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Fluorogenic probes based on polycyclic sydnone scaffolds

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ABSTRACT

We report the synthesis, photophysical characterization and kinetics of a series of polycyclic sydnone derivatives as a potential new class of fluorogenic clickable reagents. After strain-promoted cycloaddition with cyclooctyne BCN, the fluorescence generated by pyrazole products displayed up-to 115-fold fluorescence enhancement compared to reactants. These preliminary results are of interest for possible future applications in bioorthogonal chemistry.

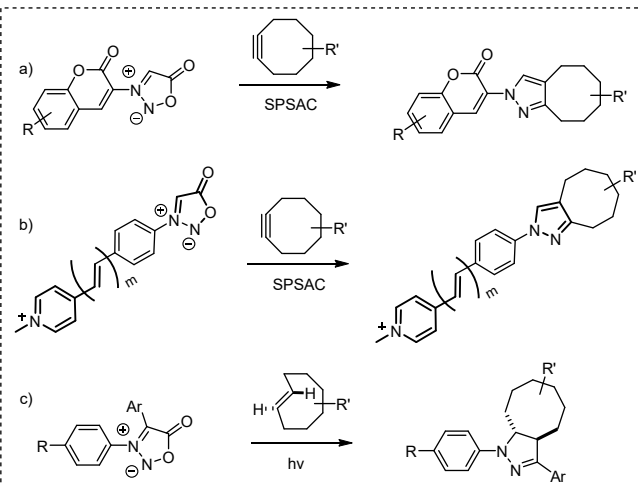
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1. Introduction

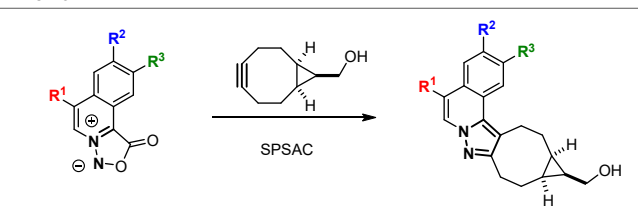
Turn-on chemical probes are organic compounds that upon a chemical transformation modify their optical and electronic properties, thus providing a high fluorescence enhancement readout.¹ Over the last two decades, this concept has been successfully explored for bioorthogonal ligation and click chemistry.² The presence of a well-designed bioorthogonal unit on the probe allows, at the same time, to suppress the fluorescence and effectively react with the target of interest. The massive interest in this technology is driven by the possibility to visualize and study drugs and biomolecules in their native environment, thus monitoring the spatiotemporal dynamics of the labeled (bio)molecules.³ In this context, a variety of fluorogenic azides⁴ and tetrazine⁵ probes have been designed to quench fluorophore moieties and react with cyclic alkynes and *trans*-cyclooctenes. Fluorogenic alkynes have been also developed following similar strategies.⁶

In the ever-growing toolbox of bioorthogonal reactions, mesoionic compounds are emerging as reliable and effective new tools.^{7,8} This family of heterocyclic dipolar compounds have been extensively synthesized and characterized over the last century, but their potential for chemical biology has been largely unexplored, until recent years. In particular, sydnones (Syd) have attracted a great deal of attention.⁹ In 2013, we reported the copper catalysed Sydnone-Alkyne Cycloaddition (CuSAC)¹⁰ and later we and others disclosed their reactivity with strained alkynes (Strained Promoted Sydnone-Alkyne Cycloaddition, SPSAC).¹¹ Both of these transformations proceed under mild reaction conditions and showcased their potential for bio-conjugation.

Previous work



This work



Scheme 1 Strategies for bioorthogonal turn-on probes development with sydnones mesoionics. SPSAC: Strained Promoted Sydnone-Alkyne Cycloaddition.

Since then, diverse applications of sydnones appeared in the literature, to provide highly reactive clickable reagents,¹² as

reporters for the visualization of the sialome in living systems¹³ and pre-targeting tools for PET imaging.¹⁴

Taking advantage of the structural and electronic modifications occurring onto the sydnone scaffold upon cycloaddition and subsequent retro Diels-Alder reaction, several groups have looked to develop turn-on photogenic probes. In 2018, we¹⁵ and others¹⁶ independently reported on sydnone-coumarins as clickable turn-on fluorescent sensors (Scheme 1a). Exploring both CuSAC and SPSAC, several coumarine derivatives were synthesized and their optical properties characterized. Recently, we published a turn-on scaffold based on a structural modification on the mesoionic (Scheme 1b).¹⁷ The best probes turned out to be based on a styryl-pyridinium scaffold, whose optical emissions could be tuned, by increasing the length of the olefin moiety. In 2018, the group of Lo, described sydnone analogues based on cyclometalated iridium(III) polypyridine complexes and explored their luminophore properties.¹⁸ On the other hand, the group of Yu discovered the fluorogenic diarylsydnone-alkene photoligation.¹⁹ In contrast to our previous reports, the authors do not explore the SPSAC, but the reactivity of sydnones upon photo-irradiation. This process involves the intermediate formation of nitrile-imine species induced by light that further react *via* [3+2]-cycloaddition to provide a substituted fluorescent pyrazoline click product (Scheme 1c).²⁰ In 2019, the same group described the photo-accelerated reaction with ring-strained alkynes.²¹

