chlorophenyl)-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide** (**5b2**) Obtained as white solid; **Yield** 0.28 g, 42%; **M.p.** 251-253 °C; **IR** (cm^{-1}): 3177, 1668, 1283; **^{1}H-NMR** (600 MHz, DMSO-d_6 with 0.03% v/v TMS) δ (ppm): 13.49 (s, 0.7H), 13.20 (s, 0.3H), 12.62 (s, 0.7H), 10.13 (s, 0.3H), 7.92 (s, 1H), 7.68 (s, 1H), 7.43 (s, 1H), 4.15-3.65 (m, 8H); **^{13}C-NMR** (125 MHz, DMSO-d_6 with 0.03% v/v TMS) δ (ppm): 164.05, 160.62, 160.26, 156.50, 137.23, 136.12, 133.67, 132.03, 129.67, 128.98, 128.57, 128.41, 127.38, 121.41, 120.83, 66.33, 66.04, 48.03, 43.19; **HRMS-ESI:** $C_{15}H_{15}ClN_4O_3$ *m/z* $[M+H]^+$ 335.0910 (Calcd.), 335.0937 (found).

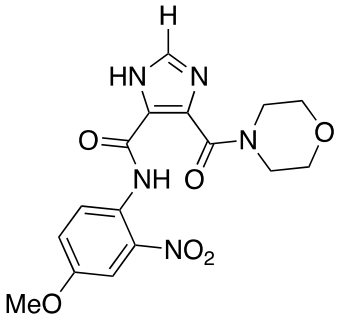
There were two conformers of this compound: intrahydrogen bonding conformer and non-intrahydrogen bonding conformer.[4]



***N*-(2-chlorophenyl)-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide** (**5b3**) Obtained as white solid; **Yield** 0.16 g, 24%; **M.p.** 187-189 °C; **IR** (cm^{-1}): 3236, 1653, 1288; **^{1}H-NMR** (600 MHz, DMSO-d_6) δ (ppm): 13.45 (s, 1H), 12.06 (s, 0.6H), 9.74 (s, 0.4H), 8.18 (s, 1H), 7.93 (s, 1H), 7.53 (dd, 1H, ^3J = 7.8 Hz, ^4J = 1.2 Hz), 7.35 (td, 1H, ^3J = 7.8 Hz, ^4J = 1.2 Hz), 7.18 (t, 1H, ^3J = 7.8 Hz, ^4J = 1.2 Hz), 4.10-3.62 (m, 8H); **^{1}H-NMR** (500 MHz, $CDCl_3$ with 0.05% v/v TMS) δ (ppm): 12.35 (s, 0.9H), 11.97 (s, 0.1H), 11.58 (s, 0.9H), 9.80 (s, 0.1H), 8.55 (d, 0.1H, J = 8.0 Hz), 8.19 (dd, 0.9H, ^3J = 8.0 Hz, ^4J = 1.5 Hz), 7.68 (s, 0.9H), 7.61 (s, 0.1H), 7.47 (dd, 0.9H, ^3J = 8.0 Hz, ^4J = 1.5 Hz), 7.43 (d, 0.1H, ^3J = 8.0 Hz), 7.32 (td, 1H, ^3J = 8.0 Hz, ^4J = 1.5 Hz), 7.15 (td, 0.9H, ^3J = 8.0 Hz, ^4J = 1.5 Hz), 7.01 (t, 0.1H, ^3J = 8.0 Hz), 4.30 (t, 1.8H, J = 5.0 Hz), 3.89-3.82 (m, 4H), 3.80 (t, 1.8H, J = 5.0 Hz), 3.76 (s, 0.2H), 3.63 (s, 0.2H); **^{13}C-NMR** (125 MHz, DMSO-d_6 with 0.03% v/v TMS) δ (ppm): 163.59, 160.22, 159.37, 157.00, 136.37,

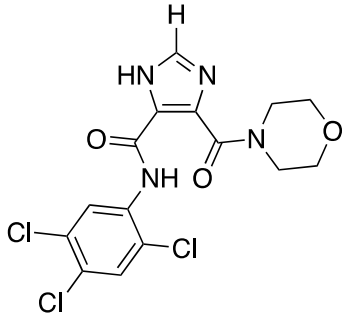
136.12, 134.75, 134.51, 134.22, 131.29, 129.54, 129.25, 128.96, 127.88, 127.45, 127.28, 125.72, 124.81, 124.35, 124.07, 122.76, 121.31, 66.44, 66.12, 65.98, 65.74, 47.81, 46.81, 42.98, 41.90; **HRMS-ESI:** $C_{15}H_{15}ClN_4O_3$ *m/z* $[M+H]^+$ 335.0910 (Calcd.), 335.0898 (found).

There were two conformers of this compound: intrahydrogen bonding conformer and non-intrahydrogen bonding conformer.[4]



***N*-(4-methoxy-2-nitrophenyl)-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide** (**5b4**) Obtained as yellow solid; **Yield** 0.29 g, 39%; **M.p.** 211-212 °C; **IR** (cm^{-1}): 3348, 1680, 1260; **^{1}H-NMR** (600 MHz, DMSO-d_6) δ (ppm): 13.31 (s, 1H), 12.24 (s, 0.3H), 11.24 (s, 0.7H), 8.45 (s, 1H), 7.93 (s, 1H), 7.62 (s, 1H), 7.40 (d, 1H, J = 9.0 Hz), 4.10-3.56 (m, 11H); **^{13}C-NMR** (125 MHz, DMSO-d_6 with 0.03% v/v TMS) δ (ppm): 160.26, 159.90, 154.70, 138.59, 136.15, 131.32, 127.68, 126.91, 124.09, 122.36, 108.89, 65.97, 65.74, 55.92, 46.77, 41.88; **HRMS-ESI:** $C_{16}H_{17}N_5O_6$ $[M+H]^+$ 376.1257 (Calcd.), 376.1276 (found).

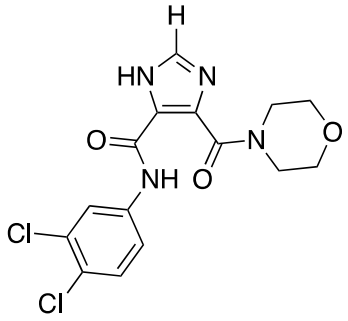
There were two conformers of this compound: intrahydrogen bonding conformer and non-intrahydrogen bonding conformer.[4]



***N*-(2,4,5-trichlorophenyl)-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide** (**5b5**) Obtained as white solid; **Yield** 0.32 g, 43%; **M.p.** 224-227 °C; **IR** (cm^{-1}): 3234, 1556, 1265; **^{1}H-NMR** (600 MHz, DMSO-d_6 with 0.03% v/v TMS) δ (ppm): 13.55 (s, 0.6H), 12.37 (s, 0.4H), 12.43 (s, 0.6H), 9.79 (s, 0.4H), 8.55 (s, 1H), 7.97-7.94 (m, 2H), 4.14-3.54 (m, 8H); **^{13}C-NMR** (125 MHz, DMSO-d_6 with 0.03% v/v TMS) δ (ppm): 163.34, 157.31,

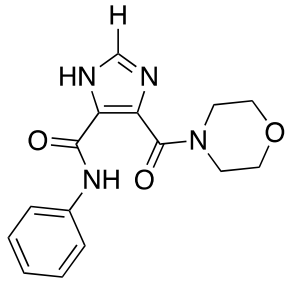
136.63, 134.91, 134.57, 130.46, 130,04, 128.65, 126.36, 123.79, 123.11, 66.27, 65.99, 47.59, 43.02; **HRMS-ESI:** $C_{15}H_{13}Cl_3N_4O_3$ *m/z* $[M-H]^-$ 400.9975 (Calcd.), 400.9936 (found).

There were two conformers of this compound: intrahydrogen bonding conformer and non-intrahydrogen bonding conformer.[4]



***N*-(3,4-dichlorophenyl)-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide** (**5b6**) Obtained as white solid, **Yield** 0.33 g, 45%; **M.p.** 258-261 °C; **IR** (cm^{-1}): 3219, 1654, 1290; **^{1}H-NMR** (600 MHz, DMSO-d_6) δ (ppm): 13.46 (s, 1H), 12.78 (s, 0.54H), 10.33 (s, 0.45H), 8.10-7.59 (m, 4H), 4.14-3.62 (m, 8H); **^{13}C-NMR** (125 MHz, DMSO-d_6 with 0.03% v/v TMS) δ (ppm): 163.99, 156.83, 138.33, 136.24, 133.98, 130.87, 129.38, 127.95, 125.19, 120.53, 119.51, 66.23, 65.97, 47.99, 43.25; **HRMS-ESI:** $C_{15}H_{14}Cl_2N_4O_3$ *m/z* $[M-H]^-$ 367.0365 (Calcd.), 367.0350 (found).

There were two conformers of this compound: intrahydrogen bonding conformer and non-intrahydrogen bonding conformer.[4]



***N*-phenyl-4-(morpholine-4-carbonyl)-1*H*-imidazole-5-carboxamide** (**5b7**) Obtained as white solid, **Yield** 0.24 g, 40%; **M.p.** 235-237 °C; **IR** (cm^{-1}): 3172, 1629, 1286; **^{1}H-NMR** (600 MHz, DMSO-d_6) δ (ppm): 13.46 (s, 0.75H), 13.15 (s, 0.25H), 12.45 (s, 0.75H), 9.91 (s, 0.25H), 7.92 (s, 0.75H), 7.89 (s, 0.25H), 7.81 (d, 0.5H, J = 7.8 Hz), 7.65 (d, 0.5H, J = 7.8 Hz), 7.39 (t, 1.5H, J = 15.6 Hz, J = 7.8 Hz), 7.32 (t, 0.5H, J = 15.6 Hz, J = 7.8 Hz), 7.13 (t, 0.75H, J = 15.6 Hz, J = 7.8 Hz), 7.07 (t, 0.25H, J = 15.6 Hz, J = 7.8 Hz), 4.14-3.66 (m, 8H); **^{13}C-NMR** (125 MHz, DMSO-d_6) δ (ppm): 164.14, 160.71, 160.10, 156.47, 138.64, 138.29 136.03, 135.65,

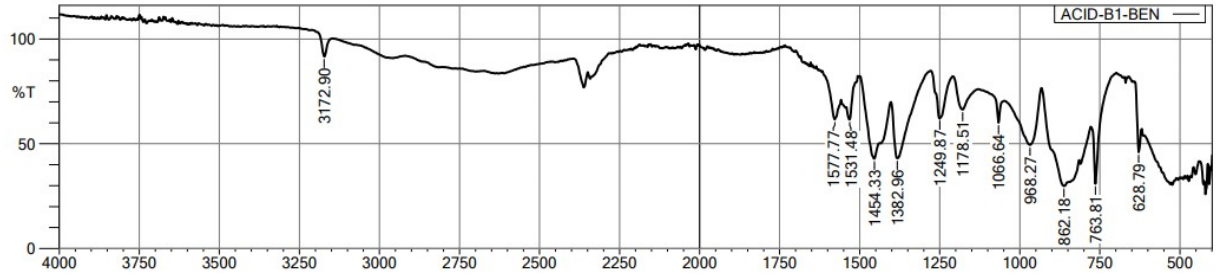
133.52, 132.26, 129.89, 129.10, 128.54, 127.08, 123.88, 123.33, 119.92, 119.30, 66.42, 66.11, 48.04, 43.19; **HRMS-ESI:** $C_{15}H_{16}N_4O_3$ *m/z* $[M+H]^+$ 301.1295 (Calcd.), 301.1275 (found).

There were two conformers of this compound: intrahydrogen bonding conformer and non-intrahydrogen bonding conformer.[4]

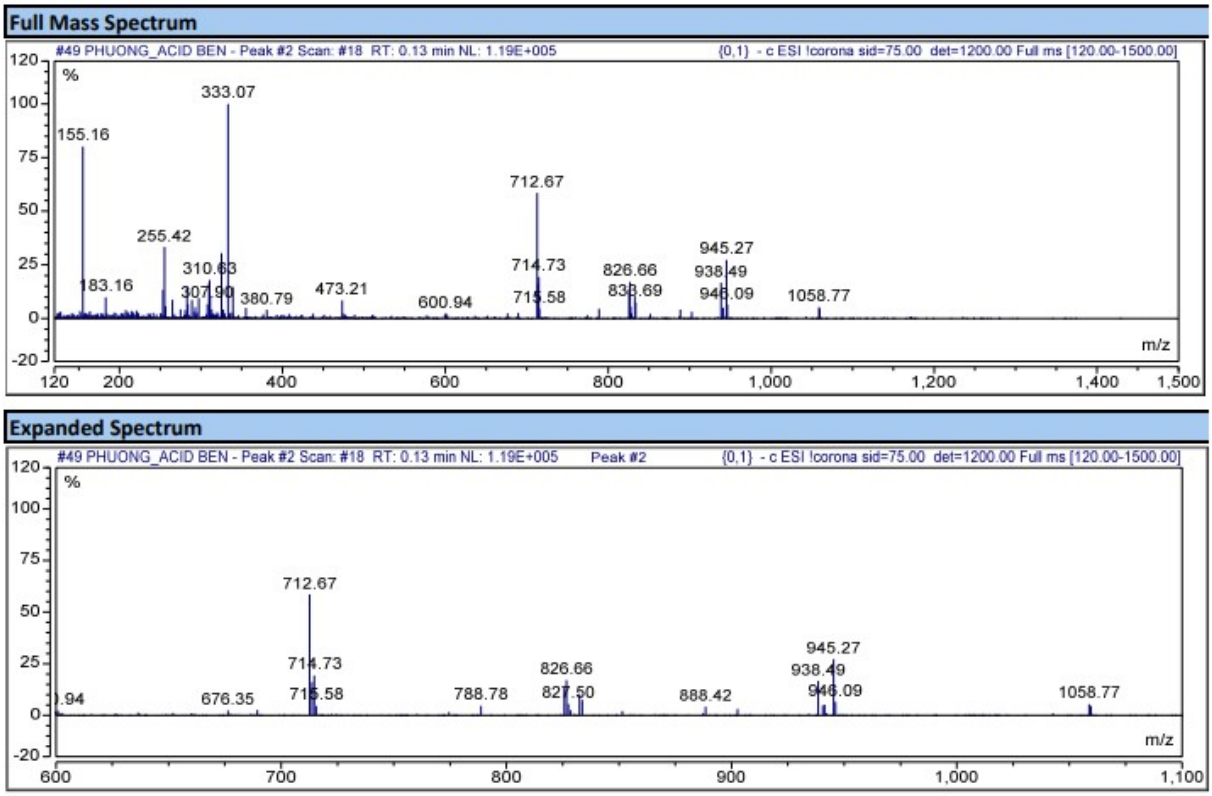
[1]H-NMR, [13]C-NMR and HRMS spectra of synthesized compounds

