

Supporting Information

Syntheses and Evaluation of Carbon-11- and Fluorine-18-Radiolabeled pan-Tropomyosin Receptor Kinases (Trk) Inhibitors: Exploration of the 4-aza-2-Oxindole Scaffold as Trk PET Imaging Agents

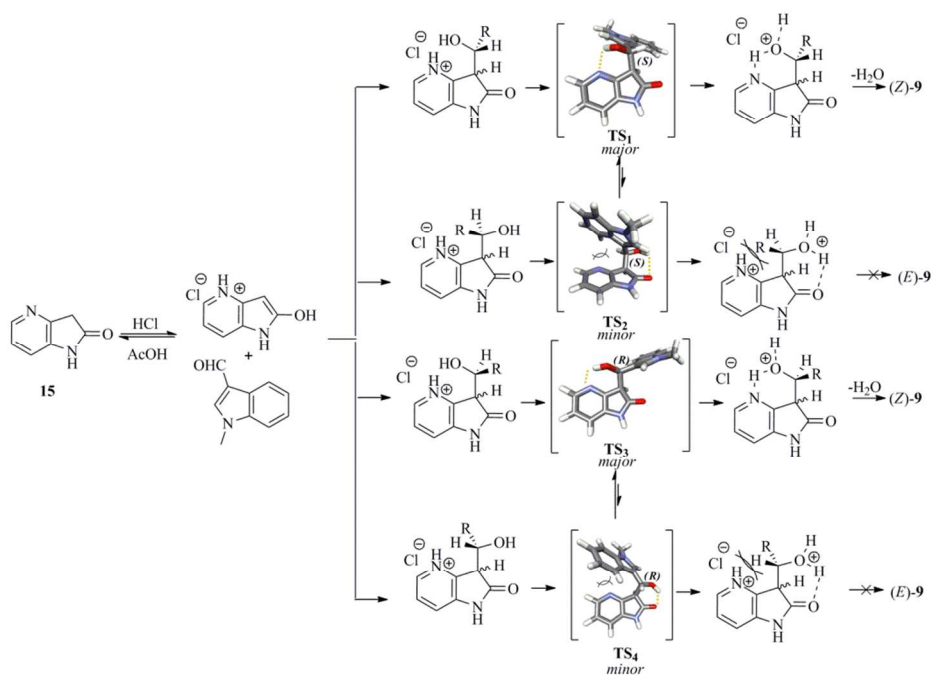
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1. Supporting Information Scheme S1 and Figures S1-S12.



Scheme S1. Mechanistic rationale for the synthesis of (Z)-9 from intermediate 15. The formation of (Z)-9 proceeds via the sterically less congested β -hydroxyketone transition states TS₁ and TS₃ which are in equilibrium with the sterically demanding states TS₂ and TS₄ respectively. The final position of the 1-methylindole moiety relative to the aza-oxindole fragment is dictated by their orientations in the depicted transition states.

We explored the isomerization of (*Z*)-**9** as it is expected to influence the potencies and kinase inhibition profile. We observed that (*Z*)-**9** isomerises within < 0.5 h under ambient condition upon incubation in mixtures of polar organic solvent and water (pH 6.0). The kinetics of isomerisation were assessed by reverse-phase HPLC. The 2 isomers were well resolved and their identity confirmed by LC-MS/MS. This rapid isomerization presumably ensues from the low rotational energy barrier of the highly conjugated (indolylmethylene)indolin-2-one system. As expected, the isomerization was prevented in the absence of light and significantly slower in slightly basic DMSO/phosphate buffer media (pH 7.4). Moreover, the photoisomerization of (*Z*)-**9** was followed by observing the UV-visible spectra at 294 K with ambient light exposure (Figure 2A). The large absorption band centered in the visible region at 438 nm, corresponding to $n-\pi^*$ transition, progressively decreased until it reached the PSS over one hour. The absorbance of the $\pi-\pi^*$ transition bands at 285 nm also decreased until reaching the PSS. The composition of the PSS was determined with the integration of the ^1H NMR spectra low field region corresponding to the N-H lactam, H-2' and vinyl protons. This *Z*:*E* ratio in DMSO- d_6 / D_2O mixture was 56:44.

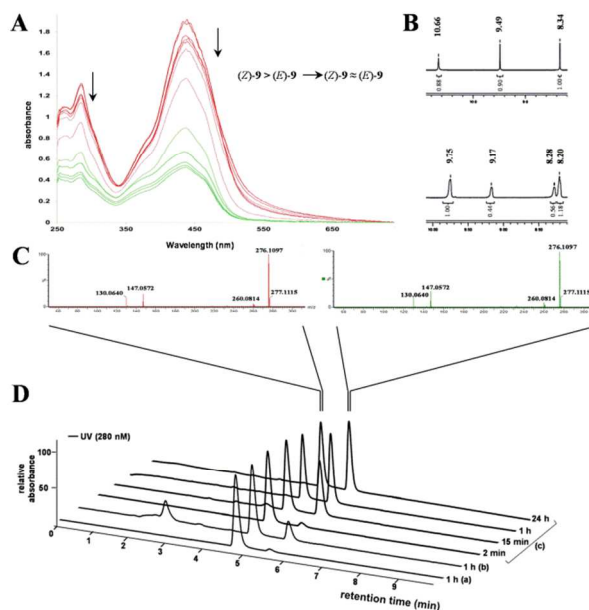


Figure S1. Assessment of the conformational equilibrium leading to the formation of (*E*)-**9** from (*Z*)-**9**. (A) Photoisomerization of a mixture (*Z*)-**9** > (*E*)-**9** in H_2O (pH 6) monitored by UV-vis spectroscopy over 60 min at 295 K (5 min intervals). (B) Downfield sections of the NMR spectra of (*Z*)-**9** in d_6 -DMSO and after 1h in $\text{D}_2\text{O}/d_6$ -DMSO (1:1). (C) LC-MS/MS analysis of (*Z*)-**9** and (*E*)-**9**. (D) Representative chromatograms (HPLC method A) from of 1.0 mM solutions of (*Z*)-**9** at 280 nm incubated (a) in MeCN/ H_2O (1:1) in absence of light (1h), (b) in DMSO/phosphate buffer (pH 7.4) (1:9) under ambient light (1h) and (c) in MeCN/ H_2O (1:1) under ambient light.



Figure S2. The structure of (*left*) the crystalized MeOH•(*Z*)-**9**, (*center*) the low-energy calculated structure of (*Z*)-**9** and (*right*) the low-energy calculated structure of (*E*)-**9** (FITTED). Black dash line represents H-bonding and black lines represent inter-atomic distances (Å). Proximity between the H-2' proton and the carbonyl in the *Z* isomer leads to H-2' deshielding. It is expected and observed that equivalent deshielding associated with the physical proximity between the H-2' proton and the nitrogen doublet should lead to even more pronounced. The same rationale applies to precursor **16**.

