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Synthesis of unsymmetrical biphenyls as potent cytotoxic agents

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ABSTRACT

Twenty-six unsymmetrical biphenyls were synthesized and evaluated for cytotoxic activity against DU145, A549, KB and KB-Vin tumor cell lines. Three compounds **27**, **35** and **40** showed very potent activity against the HTCL panel with an IC_{50} value range of 0.04–3.23 μM. In addition, fourteen active compounds were all more potent against the drug-resistant KB-Vin cell line than the parental KB cell line. Preliminary SAR analysis indicated that two bulky substituents on the 2,2′-positions of unsymmetrical biphenyl skeleton are necessary and crucial for in vitro anticancer activity, thus providing a good starting point to develop unsymmetrical biphenyls as novel anticancer agents.

Natural products continue to play a highly significant role today in the discovery and development of new drugs, new leads and new chemical entities. This fact is particularly evident in the areas of cancer and infectious diseases, where over 60% and 75% of drugs, respectively, are of natural origin.[1,2] Dibenzocyclooctandiene lignans have been identified as major bioactive constituents from the traditional Chinese medicinal plant *Schizandra chinese* and show a wide variety of interesting biological activities,[3,4] including antiviral,[5] anticancer,[6,7] hepatoprotective,[8] and anti-inflammatory.[9] Recently, it was also reported that several dibenzocyclooctadiene lignans, such as gomisin A, schisandrins A and B, and schisantherin A, have activity against cancer multidrug resistance mediated by P-glycoprotein (P-gp) and effectively restore the action of anticancer drugs,[10–12] such as vinblastine, daunorubicin, doxorubicin, and VP-16.

However, because natural lignans with multiple chiral centers are not always ideal as drug candidates, even though many total synthesis studies have been reported,[13] we were prompted to use lignans as leads for new compounds with simpler, more accessible structures. The biphenyl moiety in natural dibenzocyclooctadiene lignans is substituted with methoxy and methylenedioxy groups at different positions, resulting in either symmetrical (wuweizi C) or unsymmetrical (wuweizi B) biphenyls, as shown in Fig. 1, and this feature is crucial for biological activity. Structural simplification of the symmetrical wuweizi C to simpler biphenyl analogs led to the anti-hepatotoxic (liver injury) drugs α-DDB (methyl 4,4′-dimethoxy-5,6,5′,6′-dimethylenedioxy biphenyl-2,2-dicarboxylate) and bicyclol (Fig. 1), which are widely used medicinally in China and Asia. In our current study, we decided to focus on unsymmetrical biphenyls, as such compounds have not been previously well explored for cytotoxic activity. Our goal was to

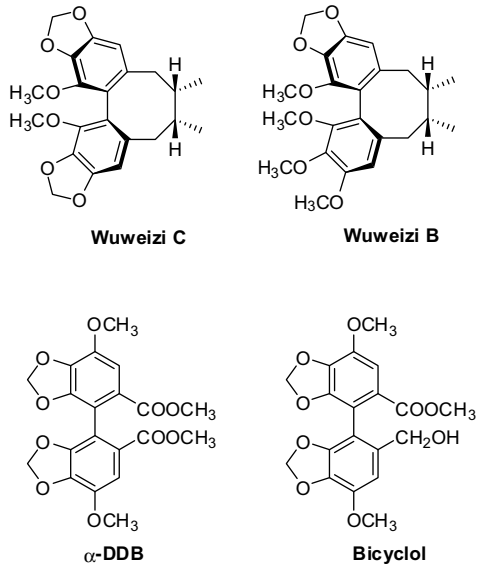

Figure 1. Structures of natural dibenzocyclooctadiene lignans and biphenyl derivatives.