Compound ***2b***

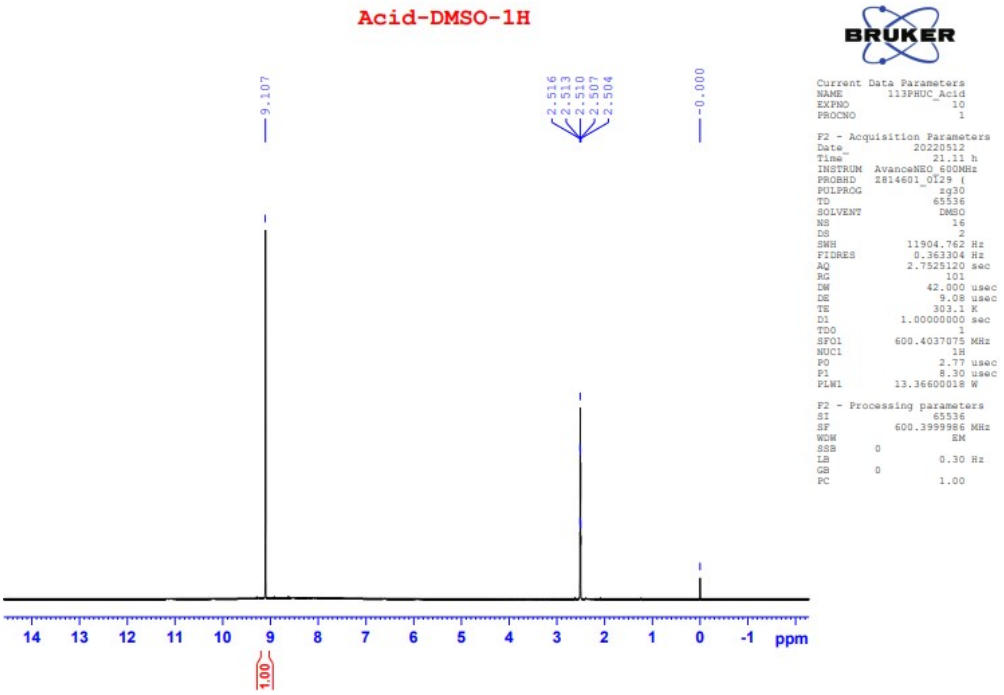
IR spectrum



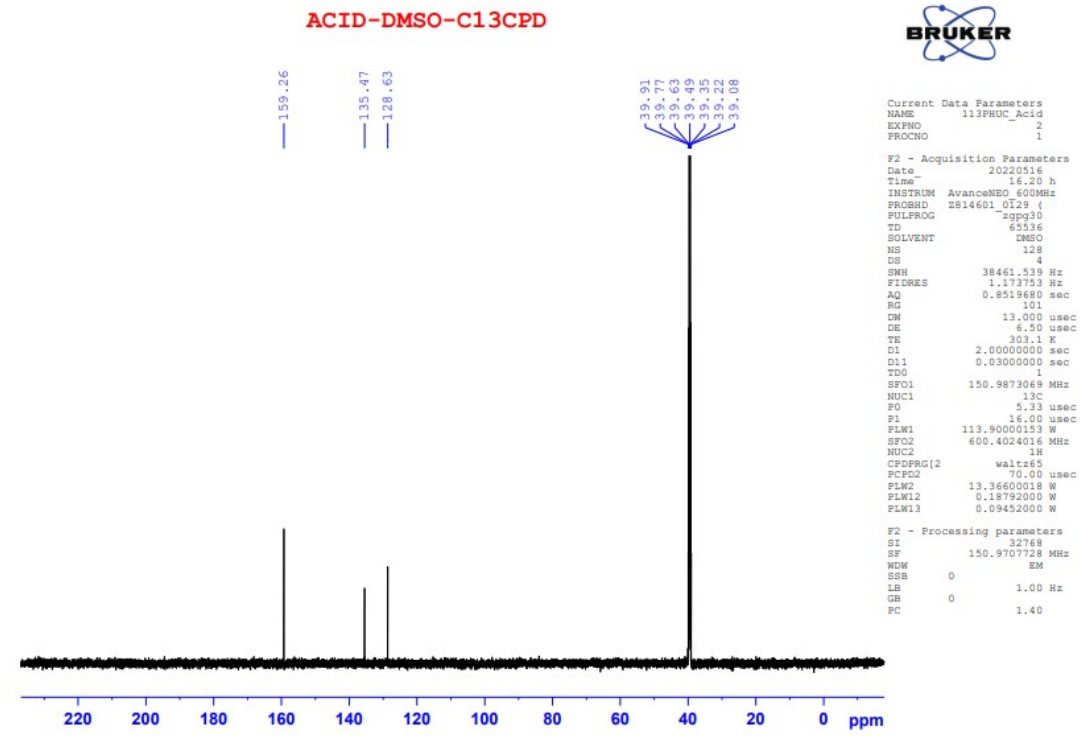
MS spectrum



[1]H-NMR spectrum

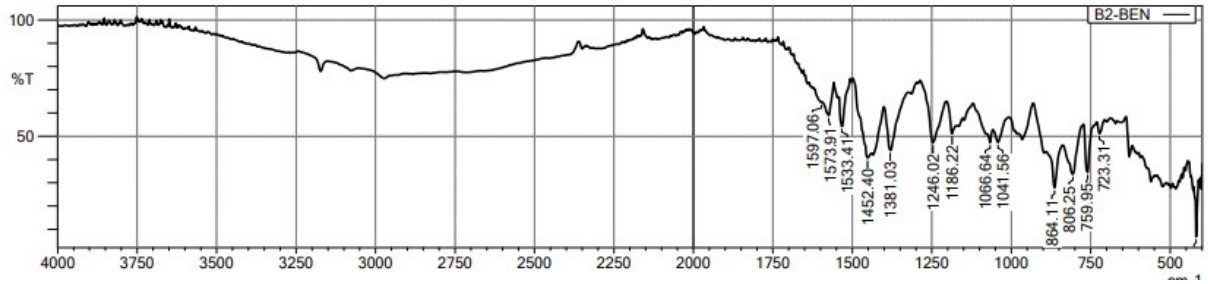


^{13}C-NMR spectrum



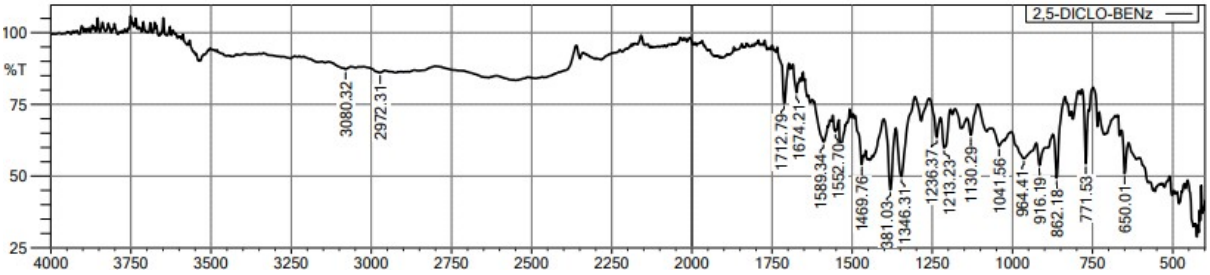
*Compound **3b***

IR spectrum



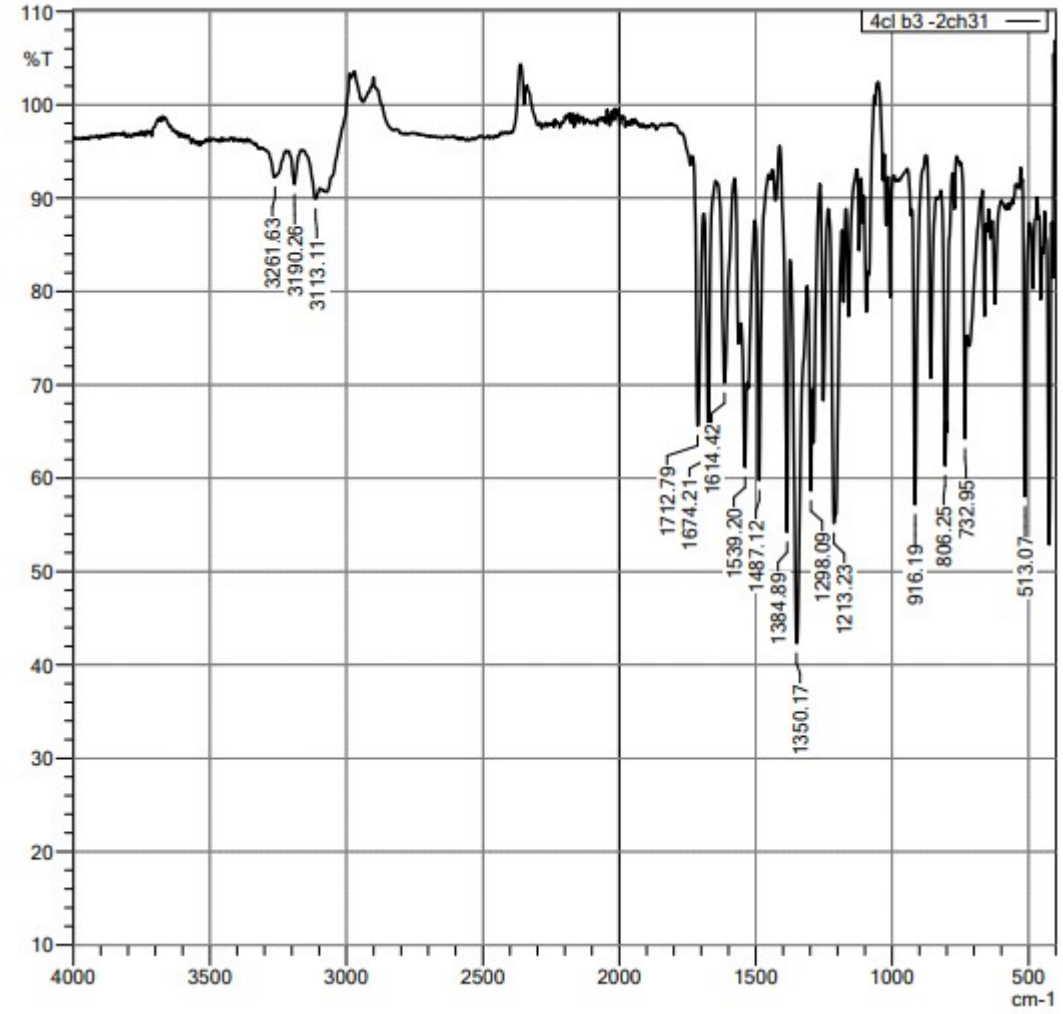
*Compound **4a1***

IR spectrum



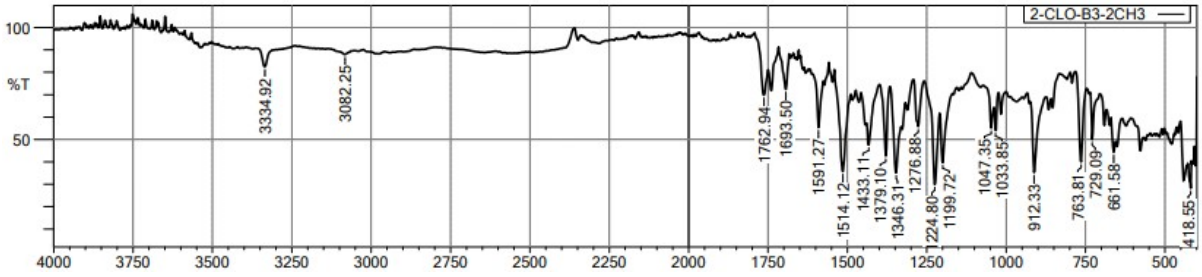
*Compound **4a2***

IR spectrum



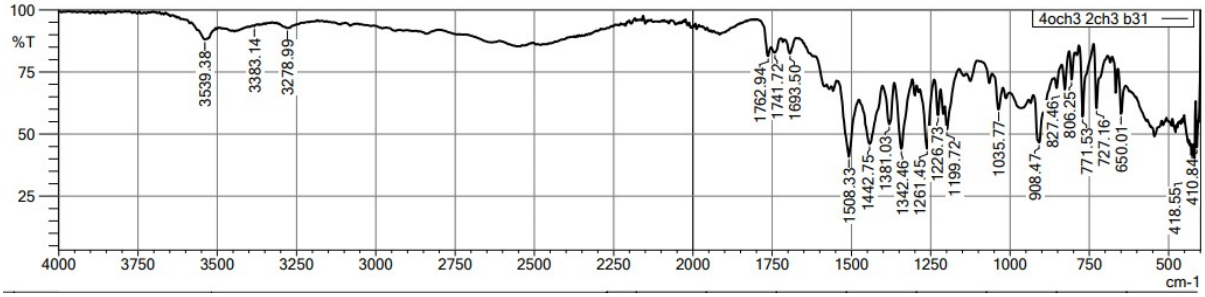
*Compound **4a3***

IR spectrum



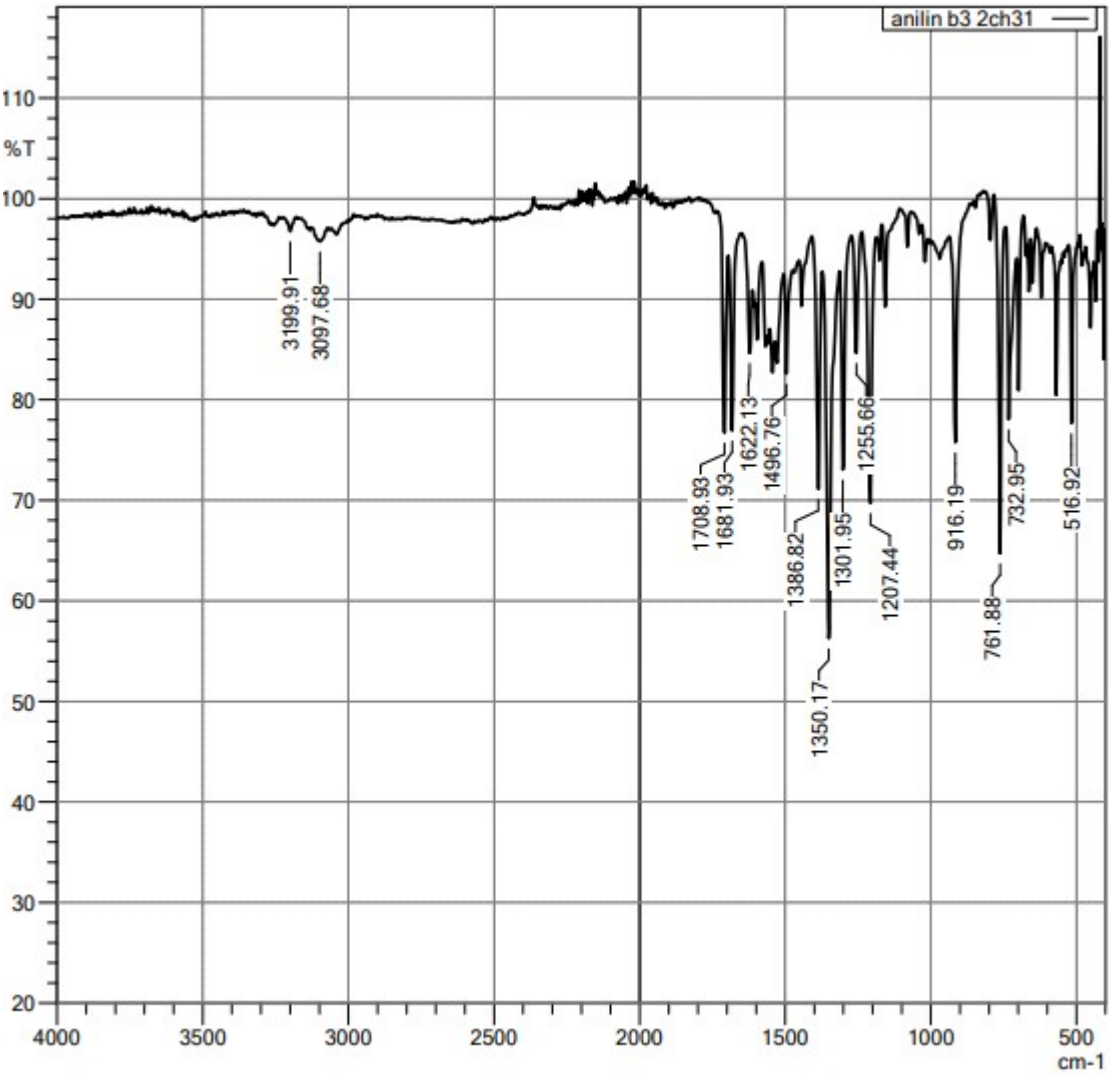
*Compound **4a4***

IR spectrum



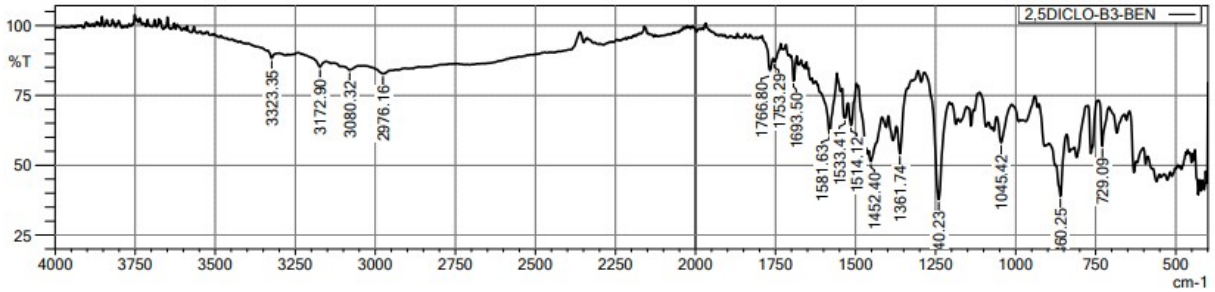
*Compound **4a7***

IR spectrum



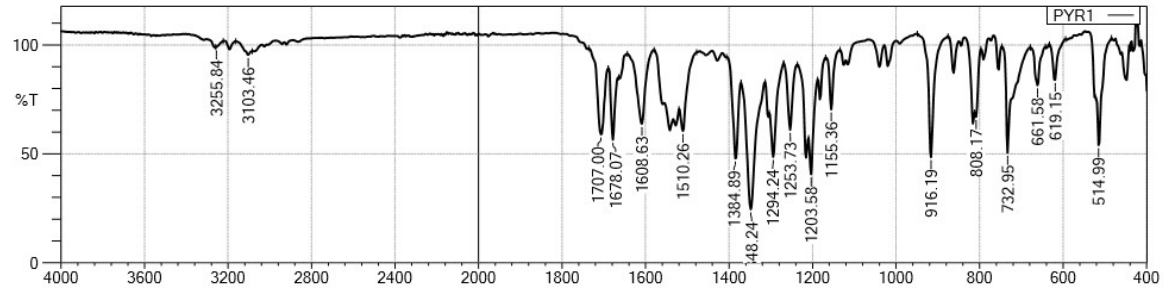
*Compound **4b1***

IR spectrum



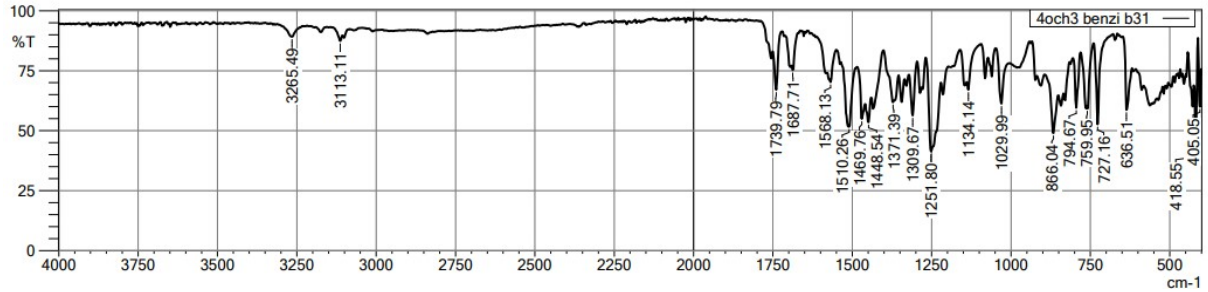
*Compound **4b2***

IR spectrum



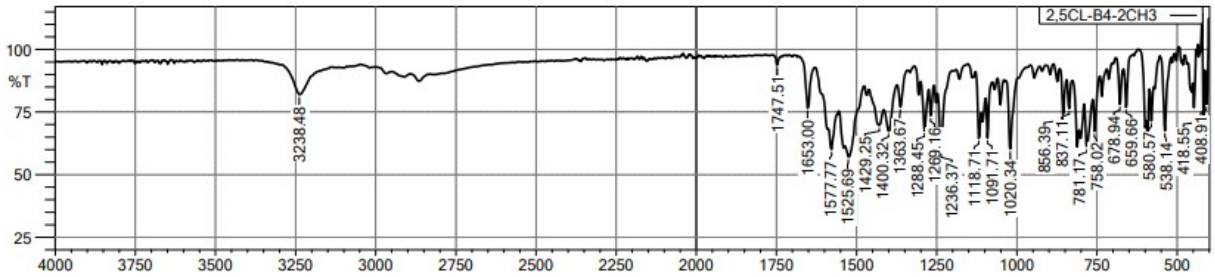
*Compound **4b4***

IR spectrum

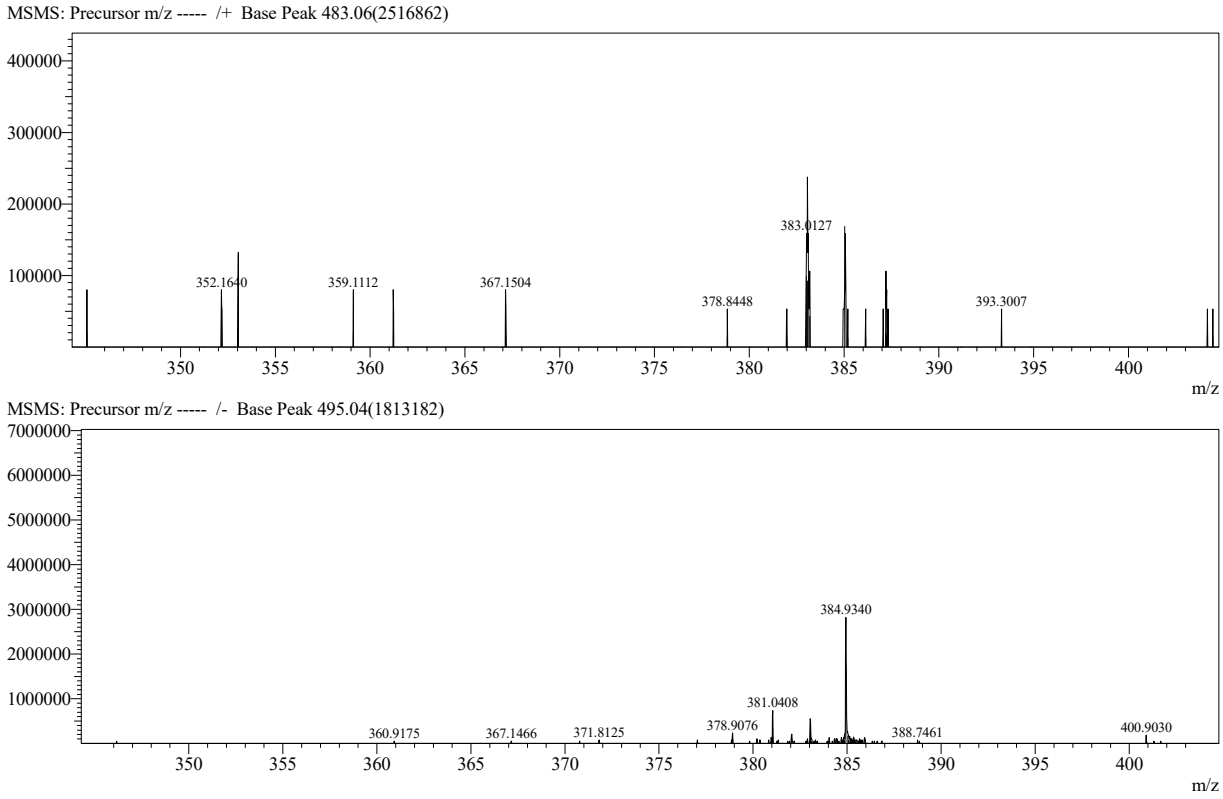


*Compound **5a1***

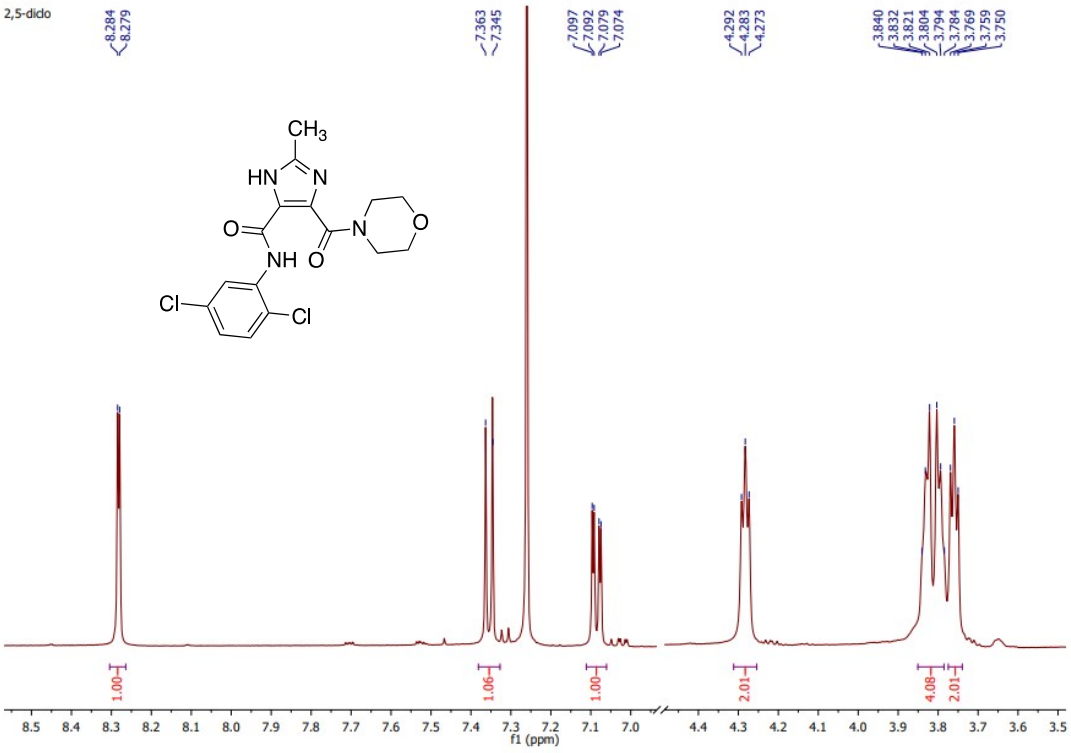
IR spectrum

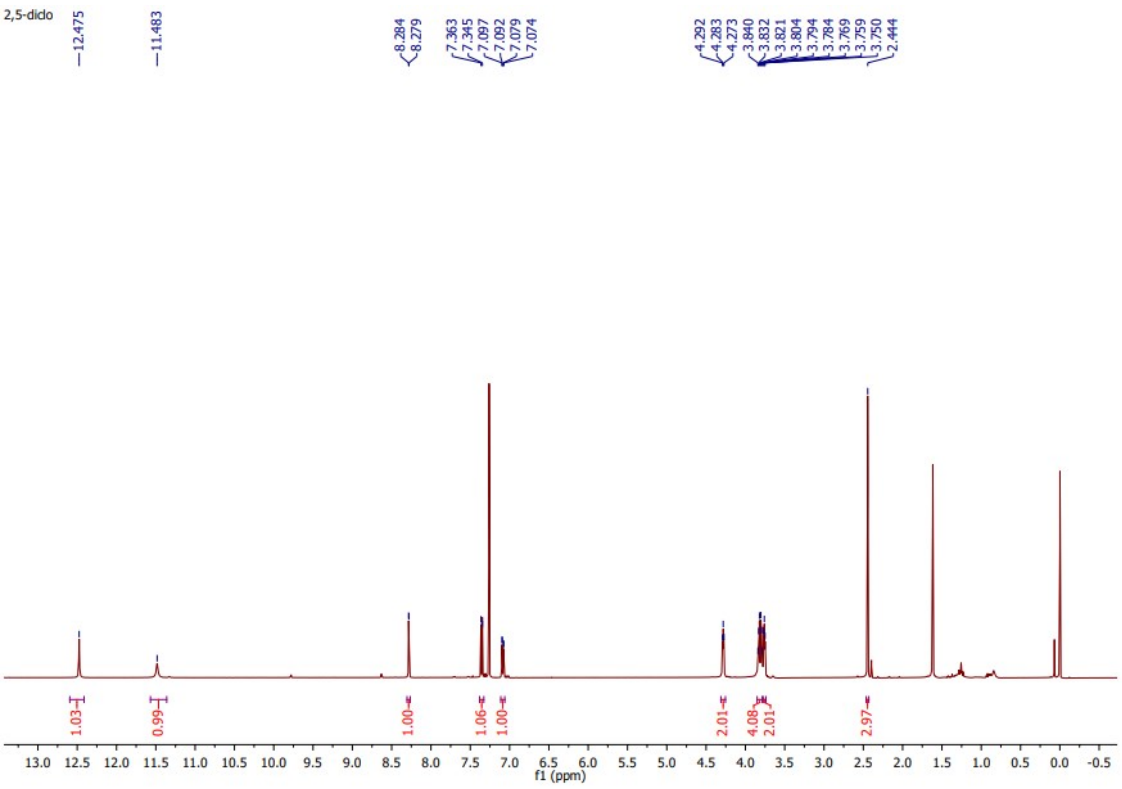


MS spectrum

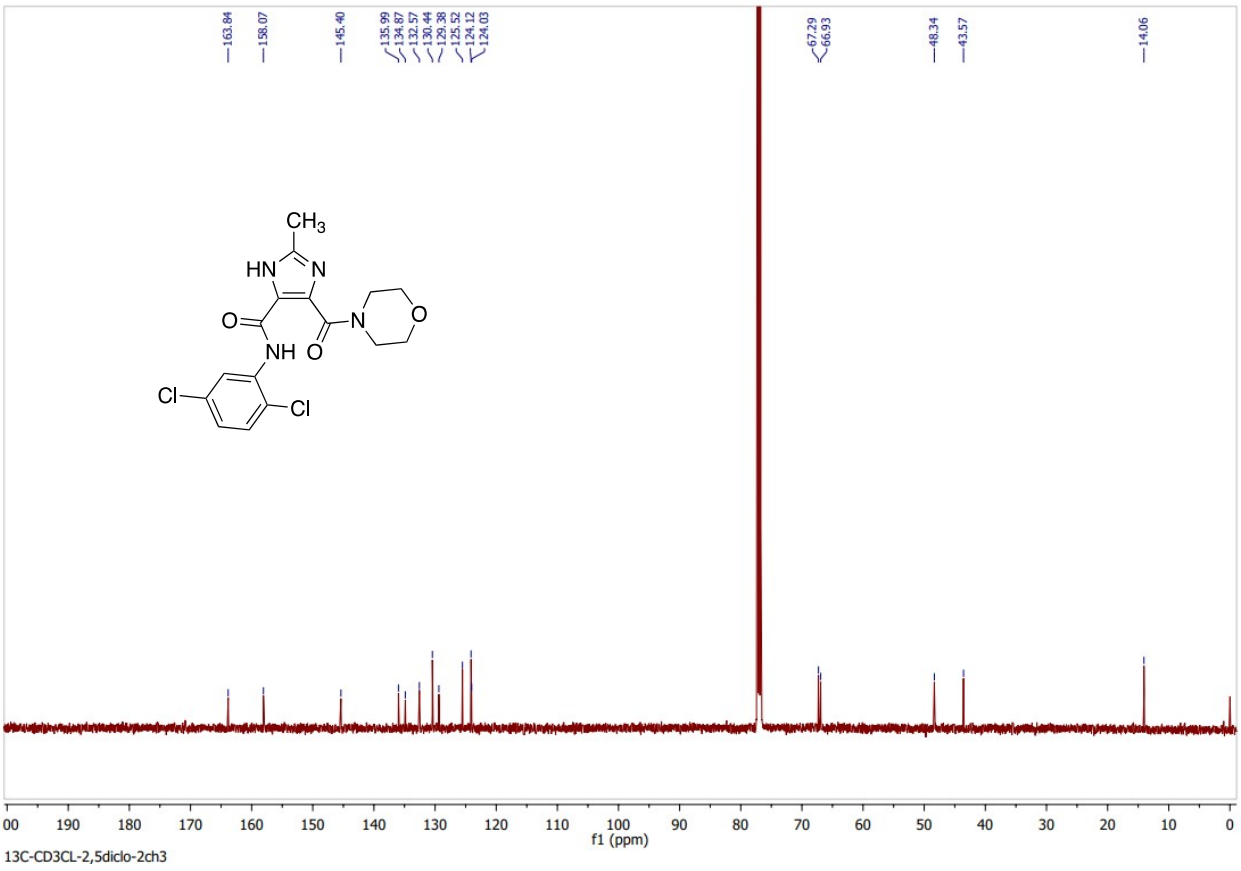


^{1}H-NMR spectrum, 500 MHz, $CDCl_3$ with 0.05% v/v TMS (TMS peak was at 0 ppm)



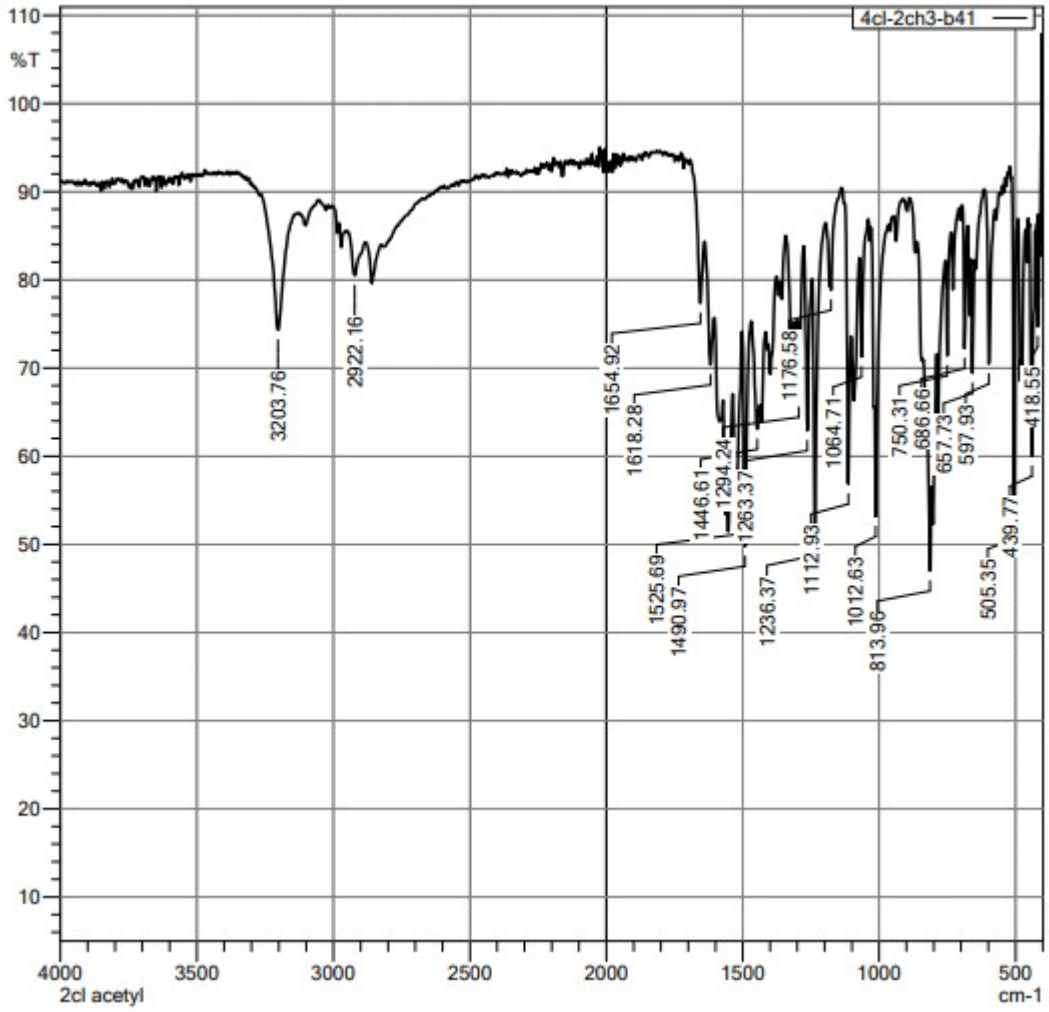


^{13}C-NMR spectrum, 125 MHz, $CDCl_3$ with 0.05% v/v TMS (TMS peak was at 0 ppm)

