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Synthesis and antibacterial activity of 4,5,6,7-tetrahydro-thieno[3,2-*c*]pyridine quinolones

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Dedicated to Late Shri Ramanbhai Patel, the founder of Zydus Research Centre, Ahmedabad.

Abstract—Synthesis and antibacterial activity of a number of substituted 4,5,6,7-tetrahydro-thieno[3,2-*c*]pyridine quinolones is reported. The antibacterial activities were evaluated in standard in vitro MIC assay method. Some of the compounds showed in vitro (MIC) antibacterial activity comparable to those of Gatifloxacin, Ciprofloxacin, and Sparfloxacin.

Fluoroquinoloneshave been the landmark discovery in the treatment of bacterial infections.[1] Ciprofloxacin introduced in the year 1986 by Bayer is one of the most potent and widely used antibacterial agents.[2]

Despite a large number of fluoroquinolones approved for the treatment of bacterial infection, there have been unabated efforts for the discovery of new quinolones[3] with specific properties and most importantly to overcome the problem of growing bacterial resistance. The major concern has been the growing incidence of resistance especially to *Staphylococci* and *Enterococci*.[4] Some of the side effects of quinolone antibacterials are unacceptable, for example, Grepafloxacin was withdrawn from market, due to increased cases of heart problems in clinical findings.[5] Similarly, Trovafloxacin was removed from the market due to liver toxicity[5] (Fig. 1).

Several drugs belonging to fluoroquinolone class having a substitution at the C-7 position attached through the N-atom are in clinical use. Recently, fluoroquinolones **6** having 4,5,6,7-tetrahydrothieno [3,2-*c*] pyridine moiety at C-7 position (Fig. 2) have been reported from Abbott laboratory[6] wherein, the substitution is linked through the carbon atom. Although good antibacterial activities have been reported against several strains such as *Staphylococcus aureus*, *Enterococcus faecalis*, *Moraxella catarrahalis*, *Escherichia coli*, *Haemophilius influenzae*, and *Streptococcus pneumoniae*, no compound is in development from this class of molecules. Interestingly, none of the quinolones having C-7 linkage through C-atom have succeeded to reach the market due to various kinds of toxicity, although some of them showed very potent antibacterial profile in preclinical evaluation.[5] Thus, we believed that safer and superior antibacterial compounds can be developed by attaching tetrahydrothieno[3,2-*c*]pyridine moiety through N-atom of the substituent at C-7 position, which would result in compounds **7**–**20**. Earlier, we have reported tetrahydrothieno[3,2-*c*]pyridine incorporated oxazolidinones, wherein compounds showed significant antibacterial activities in MIC assay.[7] In this communication we are reporting the synthesis, characterization,[8] and antibacterial activity of compounds **7**–**20** (Fig. 2), which bear the 4,5,6,7- tetrahydrothieno[3,2-*c*]pyridine moiety attached through N-atom at the C-7 position of the quinolone.

Interestingly, quinolones **7**–**20** displayed significant in vitro antibacterial activities for most of the Gram-positive strains (Tables 1 and 2).

The minimum inhibitory concentration (MIC) for 90% bacterial growth inhibition was determined by microbroth dilution technique using the National Committee