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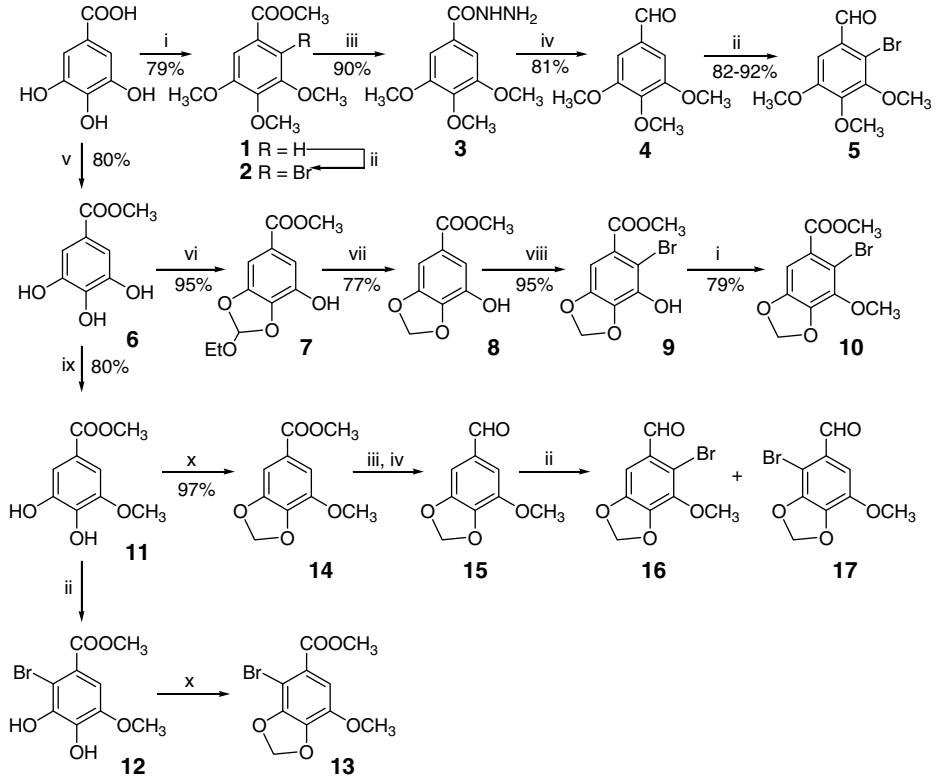
identify novel biphenyl leads with potent anticancer effects, hopefully with activity against multidrug resistance.

Herein, we report the synthesis of twenty-six unsymmetrical biphenyl compounds (**18-43**) and their cytotoxic activity against DU154, A549, KB and drug-resistant KB-Vin cell lines. Among them, three compounds (**27**, **35** and **40**) showed very promising inhibitory activity against all tested tumor cells with an IC_{50} range of 0.04–3.23 μM.

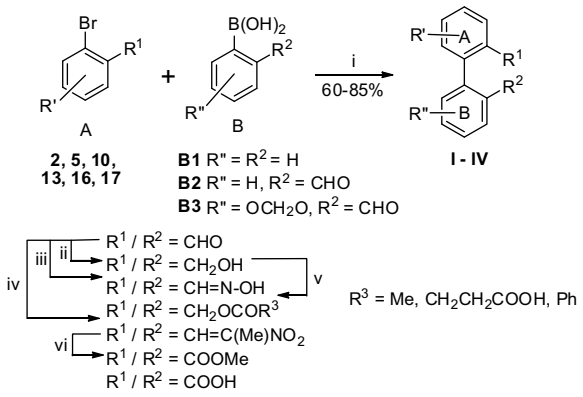
Unsymmetrical biphenyls are frequently prepared by using Stille, Suzuki, Ullmann, and Grignard cross-coupling reactions. A Suzuki cross-coupling reaction[14,15] of an aryl halide with an aryl boronic acid offers convenient access to unsymmetrical biaryls with a wide range of structural diversity. Accordingly, this approach was used to obtain our target compounds because of phenylboronic acid commercial availability, mild reaction conditions, and a little or no homocoupling by-products. The different aryl bromide precursors were synthesized as shown in Scheme 1 following literature methods.[16,17] Using methyl sulfate in strongly basic conditions, gallic acid was methylated completely to provide methyl 3,4,5-trimethoxybenzoate (**1**), followed by bromination to give the aryl bromide **2**. In methanol under acidic conditions, gallic acid was methylated only at the carboxylic acid to yield methyl gallate **6**. The three hydroxyls of **6** were then selectively modified by using different reactions to produce methylenedioxy **8** or monomethoxy **11**. Using 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) as a brominating reagent,[17] bromination of both **8** and **11** occurred regioselectively at the ortho-position to the free hydroxyl to afford **9** and **12**, respectively. Next, the remaining free hydroxyls in **9** and **12** were converted to methoxy and methylenedioxy groups, respectively, to give isomeric aryl bromide precursors **10** (methyl 2-bromo-3-methoxy-4,5-methylenedioxybenzoate) and **13** (methyl 6-bromo-3-methoxy-4,5-methylenedioxybenzoate), which are desired moieties for building different biphenyl derivatives. The benzaldehyde analogs of benzoates **2**, **10**, and **13** were prepared by the following sequence. The carboxylic esters in **1** and **14** were converted to aldehydes in **4** and **15** by reduction of an intermediate hydrazone. Bromination of **4** and **15** with Br_2 in CH_2Cl_2 then afforded 2-bromo-3,4,5-trimethoxybenzaldehyde **5** and a mixture of 2-bromo- and 6-bromo-3-methoxy-4,5-methylenedioxybenzaldehyde (**16** and **17**), respectively.

