# Glycerol as a promoting medium for electrophilic activation of aldehydes: catalyst-free synthesis of di(indolyl)methanes, xanthene-1,8(2*H*)-diones and 1-oxo-hexahydroxanthenes

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Glycerol was used, for the first time, as a green and effective promoting medium for electrophilic activation of aldehydes, and with which, a catalyst-free system for some reactions that conventionally carried out using acid catalysts, such as synthesis of di(indolyl)methanes, 3,4,5,6,7,9-hexahydro-9-aryl-1*H*-xanthene-1,8(2*H*)-dione and 1-oxo-hexahydroxanthenes, was developed.

## Introduction

The biodiesel industry generates a tremendous amount of crude glycerol as a by-product. The large surplus of glycerol, which has entered the chemical market, has caused the closure of existing glycerol plants and the discovery of processes that use glycerol as a raw material for the production of value-added chemicals and even of energy. It is undoubted that increasing demand of biodiesel will put an additional pressure upon the glycerol market in the future. Therefore, rational utilizations of glycerol have gained much attention recently. Today, most of the efforts in this area are focusing on the development of an alternative way, starting from glycerol, to prepare old chemicals that have either been prepared from petrochemicals or suffered from environmental problems during their preparation. Many successful examples could be found in some comprehensive reviews.[1] It should be noted that although some promising approaches were developed, the large-scale synthesis of new molecules starting from glycerol necessitates a systematic evaluation of toxicity, capacity and stability of the product, which will inevitably cost a lot of time and also make a hard task for researchers. Therefore, synthesis of new compounds using glycerol as starting material is, to some extent, not favorable from the perspective of industry. Although chemical conversions of glycerol have gained much attention, importance of non-transformative technologies have rarely been mentioned in literature. Confronted with huge pressure coming from biodiesel industry, more efforts are needed to allow the development of new and innovative processes by using glycerol.[2]

On the other hand, development of green solvents from renewable resources has gained much attention recently, because of the extensive uses of solvents in almost all of the chemical industry, and of the predicted disappearance of fossil oil.[3] Huge production of glycerol offers a good opportunity to chemists to use it as renewable material to prepare green and biomass-based solvents, for example, new ionic liquids.[4] Taking the inherent properties of glycerol, such as a long liquid range, nonflammability and unique solubility for polar organic compounds, into consideration, the direct use of glycerol as a solvent for organic reactions would, if realized, fit perfectly the requirements of a green solvent. It should be noted that, as a solvent, data about the toxicity and environmental compatibility have to be collected before its utilizations on a large scale. In this respect, a good understanding of glycerol, as well as positive data, is helpful for the commercialization of the processes related to glycerol solvents. However, the necessity and effectiveness of glycerol solvent have not been well-recognized yet, owing to a lack of successful examples. Wolfson's group[5] reported that glycerol could be used as alternative solvent for Pd-catalyzed Heck C–C coupling and Suzuki reactions. Although isolation of product is relatively easy, no significant improvement in terms of reaction behaviour or catalytic performance was identified in glycerol. Quite recently, we and Jérôme,[6] observed that glycerol can be used as a promising medium for organic reactions, such as the aza-Michael reaction, Fridel–Crafts type addition of indole to α,β-unsaturated ketones and ring-opening of epoxide with amine, under catalyst-free conditions. These observations verified that glycerol can indeed be used as an effective solvent for development of new synthetic methodologies. In a continuation of our research on the use of glycerol as a solvent for organic reaction, we report here that glycerol can be used as an effective medium for promoting the electrophilic activity of aldehydes. Some condensation reactions of aldehydes that are conventionally carried out using acid catalysts could be performed in catalyst-free conditions in glycerol. It is particularly useful for the synthesis of di(indolyl)methanes, 3,4,5,6,7,9-hexahydro-9-aryl-1*H*-xanthene-1,8(2*H*)-dione and 1-oxo-hexahydroxanthenes.

## Results and discussion

Initially, reaction between 4-nitrobenzaldehyde and 2-methylindole was investigated in different solvents under catalyst-free conditions, and the results are listed in Table 1.

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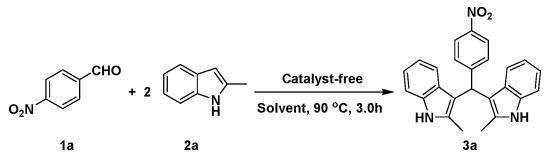
[b]*Hubei Key Laboratory of Material Chemistry and Service Failure, Huazhong University of Science and Technology, Wuhan, 430074, P R China*

**Table 1** Reaction between 4-nitrobenzaldehyde and 2-methylindole in different solvents[a]




1a 2a 3a

| Entry | Solvent | Yield (%) |
|---|---|---|
| 1 | Toluene | < 5 |
| 2 | DMF | < 5 |
| 3 | DMSO | < 5 |
| 4 | *n*-Butyl acetate | < 5 |
| 5 | No solvent | < 5 |
| 6 | *n*-Butanol | 38[e] |
| 7 | Polyethylene glycol 400 | 85 |
| 8 | Ethylene glycol | 85 |
| 9 | Water | 76[e] |
| 10 | Glycerol | 95 |
| 11[b] | Glycerol | 64[e] |
| 12[c] | Glycerol | 62[e] |
| 13[d] | Glycerol | 91 |

[a] **1a**: 1 mmol; **2a**: 2.0 mmol; solvent: 2.0 ml. [b] Glycerol: 1.0 ml. [c] 1.5 h. [d] The reaction was performed on the 10.0 mmol scale, [e] Product was obtained after PTLC.

Only a trace amount of product was detected in toluene, DMF, DMSO, *n*-butyl acetate and in neat conditions (entries 1 to 5). While the reaction proceeded sluggishly in *n*-butanol, a huge improvement was observed in polyethylene glycol and ethylene glycol (entries 6 to 8). Although water was proved to be capable of promoting the reaction, in this case, solvent extraction and silica chromatography needed to be used in order to separate and purify the product (entry 9).