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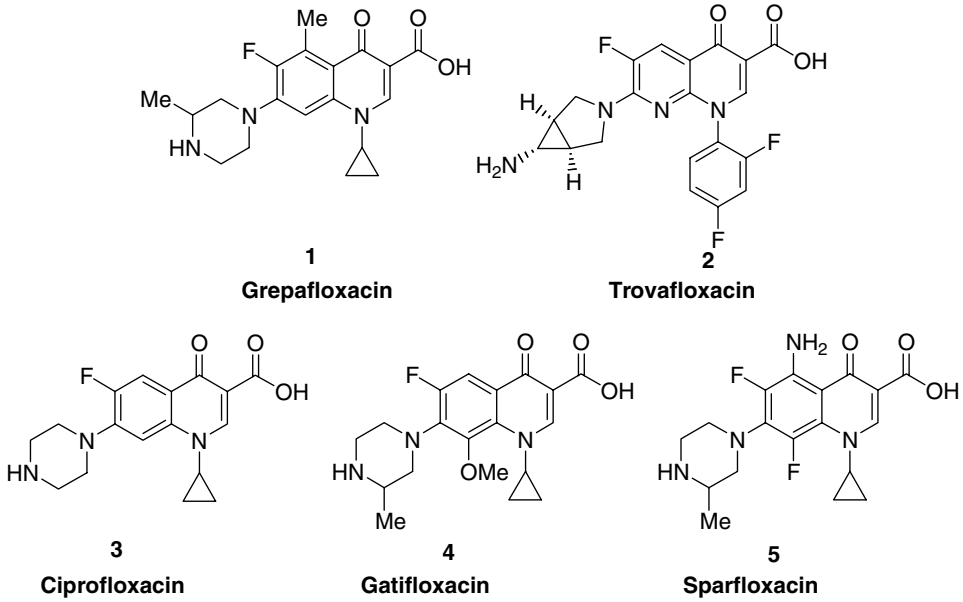


Figure 1.

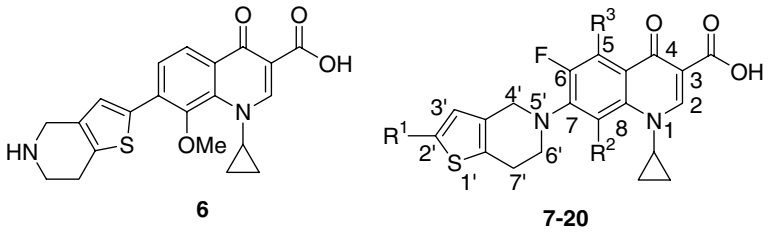


Figure 2.

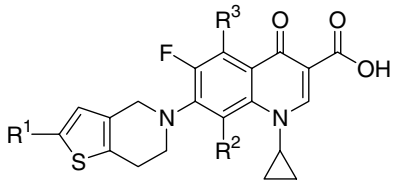
for Clinical and Laboratory Standards (NCCLS) method,[9] now known as Clinical and Laboratory Standards Institute Guidelines.

Compounds, which showed in vitro MIC values in the range of 0.25–1.0 μg/mL for most of the strains mentioned in Table 1, were further evaluated against a broader panel of susceptible and resistant Gram-positive strains (Table 2).

The syntheses of compounds have been outlined in Schemes 1 and 2. 4,5,6,7-Tetrahydro-thieno[3,2-*c*]pyridine and its derivatives **21**–**25** were synthesized by method described in the literature.[10] The difluoro derivatives **26**–**30** were synthesized conveniently using the methods described in the literature.[11] Conventional method to introduce 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine **21** or its derivatives in quinolone scaffold of **26**–**30** failed to afford the desired compounds **36**–**46**. Thus, we decided to activate the C-7 position by converting compounds **26**–**30** to fluoroborate derivatives **31**–**35** through transesterification reaction using 40% aqueous solution of tetrafluoroboric acid. The nucleophilic substitution at 7th position of fluoroborate derivatives **31**–**35** with tetrahydrothienopyridine derivatives **21**–**25** was achieved using triethylamine in dimethylsulfoxide to afford compounds **36**–**46**. Compounds **36**–**46** were hydrolyzed to the corresponding carboxylic acid derivatives **7**–**11**, **14**–**17**, **19**, and **20** by refluxing in an 80% solution of ethanol in water and triethylamine as depicted in Scheme 1. The formyl derivative **10** was oxidized to compound **12** by silver oxide and methyl alcohol derivative **11** was converted to –OCOMe derivative **13** by reacting with acetic anhydride. The aniline derivative **17** was converted to –NHCOMe derivative **18** in a similar manner (Scheme 2).

