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Discovery of piperidinyl aminopyrimidine derivatives as IKK-2 inhibitors

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ABSTRACT

A serine–threonine kinase IKK-2 plays an important role in activation of NF-κB through phosphorylation of the inhibitor of NF-κB (IκB). As NF-κB is a major transcription factor that regulates genes responsible for cell proliferation and inflammation, development of selective IKK-2 inhibitors has been an important area of anti-inflammatory and anti-cancer research. In this study, to obtain active and selective IKK-2 inhibitors, various substituents were introduced to a piperidinyl aminopyrimidine core structure. The structure–activity relationship study indicated that hydrogen, methanesulfonyl, and aminosulfonyl groups substituted at the piperidinylamino functionality provide high inhibitory activity against IKK-2. Also, morpholinosulfonyl and piperazinosulfonyl group substituted at the aromatic ring attached to the aminopyrimidine core significantly increased the inhibitory activity of the resulting derivatives. In particular, compound **17** with the aromatic piperazinosulfonyl substituent showed the most potent (IC_{50} = 1.30 μM) and selective (over other kinases such as p38α, p38β, JNK1, JNK2, JNK3, and IKK-1) inhibitory activity against IKK-2.

NF-κB is a major transcription factor that regulates genes responsible for anti-apoptosis, proliferation, and inflammation.[1–3] NF-κB suppression is beneficial in a host of animal models of inflammatory disease and many therapeutic agents including corticosteroids, leflunomide, sulfasalazine, and aspirin are known to mediate at least some of their effects through NF-κB blockade.[4–8]

NF-κB is sequestered as a dimer in the cytosol of unstimulated cells via non-covalent interactions with the inhibitor proteins (IκB), and signals that induce NF-κB activity cause phosphorylation of IκBs, their dissociation and subsequent degradation, allowing NF-κB proteins to enter the nucleus and induce gene expression.[9] Phosphorylation of IκBs and thereby activation of NF-κB is catalyzed by a serine–threonine kinase complex, IκB kinase (IKK), which is composed of three subunits, IKK-1 (IKKα), IKK-2 (IKKβ), and NEMO (IKKγ). Among the subunits, IKK-2 plays an important role in activation of NF-κB, resulting in enhanced production of TNF-α, IL-1, intercellular adhesion molecule (ICAM)-1, and cyclooxygenase (COX)-2, which indicates that this pathway is important for inflammation and the innate immune system.[9,10] Also, activation of IKK-2 stimulates anti-apoptotic and proliferative pathways. Taken together, inhibitors of IKK-2 have been being developed for treatment of inflammatory diseases such as rheumatoid arthritis (RA) and chronic obstructive pulmonary disease (COPD) as well as cancer.[11,12] IMD-1041,[13] GMX-1778 (CHS 828),[14] and teglarinad chloride (GMX-1777)[15] (Fig. 1) are three major IKK-2 inhibitors under clinical investigation for the management of COPD (IMD-1041) and solid tumors and lymphoma (CHS828 and GMX-1777).

In contrast to the elucidated role of IKK-2 in the NF-κB pathway, IKK-1 deficient mice presented an unexpected phenotype including skeletal and skin abnormalities.[16] Therefore, development of selective IKK-2 inhibitors has been an important area of anti-inflammatory and anti-cancer research. Among IKK-2 inhibitors, aminopyrimidine derivatives have been reported to possess selectivity over IKK-1.[17] Herein, we describe our initial lead optimization study of piperidinyl aminopyrimidines which led to identification of novel selective IKK-2 inhibitors.

Compounds with an aminopyrimidine core structure are competitive inhibitors of IKK-2 with respect to the cofactor, ATP.[17] As most kinases uses ATP as a cofactor, it seems to be very difficult

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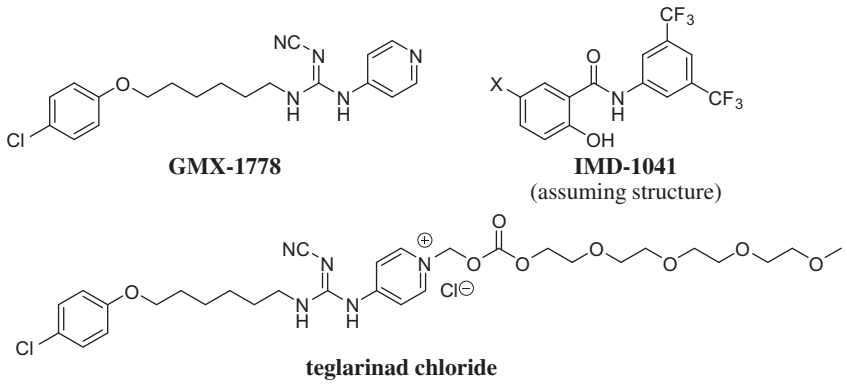


Figure 1. IKK inhibitors in clinical trials.

