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Synthesis and in vitro antibacterial activity of novel methylamino piperidinyl oxazolidinones☆

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Abstract—Design and synthesis of a few novel methylamino piperidinyl substituted oxazolidinones are reported. Their antibacterial activities have been evaluated in a MIC assay against broader panel of both susceptible and resistant Gram-positive strains. (*S*)-*N*-{3-[3-Fluoro-4-(methyl-{1-[3-(5-nitrofuran-2-yl)-acryloyl]-piperidin-4-yl}-amino)-phenyl]-2-oxo-oxazolidin-5-ylmethyl}-acetamide **4i** has shown comparable antibacterial activity to linezolid and eperezolid in the MIC assay, additionally compound **4i** showed good antibacterial activity with an in vitro MIC value of 2–4 μg/mL against linezolid resistant *Staphylococcus aureus* (linezolid ⩾16 μg/mL).

Bacterial infections have been a serious concern both in the hospital and community settings. The mortality and morbidity caused by Gram-positive bacteria has worldwide alarming impact on the human population. Oxazolidinones have been remarkable antibacterials, which act with a novel mechanism by inhibiting the protein synthesis at the bacterial ribosomal level.[1] The only drug of oxazolidinone class linezolid (Zyvox™) **1** (Fig. 1) has been approved by USFDA in April 2000.[2] The multidrug resistance is another challenge to medical fraternity. Unfortunately the linezolid is also not spared from resistance, however only few cases have been reported.[3]

Several pharmaceutical industries and academic institutions have witnessed the pace of oxazolidinone antibacterial research to get efficacious and safer drug.[4,5] Recently, we have disclosed our oxazolidinone antibacterial findings but due to unfavorable pharmacokinetic and pharmacodynamic profile none of the compounds could be selected for further development[6].

Weidner-Wells et al. investigated 4-piperidinyloxy oxazolidinone **3** (Fig. 1) with antibacterial activity against variety of susceptible as well as resistant Gram-positive organisms.[7] The results from the SAR developed by them demonstrated that replacement of piperazinyl ring of eperezolid **2** (Fig. 1) by 4-piperidinyloxy moiety is tolerable for imparting antibacterial activity. We have developed a novel series of oxazolidinones **4a**–**4i**, (Fig. 2) where piperazinyl ring of eperezolid is replaced by methylamino piperidinyl system. Ranbaxy Research Laboratories has optimized piperazinyloxazolidinones to get 5-nitrofuryl derivative **5** (**RBx-7644**),[5m] (Fig. 2) which is safer and currently in clinical development.[8] Similarly we have developed SAR and identified compound **6**, (Fig. 2) which bears 5-nitrofuryl on the distant nitrogen atom of the piperazinyl ring of the eperezolid system, show impressive in vitro MIC values against all the strains tested.[6a] Looking on the promising drugability of 5-nitrofuryl derivative, we modified methylamino piperidinyl oxazolidinone series to get 5-nitrofuryl derivative **4i**. The oxazolidinones **1**, **2**, **4a**–**4i**, **5**, and **16** were evaluated for their in vitro antibacterial activities in MIC assay by Clinical & Laboratory Standards Institute Guidelines.[9]

The syntheses of methylamino piperidinyl substituted oxazolidinones **4a**–**4i** and **16** have been outlined in Scheme 1 and achieved as reported in the literature.[6b,10] 4-Hydroxy piperidine was converted into *N*-Boc-4-pipe-

Keywords: *N*-Methylamino piperidinylaryloxazolidinones; In vitro MIC assay; Gram-positive organism; Linezolid resistant *Staphylococcus aureus*.

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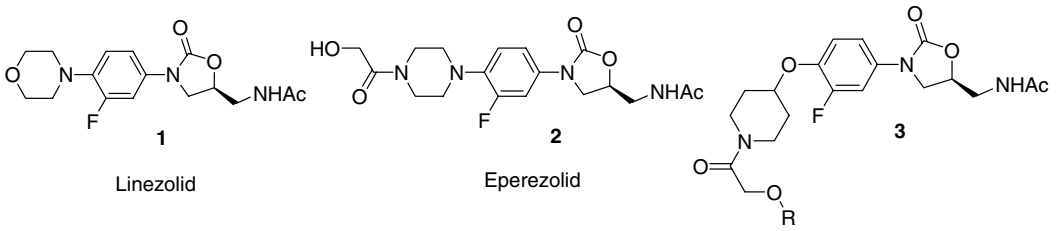


Figure 1.

