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FACILE ACCESS TO NOVEL 3-ACYLIMIDAZO[1,2-*a*]PYRIMIDINES UNDER MICROWAVE IRRADIATION

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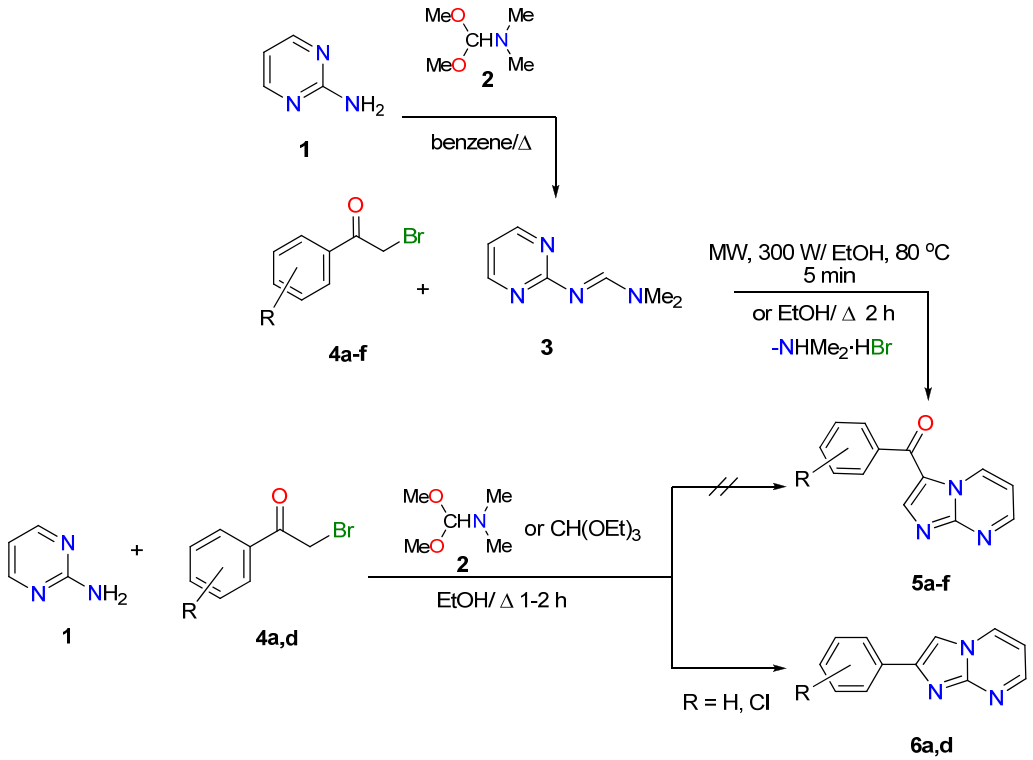
Abstract – Treatment of mono-, bis- and tris(*ω*-bromoacetophenone) derivatives with *N*,*N*-dimethylformamidine derivative of 2-aminopyrimidine, afforded the novel 3-aroyl or heteroyl derivatives of imidazo[1,2-*a*]pyrimidine, bis(imidazo[1,2-*a*]pyrimidine) and tris(imidazo[1,2-*a*]pyrimidine) derivatives, respectively, under both conventional and microwave conditions.

Imidazo[1,2-*a*]pyrimidine derivatives have received a much more attention in the field of pharmaceutical industry due to their interesting biological activities.[1] This ring system possesses important therapeutic activities such as calcium antagonists,[2] anticancer agents,[3] antifungal activity,[4] anti-inflammatory, analgesic activity,[5] antitumor agents,[6] and potent inhibitors of p38 MAP kinase.[7,8] On the other hand, bis(heterocycles) have received a great deal of attention because many biologically active natural and synthetic products have molecular symmetry.[9-16] The synthesis of the imidazo[1,2-*a*]pyrimidine ring systems has been widely investigated, they were synthesized according to Tschitschibabin reaction by cyclocondensation of 2-aminopyrimidine with the appropriate *ω*-bromoacetophenones in DME,[17] ethanol,[18] acetone and DMF.[19] Long reaction time was necessary while the yield was not very favorable. However, up to the best of our knowledge only 3-benzoylimidazo[1,2-*a*]pyrimidine from this fused system have been reported by Stanovnik group[20] using convensional methods. In addition, no synthesis of bis(imidazo[1,2-*a*]pyrimidine) derivatives and their tris analog ring systems were found in the literature,