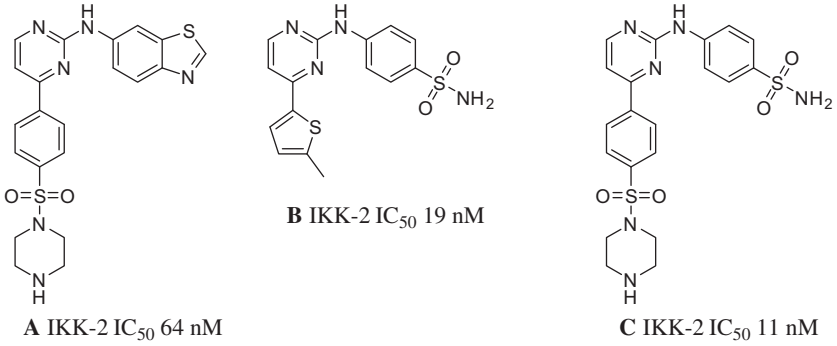


Figure 2. IKK-2 inhibitors with an aminopyrimidine core structure.

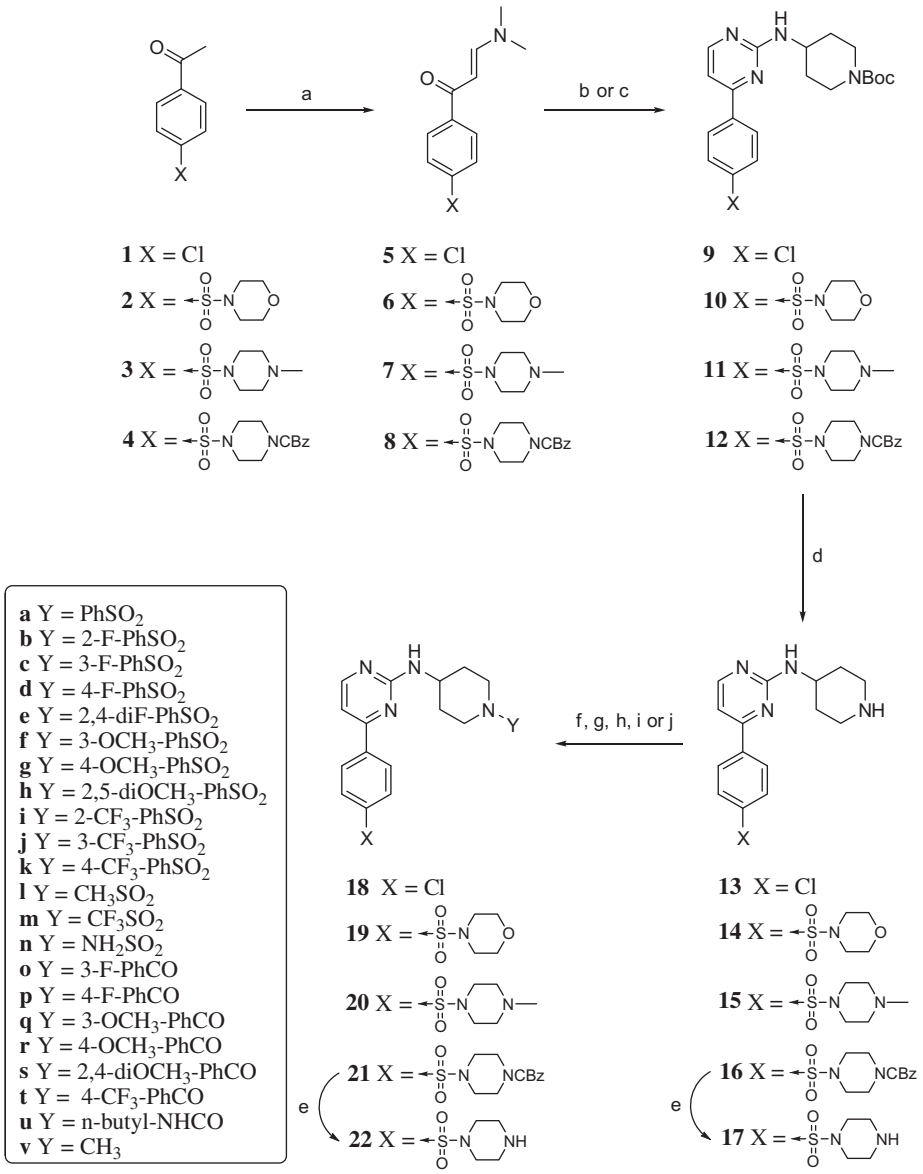
to obtain selectivity to IKK-2 over other kinases. According to the literatures, however, introduction of proper substituents to the core structure makes compounds selective to IKK-2 (Fig. 2).[17] In this study, we introduced an aryl group and a piperidin-4-yl group at C4 and 2-NH_2 position of the aminopyrimidine core structure, respectively, to obtain inhibitory activity and selectivity to IKK-2.