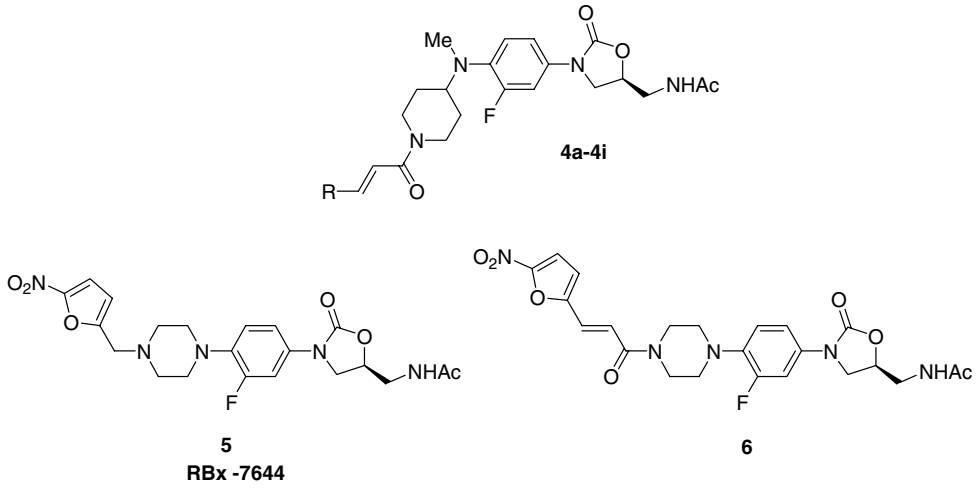
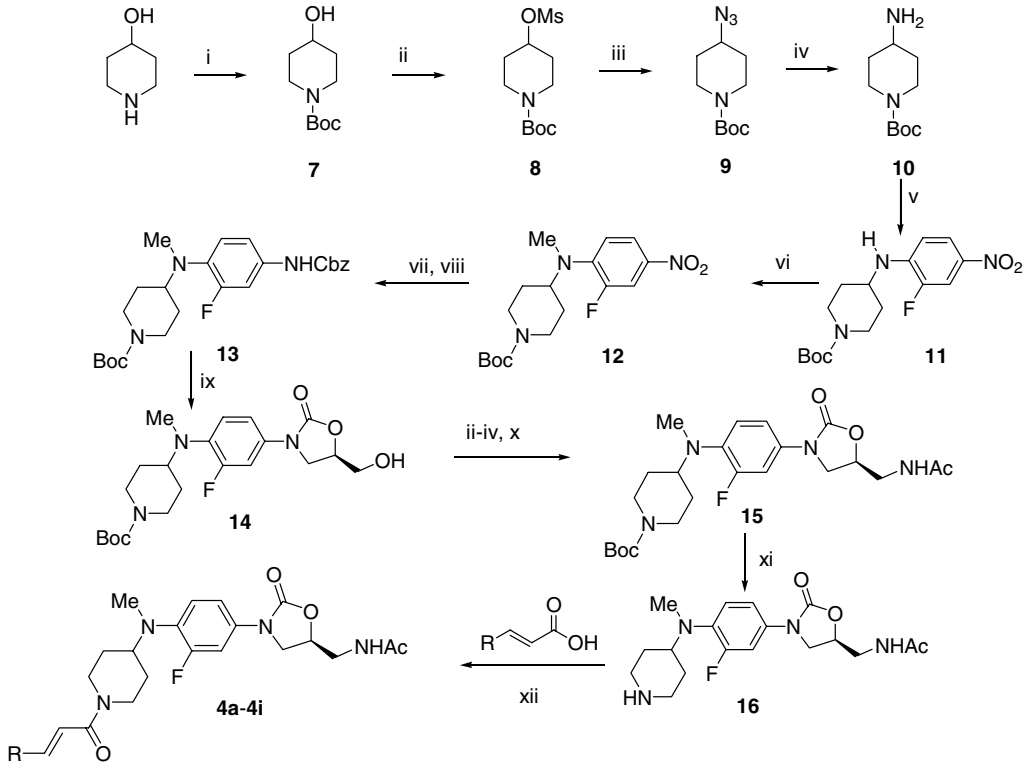


Figure 2.

