

Supplementary Information

Efficient Synthesis of New Biheterocyclic 5-[(5-Trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidines

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¹H and ¹³C nuclear magnetic resonance (NMR) and mass spectra for 5-[(5-trifluoromethyl-5-hydroxy-(3-substituted)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidines (**4a-l**) are shown.

The ¹H and ¹³C spectra were recorded at 298 K on a Bruker DPX 400 spectrometer (¹H at 400.13 MHz, ¹³C at 100.63 MHz) with a digital resolution of ± 0.01 ppm. All of the chemical shifts are expressed in ppm, and ¹H and ¹³C are reported with respect to internal tetramethylsilane

(TMS). Solutions of 0.1 mol L⁻¹ CDCl₃ were used (**1-4**) except with compound **5**, for which 0.1 mol L⁻¹ DMSO-*d*₆ was used. H-H and C-F coupling constants are in Hz. Mass spectra were registered in a HP 5973 MSD connected to a HP 6890 GC and interfaced with a Pentium PC. The gas chromatograph (GC) was equipped with a split-splitless injector, auto-sampler, and cross-linked HP-5 capillary column (30 m × 0.32 mm i.d.), and helium was used as the carrier.

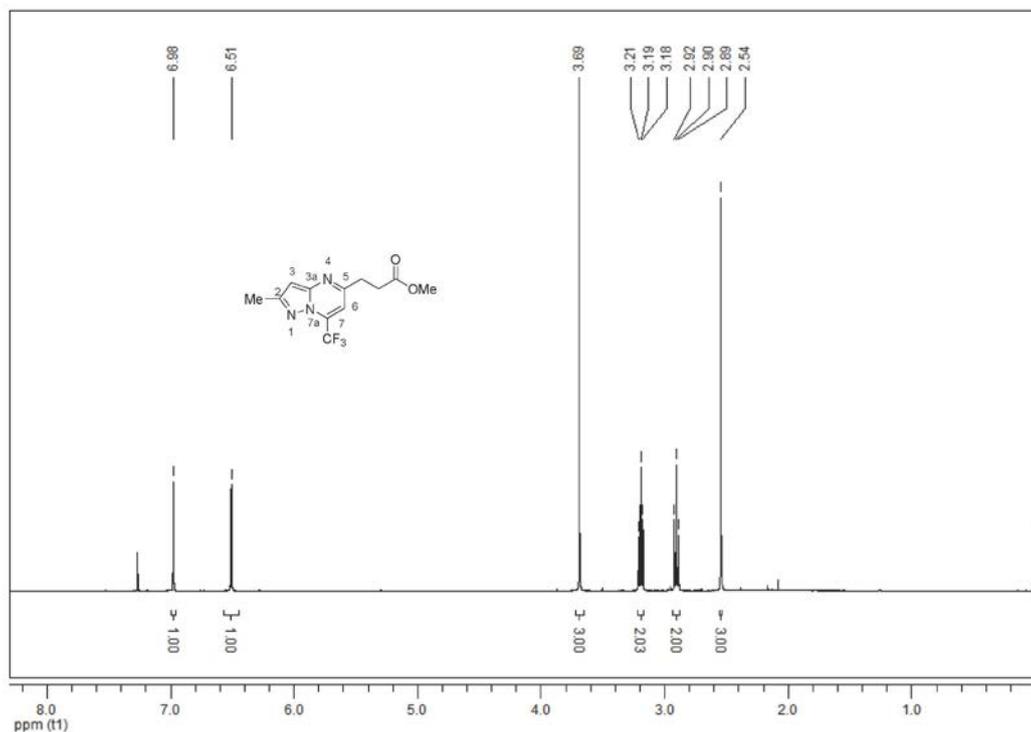


Figure S1. ¹H NMR spectrum (CDCl₃, 400 MHz) of methyl 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoate (**1**).

*e-mail: alex.fcf@ufsm.br

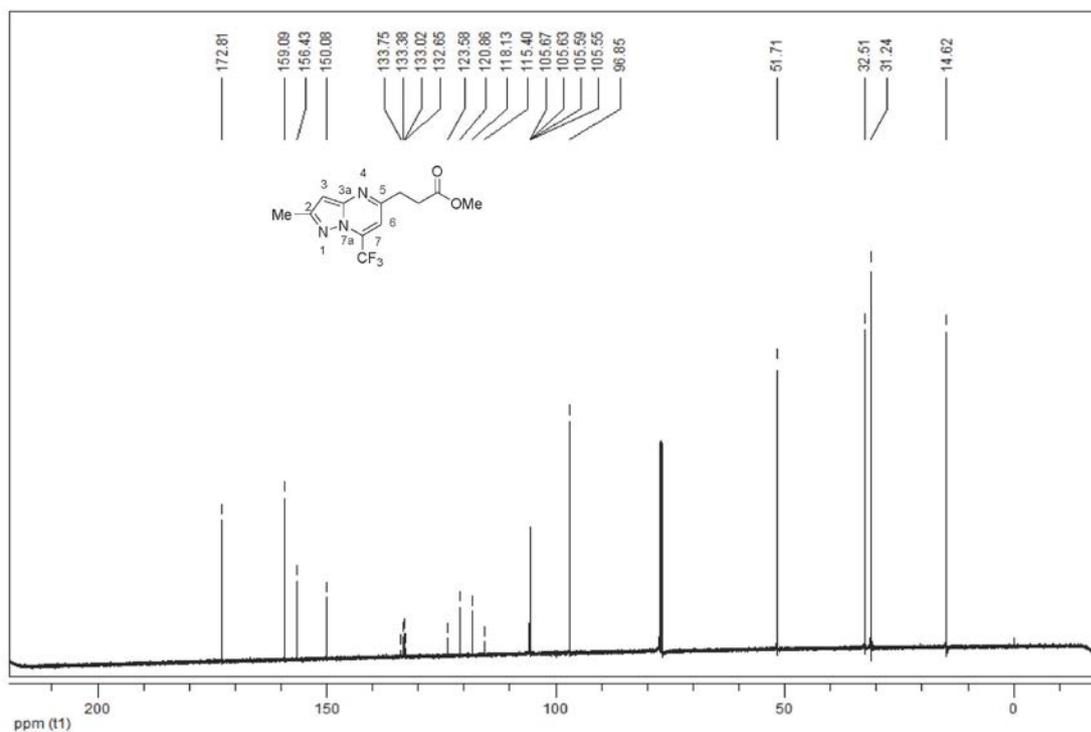


Figure S2. ¹³C NMR spectrum (CDCl₃, 100 MHz) of methyl 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoate (**1**).

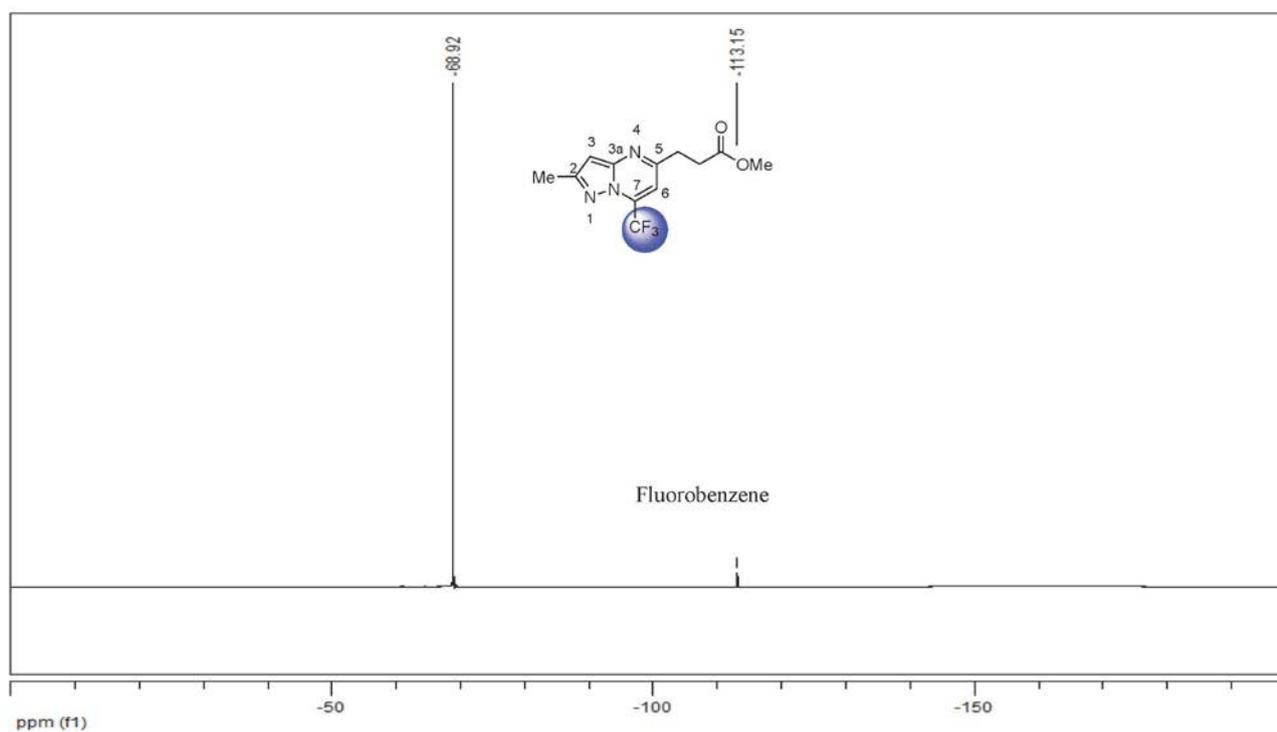


Figure S3. ¹⁹F NMR spectrum (CDCl₃, 376.4 MHz) of methyl 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoate (**1**).

User Spectra

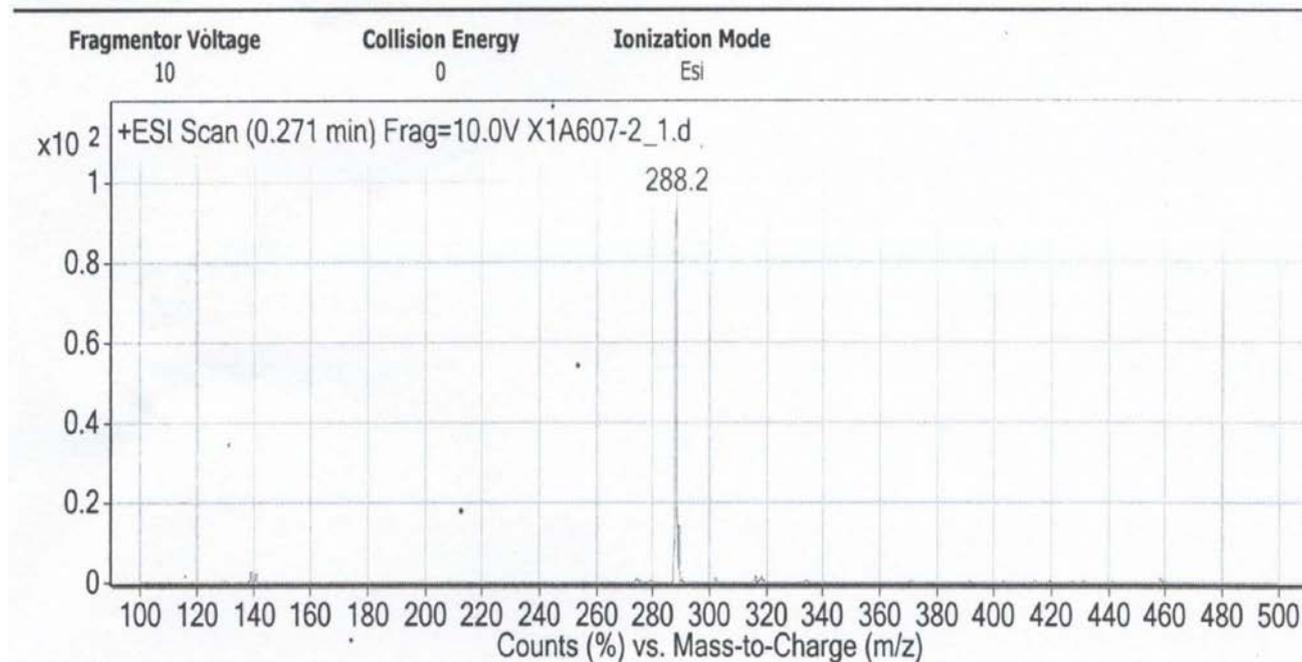


Figure S4. ESI mass spectra of 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoate (**1**).

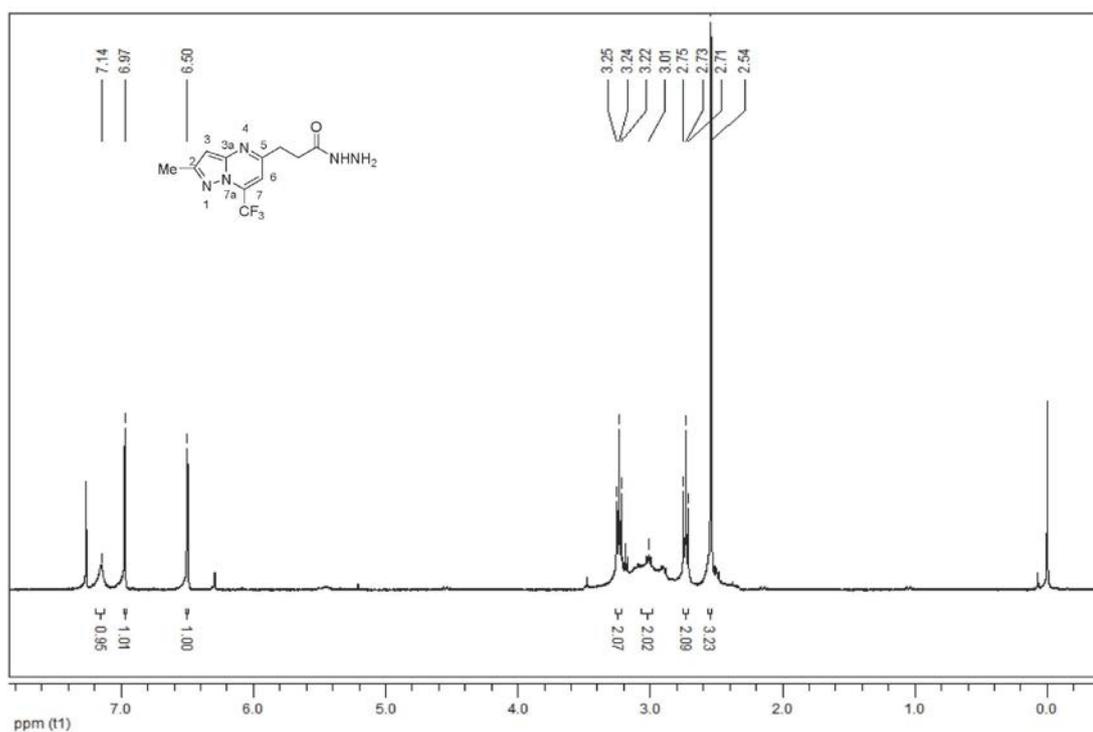


Figure S5. ¹H NMR spectrum (CDCl₃, 400 MHz) of 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoyl hydrazide (**2**).

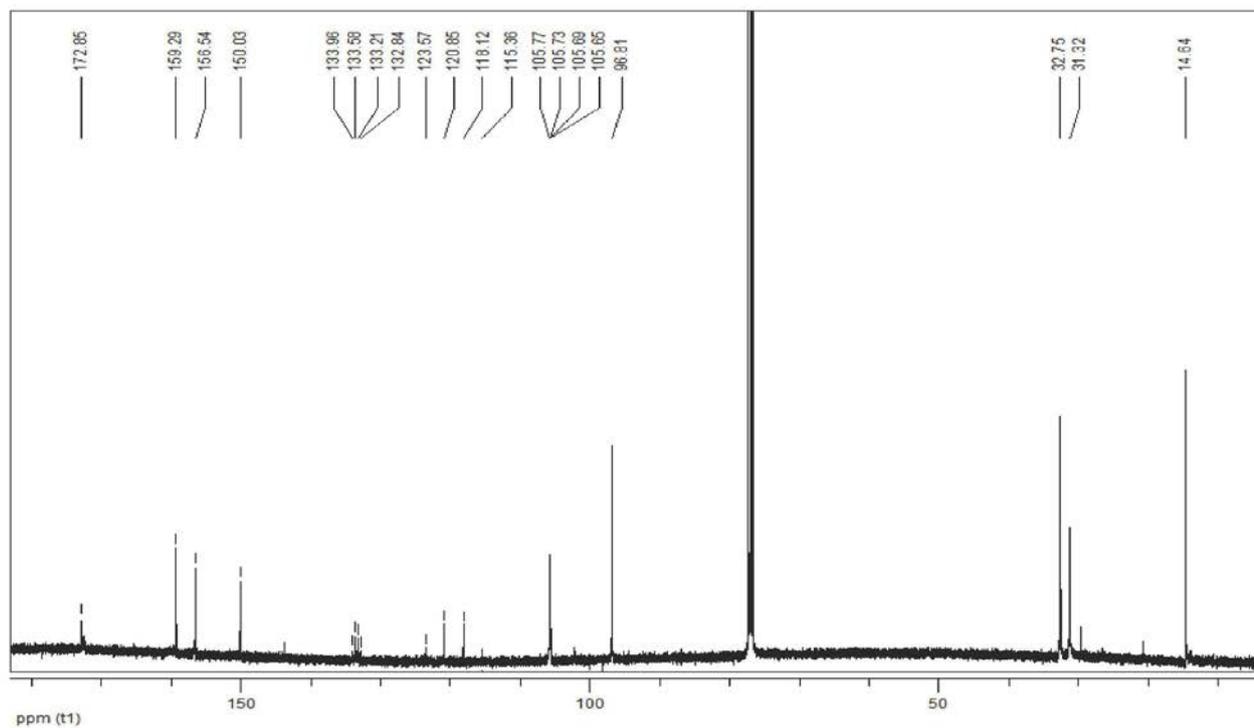


Figure S6. ¹³C NMR spectrum (CDCl₃, 100 MHz) of 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoyl hydrazide (**2**).

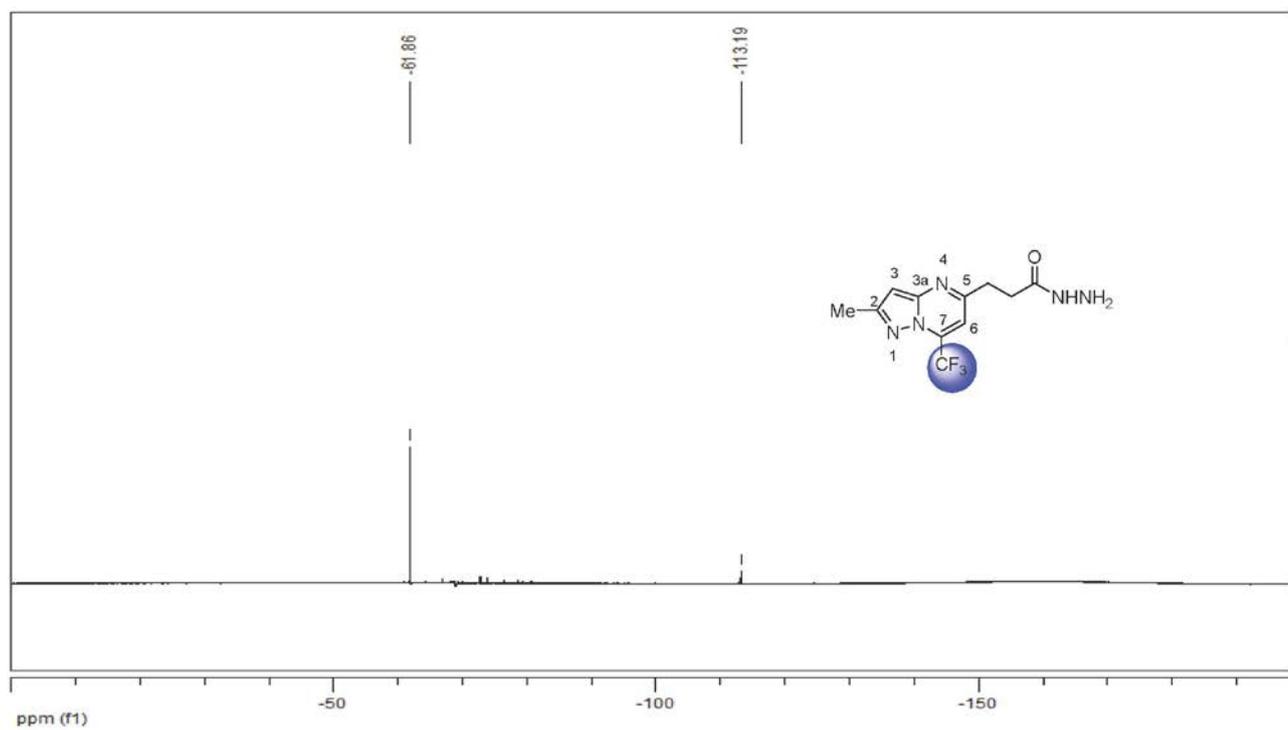


Figure S7. ¹⁹F NMR spectrum (CDCl₃, 376.4 MHz) of 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoyl hydrazide (**2**).