Herein, we report upon the reactivity and characterization of a novel family of turn-on probes based on poly-aromatic sydnone derivatives (Figure 1), their SPSAC reaction with cyclooctynes and the determination of their optical behavior.

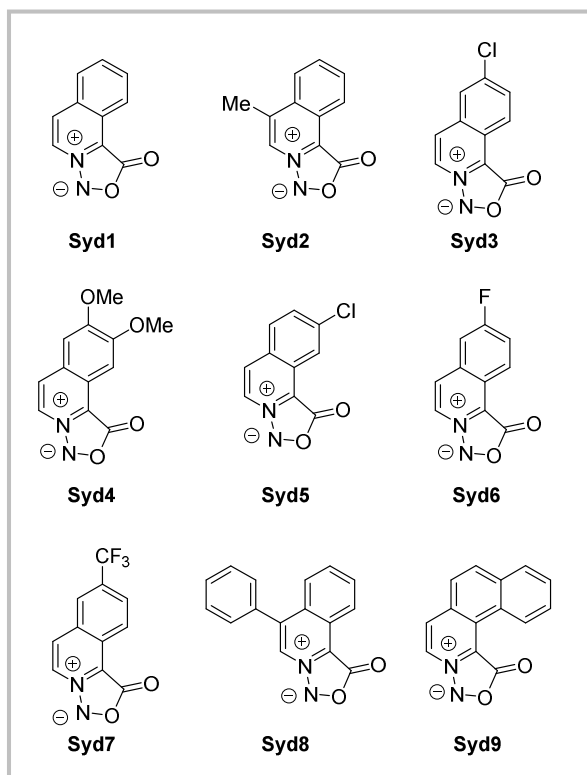


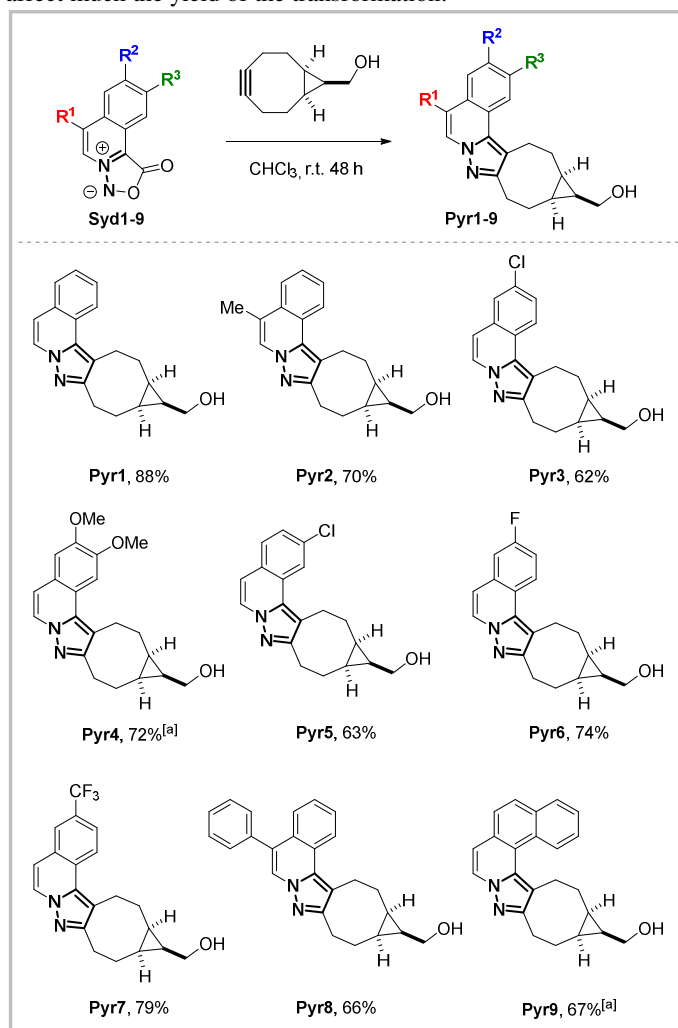
Figure 1 Polycyclic sydnone dipoles studied in this work.