The results of in vitro antibacterial activities (MIC) of compounds **7**–**20** against various bacterial strains are summarized in Tables 1 and 2. The quinolones substituted by 8-methoxy have shown better antibacterial activity than their corresponding 8-unsubstituted analogs.[12] The 8-methoxy template is present in Gatifloxacin (**4**), therefore we introduced tetrahydrothienopyridine moiety at C-7 to obtain **7**. It has been observed that introduction of tetrahydrothienopyridine led to significant loss of antibacterial activity against susceptible *Staphylococcus epidermis and Pseudomonas aeruginosa* (Table 1) compared to Gatifloxacin for compound **7**. However, in most of the *Staphylococcus aureus* and *Enterococcus faecium* strains, good antibacterial activity was observed and compound **7** is more potent than Gatifloxacin in MIC assay (Table 2). The corresponding 8-unsubstituted analog **15** showed inferior antibacterial activity (Tables 1 and 2) indicating the importance of –OMe

Table 1. In vitro MIC values of novel quinolones **7**–**20** in various Gram-positive and Gram-negative bacteria[a]



7-20

Compound	R^1	R^2	R^3	Gram-positive				Gram-negative		
				B.s.	S.e.	S.a.	E.f.	P.a.	K.p.	E.c.
7	–H	–OMe	–H	⩽0.12	>16	⩽0.12	2	>16	0.25	⩽0.12
8	–Br	–OMe	–H	⩽0.12	⩽0.12	1	0.5	>16	4	2
9	$–NO_2$	–OMe	–H	⩽0.12	4	⩽0.12	⩽0.12	1	0.25	0.5
10	–CHO	–OMe	–H	⩽0.12	⩽0.12	⩽0.12	⩽0.12	8	⩽0.12	0.25
11	$–CH_2OH$	–OMe	–H	⩽0.12	>16	2	0.5	16	⩽0.12	0.25
12	–COOH	–OMe	–H	0.5	1	2	8	>16	2	8
13	$–CH_2OAc$	–OMe	–H	⩽0.12	⩽0.12	0.25	0.5	>16	2	0.5
14	–H	–OMe	$–NO_2$	0.25	2.0	8	ND	>16	ND	16
15	–H	–H	–H	⩽0.12	8	4	ND	>16	⩽0.12	0.25
16	–Br	–H	–H	⩽0.12	0.5	4	ND	>16	2	1
17	–H	–F	$–NH_2$	⩽0.12	16	4	>16	>16	4	0.25
18	–H	–F	–NHAc	1	>16	>16	>16	>16	>16	>16
19	–H	–F	–F	0.25	2	4	>16	>16	8	0.5
20	–Br	–F	NH_2	>16	>16	ND	>16	>16	>16	>16
3				⩽0.12	⩽0.12	1	2	0.25	⩽0.12	⩽0.12
4				⩽0.12	0.25	0.5	0.5	1.0	⩽0.12	⩽0.12
5				⩽0.12	0.25	16	ND	0.25	⩽0.12	ND

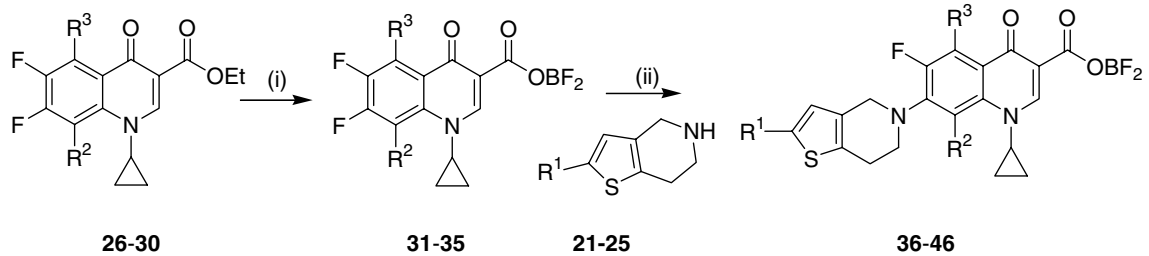
[a] MIC were determined by microbroth dilution technique and values reported in the table represent the values obtained in triplicate. B.s., *Bacillus subtilis* **ATCC 6633**; S.e., *Staphylococcus epidermidis* **ATCC 12228**; S.a., *Staphylococcus aureus* **ATCC 33591**; E.f., *Enterococcus faecalis* **ATCC 29212**; P.a., *Pseudomonas aeruginosa* **ATCC 27853**; K.p., *Klebsiella pneumoniae* **ATCC 10031**; E.c., *Escherichia coli* **ATCC 25922**.

