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Caffeoyl Naphthalenesulfonamide Derivatives as HIV Integrase Inhibitors

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Abstract—HIV-1 integrase (IN) is an essential enzyme for retroviral replication and a rational target for the design of anti-AIDS drugs. In the present study, we have designed, synthesized and tested a series of caffeoyl naphthalenesulfonamide derivatives as HIV integrase inhibitors. Among these compounds, we found that HIV integrase inhibitory activities of compounds **III-3** and **III-4** were more potent than L-chicoric acid (IC_{50} = 11.8 μg/mL) and others were comparable to L-chicoric acid. Furthermore, the structure–activity relationships of these compounds were studied. The information gathered from this paper will be useful in the development and design of HIV-1 integrase inhibitors in the future.

Introduction

The occurrence of tolerance to single target-directed anti-human immunodeficiency virus (HIV) therapies can potentially be overcome by combination treatments, which disrupt multiple points in the viral life cycle.[1] Among the most effective combination regiments are those employing reverse transcriptase and protease inhibitors;[2] however, emergence of resistant virus is also a limiting factor to reverse transcriptase and protease inhibitors. To further enhance the effectiveness of combination drug therapy, drugs targeting other steps in the life cycle of HIV are needed.

An essential step in the viral life cycle is integration of the viral DNA into the host genome.[3] This step is catalyzed by the viral enzyme, HIV integrase (HIV IN). Integrase catalyzes two separate but chemically similar reactions, known as 3′-processing and DNA strand transfer.[4,5] In 3′-processing, IN removes a dinucleotide next to conserved cytosine-adenine sequence from each 3′-end of the viral DNA. IN then attaches the processed 3′-end of the viral DNA to the host cell DNA in the strand transfer reaction. The essential role of IN has been described in experiment where IN mutants with defective catalytic capability are replication-incompetent. As there is no known human counterpart of HIV integrase, IN is an attractive target for antiviral drug design.[6]

For the past few years, extensive efforts have been made resulting in a discovery of large number of HIV IN inhibitors. Recent studies showed that L-chicoric acid (**1**) and diecaffeoyl quinic acids (**2**) display potent activity against HIV IN and can inhibit HIV replication with moderate anti-HIV activity.[7–12] Common structural features of the reported synthetic analogues are caffeic acid esters separated by aliphatic, alicyclic, or aromatic linker.[13,14] However, the synthesis of caffeic amides connected with a naphthlaenesulfonamide as HIV IN inhibitors has not been reported previously. In the present study, we synthesized new caffeoyl derivatives using functionalized naphthalenesulfonamides and tested

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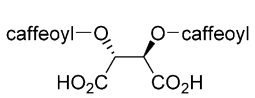
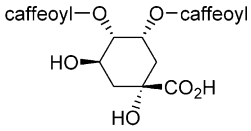
HIV IN inhibitory activities to explore the structure and activity relationships.



1, L-Chicoric acid



2, 3,4-DCQA

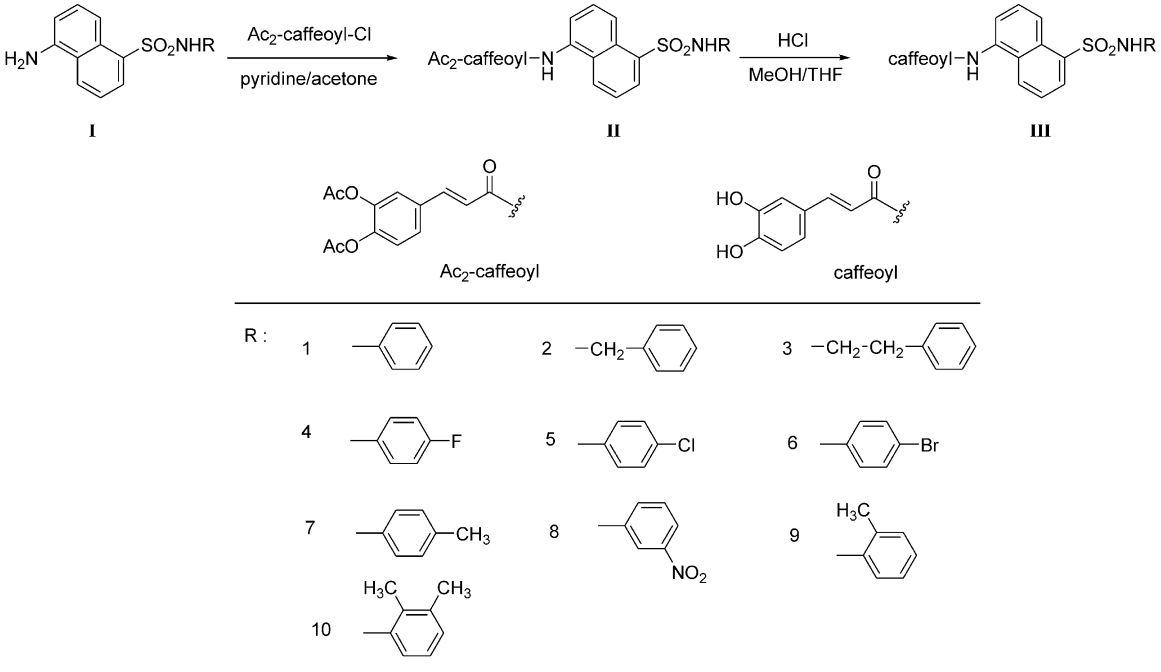
Results and Discussion

The target compounds as typified by general structure **(III)** were prepared by reacting different amines with diacetyl caffeoyl chloride in acetone at room temperature followed by removal of diacetyl protecting groups in MeOH–THF containing aqueous HCl[15] as depicted in Scheme 1. The structures and HIV IN inhibitory activities of caffeoyl naphthalenesulfonamide derivatives **(III)** are shown in Table 1.[16,17]

