Synthesis and Chemoselective Alkylation of Uracil Derivatives

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Abstract

A series of novel 1,3-dialkylpyrimidine derivatives was synthesized. Selective N1 alkylation of N3 substituted pyrimidine derivatives with different alkyl halides using K2CO3 as base in DMF at room temperature provides such compounds in good yields. This method has advantages over methods currently described in the literature for the construction of such compounds.

Introduction

Importance of uracils and its annulated substrates are well recognized by synthetic [1] as well as biological chemists [2]. With the development of clinically useful anticancer (5-fluorouracil) [3] and antiviral drugs (AZT, DDC, DDI, and BVDU) [4], there has been remarkable interest in the exploitation of uracils syntheses. Similarly, the *N*-substituted uracils possess various biological activities [5]. *N*-Glycosides of substituted uracils are widely used in therapy, mainly as antiviral and antineoplastic agents. The most prominent representatives are 5-fluorouracil and thymine derivatives [6, 7]. Uramustine, 5-[*N*,*N*-bis(2'-chloroethyl)amino]uracil is used orally in the treatment of several leukemias [8] and 5-nitrouracil derivatives exhibit microphage growth inhibition [9].

In addition, N_1, N_3-disubstituted uracils were reported to exhibit antibacter- ial and antifungal activities [10]. These N_1 or N_1, N_3-substituted uracils were synthesized *via* alkylation of the corresponding uracils [11]. It is known that substituted uracils (especially at the 5-position) play a vital role in many metabolic processes [12-14]. So far substituted 5-formyluracil analogs are quite rare in the literature, so there is considerable interest in searching for novel uracils with substituents at the N_1, N_3 positions.

Results and Discussion

Due to the tetradentate nucleophilic nature of uracils or their conjugated bases, chemoselective alkylations are a critical step and afford mixtures of N_1 and N_1 + N_3 alkyl derivatives with some *O*-substitution [15]. Considering the above facts and in continuation of our previous studies [16, 17] we report herein the synthesis of compound **2** and its selective N_1 alkylation under mild reaction conditions. The expected target molecule, **2** was accomplished *via* the method reported by *Nishiwaki et al.* [18] and *Doyle et al.* [19].

The cytosine derivative **1** when heated in DMF at 60-65 ^{0}C using isopentyl nitrite, furnished a white solid in 72 % yield after usual work up which was recrystallized from DMF/ethanol and characterized by spectroscopic methods. The IR spectrum of this solid showed sharp peaks at 1610, 1665 and 1703 cm^{-1} for three carbonyl groups and the band appeared at 3320 cm^{-1} for NH stretching. The ^{1}H NMR spectrum (DMSO-d_6) of this compound showed peaks at d 4.99 (singlet) for two methylene protons and the singlet at d 8.19 for = CH proton. The multiplet at d 7.24 to 7.33 for five aromatic protons and D_2O exchangeable broad singlet for NH proton was appeared downfield at d 12.26. The ^{13}C NMR spectrum of **2** in DMSO-d_6

showed the peaks at d 42.7 for methylene carbon and three distinct peaks at d 150.5, 161.4 and 186.6 corresponded to two amide and one formyl carbonyl carbons. The six aromatic carbons appeared between d 127.2-147.8 and olefinic carbon showed the peak at d 109.6. The mass spectrum of this solid showed the molecular ion and characteristic fragmentation patterns. Further, the elemental analysis was in agreement with molecular formula $C_{12}H_{10}N_2O_3$. On the basis of the above analyses, structure **2** was assigned to this compound. Once the structure of compound **2** was established, in order to optimize the reaction conditions for alkylation, the reaction of **2** with anilide **3a** was studied as a model reaction to provide N-alkylated product **4a**.

At first, the influence of various bases was examined to evaluate their capabilities using acetonitrile as solvent at room temperature. The results in Table 1 demonstrate that among the employed bases, an equimolar mixture of K_2CO_3 in acetonitrile afforded the best result. Higher yield and shorter reaction time was observed when K_2CO_3 was used as base. Therefore, K_2CO_3 was the base of choice for all reactions. The *t*-BuOK was not as efficient as K_2CO_3 and $NaHCO_3$ afforded the resultant product in moderate yield while Et_3N was nearly inefficient.