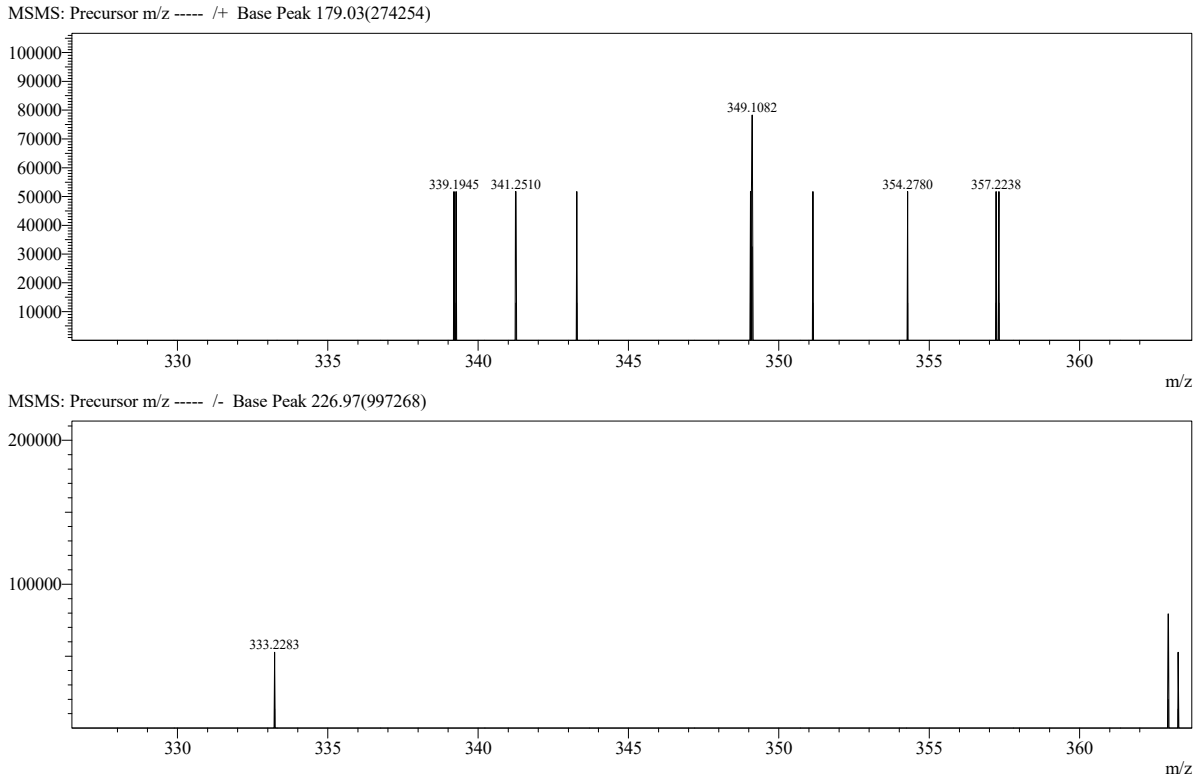


*Compound **5a2***

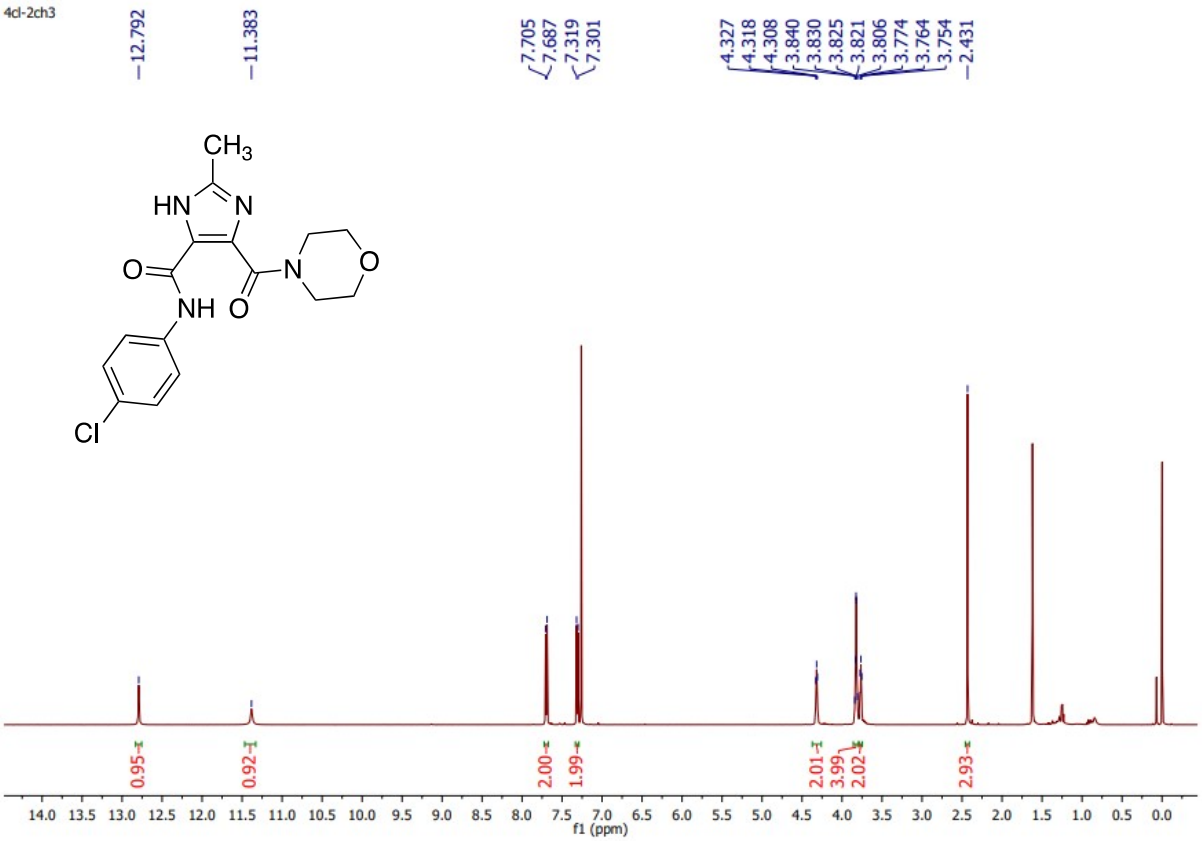
IR spectrum

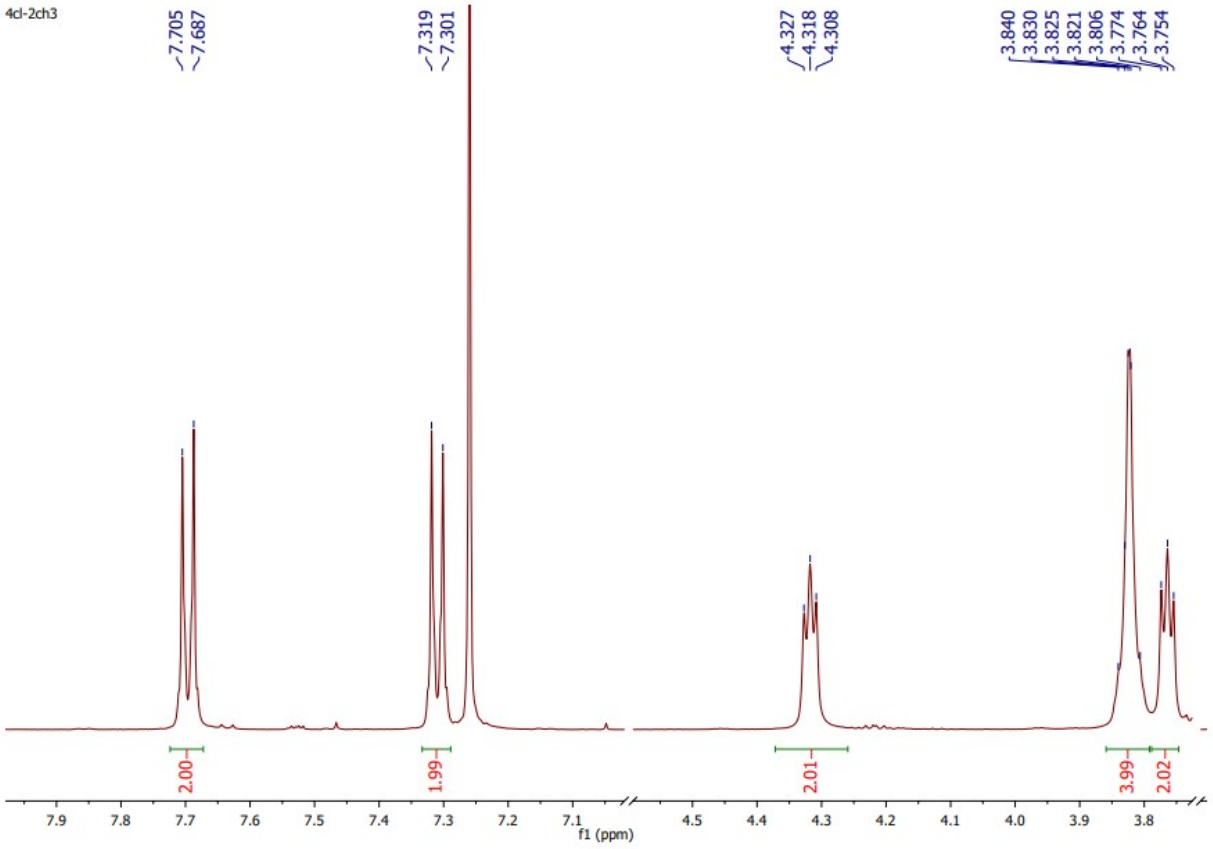

4cl-2ch3-b41
%T
110
100
90
80
70
60
50
40
30
20
10
3203.76
2922.16
1654.92
1618.28
1525.69
1490.97
1446.61
1294.24
1263.37
1236.37
1176.58
1112.93
1064.71
1012.63
813.96
750.31
686.66
657.73
597.93
505.35
439.77
418.55
4000
3500
3000
2500
2000
1500
1000
500
cm-1
2cl acetyl

MS spectrum

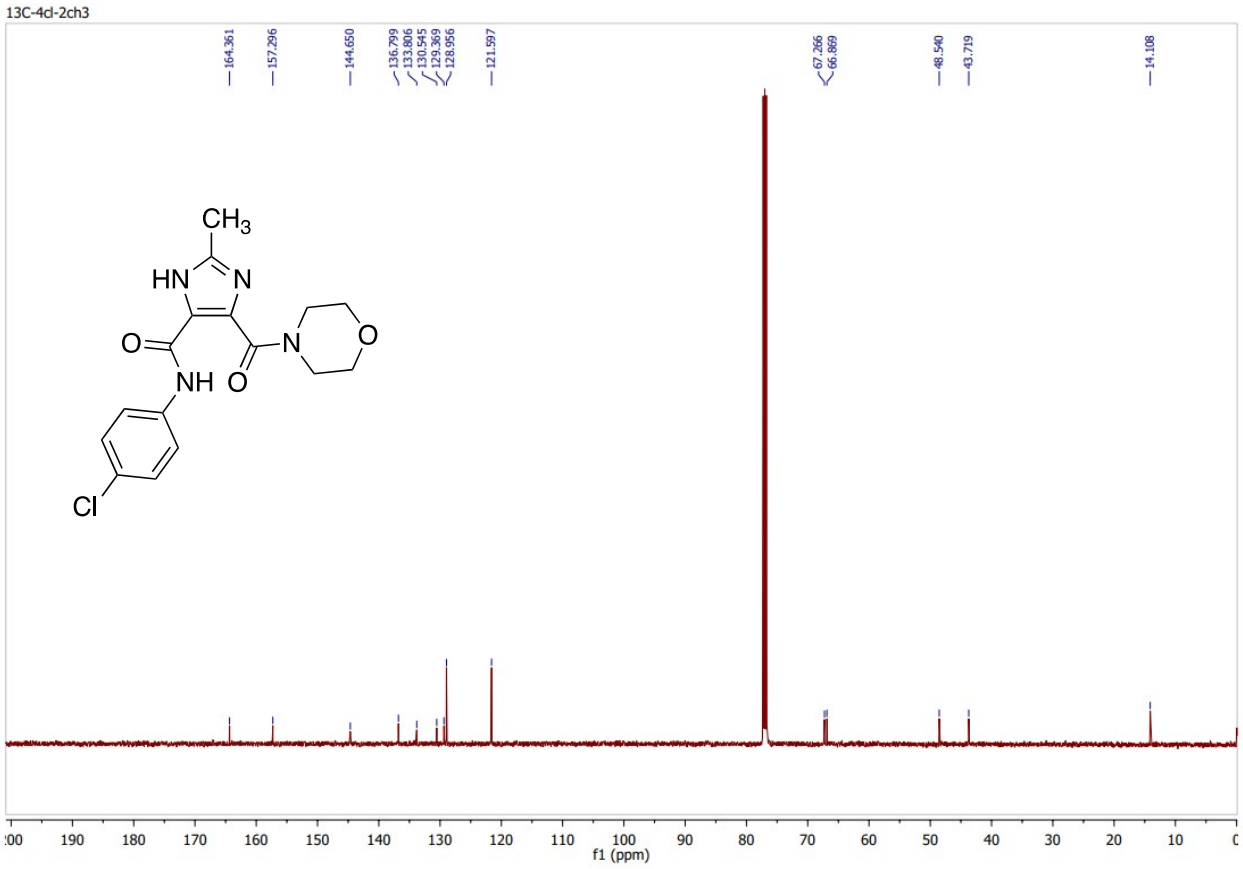


^{1}H-NMR spectrum, 500 MHz, $CDCl_3$ with 0.05% v/v TMS (TMS peak was at 0 ppm)


4cl-2ch3
12.792
11.383
7.705
7.687
7.319
7.301
4.327
4.318
4.308
3.840
3.830
3.825
3.821
3.806
3.774
3.764
3.754
2.431
CH3
HN
N
O
N
O
NH
O
Cl
0.95
0.92
2.00
1.99
2.01
3.99
2.02
2.93
f1 (ppm)

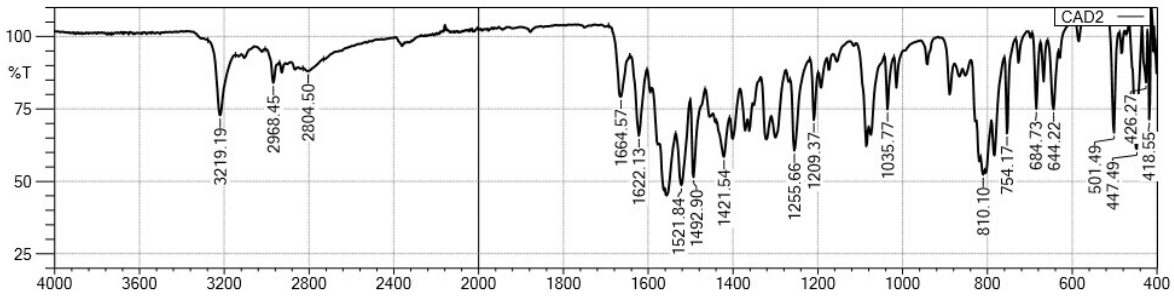

4cl-2ch3
7.705
7.687
7.319
7.301
4.327
4.318
4.308
3.840
3.830
3.825
3.821
3.806
3.774
3.764
3.754
2.00
1.99
2.01
3.99
2.02
f1 (ppm)

^{13}C-NMR spectrum, 125 MHz, $CDCl_3$ with 0.05% v/v TMS (TMS peak was at 0 ppm)

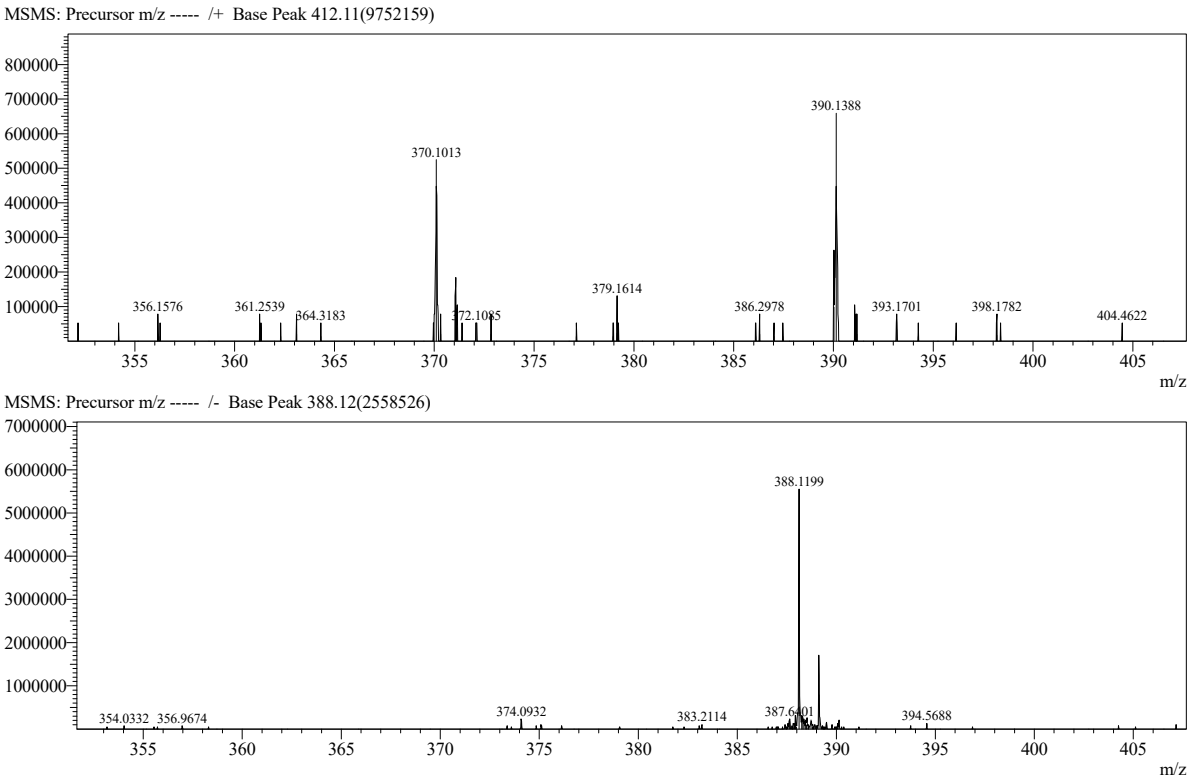


*Compound **5a4***

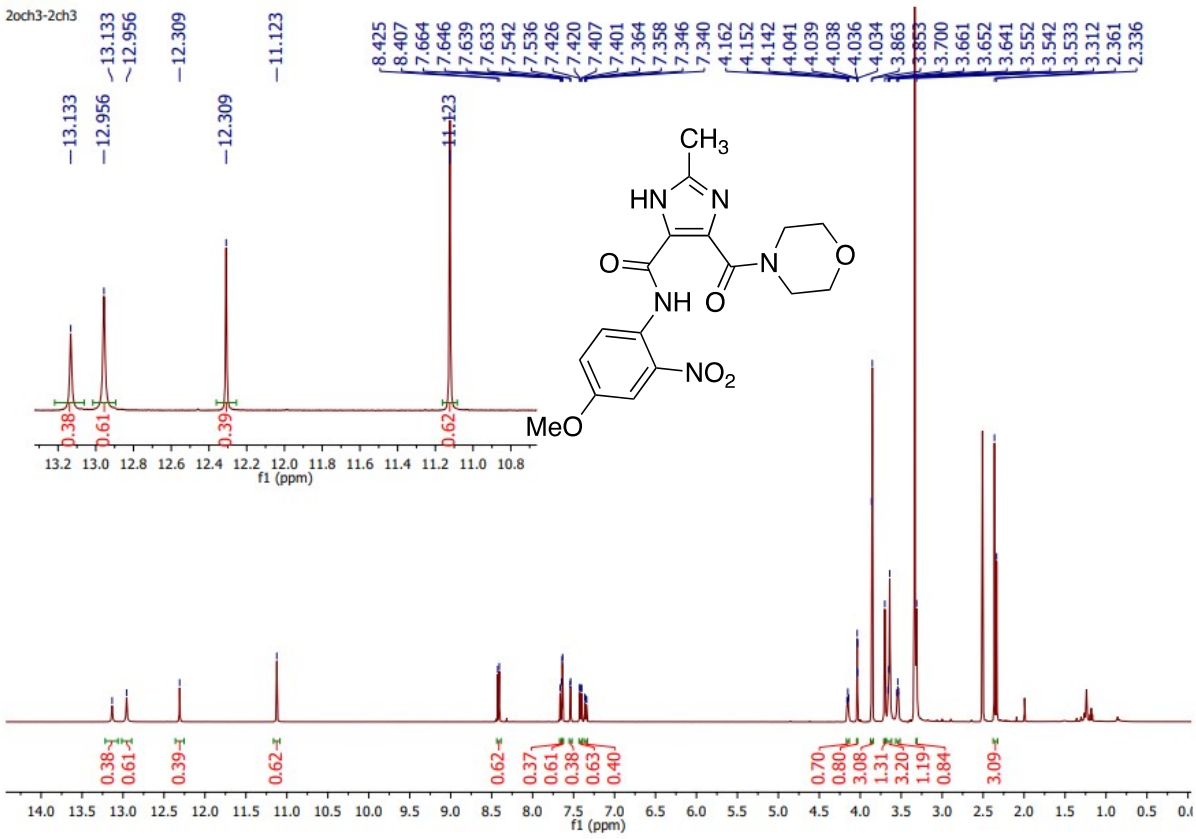
IR spectrum

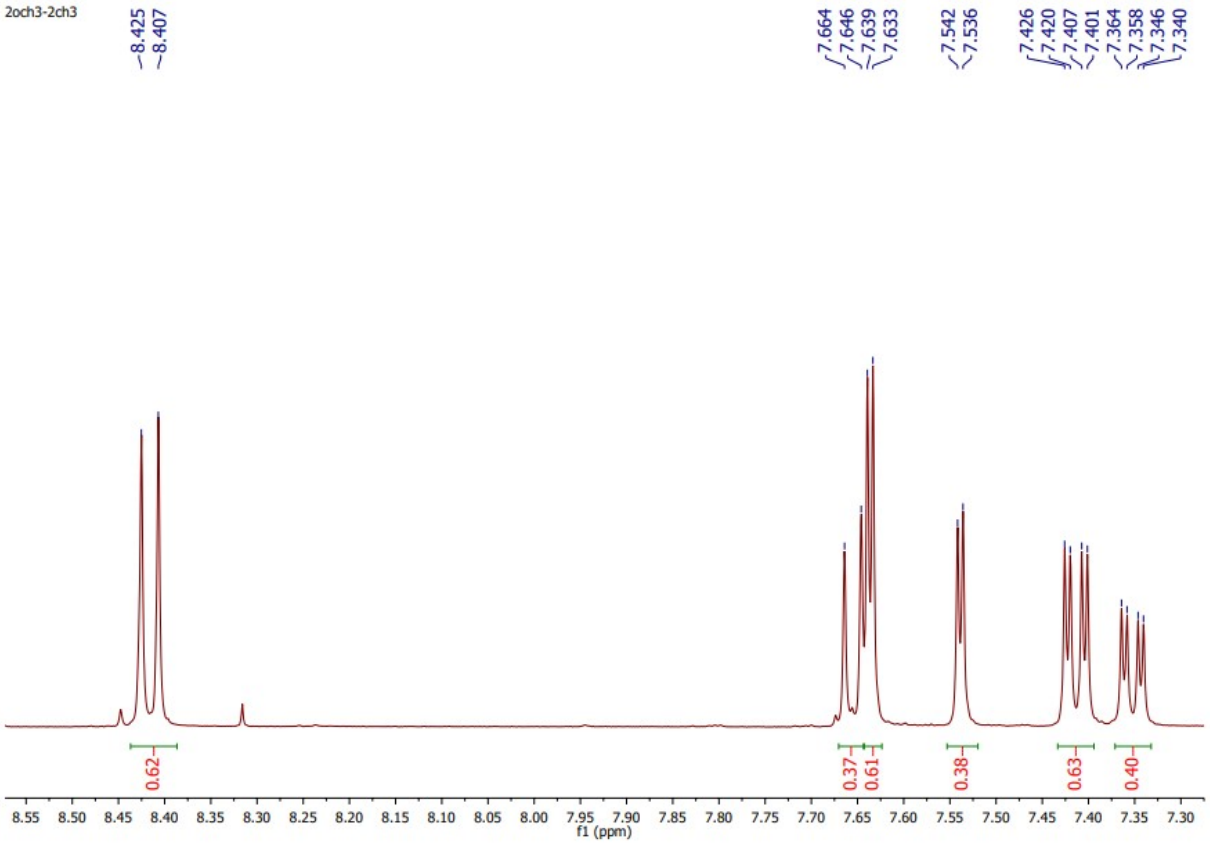


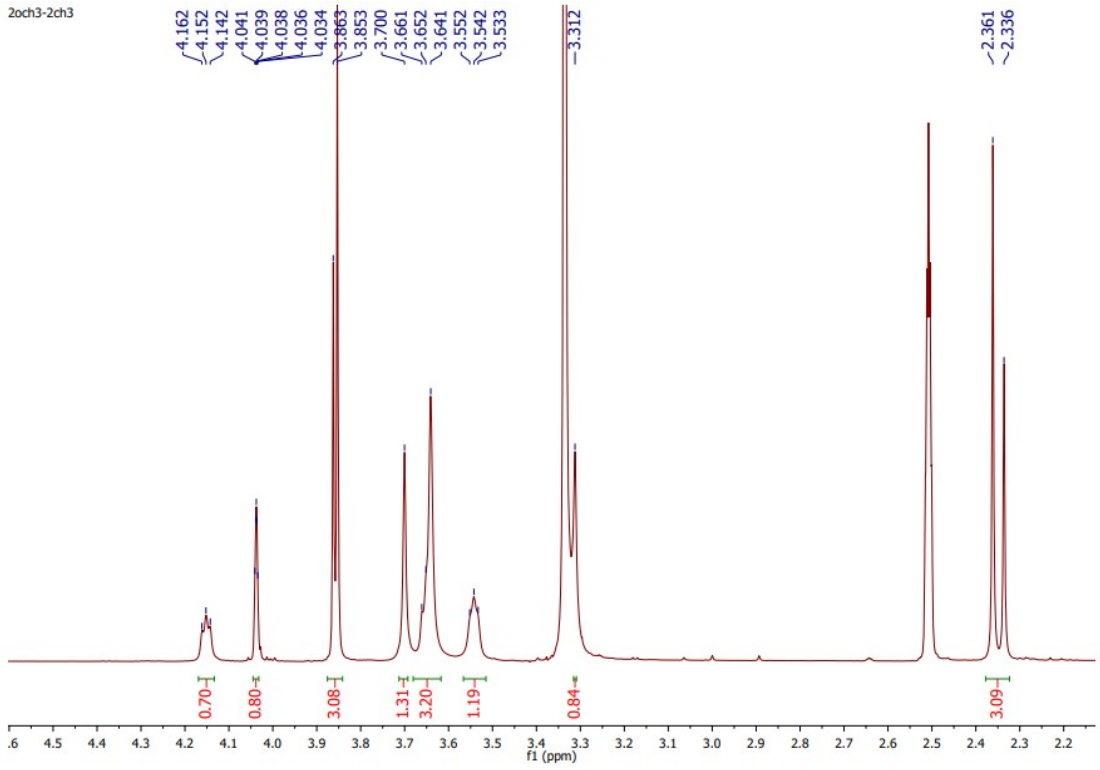
MS spectrum



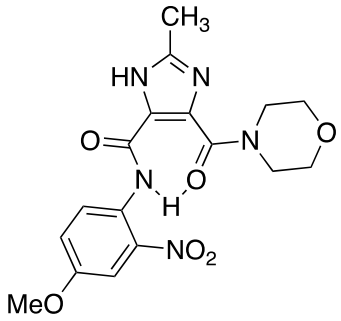
[1]H-NMR spectrum, 500 MHz, DMSO-d_6



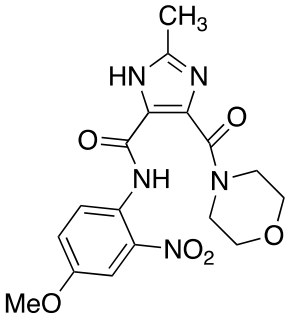

2och3-2ch3
8.425
8.407
7.664
7.646
7.639
7.633
7.542
7.536
7.426
7.420
7.407
7.401
7.364
7.358
7.346
7.340
0.62
0.37
0.61
0.38
0.63
0.40
f1 (ppm)


2och3-2ch3
4.162
4.152
4.142
4.041
4.039
4.038
4.036
4.034
3.863
3.853
3.700
3.661
3.652
3.641
3.552
3.542
3.533
3.312
2.361
2.336
0.70
0.80
3.08
1.31
3.20
1.19
0.84
3.09
f1 (ppm)

Compound **5a4** existed in the 2 conformers: the intramolecular hydrogen bonding and the non-intramolecular hydrogen bonding between 2 amide groups at approcimate ratio of 4:6.