The starting 5-amino-naphthalenesulfonamides **(I)** were prepared from 1-naphthaleneamino-5-sulfonic acid as depicted in Scheme 2. The compound **3** was purchased from Shanghai chemical reagent company. The compound **5** was prepared from compound **3** by reaction with NaOH followed by protection of amino group in Ac_2O at 100 °C. The compound **6** was synthesized at room temperature by substitution of sodium sulfonate group in compound **5** to chlorosulfonyl group with $HOSO_2Cl$. 5-Amino-naphthalenesulfonamides **(I)**[18] were synthesized from compound **7** by acylation of compound **6** with different aromatic amines followed by deprotection of acetyl groups. Ac_2-caffeoyl-Cl was prepared by treatment of 3,4-dihydroxycinnamic acid with acetic anhydride (10 equivalents) in pyridine (v/v = 5:1) in the dark overnight at room temperature, then refluxing with thionyl chloride (5 equivalents) in benzene v/v = 8:1).[19]

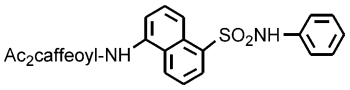
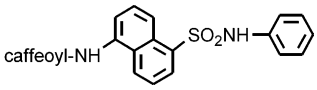
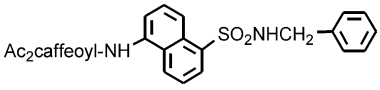
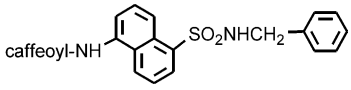
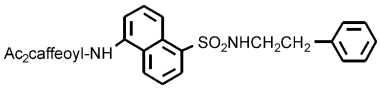
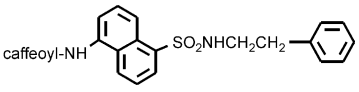
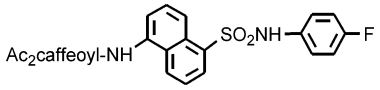
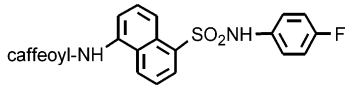
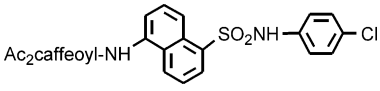
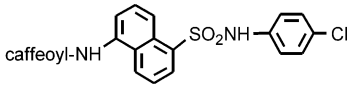
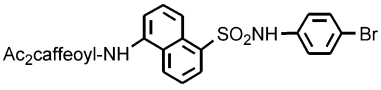
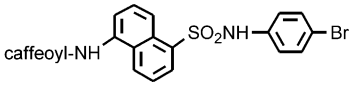
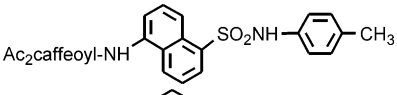
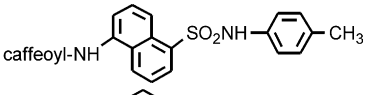
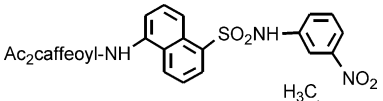
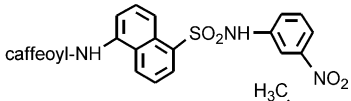
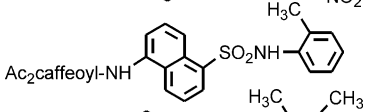
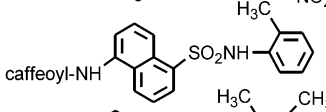
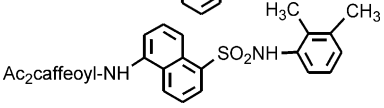
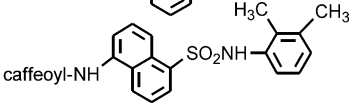
The inhibitory activity of L-choride acid has been included for comparison. In general, all compounds **III** showed moderate HIV IN inhibitory activities and are comparable or more potent than that of L-chicoric acid. The inhibitory activities of all compounds **III** were remarkably increased when compared to those compounds **II**[20] which containing acetyl protecting group. Among the synthesized compounds, compound **III-3** containing *N*-phenethylsulfonamide substitution in side chain showed the best inhibitory activity and the next order are *N*-benzylsulfoneamide and *N*-phenylsulfonamide substitution (entry 2, 1). Substitution of *p*-fluoro group (entry 4) in *N*-phenylsulfonamide derivative increased the HIV IN inhibitory activity while substitution of *p*-chloro and *p*-bromo groups decreased the inhibitory activity (entry 5, 6).

