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ORIGINAL ARTICLE

Photophysics of novel coumarin-labeled depsipeptides in solution: sensing interactions with SDS micelle via TICT model

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Abstract *N*-Acylbenzotriazoles enable the synthesis (69–92 % yield) of blue to green fluorescent coumarin-labeled depsidipeptides **8a–f** (quantum yields 0.004–0.97) and depsitripeptides **12a–d** (quantum yields 0.02–0.96). Detailed photophysical studies of fluorescent coumarin-labeled depsipeptides **8a–f** and **12a–d** are reported for both polar protic and polar aprotic solvents. 7-Methoxy and 7-diethylaminocoumarin-3-ylcarbonyl depsipeptides **8c,f** and **12d** are highly solvent sensitive. These highly fluorescent compounds could be useful for peptide assays. Further photophysical studies of 7-diethylaminocoumarin-labeled depsipeptides **8c,12d** within the micellar microenvironment of SDS reflect their ability to bind with the biological membrane, suggesting potential applications in the fields of bio- and medicinal chemistry.

Keywords Coumarin · Peptidomimetics · Depsipeptides · SDS · Micelle · TICT

Abbreviations

DCC	*N*′,*N*′-dicyclohexylcarbodiimide
SDS	Sodium dodecyl sulfate
TICT	Twisted intramolecular charge transfer

Introduction

Proteins and peptides labeled with fluorescent groups are widely applied in biology, biotechnology and medicinal chemistry for the detection and monitoring of physiochemical activity (Griffin et al. 1998; Chen et al. 2005; Dragulescu-Andrasi and Rao 2007). Fluorescent peptides have been used to label human v1b vasopressin or oxytocin receptors selectively (Corbani et al. 2011) and used in the construction of highly sensitive fluorescent tags for the detection of vascular endothelial growth factor, a biomarker for angiogenesis (Suzuki and Yokoyama 2011).

Protein engineering has inserted position-specific, non-natural amino acids into biosynthetic proteins (Hohsaka et al. 2001) and peptide analogs containing non-natural amino acids are broadly applied in structure–activity studies. Incorporation of non-natural amino or hydroxy acids into peptides and depsides expands the scope of structural perturbation and can induce specific steric properties (Scheike et al. 2007). Depsipeptides, containing both amino acid units linked by amide bonds and α-hydroxy acid units linked by ester bonds, are analogs of peptides and differ significantly in hydrogen-bonding capacity compared to natural peptides. Thus, the incorporation of hydroxy acids into a peptide chain is a useful tool

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for the diversification of peptidomimetics and for gaining a better understanding of their structural properties (Yang and Gellman 1998; Gallo and Gellman 1993). Depsipeptides exhibit useful biological (antimicrobial, antifungal, anti-inflammatory) and therapeutic activity (anticancer and anti-HIV) (Ballard et al. 2002); didemnin B and dolastatin 10 have anticarcinogenic activities (SirDeshpande and Toogood 1995; Kingston 2009). Cyclic depsipeptides such as mirabamides E–H, callipeltins A and also quinoxapeptin show promising inhibitory activities against HIV (Lu et al. 2011; Zampella et al. 1996; Boger et al. 1999). Valinomycin (Kuisle et al. 1999), a natural ionophore, can act as a non-metallic isoforming agent in potassium selective electrodes with the best K^+/Na^+ selectivity of all K^+ ionophores to date (Dudev and Lim 2009).

Coumarins afford commercially important "blue–green" fluorescent dyes which can be highly sensitive to their environment, (Wagner 2009) possess good solubility in many solvents with extended spectral ranges, high emission quantum yields and photostability (Heiner et al. 2006; Zhou and Fahrni 2004). These compounds are used to investigate ultrafast solvation dynamics and various electron transfer processes. Fluorescent coumarin-labeled peptides provide a sensitive and specific assay of matrix metalloproteinases, cathepsin D and E activity in biological samples (Knight et al. 1992; Yasuda et al. 1999). They are hydrolyzed by leucine aminopeptidase and, hence, act as inhibitors of clostridial aminopeptidase (Carmel et al. 1977).

Sodium dodecyl sulfate (SDS) micelles are capable of mimicking the tertiary interactions of protein-, lipid- and aqueous-exposed helical surfaces and are used as membrane mimetics to study the complex biological phenomena (Tulumello and Deber 2009; Maciejewski et al. 2005). They can solubilize proteins and stabilize the intramolecular interactions and, hence, are important to biosensor study (Bandyopadhyay and Saha 2008; Mishra et al. 2004). These special properties of SDS are widely used to dissolve and denature proteins, (Bhuyan 2010; Sun et al. 2012) to characterize membrane protein non-native states (Dutta et al. 2010) and to investigate solvation dynamics of coumarin dyes (Sarkar et al. 1996).

Although several literature papers concern general methods and simple photophysical studies of coumarin-labeled peptides and peptidomimetics (Avan et al. 2011; Katritzky et al. 2008a, b, 2010); a report showing their potential application inside the biological system should be interesting and useful. In this connection, depsipeptides show in contrast to their natural analogs (i) high affinity for specific receptors, (ii) good metabolic stability towards endogenous proteases, (iii) greater oral bioavailability and (iv) longer duration of action. These features interested us to explore the fields of labeled peptidomimetics and their applicability in biological system. No literature report was found on the synthesis and/or spectroscopical properties of labeled depsipeptides. Our aim in this project was to synthesize and explore the use of labeled depsipeptides, thus, showing their potential utility in biological system. Herein, we report the efficient synthesis and study of steady-state absorption, fluorescence properties of coumarin-labeled depsipeptides in polar protic and polar aprotic solvents as well as in the organized confined media of SDS micelles.

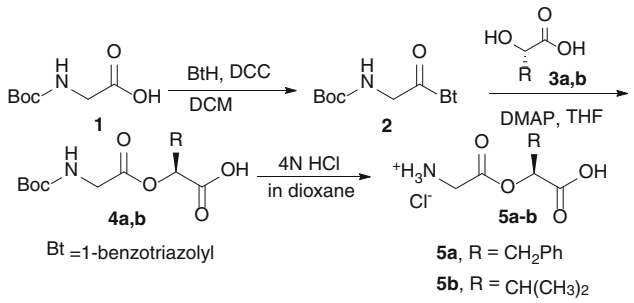
Results and discussion

Materials and methods

Melting points were determined on a capillary point apparatus equipped with a digital thermometer and are uncorrected. NMR spectra were recorded in $CDCl_3$ and DMSO–d_6 with TMS for ^1H (300 MHz) and ^{13}C (75 MHz) as an internal reference. Elemental analyses were performed on a Carlo Erba–EA 1108 Elemental Analyzer. Mass spectrometry was done on Agilent 6210 TOF–MS with electro spray ionization (ESI). CH_2Cl_2 was dried and distilled over CaH_2, whereas THF was used after distillation over Na-benzophenone. Unprotected amino acids L-phenylalanine, L-methionine and *N*-(protected)-aminoacid Boc-Gly-OH **1** were purchased from Sigma and used without further purification. Boc-Gly-Bt **2**, Hydroxycarboxylic acids **3**, Boc-protected depsidipeptide **4c** and coumarinoylbenzotriazoles **7a–c** were prepared by the reported method (Avan et al. 2011; Katritzky et al. 2008a, b, 2010). Unprotected depsidipeptides **5a**,**b** and depsitripeptides **11a–c** were characterized by ^1H, ^{13}C-NMR and used for the coupling step without further purifications. Absorption spectra were recorded on a Lambda–25 (Perkin Elmer) and fluorescence spectra were recorded on FluoroMax–3 JobinYuon Horiba Spectrofluoremeter at 23 °C. Quantum yield (Φ) was obtained by comparison of the integrated area of the corrected emission spectra of standard sample with solution of coumarin 30 in acetonitrile or stilbene in methanol. The concentration of the standard was adjusted to give the same absorbance, which is around 0.1 as the sample at the excitation wavelength.