Next, Suzuki cross-coupling reactions were performed using palladium acetate [$Pd(AcO)_2$] as catalyst in the presence of anhydrous Cs_2CO_3 to synthesize unsymmetrical biphenyls **I–IV** as shown in Scheme 2 and Table 1. Coupling between commercially available phenylboronic acid (**B1**) or 2-formylphenyl boronic acid (**B2**) and the synthetic aryl bromides described above (**2** or **5**, **13** or **17**, **10** or **16**) gave biphenyls of types **I** (**18**–**20**), **III** (**38**–**40**), and **IV** (**41**–**43**), respectively. Type II biphenyls (**28**, **29**) were prepared by reaction between **2** or **5** with 2-formyl-4,5-methylenedioxyphenyl boronic acid (**B3**), which was prepared according to literature methods.[16] After coupling, the aldehyde or methyl ester (substituents R^1 and R^2) on the biphenyls was easily converted to various functional groups, including hydroxymethyl, oxime, carboxylic acid, and various esters, by common synthetic methods, to produce additional unsymmetrical biphenyls (**21**–**27**, **30**–**37**). The spectroscopic data of all target biphenyl compounds are shown at endnote.[20]

The synthesized biphenyl compounds were tested for in vitro cytotoxic activity against a human tumor cell line (HTCL) panel, including A549 (lung), DU145 (prostate), KB (nasopharyngeal), and drug-resistant KB-Vin, according to a reported SRB method.[18] Homoharringtonine and etoposide served as reference antitumor compounds. The structures and bioassay data of all unsymmetrical biphenyls **18–43** are summarized in Table 1. Among them,



Scheme 1. Synthesis of aryl bromide precursors. Reagents and conditions: (i) Me_2SO_4/NaOH aq, rt, 1.5 h; (ii) Br_2/CH_2Cl_2, 0 °C, 1–3 h; (iii) $NH_2NH_2{\cdot}H_2O$, 95 °C, 3 h; (iv) $K_3Fe(CN)_6/NH_3{\cdot}H_2O$, toluene/$H_2O$, rt, 0.5–1.5 h; (v) MeOH/H_2SO_4, reflux, 5 days; (vi) $(EtO)_3CH/H^+$, benzene, reflux, 16 h; (vii) (a) BnBr, K_2CO_3, DMF, 70 °C, 1.5 h, 90%; (b) HCl aq. (2%), MeOH, rt, 2 h, 99%; (c) CH_2Cl_2/K_2CO_3, DMF, 105 °C, 6 h, 96%; (d) $TiCl_4/CHCl_3$, rt, 12 h, 90%; (viii) DBDMH/$CHCl_3$, rt, 10 h; (ix) Me_2SO_4/NaOH aq, $Na_2B_4O_7$, rt, 5 h; (x) CH_2Cl_2/K_2CO_3, DMF, 105 °C, 6 h.