To further study the correlation of the structural features and anti-HIV IN activities, methyl or nitro groups were substituted at phenyl ring in *N*-phenylsulfonamide derivative to result in lesser activity than that of L-chicoric acid. These results suggested that these compounds with more potent inhibitory activities consisted of two aryl units, one of which contains the 1,2-dihydroxy pattern (caffeoyl group) and the other contains different electro-attracting groups as side chain, separated by an appropriate linker segment. It was observed that in the side chain, the compounds containing electro-attracting groups on benzene ring have more potent inhibitory activities than those containing electro-donating groups. Furthermore, the presence of longer span between benzene ring and sulfonamide caused the more potent inhibitory activity. These activity differences may probably be explained as the different interaction

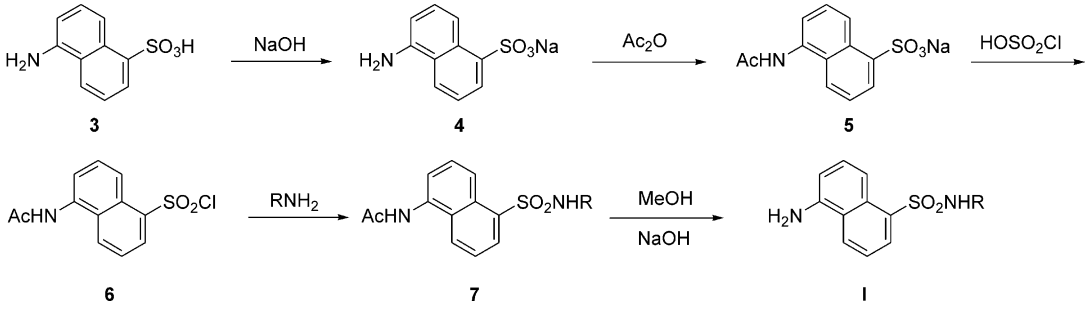


Scheme 1.

Table 1. Structures and HIV IN inhibitory activities of target compounds

Entry	Structure of **II**	IC_{50} (μg/mL)[a] of **II**	Structure of **III**	IC_{50} (μg/mL)[a] of **III**
1		>100		12.2±1.1
2		>100		8.6±4.8
3		11.9±2.2		4.5±3.4
4		24.6±6.3		7.9±4.9
5		>100		20.4±7.9
6		>100		19.5±4.5
7		>100		>100
8		>100		19.3±3.5
9		>100		20.4±3.7
10		>100		19.8±4.5
11			L-Chicoric acid(1)[b]	11.8

[a]Each value is average of at least two runs.
[b]L-Chicoric acid was prepared by known method.



3 4 5 6 7 I

Scheme 2.

between IN and the inhibitors containing different side chain through van der Waals contact or hydrophobic interaction. Although the caffeoyl compounds exhibited good inhibition against isolated HIV IN, none of the caffeoyl sulfonamide compounds could inhibit the replication of HIV in cell bases assay at nontoxic concentration (data not shown) implicating the important role of carboxylic acid in L-chicoric acid.

In conclusion, we have synthesized and tested the inhibitory activities of a new type of HIV IN inhibitors, which have a naphthalenesulfonamide as a basic skeleton. This work is the first example on the synthesis of caffeic acid amides joined a functional naphthanenesulfonamide for the development of HIV integrase inhibitiors.