2. Results and discussion

While fluorogenic sydnones have been so far built on (hetero)aromatic units conjugated to each other by single or double bonds that inherently allow for a high flexibility, we reasoned that the presence of rigid poly-aromatic motifs might

positively impact the optical properties and improve the overall turn-on process. We have recently reported the synthesis of a series of sydnones (**Syd1-9**, Figure 1), that enables a direct access to helicene-based pyrazoles through reaction with arynes.²² This peculiar family of mesoionics might have high potential for the development of fluorogenic probes if they are able to react with biocompatible cyclic alkynes such as cyclooctynes.

To test our hypothesis, tricyclic sydnones **Syd1-8** bearing a number of substituents on the aromatic scaffold and tetracyclic **Syd9** were reacted with the model cycloalkyne bicyclo-[6.1.0]-nonyne (BCN). Most of the reactions were carried on in chloroform at room temperature, while for dimethoxy substituted **Syd4** and tetracyclic **Syd9**, the temperature had to be raised to 50 °C, due to solubility issues. The desired cycloadduct products **Pyr1-9** were isolated in 62 to 88% yield (Scheme 2). Interestingly, the electronic nature of the substituents did not affect much the yield of the transformation.



Scheme 2 Strain-Promoted Sydnone Alkyne Cycloaddition with BCN. ^[a] Reaction temperature : 50 °C.

With this series of derivatives in hand, we measured the optical properties of the corresponding **Syd/Pyr** couples, in order to determine their potential as possible turn-on probes (Table 1). The λ_{ex} , λ_{em} and the quantum yields (Φ) were measured. Finally, the brightness of the **Pyr**, measured as the product of the extinction coefficient and the quantum yield ($\epsilon \times \Phi$), was reported in order to make meaningful comparisons between different fluorescent molecules. This value is directly proportional to the brightness of the dye, as it accounts for both

the amount of light absorbed and the quantum efficiency of the fluorophore.^{23,24}

Table 1. Optical properties for the polycyclic sydnones **Syd 1-9** and the corresponding pyrrole products **Pyr1-9**.

Entry	Syd	Sydnone				Pyrazole					Turn-on
		λ_{ex} (nm)	λ_{em} (nm)	Φ^b	ϵ (M ⁻¹ .cm ⁻¹)	λ_{ex} (nm)	λ_{em} (nm)	Φ^b	ϵ (M ⁻¹ .cm ⁻¹)	Bright.	
1	Syd1	280	346	0.038	13800	261	381	0.51	23800	12138	84
2	Syd2	281	342	0.014	12400	265	379	0.54	25500	13770	103
3	Syd3	275	341	0.020	13200	265	396	0.15	34900	5235	23
4 ^a	Syd4	301	370	0.006	13300	261	372	0.67	27800	18626	98
5	Syd5	273	341	0.017	11100	254	397	0.24	21800	5232	63
6	Syd6	257	336	0.011	14400	264	380	0.16	24300	3888	38
7	Syd7	263	392	0.015	15500	269	390	0.41	26500	10875	48
8 ^a	Syd8	286	347	0.016	22400	267	390	0.63	30000	18900	115
9 ^a	Syd9	263	373	0.034	25900	297	441	0.32	42500	13600	68

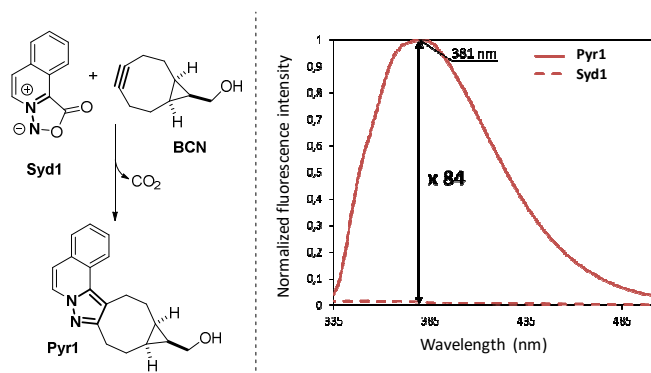
All measurements were performed in a 80:20 / DMSO:water mixture, except otherwise stated.

^a Measurements performed in a 50:50 / DMSO:water mixture.

^b Quantum yields were calculated using a solution of 2-aminopyridine in a H₂SO₄ solution (0.1 M), according to previous literature.²⁵

As shown in Table 1, both for **Syd** and **Pyr** molecules the λ_{em} do not vary much. Especially for the cycloadducts **Pyr1-8**, λ_{em} range from 372 nm to 397 nm. Only for **Pyr9**, bearing an extended aromatic structure, λ_{em} is 441 nm. As expected, quantum yields (Φ) for the **Pyr** were much higher than for the **Syd** and the values of brightness were satisfying (see Table 1).