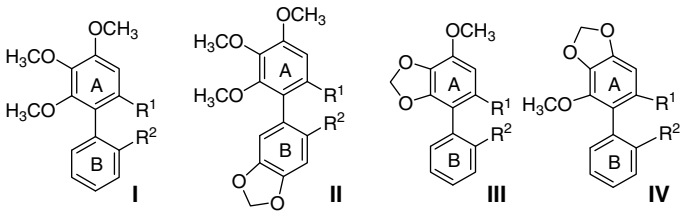
Scheme 2. Synthesis of unsymmetrical biphenyls. Reagents and conditions: (i) $Pd(OAc)_2$, PPh_3, Cs_2CO_3, DME, 70 °C, 2–10 h; (ii) $NaBH_4$/MeOH, rt, 1–2 h, 99%; (iii) $NH_2OH{\cdot}HCl$, NaOH aq /C_2H_5OH, rt, 2 h, 81–98%; (iv) $CH_3CH_2NO_2$, *n*-$BuNH_2$/HOAc, toluene, reflux, 3 days, 63%; (v) R_3COCl, Py, rt, 12 h, 90–96%; (vi) NaOH/H_2O, 100 °C, 4 h, 70%.

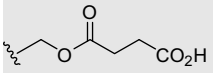
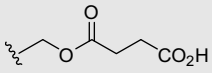
4′,5′-methylenedioxy-(4,5,6-trimethoxy-biphenyl-2,2′-diyl)bis-(methylene)dibenzoate (**35**) showed the most potent inhibitory effects with an IC_{50} value of 0.04 μM against the above four tumor cell lines. 2,3,4-Trimethoxy-2′,6-bis(2-nitroprop-1-enyl)biphenyl (**27**) and methyl 2′-formyl-4,5,6-trimethoxybiphenyl-2-carboxylate (**40**) were also significantly active with IC_{50} value ranges of 0.11–0.51 μM and 0.31–3.23 μM, respectively, against the HTCL panel. Compounds **19**, **20**, **28**, **39**, and **43** showed greater activity against DU145 and KB-Vin cell lines than against the other two cell lines.

From a structure-activity relationship (SAR) viewpoint, various patterns of methoxy and methylenedioxy substitution on the A and B ring had less impact on inhibitory potency than changes in the functional groups at the 2,2′-positions of biphenyls. With the 2,2′-substituents held constant (R^1 = CHO or COOMe, R^2 = CHO), Type III (**39** and **40**; 4-methoxy-5,6-methylenedioxy substitution) biphenyls were somewhat more potent than Type I (**19** and **20**; 4,5,6-trimethoxy substitution), II (**28** and **29**; 4,5,6-trimethoxy-4′,5′-methylenedioxy substitution), or IV (**42** and **43**; 4,5-methylendioxy-6-methoxy substitution) compounds. However, more significant changes in potency were found by changing the substituents at the 2,2′-positions as described below.

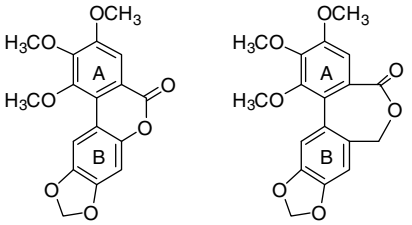
Generally, methyl carboxylate (R^1) was preferred to an aldehyde on ring A, and an aldehyde (R^2) was better than hydrogen on ring B. This trend was most apparent against DU154 and KB-Vin cell lines (compare **19**/**20**, **39**/**40**, **42**/**43**). Data for compounds **18–27** and **28–35** (Types I and II in Table 1) supported our hypothesis that variation of substituents at the biphenyl 2,2′-positions could greatly affect in vitro anticancer potency. Compounds with hydroxymethyl (**21**, **22**, **30**, **31**), dicarbaldehyde oxime (**23**, **32**), methyl acetate (**24**, **33**), and methyl 4-oxobutanoic acid (**25**, **34**) at these positions showed either no inhibitory activity or were much less potent than corresponding active compounds **19** and

