Synthesis and Use of Imidazolium Bound Rose Bengal Derivatives for Singlet Oxygen Generation

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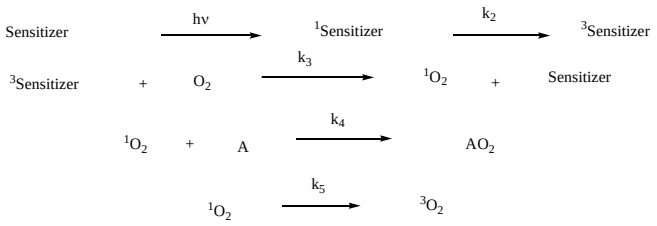
Abstract: We describe the preparation and use of two new imidazolium-bound Rose Bengal derivatives for singlet oxygen generation. Photolysis of oxygen-saturated solution of furan rings in the presence of the imidazolium-bound sensitizers provides the corresponding butenolides. The sensitizers could be recovered after the oxidation reaction.

Keywords: Ionic liquids, singlet oxygen, butenolides synthesis, rose Bengal, photooxygenation reactions.

INTRODUCTION

Singlet oxygen was originally proposed by Kautsky [1] as being an intermediate in the photosensitized oxidations. The process involves photochemical excitation of the sensitizer to its singlet excited state, intersystem crossing to triplet state, energy transfer to ground-state oxygen , and subsequent reaction of $^1O_2$ with an acceptor A to give oxygenated products AO_2 (Scheme **1**).



Scheme 1. Generation of singlet oxygen and its reaction with an acceptor A.

The chemical and photochemical generations of singlet molecular oxygen ($^1O_2$), its ready detection and its stereocontrolled chemical reactivity have made this research area very attractive and nowadays, photooxygenation reactions represent one of the most important hydrocarbon functionalization reactions for synthetic organic chemists [2]. These reactions are mild and preparatively useful because of their specificity and high yields.

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RESULTS AND DISCUSION

As part of our ongoing programme on the synthesis of biologically active natural products we applied the oxidation of furan with singlet oxygen for the preparation of oxacyclic [3], carbocyclic [4], azacyclic [5] and thiacyclic [6] systems. For the photosensitized formation of singlet oxygen, the dye we used was Rose Bengal **1**. However, one particular problem associated with this dye is its separation from the products. This has led to the synthesis of several immobilized Rose Bengal moieties using polymer or silica support [7]. Herein, we report the first synthesis of **2** and **3** (Fig. **1**), two Rose Bengal derivatives linked to an imidazolium moiety.

Compounds **2** and **3** are imidazolium salts and may be considered as ionic liquids (ILs) depending on their melting point which by definition has to be below 100º C [8]. Ionic liquids (ILs) have received much attention in recent years from the scientific community, mainly as environmentally benign reaction media [9]. Their unique properties such as high thermal and chemical stability, negligible vapour pressure, non-flammability, high loading capacity and easy recyclability make them appealing for an organic chemist. The solubility of the ionic liquids can be tuned readily by modifying the structure of the cation or the anion, so that they can phase separate from organic as well as aqueous media, rendering purifications much easier. Rose Bengal derivative **2** was prepared *via* the synthetic route shown in Scheme **2**.

Reaction of Rose Bengal **1** with propargyl bromide afforded alkyne **5** in 89% yield. Rose Bengal contains both carboxylate and phenoxide functional groups, either of which might be capable of reacting with propargyl bromide. However **5** was obtained as the major compound and could be separated from its minor isomer by column chromatography.

In order to link alkyne **5** to an ionic liquid support we needed to prepare compound **11** having an azide functional