Table 2. In vitro (MIC values in μg/mL) antibacterial activity for selected quinolone compounds against broader panel susceptible and resistant Gram-positive strains[a]

Compound	S.a.1	S.a.2	S.a.3	S.a.4	S.a.5	E.f.1	E.f.2	E.f.3	S.p
7	⩽0.125	⩽0.125	0.25	2	>16	0.25	⩽0.125	16	⩽0.125
8	2	4	2	>16	>16	>16	>16	>16	8
9	4	4	8	16	>16	>16	16	>16	0.5
10	⩽0.125	⩽0.125	⩽0.125	0.5	⩽0.12	2	0.25	>16	⩽0.12
11	2	2	ND	2	0.5	ND	0.25	ND	⩽0.12
12	2	2	0.5	>16	>16	>16	16	>16	1
13	1	4	2	4	2	ND	1	ND	⩽0.12
15	1	4	1	>16	>16	16	4	>16	0.25
16	0.5	4	4	>16	>16	>16	>16	ND	2
17	4	8	4	>16	>16	>16	16	>16	2
19	2	4	2	>16	>16	>16	16	>16	2
3	0.25	1	0.5	>16	>16	1	1	>16	0.25
4	⩽0.125	0.25	4	8	4	0.5	0.5	>16	⩽0.125
5	⩽0.125	⩽0.125	⩽0.125	8	16	>16	1	16	⩽0.125

[a] MIC were determined by microbroth dilution technique and values reported in the table represent the values obtained in triplicate. S.a.1, *Staphylococcus aureus* **ATCC 25923**; S.a.2, *Staphylococcus aureus* **ATCC 29213**; S.a.3, *Staphylococcus aureus* **ATCC 33592**; S.a.4, methicillin resistant *Staphylococcus aureus* **ATCC 700699**; S.a.5, linezolid resistant *Staphylococcus aureus* **NRS 119**; E.f.1, *Enterococcus faecalis***ATCC 14506**; E.f.2, vancomycin resistant *Enterococcus faecalis* **ATCC 700802**; E.f.3, vancomycin resistant *Enterococcus faecium* **ATCC 700221**; S.p., penicillin resistant *Streptococcus pneumoniae* **ATCC 700904**.

group at C-8. Compound **14**, where a nitro group is present at C-5 reduced the activity compared to **7**. Furthermore, we synthesized few tetrahydrothienopyridine analogues **17**, **18**, and **20**, having Sparfloxacin **5** (Fig. 1) template. However, compounds **17**, **18**, and **20** showed inferior in vitro activity than Sparfloxacin (Tables 1 and 2). When fluoro was substituted at C-5 (**19**), moderate antibacterial activity is obtained. Further, we studied the effect of a few substituents on the tetrahydrothienopyridine moiety, which subsequently furnished quinolones **8**–**13**. Quinolone containing bromo substituted tetrahydrothienopyridine as in compound **8** showed antibacterial activities against sensitive *Bacillus subtilis* and *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, and *Escherichia coli*. (Tables 1 and 2). However, **8** did not