so far even under conventional conditions. Nowadays, the use of the pressurized microwave irradiation can be very advantageous to many chemistries where the solvent can be heated up to temperatures that are 2–4 times their respective boiling points and thus providing large rate enhancement.[21-23] In addition, keeping the atmosphere from moisture that may affect the moisture sensitive reagents decreases the possibility of formation of the undesired byproducts. As a part of systematic interest in the synthesis of fused heterocyclic systems having potential unique properties,[24-27] the aim of the present work is to define versatile and expeditious route to synthesize 3-acylimidazo[1,2-*a*]pyrimidines and their bis- and tris-analogs in an efficient one step synthesis under microwave irradiation.

Treatement of the *N*,*N*-dimethyl-*N*′-pyrimidin-2-ylformamidine, obtained from the corresponding 2-aminopyrimidine (**1**) and *N*,*N*-dimethylformamide dimethylacetal (**2**), with phenacylbromide derivatives **4a-f** proceeded smoothly in anhydrous ethanol using 300 W/ 80 °C/ 5 min microwave irradiation or under conventional conditions to afford the corresponding imidazo[1,2-*a*]pyrimidine derivatives **5a-f** in good yields (Scheme 1, Table 1).



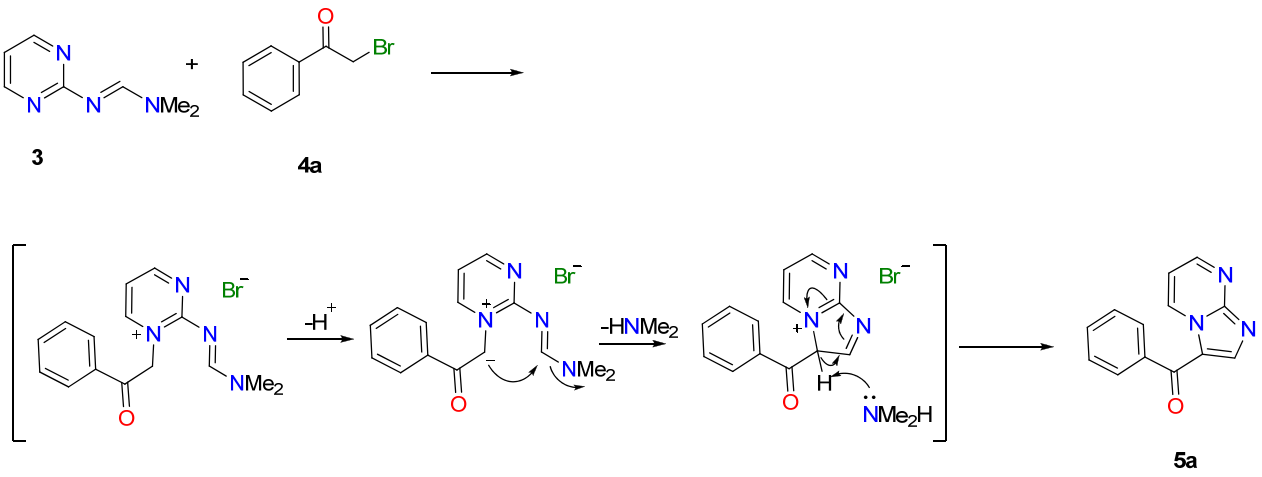
Scheme 1

Table 1. Yield % of the synthesized imidazo[1,2-*a*]pyrimidine derivatives **5a-f**

Entry	R	Product	Thermal Yield %[a]	MW Yield %[a]
1	H	**5a**	58	87
2	Me	**5b**	60	76
3	Br	**5c**	67	89
4	Cl	**5d**	62	82
5	F	**5e**	47	76
6	$NHCOCF_3$	**5f**	43	79

[a] Isolated yields

The reaction proceeds *via* first quaternization of the pyrimidines nitrogen followed by intramolecular nucleophilic attack of the anion of the methylene group to the formamidine group which followed by loss of dimethylamine to afford the fused imidazo[1,2-*a*]pyrimidine ring systems (Scheme 2).