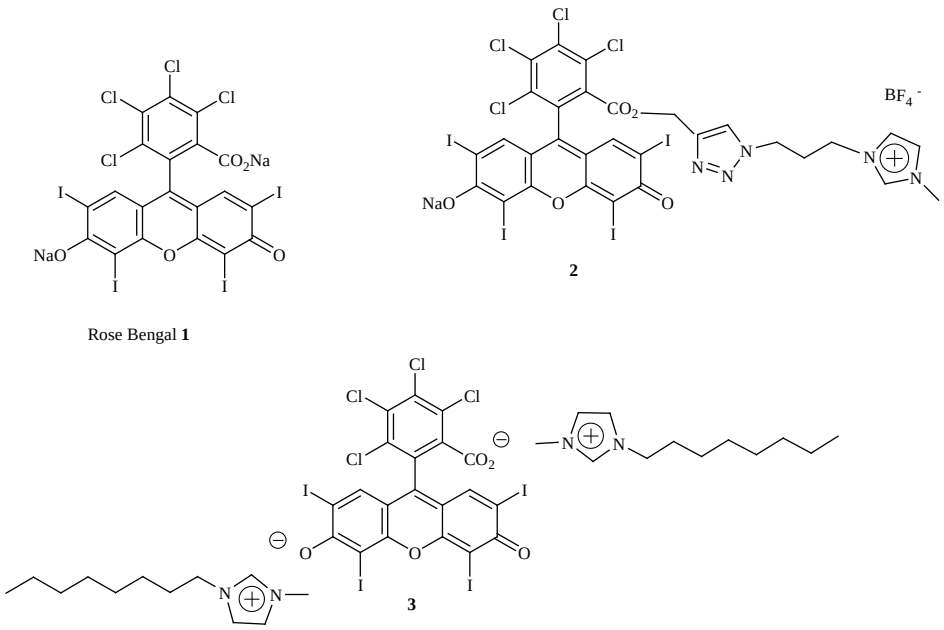
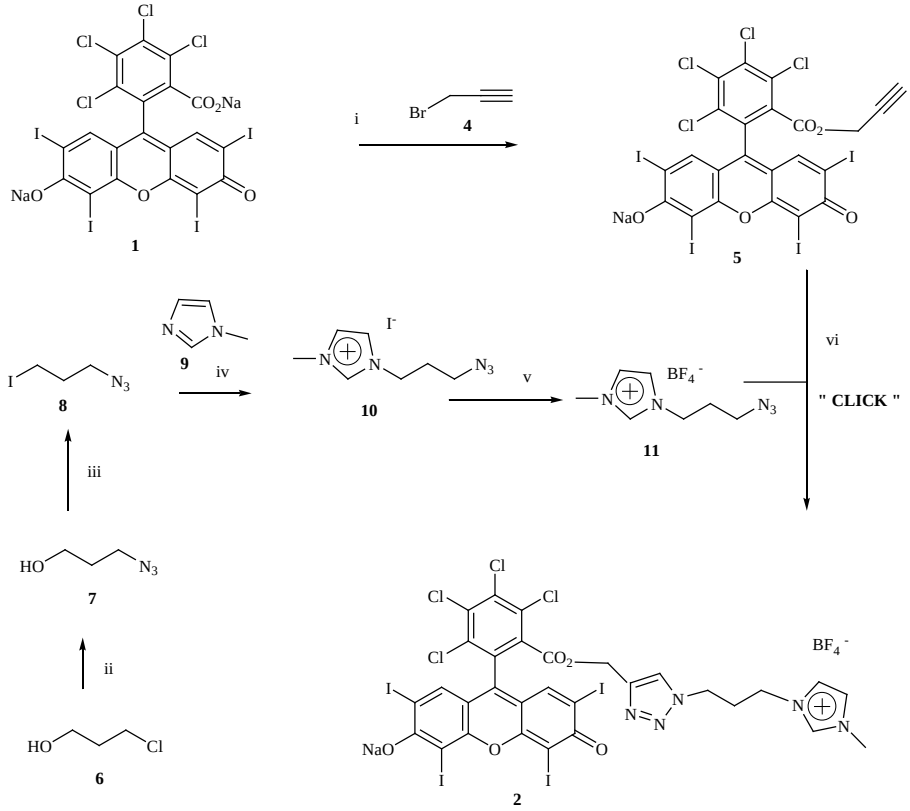


Fig. (1). Structures of Rose Bengal and two of its derivatives linked to an imidazolium moiety.



