

Copper-Catalyzed Synthesis of 9-Aryl- β -Carbolines through Tandem Oxidative Aromatization and Ullmann-Type C–N Cross-Coupling Reactions

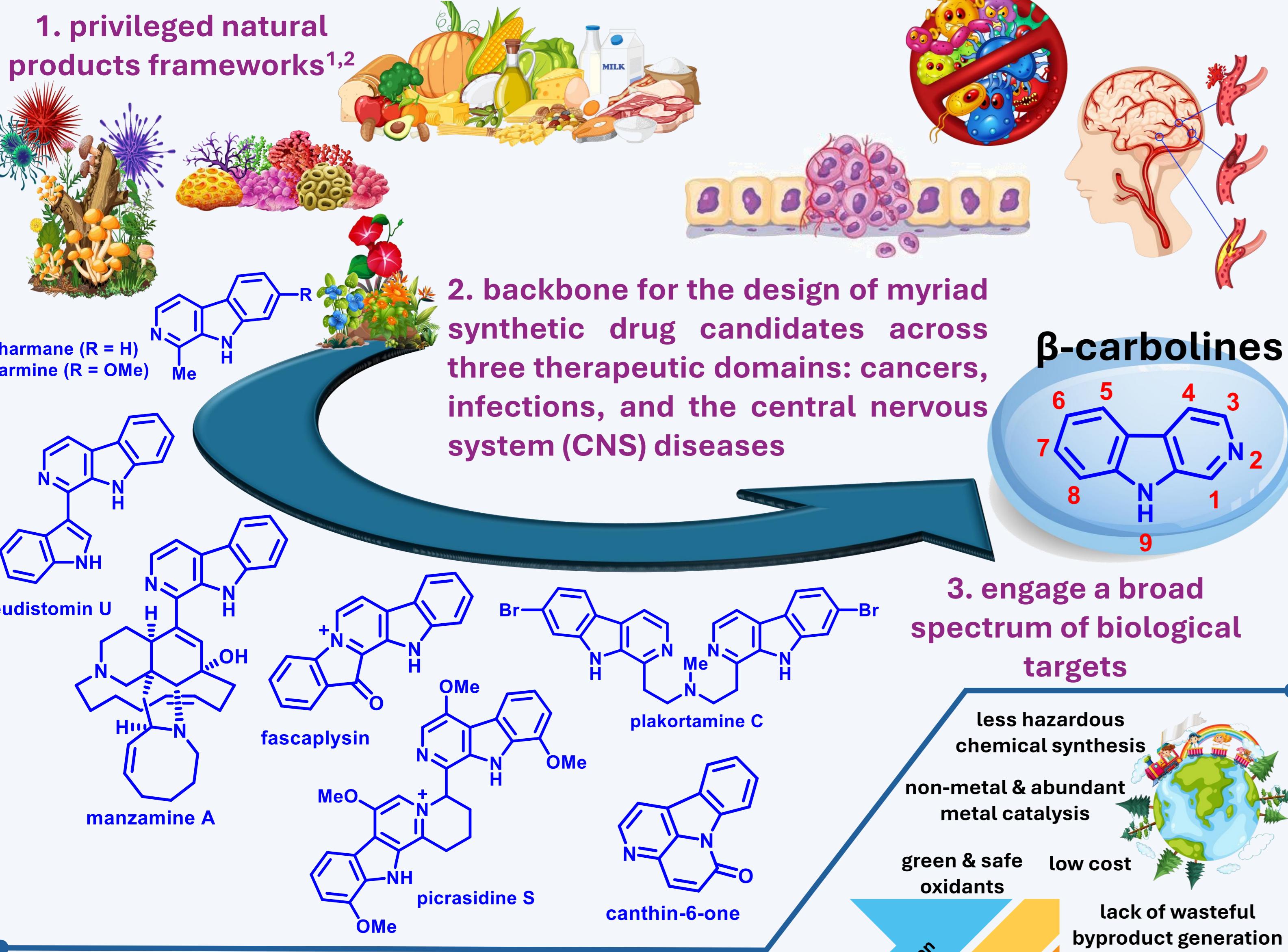


Ahmad Saifuddin Mohamad Arshad^{1*}, Nur Aziah Hanapi¹, Mohd Nizam Mordi¹
¹Centre for Drug Research, Universiti Sains Malaysia, 11800 Minden, Penang, Malaysia
 *Corresponding Author: saifudin_pudin@yahoo.com



