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A ONE-POT, GREEN SYNTHESIS OF BETTI BASE CONTAINING ADENINE DERIVATIVES IN AQUEOUS MEDIUM

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Abstract – A one-pot, three-component condensation reaction of 2-naphthol, adenine and aliphatic or aromatic aldehydes in aqueous medium to give Betti base containing adenine derivatives in the presence of *p*-toluenesulfonic acid for the first time, is described. The present approach offers several advantages such as good yields, mild conditions (80 °C), clear reaction profile and simple work-up procedure. The entitled compounds are characterized by IR, NMR and HRMS.

Betti base was first synthesized by the distinguished Italian chemist Mario Betti via a modified Mannich reaction named Betti reaction[1] which is a one-pot, three-component condensation reaction of benzaldehyde, 2-naphthol, and ammonia (Figure 1). Recently, interest in the chemistry of the Betti base[2] has intensified due to their attractive catalytic[3] and biological properties.[4] Several alternative and efficient methods have been developed for the synthesis of Betti base derivatives by multicomponent reaction of 2-naphthol, aldehyde and amide in the presence of different Lewis or Brønsted acid catalysts such as K10 clay,[5] $Ce(SO_4)_2$,[6] iodine,[7] lithium perchlorate,[8] nonionic surfactant,[9] nanocrystalline MgO,[10] $K_5CoW_{12}O_{40}\cdot 3H_2O$,[11] $HClO_4$-SiO_2,[12] ionic liquid,[13] oxalic acid,[14] sulfanilic acid[15] and *p*-toluenesulfonic acid (180 °C).[16] Although these methods are quite useful, many of these methods suffer from limitations such as the use of toxic organic solvents, high temperature (120-180 °C), tedious work-up procedures and the use of toxic, highly acidic and expensive catalysts. In addition, most of these reactions were limited to

only aromatic aldehydes. Thus, there is a need for a simple, environment-friendly efficient and more general method for the synthesis of these useful derivatives.

Organic reactions in water without use of any harmful organic solvents are of great current interest, because water is an easily available, safe, economical and environmentally benign solvent.[17] In addition the remarkable properties seen in water as a result of its specific chemical and physical properties are very useful for selectivity/reactivity that cannot be attained in organic solvents and make it an attractive solvent for many organic reactions. More recently, to the best of our knowledge, only a few Betti base derivatives were reported in aqueous medium.[18] Ahmad's group has developed one-pot synthesis of 2'-aminobenzothiazolomethyl naphthols and 5-(2'-aminobenzothiazolomethyl)-6-hydroxyquinolines with LiCl in aqueous medium.[18a] However, a large number of metal ions is not conducive to the environment. Some catalysts are expensive and not easily available.

Due to the biological activity of adenined analogues[19] and our long interest in the chemistry of heteroaromatic systems and green chemistry,[16,20] we intend to synthesize Betti base containing adenine derivatives based on the condensation between 2-naphthol, aliphatic or aromatic aldehydes and the adenine in aqueous medium conditions (Scheme 1)

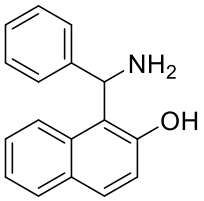
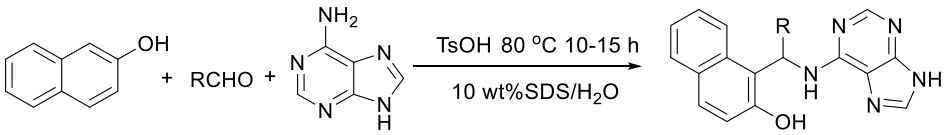


Figure 1. The structure of Betti base

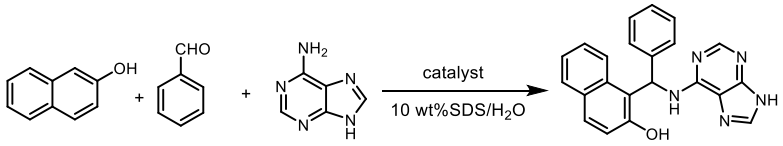


Scheme 1. The condensation between 2-naphthol, adenine and aliphatic or aromatic aldehydes in 10 wt% SDS/H_2O