Scheme 2. *Reagents and conditions*: (i) **4**, DMF, 80º C (89%); (ii) NaN_3, H_2O, reflux (98%); (iii) I_2, PPh_3, Imidazole, THF (79%); (iv) **9**, rt (95%); (v) $NaBF_4$, CH_3CN, 60º C (100%) (vi) $CuSO_4.5H_2O$, Na-ascorbate, $tBuOH/H_2O$ (99%).

group in its side chain, so that we could use the click chemistry approach [10]. **11** was readily synthesized as follows: reaction of commercially available chloropropanol **6** with sodium azide gave an hydroxyl azide which was easily converted into iodide [11] **8**. Reaction of iodide **8** with N-methyl-imidazole **9** followed by anion exchange afforded ionic liquid **11** [12] in 95% yield, setting the stage for the click chemistry reaction which occurred uneventfully to give almost quantitatively imidazolium-bound Rose Bengal **2**, [12] hereafter designated as "IM-CLICK-RB" **2**.

Diimidazolium salt **3** [12] herafter designated as Bis-[OMIM]-RB was prepared from Rose Bengal in 60% yield, *via* anion exchange according to Scheme **3**.

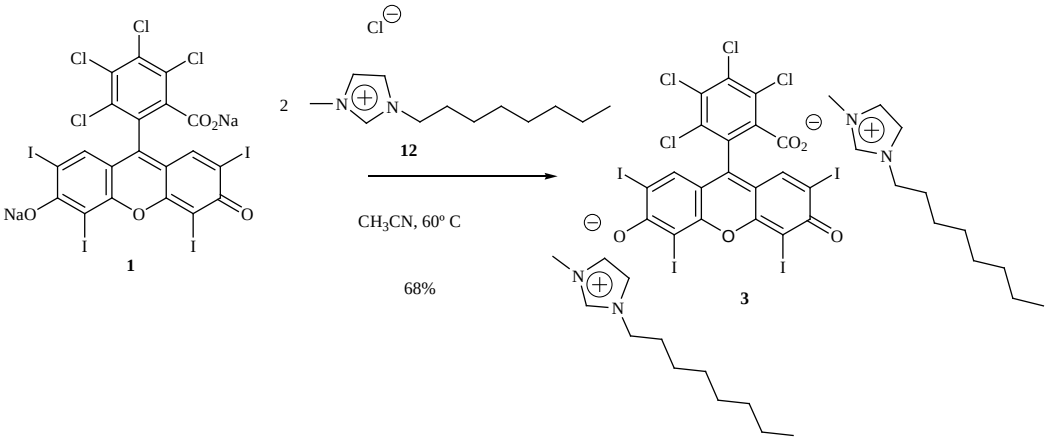
The melting points of the new Rose Bengal derivatives: IM-CLICK-RB **2** and Bis-[OMIM]-RB **3** were 252-254 ºC and 68-70º C respectively, indicating that only **3** could be considered as ionic liquid.

We were interested in exploring the photocatalytic potential of **2** and **3** for the oxidation of furans, especially in comparison with Rose Bengal disodium salt (RB). For such purpose we selected the photocatalytic oxidation of furan **13** for the preparation of methoxybutenolide **15** (Scheme **4**).

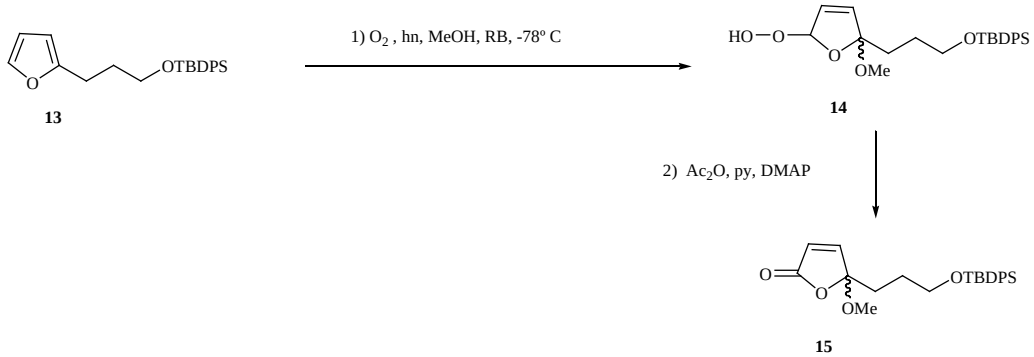
We have already reported the synthesis of methoxybutenolide **15** which was then used for the obtention of cyclic ethers.[3c] Using RB as photosensitizer, furan **13** was oxidized in 7h to the rather unstable hydroperoxide **14** which was then acetylated without further purification to afford **15** in 89% overall yield.