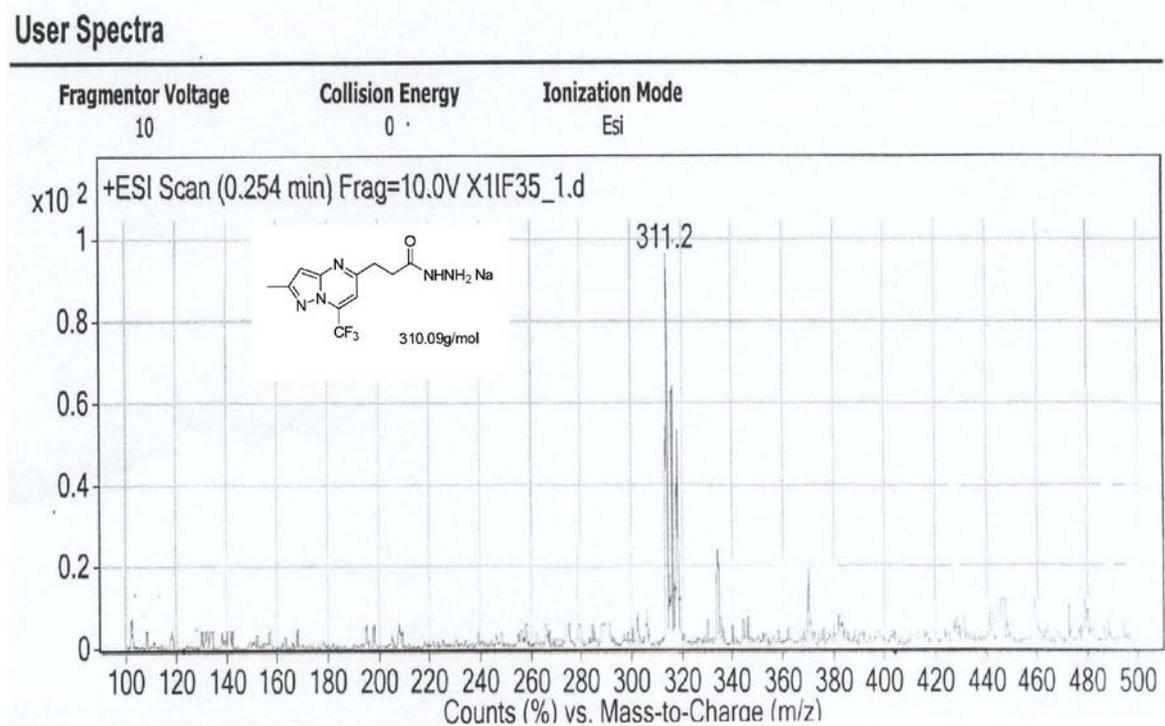


Figure S8. ESI mass spectrum of 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoyl hydrazide (**2**).

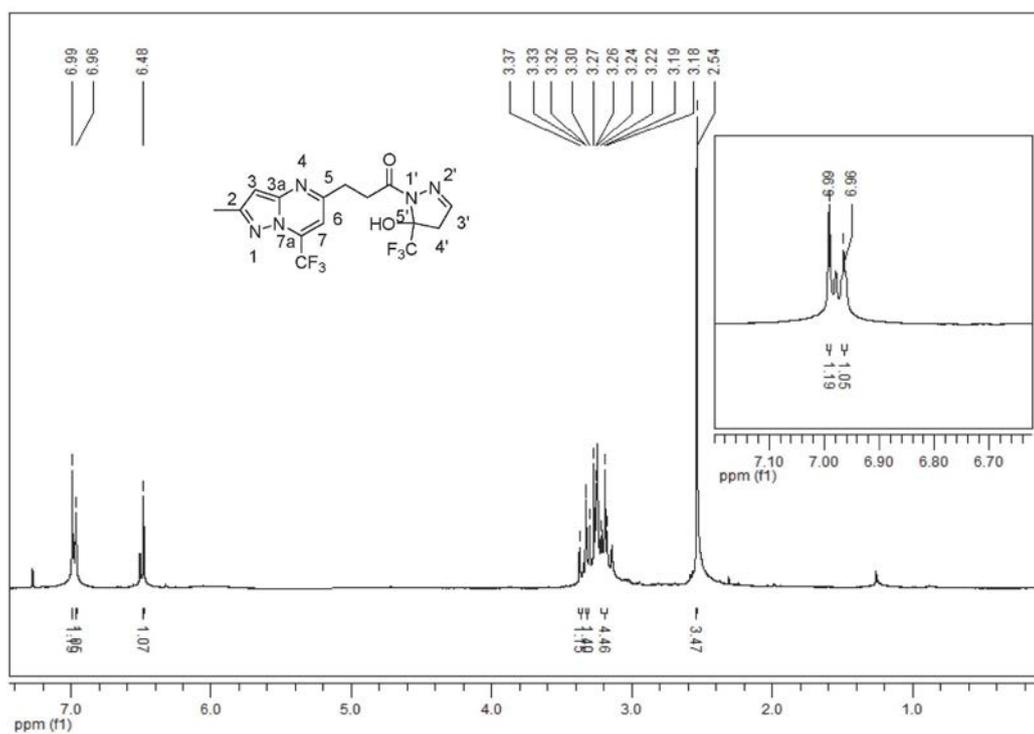


Figure S9. ¹H NMR spectrum (CDCl₃, 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4a**).

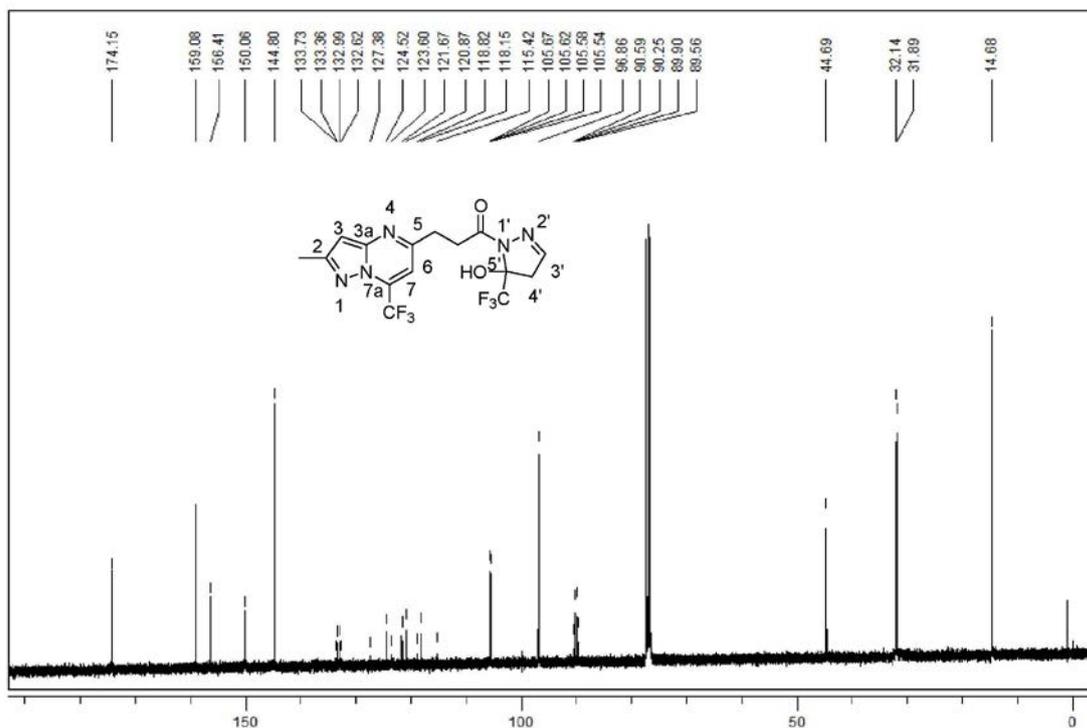


Figure S10. ^{13}C NMR spectrum (CDCl_3 , 100 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4a**).

User Spectra

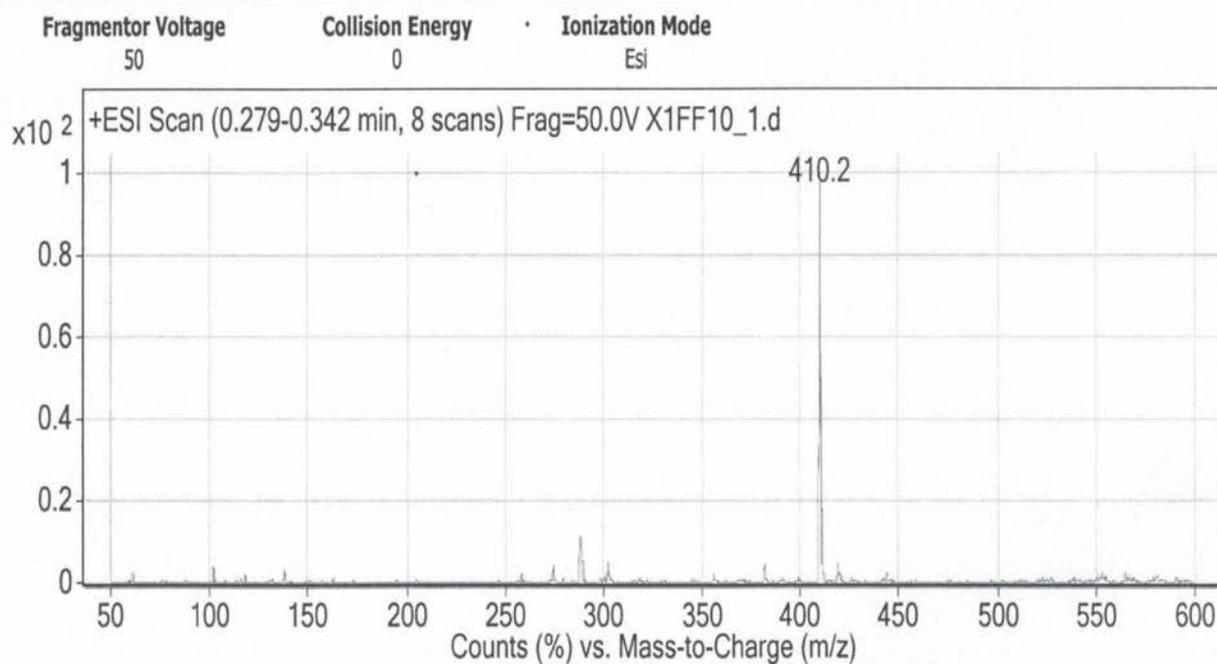


Figure S11. ESI mass spectrum of 5-[(5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4a**)

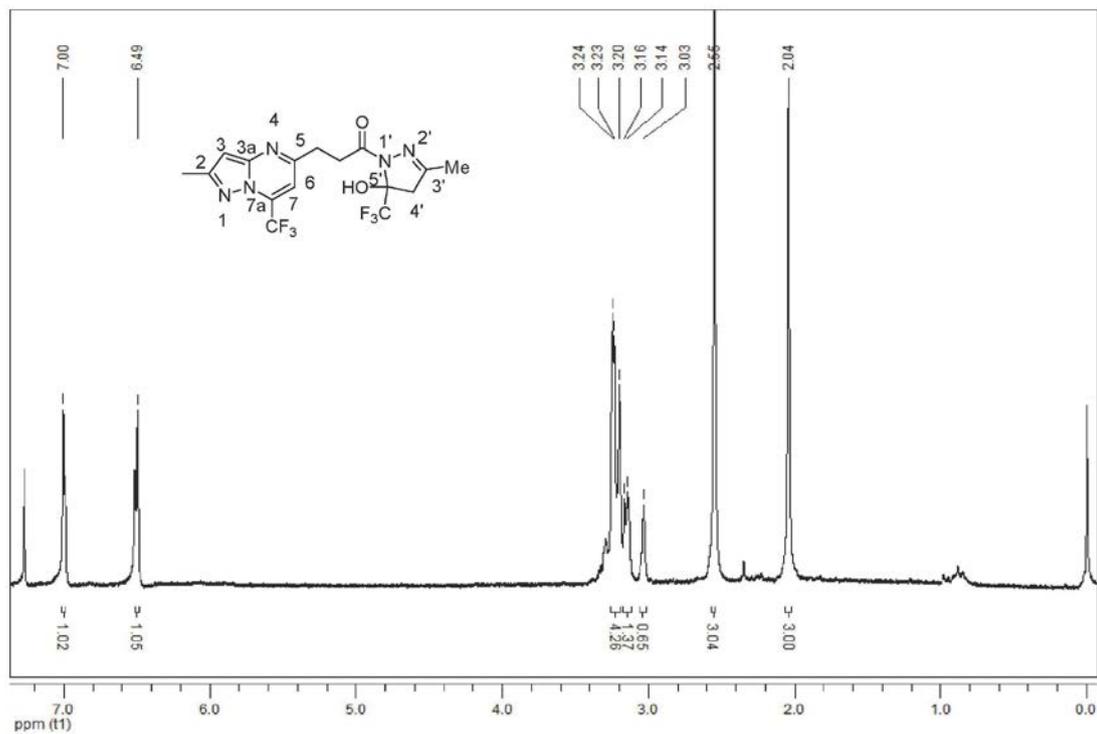


Figure S12. ^1H NMR spectrum (CDCl_3 , 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4b**).

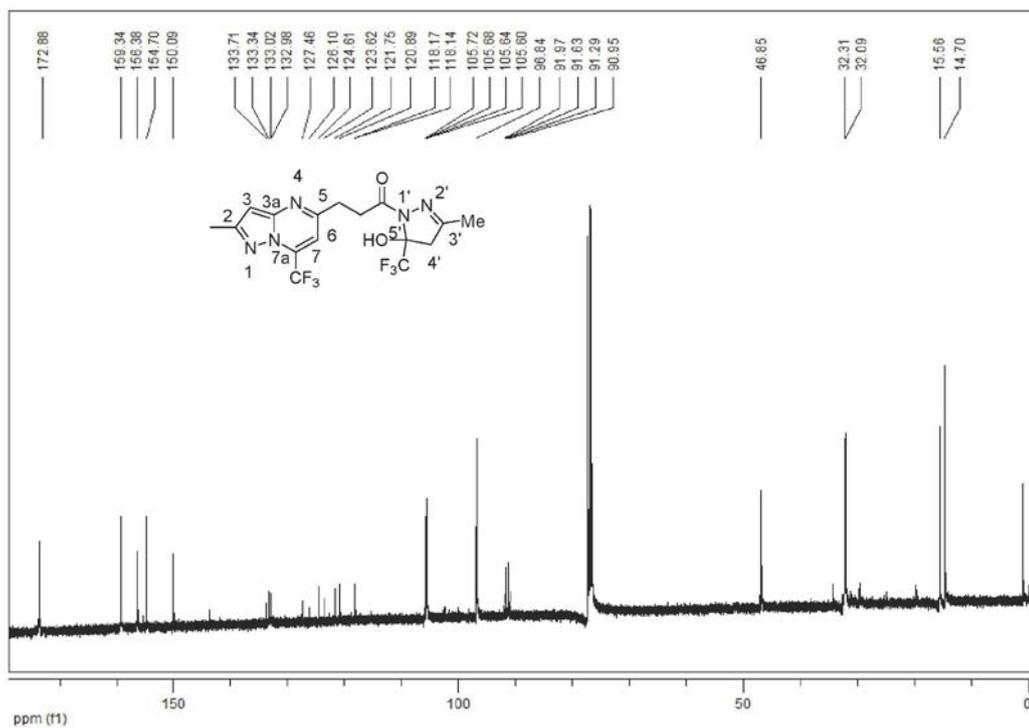


Figure S13. ^{13}C NMR spectrum (CDCl_3 , 100 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4b**).

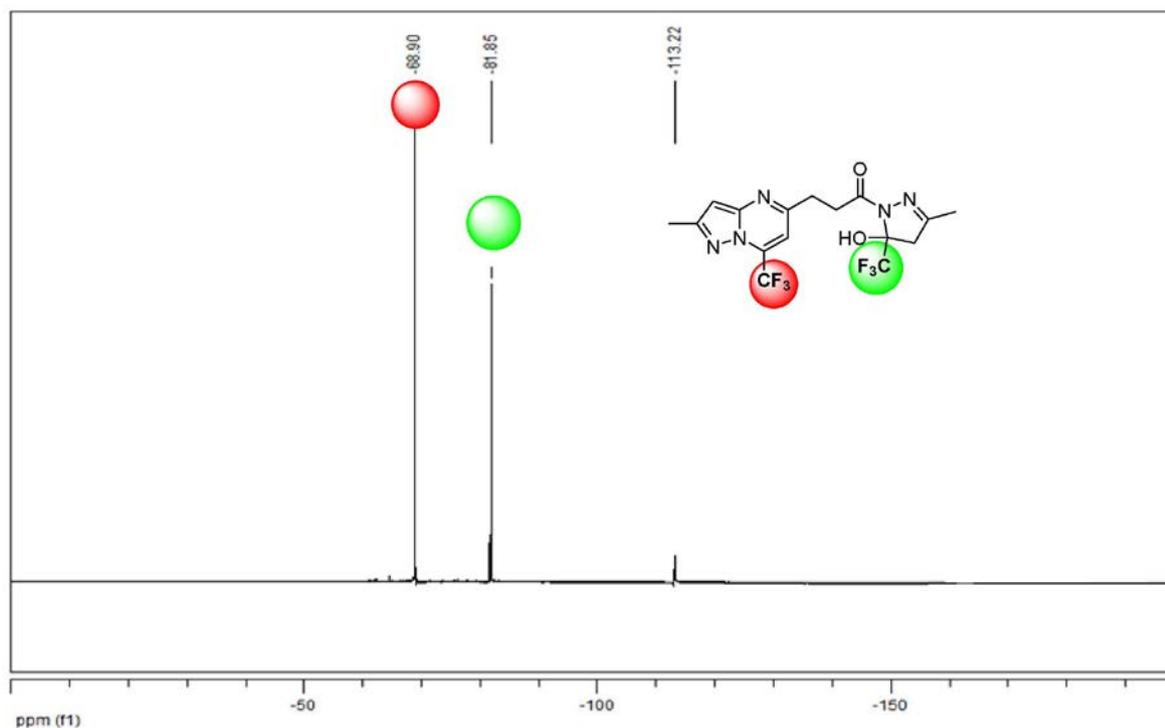


Figure S14. ^{19}F NMR spectrum (CDCl_3 , 376.4 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4b**).