The turn-on values were overall good and were directly affected by the presence of substituents. When electron withdrawing groups were present, such as in the case of **Syd/Pyr** couples **3**, **5**, **6** and **7**, lower turn-on were observed (ranging from 23 to 63). On the opposite, electron donating substituents have a positive effect (see entry 2, 4 and 8, Table 1). As representative example, the emission spectra for **Syd1** and **Pyr1** after reaction with BCN are shown in Scheme 3.

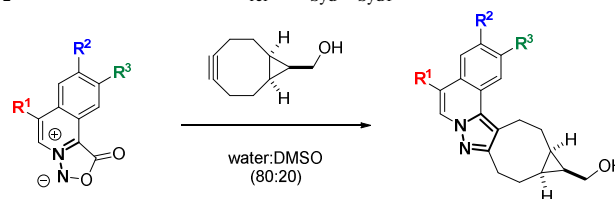


Scheme 3 (A) Fluorogenic strain-promoted cycloaddition between BCN and **Syd1**. (B) Fluorescence emission spectra of **Syd1** (dashed lines; λ_{ex} = 261 nm), and the corresponding **Pyr1** product (solid line; λ_{ex} = 261 nm) compounds in H₂O/DMSO (80/20).

The kinetic of the click reactions were next studied, at room temperature by fluorescence monitoring, determining the speed of the reactions (Table 2). For the model substrate, **Syd1**, the result ($k_{\text{Syd1}} = 0.0091 \text{ M}^{-1} \text{ s}^{-1}$) highlighted that the SPSAC on this peculiar poly-aromatic scaffold is in the same range with what

previously observed for sydnones having a C-C bond in position C₄ of the mesoionic core. For comparison, the reported values for *N*-phenyl-*C*₄-phenyl-sydnone and for *N*-phenyl-*C*₄-CF₃-sydnone with BCN are 0.027 and 0.008 M⁻¹ sec⁻¹, respectively.^{11a} For the additional substrates, it was observed that the presence of substituents did not affect much the speed of the process, as the second-order measured kinetics ranges between 0.0033 M⁻¹ s⁻¹ (**Syd2**) and 0.0123 M⁻¹ s⁻¹ (**Syd6**). Computational studies published by the groups of K.N. Houk and Y. Liang²⁶ revealed that halogen atoms in position C₄ induce a distortion of the sydnone and decrease the activation barrier of the SPSAC reaction. This phenomenon is not favoured with **Syd1-9** which adopt a rigid planar structure.

Table 2. Comparative kinetic properties of sydnones **Syd1-9** for SPSAC reactions with BCN. Reactions were conducted with 100 μM of sydnone and 150 μM of BCN in H₂O/DMSO (80/20) solution. ^a Measurements performed in a 50:50 / H₂O/DMSO solution. ^b $k_{\text{rel}} = k_{\text{Syd}}/k_{\text{Syd1}}$



Sydnone	k (M ⁻¹ s ⁻¹)	k_{rel}^b
Syd1	0.0091 ± 0.0006	1.00
Syd2	0.0033 ± 0.0002	0.36
Syd3	0.0100 ± 0.0037	1.10
Syd4 ^a	0.0055 ± 0.0001	0.60
Syd5	0.0092 ± 0.0008	1.01
Syd6	0.0123 ± 0.0005	1.35

Syd7	0.0058 ± 0.0005	0.64
Syd8^a	0.0091 ± 0.0005	1.00
Syd9^a	0.0069 ± 0.0002	0.75

3. Conclusion

In this manuscript, we reported the synthesis and characterisation of polycyclic sydnones as new fluorogenic probes based on an unconventional poly-aromatic scaffold. Their reactivities with model cyclooctyne BCN under SPSAC conditions was investigated. The optical properties of the **Syd/Pyr** couples were measured and the kinetics measured. Despite moderate reaction speed, the turn-on values are promising and might be of interest for possible application in bioorthogonal chemistry.