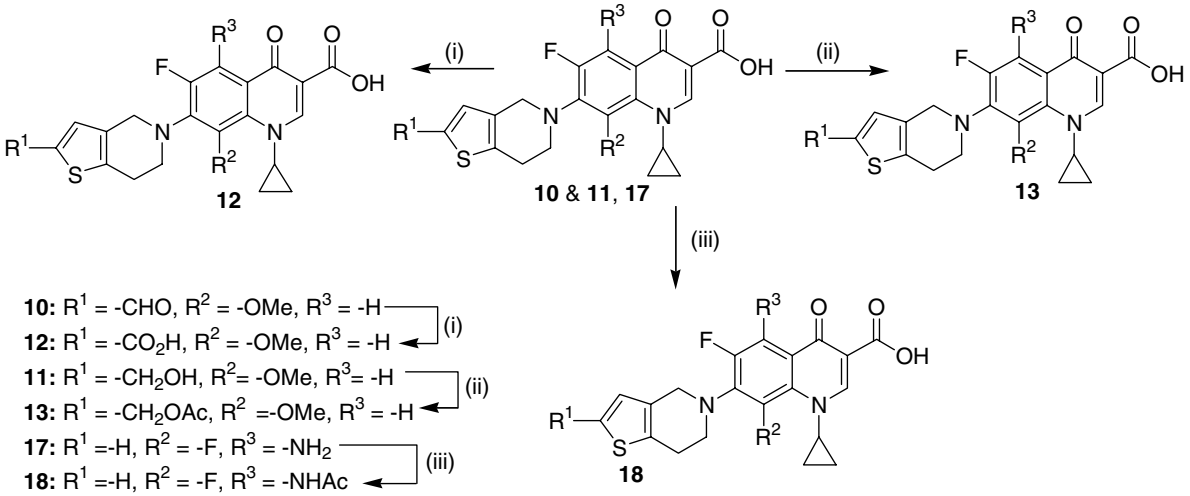
26: R^2 = -OMe, R^3 = -H
27: R^2 = -OMe, R^3 = -NO_2
28: R^2 = -H, R^3 = -H
29: R^2 = -F, R^3 = -F
30: R^2 = -F, R^3 = -NH_2

31: R^2 = -OMe, R^3 = -H
32: R^2 = -OMe, R^3 = -NO_2
33: R^2 = -H, R^3 = -H
34: R^2 = -F, R^3 = -F
35: R^2 = -F, R^3 = -NH_2

21: R^1 = -H
22: R^1 = -Br
23: R^1 = -NO_2
24: R^1 = -CHO
25: R^1 = -COOH

36: R^1 = -H, R^2 = -OMe, R^3 = -H
37: R^1 = -Br, R^2 = -OMe, R^3 = -H
38: R^1 = -NO_2, R^2 = -OMe, R^3 = -H
39: R^1 = -CHO, R^2 = -OMe, R^3 = -H
40: R^1 = -CH_2OH, R^2 = -OMe, R^3 = -H
41: R^1 = -H, R^2 = -OMe, R^3 = -NO_2
42: R^1 = -H, R^2 = -H, R^3 = -H
43: R^1 = -Br, R^2 = -H, R^3 = -H
44: R^1 = -H, R^2 = -F, R^3 = -NH_2
45: R^1 = -H, R^2 = -F, R^3 = -F
46: R^1 = -Br, R^2 = -F, R^3 = -NH_2

Scheme 1. Reagents and conditions: (i) 40% HBF_4, 90–100 °C, 3.5 h; (ii) thienopyridine, DMSO, 40 °C, 1 h; (iii) 80% EtOH, TEA, 78–80 °C, 1 h.



