

Supplementary information

**Rational design of 5-HT₆R ligands using a bioisosteric strategy:
Synthesis, biological evaluation and molecular modelling.**

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¹ H, ¹³ C NMR	S7

Parent structure	5-HT ₆ R K _i [nM]	Transformation	Bioisoster	Similarity	Ordered compound		5-HT ₆ R K _i [nM] screening
					Structure	Compound ID	
	28 ^a	5Ring Closing		1.000		VitasM STK148877	128
	32 ^b	Sulfone to Amide		0.950		VitasM STK730327	1216
				0.927		VitasM STK259601	7966
				0.911		ChemBridge 9011397	1260
				0.906		ChemBridge 9012064	16780
	1956 ^c	Sulfonamide to Urea		0.950		Enamine T6413371	1071
	1350 ^d	Fluorine to Chlorine		0.901		ChemBridge 9123171	18140
	7 ^e	Sulfone to Amide		1.000		VitasM STK327322	6509
				0.920		VitasM STK389851	12990
				0.911		VitasM STK174275	10530
				0.906		VitasM STK390087	14940

^aTasler S, Kraus J, Pegoraro S, et al. Non-competitive inhibitors of metabotropic glutamate receptor 5 (mGluR5). *Bioorg Med Chem Lett*. 2005;15(11):2876-80.

^bHolenz J, Pauwels PJ, Diaz JL, Mercè R, Codony X, Buschmann H. Medicinal chemistry strategies to 5-HT₆ receptor ligands as potential cognitive enhancers and antiobesity agents. *Drug Discov Today*. 2006;11(7-8):283-99.

^cYoon J, Yoo EA, Kim J-Y, et al. Preparation of piperazine derivatives as 5-HT₇ receptor antagonists. *Bioorg Med Chem*. 2008;16(10):5405-12.

^dRodey GE. Anti-idiotypic antibodies and regulation of immune responses. *Transfusion*. 1992;32(4):361-76.

^eSikazwe D, Bondarev ML, Dukat M, Rangisetty JB, Roth BL, Glennon R a. Binding of sulfonyl-containing arylalkylamines at human 5-HT₆ serotonin receptors. *J Med Chem*. 2006;49(17):5217-25.