The structure of compound **4a** was deduced from its elemental analysis and spectroscopic data. Its IR spectrum showed the bands at 2754, 1689, 1666, 1646 cm^{-1} and 1608 cm^{-1} for one aldehyde and three amide carbonyl groups. The band at 3273 cm^{-1} showed the presence of -NH stretching. The ^1H NMR spectrum (DMSO-d_6) showed a broad singlet at δ 10.54 for NH proton and another broad singlet which was present in compound **2** at δ 12.26 for NH proton of pyrimidine ring clearly disappeared. This clearly indicates the alkylation at N_1 position. The ^{13}C NMR spectrum (DMSO-d_6) of this solid showed the peaks at δ 43.7 and 52.0 for two CH_2 carbons, and peaks at δ 161.2 and 164.9 corresponded to two amide carbonyl carbons. The formyl carbonyl carbon was appeared at δ 186.5. The mass spectrum of this solid showed the M^+ peak at 397 and M+2 at 399 m/z due to chlorine atom. The elemental analysis was in agreement with molecular formula $C_{20}H_{16}ClN_3O_4$.

Table 1. The Influence of bases on the reaction of **2** (2.1 mmol) with anilide **3a** (2.2 mmol) in acetonitrile.

Entry	**Base**	**Time (h)**	**Yield^a (%)**
1	Et_3N	12	45
2	*t*-BuOK	10	60
3	$NaHCO_3$	11	66
4	K_2CO_3	10	85

[a] Isolated Yields

After selecting K_2CO_3 as base, several reactions were carried out to understand the influence of other solvents besides acetonitrile on the outcome of reaction. A set of anhydrous solvents was examined for the previously described model reaction. The results are depicted in Table 2. Alkylation reactions with acetone and THF occurred more slowly than DMF and DMSO. This may be due to the lower solubility of **2** and **3a** in these solvents. As Table 2 indicates, the best results were obtained with DMF.

Table 2. The effect of solvents on the reaction of **2** (2.1 mmol) with anilide **3a** (2.2 mmol) using K_2CO_3 at room temperature.

Entry	**Solvent**	**Time (h)**	**Yield[a] (%)**
1	Acetone	12	72
2	THF	11	61
3	DMF	7	87
4	DMSO	8	80

[a] Isolated Yields

3, 4	**Ar**	**3, 4**	**Ar**
a	4-ClC_6H_4	**e**	2-Cl-6-FC_6H_3
b	$4\text{-Cl-3-F}_3CC_6H_3$	**f**	2,5-*di*-$F_3CC_6H_3$
c	4-FC_6H_4	**g**	2,4-*di*-ClC_6H_3
d	4-MeC_6H_4		

With this promising system in hand, we extended the substrate scope to other anilides **3b-g**. To our delight, clean monoalkylated products were obtained without any side reactions in good yields. Application of this procedure to alkyl halides **5a-c** also proved to be successful. In compound **2**, N3 position is already substituted hence it can act as tridentate nucleophile *i.e.* either N1 alkylation or *O*-alkylation at C2 or C3 position may occur. The electronegativity of oxygen indicates that its affinity towards electrophiles is low, that is the probable reason for not obtaining any *O*-alkylated products under these reaction conditions. The desired products **6a-c** was obtained in 78-87 % yields (Scheme 3).

5, 6	**R**
a	CH_3
b	CH_2CH_3
c	$CH_2C_6H_4$-*p*-NO_2

Conclusion

In summary, we have developed an efficient and simple method for N1 alkylation of N3-alkylpyrimidine derivatives. Our method has several advantages in terms of yields, mild reaction conditions, and lack of side products. In this method 1,3-dialkylpyrimidine derivatives were synthesized in good yields. Clearly, the process can be applied to the generation of a library of uracils as a large variety of the substituted alkyl halides are readily available.