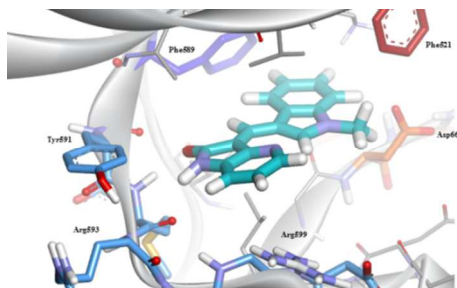


Figure S3. Top predicted binding mode of (*E*)-9 within the active site of TrkA from FITTED docking (PDB code: 4AOJ).

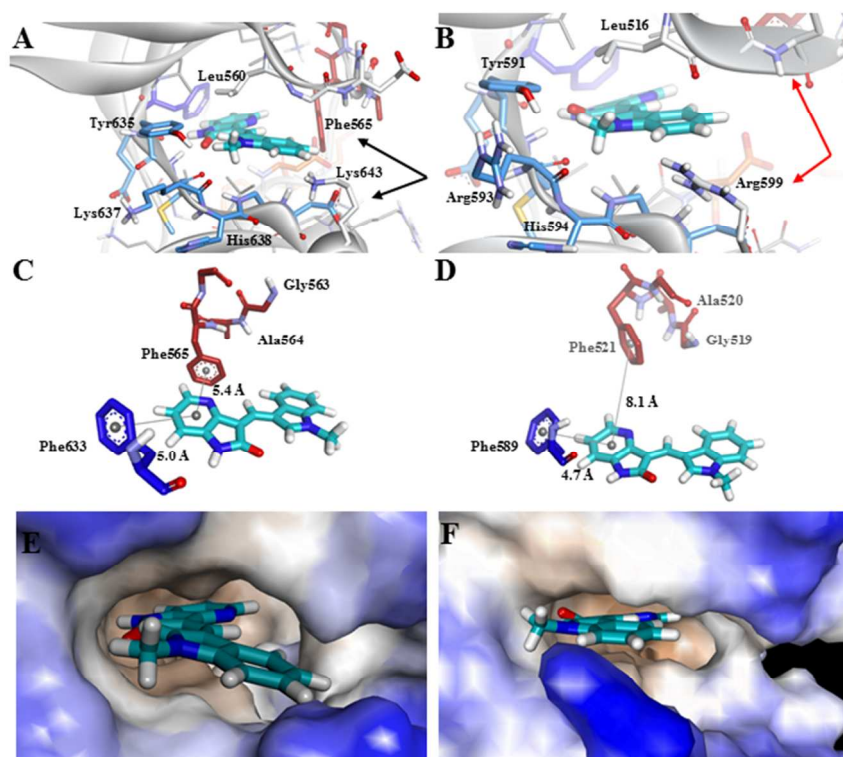


Figure S4. Comparison of the modeled binding of (Z)-9 with (A) TrkB (PDB code: 4AT3) and (B) TrkA (PDB code: 4AOJ) both in DFG-in conformation. Minor differences include the replacement of residues Lys637 and Lys643 in TrkB by Arg593 and Arg599 respectively in TrkA as well as the organization of the β -strand-1 and the glycine-rich loop (arrows). The major difference in the orientation of Phe565 (TrkB) (C) or Phe521 (TrkA) (D) from the glycine-rich loop is highlight. The ensuing differences in the ligand-protein interactions are reflected with the receptors presented in the solvent-accessible surface area (hydrophobicity); TrkB (E) and TrkA (F). Residue sequence in proximity to the ligand only differ by the replacement of TrkA Arg593 and Arg599 by two lysines residues in TrkB and TrkC. Side chains of TrkA Arg593 and the corresponding Lys637 and Lys621 in TrkB and TrkC respectively are remotely oriented vis-à-vis the ligand and most likely do influence the binding of (Z)-9 nor the orientation of the hinge. Otherwise, the charged amino acid side chains of Arg599 (TrkA), Lys643 (TrkB) and Lys627 (TrkC) lies in the in proximity of the solvent exposed face of the 1-methylindole moiety (Figure S4A,B.). Therefore, the bulkier arginine side chain may engage in unfavorable electrostatic contact with (Z)-9 compared to the lysine residues. Additionally, the pyridine ring in (Z)-9 is firmly sandwiched between Phe633 (R_{cen} 5.0 Å) and Phe565 (R_{cen} 5.4 Å) from the glycine-rich loop in TrkB whereas no corresponding hydrophobic interaction is possible between the ligand and the Phe521 (R_{cen} 8.1 Å) from the glycine-rich loop in TrkA owing to the more compact organization of the loop in TrkA – leaving the vinyl and pyridine moieties solvent exposed (Figure 4SC-E.). This difference in the ordering of the glycine-rich loop was also characterize in the structures of apo-TrkA (PDB code: 4F0I) and apo-TrkB (PDB code: 4ASZ).

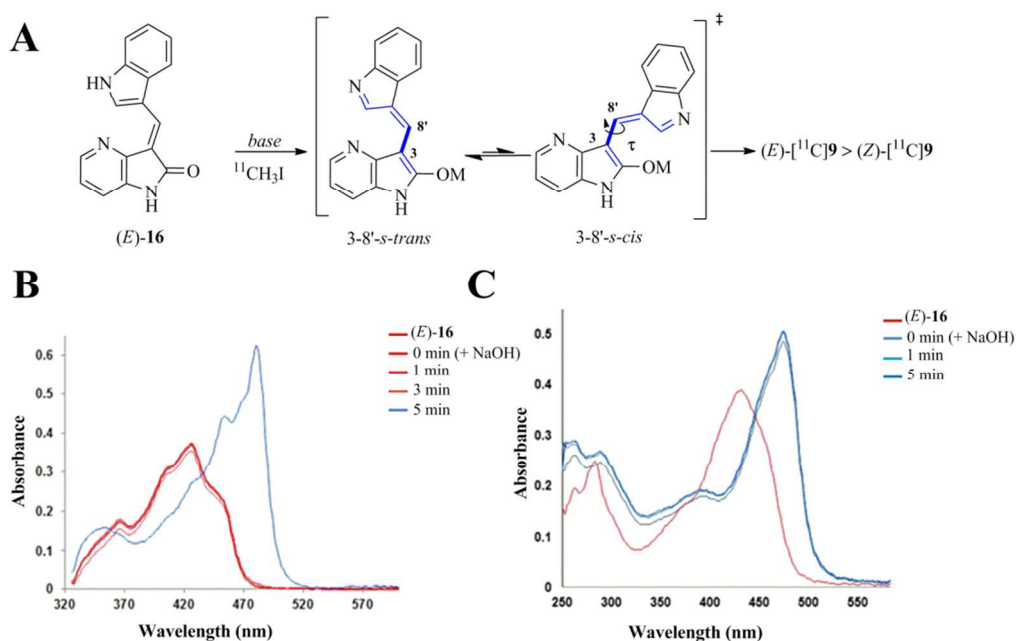


Figure S5. Plausible mechanistic explanation for the formation of (Z)-[^{11}C]9 from (E)-16. (A) ^{11}C -methylation plausibly proceeds through the more stable 3-2'-s-*trans*-azatriene enolate intermediate leading to the preferential formation of (E)-[^{11}C]9 with minor (Z)-[^{11}C]9 (M = Na, K, Cs). The formation of the proposed 3-8'-s-*trans*-azatriene and 3-8'-s-*cis*-azatriene anionic states is supported by the bathochromic shift observed in the UV-visible spectra of 16 upon addition of $\text{NaOH}_{(\text{aq})}$ in (B) acetone or (C) aqueous condition.