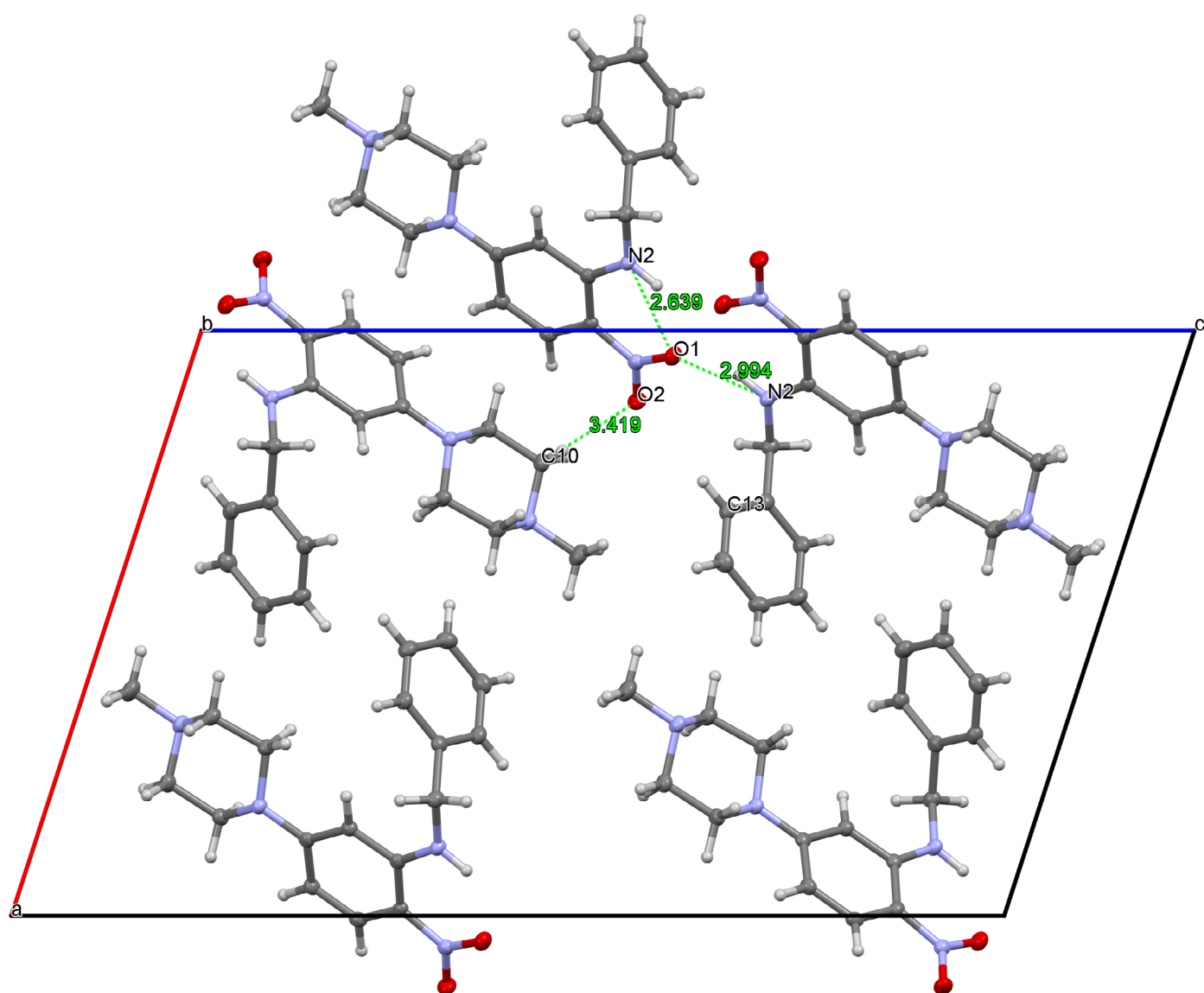


Figure S1. The crystal packing of compound 4. View along [010] axis. Unit cell $Z=4$ - additional molecule was shown in order to present selected intermolecular interactions within the crystal lattice.