*Preparation of unprotected depsidipeptides **5a–b***

Free or protected optically pure L-α-dipeptides (dipeptides) are useful building blocks for longer peptide analogs. The functions and applications of dipeptides have been poorly examined in the literature because of lack of an efficient protocol for the synthesis of dipeptide compared with proteins and amino acids (Yagasaki and Hashimoto 2008). Here, an efficient route to synthesize unprotected



Scheme 1 Preparation of depsidipeptides **5a,b**

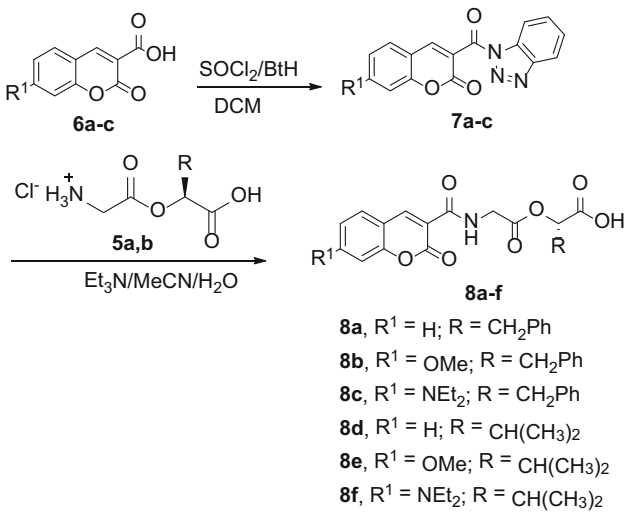
depsipeptides is reported under mild reaction conditions. Boc-protected amino acid **1** was coupled with 1*H*-benzotriazole using DCC to obtain *N*-Boc(α-aminoacyl)benzotriazole **2,** which was further reacted with L-α-hydroxycarboxylic acids **3a,b** in THF in the presence of 4-dimethylaminopyridine (DMAP) as a base to obtain Boc-protected depsidipeptides **4a,b**. Without isolation, **4a,b** were Boc-deprotected by 4 N HCl solution in dry dioxane to yield unprotected depsidipeptides **5a,b** as hydrochloride salts (Scheme 1). These free depsidipeptides were characterized by ^{1}H, ^{13}C-NMR and reacted with coumarinoylbenzotriazoles **7a–c** to prepare coumarin-labeled fluorescent depsidipeptides **8a–f** (Scheme 2).

*Preparation of N-coumarinoyl-labeled depsidipeptides **8a–f***

Coumarinoylbenzotriazoles **7a–c** were prepared from the corresponding coumarinoyl acids **6a–c** by known benzotriazole methodology (Katritzky et al. 2008a, b, 2010). *N*-Coumarinoyl-labeled depsidipeptides **8a–f** were obtained by treatment of coumarinoylbenzotriazoles **7a–c** with various unprotected depsipeptides **5a,b** in the presence of triethylamine and MeCN/H_2O (3:1 v/v) at 20 °C (Scheme 2). Novel fluorescent compounds were characterized by ^{1}H, ^{13}C-NMR and elemental analysis.

*Preparation of unprotected depsitripeptides **11a–c***

Boc-protected depsidipeptides **4a–c** (**4c** were prepared by literature method) (Avan et al. 2011) were coupled with 1*H*-benzotriazole using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) to obtain *N*-Boc(α-aminoacyl)benzotriazoles **9a,b**, which were reacted with L-phenylalanine and L-methionine in THF in the presence of triethylamine to obtain the Boc-protected depsitripeptides **10a–c**. Without isolation, **10a–c** were Boc-deprotected by 4 N HCl solution in dry dioxane to yield the unprotected depsitripeptides **11a–c** as hydrochloride salts (Scheme 3). The novel depsitripeptides **11a–c** were characterized by ^{1}H, ^{13}C-NMR and coupled with coumarinoylbenzotriazoles



Scheme 2 Preparation of coumarin-labeled depsidipeptides **8a–f**

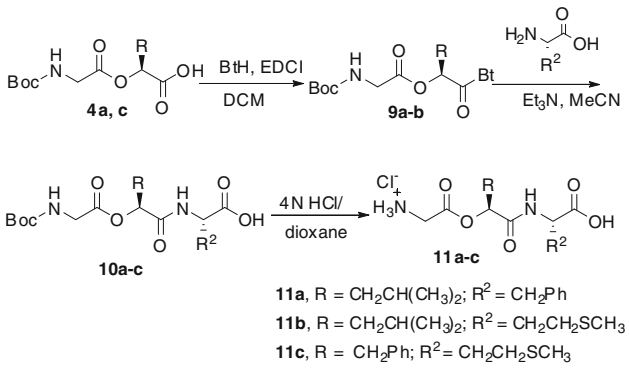
7b,c to prepare coumarin-labeled fluorescent depsitripeptides (Scheme 4).

*Preparation of N-coumarinoyl-labeled depsitripeptides **12a–d***

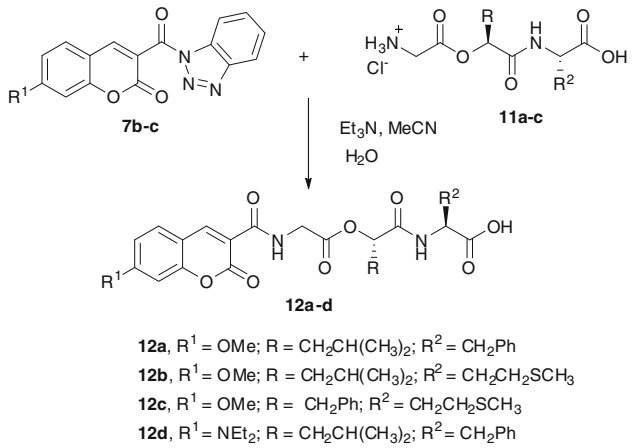
N-Coumarinoyl-labeled depsitripeptides **12a–d** were prepared by the treatment of coumarinoylbenzotriazoles **7b,c** with unprotected depsitripeptides **11a–c** in the presence of triethylamine and MeCN/H_2O (4:1 v/v) at 20 °C (Scheme 4). The novel fluorescent compounds were characterized by ^{1}H, ^{13}C-NMR and elemental analysis.

Photophysical studies of coumarin-labeled depsipeptides **8a**–**f** and **12a**–**d**

Due to a change in the dipole moments between the ground and excited electronic states of the coumarin moiety, the absorption and fluorescence maxima of coumarin-labeled conjugates are sensitive to the solvent polarity and H-bonding ability (Senthilkumar et al. 2004; Schimitschek



Scheme 3 Preparation of depsitripeptides **11a–c**



Scheme 4 Preparation of coumarin-labeled depsitripeptides **12a–d**

et al. 1976; McCarthy and Blanchard 1993; Samanta and Fessenden 2000). The spectroscopic properties of coumarins can be tuned by substituents at the positions 6 or 7, which affect the energy of the excited states (Furuta et al. 1999; Eckardt et al. 2002). This special property prompted researchers to use these fluorescent dyes as a probe to investigate many physiochemical processes. Photophysical properties of coumarin-labeled depsipeptides **8a–f** and **12a–d** were investigated in both polar protic and polar aprotic solvents over a wide range of solvent polarity. To simulate the physiological pH and gain, a better understanding of the solvent polarity effects inside a membrane-like environment, photophysical properties of two specific compounds **8c** and **12d** were studied within the micellar microenvironment of SDS in phosphate buffered saline (PBS) solution at pH 7.4.

*Absorbance, absorptivity, fluorescence and quantum yield data for coumarin-labeled depsipeptides **8a–f** and **12a–d***

The absorption and emission spectra of **8a–f** and **12a–d** in polar protic (methanol and PBS buffer) and polar aprotic (dichloromethane) solvents are shown in Figs. 1, 2, 3, 4, 5, 6 and wavelengths of absorption maxima (λ_{max}abs), fluorescence emission maxima (λ_{max}em), molar extinction coefficients (ε) and quantum yields (Φ) are listed in Tables 1, 2, 3.

