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Synthesis of new [1,2,4]triazolo[5′,1′:2,3]pyrimido[4,5-*b*]indol-2-amines

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Contents

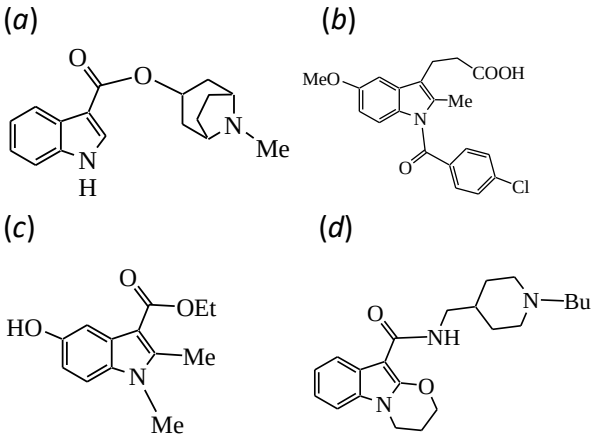


Figure S1 Structures of indole-based drugs: (*a*) Tropisetron (Navoban, antiemetic), (*b*) Indomethacin (anti-inflammatory drug), (*c*) Dimecarbine (antihypertensive), (*d*) Piboserod (antiarrhythmic).

1. General information

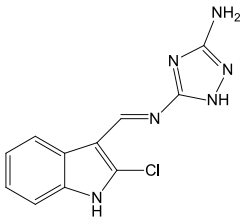
Elemental analysis was performed on a PerkinElmer 240C instrument. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX-250 spectrometers (250 and 63 MHz, respectively) in DMSO-d_6. IR spectra were recorded on a Varian 3100 FT-IR instrument. Mass spectra were obtained by direct injection on a Finnigan MAT INCOS 50 mass spectrometer. The starting 2-chloroindole-3-carbaldehydes **1a-c** and **1′a** were synthesized according to work.[S1]

2. General procedure for the synthesis of compounds 2a,b.

A mixture of 2-chloro-1*H*-indole-3-carbaldehyde **1a,b** (0.001 mol) and 3,5-diamino-1,2,4-triazole (0.001 mol) in 2.5 ml of DMF is refluxed for 4 hours. The mixture is cooled and kept at room temperature for 24 hours. The precipitate is filtered off, washed with petroleum ether, dried, and then recrystallized from butan-1-ol.

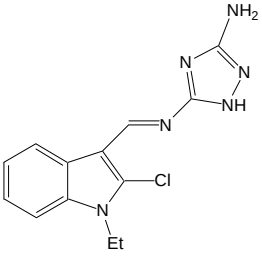
2. Characterization of compounds 2a,b.

5-[(*Z*)-(2-Chloro-1*H*-indol-3-yl)methyleneamino]-1*H*-1,2,4-triazol-3-amine 2a



Colorless crystals, yield 35%, mp 200-202°C. IR spectrum, ν_{max}, cm^{-1}: 3176, 3050, 2962, 1686, 1650, 1586, 1556. ^1H NMR (250 MHz, DMSO-d_6), δ: 11.34 (s, 1H, NH), 10.91 (s, 1H, NH), 9.38 (s, 1H, CH=N), 9.21 (s, 2H, NH_2), 8.22 (d, 1H, H_{arom}, *J* 7.5 Hz), 7.65-7.34 (m, 3H, H_{arom}). ^{13}C NMR (63 MHz, DMSO-d6), δ: 106.65, 113.40, 120.66, 121.46, 122.51, 126.23, 132.90, 147.81, 153.51, 153.97, 159.49. Calculated (%) for $C_{11}H_9N_6Cl$: C 50.69; H 3.45; N 32.25; Cl 13.60. Found: C 50.81; H 3.22; N 32.25; Cl 13.51.