XVII INTERNATIONAL POSTGRADUATE SUMMER SCHOOL ON GREEN CHEMISTRY

1. Introduction

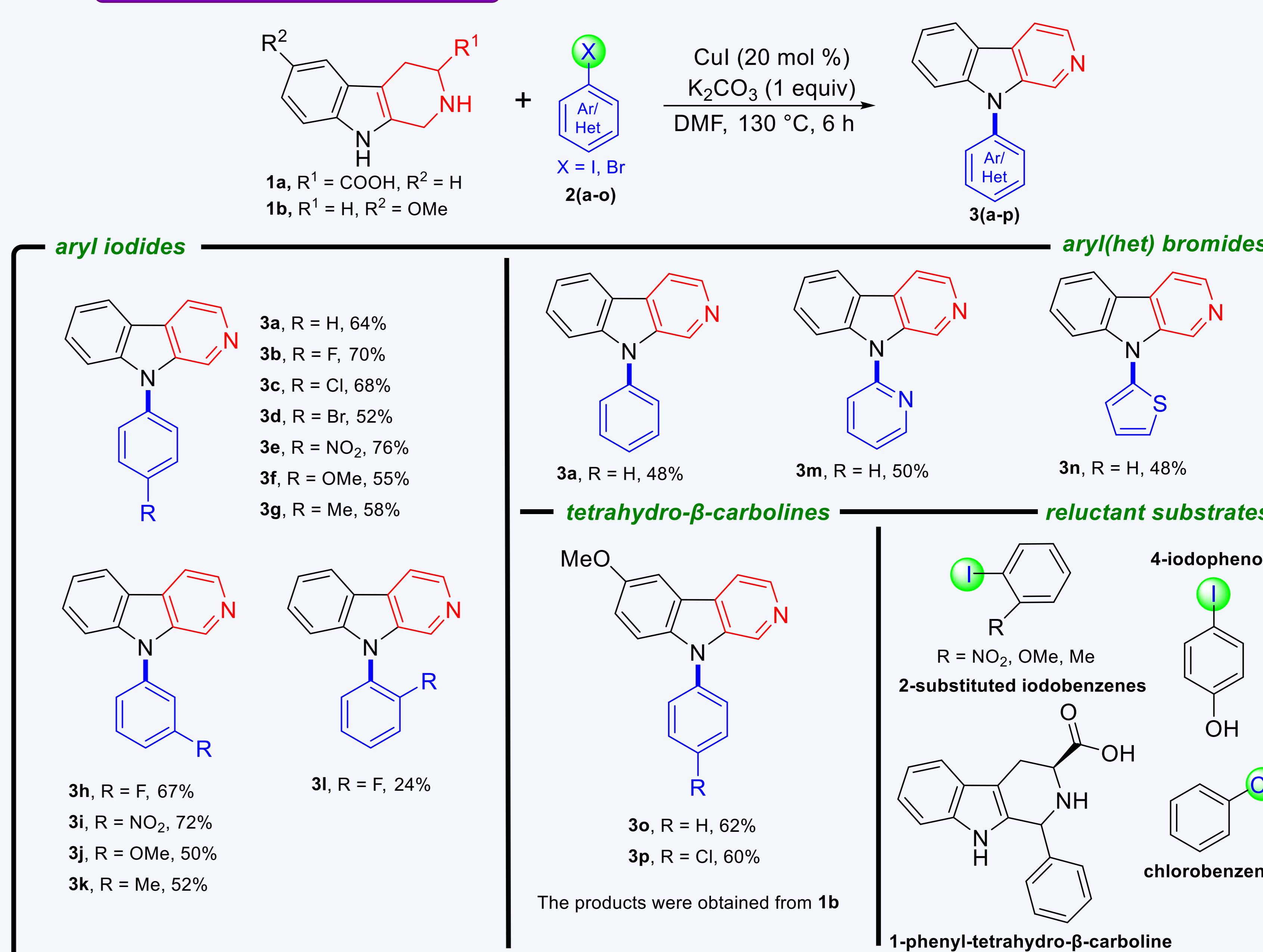


2. Reaction Optimization

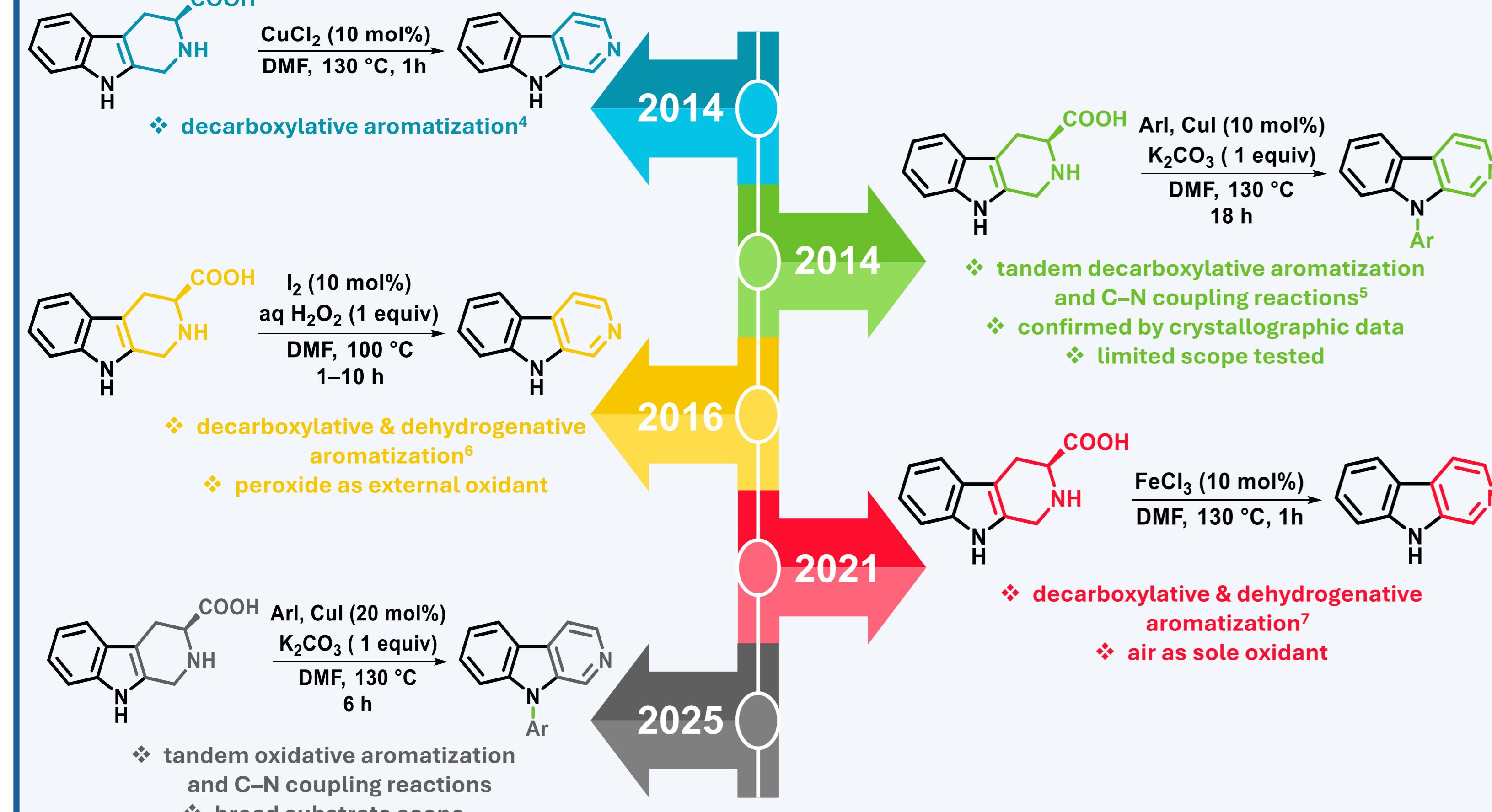
Entry	Catalyst (mol %)	Base	Solvent	Yield (%)
1	CuI (10)	None	DMF	NR
2	CuI (10)	K ₂ CO ₃	DMF	54
3	CuBr (10)	K ₂ CO ₃	DMF	50
4	CuCl (10)	K ₂ CO ₃	DMF	49
5	Cu ₂ O (10)	K ₂ CO ₃	DMF	42
6	CuBr ₂ (10)	K ₂ CO ₃	DMF	47
7	CuCl ₂ (10)	K ₂ CO ₃	DMF	45
8	CuSO ₄ (10)	K ₂ CO ₃	DMF	44
9	Cu(OAc) ₂ (10)	K ₂ CO ₃	DMF	39
10	Cu(OTf) ₂ (10)	K ₂ CO ₃	DMF	30
11	None	K ₂ CO ₃	DMF	NR
12	CuI (10)	Cs ₂ CO ₃	DMF	52
13	CuI (10)	Na ₂ CO ₃	DMF	10
14	CuI (10)	NaHCO ₃	DMF	25
15	CuI (10)	KHCO ₃	DMF	34
16	CuI (10)	K ₂ CO ₃	DMSO	46
17	CuI (10)	K ₂ CO ₃	DMA	50
18	CuI (10)	K ₂ CO ₃	1,4-dioxane	NR
19	CuI (10)	K ₂ CO ₃	toluene	NR
20	CuI (20)	K ₂ CO ₃	DMF	64
21	CuI (30)	K ₂ CO ₃	DMF	65