User Spectra

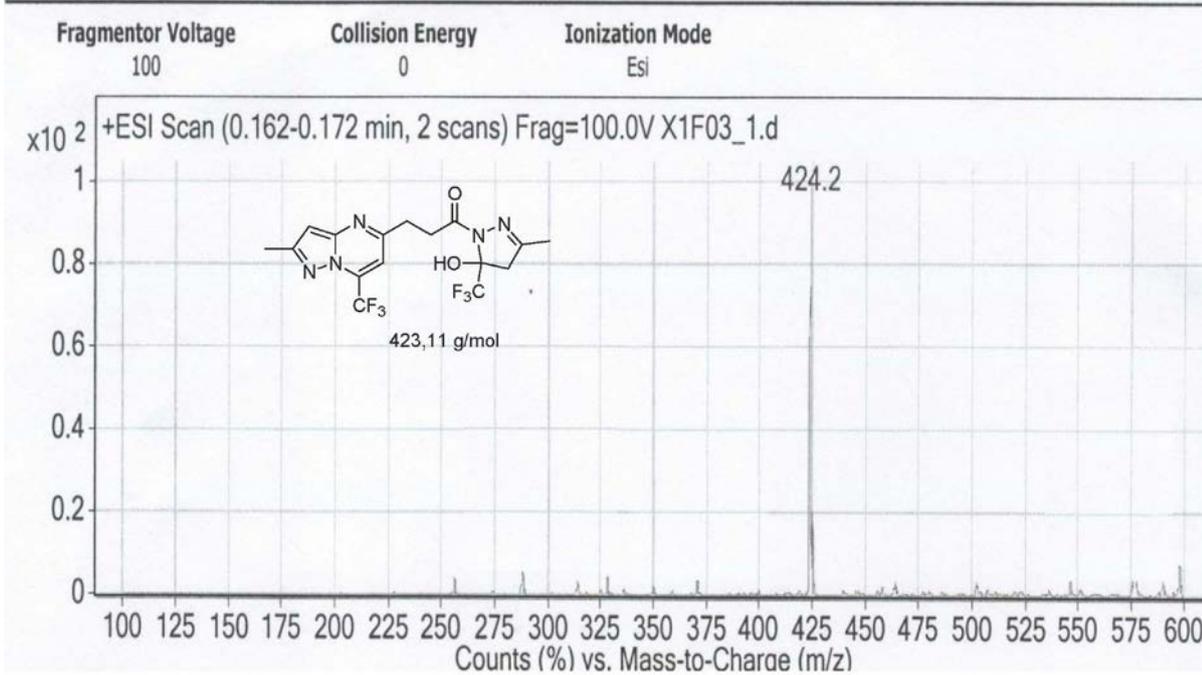


Figure S15. ESI mass spectrum of 5-[(5-trifluoromethyl-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4b**).

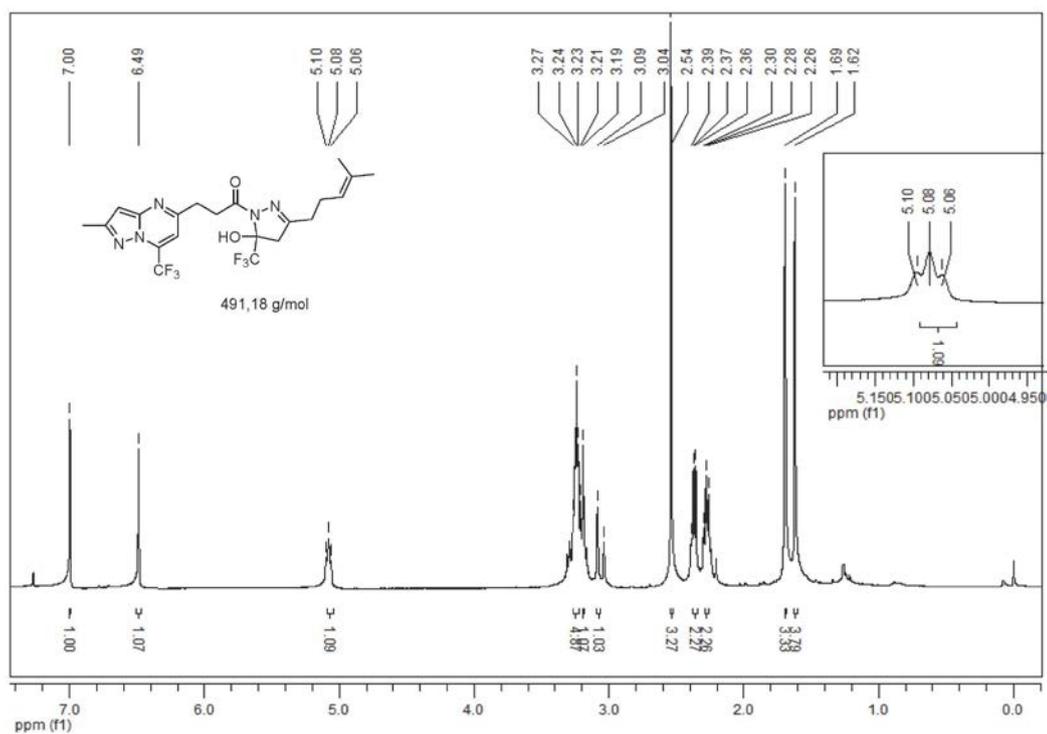


Figure S16. ¹H NMR spectrum (CDCl₃, 400 MHz) of 5-[(5-(trifluoromethyl)-5-hydroxy-3-(2-methylpent-3-enyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4c**).

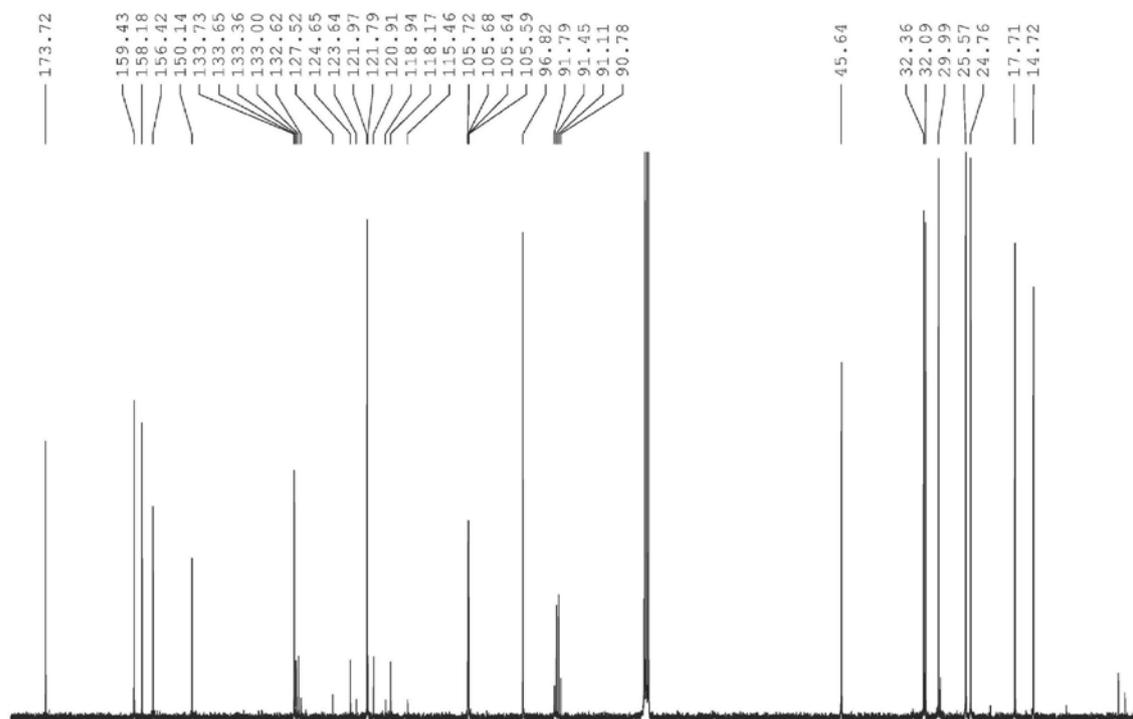


Figure S17. ¹³C NMR spectrum (CDCl₃, 100 MHz) of 5-[(5-(trifluoromethyl)-5-hydroxy-3-(2-methylpent-3-enyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4c**).

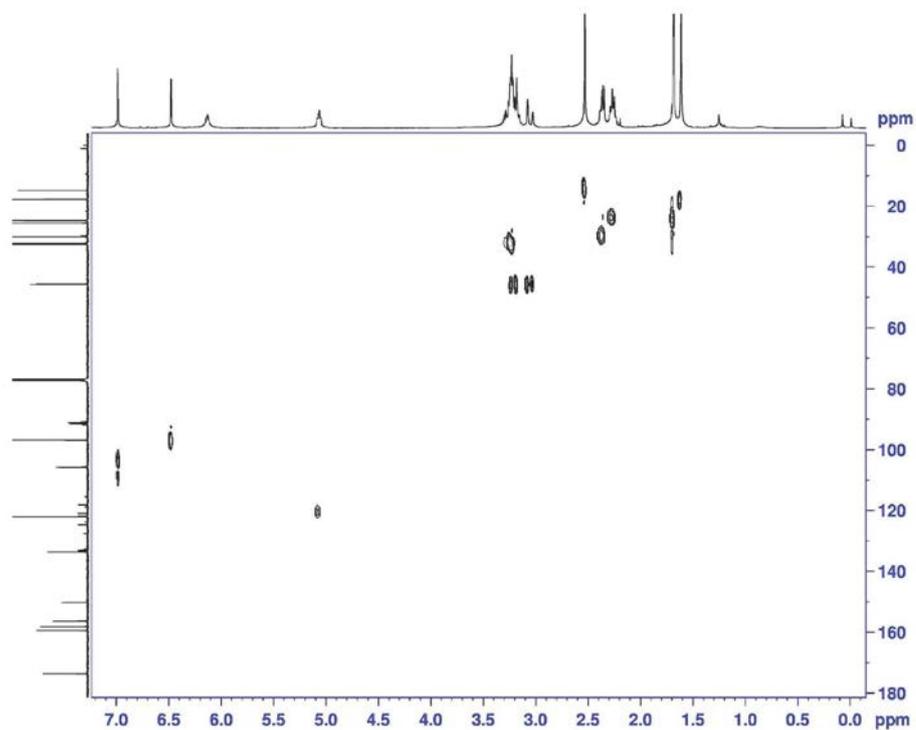


Figure S18. HSQC spectrum (CDCl₃, 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(2-methylpent-3-enyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4c**).

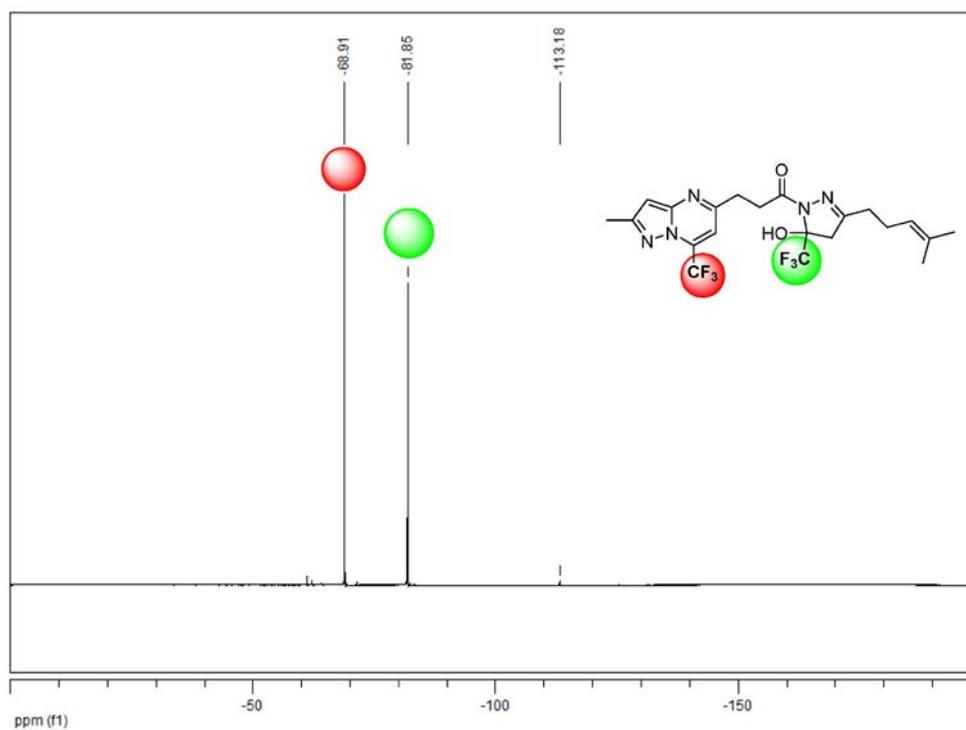


Figure S19. ¹⁹F NMR spectrum (CDCl₃, 376.4 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(2-methylpent-3-enyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4c**).

User Spectra

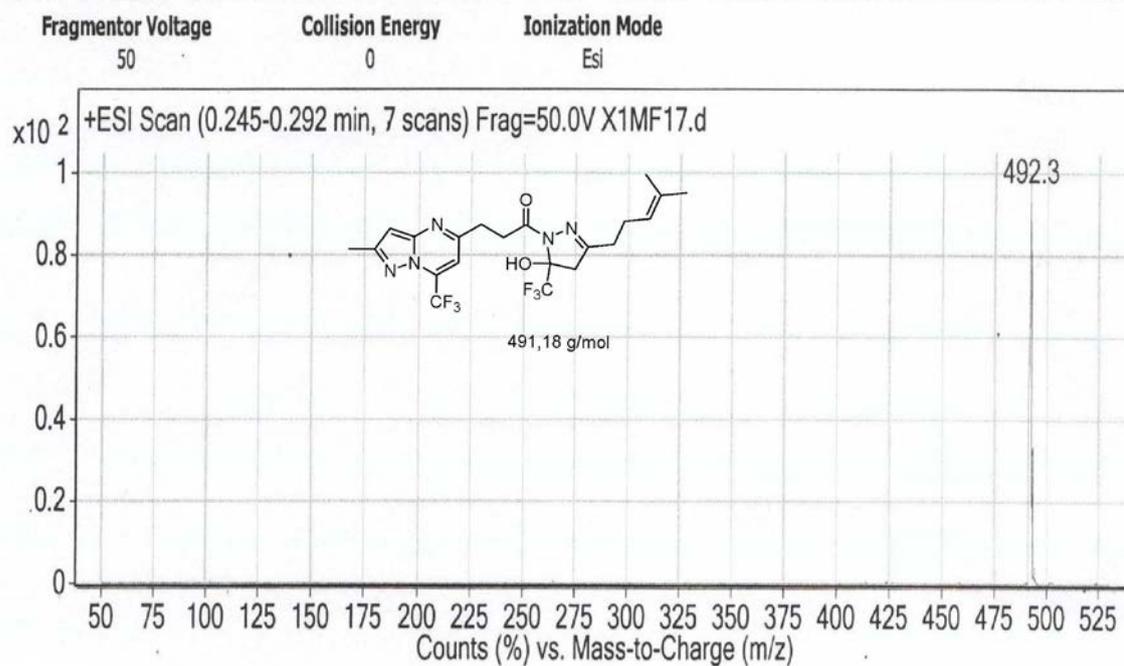


Figure S20. ESI mass spectrum of 5-[(5-trifluoromethyl-5-hydroxy-3-(2-methylpent-3-enyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4c**).

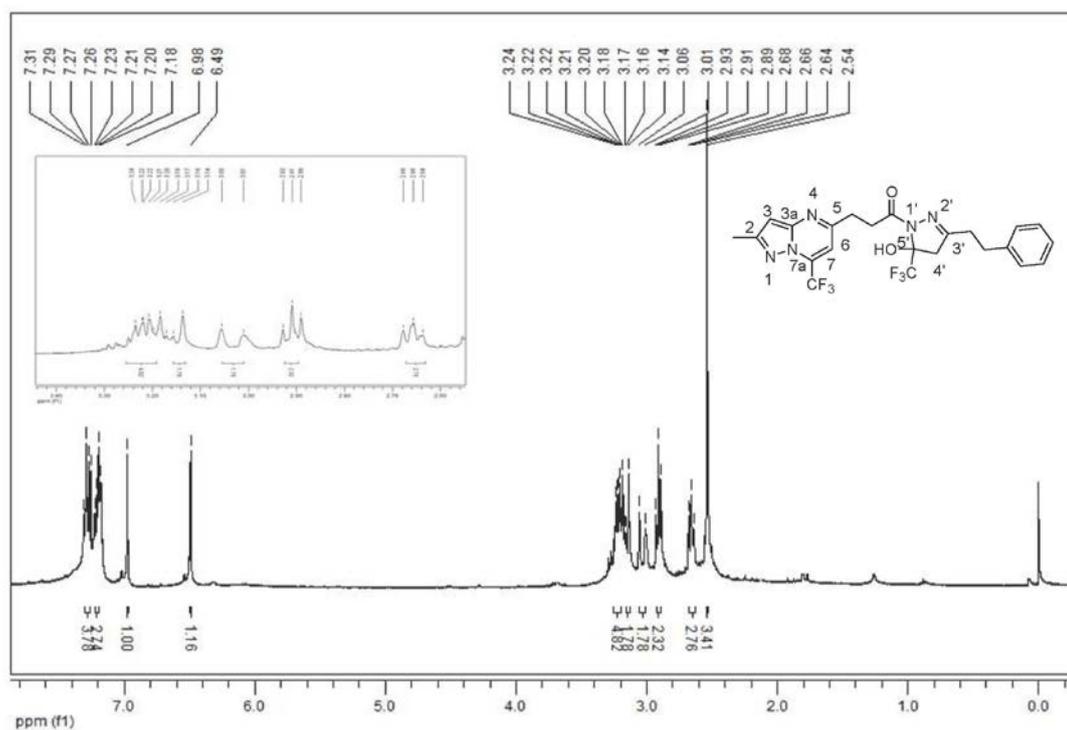


Figure S21. ^1H NMR spectrum (CDCl_3 , 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(2-phenylethyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4d**).

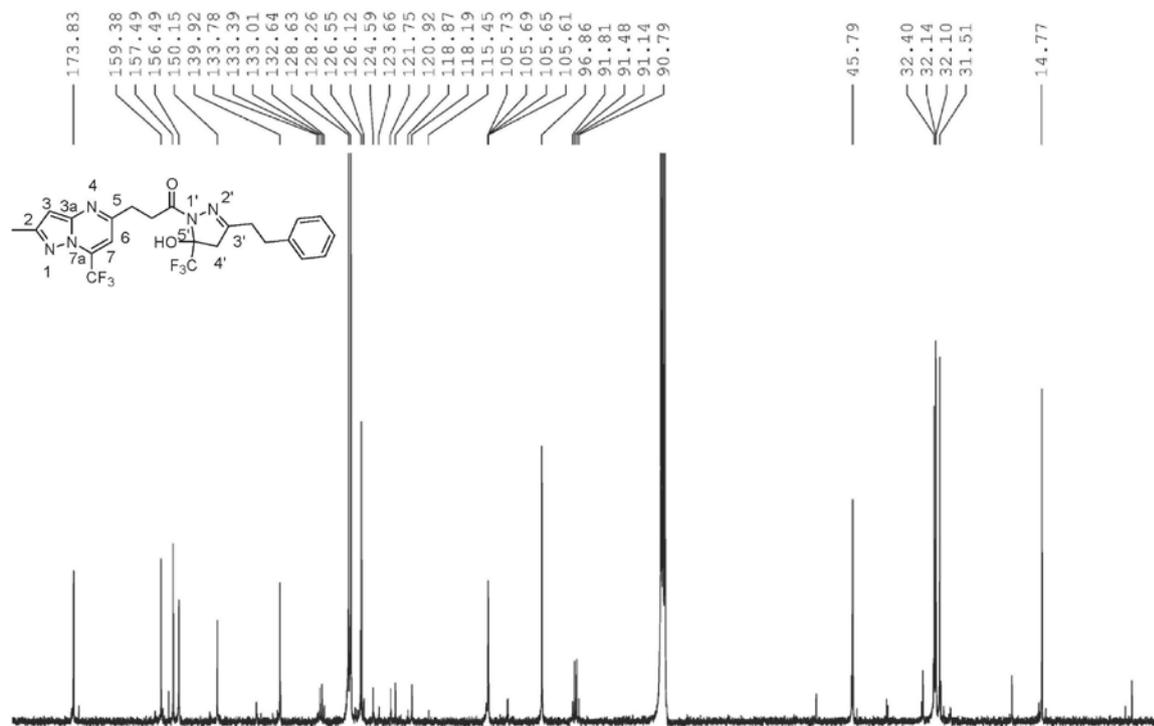


Figure S22. ^{13}C NMR spectrum (CDCl_3 , 100 MHz) of 5-[(5-(trifluoromethyl)-5-hydroxy-3-(2-phenylethyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4d**).