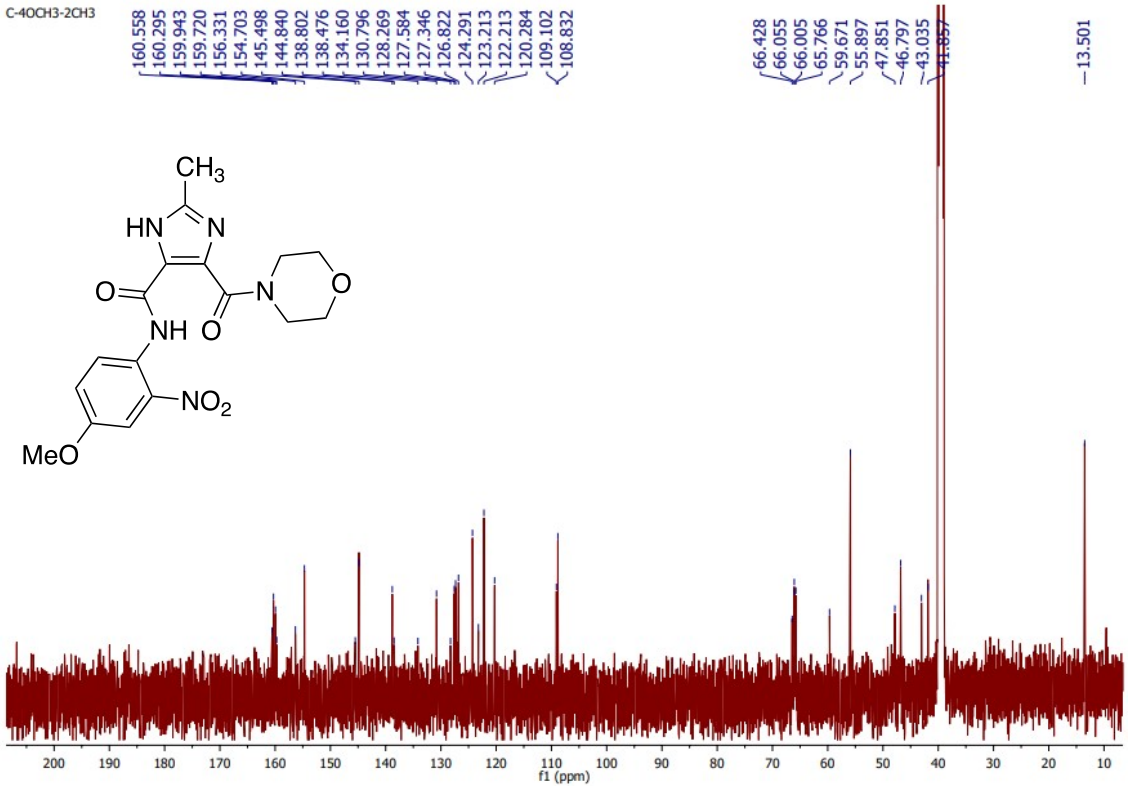


intrahydrogen bonding conformer



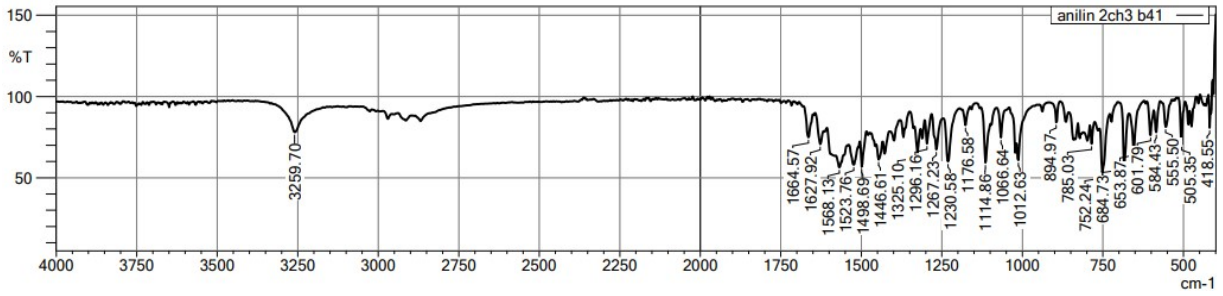
non-intrahydrogen bonding conformer

^{13}C-NMR spectrum, 500 MHz, DMSO-d_6

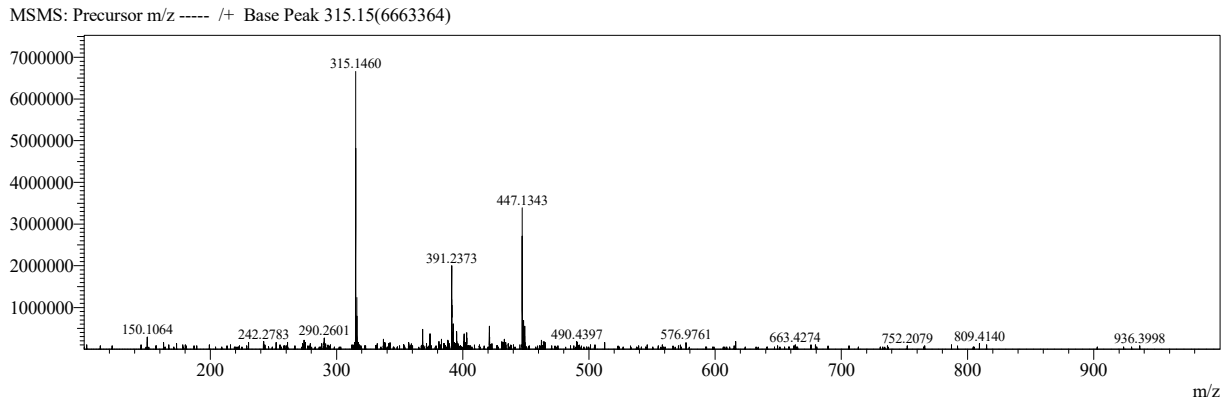


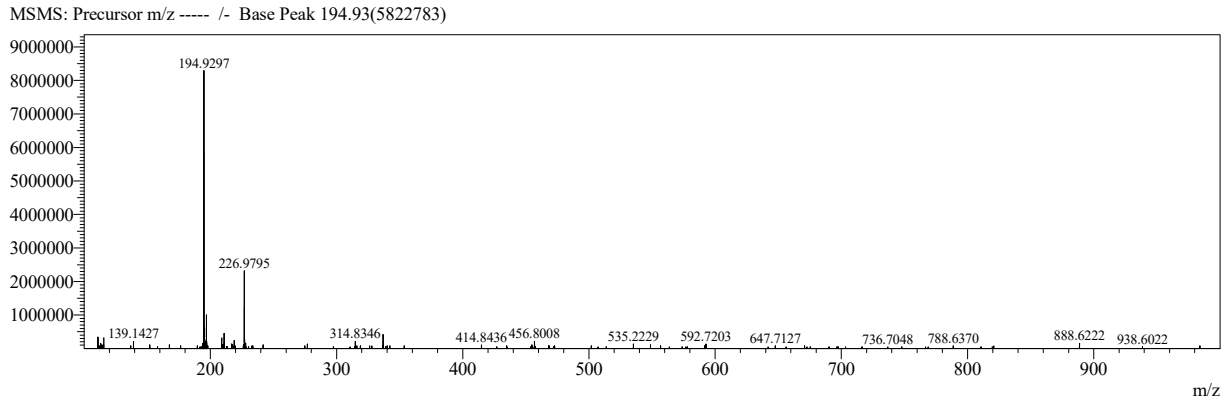
*Compound **5a7***

IR spectrum

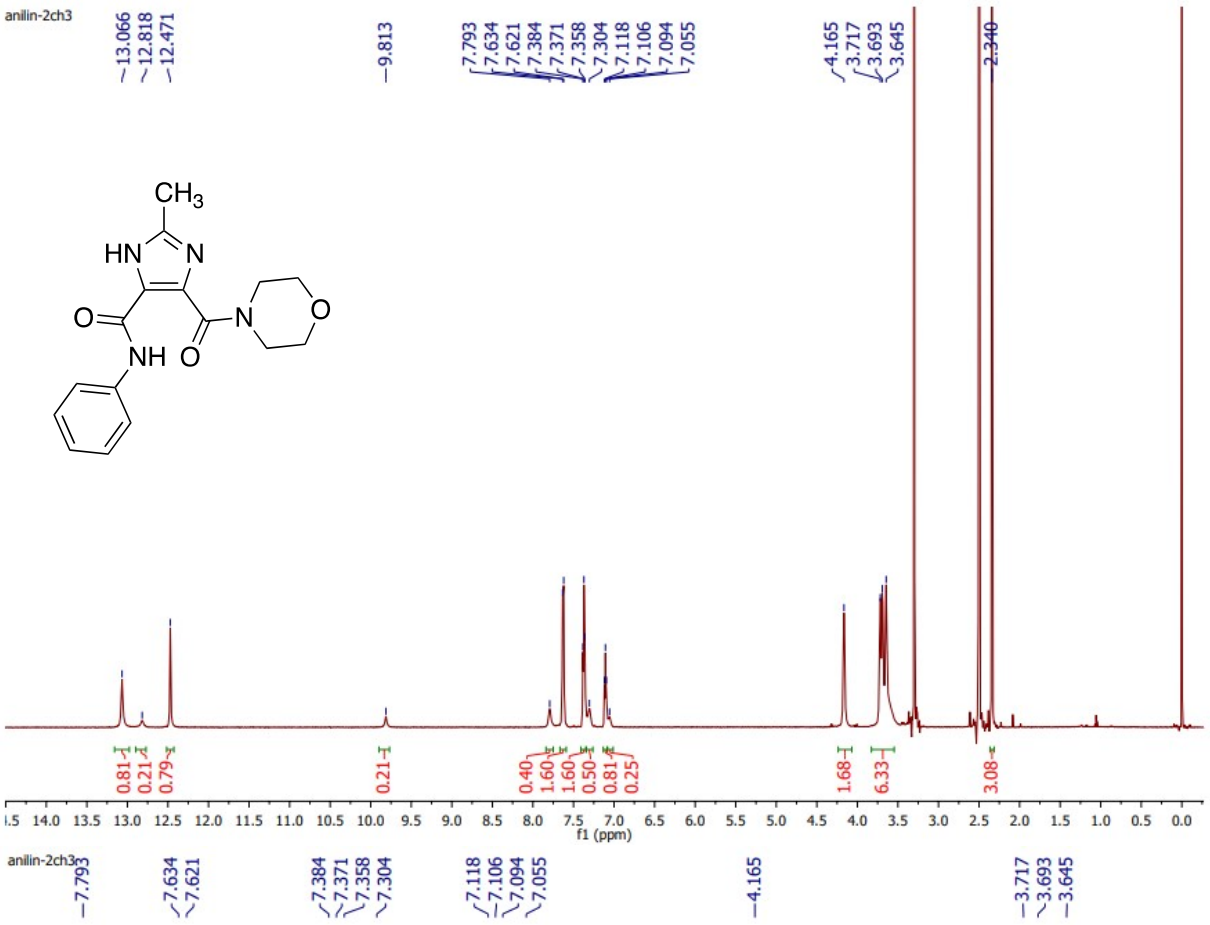


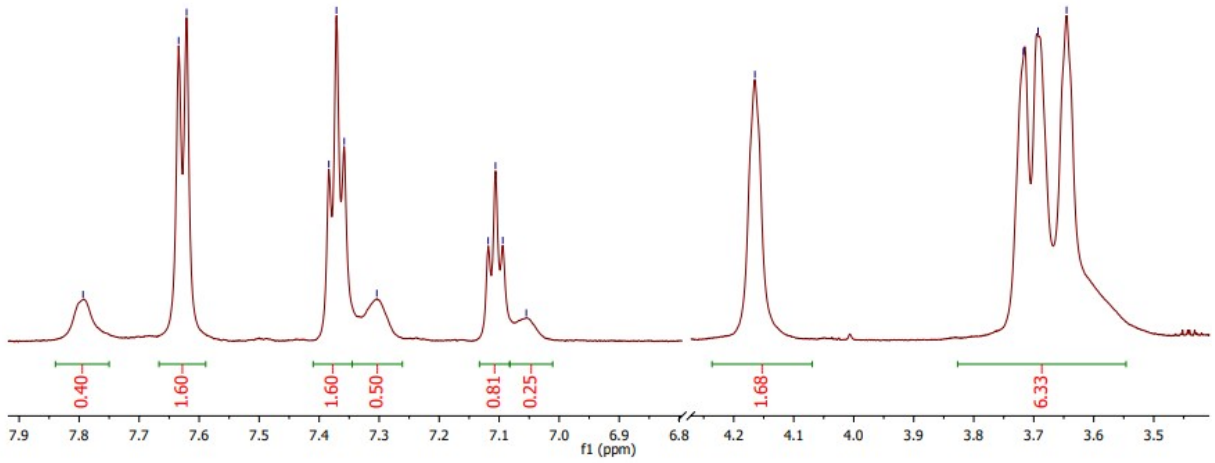
MS spectrum





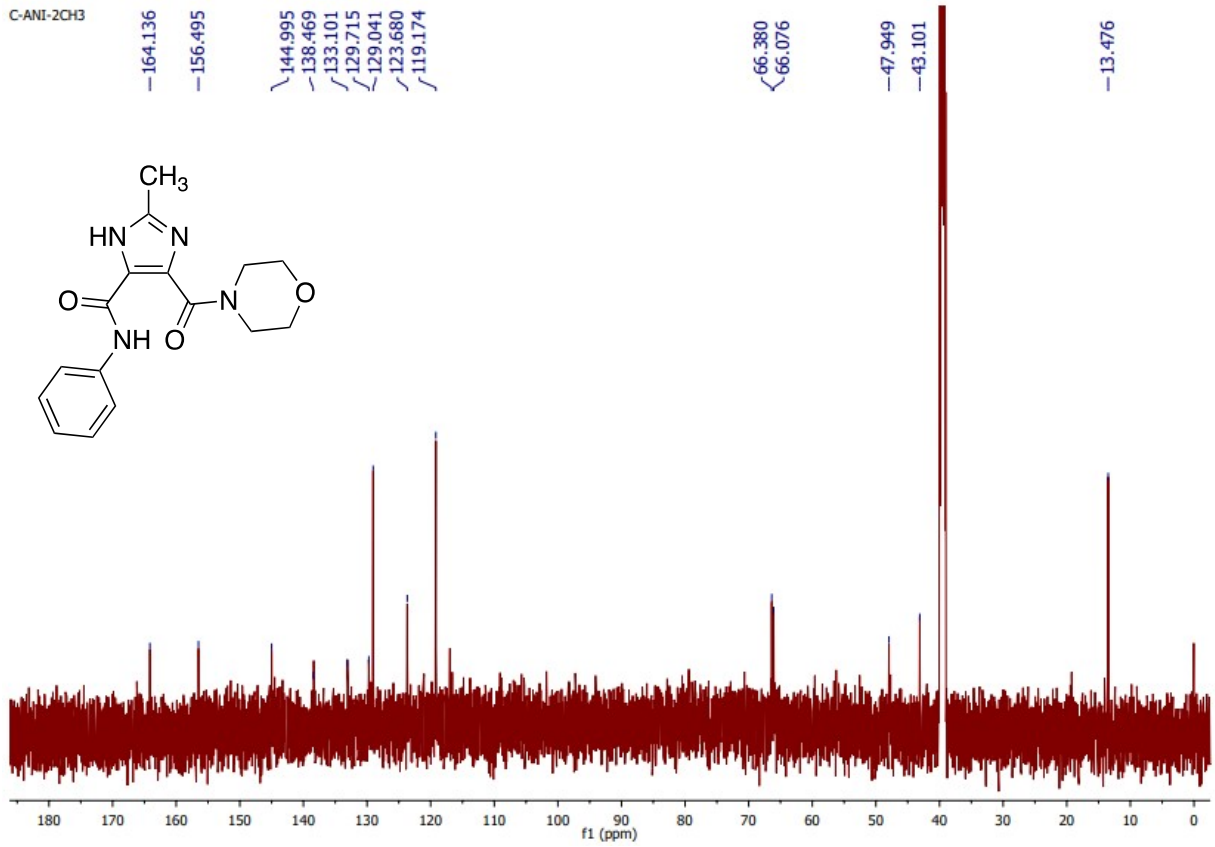
^{1}H-NMR spectrum, 500 MHz, DMSO-d_6 with 0.03% v/v TMS (TMS peak was at 0 ppm)


anilin-2ch3
13.066
12.818
12.471
9.813
7.793
7.634
7.621
7.384
7.371
7.358
7.304
7.118
7.106
7.094
7.055
4.165
3.717
3.693
3.645
2.340
CH3
HN
N
O
N
O
NH
O
0.81
0.21
0.79
0.21
0.40
1.60
1.60
0.50
0.81
0.25
1.68
6.33
3.08
f1 (ppm)


0.40
1.60
1.60
0.50
0.81
0.25
1.68
6.33
f1 (ppm)

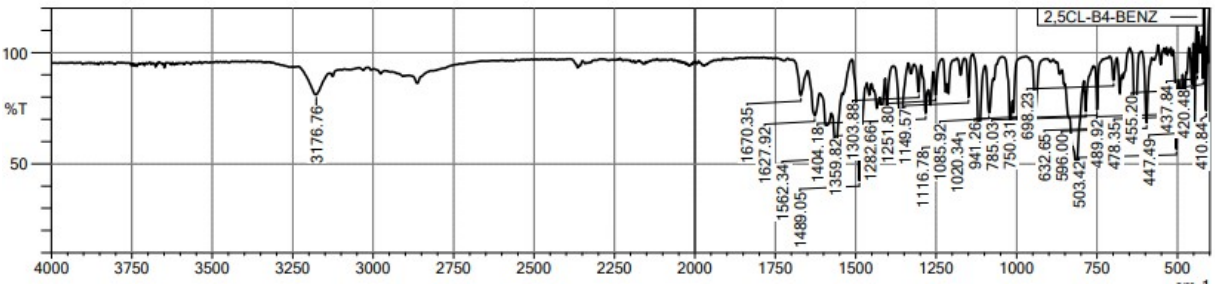
Compound **5a7** existed in the 2 conformers: the intramolecular hydrogen bonding and the non-intramolecular hydrogen bonding at approcimate ratio of 8:2.

^{13}C-NMR spectrum, 125 MHz, DMSO-d_6 with 0.03% v/v TMS (TMS peak was at 0 ppm)



*Compound **5b1***

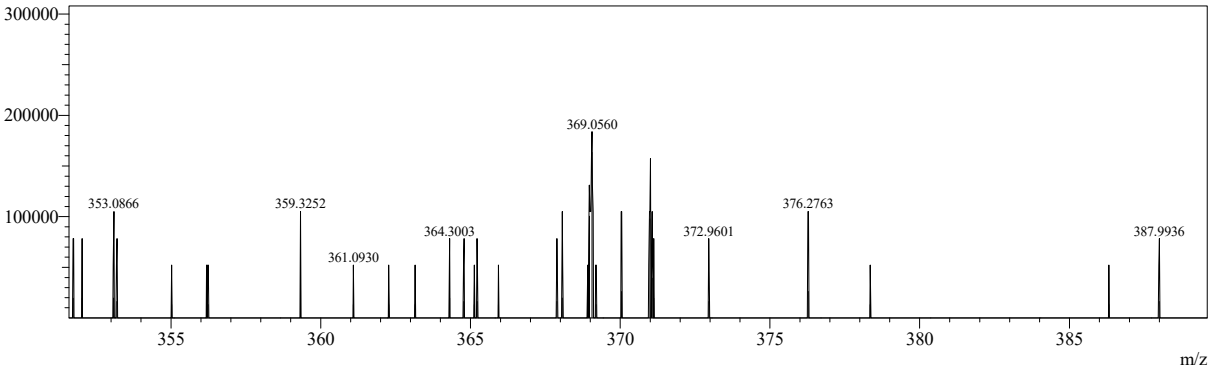
IR spectrum



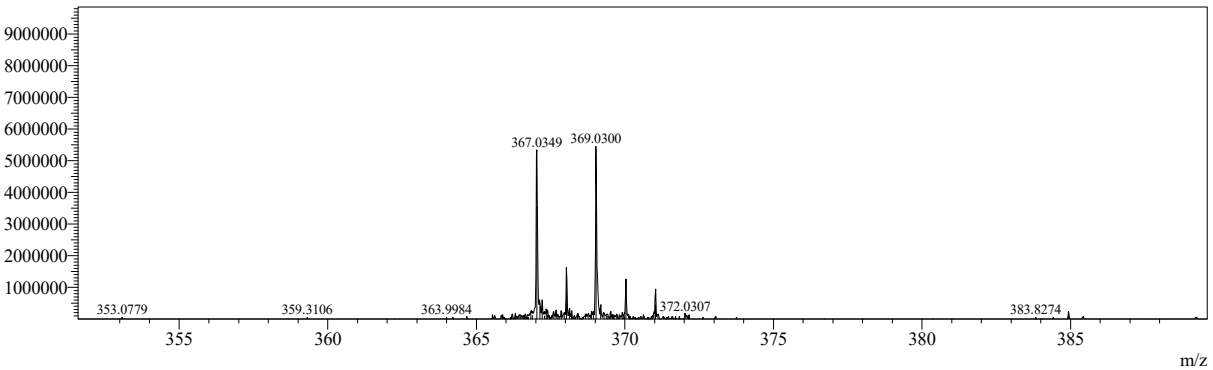
M

S spectrum

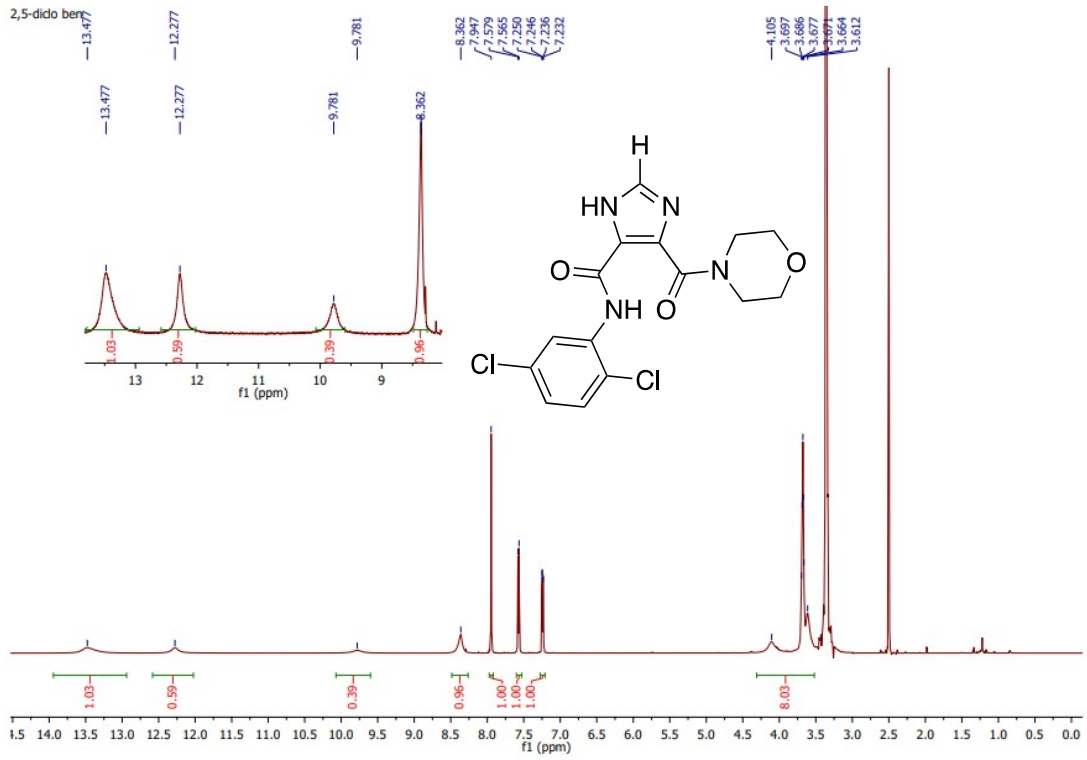
MSMS: Precursor m/z ----- /+ Base Peak 701.49(3493435)