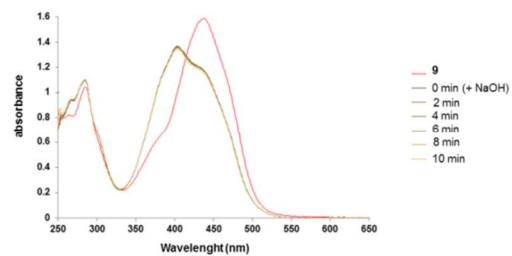


Figure S6. UV-visible spectra changes upon treatment **9** (*E/Z* mixture) with NaOH_(aq) under aqueous condition (identical condition to Figure S5) does not lead to a bathochromic shift.

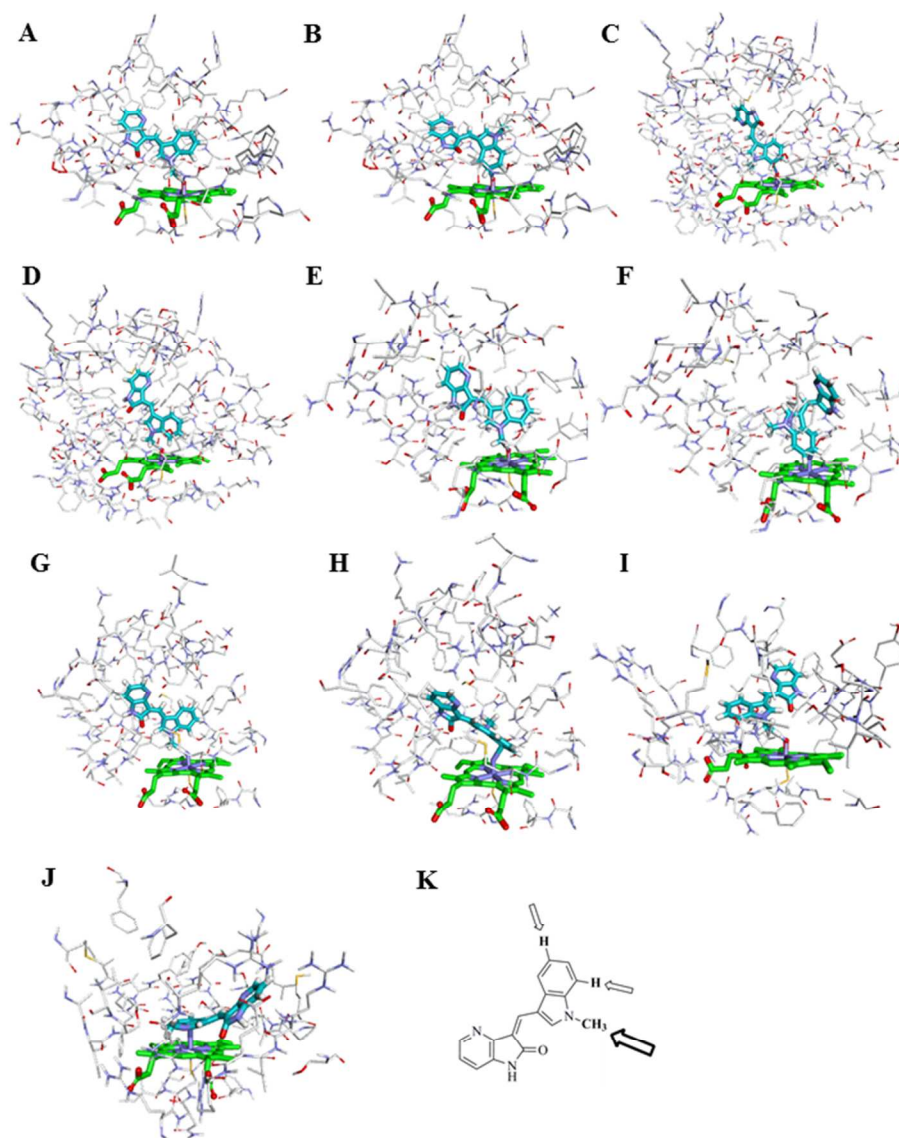


Figure S7. In silico predicted sites of metabolism using IMPACT (In-silico Metabolism Prediction by Activated Cytochromes and Transition States) with transitions states modeling exemplified for (Z)-9 (See experimental section for details).

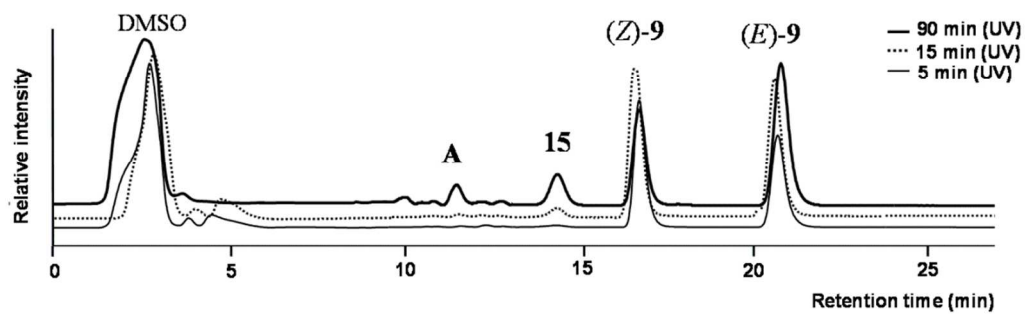


Figure S8. HPLC chromatograms over 90 min for the RLM assay with (E/Z)-9.

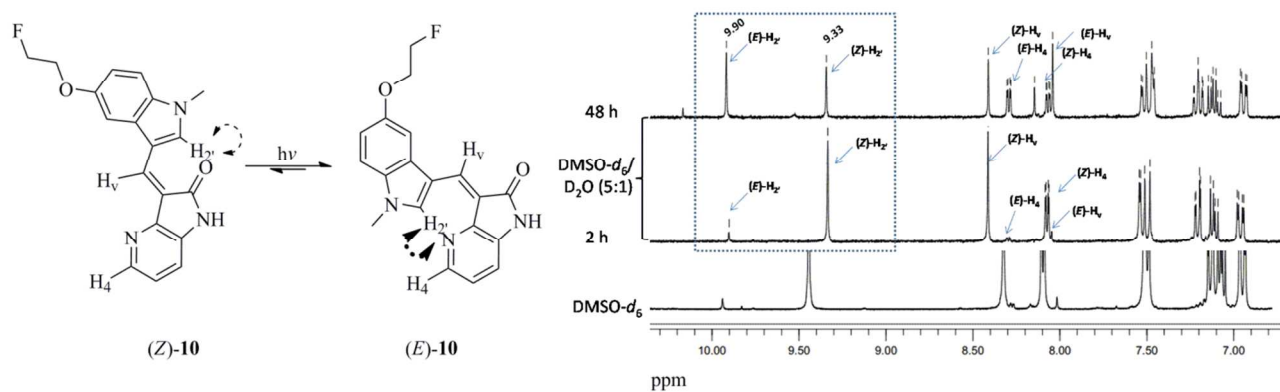


Figure S9. 1H -NMR spectra at different time points during the course of the ambient light-induced photoisomerization of (Z)-10 leading to the formation of (E)-10.

