$In(OTf)_3$ Assisted Synthesis of β-Carboline C-3 Tethered Imidazo[1,2-*a*]azine Derivatives

Nisha Devi,[a] Dharmender Singh,[a] Gurpreet Kaur,[a] Satbir Mor,[b] V. P. Rama Kishore Putta,[c] Saibabu Polina,[c] Chandi C. Malakar,[d] and Virender Singh[a]*

[a]Department of Chemistry, Dr B R Ambedkar National Institute of Technology, Jalandhar, 144011, Punjab, India

[b]Department of Chemistry, GJ University of Science and Technology, Hisar, 125001, India

[c] Department of Medicinal Chemistry, Jubilant Biosys, Bangalore - 560022, Karnataka, India.

[d]Department of Chemistry, National Institute of Technology, Manipur, Imphal-795004, India.

E mail:- singhv@nitj.ac.in; singhvirender010@gmail.com; Fax: (91) 172 2214692

Supporting Information

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General procedure for the synthesis of compounds 2a-c as exemplified for 1-(4-bromophenyl)-2,3,4,9-tetrahydro-1*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (2b)[Ref 15-16]: To a stirred suspension of L-tryptophan **1** (1.00 g, 4.89 mmol) in dry DCM (10 mL), 4-bromobenzaldehyde (**b**) (1.09 g, 5.89 mmol) was added at room temperature. Thereafter a solution of TFA (1 mL) in 5 mL dry DCM was added in small portions and the reaction was continued at room temperature till completion (45 min) which was monitored by TLC. On completion of the reaction, the excess of DCM was evaporated under reduced pressure and the crude product was washed with hexane 3-4 times (15 mL each time) to get the pure solid product as yellow solid (1.72 g from 1.00 g, 95%) which was significantly pure and utilized for the next step.

General procedure for the synthesis of compounds 3a-c as exemplified for 1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylic acid (3b) [Ref 15-16]: To a stirred solution of tetra-hydro-β-Carboline acid **2b** (1.72 g, 4.65 mmol) in dry DMF (10 mL), powdered $KMnO_4$ (3.00 g, 18.98 mmol) was added in small portions and stirred vigorously at room temperature for 45 min. After completion of the reaction as monitored by TLC, the blackish content was filtered through a bed of celite under suction to obtain a yellow filtrate. The residue over celite was further washed with a mixture of Methanol: DCM (05:95, v/v). The filtrate was concentrated *in vacuo* to yield the yellow solid product which was triturated with (hexane/EtOAc, 90:10, v/v) to obtain a light yellow solid product **3b** (1.49 g from 1.72 g, 88%).

General procedure for the synthesis of compounds 4a-c as exemplified for methyl 1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (4b) [Ref 15-16]: To a stirred solution of β-carboline-3 carboxylic acid **3b** (1.49 g, 4.07 mmol) in dry DMF (10 mL), K_2CO_3 (1.40 g, 10.13 mmol) was added in small portions and stirred the reaction at room temperature for 15 min. Thereafter, methyl iodide (0.38 mL, 6.10 mmol) dissolved in DMF (1.5 mL) was added dropwise to the reaction mixture and the content was stirred at room temperature. After the completion of reaction as monitored by TLC, ice cold water was poured in the reaction mixture and compound was extracted with $CHCl_3$ (4 x 25 mL). The organic layers were combined and washed with brine (20 mL), dried over anhydrous Na_2SO_4, concentrated *in vacuo* to yield the solid product which was triturated with (hexane/EtOAc, 90:10, v/v) to obtain a yellow solid product

4b (1.29 g from 1.49 g, 83%) which was sufficiently pure and utilized for next step without further purification.

General procedure for the synthesis of compounds 5a-c as exemplified for (1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)methanol (5b) [Ref 15-16]**:** To a stirred solution of β-carboline C-3 methyl ester (**4b)** (6.00 g, 15.75 mmol) in dry THF (70 mL), powdered LAH (1.49 g, 39.26 mmol) was added in small portions under nitrogen atmosphere and stirred the reaction at 0 ^{o}C. After 5 min of addition of LAH, the reaction was stirred room temperature till completion (10-15 min). The reaction mixture was quenched by pouring a saturated solution of NaOH drop wise into the reaction mixture under cooling conditions with constant stirring. The light grey reaction content was filtered through a bed of celite and further washed with a mixture of Methanol: DCM (05:95, v/v). The filtrate was concentrated *in vacuo* to yield the crude product which was triturated with (hexane/EtOAc, 90:10, v/v) to obtain a significantly pure yellow solid product, **5b** (5.45 g from 6.00 g, 98%).

General procedure for the synthesis of compounds 6a-c as exemplified for 1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indole-3-carbaldehyde (6b) [Ref 15-16]**:** To a stirred solution of β-Carboline alcohol, **5b** (5.45 g, 15.51 mmol) in dry DCM (60 mL), powdered MnO_2 (20 g, 230 mmol) was added in small portions and stirred vigorously at room temperature. After the completion of reaction which was monitored by TLC, the blackish contents were filtered through a bed of celite under suction to obtain a yellow filtrate. The leftover residue over celite was further washed with dichloromethane. The filtrate was concentrated *in vacuo* to yield the crude solid product which was triturated with (hexane/EtOAc, 90:10, v/v) to obtain analytically pure yellow solid product **6b** (3.95 g from 5.46 g, 73%).

General procedure for the synthesis of 1-(4-bromophenyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole-3-carbaldehyde (10b): To a cooled solution of **6b** [Ref 15-16] (1.00 g, 2.85 mmol) in dry DMF (10 mL), NaH (0.20 g, 8.25 mmol) was added in small portions and stirred the reaction at 0 ^{o}C for 15 min. Thereafter, methyl iodide (0.27 mL, 4.28 mmol) dissolved in dry DMF (2 mL) was added to the reaction mixture dropwise and reaction was transferred to room temperature and stirred till the completion (2 h) which was monitored by TLC. After the completion of reaction, the content was poured into the ice cold water and solid was precipitated out. The solid product was

filtered under vacuum and was dried in air to get the yellow solid crude which was triturated with (hexane/EtOAc, 90:10, v/v) to obtain a yellow solid product **10b** (0.86 g from 1.00 g, 83%).

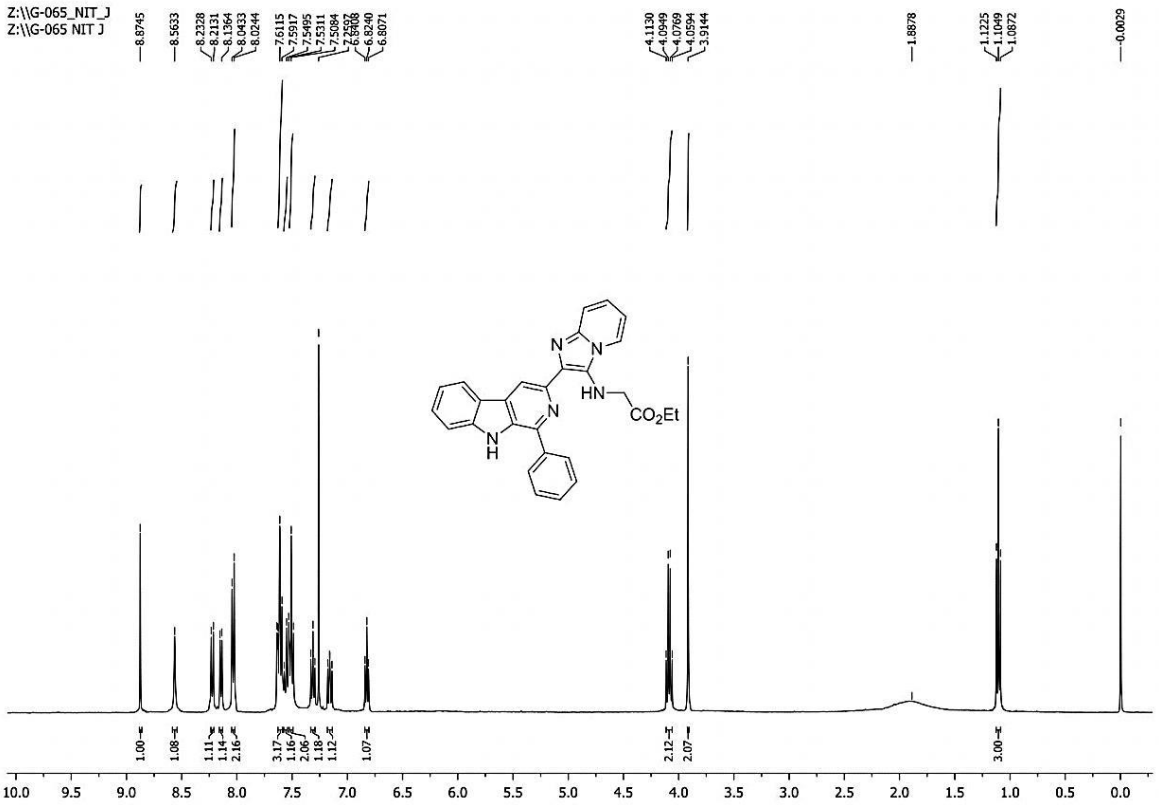

Fig. S 1. ^{1}H-NMR spectrum of ethyl 2-((2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7aAX**)**.**

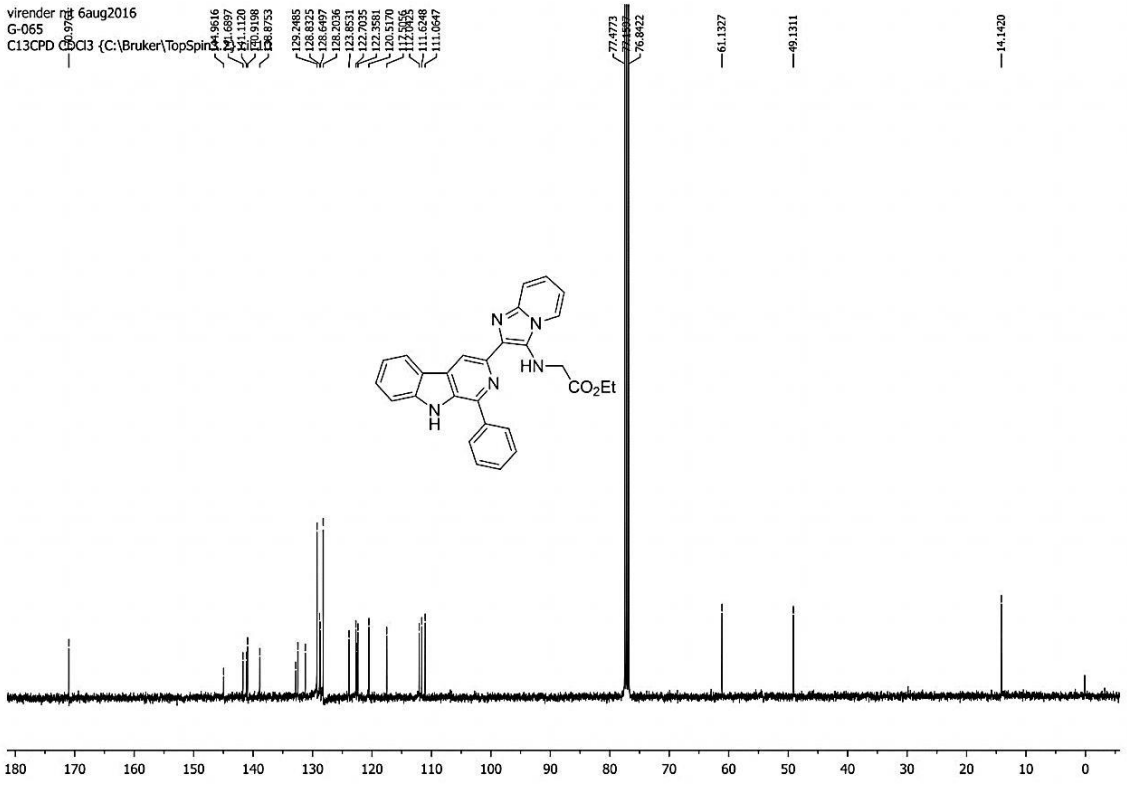

Fig. S 2 . ^{13}C-NMR spectrum of ethyl 2-((2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7aAX**)**.**

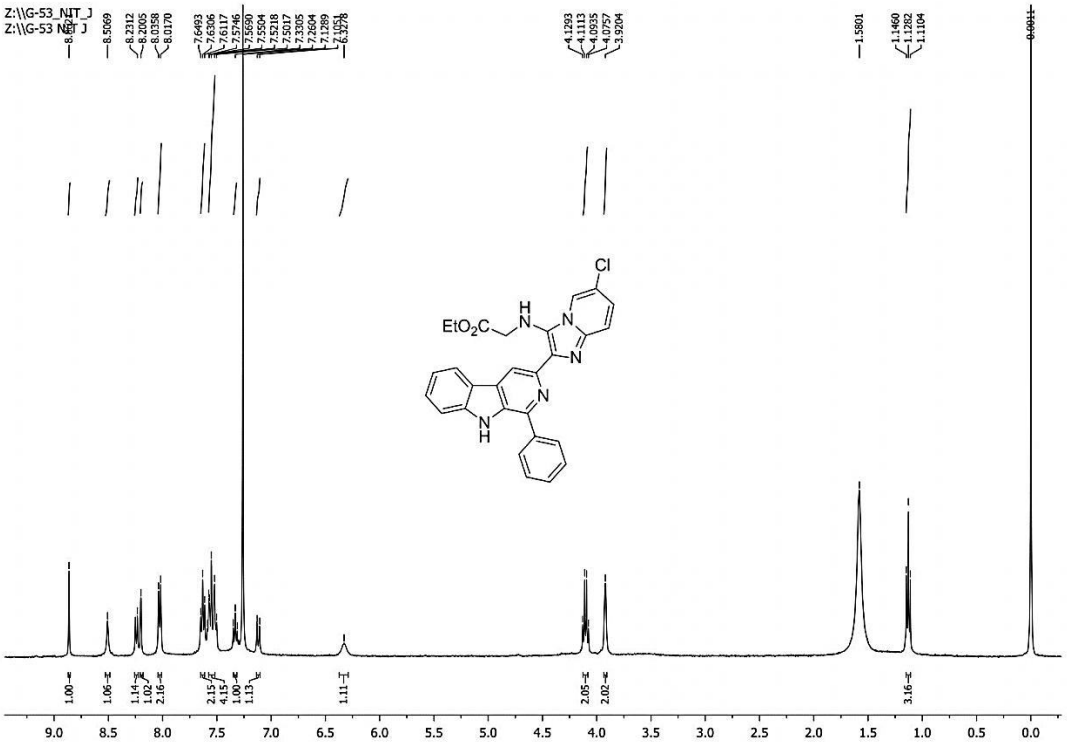

Fig. S 3. ^{1}H-NMR spectrum of ethyl 2-((6-chloro-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7aEX**).

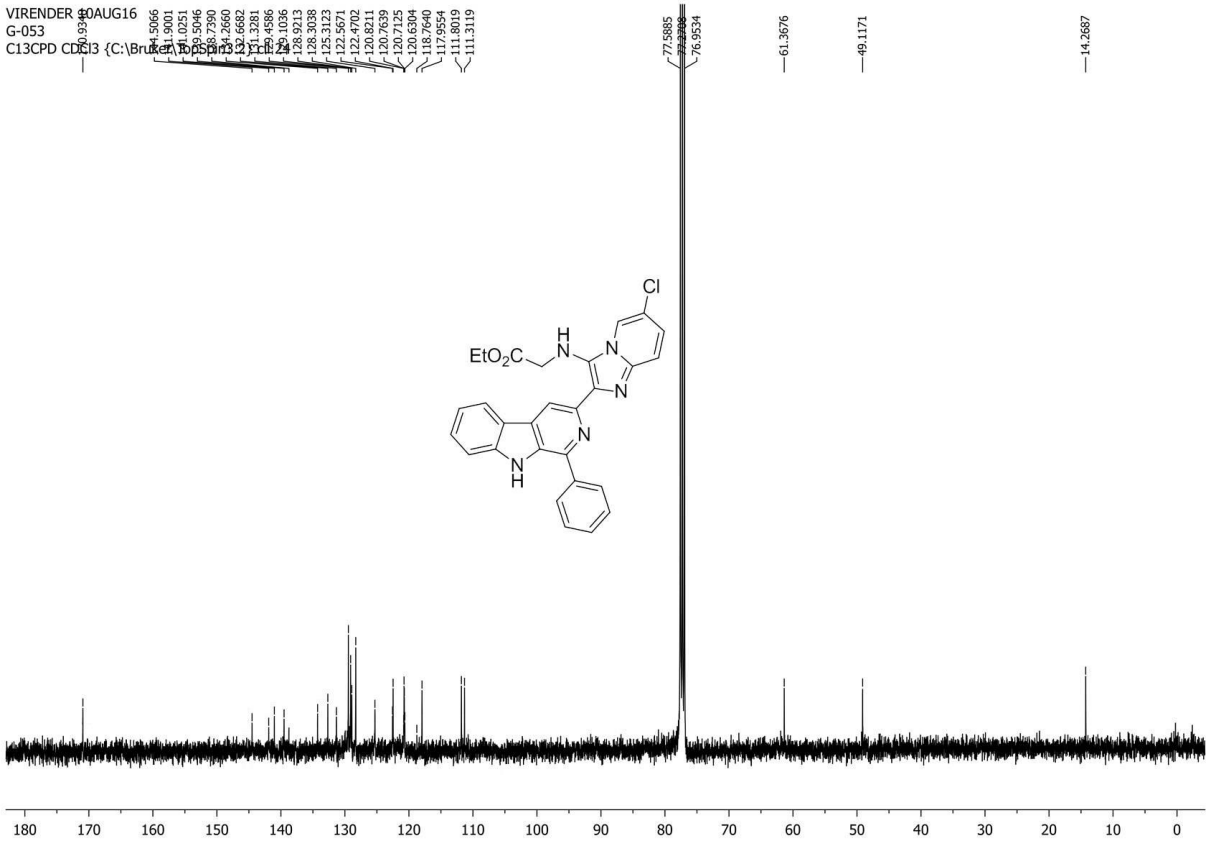

Fig. S 4 . ^{13}C-NMR spectrum of ethyl 2-((6-chloro-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7aEX**).

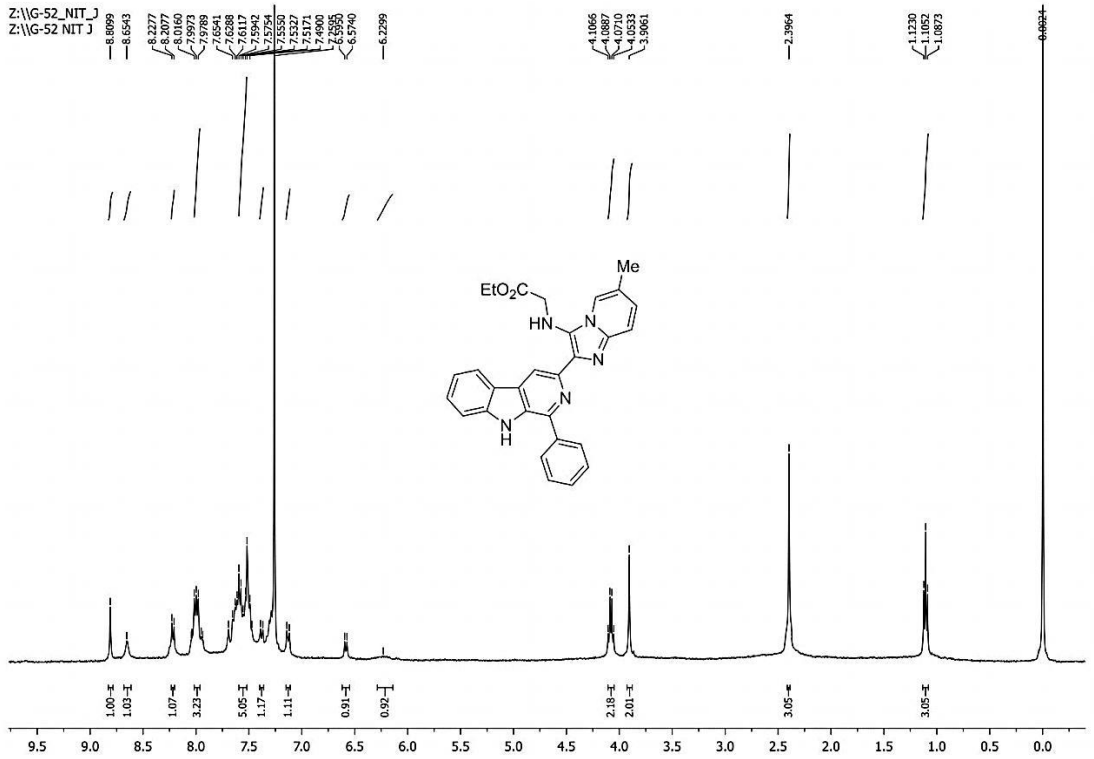

Fig. S 5. ^{1}H-NMR spectrum of ethyl 2-((6-methyl-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7aFX**)**.**

