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Original article

A solid-phase approach to DDB derivatives

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Abstract

Since the discovery of 2,2′-dimethoxycarbonyl-4,4-dimethoxy-5,6,5′,6′-biomethylenedioxy-biphenyl (**DDB**) as a potent anti-HBV agent, we have studied the structure–activity relationships of 4,4′-dimethoxy-5,6,5′,6′-dimethenedioxy-2-alkyloxycarbonyl-2′-(4-substituted benzyl piperazin-1-yl)carbonyl-biphenyl as anti-HBV agents. Therefore, it is rational to extend this study to the 3,3′-disustituted-4,4′-dimethoxy-5,6,5′,6′-dimethenedioxy-2-alkyloxycarbonyl-2′-Serine derivatives. Thus, in an attempt to develop an efficient method for the preparation of a large number of **DDB** derivatives, the reaction between a DDB acid chloride and serine derivatives on solid support was studied. The structure of resulted compounds was confirmed by LC–MS and ^{1}H NMR analysis. Compounds **2a**, **2d**, **2f**, **2j** showed in vitro anti-HBV activity without significant toxicity up to 100 μM.

Keywords: Solid-phase; Synthesis; Scaffold; DDB; Combinatorial chemistry; Anti-HBV activity

1. Introduction

Dibenzocyclooctadiene lignans are isolated from the fruit of schizandra Chinese, a creeping vine native to northern China [1]. The extracts from this lignan-rich plant have been used in Chinese and Japanese traditional medicine as protection against hepatic damage [2–5] and anti-AIDS agents [6]. This structure is interesting to organic chemists, pharmacologists, and phytochemists not only for chemical reason such as challenging synthetic targets but also for their remarkable biological activities. The active natural lignans all contain a cyclooctane ring liking a biphenyl ring system, which is substituted with methoxyl and/or methylenedioxyl groups. Since the biphenyl substitution pattern [7–9], structure–activity correlations with related synthetic biphenyl compounds that also contain bismethylenedioxyl and methoxyl group were performed. Xie et al [10,11] reported the first synthesis and liver-protective property of dimethyl-4,4′ -dimethoxy-5,6,5′,6′-dimethylenedioxy biphenyl-2,2′-dicarboxylate (**DDB**), a non-cyclooctadiene analogue. Recently, we have also reported the structure–activity relationships of 4,4′-dimethoxy-5,6,5′,6′-dimethenedioxy-2-alkyloxycarbonyl-2′-(4-substituted benzyl piperazin, 1-yl)carbonyl-biphenyl as anti-HBV agents [12]. These encouraging results promoted us to determine the optimal pattern of biphenyl amide substitution, a small library, which contained newly-built biphenyl derivatives such as alkyl-3,3′-disubstituted-4,4′-dimethoxy-5,6,5′,6′-dimethylenedioxy biphenyl-2-sustituted-2′-carboxylate **2** (Scheme 1), was synthesized by using solid-phase chemistry (Fig. 1).

2. Results and discussion

To obtain DDB derivatives library with structure **2**, the polymer-support chemistry was aimed at the synthesis of the nitro-activated phenyl esters **8** (Scheme 1). This ester **8**, which was prepared by displacing the hydroxyl group of phenol **6** by compound **7**, reacted with different Serine derivatives, such as 1-hydroxy-2-amino-3-sunstituted hydroxylamines **9** to give the expected compound **2**.