Electron-donating substituents, methoxy (–OMe) and diethylamino (–NEt_2) at position 7 of the coumarin skeleton cause a bathochromic shift of the fluorescence emission maxima (λ_{max}em) and increase quantum yields. As expected 7-methoxycoumarin-3-ylcarbonyl-labeled depsipeptides **8b**, **8e**, **12a–c** showed high quantum yields in PBS buffer (Φ = 0.20–0.24), in MeOH (Φ = 0.27–0.52) and in CH_2Cl_2 (Φ = 0.26–0.57) relative to unsubstituted coumarin-labeled depsipeptides **8a** and **8d** (Φ = 0.004–0.006).

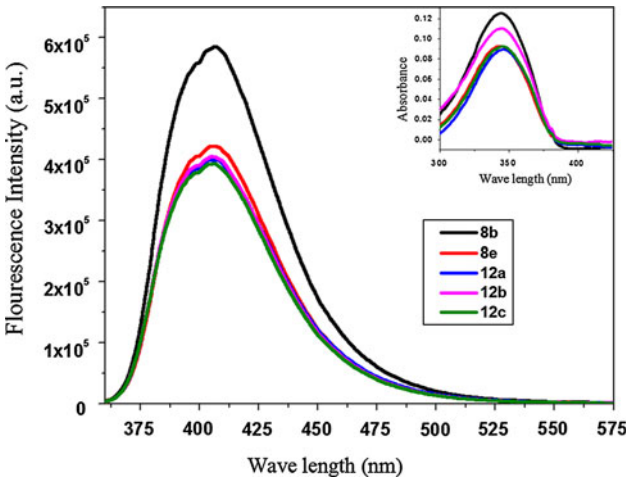


Fig. 1 Emission and absorption spectra (inset) of **8b**, **8e**, **12a–c** in PBS buffer at pH 7.4

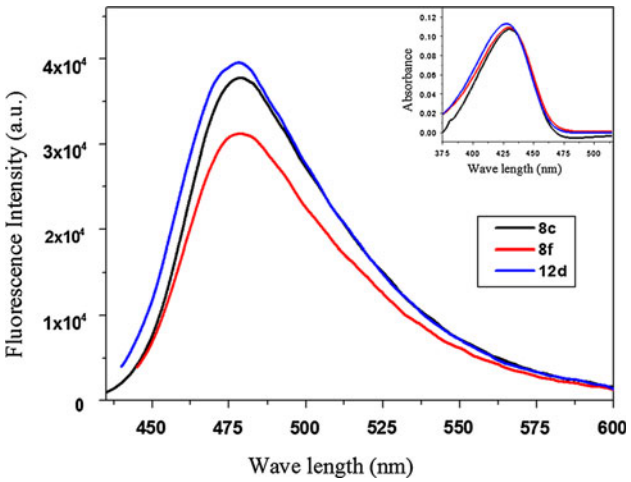


Fig. 2 Emission and absorption spectra (inset) of **8c**, **8f**, **12d** in PBS buffer at pH 7.4

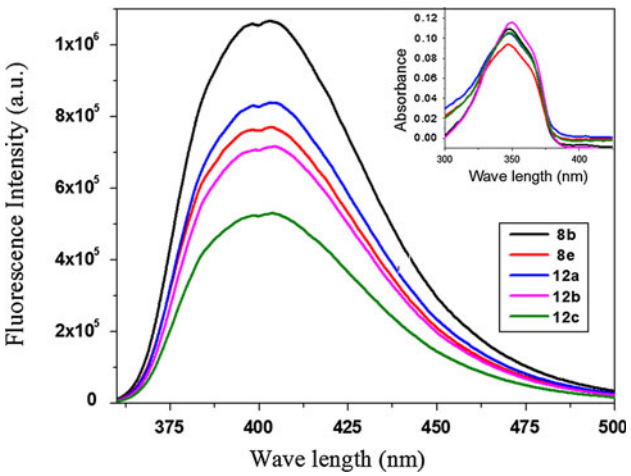


Fig. 3 Emission and absorption spectra (inset) of **8b**, **8e**, **12a–c** in MeOH

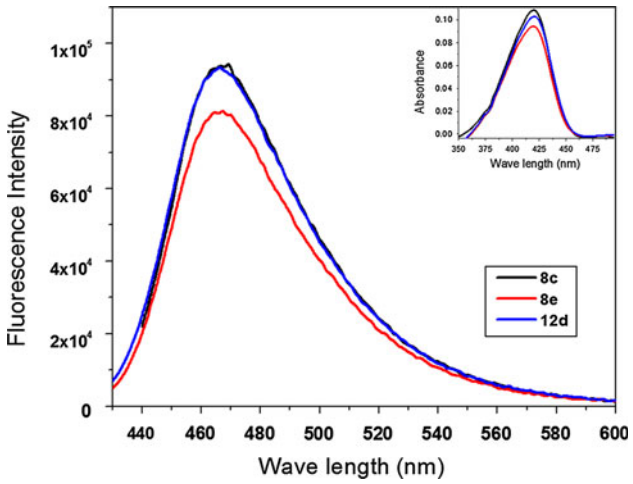


Fig. 4 Emission and absorption spectra (inset) of **8c**, **8f**, **12d** in MeOH

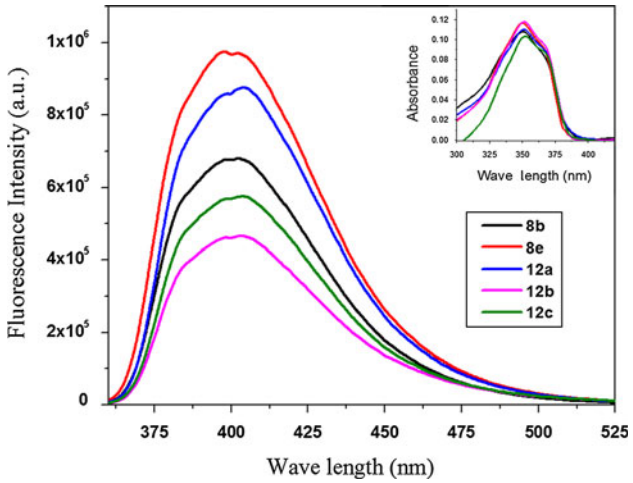


Fig. 5 Emission and absorption spectra (inset) of **8b**, **8e**, **12a–c** in DCM

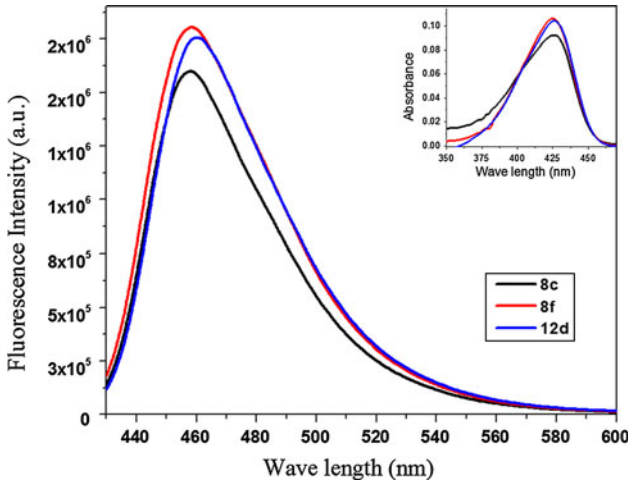


Fig. 6 Emission and absorption spectra (inset) of **8c**, **8f**, **12d** in DCM

Table 1 Absorption and emission data in PBS buffer

Entry	Comp. no.	λ_{max}abs (nm)	λ_{max}em (nm)	ε ($10^4 cm^{-1}M^{-1}$)	Φ (quantum yield)
1	**8a**	301	415.0	1.55	0.006
2	**8b**	343	407.0	2.78	0.239
3	**8c**	430	481.0	5.00	0.018
4	**8d**	301	419.0	1.91	0.006
5	**8e**	343	410.0	2.39	0.234
6	**8f**	430	480.0	4.56	0.014
7	**12a**	346	406.0	2.24	0.242
8	**12b**	345	405.0	2.30	0.197
9	**12c**	346	406.0	2.03	0.222
10	**12d**	428	480.0	6.65	0.020

The quantum yields of 7-methoxycoumarin-labeled depsipeptides are interpreted in terms of emission from an intramolecular charge transfer (ICT) excited state (Takadate et al. 2000).

