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SYNTHESIS OF NEW 1,3,8-TRISUBSTITUTED PURINE-2,6-DIONES AND 1,3,6-TRISUBSTITUTED THIAZOLO[2,3-*f*]PURINE-2,4-DIONES[1]

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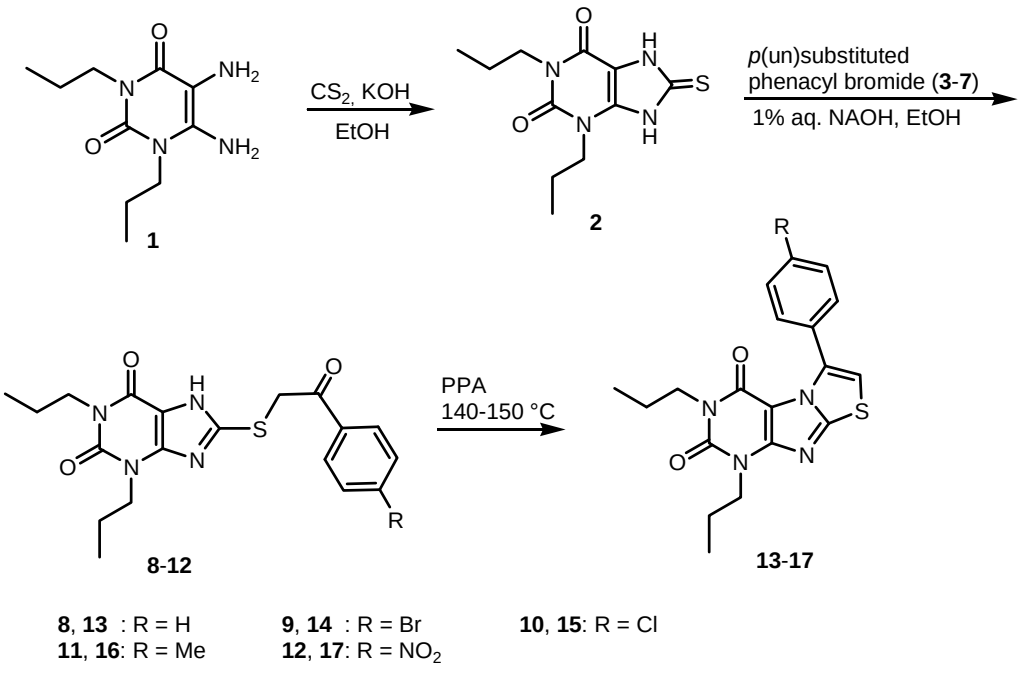
Abstract – New 1,3,8-trisubstituted purine-2,6-diones and 1,3,6-trisubstituted thiazolo[2,3-*f*]purine-2,4-diones were designed and synthesized as agents with potential biological activities. The final products were obtained by cyclization of carboxamide intermediates using 1,1,1,3,3,3,-hexamethyldisilazane. This procedure gave higher yields, and was more convenient and easier in purification compared to other methods. We also found polyphosphoric acid to be the most efficient agent in the cyclization of 8-[2-(*p*-(un)substituted-phenyl)-2-oxo-ethylsulfanyl]-1,3-dipropyl-3,7-dihydro-purine-2,6-diones to 1,3-dipropyl-6-substituted)-1*H*-thiazolo[2,3-*f*]purine-2,4-diones.

The pyrimidine and purine ring systems belong to the most ubiquitous heterocycles in nature, as they represent the main structure of many biologically active compounds. Several of these heterocycles possess a multitude of pronounced biological activities. The class of fused purines are considered to be attractive targets since their fundamental skeleton is analogous to naturally occurring purine alkaloids. Many biological activities have been reported for these classes of compounds; they can act as antitumor and anticancer amplifiers,[1] phosphodiesterase inhibitors,[2] antimicrobial agents,[3] anti-asthmatic,[4] anti-inflammatory.[5] Recently, we reported that 1,8-disubstituted purine-2,6-diones and 3,6-disubstituted thiazolo[2,3-*f*]purine-2,4-diones showed potent analgesic and anti-inflammatory activity through adenosine receptor antagonism.[7,8] Together with the very interesting recent finding by Foley *et al*. that this class of compounds has also potential antidiabetic activity through inhibition of phosphoenolpyruvate

[1]We dedicate this paper to Prof. Dr. Ekkehard Winterfeldt on the occasion of his 75 th birthday.

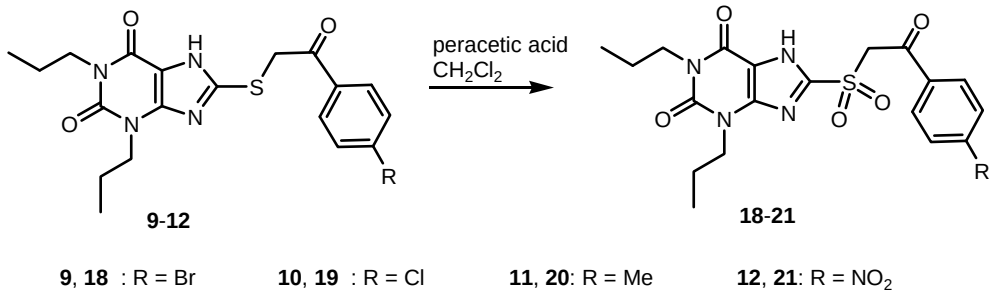
carboxykinase (PEPCK),[6] these observations motivated our interest towards the design and synthesis of new 1,3,8-trisubstituted purine-2,6-diones carrying 8-modified substituents and 1,3,6-trisubstituted thiazolo[2,3-*f*]purine-2,4-diones, on which we report in the present investigation.