The macro-porous polystyrene XE-305 from Rohm and Haas was used for making 4-hydroxy-3-nitro-benzoyl resin

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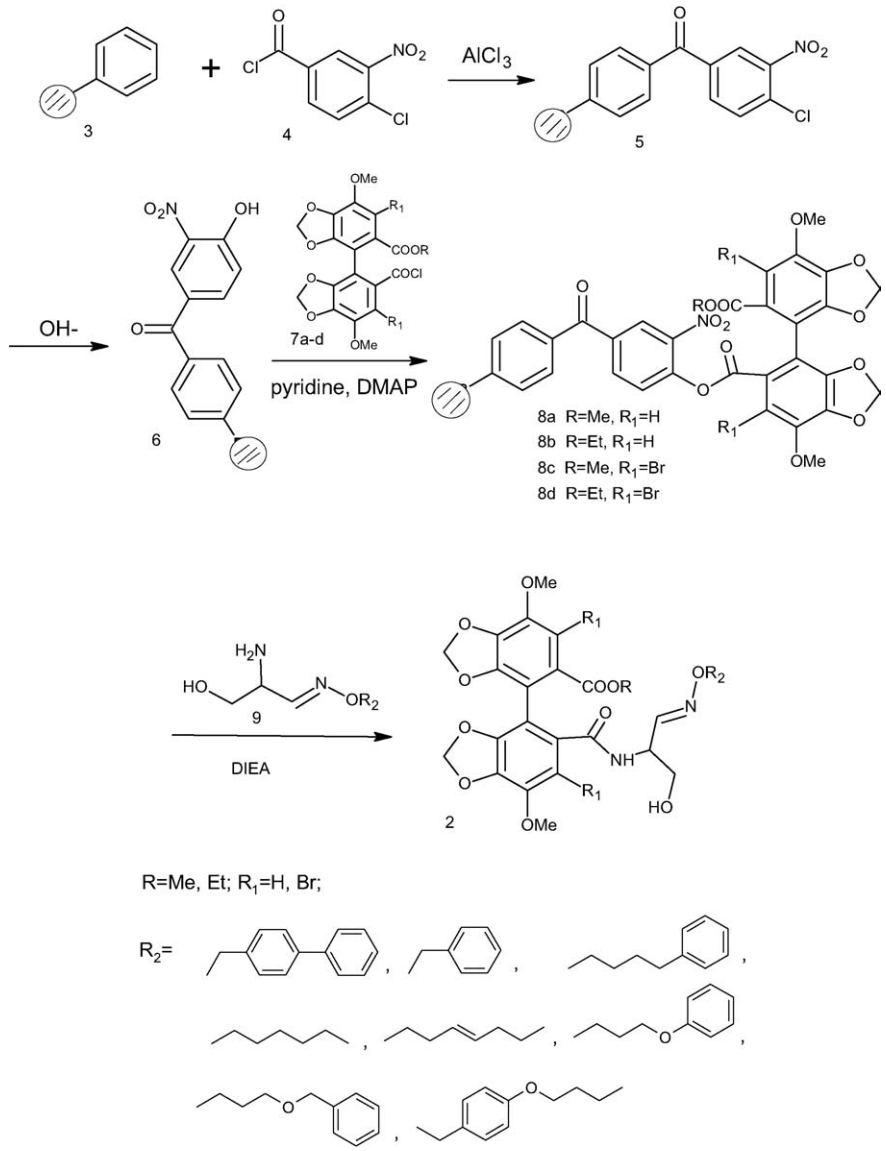


Scheme 1. Solid-phase synthesis of DDB derivatives.

6. The commercial resin **5** was reacted with 4-chloro-3-nitrobenzoyl chloride in the presence of aluminum trichloride in dry nitrobenzene at 60 °C for 5 h to give chloride **5**. The hydrolysis of **5** was carried out by using benzyltrimenthyl ammonium hydroxide in water and dioxane for 8 h at 90 °C to give resin **6** (Anal. Cl < 0.1; N 2.38; 1.7 mmol/g). The amount of available hydroxyl groups of **6** was determined by the method of esterification and amide formation.

