Disaggregation Induced ESIPT: A Novel Approach Towards Development of Sensor for Hyperglycemic Condition

Jayant Sindhu[a,#], Mayank[b,#], Aman K. K. Bhasin[a], Navneet Kaur[a], Narinder Singh[b], K.K. Bhasin[a*]

[a]Department of Chemistry, Punjab University,an Chandigarh, 160014, India.

Email: kkbhasin@pu.ac.in

[b]Department of Chemistry, Indian Institute of Technology Ropar, Punjab 140001, India.

[*]Corresponding authors

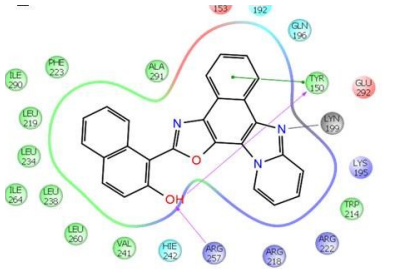
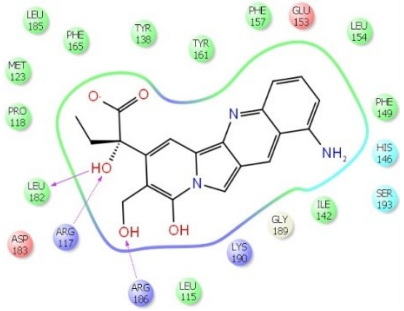
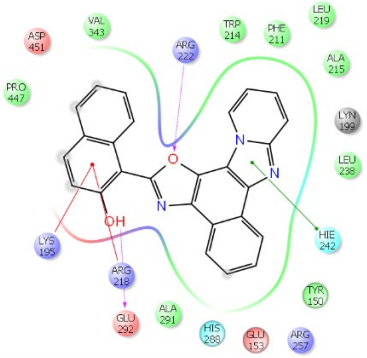
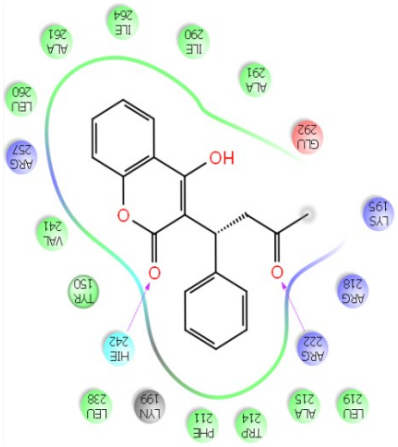
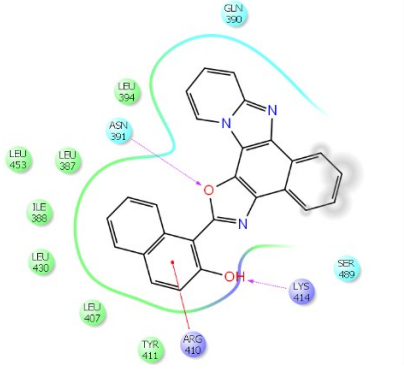
Both authors shared joint first authorship

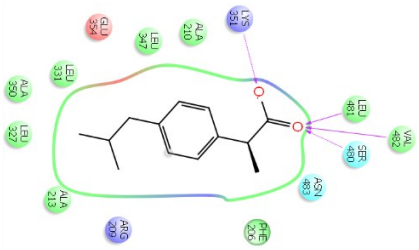
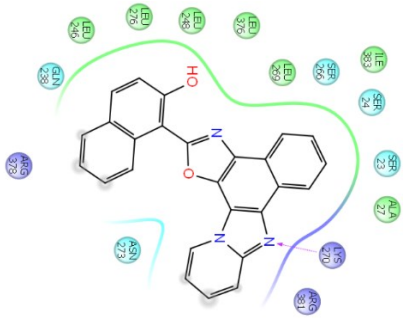
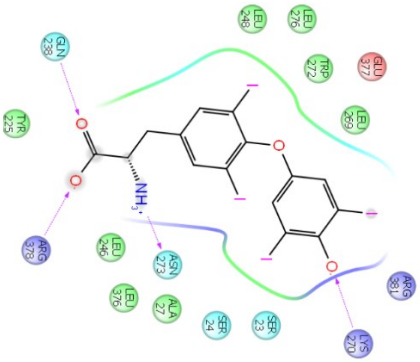
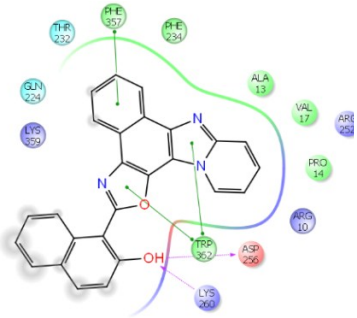
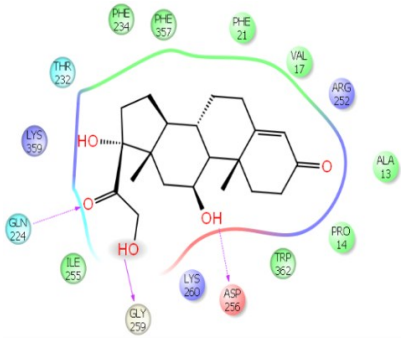
(Section A) Selectivity of ONIP1 against IB cavity of HSA protein