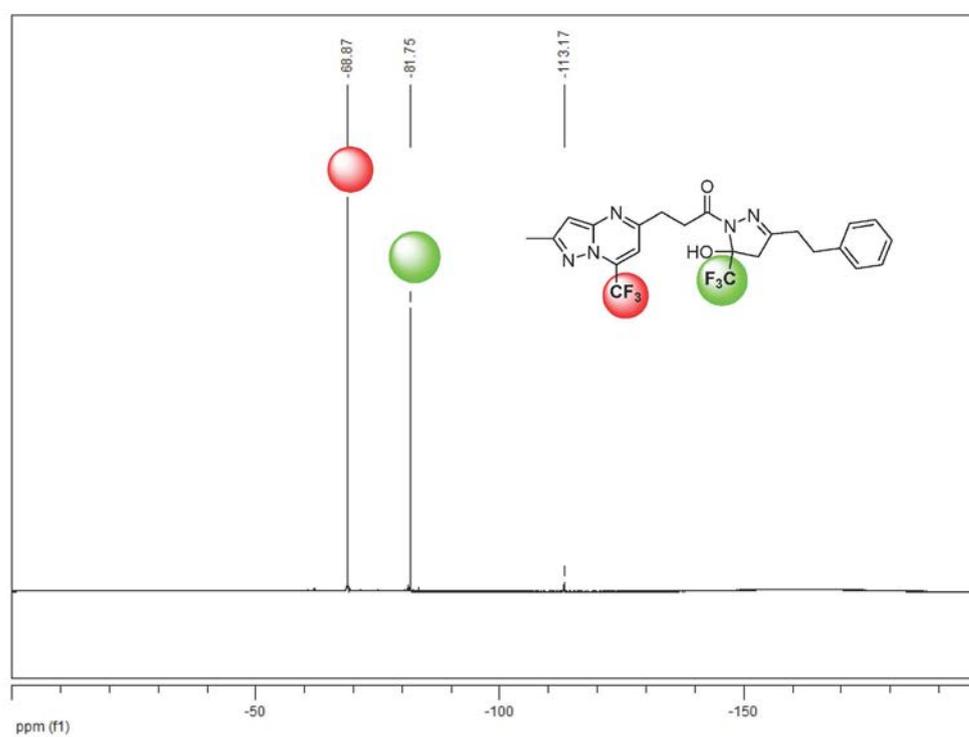


Figure S23. ^{19}F NMR spectrum (CDCl_3 , 376.4 MHz) of 5-[(5-(trifluoromethyl)-5-hydroxy-3-(2-phenylethyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4d**).

User Spectra

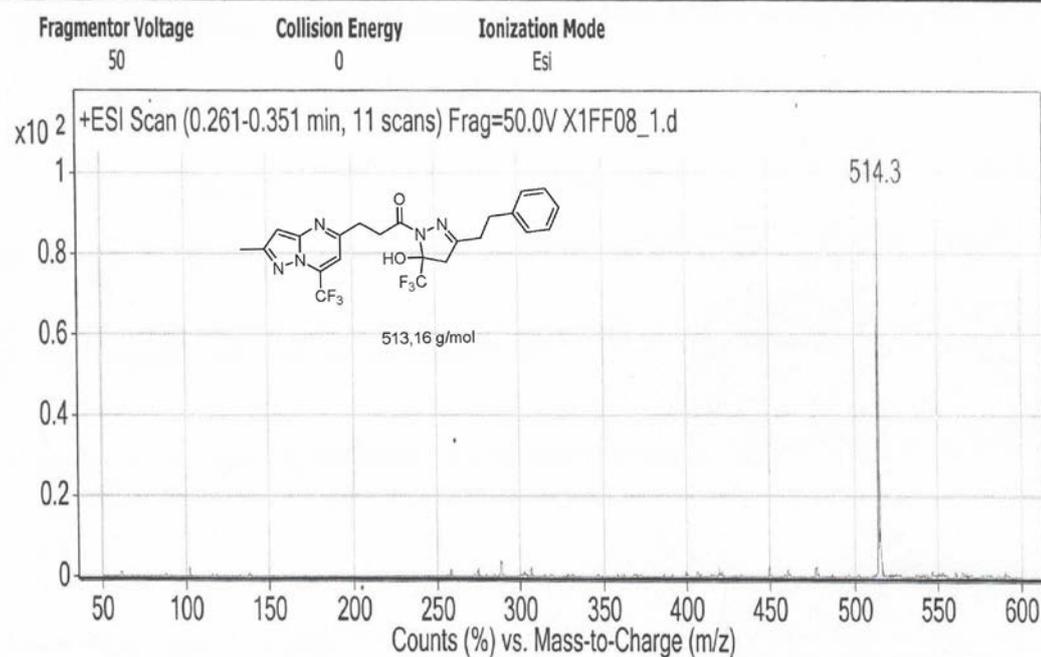


Figure S24. ESI mass spectrum of 5-[(5-trifluoromethyl-5-hydroxy-3-(2-phenylethyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4d**).

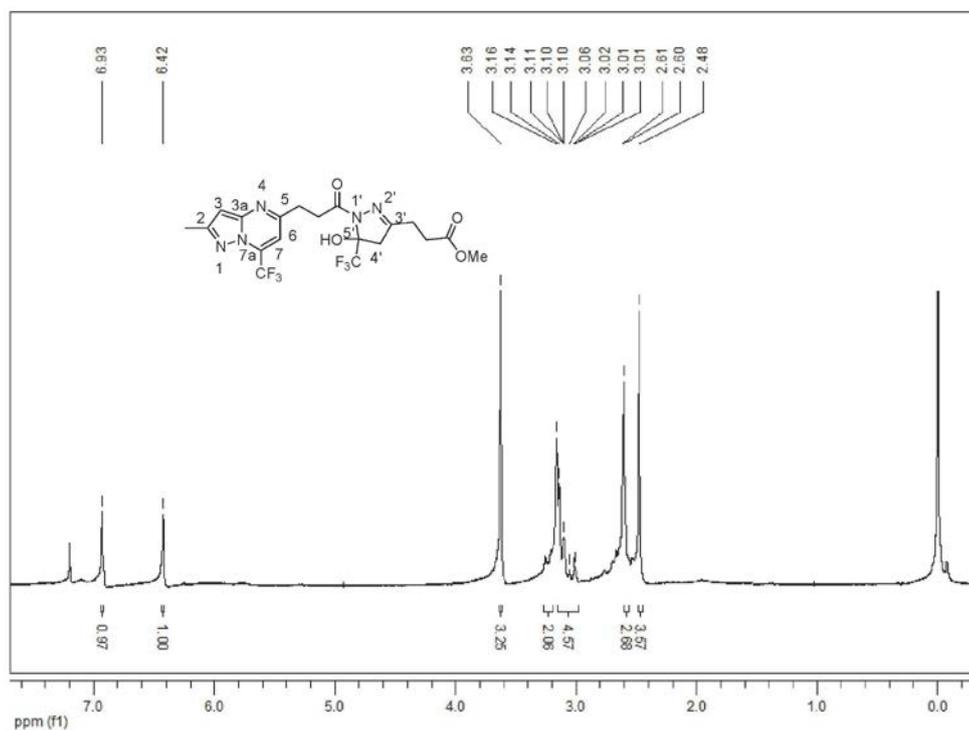


Figure S25. ¹H NMR spectrum (CDCl₃, 400 MHz) of methyl 3-(5-hydroxy-1-(3-(2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidin-5-yl)propa noyl)-5-trifluoromethyl-4,5-dihydro-1H-pyrazol-3-yl)propanoate (**4e**).

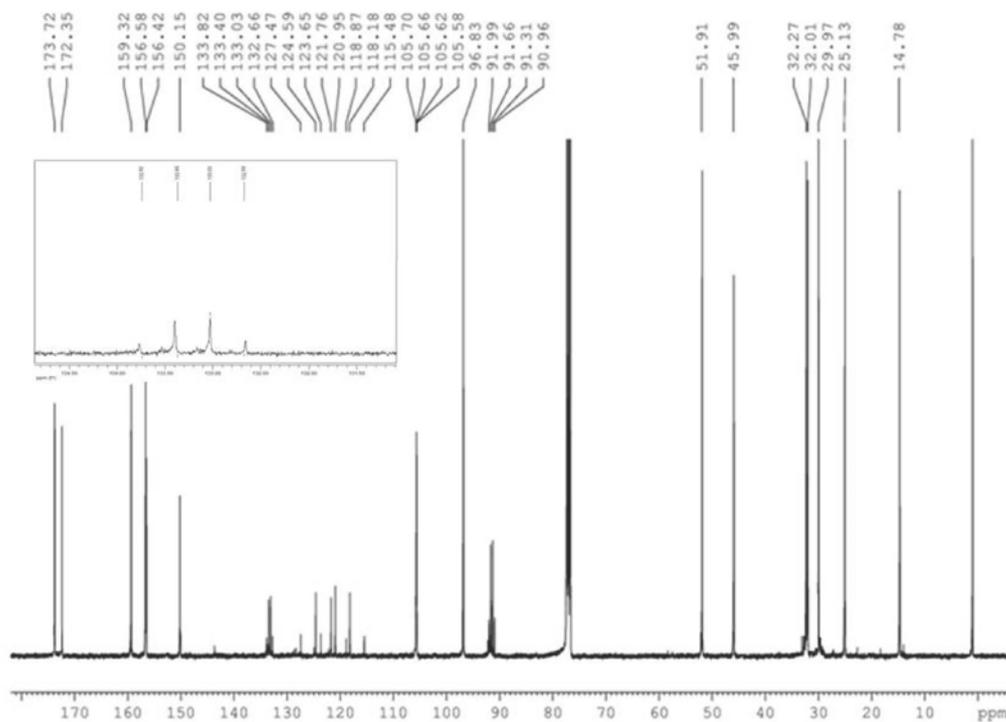


Figure S26. ^{13}C NMR spectrum (CDCl_3 , 100 MHz) of methyl 3-(5-hydroxy-1-(3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propa noyl)-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-3-yl)propanoate (**4e**).

User Spectra

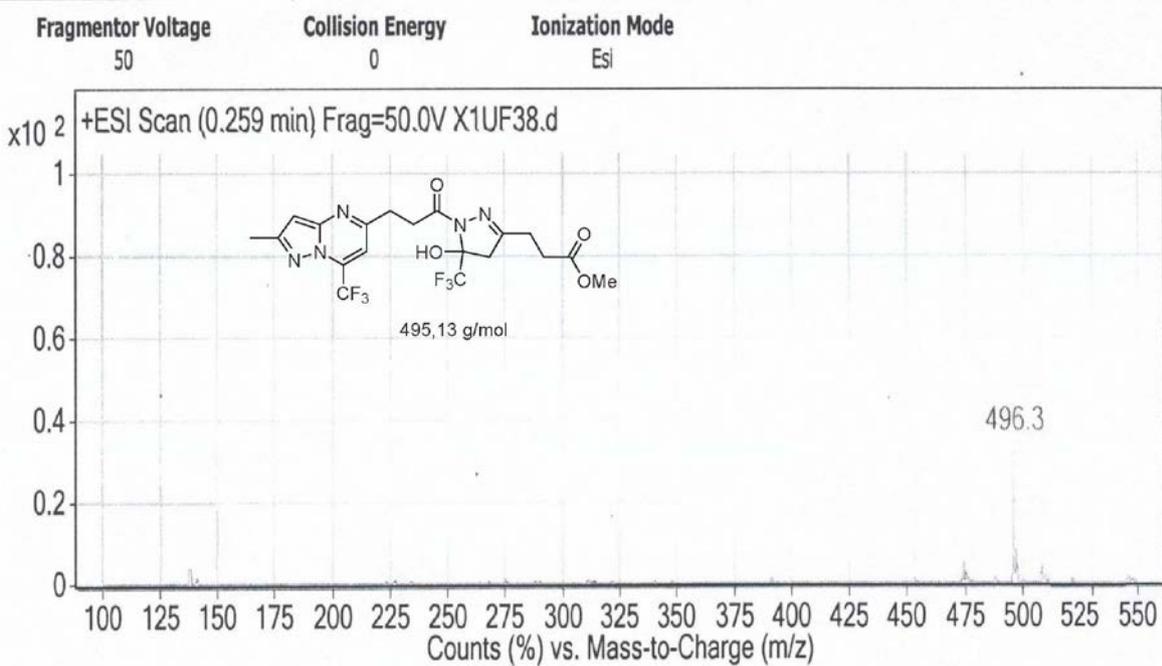


Figure S27. ESI mass spectrum of methyl 3-(5-hydroxy-1-(3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propa noyl)-5-trifluoromethyl-4,5-dihydro-1*H*-pyrazol-3-yl)propanoate (**4e**).

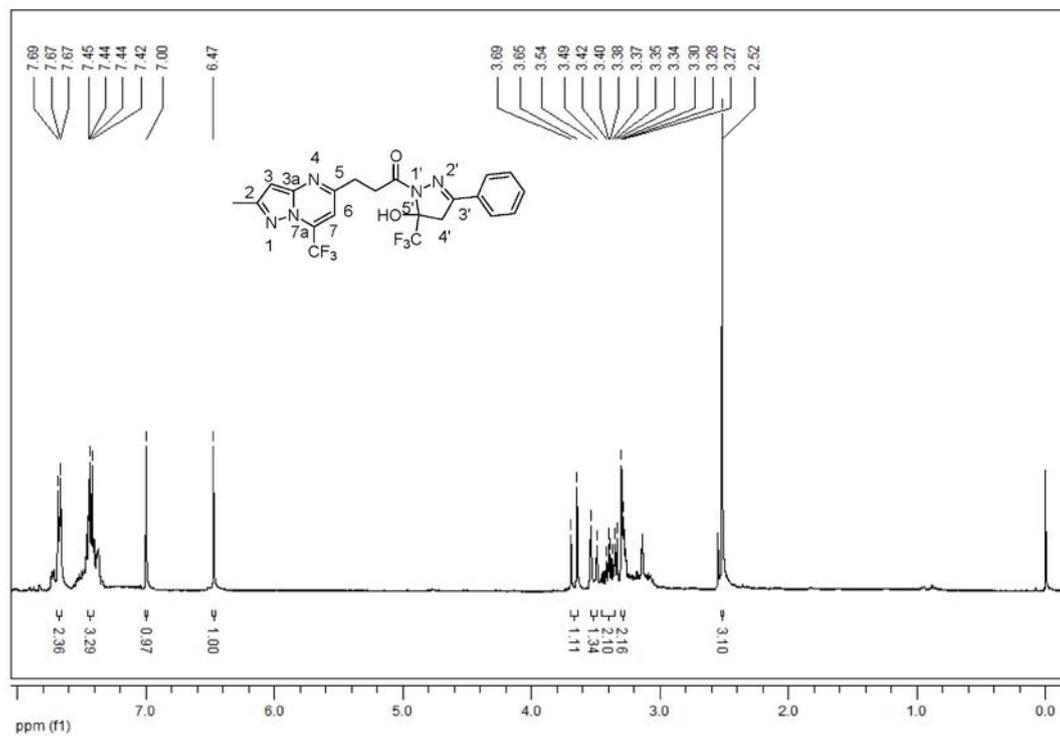


Figure S28. ^1H NMR spectrum (CDCl₃, 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4f**).

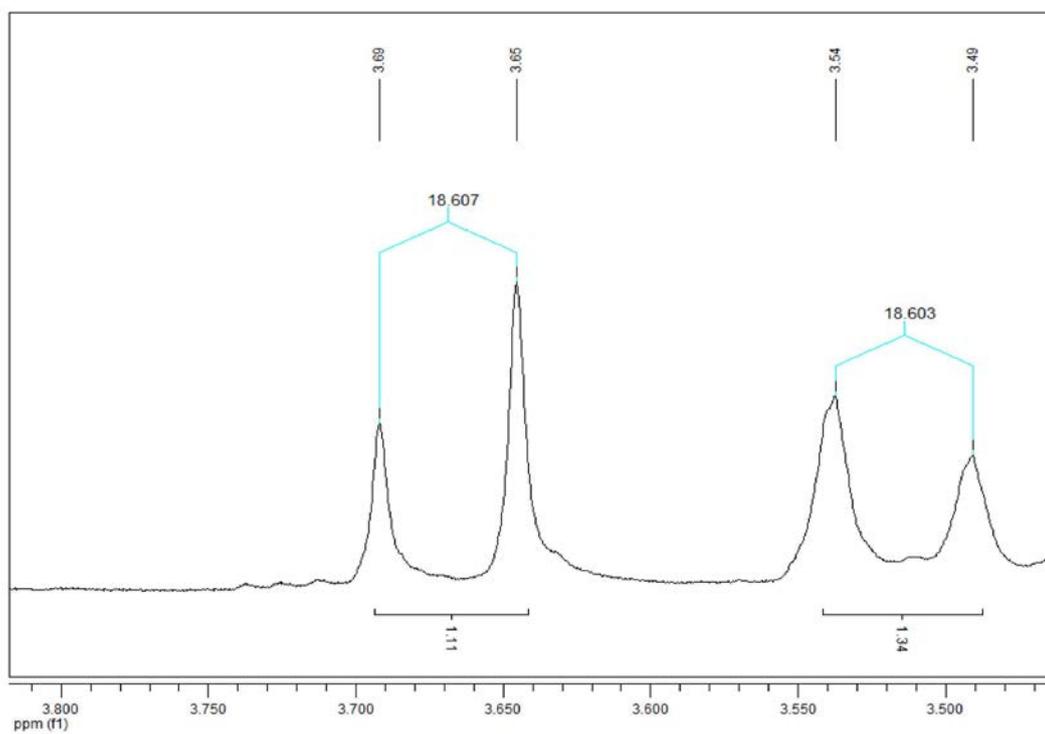


Figure S29. ^1H NMR spectrum (CDCl₃, 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4f**). Expanded between 3.47–3.82 ppm.

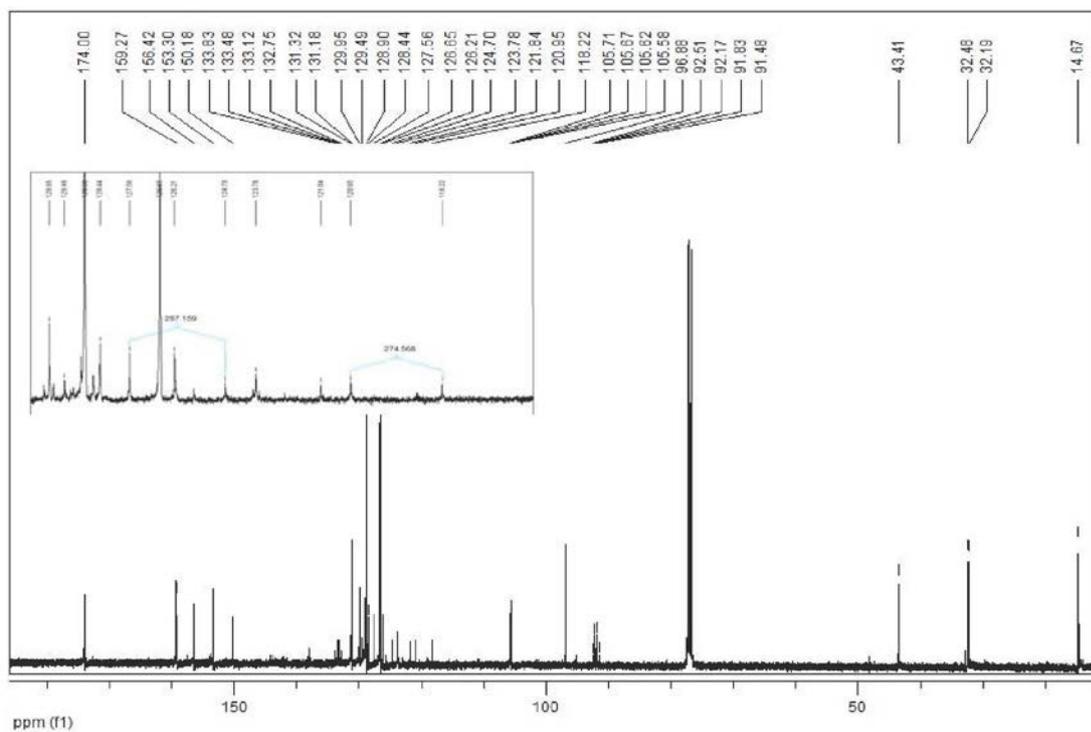


Figure S30. ¹³C NMR spectrum (CDCl₃, 100 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4f**).