Table 1
In vitro growth inhibition of DU145, A549, KB and KB-vin tumor cell lines



R^1	R^2	I/#	IC_{50} (μM)[a]				II/#	IC_{50} (μM)[a]			
			DU145	A549	KB	KBvin		DU145	A549	KB	KBvin
CHO	H	**18**	NT[c]	9.52	11.9	10.4					
CHO	CHO	**19**	4.29	9.10	16.1	9.83	**28**	3.66	20.2	15.7	4.10
COOMe	CHO	**20**	5.25	7.76	12.0	4.97	**29**	NA	NA	NA	NA
CHOH	CHOH	**21**	NA[d]	NA	NA	NA	**30**	NA	NA	NA	NA
COOMe	CH_2OH	**22**	NA	NA	NA	NA	**31**	NA	NA	NA	NA
CH=NOH	CH=NOH	**23**	NA	NA	NA	NA	**32**	NA	19.2	11.2	15.8
CH_2OCOMe	CH_2OCOMe	**24**	NA	NA	32.5	NA	**33**	NA	NA	NA	NA
		**25**	NA	NA	NA	NA	**34**	NA	NA	NA	NA
CH_2OCOPh	CH_2OCOPh	**26**	NT	NA	14.4	12.0	**35**	0.04	0.04	0.04	0.04
$CH{=}C(Me)NO_2$	$CH{=}C(Me)NO_2$	**27**	0.29[e]	0.11	0.41	0.51					
A-COO-B; See Figure 2							**36**	NA	NA	NA	NA
A-$COOCH_2$-B, See Figure 2							**37**	15.6	21.2	18.4	15.3
		III/#					**IV/#**				
CHO	H	**38**	NA	NA	NA	NA	**41**	NT	21.8	NA	18.7
CHO	CHO	**39**	3.87	7.15	6.13	2.46	**42**	9.61	9.08	9.15	6.58
COOMe	CHO	**40**	0.31	1.70	3.23	0.86	**43**	2.23	19.6	12.8	1.88
Homoharringtonine[b]				0.03	0.004	0.51					
Etoposide[b]				9.98	14.2	NA					

[a] IC_{50}: concentration that causes a 50% reduction of cell growth.
[b] Positive control.
[c] NT, not tested.
[d] NA, not active.
[e] Data obtained from PC-3 (prostate) cell line.



36 **37**

Figure 2. Structures of lactone-linked biphenyl derivatives.

28 ($R^1 = R^2$ = aldehyde), respectively. In contrast, biphenyls **27** and **35** with two bulky groups, 2-nitroprop-1-enyl and methylbenzoate, respectively, showed significant potency against all tested tumor cell lines.

These results prompted us to consider whether steric compression between adjacent 2,2′-substituents could alter the biphenyl torsional angle, resulting in a stereo-configuration that would directly affect the molecular affinity with a target receptor/enzyme and result in different inhibitory activity against tumor cell lines. Biphenyl configuration (*S*- or *R*-) in natural dibenzocyclooctandiene lignans can play an important role in antiproliferative effects. For example, wuweizisu B with R-biphenyl configuration is less potent than gomisin N with S-biphenyl configuration.[19] To obtain related information in our study, lactone-linked biphenyls **36** and **37** (Fig. 2) were evaluated in the same assays. Although neither compound showed significant potency, the latter compound with a seven-membered lactone ring was more active than the former with a six-membered lactone ring. These data suggest that both bigger torsional angles caused by two bulky substituents on the 2,2′-positions and the configuration of the biphenyls might play important roles in inhibition of tumor cell growth.

Interestingly, several active compounds (**19**, **20**, **28**, **37**, **39**, **40**, **42**, and **43**) were also 1.4–6.8 times more potent against the drug-resistant KB-Vin cell line than the KB cell line. Thus, we hypothesize that the unsymmetrical biphenyl scaffolds are relatively poor substrates for the drug efflux pump (MDR) and could be developed as novel leads with low potential for drug resistance development.

