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A water soluble light activated hydrogen sulfide donor induced by an excited state meta effect†

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We have utilized an *m*-amino benzyl based photoremovable protecting group (PRPG) to develop a new water soluble H_2S donor. It efficiently releases H_2S on demand in a spatio-temporally controlled fashion by an excited state "meta effect" with good chemical and photochemical quantum yield in an aqueous environment. The efficient photorelease of H_2S under physiological conditions was also demonstrated by *in vitro* studies.

Introduction

Hydrogen sulfide (H_2S), first discovered in 1777 by Carl Wilhelm Scheele,[1] has been traditionally known as a toxic air pollutant with the characteristic odour of rotten eggs. However, this gaseous molecule has been recently recognized as a member of the gasotransmitter family along with nitric oxide (NO) and carbon monoxide (CO).[2–6] Hydrogen sulfide (H_2S) is well known for mediating many physiological processes. H_2S gas is highly diffusive in nature and can target multiple sites within a cell. Therefore, cell signalling by H_2S is mostly complex and is dependent on its local concentration. This indicates the need for controlled generation of H_2S gas under physiological conditions. Now-a-days light activated H_2S donors are receiving much attention because of their spatio-temporal control over H_2S release.[7–12]

Chakrapani and co-workers reported the photorelease of carbonyl sulfide (COS) from a BODIPY-caged thiocarbamate upon visible light irradiation.[13] The released COS subsequently gets hydrolysed in the presence of carbonic anhydrase to yield H_2S (Fig. 1a). The limitation of this system is its requirement of carbonic anhydrase (external agent) for H_2S release. Recently, our group developed *p*-hydroxyl phenacyl based ESIPT molecules for direct release of H_2S gas upon visible light irradiation with real time monitoring (Fig. 1b).[14] However the abovementioned light activated H_2S donors have poor solubility under physiological conditions. Keeping this in mind, we were interested in designing a new light activated H_2S donor with efficient release ability and good solubility under physiological conditions.

Recently, Wang and co-workers reported an *m*-amino benzyl based photoremovable protecting group (PRPG) for the uncaging of carboxylic acids and alcohols.[15–21] The photorelease of alcohols and carboxylic acids results from selective electron transmission from an electron-donating group to the meta

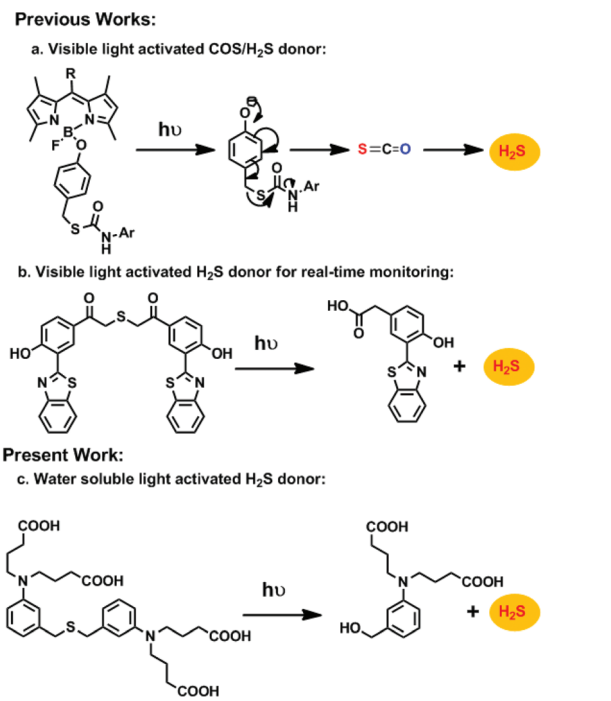

Fig. 1 Selected visible light-triggered H_2S donors: (a) a visible light activated COS/H_2S donor; (b) an ESIPT based visible light activated H_2S donor with real-time monitoring; and (c) a newly developed water soluble light activated H_2S donor.

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sites on an aromatic ring in its first excited singlet state. Upon irradiation the molecule gets excited to the singlet excited state and undergoes heterolytic cleavage of the benzylic bond to produce an ion pair, which eventually abstracts a proton from the solvent to release the corresponding alcohol. They also developed a water soluble *m*-amino benzyl based PRPG by protecting the amine group with butanoic acid.[22]

Inspired by this strategy, we designed a water soluble H_2S donor using an *m*-amino benzyl photoremovable protecting group on the basis of the excited state meta effect (Fig. 1c). This effect facilitates photochemical cleavage of the benzylic C–S bond to release the H_2S molecule. The advantages of our H_2S donors are (i) a simple synthetic procedure, (ii) fast and clean release with high quantum yield and (iii) good solubility under physiological conditions.