4. Experimental section

All reactants or reagents including dry solvents were obtained from commercial suppliers and used as received. Unless otherwise noted, all reactions were performed with dry solvents under an atmosphere of argon in oven-dried glassware using standard vacuum-line techniques. All work-up and purification procedures were carried out with reagent-grade solvents in air. Organic solvents (Aldrich) were used without further purification. THF was distilled over Na/benzophenone. Unless otherwise noted, all other commercially available reagents and solvents were used without further purification. Purifications of reactions products were carried out by flash chromatography using Merck silica gel (40–63 µm). Reactions were monitored via thin-layer chromatography (TLC) using EMD Millipore® TLC silica gel glass plates FT-ATR-IR spectra were recorded on a Perkin-Elmer UAR Two Spectrum spectrometer and are reported as wavelength numbers (cm⁻¹). ¹H NMR (400 MHz), ¹³C NMR (100 MHz) were measured on a Bruker Avance 400 MHz spectrometer. Chemical shifts are reported in parts per million (ppm, δ) downfield from residual solvents peaks and coupling constants are reported as Hertz (Hz). Splitting patterns are designated as singlet (s), broad singlet (br. s), doublet (d), triplet (t), quartet (q) and quintet (quin). Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m). Electrospray mass spectra were obtained using an ESI-Quadrupole autopurify, Waters (pump: 2545, mass: ZQ2000) mass Spectrometer. Melting points were measured on a Büchi B-545 and are reported in °C. LC-MS spectra were recorded on a Waters Acquity UPLC® equipped PDA eλ Detector and SQ Detector 2, mobile phase A: H₂O + 0.1% formic acid, mobile phase B: acetonitrile + 0.1% formic acid. Automatic chromatographies were performed with a COMBIFLASH RF 200i instrument equipped with UV detector and using flash cartridges Interchim silica 15 or 30 µm.

The preparation procedures and spectroscopic data of tricyclic sydnones are in accordance with the literature.²³

General procedure for the preparation of pyrazoles adducts with BCN

To a solution of the sydnone (1.0 equiv.) in CHCl₃ (0.1 M) was added (1*R*,8*S*,9*S*)-bicyclo[6.1.0]non-4-yn-9-ylmethanol (BCN) (1.05 equiv.). The mixture was stirred at room temperature during 48 h and evaporated under reduced pressure. The crude product was purified by flash chromatography (SiO₂, heptane/EtOAc) to obtain the desired compound.

4.1 (10,10a,11,11a,12,13-hexahydro-9H-cyclopropa[5',6']cycloocta[1',2':3,4]pyrazolo[5,1-a]isoquinolin-11-yl)methanol (Pyr1)

The title compound **Pyr1** was obtained in 88% yield (64.1 mg, 0.22 mmol) from compound **Syd1** (46.5 mg, 0.25 mmol) according to the general procedure. The crude product was purified by flash chromatography (SiO₂, heptane/EtOAc 7/3). ¹H NMR (400 MHz, CDCl₃, δ ppm): 8.28 (d, *J* = 8.0 Hz, 1H), 8.09 (4, *J* = 7.4 Hz, 1H), 7.67 (dd, *J* = 7.3 Hz, *J* = 1.0 Hz, 1H), 7.51 (m, 2H), 6.83 (d, *J* = 7.4 Hz, 1H), 3.78 (m, 2H), 3.35 (m, 1H), 3.19 (m, 2H), 3.04 (m, 1H), 2.44 (m, 1H), 2.33 (m, 1H), 1.79 (m, 2H), 1.15 (quint., *J* = 8.2 Hz, 1H), 1.02–0.92 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 154.4, 134.5, 129.6, 127.4, 127.3, 127.1, 126.4, 125.8, 123.1, 112.7, 110.7, 60.1, 27.2, 23.8, 23.4, 23.1, 21.2, 19.0, 18.9. IR (cm⁻¹): 3343, 1224, 1489, 1476, 1366, 1021, 186, 772, 729. LCMS (ESI): *m/z*: 293 [M+H]⁺. Mp.: 131–133 °C.

4.2 (5-methyl-10,10a,11,11a,12,13-hexahydro-9H-cyclopropa[5',6']cycloocta[1',2':3,4]pyrazole[5,1-a]isoquinolin-11-yl)methanol (Pyr2)

The title compound **Pyr2** was obtained in 70% yield (21.4 mg, 0.07 mmol) from compound **Syd1** (20.0 mg, 0.10 mmol) according to the general procedure. The crude product was purified by flash chromatography (SiO₂, heptane/EtOAc 7/3 → 5/5). ¹H NMR (400 MHz, CDCl₃, δ ppm): 8.33–8.28 (m, 1H), 7.97 (s, 1H), 7.81–7.75 (m, 1H), 7.55 (m, 2H), 3.77 (m, 2H), 3.33 (m, 1H), 3.75 (m, 2H), 3.02 (m, 1H), 2.45 (s, 3H), 2.49–2.38 (m, 1H), 2.36–2.26 (m, 1H), 1.85–1.73 (m, 2H), 1.40 (br. s, 1H), 1.13 (quint, *J* = 8.4 Hz, 1H), 1.00–0.86 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 153.5, 134.0, 130.4, 127.1, 127.1, 125.9, 124.7, 124.1, 123.3, 116.7, 112.3, 60.2, 27.1, 23.9, 23.5, 23.1, 21.2, 19.0, 18.9, 16.4. IR (cm⁻¹): 3330, 2923, 1477, 1402, 1364, 1024, 908, 756, 729. LCMS (ESI): *m/z*: 307 [M+H]⁺. Mp.: 171–173 °C.