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16. The enzyme inhibition assay of compounds against HIV-1 integrase was carried out as described previously: Oh, J.-W.; Shin, C.-G. *Mol. Cells* **1996**, *6*, 96.
17. **III-1**: Yield 75%, mp: 256–258 °C, R_f = 0.5 (EtOAc/petroleu mether 2:1); IR (KBr, cm^{-1}): 3346, 3250, 3037, 1664, 1598, 1516, 1493, 1284, 1147, 927–687; ^1H NMR (DMSO, 400 MHz) δ 10.69 (s, 1H), 10.16 (s, 1H), 9.53 (s, 1H), 9.23 (s, 1H), 8.59 (d, 1H, *J* = 8.8 Hz), 8.39 (d, 1H, *J* = 8.5 Hz), 8.24 (d, 1H, *J* = 6.3 Hz), 7.95 (d, 1H, *J* = 6.9 Hz), 7.74 (t, 1H, *J* = 7.7 Hz), 7.67 (t, 1H, *J* = 8.3 Hz), 7.47 (d, 1H, *J* = 15.7 Hz), 7.15 (t, 2H, *J* = 6.6 Hz), 7.07–6.90(m, 5H), 6.80 (t, 2H, *J* = 8.2 Hz). MS calcd for $C_{25}H_{20}N_2O_5S$ ($M-H^+$) 459.51, found 459.6. **III-2**: Yield 78%, mp: 242–244 °C, R_f = 0.4 (EtOAc/petroleum ether 1:1); IR (KBr, cm^{-1}): 3476, 3373, 3288, 3053, 1667, 1626, 1600, 1516, 1493, 1262, 1150, 915–699; ^1H NMR (DMSO, 400 MHz) δ 10.19 (s, 1H), 9.53 (s, 1H), 9.23 (s, 1H),8.53 (d, 1H, *J* = 8.8 Hz), 8.38 (d, 1H, *J* = 8.5 Hz), 8.16 (d, 1H, *J* = 7.1 Hz), 7.95 (d, 1H, *J* = 7.4 Hz), 7.73–7.64 (m, 4H), 7.50 (d, 1H, *J* = 15.7 Hz), 7.22–7.16 (m, 5H), 7.08 (s, 1H), 6.96 (d, 1H, *J* = 6.9 Hz), 6.83 (m, 2H), 4.04 (s, 2H) MS calcd for $C_{26}H_{22}N_2O_5S$ ($M-H^+$) 473.54, found 473.5. **III-3**: Yield 75%, mp: 244–248 °C, R_f = 0.45 (EtOAc/petroleum ether 1:1); IR (KBr, cm^{-1}): 3364, 3280, 3026, 1666, 1629, 1603, 1516, 1492, 1263, 1162, 916–699; ^1H NMR (DMSO, 400 MHz) δ 10.19 (s, 1H), 9.51 (s, 1H), 9.22 (s, 1H), 8.49 (d, 1H, *J* = 8.8 Hz), 8.39 (d, 1H, *J* = 8.5 Hz), 8.15 (d, 1H, *J* = 7.2 Hz), 7.94 (d, 1H, *J* = 7.4 Hz), 7.71–7.66 (dd, 2H, *J* = 7.9, 8.3 Hz), 7.48 (d, 1H, *J* = 15.7 Hz), 7.20–6.95 (m, 8H), 6.82 (t, 2H, *J* = 7.9 Hz), 3.03 (t, 2H, *J* = 7.7 Hz), 2.60 (t, 2H, *J* = 7.7 Hz) MS calcd for $C_{27}H_{24}N_2O_5S$ ($M-H^+$) 487.57, found 487.8. **III-4**: Yield 75%, mp: 146–150 °C, R_f = 0.6 (EtOAc/petroleum ether 1:1); IR (KBr, cm^{-1}): 3410, 3342, 3043, 1659, 1599, 1506, 1285, 1148, 975–701; ^1H NMR (DMSO, 400 MHz) δ 10.66 (s, 1H), 10.18 (s, 1H), 9.53 (s, 1H), 9.24 (s, 1H), 8.57 (d, 1H, *J* = 8.8 Hz), 8.40 (d, 1H, *J* = 8.6 Hz), 8.20 (d, 1H, *J* = 7.2 Hz), 7.96 (t, 1H, *J* = 7.1 Hz), 7.75 (t, 1H, *J* = 8.3 Hz), 7.65 (t, 1H, *J* = 8.3 Hz), 7.48 (d, 1H, *J* = 15.7 Hz), 7.07–6.96 (m, 6H), 6.81 (t, 2H, *J* = 7.9 Hz) MS calcd for $C_{25}H_{19}N_2O_5FS$ ($M-H^+$) 477.50, found 477.5. **III-5**: Yield 77%, mp: 234–236 °C, R_f = 0.35 (EtOAc/petroleum ether 1:1); IR (KBr, cm^{-1}): 450, 3330, 3057, 1656, 1603, 1516, 1490, 1285, 1148, 926–714; ^1H NMR (DMSO, 400 MHz) δ 10.91 (s, 1H), 10.21 (s, 1H), 9.57 (s, 1H), 9.27 (s, 1H), 8.56 (d, 1H, *J* = 8.5 Hz), 8.40 (d, 1H, *J* = 8.2 Hz), 8.25 (d, 1H, *J* = 7.2 Hz), 7.97 (d, 1H, *J* = 7.4 Hz), 7.76 (t, 1H, *J* = 7.2 Hz), 7.67 (t, 1H, *J* = 8.3 Hz), 7.47 (d, 1H, *J* = 15.7 Hz), 7.23 (d, 2H, *J* = 8.2 Hz), 7.05 (t, 3H, *J* = 6.3 Hz), 6.97 (d, 1H, *J* = 7.9 Hz), 6.80 (t, 2H, *J* = 6.9 Hz) MS calcd for $C_{25}H_{19}N_2O_5ClS$ ($M-H^+$)493.96, found 493.5. **III-6**: Yield 62%, mp: 162–166 °C, R_f = 0.4 (EtOAc/petroleum ether 3:2); IR (KBr, cm^{-1}): 3346, 3246, 3027, 1656, 1597, 1516, 1488, 1270, 1150, 974–709; ^1H NMR (DMSO, 400 MHz) δ 10.88 (s, 1H), 10.18 (s, 1H), 9.52 (s, 1H), 8.56 (d, 1H, *J* = 8.8 Hz), 8.41 (d, 1H, *J* = 8.5 Hz), 8.25 (d, 1H, *J* = 7.4 Hz), 7.96 (t, 1H, *J* = 7.1 Hz), 7.75 (t, 1H, *J* = 7.7 