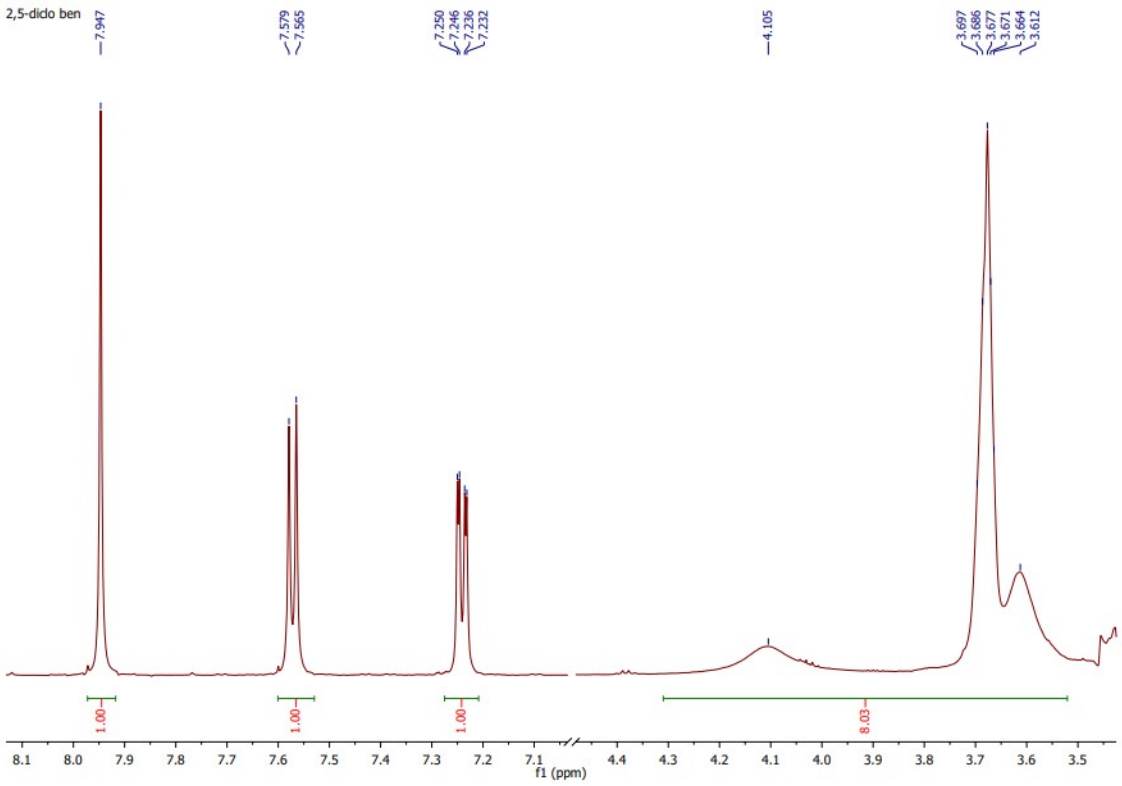


MSMS: Precursor m/z ----- /- Base Peak 367.03(3536409)



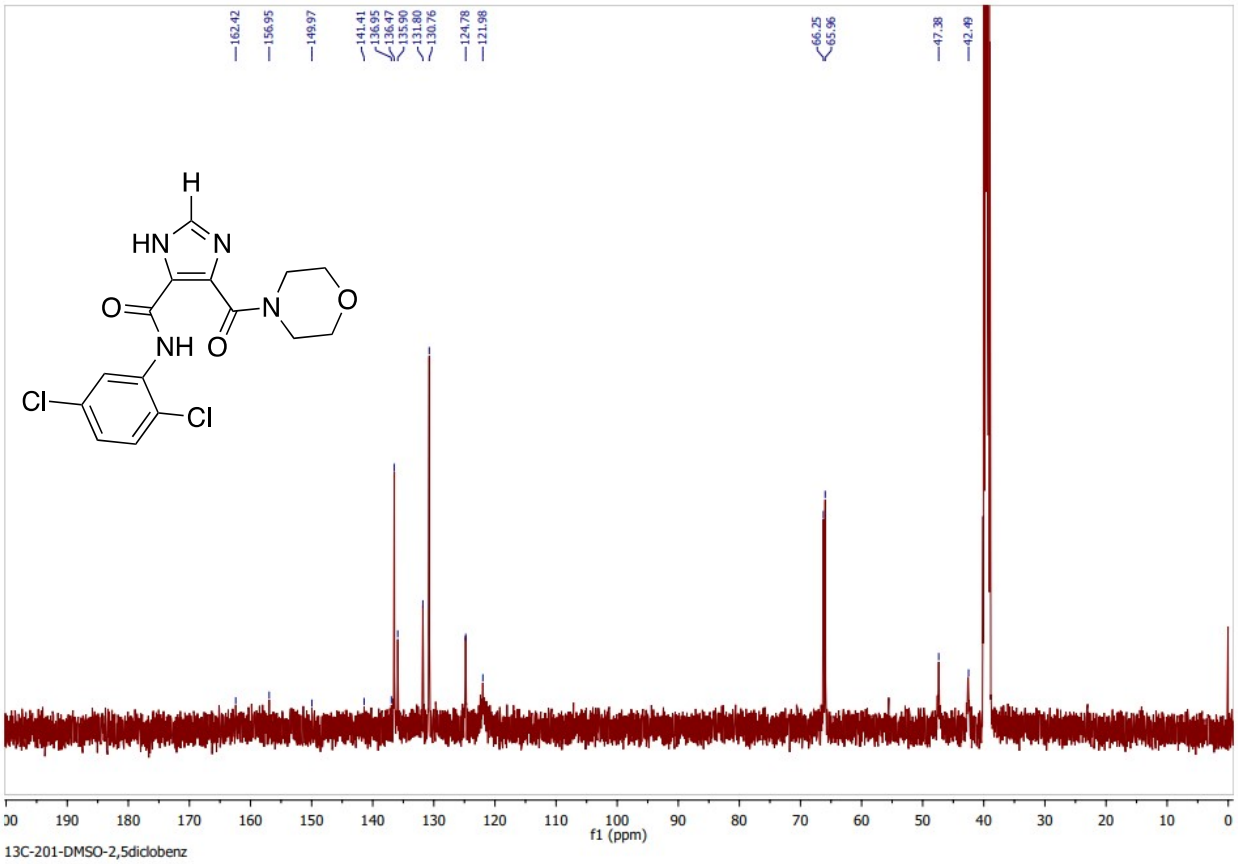
[1]H-NMR spectrum, 600 MHz, DMSO-d_6





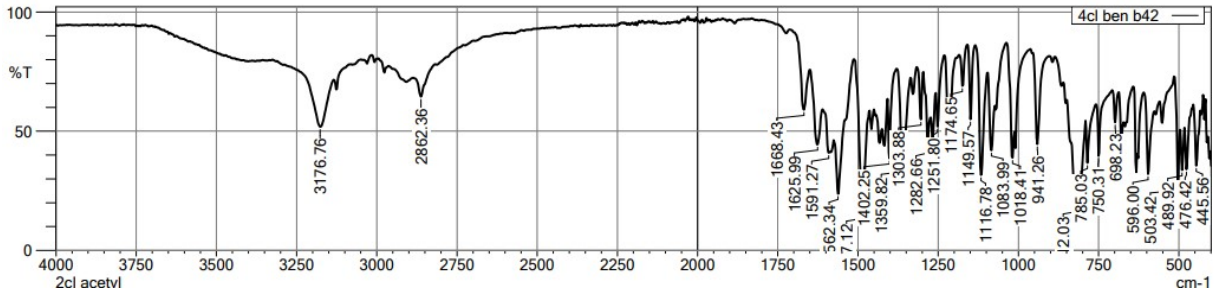
Compound **5b1** existed in the 2 conformers: the intramolecular hydrogen bonding and the non-intramolecular hydrogen bonding at approcimate ratio of 6:4.

^{13}C-NMR spectrum, 125 MHz, DMSO-d_6 with 0.03% v/v TMS (TMS peak was at 0 ppm)

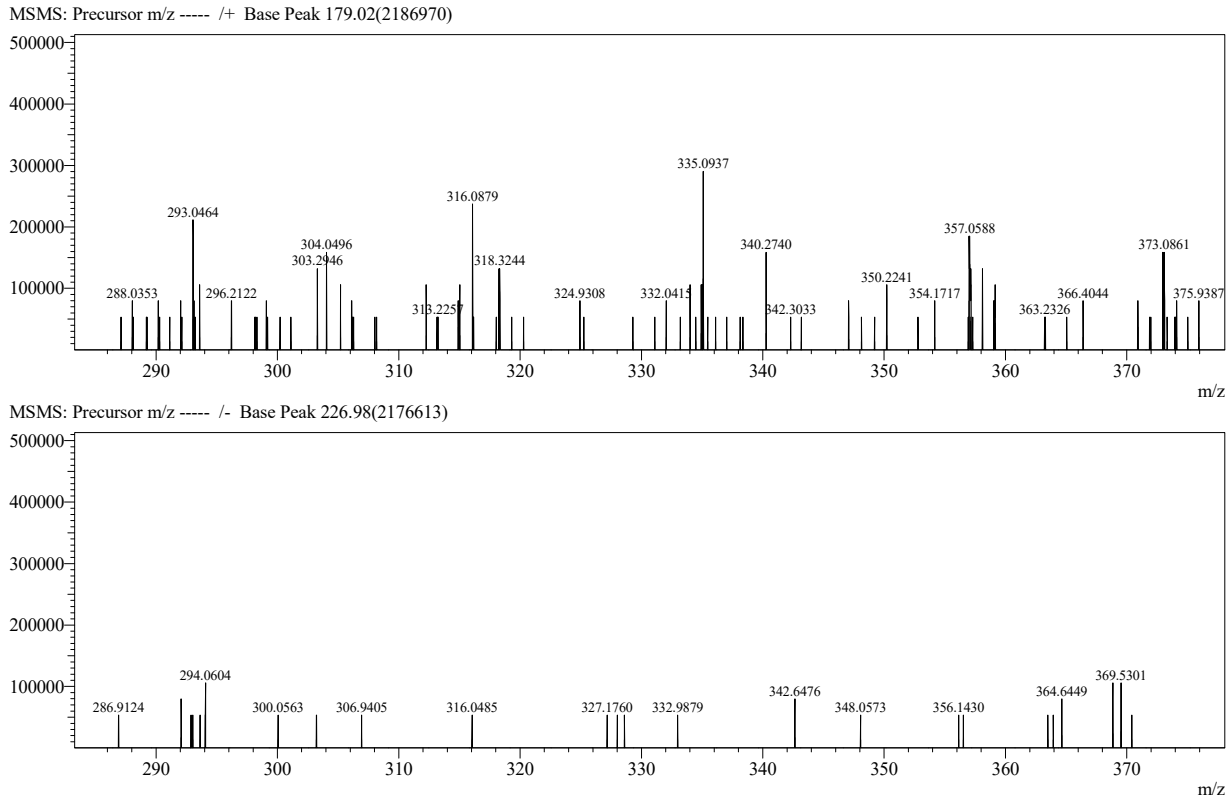


*Compound **5b2***

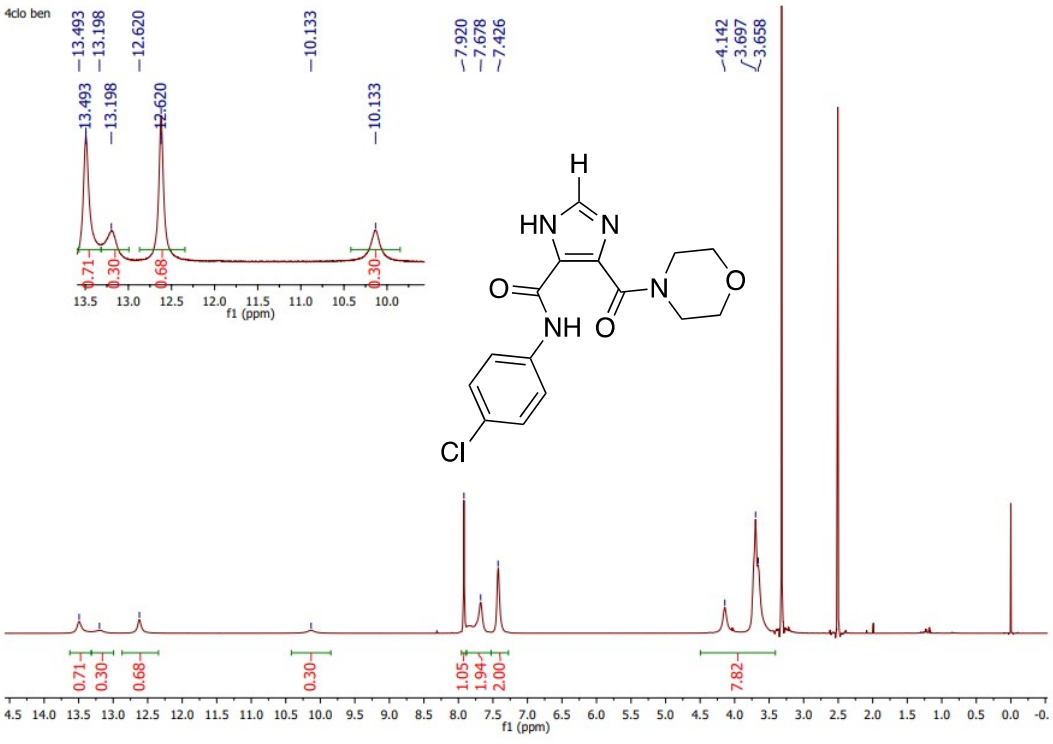
IR spectrum

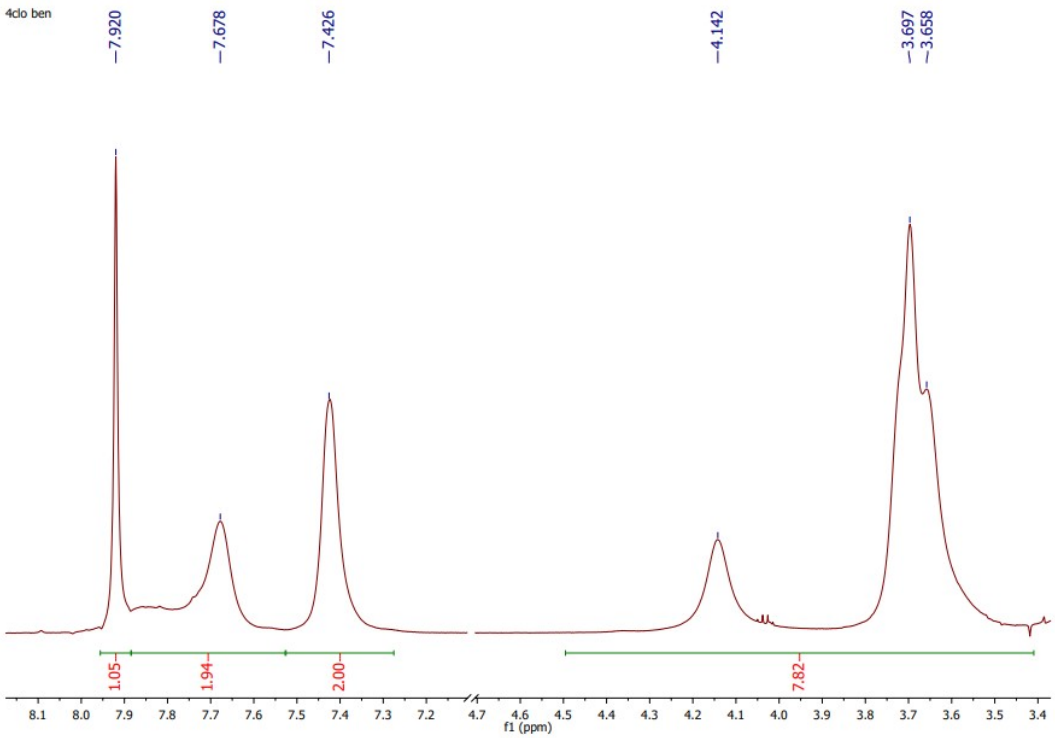


MS spectrum



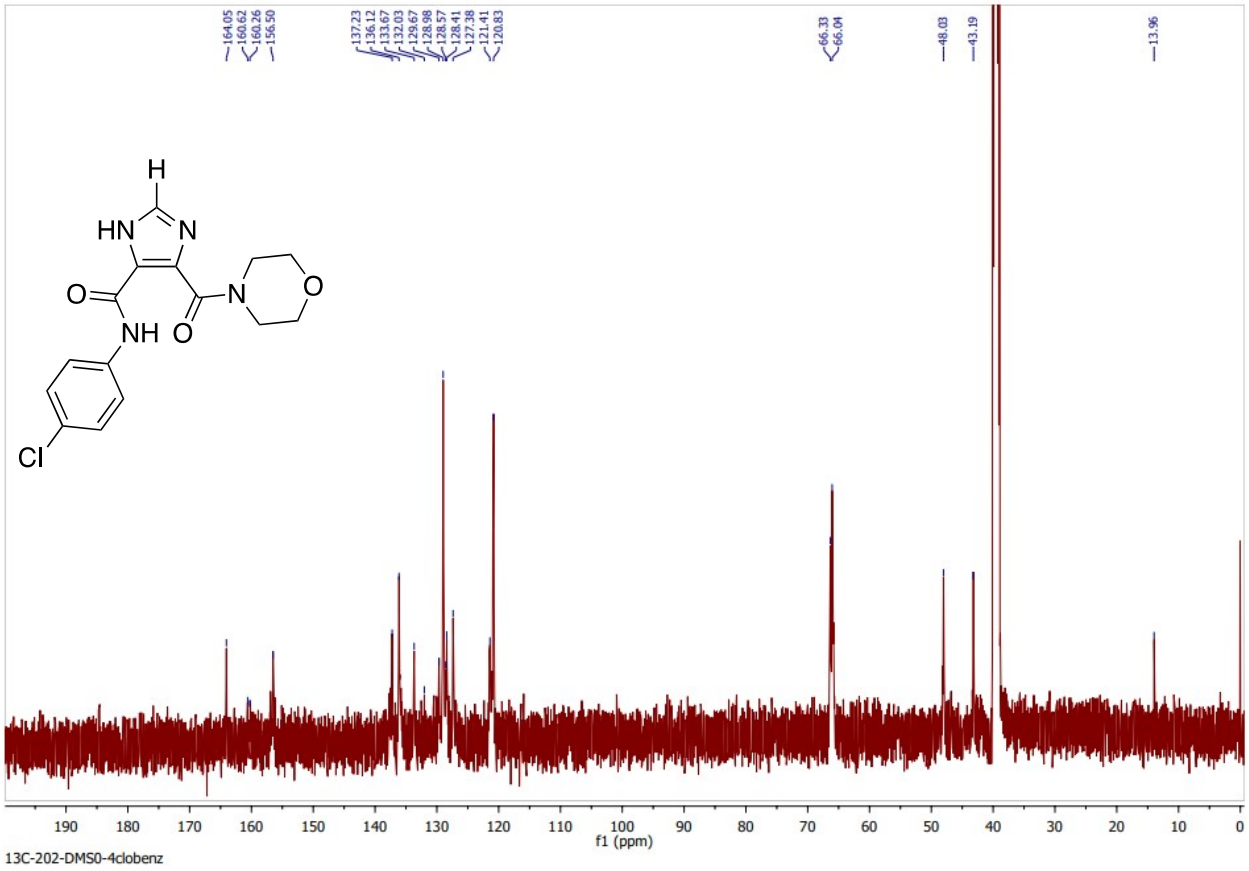
^{1}H-NMR spectrum, 125 MHz, DMSO-d_6 with 0.03% v/v TMS (TMS peak was at 0 ppm)





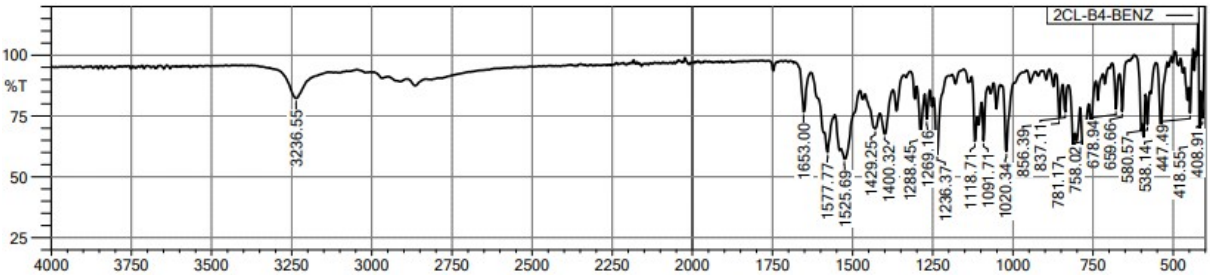
Compound **5b2** existed in the 2 conformers: the intramolecular hydrogen bonding and the non-intramolecular hydrogen bonding at approcimate ratio of 7:3.

^{13}C-NMR spectrum, 125 MHz, DMSO-d_6 with 0.03% v/v TMS (TMS peak was at 0 ppm)



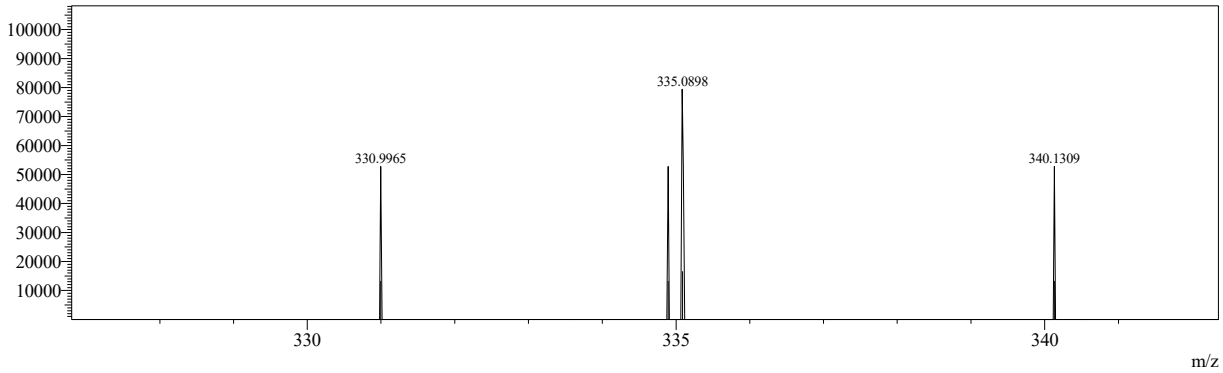
*Compound **5b3***

IR spectrum

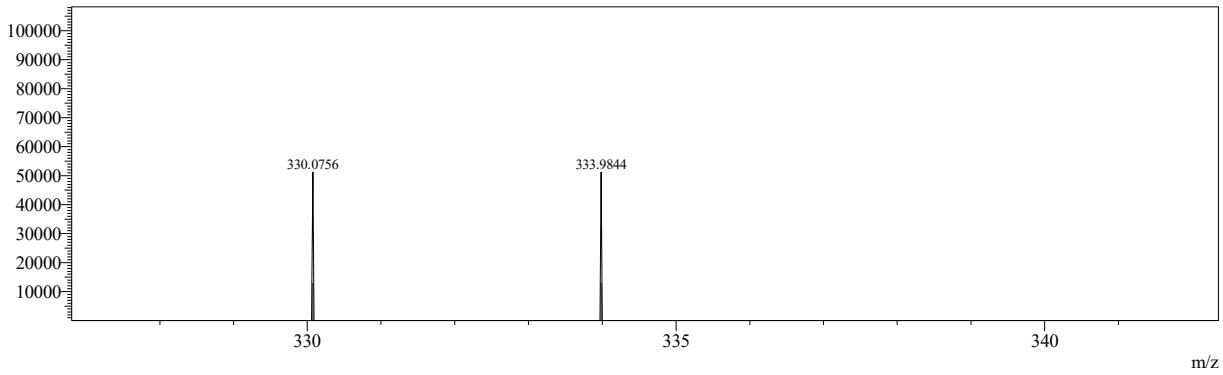


MS spectrum

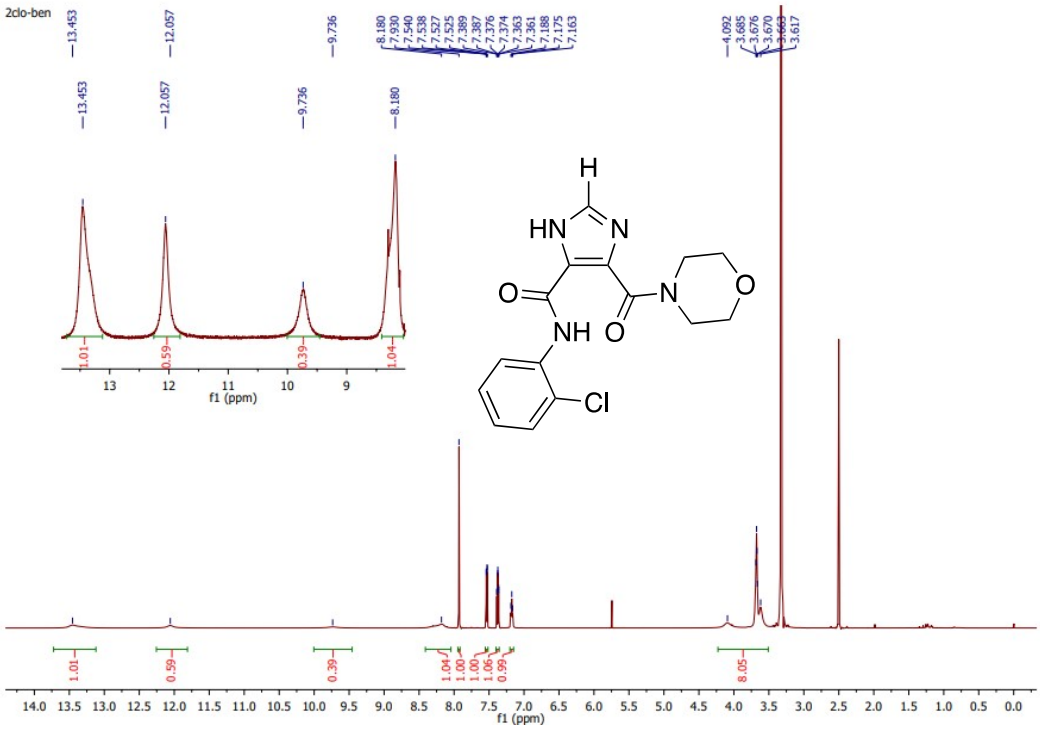
MSMS: Precursor m/z ----- /+ Base Peak 261.16(354238)

