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Synthesis of function-oriented 2-phenyl-2*H*-chromene derivatives using L-pipecolinic acid and substituted guanidine organocatalysts

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ABSTRACT

Organocatalytic domino oxa-Michael/aldol reactions between salicylaldehyde with electron deficient olefins are presented. We screened guanidine, 1,1,3,3-tetramethylguanidine (TMG) and L-pipecolinic acid as organocatalysts for this transformation. 3-Substituted 2-phenyl-2*H*-chromene derivatives are synthesized with high yields and with poor enantioselectivity (5–17% ee) using L-pipecolinic acid while TMG works well with cinnamaldehyde without using co-catalyst. These 3-substituted-2-phenyl-2*H*-chromene derivatives are further derivatized to synthesize triazole and biotin-containing chromene derivatives, to facilitate purification of protein targets.

For our ongoing chemical biology projects we are interested in developing new compounds that interact with developmentally important receptor-mediated pathways such as the TGF-β pathway, acting as antagonist or agonist.[1,2] For this purpose, we described a chemical genetic approach by testing a library of 2-substituted-2*H*-chromene derivatives for their bioactivity on developing zebrafish embryos. The zebrafish embryo provides an ideal vertebrate model system for in vivo small molecule screens because of its optical transparency, accessibility during embryonic development, and permeability to small molecules. We synthesized a small library of 2-substituted-2*H*-chromene derivatives that were screened for bioactivity using the zebrafish model.[3] Compound BT7 (**1**) (Fig. 1) was found to modulate a specific relevant pathway, namely p-SAPK/JNK, which is known to be downstream of TGF-β, and can mediate Smad-independent signaling.[3]

Our next aim is to isolate BT7-interacting protein(s) by attaching a biotin moiety, which would facilitate purification of the protein target.

For this purpose, we sought to develop function-oriented BT7 analogues and, finally, to attach biotin using functional group transformations. Domino or cascade reactions that involve the formation of multiple stereo centers comprise one-pot a rapidly growing research field with respect to the synthesis of small molecules with complex architectures.[4] However, the development of catalytic diastero- and enantioselective domino reactions is still a challenging task.[5a–c] In this context, the development of organocatalytic asymmetric domino reactions has been pursued. Nitrochromenes are versatile synthetic intermediates in organic synthesis owing to the various possible transformations of the nitro group into other useful functional groups. Useful synthetic methods reported for the preparation of 3-nitro- and 3-formyl-2-phenyl-2*H*-chromene are the domino Michael/aldol reactions of salicylaldehyde with β-nitrostyrene and cinnamaldehyde.[5d–g] Basically this involves L-proline and L-proline-based catalysts, along with a co-catalyst used for the above-mentioned purpose. However, this gives moderate to good yields and poor enantioselectivity.[6] Based on the development of these reactions and our research interest of finding catalytic domino reactions that give our function-oriented BT7 analogues (**2**, **3,** and **4**), we envisioned a reaction between differently substituted salicylaldehyde with β-nitrostyrene and cinnamaldehyde using simple catalyst like guanidine, 1,1,3,3-tetramethylguanidine (TMG)[7] and pipecolinic acid. We choose these catalysts to improve selectivity, yield, reaction time, and to use an alternative protocol in which the absence of co-catalyst can provide a better yield.[8]

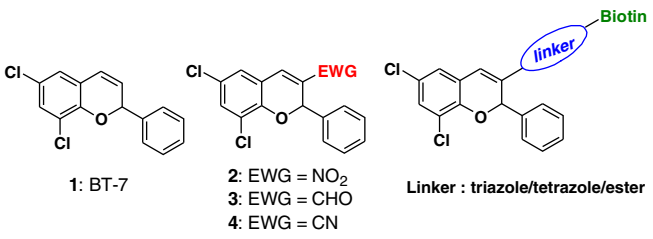

Figure 1.

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In an initial catalyst screen for the reaction between salicylaldehyde **5a** and β-nitrostyrene **6**, we found to our delight that amines **7**, **8,** and **9** were catalysts for the domino Michael/aldol reaction. In further experiments, other factors that influence the reaction were thoroughly investigated such as solvent, catalyst loading, and reaction temperature. In the beginning of our study β-nitrostyrene **6** and salicylaldehyde **5a** were taken as the model substrates. The results are listed in Table 1. Catalyst **9** gave 81% yield of **2a** at 80 °C in toluene with poor enantioselectivity (5% ee).