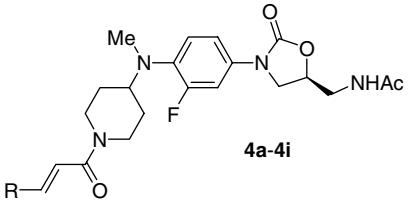
ridinol derivative **7** using *tert*-butoxy carbonyl anhydride, which was reacted with methanesulfonyl chloride to afford mesityl derivative **8**. Reaction of **8** with sodium azide gave azide derivative **9**, which was further reduced to its amino derivative **10** using triphenyl phosphine. Reaction of **10** with 3,4-difluoro nitrobenzene was carried out by nucleophilic substitution reaction at position 4 to afford **11**. The –NMe derivative **12** was synthesized from **11** employing methyl iodide and sodium hydride. The nitro group of compound **12** was reduced using Raney-Ni/hydrazine hydrate to furnish $-NH_2$, which upon subsequent protection with carboxy benzyloyl afforded intermediate **13**. The oxazolidinone ring was constituted by reacting anion of **13** with (*R*)-glycidyl butyrate to afford alcohol derivative **14**. Compound **14** was subsequently converted to $-NH_2$ derivative in the similar manner as described for compounds **7**–**10** followed by reaction with acetic anhydride to get –NHAc derivative **15**. The –Boc moiety of compound **15** was deprotected by treatment of trifluoroacetic acid to afford *N*-methyl piperidinyl oxazolidinone intermediate **16**. Finally compound **16** was reacted with appropriate acrylic acid derivatives using 1-hydroxy-benzotriazole monohydrate and [1-(3-dimethylaminopropyl)-3-ethylcarbodiimide] hydrochloride in the presence of triethylamine to furnish compounds **4a**–**4i**.

The oxazolidinones **4a**–**4i** and **16** were screened against susceptible Gram-positive strains such as *Bacillus subtilis*, *Staphylococcus epidermidis*, *Enterococcus faecalis*, and *Staphylococcus aureus*. The compound containing cinnamoyl group **4a** exhibited mild in vitro activity for susceptible *B. subtilis*, however it did not show antibacterial activity for rest of the strains mentioned in Table 1. Substitution of the phenyl ring of cinnamoyl moiety by 4-OH group **4b** also did not make any notable change in MIC values except for *E. faecalis*. Thus, substitution of electron-donating group on cinnamoyl moiety is not suitable for imparting antibacterial activities. In order to see the effect of electron-withdrawing group on phenyl ring, we substituted 4th position of the phenyl ring with electron-withdrawing $-NO_2$ group **4c**, to our surprise there was no improvement observed in antibacterial activities. Furthermore, when 3 and 4 positions were substituted as 1,2-methylenedioxy group **4d**, still no antibacterial activity was noticed. Looking on the unfavorable antibacterial activity shown by cinnamoyl compound **4a** and its derivatives **4b**–**4d**, we replaced phenyl system of cinnamoyl derivative with saturated cyclohexyl group **4e**, however it exhibited MIC 4–8 μg/mL against methicillin resistant *S. aureus* and there was complete loss of antibacterial activity for rest of the strains tested. Owing to our previous reports, where heterocycle systems displayed significant antibacterial activities against the similar set of Gram-positive strains,[6d] further we synthesized furan derivative **4f**, which also did not show appreciable change in MIC values as compared to **4e** (Table 1). Methylamino piperid-

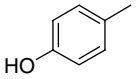
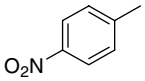
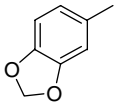