Inspired by the observed determinant effect of alcoholic solvents on the reaction, we then investigated the feasibility of using glycerol as the solvent for this reaction. As we expected, the reaction proceeded very well, and 95% yield was obtained under identical conditions (entry 10). Further investigation revealed that the result is affected by amount of glycerol and reaction time, and the optimal conditions, we found, were 2.0 ml of glycerol and 3.0 h (entries 11 and 12). Interestingly, in the beginning of the reaction, a solution, which seems to be nearly transparent, was observed because both 4-nitrobenzaldehyde and 2-methylindole are soluble in glycerol (Fig. 1a). The later formed a product, which is a solid at reaction temperature, was found to be insoluble in glycerol, and consequently, with progress of the reaction, a yellow solid was observed (Fig. 1b); and at the end of the reaction, large amount of solid product was formed. This makes stirring of the reaction mixture difficult (Fig. 1c).

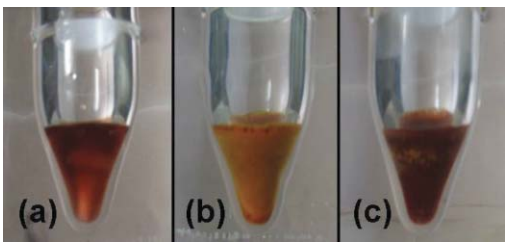
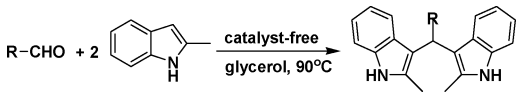



**Fig. 1** Progress of the model reaction in glycerol (a: beginning of the reaction; b: running of the reaction; c: the end of the reaction).

**Table 2** Reaction between 2-methylindole and aldehydes in glycerol[a]




| Entry | Aldehyde | Product | Time/h | Yield (%) |
|---|---|---|---|---|
| 1 | Benzaldehyde | **3b** | 21.0 | 98 |
| 2 | *p*-Tolualdehyde | **3c** | 2.5 | 98 |
| 3 | 4-Methoxybenzaldehyde | **3d** | 1.5 | 95 |
| 4 | 4-Hydroxybenzaldehyde | **3e** | 1.5 | 98 |
| 5 | 2-Methoxybenzaldehyde | **3f** | 2.0 | 97 |
| 6 | 4-Chlorobenzaldehyde | **3g** | 24.0 | 75 |
| 7 | Veratraldehyde | **3h** | 5.0 | 85 |
| 8 | Salicyladehyde | **3i** | 7.5 | 97 |
| 9 | 3-Ethoxysalicylaldehyde | **3j** | 1.5 | 93 |
| 10 | 5-Bromosalicylaldehyde | **3k** | 4.0 | 95 |
| 11 | Vanillin | **3l** | 3.0 | 98 |
| 12[b] | 4-Acetoxybenzaldehyde | **3m** | 5.0 | 96 |
| 13 | 4-Acetamidobenzaldehyde | **3n** | 9.0 | 87 |
| 14 | 2-Nitrobenzaldehyde | **3o** | 4.0 | 94 |
| 15 | 3-Phenylpropionaldehyde | **3p** | 9.0 | 90 |
| 16[b] | 4-Dimethylaminobenzaldehyde | **3q** | 15.0 | 75 |
| 17 | Furfural | **3u** | 8.0 | 98 |
| 18 | Propiophenone | — | 14.0 | 0 |

[a] 2-Methylindole: 1.0 mmol, aldehyde: 0.5 mmol; glycerol: 1.0 ml, 90 °C. [b] 100 °C.

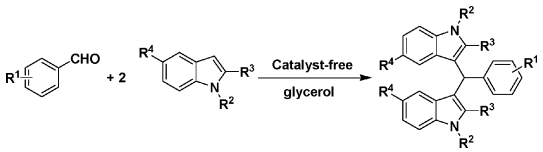
Because glycerol is highly hydrophilic, separation of the product from glycerol could be realized by adding water at 60 °C. In order to completely remove glycerol from solid product, washing with water was necessary.[7] This simple procedure allows easy scale-up of our methodology. Indeed, 91% yield was obtained in the 10.0-mmol-scale reaction (entry 13).

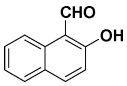
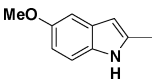
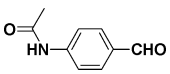
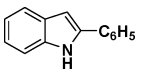
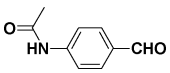
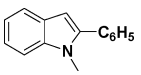
It should be noted that reactions between aldehydes and indoles are generally carried out in the presence of acids, such as HCl,[8] $P_2O_5$,[9] Amberlyst-15[10] and other solid acids,[11] or metal-containing catalysts including $Bi(NO_3)_3$,[12] $Sc(OTf)_3$,[13] $Dy(OTf)_3$[14] and $InCl_3$,[15] with the aid of organic solvents or ionic liquids.[16] Obviously, synthesis with these reported methods not only generates a lot of organic or inorganic wastes during the work-up procedure, but also suffers from the difficulty of removing trace amount of residue metal species from the product when it is applied in pharmaceutical synthesis. Particularly, when solid acids are used as catalysts, owing to the fact that both the catalyst and the product are solid, in order to separate them and recover the catalyst, a large amount of organic solvent has to be used.[17] Performing the model reaction in glycerol not only offers a high reaction yield, but also avoids: (i) generation of toxic wastes; (ii) the use of large amount of organic solvent or catalyst; and (iii) tedious post-treatment. Therefore, our system is an attractive strategy for the synthesis of the target compound from the viewpoint of green synthesis.