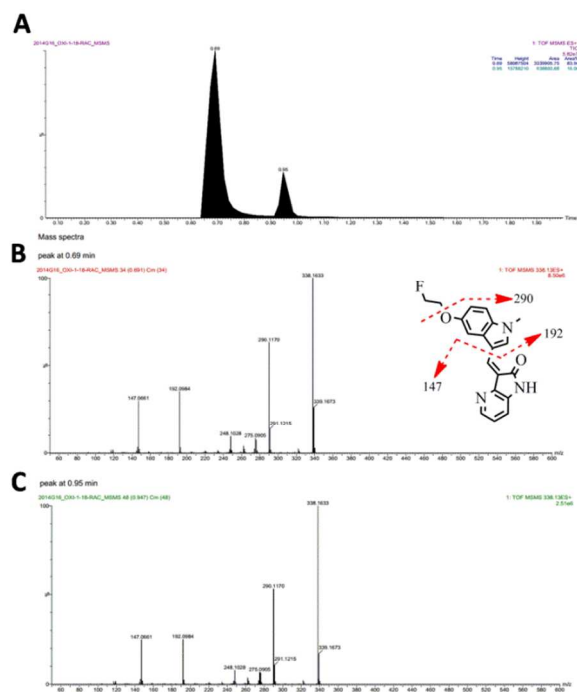


Figure S10. (A-C) LC-MS/MS analysis of the **10** *E/Z* mixture.

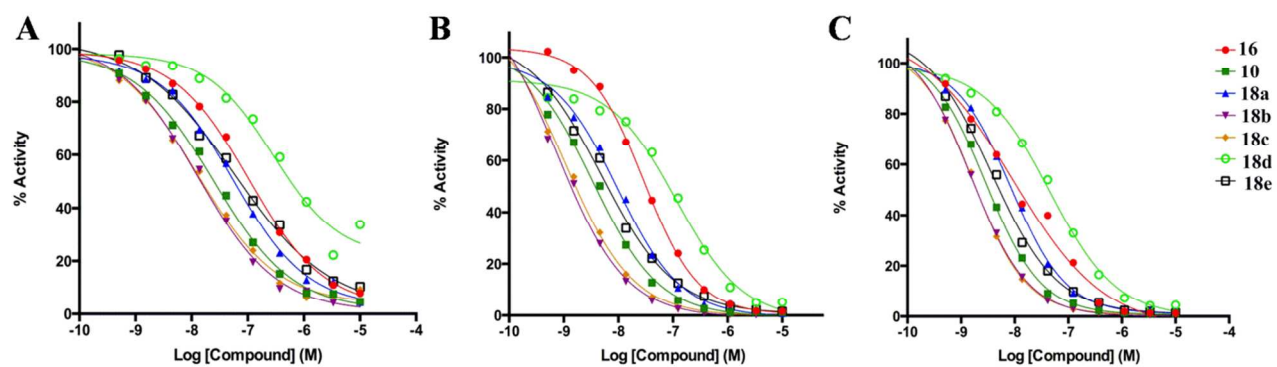


Figure S11. Dose-response curves for the $[\gamma\text{-}^{33}\text{P}]\text{ATP}$ -based enzymatic in vitro assays with **16**, **10** and **18a-e** versus (A) TrkA, (B) TrkB and (C) TrkC. The inhibitors were tested at ten different concentrations using serial dilution.

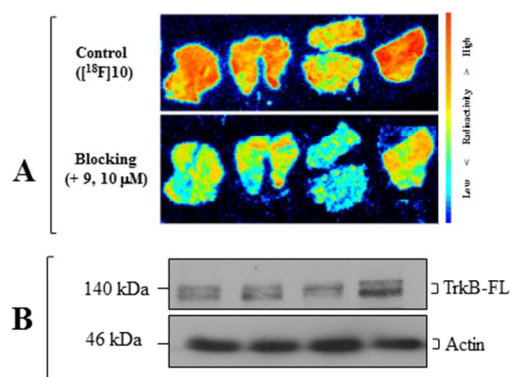


Figure S12. In vitro autoradiography of four representative sections from four human neuroblastoma tumor. (A) Autoradiography images showing the binding of [¹⁸F]**10** alone and in co-incubation with inhibitors **3** (10 μM). (B) Western blots analysis of the TrkB (FL: full length) protein levels. Actin was used as loading control.

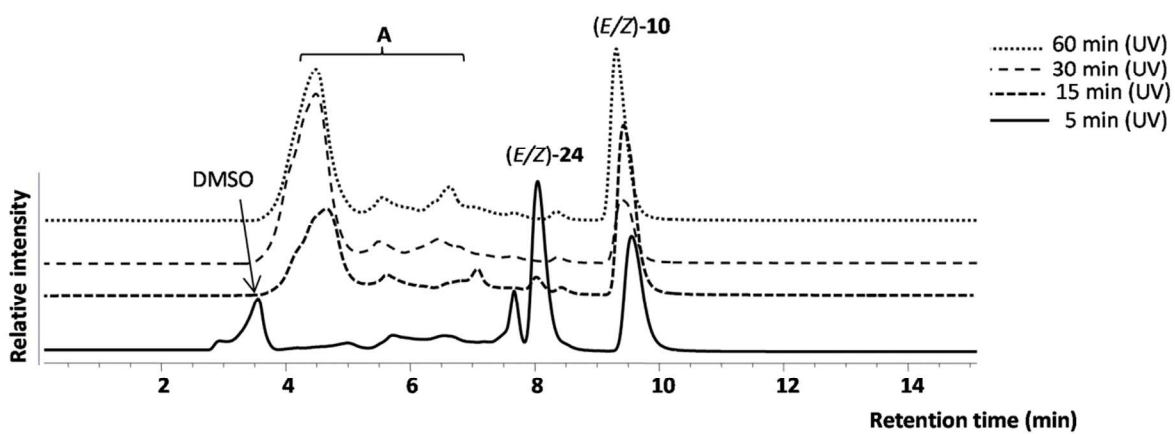
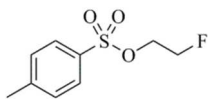


Figure S13. HPLC chromatograms over 60 min for the RLM assay with (E/Z)-10.