The methoxycoumarin-labeled depsipeptides showed reductions in quantum yields with increased solvent polarity, particularly in PBS buffer (Figs. 1, 3, 5). Interestingly, the quantum yields of 7-*N*,*N*-diethylaminocoumarin-3-ylcarbonyl containing **8c**, **8f** and **12d** were significantly higher ($\Phi = 0.85–0.97$) in CH_2Cl_2 (polar aprotic solvent) and sharply decreased in polar protic solvents ($\Phi = 0.014–0.020$ in buffer and $\Phi = 0.029–0.052$ in MeOH) (Figs. 2, 4, 6). In polar aprotic solvent (CH_2Cl_2), diethylaminocoumarin-labeled depsipeptides fluoresce from a highly emissive ICT excited state but in polar protic solvent (PBS buffer, MeOH), rotation of the diethylamino group of the ICT excited state leads to a twisted intramolecular charge transfer (TICT) excited state from which non-radiative decay to the ground state occurs (Scheme 5) (Jones et al. 1985; Krishnamoorthy and Dogra 2000). The polar solvent stabilizes charge in the twisted zwitterionic TICT and consequently the interconversion of the ICT → TICT is facilitated by an increase of the solvent polarity (Senthilkumar et al. 2004). Increasing solvent polarity stabilizes the TICT exited state relatively to ground state, which explains the bathochromic shift in emission maxima (λ_{max}em) (Figs. 7, 8). The solvatochromic shifts are directly proportional to the dipole moments of the excited and ground state.

Photophysical properties of 7-*N*, *N*-diethylaminocoumarin-labeled depsipeptides 8c and 12d in SDS micellar microenvironment

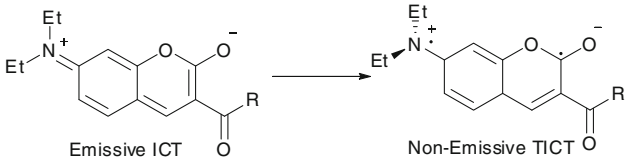
Potential applications of the coumarin-labeled depsipeptides were investigated by further photophysical study inside a membrane-like system. From the earlier experiments it was found that 7-*N*,*N*-diethylaminocoumarin-labeled depsipeptides

Table 2 Absorption and emission data in MeOH

Entry	Comp. no.	λ_{max}abs (nm)	λ_{max}em (nm)	ε ($10^4 cm^{-1}M^{-1}$)	Φ (quantum yield)
1	**8a**	291	411	1.62	0.004
2	**8b**	347.5	403	1.87	0.516
3	**8c**	420	469	4.80	0.029
4	**8d**	291	410	1.52	0.005
5	**8e**	346.5	404	2.51	0.451
6	**8f**	420	467	4.22	0.049
7	**12a**	347	403	2.41	0.413
8	**12b**	348.5	404	3.29	0.315
9	**12c**	347	404	3.67	0.274
10	**12d**	420	468	4.09	0.052

Table 3 Absorption and emission data in DCM

Entry	Comp. no	λ_{max}abs (nm)	λ_{max}em (nm)	ε ($10^4 cm^{-1}M^{-1}$)	Φ (quantum yield)
1	**8a**	291	409	1.42	0.006
2	**8b**	351	402	2.26	0.363
3	**8c**	427	458	4.86	0.849
4	**8d**	291	405	1.51	0.004
5	**8e**	350	402	3.05	0.566
6	**8f**	425	458	6.36	0.970
7	**12a**	351	404	2.94	0.494
8	**12b**	351	404	4.25	0.262
9	**12c**	352	404	3.68	0.360
10	**12d**	426	460	5.01	0.960



Scheme 5 ICT → TICT conversion

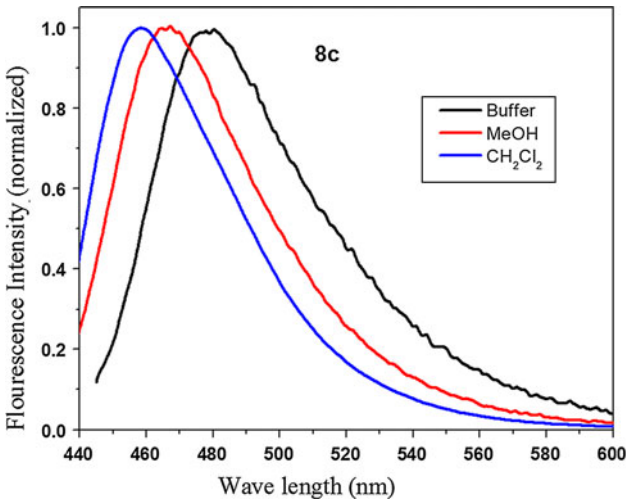


Fig. 7 Emission spectra of **8c** in PBS buffer, MeOH and DCM

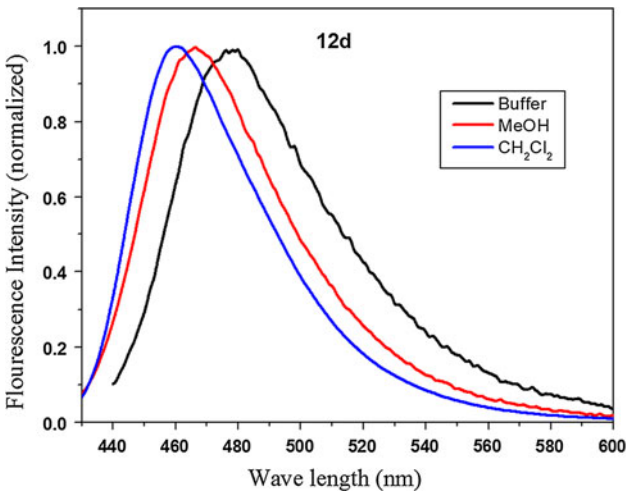


Fig. 8 Emission spectra of **12d** in PBS buffer, MeOH and DCM

are highly sensitive to the solvent polarity compared to the other coumarin-labeled depsipeptides. Two 7-*N*,*N*-diethylamino coumarin-labeled compounds **8c** and **12d** were chosen to study any change in the photophysical behavior inside a membrane-like environment. Having observed TICT for depsipeptides, our study was extended to a SDS microenvironment, since the TICT state of fluorophores is sensitive to the polarity, H-bonding ability and viscosity of the solvent (Rettig 1986; Cazeau-Dubroca et al. 1989). The steady-state absorption and fluorescence spectra of 7-*N*,*N*-diethylaminocoumarin-labeled depsidipeptide **8c** and depsitripeptide **12d** were recorded in PBS buffer solution at physiological pH 7.4 with different concentration of SDS. All data were taken with the SDS concentration (6.0–200 mM) kept well above the critical micellar concentration (CMC) of SDS micelles in PBS buffer (Fuguet et al. 2005), while the concentration of **8c** and **12d** were very low (8.63–11.15 μM); according to Poisson statistics this should allow not more than one labeled depsipeptide to interact with each SDS micelle (Tachiya 1975). The absorption spectra of **8c** and **12d** were unchanged at different SDS concentrations, but increasing SDS concentration resulted in a gradual increase in steady-state emission intensity of both **8c** and **12d** (Figs. 9, 10).