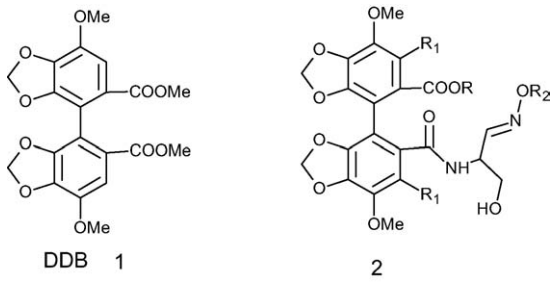
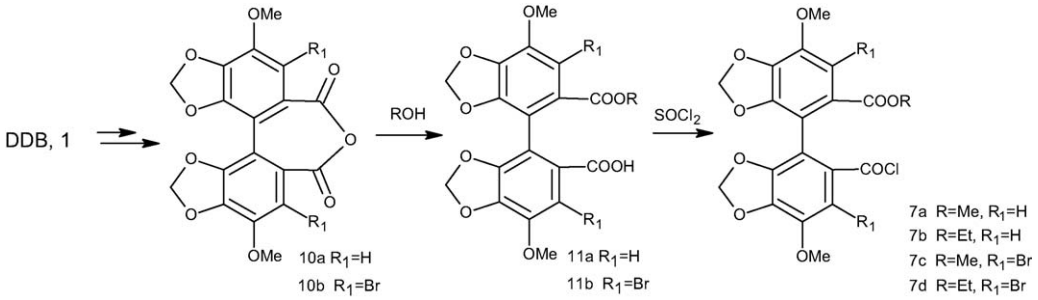


Fig. 1. Structure of DDB derivatives **1** and **2**.

Resin **6** was esterified with an excess amount of benzoyl chloride, washed with chloroform, and reacted with benzylamine. The polymer was washed with chloroform, and the unreacted benzylamine was extracted with hydrochloric acid. The organic phase afforded pure *N*-benzylbenzamide and, from its weight, the loading on the polymer was determined to be 1.7–1.8 mmol/g.

DDB acid chlorides **7a~d** were obtained as shown in Scheme 2. DDB was prepared according to a literature procedure [11]. The synthesis of 3,3′-Dibromo-DDB and their anhydride **10a–b** was reported [13]. Treatment of **8** with methanol and ethanol yielded the corresponding monoester **11a** and **11b**, respectively. Compounds **7a–d** were obtained by treatment of **11** with thionyl chloride ($SOCl_2$) under reflux.

The serine derivatives, 1-hydroxy-2-amino-3-sunstituted hydroxylamines **9**, were synthesized by the reaction of aldehyde **15** and hydroxylamine **18** (Scheme 3). Preparation of aldehyde **15** was carried out from compound **12** via several