2. Chemical synthesis of 2-fluoroethyl 4-methylbenzenesulfonate.



2-Fluoroethyl 4-methylbenzenesulfonate.² To a solution of 2-fluoroethanol (5.0 g, 78.1 mmol, 1 equiv.) in pyridine (25 mL) was added 4-methylbenzene-1-sulfonyl chloride (17.9 g, 93.7 mmol, 1.2 equiv.) in five portions over 30 min. The reaction mixture was stirred at room temperature for 24 h and the volume was reduced *in vacuo*. The residue was taken in 1N aqueous HCl (50 mL) and extracted with CHCl₃ (4 X 50 mL). The combined organic phases were dried over Na₂SO₄ and concentrated *in vacuo*. The crude product was purified by flash chromatography (30% EtOAc/hexane) to afford 10.6 g of the title compound as a colorless solid (92%). ¹H NMR (300 MHz, CDCl₃) δ 7.80 (d, *J* = 8.1 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 4.56 (dt, *J*₂ = 47.1 Hz, *J*₁ = 1.5 Hz, 2H), 4.25 (dt, *J*₂ = 27.3 Hz, *J*₁ = 3.9 Hz, 2H), 2.45 (s, 3H) ppm. ¹³C NMR (75 MHz, CDCl₃) δ 145.2, 132.6, 129.9, 128.0, 80.5 (d, *J* = 172.7 Hz), 68.5 (d, *J* = 20.8 Hz), 21.7 ppm. ¹⁹F NMR (188 MHz, DMSO-*d*₆) δ -224.66 ppm. HRMS (ESI) calcd for C₉H₁₂FO₃S (M+H)⁺ 219.04857, found 219.04849.

3. Crystallographic Data for Compounds 11 and (Z)-9.



CRYSTAL AND MOLECULAR STRUCTURE OF
C12 H14 N2 O6 COMPOUND (INSN15)

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Structure solved and refined in the laboratory of X-ray
diffraction Université de Montréal by Michel Simard.

Table 1. Crystal data and structure refinement for C12 H14 N2 O6.

Identification code	INSN15
Empirical formula	C12 H14 N2 O6
Formula weight	282.25
Temperature	100K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	$a = 19.8614(6) \text{ Å}$ $\alpha = 90^\circ$ $b = 7.8836(2) \text{ Å}$ $\beta = 95.6344(12)^\circ$ $c = 16.6615(5) \text{ Å}$ $\gamma = 90^\circ$
Volume	$2596.24(13) \text{ Å}^3$
Z	8
Density (calculated)	1.444 g/cm^3
Absorption coefficient	1.004 mm^{-1}
F(000)	1184
Crystal size	0.16 x 0.12 x 0.06 mm
Theta range for data collection	4.474 to 71.717°
Index ranges	$-24 \leq h \leq 22, -9 \leq k \leq 9, -20 \leq l \leq 20$
Reflections collected	70890
Independent reflections	2522 [$R_{\text{int}} = 0.045$]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7535 and 0.6865
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2522 / 0 / 183
Goodness-of-fit on F^2	1.046
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0337, wR_2 = 0.0860$
R indices (all data)	$R_1 = 0.0343, wR_2 = 0.0866$
Largest diff. peak and hole	0.453 and -0.240 e/Å ³

Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for C12 H14 N2 O6.

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
C(1)	4488(1)	4433(1)	6553(1)	12(1)
C(2)	5083(1)	4216(1)	6174(1)	13(1)
C(3)	5442(1)	5600(2)	5935(1)	16(1)
C(4)	5213(1)	7199(2)	6106(1)	17(1)
C(5)	4643(1)	7328(2)	6519(1)	17(1)
C(6)	4030(1)	3007(1)	6780(1)	13(1)
C(7)	3775(1)	1903(1)	6059(1)	13(1)
C(8)	3145(1)	-618(2)	5720(1)	19(1)
C(9)	2430(1)	-73(2)	5459(1)	21(1)
C(10)	3429(1)	3747(1)	7167(1)	15(1)
C(11)	2351(1)	5091(2)	6867(1)	26(1)
C(12)	1761(1)	3927(2)	6774(1)	31(1)
N(1)	4282(1)	5992(1)	6725(1)	15(1)
N(2)	5354(1)	2529(1)	6022(1)	15(1)
O(1)	5744(1)	2394(1)	5502(1)	24(1)
O(2)	5185(1)	1332(1)	6435(1)	20(1)
O(3)	3844(1)	2210(1)	5367(1)	19(1)
O(4)	3461(1)	549(1)	6328(1)	16(1)
O(5)	2948(1)	4259(1)	6603(1)	21(1)
O(6)	3402(1)	3810(1)	7884(1)	23(1)

Table 3. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for C12 H14 N2 O6.

	x	y	z	U _{eq}
H(3)	5836	5454	5661	19
H(4)	5439	8185	5944	21
H(5)	4501	8427	6664	21
H(6)	4293	2271	7188	15
H(8A)	3143	-1779	5946	23
H(8B)	3411	-638	5247	23
H(9A)	2216	-905	5079	31
H(9B)	2436	1039	5196	31
H(9C)	2174	3	5931	31
H(11A)	2248	6127	6541	31
H(11B)	2442	5433	7439	31
H(12A)	1697	3511	6218	46
H(12B)	1355	4536	6900	46
H(12C)	1843	2966	7144	46

Table 4. Anisotropic parameters ($\text{\AA}^2 \times 10^3$) for C12 H14 N2 O6.

The anisotropic displacement factor exponent takes the form:

$$-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$$

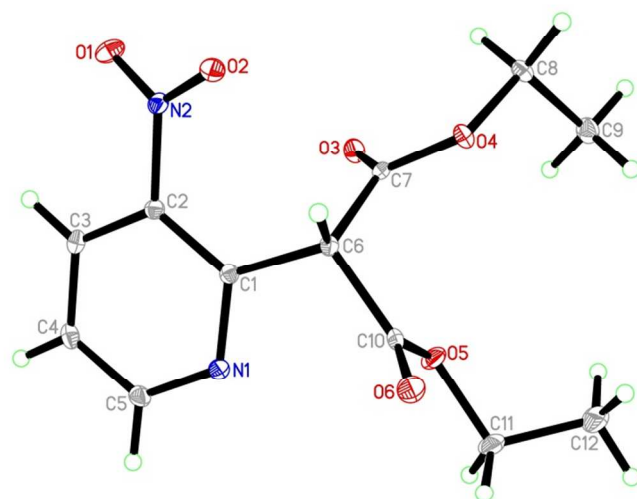
	U11	U22	U33	U23	U13	U12
C (1)	11 (1)	14 (1)	12 (1)	0 (1)	-1 (1)	0 (1)
C (2)	12 (1)	14 (1)	13 (1)	-1 (1)	-1 (1)	2 (1)
C (3)	11 (1)	20 (1)	15 (1)	1 (1)	0 (1)	-1 (1)
C (4)	15 (1)	16 (1)	20 (1)	4 (1)	-2 (1)	-4 (1)
C (5)	16 (1)	12 (1)	22 (1)	0 (1)	-2 (1)	1 (1)
C (6)	11 (1)	13 (1)	14 (1)	0 (1)	1 (1)	-1 (1)
C (7)	9 (1)	12 (1)	17 (1)	-1 (1)	2 (1)	1 (1)
C (8)	20 (1)	13 (1)	24 (1)	-6 (1)	1 (1)	-4 (1)
C (9)	20 (1)	22 (1)	21 (1)	-2 (1)	0 (1)	-4 (1)
C (10)	13 (1)	14 (1)	19 (1)	-4 (1)	4 (1)	-6 (1)
C (11)	15 (1)	29 (1)	35 (1)	-12 (1)	4 (1)	5 (1)
C (12)	17 (1)	34 (1)	42 (1)	-10 (1)	5 (1)	1 (1)
N (1)	13 (1)	14 (1)	18 (1)	-1 (1)	1 (1)	1 (1)
N (2)	12 (1)	16 (1)	17 (1)	-3 (1)	0 (1)	1 (1)
O (1)	23 (1)	28 (1)	22 (1)	-4 (1)	10 (1)	6 (1)
O (2)	19 (1)	14 (1)	29 (1)	2 (1)	4 (1)	1 (1)
O (3)	20 (1)	21 (1)	15 (1)	-2 (1)	4 (1)	-5 (1)
O (4)	17 (1)	13 (1)	18 (1)	-1 (1)	1 (1)	-4 (1)
O (5)	12 (1)	28 (1)	22 (1)	-8 (1)	1 (1)	4 (1)
O (6)	26 (1)	27 (1)	17 (1)	-4 (1)	8 (1)	-4 (1)