With these results in hand, we then investigated the substrate scopes and limitations of glycerol-mediated synthesis of di(indolyl)methane, and the results are listed in Table 2 and Table 3. Many aldehydes including benzaldehyde, *p*-tolualdehyde, 4-methoxybenzaldehyde, 4-hydroxybenzaldehyde, vanillin, 2-methoxybenzaldehyde, 4-chlorobenzaldehyde, veratraldehyde, salicylaldehyde, 5-bromosalicylaldehyde, 3-ethoxysalicylaldehyde, 4-acetoxybenzaldehyde, 4-

**Table 3** Reaction between aldehyde and different indole derivatives in glycerol[a]




| Entry | Indole | Aldehyde | Product | Temp./°C | Time/h | Yield (%) |
|---|---|---|---|---|---|---|
| 1 |  |  | **3v** | 100 | 12.5 | 82 |
| 2 |  |  | **3w** | 90 | 8.5 | 89 |
| 3 |  |  | **3r** | 90 | 7.0 | 97 |
| 4[b] |  |  | **3s** | 120 | 32.0 | 75 |
| 5[b] |  |  | **3t** | 120 | 32.0 | 65 |

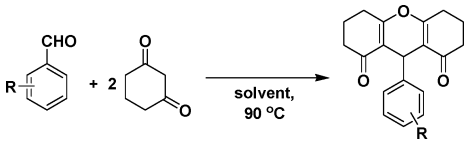
[a] aldehyde: 0.5 mmol, indole derivative: 1.0 mmol, glycerol: 1.0 ml; [b] product was obtained by PTLC.

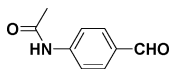
acetamidobenzaldehyde and 2-nitrobenzaldehyde reacted readily with 2-methylindole to afford the corresponding products in good to excellent yields (Table 2, entries 1 to 14). Not only aromatic aldehydes, but also aliphatic aldehydes, such as 3-phenylpropionaldehyde, were applicable in this system, and the product was obtained in 90% yield (entry 15). Because no acid or metal containing catalysts were used, our system thus allows the use of acid-labile substrates. For example, 4-dimethylaminobenzaldehyde, which tends to poison acid or metal-containing species by means of acid–base interaction or coordination, can be converted into the desired product in high yields without damage to the tertiary amine group (entry 16). Furthermore, furfural, which was known as acid-sensitive species, was also proved to be applicable in the glycerol system (entry 17), indicating the usefulness of our methodology. Limitations were found in the reactions of ketone, such as acetophenone, which is generally less reactive in the model reaction compared with aldehydes (entry 18).

When salicylaldehyde, 4-acetamidobenzaldehyde or 2-hydroxy-1-naphthaldehyde was used as substrate, the reactions of indole, 2-methyl-5-methoxyindole and 1-methylindole proceeded smoothly in glycerol to afford the corresponding products in moderate to good yields (Table 3, entries 1 to 3). However, indoles with a phenyl group in C2 position showed, unfortunately, a relatively lower reactivity compared with that of indoles with methyl group. For example, while 87% yield was obtained with 2-methylindole after 9 h at 90 °C, only 75% of yield was achieved with 2-phenylindole after 32 h of reaction at 120 °C (entry 4). The reasoning behind this low reactivity is 2-fold: (i) steric hindrance of the phenyl group; and (ii) the electron withdrawing effect.

The obtained results have clearly shown that glycerol can be used as a promoting medium for electrophilic activation of aldehydes. Encouraged by these promising results, we then investigated another electrophilic reaction of aldehyde in glycerol: condensation between aromatic aldehyde and 1,3-cyclohexanedione that gives 3,4,5,6,7,9-hexahydro-9-aryl-1*H*-xanthene-1,8(2*H*)-dione exclusively. In the literature, this reaction has been extensively investigated. The reported examples showed that either Lewis acids or protic acids have to be used in order to make the reaction proceed.[18] It was very interesting to find that reaction between 4-acetamidobenzaldehyde and 1,3-cyclohexanedione proceeded well in glycerol without the use of any catalyst, and the desired product was obtained in 85% yield (Table 4, entry 1). Glycerol was proven to be an unique promoting solvent again, as a lesser amount of product was detected in DMF, DMSO, *n*-butanol, toluene, nitromethane, polyethylene glycol, ethylene glycol and water under the identical conditions (entries 2 to 9). Because of the fact that the obtained product is not soluble in glycerol, it could be separated easily with the same procedure in the first part of this work (Fig. 2). Other aldehydes, such as benzaldehyde, *p*-tolualdehyde, 4-methoxybenzaldehyde, 2-methoxybenzaldehyde, vanillin, 4-hydroxybenzaldehyde, 4-chlorobenzaldehyde, veratraldehyde, 4-nitrobenzaldehyde and 2-nitrobenzaldehyde were proven to be applicable in this system (entries 10 to 19). Identical to the previous system, neutral conditions in the glycerol system allow the successful use of some acid-labile substrates, such as 4-acetoxybenzaldehyde, furfural, cinnamaldehyde and 4-dimethylaminobenzaldehyde, indicating again the usefulness of our system (entries 20 to 23). Other 1,3-cyclohexanediones,

**Table 4** Condensation between aldehydes and 1,3-cyclohexanedione in different solvents[a]




| Entry | Aldehyde | Product | Time/h | Yield (%) |
|---|---|---|---|---|
| 1 |  | **4a** | 1.0 | 85 |
| 2[b] | | **4a** | 1.0 | <10 |
| 3[c] | | **4a** | 1.0 | <10 |
| 4[d] | | **4a** | 1.0 | <10 |
| 5[e] | | **4a** | 1.0 | <10 |
| 6[f] | | **4a** | 1.0 | 42 |
| 7[g] | | **4a** | 1.0 | 47 |
| 8[h] | | **4a** | 1.0 | 75 |
| 9[i] | | **4a** | 1.0 | 77 |
| 10 | Benzaldehyde | **4b** | 3.0 | 87 |
| 11 | *p*-Tolualdehyde | **4c** | 2.5 | 90 |
| 12 | 4-Hydroxybenzaldehyde | **4d** | 6.0 | 92 |
| 13 | 4-Chlorobenzaldehyde | **4e** | 5.5 | 91 |
| 14 | 4-Methoxybenzaldehyde | **4f** | 2.5 | 90 |
| 15 | 2-Methoxybenzaldehyde | **4g** | 3.0 | 92 |
| 16 | Vanillin | **4h** | 2.5 | 95 |
| 17 | Veratraldehyde | **4i** | 6.0 | 99 |
| 18 | 4-Nitrobenzaldehyde | **4j** | 3.0 | 77 |
| 19 | 2-Nitrobenzaldehyde | **4k** | 4.0 | 83 |
| 20 | 4-Acetoxybenzaldehyde | **4l** | 6.0 | 82 |
| 21 | 4-Dimethylaminobenzaldehyde | **4m** | 3.0 | 88 |
| 22 | Cinnamaldehyde | **4n** | 3.5 | 50 |
| 23 | Furfural | **4o** | 6.0 | 98 |