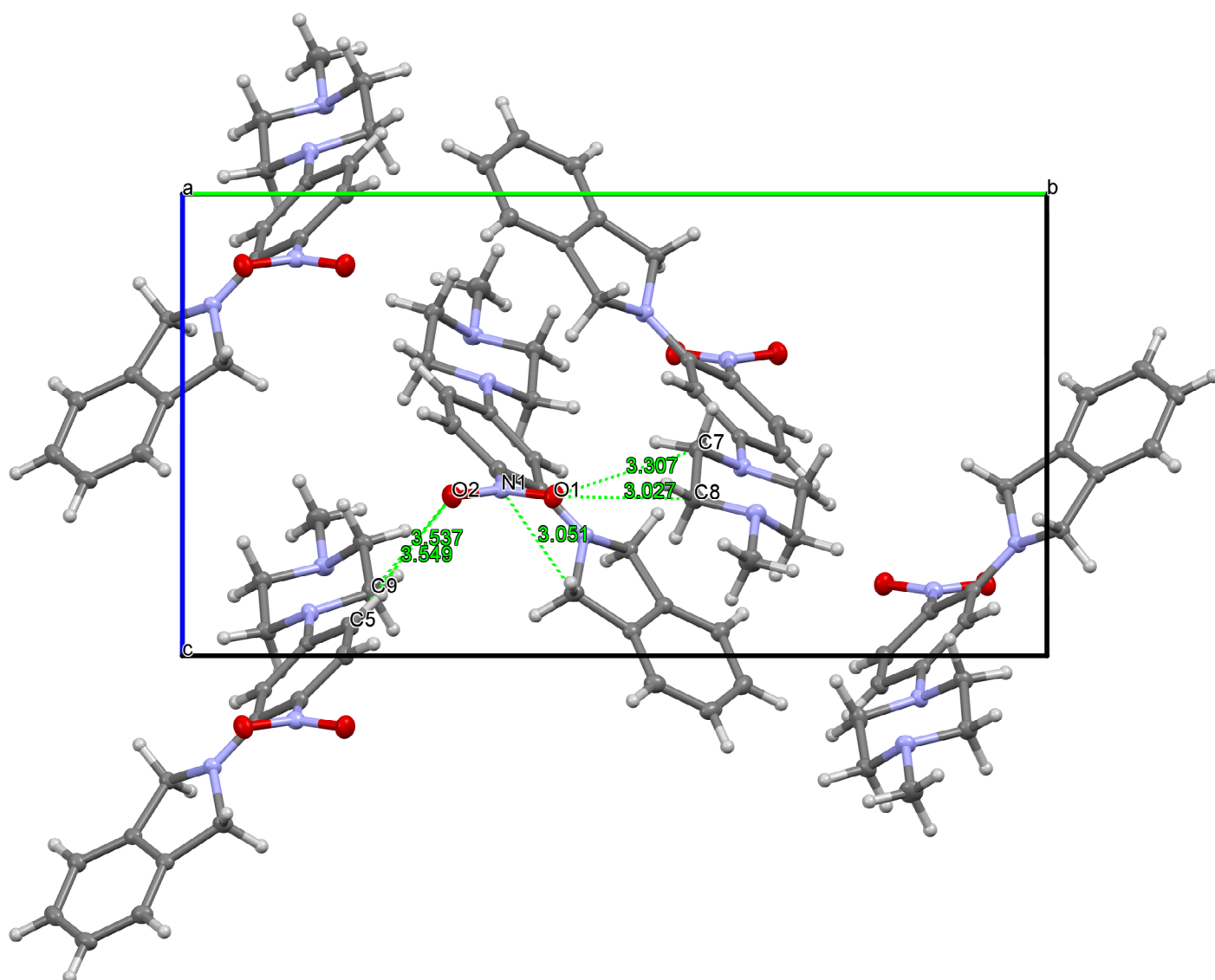


Figure S2. The crystal packing of compound 8. View along [100] axis. Unit cell $Z=4$ - additional molecule was shown in order to present selected intermolecular interactions within the crystal lattice.

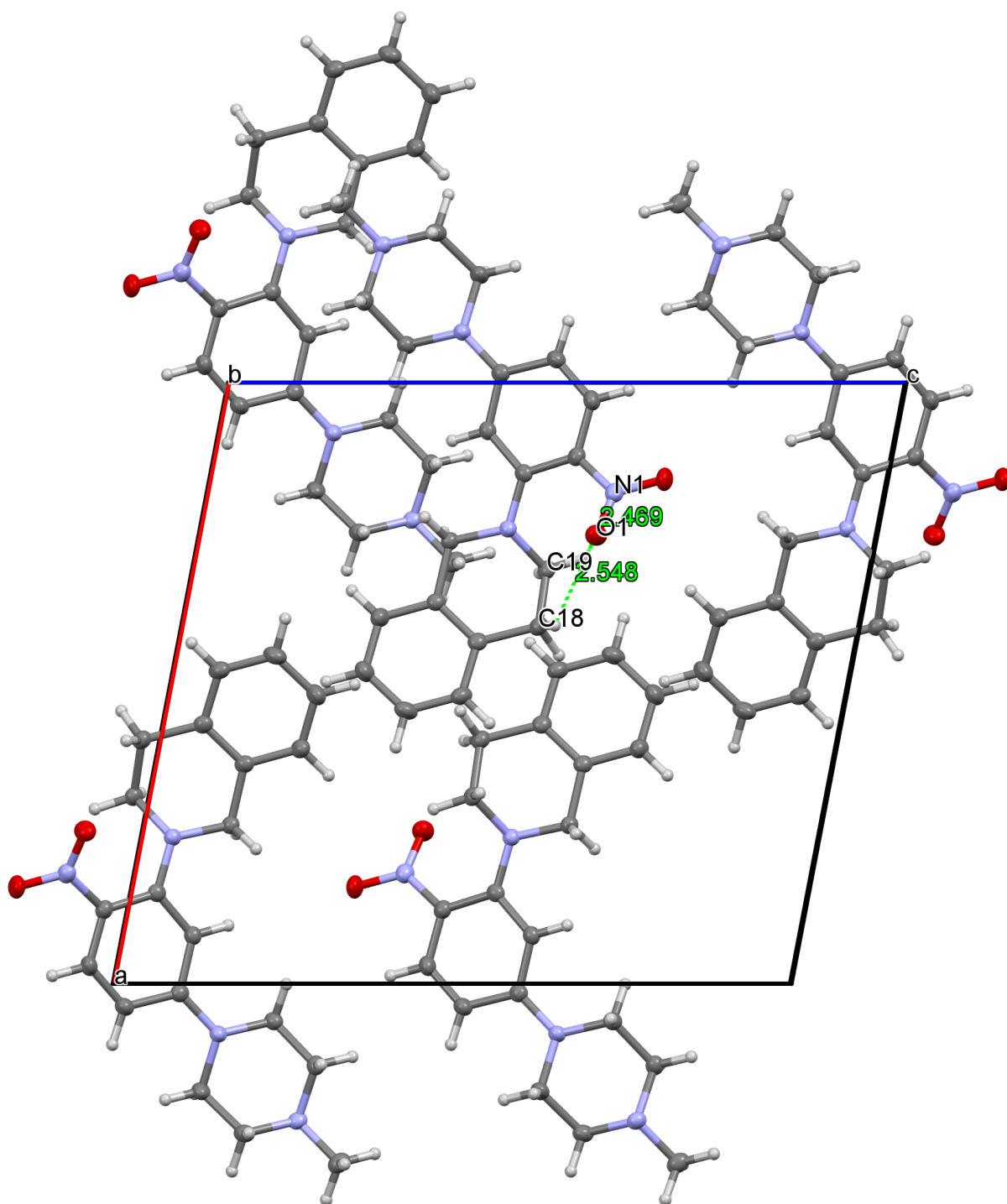


Figure S3. The crystal packing of compound 9. View along [010] axis. Unit cell $Z=4$ - additional molecule was shown in order to present selected intermolecular interactions within the crystal lattice.