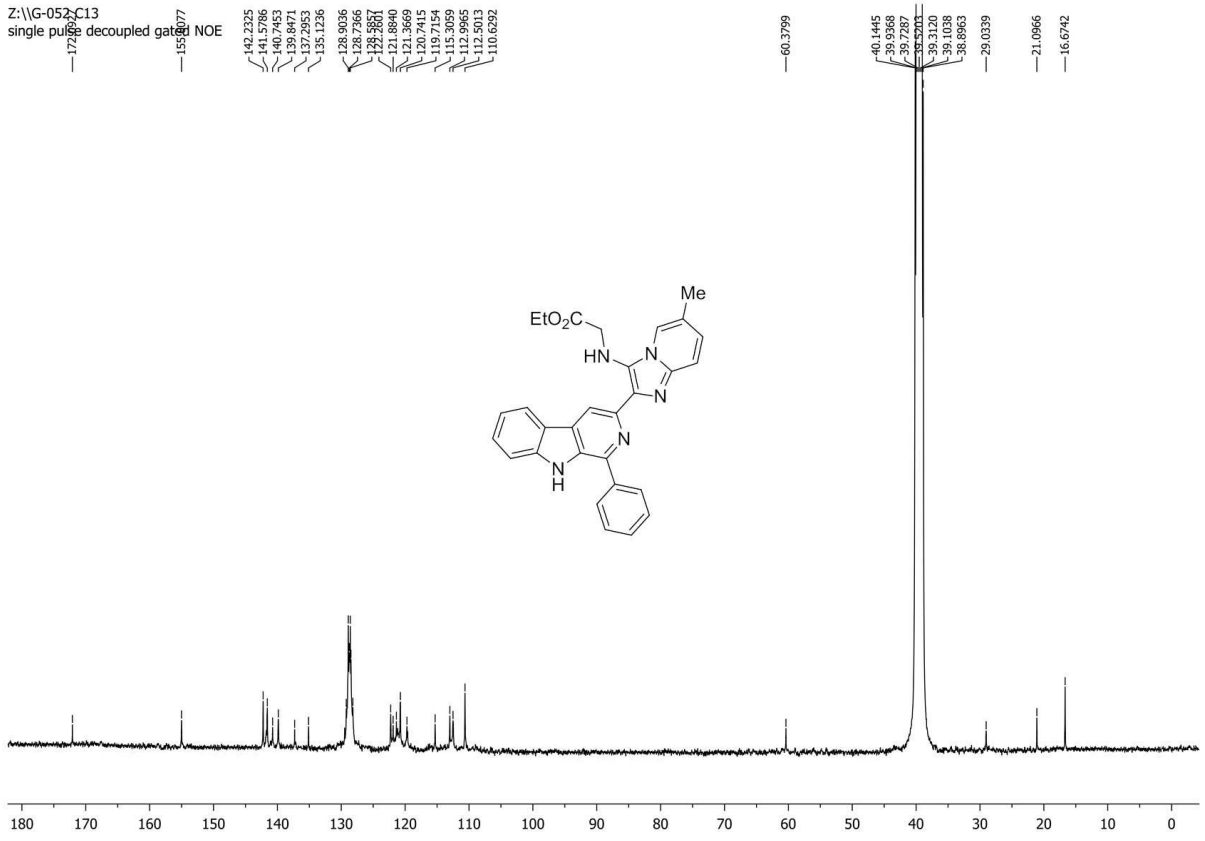

Fig. S 6. ^{13}C-NMR spectrum of ethyl 2-((6-methyl-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7aFX**)**.**

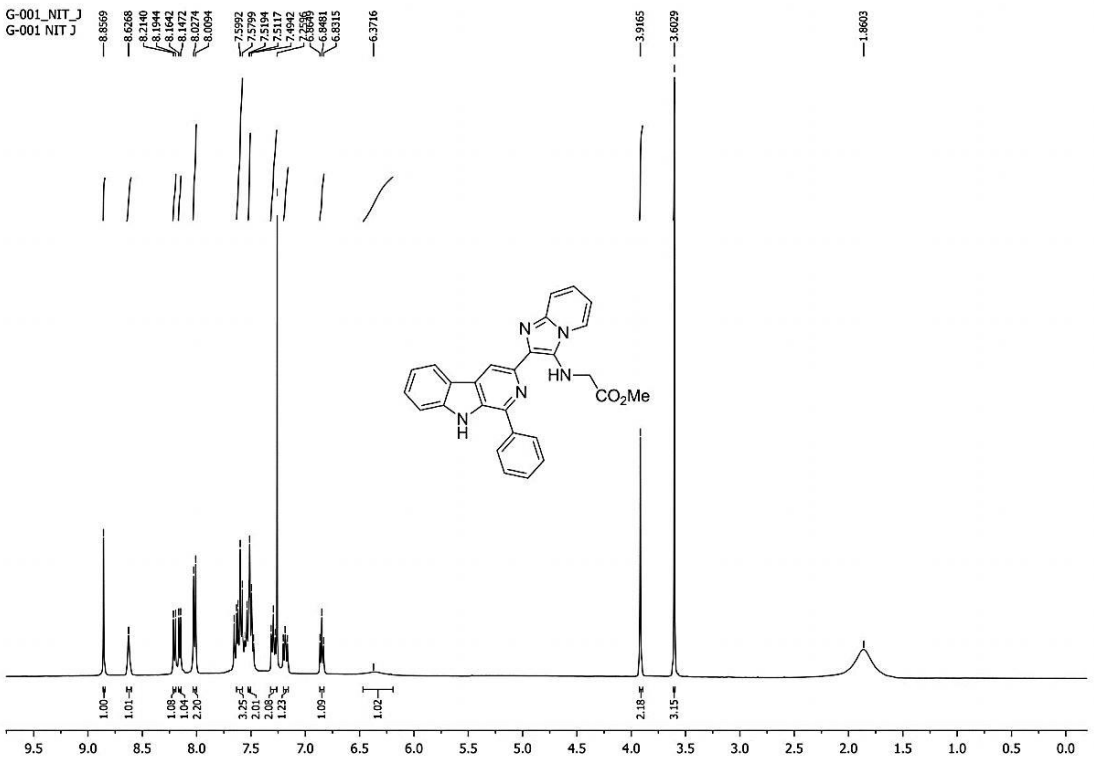

Fig. S 7. ^{1}H-NMR spectrum of methyl 2-((2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7aAY**).

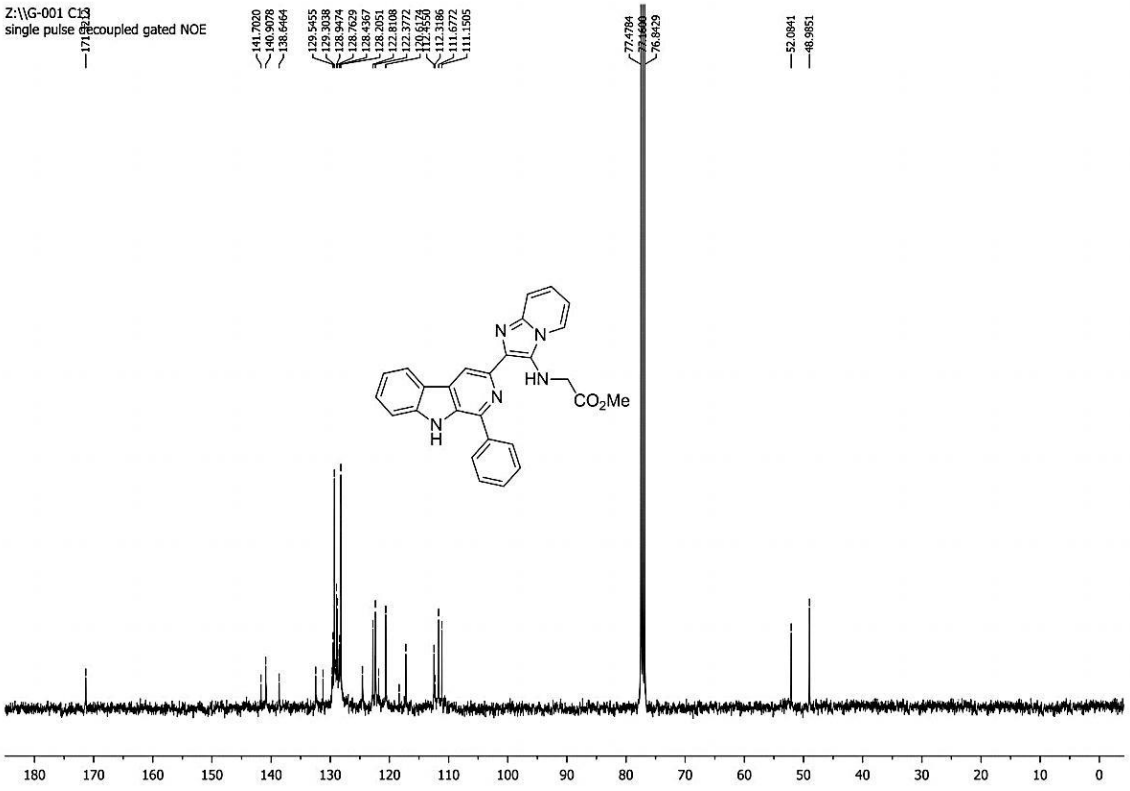

Fig. S 8. ^{13}C-NMR spectrum of methyl 2-((2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7aAY**).

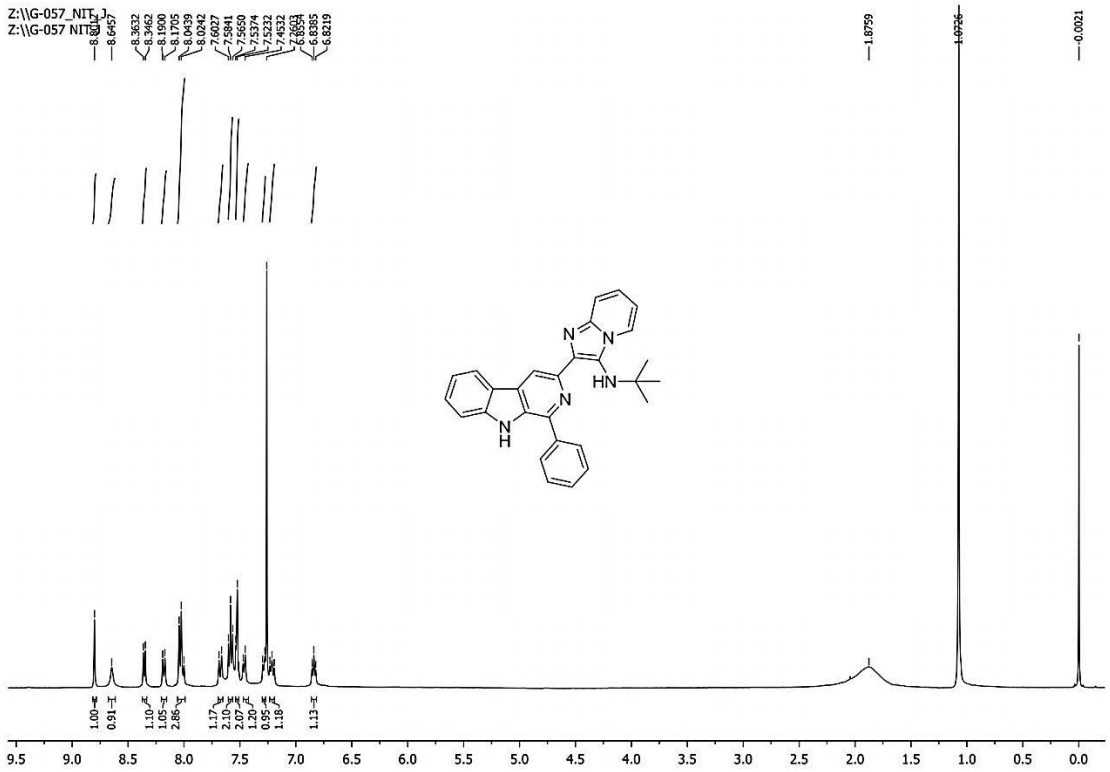

Fig. S 9. ^{1}H-NMR spectrum of *N*-(*tert*-butyl)-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-amine (**7aAZ**).

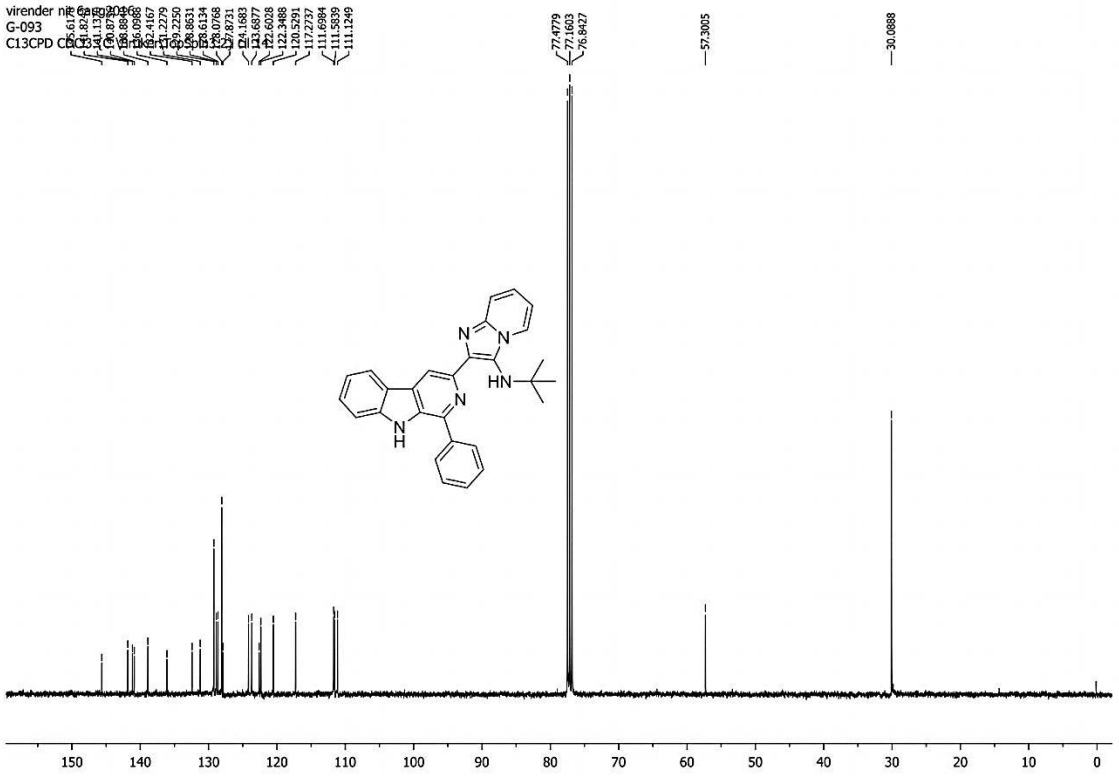

Fig. S 10. ^{13}C-NMR spectrum of *N*-(*tert*-butyl)-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-amine (**7aAZ**).

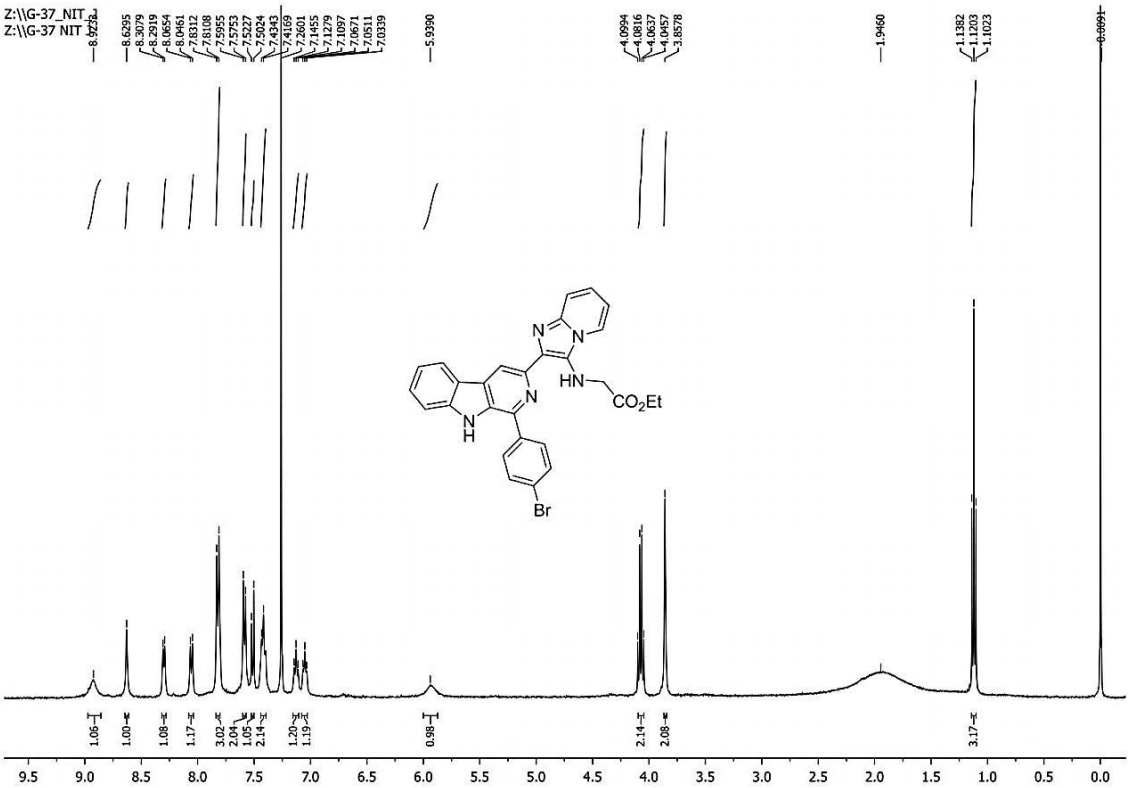

Fig. S 11. ^{1}H-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bAX**).

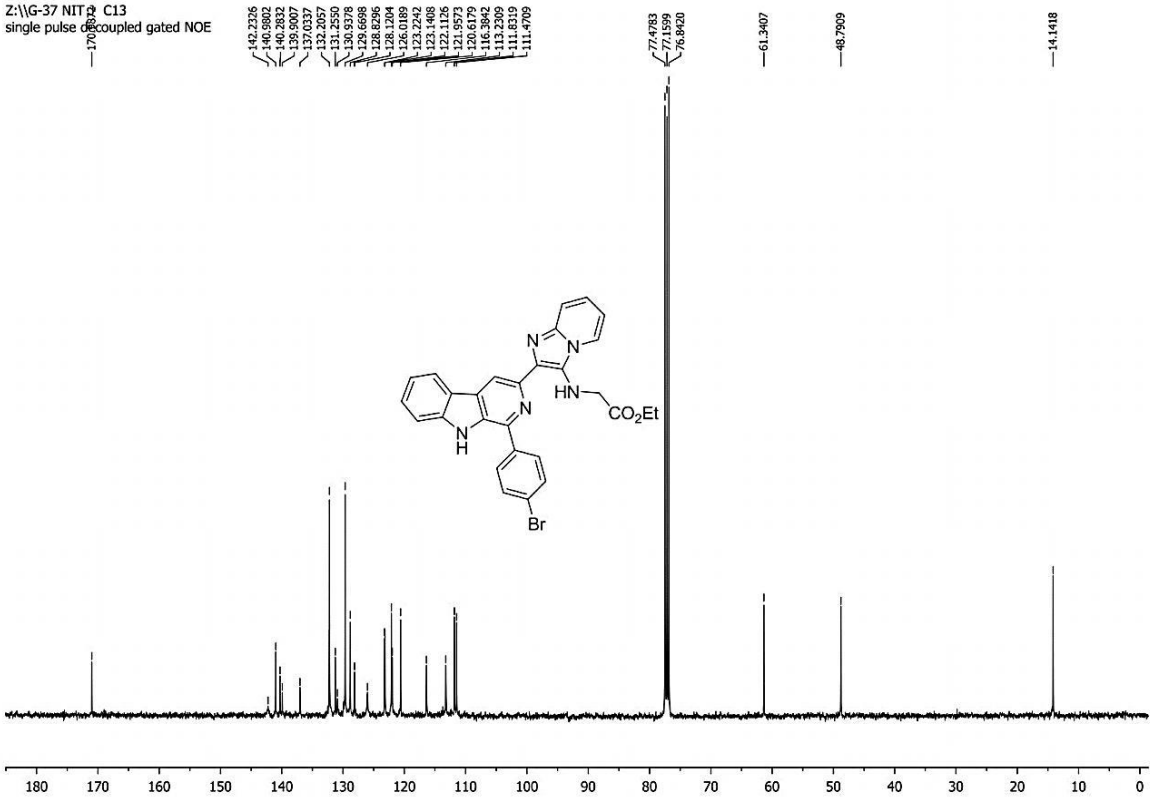

Fig. S 12. ^{13}C-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bAX**).