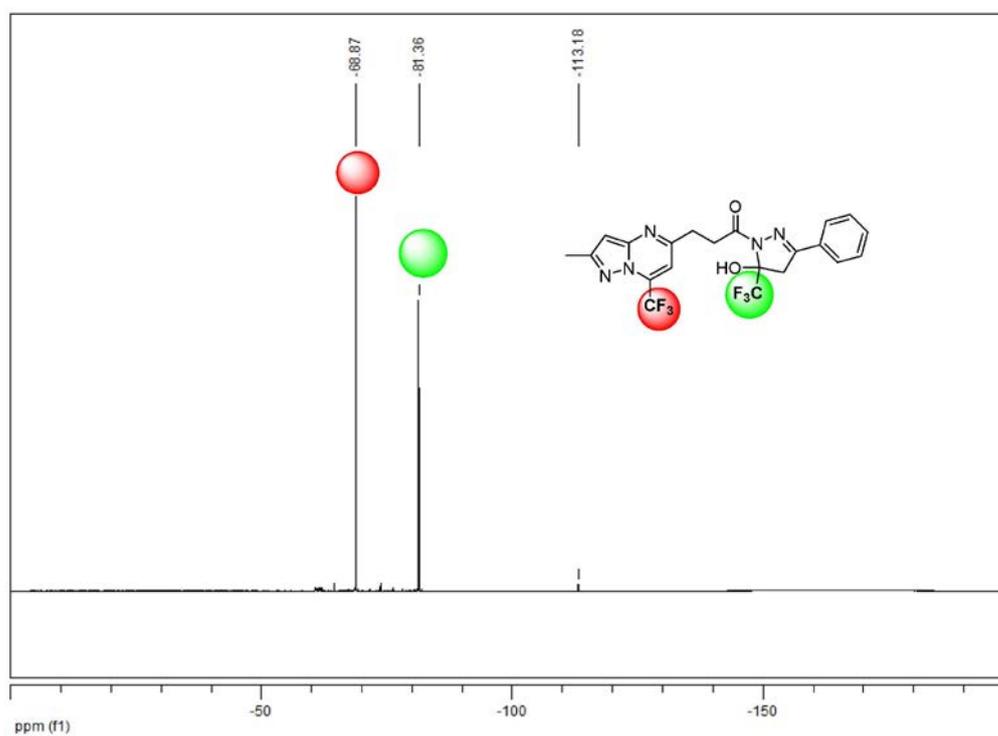


Figure S31. ¹⁹F NMR spectrum (CDCl₃, 376.4 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4f**).

User Spectra

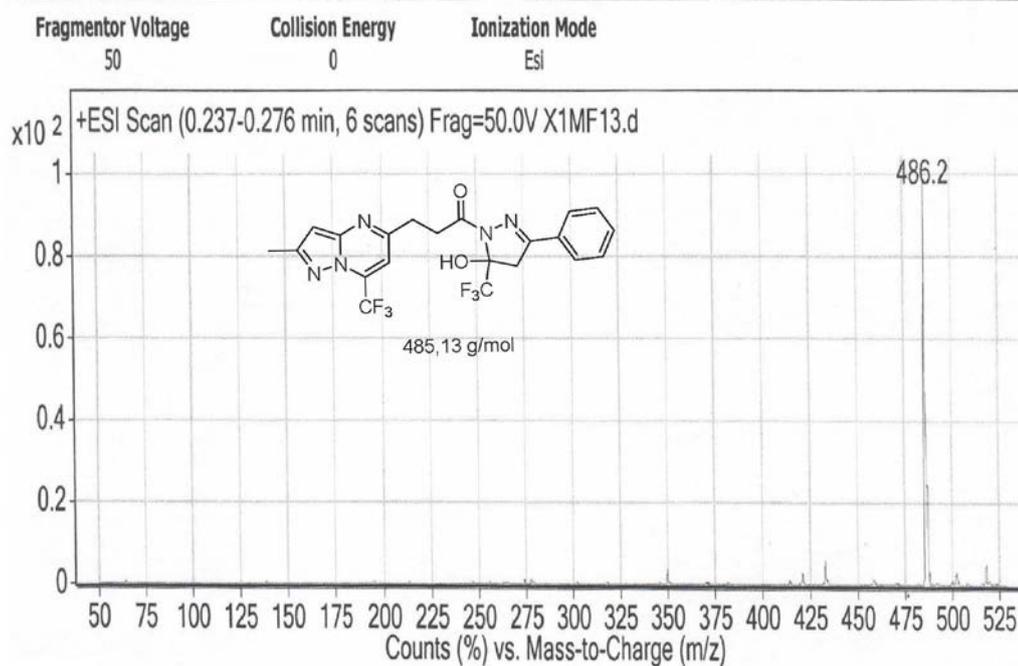


Figure S32. ESI mass spectrum 5-[(5-trifluoromethyl-5-hydroxy-3-phenyl-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4f**).

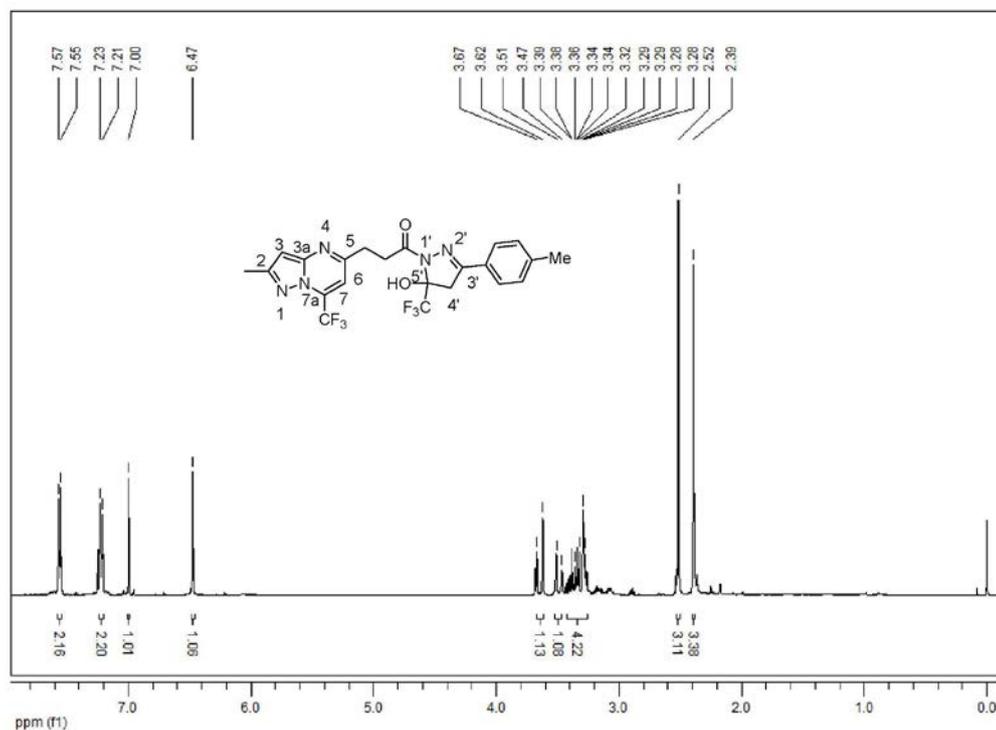


Figure S33. ¹H NMR spectrum (CDCl₃, 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(4-methylphenyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4g**).

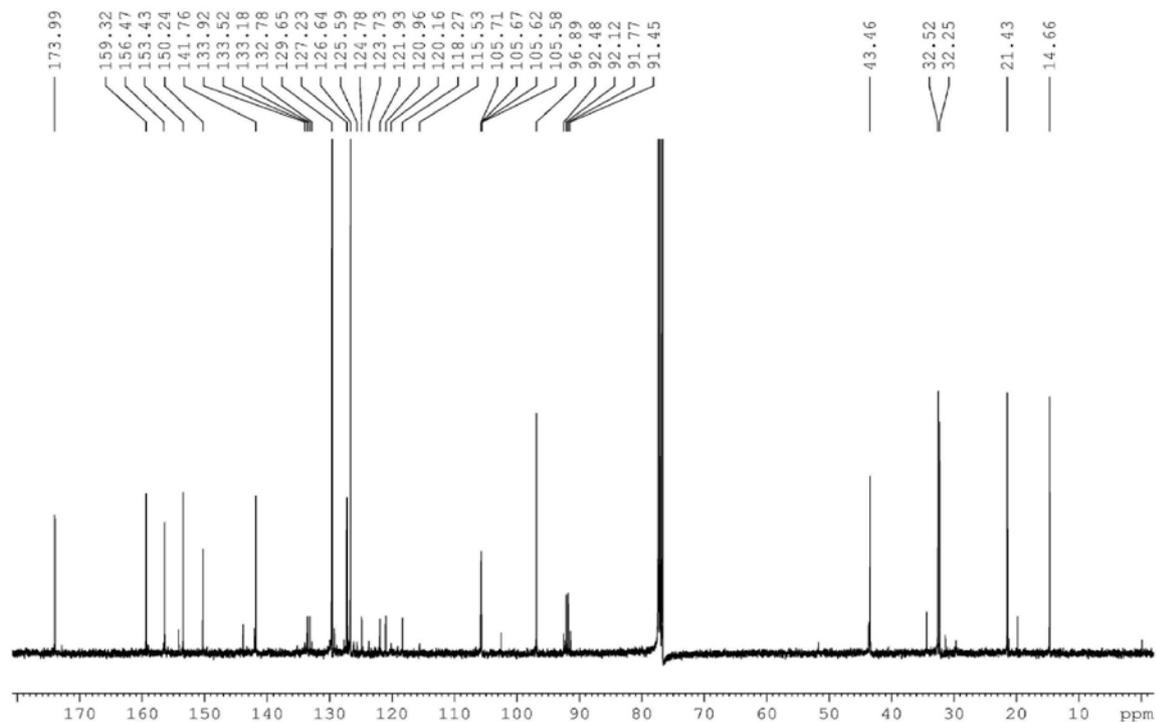


Figure S34. ^{13}C NMR spectrum (CDCl_3 , 100 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4g**).

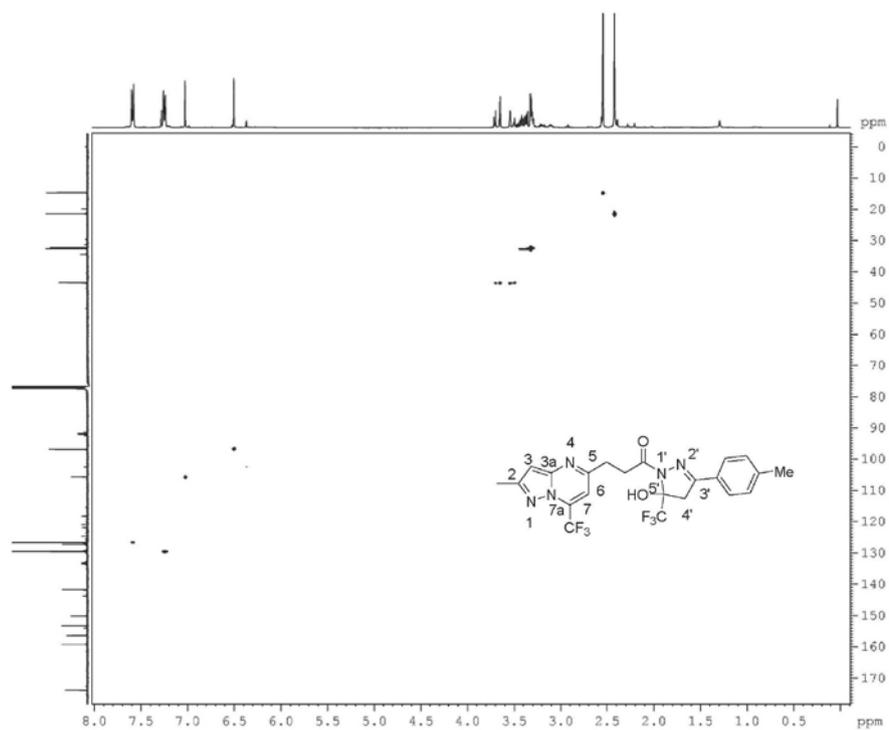


Figure S35. HSQC spectrum (CDCl_3 , 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4g**).

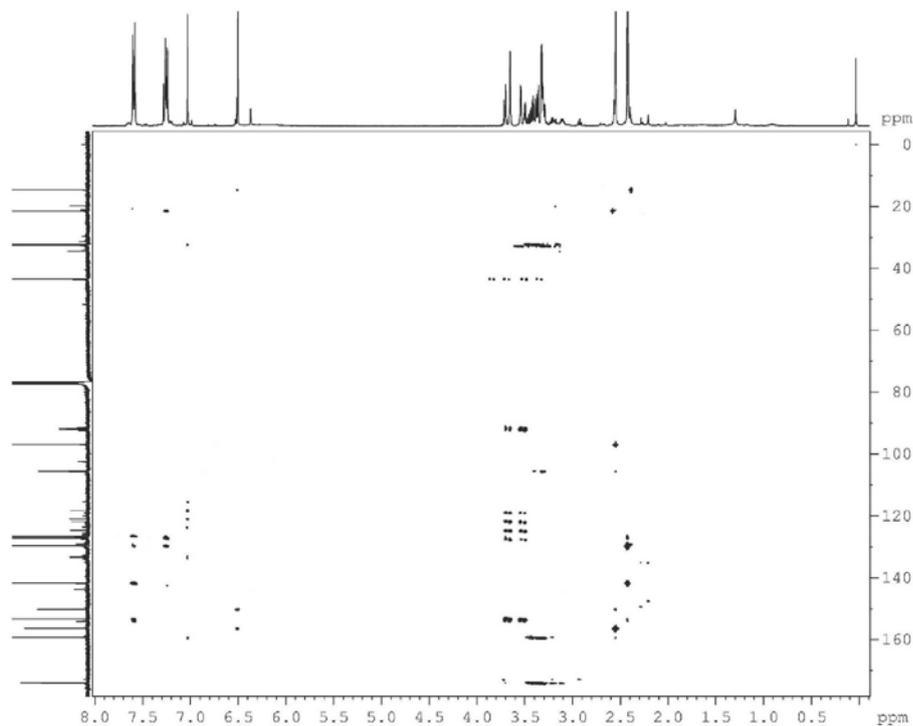


Figure S36. HMBC spectrum (CDCl₃, 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4g**).

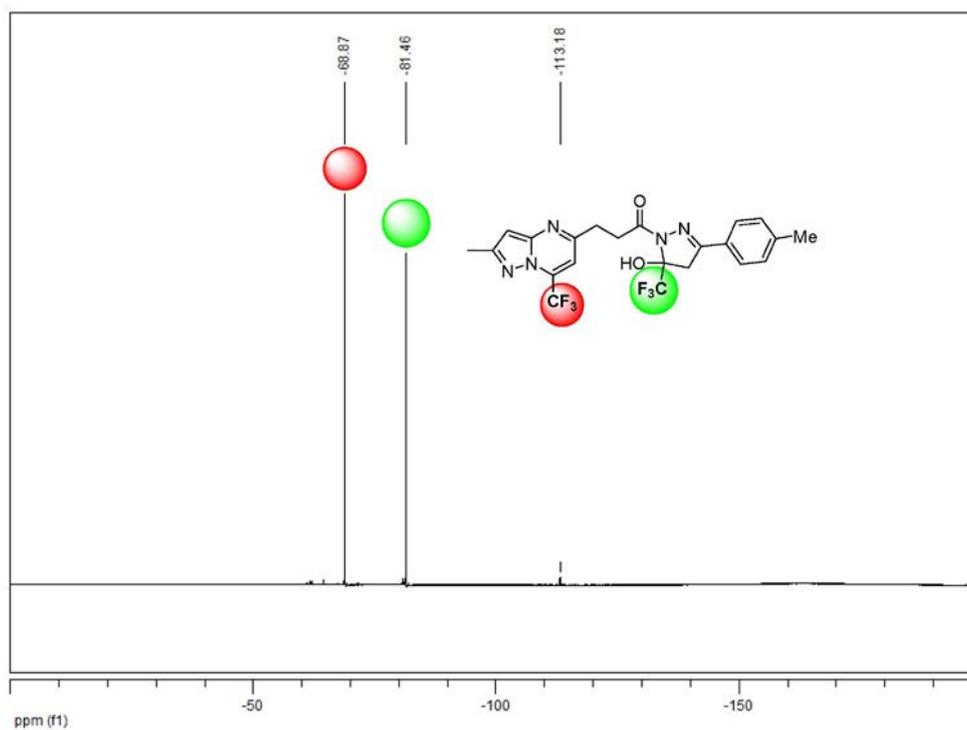


Figure S37. ¹⁹F NMR spectrum (CDCl₃, 376.4 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4g**).

User Spectra

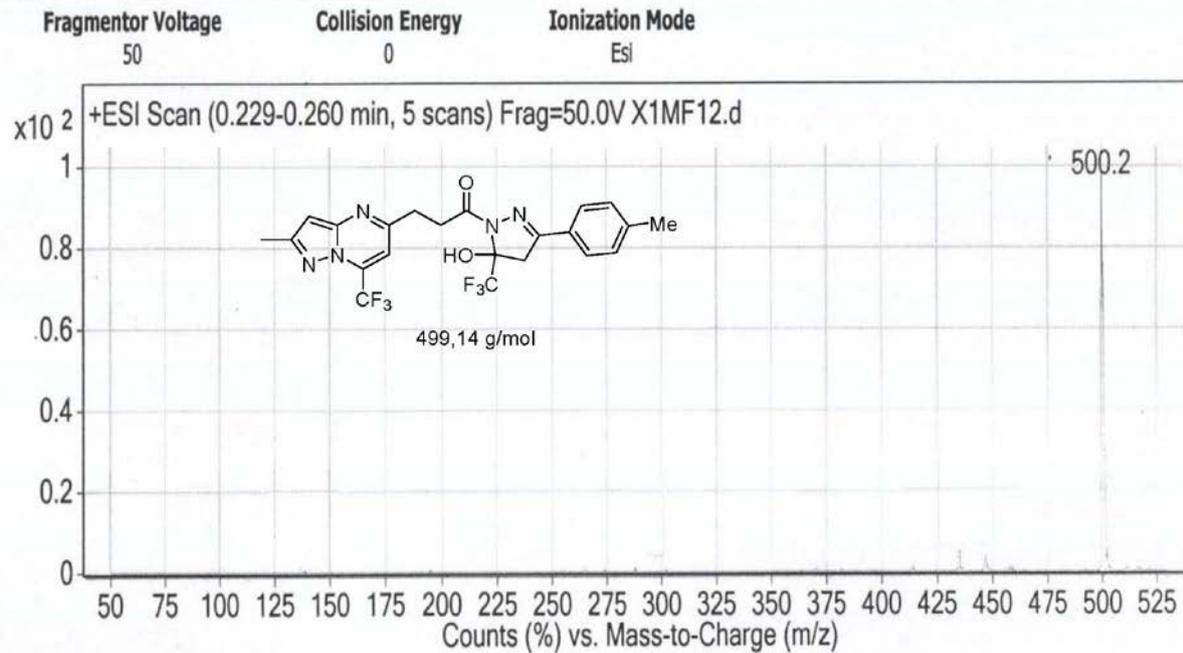


Figure S38. ESI mass spectrum of 5-[(5-trifluoromethyl-5-hydroxy-3-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (4g).