Hz), 7.67 (t, 1H, *J* = 8.2 Hz), 7.47 (d, 1H, *J* = 15.6 Hz), 7.35 (d, 2H, *J* = 7.1 Hz), 7.07 (s, 1H), 6.96 (t, 3H, *J* = 10.1 Hz), 6.80 (t, 2H, *J* = 7.9 Hz) MS calcd for $C_{25}H_{19}N_2O_5BrS$ ($M-H^+$) 539.41, found 539.5. **III-7**: Yield 78%, mp: 156–160 °C, R_f = 0.5 (EtOAc/petroleum ether 3:2); IR (KBr, cm^{-1}): 3400, 3249, 3047, 1659, 1599, 1513, 1496, 1283, 1148, 974–701; ^1H NMR (DMSO, 400 MHz) δ 10.52 (s, 1H), 10.16 (s, 1H), 9.52 (s, 1H), 9.22 (s, 1H), 8.59 (d, 1H, *J* = 8.5 Hz), 8.37 (d, 1H, *J* = 8.5 Hz), 8.19 (d, 1H, *J* = 7.2 Hz), 7.94 (t, 1H, *J* = 6.6 Hz), 7.73 (t, 1H, *J* = 7.7 Hz), 7.63 (t, 1H, *J* = 7.7 Hz), 7.47 (d, 1H, *J* = 15.7 Hz), 7.06 (s, 1H), 6.97–6.89 (m, 5H), 6.80 (t, 2H, *J* = 7.7 Hz), 2.11 (s, 3H) MS calcd for $C_{26}H_{22}N_2O_5S$ ($M-H^+$) 473.54, found 473.5. **III-8**: Yield 82%, mp: 166–170 °C, R_f = 0.5 (EtOAc/petroleum ether 3:2); IR (KBr, cm^{-1}): 3346, 3237, 3057, 1659, 1597, 1529, 1491, 1272, 1152, 972–696; ^1H NMR (DMSO, 400 MHz) δ 11.40 (s, 1H), 10.19 (s, 1H), 8.57 (d, 1H, *J* = 8.5 Hz), 8.43 (d, 1H, *J* = 8.8 Hz), 8.36 (d, 1H, *J* = 6.6 Hz), 7.96 (t, 1H, *J* = 7.1 Hz), 7.89 (s, 1H), 7.81–7.70 (m, 3H), 7.49–7.45 (m, 3H), 9.07 (s, 1H), 6.95 (d, 1H, *J* = 6.3 Hz), 6.82–6.80 (m, 2H) MS calcd for $C_{25}H_{19}N_3O_7S$ ($M-H^+$) 504.51, found 504.5. **III-9**: Yield, 70%, mp: 172–176 °C, R_f = 0.45 (EtOAc/petroleum ether 3:2); IR(KBr, cm^{-1}): 3331, 3331, 3057, 1655, 1596, 1522, 1494, 1270, 1151, 923–710; ^1H NMR (DMSO, 400 MHz) δ 10.19 (s, 1H), 9.90 (s, 1H), 9.52 (s, 1H), 9.23 (s, 1H), 8.58 (d, 1H, *J* = 8.8 Hz), 8.41 (d, 1H, *J* = 8.6 Hz), 8.04 (d, 1H, *J* = 7.2 Hz), 7.96 (t, 1H, *J* = 6.9 Hz), 7.69 (t, 1H, *J* = 7.7 Hz), 7.61 (t, 1H, *J* = 7.4 Hz), 7.48 (d, 1H, *J* = 15.4 Hz), 7.07–6.89 (m, 6H), 6.82 (m, 2H), 1.91 (s, 3H) MS calcd for $C_{26}H_{22}N_2O_5S$ ($M-H^+$) 473.54, found 473.5. **III-10**: Yield 77%, mp: 232–235 °C, R_f = 0.5 (EtOAc/petroleum ether 3:2); IR (KBr, cm^{-1}): 3356, 3356, 3065, 1663, 1598, 1515, 1491, 1267, 1151, 935–735; ^1H NMR (DMSO, 400 MHz) δ 10.22 (s, 1H), 9.89 (s, 1H), 9.55 (s, 1H), 9.26 (s, 1H), 8.57 (d, 1H, *J* = 8.8 Hz), 8.40 (d, 1H, *J* = 8.5 Hz), 8.01–7.98 (m, 2H), 7.70 (t, 1H, *J* = 7.9 Hz), 7.61 (t, 1H, *J* = 8.3 Hz), 7.48 (d, 1H, *J* = 15.4H), 7.07 (s, 1H), 6.95 (d, 1H, *J* = 7.5 Hz), 6.89–6.80 (m, 3H), 6.62 (d, 1H, *J* = 7.7 Hz), 2.10 (s, 3H), 1.86 (s, 3H) MS calcd for $C_{27}H_{24}N_2O_5S$ ($M-H^+$) 487.57, found 487.6.
18. **I-1** yellow crystal, yield 72%. mp: 170–172 °C. R_f = 0.65 (petroleum ether/Et_2O 1:1). IR (KBr, cm^{-1}): ν_{NH}: 3489, 3400, 3260, $\nu_{=CH}$: 3076, 3023, β_{NH}: 1633, 1613, $\nu_{C=C}$: 1572, 1595, 1494, ν_{SO2N}: 1322, 1155, γ_{CH}: 918–695. MS calcd for $C_{16}H_{14}N_2O_2S$ ($M-H^+$) 298.37, found 297.75. **I-2** Yellow solid, yield 72%, mp: 176–178 °C, R_f = 0.6 (petroleum ether/Et_2O 1:1), IR(KBr, cm^{-1}): ν_{NH}: 3451, 3375, 3288, $\nu_{=CH}$: 3081, 3063, 3027, β_{NH}: 1633, 1614, $\nu_{C=C}$: 1586, 1573, 1512, 1495, ν_{SO_2N}: 1301, 1154, γ_{CH}: 924–697, MS calcd for $C_{17}H_{16}N_2O_2S$ ($M-H^+$) 312.39, found 311.57. **I-3**: Brown crystal, yield 90%, mp: 116–118 °C, R_f = 0.4 (petroleum ether/Et_2O 1:1), IR (KBr, cm^{-1}): ν_{NH}: 3449, 3375, 3280, $\nu_{=CH}$: 3084, 3057, β_{NH}: 1624, 1588, $\nu_{C=C}$: 1573, 1512, 1496, ν_{SO_2N}: 1321, 1153, γ_{CH}: 933–699, MS calcd for $C_{18}H_{18}N_2O_2S$ ($M-H^+$)326.42, found 325.62. **I-4** Yellow crystal, yield 76%, mp: 168–170 °C,