1a (1 mmol), 2a (1 mmol), catalyst (indicated mol%), and base (1 equiv) were stirred in designated solvent (5 mL) at 130 °C for 6 h.

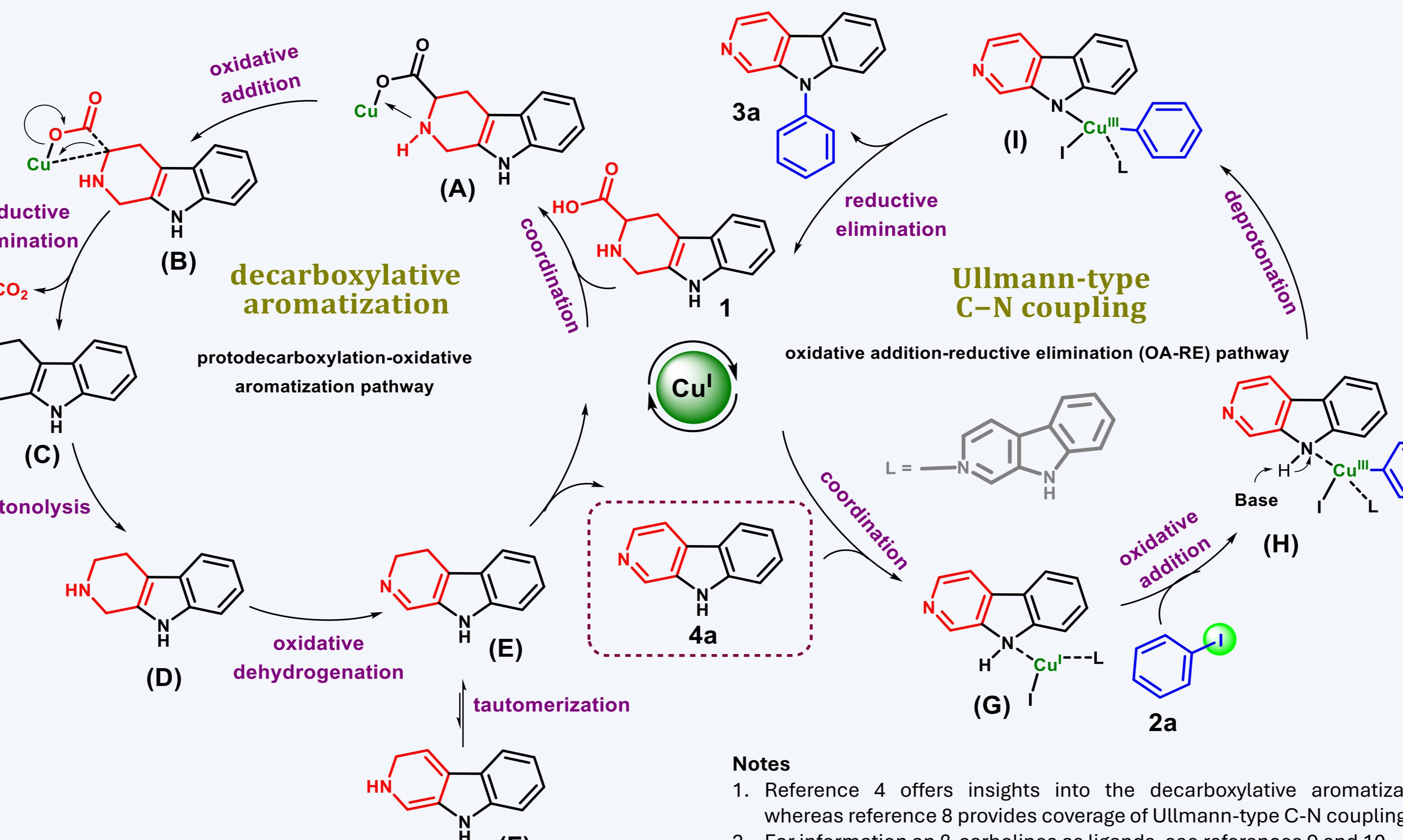
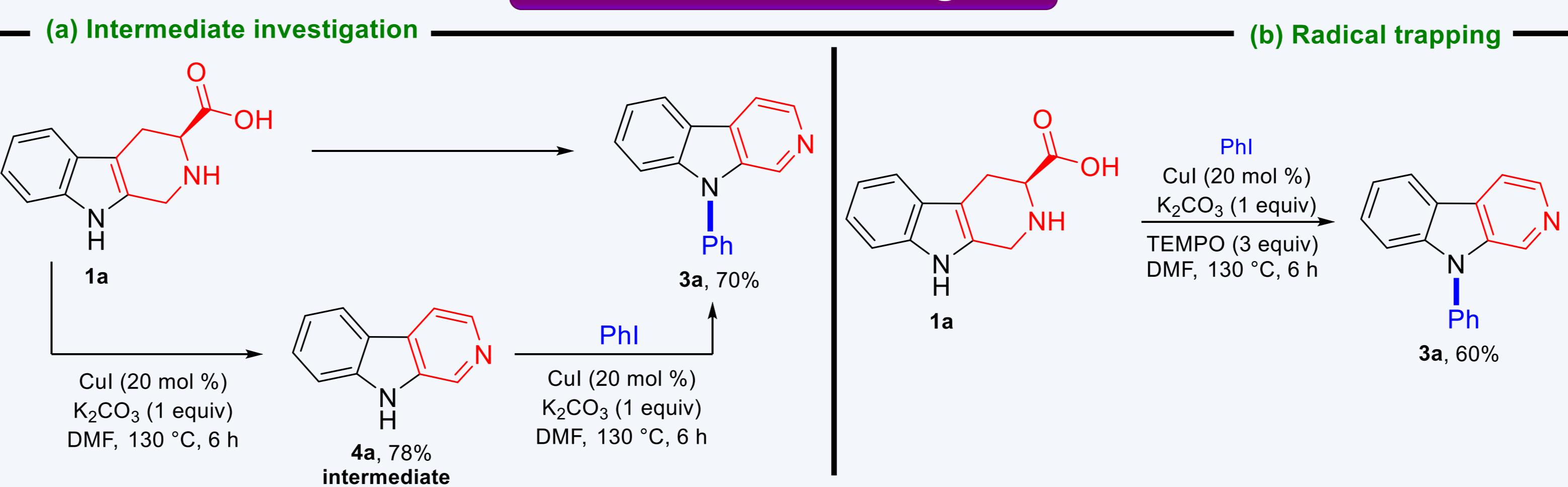
3. Substrate Scope