The selectivity of **ONIP1** towards HSA 1B cavity was further ensured using multiple studies. Herein, **ONIP1** was docked against three major cavities (*viz* warfarin, Ibuprofin and 1B heme binding cavity) of HSA protein. Herein, re-dock validation was initially performed whereby acceptable RMSD (≤ 2 Å) was obtained. In case of HSA 1B cavity, **ONIP1** showed remarkable dock score of -8.8, *i.e*. comparable to -9.5 as obtained for re-docked co-crystallized. Furthermore, MM_GBSA binding energy was also calculated for the same and found higher binding affinity for **ONIP1** compared to its co-crystallized ligand. Thus, binding affinity of **ONIP1** was found highly favourable for target 1B cavity of HSA protein. Whereas, in case of other drug binding cavities of HSA, the dock score as well as MM_GBSA binding energy score obtained for **ONIP1** was found very weak compared to co-crystallized ligand. Thus, confirming its selectivity towards IB cavity of HSA protein. In the similar manner, binding affinity of **ONIP1** was also investigated towards blood globulin protein too. Herein also, **ONIP1** has produced very weak dock score as well as MM_GBSA binding energy score compared to that of co-crystallized ligand. Thus, designing prospective and binding energy data ensured us about **ONIP1**selectivity towards IB cavity of HSA with respect to its other cavities as well as blood globulin protein. All the results have been mentioned in Table ST1.

Table ST1: Comparison of dock score, binding energy and RMSD for ONIP1 with different proteins

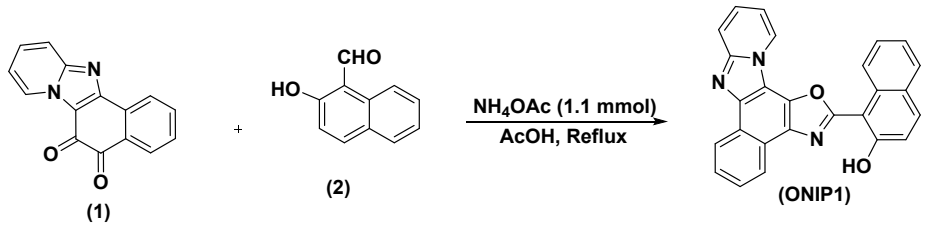
S. No	Title	Protein (PDB ID)	Re-dock RMSD	Dock Score	MM_GBSA_dG_Bind	Docked Pose

1	**ONIP1**	HSA (4L8U) Heme binding Site	ND	-8.8	-78.979	
2	**Internal Ligand**	HSA (4L8U) Heme binding Site	2Å	-9.5	-76.992	
3	**ONIP1**	HSA (2BXD) Warfarin binding site	ND	-3.8	-27.778	
4	**Internal Ligand**	HSA (2BXD) Warfarin binding site	2 Å	-7	-68.666	
5	**ONIP1**	HSA (2BXG) Ibuprofin binding site	ND	-2.974	-36.278	

6	**Internal Ligand**	HSA (2BXG) Ibuprofin binding site	1.243 Å	-8.831	-81.013	
7	**ONIP1**	Globulin (2CEO) Tyroxine Binding Site	ND	-4.1	-59.999	
8	**Internal Ligand**	Globulin (2CEO) Tyroxine Binding Site	1.8Å	-7.9	-103.383	
9	**ONIP1**	Globulin (2V95) Corticol Binding Site	ND	-5.772	-58.215	
10	**Internal Ligand**	Globulin (2V95) Corticol Binding Site	1.2 Å	9.6	-100.161	