The synthesis of title compounds, piperidinyl aminopyrimidines, was started with 1-acetyl-4-substituted benzenes **1**–**4** (Scheme 1). The compounds **1**–**4** were treated with DMF-DMA (*N*,*N*-dimethylformamide dimethyl acetal) at 150 °C to afford the corresponding *N*,*N*-dimethylamino derivatives **5**–**8** in 82–98% yields, which were converted to the compounds **9**–**12** with the aminopyrimidine core structure. Treatment of one vinylogous amide **5** with guanidine provided the aminopyrimidine core via addition–elimination to the vinylogous amide **5** followed by cyclization. Reductive amination of *N*-Boc-4-piperidone with the free aminopyrimidine intermediate thus obtained, in the presence of $TiCl(O^iPr)_3$ and $NaBH(OAc)_3$ provided **9** in 20% yield for two steps. On the other hand, direct condensation of the other vinylogous amides **6**–**8** with *N*-(*N*-Boc-4-piperidinyl)-guanidinium chloride in EtOH gave the corresponding aminopyrimidine derivatives **10**–**12** in 34–46% yields. The Boc protecting groups of the compounds **9**–**12** were removed under acidic conditions with 30% TFA in CH_2Cl_2 to give **13**–**16** in 66–99% yields. The carbobenzyloxy (Cbz) protecting group in **16** was also removed by hydrogenolysis to afford a piperazine-substituted compound **17**.

Various substituents such as sulfonyl, benzoyl, urea, and methyl group were introduced to the free piperidinylamino functionality of the compound **13**. Thus, the compound **13** was treated with various benzenesulfonyl chlorides with aromatic substituents or alkylsulfonyl chlorides such as CH_3SO_2Cl and CF_3SO_2Cl under basic conditions to give the corresponding sulfonylated derivatives **18a**–**18m** in 27–75% yields. Also, treatment of **13** with chlorosulfonyl isocyanate and *t*-BuOH in CH_2Cl_2 followed by Boc-deprotection under acidic conditions (30% TFA) provided the aminosulfonyl-substituted derivative **18n** in 80% yield. The compound **13** was converted to the corresponding benzoylated compounds such as 3-F-, 4-F-, 3-OMe-, 4-OMe-, 2,4-di-OMe-, and 4-CF_3-benzoylated compounds (**18o**–**18t**) in 28–75% yields by using the appropriately substituted benzoyl chlorides in the presence of pyridine and DMAP in CH_2Cl_2 at −78 °C. *N*-Butylaminocarbonyl-piperidinyl aminopyrimidine derivative **18u** was obtained in 35% yield by reacting **13** with *n*-butyl isocyanate in pyridine at 120 °C. Reductive amination of formaldehyde with **13** afforded the methylated derivative **18v** in 47% yield.

A selected group of the substituted aminopyrimidine derivatives were prepared from compounds **14**–**16**. Thus, the compound **14** was converted to **19l**, **19n**, and **19v** with methanesulfonyl, aminosulfonyl, and methyl groups substituted at the piperidinylamino functionality. The compound **15** also underwent methanesulfonylation and aminosulfonylation to afford the derivatives **20l** and **20n**, respectively, and the same reactions with **16** followed by Cbz deprotection furnished **22l** and **22n**.