Results and discussion

Synthesis of the H_2S donor

Light activated H_2S donor **4** was synthesized as shown in Scheme 1. Compound **2** was prepared by chlorinating the 3-nitro benzyl alcohol **1** to its corresponding benzyl chloride using $SOCl_2$ in dry DCM followed by condensation reaction with Na_2S for 4 h in an acetone–water mixture. Then compound **2** was reduced with iron and acetic acid in ethanol by sonicating for 2 h at room temperature. Finally, protection of the amine group of compound **3** in the presence of K_2CO_3 using 4-bromobutyric acid produced H_2S donor **4**. The product obtained in each step was characterized by ^{1}H NMR and ^{13}C NMR spectroscopy (see Fig. S1–S3 in the ESI†).

Photophysical properties of H_2S donor 4

The photophysical properties of H_2S donor **4** was investigated. The UV-Vis spectrum of H_2S donor **4** (Fig. 2a) shows a strong absorption band at λ_{max} = 314 nm (ε = 4960 M^{-1} cm^{-1}) in water. The donor **4** also exhibited an emission maximum (excitation wavelength = 314 nm) at λ_{max} = 370 nm (Fig. 2b).

Photochemical properties of H_2S donor 4

We studied the photochemical properties of our water soluble H_2S donor using 1×10^{-4} M solution of H_2S donor **4** in PBS buffer (pH ~ 7.4). We performed the photolysis of **4** under a nitrogen atmosphere under a medium-pressure mercury lamp (125 W, incident intensity (I_0) = 1.55×10^{17} quanta per s) as the source of light ($\lambda \geq 365$ nm) using 1 M $CuSO_4$ solution as a UV cut-off filter with continuous stirring for 30 min. We analysed the photodecomposition of H_2S donor **4** and formation of the photoproduct by reversed-phase HPLC. As shown in Fig. 3a, the gradual disappearance of a peak at t_R = 6.15 min corresponding to **4** indicates gradual photodecomposition of the H_2S donor with the increase in the irradiation time. On the other hand, the appearance and the gradual increase in the intensity of the new peak at t_R = 3.83 min indicate the formation of the photoproduct, **6**. The newly formed peak at t_R = 3.83 was assigned to the photoproduct (**6**) by co-injection of authentic synthesized compound **6** and further confirmed by isolation and characterization by ^{1}H & ^{13}C NMR spectroscopy (see Fig. S4, ESI†). The photodecomposition of donor **4** was also confirmed by UV-Vis and fluorescence spectroscopy (Fig. 4).

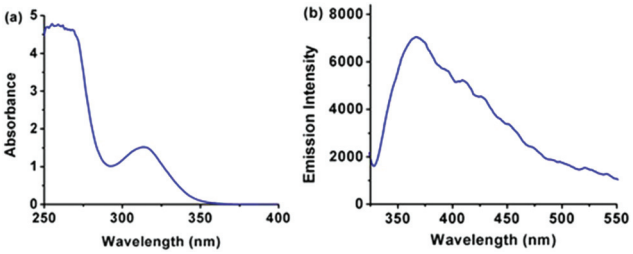


Fig. 2 (a) UV-Vis absorption spectra and (b) emission spectra of **4** (1×10^{-4} M) in water.

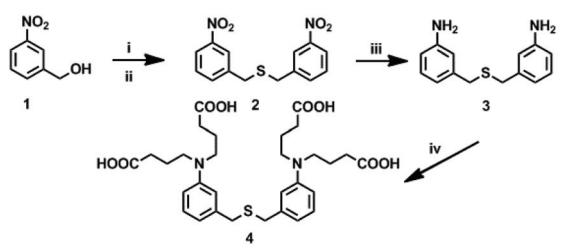
Furthermore, we observed about 95% of photorelease, calculated from the increase in the HPLC peak area of the photoproduct formed from **4** due to the release of H_2S after 30 min of irradiation (Fig. 3b).