After successfully optimizing the catalyst **9**, solvent (toluene), temperature (80 °C) and reaction time (24 h), we further explored to generalize this reaction. For this purpose we used substituted salicylaldehyde as substrates. Table 2 shows a number of examples of this chemistry. Significant variation in the electronic and steric features of salicylaldehydes is tolerated for the L-pipecolinic acid **9** catalyzed cascade process. The reaction between 3,5-dichlorosalicylaldehyde **5b** with β-nitrostyrene **6** in the presence of 20 mol % of L-pipecolinic acid **9** furnished our target BT7 nitro chromene derivative **2b** in 76% yield with poor enantioselectivity ee 2% (Table 2, entry 2). We then screened the 5-substituted salicylaldehydes, 5-chloro (**5c**), 5-bromo (**5d**) and β-nitrostyrene **6** under optimized conditions, which gave the corresponding chromene derivatives **9c** and **9d** in 79%, and 80% yields with poor enantioselectivity 17% and 18% ee, respectively (Table 2, entries 3 and 4). 5-hydroxy salicylaldehyde 5e gave the corresponding nitrochromene derivative in moderate yield 60% with 13% ee (Table 2, entry 5).

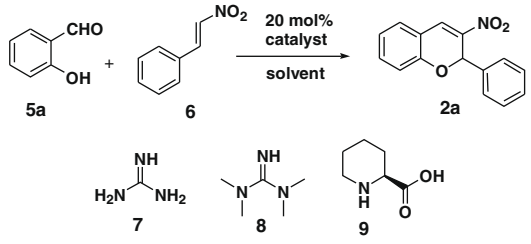
The catalytic activity of **9** was further examined with the 2-amino-benzaldehyde **10** and β-nitrostyrene **6** under the same reaction conditions and gave the 3-nitro-2-phenyl-1,2-dihydro-quinoline[10] **11** in 85% yield and 26% ee (Scheme 1).

Having succeeded in synthesizing the BT7 nitrochromene derivative **2b**, our attention was next focused on the attachment of biotin. Yao and co-workers reported the [3+2] cycloaddition of 3-nitro-2-phenyl-2*H*-chromene with sodium azide under catalyst free conditions at 80 °C in DMSO.[11] Following this procedure we synthesized the BT7 triazole **12** by using 6,8-dichloro-3-nitro-2-phenyl-2*H*-chromene **2b** and sodium azide at 80 °C in DMSO in 82% yield. We next examined the feasibility of attaching biotin to the BT7 triazole analogue **12** via triazole moiety using DCC under various reaction conditions, however, we did not observe the expected product formation (Scheme 2).

As we failed to make amide linkage of d-biotin with **12**, we then decided instead of acid–amine coupling, alkyne-azide click chemistry could be implemented. Keeping this idea in mind we planned to synthesize **14**. According to Scheme 3 and **14** could be synthesized from Michael adduct **3**.

To synthesize compound **3**, we screened the catalyst, **7, 8, 9,** and L-proline with 3,5-dichlorosalicylaldehyde **5b** and cinnamaldehyde **13** as substrates. To our surprise, the reaction proceeded only with **8** and gave **3** in 78% yield.[12] After 72 h with L-proline only 10% conversion was observed. Reaction of **5b** with **13** in the presence of L-pipecolinic acid and **7** was carried out but this failed to proceed at all even after 72 h. It is very interesting to note that in the case of β-nitrostyrene, all four catalysts gave 3-nitro-substituted chromene derivatives in moderate to good yields, but in the case of cinnamaldehyde, only catalyst **8** (TMG) gave 3-formyl substituted chromene derivatives. The detailed mechanism of this transformation is cur-

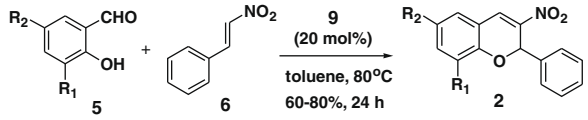
Table 1
Catalyst screen for the amine-catalyzed enantioselective domino reactions between **5a** and **6**