Table 5. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for C12 H14 N2 O6

C(1)-N(1)	1.3366(15)	C(3)-C(2)-C(1)	120.91(10)
C(1)-C(2)	1.4023(16)	C(3)-C(2)-N(2)	117.16(10)
C(1)-C(6)	1.5182(15)	C(1)-C(2)-N(2)	121.93(10)
C(2)-C(3)	1.3844(16)	C(4)-C(3)-C(2)	118.11(10)
C(2)-N(2)	1.4661(14)	C(3)-C(4)-C(5)	118.17(11)
C(3)-C(4)	1.3793(17)	N(1)-C(5)-C(4)	123.79(11)
C(4)-C(5)	1.3837(17)	C(1)-C(6)-C(10)	109.59(9)
C(5)-N(1)	1.3386(15)	C(1)-C(6)-C(7)	112.66(9)
C(6)-C(10)	1.5271(15)	C(10)-C(6)-C(7)	109.71(9)
C(6)-C(7)	1.5290(15)	O(3)-C(7)-O(4)	125.77(10)
C(7)-O(3)	1.1996(14)	O(3)-C(7)-C(6)	125.53(10)
C(7)-O(4)	1.3365(13)	O(4)-C(7)-C(6)	108.70(9)
C(8)-O(4)	1.4633(14)	O(4)-C(8)-C(9)	110.39(10)
C(8)-C(9)	1.5064(17)	O(6)-C(10)-O(5)	126.13(11)
C(10)-O(6)	1.2012(15)	O(6)-C(10)-C(6)	123.20(11)
C(10)-O(5)	1.3345(15)	O(5)-C(10)-C(6)	110.65(9)
C(11)-O(5)	1.4610(14)	O(5)-C(11)-C(12)	110.30(11)
C(11)-C(12)	1.4838(19)	C(1)-N(1)-C(5)	118.92(10)
N(2)-O(1)	1.2217(13)	O(1)-N(2)-O(2)	123.74(10)
N(2)-O(2)	1.2343(13)	O(1)-N(2)-C(2)	118.13(10)
		O(2)-N(2)-C(2)	118.12(9)
N(1)-C(1)-C(2)	119.96(10)	C(7)-O(4)-C(8)	116.92(9)
N(1)-C(1)-C(6)	115.01(10)	C(10)-O(5)-C(11)	117.98(10)
C(2)-C(1)-C(6)	125.02(10)		

Table 6. Torsion angles [$^{\circ}$] for C12 H14 N2 O6.

N(1)-C(1)-C(2)-C(3)	-3.56(16)
C(6)-C(1)-C(2)-C(3)	175.14(10)
N(1)-C(1)-C(2)-N(2)	175.85(10)
C(6)-C(1)-C(2)-N(2)	-5.46(17)
C(1)-C(2)-C(3)-C(4)	2.31(16)
N(2)-C(2)-C(3)-C(4)	-177.13(10)
C(2)-C(3)-C(4)-C(5)	1.13(16)
C(3)-C(4)-C(5)-N(1)	-3.65(18)
N(1)-C(1)-C(6)-C(10)	-0.30(13)
C(2)-C(1)-C(6)-C(10)	-179.05(10)
N(1)-C(1)-C(6)-C(7)	122.14(10)
C(2)-C(1)-C(6)-C(7)	-56.62(14)
C(1)-C(6)-C(7)-O(3)	-9.30(16)
C(10)-C(6)-C(7)-O(3)	113.07(12)
C(1)-C(6)-C(7)-O(4)	171.07(9)
C(10)-C(6)-C(7)-O(4)	-66.56(11)
C(1)-C(6)-C(10)-O(6)	-98.76(13)
C(7)-C(6)-C(10)-O(6)	137.06(11)
C(1)-C(6)-C(10)-O(5)	82.61(11)
C(7)-C(6)-C(10)-O(5)	-41.57(12)
C(2)-C(1)-N(1)-C(5)	1.17(16)
C(6)-C(1)-N(1)-C(5)	-177.65(10)
C(4)-C(5)-N(1)-C(1)	2.46(17)
C(3)-C(2)-N(2)-O(1)	-21.33(14)
C(1)-C(2)-N(2)-O(1)	159.24(10)
C(3)-C(2)-N(2)-O(2)	157.51(10)
C(1)-C(2)-N(2)-O(2)	-21.92(15)
O(3)-C(7)-O(4)-C(8)	-3.10(16)
C(6)-C(7)-O(4)-C(8)	176.52(9)
C(9)-C(8)-O(4)-C(7)	-88.32(12)
O(6)-C(10)-O(5)-C(11)	4.83(18)
C(6)-C(10)-O(5)-C(11)	-176.59(10)
C(12)-C(11)-O(5)-C(10)	-105.81(13)



ORTEP view of the C₁₂ H₁₄ N₂ O₆ compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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CRYSTAL AND MOLECULAR STRUCTURE OF
C18 H17 N3 O2 COMPOUND (INSN14)

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Structure solved and refined in the laboratory of X-ray
diffraction Université de Montréal by Michel Simard.

Table 1. Crystal data and structure refinement for C₁₈ H₁₇ N₃ O₂.

Identification code	INSN14
Empirical formula	C ₁₈ H ₁₇ N ₃ O ₂
Formula weight	307.34
Temperature	100K
Wavelength	1.54178 Å
Crystal system	Monoclinic
Space group	P2 ₁
Unit cell dimensions	$a = 8.6286(5) \text{ Å}$ $\alpha = 90^\circ$ $b = 6.1649(4) \text{ Å}$ $\beta = 99.9863(19)^\circ$ $c = 14.2037(9) \text{ Å}$ $\gamma = 90^\circ$
Volume	744.11(8) Å ³
Z	2
Density (calculated)	1.372 g/cm ³
Absorption coefficient	0.741 mm ⁻¹
F(000)	324
Crystal size	0.18 x 0.16 x 0.05 mm
Theta range for data collection	3.159 to 71.540°
Index ranges	$-10 \leq h \leq 10, -7 \leq k \leq 7, -17 \leq l \leq 17$
Reflections collected	30266
Independent reflections	2851 [$R_{\text{int}} = 0.036$]
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.7535 and 0.6788
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2851 / 1 / 218
Goodness-of-fit on F^2	1.076
Final R indices [$I > 2\sigma(I)$]	$R_1 = 0.0269, wR_2 = 0.0706$
R indices (all data)	$R_1 = 0.0270, wR_2 = 0.0706$
Absolute structure parameter	0.08(4)

Largest diff. peak and hole	0.198 and -0.150 e/Å ³
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Table 2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for C18 H17 N3 O2.