Scheme 1. Reagents and conditions: (i) Boc_2O, THF, 0 °C, 3–4 h, 85%; (ii) $MeSO_2Cl$, TEA, CH_2Cl_2, 0–5 °C, 1 h, 63%; (iii) NaN_3, DMF, 70–80 °C, 2–3 h, 45%; (iv) PPh_3, 1,4-dioxane, MeOH, NH_3 aq, 27–28 °C, 30 min, 44%; (v) $C_6H_3F_2NO_2$, CH_3CN, 75–80 °C, 1–2 h, 76%; (vi) NaH, MeI, DMF, 27–28 °C, 30 min, 23%; (vii) Raney Ni, $N_2H_4{\cdot}H_2O$, MeOH, 27–78 °C, 30 min, 50%; (viii) CbzCl, $NaHCO_3$, $(CH_3)_2CO$, H_2O, 0–27 °C, 35%; (ix) *n*-BuLi (1.6 M sol. in hexane), (*R*)-glycidyl butyrate,THF, −78 °C, 3 h, 40%; (x) Ac_2O, pyridine, 27–28 °C, 30 min, 85%; (xi) TFA, CH_2Cl_2, 27–28 °C, 1–2 h, 65%; (xii) EDC·HCl, $HOBt{\cdot}H_2O$, TEA, CH_2Cl_2, 27–28 °C, 0.5–1 h, (15–76%).

Table 1. In vitro MIC [minimum inhibitory concentration in μg/mL] values of novel methylamino piperidinyl oxazolidinones **4a**–**4i** in various susceptible Gram-positive strains[a]

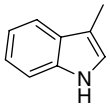
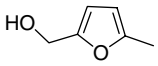
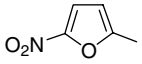


4a-4i

Compound	R	B.s.	S.e.	E.f.	E.f. 1	S.a.	S.a. 1	S.a. 2
4a		2–4	8–16	>16	>16	8–16	8–16	4–8
4b		2–4	8–16	4–8	>16	8–16	>16	>16
4c		4–8	8–16	>16	>16	>16	>16	>16
4d		2–4	8–16	8–16	>16	8–16	>16	>16

(*continued on next page*)

Table 1 (*continued*)

Compound	R	B.s.	S.e.	E.f.	E.f. 1	S.a.	S.a. 1	S.a. 2
4e		8–16	>16	>16	8–16	>16	8–16	8–16
4f		2–4	>16	>16	>16	>16	>16	>16
4g		2–4	4–8	8–16	>16	8–16	>16	>16
4h		>16	>16	>16	>16	>16	>16	>16
4i		0.5–1	1–2	2–4	4–8	1–2	2–4	1–2
1		1–2	2–4	2–4	1–2	1–2	2–4	ND
2		0.5–1	2–4	2–4	2–4	1–2	2–4	ND
5		0.25–0.5	0.5–1	ND	2–4	1–2	1–2	1–2
16		>16	>16	>16	>16	>16	>16	>16

[a] MIC were determined by broth micro dilution technique. B.s., *Bacillus subtilis* **ATCC 6633**; S.e., *Staphylococcus epidermidis* **ATCC 12228**; E.f., *Enterococcus faecalis* **ATCC 29212**; E.f. 1, *Enterococcus faecalis* **ATCC 14506**; S.a., *Staphylococcus aureus* **ATCC 33591**; S.a. 1, *Staphylococcus aureus* **ATCC 29213**; S.a. 2, *Staphylococcus aureus* **ATCC 33592**; ND, not done.

inyl oxazolidinone with 3-indoyl moiety resulted in compound **4g**, which was found to be mediocre against *B. subtilis*, *S. epidermidis*, while hydroxymethyl derivative of furan **4h** showed no antibacterial activities against susceptible strains (Table 1). The 5-nitrofuryl derivative **4i** exhibited comparable in vitro MIC values as those of linezolid **1**, eperezolid **2**, and RBx-7644 **5**. Replacement of piperazinyl system of compound **6** by *N*-methyl piperidinyl as in **4i** resulted in a slightly lesser potent compound.[6a] The unmasked *N*-methyl piperidinyl derivatives **16** were found to be inactive against all the strains tested (Tables 1 and 2). Encouraged by