[a] Aldehyde: 0.5 mmol, 1,3-cyclohexanedione: 1.0 mmol, glycerol: 2.0 g, 90 °C. [b] Solvent: toluene. [c] Solvent: DMF. [d] Solvent: DMSO. [e] $CH_3NO_2$. [f] Solvent: *n*-butyl acetate. [g] Solvent: polyethylene glycol. [h] Ethylene glycol. [i] Solvent: water.

such as dimedone and 5-methyl-cyclohexane-1,3-dione, also reacted readily with 4-nitrobenzaldehyde in glycerol to afford the corresponding products in excellent yields (Scheme 1).

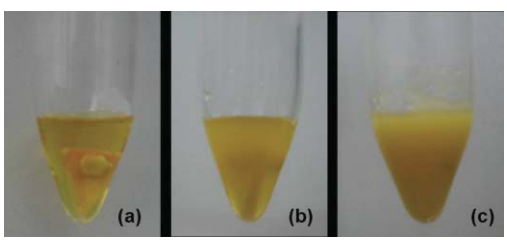
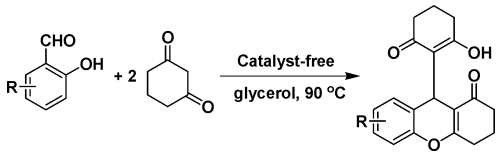
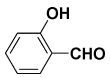
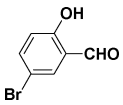
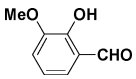
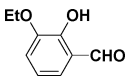
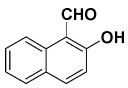



**Fig. 2** Progress of the reaction between 4-acetamidobenzaldehyde and 1,3-cyclohexanedione in glycerol without any catalysts [(a): beginning of the reaction; (b): after 30–40 min of reaction at 90 °C; (c): the end of the reaction].

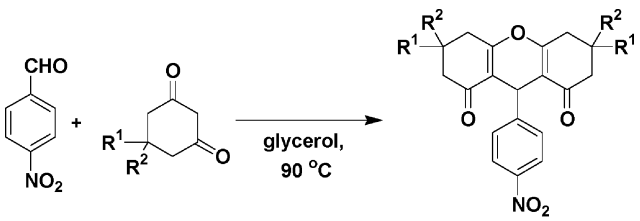
Furthermore, when salicylaldehyde was used in the reaction of 1,3-cyclohexanedione, 1-oxo-hexahydroxanthene, which has been proven to be bioactive recently,[19] was obtained instead of 3,4,5,6,7,9-hexahydro-9-(2-hydroxyphenyl)-1*H*-xanthene-1,8(2*H*)-dione (Table 5, entry 1). This reaction has been recognized as an acid-catalyzed reaction, and the aid of organic solvents is necessary in the previous reported systems.[20] Our system offers a catalyst-free method for the synthesis of

**Table 5** Reaction between salicylaldehydes and 1,3-cyclohexanedione in glycerol[a]




| Entry | Indole | Product | Time/h | Yield (%) |
|---|---|---|---|---|
| 1 |  | **5a** | 12.5 | 84 |
| 2 |  | **5b** | 12.5 | 90 |
| 3 |  | **5c** | 6.0 | 88 |
| 4 |  | **5d** | 12.5 | 78 |
| 5[b] |  | **5e** | 3.5 | 98 |

[a] Salicylaldehyde: 0.5 mmol, 1,3-cyclohexanedione: 1.0 mmol, glycerol: 1.0 ml. [b] 100 °C.




$R^1 = R^2 = Me$, 2.5 h, Yield = 94% (4p);
$R^1 = Me$, $R^2 = H$, 1.0 h, Yield = 96% (4q).

**Scheme 1** Reactions between 4-nitrobenzaldehyde and different 1,3-cyclohexanediones in glycerol.

1-oxo-hexahydroxanthenes, which makes the methodology quite attractive from the viewpoints of waste minimization and convenient product separation. In glycerol system, other salicylaldehydes, such as 5-bromosalicylaldehyde, 3-methoxysalicylaldehyde, 3-ethoxysalicylaldehyde and 2-hydroxy-1-naphthaldehyde have also been converted smoothly, and the desired 1-oxo-hexahydroxanthenes were obtained in moderate to high yields (entries 2 to 5). These results further verified the effectiveness of glycerol solvent in promoting electrophilic activity of aldehydes.

## Conclusions

In conclusion, glycerol was proved to be an effective medium to promote electrophilic activity of aldehydes. In glycerol and in the absence of any catalyst, many aldehydes reacted readily with indoles and 1,3-cyclohexanedione to afford the corresponding

di(indolyl)methane derivatives, 3,4,5,6,7,9-hexahydro-9-aryl-1*H*-xanthene-1,8(2*H*)-diones and 1-oxo-hexahydroxanthenes in good to excellent yields. Compared with previously reported systems composed of acid catalysts and organic solvents, glycerol solvent not only makes the product separation much easier, but also shows higher environmental compatibility and sustainability considering the following two factors: (i) avoidance of quenching step allows the use of less amount of toxic organic solvent and minimization of waste; and (ii) glycerol is, currently, a by-product of the biodiesel industry and its utilization needs to be extended urgently. These observations also promote the advance of solvent innovations. Despite these good results, we are uncertain as to the reasons behind the significant effects of glycerol on these reactions, though it is likely due to the strong hydrogen bonds between the carbonyl of the aldehyde and the alcoholic solvent. This is, no doubt, the next issue needing to be addressed. The unique ability of glycerol might also be useful for other catalytic or organic reactions, and the investigations on these lines are underway in our group.