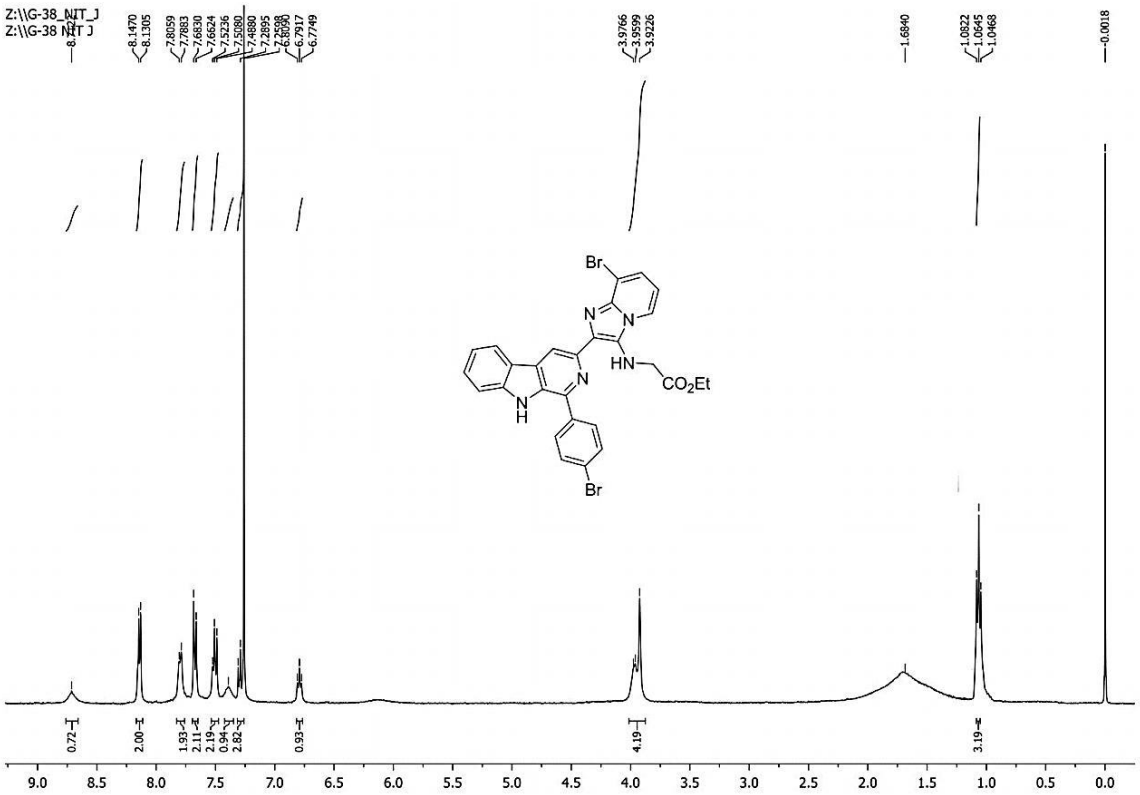

Fig. S 13. ^{1}H-NMR spectrum of ethyl 2-((8-bromo-2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bBX**).

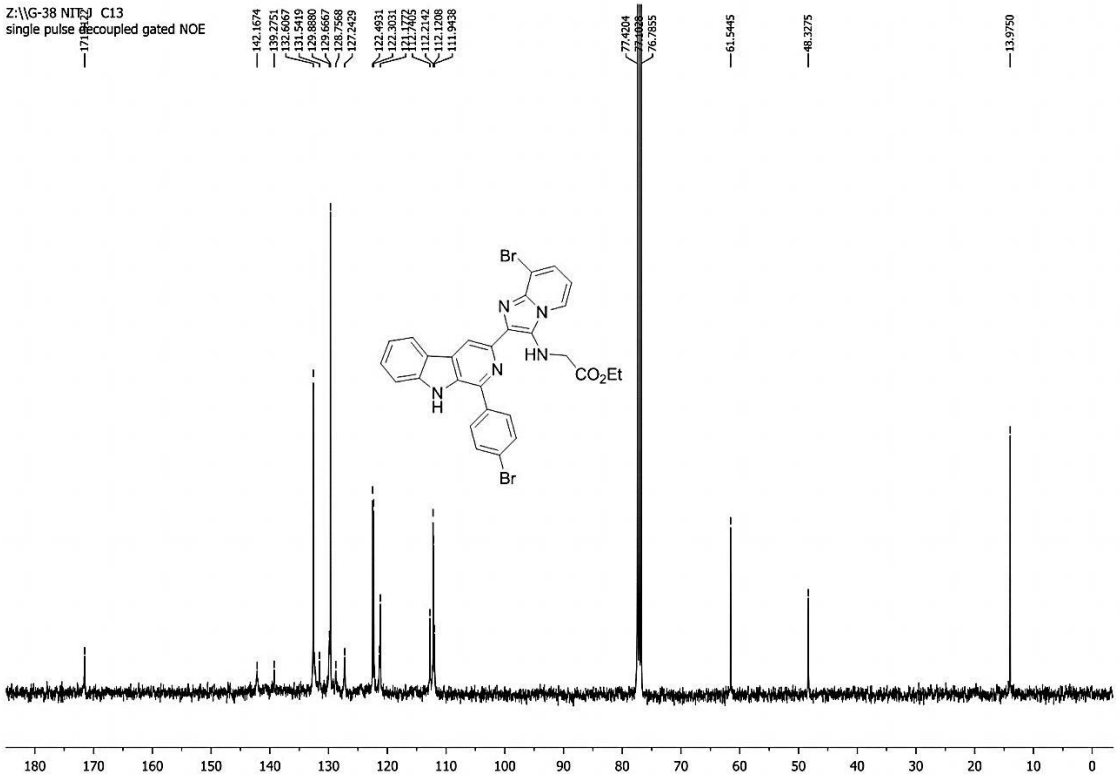

Fig. S 14. ^{13}C-NMR spectrum of ethyl 2-((8-bromo-2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bBX**).

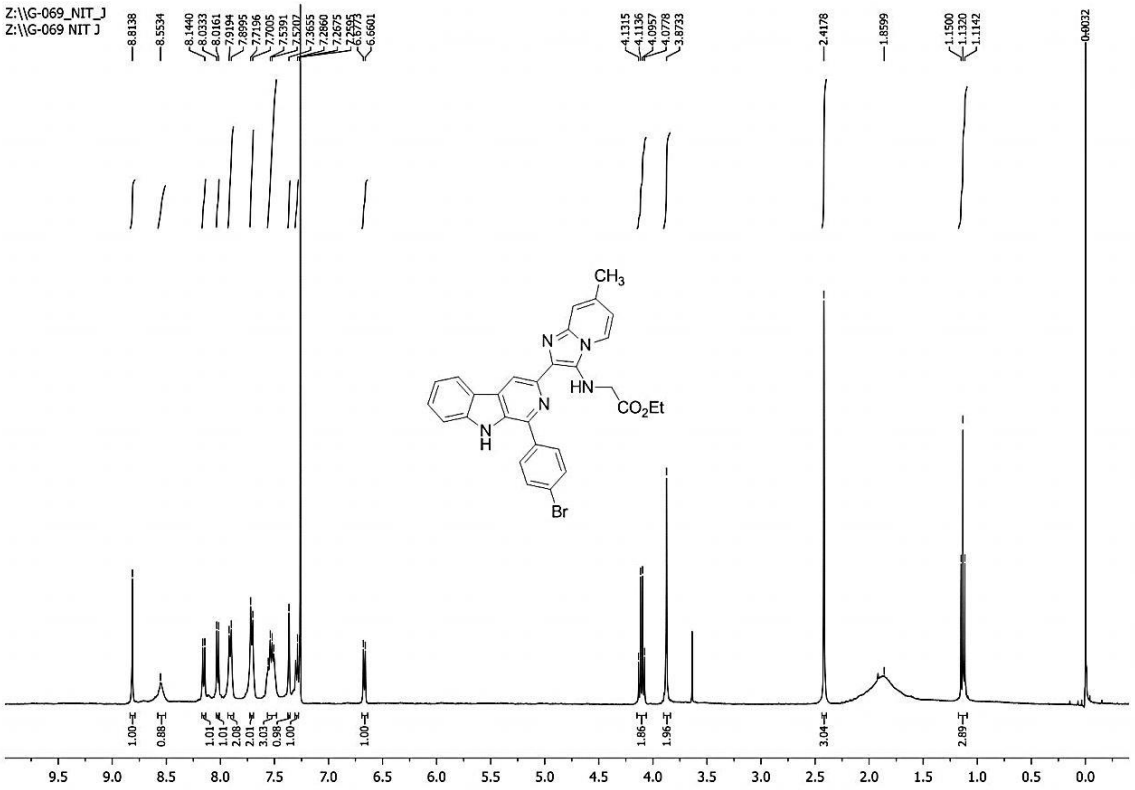

Fig. S 15. ^{1}H-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bCX**).

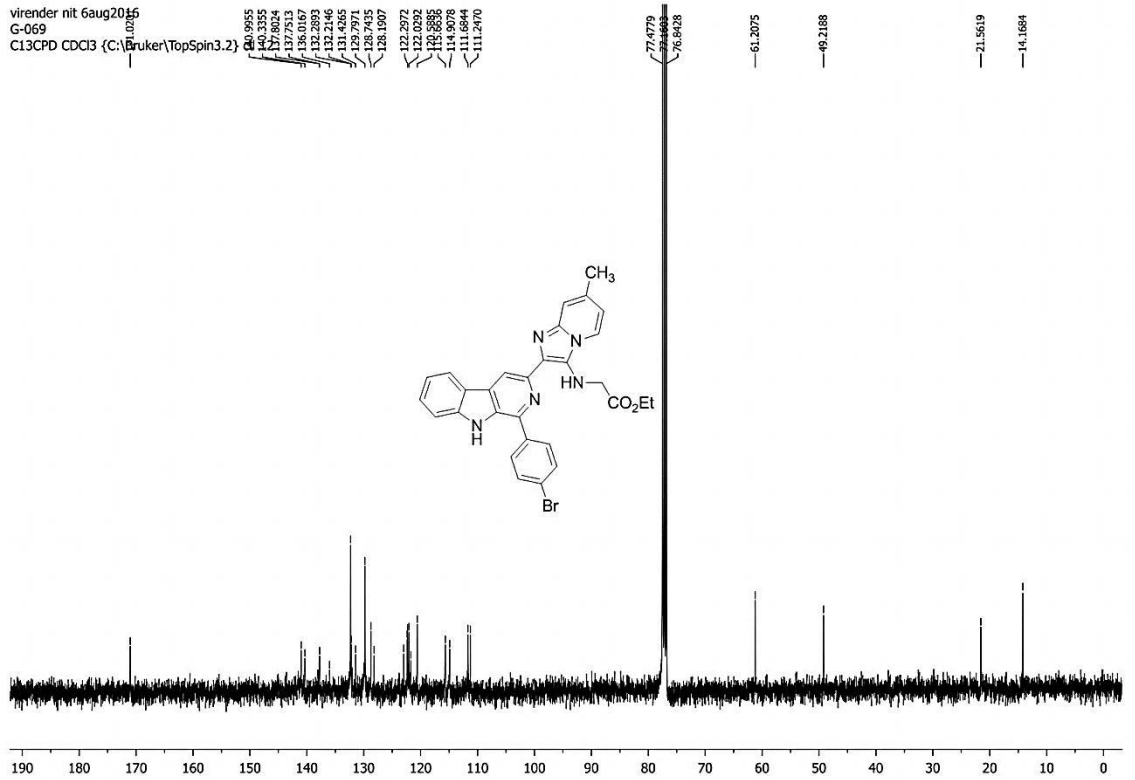

Fig. S 16. ^{13}C-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-7-methylimidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bCX**).

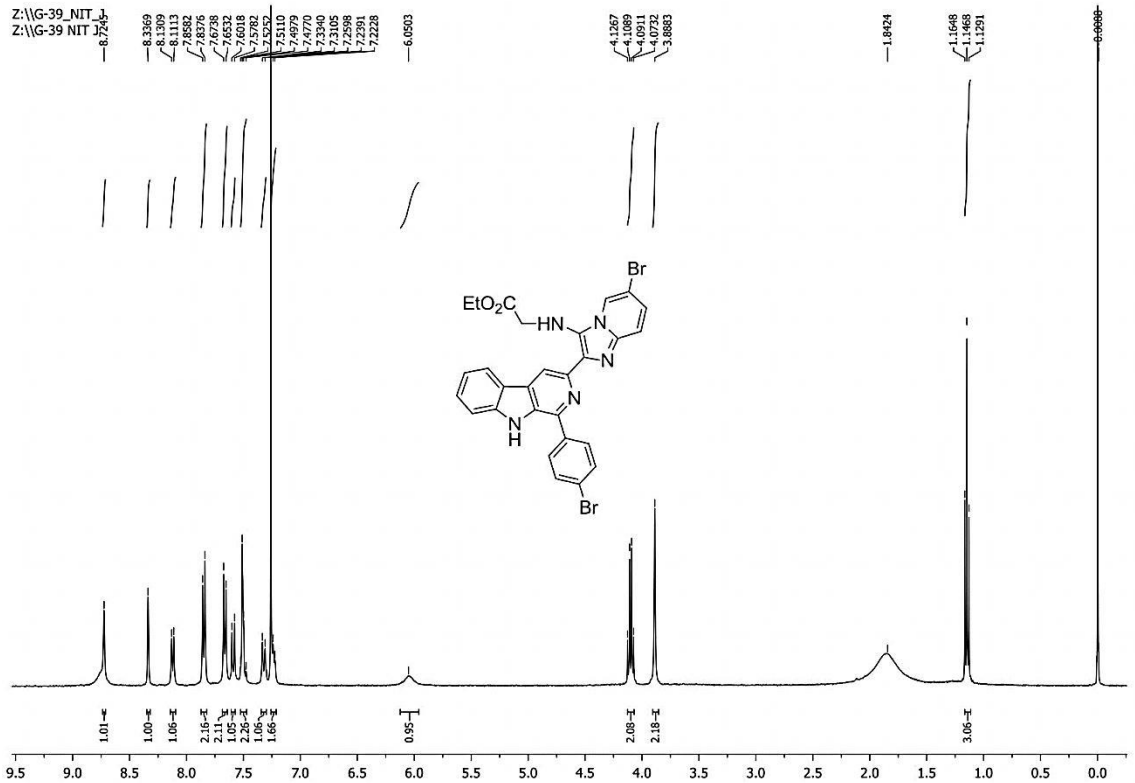

Fig. S 17. ^{1}H-NMR spectrum of ethyl 2-((6-bromo-2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bDX**).

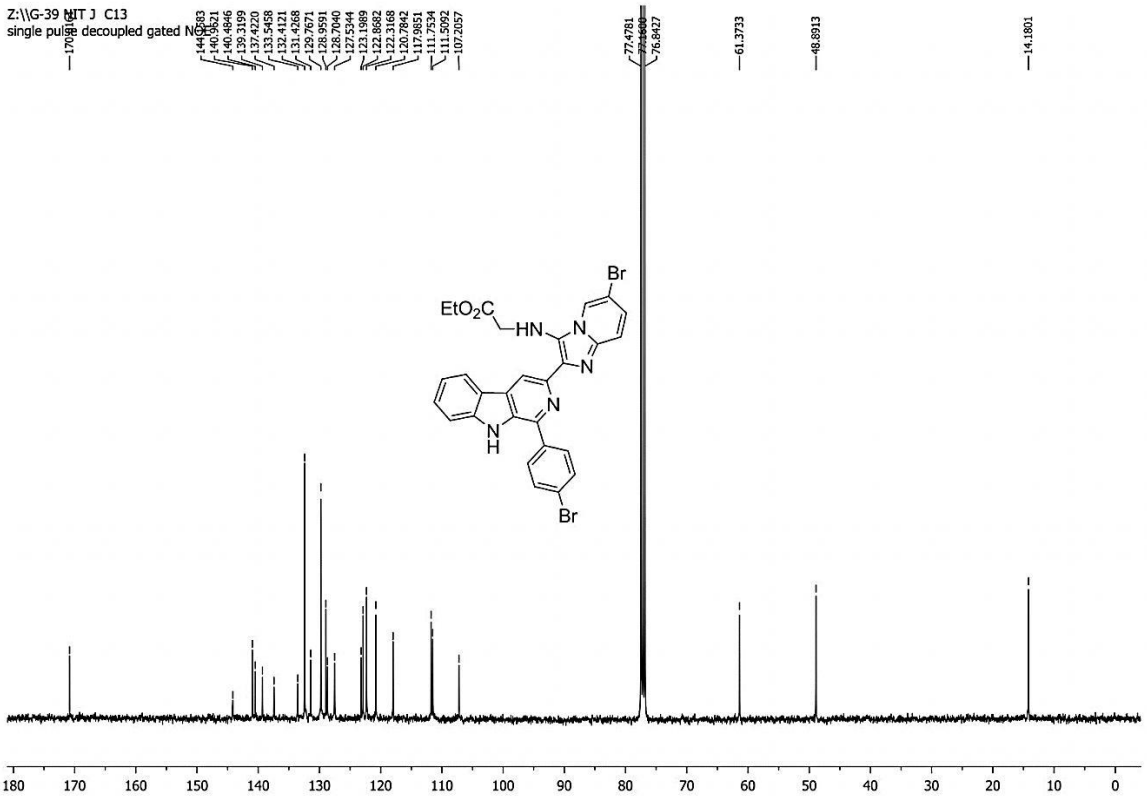

Fig. S 18. ^{13}C-NMR spectrum of ethyl 2-((6-bromo-2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bDX**).

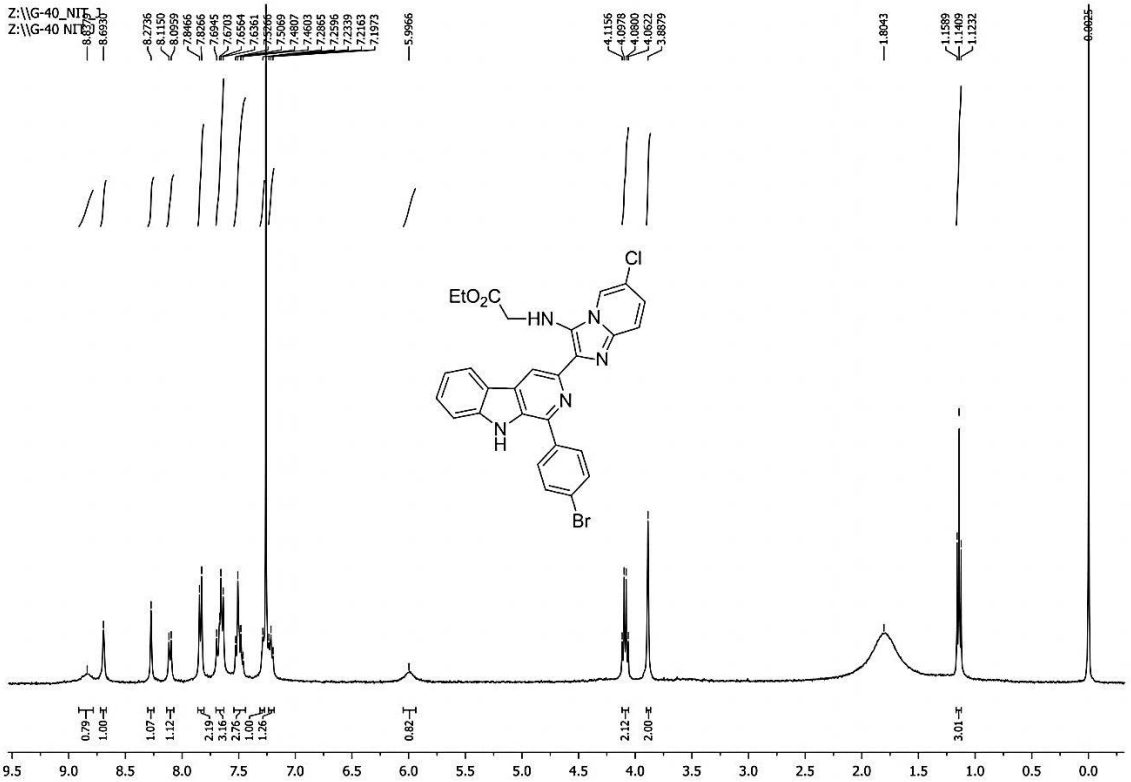

Fig. S 19. ^{1}H-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-6-chloroimidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bEX**).

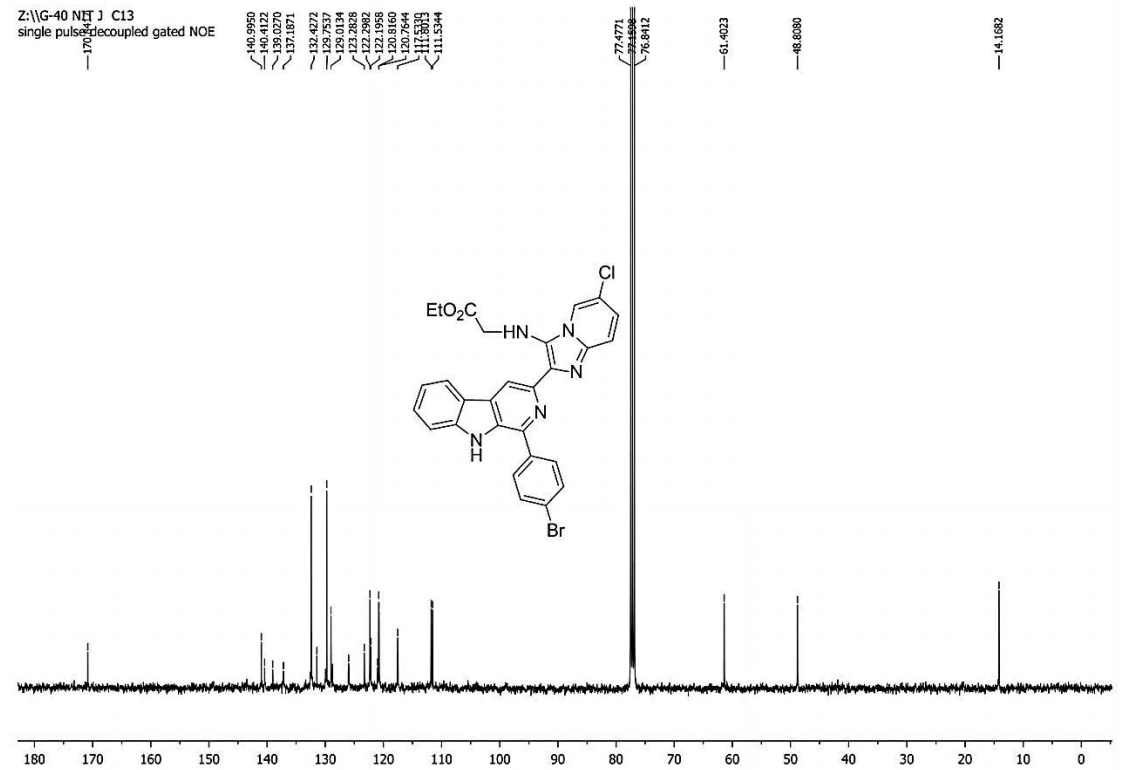

Fig. S 20. ^{13}C-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-6-chloroimidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bEX**).

