Synthesis of some aryl (pyrimidin-3-yl)methyl ureas, hydrazones and semicarbazones

Virginija Jakubkiene,* Justinas Zurba, and Milda M. Burbuliene

Department of Organic Chemistry, Faculty of Chemistry, Vilnius University
Naugarduko 24, LT-03225, Vilnius, Lithuania
E-mail: virginija.jakubkiene@chf.vu.lt

DOI: http://dx.doi.org/10.3998/ark.5550190.p009.620

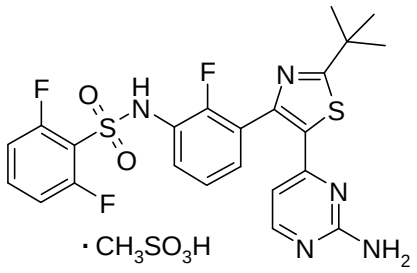
Abstract

Two methods of synthesis of aryl (pyrimidin-3-yl)methyl ureas were investigated. One of them involved reaction sequence starting with (pyrimidin-3-yl)acetohydrazides to give the corresponding azides, which reacted with aryl amines to form aryl (pyrimidin-3-yl)methyl ureas. The second one was based on a one-pot reaction of (pyrimidin-3-yl)acetic acids with diphenyl phosphoryl azide followed by reaction with aryl amines. Also, some new aryl and (pyrimidin-3-yl) moiety bearing hydrazones and semicarbazones were synthesized.

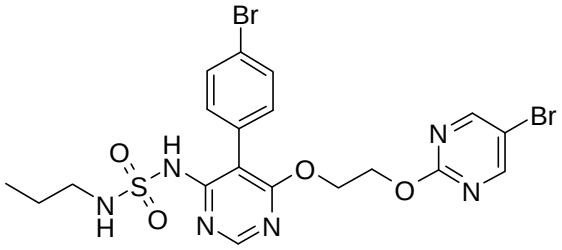
Keywords: (Pyrimidin-3-yl)acetyl azides, aryl (pyrimidin-3-yl)ureas, hydrazones, semicarbazones

Introduction

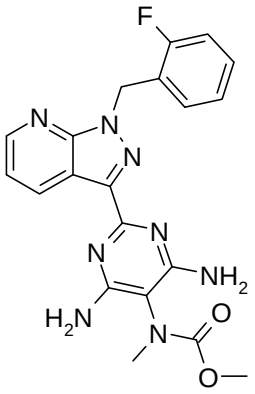
Pyrimidines represent an important group of heterocyclic compounds exhibiting broad spectrum of biological activity.[1-5] Moreover, pyrimidine moiety is a building block for some new drug introduced to the market every year (Figure 1). Thus, dabrafenib mesylate (Tafinlar®) was approved in 2013 for the treatment of metastatic BRAF-mutant melanoma, macitentan (Opsumit®) and riociguat (Adempas®) – for the treatment of pulmonary arterial hypertension (PAH), sofosbuvir (Sovaldi®) – for the treatment of the hepatits C virus (HCV) across several genotypes.[6] On the other hand, compounds with the moiety of urea, hydrazone and semicarbazone are citied to show anticancer,[7-9] antimicrobial,[1,3-5,10-13] antithrombotic,[14] analgesic[15,16] and anti-inflammatory activity.[1,5,13,16]