This result clearly indicates that there is interaction between the 7-*N*,*N*-diethylaminocoumarin-labeled depsipeptides and SDS micelle. To get a better understanding of the phenomena, the emission and absorption spectra of both the compounds were recorded in PBS buffer solution (SDS free condition) and in SDS solution made in PBS

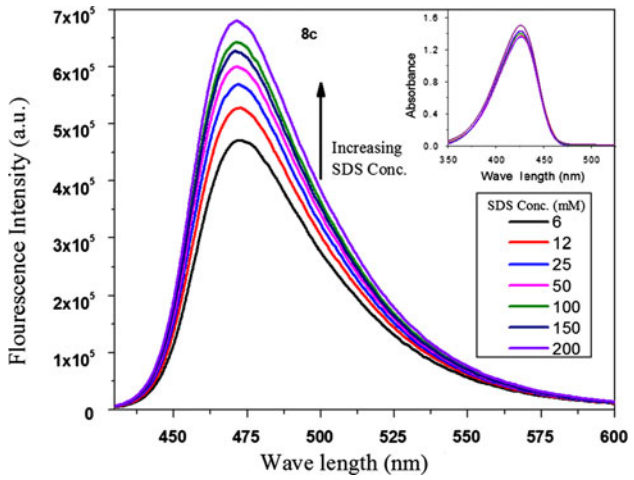


Fig. 9 Emission and absorption spectra (inset) of **8c** in PBS with different SDS conc

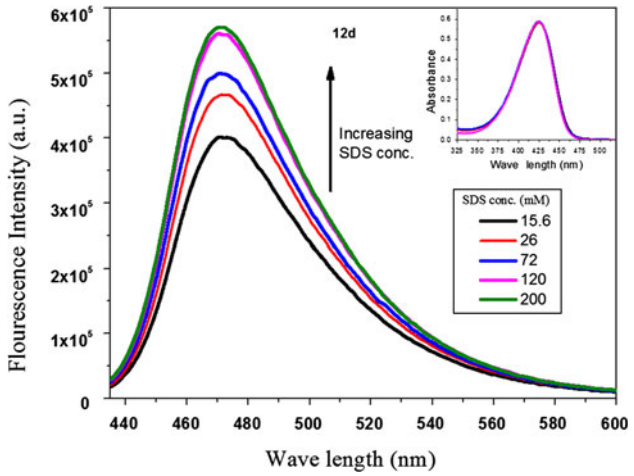


Fig. 10 Emission and absorption spectra (inset) of **12d** in PBS with different SDS conc

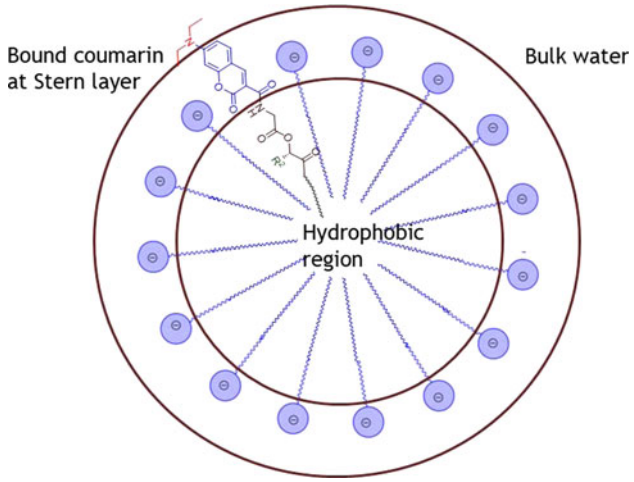


Fig. 11 Binding of coumarin moiety to the Stern layer

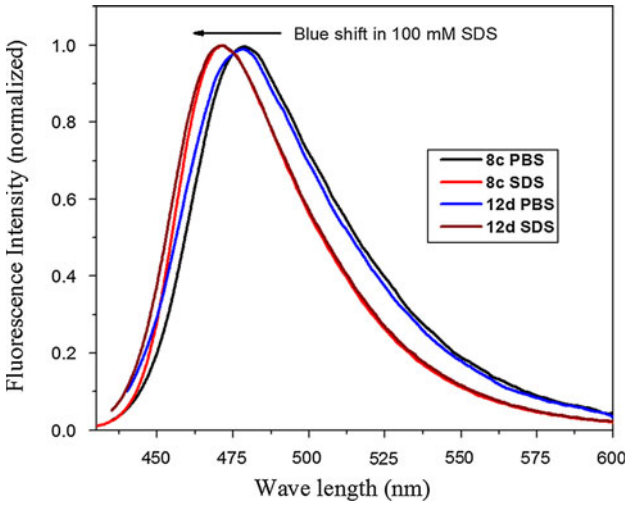


Fig. 12 Blue shift in the emission spectra **8c** and **12d** in PBS, and 100 mM SDS solution

buffer keeping the same 50 nM concentration in both cases. It was found that the quantum yields of **8c** and **12d** were significantly higher (around four times) even in very low 50 mM concentration of SDS solution ($\Phi = 0.073$ and 0.093, respectively) than in SDS free PBS buffer solution ($\Phi = 0.018$ and 0.020, respectively). The concentration-dependent enhancement of fluorescence by SDS can be explained by the diffusion of the 7-*N,N*-diethylaminocoumarin-labeled depsipeptides to the micellar Stern layer. The hydrophobic depsipeptide chains of **8c** and **12d** make them less soluble in a polar solvent such as water, thereby; they prefer the hydrophobic inner core of the micelle. The microenvironment around the 7-*N,N*-diehtylaminocoumarin moiety, however, is polar and it remains bound to Stern layer of the SDS micelle (Shirota et al. 2004; Dhenadhayalan et al. 2011) (Fig. 11). This hypothesis was further supported for both the compounds **8c** and **12d** by a $\lambda = 15$ nm blue shift of the emission maxima in SDS solution compared to PBS buffer solution (Fig. 12).

Since, TICT requires twisting of the donor diethylamino group (Scheme 5), an organized SDS Stern layer will restrict this twisting motion and retard TICT (Bhattacharyya and Chowdhury 1993). Conversion of ICT to non-emissive TICT state was restricted by simultaneous decreased polarity and increased confinement at the Stern layer of the SDS micelle resulting in an increased emission intensity with increasing SDS concentration. This significant change of the fluorescence property in the SDS micelle could make these compounds useful to monitor the reaction dynamics of a peptide-based drug inside a biological system.

Conclusion

In this paper, we have documented the synthesis and photophysical studies of novel coumarin-labeled depsipeptides. We believe that the present study complements on dye-labeled natural peptides and facilitated application of labeled peptidomimetics or depsipeptides. Variations of quantum yields in different solvents are reported and rationalized in terms of ICT–TICT excited states. 7-Methoxycoumarin-labeled depsipeptides are efficient for probes, since they exhibit high quantum yield values. Moreover, 7-diethylaminocoumarin-labeled depsipeptides, with their unique TICT state in polar protic solvents, are highly sensitive to solvent polarity, H-bonding ability and organized nature of the solvent medium such as an SDS micelle. Thus, 7-diethylaminocoumarin-labeled depsipeptides may be good candidates for the real-time monitoring of physiological processes. Their drastic change in fluorescence properties due to binding with the Stern layer of SDS micelle suggests potential utility in investigating reaction dynamics in biological membrane interfaces as well as for the monitoring of drug delivery.