Experimental

Melting points were determined on a Buchi melting point apparatus, Mod. B-545 and are uncorrected. The ^{1}H (500 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on a Varian VXR spectrometer. Chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane (TMS), and multiplicities are given as s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). The solvent for NMR spectra was DMSO unless otherwise stated. Infrared spectra were taken on Thermo Electron Corporation NICOLET 380 FTIR instrument in potassium bromide pellets unless otherwise stated. Mass spectrum was recorded on Shimadzu GC-MS QP 2010A mass spectrometer with an ionization potential of 70 eV. An elemental analysis was performed on a Hosli CH-Analyzer and is within ± 0.4 of the theoretical percentage. All reactions were monitored by thin layer chromatography, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light (254 and 366 nm) for detection. Common reagents are either commercially available and were used without further purification or prepared by standard literature procedures.

Synthesis of 3-Benzyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidine-5-carbaldehyde (2)

To a stirred solution of **21** (2.29 g, 10 mmol) in DMF (20 mL), a solution of isopentyl nitrite (1.17 g, 10 mmol) in DMF (1.5 mL) was added over a period of 10 min and the reaction mixture was stirred for 2 h at 60-65^{0}C. After completion of reaction (TLC check, chloroform: methanol, 9.5: 0.5), the solvent was removed under reduced pressure, oily residue was triturated with acetonitrile. The solid obtained was collected by filtration, washed with cold acetonitrile, dried and recrystallized from DMF/ethanol to afford **2** in (1.65 g) 72 % yield.

White solid, m. p. 180-182^{0}C; IR (KBr): 3320, 3055, 2960, 2737, 1703, 1665, 1610, 1480, 1350, 1100 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 12.26 (bs, 1H, NH, exchangeable with D_2O), 9.78 (s, 1H, CHO), 8.19 (s, 1H, CH), 7.24-7.33 (m, 5H, ArH), 4.99 (s, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 186.6, 161.4, 150.5, 147.8, 136.7, 128.3, 127.6, 127.2, 109.6, 42.7. MS: m/z (%) = 230 [M^{+}]. *Anal*. Calcd. for $C_{12}H_{10}N_2O_3$: C, 62.61; H, 4.38; N, 12.17. Found. C, 62.87; H, 4.25; N, 12.40.

Synthesis of 2-[3-Benzyl-5-formyl-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl]-*N*-(4-aryl)acetamide (4a-g)

General Procedure

A suspension of **2** (0.5 gm, 2.1 mmol), K_2CO_3 (0.3 g, 2.1 mmol) and alkyl halides **3** (2.2 mmol) in DMF (4 mL) was stirred at room temperature for 6-8 h (TLC monitoring, chloroform: methanol, 9.5: 0.5). Reaction mass was then quenched in ice-cold water and solid obtained was filtered, washed with water, dried and crude solid was recrystallized from DMF/ethanol to afford **4** in 78-90 % yield.

2-(3-Benzyl-5-formyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-*N*-(4-chlorophenyl)-acetamide (4a)

At rt. for 7 h., White solid, m.p 198-200^{0}C; Yield 0.74 g (87 %). IR (KBr): 3273, 3122, 3061, 2754, 1689, 1666, 1646, 1608, 1543, 1492, 1460, 1383, 1226 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.54 (bs, 1H, NH), 9.87 (s, 1H, CHO), 8.62 (s, 1H, CH), 7.57 (d, *J* = 7.0 Hz, 2H, ArH), 7.37 (d, *J* = 7.0 Hz, 2H, ArH), 7.25-7.31 (m, 5H, ArH), 5.02 (s, 2H, CH_2), 4.80 (s, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 186.5, 164.9, 161.2, 151.1, 150.4, 137.3, 136.3, 128.8, 128.3, 127.6, 127.3, 127.2, 120.6, 109.4, 52.0, 43.7. MS: m/z (%) = 397 [M$^+$], 399 [M+2]. *Anal*. Calcd. for $C_{20}H_{16}ClN_3O_4$: C, 60.38; H, 4.05; N, 10.56. Found. C, 60.60; H, 4.32; N, 10.73.