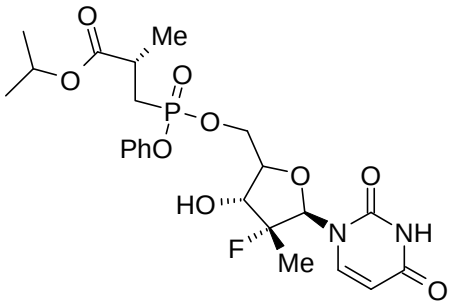
Dabrafenib mesylate



Macitentan



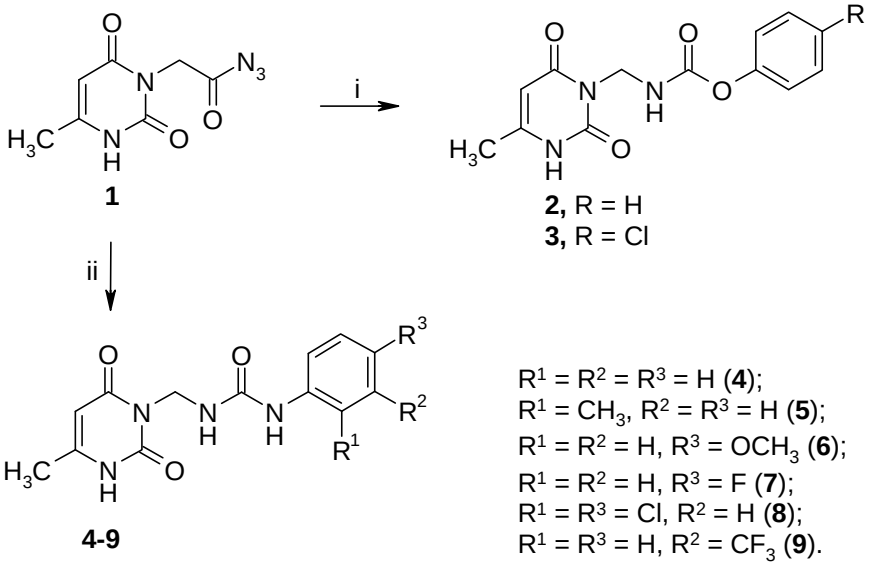
Riociguat



Sofosbuvir

Figure 1. New drugs having a pyrimidine skeleton.

Earlier we have synthesised arylpyrimidinylureas and carbamates, which showed anti-inflammatory activity against endotoxin-induced airway epithelial cell injury[17,18] (Scheme 1).

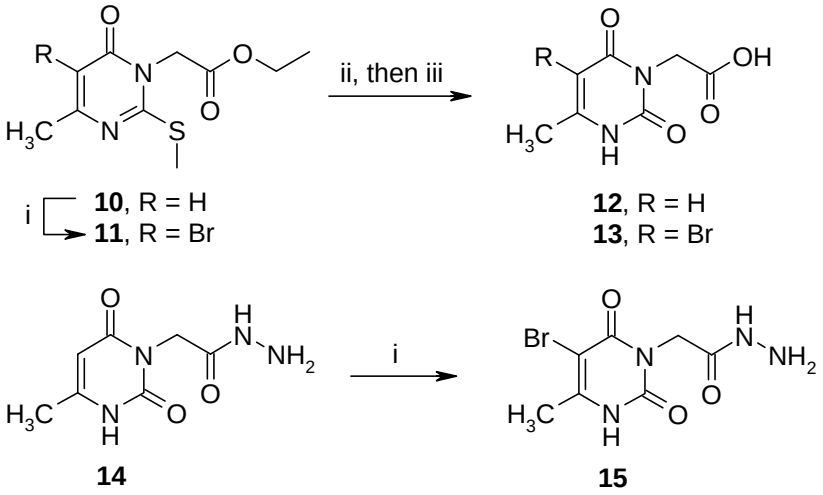


Scheme 1. *Reagents and conditions:* (i) corresp. phenol, dry dioxane, reflux, 5 h; (ii) corresp. aniline, dry dioxane, reflux, 1 h.

N-(2,4-Dichlorophenyl)-*N'*-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]urea (**8**) showed especially high activity compared to that of emodin and rhein.[18] On the basis of the above mentioned structures, bearing urea bridged 2,4-dioxopyrimidine and halo aryl fragment, the goal of our reasearch was to synthesize series of new structurally relative compounds as well as to find out the most effective methods for their synthesis.

Results and Discussion

The synthesis of the starting compounds **12**, **13** and **15** is described in Scheme 2. Thus, compound **11** was synthesized by bromination of ester **10** according to the known procedure.[19] Compound **15** was synthesized by analogous bromination from hydrazide **14** which synthesis has already been described.[20] Hydrolysis of esters **10**, **11** with 20% NaOH solution, then acidification with conc. HCl gave the corresponding acids **12**, **13**. Acids **12**, **13** and hydrazides **14**, **15** were further used for acyl azide **1**, **16** synthesis.