The photochemical quantum yield (ϕ_p) of the photorelease of H_2S from **4** was determined to be 0.14 ± 0.05 using potassium ferrioxalate as an actinometer (see the ESI† for further details).

H_2S detection using fluorescent probe *N*,*N*-dimethylaniline–hemicyanine dye

To detect H_2S generation from **4**, we used the *N*,*N*-dimethylaniline–hemicyanine dye (D1) as a photostable (see Fig. S9, ESI†) and H_2S-sensitive probe. The *N*,*N*-dimethylaniline–hemicyanine dye reacts with H_2S to form P1 (Scheme 2). It shows an intense red colour visible to the naked eye and bright red fluorescence.

The dye (10 μM) was irradiated with UV-Vis light ($\lambda \geq$ 365 nm) in the presence of H_2S donor **4** (100 μM) in PBS buffer (10 mM) (pH ~ 7.4) with continuous stirring. The UV-Vis absorption spectrum of the D1 dye displayed an absorption maximum at 521 nm. With the increase in the irradiation time from 0 min to 30 min, we observed that the intensity of the absorption peak at 521 nm decreased with a concomitant increase in the new absorption maximum at around 431 nm (Fig. 4a). This hypsochromic shift in the absorption spectra in



Scheme 1 Synthesis procedure of the water soluble light activated H_2S donor. Reagents and conditions: (i) $SOCl_2$, dry DCM, 4 h; (ii) Na_2S, acetone–H_2O, rt, 4 h (70%); (iii) iron powder, acetic acid, ethanol, rt, 2 h (70%); and (iv) 4-bromobutyric acid, K_2CO_3, acetone, reflux, 24 h (55%).

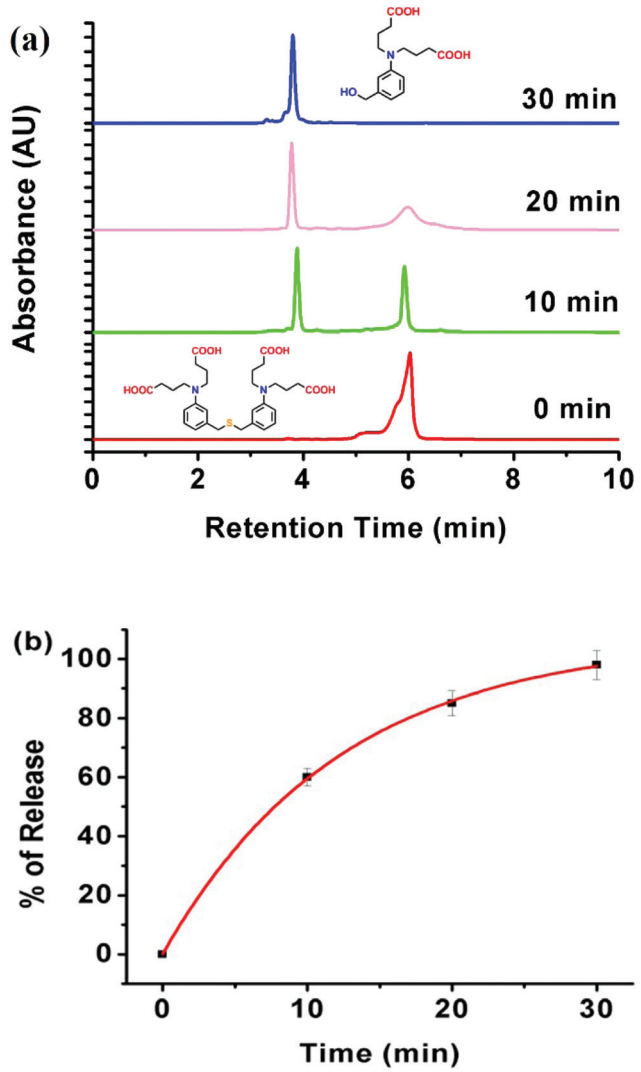


Fig. 3 (a) Overlay of HPLC chromatograms of **4** at regular time intervals (0–30 min) of irradiation with light ($\lambda \geq 365$ nm). (b) % of photorelease with respect to the increase in the HPLC peak area of the photoproduct formed from **4** due to the release of H_2S at different time intervals.