5-[(*E*)-(2-Chloro-1-ethylindol-3-yl)methyleneamino]-1*H*-1,2,4-triazol-3-amine 2b



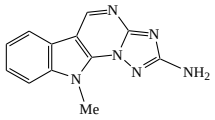
Colorless crystals, yield 37%, mp 150-152°C. IR spectrum, ν_{max}, cm^{-1}: 3157, 3055, 3027, 1698, 1636, 1615, 1561, 1524, 1500. NMR ^1H (250 MHz, DMSO-d_6), δ: 11.38 (s, 1H, NH_2), 10.91 (s, 1H, NH), 9.40 (s, 1H, CH=N), 9.25 (s, 1H, NH_2), 8.27 (d, 1H, H_{arom}, *J* 7.5 Hz), 7.85 (d, 1H, H_{arom}, *J* 7.5 Hz), 7.59-7.41 (m, 2H, H_{arom}), 4.96 (q, 1H, CH_2, *J* 5.0 Hz), 1.46 (t, 3H, CH_3, *J* 5.0 Hz). ^{13}C NMR (63 MHz, DMSO-d_6) δ: 14.04, 18.82, 106.65, 113.56, 120.66, 121.45, 122.51, 126.23, 147.81, 153.97, 159.49. Calculated (%) for $C_{13}H_{13}N_6Cl$: C 54.09; H 4.50; N 29.12; Cl 12.28. Found: C 54.35; H 4.77; N 29.38; Cl 12.08.

3. General procedure for the synthesis of compounds 3a-c.

A mixture of 2-chloro-1*H*-indole-3-carbaldehyde **1′a** or **1b,c** (0.002 mol), 3,5-diamino-1,2,4-triazole (0.002 mol), and a solution of NaOH (0.002 mol in 0.2 ml of water) in 2.5 ml of DMF was refluxed for 2 hours. The mixture was cooled and kept at room temperature for 24 hours. The precipitate was filtered off, washed with petroleum ether, dried, and then recrystallized from butan-1-ol.

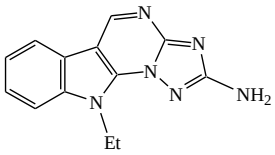
4. Characterization of compounds 3a-c.

10-Methyl-10*H*-[1,2,4]triazolo[5′,1′:2,3]pyrimido[4,5-*b*]indol-2-amine 3a



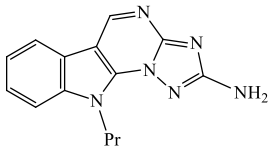
Colorless crystals, yield 41%, mp 283-285°C. IR spectrum, ν_{max}, cm^{-1}: 3370, 3211, 1638, 1613, 1586, 1534, 1523, 1485. NMR ^1H (250 MHz, DMSO-d_6), δ: 9.12 (s, 1H, CH=N), 8.15 (d, 1H, H_{arom}, *J* 7.5 Hz), 7.66 (d, 1H, H_{arom}, *J* 7.5 Hz), 7.53-7.35 (m, 2H, H_{arom}), 6.21 (s, 2H, NH_2), 4.30 (t, 3H, CH_3) ppm. ^{13}C NMR (63 MHz, DMSO-d_6), δ: 31.23, 105.40,111.22,120.27, 120.65, 123.03, 126.21, 138.17, 139.00, 145.94, 155.75, 166.66. Calculated (%) for $C_{12}H_{10}N_6$: C 60.51; H 4.20; N 35.29. Found: C 60.69; H 4.39; N 35.18.

10-Ethyl-10*H*-[1,2,4]triazolo[5′,1′:2,3]pyrimido[4,5-*b*]indol-2-amine 3b.



Colorless crystals, yield 51%, mp 308-310°C. IR spectrum, ν_{max}, cm^{-1}: 3358, 3214, 1698, 1636, 1615,1613,1584, 1524. NMR ^1H (250 MHz, DMSO-d_6), δ: 9.18 (s, 1H, CH=N), 8.20 (d, 1H, H_{arom}, *J* 7.5 Hz), 7.78 (d, 1H, H_{arom}, *J* 7.5 Hz), 7.51-7.37 (m, 2H, H_{arom}), 6.34 (s, 2H, NH_2), 4.94 (q, 2H, CH_2, *J* 7.5 Hz),1.43 (t, 3H, CH_3, *J* 7.5 Hz) ppm. ^{13}C NMR (63 MHz, DMSO-d_6), δ: 15.97, 23.92, 105.30, 111.28, 120.46, 121.06, 122.83, 126.04, 136.89, 138.44, 145.93, 155.77,167.15. Calculated (%) for $C_{13}H_{12}N_6$: C 61.90; H 4.76; N 33.31 Found: C 60.83; H 4.59; N 33.28.