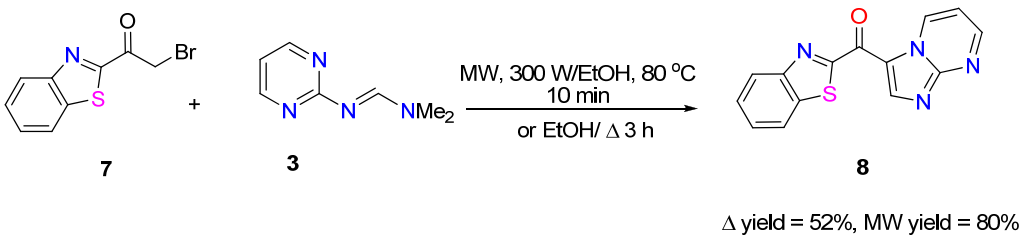


Scheme 2

The structure of the products **5a-f** were confirmed by their spectral data as well as their elemental analyses. The ^{1}H NMR spectra of compounds **5a-f** showed a characteristic signals due to the pyrimidine ring protons at the expected chemical shifts and integral values. However it should be noted that the value of the chemical shift for C5-*H* proton in the pyrimidines ring of in all products is downfield (δ around 9.8 ppm) than the corresponding expected value for the non acylated imidazopyrimidine (δ around 8.8 ppm),[28] due to the carbonyl group anisotropy.

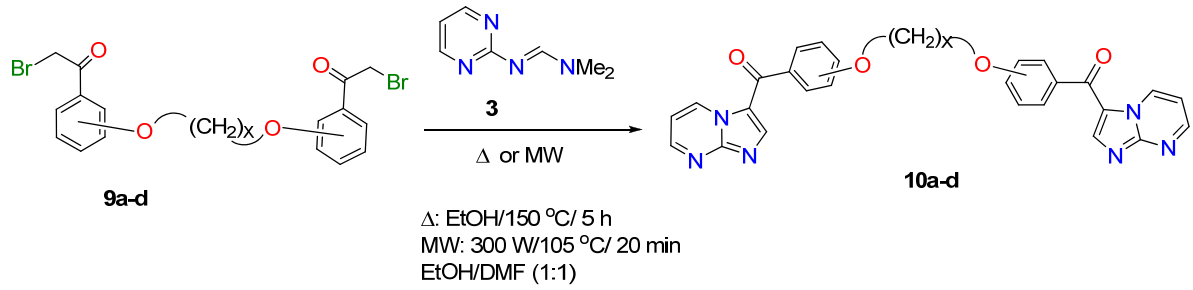
Attempts were made to obtain the imidazo[1,2-*a*]pyrimidines **5** *via* the alternative one pot three component reaction of the *ω*-bromoacetophenone derivatives **4**, 2-aminopyrimidine (**1**), and dimethylformamide dimethylacetal (**2**) or triethylorthoformate under solvent free conditions. The reaction afforded well known non carbonyl analogue imidazopyrimidines **6** instead of **5** as shown in Scheme 1.

In the same manner, when 2-bromoacetylbenzothiazole (**7**) was reacted with *N*,*N*-dimethyl-*N*′-pyrimidin-2-ylformamidine (**3**), under thermal as well as microwave conditions, it afforded the corresponding 3-(benzothiazol-2-oyl)imidazo[1,2-*a*]pyrimidine **8** in good yield (Scheme 3).



Scheme 3

When the bis(*ω*-bromoacetophenone) derivatives **9a-d** was treated with *N*,*N*-dimethyl-*N*′-pyrimidin-2-ylformamidine (**3**), in anhydrous ethanol using 300 W/ 105 °C/ 20 min microwave irradiation conditions or conventionally it afforded the corresponding bis(imidazo[1,2-*a*]pyrimidine) derivatives **10a-d** (Scheme 4).