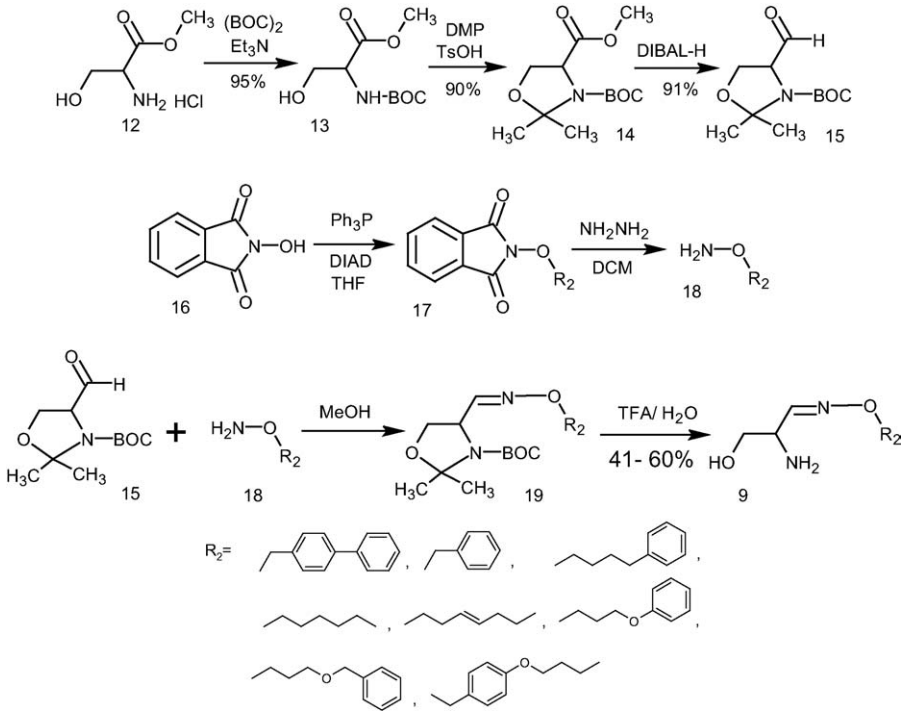


Scheme 2.

simple reactions: Boc-amimo protection, and hydroxyl protection and DIBAL reaction [14,15]. *O*-alkylated hydroxylamines **18** were also routinely prepared from the Mitsunobu reaction of **16** with alcohol and subsequent hydrazine treatment [16]. The coupling step of **15** and **18** was carried out in methanol to give **19**, which was hydrolyzed to **9** by acid deprotection of both amine and alcohol groups.

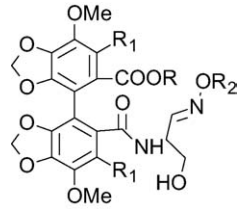
The **DDB**-attached polymeric active ester resin **8** was obtained by the DMAP (4-dimethylamino pyridine)-catalyzed reaction of resin **6** with four DDB–acid chlorides **7a~d**, methyl 2′-chlorocarbonyl-4,4′-dimethoxy-5,6,5′,6′-dimethylenedioxy biphenyl-2-carboxylate, ethyl 2′-chlorocarbonyl-4,4′-dimethoxy-5,6,5′,6′-dimethylenedioxy biphenyl-2-carboxylate, methyl 2′-chlorocarbonyl-3,3′-dibromo-4,4′-dimethoxy-5,6,5′,6′-dimethylenedioxy biphenyl-2-carboxylate, ethyl 2′-chlorocarbonyl-3,3′-dibromo-4,4′-dimethoxy-5,6,5′,6′-dimethylenedioxy biphenyl-2-carboxylate, respectively. The above-mentioned benzylamine method was used for the determination of the DDB loading and weighing the resulting amide showed that 70–80% of the available OH groups underwent ester. Polymeric active esters **8** reacted with different serine derivatives, 1-hydroxy-2-amino-3-sunstituted hydroxylamines **9** in the presence of diisopropyl ethylamine (DIEA) at room temperature for 48 h to give alkyl-3,3′-disubstituted-4,4′-dimethoxy-5,6,5′,6′-dimethylenedioxy biphenyl-2-sustituted-2′-carboxylate **2** in 71~91% yield. Analysis with IR spectrum and LC–MS/MS showed that the biphenyls coupled with **9** selectively by the NH_2 group of **9**, not OH group. Table 1 summarizes yield and purity data from a set of representing compounds that were selected from a synthesized library.

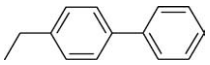
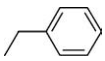
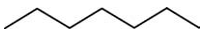
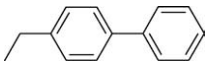
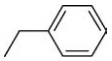
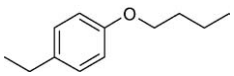
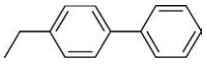
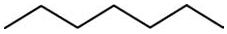
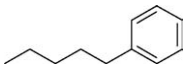
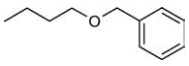
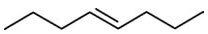
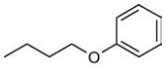
In conclusion, we have shown that polymer-bound 4-hydroxy-3-nitrobenzophenone can be utilized as a versatile precursor for the construction of the **DDB** derivatives. Those derivatives, are substituted with alkylamino amides at the 2-position, which are normally the methyl carboxylate group. All the synthesized **DDB** derivatives were evaluated for anti-HBV. The compounds **2a**, **2d**, **2f**, **2j** showed in vitro moderate activity against HBV(EC_{50} = 5.8, 2.3, 1.9, and 3.8 μM, respectively) using the HepG2 2.2.15 cells. The



Scheme 3.