10-Propyl-10*H*-[1,2,4]triazolo[5′,1′:2,3]pyrimido[4,5-*b*]indol-2-amine 3c



Colorless crystals, yield 37%, mp 318-320°C. IR spectrum, ν_{max}, cm^{-1}: 3287, 3215, 1679, 1633, 1575, 1535, 1485. ^1H NMR (250 MHz, DMSO-d_6), δ: 9.15 (с, 1H, CH=N), 8.16 (д, 1H, $H_{аром}$ *J* 7.5 Hz), 7.74 (д, 1H, $H_{аром}$, *J* 7.5 Hz), 7.49 -7.32 (м, 2H, $H_{аром}$), 6.29 (с, 2H, NH_2), 4.83 (т, 2H, NCH_2, *J* 7.5 Hz), 1.86 (к, 2H, CH_2, *J* 7.5 Hz), 0.83 (т, 3H, CH_3. *J* 7.5 Hz) ppm. ^{13}C NMR (63 MHz, DMSO-d_6), δ: 11.07, 23.49, 45.73, 105.16, 111.55, 120.38, 120.94, 122.76, 125.92, 137.32, 138.76, 145.93, 156.02, 167.04. Calculated (%) for $C_{14}H_{14}N_6$: C 63.16; H 5.26; N 31.58. Found: C 63.28; H 5.51; N 31.20.

5. X-ray diffraction data CCDC 2409128 (3c)

$C_{14}H_{14}N_6$ (M =266.31 g mol^{-1}): triclinic, space group P-1 (no. 2), a =7.34500(10) Å, b = 13.2195(3) Å, c =13.6533(3) Å, α =102.524(2)°, β =103.771(2)°, γ =90.269(2)°, V = 1254.73(5) Å^3, Z = 4, T = 101(2) K, μ(CuKα) = 0.735 mm^{-1}, d_{calc} = 1.410 g cm^{-3}, 25935 reflections measured (6.862° ≤ 2Θ ≤ 152.298°), 5228 unique (R_{int} = 0.0256, R_{sigma} = 0.0168) which were used in all calculations. The final R_1 was 0.0472 ($I > 2\sigma(I)$) and wR_2 was 0.1245 (all data). The X-ray diffraction data set was recorded on an Agilent SuperNova diffractometer using a microfocus X-ray radiation source with copper anode and Atlas S2 two-dimensional CCD detector. The reflections were collected, unit cell parameters determined and refined using the specialized CrysAlisPro software suite (Rigaku Oxford Diffraction, 2015).[S2] The structures were solved using the ShelXT program (Sheldrick, 2015)[S3] and refined with the ShelXL program (Sheldrick, 2015).[S4] Molecular graphics and presentation of structures for the publication were performed with the Olex2 ver. 1.5 software suite.[S5]

CCDC 2409128 (**3c**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

7. References

S1. K. F. Suzdalev, N. I. Vikrishchuk, K. A. Prikhodko, E. Yu. Shasheva, S. V. Kurbatov, S. K. Bogus and P. A. Galenko-Yaroshevsky, *Chem. Heterocycl. Compd*., 2016, **52**, 303; https://doi.org/10.1007/s10593-016-1882-y.

S2. CrysAlisPro, version 1.171.38.41, Rigaku Oxford Diffraction, Oxford, 2015.

S3. G. M. Sheldrick, *Acta Crystallogr*., *Sect. A: Found. Adv.*, 2015, **71**, 3; https://doi.org/10.1107/S2053229614024218.