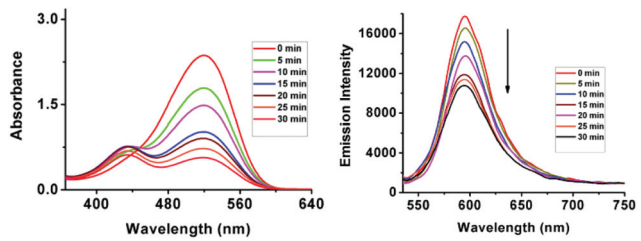
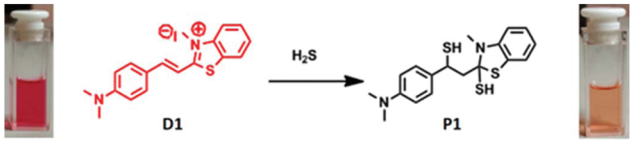


Fig. 4 Detection of released H_2S from **4** using (a) UV-vis and (b) fluorescence spectra with the probe D1.

the presence of H_2S was due to the loss in conjugation of D1 when H_2S reacted with it to form P1 (Scheme 2).

We also showed that the photoproduct had no influence in the quenching of the fluorescence of the dye (D1) (see Fig. S8, ESI†).



Scheme 2 H_2S detection from **4** by using H_2S-sensitive fluorescent probe dye D1.

We further investigated the release of H_2S from **4** in aqueous buffer by fluorescence spectroscopy using the same H_2S sensitive fluorescent probe D1. The dye D1 exhibited red fluorescence (excitation wavelength = 521 nm) at 595 nm in the absence of H_2S. With the increase in the irradiation time from 0 to 30 min, H_2S was gradually released and it reacted with the probe (D1) leading to its decomposition, and as a result a decrease in the fluorescence intensity was observed (Fig. 4b). The accurate determination of H_2S from **4** was not possible. However, the changes in the absorption spectra and the decrease in the fluorescence intensity indicated the generation of H_2S from **4**. No detectable fluorescence change was observed when the donor (**4**) and probe (D1) were incubated under similar conditions in the absence of light.

To quantify the amount of H_2S released from **4**, we used the standard methylene blue assay (see Fig. S6, ESI†). In this study, a 100 μM solution of **4** in pH 7.4 PBS buffer was prepared and mixed with the methylene blue cocktail. Upon irradiation of light ($\lambda \geq 365$ nm), the solution exhibited an increase in absorption at 663 nm at different time intervals corresponding to the formation of methylene blue, confirming the ability of **4** to produce H_2S (Fig. 5). We found that the concentrations of released H_2S from **4** reached a maximum of ~45 μM in about 30 min.

To show the precise control over H_2S release by light, we monitored the release of H_2S by periodically switching the light source on and off. Fig. 6 clearly indicates that whenever the light source was switched off, H_2S release stopped; this clearly indicates that only an external stimulus light induces H_2S release.

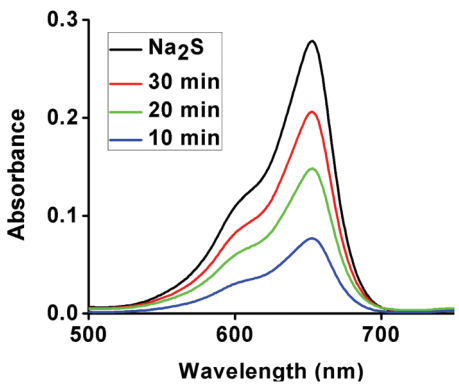


Fig. 5 Spectra of methylene blue assay. Black line: Na_2S (50 μM). Other lines: H_2S release from **4** upon irradiation at different times.