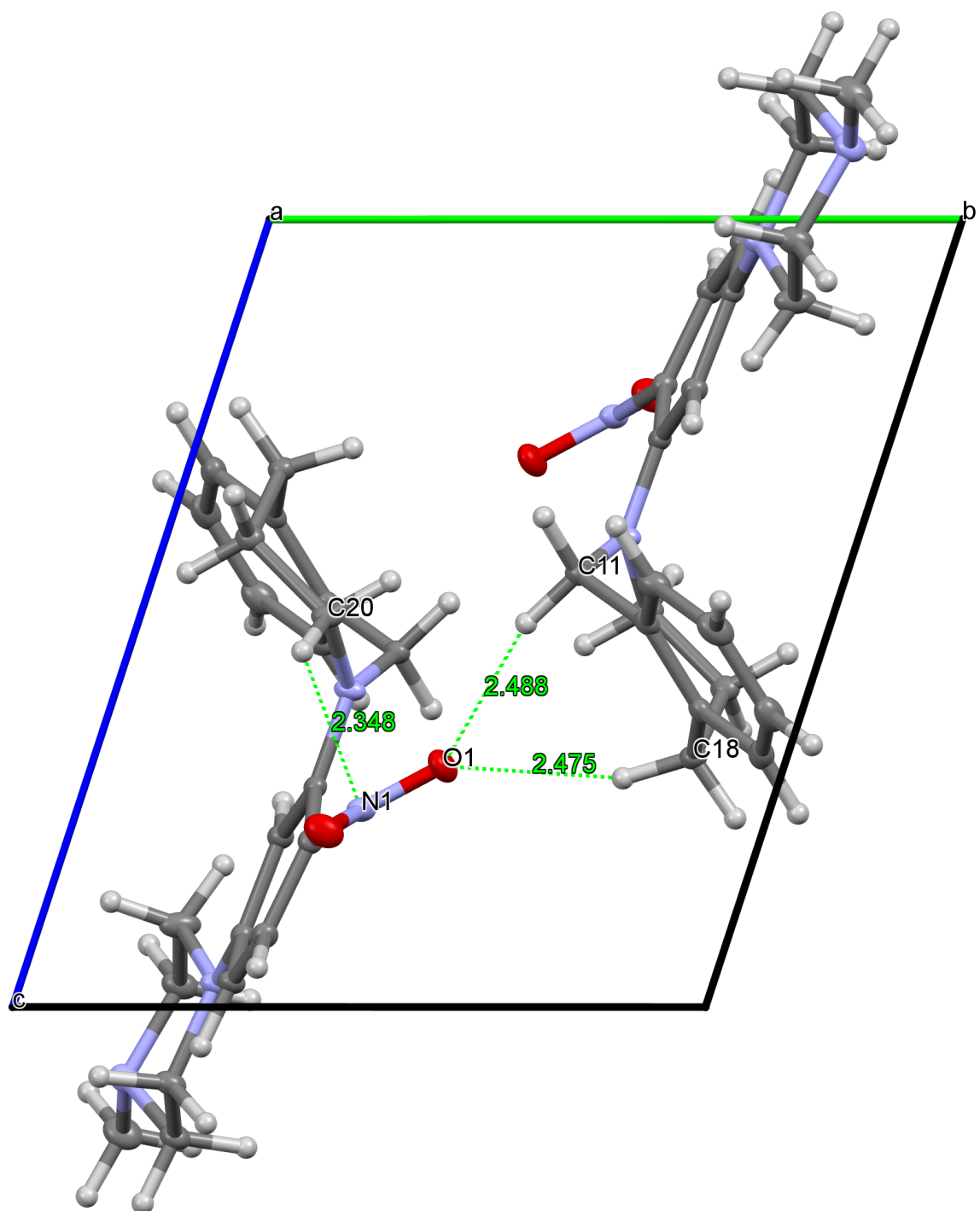


Figure S4. The crystal packing of compound 10 and selected interactions within the crystal lattice. View along [100] axis. Unit cell $Z=2$.