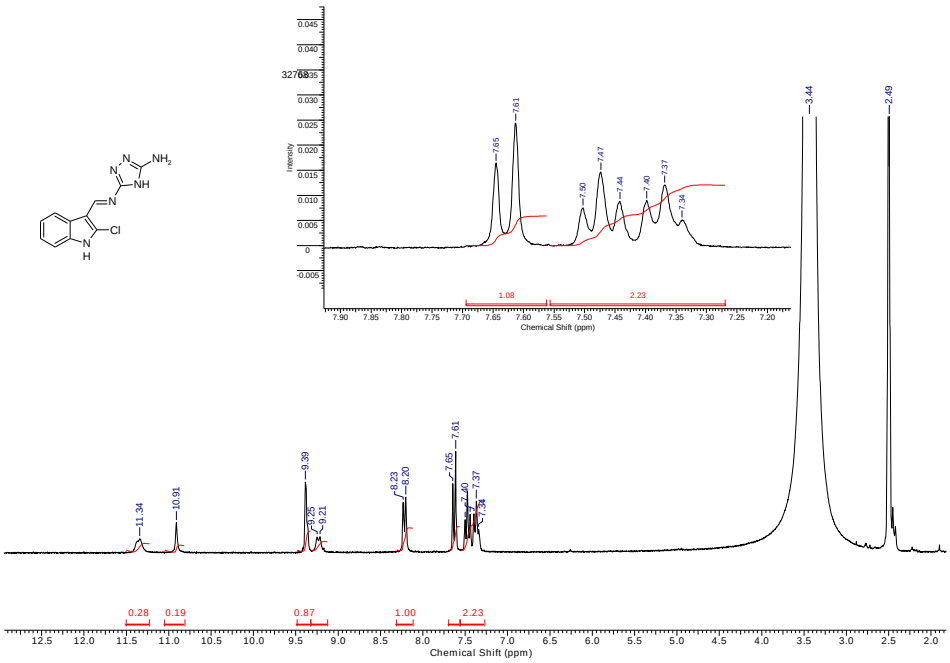
S4. G. M. Sheldrick, *Acta Crystallogr*., *Sect. C: Struct. Chem.*, 2015, **71**, 3; https://doi.org/10.1107/S2053229614024218.

S5. O. V. Dolomanov, L. J. Bourhis, R. J. Gildea, J. A. K. Howard and H. J. Puschmann, *J. Appl. Crystallogr.*, 2009, **42**, 339; https://doi.org/10.1107/S0021889808042726.

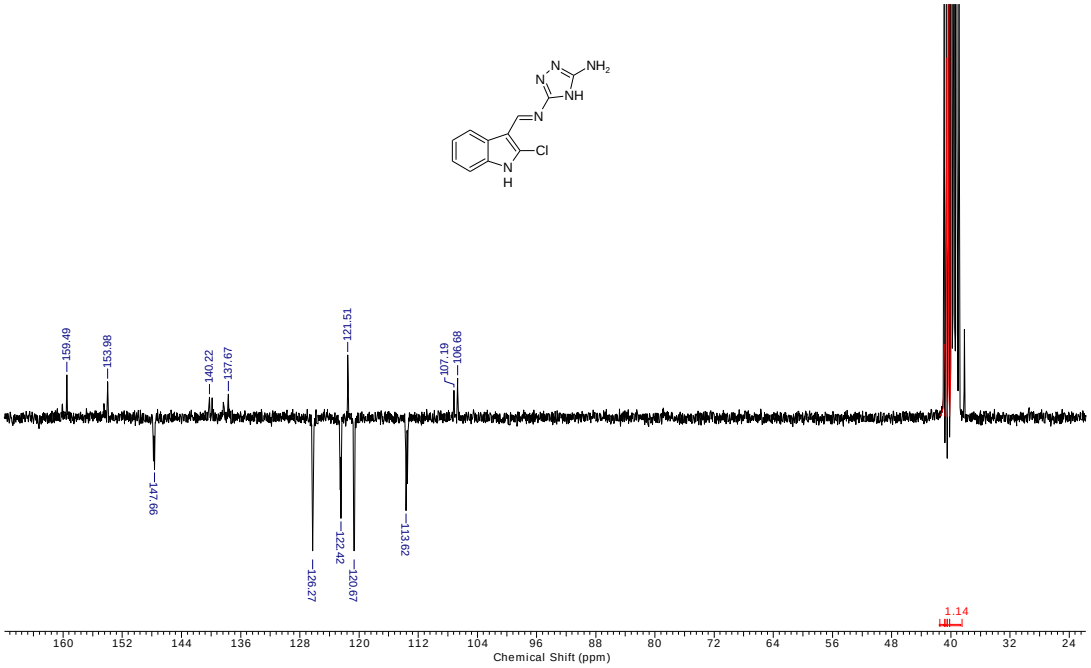
8. NMR spectra of compounds 2a,b and 3a-c.