10: R^1 = -CHO, R^2 = -OMe, R^3 = -H
12: R^1 = -CO_2H, R^2 = -OMe, R^3 = -H
11: R^1 = -CH_2OH, R^2= -OMe, R^3= -H
13: R^1 = -CH_2OAc, R^2 =-OMe, R^3 = -H
17: R^1 =-H, R^2 = -F, R^3 = -NH_2
18: R^1 =-H, R^2 = -F, R^3 = -NHAc

Scheme 2. Reagents and conditions: (i) NaOH, $AgNO_3$, H_2O, 27–28 °C, 16 h; (ii) Ac_2O, C_5H_5N, 0–5 °C, 1.5 h; (iii) AcOH, Ac_2O, 110 °C, 30 min.

show activity against resistant strains (Table 2) as well as against *Pseudomonas aeruginosa* (Table 1). The corresponding C-8 unsubstituted analog **16** did not appreciably alter the antibacterial activities. Compound **9** with an electron withdrawing –NO_2 group on the tetrahydrothienopyridine exhibited comparable antibacterial activities with that of Gatifloxacin against the strains of Table 1, but the same trend was not observed against the strains mentioned in Table 2. When the –CHO group was introduced in the thienopyridine system, the quinolone **10** showed excellent in vitro antibacterial activity against all the bacteria strains (Table 1). In view of emerging resistance to linezolid, we wanted to test a few selected quinolone derivatives against linezolid resistant strains, which has G 2576-U mutations in the 23S rRNA and these mutations have been reported to develop microorganism having linezolid resistance.[13] Thus, we tested these compounds in linezolid resistant *Staphy-*

lococcus aureus strains NRS 119 from NARSA, USA. (We are registered user of Network on Antimicrobial Resistance in Staphylococcus aureus, www.narsa.net). The compound **10** was found to be active against the resistant strains such as methicillin resistant *staphylococcus aureus*, vancomycin resistant *enterococcus faecalis*, penicillin resistant *streptococcus pneumoniae* as well as against linezolid resistant *staphylococcus aureus* (Table 2). A hydroxymethyl analog **11** in general has been found to be less potent than its –CHO derivative **10**. On the other hand, the corresponding carboxylic acid derivative **12** showed moderate antibacterial activity in some of the strains. When the –OH group of hydroxymethyl group in **11** is protected by acetyl group, the –$OCOCH_3$ derivative **13** showed comparable in vitro activities to its parent alcohol **11**.

In summary, tetrahydrothienopyridine substitution at the 7th position of quinolone moiety **7** showed in vitro antibacterial activities against both susceptible and resistant strains of bacteria. The bromo derivative **8** has inferior potency than its desbromo derivative **7**. The nitro derivative **9** displayed similar in vitro MIC values as that of bromo derivative **8**. However, formyl derivative **10** emerged as the best compound as indicated by low MIC values and among some of the resistant strains tested. The compound **10** exhibited 4–8 times superior antibacterial activity than Gatifloxacin, Ciprofloxacin, and Sparfloxacin. The hydroxymethyl derivative **11** exhibited deterioration in antibacterial activities than its precursor formyl derivative **10** and the corresponding carboxylic acid derivative **12** did not show activities for resistant strains. The –$OCOCH_3$ derivative **13** is as good as its hydroxy counterpart **11**. The modifications in quinolone nucleus, which resulted compounds **14**–**20**, showed significant loss of antibacterial activity. The unsubstituted and substituted thienopyridine incorporated quinolones have shown a remarkable influence on the antibacterial activities.

Acknowledgments

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8. **7**. 99% purity by HPLC; mp 175 °C; IR (KBr): 3429, 1732, 1622 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 14.98 (s, 1H), 8.70 (s, 1H), 7.77 (d, J = 10.95 Hz, 1H), 7.35 (d, J = 5.13 Hz, 1H), 6.91 (d, J = 5.13 Hz, 1H), 4.42 (s, 2H), 4.17 (m, 1H), 3.70 (s, 3H), 3.65 (t, J = 4.65 Hz, 2H), 2.98 (br s, 2H), 1.14–1.07 (m, 4H); ESI-MS: 415 $(M+H)^+$. Compound **8**. 95.41% purity by HPLC; mp 180 °C (with dec); IR (KBr): 3431, 1730, 1620 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 14.90 (s, 1H), 8.70 (s, 1H), 7.78 (d, J = 12.13 Hz, 1H), 7.05 (s, 1H), 4.36 (s, 2H), 4.18 (m, 1H), 3.70 (s, 3H), 3.63 (t, J = 4.92 Hz, 2H), 2.91 (br s, 2H),