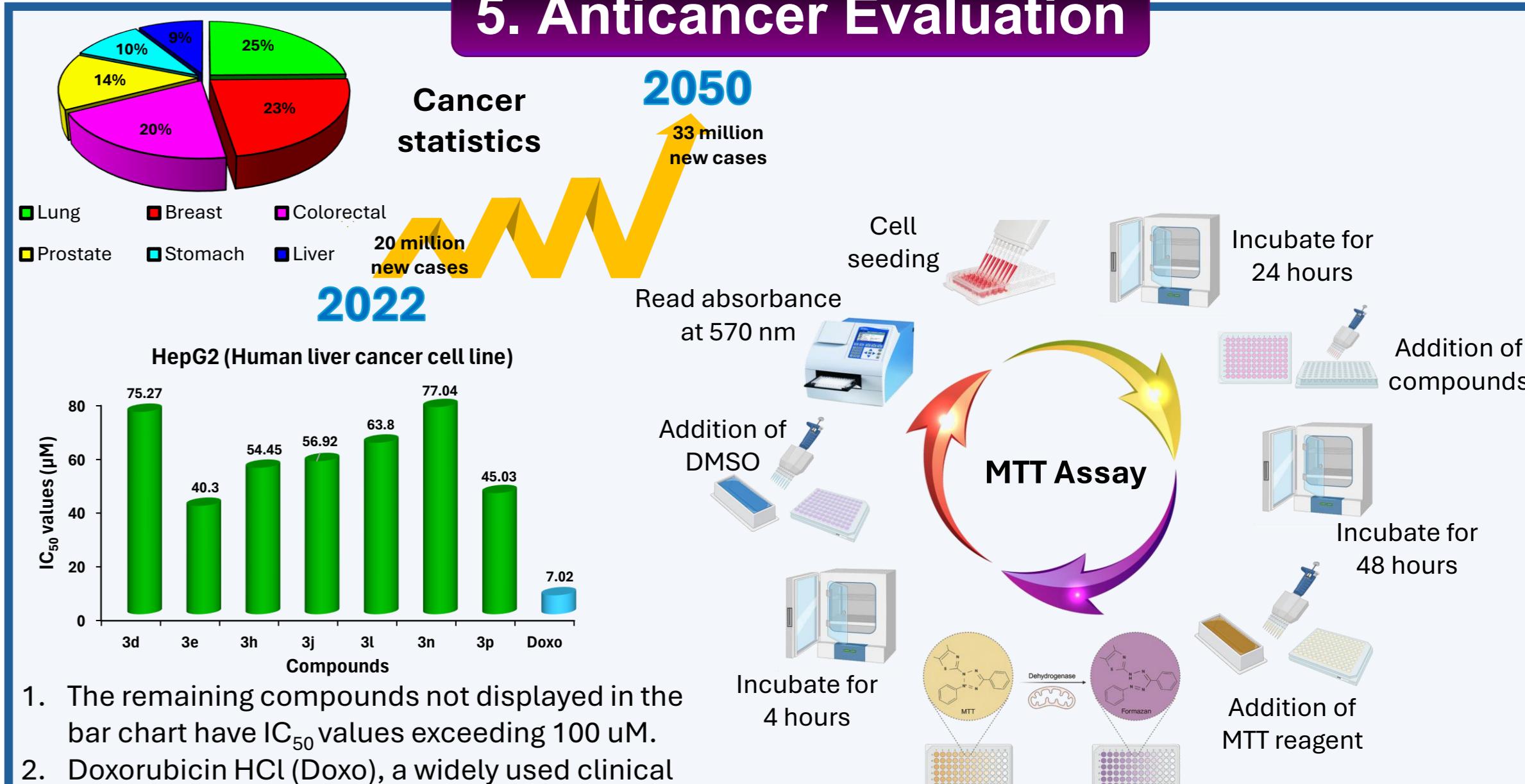
Our synthetic timeline



4. Mechanistic Insights



5. Anticancer Evaluation



6. Conclusion

A copper-catalyzed tandem oxidative aromatization and Ullmann-type C–N cross-coupling reactions has been developed for the straightforward synthesis of 9-aryl- β -carbolines from tetrahydro- β -carbolines.

References

- R. Cao, W. Peng, Z. Wang, A. Xu, *Curr. Med. Chem.* 2007, 14, 479–500.
- A. S. M. Arshad, M. N. Mordi, *Adv. Synth. Catal.* 2023, 365, 2126–2146.
- S. Gaikwad, L. Kováčiková, P. Pawar, M. Gaikwad, A. Boháč, B. Dawane, *Tetrahedron* 2024, 155, 133903.
- R. Meesala, M. N. Mordi, S. M. Mansor, *Synlett* 2014, 25, 120–122.
- R. Meesala, M. N. Mordi, S. M. Mansor, M. M. Rosli, *Mol. Cryst. Liq. Cryst.* 2014, 605, 125–134.
- R. Meesala, A. S. M. Arshad, R. Meesala, M. N. Mordi, S. M. Mansor, *Tetrahedron* 2016, 72, 8537–8541.
- A. S. M. Arshad, R. Meesala, M. N. Mordi, S. M. Mansor, *Tetrahedron* 2021, 83, 131960.
- Y. Li, J. Peng, X. Chen, B. Mo, X. Li, P. Sun, C. Chen, *J. Org. Chem.* 2018, 83, 5288–5294.
- I. Maisuls, E. Wolcan, P. M. David-Gara, F. M. Cabrerizo, G. J. Ferraudi, G. T. Ruiz, *J. Photochem. Photobiol. B* 2021, 8, 100078.
- I. Maisuls, E. Wolcan, O. E. Piro, E. E. Castellano, G. Petroselli, R. Erra-Balsells, F. M. Cabrerizo, G. T. Ruiz, *ChemistrySelect* 2017, 2, 8666–8672.

Acknowledgment

We gratefully acknowledge financial support from the Ministry of Higher Education Malaysia for Fundamental Research Grant Scheme with Project Code: FRGS/1/2020/STG04/USM/01/1. Ahmad Saifuddin Mohamad Arshad thanks the Institute of Postgraduate Studies, Universiti Sains Malaysia for the USM Fellowship.