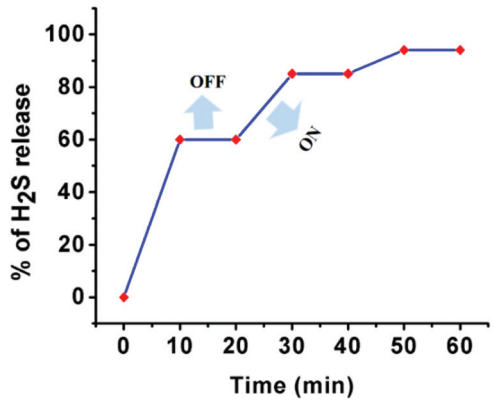


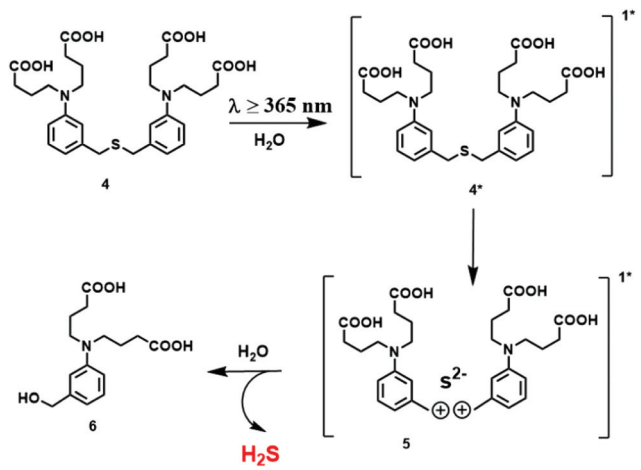
Fig. 6 Progress of the photodegradation of H_2S donor **4** under light and dark conditions calculated from the HPLC peak area (ON indicates the start of light irradiation and OFF indicates the end of light irradiation).

Furthermore, the spatiotemporal control ability of our H_2S donor was also investigated (see Fig. S7, ESI†).

The hydrolytic stability of the H_2S donor **4** was examined individually in PBS buffer (pH ~ 7.4) by keeping them under darkness for a period of 20 days. The fate of the H_2S donor **4** was studied using ^1H NMR. We observed only 4% decomposition of the H_2S donor **4**. The aqueous solubility of the H_2S donor **4** is found to be 22.5 g per 100 mL at 25 °C.

Mechanism of H_2S release from 4

The photorelease of H_2S from **4** was investigated. Based on the literature studies, we proposed the mechanism of the release of H_2S from **4** as shown in Scheme 3. H_2S donor **4**, upon irradiation, initially gets excited to the singlet excited state (**4***). At this excited sate, the benzylic C–O bond undergoes heterolytic cleavage due to electron transmission from the amine group (meta effect) to produce ion pairs. These ion pairs in the presence of water result in the release of H_2S and the corresponding benzylic alcohol (**6**) as the photoproduct.



Scheme 3 Proposed mechanism of H_2S release from **4**.

Cellular internalization and cell viability study

The roles of H_2S in cancer development and progression are still controversial. A clear relationship between the H_2S level and cancer progression remains to be understood. Still a deeper understanding of whether and how H_2S plays a role in cancer etiology and progression is needed.[23,24] Hence, we thought that our H_2S donor can be used in the future to understand the role of H_2S in cancer biology. Because of this reason, we used HeLa cells for our studies.

The H_2S releasing ability of **4** was studied in live cells using H_2S-sensitive probe D1 by confocal microscopy imaging. Cervical cancer cells (HeLa) were incubated with **4** and D1 for 6 h followed by irradiation with light ($\lambda \geq 365$ nm) for 30 min. Initially the cells emitted bright red fluorescence (excitation wavelength = 540 nm) from the incubated dye (D1) (Fig. 7a). With the increase in the irradiation time from 0 to 30 min a gradual decrease in the fluorescence intensity of the cells was observed, indicating a steady time dependent release of H_2S from **4** (Fig. 7a–c). The cells did not show any significant decrease in fluorescence in the absence of either light or the H_2S donor **4** (see Fig. S10, ESI†). Furthermore, we also calculated the changes in the fluorescence intensities at different irradiation times from the confocal microscopy images (see Fig. S11, ESI†).

For our H_2S donor **4** to be useful as a H_2S releasing biological tool, it should be biocompatible. Therefore, we evaluated the cytotoxicity of **4** using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay on HeLa cells before and after photolysis (Fig. 8a and b). Briefly, HeLa cells

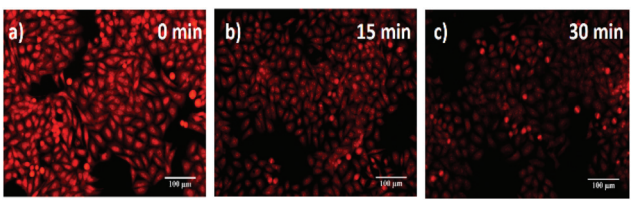


Fig. 7 Confocal microscopy images of H_2S release from **4**. Gradual release of H_2S from **4** was monitored using an H_2S sensitive fluorescent probe (D1) at different time intervals during irradiation with light ($\lambda \geq 365$ nm), (a) 0 min; (b) 15 min; and (c) 30 min.