A total of 33 compounds with the aminopyrimidine core structure were synthesized and biologically evaluated against IKK-2. Assay for IKK-2 inhibitors was done by using TR-FRET (Time-Resolved Fluorescence Resonance Energy Transfer) method on IMAP® platform.[18] For the assay, 5-carboxyfluoresceinylated (5-FAM) IκBα-derived peptide, 5-FAM-GRHDSGLDSMK-NH_2, was used as substrate of IKK-2 and IMAP binding reagent and terbium donor were added for detection reaction. In the primary assay, % inhibition of each compound at fixed concentration (10 μM) against IKK-2 was measured and, only for those compounds which showed more than 50% inhibition, the half maximal inhibitory



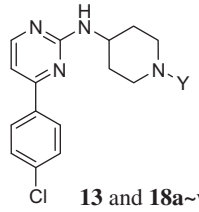
Scheme 1. Synthesis of piperidinyl aminopyrimidine derivatives. Reagents and conditions: (a) DMF-DMA, 150 °C; (b) guanidine, EtOH, 80 °C; *N*-Boc-4-piperidone, $TiCl(O^iPr)_3$, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, rt; (c) *N*-(*N*-Boc-4-piperidinyl)-guanidinium chloride, EtOH, 80 °C; (d) 30% TFA in CH_2Cl_2, rt; (e) $Pd(OH)_2/C$, H_2, MeOH, EtOAc, H_2O, AcOH, rt; (f) various sulfonyl chlorides, DIPEA, CH_2Cl_2, rt; (g) chlorosulfonyl isocyanate, *t*-BuOH, CH_2Cl_2; 30% TFA in CH_2Cl_2, rt; (h) substituted benzoyl chlorides, DMAP, pyr, CH_2Cl_2, −78 °C; (i) *N*-butyl isocyanate, pyr, 120 °C; (j) 37% HCHO, MeOH, $NaBH(OAc)_3$, rt.

concentration (IC_{50}) was evaluated. The inhibitory activity of the piperidinyl aminopyrimidine derivatives with 4-chlorophenyl group and various substituents at nitrogen of the piperidine ring (**13** and **18a**–**v**) are summarized in Table 1. Among the piperidinyl aminopyrimidine derivatives, only three compounds (**13**, **18l**, and **18n**) showed more than 50% inhibition with 75.03%, 73.58%, and 70.86% inhibitions, respectively. Compounds **18a**–**18k** with benzenesulfonyl groups did not inhibit IKK-2 activity significantly. On the other hand, compounds **18l** and **18n** with methanesulfonyl and aminosulfonyl groups were potent inhibitors of the IKK-2 with IC_{50} values of 3.67 and 3.80 μM, respectively. In contrast, the compound **18m** with a trifluoromethanesulfonyl group showed low inhibitory activity (% inhibition at 10 μM is only 13.90%). Compounds **18o**–**18t** with benzoyl groups showed as low activities as the benzenesulfonyl-substituted derivatives (**18a**–**18k**). The compound **18u** with *n*-butylaminocarbonyl group showed low activity with 32.16% inhibition. The compound **18v** with methyl group also showed low activity with 38.68% inhibition and an IC_{50} value of 19.70 μM. From these results, it was clear that the piperidinyl aminopyrimidine derivatives with substituents such as H, CH_3SO_2, NH_2SO_2, and CH_3 at the piperidine moiety showed potent inhibitory activity against the target enzyme.

With the optimized piperidinyl substituents (Y = H, CH_3SO_2, NH_2SO_2, CH_3) in hand, the structure–activity relationship of the aromatic substituent at the chlorine position was then investigated. Thus, instead of the chlorine atom, morpholinosulfonyl, *N*-methylpiperazinosulfonyl, and piperazinosulfonyl groups were introduced at the X position of the aromatic substituent of the aminopyrimidine core structure, and the inhibitory activity against IKK-2 of the resulting piperidinyl aminopyrimidine derivatives was evaluated (Table 2). The inhibitory activity of the morpholinosulfonyl-substituted derivatives **14** (Y = H) and **19l** (Y = CH_3SO_2) was as potent as the corresponding compounds **13** and **18l** (X = Cl). The compounds **19n** (Y = NH_2SO_2, IC_{50} = 0.92 μM) and **19v** (Y = CH_3, IC_{50} = 5.60 μM) showed improved activities compared with the corresponding chlorine-substituted derivatives **18n**