Initially, we chose the reaction of 2-naphthol (2 mmol), benzaldehyde (2 mmol) and adenine (2 mmol) in 10 wt% SDS (sodium dodecyl sulfate)/H_2O (3 mL) under catalyst-free conditions as a model reaction trying every order of the addition of starting materials, but no targeted product was obtained (entry 1, Table 1). Then we used the commercially available *p*-toluenesulfonic acid (20% mmol) as the catalyst to

get the desired products (entries 12–14, Table 1). Next, several catalysts such as Lewis acid catalysts ($FeCl_3·6H_2O$, $AlCl_3$, $CeCl_3$, $SnCl_2$, etc.) (20% mmol, respectively) and Brønsted acid (20% mmol, respectively) were examined for optimization of reaction at 80 ^oC in 10 wt% SDS/H_2O (entries 2–11, Table 1). So we chose *p*-toluenesulfonic acid as the best catalyst to optimize the model reaction (entry 13, Table 1).

Table 1. Optimization of the reaction conditions[a]



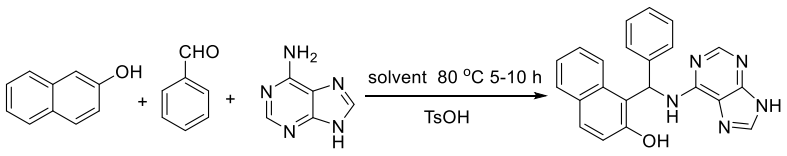
Entry	Catalyst	t (h)	Yield[b](%)
1	-	24	0
2	$FeCl_3·6H_2O$	10	0
3	$AlCl_3$	10	0
4	MgO	10	0
5	Yb_2O_3	10	0
6	$SnCl_2$	10	0
7	$CeCl_3$	10	0
8	sulfanilic acid	10	50
9	H_2SO_4	10	46
10	vitamin B1	10	37
11	L -proline	10	48
12	TsOH[c]	5	47
13	TsOH	10	80
14	TsOH	15	78

a. Reaction conditions: adenine (2 mmol), benzaldehyde (2 mmol), 2-naphthol (2 mmol) and catalyst (20% mmol) in 10 wt% SDS/H_2O (3 mL) was stirred at 80 °C for 5-24 h
b. Isolated yield of product.
c. TsOH= *p*-toluenesulfonic acid.

With the best promotor in hand, we also studied the solvent effect. We tried a variety of solvents. To our surprise, the reaction in some solvents such as EtOH, DMF, THF, MeOH, toluene, MeCN and DMSO nearly did not proceed (entries 1–5, 11-12, Table 2,). When the reaction was carried out in pure water and

EtOH/H_2O, it was found that a moderate yield of 48% and 40% could be obtained after 10 h (entries 6–7, Table 2). Our studies suggested that 10 wt% SDS/H_2O was the ideal solvent for this reaction and SDS could promote the reaction in water due to lower mass transfer resistance and enlargement of the interfacial area (entry 9, Table 2).

Table 2. Optimization of the reaction solvent[a]



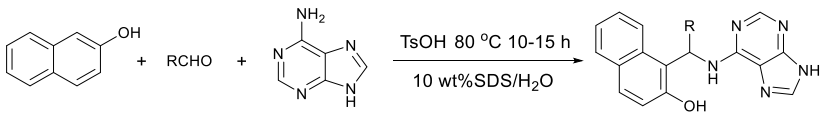
Entry	Solvent	t (h)	Yield[b] (%)
1	EtOH	10	0
2	DMF	10	trace
3	THF	10	0
4	MeOH	10	0
5	toluene	10	0
6	EtOH/H_2O	10	40
7	H_2O	10	48
8	10 wt% SDS/H_2O	5	50
9	10 wt% SDS/H_2O	10	80
10	10 wt% SDS/H_2O	15	78
11	MeCN	10	0
12	DMSO	10	trace

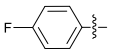
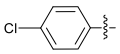
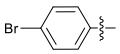
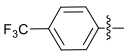
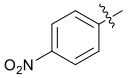
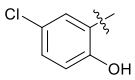
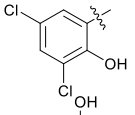
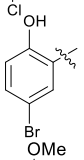
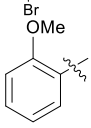
a. Reaction conditions: adenine (2 mmol), benzaldehyde (2 mmol), 2-naphthol (2 mmol) and TsOH (20% mmol) in solvent (3 mL) was stirred at 80 °C for 5-15 h

b. Isolated yield of product

To demonstrate the scope and limitations of the procedure, a wide range of structurally diverse aldehydes underwent condensation by this reaction to provide Betti base containing adenine derivatives in good yields. The results are summarized in Table 3. As evident from the results, this procedure is uniformly effective for both aliphatic and aromatic aldehydes. The aliphatic aldehydes such as propyl aldehyde,