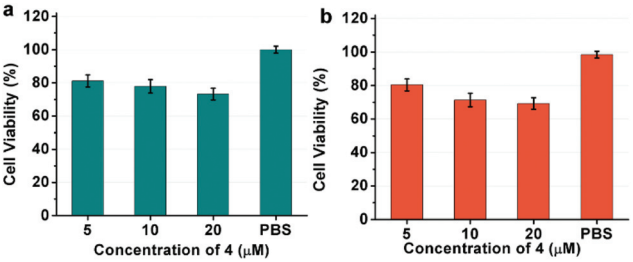


Fig. 8 Cell viability assay of **4** on the HeLa cell line (72 h MTT assay): (a) before and (b) after photolysis for 30 min. Values are presented as mean ± standard deviation from three independent experiments.

were incubated with 20 μM, 10 μM and 5 μM concentrations of **4** for 6 h and subjected to photolysis under $\lambda \geq 365$ nm light for 30 min. After 72 h of incubation, MTT was added to the cells at 0.4 mg mL^{-1} and incubated for another 4 h. From the results, we observed that there is no evidence of the inhibition of proliferation of HeLa cells by **4** before (Fig. 8a) and after (Fig. 8b) photolysis, suggesting that H_2S donor **4** is not cytotoxic at the studied concentrations.

Conclusions

In conclusion, we have developed a water soluble H_2S donor that generates H_2S under UV-Vis light ($\lambda \geq 365$ nm) irradiation, with the release of a bio-compatible photoproduct. The meta effect of the *N*,*N*-dibutyl acid amine group helped in efficient uncaging of H_2S with high quantum yield. *In vitro* studies revealed that our H_2S donor exhibited good biocompatibility and cellular internalisation. Furthermore, the H_2S release ability of our donor at the cellular level was also demonstrated. Thus, our newly developed H_2S donor played a dual role: (i) controlled release of H_2S under UV-Vis light ($\lambda \geq 365$ nm) without the aid of any additional reagent and (ii) being soluble under physiological conditions.

Experimental section

Chemicals and starting materials

All reagents were purchased from Sigma-Aldrich and were used without further purification. Dichloromethane was distilled from CaH_2 before use. All anhydrous reactions were performed under a dry nitrogen atmosphere.

Methods and techniques

^{1}H NMR spectra were recorded on a Bruker-AC 600 MHz spectrophotometer. The chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: 7.26 ppm, D_2O: 4.79 ppm). The data were reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet), and coupling constant (Hz). The ^{13}C NMR (150 MHz) spectra were recorded on a Bruker-AC 600 MHz spectrometer with complete proton decoupling. The chemical shifts were reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (deuterochloroform: 77.0 ppm). UV/Vis absorption spectra were recorded on a Shimadzu UV-2450 UV/Vis spectrophotometer; the fluorescence emission spectra were recorded on a Hitachi F-7000 fluorescence spectrophotometer. The photolysis of the caged compounds was carried out using a 125 W medium-pressure Hg lamp supplied by SAIC (India). Chromatographic purification was done with 60–120-mesh silica gel (Merck). For reaction monitoring, precoated silica gel 60 F254 TLC sheets (Merck) were used. RP-HPLC was performed using acetonitrile as the mobile phase, at a flow rate of 1 mL min^{-1}.

General procedure for the preparation of the H_2S donor

Synthesis of bis(3-nitrobenzyl)sulfane (2). 3-Nitrobenzyl alcohol (612 mg, 4 mmol) was dissolved in dry CH_2Cl_2 (20 mL) with Et_3N (1.1 mL) into a round bottom flask. Then $SOCl_2$ (0.5 ml, 4 mmol) was slowly added with stirring over 10 min. After 4 h, the solvent was removed by rotary evaporation at 45 °C and subjecting to high vacuum, respectively. Then the residue was dissolved in 10 ml acetone and add to a stirred and ice-cooled solution of sodium sulfide nonahydrate ($Na_2S{\cdot}9H_2O$) (600 mg, 2.5 mmol) in water (20 ml). After completion of the addition, the mixture was warmed to room temperature for an hour. The completion of the reaction was monitored by TLC and the mixture was extracted with EtOAc and washed with water. The collected organic layer was dried over Na_2SO_4 and the solvent was removed by rotary evaporation under reduced pressure. The crude product was purified by column chromatography using 10% EtOAc in petroleum ether to give the product as a yellow solid (0.345 g, 70%). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 (d, J = 8.0 Hz, 4H), 7.59 (d, J = 7.6 Hz, 2H), 7.50 (t, J = 7.7 Hz, 2H), 3.71 (s, 4H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 148.38 (s), 139.81 (s), 134.98 (s), 129.63 (s), 123.75 (s), 122.38 (s), 35.36 (s).