In conclusion, twenty-six unsymmetrical biphenyls were synthesized and evaluated in DU145, A549, KB and KB-Vin tumor cell lines. Three compounds **27**, **35** and **40** showed very potent activity against the HTCL panel with an IC_{50} value range of 0.04–3.23 μM. In addition, fourteen active compounds were all more potent against the drug-resistant KB-Vin cell line than the parental KB cell line. Preliminary SAR analysis indicated that two bulky substituents on the 2,2′-positions of unsymmetrical biphenyl skeleton are necessary and crucial for in vitro anticancer activity. Current studies provide a good starting point to develop unsymmetrical biphenyls as novel anticancer agents. Further lead optimization is ongoing.

Acknowledgments

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20. Compound **18**: Yield 71%; white solid, mp 88–90 °C; ^{1}H NMR 9.65 (1H, s), 7.43 (3H, m), 7.34 (3H, m), 4.00 (3H, s), 3.97 (3H, s), 3.60 (3H, s); ESI-MS m/z: 295 ($M+Na^+$).
Compound **19**: Yield 65%; white solid, mp 71–72 °C; ^{1}H NMR 9.88 (1H, s), 9.60 (1H, s), 8.09 (1H, dd, J = 1.6 and 7.6 Hz), 7.68 (1H, dd, J = 1.6 and 7.6 Hz), 7.60 (1H, dd, J = 1.6 & 7.6 Hz), 7.42 (1H, s), 7.32 (1H, dd, J = 1.6 and 7.6 Hz), 4.00 (6H, s), 3.55 (3H, s); ESI-MS m/z: 323 ($M+Na^+$).
Compound **20**: Yield 65%; white solid, mp 78–79 °C; ^{1}H NMR 9.82 (1H, s), 8.02 (1H, dd, J = 1.2 and 8.0 Hz), 7.59 (1H, dd, J = 1.2 and 8.0 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.38 (1H, s), 7.19 (1H, d, J = 8.0 Hz), 3.96 (6H, s), 3.52 (6H, s); ESI-MS m/z: 353 ($M+Na^+$).
Compound **21**: Yield 96%; white solid, mp 106–108 °C; ^{1}H NMR 7.48 (1H, d, J = 7.2 Hz), 7.37 (2H, m), 7.13 (1H, d, J = 7.2 Hz), 6.88 (1H, s), 4.31 (2H, s), 4.22 (2H, s), 3.92 (3H, s), 3.90 (3H, s), 3.54 (3H, s); ESI-MS m/z: 327 ($M+Na^+$).
Compound **22**: Yield 97%, white solid, mp 68–69 °C; ^{1}H NMR: 7.54 (1H, d, J = 8.0 Hz), 7.40 (1H, s), 7.30 (2H, m), 7.03 (1H, d, J = 8.0 Hz), 4.38 (2H, m), 3.96 (6H, s), 3.58 (3H, s), 3.52 (3H, s); ESI-MS m/z 355 ($M+Na^+$).
Compound **23**: Yield 90%, pale yellow solid, mp 123–124 °; ^{1}H NMR (DMSO) 11.33 (1H, s), 11.27 (1H, s), 7.89 (1H, m), 7.57 (1H, s), 7.47 (2H, m), 7.35 (1H, s), 7.26 (1H, s), 7.20 (1H, s), 3.90 (3H, s), 3.84 (3H, s), 3.49 (3H, s); ESI-MS m/z 353 ($M+Na^+$).
Compound **24**: Yield 80%, white solid, mp 68–70 °C, ^{1}H NMR 7.46 (1H, dd, J = 1.2 & 7.2 Hz), 7.39 (2H, m), 7.18 (1H, dd, J = 1.2 and 7.2 Hz), 6.80 (1H, s), 4.71–4.87 (4H, m), 3.91 (6H, s), 3.59 (3H, s), 2.01 (6H, s); ESI-MS m/z: 411 ($M+Na^+$).