Experimental section

General preparation of unprotected depsidipeptides 5**a**,**b**

4–Dimethylaminopyridine (1.2 mmol) was added to a stirred solution of Boc–Gly–Bt **2** (1.0 mmol) and α–hydroxycarboxylic acid **3a,b** (1.2 mmol) in dry THF (5.0 mL) at 4 °C. The reaction mixture was stirred for 4 h at room temperature until the reaction was completed by TLC [EtOAc-hexanes (1:2)]. The solvent was evaporated under reduced pressure, and the residue was taken into EtOAc (10.0 mL), washed with saturated citric acid solution (3 × 5 mL) and brine (5 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to yield the crude product as oil. Without isolation, Boc-deprotection was conducted by 4 N HCl solution in dry dioxane (5.0 mL) for 2 h. Boc-protected depsidipeptides **4a** (0.31 g, 1.0 mmol for **4a**) or **4b** (0.27 g, 1.0 mmol for **4b**) was dissolved in dry dioxane (2.0 mL) and cooled to 0 °C. Then dry 4 N HCl in dioxane (3.0 mL) was added into the solution through a syringe for 5 min at 0 °C. The mixture was stirred for another 2 h at 0 °C. The solvent was evaporated and the precipitate was washed with dry diethyl ether to yield unprotected depsidipeptides **5a**,**b** as hydrochloride salts.

(S)–2–(1–carboxy–2–phenylethoxy)–2–oxoethanaminium chloride (**5a**) White microcrystals (54 %), mp 150–152 °C; $[\alpha]_D^{23} = -29.0$ (c 1.0, CH_3OH); ^1H NMR (DMSO–d_6) δ 3.08 (dd, $J = 14.4$, 8.1 Hz, 1H), 3.19 (dd, $J = 14.2$, 4.2 Hz, 1H), 3.75–3.88 (m, 2H), 5.23–5.27 (m, 1H), 7.19–7.35 (m, 5H), 8.54 (br s, 3H); ^{13}C NMR (DMSO–d_6) δ 36.3, 73.9, 126.9, 128.4, 129.4, 136.1, 167.3, 169.7.

(S)–2–(1–carboxy–2–methylpropoxy)–2–oxoethanaminium chloride (**5b**) White microcrystals (79 %), mp 165–168 °C; $[\alpha]_D^{23} = -35.0$ (c 1.0, CH_3OH); ^1H NMR (DMSO–d_6) δ 0.91–0.98 (m, 6H), 2.14–2.24 (m, 1H), 3.78–4.00 (m, 2H), 4.83 (d, $J = 3.9$ Hz, 1H), 8.60 (br s, 3H); ^{13}C NMR (DMSO–d_6) δ 17.0, 18.6, 29.5, 77.5, 167.5, 169.9.

General preparation of *N*-coumarinoyl-labeled depsidipeptides **8a–f**

Hydrochloride salts of Gly-L-(*O*-Phe) **5a** (0.04 g, 0.16 mmol, 1.2 equiv) or Gly-L-(*O*-Val) **5b** (0.03 g, 0.16 mmol) and TEA (0.04 g, 0.32 mmol, 2.0 equiv) were dissolved in minimum amount of cold water (2 mL). Acetonitrile (6 mL) was added to this solution and cooled to 10 °C. A solution of *N*-acylcoumarinoyl-Bt **7a–c** (0.04–0.06 g, 1.0 equiv) was added and stirred for 1 h at 25 °C. The reaction mixture was monitored with TLC [EtOAc-Hexanes (1:2)]. After the completion of reaction, solvent was evaporated. 4 N HCl solution (5 mL) was added drop wise just to acidify the reaction mixture. The precipitate was filtered and washed with 1 N HCl (5 mL) and water (5 mL) to afford desired ***N*-**Coumarinoyl-labeled depsidipeptides **8a–f** (Note: for **8c** and **8f** acidification was done carefully just to neutralize the solution).

(S)–2–(2–(2–oxo–2H–chromene–3–carboxamido)acetoxy) –3–phenylpropanoic acid (**8a**) White microcrystals (86 %), mp 185–187 °C; $[\alpha]_D^{23} = -17.0$ (c 1.0, CH_3OH); ^1H NMR (DMSO-d_6) δ 3.07 (dd, $J = 14.6$, 8.0 Hz, 1H), 3.14 (dd, $J = 14.6$, 4.7 Hz, 1H), 4.17 (d, $J = 6.0$ Hz, 2H), 5.14 (dd, $J = 7.7$, 4.5 Hz, 1H), 7.14–7.30 (m, 5H), 7.45 (t, $J = 7.3$ Hz, 1H), 7.52 (d, $J = 8.1$ Hz, 1H), 7.77 (t, $J = 7.9$ Hz, 1H), 8.00 (dd, $J = 8.0$, 1.4 Hz, 1H), 8.89 (s, 1H), 9.07 (t, $J = 5.6$ Hz, 1H), 13.22 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 36.5, 41.3, 73.1, 116.2, 118.1, 118.4, 125.3, 126.7, 128.2, 129.4, 130.5, 134.4, 136.2, 148.3, 154.0, 160.3, 161.4, 169.0, 170.2; Anal. Calcd for $C_{21}H_{17}NO_7$: C, 63.80; H, 4.33, N, 3.54. Found: C, 63.51; H, 4.50; N, 3.51.

(S)–2–(2–(7–methoxy–2–oxo–2H–chromene–3–carboxamido) acetoxy)–3–phenylpropanoic acid (**8b**) White microcrystals (89 %), mp 184–187 °C; $[\alpha]_D^{23} = -20.0$ (c 1.0, CH_3OH); ^1H NMR (DMSO–d_6) δ 3.00–3.18 (m, 2H), 3.91 (s, 3H), 4.16 (d, $J = 5.7$ Hz, 2H), 5.13 (dd, $J = 7.7$, 4.7 Hz, 1H), 7.02–7.14 (m, 2H), 7.15–7.29 (m, 5H), 7.93

(d, $J = 8.7$ Hz, 1H), 8.84 (s, 1H), 9.01 (t, $J = 5.4$ Hz, 1H), 13.25 (br s, 1H);^{13}C NMR (DMSO–d_6) δ 36.4, 41.2, 56.3, 73.1, 100.3, 112.1, 113.8, 114.0, 126.7, 128.2, 129.4, 131.8, 136.2, 148.5, 156.4, 160.7, 161.7, 164.7, 169.1, 170.2 Anal. Calcd for $C_{22}H_{19}NO_8$: C, 62.12; H, 4.50, N, 3.29. Found: C, 61.97; H, 4.40; N, 3.24.

(S)–2–(2–(7–(diethylamino)–2–oxo–2H–chromene–3–carboxamido)acetoxy)–3–phenylpropanoic acid (**8c**) Yellow microcrystals (86 %), mp 191–193 °C; $[\alpha]_D^{23} = -39.0$ (c 1.0, CH_3OH); ^{1}H NMR (DMSO–d_6) δ 1.14 (t, $J = 6.9$ Hz, 6H), 3.00–3.17 (m, 2H),3.48 (q, $J = 6.9$ Hz, 4H), 4.14 (d, $J = 5.7$ Hz, 2H), 5.12 (dd, $J = 7.4$, 4.5 Hz, 1H), 6.63 (s, 1H), 6.81 (d, $J = 8.7$ Hz, 1H), 7.17–7.26 (m, 5H), 7.69 (d, $J = 9.0$ Hz, 1H), 8.65 (s, 1H), 8.98 (t, $J = 5.6$ Hz, 1H), 13.22 (br s, 1H); ^{13}C NMR (DMSO–d_6) δ 12.3, 36.4, 41.0, 44.4, 73.0, 95.8, 107.6, 108.5, 110.2, 126.7, 128.2, 129.4, 131.8, 136.2, 148.2, 152.6, 157.4, 161.6, 162.5, 169.3, 170.2; Anal. Calcd for $C_{25}H_{26}N_2O_7$: C, 64.37; H, 5.62, N, 6.01. Found: C, 64.21; H, 5.50; N, 6.08.