Table 1
Synthesis of DDB amide



Number	R	R_1	R_2	Yield[a] (%)	Purity[b] (%)
2a	Me	H		91	95
2b	Me	H		82	90
2c	Me	H		75	87
2d	Et	H		90	96
2e	Et	H		83	90
2f	Et	H		71	85
2g	Me	Br		93	95
2h	Me	Br		82	91
3i	Me	Br		84	90
2j	Et	Br		89	92
2k	Et	Br		81	89
2m	Et	Br		91	90

[a] Determined by weight of the crude products (TFA Salt) based on the loading of the resins.

[b] Determined by LC–MS using both UV detectors and further confirmed by ^{1}H NMR analysis.

2.2.15 cells were grown to confluence in minimal essential medium with 10% fetal bovine serum. At confluence the treatment with the drugs was initiated, and it was then continued for 6 days with medium changes at 3-day intervals. After the 6-day treatment, the medium was harvested, and the viral particles were precipitated with polyethylene glycol, digested, and then processed for Southern blot analysis. The blots were hybridized to an HBV-specific probe, and amounts of viral DNA were assessed in comparison with levels of DNA from cultures not treated with the compounds. Further confirmation of the viral DNA levels was obtained by processing the cells treated with the compounds. The genomic DNA was digested with *Hin*dIII and subjected to Southern analysis. Levels of the episomal DNA were determined in relation to those of the integrated HBV DNA. Densitometric scans were performed on autoradiographs. The compounds concentrations that caused 50% inhibition of the DNA compared with the controls were calculated.

3. Experimental part

*3.1. The preparation of the polymer-bound precursor **6** was briefly discussed in Ref. [17]. The detailed experimental procedures are illustrated as follows*

3.1.1. Preparation of the polymer

To a mixture of 50 g of macroreticular polystyrene (XE-305, Rohm and Haas) and 100 g of 4-chloro-3-nitrobenzoyl chloride was added a solution of 25 g of aluminum trichloride in 300 ml of dry nitrobenzene. The mixture was stirred mechanically at 60 °C for 5 h and poured into a mixture of 150 ml of DMF, 100 ml of concentrated HCl, and 150 g of ice.

The beads slowly turned white. They were washed with 300 ml portions of DMF/water (3:1) until the washings were colorless, then with warm (60 °C) DMF, and finally with six portions of 300 ml of DCM/MeOH (2:1). The dried polymer weighed 82 g (1.88 mmol/g). Hydrolysis was carried out with a mixture of 130 ml of 40% benzyltrimenthylammonium hydroxide in water, 130 ml of water, and 260 ml of dioxane for 8 h at 90 °C. The polymer was filtered, and the process was repeated. The beads were then washed with four portions of warm (60 °C) dioxane. Acetic acid (30 ml) was added with stirring for 15 min. The polymer was washed with dioxane until the washings were neutral, followed by six portions of 300 ml of DCM/MeOH (2:1). Anal. calcd: Cl, < 0.1; N, 2.38 (1.7 mmol/g). The amount of available hydroxide groups was determined by esterifying with a three fold excess of benzoyl chloride and pyridine in dry chloroform at 0–10 °C for 30 min, washing with chloroform, and reacting with excess benzylamine. The polymer was washed with chloroform, and excess benzylamine was extracted with hydrochloric acid. The organic phase afforded pure N-benzylbenzamide, and from its weight the loading on the polymer was determined to be 1.7–1.8 mmol/g, assuming quantitative reactions.