Compound **25**: Yield 20%; yellow oil, ^{1}H NMR 7.45 (1H, m), 7.37 (2H, m), 7.15 (1H, dd, J = 1.2 and 6.8 Hz), 6.78 (1H, s), 4.93 (2H, s), 4.78 (2H, s), 3.90 (6H, s), 3.56 (3H, s), 2.58 (8H, m); ESI-MS m/z 527 ($M+Na^+$).
Compound **26**: Yield 99%, yellow oil; ^{1}H NMR 7.97 (4H, m), 7.57 (1H, d, J = 7.2 Hz), 7.35–7.52 (8H, m), 7.27 (1H, dd, J = 7.2 and 2.8 Hz), 6.86 (1H, s), 5.17 (2H, d, J = 7.6), 5.00 (2H, s), 3.89 (6H, s), 3.61 (3H, s);ESI-MS m/z: 535 ($M+Na^+$).
Compound **27**: Yield 63%, brown solid, mp 57–58 °C, ^{1}H NMR 7.62 (1H, s), 7.49 (2H, m), 7.47 (2H, m), 7.26 (1H, m), 6.67 (1H, s), 3.95 (3H, s), 3.93 (3H, s), 3.61 (3H, s), 2.30 (3H, s), 2.28 (3H,s); ESI-MS 437 [$M+Na^+$].
Compound **28**: Yield 69%, white solid, mp 129–130 °C; ^{1}H NMR 9.64 (1H, s), 9.58 (1H, s), 7.51 (1H, s), 7.38 (1H, s), 6.74 (1H, s), 6.15 (2H, s), 4.00 (6H, s), 3.63 (3H, s); ESI-MS m/z: 367 ($M+Na^+$).
Compound **29**: Yield 63%; pale yellow solid, mp 102–103 °C; ^{1}H NMR 9.55 (1H, s), 7.46 (1H, s), 7.36 (1H, s), 6.63 (1H, s), 6.10 (2H, s), 3.97 (6H, s), 3.63 (3H, s), 3.61 (3H, s); ESI-MS m/z: 397 ($M+Na^+$).
Compound **30**: Yield 90%; white solid, mp 109–110 °C; ^{1}H NMR 7.00 (1H, s), 6.87 (1H, s), 6.62 (1H, s), 6.00 (2H, s), 4.31 (2H, d, J = 4 Hz), 4.21 (2H, d, J = 4 Hz), 3.90 (6H, s), 3.61 (3H, s); ESI-MS m/z: 371 ($M+Na^+$).
Compound **31**: Yield 93%; white solid, mp 81 °C; ^{1}H NMR 7.25 (1H, s), 7.02 (1H, s), 6.51 (1H, s), 6.01 (2H, s), 4.26 (2H, m), 3.96 (6H, s), 3.67 (3H, s), 3.58 (3H, s); ESI-MS m/z: 399 ($M+Na^+$).
Compound **32**: Yield 81%, pale yellow solid, mp 82–84 °C, ^{1}H NMR (DMSO-d_6) 11.28 (1H, s), 11.15 (1H, s), 7.42 (1H, s), 7.40 (1H, s), 7.30 (1H, s), 7.23 (1H, s), 6.77 (1H, s), 6.14 (2H, ds), 3.87 (3H, s), 3.83 (3H, s), 3.53 (3H, s); ESI-MS m/z: 397 ($M+Na^+$).
Compound **33**: Yield 92%, white solid, mp 154–155 °C; ^{1}H NMR 6.95 (1H, s), 6.78 (1H, s), 6.64 (1H, s), 6.02 (2H, s), 4.73–4.76 (4H, m), 3.92 (3H, s), 3.89 (3H, s), 3.64 (3H, s), 2.04 (3H, s), 2.00 (3H, s); ESI-MS m/z: 455 ($M+Na^+$).
Compound **34**: Yield 91%, ^{1}H NMR 7.00 (1H, s), 6.89 (1H, s), 6.71 (1H, s), 6.07 (2H, s), 4.63 (4H, m), 3.84 (3H, s), 3.76 (3H, s), 3.51 (3H, s), 2.40 (8H, m); ESI-MS m/z: 571 ($M+Na^+$).
Compound **35**: Yield 94%; white gum; ^{1}H NMR 7.96 (4H, m), 7.50 (2H, m), 7.38 (4H, m), 7.05 (1H, s), 6.86 (1H, s), 6.73 (1H, s), 6.00 (2H, ds), 5.06–5.03 (4H, m), 3.89 (6H, s), 3.66 (3H, s); ESI-MS m/z: 579 ($M+Na^+$).
Compound **36**: Yield 11%; pale yellow solid, mp 191–194 °C; ^{1}H NMR 8.33 (1H, s), 7.72 (1H, s), 6.87 (1H, s), 6.07 (2H, s), 4.04 (3H, s), 4.00 (3H, s), 3.96 (3H, s); ESI-MS m/z: 353 ($M+Na^+$).