Table 3. The study of the scope and limitations of this transformation using a series of aldehydes



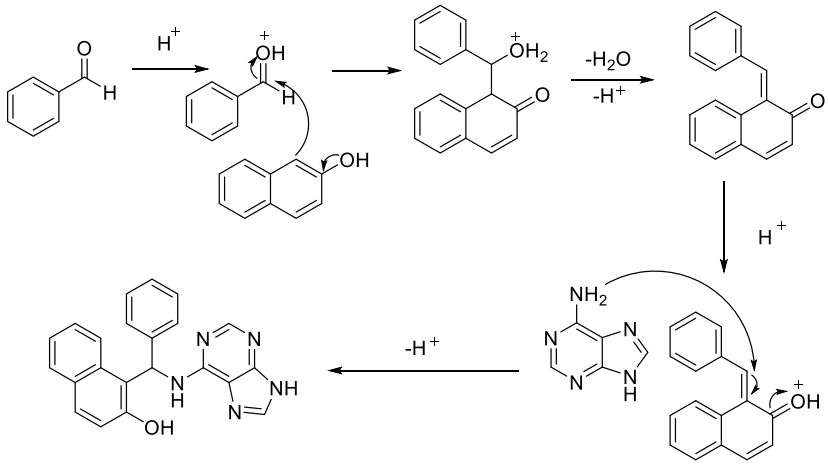
Entry (compound)	Aldehyde R	t (h)	yield[a] (%)
1		10	80.0
2		10	88.0
3		10	85.0
4		10	90.0
5		10	86.0
6		10	70.3
7		10	65.0
8		10	75.0
9		10	64.0
10		10	60.0
11		10	83
12		15	68
13		15	65.2
14		14	64.5
15		15	69

a. Isolated yield of product

n-butyraldehyde, and 3-methylbutanal were subjected under the reaction conditions and corresponding desired products were isolated in moderate yields (entries 13-15, Table 3). Aromatic aldehydes with electron donating groups (entries 12, Table 3) showed poor reactivity compared with that with electron withdrawing groups or without any groups (entries 1, 2-8, Table 3). Whatever type of aromatic

aldehydes with electron withdrawing groups or electron donating groups at the ortho-position, the yield is low which may be due to the large space hindrance (entries 6, 7, 9-10, Table 3). Next, we extended this reaction to phenols, *p*-nitrophenol on reaction under similar conditions. It was found that no conversion to product was obtained even after 24 h of heating.

A reasonable reaction path based on our results, and other people's research works[18c-e] was proposed (Scheme 2). As depicted in Scheme 2, at first, the condensation of β-naphthol and benzaldehyde produced the α,β-unsaturated carbonyl compound intermediate promoted by *p*-toluenesulfonic acid, then the entitled compound is obtained by the Michael addition of adenine to α, β-unsaturated carbonyl compound.



Scheme 2. A proposed reasonable reaction path

In conclusion, we have developed a facile, green, and effective method for the synthesis of Betti base containing adenine derivatives catalyzed by *p*-toluenesulfonic acid in aqueous medium. From the condition of green chemistry, the advantages of the present procedure are experimental simplicity and easy work-up.

EXPERIMENTAL

General information: All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker Avance III (^{1}H: 400 MHz, ^{13}C: 100 MHz,), chemical shifts (δ) are expressed in ppm, and J values are given in Hz, and DMSO-d_6 was used as solvent. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF254. HRMS (ESI) analysis was measured on a LCMS-IT-TOF instrument. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using KBr pellet. All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (200–300 mesh).

General procedure: To a solution of 10 wt% SDS/H_2O (3 mL) were added adenine (2 mmol), aldehyde (2 mmol), 2-naphthol (2 mmol) and TsOH (20% mmol). The mixture was stirred at 80 °C for several hours and monitored by TLC. After the reaction was complete, the reaction mixture was filtered and the precipitate washed with hot H_2O. The crude products were purified by recrystallization from EtOH.