(S)–3–methyl–2–(2–(2–oxo–2H–chromene–3–carboxamido) acetoxy)butanoic acid (**8d**) White microcrystals (69 %), mp 137–140 °C; $[\alpha]_D^{23} = -26.0$ (c 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.03 (d, $J = 6.6$ Hz, 3H), 1.06 (d, $J = 8.1$ Hz, 3H), 2.26–2.40 (m, 1H), 4.28–4.46 (m, 2H), 5.04 (d, $J = 3.9$ Hz, 1H), 7.36–7.44 (m, 2H), 7.64–7.74 (m, 2H), 8.95 (s, 1H), 9.35 (t, $J = 6.0$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.2, 19.0, 30.2, 42.0, 77.4, 116.9, 117.8, 118.7, 125.6, 130.3, 134.6, 149.4, 154.8, 161.4, 162.5, 169.1, 173.1; Anal. Calcd for $C_{17}H_{17}NO_7$: C, 58.79; H, 4.93, N, 4.03. Found: C, 58.53; H, 4.87; N, 4.07.

(S)–2–(2–(7–methoxy–2–oxo–2H–chromene–3–carboxamido) acetoxy)–3–methylbutanoic acid (**8e**) White microcrystals (90 %), mp 182–185 °C; $[\alpha]_D^{23} = -24.0$ (c 1.0, CH_3OH); ^{1}H NMR (DMSO–d_6) δ 0.91 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 2.11–2.22 (m, 1H),3.90 (s, 3H), 4.22 (d, $J = 5.7$ Hz, 2H),4.76 (d, $J = 4.2$ Hz, 1H), 7.02–7.07 (m, 1H), 7.11 (d, $J = 2.4$ Hz, 1H), 7.91 (dd, $J = 8.6$, 2.9 Hz, 1H), 8.86 (d, $J = 2.7$ Hz, 1H), 9.06 (t, $J = 5.6$ Hz, 1H), 13.11 (br s, 1H); ^{13}C NMR (DMSO–d_6) δ 16.9, 18.6, 29.4, 41.2, 56.3, 76.7, 100.3, 112.1, 113.7, 114.0, 131.7, 148.5, 156.3, 160.7, 161.8, 164.7, 169.3; 170.3, Anal. Calcd for $C_{18}H_{19}NO_8$: C, 57.29; H, 5.08, N, 3.71. Found: C, 57.20; H, 5.08; N, 3.63.

(S)–2–(2–(7–(diethylamino)–2–oxo–2H–chromene–3–carboxamido)acetoxy)–3–methylbutanoic acid (**8f**) Yellow microcrystals (92 %), mp 174–176 °C; $[\alpha]_D^{23} = -19.0$ (c 1.0, CH_3OH); ^{1}H NMR (DMSO–d_6) δ 0.91 (d, $J = 6.6$ Hz, 3H), 0.95 (d, $J = 6.6$ Hz, 3H), 1.14 (t, $J = 7.1$ Hz, 6H), 2.12–2.19 (m, 1H), 3.48 (q, $J = 7.0$ Hz, 4H), 4.20 (d, $J = 6.0$ Hz, 2H), 4.75 (d, $J = 4.2$ Hz, 1H), 6.61 (d, $J = 2.1$ Hz, 1H), 6.79–6.83 (m, 1H), 7.69 (d, $J = 9.0$ Hz, 1H), 8.67 (s, 1H), 9.02 (t, $J = 5.7$ Hz, 1H), 13.07 (br s, 1H); ^{13}C NMR (DMSO–d_6) δ 12.3,16.9, 18.5, 29.4, 41.1, 44.4, 76.6, 95.9, 107.5, 107.6, 110.2, 131.7, 148.1, 152.6, 157.3, 162.6, 169.5, 170.3, Anal. Calcd for $C_{21}H_{26}N_2O_7$: C, 60.28; H, 6.26, N, 6.69. Found: C, 59.73; H, 6.12, N, 7.45.

General preparation of unprotected depsidipeptides **11a–c**

A solution of EDCI (1.10 g, 5.80 mmol, 1.0 equiv.) was added to a stirred solution of **4a**, and **4c** (1.0 equiv.) and benzotriazole (0.69 g, 5.80 mmol) in CH_2Cl_2 (50 mL) at 0 °C. The reaction mixture was stirred for 16 h at room temperature. Then reaction was quenched with water. The reaction mixture was washed with 20 % citric acid solution (3 × 10 mL), saturated Na_2CO_3 (3 × 15 mL), water (2 × 10 mL) and brine (15 mL), dried over $MgSO_4$ and solvent was evaporated under reduced pressure to yield the desired product **9a–b**. L-Phenylalanine (0.50 g, 3.0 mmol, 1.5 equiv) or L-methionine (0.22 g, 1.5 mmol) and TEA (300 mg, 3.0 mmol, 1.5 equiv) were dissolved in minimum amount of cold water (5 mL). Acetonitrile (10 mL) was added to the solution and cooled to 10 °C. A solution of **9a–b** (1.0 equiv., 2.0 mmol) in acetonitrile (5 mL) was added and stirred for 2 h at 25 °C. The reaction mixture was monitored with TLC [EtOAc-Hexanes (1:2)]. After the completion of the reaction, solvent was evaporated. The residue was dissolved in CH_2Cl_2 (30 mL) and washed with saturated citric acid solution (4 × 10 mL), water (10 mL) and brine (10 mL), dried over $MgSO_4$ and evaporated to give **10a–c**. Crude **10a–c** (1.0 mmol) was dissolved in dry dioxane (2 mL) and cooled to 0 °C. Then dry 4 N HCl in dioxane (3 mL) was added into the solution through a syringe for 5 min at 0 °C and stirred for another 2 h at 0 °C. The solvent was evaporated and the precipitate was washed with dry diethyl ether to give the desired product **11a–c** as white microcrystals.

(S)–2–((S)–2–(2–aminoacetoxy)–4–methylpentanamido)–3–phenylpropanoic acid hydrochloride (**11a**) White microcrystals (42 %), mp 175–178 °C; $[\alpha]_D^{23} = -43.0$ (c 1.0, CH_3OH); ^{1}H NMR (DMSO–d_6) δ 0.82 (d, $J = 5.1$ Hz, 3H) 0.84 (d, $J = 4.5$ Hz, 3H) 1.40–1.64 (m, 3H), 2.94 (dd, $J = 13.8$, 9.0, 1H), 3.07 (dd, $J = 13.7$, 5.0 Hz, 1H), 3.70–3.90 (m, 2H), 4.40–4.56 (m, 1H), 5.04 (dd, $J = 8.7$, 3.5 Hz, 1H), 7.18–7.36 (m, 5H), 8.34–8.46 (br s, 3H), 8.52 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (DMSO–d_6) δ 21.5, 23.1, 23.8, 24.5 36.5, 53.2, 73.0, 126.5, 128.2, 129.2, 137.5, 167.1, 168.9, 172.5.

(S)–2–((S)–2–(2–aminoacetoxy)–4–methylpentanamido)–4–(methylthio)butanoic acid hydrochloride (**11b**) White microcrystals (30 %), mp 104–107 °C; $[\alpha]_D^{23} = -32.0$ (c 1.0, CH_3OH); ^{1}H NMR (DMSO–d_6) δ 0.84 (d, $J = 5.7$ Hz,

3H); 0.86 (d, $J = 6.3$ Hz, 3H); 1.44–1.74 (m, 3H), 1.80–2.00 (m, 5H), 2.34–2.45 (m, 2H), 3.70–3.93 (m, 2H), 4.23–4.32 (m, 1H), 5.01 (dd, $J = 9.5$, 4.1 Hz, 1H), 8.40–8.62 (m, 4H); ^{13}C NMR (DMSO–d_6) δ 14.7, 21.6, 23.2, 23.8, 29.8, 30.7, 50.8, 73.1, 167.2, 169.1, 172.9.