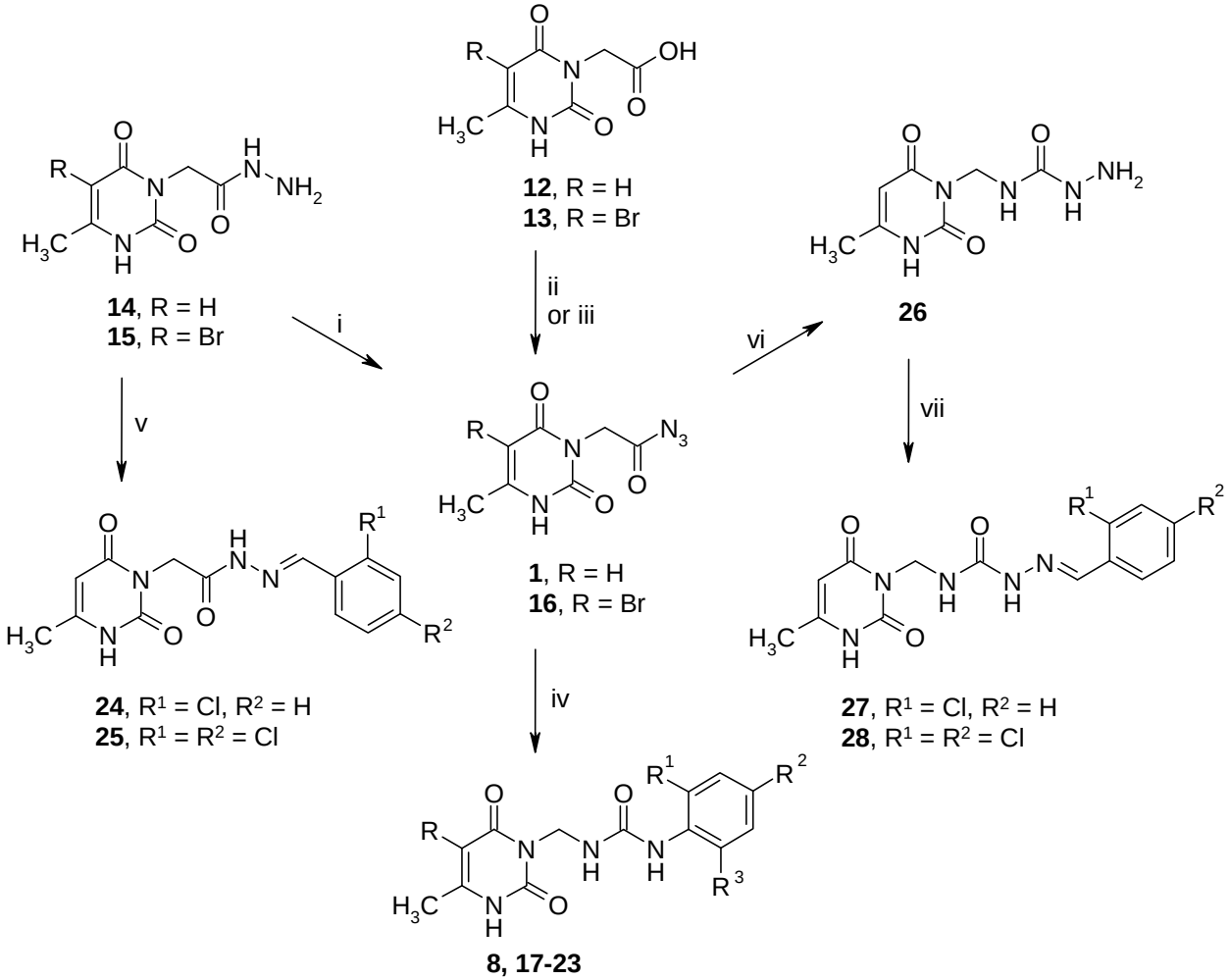


Scheme 2. *Reagents and conditions:* (i) Br_2, CH_3COOH, rt, 1 h; (ii) 20% NaOH, reflux, 1 h; (iii) conc. HCl, pH = 2.

Acyl azides commonly are prepared from carboxylic acids *via* mixed anhydrides[21-24] or directly using diphenyl phosphoryl azide[25] or from acyl chlorides.[21] They can also been prepared by nitrosation of hydrazides.[26,27]

Hydrazide nitrosation was used in a previous work[17] to synthesize azide **1**. In the present study, the same procedure was used for the synthesis of **16** which was obtained in a moderate 61% yield from hydrazide **15**. According to the same nitrosation procedure from hydrazide **14**, the desired azide **1** was isolated in a 73% yield. We performed, however, one-pot two-step reaction beginning with acid **12** to synthesize azide **1**. Treatment of acid **12** with

ethylchloroformate in the presence of triethylamine followed by reaction with sodium azide, yielded only 35% of azide **1**. Therefore, acyl azides **1** and **16** to be used for the synthesis of ureas **17**−**23**, were prepared from corresponding hydrazides **14**, **15** (Scheme 3).