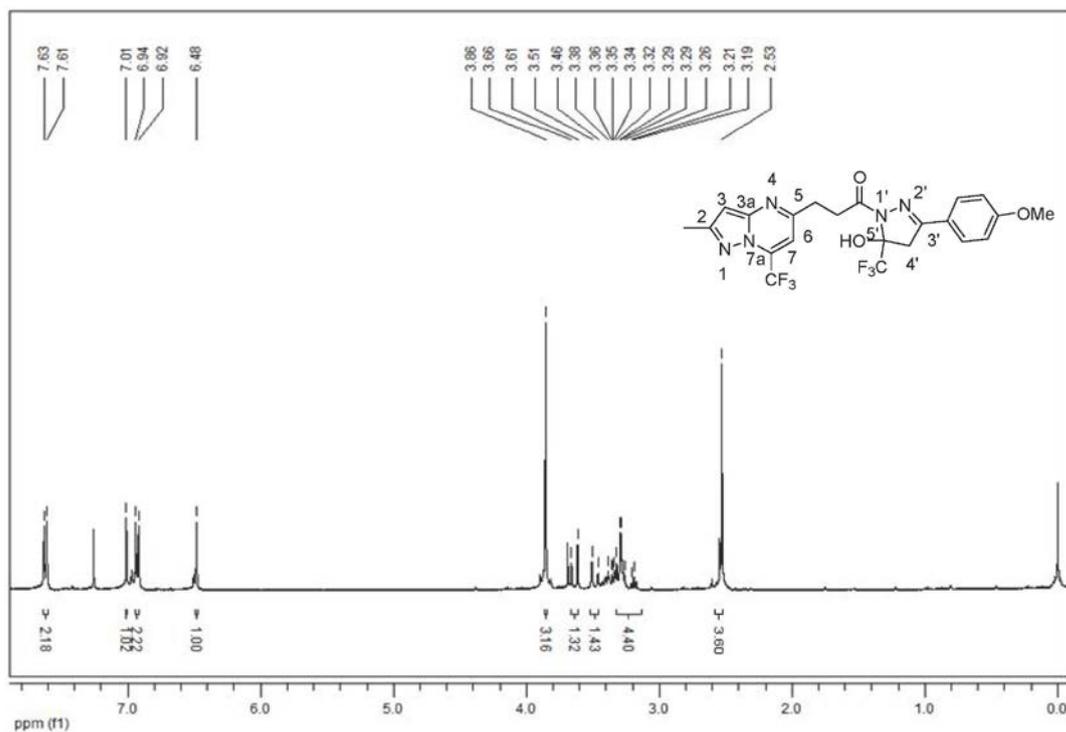


Figure S39. ¹H NMR spectrum (CDCl₃, 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (4h).

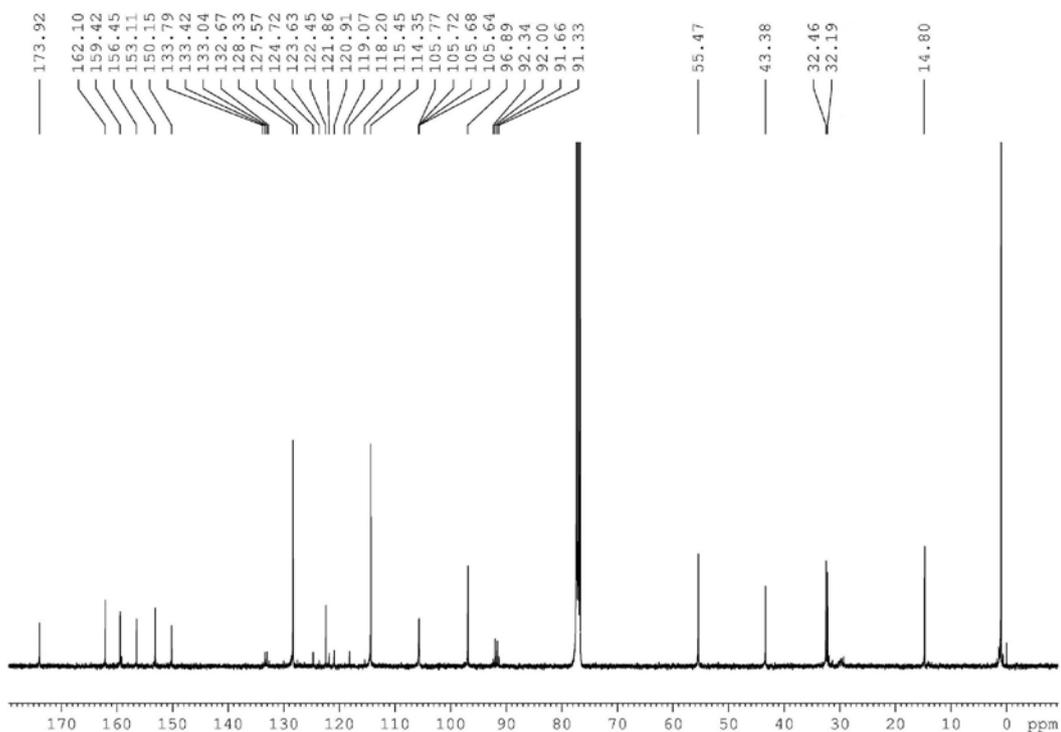


Figure S40. ¹³C NMR spectrum (CDCl₃, 100 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4h**).

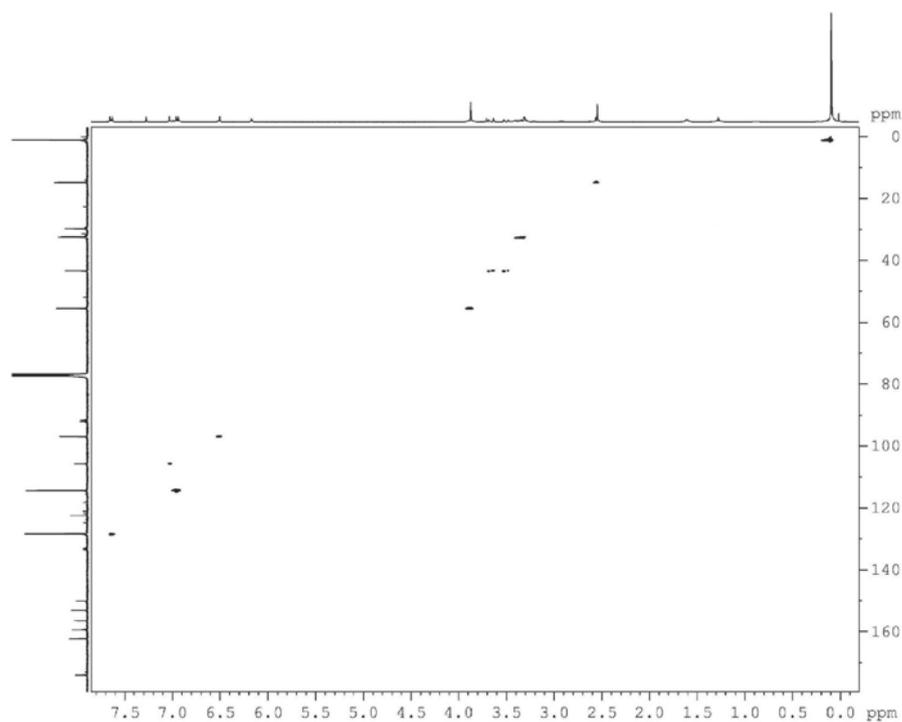


Figure S41. HSQC spectrum (CDCl₃, 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4h**).

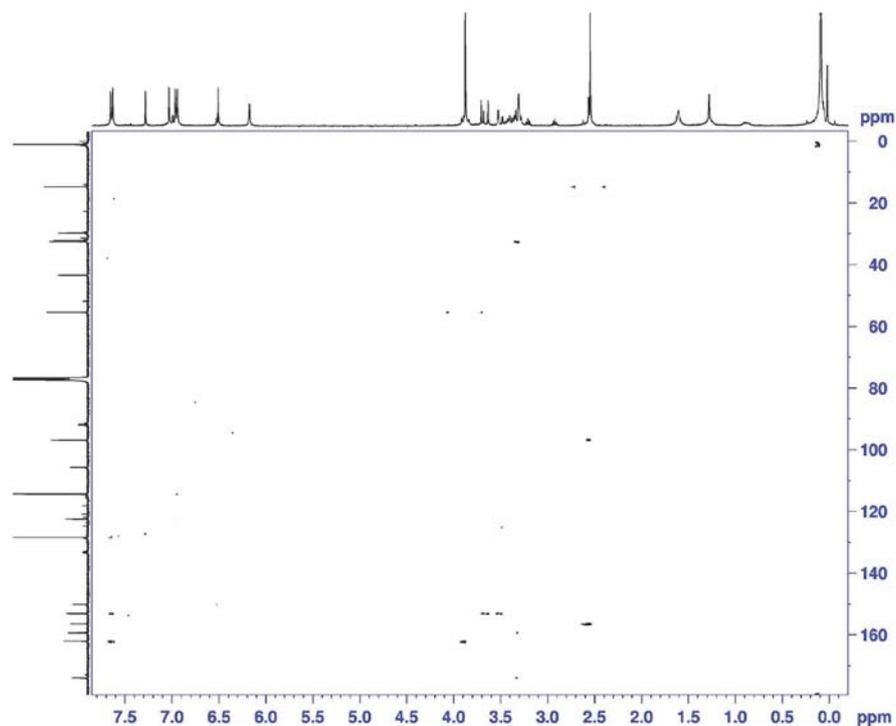


Figure S42. HMBC spectrum (CDCl₃, 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4h**).

User Spectra

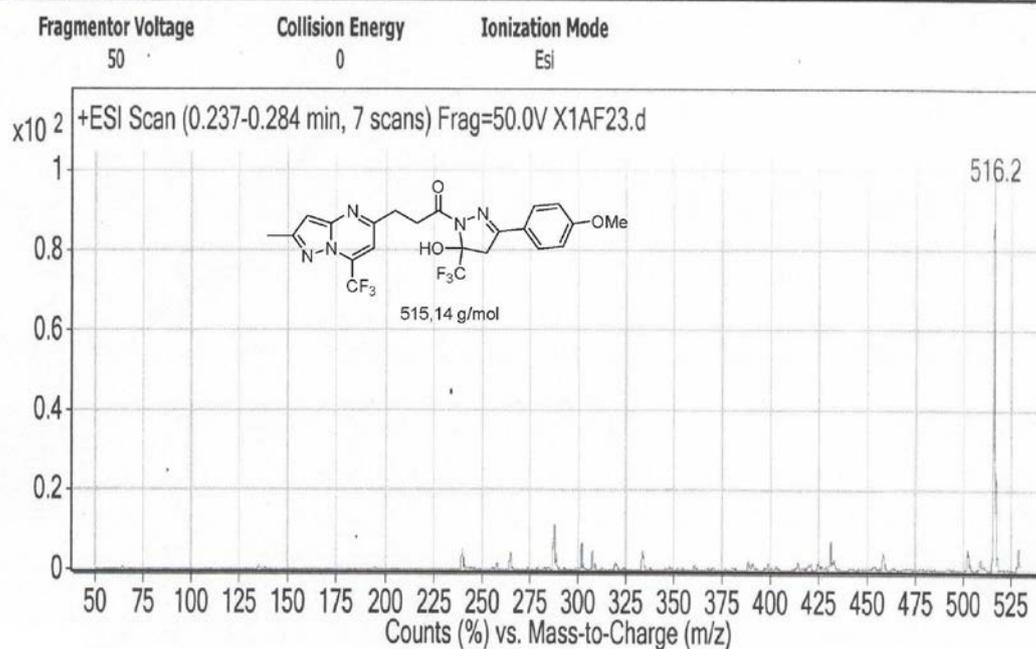


Figure S43. ESI mass spectrum of 5-[(5-trifluoromethyl-5-hydroxy-3-(4-methoxyphenyl)-4,5-dihydro-1H-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4h**).

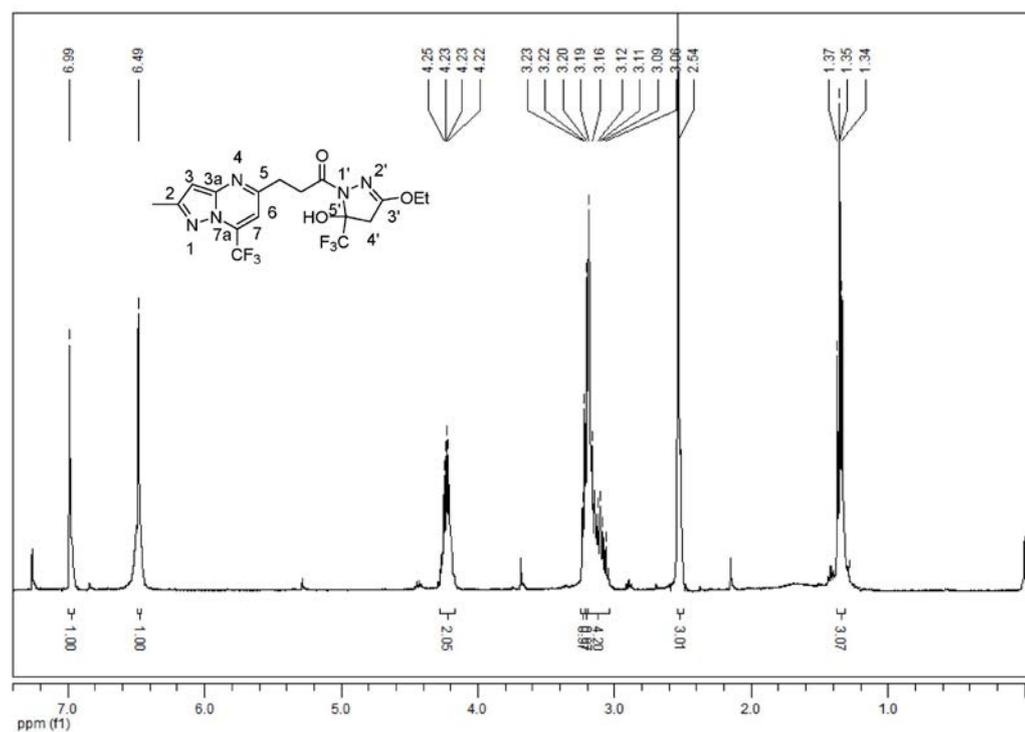


Figure S44. ^1H NMR spectrum (CDCl_3 , 400 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-ethoxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4i**).

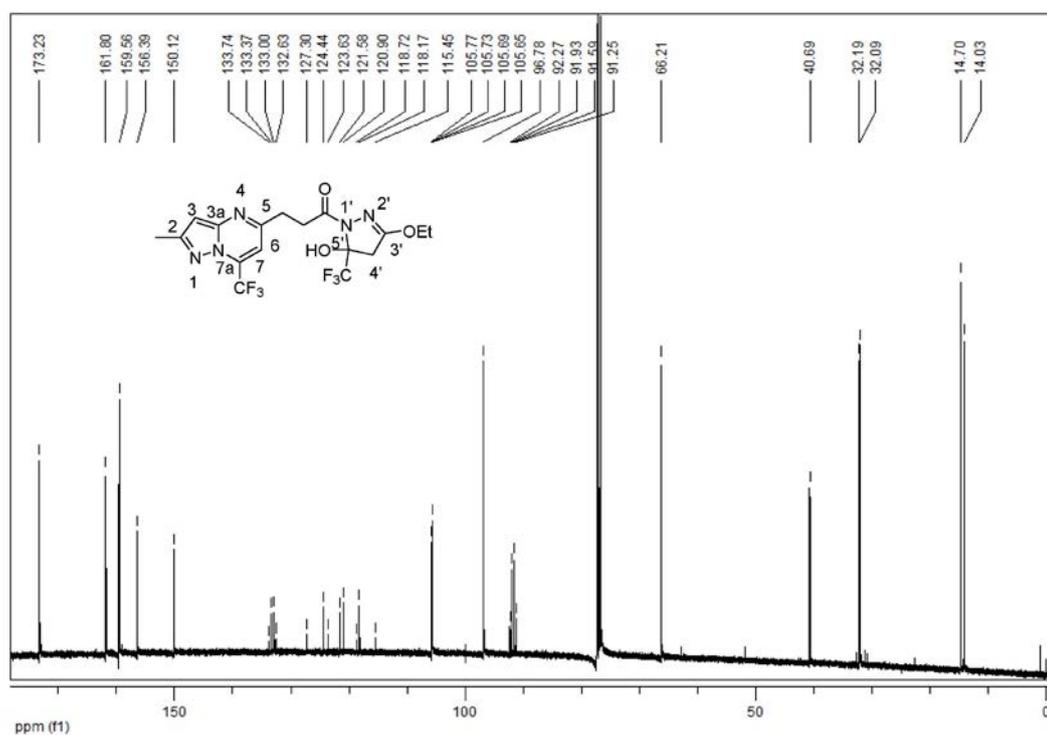


Figure S45. ^{13}C NMR spectrum (CDCl_3 , 100 MHz) of 5-[(5-trifluoromethyl-5-hydroxy-3-ethoxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4i**).

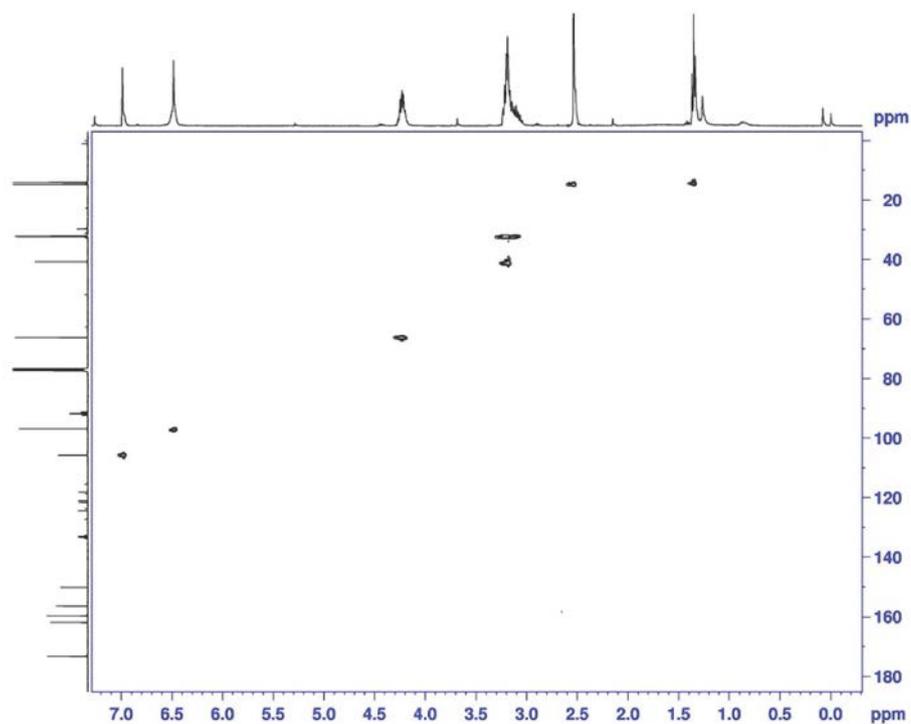


Figure S46. HSQC spectrum (CDCl₃, 400 MHz) of 5-[(3-ethoxy-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4i**).

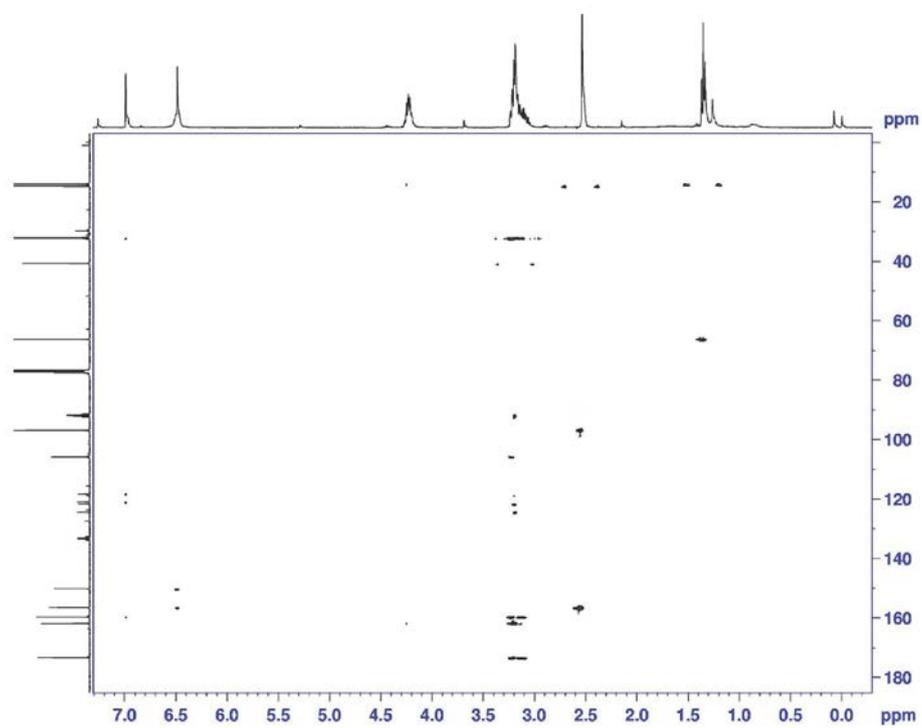


Figure S47. HMBC spectrum (CDCl₃, 400 MHz) of 5-[(3-ethoxy-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4i**).