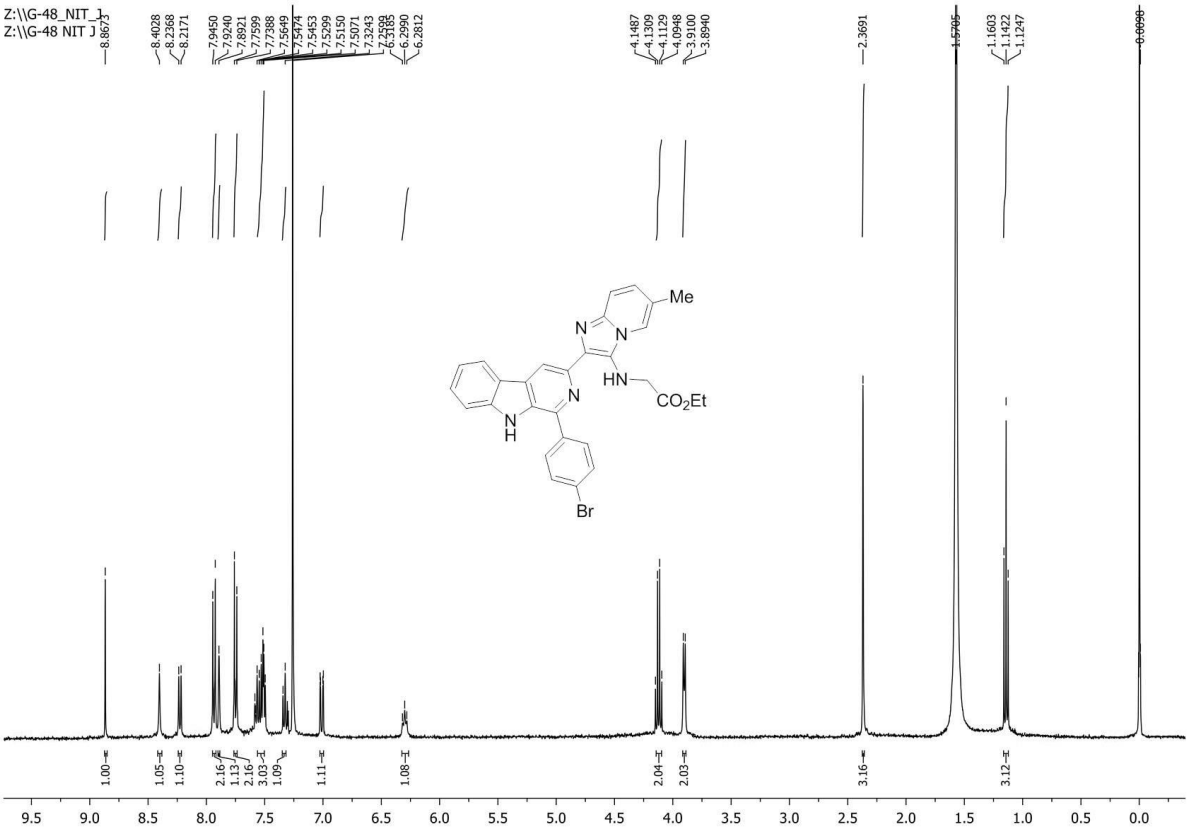

Fig. S 21. ^{1}H-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-6-methylimidazo[1,2-a]pyridin-3-yl)amino)acetate (**7bFX**).

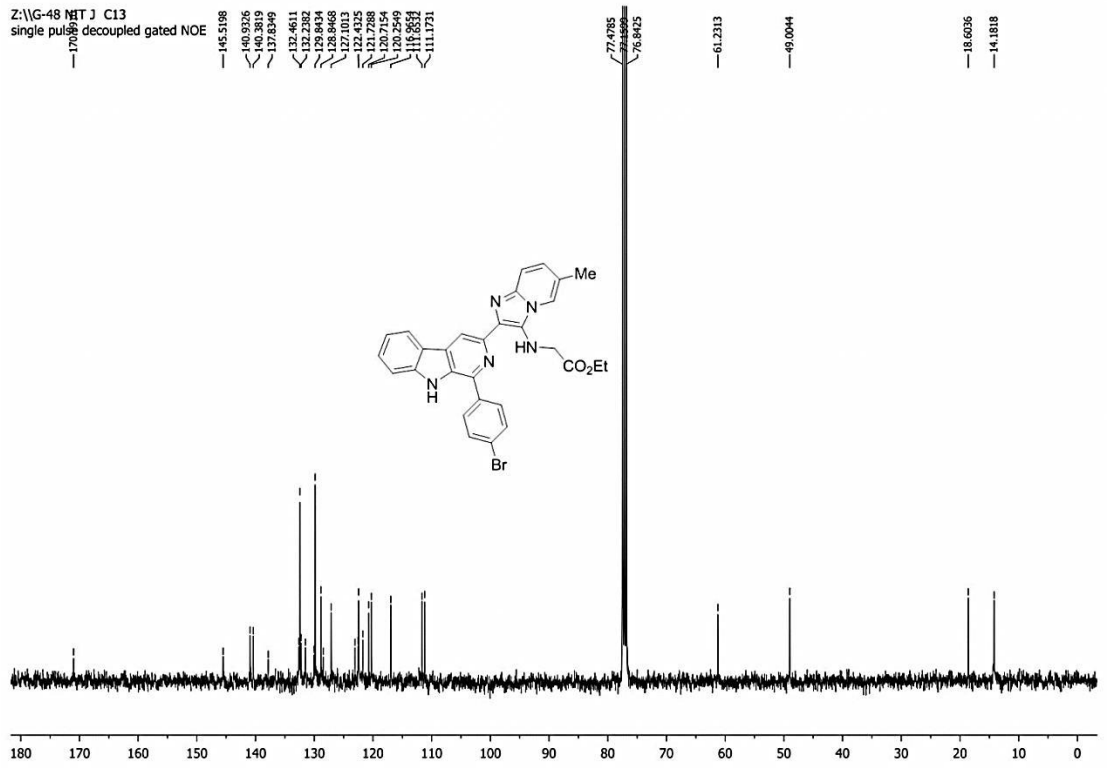

Fig. S 22. ^{13}C-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-6-methylimidazo[1,2-a]pyridin-3-yl)amino)acetate (**7bFX**).

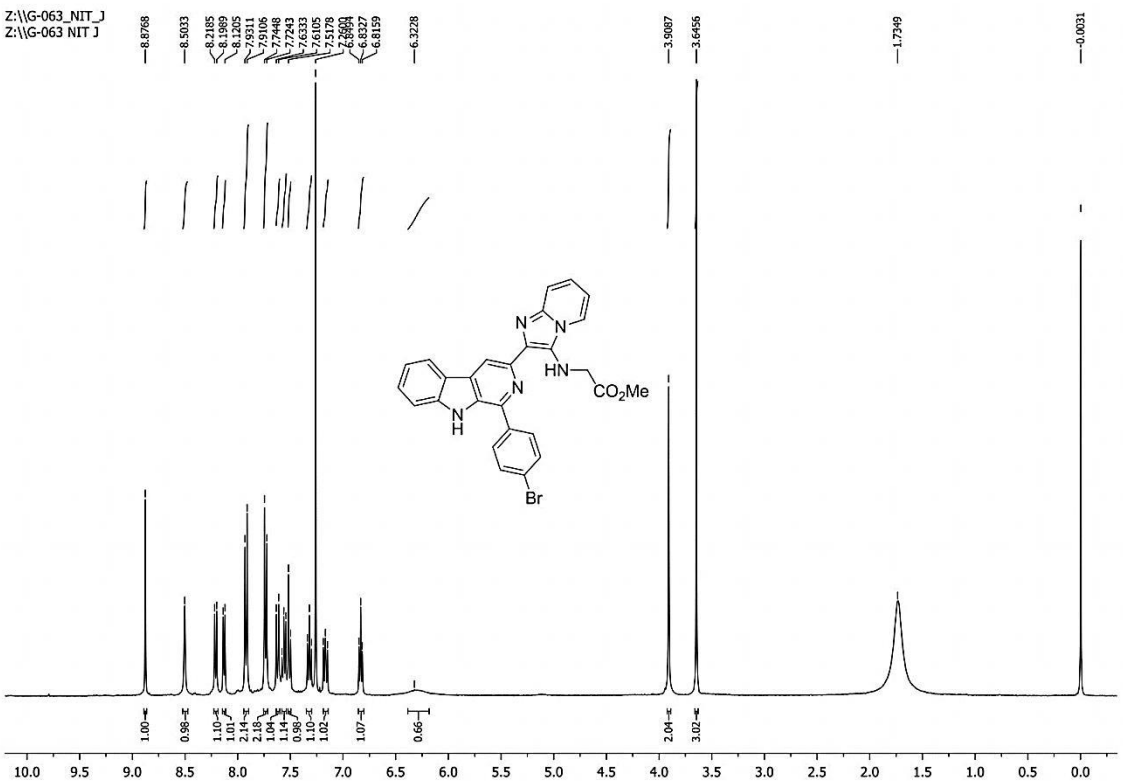

Fig. S 23. ^{1}H-NMR spectrum of methyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bAY**).

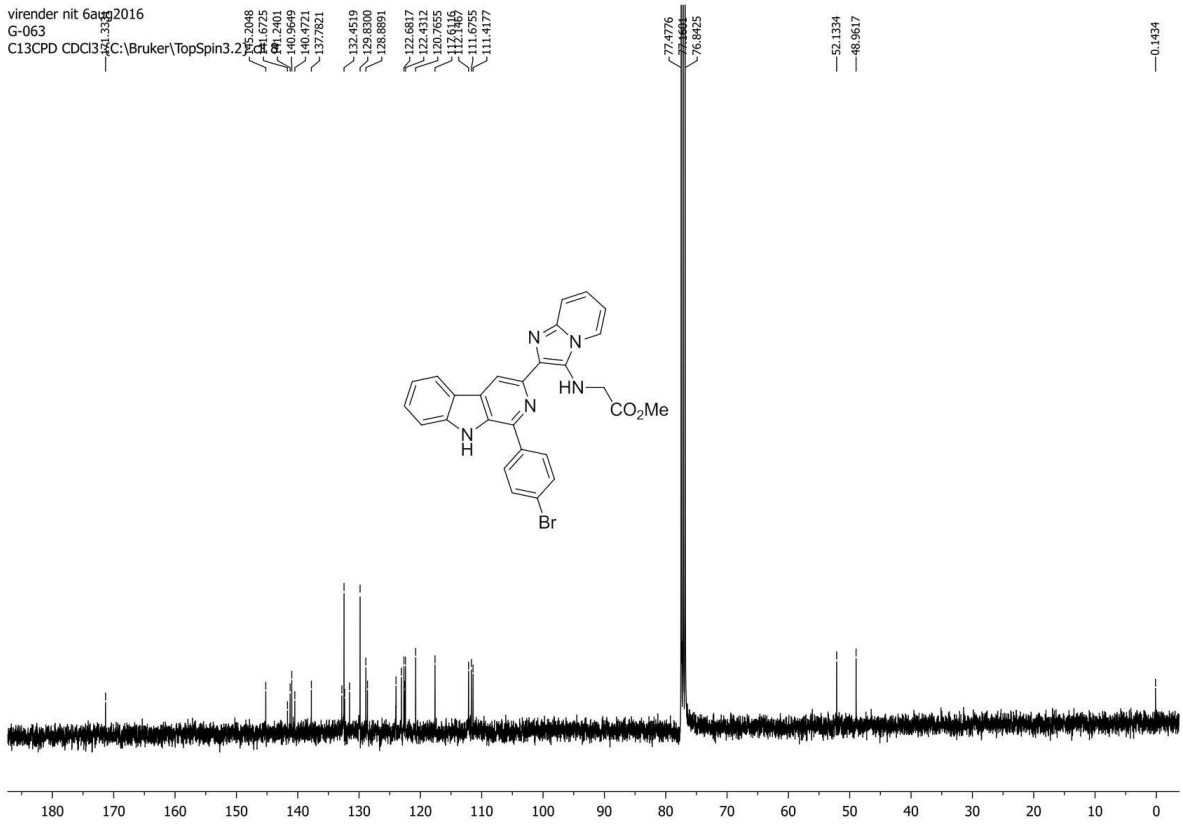

Fig. S 24. ^{13}C-NMR spectrum of methyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7bAY**).

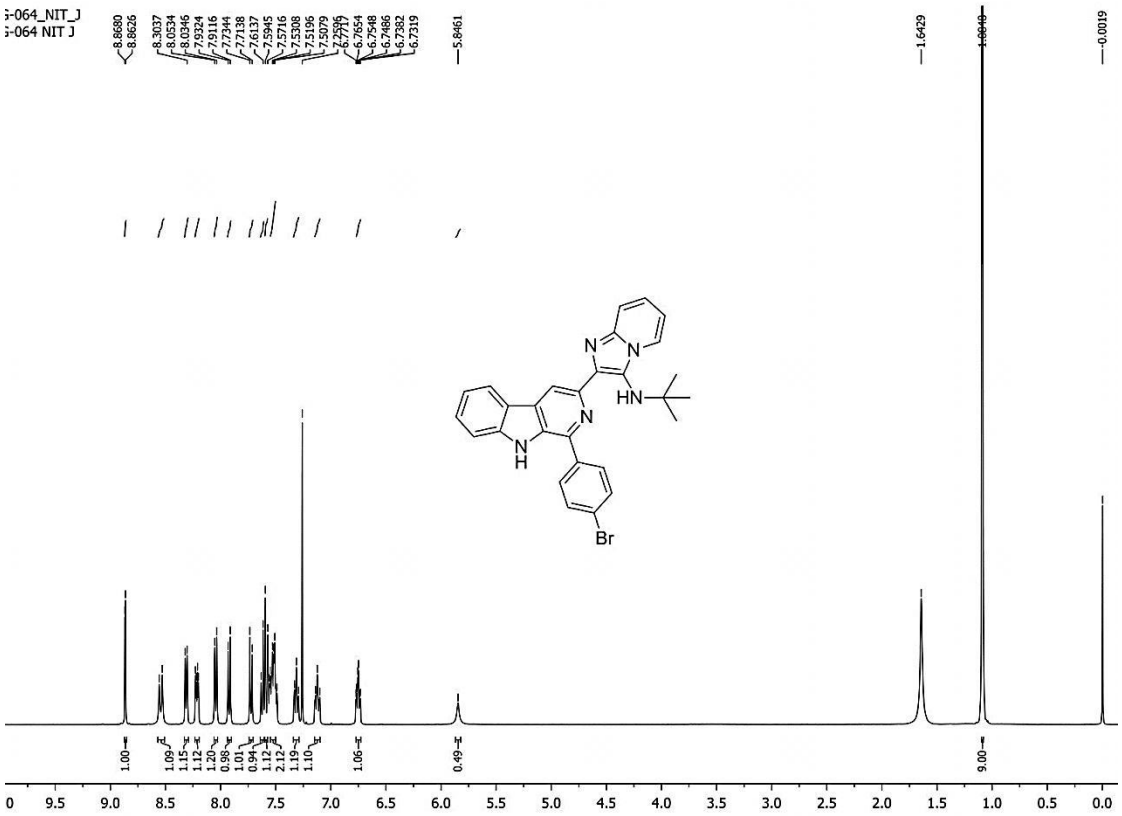

Fig. S 25. ^{1}H-NMR spectrum of 2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-N-(*tert*-butyl)imidazo[1,2-*a*]pyridin-3-amine (**7bAZ**).

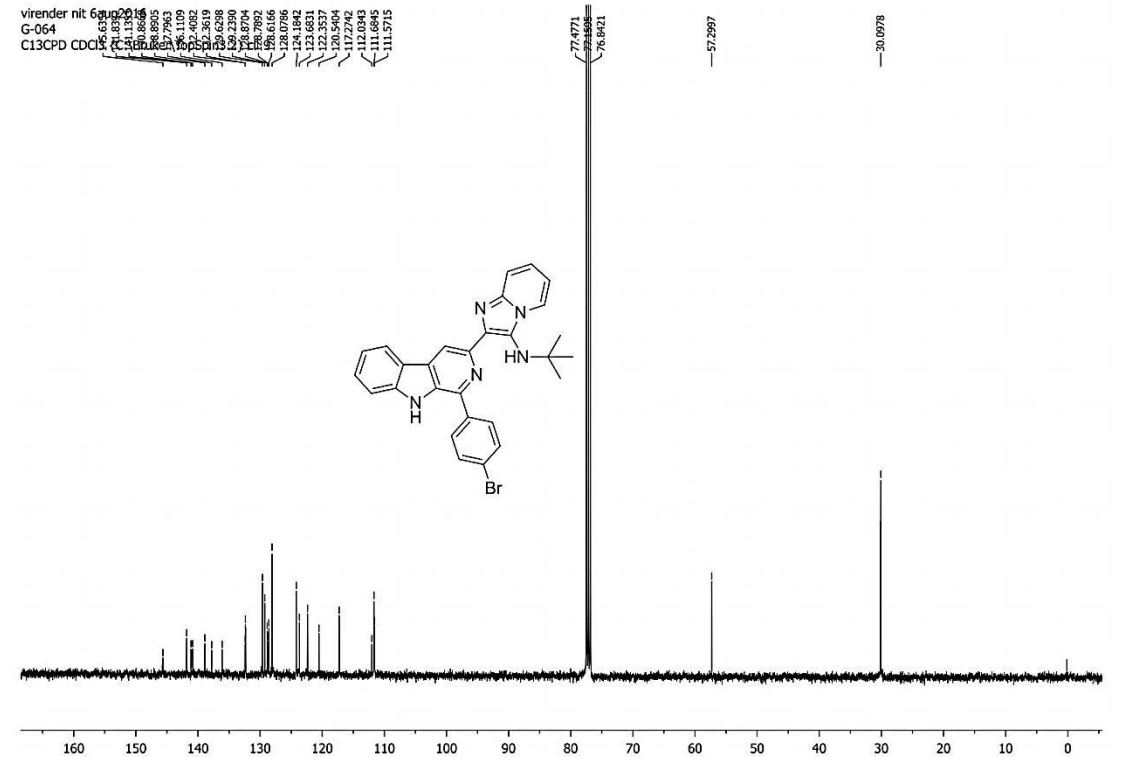

Fig. S 26. ^{13}C-NMR spectrum of 2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-N-(*tert*-butyl)imidazo[1,2-*a*]pyridin-3-amine (**7bAZ**).

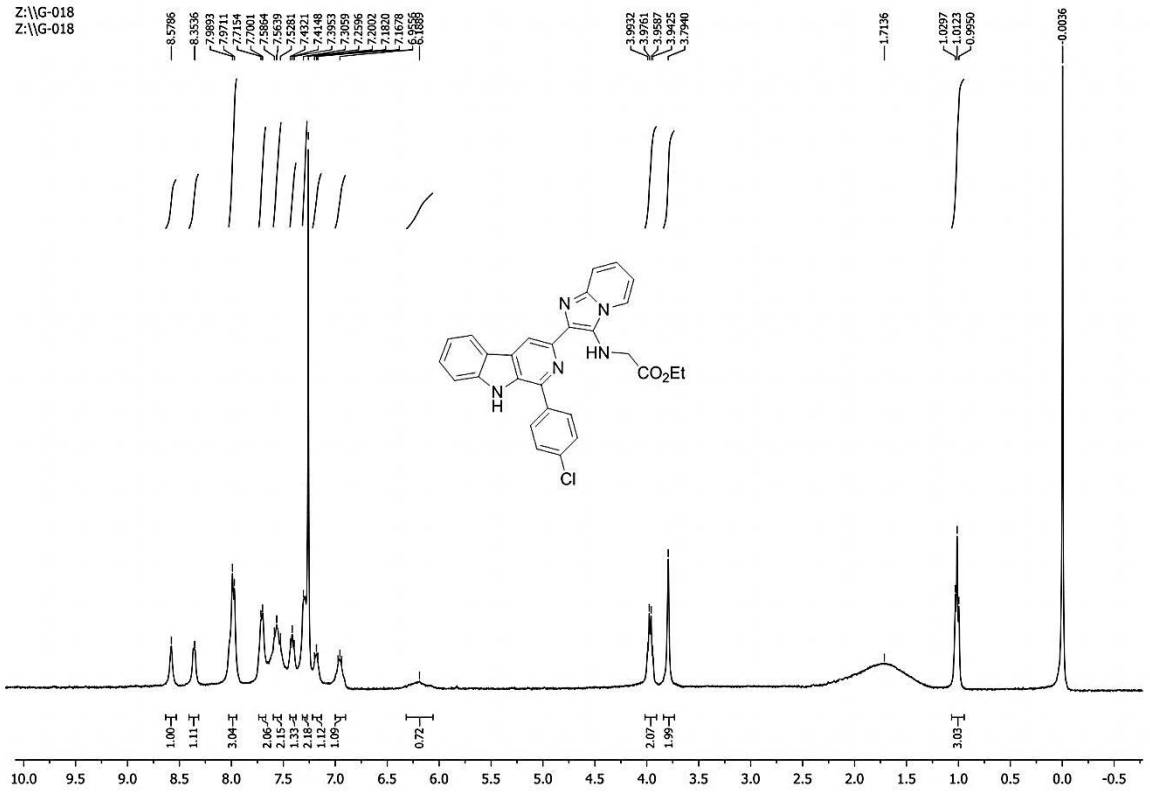

Fig. S 27. ^{1}H-NMR spectrum of ethyl 2-((2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7cAX**).