(X = Cl, Y = NH_2SO_2, IC_{50} = 3.80 μM) and **18v** (X = Cl, Y = CH_3, IC_{50} = 19.70 μM). On the other hand, the compounds **15**, **20l**, and **20n** with *N*-methylpiperazinosulfonyl group showed lower inhibitory activities than the corresponding compounds **13**, **18l**, and **18n** with aromatic chlorine substituent. The IC_{50} values of **15** and **20n** were 7.02 and 4.25 μM, respectively. In case of the piperazinosulfonyl-substituted derivatives (**17**, **22l**, and **22n**), the compound **17** (Y = H) was a potent inhibitor with an IC_{50} value of 1.30 μM. However, the compounds **22l** and **22n** with methanesulfonyl and aminosulfonyl group as X showed similar activities as the corresponding compounds **18l** (X = Cl, Y = CH_3SO_2) and **18n** (X = Cl, Y = NH_2SO_2) with IC_{50} values of 3.14 and 3.85 μM, respectively.

Table 1
IKK-2 inhibitory activities of piperidinyl aminopyrimidine derivatives with 4-chlorophenyl group



13 and **18a~v**

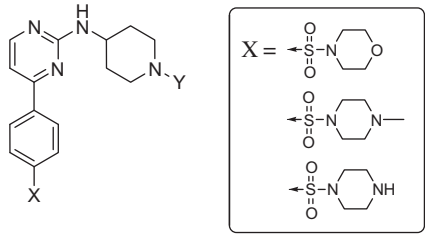
Entry	Compounds	Y	% Inhibition at 10 μM (%)	IC_{50} (μM)
1	**13**	H	75.03	3.20
2	**18a**	$PhSO_2$	—[a]	
3	**18b**	2-F-$PhSO_2$	20.31	—[a]
4	**18c**	3-F-$PhSO_2$	15.12	—[a]
5	**18d**	4-F-$PhSO_2$	13.47	—[a]
6	**18e**	2,4-Di-F-$PhSO_2$	19.68	—[a]
7	**18f**	3-OCH_3-$PhSO_2$	12.74	—[a]
8	**18g**	4-OCH_3-$PhSO_2$	26.15	—[a]
9	**18h**	2,5-Di-OCH_3-$PhSO_2$	19.58	—[a]
10	**18i**	2-CF_3-$PhSO_2$	26.57	—[a]
11	**18j**	3-CF_3-$PhSO_2$	14.10	—[a]
12	**18k**	4-CF_3-$PhSO_2$	15.60	—[a]
13	**18l**	CH_3SO_2	73.58	3.67
14	**18m**	CF_3SO_2	13.90	—[a]
15	**18n**	NH_2SO_2	70.86	3.80
16	**18o**	3-F-PhCO	38.79	—[a]
17	**18p**	4-F-PhCO	39.04	—[a]
18	**18q**	3-OCH_3-PhCO	40.15	—[a]
19	**18r**	4-OCH_3-PhCO	32.25	—[a]
20	**18s**	2,4-Di-OCH_3-PhCO	42.79	—[a]
21	**18t**	4-CF_3-PhCO	24.29	—[a]
22	**18u**	*n*-C_4H_9NHCO	32.16	—[a]
23	**18v**	CH_3	38.68	19.70
24	Reference compound[19]	—[a]	0.15	

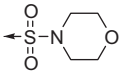
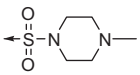
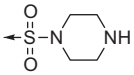
[a] Not determined.

The most active compounds **19n** and **17**[20] were biologically evaluated against other kinases such as IKK-1, p38α, p38β, JNK1, JNK2, and JNK3 to obtain selectivity information. The results are shown in Table 3. Selectivity to IKK-2 is necessary to reduce side effects possibly occurring with inhibition of other kinases. The compound **19n** (X = morpholinosulfonyl, Y = NH_2SO_2) did not show significant inhibitory activity against IKK-1 but no selectivity was observed over the other kinases such as p38α, p38β, JNK1, JNK2, and JNK3. On the other hand, the compound **17** (X = piperazinosulfonyl, Y = H) showed good selectivity over p38α, p38β, JNK1, JNK2, and JNK3 as well as IKK-1. Therefore, the selectivity to IKK-2 seems to be more dependent on the X substituent but the role of the piperazinosulfonyl group of **17** in the inhibitory activity as well as selectivity to IKK-2 necessitates further investigation.