5-[(*Z*)-(2-Chloro-1*H*-indol-3-yl)methyleneamino]-1*H*-1,2,4-triazol-3-amine 2a

^{1}H NMR spectrum

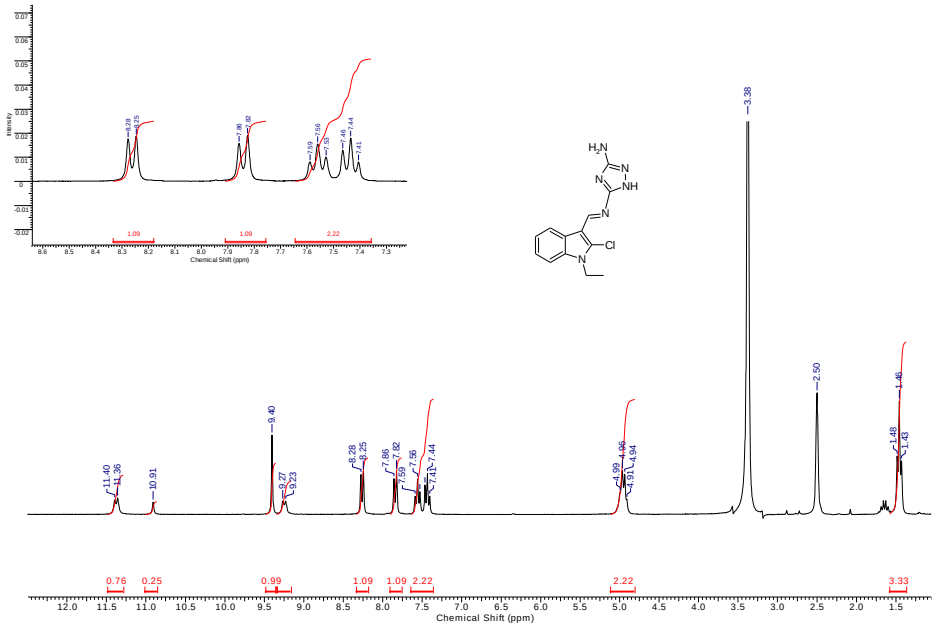


^{13}C NMR spectrum



5-[(*E*)-(2-Chloro-1-ethyl-indol-3-yl)methyleneamino]-1*H*-1,2,4-triazol-3-amine 2b