1-(((9*H*-Purin-6-yl)amino)(phenyl)methyl)naphthalen-2-ol (**compound 1**): White solid, mp 227~229 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.10 (1H, s, adenine-NH), 10.54 (1H, s, OH), 7.16-8.32 (15H, m, CHNH, Ph-H, adenine-H and methine-H); ^{13}C NMR (DMSO-d_6, 100.6 MHz): δ: 154.18, 153.67, 153.01, 150.19, 143.21, 140.08, 132.72, 129.93, 129.21, 128.76, 128.69, 127.65, 127.00, 126.59, 123.32, 122.58, 119.37, 119.28, 49.61; IR (KBr) ν: 3417, 1604, 1515, 1296, 1254, 818, 744; HRMS(ESI) $[M+H]^+$ Calcd for $C_{22}H_{18}N_5O$ 368.1506, found 368.1489.

1-(((9*H*-Purin-6-yl)amino)(4-fluorophenyl)methyl)naphthalen-2-ol (**compound 2**): White solid, mp 166~167 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.08 (1H, s, adenine-NH), 10.57 (1H, s, OH), 7.08-8.30 (14H, m, CHNH, Ph-H, adenine-H and methine-H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 159.90,153.69, 152.95, 140.14, 139.37, 139.33, 132.61, 130.06, 129.24, 128.79, 128.55, 128.47, 127.71, 123.34, 122.40, 119.25, 115.52, 115.31, 49.19; IR (KBr) ν: 3403, 1609, 1507, 1234, 818; HRMS(ESI) $[M+H]^+$ Calcd for $C_{22}H_{17}FN_5O$ 386.1412, found 386.1395.

1-(((9*H*-Purin-6-yl)amino)(4-chlorophenyl)methyl)naphthalen-2-ol (**compound 3**): White solid, mp 234~235 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.11 (1H, s, adenine-NH), 10.58 (1H, s, OH), 7.11-8.32 (14H, m, CHNH, Ph-H, adenine-H and methine-H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 153.72, 152.96, 142.23, 140.17, 132.61, 131.63, 130.16, 129.83, 129.25, 128.65, 128.46, 127.74, 126.57, 123.38, 123.11, 122.51, 119.25, 109.11, 49.19; IR (KBr) ν: 3403, 1607, 1515, 1248, 816, 744; HRMS(ESI) $[M+H]^+$ Calcd for $C_{22}H_{17}ClN_5O$ 402.1116, found 402.1122.

1-(((9*H*-Purin-6-yl)amino)(4-bromophenyl)methyl)naphthalen-2-ol (**compound 4**): White solid, mp 231~ 233 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.10 (1H, s, adenine-NH), 10.57 (1H, s, OH), 7.24-8.30 (14H, m, CHNH, Ph-H, adenine-H and methine-H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 153.73, 152.96, 142.23, 140.18, 132.58, 131.56, 130.16, 129.76, 129.24, 128.82, 127.99, 127.75, 126.56, 123.37, 123.09, 122.48, 119.23, 109.14, 49.19; IR (KBr) ν: 3399, 1605, 1512, 1248, 812, 743; HRMS(ESI) $[M+H]^+$ Calcd for $C_{22}H_{17}BrN_5O$ 446.0611, found 446.0600.

1-(((9*H*-Purin-6-yl)amino)(4-(trifluoromethyl)phenyl)methyl)naphthalen-2-ol (**compound 5**): White solid, mp 204~206 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.15 (1H, s, adenine-NH), 10.59 (1H, s, OH), 7.27-8.35 (14H, m, CHNH, Ph-H, adenine-H and methine-H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 153.81, 152.92, 148.20, 140.31, 132.68, 130.35, 129.28, 128.83, 127.78, 127.29, 126.18, 125.65, 125.62,

123.48, 123.39, 122.51, 119.21, 118.89, 49.43; IR (KBr) ν: 3411, 1612, 1517, 1326, 1125, 817; HRMS(ESI) $[M+H]^+$ Calcd for $C_{23}H_{17}F_3N_5O$ 436.1380, found 436.1372.