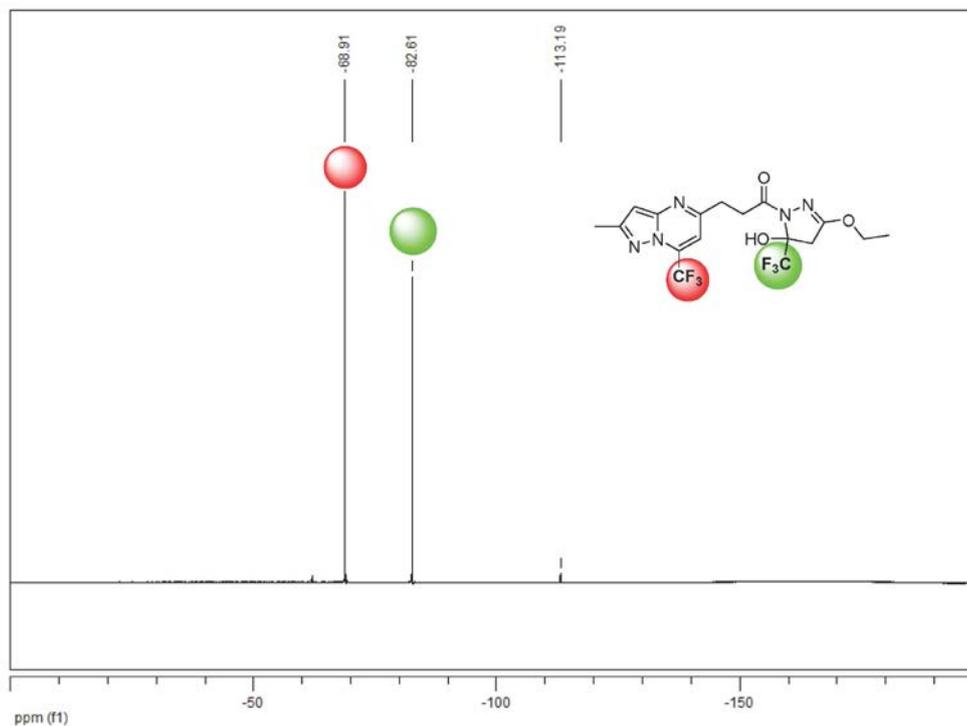


Figure S48. ^{19}F NMR spectrum (CDCl_3 , 376.4 MHz) of 5-[(3-ethoxy-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4i**).

User Spectra

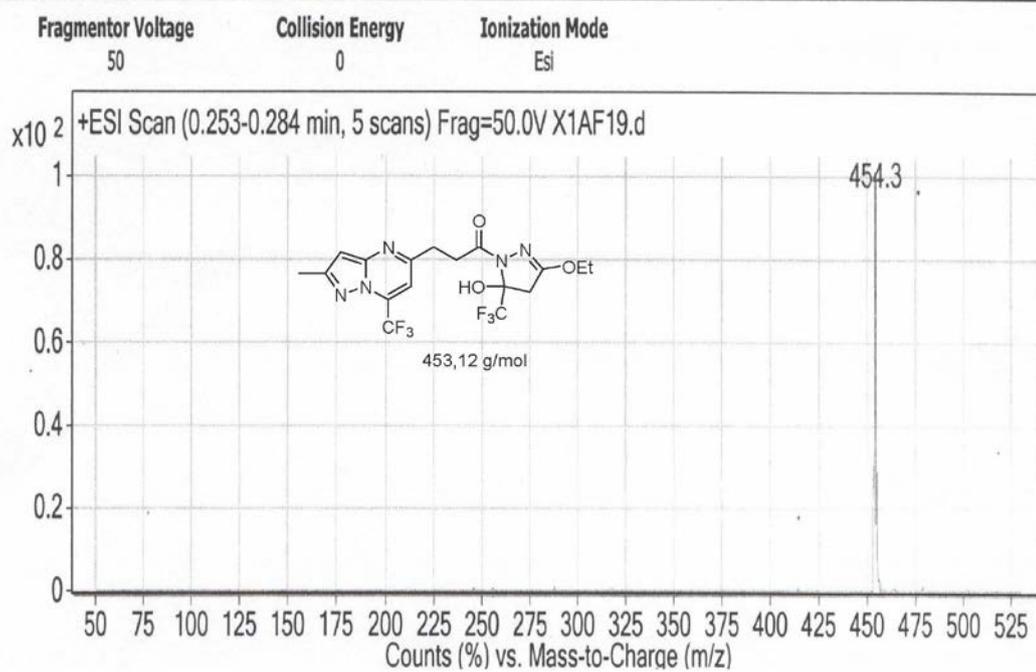


Figure S49. ESI mass spectrum of 5-[(3-ethoxy-5-trifluoromethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4i**).

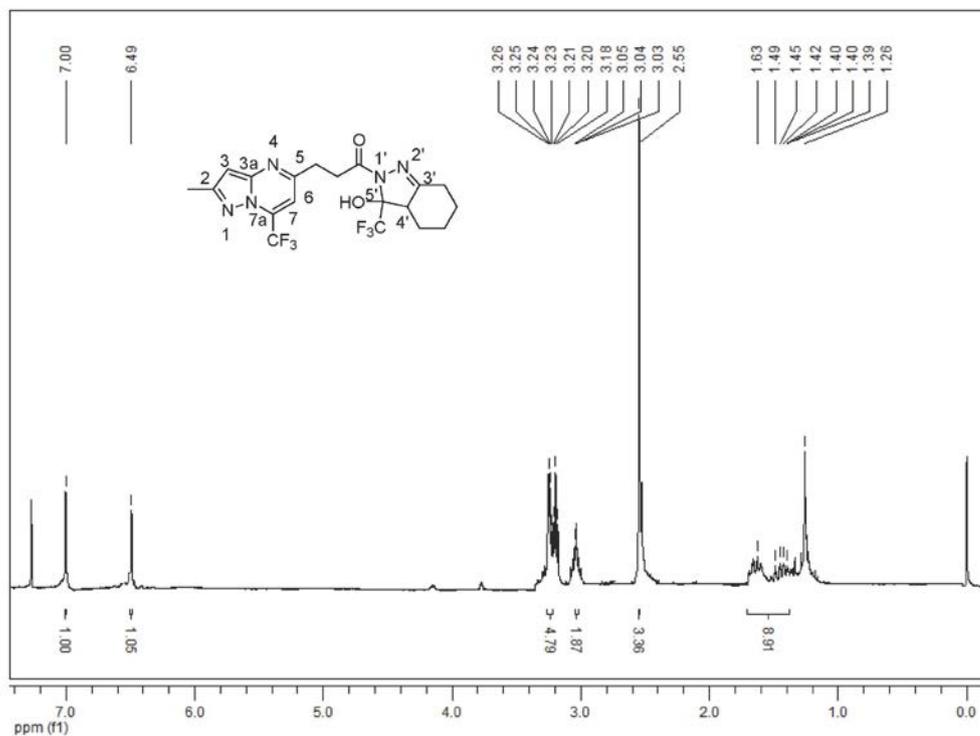


Figure S50. ^1H NMR spectrum (CDCl_3 , 400 MHz) of 5-[1-(3-hydroxy-3-trifluoromethyl-3,3a,4,5,6,7-hexahydroindazol-2-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4j**).

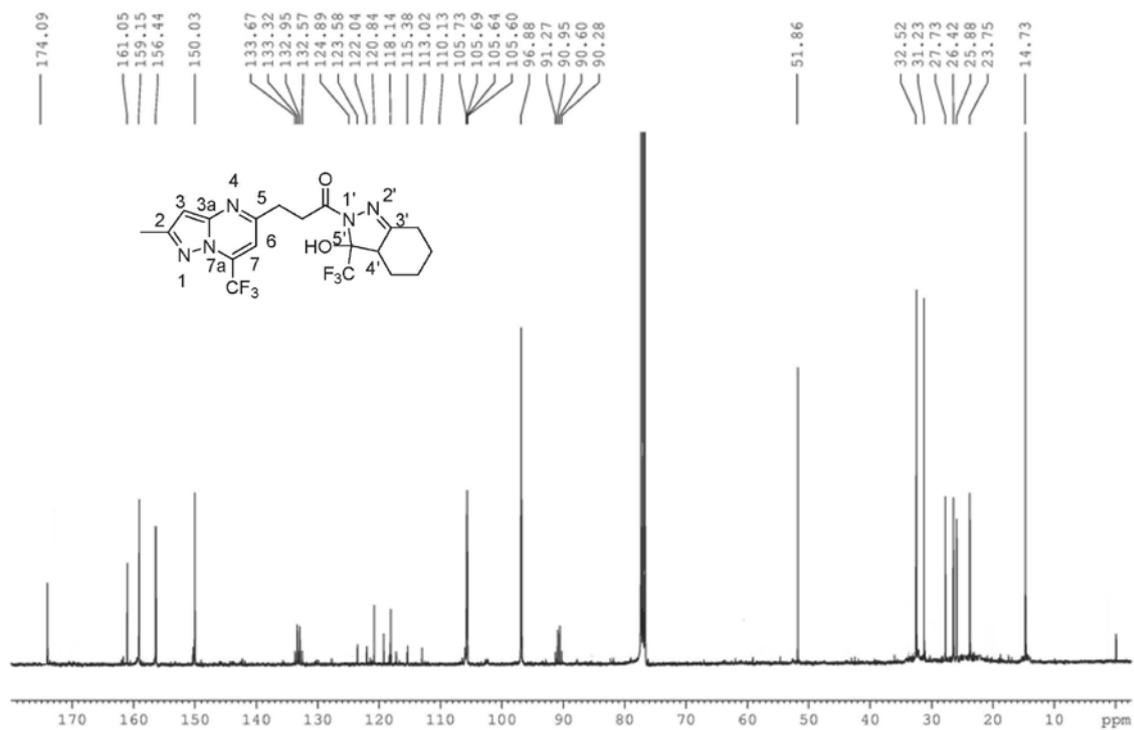


Figure S51. ^{13}C NMR spectrum (CDCl_3 , 100 MHz) of 5-[1-(3-hydroxy-3-trifluoromethyl-3,3a,4,5,6,7-hexahydroindazol-2-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4j**).

User Spectra

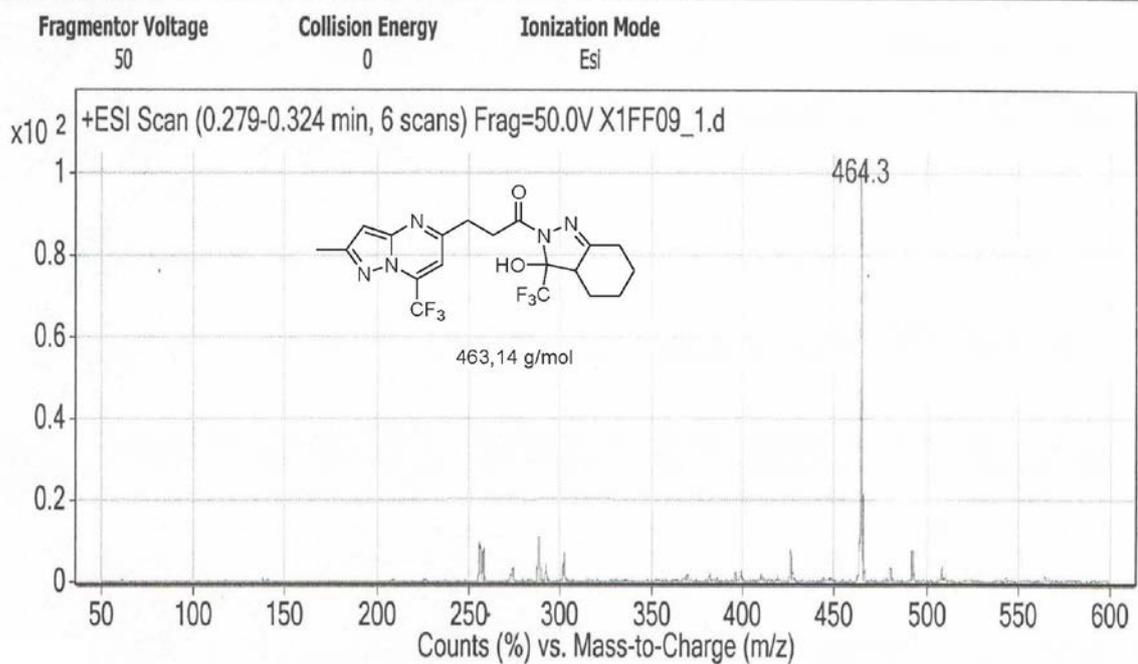


Figure S52. ESI mass spectrum of 5-[1-(3-hydroxy-3-trifluoromethyl-3,3a,4,5,6,7-hexahydroindazol-2-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4j**).

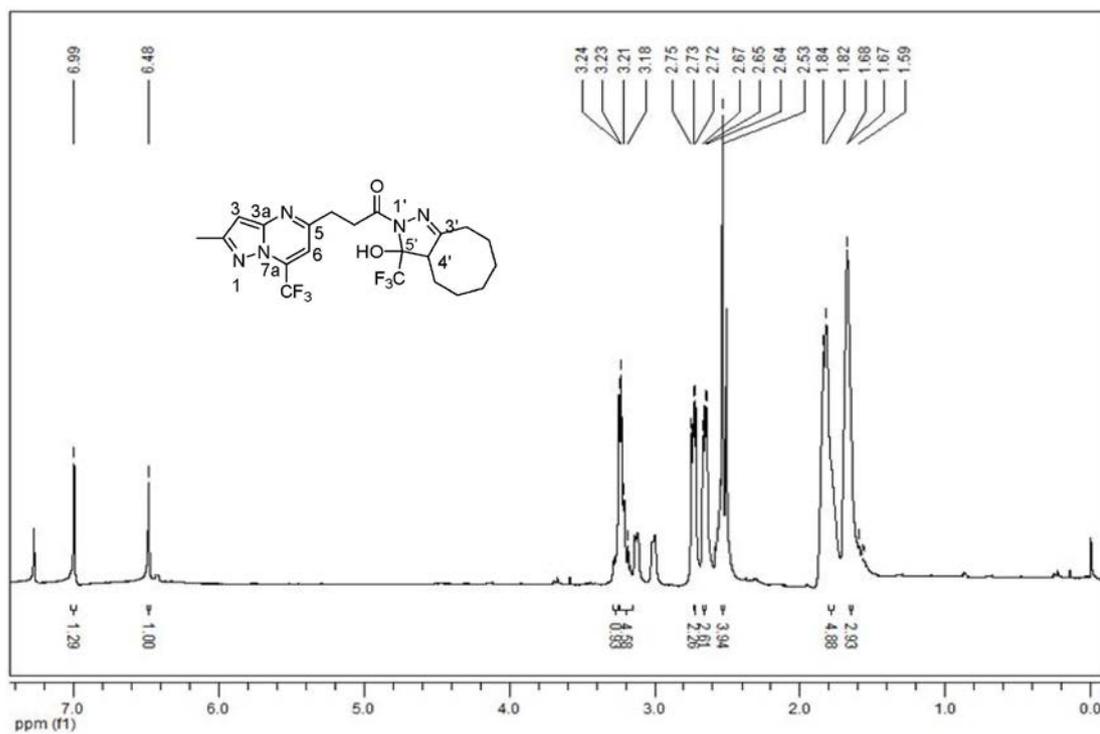


Figure S53. ^1H NMR spectrum (CDCl_3 , 400 MHz) of 1-(3-hydroxy-3-trifluoromethyl-3,3a,4,5,6,7,8,9-octahydrocycloocta[*c*]pyrazol-2-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4k**).

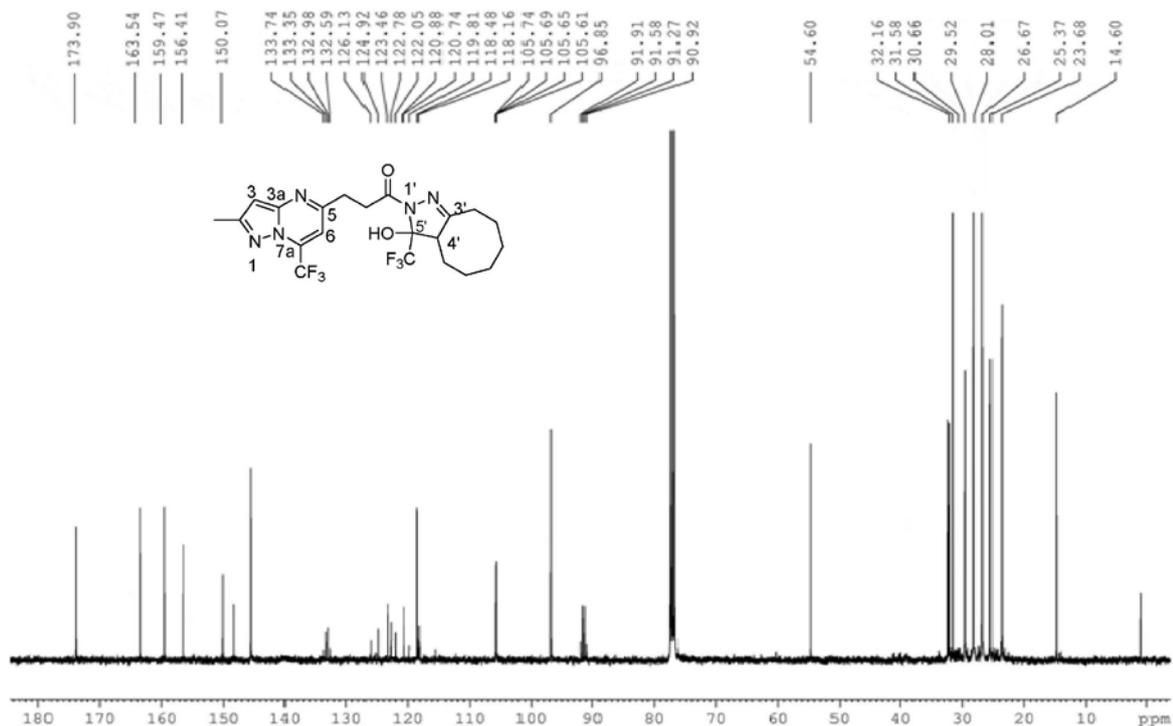


Figure S54. ¹³C NMR spectrum (CDCl₃, 100 MHz) of 1-(3-hydroxy-3-trifluoromethyl-3,3a,4,5,6,7,8,9-octahydrocycloocta[c]pyrazol-2-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4k**).