2-(3-Benzyl-5-formyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-*N*-(4-chloro-3-trifluoromethylphenyl)-acetamide (4b)

At rt. for 8 h., White solid, m.p 168-170^{0}C; Yield 0.85 g (85 %). IR (KBr): 3317, 3128, 3072, 2960, 2758, 1693, 1658, 1606, 1548, 1481, 1421, 1333, 1226 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.86 (bs, 1H, NH), 9.88 (s, 1H, CHO), 8.63 (s, 1H, CH), 8.14 (d, *J* = 8.5 Hz, 1H, ArH), 7.78 (d, *J* = 2.5 Hz, 1H, ArH), 7.68 (dd, *J* = 2.5 Hz, and 8.5 Hz, 1H, ArH), 7.25-7.33 (m, 5H, ArH), 5.02 (s, 2H, CH_2), 4.85 (s, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 186.5, 165.6, 161.1, 150.9, 150.5, 137.9, 136.3, 132.2, 128.3, 127.5, 126.9, 125.3, 124.4, 123.9, 123.6, 121.5, 117.7, 109.4, 52.1, 43.7. MS: m/z (%) = 465 [M$^+$], 467 [M+2]. *Anal*. Calcd. for $C_{21}H_{15}ClF_3N_3O_4$: C, 54.15; H, 3.25; N, 9.02. Found. C, 54.38; H, 3.50; N, 9.25.

2-(3-Benzyl-5-formyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-*N*-(4-fluorophenyl)-acetamide (4c)

At rt. for 6 h., White solid, m.p 232-235^{0}C; Yield 0.68 g (84 %). IR (KBr): 3275, 3155, 3064, 2700, 1693, 1666, 1612, 1554, 1508, 1460, 1384, 1226 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.44 (bs, 1H, NH), 9.87 (s, 1H, CHO), 8.62 (s, 1H, CH), 7.56 (dd, *J* = 5.0 Hz, and 6.5 Hz, 2H, ArH), 7.17-7.55 (m, 5H, ArH), 7.15 (dd, *J* = 2.0 Hz, and 6.5 Hz, 2H, ArH), 5.03 (s, 2H, CH_2), 4.79 (s, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 186.5, 164.7, 161.1, 159.6, 157.2, 151.1, 150.4, 136.3, 134.7, 128.3, 127.6, 127.3, 120.8, 115.3, 109.3, 51.9, 43.6. MS: m/z (%) = 381 [M$^+$]. *Anal*. Calcd. for $C_{20}H_{16}FN_3O_4$: C, 62.99; H, 4.23; N, 11.02. Found. C, 62.71; H, 4.41; N, 10.87.

2-(3-Benzyl-5-formyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-*N*-*p*-tolylacetamide (4d)

At rt. for 8 h., White solid, m.p 243-245^{0}C; Yield 0.72 g (89 %). IR (KBr): 3269, 3057, 2756, 1722, 1689, 1664, 1608, 1546, 1460, 1379, 1344 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.30 (bs, 1H, NH), 9.88 (s, 1H, CHO), 8.62 (s, 1H, CH), 7.43 (d, *J* = 8.5 Hz, 2H, ArH), 7.24-7.33 (m, 5H, ArH), 7.11 (d, *J* = 8.5 Hz, 2H, ArH), 5.03 (s, 2H, CH_2), 4.79 (s, 2H, CH_2), 2.25 (s, 3H, CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ 186.5, 164.4, 161.2, 151.2, 150.4, 136.3, 135.8, 132.6, 129.2, 128.3, 127.6, 127.3, 119.0, 109.3, 51.9, 43.6, 20.4. MS: m/z (%) = 377 [M^+]. *Anal*. Calcd. for $C_{21}H_{19}N_3O_4$: C, 66.83; H, 5.07; N, 11.13. Found. C, 66.67; H, 5.30; N, 10.89.

2-(3-Benzyl-5-formyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-*N*-(2-chloro-6-fluoro-phenyl) acetamide (4e)

At rt. for 8 h., White solid, m.p 255-257^{0}C; Yield 0.81 g (91 %). IR (KBr): 3227, 3059, 2716, 1726, 1683, 1670, 1608, 1548, 1458, 1377, 1342 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.22 (bs, 1H, NH), 9.86 (s, 1H, CHO), 8.66 (s, 1H, CH), 7.25-7.39 (m, 8H, ArH), 5.03 (s, 2H, CH_2), 4.89 (s, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 186.5, 165.2, 161.2, 159.0, 157.0, 151.0, 150.3, 136.3, 132.0, 129.0, 128.3, 127.3, 125.3, 122.9, 115.1, 109.4, 51.4, 43.6. MS: m/z (%) = 415 [M^+], 417 [M+2]. *Anal*. Calcd. for $C_{20}H_{15}ClFN_3O_4$: C, 57.77; H, 3.64; N, 10.11. Found. C, 57.50; H, 3.48; N, 10.33.