U_{eq} is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U_{eq}
C(2)	-808(2)	2667(3)	2495(1)	15(1)
C(3)	851(2)	2457(3)	2344(1)	14(1)
C(4)	880(2)	506(3)	1767(1)	14(1)
C(6)	1772(2)	-2219(3)	918(1)	18(1)
C(7)	307(2)	-3215(3)	749(1)	18(1)
C(8)	-955(2)	-2300(3)	1101(1)	18(1)
C(9)	-651(2)	-389(3)	1605(1)	15(1)
C(10)	2123(2)	3733(3)	2660(1)	14(1)
C(11)	2309(2)	5685(3)	3207(1)	14(1)
C(12)	1218(2)	6864(3)	3609(1)	15(1)
C(14)	3456(2)	8764(3)	3921(1)	14(1)
C(15)	4580(2)	10365(3)	4221(1)	17(1)
C(16)	6063(2)	10036(3)	3995(1)	19(1)
C(17)	6405(2)	8165(3)	3505(1)	18(1)
C(18)	5280(2)	6587(3)	3214(1)	16(1)
C(19)	3766(2)	6895(3)	3416(1)	14(1)
C(20)	1134(2)	10217(3)	4590(1)	18(1)
N(1)	-1618(2)	929(3)	2040(1)	17(1)
N(5)	2082(2)	-368(2)	1426(1)	16(1)
N(13)	1889(2)	8679(2)	4034(1)	14(1)
O(2)	-1414(1)	4056(2)	2935(1)	22(1)
C(21)	4901(2)	2878(4)	792(2)	31(1)
O(21)	5123(2)	1077(3)	1404(1)	31(1)

Table 3. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for C18 H17 N3 O2.

	x	y	z	U _{eq}
H(6)	2604	-2877	662	21
H(7)	165	-4525	393	21
H(8)	-1967	-2955	999	22
H(10)	3070	3225	2481	17
H(12)	151	6456	3588	18
H(15)	4341	11612	4561	20
H(16)	6861	11093	4174	23
H(17)	7437	7975	3370	21
H(18)	5531	5329	2885	19
H(20A)	1538	10005	5272	28
H(20B)	-6	9979	4465	28
H(20C)	1362	11700	4407	28
H(1)	-2640 (30)	830 (40)	1969 (16)	24 (6)
H(21A)	4815	2392	128	46
H(21B)	5798	3866	949	46
H(21C)	3933	3635	872	46
H(21)	4160 (30)	640 (50)	1468 (18)	38 (7)

Table 4. Anisotropic parameters ($\text{\AA}^2 \times 10^3$) for C18 H17 N3 O2.

The anisotropic displacement factor exponent takes the form:

$$-2 \pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$$

	U11	U22	U33	U23	U13	U12
C(2)	13(1)	17(1)	17(1)	2(1)	4(1)	0(1)
C(3)	14(1)	15(1)	14(1)	2(1)	3(1)	0(1)
C(4)	13(1)	14(1)	13(1)	2(1)	1(1)	-1(1)
C(6)	19(1)	17(1)	17(1)	1(1)	3(1)	4(1)
C(7)	23(1)	14(1)	15(1)	0(1)	0(1)	0(1)
C(8)	17(1)	19(1)	17(1)	1(1)	-1(1)	-5(1)
C(9)	14(1)	15(1)	15(1)	3(1)	2(1)	-1(1)
C(10)	12(1)	16(1)	14(1)	2(1)	2(1)	3(1)
C(11)	13(1)	14(1)	13(1)	2(1)	2(1)	-1(1)
C(12)	15(1)	16(1)	14(1)	1(1)	2(1)	-2(1)
C(14)	13(1)	14(1)	13(1)	2(1)	1(1)	1(1)
C(15)	19(1)	15(1)	15(1)	-1(1)	0(1)	0(1)
C(16)	16(1)	18(1)	21(1)	1(1)	-2(1)	-4(1)
C(17)	12(1)	21(1)	20(1)	3(1)	2(1)	1(1)
C(18)	16(1)	16(1)	15(1)	1(1)	2(1)	2(1)
C(19)	15(1)	13(1)	13(1)	2(1)	0(1)	0(1)
C(20)	19(1)	19(1)	19(1)	-4(1)	6(1)	2(1)
N(1)	10(1)	19(1)	23(1)	-3(1)	4(1)	-3(1)
N(5)	15(1)	16(1)	16(1)	0(1)	2(1)	1(1)
N(13)	14(1)	14(1)	15(1)	-1(1)	3(1)	0(1)
O(2)	16(1)	22(1)	29(1)	-6(1)	8(1)	-1(1)
C(21)	26(1)	36(1)	31(1)	4(1)	6(1)	2(1)
O(21)	12(1)	36(1)	45(1)	12(1)	2(1)	-3(1)

Table 5. Bond lengths [Å] and angles [°] for C18 H17 N3 O2

C(2)-O(2)	1.229(2)	C(4)-C(3)-C(2)	105.28(14)
C(2)-N(1)	1.378(2)	N(5)-C(4)-C(9)	123.19(16)
C(2)-C(3)	1.490(2)	N(5)-C(4)-C(3)	128.94(15)
C(3)-C(10)	1.362(2)	C(9)-C(4)-C(3)	107.88(14)
C(3)-C(4)	1.458(2)	N(5)-C(6)-C(7)	123.75(16)
C(4)-N(5)	1.332(2)	C(6)-C(7)-C(8)	120.26(17)
C(4)-C(9)	1.414(2)	C(9)-C(8)-C(7)	116.20(16)
C(6)-N(5)	1.352(2)	C(8)-C(9)-N(1)	131.13(16)
C(6)-C(7)	1.388(3)	C(8)-C(9)-C(4)	120.39(16)
C(7)-C(8)	1.394(3)	N(1)-C(9)-C(4)	108.46(15)
C(8)-C(9)	1.380(3)	C(3)-C(10)-C(11)	132.42(15)
C(9)-N(1)	1.384(2)	C(12)-C(11)-C(10)	130.25(16)
C(10)-C(11)	1.427(2)	C(12)-C(11)-C(19)	105.83(15)
C(11)-C(12)	1.388(3)	C(10)-C(11)-C(19)	123.87(15)
C(11)-C(19)	1.448(2)	N(13)-C(12)-C(11)	110.40(15)
C(12)-N(13)	1.353(2)	N(13)-C(14)-C(15)	128.95(16)
C(14)-N(13)	1.390(2)	N(13)-C(14)-C(19)	107.62(14)
C(14)-C(15)	1.397(2)	C(15)-C(14)-C(19)	123.43(16)
C(14)-C(19)	1.407(2)	C(16)-C(15)-C(14)	116.44(16)
C(15)-C(16)	1.387(2)	C(15)-C(16)-C(17)	121.06(17)
C(16)-C(17)	1.404(3)	C(18)-C(17)-C(16)	121.87(16)
C(17)-C(18)	1.386(2)	C(17)-C(18)-C(19)	118.33(16)
C(18)-C(19)	1.398(2)	C(18)-C(19)-C(14)	118.84(15)
C(20)-N(13)	1.458(2)	C(18)-C(19)-C(11)	134.22(16)
C(21)-O(21)	1.402(3)	C(14)-C(19)-C(11)	106.93(15)
		C(2)-N(1)-C(9)	111.75(14)
O(2)-C(2)-N(1)	123.74(16)	C(4)-N(5)-C(6)	116.17(15)
O(2)-C(2)-C(3)	129.62(16)	C(12)-N(13)-C(14)	109.21(14)
N(1)-C(2)-C(3)	106.63(15)	C(12)-N(13)-C(20)	125.64(15)
C(10)-C(3)-C(4)	124.76(15)	C(14)-N(13)-C(20)	124.98(14)
C(10)-C(3)-C(2)	129.96(16)		