## Experimental

All the reactions were conducted in a 10 mL V-type flask equipped with triangle magnetic stirring. In a typical reaction, glycerol (2.0 ml) was mixed with 2-methylindole (262 mg, 2.0 mmol) and *p*-nitrobenzaldehyde (151 mg, 1.0 mmol) under air. The mixture was stirred for 3.0 h at 90 °C. After reaction, the mixture was mixed at 60 °C with water (6 mL). After 15 min of stirring, the crude mixture was filtered and washed with water. After drying at room temperature, the product was obtained in 95% of yield.

### Spectroscopic data of new compounds

**Bis(2-methyl-3-indolyl)(2-methoxyphenyl)methane (3f).** White solid, mp: 240–242 °C; $^1$H NMR (DMSO-$d_6$): 1.92 (s, 3H), 3.59 (s, 3H), 6.04 (s, 1H), 6.60 (t, $J$ = 7.2 Hz, 2H), 6.74 (t, $J$ = 6.8 Hz, 3H), 6.81 (t, $J$ = 7.2 Hz, 2H), 6.91 (d, $J$ = 7.6 Hz, 1H), 7.01 (d, $J$ = 7.2 Hz, 1H), 7.14 (d, $J$ = 7.6 Hz, 3H), 10.59 (s, 2H); $^{13}$C NMR: 12.3, 33.1, 56.0, 110.7, 111.2, 112.4, 118.3, 118.7, 119.9, 120.3, 127.8, 129.1, 130.2, 132.1, 132.7, 135.4; IR (cm$^{-1}$): 3392, 3055, 2919, 2835, 1619, 1596, 1488, 1461, 1434, 1346, 1302, 1244, 1163, 1103, 1018, 783, 744, 603; anal. calcd for $C_{27}H_{24}N_2O_2$: C: 82.07; H: 6.36; N: 7.36; found: C: 82.21; H: 6.24; N: 6.33.

**2-[Bis(2-methyl-1*H*-indol-3-yl)methyl]-3-ethoxyphenol (3j).** White solid, mp: 248–250 °C; $^1$H NMR (DMSO-$d_6$):1.31 (t, $J$ = 6.4 Hz, 3H), 2.02 (s, 6H), 4.0 (dd, $J_a$ = 6.8 Hz, $J_b$ = 12.8 Hz, 2H), 6.09 (s, 1H), 6.59 (t, $J$ = 7.6 Hz, 1H), 6.65 (t, $J$ = 7.6 Hz, 1H), 6.83 (quint, $J$ = 7.2 Hz, 5H), 7.18 (d, $J$ = 8.0 Hz, 2H), 8.09 (s, 1H), 10.61 (s, 2H), $^{13}$C NMR: 12.3, 15.2, 33.2, 64.6, 110.6, 111.3, 112.7, 118.2, 118.3, 118.8, 119.8, 122.5, 129.2, 131.3, 132.1, 135.4, 144.8, 146.5; IR (cm$^{-1}$): 3473, 3389, 3052, 2980, 1612, 1463, 1344, 1271, 1220, 1057, 742; anal. calcd for $C_{27}H_{26}N_2O_2$: C: 79.00; H: 6.38; N: 6.82; found: C: 79.32; H: 6.21; N: 7.03.

**2-[Bis(2-methyl-1*H*-indol-3-yl)methyl]-4-bromophenol (3k).** White solid, mp: 228–230 °C, $^1$H NMR (DMSO-$d_6$): 2.08 (s, 6H), 6.01 (s, 1H), 6.73 (t, $J$ = 6.8 Hz, 2H), 6.79 (dd, $J_a$ = 8.0 Hz, $J_b$= 10.0 Hz, 3H), 6.89 (t, $J$ = 7.2 Hz, 2H), 7.05 (d, $J$ = 2.4 Hz, 1H), 7.21 (d, $J$ = 8.4 Hz, 3H), 9.55 (s, 1H), 10.70 (s, 2H); $^{13}$C NMR: 12.3, 33.4, 110.1, 110.8, 111.8, 117.5, 118.5, 120.0, 128.9, 130.0, 132.3, 132.5, 133.9, 135.4, 155.1; IR (cm$^{-1}$): 3398, 3055, 2916, 1616.3, 1460, 1426, 1340, 1303, 1263, 1221, 1103, 1017, 819, 744; anal. calcd for $C_{25}H_{21}BrN_2O$: C: 67.42; H: 4.75; N: 6.29; found: C: 67.09; H: 4.56; N: 6.51.

**Bis(2-methyl-3-indolyl)(4-acetoxyphenyl)methane (3m).** White solid, mp: 284–286 °C; 1H NMR (DMSO-$d_6$): 2.10 (s, 6H), 2.24 (s, 3H), 5.96 (s, 1H), 6.70 (t, $J$ = 7.2 Hz, 2H), 6.85 (d, $J$ = 8.0 Hz, 2H), 6.90 (t, $J$ = 7.2 Hz, 2H), 7.01 (d, $J$ = 8.4 Hz, 2H), 7.23 (t, $J$ = 7.6 Hz, 4H), 10.76 (s, 2H); $^{13}$C NMR: 12.4, 21.3, 38.6, 110.8, 112.6, 118.5, 119.0, 120.1, 121.7, 128.7, 130.0, 132.6, 135.6, 142.2, 149.0, 169.7; IR (cm$^{-1}$): 3391, 3058, 1737, 1503, 1461, 1428, 1369, 1347, 1304, 1224, 1194, 1164, 1097, 1016, 941, 915, 866, 844, 745, 611, 597; anal. calcd for $C_{27}H_{24}N_2O_2$: C: 79.39; H: 5.92; N: 6.86; found: C: 79.61; H: 5.94; N: 6.83.