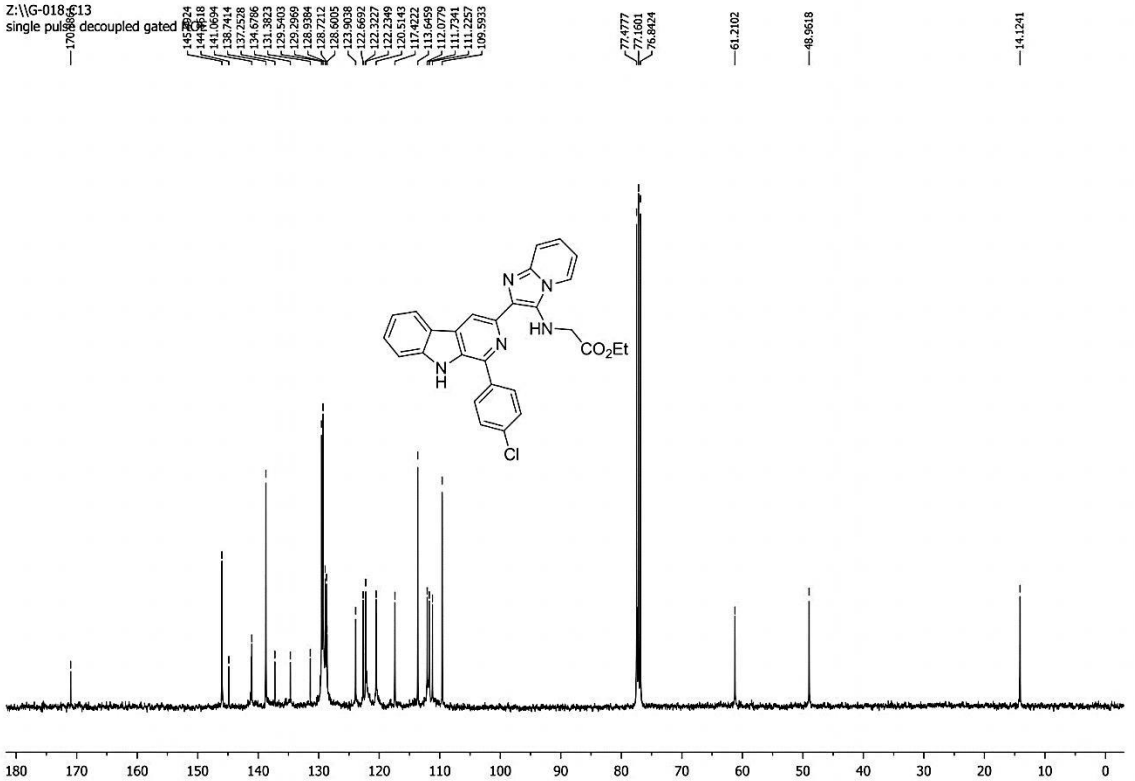

Fig. S 28. ^{13}C-NMR spectrum of ethyl 2-((2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7cAX**).

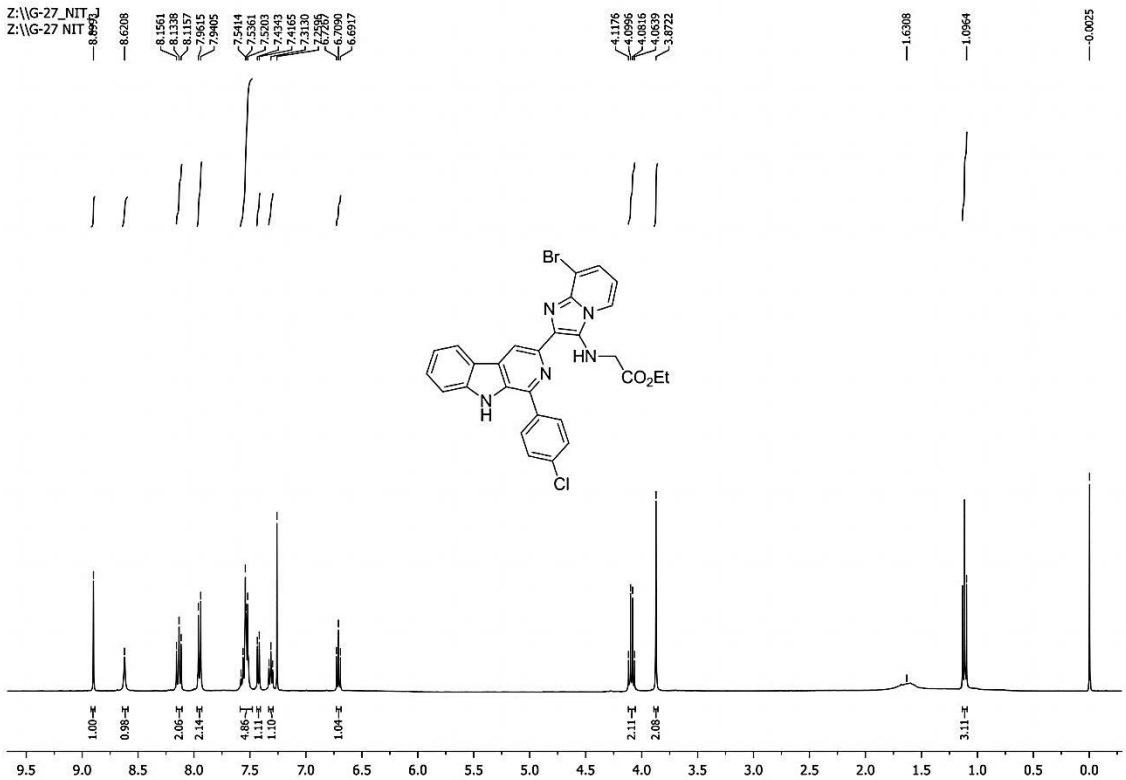

Fig. S 29. ^{1}H-NMR spectrum of ethyl 2-((8-bromo-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7cBX**).

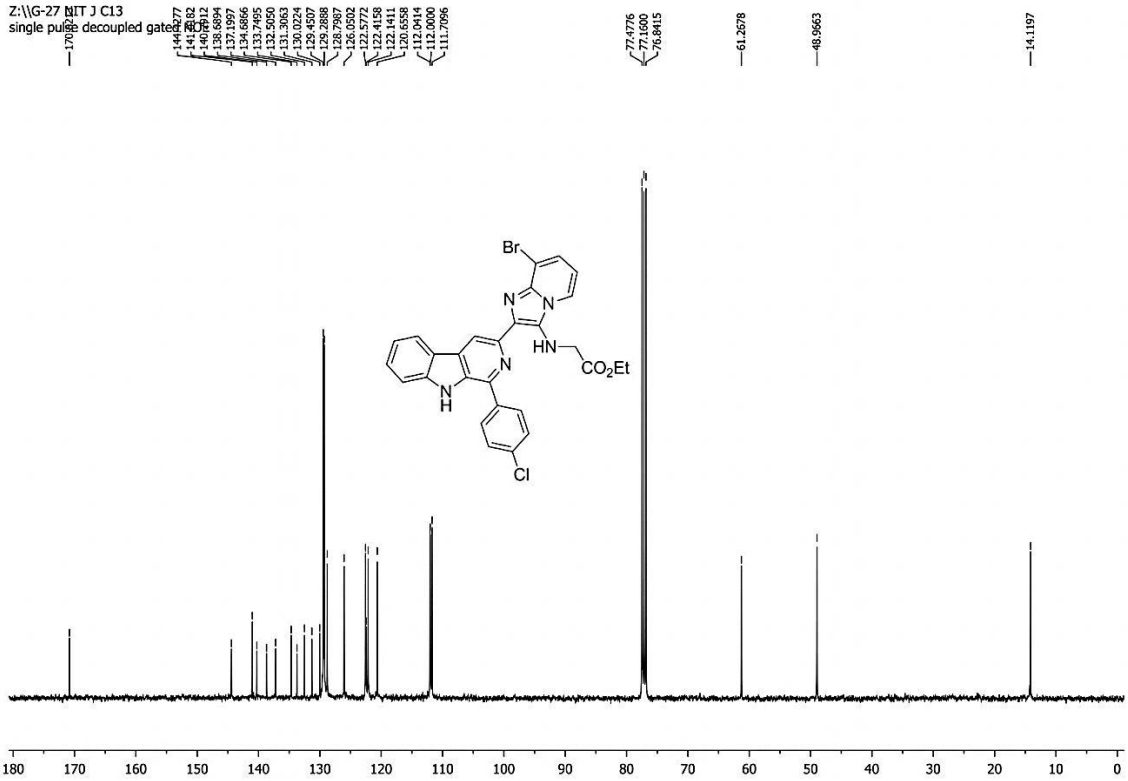

Fig. S 30. ^{13}C-NMR spectrum of ethyl 2-((8-bromo-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7cBX**).

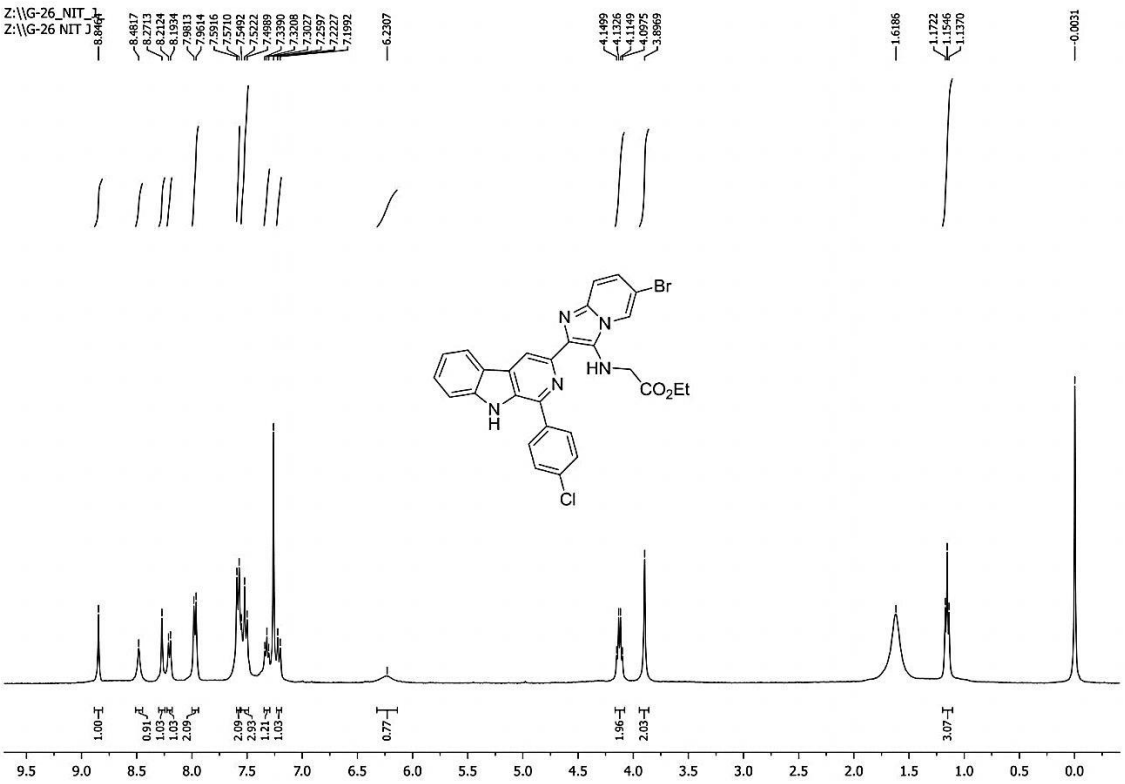

Fig. S 31. ^{1}H-NMR spectrum of ethyl 2-((6-bromo-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7cDX**).

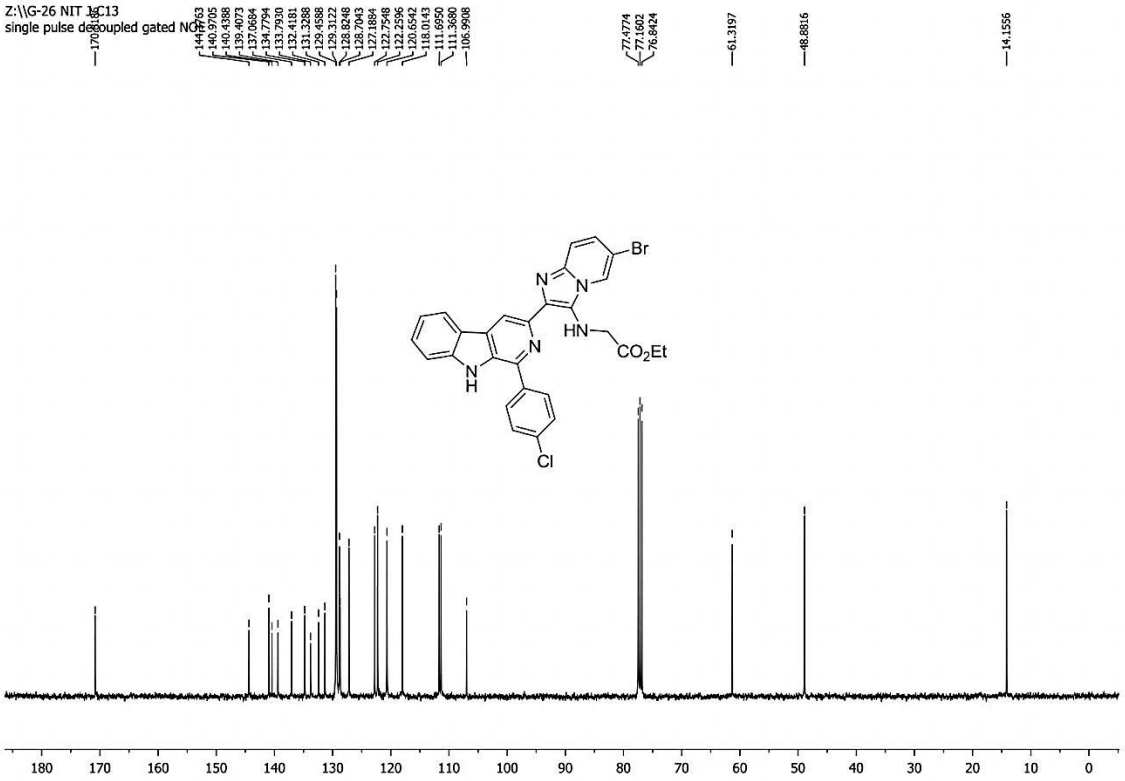

Fig. S 32. ^{13}C-NMR spectrum of ethyl 2-((6-bromo-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7cDX**).

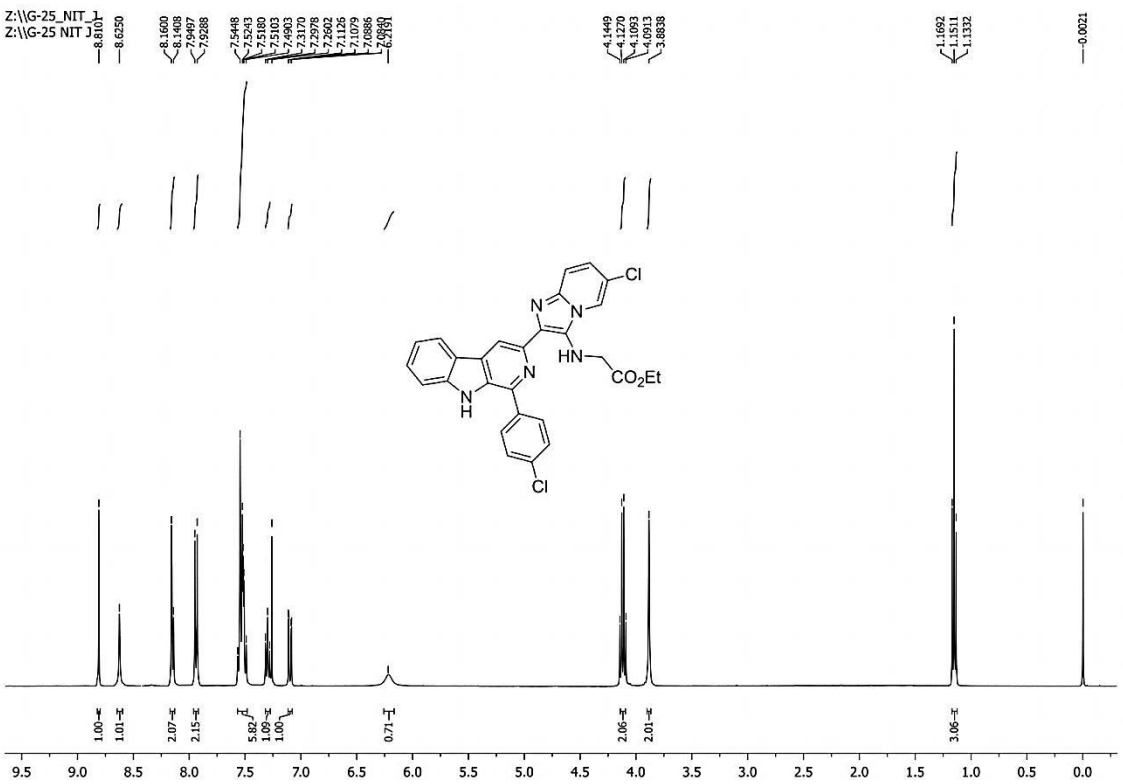

Fig. S 33. ^{1}H-NMR spectrum of ethyl 2-((6-chloro-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7cEX**).

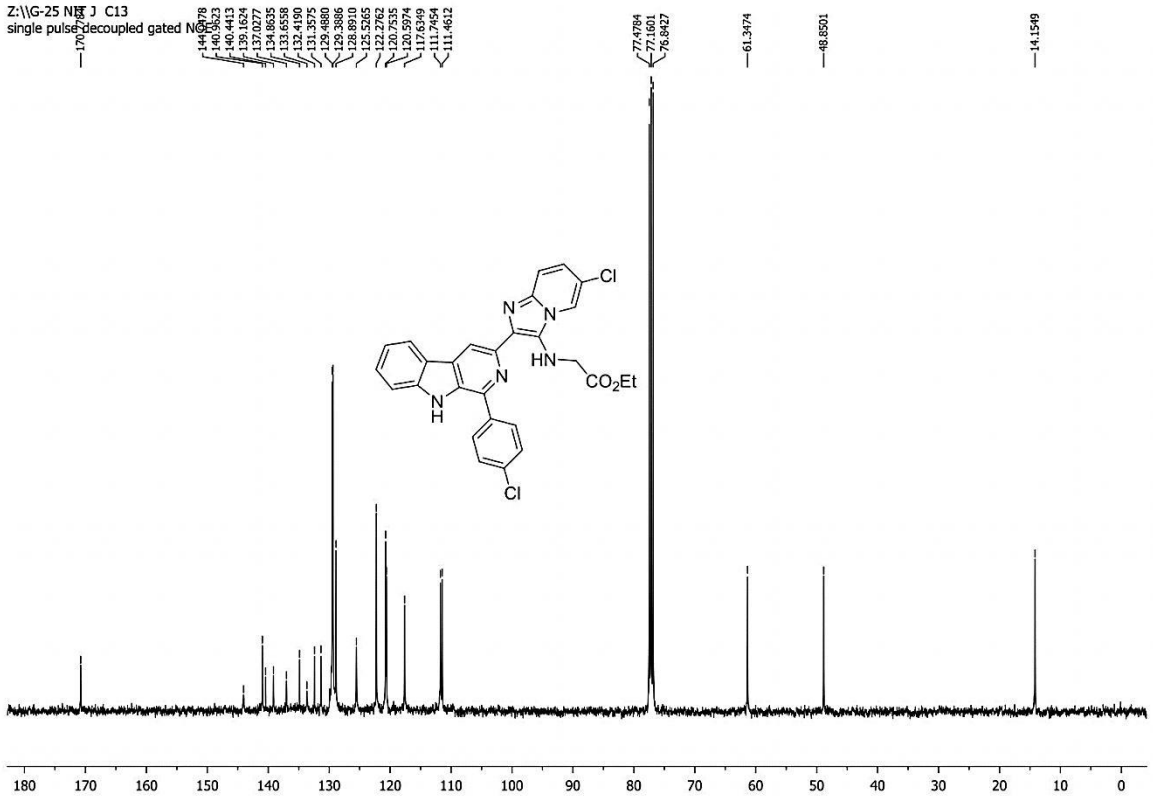

Fig. S 34. ^{13}C-NMR spectrum of ethyl 2-((6-chloro-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**7cEX**).