In summary, in order to obtain active and selective IKK-2 inhibitors, various substituents were introduced to the piperidinyl aminopyrimidine core structure. First, the structure–activity relationship of the piperidinyl amino substituent (Y) was investigated (**13** and **18a–18v**, Table 1), which indicated that the relatively small substituents such as hydrogen, methanesulfonyl and aminosulfonyl group show better inhibitory activity against IKK-2. Then, substituents such as morpholinosulfonyl, *N*-methylpiperazinosulfonyl, and piperazinosulfonyl group were introduced at the 4-position of the aromatic ring attached to the aminopyrimidine core (X) (**14**, **15**, **17**, and **19–21**, Table 2). Among the derivatives thus prepared, compounds **19n** and **17** showed the most potent inhibitory activity against IKK-2. In addition, the compound **17** showed good selectivity over other kinases such as IKK-1, p38α, p38β, JNK1, JNK2, and JNK3. Based on this information, further optimization study of the inhibitory activity as well as

Table 2
IKK-2 inhibitory activities of piperidinyl aminopyrimidine derivatives



Entry	Compounds	X	Y	% Inhibition at 10 μM (%)	IC_{50} (μM)
1	**14**		H	82.51	2.09
2	**19l**		CH_3SO_2	61.51	2.20
3	**19n**		NH_2SO_2	89.55	0.92
4	**19v**		CH_3	67.06	5.60
5	**15**		H	59.35	7.02
6	**20l**		CH_3SO_2	43.15	—[a]
7	**20n**		NH_2SO_2	67.11	4.25
8	**17**		H	84.08	1.30
9	**22l**		CH_3SO_2	76.09	3.14
10	**22n**		NH_2SO_2	70.90	3.85
11	Reference compound[19]			—[a]	0.15

[a] Not determined.

Table 3
Selectivity of compounds **19n** and **17** over other kinases (IC_{50} values in μM)

Entry	Compounds	IKK-2	IKK-1	p38α	p38β	JNK1	JNK2	JNK3
1	**19n**	0.92	20.37	4.7	0.21	0.48	1.9	0.88
2	**17**	1.30	>30	>30	>30	19.73	>30	>30

selectivity for IKK-2 of the piperidinyl aminopyrimidine derivatives will be performed in due course.

Acknowledgment

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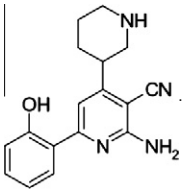
19. Murata, T.; Shimada, M.; Kadono, H.; Sakakibara, S.; Yoshino, T.; Masuda, T.; Shimazaki, M.; Shintani, T.; Fuchikami, K.; Bacon, K. B.; Ziegelbauer, K. B.; Lowinger, T. B. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4013and the structure of the reference compound is as follows:



20. Spectral data of compound **19n**: ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.45 (d, J = 5.00 Hz, 1H), 8.34 (d, J = 8.26 Hz, 2H), 7.86 (d, J = 8.41 Hz, 2H), 7.36 (d, J = 7.43 Hz, 1H), 7.24 (d, J = 5.15 Hz, 1H), 6.74 (s, 2H), 3.82–3.97 (m, 1H), 3.65 (t, J = 4.26 Hz, 4H), 3.44–3.53 (m, 2H), 2.92 (t, J = 4.51 Hz, 4H), 2.60–2.77 (m, 2H), 1.92–2.06 (m, 2H), 1.51–1.70 (m, 2H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 162.36, 160.04 (2C), 141.96, 136.49, 128.57, 128.12, 106.77, 65.76, 47.61, 46.35, 45.64, 30.93; MS (TOF, ES+, M+Na) 505.2, and spectral data of compound **17**: ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.40 (d, J = 5.27 Hz, 1H), 8.34 (d, J = 8.43 Hz, 2H), 7.89 (d, J = 8.30 Hz, 2H), 7.22 (d, J = 5.18 Hz, 1H), 4.08–4.25 (m, 1H), 3.32–3.46 (m, 2H), 2.96–3.13 (m, 6H), 2.84–2.95 (m, 4H), 2.16–2.31 (m, 2H), 1.67–1.77 (m, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 163.35, 161.91, 158.92, 141.67, 137.17, 127.92, 127.47, 106.36, 46.58, 46.26, 44.46, 43.55, 29.97; MS (TOF, ES+, M+H) 403.0.