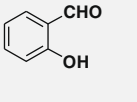
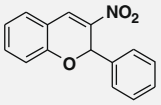
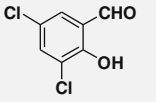
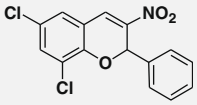
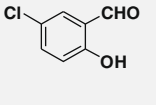
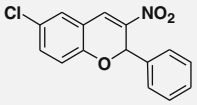
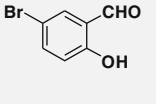
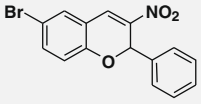
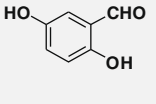
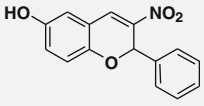


Entry	Catalyst	Reaction condition	Yield[a,b] (%)
1	7	Toluene, rt, 5 d	11
2	7	Toluene, 80 °C, 48 h	68
3	8	Toluene, rt, 5 d	30
4	8	Toluene, 80 °C, 48 h	75
5	**9**	**Toluene, 80°C, 24 h**	**81 (5%, ee)**[b]

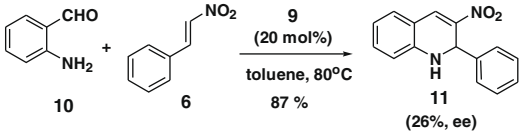
[a] Reaction with **5** (1 mmol), **6** (1.2 mmol) in 2 ml toluene, isolated yield after column purified.
[b] Determined by chiral-HPLC analyses using chiralpak AD.

Table 2
Scope of the domino Michael/aldol reaction between various salicylaldehydes with *E*-β-nitrostyrene[9] **6**[a]

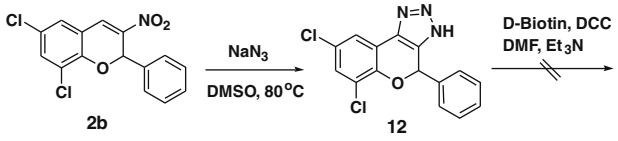


Entry	Aldehyde (**5a–e**)	Product (**2a–e**)	Yield[b] (%)	ee[c] (%)
1			81	5
2			76	2
3			79	17
4			80	16
5			60	13

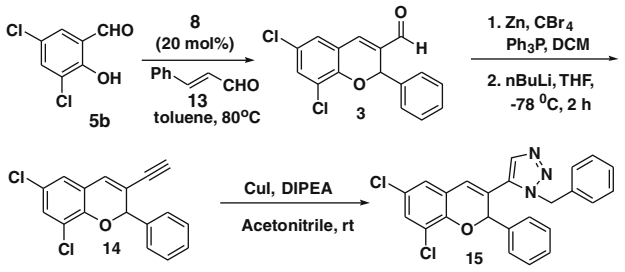
[a] Reaction with **5** (1 mmol), **6** (1.2 mmol) and catalyst (20 mol %) in toluene.
[b] Isolated yield of pure copmpound.
[c] Determined by chiral-HPLC analyses using chiralpak AD.



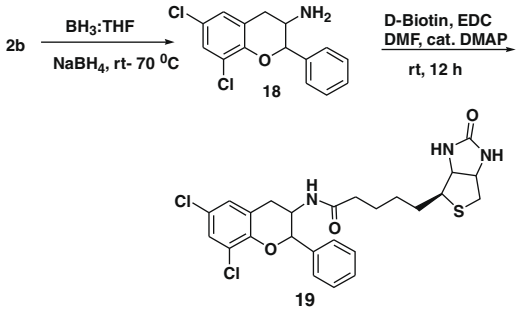
Scheme 1.



Scheme 2.



Scheme 3.



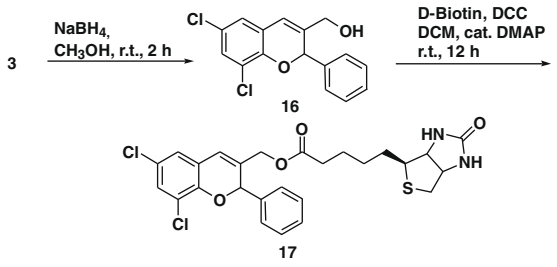
Scheme 5.