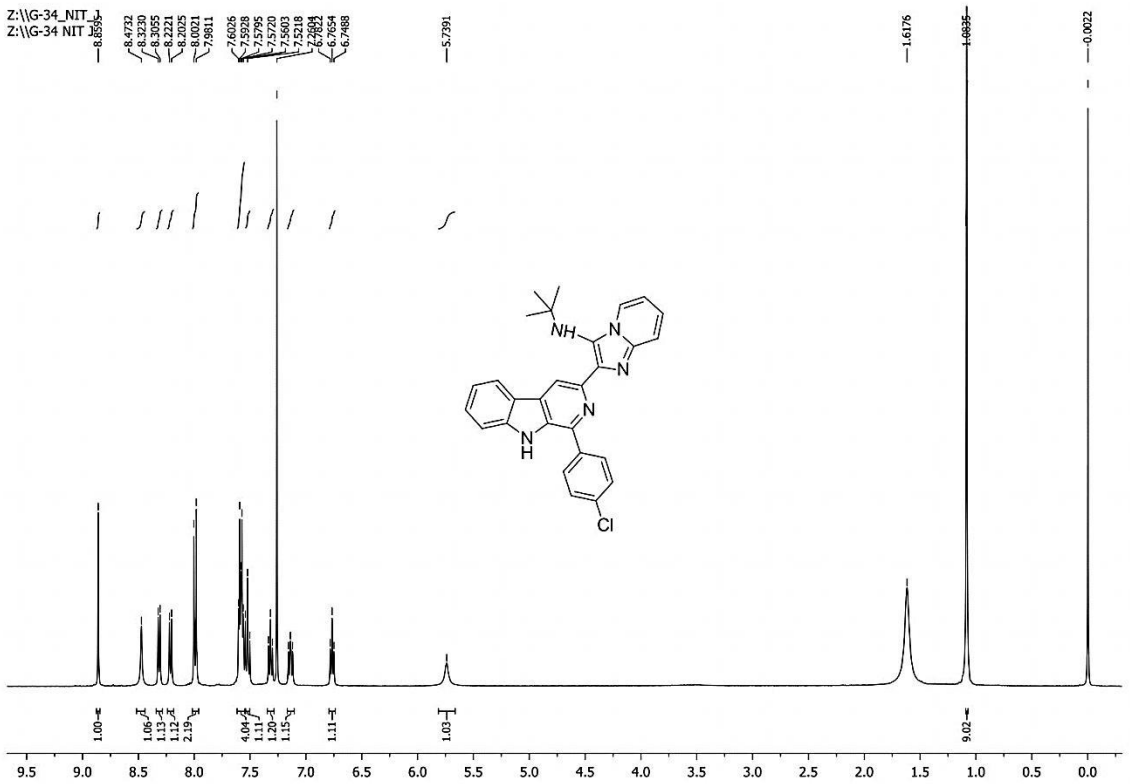

Fig. S 35. ^{1}H-NMR spectrum of *N*-(*tert*-butyl)-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-amine (**7cAZ**).

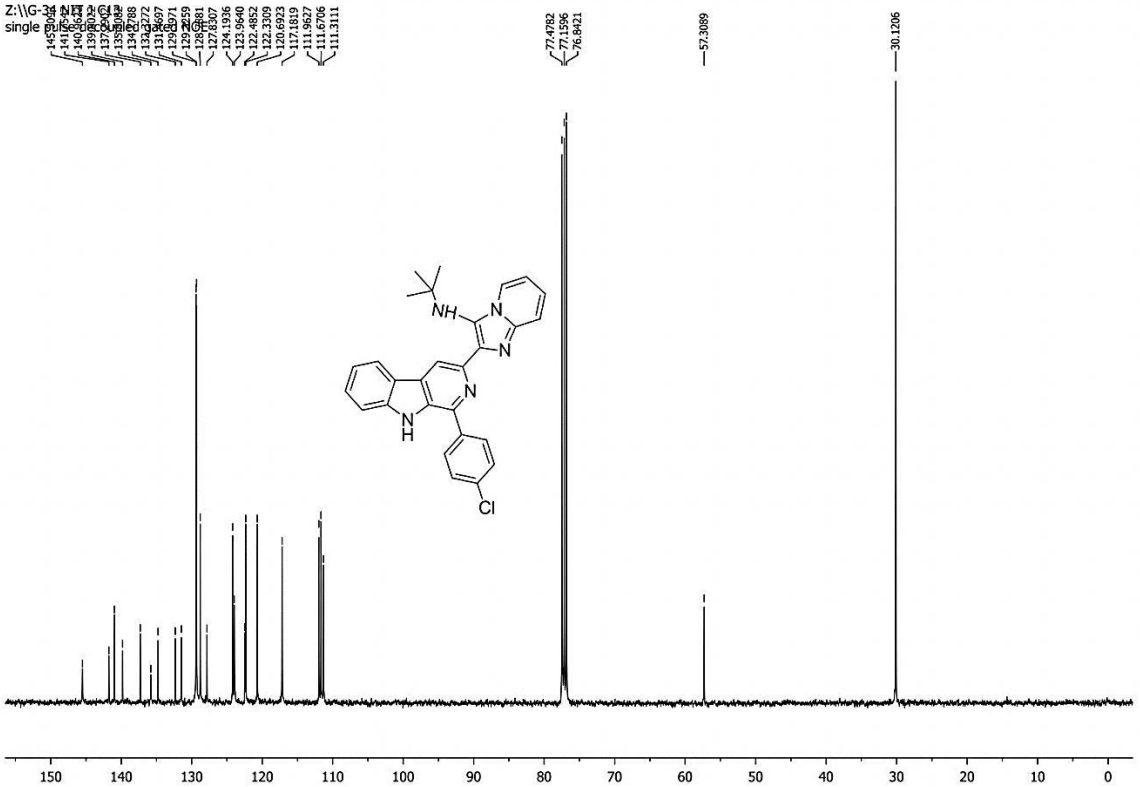

Fig. S 36. ^{13}C-NMR spectrum of *N*-(*tert*-butyl)-2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-amine (**7cAZ**).

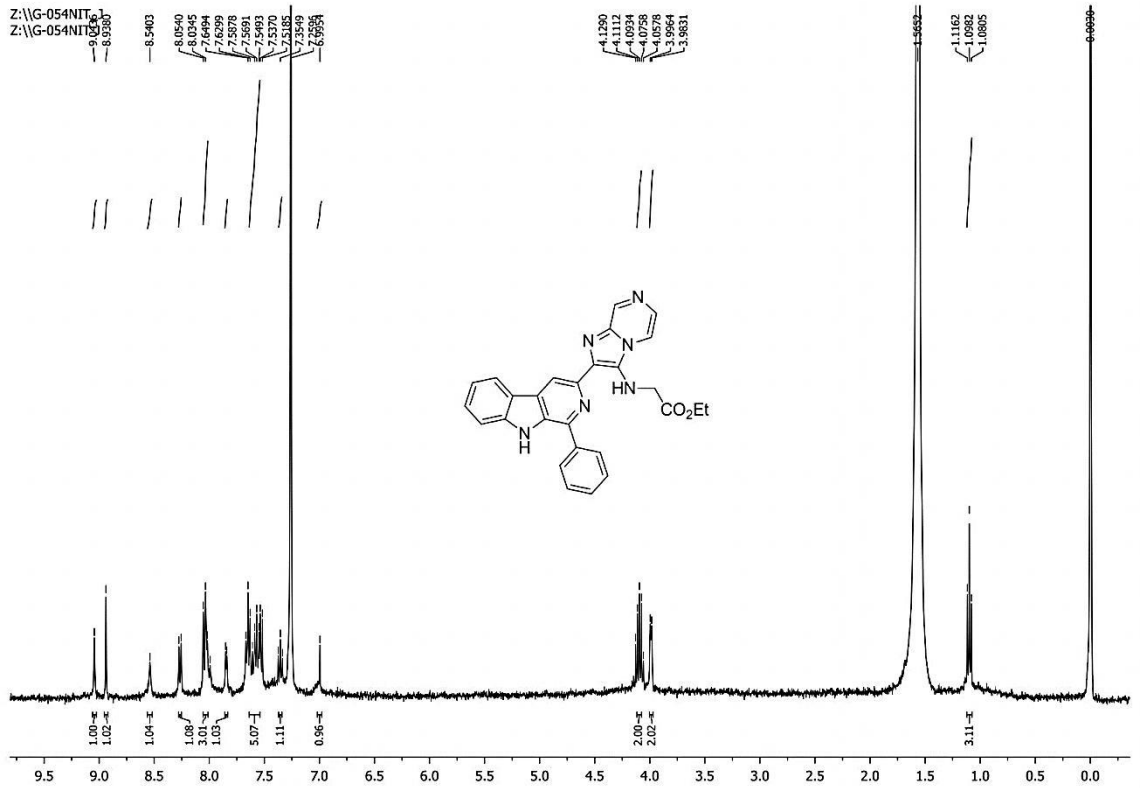

Fig. S 37. ^{1}H-NMR spectrum of ethyl 2-((2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (**8aGX**).

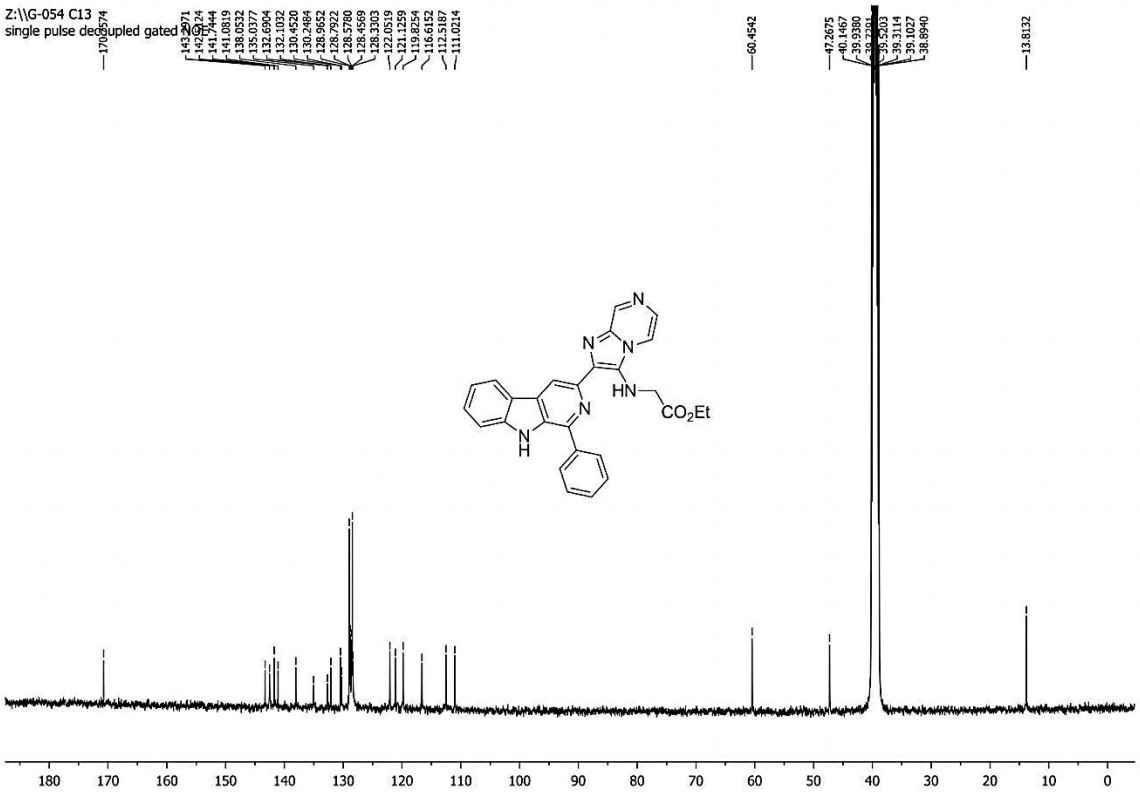

Fig. S 38. ^{13}C-NMR spectrum of ethyl 2-((2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (**8aGX**).

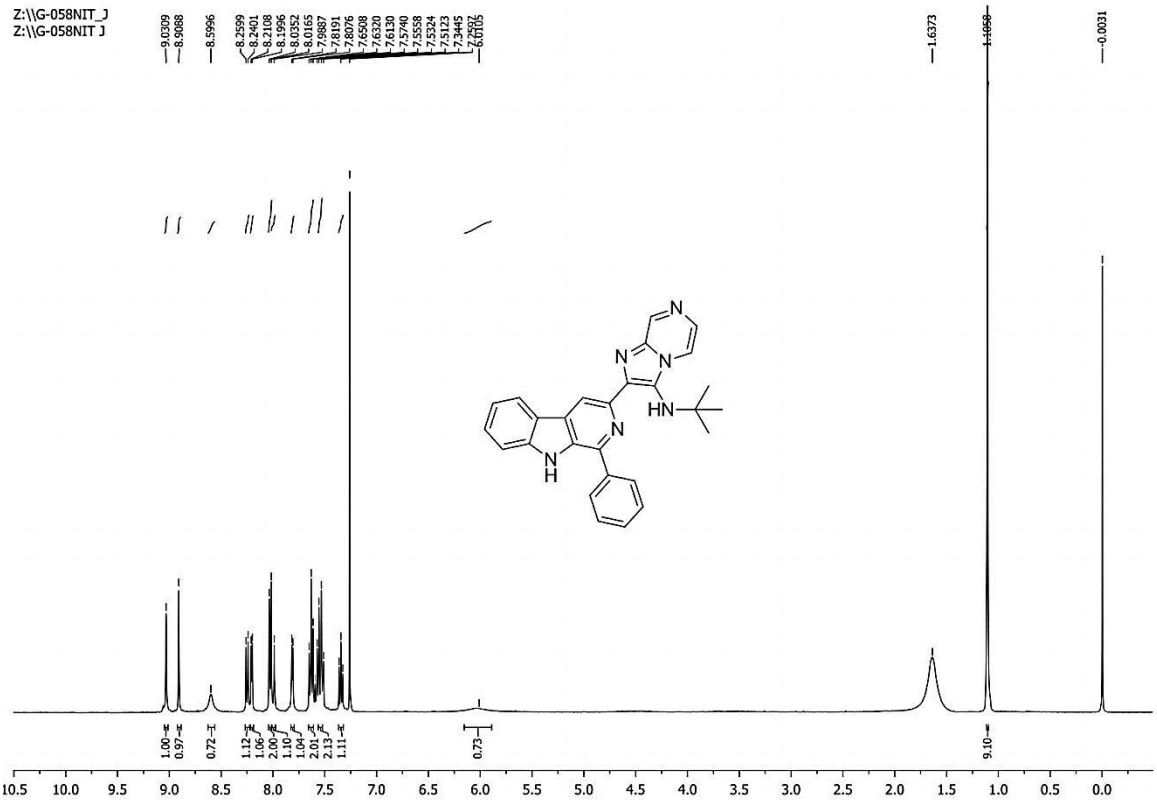

Fig. S 39. ^{1}H-NMR spectrum of *N*-(*tert*-butyl)-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-amine (**8aGZ**).

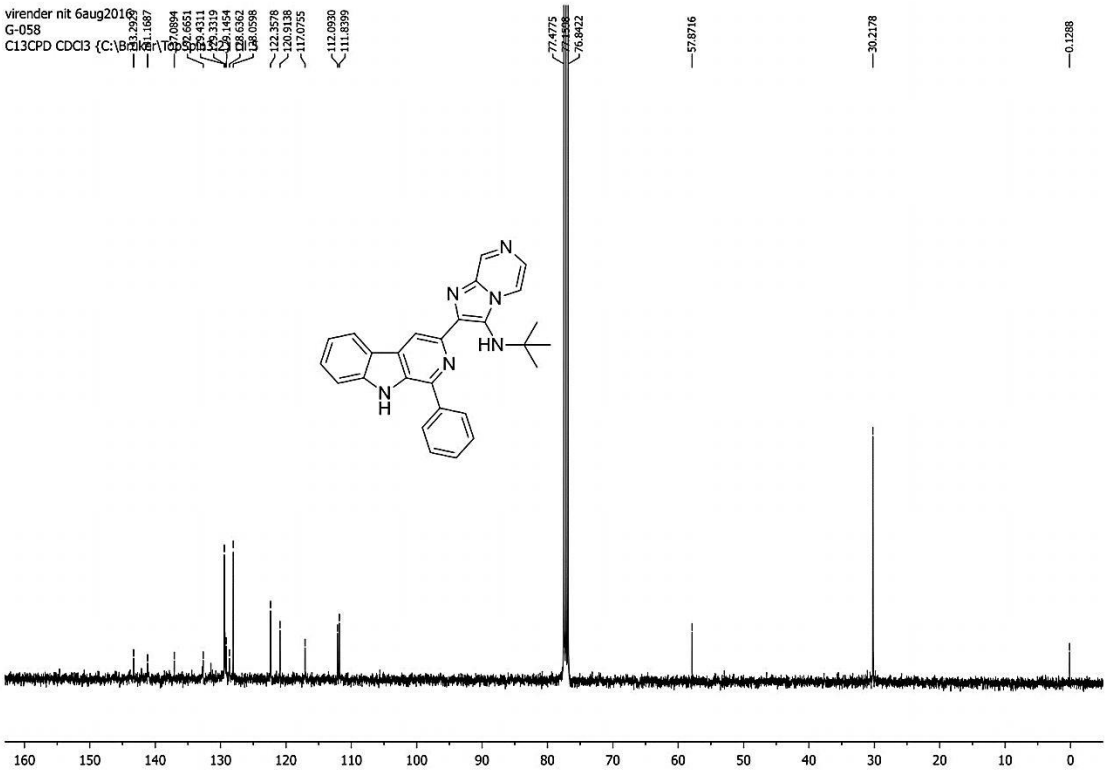

Fig. S 40. ^{13}C-NMR spectrum of *N*-(*tert*-butyl)-2-(1-phenyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-amine (**8aGZ**).

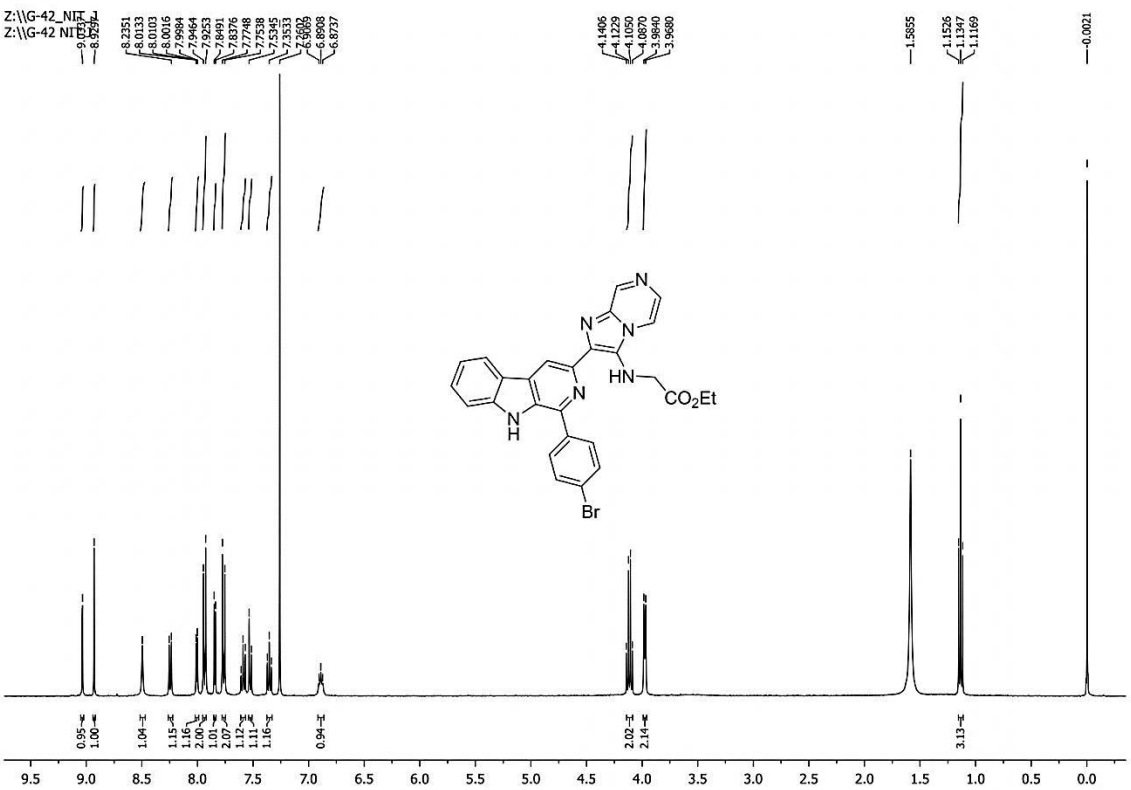

Fig. S 41. ^{1}H-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (**8bGX**).

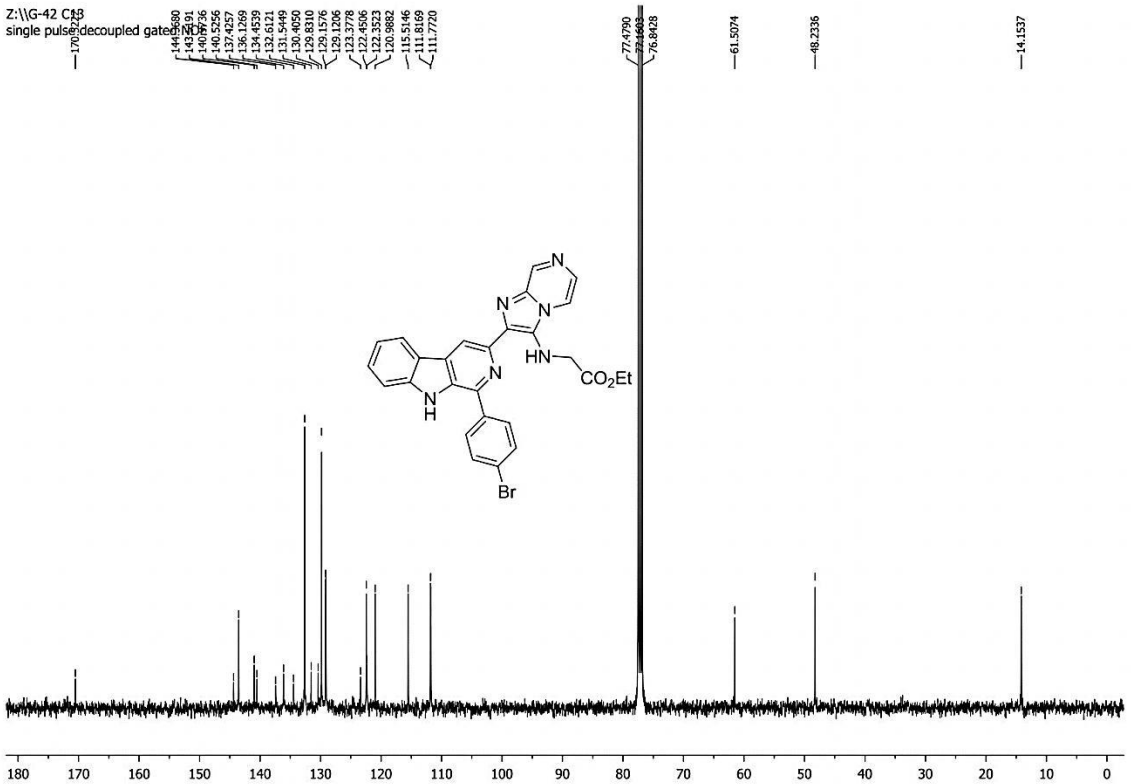

Fig. S 42. ^{13}C-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (**8bGX**).