R_f = 0.64 (petroleum ether/Et_2O 1:1), IR(KBr, cm^{-1}): ν_{NH}: 3394, 3323, 3252, $\nu_{=CH}$: 3059, 3106, β_{NH}: 1621, $\nu_{C=C}$: 1593, 1573, 1508, ν_{SO_2N}: 1314, 1139, γ_{CH}: 937–702, MS calcd for $C_{16}H_{13}N_2O_2FS$ ($M-H^+$) 316.36, found 315.41. **I-5**: Yellow solid, yield 75%, mp: 202–204 °C, R_f = 0.65 (petroleum ether/Et_2O 1:1), IR (KBr, cm^{-1}): ν_{NH}: 3390, 3322, 3102, $\nu_{=CH}$: 3047, β_{NH}: 1622, $\nu_{C=C}$: 1596, 1573, 1512, 1491, ν_{SO_2N}: 1316, 1139, γ_{CH}: 934–681, MS calcd for $C_{16}H_{13}N_2O_2ClS$ ($M-H^+$) 332.81, found 331.49. **I-6**: Yellow solid, yield 34%, mp: 212-214 °C, R_f = 0.7 (petroleum ether/Et_2O 1:1), IR (KBr, cm^{-1}): ν_{NH}: 3451, 3391, 3312, $\nu_{=CH}$: 3102, 3042, β_{NH}: 1621, $\nu_{C=C}$: 1589, 1573, 1512, 1489, ν_{SO_2N}: 1315, 1139, γ_{CH}: 935–701, MS calcd for $C_{16}H_{13}N_2O_2BrS$ ($M-H^+$) 376.26, found 375.45. **I-7**: Yellow crystal, yield 65%, mp: 194–196 °C, R_f = 0.6 (petroleum ether/Et_2O 1:1), IR (KBr, cm^{-1}): ν_{NH}: 3447, 3393, 272, $\nu_{=CH}$: 3104, 3025, β_{NH}: 1632, $\nu_{C=C}$: 1589, 1573, 1510, ν_{SO_2N}: 1298, 1153, γ_{CH}: 926–703, MS calcd for $C_{17}H_{16}N_2O_2S$ ($M-H^+$) 312.39, found 311.64. **I-8** Red crystal, yield 47%, mp: 196–198 °C, R_f = 0.7 (petroleum ether/Et_2O 1:1), IR (KBr, cm^{-1}): ν_{NH}: 3470, 3387, 3283, $\nu_{=CH}$: 3095, β_{NH}: 1643, 1613, $\nu_{C=C}$: 1583, 1570, 1529, ν_{SO_2N}: 1343, 1160 γ_{CH}: 949–735, MS calcd for $C_{16}H_{13}N_3O_4S$ ($M-H^+$) 343.37, found 342.45. **I-9**: Brown crystal, yield 75%, mp: 178–180 °C, R_f = 0.5 (petroleum ether/Et_2O 1:1), IR(KBr, cm^{-1}): ν_{NH}: 3447, 3374, 3272, $\nu_{=CH}$: 3059, 3024, β_{NH}: 1634, 1616, $\nu_{C=C}$: 1587, 1573, 1513, 1492, ν_{SO_2N}: 1303, 1150, γ_{CH}: 921–721, MS calcd for $C_{17}H_{16}N_2O_2S$ ($M-H^+$) 312.39, found 311.50. **I-10** Yellow solid, yield 70%, mp: 198–200 °C, R_f = 0.6 (petroleum ether/Et_2O 1:1), IR (KBr, cm^{-1}): ν_{NH}: 3414, 3347, $\nu_{=CH}$: 3168, β_{NH}: 1632, $\nu_{C=C}$: 1589, 1574, 1513, 1486, ν_{SO_2N}: 1311, 1156, γ_{CH}: 936–703, MS calcd for $C_{18}H_{18}N_2O_2S$ ($M-H^+$)326.42, found 325.61.