The general synthetic route to obtain the designed 1,3,8-trisubstituted purine-2,6-diones **(10-14)** and 1,3,6-trisubstituted thiazolo[2,3-*f*]purine-2,4-diones **(15-19)** is presented in Scheme 1. 1,3-Dipropyl-8-thioxo-3,7-dihydropurine-2,6-dione **(2)** was synthesized by reaction of 5,6-diamino-1,3-dipropyl-1*H*-pyrimidine-2,4-dione **(1)** with carbon disulfide in the presence of potassium hydroxide.[9] The compound **2** was subjected to the interaction with the prepared phenacyl bromide **3-7**[10] in the presence of potassium hydroxide to give the required 1,3,8-trisubstituted purine-2,6-diones **8-12**. The structure elucidation of these newly synthesized derivatives was confirmed by elemental analysis and spectral data (see exp. part). The ^{1}H- NMR spectra of compounds **8-12** are characterized by the appearance of the methylene protons of the S-CH_2-CO moiety at 4.88 to 4.96 ppm and at 39.27-39.67 ppm in ^{1}H-NMR and ^{13}C-NMR spectra, respectively. Together with the presence of N9-H or N7-H signals this strongly supported that alkylation took place at the S- rather than at the N-atom. It is well known that mercaptopurines undergo S-alkylation at lowered temperatures while at elevated temperatures, the N7-H is also attacked.[11] We applied three methods for the cyclodehydration of compounds **8-12** to obtain the required 1,3,6-trisubstituted thiazolo[2,3-*f*]purine-2,4-diones **13-17**: a) use of ethanolic solution of hydrochloric acid[12] which was not successful in our hands, b) the reflux in glacial acetic acid for 2 days, which gave the cyclized derivative.[13]



Scheme 1 Synthesis of 8-[2-(*p*-(un)substituted phenyl)-2-oxo-ethyl-sulfanyl]-1,3-dipropyl-3,7-dihydro-purine-2,6-diones **8-12** and 1,3-dipropyl-6-substituted)-1*H*-thiazolo[2,3-*f*]purine-2,4-diones **13-17**.

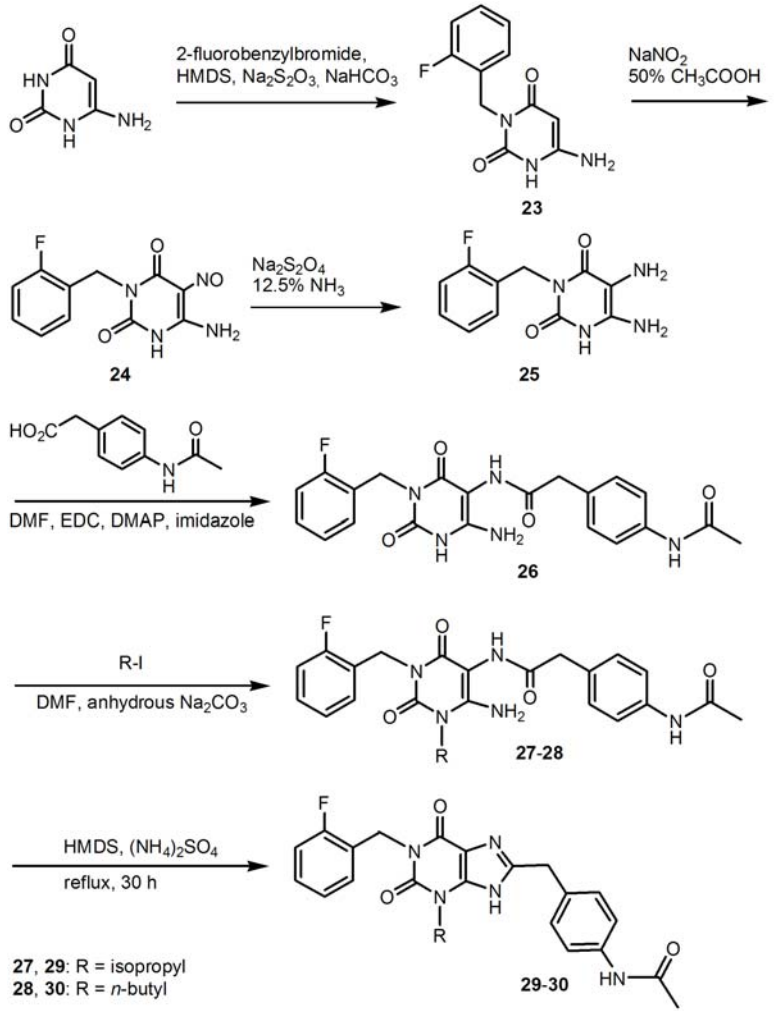
However, column chromatography was needed for purification and also the yield did not exceed 50%, which proved this method as tedious and time consuming. Considerably better results were obtained when using method c), the cyclodehydration of compounds **9-12** in polyphosphoric acid (PPA) at 140-150 °C to give the new 1,3,6-trisubstituted thiazolo[2,3-*f*]purine-2,4-diones **13-17** in yields between 73 and 81%.
The advantages of method c were that the yields were considerably higher, and the method was less time-consuming, and it was possible to purify the product by recrystallization due to fewer side products. The ^{1}H-NMR data of compounds **13-17**, show the disappearance of both methylene protons of S-CH_2-CO and N7-H (or N9-H) proton, in addition to the appearance of C7-H as downfield proton 7.30-7.55 ppm this provides strong evidence for ring cyclization.



Scheme 2 Synthesis of 8-[2-(*p*-substituted phenyl)-2-oxoethyl-sulfonyl]-1,3-dipropyl-3,7-dihydropurine-2,6-dione **18-21**.

The conversion of 8-[2-(*p*-substitutedphenyl)-2-oxoethylsulfanyl]-1-propyl-3,7,8,9-tetrahydropurine-2,6-dione **9-12** into 8-[2-(*p*-substitutedphenyl)-2-oxoethylsulfonyl]-1-propyl-3,7,8,9-tetrahydropurine-2,6-diones **(18-21)** was achieved by using peracetic acid (39% in acetic acid) in dichloromethane[14] as illustrated in Scheme 2. The NMR spectra of the oxidised derivatives **20-23** were characterized by downfield shift of the methylene group (-SO_2**CH_2**CO-) to 5.53-5.64 ppm in the ^{1}H-NMR, and to 61.95-62.48 ppm in the ^{13}C-NMR spectra, respectively.
Our attempts to prepare the 3-substitituted *N*-{4-[1-(2-fluorobenzyl)-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-8-ylmethyl]phenyl}acetamide derivatives (**29-30**) by reported procedures[6] via 6-amino-1-butyl-3-(2-fluorobenzyl)-1*H*-pyrimidine-2,4-dione either by alkylation of 6-amino-1-butyl-1*H*-pyrimidine-2,4-dione or by alkylation of 3-(2-fluorobenzyl)-1*H*-pyrimidine-2,4-dione failed. In our hands, these reactions yielded three products with similar mobility in thin layer chromatography (TLC), that also were difficult to separate by column chromatography. This may be due to the formation of the *N*,5-disubstituted and 5-substituted derivatives in addition to the starting material because the 5-H is prone to substitution.
The synthesis of the 3-substituted *N*-{4-[1-(2-fluorobenzyl)-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-8-yl-methyl]phenyl}acetamide derivatives **29-30**, was carried out by using the modified procedure shown in (Scheme 3).