rently being investigated in our laboratory. Aldehyde **3** was further derivatized to **14**. Compound **3** was treated with triphenylphosphine, CBr_4 in Zn, resulting in dibromo derivative, which was further treated with *n*-BuLi in −78 °C to furnish alkyne **14**.[13] Before doing click chemistry with d-biotin azide, we initially attempted a model reaction, using simple benzyl azide in the presence of CuI and DIPEA, as base and successfully achieved the triazole **15** (Scheme 3).[14] After obtaining the triazole derivative we also planned to synthesize ester and amide linkage of d-biotin. Thus, the aldehyde **3** was reduced by sodium borohydride in methanol, which produced the corresponding alcohol **16** in 92% yield.[15]

We then esterified this alcoholic derivative of BT7 **16** with d-biotin using DCC, DMAP in dichloromethane and produced the d-biotin-attached BT7 analogue **17** in 74% yield (Scheme 4).[15] After synthesizing **17**, we focused to synthesize d-biotin-attached amide (Scheme 5).[16] It is interesting to note that we tried with many reducing agents (but not by enzymatic process) to reduce only nitro group to amine keeping the vinylic double bond intact in the compound **2b** but failed. However, the nitro compound **2b** was reduced with BH_3/THF to form the amine **18** which was isolated by crystallization using ether–hexane system in 82% yield. We observed both double bond and nitro group were reduced.[8e] The amine **18** was coupled with biotin using EDCI and DMAP in DMF to give BT7 biotin amide **19**, which was purified by crystallization using ether and hexanes in 78% yield.[16]

After synthesizing of BT7 nitro **2b** and aldehyde **3**, we next turned our attention to functionalize BT7-carbonitrile **4**. For this purpose the reaction between **5b** and phenyl-acrylonitrile was executed with catalysts **7**, **8**, **9,** and L-proline, to our surprise in all cases we failed to achieve the synthesis of compound **4**. From this observation, it might be possible that, Michael acceptors playing crucial role in this domino oxa-Michael/aldol reaction, because in the case of β-nitrostyrene, all four catalysts worked well, for cinnamaldehyde only catalyst **8** worked, for acrylonitrile, L-proline worked (data not shown), but in the case of cinnamonitrile none of the four catalysts worked.

In summary, we report an organocatalytic domino oxa-Michael/aldol reaction that gives chromenes in high yields without using co-catalyst and in less reaction time. Hence, the reaction constitutes a simple catalytic high yield entry to pharmaceutically valuable 2*H*-chromene and 1,2-dihydro-quinoline derivatives. We successfully attached the biotin moiety to our lead compound BT7. For the first time, we observed the catalytic activity of L-pipecolinic acid to synthesize 3-substituted 2-phenyl chromene derivatives with poor enantioselectivities (5–117% ee). We are in the process of developing chiral L-pipecolinic acid-based and TMG-based catalysts to improve activity, improve stereoselectivity in various organic transformations and other enantioselective domino reactions. The detailed biological study of these compounds as possible TGF-β pathway modulators is ongoing in our laboratory.



Scheme 4.

Acknowledgments

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Supplementary data

Supplementary data (copies of ^1H, ^{13}C NMR and mass spectra) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.02.143.