Synthesis of 3,3′-(thiobis(methylene))dianiline (3). To a suspension of bis(3-nitrobenzyl)sulfane (2) (600 mg, 2 mmol) in a mixture of glacial acetic acid (5 mL), ethanol (5 mL) and water (1 mL) was added reduced iron powder (560 mg, 10 mmol). The resulting suspension was stirred for 1 h at room temperature with TLC analysis monitoring for the completion of the reaction. The reaction mixture was filtered to remove the iron residue which was washed with ethyl acetate (30 mL). The filtrate was partitioned with 2 M KOH and the basic layer was further extracted with ethyl acetate (3 × 25 mL). The combined organic extracts were washed with brine (2 × 25 mL) and water (3 × 50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was then subjected to flash silica gel column chromatography (40% ethyl acetate in hexane) yielding **3** (89%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (t, J = 8 Hz, 2H), 6.68 (d, J = 8 Hz, 2H), 6.64 (s, 2H), 6.57 (d, J = 8 Hz, 2H), 3.53 (s, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.50 (s), 139.42 (s), 129.30 (s), 119.44 (s), 115.72 (s), 113.93 (s), 35.72 (s).

Synthesis of bis(4,4′-(phenylazanediyl)dibutanoic acid) sulfane (4). Compound **3** (2.5 g, 10 mmol) was dissolved in 30 mL of dry DMF in an ice-bath and then Na_2HPO_4 (5.5 g, 40 mmol) was added. To this mixture 4-bromobutyric acid (4.1 ml, 40 mmol) was added dropwise. Finally, the mixture was refluxed overnight until all the starting material was consumed. The reaction mixture was then cooled to room temperature, neutralized by dropwise addition of $NaHCO_3$ solution and extracted with EtOAc. The combined organic extracts were washed with saturated brine. Next, purification was done by column chromatography (methanol : DCM = 1 : 5) to afford the pure product as a pale yellow gel (2.3 g, yield 40%).

^{1}H NMR (600 MHz, D_2O–CD_3OD) δ 7.05 (s, 2H), 6.81–6.35 (m, 6H), 3.61 (s, 4H), 3.12–3.05 (m, 8H), 2.06–1.95 (m, 8H), 1.64–1.57 (m, 8H). ^{13}C NMR (151 MHz, D_2O) δ 182.94 (s),

148.21 (s), 139.23 (s), 129.92 (s), 117.61 (s), 114.03 (s), 112.61 (s), 50.64 (s), 35.37 (s), 34.93 (s), 23.10 (s). HRMS (ESI+) calcd for $C_{30}H_{40}N_2O_8S$ $[M + H]^+$, 588.2505; found: 588.2586.

Photolysis of H_2S donor 4. A solution of 10^{-4} M H_2S donor **4** was prepared in PBS buffer. Half of the solution was kept in the dark and to the remaining half, nitrogen was passed through and it was irradiated under UV light (≥365 nm), using a 125 W medium pressure Hg lamp filtered by using suitable filters with continuous stirring. At regular intervals of time, 20 μl of the aliquot was taken and analyzed by absorption spectroscopy, fluorescence spectroscopy and RP-HPLC using acetonitrile as the mobile phase, at a flow rate of 1 ml min^{-1} (detection: UV 254 nm). Peak areas were determined by RP-HPLC with an average of three runs, which indicated a gradual decrease of H_2S donor **4** with time. The reaction was followed until the consumption of H_2S donor **4** was less than 5% of the initial content. Based on the HPLC data for each compound, we plotted normalized [A] (HPLC peak area) *versus* irradiation time.