We prepared 6-Amino-3-(2-fluorobenzyl)-1*H*-pyrimidine-2,4-dione **23** by regioselective alkylation of 6-aminouracil in 1,1,1,3,3,3,-hexamethyldisilazane (HMDS) by modifying the reported procedure[15] in the following way: we used slightly less than one equivalent of alkyl halide instead of one equivalent and heated carefully to avoid the disubstitution at N-1 and 5-substitution. The reaction progress was monitored using thin layer chromatography (TLC) and the reaction was stopped as soon as the disubstituted started to appear although there was still unreacted starting material left (see exp. part). After several test reactions, this method was found to give the best results for the preparation of this compound. Nitrosation of **23** followed by reduction of compound **24** afforded compound **25** respectively using a reported procedure for similar derivatives.[16]



Scheme 3 Synthesis of 3-substitituted *N*-{4[1-(2-fluorobenzyl)-2,3,6,7-tetrahydro-1*H*-purin-8-yl methyl]phenyl}acetamide derivatives **31-32**.

Compound **25** was used directly for the next reaction without further purification. 5,6-Diamino-3-(2-fluorobenzyl)-1*H*-pyrimidine-2,4-dione **25** was treated with (4-acetylaminophenyl)acetic acid[17] in

presence of *N*1-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDC), dimethylaminopyridine (DMAP), and imidazole to obtain 2-(4-acetylaminophenyl)-*N*-[6-amino-3-(2-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetamide **26**. The amide derivative **26** was alkylated at position 1 in dimethylformamide (DMF) in the presence of anhydrous potassium carbonate and i-PrI or BuI under argon atmosphere to give compounds **(27-28)** in analogy to reported procedures.[18] The 1-substituted 2-(4-acetylaminophenyl)-*N*-[6-amino-3-(2-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]acetamide derivatives **27** or **28** were refluxed in HMDS in presence of catalytic amounts of ammonium sulphate to afford *N*-{4[1-(2-fluorobenzyl)-3-isopropyl-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-8-ylmethyl]-phenyl}acetamide **29** and *N*-{4[1-(2-fluorobenzyl)-3-butyl-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-8-ylmethyl]phenyl}acetamide **30,**[6] respectively, in good yields. This ring cyclization using HMDS could readily be applied for further derivatization and turned out to be more convenient than alkaline dehydration.

We are currently investigating the biological activities of these new compounds and will report on these results elsewhere in due course.

EXPERIMENTAL

General: The Melting points were measured using a Stuart Scientific melting point apparatus SMP3 (U.K.) and are uncorrected. The NMR spectra were taken using Bruker DPX 300 MHz instrument. DMSO-d_6 was used as solvent and the chemical shifts are given in δ (ppm) values. The chemical shifts of the remaining protons of the deuterated solvent served as internal standard: δ ^{1}H: 2.49 ppm, ^{13}C: 39.7 ppm. The EI-MS was obtained using EI- Finnigan MAT 95XL (Thermo Finnigan, Bremen) and FAB-MS was obtained using Concept 1H (Kratos, Hofheim), with *m*-Nitrobenzyl alcohol as matrix. Elemental microanalyses were performed using VarioEL apparatus. Silica gel column chromatography was carried out using kieselgel 60 (Merck). TLC analysis was performed on kieselgel 60 F_{254} (Merck) aluminum plates.

5,6-Diamino-1,3-dipropyl uracil **1** was prepared from dipropyl urea followed by nitrosation and reduction as described.[16,21] Phenacyl bromides **3-7** were prepared from *p*-(un)substituted acetophenone derivatives by bromination in Et_2O-dioxan (2:1) in presence of $AlCl_3$ as catalyst.[10] (4-Acetylaminophenyl)acetic acid was prepared according to the reported procedure.[17]

1,3-Dipropyl-8-thioxo-3,7,8,9-tetrahydropurine-2,6-dione (2)[9]

KOH (1.5 g, 27 mmol) was dissolved in EtOH (40 mL) then carbon disulfide (2.05 g, 27 mmol) was added followed by addition of 5,6-diamino-1,3-dipropyluracil **3a** (6.11 g, 27 mmol). The reaction mixture was refluxed for 4 h, diluted with warm water (30 mL) and stirred well, then AcOH (3 mL) in water (5

mL) was added portionwise . The reaction mixture was allowed to cool in refrigerator for 3 h, the product was collected by filtration. Recrystallization from EtOH to afforded the compound (6.01 g, 83%) in white color: mp 313-315 ºC. ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.67 (3H, t, J = 7.4 Hz, 3′-CH_3), 0.88 (3H, t, J = 7.4 Hz, 3″-CH_3), 1.51 (4H, m, 2′-CH_2 & 2″-CH_2), 3.74 (2H, t, J = 7.4 Hz, 1′-CH_2), 3.78 (2H, t, J = 7.4 Hz, 1″-CH_2), 12.09 (2H, br s, H-7 & H-9).

General procedure for preparation of 8-[2-(*p*-(un)substitutedphenyl)-2-oxoethylsulfanyl]-1,3-dipropyl-3,7-dihydropurine-2,6-dione (8-12). To a solution of 1,3-dipropyl-8-thioxo-3,7,8,9-tetrahydropurine-2,6-diones **2** (0.78 g, 2.9 mmol), dissolved in aqueous NaOH (1%, 20 mL) was added portionwise with stirring a solution of the appropriately *p*-(un)substituted phenacyl bromide **3, 4, 5, 6 or 7** (2.9 mmol) in EtOH (5 mL). The reaction mixture was stirred at ambient temperature for 4-5 h. The reaction mixture was kept at rt overnight and the product was collected by filtration, washed with water and crystallized from EtOH/water to afford the compounds **8-12**.