Table 2. In vitro MIC values of novel methylamino piperidinyl oxazolidinones **4a**–**4i** in various susceptible and resistant Gram-positive strains[a]

Compound	E.f. 2	E.f. 3	S.a. 3	S.a. 4	S.a. 5	S.p.	S.p. 1	S.e. 1
4a	8–16	4–8	8–16	>16	8–16	8–16	8–16	4–8
4b	8–16	8–16	8–16	>16	4–8	8–16	8–16	8–16
4c	>16	>16	>16	>16	8–16	>16	>16	8–16
4d	>16	>16	>16	>16	>16	>16	>16	>16
4e	8–16	8–16	8–16	>16	4–8	>16	8–16	8–16
4f	>16	8–16	>16	>16	8–16	>16	>16	>16
4g	8–16	8–16	8–16	>16	2–4	8–16	8–16	4–8
4h	>16	>16	>16	>16	>16	>16	>16	>16
4i	1–2	1–2	2-4	2–4	1–2	2–4	0.25–0.5	0.25–0.5
1	1–2	ND	1–2	>16	1–2	0.5–1	0.5–1	1–2
2	1–2	ND	2–4	>16	1–2	0.25–0.5	0.25–0.5	ND
5	1–2	2–4	1–2	>16	0.5–1	2–4	0.25–0.5	0.25–0.5
16	>16	>16	>16	>16	>16	>16	>16	>16

[a] MIC were determined by broth micro dilution technique. E.f. 2, multi-resistant *Enterococcus faecalis* **ATCC 700802**; E.f. 3, vancomycin resistant *Enterococcus faecium* **ATCC 700221**; S.a. 3, *Staphylococcus aureus* **ATCC 25923**; S.a. 4, linezolid resistant *Staphylococcus aureus* **NRS 119**; S.a. 5, methicillin resistant *Staphylococcus aureus* **ATCC 700699**; S.p., *Streptococcus pyogens* **ATCC 14289**; S.p. 1, multi-resistant *Streptococcus pneumoniae* **ATCC 700904**; S.e. 1, *Staphylococcus epidermidis* **ATCC 155**; ND, not done.

MIC values obtained for compound **4i**, we tested all the compounds against broader panel of susceptible and resistant Gram-positive strains (Table 2). Compounds **4a**–**4h** and **16** displayed similar inferior potency against various strains mentioned in Table 2 as exhibited for strains mentioned in Table 1 except for compound **4i**, which was found to be potent against all the strains mentioned in Table 2.

In the view of emerging resistance to linezolid, we tested oxazolidinone derivatives **4a**–**4i** against linezolid resistant *S. aureus* strain NRS 119 (we are registered user of Network on Antimicrobial Resistance in *S. aureus*, www.narsa.net), which has G 2576T mutations in DNA encoding the central loop of domain V of 23S rRNA and these mutations have been reported to develop microorganisms having linezolid resistance.[3d] Compound **4i** showed antibacterial activity with in vitro MIC values in the range of 2–4 μg/mL against linezolid resistant *S. aureus* (Table 2, linezolid $\geqslant$16 μg/mL). Thus, appropriate substitution on oxazolidinone would give compounds, which may even work against linezolid resistant organisms.

In summary, replacement of piperazinyl ring of eperezolid by methylamino piperidinyl system resulted in compounds which were tolerable for antibacterial activity in MIC assay. The cinnamoyl derivative **4a** and different substituents on the phenyl ring **4b** and **4c** are poor antibacterial agents. However, the heterocyclic derivatives **4f**–**4i** are still suitable for imparting antibacterial activity particularly 5-nitrofuryl derivative **4i** is comparable in antibacterial MIC values to linezolid, eperezolid, and RBx-7644. Optimization of the methylamino piperidinyl oxazolidinone resulted in compound **4i**, which was also active against linezolid resistant strains.