^{1}H NMR spectrum



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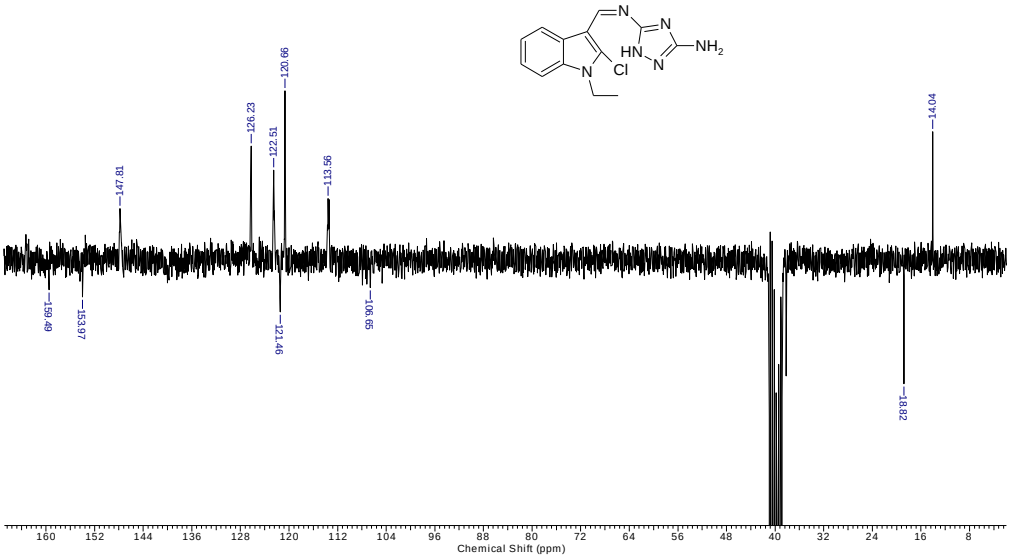
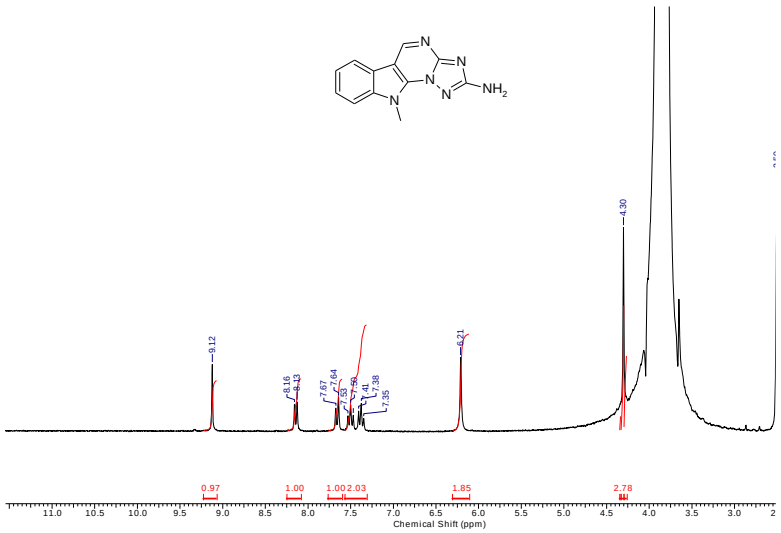