1.14–1.04 (m, 4H); ESI-MS: 494 $(M+H)^+$. Compound **9**. 94.35% purity by HPLC; mp 220 °C (with dec); IR (KBr): 3398, 1732, 1624 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 14.64 (s, 1H), 8.85 (s, 1H), 7.95(d, J = 12.0 Hz, 1H), 7.70 (s, 1H), 4.45 (s, 2H), 4.05 (m, 1H), 3.74 (t,J = 5.28 Hz, 2H), 3.71 (s, 3H), 3.12 (t, J = 5.46 Hz, 2H), 1.27 (m, 4H); ESI-MS: 459.7 $(M+H)^+$. Compound **10**. 95.39% purity by HPLC; mp 230–232 °C (with dec); IR (KBr): 3459, 1676, 1624 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 14.93 (s, 1H), 9.85 (s, 1H), 8.71 (s, 1H), 7.85 (s, 1H), 7.77 (d, J = 12.09 Hz, 1H), 4.48 (s, 2H), 4.17 (m, 1H), 3.71 (s, 3H), 3.67 (t, J = 5.23 Hz, 2H), 3.10 (t, J = 5.04 Hz, 2H), 1.14–1.05 (m, 4H); ESI-MS: 443 $(M+H)^+$. Compound **11**. 94.95% purity by HPLC; mp 172–174 °C; IR (KBr): 3354, 1706, 1618 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + few drops of CD_3OD): δ 14.89 (s, 1H), 8.83 (s, 1H), 7.88(d, J = 12.13 Hz, 1H), 6.73 (s, 1H), 5.33 (s, 1H), 4.74 (s, 2H), 4.42 (s, 2H), 4.0 (m, 1H), 3.75 (s, 3H), 3.72 (br s, 2H), 3.04 (br s, 2H), 1.15–1.05 (m, 4H); ESI-MS: 445 $(M+H)^+$. Compound **12**. 98.52% purity by HPLC; mp 235–240 °C (with dec); IR (KBr): 3435, 1730, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$ + few drops of CD_3OD): δ 8.84 (s, 1H), 7.91 (d, J = 12.09 Hz, 1H), 7.54 (s, 1H), 4.47 (s, 2H), 4.15 (m, 1H), 3.75 (s, 3H), 3.74 (t, J = 5.58 Hz, 2H), 3.09 (t, J = 5.70 Hz, 2H), 1.26 (m, 2H), 1.05 (br s, 2H); ESI-MS: 459.0 $(M+H)^+$. Compound **13**. 95.28% purity by HPLC; mp 202-204 °C (with dec); IR (KBr): 3435, 1624,1512 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 14.50 (s, 1H), 8.82 (s, 1H), 7.89 (d, J = 9.0 Hz, 1H), 6.81 (s, 1H), 5.18 (s, 2H), 4.40 (s, 2H), 4.03 (m, 1H), 3.75 (s, 3H), 3.69 (t, J = 5.43 Hz, 2H), 3.03 (t, J = 5.33 Hz, 2H), 2.08 (s, 3H), 1.13 (m, 2H), 1.02 (m, 2H); ESI-MS: 487.0 $(M+H)^+$. Compound **14**. 94.03% purity by HPLC; mp 180 °C (with dec); IR (KBr): 3431, 1620, 1544 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 13.8 (s, 1H), 8.74 (s, 1H), 7.36 (d, J = 5.13 Hz, 1H), 6.91 (d, J = 5.16 Hz, 1H), 4.48 (s, 2H), 4.17 (m, 1H), 3.71 (s, 3H), 3.70 (br s, 2H), 2.99 (br s, 2H), 1.14–1.03 (m, 4H); ESI-MS: 460.0 $(M+H)^+$. Compound **15**. 