8-(2-Oxo-2-phenylethylsulfanyl)-1,3-dipropyl-3,7-dihydropurine-2,6-dione (8)

White solid, yield 69%, mp 174-176 ºC (EtOH/water). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.66 (3H, t, J = 7.4 Hz, 3′-CH_3), 0.88 (3H, t, J = 7.4 Hz, 3″-CH_3), 1.51 (4H, m, 2′-CH_2 & 2″-CH_2), 3.73 (2H, t, J = 7.4 Hz, 1′-CH_2), 3.79 (2H, t, J = 7.4 Hz, 1″-CH_2), 4.93 (2H, s, CH_2), 7.65 (3H, m, Ar-H), 8.03 (2H, m, Ar-H), 13.51 (1H, s, H-7). ^{13}C-NMR: (75 MHz, DMSO-d_6) δ: 11.0, 11.5, 21.1, 21.2, 39.5, 42.4, 44.7, 108.2, 128.7, 129.1, 134.0, 136.1, 148.4, 149.1, 150.7, 153.5, 193.8. *Anal*. Calcd for $C_{19}H_{22}N_4O_3S$ 1/2 H_2O: C, 57.70; H, 5.87; N, 14.17. Found: C, 57.37; H, 5.66; N, 13.68. MS (FAB, positive mode) *m/z*: 387 $[M+1]^+$.

8-[2-(*p*-Bromophenyl)-2-oxoethylsulfanyl]-1,3-dipropyl-3,7-dihydropurine-2,6-dione (9)

White solid, yield 70%, mp 210-212 ºC (EtOH/water). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.66 (3H, t, J = 7.4 Hz, 3′-CH_3), 0.82 (3H, t, J = 7.4 Hz, 3″-CH_3), 1.49 (4H, m, 2′-CH_2 & 2″-CH_2), 3.71 (2H, t, J = 7.4 Hz, 1′-CH_2), 3.79 (2H, t, J = 7.4 Hz, 1″-CH_2), 4.88 (2H, s, CH_2), 7.88 (2H, d, J = 8.5 Hz), 7.97 (2H, d, J = 8.5 Hz), 13.51 (1H, s, H-7). ^{31}C-NMR: (75 MHz, DMSO-d_6) δ: 11.1, 11.5, 21.1, 21.2, 39.3, 42.4, 44.7, 108.4, 128.2, 130.7, 132.3, 135.2, 148.3, 148.9, 150.7, 153.5, 193.2. *Anal*. Calcd for $C_{19}H_{21}BrN_4O_3S$: C, 49.04; H, 4.55; N, 12.04. Found: C, 48.66; H, 4.63; N, 12.00.

8-[2-(*p*-Chlorophenyl)-2-oxoethylsulfanyl]-1,3-dipropyl-3,7-dihydropurine-2,6-dione (10)

White solid, yield 69%, mp 200-202 ºC (EtOH/water). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.66 (3H, t, J = 7.4 Hz, 3′-CH_3), 0.82 (3H, t, J = 7.4 Hz, 3″-CH_3), 1.48 (4H, m, 2′-CH_2 & 2″-CH_2), 3.71 (2H, t, J = 7.4 Hz, 1′-CH_2), 3.79 (2H, t, J = 7.4 Hz, 1″-CH_2), 4.89 (2H, s, CH_2), 7.63 (2H, d, J = 8.5 Hz), 8.04 (2H, d, J =

8.5 Hz), 13.52 (1H, s, H-7). ^{31}C-NMR: (75 MHz, DMSO-d_6) δ: 11.2, 11.5, 21.1, 21.2, 39.7, 42.4, 44.7, 108.1, 129.3, 130.7, 134.8, 139.0, 148.6, 149.0, 150.7, 153.5, 193.0. *Anal*. Calcd for $C_{19}H_{21}ClN_4O_3S.1/2\ H_2O$: C, 53.08; H, 5.17; N, 13.03. Found: C, 52.75; H, 5.01; N, 12.57.

8-(2-Oxo-2-*p*-tolylethylsulfanyl)-1,3-dipropyl-3,7-dihydropurine-2,6-dione (11)

White solid, yield 71%, mp 178-180ºC (EtOH/water). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.68 (3H, t, J = 7.4 Hz, 3′-CH_3), 0.83 (3H, t, J = 7.4 Hz, 3″-CH_3), 1.51 (4H, m, 2′-CH_2 & 2″-CH_2), 2.38 (3H, s, 4‴-CH_3), 3.77 (4H, m, 1′-CH_2 & 1″-CH_2), 4.89 (2H, s, CH_2), 7.35 (2H, d, J = 8.4 Hz), 7.93 (2H, d, J = 8.4 Hz),13.49 (1H, s, H-7). ^{31}C-NMR: (75 MHz, DMSO-d_6) δ: 11.2, 11.5, 21.1, 21.6, 39.5, 42.4, 44.7, 108.2, 128.9, 129.7, 133.6, 144.5, 148.4, 149.1, 150.8, 153.5, 193.3. *Anal*. Calcd for $C_{20}H_{24}N_4O_3S$: C, 59.98; H, 6.04; N, 13.99. Found: C, 59.49; H, 6.06; N, 13.80.

8-[2-(*p*-Nitrophenyl)-2-oxoethylsulfanyl]-1,3-dipropyl-3,7-dihydropurine-2,6-dione (12)

White solid, yield 66%, mp 189-191 ºC (EtOH/water). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.65 (3H, t, J = 7.4 Hz, 3′-CH_3), 0.82 (3H, t, J = 7.3 Hz, 3″-CH_3), 1.46 (4H, m, 2′-CH_2 & 2″-CH_2), 3.70 (2H, t, J = 7.3 Hz, 1′-CH_2), 3.79 (2H, t, J = 7.4 Hz, 1″-CH_2), 4.96 (2H, s, CH_2), 8.26 (2H, d, J = 8.5 Hz), 8.37 (2H, d, J = 8.5 Hz), 13.55 (1H, s, H-7). ^{31}C-NMR: (75 MHz, DMSO-d_6) δ: 11.2, 11.5, 21.1, 21.2, 39.5, 42.5, 44.7, 108.1, 124.3, 130.2, 140.9, 148.4, 148.7, 150.5, 150.7, 153.5, 193.3 *Anal*. Calcd for $C_{19}H_{21}N_5O_5S.H_2O$: C, 50.77; H, 5.17; N, 15.58. Found: C, 51.10; H, 4.73; N, 15.20.