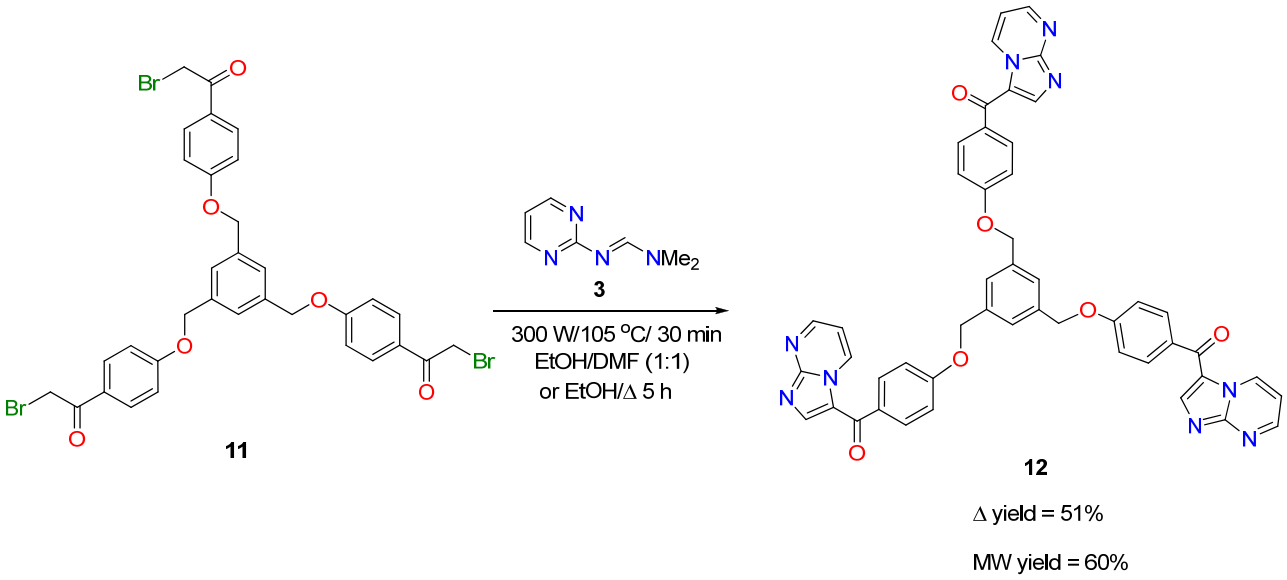
Scheme 4

Table 2. Yield % of the synthesized bis(imidazo[1,2-*a*]pyrimidine) derivatives **10a-d**

Entry	X	**10a,b** (*o*-isomer)	Yield %[a] Δ	Yield %[a] MW
1	3	**10a**	56	81
2	4	**10b**	61	74
		10c,d (*p*-isomer)		
3	3	**10c**	49	69
4	4	**10d**	53	78

[a] Isolated yields

Also, when the tris(*ω*-bromoacetophenone) derivative **11** was treated with *N*,*N*-dimethyl-*N*′-pyrimidin-2-ylformamidine (**3**), in a mixture of EtOH and DMF under the same experimental conditions, it afforded the tripodal imidazo[1,2-*a*]pyrimidine derivative **12** (Scheme 5), however the yield of the reaction product was moderate after 30 min of irradiation.



Scheme 5

In summary, a facile synthesis of novel series of mono-, bis- and tris(imidazopyrimidine) derivatives *via* the reaction of *ω*-bromoacetophenone derivatives with *N*,*N*-dimethyl-*N*′-pyrimidin-2-yl-formamidine was achieved under microwave irradiation. The synthesized mono-, bis-, and tris(fused-heterocycles) offer an advantage of their easy eco-friendly synthesis on a large scale quantities in a simple efficient procedure from inexpensive starting materials and it is expected that they would be useful compounds with potentially high pharmacological and biological activities.

EXPERIMENTAL

All melting points were measured on a Gallenkamp melting point apparatus. The infrared spectra were recorded in potassium bromide discs on a Pye Unicam SP 3- 300 and Shimadzu FT IR 8101 PC infrared spectrophotometers. The NMR spectra were recorded on a Varian Mercury VXR-300 NMR spectrometer (^{1}H NMR (300 MHz) and ^{13}C NMR (75.46 MHz)) and Bruker-500 NMR spectrometer (^{1}H NMR (500 MHz) and ^{13}C NMR (125.77 MHz)) were run in deuterated chloroform ($CDCl_3$) or dimethyl sulfoxide (DMSO-d_6). Chemical shifts were related to that of the solvent. Mass spectra were recorded on a Shimadzu GCMS-QP1000 EX mass spectrometer at 70 eV. Elemental analyses were carried out at the Micro-analytical Centre of Cairo University, Giza, Egypt and recorded on Elementar-Vario EL automatic

analyzer. Microwave irradiation was performed using the MARS system of CEM which is a multi-mode platform equipped with a magnetic stirring plate and a rotor that allows the parallel processing of several vessels per batch. We used the HP-500 (teflon (TFA) insert) (vessel volume 80 mL, max pressure 350 psi, max temperature 210 ^{o}C) in order to get the maximum save operation.