References and notes

1. MacRae, C. A.; Peterson, R. T. *Chem. Biol.* **2003**, *10*, 901–908.
2. Peterson, R. T.; Link, B. A.; Dowling, J. E.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 12965–12969.
3. Torregroza, I.; Evans, T.; Das, B. C. *Chem. Biol. Drug. Des.* **2009**, *73*, 339–345.
4. (a) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006. p. 672; (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115; (c) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem., Int. Ed.* **2006**, *45*, 7134; (d) Guo, H.; Ma, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 354; (e) Pellieser, H. *Tetrahedron* **2006**, *62*, 2143; (f) Ramon, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (g) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1570–1581.
5. (a) Rios, R.; Sundén, H.; Vesely, J.; Zhao, G.-L.; Dziedzic, P.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 1028; (b) Penon, O.; Carlone, A.; Mazzanati, A.; Locatelli, M.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem. Eur. J.* **2008**, *14*, 4788; (c) Enders, D.; Wang, C.; Bats, D. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 3579; (d) Luo, S.-P.; Li, Z.-B.; Wang, L.-P.; Guo, Y.; Xia, A.-B.; Xu, D.-Q. *Org. Biomol. Chem.* **2009**, *7*, 4539–4546; (e) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354–10355; (f) Li, H.; Wang, J.; E-Nunu, T.; Zu, L.; Jiang, W.; Wei, S.; Wang, W. *Chem. Commun.* **2007**, 507–509; (g) Sunden, H.; Rios, R.; Ibrahem, I.; Zhao, G-L.; Eriksson, L.; Córdova, A. *Adv. Synth. Catal.* **2007**, *349*, 827–832; (h) Sundén, H.; Ibrahem, I.; Zhao, G.-L.; Eriksson, L.; Córdova, A. *Chem Eur. J* **2007**, *13*, 574; (i) Ibrahem, I.; Sundén, H.; Rios, R.; Zhao, G.-L.; Córdova, A. *Chimia* **2007**, *61*, 219.
6. (a) Xu, D.-Q.; Wang, Y.-F.; Luo, S.-P.; Zhang, S.; Zhong, A.-G.; Chen, H.; Xu, Z.-Y. *Adv. Synth. Catal.* **2008**, *350*, 2610–2616; (b) Karthikeyan, T.; Sankararaman, S. *Tetrahedron: Asymmetry* **2008**, *19*, 2741–2745.