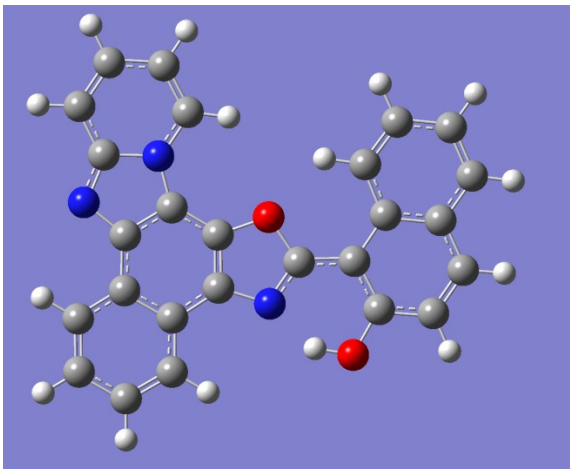
Section B, (Synthesis of ONIP1)

ONIP1 was synthesised by attempting a multicomponent reaction of naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5,6-dione **(1)** (1.00 mmol), 2-hydroxy-1-naphthaldehyde (2) and NH_4OAc (1.10 mmol) in AcOH for 24 h under reflux (Scheme SC1). The compounds was thoroughly characterised with satisfactory ^{1}H, ^{13}C NMR and HRMS.



Scheme SC1: Synthesis of 2-(aryl)oxazolo[5'',4'':3',4']naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (**ONIP1**)

(A)



(B)

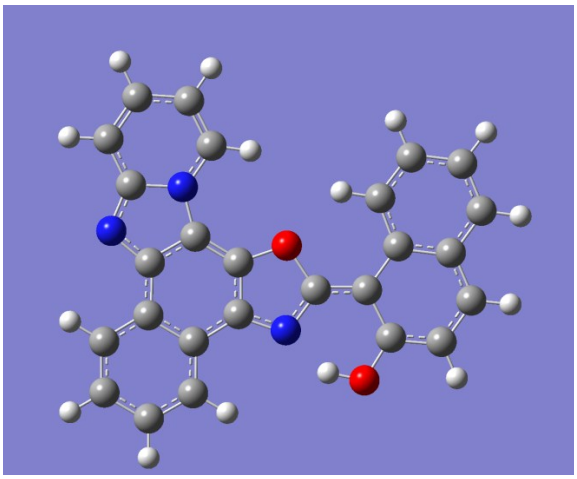


Figure SF1: Optimized structures for **ONIP1** in ground state **(A)** and in excited state **(B).**

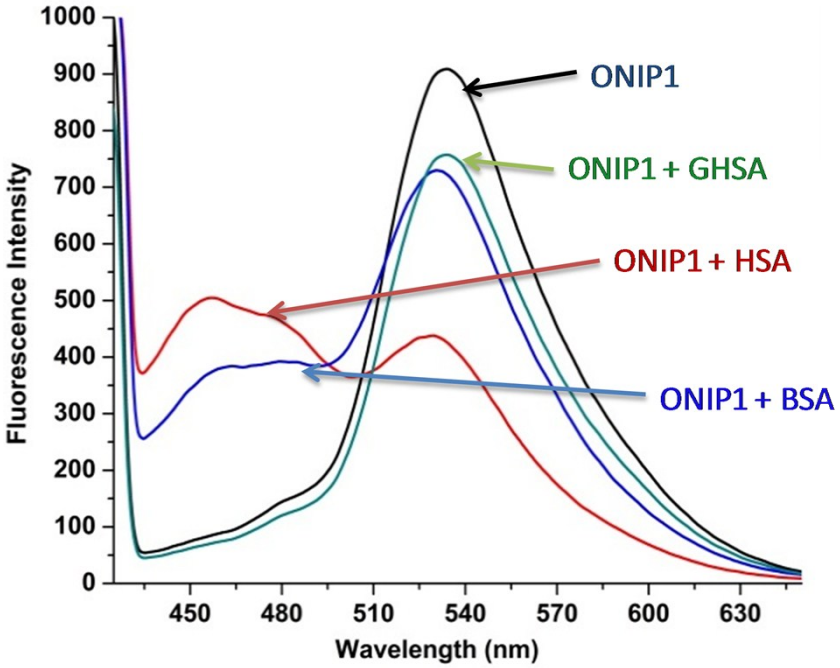


Figure ST2: (A) Fluorescence spectra of 2 Mm **ONIP1** (λ_{ex} = 415 nm) in the presence of 3.31 µM BSA, HSA, and GHSA, respectively.