10-Methyl-10*H*-[1,2,4]triazolo[5′,1′:2,3]pyrimido[4,5-*b*]indol-2-amine 3a

^{1}H NMR spectrum



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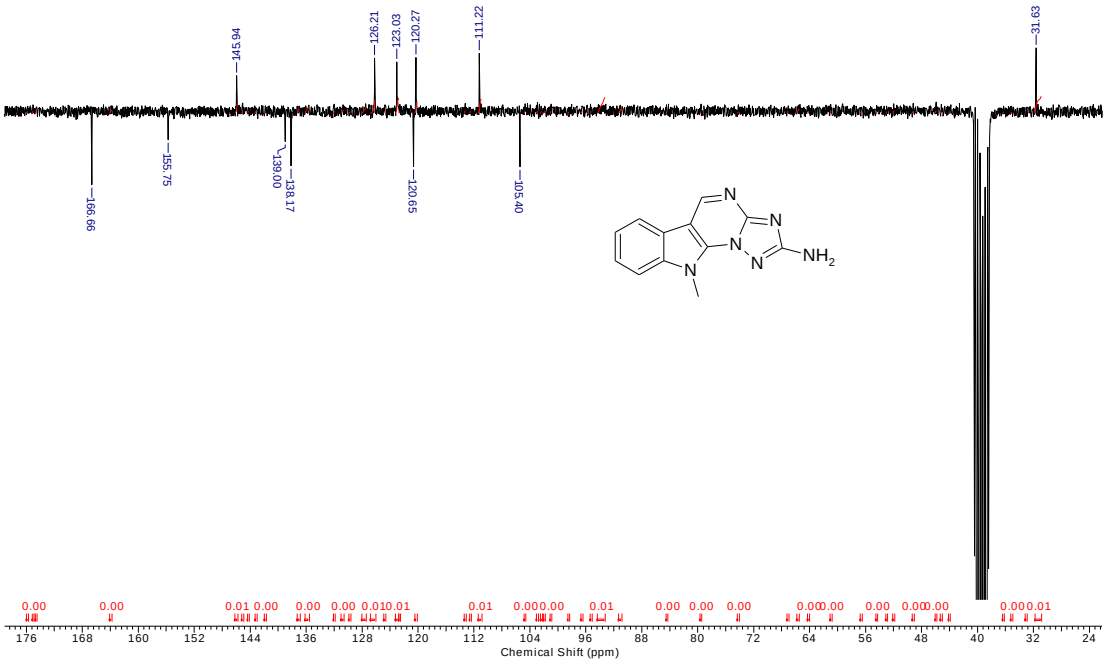
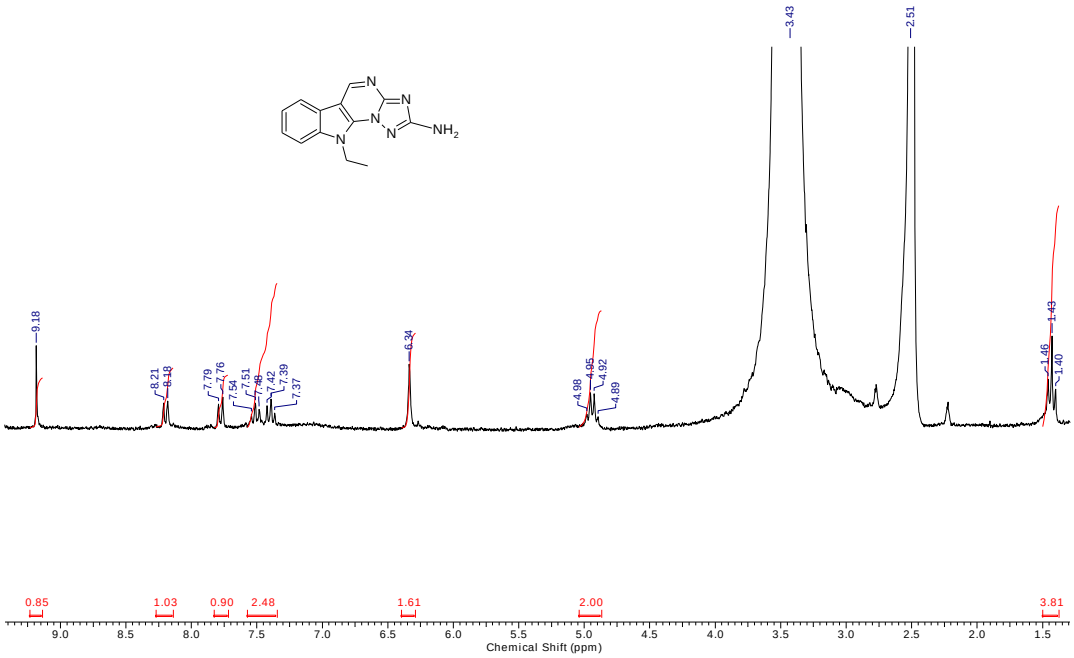


10-Ethyl-10*H*-[1,2,4]triazolo[5′,1′:2,3]pyrimido[4,5-*b*]indol-2-amine 3b.