2-(3-Benzyl-5-formyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-*N*-(2,5-bistrifluoromethyl-phenyl) acetamide (4f)

At rt. for 8 h., off white solid, m.p 224-226^{0}C; Yield 0.86 g (79 %). IR (KBr): 3333, 3070, 3001, 2710, 1697, 1664, 1600, 1550, 1460, 1380 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.33 (bs, 1H, NH), 9.87 (s, 1H, CHO), 8.63 (s, 1H, CH), 7.82-8.00 (m, 3H, ArH), 7.25-7.31 (m, 5H, ArH), 5.04 (s, 2H, CH_2), 4.90 (s, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 186.6, 165.3, 162.1, 151.3, 150.5, 137.8, 136.6, 128.8, 128.5, 127.4, 127.0, 126.7, 123.5, 120.8, 117.5, 110.4, 52.0, 43.7. MS: m/z (%) = 499 [M^+]. *Anal*. Calcd. for $C_{22}H_{15}F_6N_3O_4$: C, 52.92; H, 3.03; N, 8.41. Found. C, 52.78; H, 3.28; N, 8.65.

2-(3-Benzyl-5-formyl-2,4-dioxo-3,4-dihydro-2*H*-pyrimidin-1-yl)-*N*-(2,4-dichlorophenyl)-acetamide (4g)

At rt. for 8 h., White solid, m.p 182-184^{0}C; Yield 0.81 g (86 %). IR (KBr): 3275, 3082, 2926, 2722, 1689, 1666, 1610, 1585, 1525, 1460, 1383 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.12 (bs, 1H, NH), 9.83 (s, 1H, CHO), 8.63 (s, 1H, CH), 7.19-7.81 (m, 8H, ArH), 5.03 (s, 2H, CH_2), 4.96 (s, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 186.3, 165.3, 164.2, 151.7, 150.6, 137.4, 136.1, 129.2, 129.0, 127.8, 127.6, 126.2, 121.6, 111.5, 53.0, 44.0. MS: m/z (%) = 432 [M^+], 436 [M+4]. *Anal*. Calcd. for $C_{20}H_{15}Cl_2N_3O_4$: C, 55.57; H, 3.50; N, 9.72. Found. C, 55.35; H, 3.75; N, 10.00.

Synthesis of 2-[3-Benzyl-1-alkyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin e-5-carbaldehyde (6a-c)

General Procedure

A suspension of **2** (0.5 gm, 2.1 mmol), K_2CO_3 (0.3 g, 2.1 mmol) and alkyl halides **5** (2.2 mmol) in DMF (4 mL) was stirred at room temperature for 6-8 h (TLC monitoring, chloroform: methanol, 9.5: 0.5). Reaction mass was then quenched in ice-cold water and solid obtained was filtered, washed with water, dried and crude solid was recrystallized from DMF/ethanol to afford **6** in 78-90 % yield.

3-Benzyl-1-methyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidine-5-carbaldehyde (6a)

At rt. for 6 h., White solid, m.p 162-164^{0}C; Yield 0.41 g (78 %). IR (KBr): 3360, 3055, 2956, 2737, 1695, 1653, 1602, 1545, 1483, 1444, 1352 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.82 (s, 1H, CHO), 8.56 (s, 1H, CH), 7.25-7.31 (m, 5H, ArH), 5.01 (s, 2H, CH_2), 3.44 (s, 3H, -CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 186.4, 161.3, 151.2, 150.7, 136.5, 128.3, 127.7, 127.2, 109.1, 43.5, 37.3. MS: m/z (%) = 244 [M$^+$]. *Anal*. Calcd. for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found. C, 63.70; H, 5.17; N, 11.74.