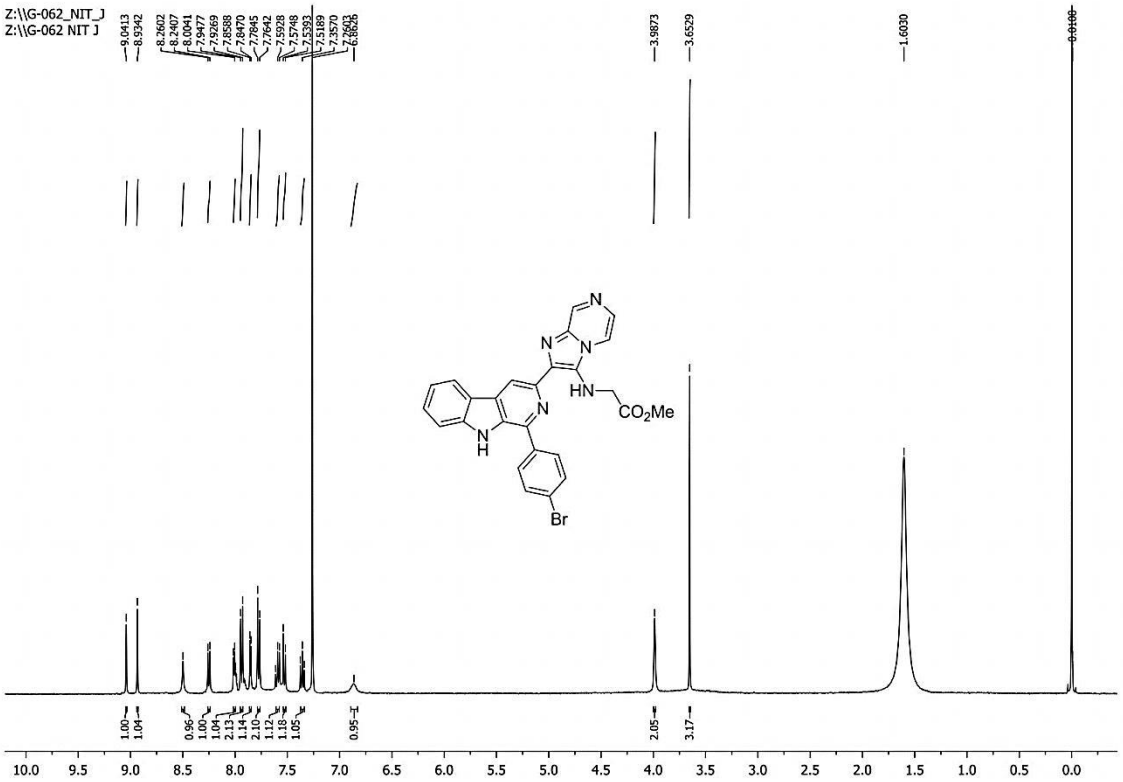

Fig. S 43. ^{1}H-NMR spectrum of methyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (**8bGY**).

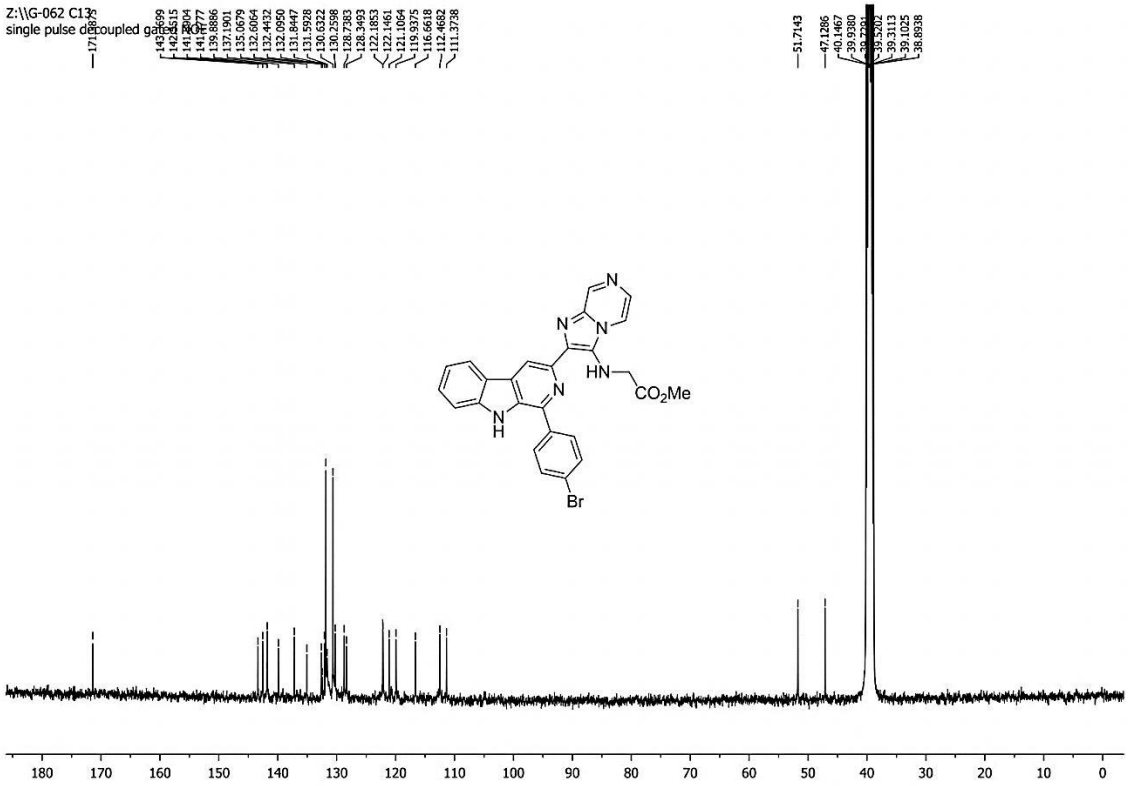

Fig. S 44. ^{13}C-NMR spectrum of methyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (**8bGY**).

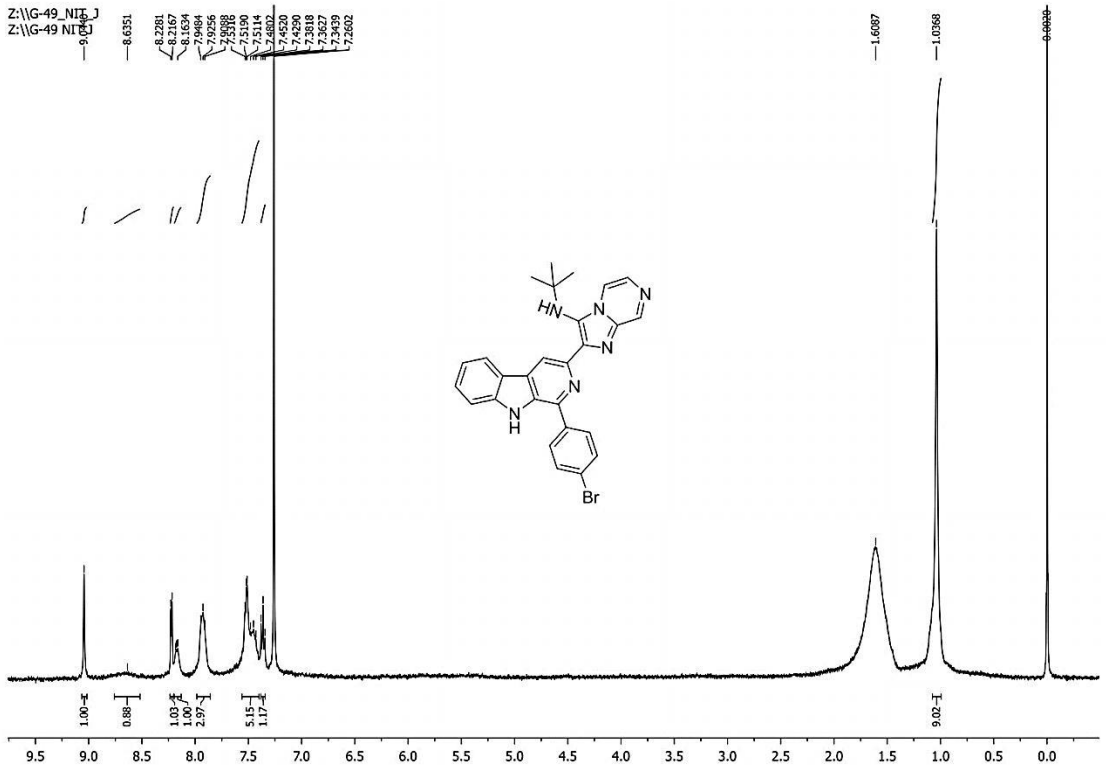

Fig. S 45. ^{1}H-NMR spectrum of 2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-N-(tert-butyl)imidazo[1,2-*a*]pyrimidin-3-amine (**8bGZ**).

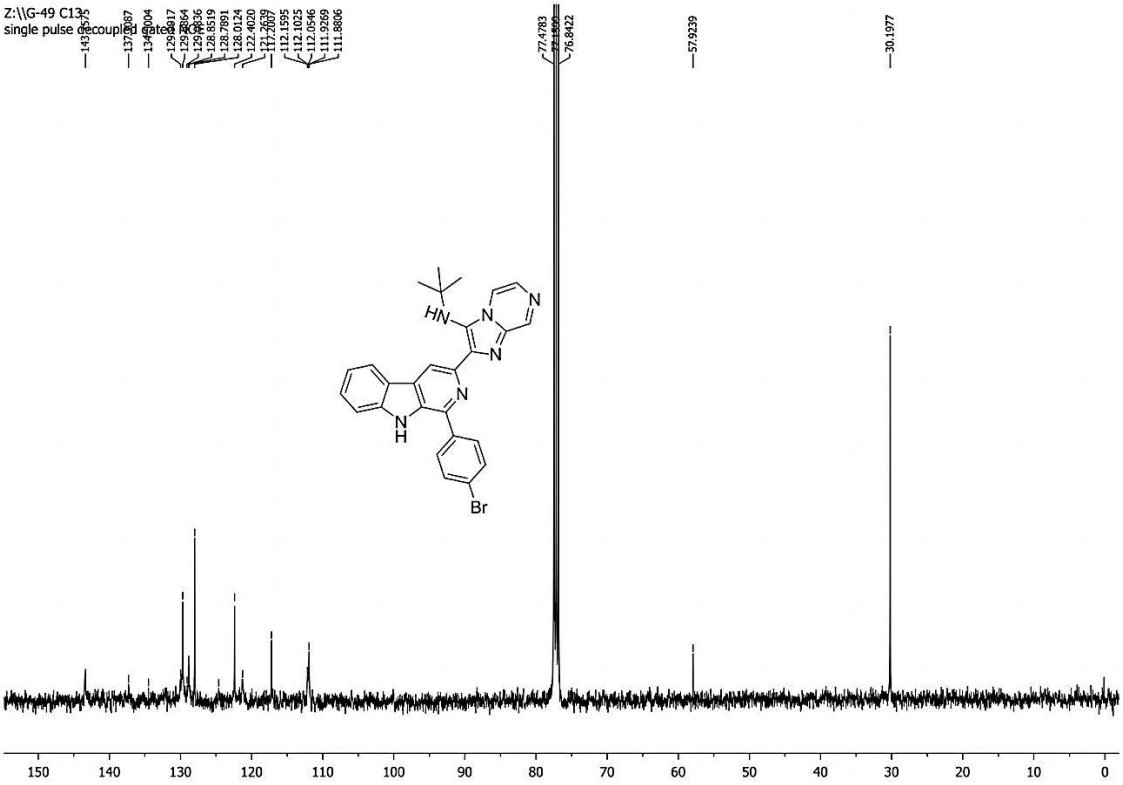

Fig. S 46. ^{13}C-NMR spectrum of 2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-N-(tert-butyl)imidazo[1,2-*a*]pyrimidin-3-amine (**8bGZ**).

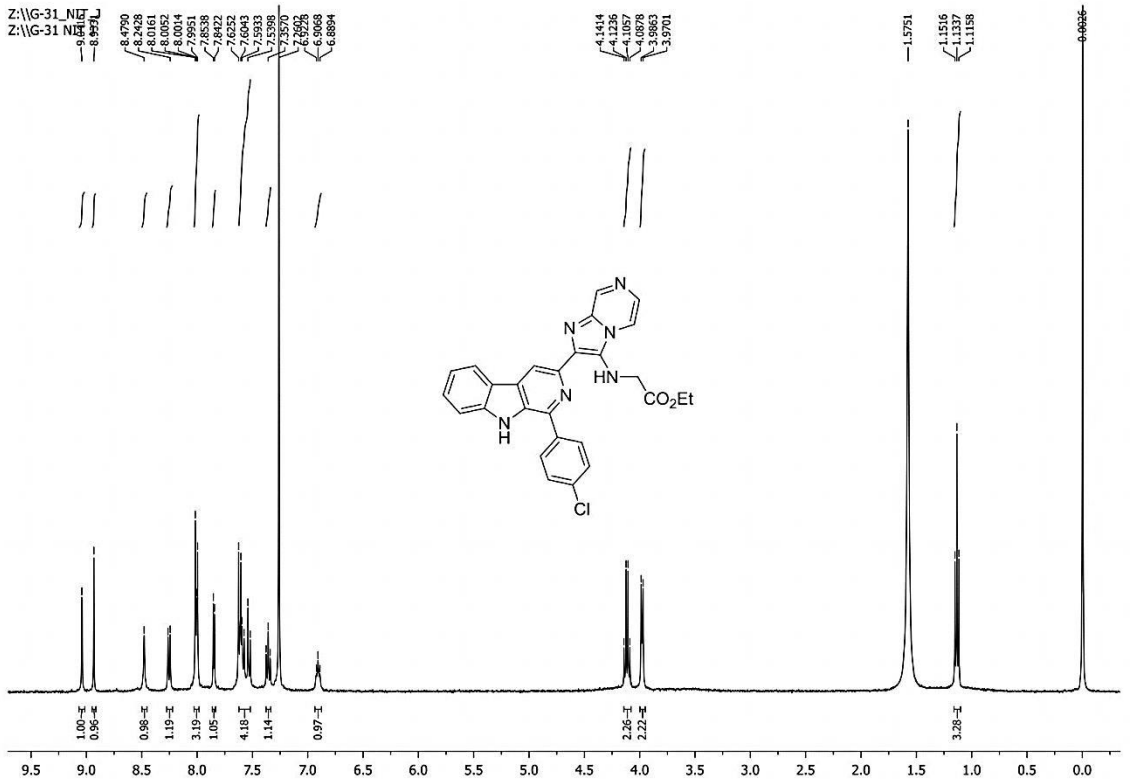

Fig. S 47. ^{1}H-NMR spectrum of ethyl 2-((2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (**8cGX**).

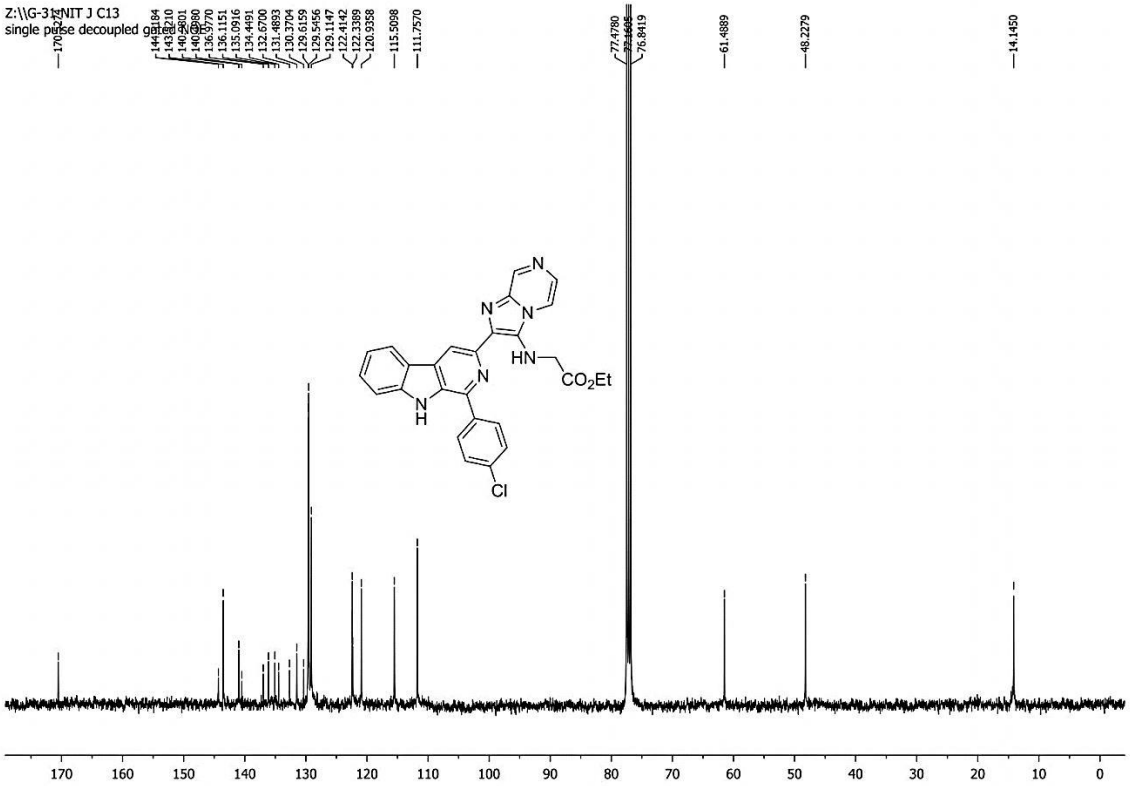

Fig. S 48. ^{13}C-NMR spectrum of ethyl 2-((2-(1-(4-chlorophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrazin-3-yl)amino)acetate (**8cGX**).

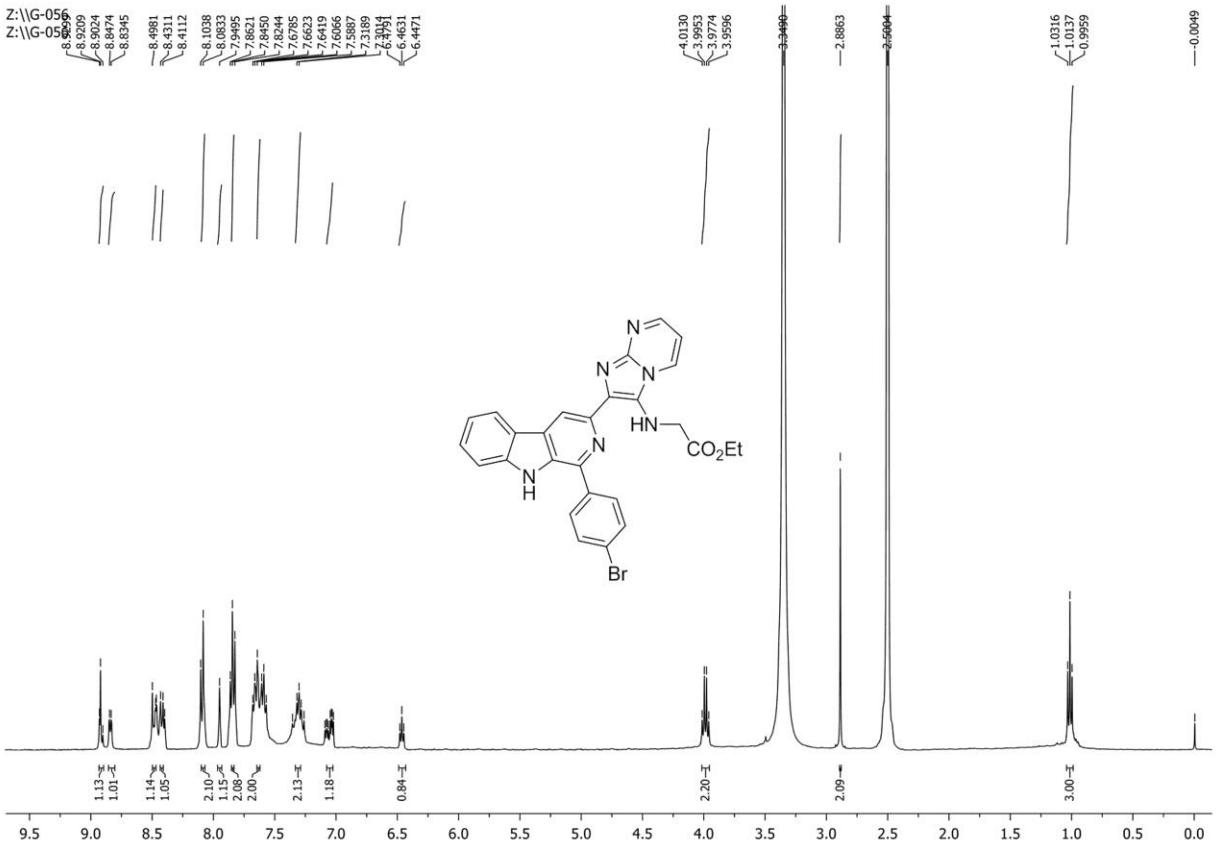

Fig. S 49. ^{1}H-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrimidin-3-yl)amino)acetate (**9bHX**).