User Spectra

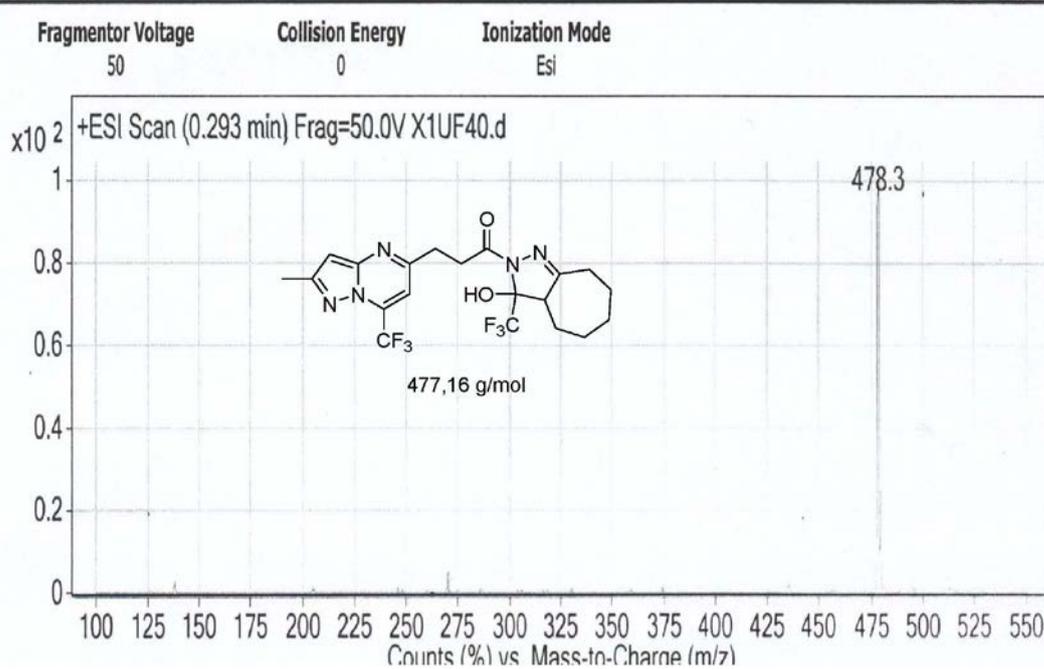


Figure S55. ESI mass spectrum of 1-(3-hydroxy-3-trifluoromethyl-3,3a,4,5,6,7,8,9-octahydrocycloocta[c]pyrazol-2-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-a]pyrimidine (**4k**).

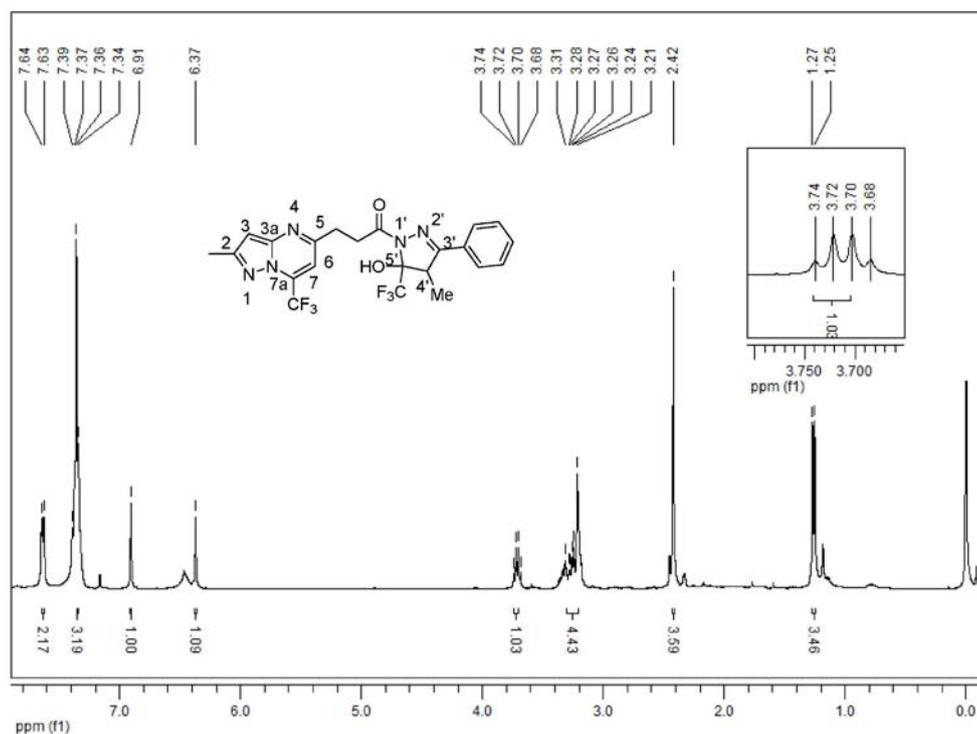


Figure S56. ^1H NMR spectrum (CDCl_3 , 400 MHz) of 1-(5-trifluoromethyl-5-hydroxy-4-methyl-3-phenyl-4,5-dihydropyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4l**).

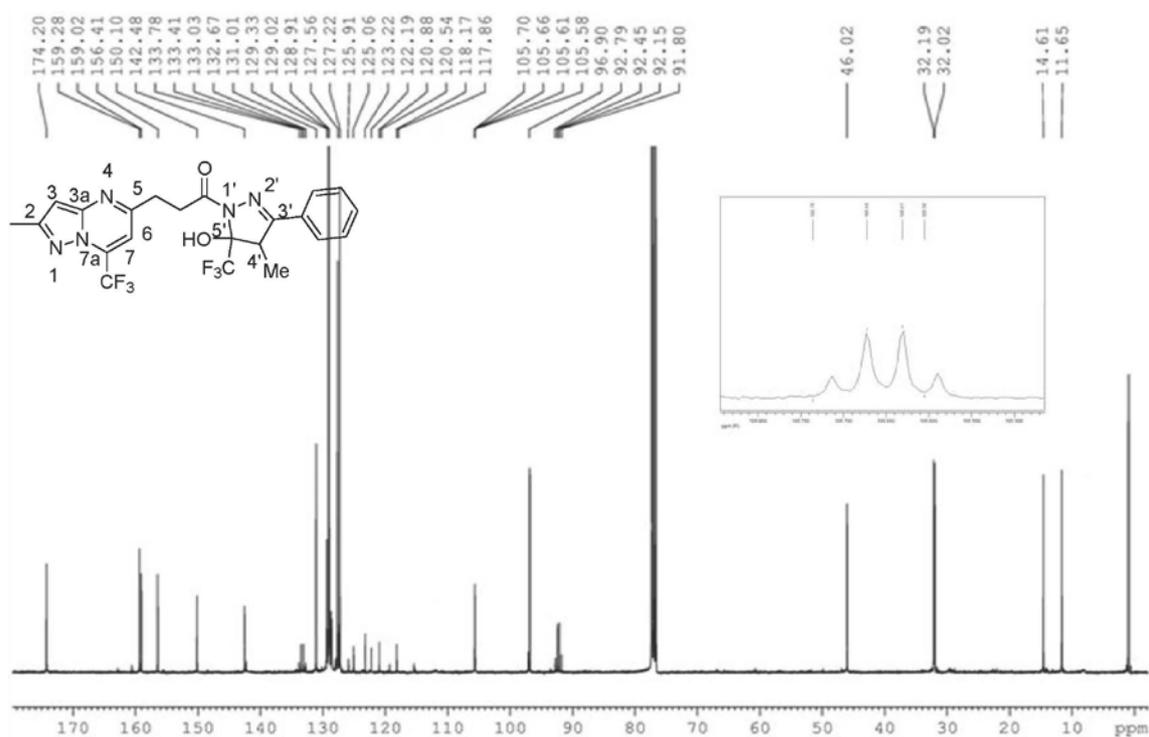


Figure S57. ^{13}C NMR spectrum (CDCl_3 , 400 MHz) of 1-(5-trifluoromethyl-5-hydroxy-4-methyl-3-phenyl-4,5-dihydropyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4l**).

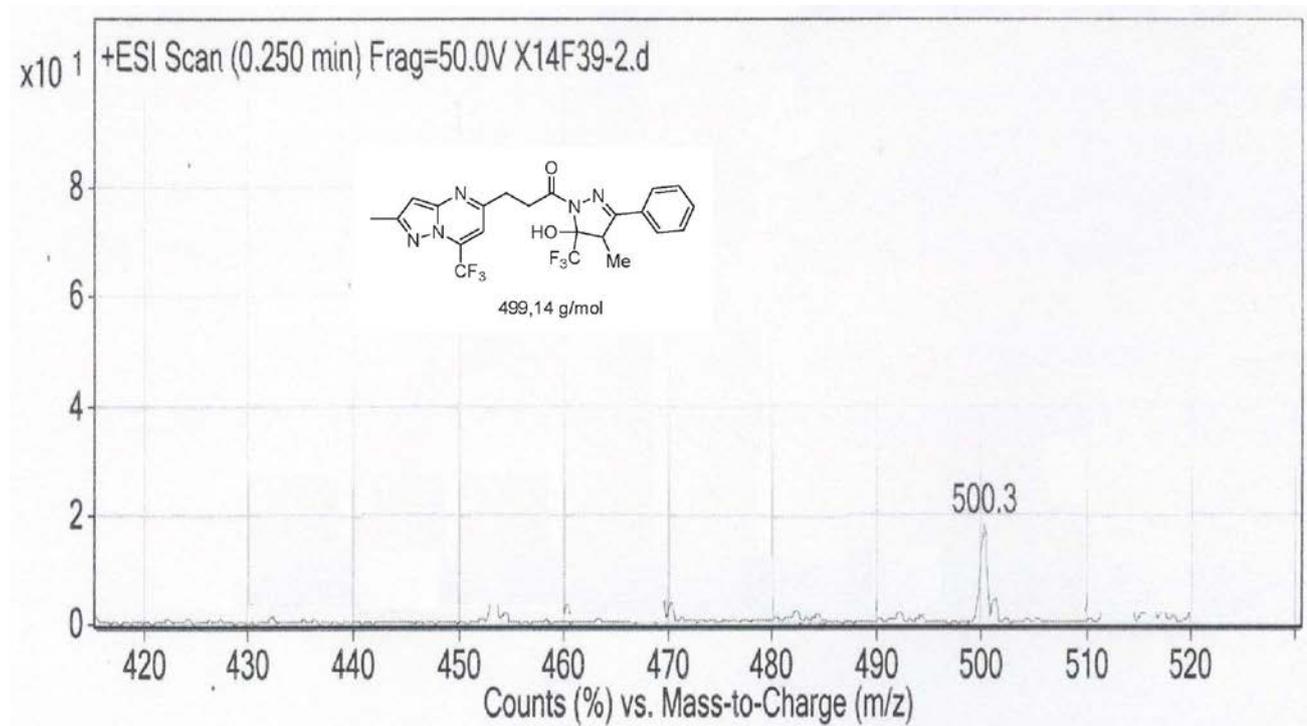


Figure S58. ESI mass spectrum of 1-(5-(trifluoromethyl)-5-hydroxy-4-methyl-3-phenyl-4,5-dihydropyrazol-1-yl)-1-propan-1-one-3-yl]-2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidine (**4l**)

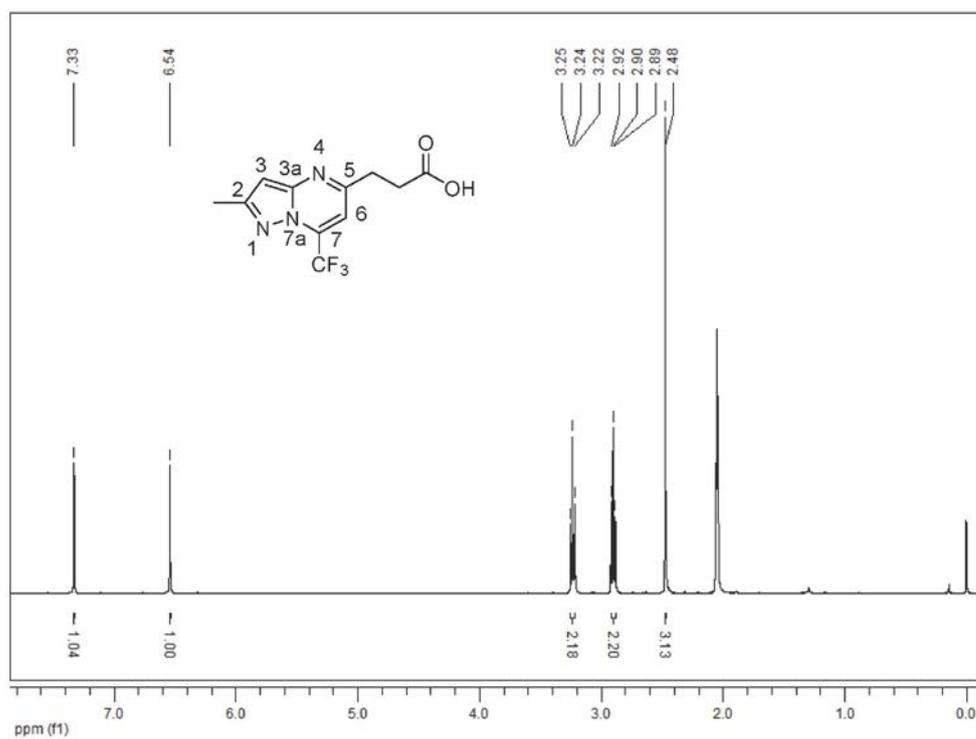


Figure S59. ^1H NMR spectrum (DMSO- d_6 , 400 MHz) of 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoic acid.

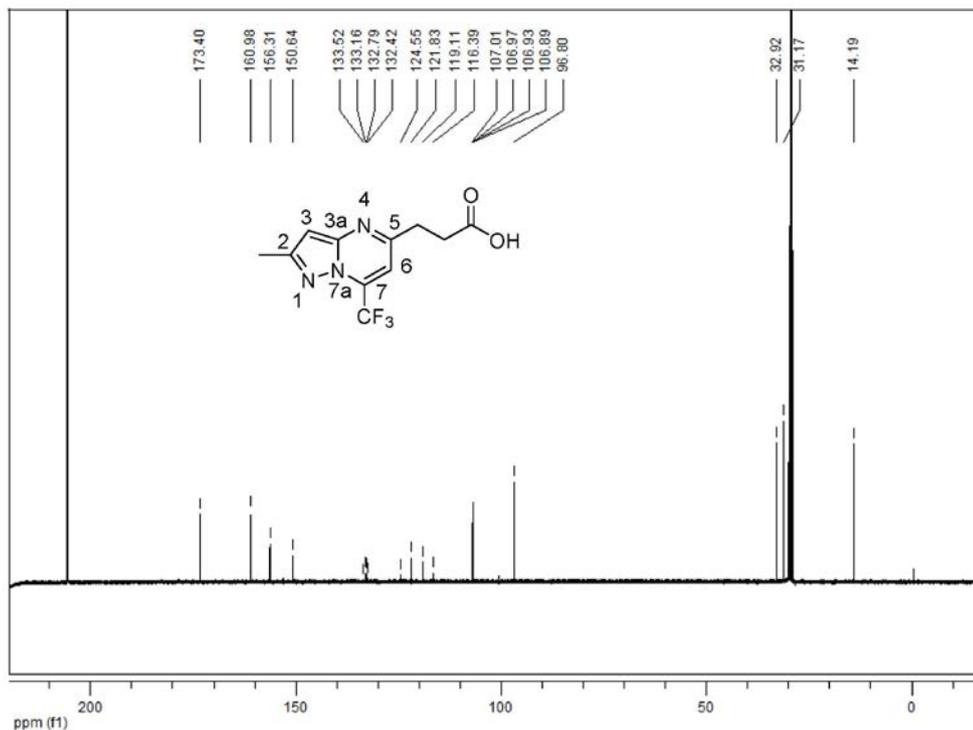


Figure S60. ^{13}C NMR spectrum (DMSO- d_6 , 100 MHz) of 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoic acid.

User Spectra

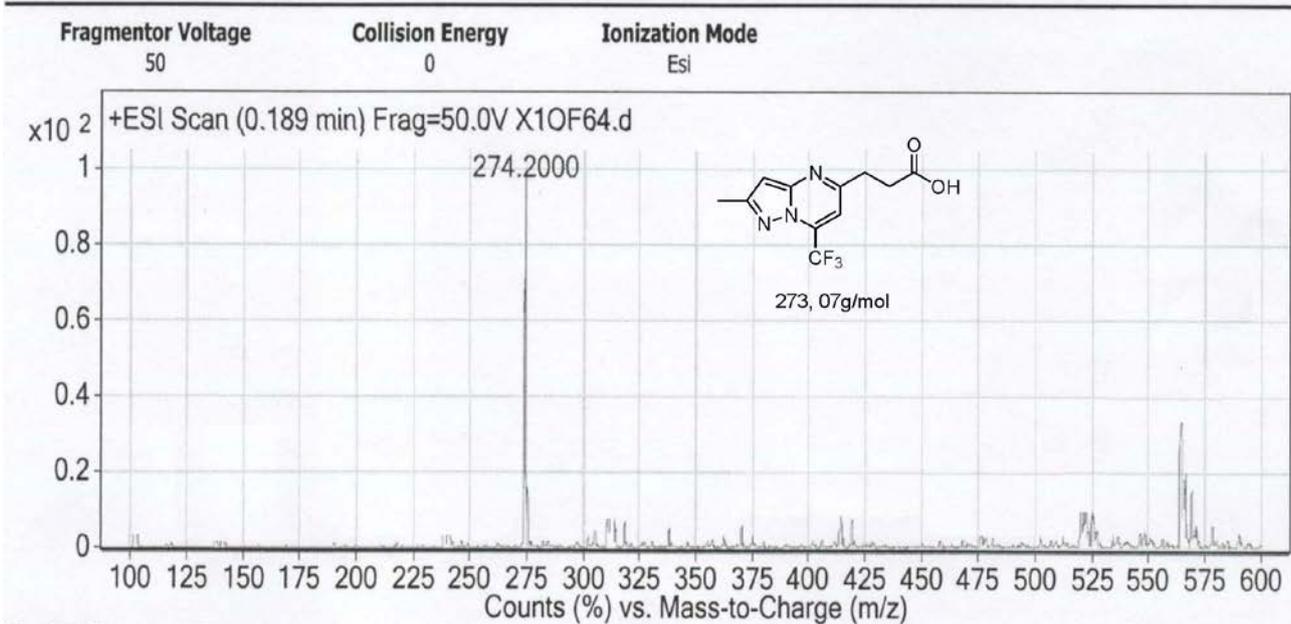


Figure S61. ESI mass spectrum of 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoic acid (5).

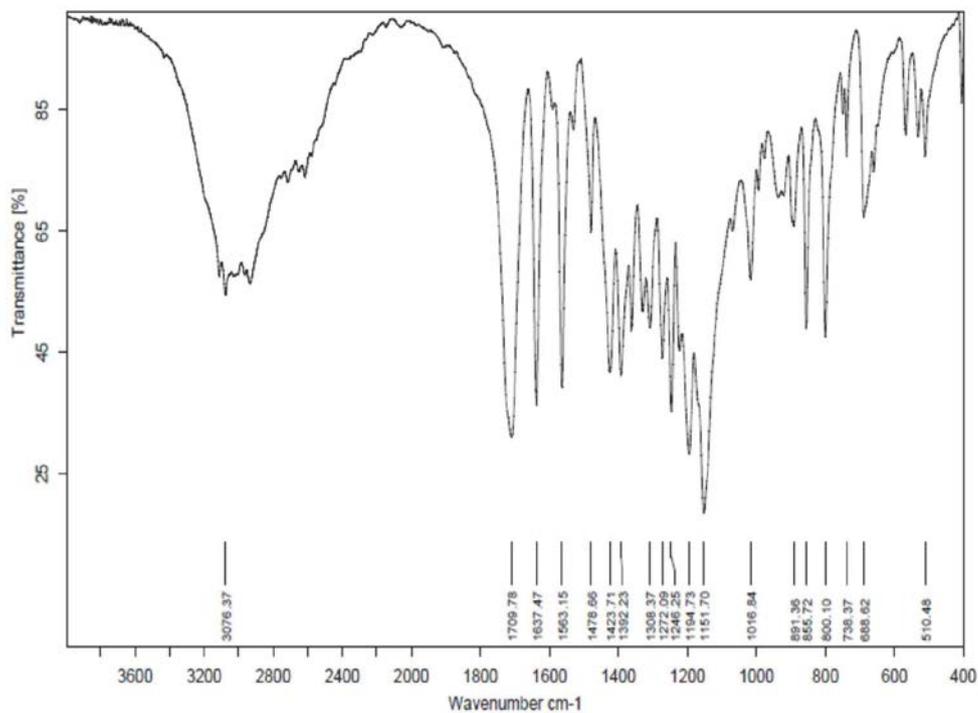


Figure S62. IR spectrum (KBr) of 3-(2-methyl-7-trifluoromethylpyrazolo[1,5-*a*]pyrimidin-5-yl)propanoic acid (**5**).