We carried out the same reaction on a 2 mmol scale, using RB **1**, IM-CLICK-RB **2** and Bis-[OMIM]-RB **3** as photosensitizers in order to compare the overall yields and the reaction time for the oxidation of furan **13** to hydroperoxide **14**. The results are summerized in Table **1**.

As can be seen from Table **1**, the photocatalytic performance of Bis-[OMIM]-RB **3** is superior to that of IM-

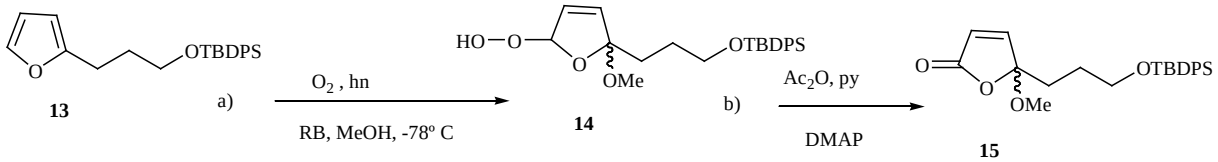


Scheme 3. Preparation of diimidazolium salt **3.**



Scheme 4. Synthesis of methoxybutenolide **15** by photocatalytic oxidation of furan **13.**

Table 1. Comparison of the Photocatalytic Performance of Photosensitizers RB 1**, IM-CLICK-RB** 2 **and Bis-[OMIM]-RB** 3



Entry	Catalyst	Reaction time for step a (h)	Overall Yield (%)
1	RB	2	71
2	IM-CLICK-RB (**2**)	3	75
3	Bis-[OMIM]-RB (**3**)	2	87

CLICK-RB **2** and RB, as indicated by the higher yield obtained for final butenolide **15**.

One noticeable difference between free RB **1** and its two derivatives IM-CLICK-RB **2** and Bis-[OMIM]-RB **3** is that in the case of RB the catalyst could not be recovered, whereas **2** and **3** were recovered as follows: after completion of the oxidation reaction (tlc), the methanol was rotatory evaporated and the residue taken up with ether (15 ml). In this solvent , **2** and **3** were not soluble and were recovered by decantation, ready for another run.. The ether phase was concentrated and the resulting crude hydroperoxide **14** was further acetylated to afford methoxybutenolide **15**.

Recyclability studies were carried out for Bis-[OMIM]-RB **3** as follows. We decided to use the same time (2 h) in the oxidation step for all the runs. After the first run the catalyst was recovered as above and reused after vacuum drying. The results are summarized in Table **2**.

Table 2. Reuse of Bis-[OMIM]-RB 3 in Successive Reaction Cycles

Cycle	Time[h] [a]	Yield [%] [b]
1	2	87
2	2	84
3	2	85
4	2	84
5	2	83
6	2	80

[a] Reaction time for step a. [b]Yields referred to pure isolated 15.

After a total of six such cycles, yield was still high.

CONCLUSIONS

In conclusion, we have synthesized two new Rose Bengal derivatives, IM-CLICK-RB **2** and Bis-[OMIM]-RB **3** and used them as sensitizers for the generation of singlet oxygen. Bis-[OMIM]-RB **3** is an easily available ionic liquid which shows better photocatalytic performance than RB and IM-CLICK-RB **2**. Work is now in progress on the use of Bis-[OMIM]-RB **3**, in conjunction with ionic liquid as solvent for the singlet oxygen oxidation of furans.

EXPERIMENTAL SECTION

General information

Solvents were purified and dried by standard procedures before use. Melting points uncorrected.

^{1}H and ^{13}C NMR spectra were recorder in a Bruker ARX-400 spectromer (400MHz ^{1}H, 100.61MHz ^{13}C) using TMS as internal standard (chemical shifts in δ values, *J* in Hz). Mass spectrometry was carried out with a Hewlett Packard 5988A spectrometer. Flash chromatography (FC) was performed on silica gel (Merck 60, 230-400 mesh); analytical TLC was peformed on plates precoated with silica gel (Merck 60 F254, 0.25mmm).