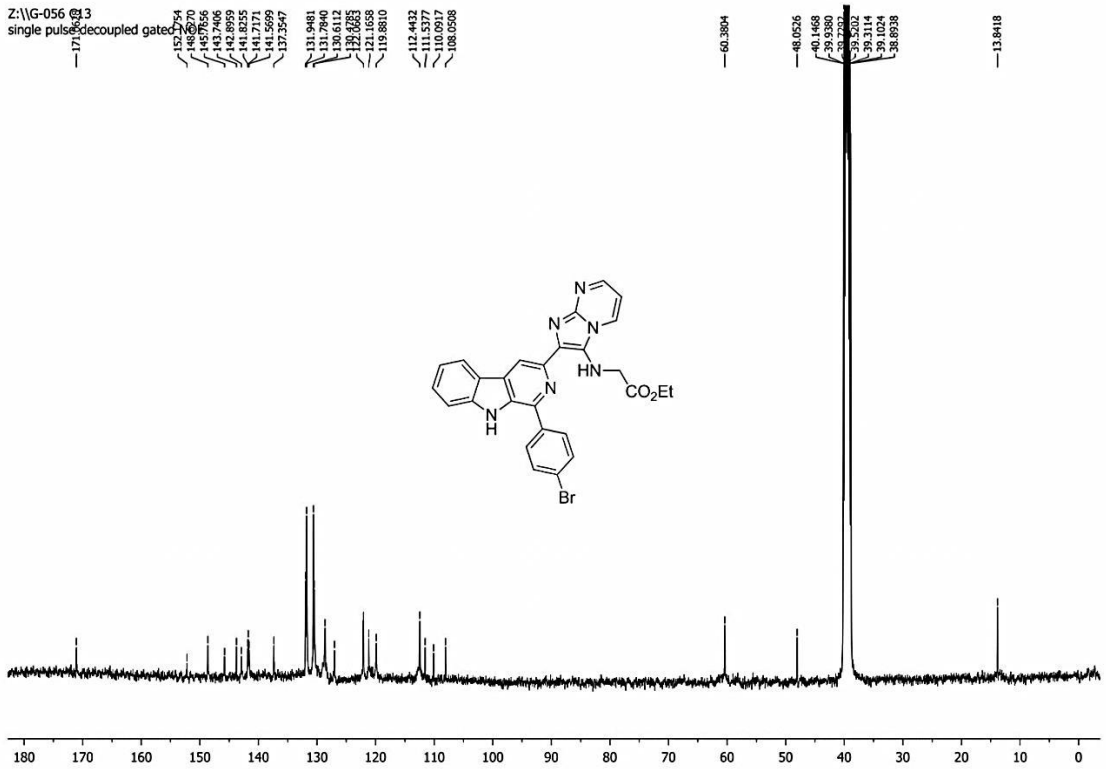

Fig. S 50. ^{13}C-NMR spectrum of ethyl 2-((2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyrimidin-3-yl)amino)acetate (**9bHX**).

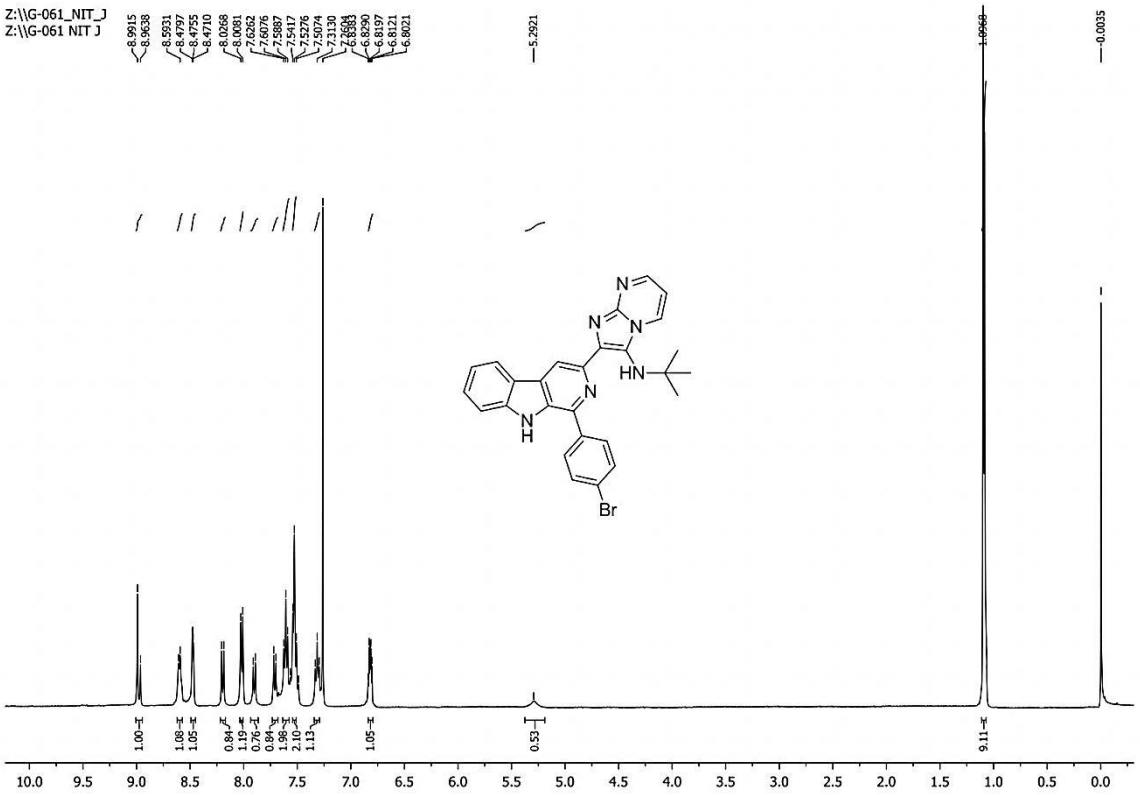

Fig. S 51. ^{1}H-NMR spectrum of 2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-N-(*tert*-butyl)imidazo[1,2-*a*]pyrimidin-3-amine (**9bHZ**).

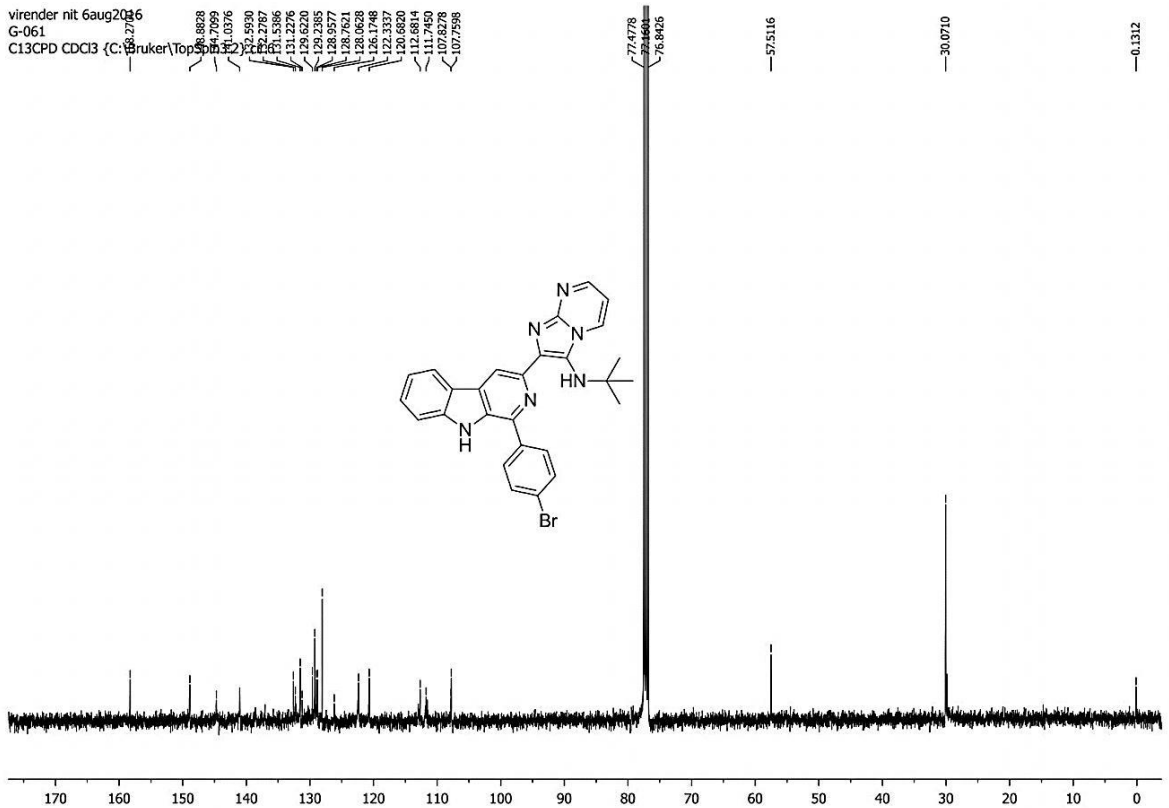

Fig. S 52. ^{13}C-NMR spectrum of 2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)-N-(*tert*-butyl)imidazo[1,2-*a*]pyrimidin-3-amine (**9bHZ**).

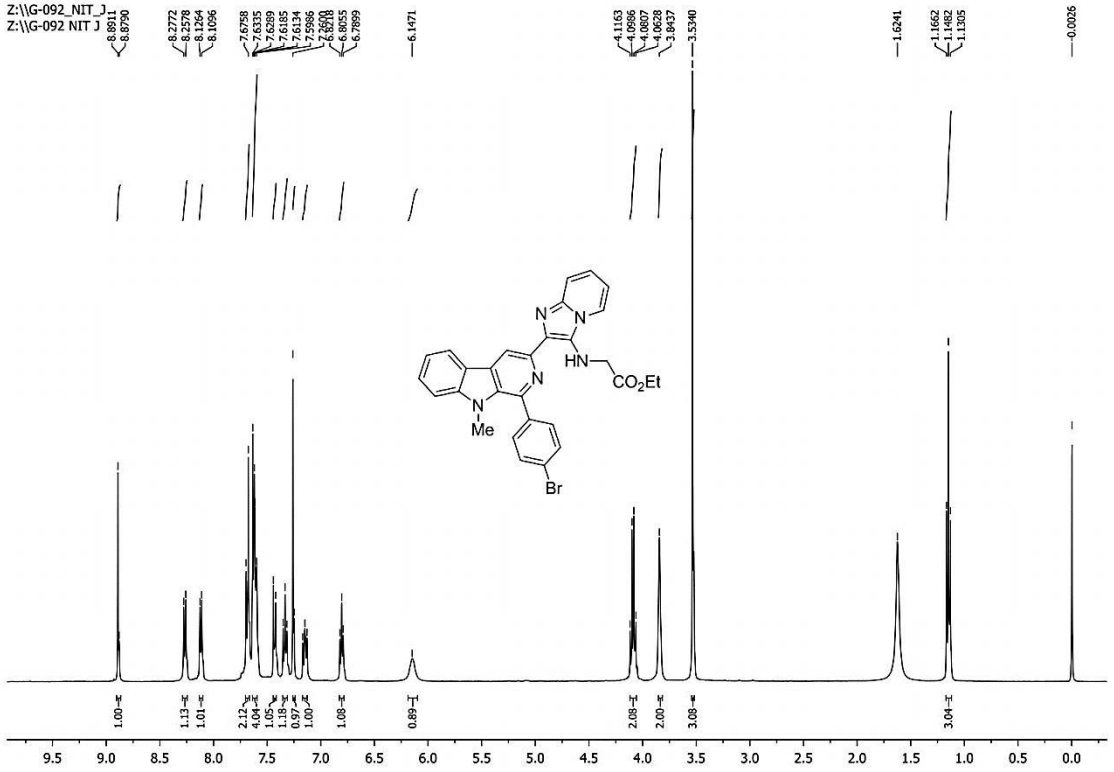

Fig. S 53. ^{1}H-NMR spectrum of Ethyl 2-((2-(1-(4-bromophenyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**11bAX**).

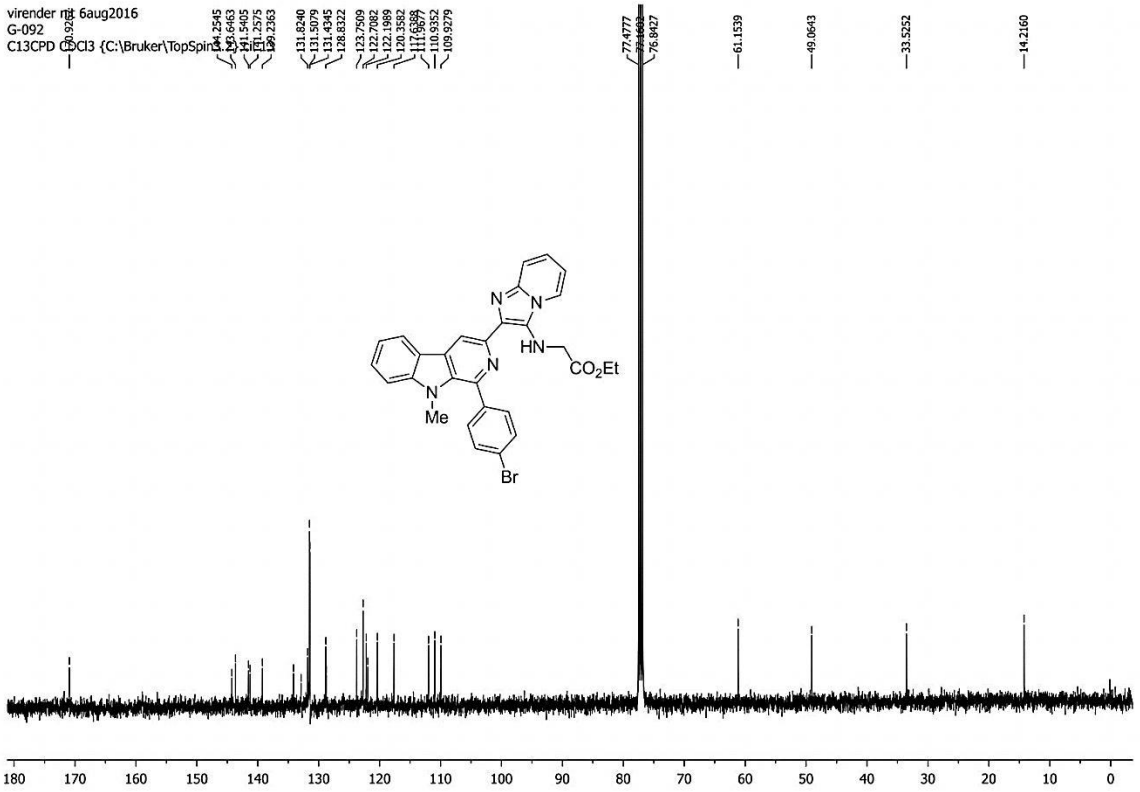

Fig. S 54. ^{13}C-NMR spectrum of Ethyl 2-((2-(1-(4-bromophenyl)-9-methyl-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-yl)amino)acetate (**11bAX**).

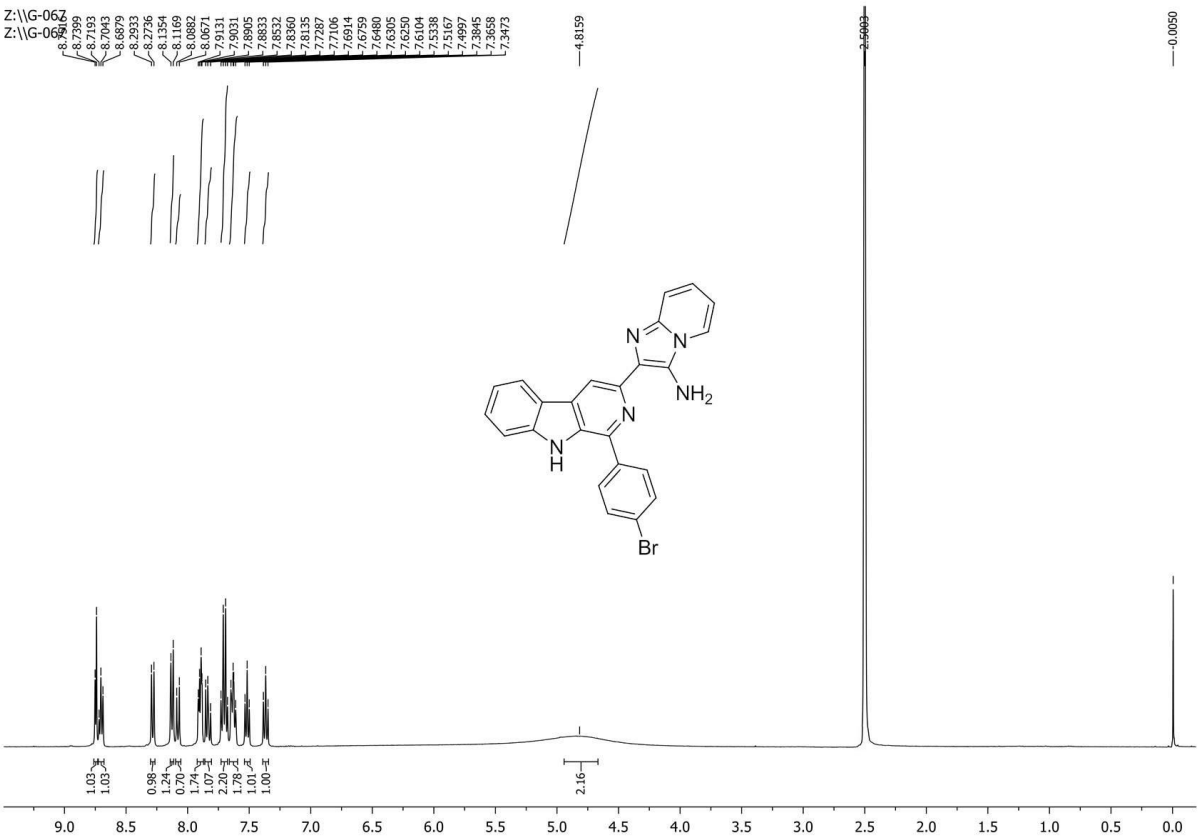

Fig. S 55. ^{1}H-NMR spectrum of 2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-amine (**12bAZ**).

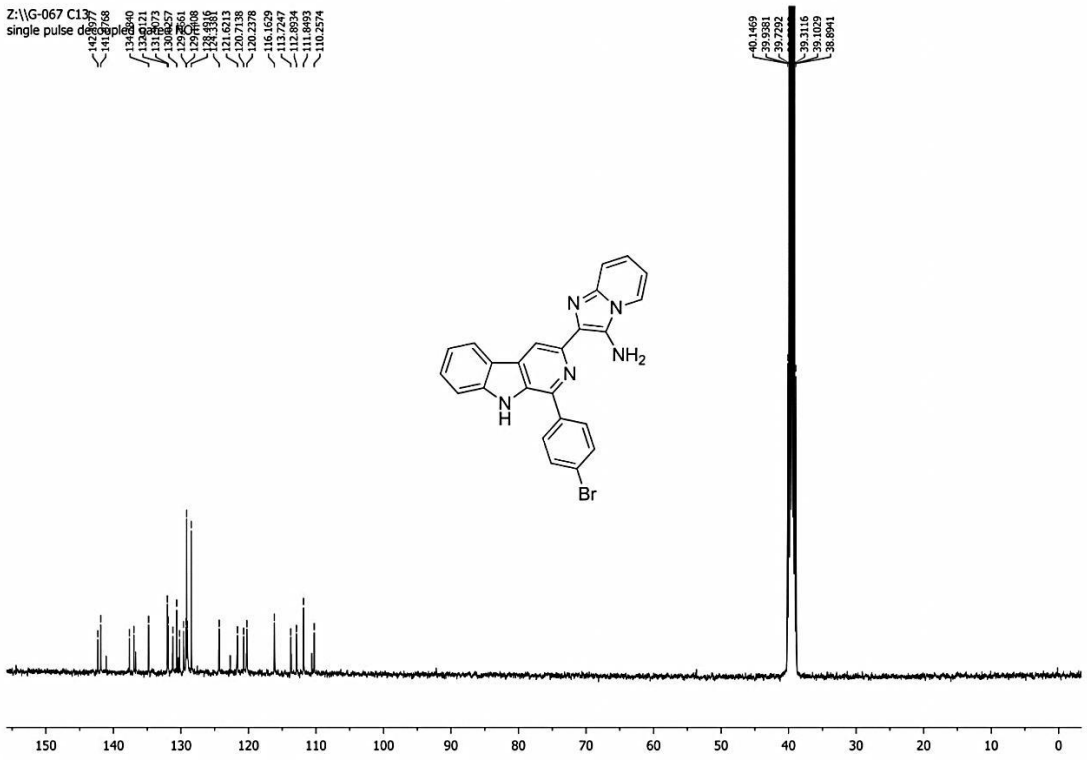

Fig. S 56. ^{13}C-NMR spectrum of 2-(1-(4-bromophenyl)-9*H*-pyrido[3,4-*b*]indol-3-yl)imidazo[1,2-*a*]pyridin-3-amine (**12bAZ**).