General procedure for preparation of 1,3-dipropyl-6-substituted)-1*H*-thiazolo[2,3-*f*]purine-2,4-diones (13-17).

To a stirred freshly prepared polyphosphoric acid from phosphorus pentaoxide (8 g) and phosphoric acid (6 mL) was added the appropriate 8-(2-oxo-2-(un)substitutedphenylethylsulfanyl)-1-3-dipropyl-3,7-dihydropurine-2,6-dione **8, 9, 10, 11 or 12** (5.3 mmol) and the reaction mixture was heated at 140-150 °C for 5-6 h. The reaction mixture was cooled, poured into ice-water and neutralized with aqueous sodium carbonate solution. The precipitate solid was filtered off, washed with water and crystallized from DMF/water to afford the final compounds **13-17**.

6-Phenyl-1,3-dipropyl-1*H*-thiazolo[2,3-*f*]purine-2,4-dione (13)

White solid, yield 76%, mp 187-189 ºC (DMF/water). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.79(3H, t, J = 7.4 Hz, 3′-CH_3), 0.89(3H, t, J = 7.3 Hz, 3″-CH_3), 1.44 (2H, m, 2′-CH_2) 1.72 (2H, m, 2″-CH_2), 3.79 (2H, t, J = 7.4 Hz, 1′-CH_2), 4.00 (2H, t, J = 7.4 Hz, 1″-CH_2), 7.30 (1H, s, 7-H), 7.45 (5H, m, Ar-H). ^{31}C-NMR: (75 MHz, DMSO-d_6) δ: 11.4, 11.5, 21.1, 21.2, 42.6, 44.9, 105.3, 111.7, 127.9, 129.6, 129.8, 135.4, 150.7,

152.1, 152.7, 156.1. *Anal*. Calcd for $C_{19}H_{20}N_4O_2S.1/2\ H_2O$: C, 60.45; H, 5.62; N, 14.85. Found: C, 60.67; H, 5.29; N, 14.57.

6-(4-Bromophenyl)-1,3-dipropyl-1*H*-thiazolo[2,3-*f*]purine-2,4-dione (14)

White solid, yield 73%, mp 208-210 ºC (DMF/water). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.80 (3H, t, J = 7.4 Hz, 3′-CH_3), 0.90 (3H, t, J = 7.4 Hz, 3″-CH_3), 1.45 (2H, m, 2′-CH_2) 1.73 (2H, m, 2″-CH_2), 3.72 (2H, t, J = 7.4 Hz, 1′-CH_2), 4.01 (2H, t, J = 7.4 Hz, 1″-CH_2), 7.36 (1H, s, 7-H), 7.49 (2H, d, J = 8.5 Hz), 7.62 (2H, d, J = 8.5 Hz). ^{31}C-NMR: (75 MHz, DMSO-d_6) δ: 11.4, 11.5, 21.1, 21.2, 42.6, 45.0, 105.3, 112.4, 123.3, 129.1, 130.9, 131.8, 134.1, 150.7, 152.3, 152.7, 156.1 *Anal*. Calcd for $C_{19}H_{19}BrN_4O_2S$: C, 51.01; H, 4.28; N, 12.52. Found: C, 51.23; H, 4.11; N, 12.63.

6-(4-Chlorophenyl)-1,3-dipropyl-1*H*-thiazolo[2,3-*f*]purine-2,4-dione (15)

White solid, yield 77%, mp 163-165 ºC (DMF/water). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.80 (3H, t, J = 7.4 Hz, 3′-CH_3), 0.90 (3H, t, J = 7.4 Hz, 3″-CH_3), 1.46 (2H, m, 2′-CH_2) 1.72 (2H, m, 2″-CH_2), 3.70 (2H, t, J = 7.4 Hz, 1′-CH_2), 4.00 (2H, t, J = 7.4 Hz, 1″-CH_2), 7.35 (1H, s, 7-H), 7.47 (2H, d, J = 8.5 Hz), 7.57 (2H, d, J = 8.5 Hz). ^{31}C-NMR: (75 MHz, DMSO-d_6) δ: 11.4, 11.5, 21.1, 21.2, 42.6, 45.0, 105.3, 112.4, 127.9, 128.7, 129.6, 131.6, 134.0, 134.6, 150.7, 152.3, 152.7, 156.1 *Anal*. Calcd for $C_{19}H_{19}ClN_4O_2S$: C, 56.64; H, 4.75; N, 13.91. Found: C, 56.48; H, 4.79; N, 14.12. MS (FAB, positive mode) m/z: 403 $[M+1]^+$.

1,3-Dipropyl-6-*p*-tolyl-1*H*-thiazolo[2,3-*f*]purine-2,4-dione (16)

White solid, yield 81%, mp 173-175 ºC (DMF/water). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.79 (3H, t, J = 7.4 Hz, 3′-CH_3), 0.90 (3H, t, J = 7.4 Hz, 3″-CH_3), 1.45 (2H, m, 2′-CH_2) 1.72 (2H, m, 2″-CH_2), 2.39 (3H, s, 4‴-CH_3), 3.71 (2H, t, J = 7.4 Hz, 1′-CH_2), 4.00 (2H, t, J = 7.4 Hz, 1″-CH_2), 7.24 (3H, m, H-7), 7.44 (2H, d, J = 8.5 Hz). ^{31}C-NMR: (75 MHz, DMSO-d_6) δ: 11.4, 11.5, 21.1, 21.2, 21.5, 42.6, 45.0, 105.3, 111.2, 127.0, 128.5, 129.5, 135.5, 139.3, 150.7, 152.1, 152.7, 156.1 *Anal*. Calcd for $C_{20}H_{22}N_4O_2S.1/2\ H_2O$: C, 61.35; H, 5.93; N, 14.31. Found: C, 61.79; H, 5.86; N, 14.24.