Synthesis and Characterization: Imidazopyrimidine, bis(imidazopyrimidine) and tris(imidazopyrimidine) derivatives 8a-e, 9a-d and 10.

General procedure:

Thermal Method

A mixture of the appropriate *ω*-bromoacetophenones **4a-f** (3 mmole), 2-bromoacetylbenzothiazole (**7**) (3 mmole), bis(*ω*-bromoacetophenones)[29] **9a-d** (1.5 mmole) or tris(*ω*-bromoacetophenone) **11** (1 mmole) and *N*,*N*-dimethyl-*N′*-pyrimidin-2-ylformamidine **7a,b** (3 mmole) in absolute EtOH (50 mL) was heated at refluxing temperature for 1-4 h. The reaction mixture was then left to cool and the resulting solid was collected by filtration, washed thoroughly with EtOH and dried. Recrystallization from EtOH or EtOH/DMF afforded the corresponding mono-, bis- and tris(imidazopyrimidine) derivatives **5a-f**, **8**, **10a-d** and **12**, respectively.

Microwave Method

A mixture of the appropriate *ω*-bromoacetophenones **4a-f** (3 mmole), 2-bromoacetylbenzothiazole (**7**) (3 mmole), bis(*ω*-bromoacetophenones)[29] **9a-d** (1.5 mmole) or tris(*ω*-bromoacetophenone) **11** (1 mmole) and *N*,*N*-dimethyl-*N′*-pyrimidin-2-ylformamidine **7a,b** (3 mmole) in absolute EtOH (30 mL) or EtOH/DMF mixture (30 mL) were mixed in a HP-500 process vial. The vial was capped properly and irradiated by microwaves (300 W) using pressurized conditions at 80 or 105 ^{o}C for 5, 20 or 30 min. Microwave irradiation was performed using the MARS system of CEM which is a multi-mode platform equipped with a magnetic stirring plate and a rotor that allows the parallel processing of several vessels per batch. The reaction mixture was then left to cool and the resulting solid was recrystallized from EtOH, DMF or a mixture of EtOH/DMF to afford the corresponding mono-, bis- and tris(imidazopyrimidine) derivatives **5a-f**, **8**, **10a-d** and **12**, respectively. The physical and spectral data of the newly synthesized compounds are listed below.

3-Benzoylimidazo[1,2-*a*]pyrimidine (5a): mp 234-235 ˚C [Lit. mp 234][20]; IR (KBr) ν_{max}/cm^{-1} 1611 (C=O); ^{1}H NMR (DMSO-d_6) δ 7.46 (t, 2H, J = 9 Hz), 7.57 (t, 1H, J = 7.2 Hz), 7.68 (t, 1H, J = 9 Hz), 7.90 (d, 2H, J = 7.2 Hz), 8.43 (s, 1H), 8.89 (d, 1H, J = 4.5 Hz), 9.89 (d, 1H, J = 6.9 Hz); ^{13}C NMR (DMSO-d_6) δ 112.39, 121.54, 129.32, 132.95, 137.39, 139.43, 143.50, 146.38, 151.26, 154.88, 184.11. MS *m/z* 223 (M^+). Anal. Calcd for $C_{13}H_9N_3O$: C, 69.95; H, 4.06; N, 18.82. Found: C, 69.93; H, 4.05; N, 18.85%.

3-(4-Methylbenzoyl)imidazo[1,2-*a*]pyrimidine (5b): mp 208 ˚C; IR (KBr) ν_{max}/cm^{-1} 1611 (C=O); ^{1}H

NMR (DMSO-d_6) δ 2.43 (s, 3H), 7.39 (d, 2H, J = 7.8 Hz), 7.46 (t, 1H, J = 2.4 Hz), 7.82 (d, 2H, J = 7.8 Hz), 8.42 (s, 1H), 8.86 (d, 1H, J = 3.6 Hz), 9.87 (d, 1H, J = 6.9 Hz); ^{13}C NMR (DMSO-d_6) δ 21.62, 112.26, 121.84, 129.48, 129.83, 135.79, 137.35, 143.30, 146.00, 151.36, 154.73, 184.21. MS *m/z* 237 (M^+). Anal. Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 70.84; H, 4.63; N, 17.68%.