**Bis(2-methyl-3-indolyl)(4-acetamidophenyl)methane (3n).** White solid, mp: 275–277 °C; $^1$H NMR (DMSO-$d_6$): 2.04 (s, 3H), 2.09 (s, 6H), 5.89 (s, 1H), 6.70 (t, $J$ = 7.2 Hz, 2H), 6.85 (d, $J$ = 8.0 Hz, 2H), 6.90 (t, $J$ = 8.0 Hz, 2H), 7.11 (d, $J$ = 8.0 Hz, 2H), 7.23 (d, $J$ = 8.0 Hz, 2H), 7.48 (d, $J$ = 8.0 Hz, 2H), 9.89 (s, 1H), 10.73 (s, 2H); $^{13}$C NMR: 12.4, 24.4, 38.6, 110.8, 112.8, 118.4, 119.0, 119.2, 120.0, 128.8, 129.3, 132.5, 135.5, 137.6, 139.3, 168.5; IR (cm$^{-1}$): 3386, 3294, 3052, 2918, 2868, 1672, 1613, 1556, 1513, 1458, 1405, 1356, 1305, 1246, 1180, 1155, 1128, 1096, 1015, 836, 750, 669, 629, 501; anal. calcd for $C_{27}H_{25}N_3O$: C: 79.58; H: 6.18; N: 10.31; found: C: 79.66; H: 6.01; N: 10.42.

**3,3′-(3-Phenyl)propylidenebis[2-methyl-1*H*-indole] (3p).** White solid, mp: 188–190 °C, $^1$H NMR (DMSO-$d_6$): 2.31 (s, 6H), 2.62 (s, 4H), 4.39 (s, 1H), 6.82 (t, $J$ = 7.6 Hz, 2H), 6.91 (t, $J$ = 7.2 Hz, 2H), 7.09-7.18 (m, 3H), 7.18-7.27 (m, 4H), 7.49 (d, $J$ = 8.0 Hz, 2H), 10.65 (s, 2H); $^{13}$C NMR: 12.8, 34.1, 34.8, 36.6, 118.4, 119.0, 119.9, 126.1, 128.2, 128.7, 128.7, 131.7, 135.6, 142.8; IR (cm$^{-1}$): 3497, 3058, 3044, 2932, 1590, 1551, 1479, 1452, 1426, 1369, 1327, 1269, 1236, 1226, 1201, 1178, 1162, 1152, 1129, 1117, 1084, 1058, 1010, 868, 805, 747, 553; anal. calcd for $C_{27}H_{26}N_2$: C: 85.68; H: 6.92; N: 7.40; found: C: 85.89; H: 6.71; N: 7.66.

**1-(Di-1*H*-indol-3-ylmethyl)-2-naphthalenol (3v).** White solid, mp: 224–226 °C; $^1$H NMR (DMSO-$d_6$): 6.83 (t, $J$ = 7.6 Hz, 4H), 6.91 (s, 1H), 7.01 (t, $J$ = 7.2 Hz, 2H), 7.05-7.15 (m, 2H), 7.32 (t, $J$ = 8.8 Hz, 5H), 7.68 (dd, $J_a$ = 4.0 Hz, $J_b$ = 9.2 Hz, 2H), 8.34 (t, $J$ = 4.4 Hz, 1H), 9.91 (bs, 1H), 10.72 (d, $J$ = 1.6 Hz, 2H); $^{13}$C NMR: 30.6, 111.8, 117.4, 118.5, 118.8, 119.7, 121.3, 121.7, 122.3, 124.3, 125.0, 127.8, 128.5, 128.7, 129.4, 134.1, 136.8, 152.3; IR (cm$^{-1}$): 3469, 3407, 3050, 1620, 1600, 1517, 1455, 1414, 1398, 1356, 1337, 1263, 1211, 1148, 1121, 1093, 1027, 1009, 949, 826, 780, 750, 598, 512; anal. calcd for $C_{27}H_{20}N_2O$: C: 83.48; H: 5.19; N: 7.21; found: C: 82.44; H: 5.01; N: 7.50.

**2-[Bis(2-methyl-5-methoxy-1*H*-indol-3-yl)methyl]phenol (3w).** White solid, mp: 246–248 °C, $^1$H NMR (DMSO-$d_6$): 2.08 (s, 6H), 3.34 (s, 6H), 5.92 (s, 1H), 6.24 (d, $J$ = 2.4 Hz), 6.50 (dd,

$J_a$ = 2.4 Hz, Jb = 8.8 Hz, 2H), 6.68 (t, $J$ = 7.6 Hz, 1H), 6.80 (d, $J$ = 7.6 Hz, 1H), 7.05 (dd, $J_a$ = 8.8 Hz, $J_b$ = 14.4 Hz, 4H), 9.07 (s, 1H), 10.47 (s, 2H); $^{13}$C NMR: 12.3, 33.3, 55.1, 101.6, 109.0, 111.1, 112.5, 115.4, 118.7, 127.3, 129.5, 130.3, 130.6, 130.9, 132.9, 152.7, 155.7; IR (cm$^{-1}$): 3475, 3383, 2950, 2832, 1622, 1583, 1484, 1451, 1350, 1298, 1252, 1212, 1087, 1033, 963, 841, 803, 618; anal. calcd for $C_{27}H_{26}N_2O_3$: C: 76.03; H: 6.14; N: 6.57; found: C: 76.27; H: 5.98; N: 6.79.

**3,3′-[(4-Acetamidophenyl)methylene]bis[1-methyl-1*H*-indole] (3r).** White solid, mp: 198–200 °C; $^1$H NMR (DMSO-$d_6$): 2.02 (s, 3H), 3.67 (s, 6H), 5.78 (s, 1H), 6.79 (s, 2H), 6.90 (t, $J$ = 7.6 Hz, 2H), 7.09 (t, $J$ = 7.6 Hz, 2H), 7.28 (dd, $J_a$ = 8.0 Hz, $J_b$ = 13.2 Hz, 4H), 7.35 (d, $J$ = 8.4 Hz, 2H), 7.49 (d, $J$ = 8.4 Hz, 2H), 9.87 (s, 1H); $^{13}$C NMR: 24.4, 32.7, 118.0, 118.8, 119.4, 119.7, 121.5, 127.4, 128.3, 128.9, 137.5, 137.7, 139.9, 168.5; IR (cm$^{-1}$): 3316, 3049, 2932, 2827, 1666, 1600, 1539, 1513, 1473, 1406, 1370, 1323, 1267, 1233, 1155, 1119, 1061, 1013, 862, 794, 740, 526; anal. calcd for $C_{27}H_{25}N_3O$: C: 79.58; H: 6.18; N: 10.31; found: C: 79.81; H: 6.33; N: 10.55.