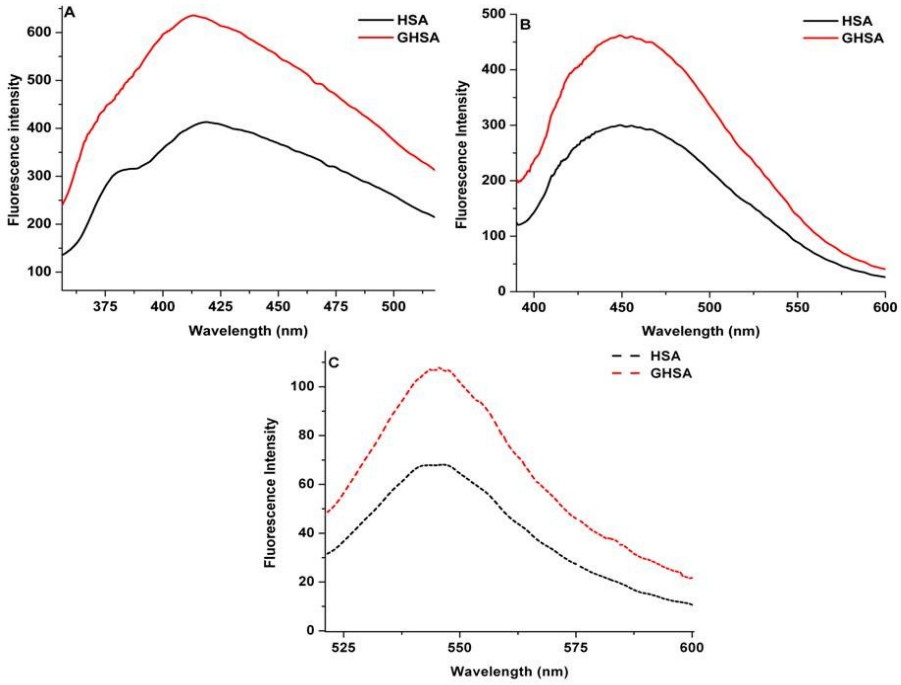


Figure SF3: Emission fluorescence spectra of HAS and GHSA; A, λex = 335 nm; B, λex = 370 nm; C, λex = 485 nm. Herein, the fluorescence intensity of both the entities *viz* HSA and GHSA were recorded upon excitationat 335 (Figure S3 A), 370 (Figure. S3 B) and 485 nm (Figure S3 C). The result obtained revealed the increase in fluorescence intensityin case of GHSA compared to HSAat all the three excitation wavelength. The increase in fluorescence intensity of GHSA at λex = 335 nm was further found to be associated with a significant blue shift (Figure 3S A). Furthermore, in case of figure 3S B (λex = 370 nm), no shift was observed in case of GHSA whereas in case of figure 3S C (λex = 485 nm) a redshift of about 7 nm was obtained for GHSA. Thus, considering the above-mentioned fluorescence trend and literature based evidence glycation of HSA and thus GHSA formation is confirmed.[1]