3-(4-Bromobenzoyl)imidazo[1,2-*a*]pyrimidine (5c): mp 248 ˚C; IR (KBr) ν_{max}/cm^{-1} 1698 (C=O); ^{1}H NMR (DMSO-d_6) δ 7.45 (t, 1H, J = 7.8 Hz), 7.77-7.81 (m, 4H), 8.46 (s, 1H), 8.88 (d, 1H, J = 3.6 Hz), 9.85 (d, 1H, J = 6.9 Hz). MS *m/z* 302 (M^+). Anal. Calcd for $C_{13}H_8BrN_3O$: C, 51.68; H, 2.67; N, 13.91. Found: C, 51.65; H, 2.66; N, 13.93%.

3-(4-Chlorobenzoyl)imidazo[1,2-*a*]pyrimidines (5d): mp 240 ˚C; IR (KBr) ν_{max}/cm^{-1} 1699 (C=O); ^{1}H NMR (DMSO-d_6) δ 7.46 (t, 1H, J = 2.4 Hz), 7.66 (d, 2H, J = 7.8 Hz), 7.92 (d, 2H, J = 7.8 Hz), 8.46 (s, 1H), 8.88 (d, 1H, J = 3.6 Hz), 9.86 (d, 1H, J = 6.9 Hz). MS *m/z* 257 (M^+). Anal. Calcd for $C_{13}H_8ClN_3O$: C, 60.60; H, 3.13; N, 16.31. Found: C, 60.62; H, 3.11; N, 16.34%.

3-(4-Fluorobenzoyl)imidazo[1,2-*a*]pyrimidine (5e): mp 256 ˚C; IR (KBr) ν_{max}/cm^{-1} 1698 (C=O); ^{1}H NMR (DMSO-d_6) δ 7.39 (t, 1H, J = 2.4 Hz), 7.46 (d, 2H, J = 7.8 Hz), 7.98 (d, 2H, J = 7.8 Hz), 8.44 (s, 1H), 8.88 (d, 1H, J = 3.6 Hz), 9.86 (d, 1H, J = 6.9 Hz). MS *m/z* 241 (M^+). Anal. Calcd for $C_{13}H_8FN_3O$: C, 64.73; H, 3.34; N, 17.42. Found: C, 64.70; H, 3.32; N, 17.40%.

3-(4-Trifluoroacetamidobenzoyl)imidazo[1,2-*a*]pyrimidine (5f): mp 235 ˚C; IR (KBr) ν_{max}/cm^{-1} 3568, (NH), 1737 (C=O), 1615 (C=O); ^{1}H NMR (DMSO-d_6) δ 7.46 (t, 1H, J = 2.4 Hz), 7.93 (d, 2H, J = 7.8 Hz), 7.99 (d, 2H, J = 7.8 Hz), 8.48 (s, 1H), 8.87 (d, 1H, J = 3.6 Hz), 9.87 (d, 1H, J = 6.9 Hz), 11.57 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 111.79, 117.53, 115.29, 121.06, 12171, 130.50, 135.12, 137.08, 140.57, 146.16, 150.74, 154.17 (q), 183.18. MS *m/z* 334 (M^+). Anal. Calcd for $C_{15}H_9F_3N_4O_2$: C, 53.90; H, 2.71; N, 16.76. Found: C, 53.88; H, 2.73; N, 16.72%.

3-(Benzothiazol-2-oyl)imidazo[1,2-*a*]pyrimidine (8): mp 258 ˚C; IR (KBr) ν_{max}/cm^{-1} 1686 (C=O); ^{1}H NMR (DMSO-d_6) δ 7.52-7.54 (m, 2H), 7.63 (t, 1H, J = 7.8 Hz), 8.29 (d, 1H, J = 7.8 Hz), 8.35 (d, 1H), 8.94 (d, 1H, J = 3.6 Hz), 9.59 (s, 1H), 9.96 (s, 1H). MS *m/z* 280 (M^+). Anal. Calcd for $C_{14}H_8N_4OS$: C, 59.99; H, 2.88; N, 19.99. Found: C, 59.97; H, 2.85; N, 19.96%.