95% purity by HPLC; mp 230 °C (with dec); IR (KBr): 3421, 1629, 1490 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 15.26 (s, 1H), 8.64 (s, 1H), 7.93 (d, J = 13.35 Hz, 1H), 7.60 (d, J = 7.59 Hz, 1H), 7.39 (d, J = 5.07 Hz, 1H), 6.97 (d, J = 5.10 Hz, 1H), 4.51 (s, 2H), 3.78 (m, 1H), 3.74 (t,J = 5.41 Hz, 2H), 2.98 (br s, 2H), 1.24 (m, 2H), 1.14 (m, 2H); ESI-MS: 385 $(M+H)^+$. Compound **16**. 95.11% purity by HPLC; mp 235–238 °C (with dec); IR (KBr): 3404, 1624, 1585 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 15.23 (s, 1H), 8.64 (s, 1H), 7.92 (d, J = 13.32 Hz, 1H), 7.57 (d, J = 7.56 Hz, 1H), 7.09 (s, 1H), 4.45 (s, 2H), 3.79 (m, 1H), 3.73 (t, J = 5.43 Hz, 2H), 2.71 (br s, 2H), 1.14–1.12 (m, 4H); ESI-MS: 463.0 $(M+H)^+$. Compound **17**. 97.58% purity by HPLC; mp 277–280 °C (with dec); IR (KBr): 3338, 1683 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 14.68 (s, 1H), 8.66 (s, 1H), 7.16 (d, J = 5.13 Hz, 1H), 6.81 (d, J = 5.16 Hz, 1H), 6.51 (br s, 2H), 4.52 (s, 2H), 3.97 (m, 1H), 3.68 (t, J = 5.44 Hz, 2H), 3.05 (t, J = 5.32 Hz, 2H), 1.22 (m, 2H), 1.09 (m, 2H); ESI-MS: 418.0 $(M+H)^+$. Compound **18**. 94.47% purity by HPLC; mp above 275 °C (with dec); IR (KBr): 3325, 1629, 1517 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 14.85 (s, 1H), 10.09 (s, 1H), 8.65 (s, 1H), 7.35 (d, J = 5.13 Hz, 1H), 6.90 (d, J = 5.16 Hz, 1H), 4.49 (s, 2H), 4.13 (m, 1H), 3.64 (br s, 2H), 2.97 (br s, 2H), 2.10 (s, 3H), 1.18–1.13 (m, 4H); ESI-MS: 460.0 $(M+H)^+$. Compound **19**. 97.57% purity by HPLC; mp 250–253 °C; IR (KBr): 3431, 1732, 1633 cm^{-1};^1H NMR (300 MHz, DMSO-d_6): δ 14.74 (s, 1H), 8.64 (s, 1H), 7.36 (d, J = 5.16 Hz, 1H), 6.90 (d, J = 5.16 Hz, 1H), 4.54 (s, 2H), 4.11 (m, 1H), 3.69 (t, J = 5.04 Hz, 2H), 2.98 (br s, 2H), 1.16–1.14 (m, 4H); ESI-MS: 421 $(M+H)^+$. Compound **20**. 97.5% purity by HPLC; mp 265–268 °C (with dec); IR (KBr): 3446, 1645, 1587 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ 14.68 (s, 1H), 8.51 (s, 1H), 7.30 (br s, 2H), 7.03 (s, 1H), 4.38 (s, 2H), 4.02 (m, 1H), 3.59 (br s, 2H), 2.86 (br s, 2H), 1.16–1.09 (m, 4H); ESI-MS: 498.0 $(M+H)^+$.

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