3-Benzyl-1-ethyl-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidine-5-carbaldehyde (6b)

At rt. for 6 h., White solid, m.p 116-118^{0}C; Yield 0.45 g (82 %). IR (KBr): 3367, 3050, 2952, 2737, 1698, 1655, 1605, 1555, 1489, 1448, 1353 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 9.82 (s, 1H, CHO), 8.59 (s, 1H, CH), 7.25-7.32 (m, 5H, ArH), 5.02 (s, 2H, CH_2), 3.89 (q, *J* = 7.0 Hz, 2H, -CH_2), 1.22 (t, *J* = 7.0 Hz, 3H, -CH_3). ^{13}C NMR (125 MHz, DMSO-d_6): δ = 187.2, 161.1, 159.1, 134.7, 125.5, 121.6, 119.3, 111.4, 100.7, 51.3, 29.4, 28.6. MS: m/z (%) = 258 [M$^+$]. *Anal*. Calcd. for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found. C, 64.87; H, 5.27; N, 11.09.

3-Benzyl-1-(4-nitrobenzyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrimidine-5-carbaldehyde (6c)

At rt. for 8 h., Yellow solid, m.p 125-127^{0}C; Yield 0.68 g (87 %). IR (KBr): 3375, 3076, 2956, 2744, 1693, 1662, 1606, 1521, 1460, 1346, 1220 cm^{-1}. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.87 (s, 1H, CHO), 8.81 (s, 1H, CH), 8.20 (d, *J* = 9 Hz, 2H, ArH), 7.62 (d, *J* = 9 Hz, 2H, ArH), 7.14-7.35 (m, 5H, ArH), 5.24 (s, 2H, CH_2), 4.99 (s, 2H, CH_2). ^{13}C NMR (125 MHz, DMSO-d_6): δ 186.5, 161.1, 157.6, 150.4, 147.0, 143.4, 136.3, 128.7, 128.5, 128.1, 127.6, 127.4, 127.2, 123.6, 110.1, 52.4, 43.7. MS: m/z (%) = 365 [M$^+$]. *Anal*. Calcd. for $C_{19}H_{15}N_3O_5$: C, 62.46; H, 4.14; N, 11.50. Found. C, 62.63; H, 4.31; N, 11.23.

Declarations

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References

1. (a) Lunt. E; *Comprehensive Organic Chemistry,* ed. Barton, D. and W. D. Ollis, Pergamon Press. Oxford, 1974,vol. 4, p. 493. (b) Brown, J. D; *Comprehensive Heterocyclic Chemistry,* ed. Katritzky, A. R. and Rees, C. W. Pergamon Press. Oxford. 1984,vol. 3, p. 57. (c) Sasaki, T; Minamoto, K; Suzuki, T. and

Yamashita, S. *Tetrahedron.* **1980**, *36*, 865. (d) Bradshaw, T. K. and Hutchison D. W. *Client. Soc. Rev.,* **1977**,*6*, 43. (e) Bhuyan, P. J; Boruah, R. C. and Sandhu, J. S. *J. Org. Chem.,* **1990**, *55*, 568. (f) Bhuyan, P. J; Sandhu, J. S. and Ghosh, A. C. *Tetrahedron Lett.,* **1996**, *37*, 1853. and references therein.