Synthesis of iodide Bis-[OMIM]-RB 3

To a stirred solution of [OMIM][Cl] **12** (568 mg, 2.5 mmol) in acetonitrile (15 mL) was added Rose Bengal **1** (1.25 g, 1.23 mmol). The mixture was stirred at 60 ºC for 24 h then allowed to reach room temperature. The resulting precipitate was filtered, washed with acetonitrile (3 x 20 mL) and the filtrate was concentrated under reduced pressure to afford a deep purple powder which was washed with AcOEt (3 x 20 mL), dried under vacuum to afford **3** (1.14 g, 68%). mp 68-70 °C; IR ($CDCl_3$) 2923 ; 22852 ; 1614 ; 1545; 1460; 1349; 1225; 1164; 950; 755; 623; 530; 448; 369 cm^{1}; **UV (MeOH, λ(nm))**: 555; 518; 318; 211; **^{1}H-NMR ($CDCl_3$) δ(ppm):** 9.85 (2H, s, **H**-23); 7.54 (2H, s, **H**-6,10); 7.27 (2H, s, **H**-25); 7.20 (2H, s, **H**-26); 4.08 (4H, t, J = 7.51 Hz, **H**-28); 3.83 (6H, s, **H**-36); 1.98 (4H,m, **H**-29); 1.77 (4H, m, **H**-30); 1.29 – 1.22 (8H, m, **H**-31,32,33,34); 0.85 (6H, t, J =7.09Hz, **H**-35).**^{13}C-NMR ($CDCl_3$) δ(ppm):** 172.76 (**C**-4,12); 167.12 (**C**-21); 157.74 (**C**-2,14); 144.80; 144.00; 134.29; 131.02; 130.61; 128.36; 127.56 (**C**-20,15,16,17,18,19,8); 137.79 (**C**H-23); 137.71 (**C**H-6,10); 111.92 (**C**-7,9); 96.44 (**C**-3,13); 75.35 (**C**-5,11); 50.13 (**C**H_2-28); 36.63 (**C**H_3-36); 31.70; 30.34; 29.08; 29.00; 26.33; 22.61 (**C**H_2-29, 30, 31, 32, 33, 34); 14.12 (**C**H_3-35). **MS (ESI) (m/z, %):** ESI^+ 391.28 (cation, 61). ESI^- 972.48 (anion, 100); 1166.65 (1cation + anion, 13).

Synthesis of compound 5

To a stirred solution of Rose Bengale (3.5 g, 3.5 mmol) in DMF (150 mL) was added propargyl bromide **4** (1,12 g, 9.4 mmol). The resulting mixture was stirred at 80 ºC for 3 h. The DMF was distilled off under vacuo and the residue stirred in diethyl ether overnight. After filtration and thorough washing with diethyl ether, the residue was stirred with water for 6 h and filtered, to afford a deep purple powder which was dried under vacuum and purified by column chromatography on silica ($MeOH/CH_2Cl_2$, 5/95) to afford compound **5** (3.2 g, 89%). R_f = 0.11 ($MeOH/CH_2Cl_2$ 1:9)); IR ($CDCl_3$) 2348 ; 2301 ; 2100 ; 1740 (C=O ester);1613; 1541; 1455; 1339; 1236; 1011 cm^{-1};^{1}H NMR (DMSO-d6, 400 MHz) δ 7.47 (2H, s, CH-Ph); 4.64 (2H, d, J = 2.5 Hz, CH2); 2.98 (1H, t, J = 2.4 Hz, CH-alcyne); ^{13}C NMR (DMSO-d6, 400 MHz) δ 171.62 (C-3,5); 162.29 (C=O); 156.98 (C-4a,4b); 138.93; 135.21; 134.35; 132.64; 131.87; 130.12; 128.79 (C-1´, 2´, 3´, 4´, 5´,6´, 9);135.96 (C-1,8); 110.46 (C-8a, 8b); 97.23 (C-4,5); 77.30 (CH-alcyne); 76.24 (C-2,7); 53.43 (CH2). ; EI-HRMS calcd for $C_{23}H_5Cl_4I_4NaO_5$ (*m/z*) [M^+] 1033.7025, found 1033.5074.