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10. Spectroscopic data for compounds **4a**–**4i**:
Compound **4a**. 98.8% purity by HPLC; mp 74–76 °C; IR (KBr) 3292, 1751, 1647, 1598 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$), δ 7.65 (d, J = 15.36 Hz, 1H), 7.54–7.51 (dd, J = 7.77 and 2.34 Hz, 2H), 7.40–7.35 (m, 4H), 7.05 (d, J = 2.46 Hz, 1H), 6.99 (d, J = 8.97 Hz, 1H), 6.90 (d, J = 15.4 Hz, 1H), 6.02 (bs, 2H), 4.78–4.75 (m, 2H), 4.10–4.08 (d, 1H), 4.02 (t, J = 8.95 Hz, 1H), 3.77–3.64 (m, 3H), 3.42–3.37 (t, 1H), 3.16–3.12 (bs, 1H), 2.71 (s, 3H), 2.03 (t, 3H), 1.89–1.81 (bs, 2H), 1.68–1.62 (dd, J = 11.88 and 4.41 Hz, 2H); ESI-MS: 495.2 $(M+H)^+$.
Compound **4b**. 98% purity by HPLC; mp 128–130 °C; IR (KBr) 3292, 1747, 1639, 1606 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.60 (d, J = 15.36 Hz, 1H), 7.42 (d, J = 8.67 Hz, 3H), 7.04–6.97 (m, 2H), 6.83 (d, J = 8.55 Hz, 2H), 6.75 (d, J = 15.36 Hz, 1H), 6.06 (bs, 1H), 5.84 (bs, 1H), 4.78–4.75 (m, 2H), 4.16–4.12 (d, 1H), 4.02 (t, J = 8.97 Hz, 1H), 3.74–3.60 (m, 3H), 3.35–3.28 (t, 1H), 3.12–3.08 (bs, 1H), 2.70 (s, 3H), 2.03 (s, 3H), 1.85–1.78 (bs, 2H), 1.28–1.25 (bs, 2H); ESI-MS: 511.2 $(M+H)^+$.
Compound **4c**. 96.7% purity by HPLC; mp 153–155 °C; IR (KBr) 3292, 1647, 1608 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (d, J = 8.58 Hz, 2H), 7.7–7.64 (t, J = 8.42 Hz, 3H), 7.45–7.39 (dd, J = 14.01 and 2.01 Hz, 1H), 7.06–6.95 (m, 3H), 6.16 (bs, 1H), 4.77–4.76 (m, 2H), 4.16–4.12 (d, 1H), 4.03 (t, J = 8.95 Hz, 1H), 3.78–3.58 (m, 3H), 3.40–3.36 (t, 1H), 3.20–3.14 (bs, 1H), 2.72 (s, 3H), 2.03 (s, 3H), 1.88–1.84 (bs, 2H), 1.67–1.65 (bs, 2H); ESI-MS: 540.2 $(M+H)^+$.
Compound **4d**. 98.4% purity by HPLC; mp 76–78 °C; IR (KBr) 3292, 1643, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (d, J = 15.54 Hz, 1H), 7.44–7.38 (dd, J = 14.01 and 2.43 Hz, 1H), 7.05–6.97 (m, 2H), 6.81–6.70 (m, 1H), 6.07 (bs, 1H), 5.99 (s, 2H), 4.78–4.76 (m, 2H), 4.18–4.14 (d, 1H), 4.02 (t, J = 8.97 Hz, 1H), 3.77–3.60 (m, 3H), 3.38–3.35 (t, 1H), 3.20–3.14 (bs, 1H), 2.70 (s, 3H), 2.69–2.68 (m, 1H), 2.02 (s, 3H), 1.84–1.78 (bs, 2H), 1.67–1.65 (bs, 2H); ESI-MS: 539.2 $(M+H)^+$.