2–(((S)–1–(((S)–1–carboxy–3–(methylthio)propyl)amino)–1–oxo–3–phenylpropan–2–yl)oxy)–2–oxoethanaminium chloride (**11c**) White microcrystals (35 %), mp 180–182 °C; $[\alpha]_D^{23} = -21.0$ (c 1.0, CH_3OH); ^{1}H NMR (DMSO–d_6) δ 1.80–2.02 (m, 2H), 2.04 (s, 3H), 2.32–2.48 (m, 2H), 2.99 (dd, $J = 14.3$, 8.9 Hz, 1H), 3.14 (dd, $J = 14.4$, 3.6 Hz, 1H), 3.72 (d, $J = 17.3$, 1H), 3.89 (d, $J = 18.2$, 1H), 4.31–4.39 (m, 1H), 5.29 (dd, $J = 8.1$, 3.6 Hz, 1H), 7.20–7.36 (m, 5H), 8.65 (d, $J = 7.8$ Hz, 1H); ^{13}C NMR (DMSO–d_6) δ 14.6, 29.7, 30.6, 37.1, 50.9, 75.0, 126.7, 128.3, 129.4, 136.3, 167.1, 168.2, 172.9.

General preparation of *N*-coumarinoyl-labeled depsitripeptides **12a–d**

Hydrochloride salts of **11a–c** (0.050-0.055 g, 0.11 mmol, 1.1 equiv.) and TEA (0.04 g, 0.22 mmol, 2.0 equiv.) were dissolved in minimum amount of cold water (1 mL). Acetonitrile (4 mL) was added to the solution and cooled to 10 °C. A solution of *N*-coumarinoyl-Bt **7a–c** (0.04–0.05 g, 1.0 equiv.) was added and stirred for 1 h at 25 °C. The reaction mixture was monitored with TLC [EtOAc-Hexanes (1:2)]. After the completion of reaction, solvent was evaporated. 4 N HCl solution (5 mL) was added drop wise just to acidify the reaction mixture. The precipitated was filtered and washed with 1 N HCl (5 mL) and water (5 mL) to afford desired ***N*-**Coumarinoyl-labeled depsidipeptides **12a–d**. (Note: for **12d** acidification was done carefully just to neutralize the solution, at neutralization point thick precipitate was formed and it was filtered off). The crude compound was recrystallized from EtOAc-hexanes.

(S)–2–((S)–2–(2–(7–methoxy–2–oxo–2H–chromene–3–carboxamido)acetoxy)–4–methylpentanamido)–3–phenylpropanoic acid (**12a**) White microcrystals (88 %), mp 160–163 °C; $[\alpha]_D^{23} = -22.0$ (c 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.86 (d, $J = 6.3$ Hz, 3H), 0.87 (d, $J = 6.0$ Hz, 3H), 1.54–1.66 (m, 3H), 3.16 (dd, $J = 13.8$, 8.4 Hz, 1H), 3.32 (dd, $J = 14.3$, 5.3 Hz, 1H), 3.92 (s, 3H), 4.16–4.20 (m, 2H), 4.76–4.88 (m, 1H), 5.27 (t, $J = 6.5$ Hz, 1H), 6.85 (d, $J = 2.4$ Hz, 1H), 6.95 (dd, $J = 8.7$, 2.4 Hz, 1H), 7.14–7.30 (m, 6H), 7.59 (d, $J = 8.7$ Hz, 1H), 8.75 (s, 1H), 9.31 (t, $J = 5.9$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 23.3, 24.7, 37.3, 40.6, 42.5, 53.7, 56.3, 73.8, 100.5, 112.4, 113.6, 114.5, 127.2, 128.7, 129.5, 131.6, 136.4, 149.4, 157.0, 161.8, 163.7, 165.5, 168.5, 170.8, 173.4; HRMS, $[M + Na]^+$: Calcd for $[C_{28}H_{30}N_2O_9Na]^+$: 561.1844. Found: 561.1847.

(S)–2–((S)–2–(2–(7–methoxy–2–oxo–2H–chromene–3–carboxamido)acetoxy)–4–methylpentanamido)–4–(methylthio)-butanoic acid (**12b**) White microcrystals (92 %), mp 182–184 °C; $[\alpha]_D^{23} = -17.0$ (c 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.92 (d, $J = 6$ Hz, 3H), 0.94 (d, $J = 6.3$ Hz, 3H), 1.65–1.82 (m, 3H), 2.10 (s, 3H), 2.10–2.31(m, 2H), 2.55–2.61 (m, 2H), 3.92 (s, 3H), 4.17–4.35 (m, 2H), 4.60–4.69 (m, 1H), 5.35 (t, $J = 6.5$ Hz, 1H), 6.85 (d, $J = 2.4$ Hz, 1H), 6.95 (dd, $J = 8.7$, 2.4 Hz, 1H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.65 (d, $J = 8.7$ Hz, 1H), 8.83 (s, 1H), 9.38 (t, $J = 5.6$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.4, 21.6, 23.2, 24.6, 30.2, 30.8, 40.4, 42.4, 51.8, 56.1, 73.5, 100.3, 112.2, 113.3, 114.3, 131.5, 149.3, 156.9, 161.7, 163.8, 165.4, 168.3, 171.1, 173.7; HRMS, $[M + Na]^+$: Calcd for $[C_{28}H_{30}N_2O_9Na]^+$: 545.1564. Found: 545.1562.

(S)–2–((S)–2–(2–(7–methoxy–2–oxo–2H–chromene–3–carboxamido)acetoxy)–3–phenylpropanamido)–4–(methylthio)butanoic acid (**12c**) White microcrystals (83 %), mp 170–172 °C; $[\alpha]_D^{23} = -43.0$ (c 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 3H), 2.02–2.25 (m, 4H), 3.14 (dd, $J = 14.7$, 4.5 Hz, 1H), 3.24 (dd, $J = 14.3$, 5.2 Hz, 1H), 3.95 (s, 3H), 4.09 (dd, $J = 17.4$, 5.7 Hz, 1H), 4.32 (dd, $J = 17.4$, 5.7 Hz, 1H), 4.52–4.62 (m, 1H), 5.55 (t, $J = 4.7$ Hz, 1H), 6.80–7.14 (m, 7H), 7.39 (d, $J = 7.8$ Hz, 1H), 7.67 (d, $J = 8.7$ Hz, 1H), 8.69 (s, 1H), 9.39 (t, $J = 5.4$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 15.4, 30.0, 30.6, 37.4, 42.7, 52.0, 56.4, 74.6, 100.6, 112.5, 113.5, 114.6, 127.0, 128.4, 130.0, 131.8, 135.5, 149.5, 157.1, 162.0, 164.3, 165.7, 167.7, 169.9, 173.7; Anal. Calcd for $C_{27}H_{28}N_2O_9S$: C, 58.26; H, 5.07, N, 5.03. Found: C, 57.97; H, 5.20; N, 4.60.

(S)–2–((S)–2–(2–(7–(diethylamino)–2–oxo–2H–chromene–3–carboxamido)acetoxy)–4–methylpentanamido)–3–phenylpropanoic acid (**12d**) Yellow microcrystals (90 %), mp 162–165 °C; $[\alpha]_D^{23} = -25.0$ (c 1.0, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 0.83 (s, 3H), 0.91 (s, 3H), 1.23(t, $J = 6.9$, 6H), 1.57 (s, 3H), 3.17(dd, $J = 14.2$, 8.4, 1H), 3.33 (dd, $J = 14.2$,4.5,1H) 3.44 (d, J = 6.9 4H), 4.11 (d, $J = 4.8$ Hz, 2H), 4.72–4.85 (m, 1H), 5.25 (br s, 1H), 6.46 (s, 1H), 6.45 (d, $J = 8.4$ Hz, 1H), 7.10–7.28 (m, 6H), 7.35–7.45 (m, 2H), 8.56 (s, 1H), 9.37 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.7, 21.9, 23.3, 24.7, 37.3, 40.5, 42.7, 45.4, 54.3, 73.6, 96.7, 108.5, 110.5, 127.1, 128.7, 129.5, 131.9, 136.6, 149.0, 153.3, 158.1, 162.8, 165.2, 168.7, 171.3, 172.8, HRMS, $[M + Na]^+$: Calcd for: $[C_{31}H_{37}N_2O_8Na]^+$: 602.2473. Found: 602.2467.

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Conflict of interest The authors declare that they have no conflict of interest.

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