6-(4-*p*-Nitrophenyl)-1,3-dipropyly-1*H*-thiazolo[2,3-*f*]purine-2,4-dione (17)

White solid, yield 78%, mp 200-202 ºC (DMF/water). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.79 (3H, t, J = 7.4 Hz, 3′-CH_3), 0.91 (3H, t, J = 7.4 Hz, 3″-CH_3), 1.45 (2H, m, 2′-CH_2) 1.72 (2H, m, 2″-CH_2), 3.71 (2H, t, J = 7.4 Hz, 1′-CH_2), 4.02 (2H, t, J = 7.4 Hz, 1″-CH_2), 7.55 (1H, s, 7-H), 7.84 (2H, d, J = 8.5 Hz), 8.26 (2H, d, J = 8.5 Hz). ^{31}C-NMR: (75 MHz, DMSO-d_6) δ: 11.4, 11.5, 21.1, 21.2, 42.6, 45.1, 105.4, 113.6, 122.9, 131.0, 133.0, 136.1, 148.3, 150.7, 152.4, 152.7, 156.2 *Anal*. Calcd for $C_{19}H_{19}N_5O_4S$: C, 55.20; H, 4.63; N, 16.94. Found: C, 55.16; H, 4.85; N, 16.50.

General procedure for preparation of 8-[2-(*p*-(un)substitutedphenyl)-2-oxoethylsulfonyl]-1-propyl-3,7,8,9-tetrahydropurine-2,6-dione (18-21)

To a stirred solution of 8-[2-(*p*-(un)substitutedphenyl)-2-oxoethylsulfanyl]-1-propyl-3,7,8,9-tetrahydropurine-2,6-dione **9, 10, 11 or 12 (**0.344 mmol) in CH_2Cl_2 (5 mL) was added a solution of peracetic acid (39% in AcOH, 172 mg, 1.07 mmol). The reaction was stirred for 7 h before being extracted with CH_2Cl_2 (20 mL) and water (20 mL). The organic phase was washed with water (2 × 20 mL) and the combined aqueous phases were extracted with CH_2Cl_2 (50 mL). The combined organic phases were dried over $MgSO_4$ and evaporated in *vacuo* to yield the product as white powder. Purification with silica gel chromatography (CH_2Cl_2:MeOH = 9:1) gave compounds **18-21** in the pure form.

8-[2-(*p*-Bromophenyl)-2-oxoethylsulfonyl]-1,3-dipropyl-3,7-dihydropurine-2,6-dione (18)

White crystals, yield 87%, mp 221-223 ºC (CH_2Cl_2/MeOH). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.83 (6H, m, 3′-CH_3 & 3″-CH_3), 1.58 (4H, m, 2′-CH_2 & 2″-CH_2), 3.83 (4H, m, 1′-CH_2 & 1″-CH_2), 5.54 (2H, s, CH_2), 7.72 (2H, d, J = 8.5 Hz), 7.86 (2H, d, J = 8.5 Hz).^{1}C-NMR: (75 MHz, DMSO-d_6) δ: 11.3, 11.6, 21.1, 21.2, 42.9, 45.2, 62.1, 108.2, 129.1, 131.3, 132.2, 134.9, 145.5, 146.4, 150.8, 154.9, 188.1. HRMS (EI) calcd. for $C_{19}H_{21}Br\ N_4O_5S^+$: 496.0416, found 496.0419.

8-[2-(*p*-Chlorophenyl)-2-oxoethylsulfonyl]-1,3-dipropyl-3,7-dihydropurine-2,6-dione (19)

White crystals, yield 86%, mp 217-219 ºC (CH_2Cl_2/MeOH). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.83 (6H, m, 3′-CH_3 & 3″-CH_3), 1.58 (4H, m, 2′-CH_2 & 2″-CH_2), 3.83 (4H, m, 1′-CH_2 & 1″-CH_2), 5.54 (2H, s, CH_2), 7.72 (2H, d, J = 8.5 Hz), 7.86 (2H, d, J = 8.5 Hz).^{1}C-NMR: (75 MHz, DMSO-d_6) δ: 11.2, 11.6, 21.1, 21.2, 42.9, 45.2, 62.2, 108.2, 129.3, 130.3, 134.6, 139.9, 145.6, 147.4, 150.8, 155.0, 187.9. HRMS (EI) calcd. for $C_{19}H_{21}Cl\ N_4O_5S^+$: 452.0921, found 452.0927.

8-(2-Oxo-2-*p*-tolylethylsulfonyl)-1,3-dipropyl-3,7-dihydropurine-2,6-dione (20)

White crystals, yield 89%, mp 214-216 ºC (CH_2Cl_2/MeOH). 0.83 (6H, m, 3′-CH_3 & 3″-CH_3), 1.56 (4H, m, 2′-CH_2 & 2″-CH_2), 2.35 (3H, s, 4‴-CH3), 3.84 (4H, m, 1′-CH_2 & 1″-CH_2), 5.54 (2H, s, CH_2), 7.58 (2H, d, J = 8.5 Hz), 7.95 (2H, d, J = 8.5 Hz). ^{1}C-NMR: (75 MHz, DMSO-d_6) δ: 11.3, 11.6, 21.1, 21.2, 21.6, 42.9, 45.2, 62.0, 108.4, 121.3, 129.5, 129.7, 133.5, 145.6, 150.8, 154.9, 188.3. HRMS (EI) calcd. for $C_{20}H_{24}\ N_4O_5S^+$: 432.1467, found 432.1471.

8-[2-(*p*-Nitrophenyl)-2-oxoethylsulfonyl]-1,3-dipropyl-3,7-dihydropurine-2,6-dione (21)

White crystals, yield 90%, mp 204-206 ºC (CH_2Cl_2/MeOH). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.81 (6H, m, 3′-CH_3 & 3″-CH_3), 1.57 (4H, m, 2′-CH_2 & 2″-CH_2), 3.84 (4H, m, 1′-CH_2 & 1″-CH_2), 5.64 (2H, s,

CH_2), 8.18 (2H, d, J = 8.5 Hz), 8.31 (2H, d, J = 8.5 Hz).[1]C-NMR: (75 MHz, DMSO-d_6) δ: 11.2, 11.6, 21.1, 21.2, 42.9, 45.2, 62.5, 108.7, 124.2, 130.5, 130.8, 140.34, 150.8, 151.2, 155.1, 188.3. HRMS (EI) calcd. for $C_{19}H_{21}N_5O_7S^+$: 463.1162, found 463.1167.