Compound **4e**. 97% purity by HPLC; mp 61–63 °C; IR (KBr) 3292, 1652, 1604 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.38 (dd, J = 14.01 and 2.43 Hz, 1H), 7.04 (d, J = 2.43 Hz, 1H), 6.99 (d, J = 9.03 Hz, 1H), 6.85–6.78 (m, 1H), 6.21–6.16 (dd, J = 15.24, 1.05 Hz, 1H), 6.02 (bs, 1H), 4.78–4.76 (m, 2H), 4.10–4.08 (d, 1H), 4.02 (t, J = 8.97 Hz, 1H), 3.77–3.60 (m, 3H), 3.42–3.38 (m, 1H), 3.02–2.98 (t, 1H), 2.69 (s, 3H), 2.12–2.08 (m, 1H), 2.02 (s, 3H), 1.78–1.60 (bs, 6H), 1.58–1.54 (bs, 2H), 1.28–1.16 (m, 4H), 1.14–1.12 (m, 2H); ESI-MS: 501.2 $(M+H)^+$.
Compound **4f**. 96.9% purity by HPLC; mp 118–120 °C; IR (KBr) 3292, 1647, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.47–7.38 (m, 3H), 7.05 (d, J = 2.37 Hz, 1H), 6.99 (d, J = 9.03 Hz, 1H), 6.82 (d, J = 15.12 Hz, 1H), 6.53 (d, J = 3.36 Hz, 1H), 6.45 (d, J = 3.36 Hz, 1H), 6.0 (bs, 1H), 4.79–4.75 (m, 2H), 4.12–4.08 (d, 1H), 4.02 (t, J = 8.97 Hz, 1H), 3.77–3.60 (m, 3H), 3.42–3.36 (t, 1H), 3.08 (bs, 1H), 2.70 (s, 3H), 2.03 (s, 3H), 1.85–1.81 (bs, 2H), 1.69–1.59 (bs, 2H); ESI-MS: 485.3 $(M+H)^+$.
Compound **4g**. 93.8% purity by HPLC; mp 120–122 °C; IR (KBr) 3269, 1635, 1573 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.63 (bs, 1H), 7.89 (d, J = 2.61 Hz, 1H), 7.48–7.39 (m, 3H), 7.28–7.24 (m, 2H), 7.05–6.9 (m, 3H), 6.10 (bs, 1H), 4.77–4.76 (m, 2H), 4.18–4.14 (d, 1H), 4.02 (t, J = 8.97 Hz, 1H), 3.76–3.62 (m, 3H), 3.42–3.38 (t, 1H), 3.16–3.12 (bs, 1H), 2.71 (s, 3H), 2.10–2.06 (bs, 1H), 2.02 (s, 3H), 1.86–1.82 (bs, 2H), 1.74–1.70 (bs, 2H); ESI-MS: 534.2 $(M+H)^+$.
Compound **4h**. 94.1% purity by HPLC; oil; IR (neat) 3303, 1645, 1595 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.43–7.37 (m, 2H), 7.04 (d, J = 2.16 Hz, 1H), 6.99 (d, J = 8.97 Hz, 1H), 6.82 (d, J = 15.06 Hz, 1H), 6.47 (d, J = 3.21 Hz, 1H), 6.35 (d, J = 3.37 Hz, 1H), 6.3 (bs, 1H), 4.77–4.75 (m, 2H), 4.63 (s, 2H), 4.16–4.12 (d, 1H), 4.02 (t, J = 8.97 Hz, 1H), 3.77–3.61 (m, 3H), 3.42–3.38 (t, 1H), 3.1 (t, 1H), 2.70 (s, 3H), 2.36–2.32 (bs, 1H), 2.02 (s, 3H), 1.86–1.80 (bs, 2H), 1.75–1.69 (bs, 2H); ESI-MS: 515.3 $(M+H)^+$.
Compound **4i**. 98% purity by HPLC; mp 175–177 °C; IR (KBr) 3292, 1647, 1600 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46–7.40 (dd, J = 15.18 and 3.66 Hz, 2H), 7.35 (d, J = 3.92 Hz, 1H), 7.15 (d, J = 15.21 Hz, 1H), 7.05 (d, J = 2.47 Hz, 1H), 7.01 (d, J = 3.91 Hz, 1H), 6.69 (d, J = 3.95 Hz, 1H), 6.0 (bs, 1H), 4.77–4.75 (m, 2H), 4.16–4.12 (d,1H), 4.03 (t, J = 8.97 Hz, 1H), 3.78–3.58 (m, 3H), 3.42–3.36 (t, 1H), 3.16 (bs, 1H), 2.71 (s, 3H), 2.03 (s, 3H), 1.85–1.81 (bs, 2H), 1.69–1.65 (bs, 2H); ESI-MS: 530.1 $(M+H)^+$.