1-(((9*H*-Purin-6-yl)amino)(2-chlorophenyl)methyl)naphthalen-2-ol (**compound 6**): White solid, mp 190~192 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.99 (1H, s, adenine-NH), 10.31 (1H, s, OH), 7.12-8.27 (14H, m, CHNH, Ph-H, adenine-H and methine-H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 154.29, 152.93, 152.85, 139.83, 133.16, 133.07, 130.35, 130.15, 129.94, 129.12, 129.06, 129.05, 128.76, 127.14, 123.08, 122.93, 119.31, 117.80, 49.12 ; IR (KBr) ν: 3387, 1604, 1537, 1439, 1262, 744; HRMS(ESI) $[M+H]^+$ Calcd for $C_{22}H_{17}ClN_5O$ 402.1116, found 402.1098.

1-(((9*H*-Purin-6-yl)amino)(2-fluorophenyl)methyl)naphthalen-2-ol (**compound 7**): White solid, mp 220~221 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.07 (1H, s, adenine-NH), 10.57 (1H, s, OH), 7.06-8.29 (14H, m, CHNH, Ph-H, adenine-H and methine-H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 153.64, 152.96, 140.11, 139.28, 132.57, 130.06, 129.24, 128.77, 128.54, 128.46, 127.73, 123.36, 122.48, 119.25, 119.15, 115.52, 115.31, 100.00, 49.16; IR (KBr) ν: 3405, 1607, 1508, 1248, 1159, 818, 743; HRMS(ESI) $[M+H]^+$ Calcd for $C_{22}H_{17}FN_5O$ 386.1412, found 386.1404.

1-(((9*H*-Purin-6-yl)amino)(4-nitrophenyl)methyl)naphthalen-2-ol (**compound 8**): yellow solid, mp 221~222 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.13 (1H, s, adenine-NH), 10.62 (1H, s, OH), 7.25-8.41 (14H, m, CHNH, Ph-H, adenine-H and methine-H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 192.74, 153.84, 152.89, 146.71, 140.55, 140.37, 132.57, 131.09, 130.54, 129.32, 128.83, 127.92, 127.71, 124.72, 123.96, 123.47, 122.45, 119.13, 99.99, 49.51; IR (KBr) ν: 3389, 1622, 1517, 1344, 820, 741; HRMS(ESI) $[M+H]^+$ Calcd for $C_{22}H_{17}N_6O_3$ 413.1357, found 413.1346.

1-(((9*H*-Purin-6-yl)amino)(5-chloro-2-hydroxyphenyl)methyl)naphthalen-2-ol (**compound 9**): White solid, mp 223~225 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.07 (1H, s, adenine-NH), 10.60 (1H, s, OH), 10.29 (1H, s, OH), 6.76-8.28(13H, m, CHNH, Ph-H, adenine-H and methine-H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 154.08, 153.63, 152.69, 151.06, 140.13, 132.62, 131.26, 129.83, 128.88, 128.73, 128.48, 128.07, 127.81, 126.94, 123.37, 123.27, 122.69, 119.29, 46.37; IR (KBr) ν: 3348, 3063, 1613, 1519, 1470, 1259, 811, 745; HRMS(ESI) $[M+H]^+$ Calcd for $C_{22}H_{17}ClN_5O_2$ 418.1065, found 418.1081.

1-(((9*H*-Purin-6-yl)amino)(3,5-dichloro-2-hydroxyphenyl)methyl)naphthalen-2-ol (**compound 10**): White solid, mp 201~203 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.07 (1H, s, adenine-NH), 10.60 (1H, s, OH), 10.29 (1H, s, OH), 6.76-8.28 (13H, m, CHNH, Ph-H, adenine-H and methine-H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 192.41, 153.50, 152.16, 150.18, 140.80, 133.63, 132.44, 130.40, 129.14, 128.83, 128.38, 127.64, 123.57, 123.52, 123.06, 122.42, 119.37, 117.26, 100.00, 47.90; IR (KBr) ν: 3363, 3067, 2360, 1622, 1518, 1331, 1253, 810, 748; HRMS(ESI) $[M+H]^+$ Calcd for $C_{22}H_{14}Cl_2N_5O_2$ 450.0530, found 450.0515.