Synthesis of azide 7

To a solution of NaN_3 (5.82 g, 89.6 mmol) in H_2O (70 mL) was added portionwise **6 (**3.00 mL, 44.8mmol). The mixture was refluxed for 16h then allowed to reach room temperature and extracted with CH_2Cl_2 (80 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered and the solvent rotatory evaporated to afford azide **7** as a colourless liquid (2.37 g, 98%). R_f = 0.46 (EtOAc/hexane 3:7); **^{1}H-NMR ($CDCl_3$, δ):** 3.63 (2H, q, J = 5.07, **H**-1); 3.35 (2H, t, J = 6.66, **H**-3); 2.95 (1H, s, O**H**); 1.74 (2H, m, **H**-2); **^{13}C-NMR ($CDCl_3$, δ):** 59.30 (**C**H_2-1); 48.14 (**C**H_2-3); 31.22 (**C**H_2-2); **MS (EI^+)(m/z, %) :** 86.06 ($[C_3H_6ON_2]^+$, 100).

Synthesis of iodide 8

To a vigourously stirred solution of azide **7** (8.14 g, 80.6 mmol) in THF (150 mL) and under argon atmosphere were added PPh_3 (25.36 g, 96.36 mmol) and imidazole (16.46 g, 241.8 mmol). The mixture was stirred until total dissolution of the reagents, then cooled to -20 ºC, before adding portionwise I_2 (26.59 g, 104.78 mmol) dissolved in THF (50 mL). The reaction mixture was stirred at -20 ºC for 10 mn, then allowed to reach room temperature for 30 mn. The reaction mixture was spurred into ice-water and an saturated aqueous solution of $NaHCO_3$ (100mL) was added. A precipitate was formed, which was filtered and the filtrate extracted with ether (3 x 120 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent rotatory evaporated to afford a residue which was purified by column chromatography on silica (hexane/EtOAc, 7/3) to afford compound **8** (13.4 g, 99%) as a yellow oil. R_f = 0.78 (hexane/EtOAc, 7/3); **^{1}H-NMR ($CDCl_3$, δ):** 3.42 (2H, t, J = 6.34Hz, **H**-3); 3.24 (2H, t, J = 6.64Hz, **H**-1); 2.03 (2H, m, H-2)**; ^{13}C-NMR ($CDCl_3$, δ):** 51.48 (**C**H_2-3); 32.34 (**C**H_2-2); 2.49 (**C**H_2-1).

Synthesis of ionic liquid 10

To iodide **8** **(**3.31 g, 16.82 mmol) was added methylimidazole **9** (1.47mL, 18.5 mmol) and the mixture stirred at room temperature for 48h. The resulting yellow and viscous oil was washed with EtOAc AcOEt (5 x 25 mL) to yield ionic liquid **10** (4.37 g; 95 %); **^{1}H-NMR (D_2O, δ) :** 8.69 (1H, s, **H**-2) ; 7.42 (1H, s, **H**-4); 7.35 (1H, s, **H**-5); 4.21(2H, t, J = 6.9 Hz, **H**-6); 3.80 (3H, s, **H**-9); 3.33 (2H, t, J = 6.9, **H**-8); 2.06 (2H, q, J = 6.7 Hz, **H**-7); **^{13}C-NMR (D_2O, δ):** 136.28 (**C**H-2); 123.95 (**C**H-4); 122.49 (**C**H-5); 47.84 (**C**H_2-6); 47.04 (**C**H_2-8); 36.37 (**C**H_3-9); 28.78 (**C**H_2-7); **IR-($CDCl_3$, ν(**cm^{-1}**)):** 3463; 3081; 2871; 2102; 1569; 1455; 1455; 1265; 1166; 1062; 829; 752; 619; **MS (ESI^+) (m/z, %):** 166.11 (cation, 100).