Compound **37**: Yield 98%; white solid, mp 163–164 °C; ^{1}H NMR 7.26 (1H, s), 7.21 (1H, s), 6.92 (1H, s), 6.03 (2H, ds), 4.93 (1H, d, J = 12 Hz), 4.81 (1H, s), 3.99 (3H, s), 3.95 (3H, s), 3.66 (3H, s); ESI-MS m/z 367 ($M+Na^+$).
Compound **38**: Yield 80%; white solid, mp 106–107 °C; ^{1}H NMR 9.78 (1H, s), 7.48 (3H, m), 7.42 (2H, m), 7.36 (1H, s), 6.11 (2H, s), 4.00 (3H, s); ESI-MS m/z: 279 ($M+Na^+$).
Compound **39**: Yield 70%; white solid, mp 112–114 °C; ^{1}H NMR 9.95 (1H, s), 9.68 (1H, s), 8.07 (1H, dd, J = 1.6 and 7.6 Hz), 7.70 (1H, dd, J = 1.6 and 7.6 Hz), 7.61(1H, d, J = 7.6 Hz), 7.39 (1H, s), 7.37 (1H, dd, J = 1.6 and 7.6 Hz), 6.13 (2H, s), 3.83 (3H, s); ESI-MS m/z: 307 ($M+Na^+$).
Compound **40**: Yield 84%; white solid, mp 121–122 °C; ^{1}H NMR 9.89 (1H, s), 8.02 (1H, dd, J = 1.2 and 7.6 Hz), 7.63 (1H, dd, J = 1.2 and 7.6 Hz), 7.52 (1H, d, J = 7.6 Hz), 7.40 (1H, s), 7.27 (1H, d, J = 7.6 Hz), 6.01 (2H,s), 4.00 (3H, s), 3.58 (3H, s); ESI-MS m/z: 337 ($M+Na^+$).
Compound **41**: Yield 80%; white solid, mp 89–91 °C; ^{1}H NMR 9.52 (1H, s), 7.43 (3H, m), 7.30 (2H, m), 7.24 (1H, s), 6.10 (2H, s), 3.82 (3H, s). ESI-MS m/z: 279 ($M+Na^+$).
Compound **42**: Yield 70%; white solid, mp 125–126 °C; ^{1}H NMR 9.86 (1H, s), 9.47 (1H, s), 8.06 (1H, dd, J = 1.6 and 7.6 Hz), 7.67 (1H, dd, J = 1.6 and 7.6 Hz), 7.64 (1H, d, J = 7.6 Hz), 7.27 (1H, s), 7.25 (1H, d, J = 7.6 Hz), 6.13 (2H, s), 3.83 (3H, s); ESI-MS m/z: 295 ($M+Na^+$).
Compound **43**: Yield 70%; white solid, mp 88–90 °C; ^{1}H NMR 9.84 (1H, s), 8.02 (1H, dd, J = 1.2 and 7.6 Hz), 7.58 (1H, dd, J = 1.2 and 7.6 Hz), 7.50 (1H, d, J = 7.6 Hz), 7.24 (1H, s), 7.15 (1H, d, J = 7.6 Hz), 6.10 (2H, s), 3.78 (3H, s), 3.52 (3H, s); ESI-MS m/z: 337 ($M+Na^+$). All ^{1}H NMR were measured in solvent $CDCl_3$ unless indicated.