4.3 (3-chloro-10,10a,11,11a,12,13-hexahydro-9H-cyclopropa[5',6']cycloocta[1',2':3,4]pyrazolo[5,1-a]isoquinolin-11-yl)methanol (Pyr3)

The title compound **Pyr3** was obtained in 62% yield (20.2 mg, 0.06 mmol) from compound **Syd3** (22.1 mg, 0.10 mmol) according to the general procedure. The crude product was purified by flash chromatography (SiO₂, heptane/EtOAc 5/5). ¹H NMR (400 MHz, CDCl₃, δ ppm): 8.20 (d, *J* = 8.7 Hz, 1H), 8.11 (d, *J* = 7.4 Hz, 1H), 7.65 (d, *J* = 1.9 Hz, 1H), 7.49 (dd, *J* = 8.7 Hz, *J* = 1.9 Hz, 1H), 6.75 (d, *J* = 7.4 Hz, 1H), 3.78 (m, 2H), 3.33 (m, 1H), 3.16 (m, 2H), 3.04 (m, 1H), 3.43 (m, 1H), 2.34 (m, 1H), 1.86–1.74 (m, 2H), 1.68 (br. s, 1H), 1.15 (quint, *J* = 8.4 Hz, 1H), 1.02–0.90 (m, 2H). ¹³C NMR (100 MHz, CDCl₃, δ ppm): 154.8, 134.1, 132.9, 131.0, 127.6, 127.5, 126.6, 124.5, 124.2, 112.9, 109.7, 60.2, 27.2, 23.9, 23.4, 23.0, 21.2, 19.1, 18.9. IR (cm⁻¹): 3338, 2923, 1477, 1365, 1023, 908, 876, 814, 777, 730. LCMS (ESI): *m/z*: 327 [M(³⁵Cl)+H]⁺, 329 [M(³⁷Cl)+H]⁺. Mp.: 175–177 °C.

4.4 (2,3-dimethoxy-10,10a,11,11a,12,13-hexahydro-9H-cyclopropa[5',6']cycloocta[1',2':3,4]pyrazole [5,1-a]isoquinolin-11-yl)methanol (Pyr4)

The title compound **Pyr4** was obtained in 72% yield (25.4 mg, 0.07 mmol) from compound **Syd4** (24.6 mg, 0.10 mmol) according to a modification of the procedure, and the temperature was raised to 50 °C. The crude product was purified by flash chromatography (SiO₂, heptane/EtOAc 2/8). ¹H NMR (400 MHz, CDCl₃, δ ppm): 8.04 (d, *J* = 7.3 Hz, 1H), 7.69 (s, 1H), 7.06 (s, 1H), 6.75 (d, *J* = 7.3 Hz, 1H), 4.02 (s, 3H), 3.99 (s, 3H), 3.78 (m, 2H), 3.34 (m, 1H), 3.17 (m, 2H), 3.02 (m, 1H), 2.43 (m, 1H),

2.32 (m, 1H), 1.89–1.72 (m, 2H), 1.59 (br. s, 1H), 1.14 (quint, $J = 8.3$ Hz, 1H), 1.02–0.89 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 154.2, 149.3, 149.2, 134.5, 125.0, 124.3, 120.0, 110.6, 110.2, 108.0, 104.3, 60.2, 56.1 (2C), 27.2, 23.8, 23.5, 23.4, 21.2, 19.1, 18.8. IR (cm^{-1}): 3337, 2927, 1509, 1484, 1417, 1360, 1263, 1223, 1162, 1026, 911, 851, 727. LCMS (ESI): m/z : 353 $[\text{M}+\text{H}]^+$. Mp.: 158–160 °C.

4.5 (2-chloro-10,10a,11,11a,12,13-hexahydro-9H-cyclopropa[5',6']cycloocta[1',2':3,4]pyrazolo[5,1-a]isoquinolin-11-yl)methanol (**Pyr5**)