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20. **II-1**: Yield 63%, mp: 206–208 °C, R_f = 0.4 (EtOAc/petroleum ether 1:1); IR (KBr, cm^{-1}): 3314, 3070, 1763, 1738, 1658, 1597, 1531, 1497, 1216, 1153, 906–693; ^1H NMR (DMSO, 400 MHz) δ 10.74 (s, 1H), 10.34 (s, 1H), 8.61 (d, 1H, J = 8.6 Hz), 8.39 (d, 1H, J = 8.5 Hz), 8.26 (d, 1H, J = 7.2 Hz), 7.97 (t, 1H, J = 6.9 Hz), 7.76 (t, 1H, J = 8.2 Hz), 7.68–7.59 (m, 4H), 737 (d, 1H, J = 8.2 Hz), 7.17–7.02 (m, 5H), 6.93 (t, 1H, J = 7.4 Hz), 2.31 (s, 6H) Ms calcd for $C_{29}H_{24}N_2O_7S$ ($M-H^+$) 543.58, found 543.7. **II-2**: Yield 67%, mp: 188–190 °C, R_f = 0.5 (EtOAc/petroleum ether 1:1); IR (KBr, cm^{-1}): 3288, 3031, 1770, 1665, 1622, 1595, 1527, 1500, 1207, 1151, 899–699; ^1H NMR (DMSO, 400 MHz) δ 10.33 (s, 1H), 8.55 (d, 1H, J = 8.3 Hz), 8.38 (d, 1H, J = 8.8 Hz), 8.16 (d, 1H, J = 7.2 Hz), 7.96 (t, 1H, J = 7.29 Hz), 7.74–7.60 (m, 5H), 7.37 (d, 1H, J = 8.3 Hz), 7.19–7.15 (m, 6H), 4.04 (s, 2H), 2.32 (s, 6H) MS calcd for $C_{30}H_{26}N_2O_7S$ ($M-H^+$) 557.61, found 557.5. **II-3**: Yield 65%, mp: 212–216 °C, R_f = 0.6 (EtOAc/petroleum ether 1:1); IR (KBr, cm^{-1}): 3318, 3061, 1771, 1668, 1629, 1596, 1532, 1499, 1205, 1150, 900–700; ^1H NMR (DMSO, 400 MHz) δ 10.34 (s, 1H), 8.52 (d, 1H, J = 8.5 Hz), 8.41 (d, 1H, J = 9.5 Hz), 8.16 (d, 1H, J = 7.4 Hz), 7.87 (d, 1H, J = 8.3 Hz), 7.73–7.61 (m, 5H) 7.39 (d, 1H, J = 8.2 Hz), 7.20–7.04 (m, 6H), 3.04 (t, 2H, J = 7.1 Hz), 2.60 (t, 2H, J = 7.4 Hz), 2.32 (s, 6H) MS calcd for $C_{31}H_{28}N_2O_7S$ ($M-H^+$) 571.64, found 571.7. **II-4**: Yield 57%, mp: 186–188 °C, R_f = 0.6 (EtOAc/petroleum ether 3:2); IR (KBr, cm^{-1}): 3318, 3061, 1771, 1668, 1629, 1596, 1532, 1499, 1205, 1150, 900–700; ^1H NMR (DMSO, 400 MHz) δ 10.34 (s, 1H), 8.52 (d, 1H, J = 8.5 Hz), 8.41 (d, 1H, J = 9.5 Hz), 8.16 (d, 1H, J = 7.4 Hz), 7.87 (d, 1H, J = 8.3 Hz), 7.73–7.61 (m, 5H) 7.39 (d, 1H, J = 8.2 Hz), 7.20–7.04 (m, 6H), 3.04 (t, 2H, J = 7.1 Hz), 2.60 (t, 2H, J = 7.4 Hz), 2.32 (s, 6H) MS calcd for $C_{29}H_{23}N_2O_7FS$ ($M-H^+$) 561.57, found 561.0. **II-5**: Yield 72%, mp: 190–192 °C, R_f = 0.45 (EtOAc/petroleum ether 1:1); IR (KBr, cm^{-1}): 3254, 3047, 1770, 1667, 1630, 1596, 1532, 1496, 1224, 1185, 898–715; ^1H NMR (DMSO, 400 MHz) δ 10.91 (s, 1H), 10.35 (s, 1H), 8.58 (d, 1H, J = 8.8 Hz), 8.41 (d, 1H, J = 8.8 Hz), 8.25 (d, 1H, J = 7.4 Hz), 7.97 (t, 1H, J = 7.5 Hz), 7.77 (t, 1H, J = 8.5 Hz), 7.68–7.59 (m, 4H), 7.37 (d, 1H, J = 8.2 Hz), 7.22 (d, 2H, J = 4.9 Hz), 7.04 (t, 3H, J = 6.9 Hz), 2.32 (s, 6H) Ms calcd for $C_{29}H_{23}N_2O_7ClS$ ($M-H^+$) 578.03, found 