1-(((9*H*-Purin-6-yl)amino)(5-bromo-2-hydroxyphenyl)methyl)naphthalen-2-ol (**compound 11**): White solid, mp 234~236 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.08 (1H, s, adenine-NH), 10.63 (1H, s, OH), 10.31 (1H, s, OH), 6.72-8.29 (13H, m, CHNH, Ph-H, adenine-H and methine-H); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 154.51, 153.62, 152.68, 14021, 132.64, 131.84, 131.36, 130.96, 129.81, 128.86, 128.72, 126.92, 123.40, 123.20, 119.27, 118.77, 118.36, 110.39, 46.22; IR (KBr) ν: 3345, 3063, 1611, 1471, 1259, 812, 744; HRMS(ESI) $[M+H]^+$ Calcd for $C_{22}H_{15}BrN_5O_2$ 460.0415, found 460.0431.

1-(((9*H*-Purin-6-yl)amino)(2-methoxyphenyl)methyl)naphthalen-2-ol (**compound 12**): White solid, mp 222~ 224 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.05 (1H, s, adenine-NH), 10.38 (1H, s, OH), 6.88-8.45 (14H, m, CHNH, Ph-H, adenine-H and methine-H), 3.58 (3H, s, OCH_3); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 157.14, 153.88, 152.98, 139.88, 132.74, 130.57, 129.51, 128.77, 128.73, 128.44, 126.61, 123.73, 123.01, 120.32, 119.60, 119.52, 119.23, 111.42, 55.73, 20.42; IR (KBr) ν: 3385, 1605, 1448, 1246, 1024, 803, 749; HRMS(ESI) $[M+H]^+$ Calcd for $C_{23}H_{20}N_5O_2$ 398.1612, found 398.1609.

1(1-((9*H*-Purin-6-yl)amino)propyl)naphthalen-2-ol (**compound 13**): White solid, mp 211~ 213 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.94 (1H, s, adenine-NH), 10.45 (1H, s, OH), 6.44-8.23 (9H, m, Ph-H and adenine-H), 6.33 (1H, s, methine-H) 2.07-2.14 (2H, m, CH_2), 0.88-1.05 (3H, m, CH_3); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 153.61, 152.88, 139.60, 132,80 129.15, 129.00, 128.71, 127.01, 126.99, 123.04, 122.88, 120.04, 119.28, 56.54, 19.03, 11.81; IR (KBr) ν: 3381, 2957, 1608, 1517, 1255, 816, 744; HRMS(ESI) $[M+H]^+$ Calcd for $C_{18}H_{18}N_5O$ 320.1506, found 320.1528.

1-(1-((9*H*-Purin-6-yl)amino)butyl)naphthalen-2-ol (**compound 14**): White solid, mp 212~214 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 12.97 (1H, s, adenine-NH), 10.43 (1H, s, OH), 7.11-8.24 (9H, m, Ph-H and adenine-H), 6.44 (1H, s, methine-H), 1.98-2.11 (2H, m, CH_2), 1.19-1.43 (2H, m, CH_2), 0.89 (3H, t, J=8Hz, CH_3); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 153.59, 152.86, 139.77, 132.61, 129.09, 128.99, 128.71, 126.98, 123.02, 120.39, 119.28, 47.10, 20.09, 19.03, 14.37; IR (KBr) ν: 3381, 2957, 1608, 1517, 1255, 816, 744; HRMS(ESI) $[M+H]^+$ Calcd for $C_{19}H_{20}N_5O$ 334.1662, found 334.1666.

1-(1-((9*H*-Purin-6-yl)amino)-3-methylbutyl)naphthalen-2-ol (**compound 15**): White solid, mp 216~ 218 °C; ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 13.04 (1H, s, adenine-NH), 10.51 (1H, s, OH), 7.24-8.31 (9H, m, Ph-H and adenine-H), 6.60 (1H, s, methine-H), 2.25 (1H, brs, CH_2), 1.74 (1H, brs, CH_2), 1.65-1.66 (1H, m, CH_3CH), 0.91-1.00 (6H, m, $2CH_3$); ^{13}C NMR (DMSO-d_6, 100.6 MHz) δ: 154.94, 153.65, 153.02, 139.65, 133.64, 133.49, 129.24, 129.06, 128.75, 127.03, 123.12, 120.38, 119.29, 53.33, 33.06, 20.83; IR (KBr) ν: 3416, 2955, 1606, 1517, 1258, 815, 741; HRMS(ESI) $[M+H]^+$ Calcd for $C_{20}H_{22}N_5O$ 348.1819, found 348.1818.

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