The title compound **Pyr5** was obtained in 63% yield (20.6 mg, 0.06 mmol) from compound **Syd5** (22.1 mg, 0.10 mmol) according to the general procedure. The crude product was purified by flash chromatography (SiO_2 , heptane/EtOAc 6/4 \rightarrow 4/6). ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.21 (d, $J = 1.7$ Hz, 1H), 8.08 (d, $J = 7.4$ Hz, 1H), 7.60 (d, $J = 8.6$ Hz, 1H), 7.43 (dd, $J = 8.6$ Hz, $J = 1.7$ Hz, 1H), 6.79 (d, $J = 7.4$ Hz, 1H), 3.78 (m, 2H), 3.33 (m, 1H), 3.16 (m, 2H), 3.03 (m, 1H), 2.46 (m, 1H), 2.33 (m, 1H), 1.86–1.74 (m, 2H), 1, 65 (br. s, 1H), 1.15 (quint, $J = 8.3$ Hz, 1H), 1.01–0.86 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 154.7, 133.5, 133.0, 128.7, 128.0, 127.5, 126.9, 126.7, 122.6, 113.3, 110.1, 60.2, 27.1, 23.9, 23.4, 23.0, 21.2, 16.2, 18.8. IR (cm^{-1}): 3336, 2923, 1601, 1488, 1475, 1366, 1099, 1024, 907, 826, 728. LCMS (ESI): m/z : 327 $[\text{M}(^{35}\text{Cl})+\text{H}]^+$, 329 $[\text{M}(^{37}\text{Cl})+\text{H}]^+$. Mp.: 132–134 °C

4.6 (3-fluoro-10,10a,11,11a,12,13-hexahydro-9H-cyclopropa[5',6']cycloocta[1',2':3,4]pyrazolo[5,1-a]isoquinolin-11-yl)methanol (**Pyr6**)

The title compound **Pyr6** was obtained in 74% yield (22.9 mg, 0.07 mmol) from compound **Syd6** (20.4 mg, 0.10 mmol) according to the general procedure. The crude product was purified by flash chromatography (SiO_2 , heptane/EtOAc 5/5 \rightarrow 3/7). ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.85 (dd, $J = 8.8$ Hz, $J = 5.4$ Hz, 1H), 8.10 (d, $J = 7.3$ Hz, 1H), 7.82 (dd, $J = 9.4$ Hz, $J = 2.5$ Hz, 1H), 7.26 (td, $J = 8.8$ Hz, $J = 2.5$ Hz, 1H), 6.77 (d, $J = 7.3$ Hz, 1H), 3.78 (m, 2H), 3.32 (m, 1H), 3.15 (m, 2H), 3.02 (m, 1H), 2.42 (m, 1H), 2.33 (m, 1H), 1.85–1.73 (m, 2H), 1.65 (br. s, 1H), 1.14 (quint, $J = 8.4$ Hz, 1H), 1.02–0.85 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 161.4 ($J = 247$ Hz), 154.8, 134.3, 131.6 ($J = 8.9$ Hz), 127.5, 125.2 ($J = 8.4$ Hz), 122.5, 115.6 ($J = 23.1$ Hz), 112.4 ($J = 21.5$ Hz), 112.3, 109.9 ($J = 3.0$ Hz), 60.1, 27.2, 23.9, 23.4, 23.0, 21.2, 19.1, 18.9. IR (cm^{-1}): 3342, 2924, 1559, 1479, 1365, 1252, 1133, 1022, 908, 867, 776, 729. LCMS (ESI): m/z : 311 $[\text{M}+\text{H}]^+$. Mp.: 131–133 °C

4.7 (3-(trifluoromethyl)-10,10a,11,11a,12,13-hexahydro-9H-cyclopropa[5',6']cycloocta[1',2':3,4]pyrazolo[5,1-a]isoquinolin-11-yl)methanol (**Pyr7**)

The title compound **Pyr7** was obtained in 79% yield (28.4 mg, 0.08 mmol) from compound **Syd7** (25.4 mg, 0.10 mmol) according to the general procedure. The crude product was purified by flash chromatography (SiO_2 , heptane/EtOAc 6/4 \rightarrow 4/6). ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.37 (d, $J = 8.5$ Hz, 1H), 8.17 (d, $J = 7.3$ Hz, 1H), 7.94 (s, 1H), 7.74 (dd, $J = 8.5$ Hz, $J = 1.4$ Hz, 1H), 6.88 (d, $J = 7.3$ Hz, 1H), 3.78 (m, 2H), 3.36 (m, 1H), 3.19 (m, 2H), 3.06 (m, 1H), 2.50–2.30 (m, 2H), 1.87–1.75 (m, 2H), 1.60 (br. s, 1H), 1.15 (quint, $J = 8.2$ Hz, 1H), 1.02–0.84 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 155.0, 133.8, 129.4, 128.9 (q, $J = 33.0$ Hz), 128.0, 127.7, 124.5 (q, $J = 3.7$ Hz), 124.1 (q, $J = 27.2$ Hz), 123.7, 123.5 (q, $J = 3.0$ Hz), 114.0, 110.3, 60.1, 27.2, 23.9, 23.3, 23.0, 21.2, 19.0, 18.9. IR (cm^{-1}): 3352, 2926, 1485, 1367, 1238, 1311, 1122, 1074, 1021, 899, 825, 747, 690, 665. LCMS (ESI): m/z : 361 $[\text{M}+\text{H}]^+$.