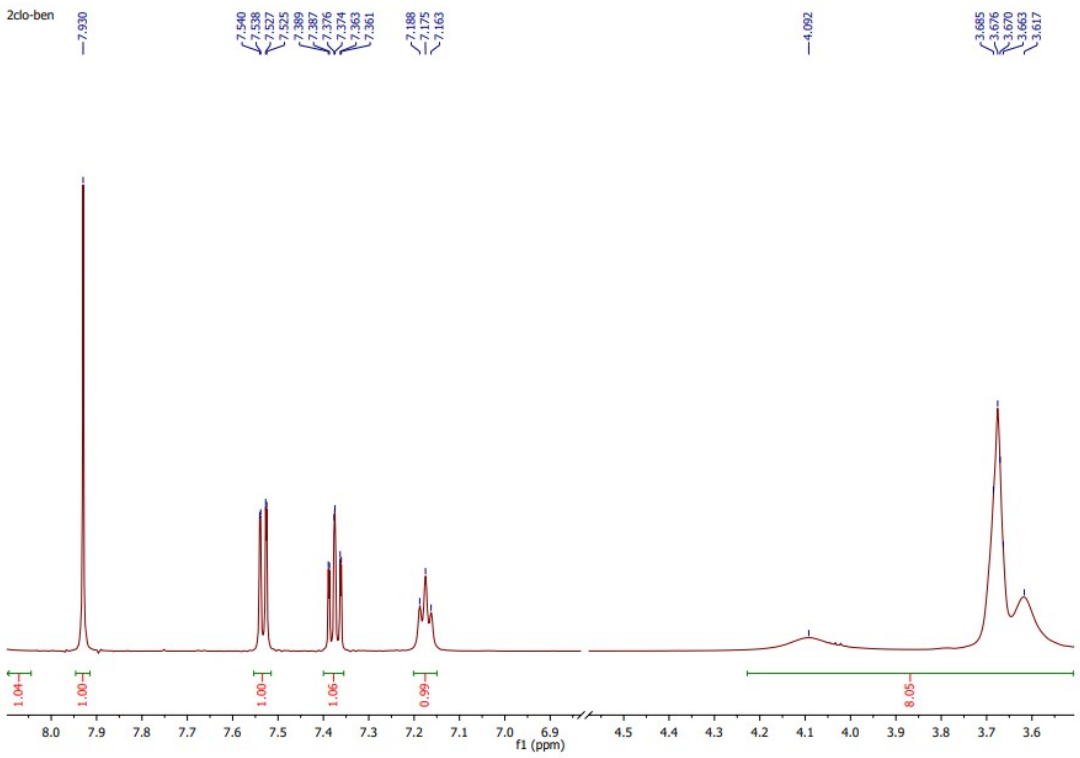


MSMS: Precursor m/z ----- /- Base Peak 226.97(1359507)



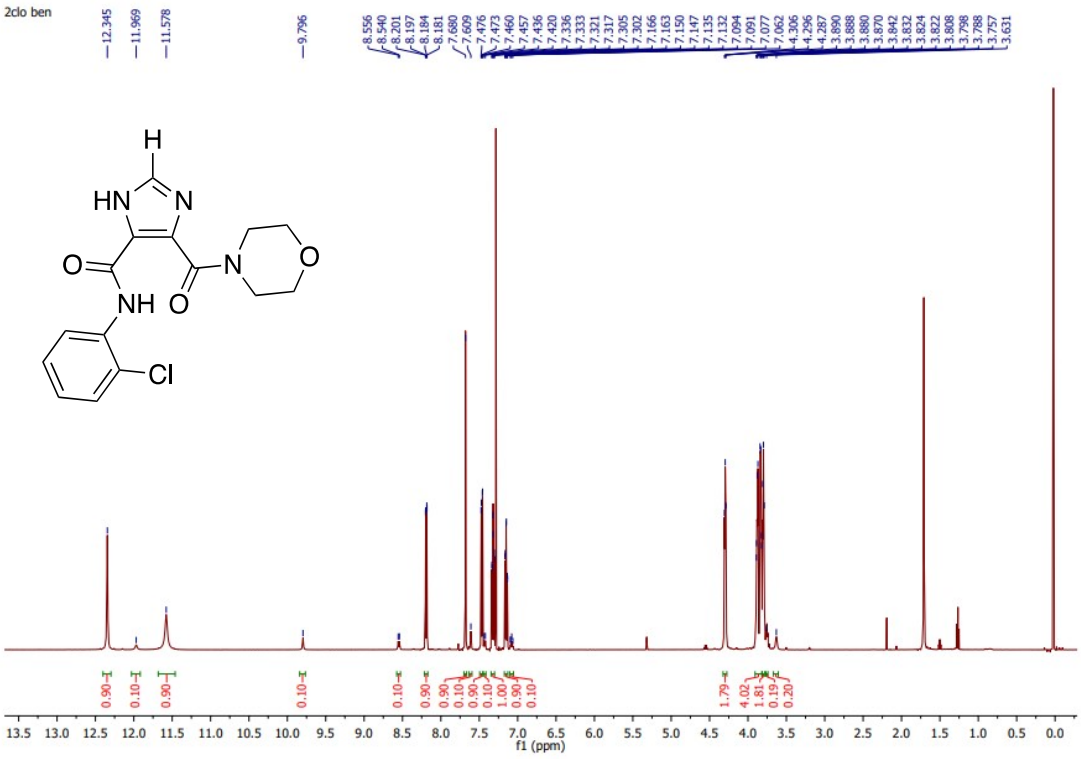
^{1}H-NMR spectrum, 600 MHz, DMSO-d_6

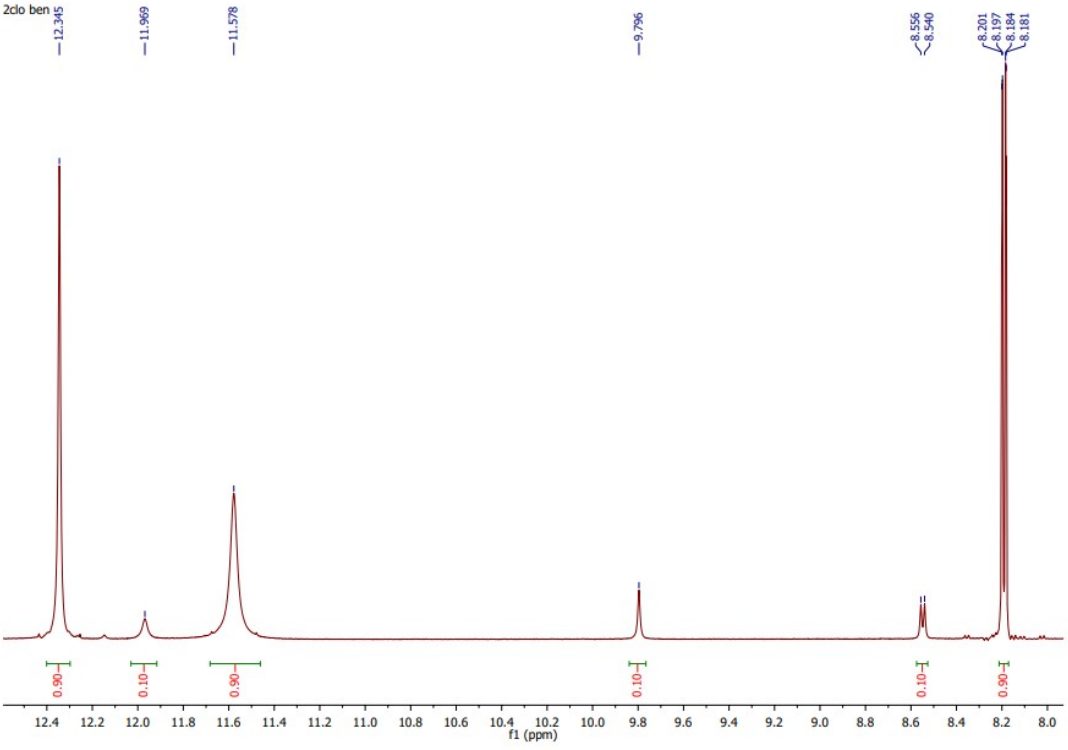


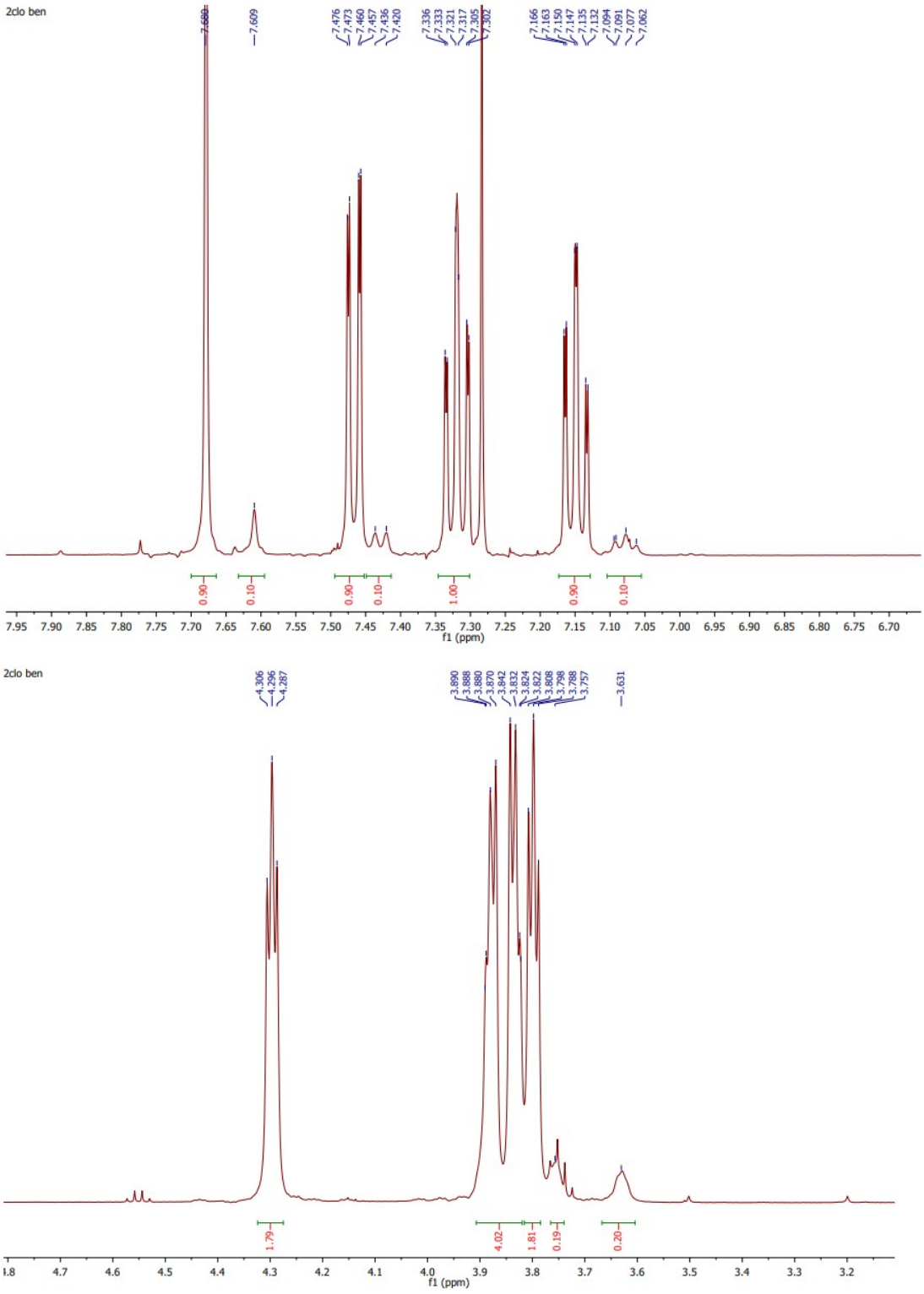


Compound **5b3** existed in the 2 conformers in DMSO: the intramolecular hydrogen bonding and the non-intramolecular hydrogen bonding at approcimate ratio of 6:4.

^{1}H-NMR spectrum, 500 MHz, $CDCl_3$ with 0.05% v/v TMS (TMS peak was at 0 ppm)

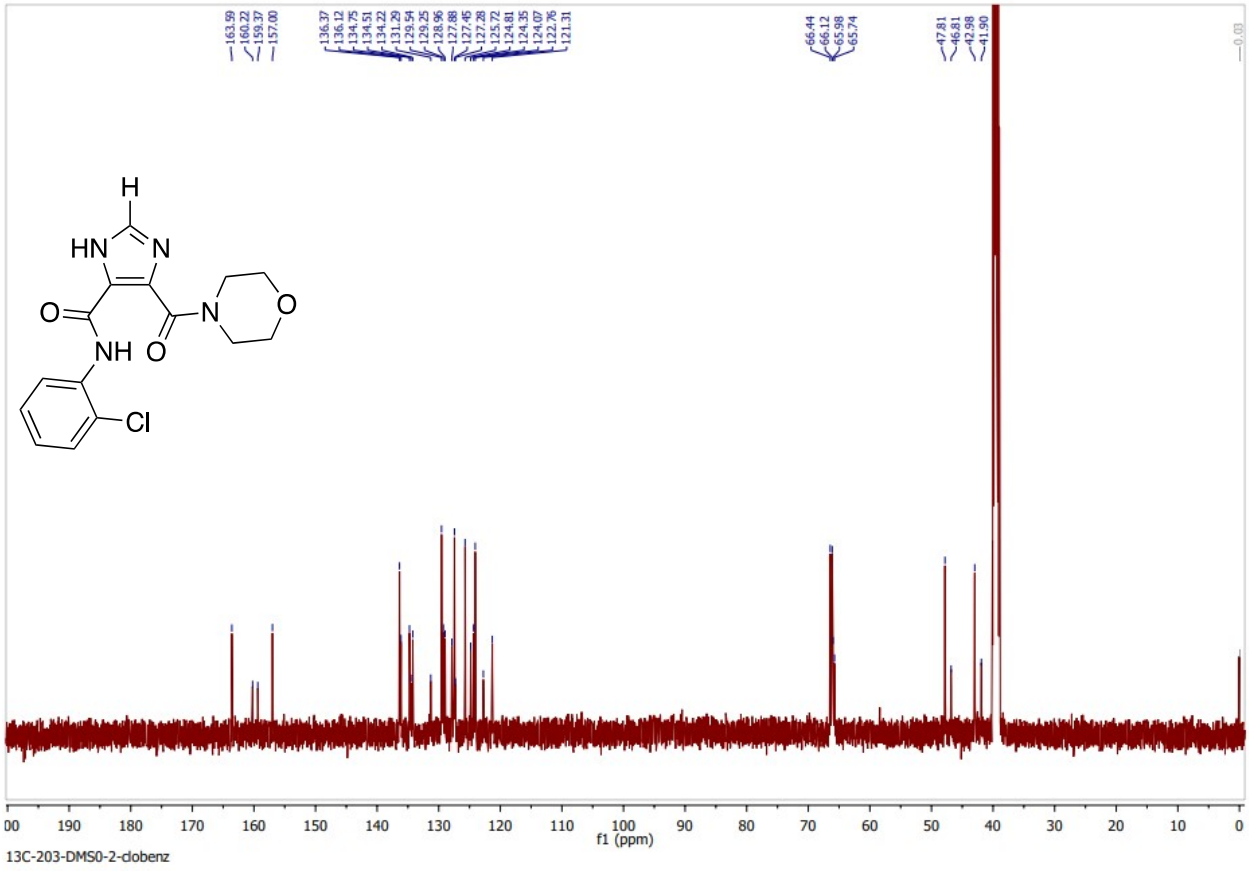

2clo ben
12.345
11.969
11.578
9.796
8.556
8.540
8.201
8.197
8.184
8.181
7.680
7.609
7.476
7.473
7.460
7.457
7.436
7.420
7.336
7.333
7.321
7.317
7.305
7.302
7.166
7.163
7.150
7.147
7.135
7.132
7.094
7.091
7.077
7.062
4.306
4.296
4.287
3.890
3.888
3.880
3.870
3.842
3.832
3.824
3.822
3.808
3.798
3.788
3.757
3.631
H
HN
N
O
N
O
NH
O
Cl
0.90
0.10
0.90
0.10
0.10
0.90
0.90
0.10
0.90
0.10
1.00
0.90
0.10
1.79
4.02
1.81
0.19
0.20
13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


2clo ben
12.345
11.969
11.578
9.796
8.556
8.540
8.201
8.197
8.184
8.181
0.90
0.10
0.90
0.10
0.10
0.90
12.4 12.2 12.0 11.8 11.6 11.4 11.2 11.0 10.8 10.6 10.4 10.2 10.0 9.8 9.6 9.4 9.2 9.0 8.8 8.6 8.4 8.2 8.0
f1 (ppm)



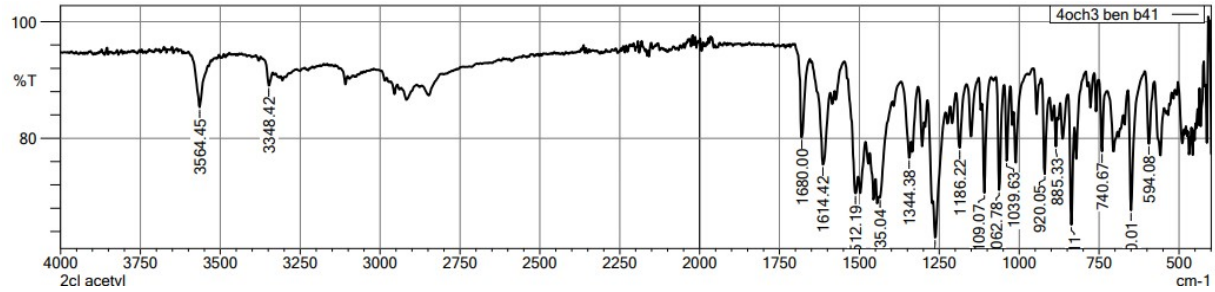
Compound **5b3** existed in the 2 conformers in $CDCl_3$: the intramolecular hydrogen bonding and the non-intramolecular hydrogen bonding at approcimate ratio of 9:1.

^{13}C-NMR spectrum, 125 MHz, DMSO-d_6 with 0.03% v/v TMS (TMS peak was at 0 ppm)



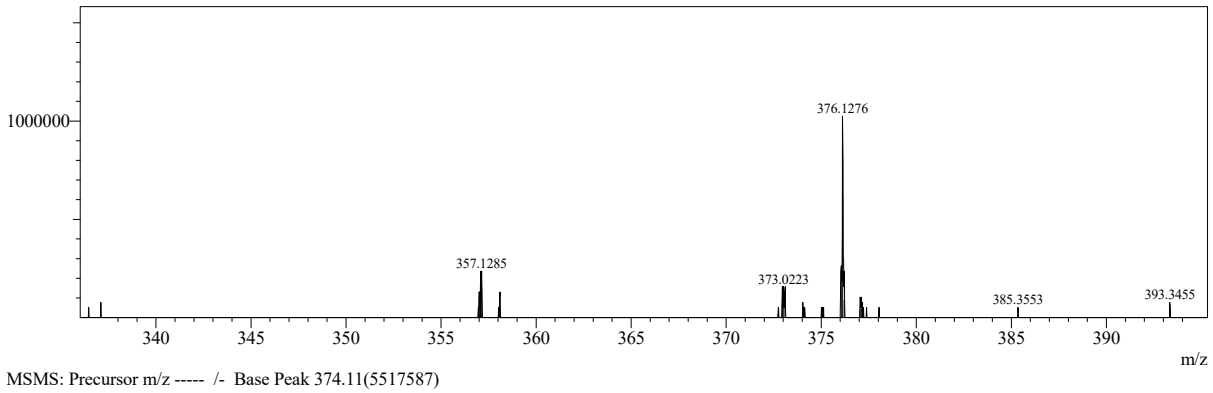
Compound ***5b4***

IR spectrum

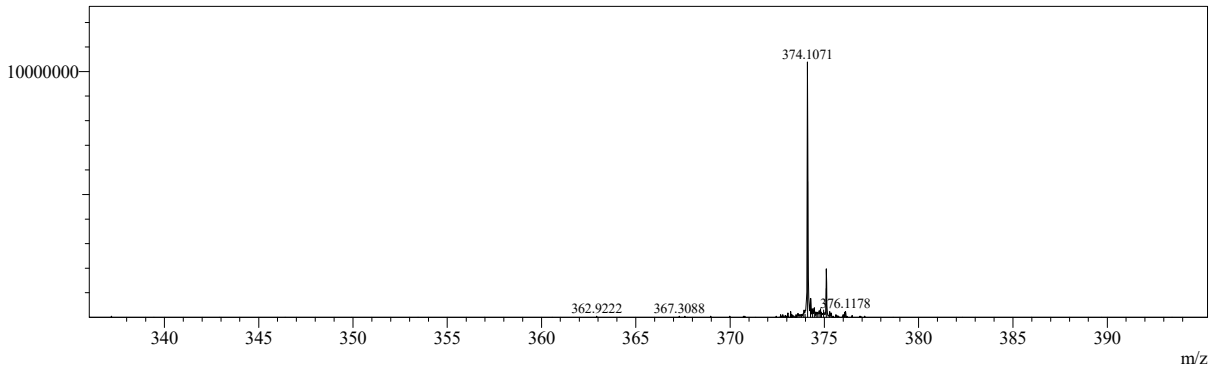


MS spectrum

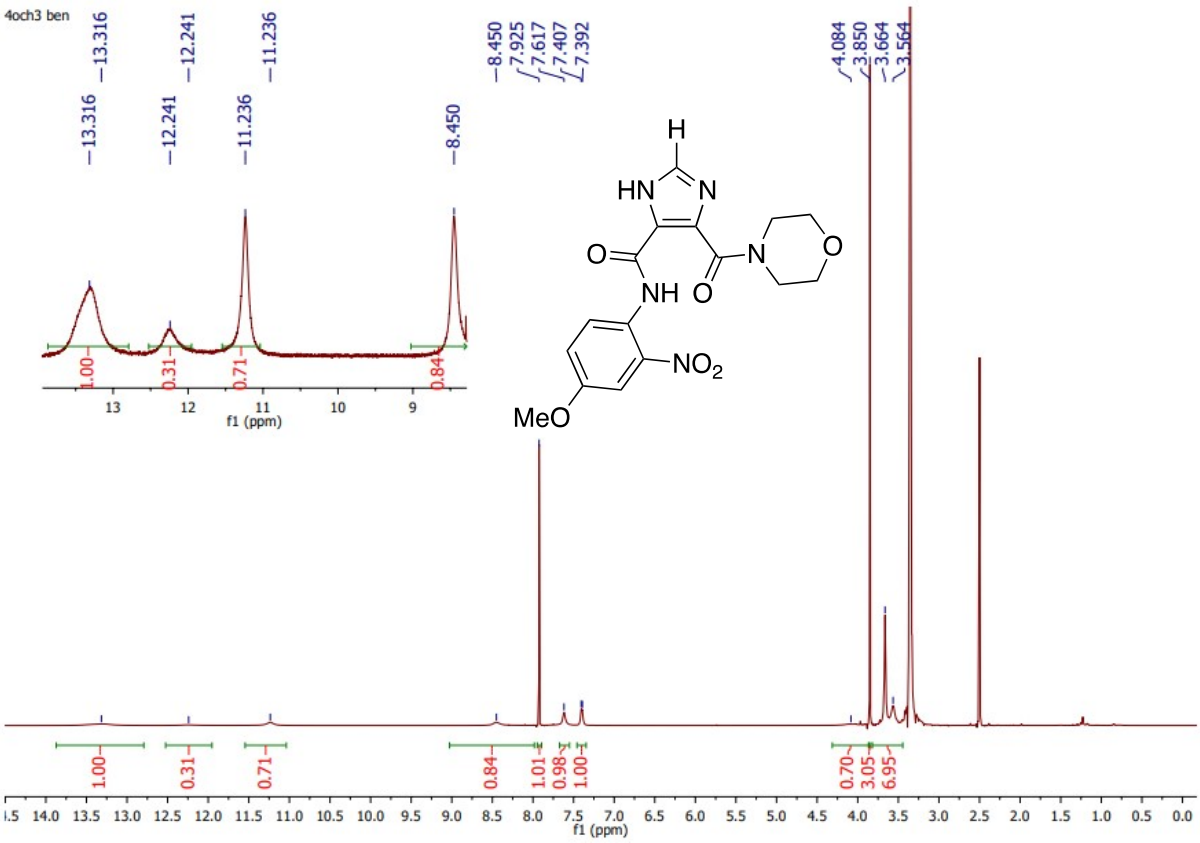
MSMS: Precursor m/z ----- /+ Base Peak 414.03(4690447)

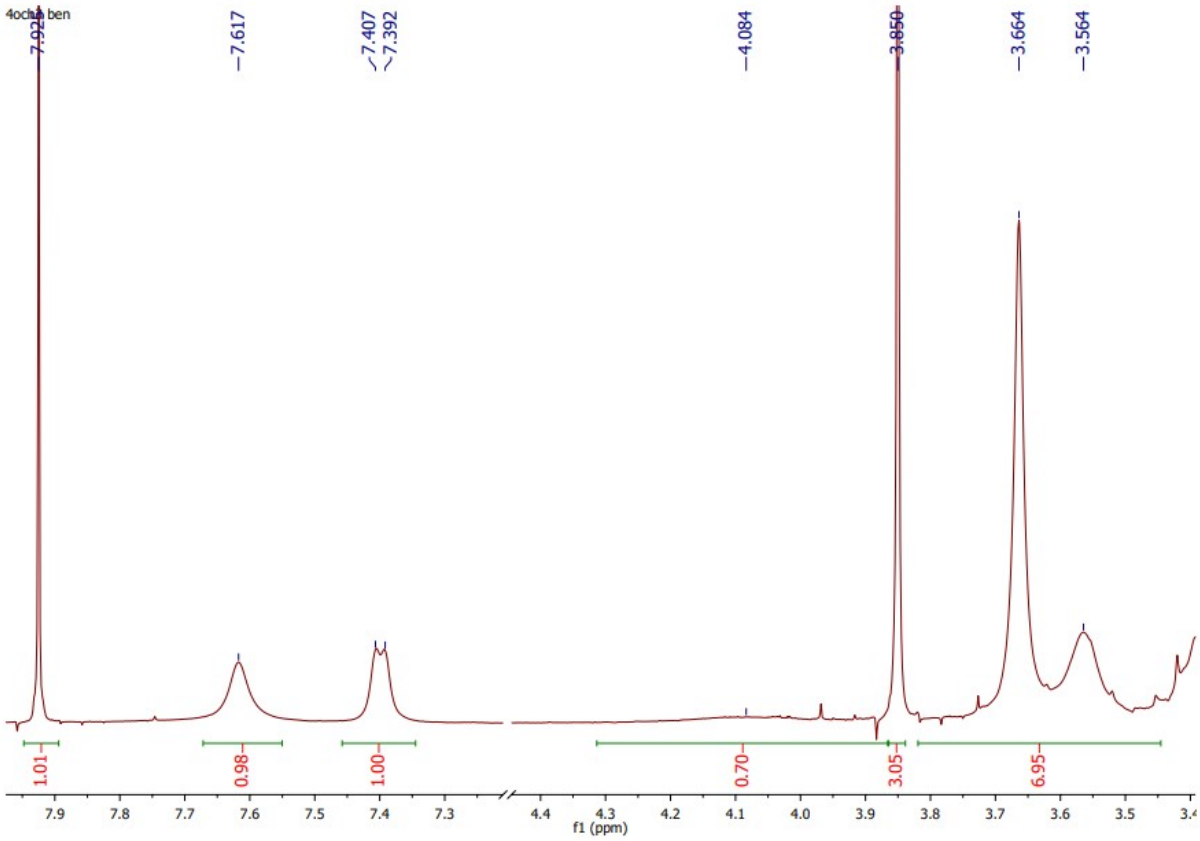


MSMS: Precursor m/z ----- /- Base Peak 374.11(5517587)