Characterisation of photoproduct (6). ^{1}H NMR (600 MHz, D_2O) δ 7.19 (t, J = 6.7 Hz, 1H), 6.80–6.70 (m, 2H), 6.65 (d, J = 6.5 Hz, 1H), 4.47 (s, 2H), 3.19 (s, 4H), 2.09 (d, J = 6.0 Hz, 4H), 1.69 (s, 4H). ^{13}C NMR (151 MHz, D_2O) δ 182.98 (s), 148.46 (s), 141.73 (s), 129.89 (s), 115.78 (s), 113.00 (s), 112.54 (s), 64.19 (s), 48.74 (s), 34.89 (s), 23.09 (s).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 M. S. Vandiver and S. H. Snyder, *J. Mol. Med.*, 2012, **90**, 255–263.
2 R. Wang, *Physiol. Rev.*, 2012, **92**, 791–896.
3 C. Szabó, *Nat. Rev. Drug Discovery*, 2007, **6**, 917–935.
4 J. M. Fukuto, S. J. Carrington, D. J. Tantillo, J. G. Harrison, L. J. Ignarro, B. A. Freeman, A. Chen and D. A. Wink, *Chem. Res. Toxicol.*, 2012, **25**, 769–793.
5 K. R. Olson, J. A. Donald, R. A. Dombkowski and S. F. Perry, *Respir. Physiol. Neurobiol.*, 2012, **184**, 117–129.
6 Y. Zhao and M. D. Pluth, *Angew. Chem., Int. Ed.*, 2016, **55**, 14638–14642.
7 N. O. Devarie-baez, P. E. Bagdon, B. Peng, Y. Zhao, C. Park and M. Xian, *Org. Lett.*, 2013, **15**, 2786–2789.
8 Y. Zhao, S. G. Bolton and M. D. Pluth, *Org. Lett.*, 2017, **19**, 2278–2281.
9 W. Chen, M. Chen, Q. Zang, L. Wang, F. Tang, Y. Han, C. Yang, L. Deng and Y.-N. Liu, *Chem. Commun.*, 2015, **51**, 9193–9196.
10 N. Fukushima, N. Ieda, K. Sasakura, T. Nagano, K. Hanaoka, T. Suzuki, N. Miyata and H. Nakagawa, *Chem. Commun.*, 2014, **50**, 587–589.
11 N. Fukushima, N. Ieda, M. Kawaguchi, K. Sasakura, T. Nagano, K. Hanaoka, N. Miyata and H. Nakagawa, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 175–178.
12 Z. Xiao, T. Bonnard, A. Shakouri-Motlagh, R. A. L. Wylie, J. Collins, J. White, D. E. Heath, C. E. Hagemeyer and L. A. Connal, *Chem. – Eur. J.*, 2017, **23**, 11294–11300.
13 A. K. Sharma, M. Nair, P. Chauhan, K. Gupta, D. K. Saini and H. Chakrapani, *Org. Lett.*, 2017, **19**, 4822–4825.
14 Y. Venkatesh, J. Das, A. Chaudhuri, A. Karmakar, T. K. Maiti and N. D. Pradeep Singh, *Chem. Commun.*, 2018, **54**, 3106–3109.
15 X. Ding and P. Wang, *J. Org. Chem.*, 2017, **82**, 7309–7316.
16 P. Wang, *J. Photochem. Photobiol., A*, 2017, **335**, 300–310.
17 P. Wang, D. Devalankar, Q. Dai, P. Zhang and S. Michalek, *J. Org. Chem.*, 2016, **81**, 9560–9566.
18 X. Ding, D. Devalankar and P. Wang, *Org. Lett.*, 2016, **18**, 5396–5399.
19 P. Wang, D. Devalankar and W. Lu, *J. Org. Chem.*, 2016, **81**, 6195–6200.
20 P. Wang, W. Lu, D. A. Devalankar and Z. Ding, *Org. Lett.*, 2015, **17**, 2114–2117.
21 P. Wang, W. Lu, D. Devalankar and Z. Ding, *Org. Lett.*, 2015, **17**, 170–172.
22 X. Ding and P. Wang, *J. Org. Chem.*, 2018, **83**, 7459–7466.
23 D. Wu, W. Si, M. Wang, S. Lv, A. Ji and Y. Li, *Nitric Oxide*, 2015, **50**, 38–45.
24 M. R. Filipovic, J. Zivanovic, B. Alvarez and R. Banerjee, *Chem. Rev.*, 2018, **118**, 1253–1337.