4.8 (5-phenyl-10,10a,11,11a,12,13-hexahydro-9H-cyclopropa[5',6']cycloocta[1',2':3,4]pyrazolo[5,1-a]isoquinolin-11-yl)methanol (**Pyr8**)

The title compound **Pyr8** was obtained in 66% yield (24.6 mg, 0.07 mmol) from compound **Syd8** (26.3 mg, 0.10 mmol) according to the general procedure. The crude product was purified by flash chromatography (SiO_2 , heptane/EtOAc 9/1 \rightarrow 7/3). ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.37 (d, $J = 8.1$ Hz, 1H), 8.08 (s, 1H), 7.69 (dd, $J = 8.1$ Hz, $J = 0.6$ Hz, 1H), 7.57 (dd, $J = 7.1$ Hz, $J = 0.6$ Hz, 1H), 7.54–7.41 (m, 6H), 3.80 (m, 2H), 3.40 (m, 1H), 3.23 (m, 2H), 3.07 (m, 2H), 2.49 (m, 1H), 2.36 (m, 1H), 1.89–1.77 (m, 2H), 1.16 (d, $J = 8.3$ Hz, 1H), 1.05–0.88 (m, 2H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 154.7, 136.8, 134.1, 130.4 (2C), 129.5, 128.7 (2C), 127.9, 127.3, 127.1, 126.1, 126.0, 125.5, 123.8, 123.3, 112.5, 60.2, 27.2, 23.8, 23.4, 23.1, 21.2, 19.0 (2C). IR (cm^{-1}): 3344, 2923, 1631, 1473, 1401, 1358, 1025, 855, 756, 701. LCMS (ESI): m/z : 369 $[\text{M}+\text{H}]^+$. Mp.: 106–108 °C.

4.9 (12,12a,13,13a,14,15-hexahydro-11H-benzo[h]cyclopropa[5',6']cycloocta[1',2':3,4]pyrazolo[5,1-a]isoquinolin-13-yl)methanol (**Pyr9**)

The title compound **Pyr9** was obtained in 67% yield (23.0 mg, 0.07 mmol) from compound **Syd9** (23.6 mg, 0.10 mmol) according to a modification of the procedure, and the temperature was raised to 50 °C. The crude product was purified by flash chromatography (SiO_2 , heptane/EtOAc 9/1 \rightarrow 2/8). ^1H NMR (400 MHz, CDCl_3 , δ ppm): 8.44–8.37 (m, 1H), 8.25 (d, $J = 7.2$ Hz, 1H), 7.96–7.91 (m, 1H), 7.88 (d, $J = 8.4$ Hz, 1H), 7.64 (d, $J = 8.4$ Hz, 1H), 7.62–7.56 (m, 2H), 6.91 (d, $J = 7.2$ Hz, 1H), 3.83 (m, 2H), 3.38 (ddd, $J = 15.4$ Hz, $J = 8.3$ Hz, $J = 3.6$ Hz, 1H), 3.29 (ddd, $J = 14.9$ Hz, $J = 8.5$ Hz, $J = 3.4$ Hz, 1H), 2.98 (ddd, $J = 14.9$ Hz, $J = 7.9$ Hz, $J = 3.4$ Hz, 1H), 2.76 (ddd, $J = 15.5$ Hz, $J = 7.0$ Hz, $J = 3.6$ Hz, 1H), 2.69–2.58 (m, 1H), 2.50–2.39 (m, 1H), 1.76–1.69 (m, 2H), 1.30–1.17 (m, 4H). ^{13}C NMR (100 MHz, CDCl_3 , δ ppm): 156.9, 136.0, 133.0, 129.1, 128.4, 128.3, 128.1, 127.7, 127.0, 126.3, 125.2, 125.0, 122.0, 114.7, 110.9, 60.0, 27.5, 26.1, 24.5, 23.9, 22.5, 21.3, 20.9. IR (cm^{-1}): 3355, 2945, 1481, 1354, 1135, 1025, 826, 750, 655. LCMS (ESI): m/z : 342 $[\text{M}+\text{H}]^+$. Mp.: 149–151 °C.

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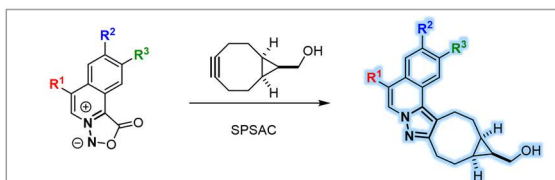
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Fluorogenic probes based on polycyclic sydnone scaffolds

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