Table 6. Torsion angles [$^{\circ}$] for C18 H17 N3 O2.

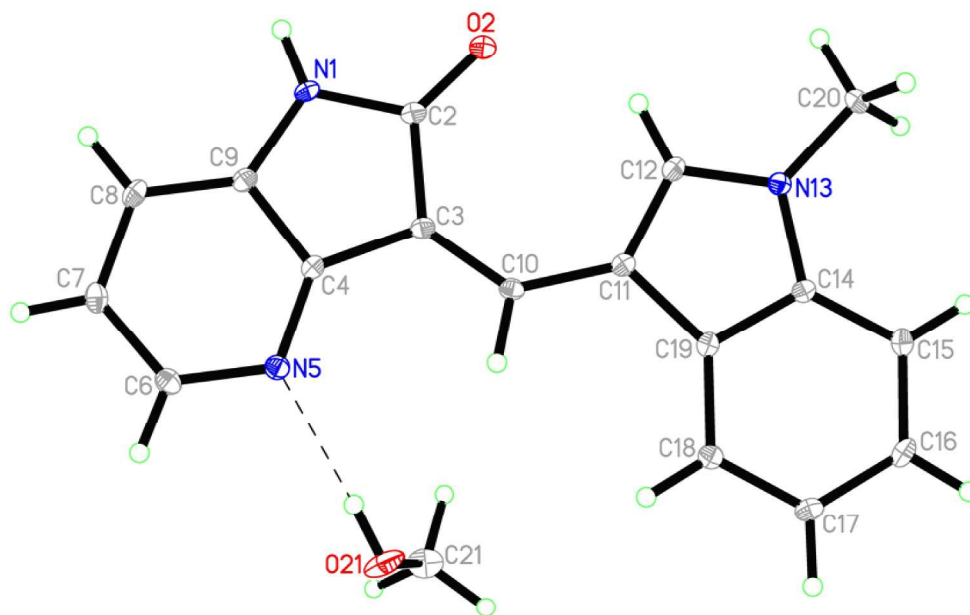
O(2)-C(2)-C(3)-C(10)	0.6(3)
N(1)-C(2)-C(3)-C(10)	-178.79(17)
O(2)-C(2)-C(3)-C(4)	-179.90(17)
N(1)-C(2)-C(3)-C(4)	0.68(18)
C(10)-C(3)-C(4)-N(5)	-1.7(3)
C(2)-C(3)-C(4)-N(5)	178.78(17)
C(10)-C(3)-C(4)-C(9)	178.57(15)
C(2)-C(3)-C(4)-C(9)	-0.94(17)
N(5)-C(6)-C(7)-C(8)	0.7(3)
C(6)-C(7)-C(8)-C(9)	0.5(2)
C(7)-C(8)-C(9)-N(1)	179.69(17)
C(7)-C(8)-C(9)-C(4)	-1.9(2)
N(5)-C(4)-C(9)-C(8)	2.4(2)
C(3)-C(4)-C(9)-C(8)	-177.87(14)
N(5)-C(4)-C(9)-N(1)	-178.87(16)
C(3)-C(4)-C(9)-N(1)	0.86(18)
C(4)-C(3)-C(10)-C(11)	178.80(16)
C(2)-C(3)-C(10)-C(11)	-1.8(3)
C(3)-C(10)-C(11)-C(12)	1.7(3)
C(3)-C(10)-C(11)-C(19)	-175.42(17)
C(10)-C(11)-C(12)-N(13)	-177.17(16)
C(19)-C(11)-C(12)-N(13)	0.34(18)
N(13)-C(14)-C(15)-C(16)	-179.06(16)
C(19)-C(14)-C(15)-C(16)	0.0(2)
C(14)-C(15)-C(16)-C(17)	-1.1(3)
C(15)-C(16)-C(17)-C(18)	1.0(3)
C(16)-C(17)-C(18)-C(19)	0.2(2)
C(17)-C(18)-C(19)-C(14)	-1.2(2)
C(17)-C(18)-C(19)-C(11)	177.71(17)
N(13)-C(14)-C(19)-C(18)	-179.60(14)
C(15)-C(14)-C(19)-C(18)	1.1(2)
N(13)-C(14)-C(19)-C(11)	1.20(17)
C(15)-C(14)-C(19)-C(11)	-178.07(15)
C(12)-C(11)-C(19)-C(18)	-179.97(18)
C(10)-C(11)-C(19)-C(18)	-2.3(3)
C(12)-C(11)-C(19)-C(14)	-0.95(18)
C(10)-C(11)-C(19)-C(14)	176.76(15)
O(2)-C(2)-N(1)-C(9)	-179.63(16)
C(3)-C(2)-N(1)-C(9)	-0.17(19)
C(8)-C(9)-N(1)-C(2)	178.11(17)
C(4)-C(9)-N(1)-C(2)	-0.44(19)
C(9)-C(4)-N(5)-C(6)	-1.2(2)
C(3)-C(4)-N(5)-C(6)	179.14(16)
C(7)-C(6)-N(5)-C(4)	-0.3(2)
C(11)-C(12)-N(13)-C(14)	0.42(18)
C(11)-C(12)-N(13)-C(20)	-175.06(15)
C(15)-C(14)-N(13)-C(12)	178.19(17)
C(19)-C(14)-N(13)-C(12)	-1.02(17)
C(15)-C(14)-N(13)-C(20)	-6.3(3)
C(19)-C(14)-N(13)-C(20)	174.50(15)

Table 7. Bond lengths [$\text{\AA}$] and angles [$^\circ$] related to the hydrogen bonding for C18 H17 N3 O2.

D-H	..A	d(D-H)	d(H..A)	d(D..A)	<DHA
N(1)-H(1)	O(21)#1	0.87(3)	1.96(3)	2.802(2)	161(2)
O(21)-H(21)	N(5)	0.89(3)	1.89(3)	2.777(2)	172(2)

Symmetry transformations used to generate equivalent atoms:

#1 $x-1, y, z$



ORTEP view of the C₁₈ H₁₇ N₃ O₂ compound with the numbering scheme adopted. Ellipsoids drawn at 30% probability level. Hydrogen atoms are represented by sphere of arbitrary size.

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