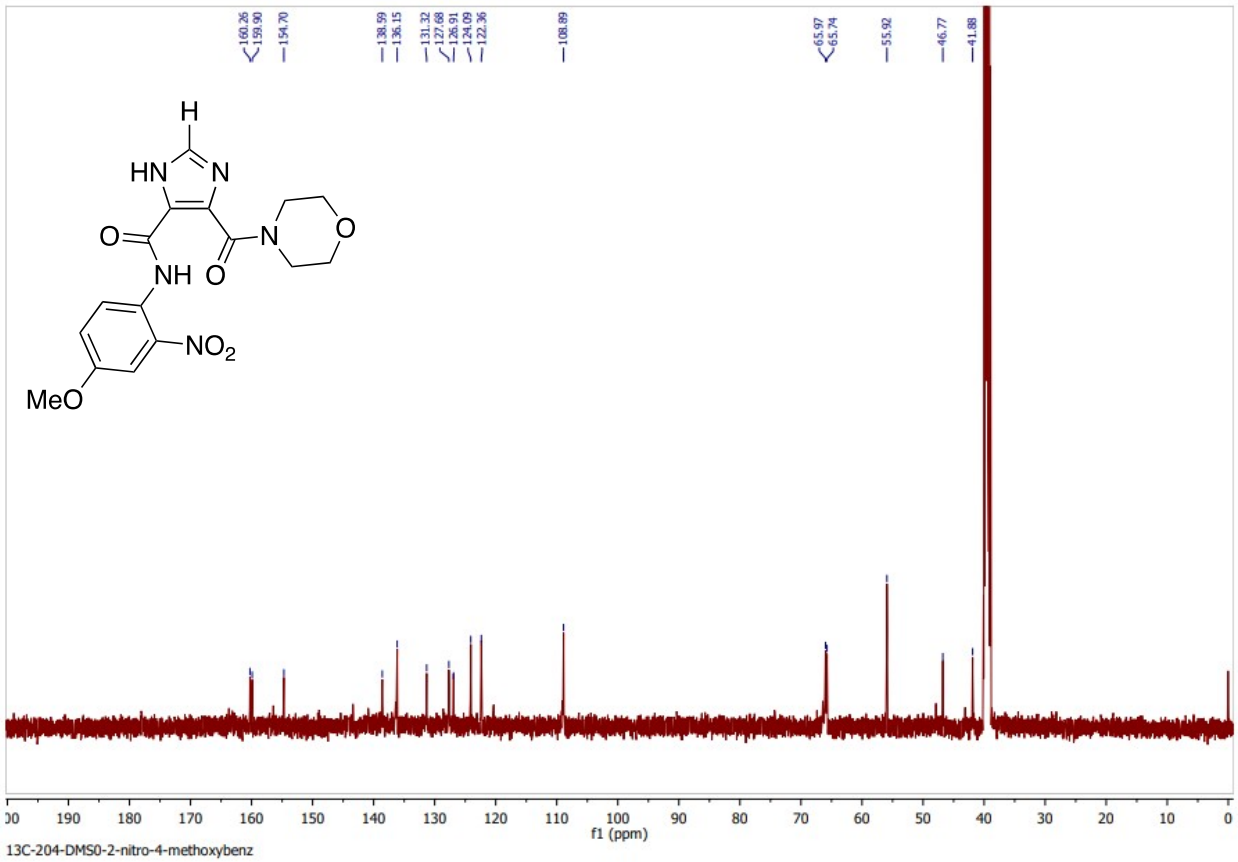
^{1}H-NMR spectrum, 600 MHz, DMSO-d_6





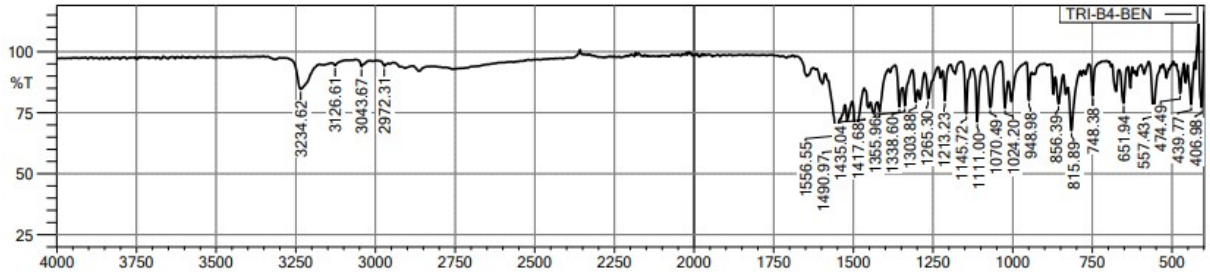
Compound **5b4** existed in the 2 conformers: the intramolecular hydrogen bonding and the non-intramolecular hydrogen bonding at approcimate ratio of 3:7.

^{13}C-NMR spectrum, 125 MHz, DMSO-d_6 with 0.03% v/v TMS (TMS peak was at 0 ppm)

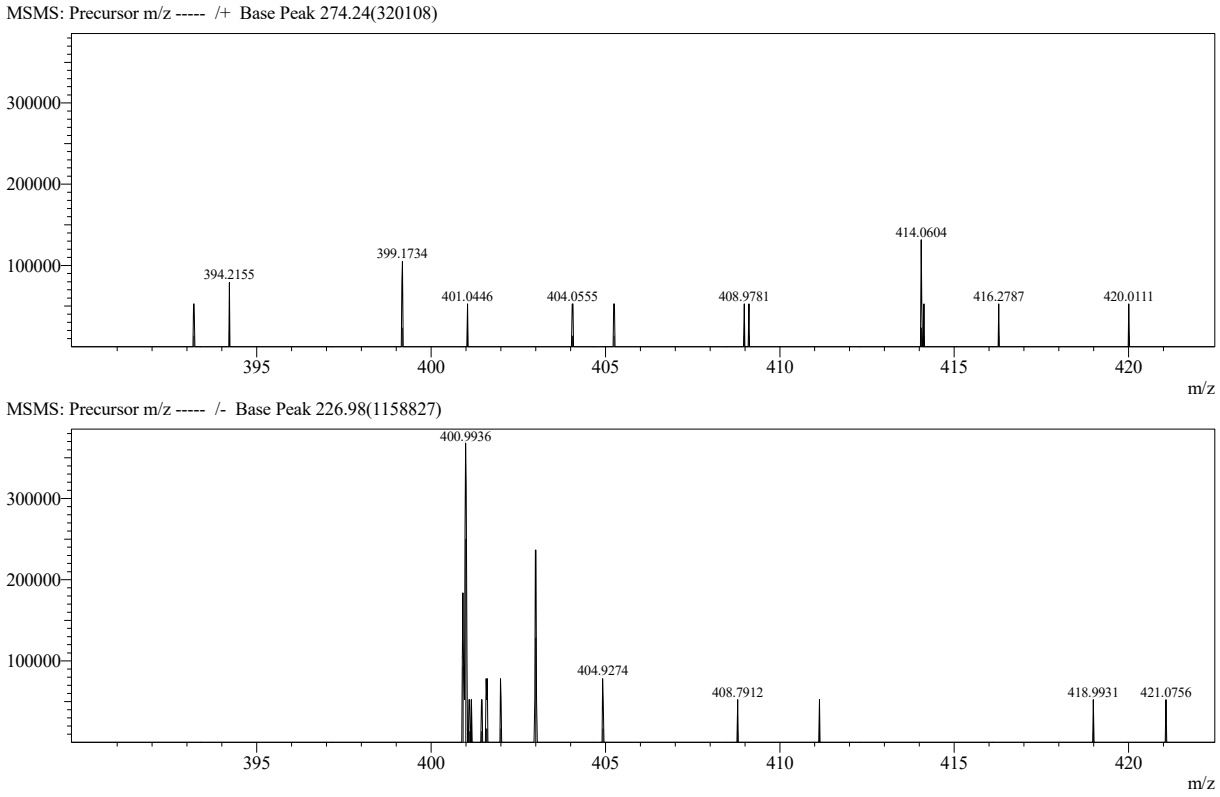


Compound ***5b5***

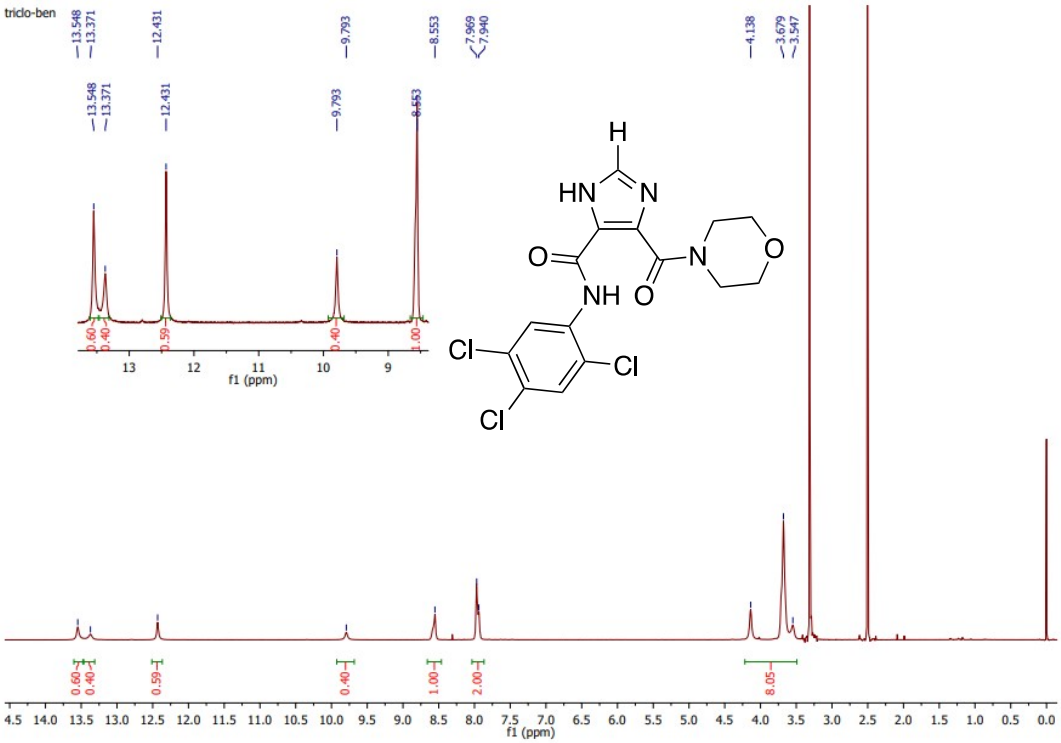
IR spectrum

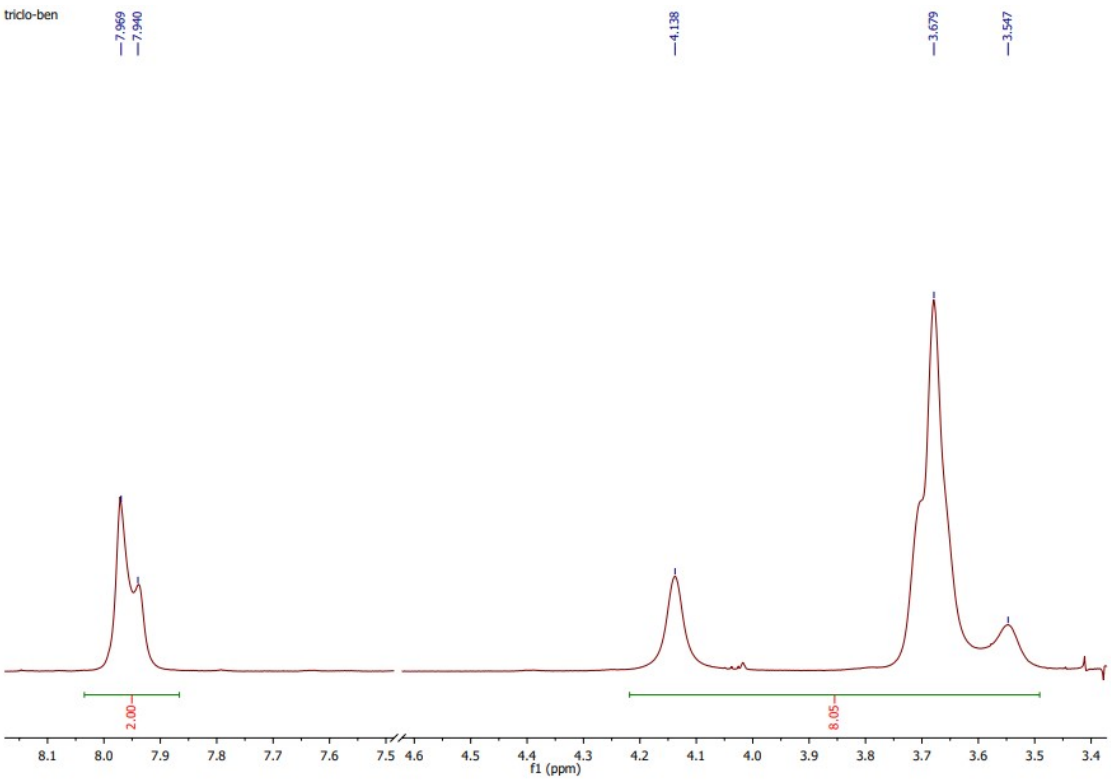


MS spectrum



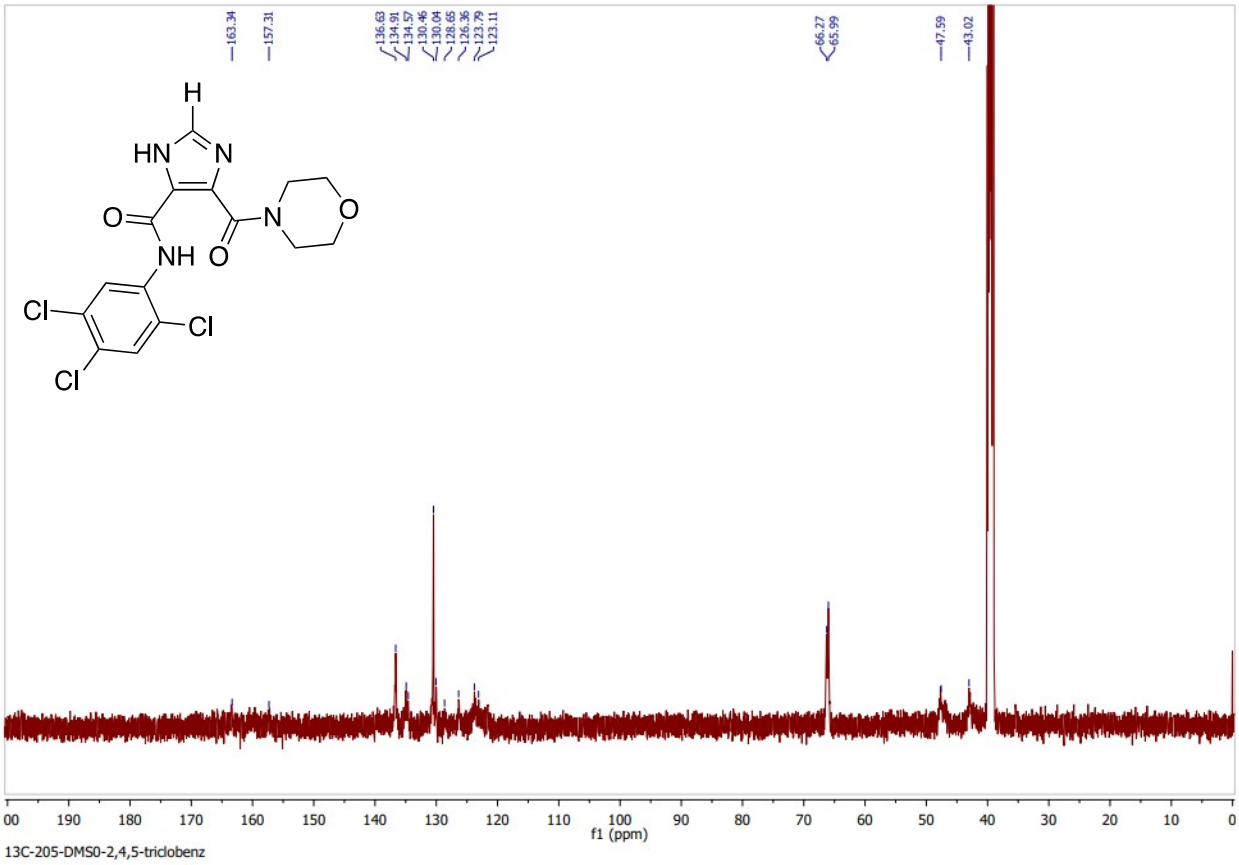
^{1}H-NMR spectrum, 125 MHz, DMSO-d_6 with 0.03% v/v TMS (TMS peak was at 0 ppm)





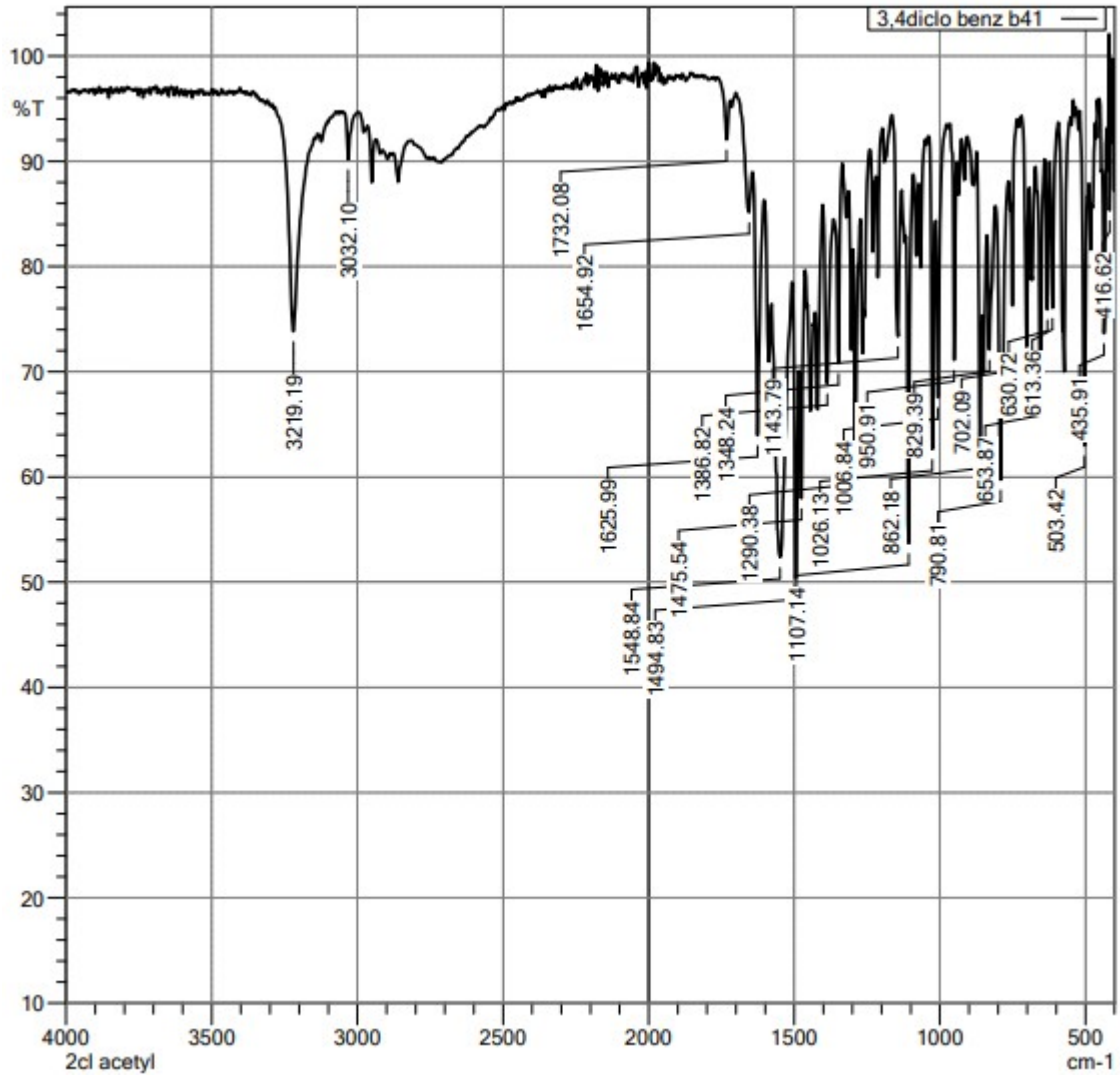
Compound **5b5** existed in the 2 conformers: the intramolecular hydrogen bonding and the non-intramolecular hydrogen bonding at approcimate ratio of 6:4.

^{13}C-NMR spectrum, 125 MHz, DMSO-d_6 with 0.03% v/v TMS (TMS peak was at 0 ppm)