**3,3′-[(4-Acetamidophenyl)methylene]bis[2-phenyl-1*H*-indole (3s).** White solid, mp > 300 °C (decomposed); $^1$H NMR (DMSO-$d_6$): 2.04 (s, 3H), 5.96 (s, 1H), 6.72 (t, $J$ = 7.6 Hz, 2H), 6.98 (d, $J$ = 8.0 Hz, 2H), 7.03 (t, $J$ = 8.0 Hz, 2H), 7.09 (d, $J$ = 8.0 Hz, 2H), 7.16–7.29 (m, 6H), 7.35 (d, $J$ = 2.4 Hz, 2H), 7.33 (s, 2H), 7.40 (d, $J$ = 8.0 Hz, 2H), 7.51 (d, $J$ = 8.0 Hz, 2H), 9.93 (s, 1H), 11.35 (s, 2H); $^{13}$C NMR: 19.0, 24.4, 111.8, 114.9, 119.0, 119.4, 121.4, 121.4, 127.7, 128.5, 128.7, 128.8, 129.3, 133.3, 135.8, 136.8, 137.7, 140.6, 168.6; IR (cm$^{-1}$): 3392, 3058, 1675, 1657, 1603, 1543, 1512, 1452, 1425, 1405, 1373, 1315, 1273, 1042, 1024, 823, 767, 745, 698, 509; anal. calcd for $C_{37}H_{29}N_3O$: C: 83.59; H: 5.50; N: 7.90; found: C: 83.66; H: 5.39; N: 8.05.

**2-[Bis(1-methyl-2-phenylindol-3-yl)methyl]phenol (3t).** Yellow solid, mp: 170–172 °C, $^1$H NMR: 3.42 (s, 6H), 5.09 (s, 1H), 5,68 (s, 1H), 6.74 (d, $J$ = 7.6 Hz, 1H), 6.77–6.88 (m, 7H), 7.03 (d, $J$ = 8.0 Hz, 2H), 7.09–7.17 (m, 8H), 7.19–7.21 (m, 1H), 7.22 (s, 1H), 7.23–7.26 (m, 2H); $^{13}$C NMR: 30.8, 35.7, 109.3, 116.1, 119.5, 120.6, 120.9, 121.4, 127.5, 127.7, 127.9, 128.0, 129.8, 130.3, 130.6, 131.4, 137.3, 154.4; anal. calcd for $C_{37}H_{30}N_2O$: C: 85.68; H: 5.83; N: 5.40; found: C: 85.89; H: 5.69; N: 5.67.

**3,4,5,6,7,9-Hexahydro-9-(4-acetamidophenyl)-1*H*-xanthene-1,8(2*H*)-dione (4a).** White solid, mp: 226–228 °C; $^1$H NMR (DMSO-$d_6$): 1.77–1.90 (m, 2H), 1.90–1.97 (m, 2H), 1.95 (s, 3H), 2.19–2.35 (m, 4H), 2.53–2.71 (m, 4H), 4.53 (s, 1H), 7.08 (d, $J$ = 8.4 Hz, 2H), 7.37 (d, $J$ = 8.4 Hz, 2H), 9.81 (s, 1H); $^{13}$C NMR: 20.3, 24.3, 26.9, 30.7, 36.9, 39.4, 116.0, 119.4, 128.6, 137.8, 139.8, 165.1, 168.5, 196.8; IR (cm$^{-1}$): 3536, 3306, 2959, 2926, 1665, 1607, 1548, 1512, 1413, 1358, 1326, 1274, 1201, 1175, 1130, 1014, 958, 905, 762; anal. calcd for $C_{22}H_{23}NO_3$: C: 75.62; H: 6.63; N: 4.01; found: C: 75.83; H: 6.49; N: 4.27.

**3,4,5,6,7,9-Hexahydro-9-(4-acetoxyphenyl)-1*H*-xanthene-1,8(2*H*)-dione (4l).** White solid, mp: 227–228 °C; $^1$H NMR (DMSO-$d_6$): 1.78–1.91 (m, 2H), 1.91–2.01 (m, 2H), 2.05–2.13 (m, 2H), 2.22 (s, 3H), 2.25–2.33 (m, 3H), 2.55–2.72 (m, 3H), 4.60 (s, 1H), 6.95 (d, $J$ = 8.4 Hz, 2H), 7.21 (d, $J$ = 8.4 Hz, 2H); $^{13}$C NMR: 20.3, 21.3, 26.9, 30.9, 36.8, 115.9, 121.7, 129.4, 142.4, 149.2, 165.4, 169.7, 196.8; IR (cm$^{-1}$): 2959, 2929, 1748, 1664, 1628, 1506, 1423, 1360, 1221, 1201, 1173, 1129, 1015, 957, 920, 856, 537; anal. calcd for $C_{22}H_{22}O_4$: C: 75.41; H: 6.33; found: C: 75.58; H: 6.09.