Synthesis of ionic liquid 11

To a solution of **10** (5.23 g, 17.86 mmol) in acetonitrile (40mL) was added $NaBF_4$ (2.20 g, 19.64 mmol). The mixture was stirred at 60º C for 48 h and the resulting precipitate was filtered off, washed with acetonitrile and the filtrate concentrated under vacuum to afford a yellow viscous oil **11** (4.51 g, 100%); **^{1}H-NMR (D_2O, δ):** 8.71 (1H, s, **H**-2) ; 7.45 (1H, s, **H**-4); 7.39 (1H, s, **H**-5); 4.25 (2H, t, J = 6.9 Hz, **H**-6); 3.83 (3H, s, **H**-9); 3.37 (2H, t, J = 6.4 Hz, **H**-8); 2.10 (2H, q, J = 6.6 Hz, **H**-7); **^{13}C-NMR (D_2O, δ):** 136.18 (**C**H-2); 123.82 (**C**H-4); 122.34 (**C**H-5); 47.70 (**C**H_2-7); 46.88 (**C**H_2-8); 36.02 (**C**H_3-9); 28.58 (**C**H_2-7); **IR-($CDCl_3$, ν(**cm^{-1}**)):** 3463; 3081; 2102; 1569; 1455; 1265; 1166; 1058; 831; 769; 619; **MS (ESI^+) (m/z, %):** 166.12 (cation, 100); 167.11 (12); 225.15(2.35).

Synthesis of IM-CLICK-RB 2

To a solution of ionic liquid **11** (528.7 mg, 2.09 mmol) in 30 mL of tBuOH/H_2O (2/1) was added compound **5** (2.33 g, 5.95 mmol) a catalytic amount of $CuSO_4.5H_2O$ (5 %), sodium ascorbate (0.42 mL, 0.42 mmol of an 1M solution). The reaction mixture was stirred at room temperature overnight. At the end of the reaction, the solvent was evaporated and the resulting solid was washed with Et_2O (3 x 15 mL), EtOAc (3 x 15 mL), MeOH (3 x 15 mL) then dried under vacuum to afford 2 (2.3 g, 86%) as a rose solid. mp 235-237 ˚C; **^{1}H-NMR (DMSO-d_6) δ(ppm):** 9.50 (1H, s, **H**-32); 7.90 (1H, t, J =1.75 Hz, C**H**-27); 7.80; 7.79 (2H, s, **H**-34,35); 7.63 (2H, s, **H**-6,10); 4.68 (2H, d, J = 2.46 Hz, **H**-22); 4.56 (2H, t, J = 7.15 Hz, **H**-30); 4.12 (3H, s, **H**-35); 3.57 (2H, t, J = 6.57 Hz, **H**-28); 2.29 (2H, m, **H**-29); **^{13}C-NMR (DMSO-d_6) δ(ppm):** 174.19 (**C**-4,12); 164.21 (**C**=O); 159.66 (**C**-2,14); 141.29; 137.45; 136.61; 135.47; 134.32; 132.86; 131.47 (**C**-20, 15, 16, 17, 18, 19, 8); 138.39(**C**H-6,10); 125.81 (**C**H-27); 124.67; 124.45 (**C**H-34,35); 112.82 (**C**-7,9);98.35 (**C**-3,13); 75.99 (**C**-5,11) ; 54.89 (**C**H_2-22); 49.73; 48.88 (C-28,30); 37.93 (C-35); 31.52 (CH_2-29); **IR-($CDCl_3$, ν(**cm^{-1}**)):** 2360; 2098; 1743 (C=O); 1614; 1546; 1459; 1344; 1247; 1168; 952; 754; 663; 522; 435; **UV (MeOH, λ(nm)**): 564; 285; 273; 266; 207; **MS (EI^+)[m/z,(%)]:** X = I: 1175.62($[C_{33}H_{19}Cl_4I_4N_3NaO_3]^+$, 100); X = BF_4: 1177.6182 ($[M - Na]^+$ 100); 1175.62($[C_{11}H_{10}Cl_4I_4N_{23}NaO_4]^+$, 86).

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CONFLICT OF INTEREST

None declared.

SUPPORTING INFORMATION

Supporting Information is available on the publisher's web site along with the published article.

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[12] The spectral data of **2** and **3** can be found in the supplementary material.

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