577.6. **II-6**: Yield 80%, mp: 192–194 °C, R_f = 0.4 (EtOAc/petroleum-ether 1:1); IR (KBr, cm^{-1}): 3258, 3037, 1770, 1667, 1628, 1594, 1533, 1491, 1207, 1153, 901–709; ^1H NMR (DMSO, 400 MHz) δ 10.89 (s, 1H), 10.32 (s, 1H), 8.58 (d, 1H J = 8.5 Hz), 8.42 (s, 1H, J = 8.5 Hz), 8.26 (d, 1H, J = 7.4 Hz), 7.98 (t, 1H, J = 7.4 Hz), 7.77 (t, 1H, J = 8.5 Hz), 7.70–7.66 (m, 4H), 7.39–7.34 (m, 3H), 7.10–6.98 (m, 3H), 2.32 (s, 6H) MS calcd for $C_{29}H_{23}N_2O_7BrS$ ($M-H^+$) 623.48, found 623.5. **II-7**: Yield 70%, mp: 170–174 °C, R_f = 0.5 (EtOAc/petroleum ether 1:1); IR (KBr, cm^{-1}): 3278, 3067, 1772, 1668, 1627, 1596, 1532, 1503, 1206, 1152, 902–704; ^1H NMR (DMSO, 400 MHz) δ 10.55 (s, 1H), 10.33 (s, 1H), 8.61 (d, 1H, J = 8.5 Hz), 8.37 (d, 1H, J = 8.6 Hz), 7.97 (t, 1H, J = 6.8 Hz), 7.75 (t, 1H, J = 8.2 Hz), 7.66–7.609 (m, 4H), 7.37 (t, 1H, J = 8.2 Hz), 7.06 (d, 1H, J = 15.7 Hz), 6.96–6.89 (dd, 4H, J = 9.9, J = 8.5 Hz), 2.31 (s, 6H), 2.11 (s, 3H) MS calcd for $C_{30}H_{26}N_2O_7S$ ($M-H^+$) 557.61, found 557.5. **II-8**: Yield 56%, mp: 138–140 °C, R_f = 0.5 (EtOAc/petroleum ether 1:1); IR (KBr, cm^{-1}): 3266, 3067, 1771, 1666, 1622, 1531, 1501, 1206, 1154, 900–696; ^1H NMR (DMSO, 400 MHz) δ 11.43 (s, 1H), 10.35 (s, 1H), 8.58 (d, 1H, J = 8.5 Hz), 8.43 (d, 1H, J = 8.6 Hz), 8.36 (d, 1H, J = 7.2 Hz), 7.97 (d, 1H, J = 7.7 Hz), 7.88 (s, 1H), 7.82–7.59 (m, 6H), 7.47 (d, 2H, J = 5.1 Hz), 7.37 (d, 1H, J = 8.2 Hz), 7.06 (d, 1H, J = 15.7 Hz), 2.31 (s, 6H) MS calcd for $C_{29}H_{23}N_3O_9S$ ($M-H^+$) 588.58, found 588.5. **II-9**: Yield 55%, mp: 196–198 °C, R_f = 0.5 (EtOAc/petroleum ether 1:1); IR (KBr, cm^{-1}): 3266, 3060, 1773, 1662, 1628, 1533, 1497, 1208, 1151, 900–712; ^1H NMR (DMSO, 400 MHz) δ 10.34 (s, 1H), 9.91 (s, 1H), 8.60 (d, 1H, J = 8.5 Hz), 8.41 (d, 1H, J = 8.5 Hz), 8.05 (d, 1H, J = 6.6 Hz), 7.99 (t, 1H, J = 7.4 Hz), 7.71–7.55 (m, 5H), 7.37 (d, 1H, J = 8.2 Hz), 7.36–6.99 (m, 4H), 6.90 (m, 1H), 2.31 (s, 6H), 1.91 (s, 3H) MS calcd for $C_{30}H_{26}N_2O_7S$ ($M-H^+$) 557.61, found 557.5. **II-10**: Yield 60%, mp: 200–204 °C, R_f = 0.6 (EtOAc/petroleum ether 3:2); IR (KBr, cm^{-1}): 3285, 3075, 1754, 1664, 1625, 1587, 1524, 1505, 1219, 1149, 901–737; ^1H NMR (DMSO, 400 MHz) δ 10.35 (s, 1H), 9.87(s, 1H), 8.59 (d, 1H, J = 8.8 Hz), 8.41(d, 1H, J = 8.5 Hz), 8.01 (t, 2H, J = 6.4 Hz), 7.72–7.60 (m, 5H), 7.38 (d, 1H, J = 8.3 Hz), 7.10 (d, 1H, J = 8.5 Hz), 6.96 (d, 1H, J = 7.4 Hz), 6.87 (t, 1H, J = 7.4 Hz), 6.61 (d, 1H, J = 7.9 Hz), 2.31 (s, 6H), 2.10 (s, 3H), 1.86 (d, 3H) MS calcd for $C_{31}H_{28}N_2O_7S$ ($M-H^+$) 571.64, found 571.7.