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## Notes and references

1 (*a*) M. Pagliaro, R. Ciriminna, H. Kimura, M. Rossi and C. D. Pina, *Angew. Chem., Int. Ed.*, 2007, **46**, 4434–4440; (*b*) A. Corma, S. Iborra and A. Velty, *Chem. Rev.*, 2007, **107**, 2411–2502; (*c*) N. Armaroli and V. Balzani, *Angew. Chem., Int. Ed.*, 2007, **46**, 52–66.
2 (*a*) F. Jérôme, Y. Pouilloux and J. Barrault, *ChemSusChem*, 2008, **1**, 586–613; (*b*) C. -H. Zhou, J. N. Beltramini, Y. -X. Fan and G. Q. Lu, *Chem. Soc. Rev.*, 2008, **37**, 527–549; (*c*) A. Behr, J. Eilting, K. Irawadi, J. Leschinski and F. Lindner, *Green Chem.*, 2008, **10**, 13–30.
3 (*a*) S. T. Handy, *Chem.–Eur. J.*, 2003, **9**, 2938–2944; (*b*) W. Leitner, *Green Chem.*, 2007, **9**, 923; (*c*) I. T. Horváth, *Green Chem.*, 2008, **10**, 1024–1028; (*d*) I. Giovanni, H. Silke, L. Dieter and K. Burkhard, *Green Chem.*, 2006, **8**, 1051–1055.
4 F. Bellina, A. Bertoli, B. Melai, F. Scalesse, F. Signori and C. Chiappe, *Green Chem.*, 2009, **11**, 622.
5 (*a*) A. Wolfson, C. Dlugy and Y. Shotland, *Environ. Chem. Lett.*, 2007, **5**, 67–71; (*b*) A. Wolfson and C. Dlugy, *Chem. Pap.*, 2007, **61**, 228–232.
6 (*a*) Y. Gu, J. Barrault and F. Jérôme, *Adv. Synth. Catal.*, 2008, **350**, 2007–2012; (*b*) A. Karam, N. Villandier, M. Delample, C. K. Koerkamp, J. -P. Douliez, R. Granet, P. Krausz, J. Barrault and F. Jérôme, *Chem.–Eur. J.*, 2008, **14**, 10196–10200.
7 The used glycerol could be recovered by removing water under vacuum conditions. However, it requires a lot of energy. Furthermore, low cost of glycerol makes the recycling of glycerol economically insignificant. Fortunately, good biocompatibility and low toxicity of glycerol are helpful for us to find a suitable and environmentally acceptable way to use or treat the generated aqueous solution of glycerol.
8 T. N. Parac-Vogt, K. Kimpe, S. Laurent, E. L. Vander, C. Burtea, F. Chen, R. N. Muller, Y. Ni, A. Verbruggen and K. Binnemans, *Chem.–Eur. J.*, 2005, **11**, 3077–3086.
9 A. Hasaninejad, A. Zare, H. Sharghi, K. Niknam and M. Shekouhy, *ARKIVOC*, 2007, (14), 39–50.
10 (*a*) C. Ramesh, J. Banerjee, R. Pal and B. Das, *Adv. Synth. Catal.*, 2003, **345**, 557–559; (*b*) S. A. Farhanullah, P. R. Maulik and V. Ji. Ram, *Tetrahedron Lett.*, 2004, **45**, 5099–5102.
11 (*a*) A. K. Maiti and P. Bhattacharyya, *J. Chem. Res. (S)*, 1997, **11**, 424–425; (*b*) M. Chakrabarty, N. Ghosh, R. Basak and Y. Harigaya, *Tetrahedron Lett.*, 2002, **43**, 4075–4078; (*c*) C. J. Magesh, R. Nagarajan, M. Karthik and P. T. Perumal, *Appl. Catal., A*, 2004, **266**, 1–10.
12 M. M. Khodaei, I. Mohammadpoor-Baltork, H. R. Memarian, A. R. Khosropour, K. Nikoofar and P. Ghanbary, *J. Heterocycl. Chem.*, 2008, **45**, 377–381.
13 S. Sato and T. Sato, *Carbohydr. Res.*, 2005, **340**, 2251–2255.
14 X. Mi, S. Luo, J. He and J. -P. Cheng, *Tetrahedron Lett.*, 2004, **45**, 4567–4570.
15 (*a*) G. Babu, N. Sridhar and P. T. Perumal, *Synth. Commun.*, 2000, **30**, 1609–1614; (*b*) R. Nagarajan and P. T. Perumal, *Tetrahedron*, 2002, **58**, 1229–1232.
16 (*a*) J. S. Yadav, B. V. S. Reddy and S. Sunitha, *Adv. Synth. Catal.*, 2003, **345**, 349–352; (*b*) D. -G. Gu, S. -J. Ji, Z. -Q. Jiang, M. -F. Zhou and T. -P. Loh, *Synlett*, 2005, 959–962.
17 V. T. Kamble, K. R. Kadam, N. S. Joshi and D. B. Muley, *Catal. Commun.*, 2007, **8**, 498–502.

 

18 (*a*) B. Das, M. Krishnaiah, K. Laxminarayana, K. Damodar and D. N. Kumar, *Chem. Lett.*, 2008, **37**, 1000–1001; (*b*) S. Kantevari, R. Bantu and L. Nagarapu, *J. Mol. Catal. A: Chem.*, 2007, **269**, 53–57; (*c*) G. I. Shakibaei, P. Mirzaei and A. Bazgir, *Appl. Catal., A*, 2007, **325**, 188–192; (*d*) A. John, P. J. P. Yadav and S. Palaniappan, *J. Mol. Catal. A: Chem.*, 2006, **248**, 121–125; (*e*) B. Das, P. Thirupathi, I. Mahender, V. S. Reddy and Y. K. Rao, *J. Mol. Catal. A: Chem.*, 2006, **247**, 233–239.

19 N. Sato, M. Jitsuoka, T. Shibata, T. Hirohashi, K. Nonoshita, M. Moriya, Y. Haga, A. Sakuraba, M. Ando, T. Ohe, H. Iwaasa, A. Gomori, A. Ishihara, A. Kanatani and T. Fukami, *J. Med. Chem.*, 2008, **51**, 4765–4770.

20 (*a*) G. Sabitha, K. Arundhathi, K. Sudhakar, B. S. Sastry and J. S. Yadav, *Synth. Commun.*, 2008, **38**, 3439–3446; (*b*) P. Zhang, Y. -D. Yu and Z. -H. Zhang, *Synth. Commun.*, 2008, **38**, 4474–4479.