6-Amino-3-(2-fluorobenzyl)-1*H*-pyrimidine-2,4-dione (23)

A suspension 6-aminouracil 4 g (31.47 mmol) and 0.20 g of ammonium sulphate were refluxed in HMDS (40 mL) for 5 h, within this time the mixture became clear homogenous. Excess HMDS was distilled off at first under atmospheric pressure, then in *vacuo.* The product was allowed to cool to ca. 40-70 °C, the required amount of the 2-flourobenzyl bromide (5.47 g, 29.00 mmol) was added. The reaction mixture heated carefully (increase of temperature lead to formation of disubstituted derivative) in oil bath for 2 h, the reaction progress was monitored with TLC (eluent: CH_2Cl_2: MeOH, 9:1). The reaction was stopped when the disubstituted product started to appear on TLC. The mixture was allowed to cool to rt. and a solution of $Na_2S_2O_3$ in water was added. The flask was cooled in an ice bath, and a saturated solution of $NaHCO_3$ in water was added in small portions until effervescence ceased. The formed precipitate was filtered and washed with cold water then with Et_2O. The product was purified using column chromatography (MeOH:CH_2Cl_2 = 1:99 to 7:93) to give the compound **23** (5.26 g, 71%) as white crystals, mp >300 ºC (EtOH). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 4.63 (1H, s, 5-CH), 4.91 (2H, s, CH_2), 6.31 (2H, br s, NH_2), 7.12 (4H, m, Ar-H), 10.52 (1H, br s, N1-H). ^{13}C-NMR (75 MHz, DMSO-d_6): 36.2, 74.3, 115.6, 124.7, 125.6, 128.2, 128.9, 151.4, 154.4, 158.6, 161.8. *Anal*. Calcd for $C_{11}H_{10}FN_3O_2$: C, 56.17; H, 4.29; N, 17.86. Found: C, 56.59; H, 4.18; N, 17.47.

6-Amino-3-(2-fluorobenzyl)-5-nitroso-1*H*-pyrimidine-2,4-dione (24)

A solution of 6-Amino-3-(2-fluorobenzyl)-1*H*-pyrimidine-2,4-dione **23**, (3.5 g, 14.89 mmol) in 50% aqueous AcOH (70 mL) was prepared by heating to 70-90 ºC. $NaNO_2$ (2.1 g, 29.78 mmol) was added in small portions over a period of 15 min. The mixture was further stirred for 30 min and then allowed to cool. The yellow product was precipitated and was collected by filtration and washed with water to give compound **24** (3.3g, 84%) as yellow crystals, mp >300 ºC (EtOH). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 5.09 (2H, s, CH_2), 7.21 (4H, m, Ar-H), 8.06 (2H, br s, NH_2), 11.39 (1H, br s, N1-H). ^{13}C-NMR (75 MHz, DMSO-d_6): 37.5, 115.4, 124.8, 124.8, 128.8, 128.9, 140.2, 149.6, 158.6, 161.6, 161.8. *Anal*. Calcd for $C_{11}H_9FN_4O_3.1/2\ H_2O$: C, 48.35; H, 3.70; N, 20.51. Found: C, 48.29; H, 3.86; N, 20.38.

2-(4-Acetylaminophenyl)-*N*-[6-amino-3-(2-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetamide (26)

To a stirred solution of *p*-acetamidophenylacetic acid (1.25 g, 6.47 mmol) in anhydrous DMF (20 mL), 1-ethyl-3-[3-dimethylaminopropyl]carbodiimide hydrochloride (1.23 g 1.55 mmol), DMAP (0.04 g) and

imidazole (0.03 g) were added under argon atmosphere then 5,6-diamino-3-(2-fluorobenzyl)-1*H*-pyrimidine-2,4-dione **25** (1.62 g, 6.47 mmol) was added. The reaction mixture was stirred overnight at rt. Water was added to the reaction mixture and the formed precipitate was separated by filtration. The product was recrystallized from EtOH to give the product as pale yellow crystals (2.04 g, 74%), mp 198-200 ºC (EtOH). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 2.01 (3H, s, CH_3), 3.49 (2H, s, CH_2), 4.92 (2H, s, CH_2), 6.09 (2H, br s, 6-NH_2), 7.09 (3H, m, Ar-H), 7.21 (2H, d, J = 8.3, Ar-H), 7.22 (1H, m, Ar-H), 7.46 (2H, d, J = 8.3, Ar-H), 8.06 (1H, s, amide-H), 9.84 (1H, s, amide-H), 10.36 (1H, br s, 3-H,). ^{13}C-NMR: (75 MHz, DMSO-d_6) δ: 24.4, 36.8, 41.8, 87.5, 115.6, 119.2, 124.7, 128.4, 129.1, 129.8, 131.3, 138.0, 150.3, 150.9, 159.0, 160.9, 161.4, 168.5, 171.10. MS (FAB, positive mode) m/z: 426 $[M+1]^+$.

General procedure of 1-substituted 2-(4-acetylaminophenyl)-*N*-[6-amino-3-(2-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl]acetamide derivatives (27-28)

2-(4-Acetylaminophenyl)-*N*-[6-amino-3-(2-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl]-acetamide **28** (1.2 g, 2.82 mmol) was dissolved in anhydrous DMF (20 mL) under argon atmosphere then K_2CO_3 (0.79 g, 5.7 mmol) was added and the reaction mixture was stirred for 1 hour at 60 °C. After cooling to rt the appropriate alkyl iodide (5.2 g, 3.2 mL, 28.2 mmol) was added and then the reaction mixture was stirred for 4 h at rt and then was further stirred at 60 °C for 12 h. The mixture was concentrated under reduced pressure then water was added and the formed precipitate was filtered and washed with water. Purification with silica gel column chromatography (MeOH:CH_2Cl_2 = 5:95 to 8:92) gave the compounds **29-30** as white crystals.