7. (a) Yanqing, P.; Gonghua, S.; Feifei, H. *Monatsh. Chem.* **2005**, *136*, 727–731; (b) Nirmal, K. P.; Hitoshi, U.; Masahiro, T. *Tetrahedron Lett.* **2007**, *48*, 8700–8703; (c) Junjie, H.; Yanfen, X.; Yingpeng, S.; Xuegong, S.; Xinfu, P. *Catal. Commun.* **2008**, *9*, 2077–2079.
8. (a) Carrie, E. A.; Melissa, M. V.; Scott, J. M. *Org. Lett.* **2005**, *7*, 3849–3851; (b) Zhouyu, W.; Xiaoxia, Y.; Siyu, W.; Pengcheng, W.; Anjiang, Z.; Jian, S. *Org. Lett.* **2006**, *8*, 999–1001; (c) Fatome, M.; Andrieu, L.; Laval, J. D.; Royer, R. L. *Eur. J. Med. Chem.* **1976**, *11*, 81–82; (d) Rene, L.; Royer, R. *Eur. J. Med. Chem.* **1975**, *10*, 72–78; (e) Varma, R. S.; Kadkhodayan, M.; Kabalka, G. W. *Heterocycles* **1986**, *24*, 1647–1652.
9. *General procedure for synthesis 3-nitro-2-phenyl-2H-chromenes*: A mixture of salicylaldehyde (1 mmol) and β-nitrostyrene (1.2 mmol) in dry toluene under nitrogen atmosphere was added 20 mol % L-pipecolinic acid at room temperature. The reaction mixture was stirred at 80 °C under nitrogen atmosphere for 24 h. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate (3 × 10 mL). The extracts were washed with H_2O and brine, then dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography using hexanes/ethyl acetate (8:1) as the eluent to give 3-nitro-2-phenyl-2*H*-chromenes. The enantiomeric excess was determined by HPLC with chiralpak AD column.
10. (a) Ballini, R.; Bosica, G.; Fiorini, D.; Palmieri, A. *Green Chem.* **2005**, *7*, 825–827; (b) Yan, M.-C.; Tu, Z.; Lin, C.; Ko, S.; Hsu, J.; Yao, C.-F. *J. Org. Chem.* **2004**, *69*, 1565–1570.
11. Pateliya, M. H.; Rama Raju, B.; Kavala, V.; Kuo, C.-W.; Yao, C.-F. *Tetrahedron* **2009**, *65*, 5799–5804.
12. *Synthesis of 6,8-dichloro-2-phenyl-2H-chromene-3-carbaldehyde* (**3**): A mixture of 3,5-dichloro salicylaldehyde (1 mmol) and cinnamaldehyde (1.2 mmol) in dry toluene under nitrogen atmosphere was added 20 mol % 1,1,3,3-tetramethylguanidine at room temperature. The reaction mixture was stirred at 80 °C for 48 h under nitrogen atmosphere till the complete disappearance of starting material monitored by TLC. The reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate (3 × 10 mL). The extracts were washed with H_2O (2 × 10 mL) and brine, then dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography using hexanes/ethyl acetate (8:1) as the eluent to give 6,8-dichloro-2-phenyl-2*H*-chromene-3-carbaldehyde **3**. 78% yield, ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.75 (s, 1H), 7.35–7.39 (m, 2H), 7.41–7.28 (m, 5H), 7.17–7.18 (d, 1H, J = 3 Hz), 6.49 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.9, 150.0, 139.4, 138.2, 136.1, 133.3, 129.4, 129.1, 127.4, 126.8, 124.0, 122.3, 75.1.
13. Alami, M.; Peyrat, J.-F.; Belachmi, L.; Brion, J.-D. *Eur. J. Org. Chem.* **2001**, 4207–4212.
14. Hotha, S.; Kashyap, S. *J. Org. Chem.* **2006**, *71*, 364–367.
15. *Synthesis of biotin attached BT7 analogue* **17**: To a solution of 6, 8-dichloro-2-phenyl-2*H*-chromene-3-carbaldehyde **3** (1 mmol) in methanol was added sodium borohydride (2 mmol). The mixture was then stirred at room temperature for 2 h and the reaction completion was indicated by TLC. After evaporation of the solvent, water was added and the product was extracted using ethyl acetate (3 × 10 mL). The extracts were washed with H_2O (2 × 10 mL) and brine, then dried over Na_2SO_4, and evaporated. The residue was purified by flash column chromatography using hexanes/ethyl acetate (8:2) as the eluent to give the alcohol **16** as an oil. Compound **16** was directly used for next step. To a stirred solution of d-biotin in DCM was added DCC under nitrogen atmosphere and stirred for 2 h at room temperature. To this stirred solution was added alcohol **16** in DCM and stirring continued for over night at room temperature under nitrogen atmosphere. After evaporation of the solvent, the product **17** was purified by silica gel chromatography (hexanes/ethyl acetate). 74% yield, ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.95 (s, 1H), 7.35–7.38 (m, 5H), 7.31–7.34 (m, 1H), 6.82 (s, 1H), 6.43 (s, 1H), 6.37 (s, 1H), 6.10 (s, 1H), 4.59 (s, 2H), 4.25–4.32 (m, 1H), 4.12–4.18 (m, 1H), 3.04–3.13 (m, 1H), 2.78–2.87 (m, 1H), 2.56–2.60 (d, 1H, J = 12 Hz), 2.18–2.25 (t, 2H, J = 6 Hz), 1.43–1.48 (m, 4H), 1.27–1.29 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 163.5, 163.2, 147.0, 138.4, 134.1, 130.0, 129.6, 128.3, 126.0, 124.8, 121.6, 120.9, 78.2, 63.8, 56.2, 48.3, 36.6, 33.8, 31.6, 28.8, 25.3, 25.0. ESI MS: [M+H] 533.1055, calcd 533.0990 for $C_{26}H_{26}Cl_2N_2O_4S$.
16. *Synthesis of biotin attached BT7 analogue* **19**: To a stirred solution of d-biotin (1.1 mmol) in DMF was added EDCI (3 mmol), DMAP (3 mmol) and compound **18** (1 mmol) under nitrogen atmosphere and stirred for overnight at room temperature. Reaction mixture was diluted with water and extracted with ethyl acetate (3 × 10 mL) and dried over Na_2SO_4. After evaporation of the solvent, the product was crystallized over ether–hexanes system resulted in compound **19** in 78% yield.^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (m, 1H), 7.71–7.21 (m, 7H), 6.61 (br s, 1H), 6.35 (s, 2H), 5.41 (s, 1H), 4.71 (m, 1H), 4.35 (m, 1H), 4.21 (m, 1H), 3.32 (m, 2H), 2.92–2.51 (m, 2H), 2.22–1.91 (m, 2H), 0.9–1.71 (m, 6H); ^{13}CNMR (75 MHz, $CDCl_3$): 173.0, 163.6, 149.8, 138.8, 129.4, 128.5, 127.9, 127.0, 125.0, 124.7, 122.4, 79.1, 61.9, 60.0, 56.3, 45.0, 39.5, 35.5, 32.5, 28.8, 26.1 ESI MS:$[M+H]^+$: 520.1151, calcd 519.1150 for $C_{25}H_{27}Cl2N_3O_3S$.