^{1}H NMR spectrum



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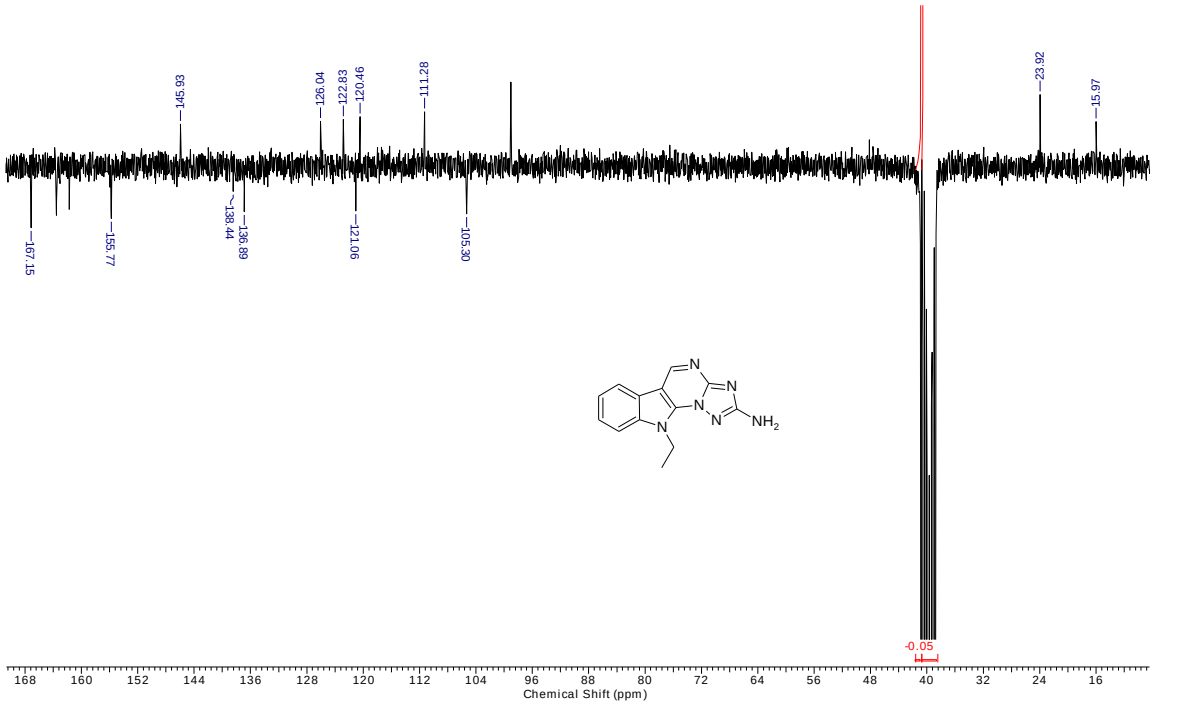

10-Propyl-10*H*-[1,2,4]triazolo[5′,1′:2,3]pyrimido[4,5-*b*]indol-2-amine 3c

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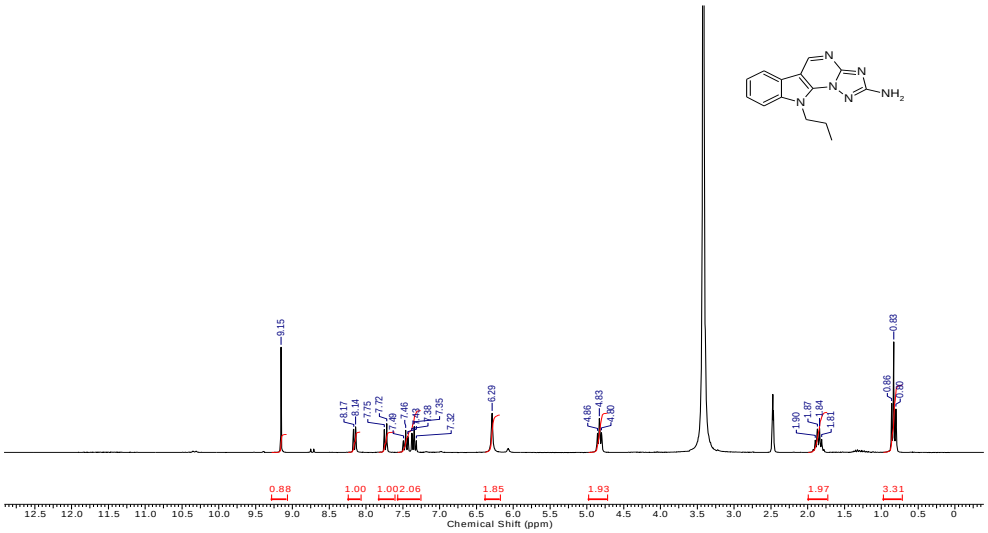

^{13}C NMR spectrum