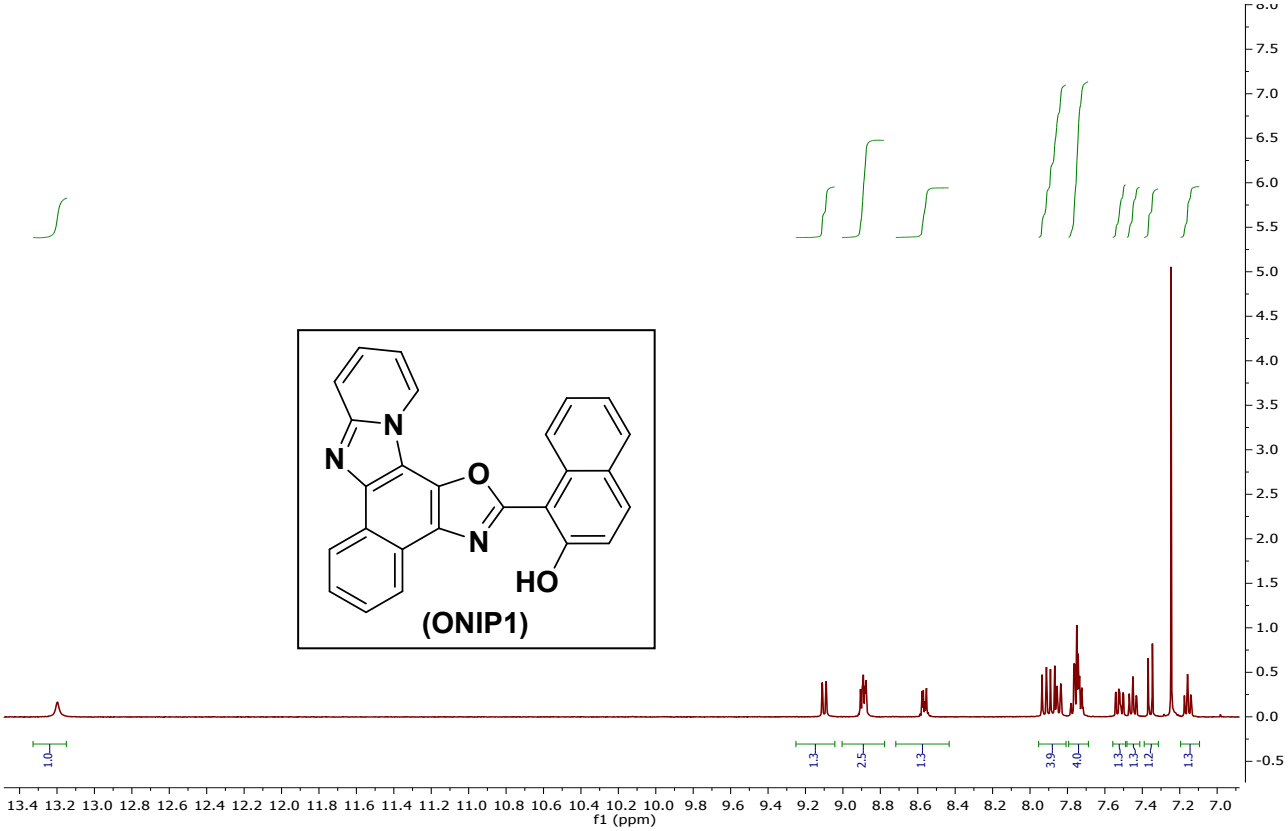


Figure SF4: ^{1}H NMR spectrum of 1-(oxazolo[5",4":3',4']naphtho[1',2':4,5]imidazo[1,2-a]pyridin-2-yl)naphthalen-2-ol (**ONIP1**).