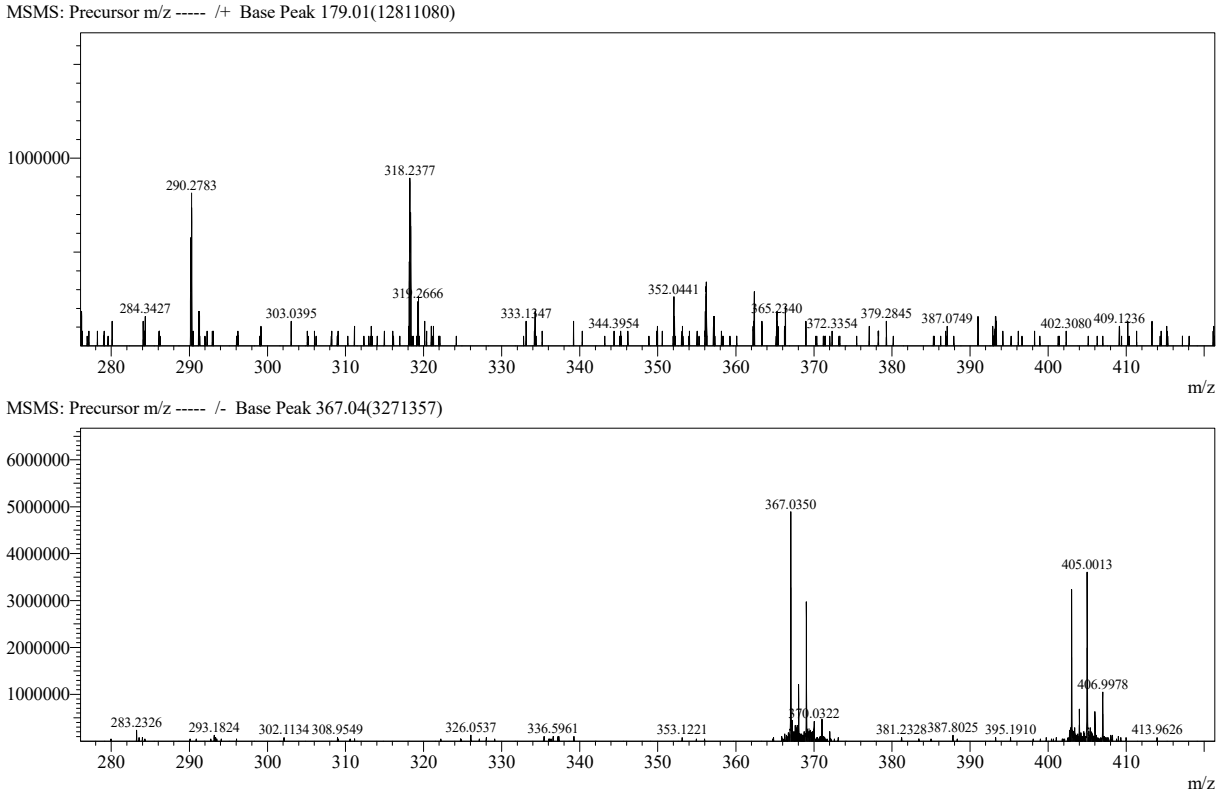


Compound ***5b6***

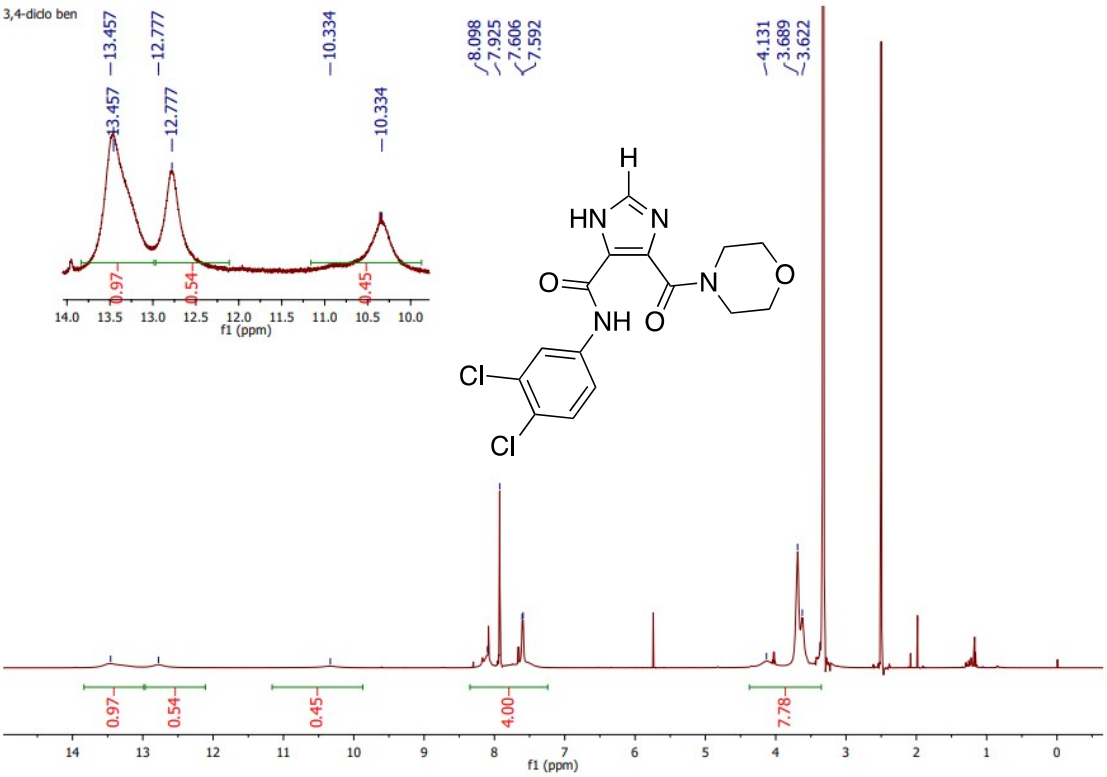
IR spectrum

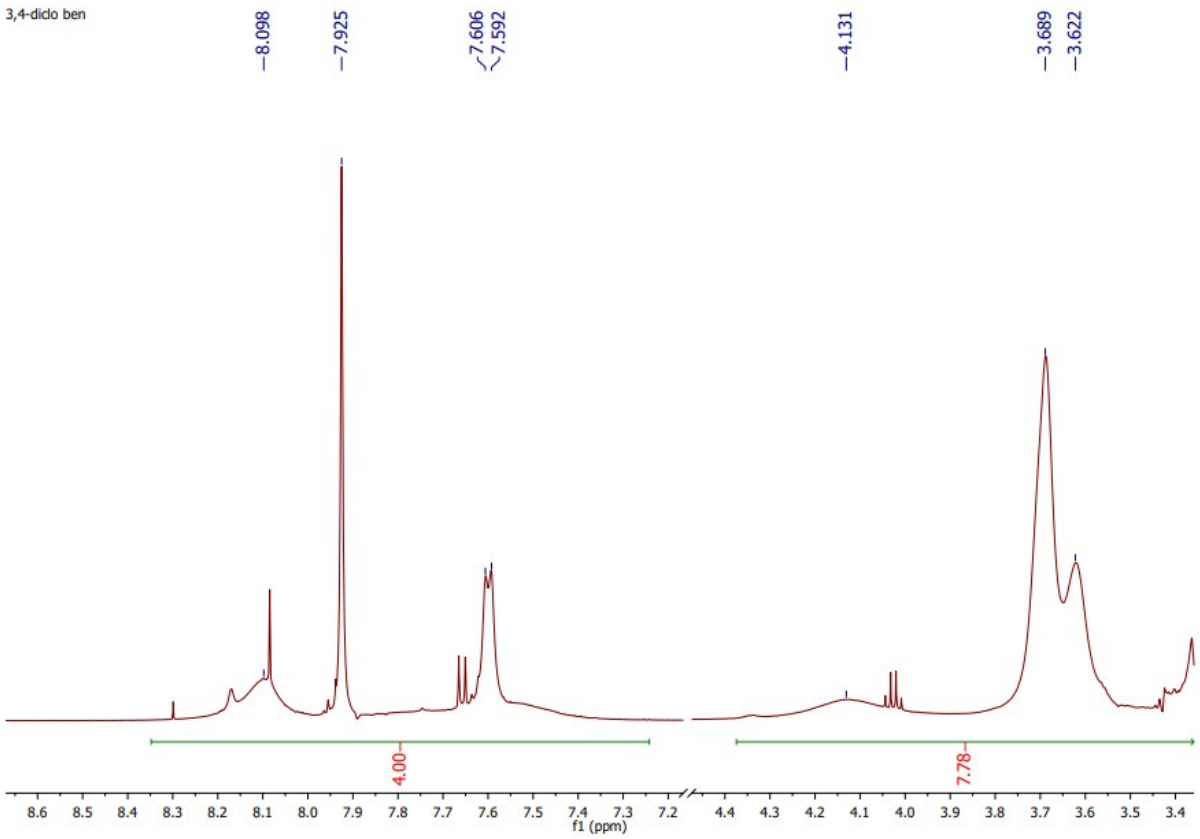

3,4diclo benz b41
%T
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
500
cm-1
2cl acetyl
3219.19
3032.10
1732.08
1654.92
1625.99
1548.84
1494.83
1475.54
1386.82
1348.24
1290.38
1143.79
1107.14
1026.13
1006.84
950.91
862.18
829.39
790.81
702.09
653.87
630.72
613.36
503.42
435.91
416.62

MS spectrum



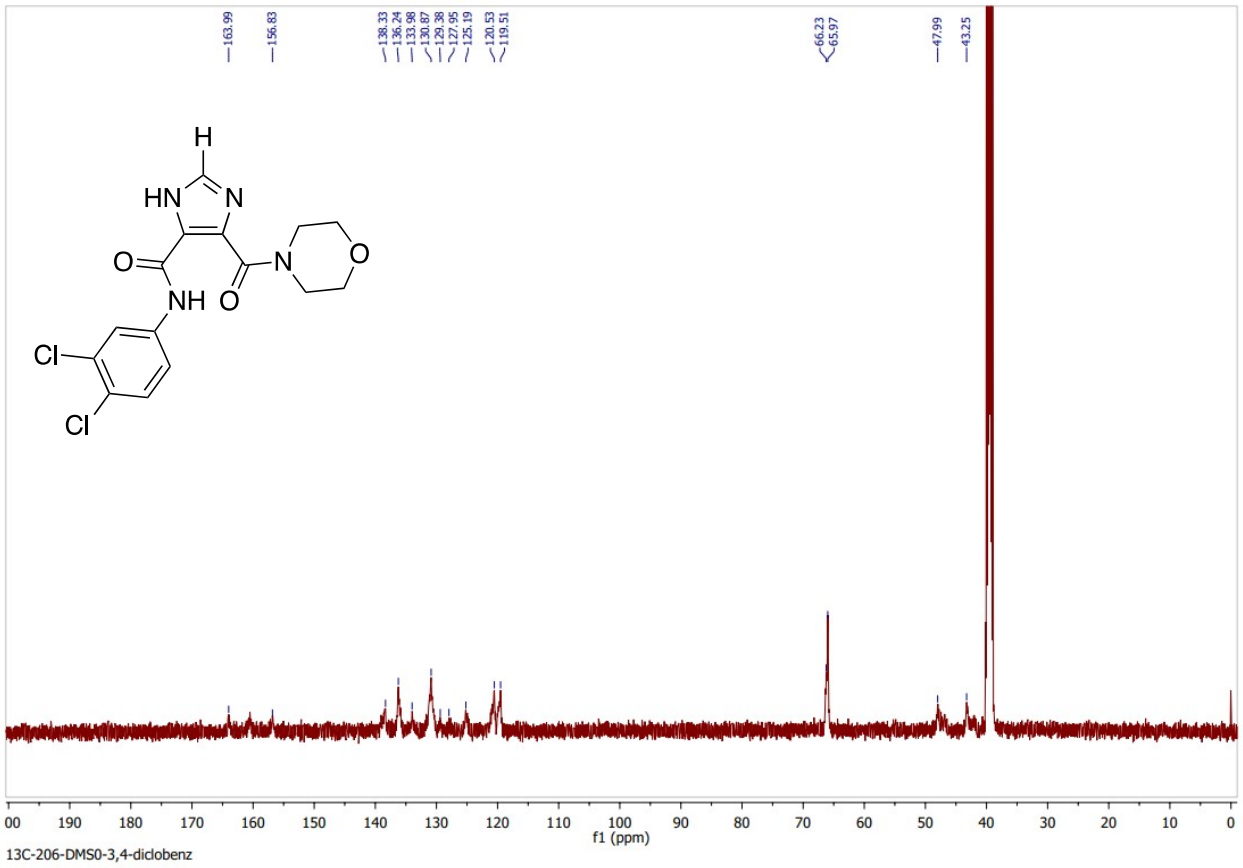
^{1}H-NMR spectrum, 600 MHz, DMSO-d_6





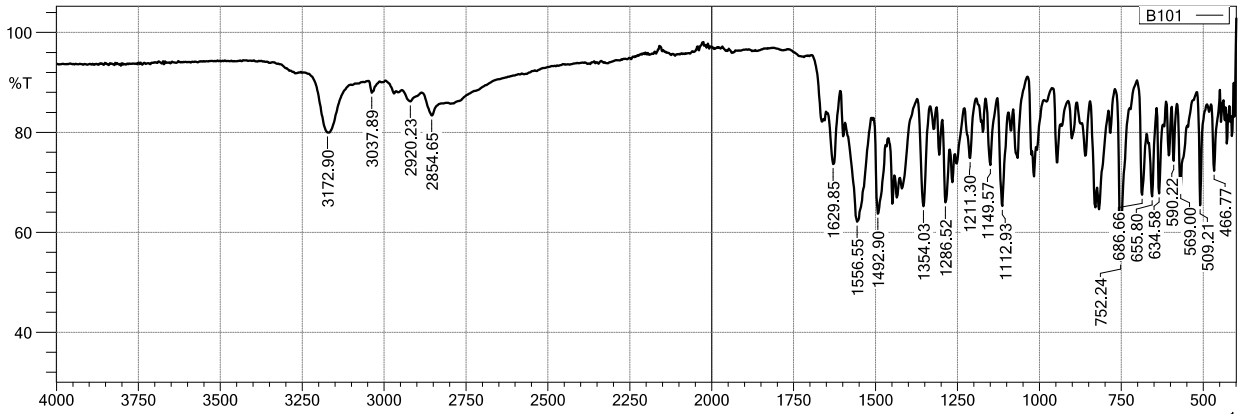
Compound **5b6** existed in the 2 conformers: the intramolecular hydrogen bonding and the non-intramolecular hydrogen bonding at approcimate ratio of 5.4:4.5.

^{13}C-NMR spectrum, 125 MHz, DMSO-d_6 with 0.03% v/v TMS (TMS peak was at 0 ppm)

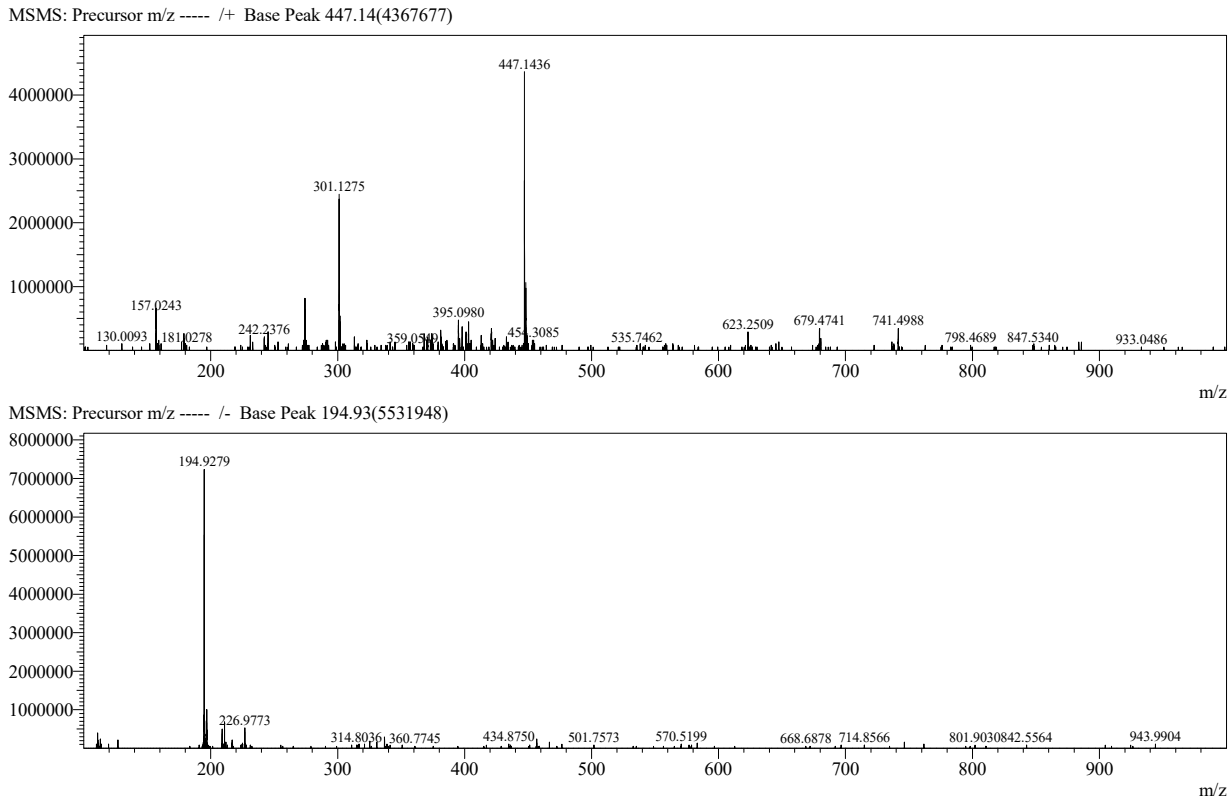


*Compound **5b7***

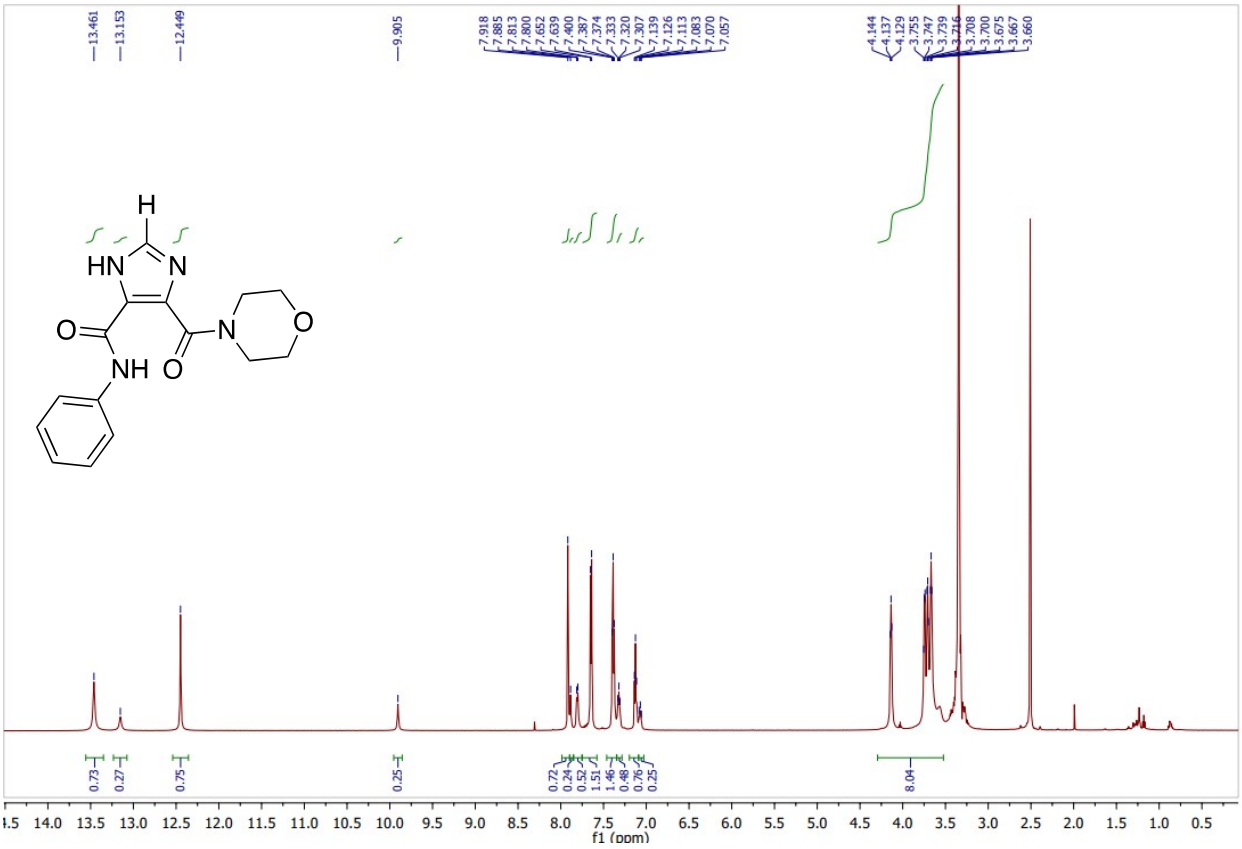
IR spectrum



MS spectrum

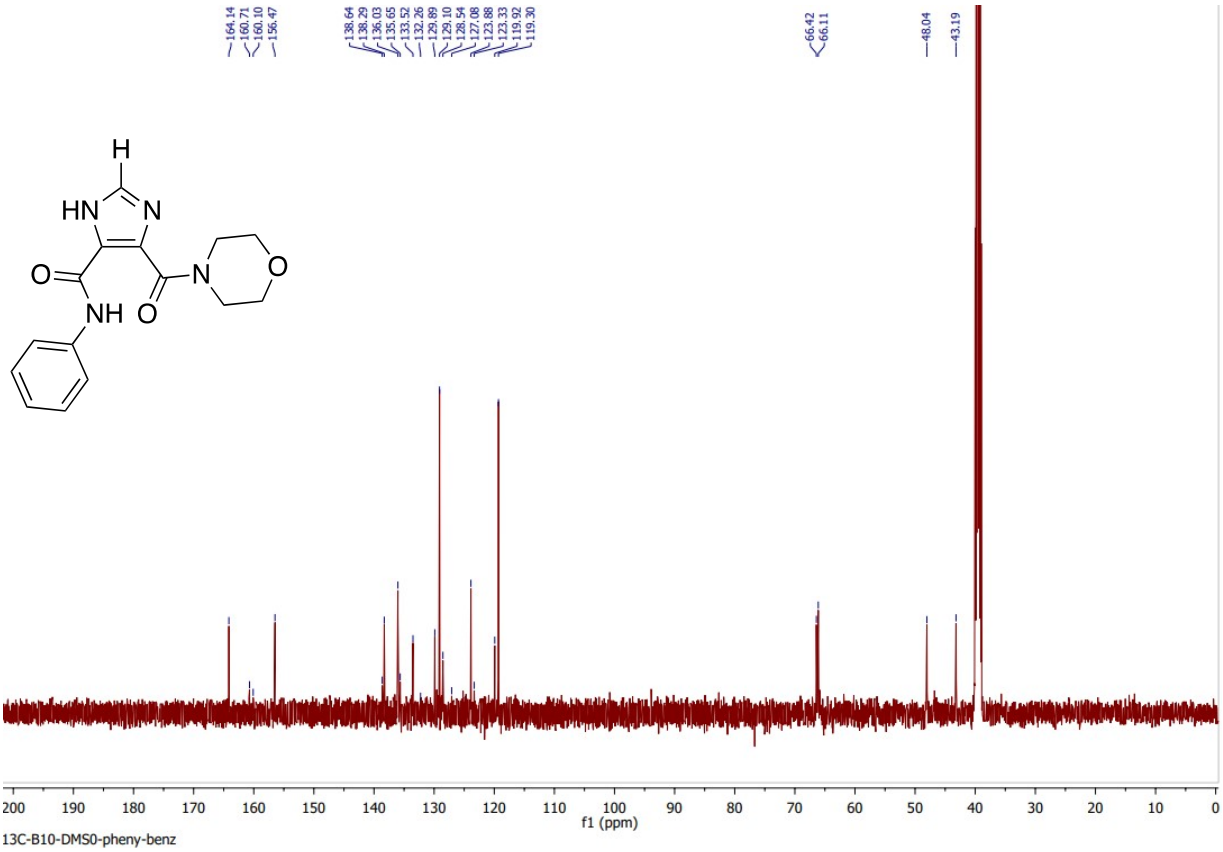


^{1}H-NMR spectrum, 600 MHz, DMSO-d_6



Compound **5b7** existed in the 2 conformers: the intramolecular hydrogen bonding and the non-intramolecular hydrogen bonding at approcimate ratio of 7.5:2.5.

^{13}C-NMR spectrum, 125 MHz, DMSO-d_6



2. Screening for M^{pro} inhibitory activity at 1 μM

Compound	I%	Compound	I%	Compound	I%
5a1	38%	**5b1**	18%	**Ritonavir**	24%
5a2	38%	**5b2**	3%	**Lopinavir**	33%
5a3	25%	**5b3**	28%	**Ebselen**	100%
5a4	28%	**5b4**	30%		
5a5	39%	**5b5**	16%		
5a6	33%	**5b6**	33%		
5a7	24%	**5b7**	15%		

3. Dose-response inhibition data

5a1

LogC (μM)	Mean (%)	SD (%)
-0.61	0.00	0.00
-0.31	0.00	0.00

-0.01	0.00	0.00
0.29	5.09	7.19
0.59	23.49	9.66
0.89	41.34	3.83
1.19	79.47	7.10
1.49	93.39	9.35
1.80	100.00	0.00
2.10	100.00	0.00
2.40	100.00	0.00
2.70	100.00	0.00

5a2

LogC (µM)	Mean (%)	SD (%)
-0.61	0.00	0.00
-0.31	1.81	2.56
0.29	28.19	0.51
0.59	39.44	5.27
0.89	52.69	3.99
1.49	74.10	7.32
1.80	84.33	10.04
2.10	96.59	4.82
2.40	100.00	0.00
2.70	100.00	0.00

5a5

LogC (µM)	Mean (%)	SD (%)
0.19	0.00	0.00
0.49	0.00	0.00
0.80	5.56	7.86
1.10	46.94	4.95
1.70	100.00	0.00

2.00	100.00	0.00

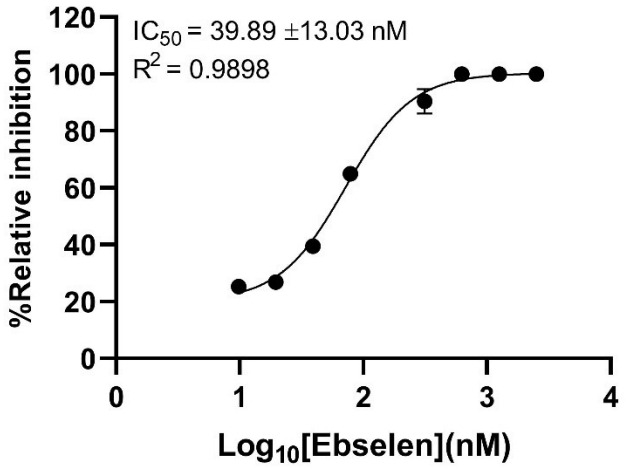
5a6

LogC (μM)	Mean (%)	SD (%)
-1.31	11.00	10.42
-1.01	6.67	9.43
-0.71	14.67	7.13
-0.41	9.33	6.80
-0.11	15.00	5.66
0.19	37.00	7.79
0.80	55.00	7.79
1.10	42.00	3.56
1.40	54.67	1.70
1.70	100.00	0.00
2.00	100.00	0.00

5b6

LogC (μM)	Mean (%)	SD (%)
0.29	8.61	6.12
0.59	9.88	7.01
0.89	10.75	7.71
1.19	37.58	2.54
1.49	38.76	6.42
1.80	62.88	6.52
2.10	100.00	0.00
2.40	100.00	0.00
2.70	100.00	0.00

4. Dose-response Inhibition of ebselen against SARS-CoV-2 M^{pro}



5. Enzyme kinetic inhibition plots of SARS-CoV-2 M^{pro} inhibition by 5a2 (Mean±SD%)

[S] (μM)	[I] (μM)		
	0	2.5	5
80	0.269±0.055	0.282±0.056	0.313±0.064
60	0.363±0.085	0.412±0.126	0.409±0.082
40	0.452±0.047	0.486±0.023	0.570±0.050
20	0.571±0.025	0.690±0.066	0.850±0.036
10	1.081±0.056	1.272±0.158	1.558±0.236

6. The cytotoxic effect on 16HBE14o cell line of potential compounds

Compound	Mean (%)	SD (%)
0.2%DMSO	100.00	4.02
5a1	100.84	7.78
5a2	91.65	3.53
5a5	99.52	9.13
5a6	97.02	1.89
5a7	95.35	1.61

7. The distribution of the four substituents of the native ligand across the four pockets (S1-4) of the binding site in SARS-CoV-2's Mpro

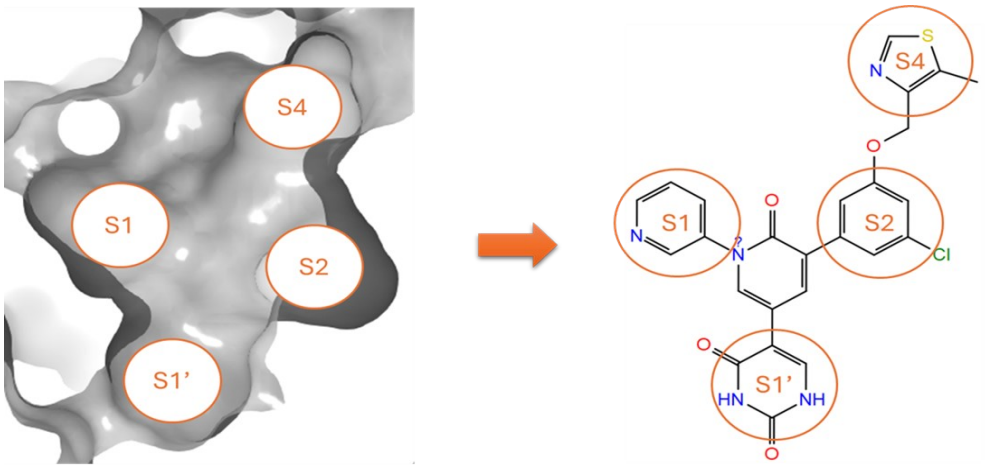


Figure S1. The distribution of the four substituents of the native ligand across the four pockets (S1-4) of the binding site (gray shape) (PDB: 7N44).