3.1.2. Polymeric active esters

Esters of simple acids were prepared from the acid chloride and pyridine as described. Active esters of Boc-protected amino acids were prepared by the symmetric anhydride method as follows: 4 mmol of the Boc-protected amino acid

was dissolved in 6 ml of DCM (THF was added in case of poor solubility). The solution was cooled to –10 to 0 °C and 2 mmol of DDC was added. After 30 min at 0 °C, the mixture was filtered directly into a vessel containing 1 g of the polymer-bonund-4-hydroxy-3-nitrobenzophenone. Pyridine (0.5 ml) was added, and the mixture was shaken for 1 h at room temperature. The polymer was washed with six to eight 10-ml portions of chloroform. Active esters of Boc-glycine, Boc-phenylalanine, and Boc-*o*-benzyl-tyrosine were thus prepared. Determination of the loading by reacting the polymers with an excess of benzylamine and weighing the resulting amide showed that 70–80% of the available OH groups underwent esterfication.

3.2. General procedure

*3.2.1. Synthesis of [N-[(1,1-dimethylethoxy) carbonyl]-serine, methyl ester] (**13**)*

H-Ser-OMe-HCl (15 g, 96.5 mmol) was dissolved in dichloromethane (200 ml) and 2.2 equiv of triethylamine added, then tert-butylpyrocarbonate (23.2 g, 0.106 mol) were slowly added with vigorous stirring and cooling in an ice bath. After stirring at 0 °C for 30 min in the solution was stirred at room temperature for 3 h. The reaction mixture was then evaporated and partitioned between 200 ml of ethyl acetate and 100 ml of $KHSO_4$ (1 M) and washed with 1 M $KHSO_4$ (100 ml, 1 M), $NaHCO_3$ (100 ml) and brine (3 × 50 ml). After drying over $MgSO_4$, the extract was taken to dryness at reduced pressure to give **13** 20.1 g as oil (yield 95%).

^{1}H NMR (acetic-d_6) δ ppm: 1.43 (s, 9H, CH_3, Boc), 2.50 (br, s, H, exchanged with D_2O), 3.76(s, 3H, CH_3, OMe), 3.85–4.98 (m, 2H, CH_2, Ser), 4.39 (m, 1H, CH, ser), 5.49 (br, 1H, NH, exchanged with D_2O).

*3.2.2. 3-(1,1-Dimethylethyl)4-methyl-2,2-dimethyl-3,4-oxazolidinedicarboxylate (**14**)*

To a stirred solution of Boc-Ser-OMe (**13**, 35.8 g, 163 mmol) in CH_2Cl_2 (200 ml) were added DMP (100 ml, 820 mmol) and *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O, 3.2 g, 16.4 mmol) at 0 °C. After stirring at r.t. for 12 h, the mixture was poured into statured aq. $NaHCO_3$ (200 ml) and then the resulting solution was extracted with Et_2O (3 × 150 ml). The organic layer was washed with statured aq. $NaHCO_3$ (3 × 100 ml), brine (3 × 100 ml), and then dried (Na_2SO_4). Concentration in vacuo gave a crude oil, which was distilled in vacuo to give **14** as a colorless oil 39.1 g (90%), b.p. 110–112 °C per 4 Torr. ^{1}H NMR ($CDCl_3$) δ ppm: 1.39(s, 9H), 1.48(br, s, 3H), 1.65(br, s, 3H), 3.74(s, 3H), 4.11(dd, J = 8.5 and 8.1 Hz, 1H), 4.35(dd, J = 8.5 and 3.5 Hz, H), 4.47(m, H).