Bis(imidazo[1,2-*a*]pyrimidines) 10a-d

10a: mp 261-262 ˚C; IR (KBr) ν_{max}/cm^{-1} 1624 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.98 (m, 2H), 4.26 (m, 4H), 6.97 (d, 2H, J = 9 Hz), 7.03 (t, 2H, J = 9 Hz), 7.39-7.49 (m, 6H, J = 9 Hz), 8.08 (s, 2H), 8.86 (d, 2H, J = 9 Hz), 9.87 (d, 2H, J = 9 Hz); ^{13}C NMR (DMSO-d_6) δ 28.55, 65.44, 113.91, 120.94, 122.65, 128.08, 129.74, 132.62, 134.17, 136.98, 137.32, 146.89, 154.65, 156.20, 184.17. MS *m/z* 518 (M^+). Anal. Calcd for $C_{29}H_{22}N_6O_4$: C, 67.17; H, 4.28; N, 16.21. Found: C, 67.15; H, 4.25; N, 16.24%.

10b: mp 269-270 ˚C; IR (KBr) ν_{max}/cm^{-1} 1658 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.47 (m, 4H), 3.92 (m, 4H), 6.98-7.09 (m, 4H, J = 9 Hz), 7.40-7.56 (m, 6H, J = 9 Hz), 8.07 (s, 2H), 8.84 (d, 2H, J = 9 Hz), 9.86 (d, 2H,

J = 9 Hz). MS *m/z* 532 (M^+). Anal. Calcd for $C_{30}H_{24}N_6O_4$: C, 67.66; H, 4.54; N, 15.78. Found: C, 67.63; H, 4.52; N, 15.81%.

10c: mp 208-209 ˚C; IR (KBr) ν_{max}/cm^{-1} 1624 (C=O); ^{1}H NMR (DMSO-d_6) δ 2.28 (m, 2H), 4.29-4.33 (m, 4H), 7.14-7.18 (d, 4H, *J* = 9 Hz), 7.40-7.43 (t, 2H, *J* = 9 Hz), 7.89-7.92 (d, 4H, *J* = 9 Hz), 8.42 (s, 2H), 8.84-8.86 (d, 2H, *J* = 9 Hz), 9.82-8.85 (d, 2H, *J* = 9 Hz). MS *m/z* 518 (M^+). Anal. Calcd for $C_{29}H_{22}N_6O_4$: C, 67.17; H, 4.28; N, 16.21. Found: C, 67.15; H, 4.26; N, 16.20%.

10d: mp 299-300 ˚C; IR (KBr) ν_{max}/cm^{-1} 1625 (C=O); ^{1}H NMR (DMSO-d_6) δ 1.94 (m, 4H), 4.18 (m, 4H), 7.12-7.15 (d, 4H, *J* = 9 Hz), 7.41-7.43 (t, 2H, *J* = 9 Hz), 7.90-7.93 (m, 4H, *J* = 9 Hz), 8.42 (s, 2H), 8.84-8.86 (d, 2H, *J* = 9 Hz), 9.84-8.86 (d, 2H, *J* = 9 Hz). MS *m/z* 532 (M^+). Anal. Calcd for $C_{30}H_{24}N_6O_4$: C, 67.66; H, 4.54; N, 15.78. Found: C, 67.64; H, 4.53; N, 15.75%.

Tris(imidazo[1,2-*a*]pyrimidine) 12: mp > 300 ˚C; IR (KBr) ν_{max}/cm^{-1} 1626 (C=O); ^{1}H NMR (DMSO-d_6) δ 5.27 (s, 6H), 7.11-7.24 (m, 6H), 7.42 (d, 3H), 7.55 (s, 3H), 7.92 (d, 6H), 8.44 (s, 3H), 8.86 (d, 3H), 9.82 (d, 3H). Anal. Calcd for $C_{48}H_{33}N_9O_6$: C, 69.31; H, 4.00; N, 15.15. Found: C, 69.28; H, 4.01; N, 15.12%.

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