2. (a) Marumoto, R. and Furukawa, Y. *Chem. Pharm. Bull.,* **1977**,*25*, 2974. (b) Cheng, C. C. and Roth, B. *Prog. Med. Chem.,* **1971**, *8*, 61. (c) Clercq, E. D. and Bernaens, R. *J. Biol. Chem.,* **1987**,*262*, 14905. (d) Jones, A. S; Sayers, J. R; Walker, R. T. and Clercq, E. D. *J. Med Chem.,* **1988**,*31*, 268.
3. (a) Baba, M; Pauuels, R; Herdwig, P; Ciercq, E. D; Desmyster, J. and Vandepulfe, M. *Biochem. Res. Cof. mun.,* **1957**,*142*, 128. (b) Clercq, E. D. *J. Med. Chem.,* **1986**,*29*, 1561.
4. (a) Clercq, E. D. *Anticancer Res.,* **1986**,*6*, 549. (b) Jones, A. S; Verhalst, G. and Walker, R. T. *Tetrahedron Lett.,* **1974**,4415.
5. Block, J. H; Beal, J. M; In *Organic Medicinal and Pharmaceutical Chemistry,* 11th ed.; Lippincott Williams & Wilkins: London, **2004**, pp. 375, 406.
6. Longley, D. B; Harkin, D. P; Johnston, P. G. *Nat. Rev.,* **2003**,*3*, 330.
7. Hoffmann, C; Rockstroh, J. K; Kamps, B. S. *HIV Medicine **2005**,* Flying Publisher; Steinhauser: Paris, **2005**, 620.
8. Baraldi, P. G; Romagnoli, R; Gaudix, A. E; Pineda, de las Infantas, M. J. P; Gallo, M. A; Espinosa, A; Martinez, A; Bingham, J. P; Hartley, J. A. *J. Med. Chem*., **2002**,*45*, 3630.
9. Copik, A; Suwinski, J; Walczak, K; Bronikowska, J; Czuba, Z; Krol, W. *Nucleosides, Nucleotides Nucleic Acids Res*. **2002**, *21*, 377.
10. Semenov, V. E; Voloshina, A. D; Toroptzova, E. M; Kulik, N. V; Zobov, V. V; Giniyatullin, R. K; Mikhailov, A. S; Nikolaev, A. E; Akamsin, V. D; Reznik, V. S. *Eur. J. Med. Chem.* **2006**, *41*, 1093.
11. Zenker, N. Thyroid function and thyroid drugs. In: Principles of Medicinal Chemistry. Foye W. O; editor, 3rd ed.; Lea & Febiger: Philadelphia, London, UK, 1990. p. 603-621.
12. Kamalakannan, P; Venkappayya, D; Balsubramanian, T. *J. Chem. Soc., Dalton Trans.* **2002**, 3381.
13. Motawia, M. S; Abdel-Megied, A. E. S; Pedersen, E. B; Nielsen, C. M; Ebbesen, P. *Acta Chem. Scand.* **1992**, *46*, 77.
14. Fabrissim, S; de Nardo, M; Nisi, C; Morasca, L; Dolfini, E; Franchi, G. *J. Med. Chem.* **1976**, *19*, 639.
15. (a) See for example Brown, D. J. in *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R; Rees, C. W; chairmen, eds.; Boulton, A. J; McKillop, A.: Pergamon Press, Oxford, 1984, vol. 3, p. 89-93 and references cited therein. (b) Efimitseva, E. V; Mikhailov, S. N; Meshkov, S. V; Lonnberg, H. *Acta Chem. Scand*. **1992**, 46, 1122. (c) Kundu, N. G; Sikdar, S; Hertzberg, R. P; Schmitz, S. A; Khatri, S. G; *J. Chem. Soc. Perkin Trans. 1* **1985**, 1295. (d) Singh, H; Aggarwal, P; Kumar, S. *Synthesis* **1990**, 520. (e) Ogilvie, K. K; Beaucage, S. L. *Tetrahedron Lett*. **1978**, *19*, 1663. (f) Wong, J. L; Fuchs, D. S. *J. Org. Chem*. **1971**, *36*, 848. (g) Kusmierek, Z. A; Singer, B. *Nucleic Acid Research* **1976**, *3*, 989. (h) Martirosyan, Z. A; Gunar, V. I; Zavyalov, S. I. *Izvestiya Akademii Nauk. SSSR Seriya Khimickesaya* **1970**, *5*, 1127.
16. Birari, D. R; Ghagare, M. G; Bagul, S. M; Ghotekar, B. K; Kazi, M. A; Toche, R. B. and Jachak, M. N. *Org. Prep. Proced. Int*. **2009**, *41*, 515.

17. Birari D. R., Ghagare M. G., Bagul S. M., Toche R. B. and Jachak M. N*. Monatsh. Chem. **2010**, *141*, 451.
18. Nishiwaki, T; Fusko, F. and Minamisono, E. *J. Chem. Soc. Perkin Trans.*, **1974**,*1*, 1871.
19. Doyle, M. P; Deliria, J. F; Siegfried, B. Jr. and Bishop, S. W. *J. Org. Chem.,* **1977**,*42*, 3494.

Schemes

Schemes 1 to 3 are available in the Supplementary Files section.

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