2-(4-Acetylaminophenyl)-*N*-[6-amino-1-isopropyl-3-(2-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]acetamide (27)

mp 256-258 ºC, yield (71%). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 1.15 (6H, d, J = 6.04 Hz, 2 CH_3), 2.04 (3H, s, CH_3), 3.51 (2H, s, CH_2), 5.02 (2H, s, N3-CH_2), 5.15 (1H, m, N1-CH), 6.21 (2H, br s, 6-NH_2), 7.22 (6H, m, Ar-H), 7.48 (2H, d, J = 8.4, Ar-H), 8.97 (1H, s, amide-H), 9.85 (1H, s, amide-H). ^{13}C-NMR: (75 MHz, DMSO-d_6) δ: 21.7, 24.4, 37.3, 41.9, 72..0, 92.48, 115.5, 119.2, 124.8, 129.1, 129.8, 131.5, 138.0, 153.5, 158.1, 158.6, 159.8, 161.9, 168.5, 170.6. MS (FAB, positive mode) m/z: 468 $[M+1]^+$. Anal. Calcd for $C_{24}H_{26}FN_5O_4$: C, 61.66; H, 5.61; N, 14.98. Found: C, 61.29; H, 5.89; N, 15.09.

2-(4-Acetylaminophenyl)-*N*-[6-amino-1-butyl-3-(2-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]acetamide (28)[18]

mp 239-241 ºC, yield (68%). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.87 (3H, t, J = 7.3 Hz, 4′-CH_3), 1.27 (2H, m, 3′-CH_2), 1.47 (2H, m, 2′-CH_2), 2.01 (3H, s, CH_3), 3.51 (2H, s, CH_2), 3.85 (2H, t, J = 7.3, 1′-CH_2),

4.98 (2H, s, N3-CH_2), 6.64 (2H, br s, 6-NH_2), 6.97 (1H, m, Ar-H), 7.13 (3H, m, Ar-H), 7.23 (2H, d, *J* = 8.4, Ar-H), 7.47 (2H, d, *J* = 8.4, Ar-H), 8.60 (1H, s, amide-H), 9.85 (1H, s, amide-H). ^{13}C-NMR: (75 MHz, DMSO-d_6) δ: 14.1, 19.6, 24.4, 30.1, 37.7, 41.9, 42.8, 87.8, 115.6, 119.2, 124.7, 128.3, 129.0, 129.9, 131.4, 138.0, 150.7, 152.2, 159.0, 159.4, 161.4, 168.5, 171.3. MS (FAB, positive mode) m/z: 482 $[M+1]^+$. Anal. Calcd for $C_{25}H_{28}FN_5O_4$: C, 62.36; H, 5.86; N, 14.54. Found: C, 62.14; H, 5.57; N, 14.19.

General procedure for preparation of 3-substitituted *N*-{4-[1-(2-fluorobenzyl)-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-8-ylmethyl]phenyl}acetamide derivatives (29-30)

1-substituted 2-(4-acetylaminophenyl)-*N*-[6-amino-3-(2-fluorobenzyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]acetamide derivative (**27**) or (**28**) (37 mmol) and catalytic amounts of $(NH_4)_2SO_4$ were suspended in HMDS (15 mL). The reaction mixture was refluxed at 130-135 °C for 48 h. The reaction progress was monitored by TLC until the starting material was disappeared, the HMDS was evaporated under reduced pressure and the residue was suspended in 10 mL (MeOH:H_2O, 1:1). The formed precipitate was collected by filtration and washed with water. Purification using silica gel chromatography (MeOH:CH_2Cl_2 = 9:1) gave the compounds **29-30** as white crystals.

***N*-{4-[1-(2-Fluorobenzyl)-3-isopropyl-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-8-ylmethyl]phenyl}-acetamide (29)**

mp 284-286 ºC, yield (78%). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 1.14 (6H, d, *J* = 6.05 Hz, 2CH_3), 2.01 (3H, s, CH_3), 3.97 (2H, s, CH_2), 5.13 (1H, m, N1-CH), 5.19 (2H, s, N3-CH_2), 7.04 (3H, m, Ar-H), 7.20 (2H, d, *J* = 8.4, Ar-H), 7.25 (1H, m, Ar-H), 7.49 (2H, d, *J* = 8.4, Ar-H), 9.88 (1H, s, amide-H), 13.28 (1H, be s, 7-H). ^{13}C-NMR: (75 MHz, DMSO-d_6) δ: 21.5, 24.4, 34.6, 37.8, 72..6, 115.5, 119.5, 124.9, 128.9, 129.3, 132.1, 138.3, 153.1, 158.7, 161.9, 168.6. HR-ESI-MS: 450.1937 (100%, $[M+H]^+$, $C_{24}H_{25}FN_5O_3^+$; calcd. 450.1941).

***N*-{4-[1-(2-Fluorobenzyl)-3-butyl-2,6-dioxo-2,3,6,9-tetrahydro-1*H*-purin-8-ylmethyl]phenyl}-acetamide (30)**[20]

mp 289-291 ºC, yield (82%). ^{1}H-NMR: (300 MHz, DMSO-d_6) δ: 0.82 (3H, t, *J* = 7.3 Hz, 4′-CH_3), 1.24 (2H, m, 3′-CH_2), 1.57 (2H, m, 2′-CH_2), 1.96 (3H, s, CH_3), 3.51 (2H, s, CH_2), 3.92 (2H, t, *J* = 7.3, 1′-CH_2), 5.05 (2H, s, N3-CH_2), 7.19 (6H, m, Ar-H), 7.13 7.42 (2H, d, *J* = 8.4, Ar-H), 9.83 (1H, s, amide-H), 13.29 (1H, br s, 7-H). ^{13}C-NMR: (75 MHz, DMSO-d_6) δ: 14.3, 19.7, 24.4, 30.1, 34.2, 38.2, 41.9, 43.2, 106.7, 115.4, 119.6, 124.8, 128.2, 129.1, 129.2, 131.8, 138.4, 148.8, 151.0, 153.6, 154.2, 159.1, 161.5, 168.6. MS (FAB, positive mode) m/z: 464 $[M+1]^+$. HR-ESI-MS: 464.2088 (20%, $[M+H]^+$, $C_{25}H_{27}FN_5O_3^+$; calcd. 464.2098); 486.1907 (100%, $[M+Na]^+$, $C_{25}H_{26}FN_5NaO_3^+$; calcd. 486.1917).

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