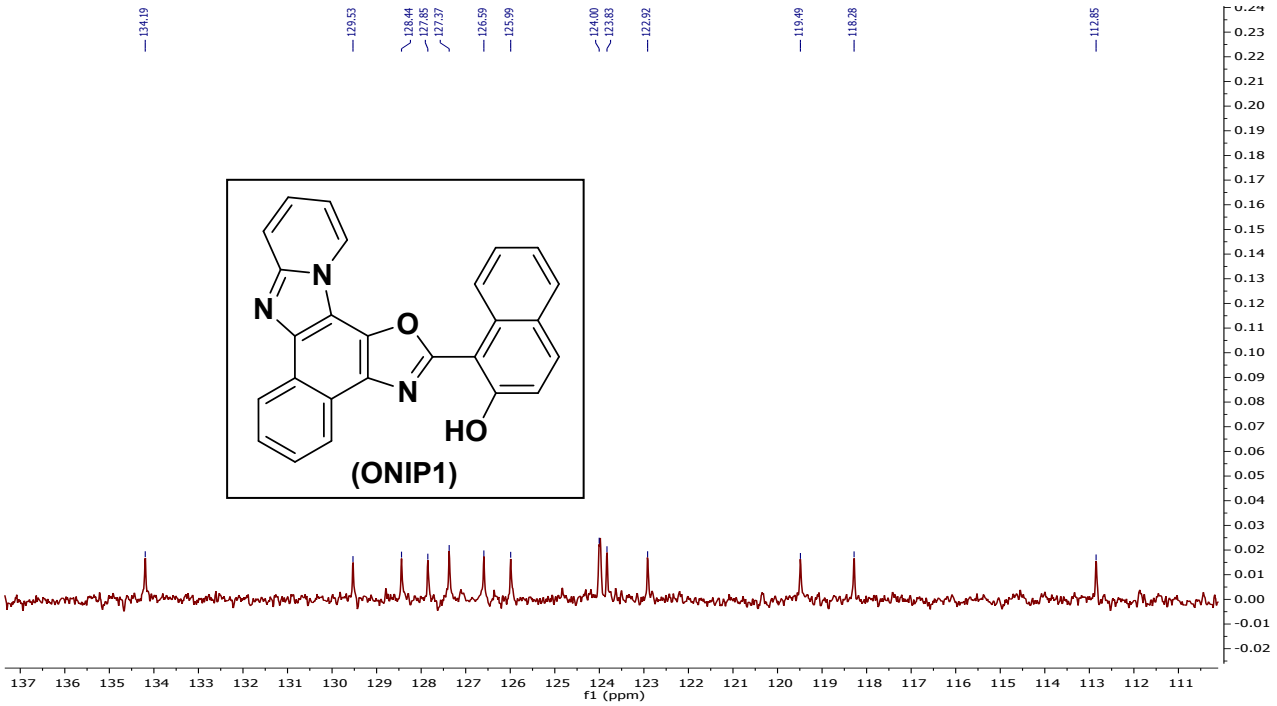


Figure SF5: ^{13}C NMR spectrum of 1-(oxazolo[5",4":3',4']naphtho[1',2':4,5]imidazo[1,2-a]pyridin-2-yl)naphthalen-2-ol (**ONIP1**)

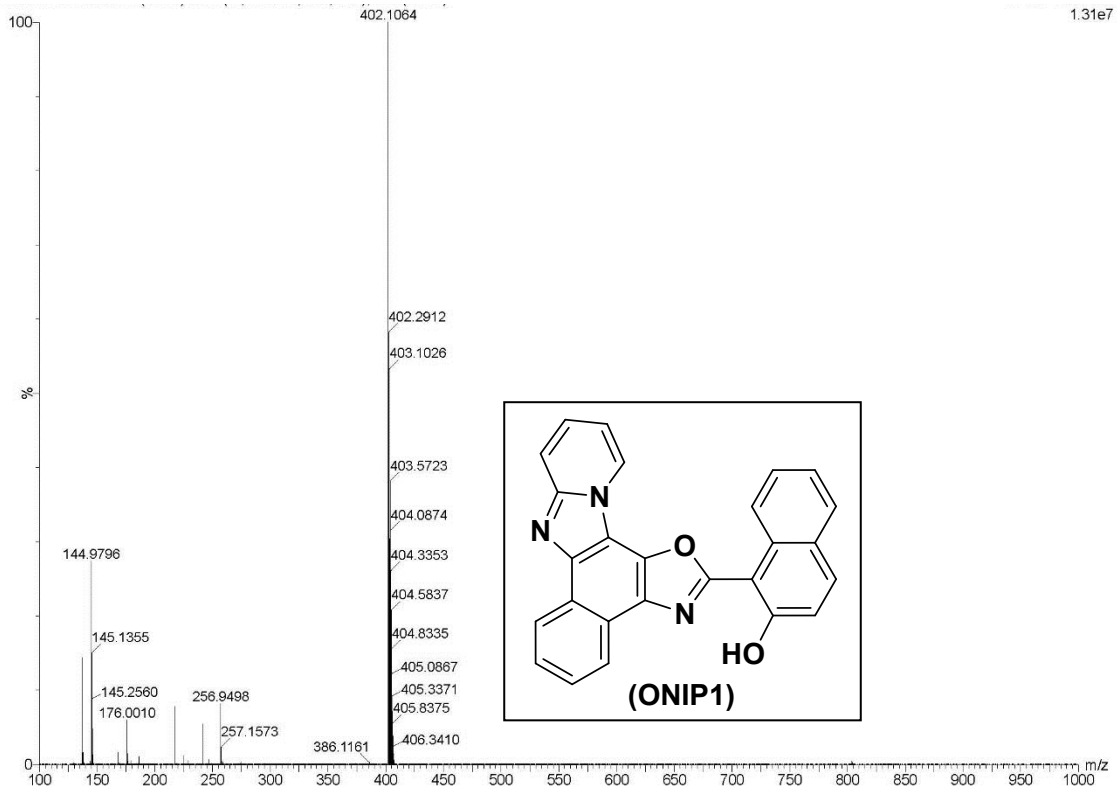


Figure SF6: HRMS of 1-(oxazolo[5",4":3',4']naphtho[1',2':4,5]imidazo[1,2-a]pyridin-2-yl)naphthalen-2-ol (**ONIP1**)

Reference

1. A. Szkudlarek, M. Maciążek-Jurczyk, M. Chudzik, J. Równicka-Zubik and A. Sułkowska, *Spectrochim. Acta Mol. Biomol. Spectrosc.*, **2016**, *153*, 560-565.