*3.2.3. 1,1-Dimethylethyl-4-formyl-2,2-dimethyl-3-oxazolidinecarboxylate (**15**)*

To a stirred –78 °C solution of **14** (40.2 g, 0.155 mol) in dry toluene (300 ml) was add ed a –78 °C solution of 1.5 M DIBAL-H in toluene (175 ml) *via* cannula (using positive N_2 pressure). The rate of addition was adjusted so as to keep the internal temperature below –70 °C. After of addition, the reaction mixture was stirred for an additional 2.5 h at –78 °C (under an N_2 atmosphere) when the TLC showed the clean formation of product **15**. The reaction was quenched by slowly adding 70 ml of cold (–78 °C) CH_3OH($H_2\uparrow$ evolution) to keep the internal temperature below –65 °C. The resulting white emulsion was slowly poured into 1000 ml of ice-cold 1 N HCl with swirling over 15 min, and the aqueous mixture was then extracted with EtOAc (3 × 1000 ml), dried with $MgSO_4$, filtered and concentrated in vacuo to give crude product **15** as a colorless oil, which was vacuum distilled to give **15** 32.2 g (91.0%) as a colorless liquid. ^{1}H NMR($CDCl_3$) δppm: 1.42(s, 9H), 1.50–1.64 (br, m, 6H), 4.06–4.09 (m, 2H), 4.20–4.35 (m, 1H), 9.53 (br, s, H).

*3.2.4. General procedure representative prexperimental procedure for mitsunobu reaction bibenzyl phthalimidooxy (**18**)*

To a stirred solution of **17a** (6.6 g, 36 mmol) PPh_3 (12.3 g, 47.0 mmol, 1.3 equiv) and PhthNOH (7.0 g, 43.2 mmol,1.2 equiv) in THF (100 ml) was added DIAD (9.5 g, 47.0 mmol, 1.3 equiv) dropwise over 30 min. The mixture was stirred at r.t. for 6 h. TLC showed without of starting material. The reaction mixture was concentrated and then the residue was dissolved in ethanol (30 ml) to get **18a** as a solid. The solid was washed with ethanol to afford a pure **18a** in 93% yield as a solid. ^{1}H NMR($CDCl_3$) δ ppm: 5.07 (s, 2H), 7.41–7.83 (m, 13H).

*3.2.5. Preparation of compound **19a***

To a stirred solution of **18a** (7.2 g, 22 mmol) in CH_2Cl_2 (150 ml) was added dropwise NH_2NH_2 (1.4 ml, 44 mmol). The reaction mixture was stirred at r.t. for 4 h. Lots of solid appeared, the mixture was filtered through celite. The filtrate was washed by 2 N NaOH, concentrated. The residue was purified by flash column chromatography (1:1 hexane/EtOAc) to give **19a** 2.8 g (63.9%) as oil. ^{1}H NMR ($CDCl_3$) δppm: 4.74 (s, 2H), 5.43 (br, s, 2H), 7.33–7.61 (m, 9H).

To a solution of **19a** (2.0 g, 10 mmol) in MeOH(50 ml) was added **15** (2.3 g, 10 mmol). The resulting mixture was heated at 50 °C for 12 h. TLC showed without of starting materials. After concentration under reduced pressure, the residue was dissolved in TFA (15 ml) and H_2O (50 ml) and the mixture was stirred at r.t. for 1 h. The solvent was evaporated in vacuo and statured aq $NaHCO_3$ was added. The mixture was extracted with EtOAc, dried with Na_2SO_4 and concentrated in vacuo to give **9a** 1.0 g (36.2% in two steps) as yellow oil. ^{1}H NMR($CDCl_3$) δ ppm: 3.28 (br, s, 2H), 3.56–3.76 (m, 3H), 5.08 (s, 2H), 7.34–7.57 (m, 10H).

*3.2.6. Preparation of compound **2***

In a single 96-well microtiter plate to produce one product per well. For the reaction, 0.014 mmol of **8** per well in DCM, and compound **9** (1.1 equiv). The plate was capped for 48 h at r.t. The products were removed from the resin, washed into

a second 96-well plate with DCM (2 × 600 μl). The solvents were then removed in a reduced-pressure oven to obtained compound **2** (Table 1 summarize compound **2a**–**2m** of yield and purity data from a set of representing compounds that were selected from a library synthesized).

Acknowledgements

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