R = R^1 = H, R^2 = R^3 = Cl (**8**); R = R^1 = R^2 = H, R^3 = Cl (**17**); R = R^1 = R^3 = H, R^2 = Cl (**18**); R = R^2 = H, R^1 = R^3 = Cl (**19**); R = R^1 = R^3 = H, R^2 = Br (**20**); R = R^1 = H, R^2 = R^3 = Br (**21**); R = Br, R^1 = H, R^2 = R^3 = Cl (**22**); R = R^1 = R^2 = Br, R^3 = H (**23**).

Scheme 3. *Reagents and conditions:* (i) aq. HCl, $NaNO_2/H_2O$, 0–5 °C, 30 min.; (ii) abs. acetone, TEA, $ClCO_2Et$, -5–5 °C, 30 min., then NaN_3/H_2O, 0–5 °C, 7 h, later 5–10 °C overnight – yield **1**; (iii) dry benzene, TEA, rt, 10 min., then DPPA, rt, 24 h: (iv) dry benzene, corresp. aniline, reflux, 3 h; (v) *i*-PrOH, reflux, 3 min., then 70–75 °C, corresp. benzaldehyde; (vi) dry benzene, reflux, 2 h, then diethyl ether, $N_2H_4 \cdot H_2O$, rt, 1 h; (vii) abs. EtOH, corresp. benzaldehyde, rt, 24 h.

Acyl azides undergo thermal rearrangement in an inert solvents to give isocyanates (Curtius rearrangement), which on reaction with amines lead to the formation of ureas.[22,23,25,27] Thus, heating at reflux acyl azides **1**, **16** and arylamines in dry benzene produced ureas **8**, **17**–**23** in 53–

76% yields. The structure of these compounds was confirmed by NMR data. The number of signals and their chemical shifts are in accordance with the given structures. For example, in the ^{1}H NMR spectra of ureas **8**, **17**–**23** the characteristic splitting of NCH_2 group protons into doublets (5.20−5.28 ppm) and neighbour NH protons triplets (6.90−7.93 ppm) are observed. The NH protons close to aromatics resonate at 8.25−8.90 ppm.

It should be noted, that the yield and the reaction time are dependent on the number of halogen atoms and their position in an aryl amine ring, e.g., azide **1** reaction with 2,6-dichloroaniline occurred within 4 h, while it needs only 2 h in the other cases. In addition, urea **19** is obtained in a lower yield (53%), and 2,4,6-trichloroaniline did not react with azide **1** under given conditions.

Searching for more efficient synthesis of ureas, we tried one-pot synthetic pathway from acids **12**, **13**. Treatment of acids **12**, **13** with diphenyl phosphoryl azide in the presence of triethylamine in dry benzene at room temperature to form acyl azides **1**, **16**, which without isolation from the reaction mixture further were allowed to react with corresponding anilines. According to this procedure ureas **8, 19, 21–23** were synthesized.

This synthetic pathway compared to the synthesis of ureas from hydrazides, has some advantages (less stages and shorter time), however it has disadvantages as well. First of all, to full conversion of starting acids **12**, **13** it is necessary to use a large excess of reagents (4 equiv. of DPPA and 1 equiv. of TEA per 1 equiv. of acid). On the other hand, the output of these reactions is much lower (8-52%). Thus, the discussed synthesis of ureas from acids would be better, presumably, only if the synthesis of the starting acids could be more convenient than synthesis of the corresponding hydrazides.

With the purpose to modify the linkage between the pyrimidine ring and aryl substituents we synthesized hydrazones **24**, **25**. Good yields (77 and 86%) of hydrazones were obtained under treatment of hydrazide **14** with the corresponding benzaldehydes in hot isopropanol. In the ^{1}H NMR spectra of hydrazones **24**, **25** along with others the characteristic two sets of signals of NCH_2 (4.47−4.88 ppm), 6'-ArH (7.93–8.02), N=CH (8.34−8.58 ppm), CONH (11.24−11.27 ppm) and NH group of the pyrimidine ring (11.81−11.94 ppm) protons were observed. According to the literature acyl hydrazones in solutions may exist as *Z*/*E* geometrical isomers about C=N double bond and *syn/anti* conformers arising from the hindered rotation about amide C−N linkage.[28] In dimethyl-d_6 sulfoxide solution hydrazones are present in the form of *E* isomers,[29] so the above signals were assigned to *syn/anti* conformers of the *E* geometrical isomers.

Structurally related to ureas semicarbazones also can be synthesized from acyl azides. Thus, acetyl azide **1** rearranged to isocyanate in benzene at reflux and then was allowed to react with hydrazine hydrate to form semicarbazide **26**. Reaction of **26** with benzaldehydes yielded the corresponding semicarbazones **27**, **28**. In the ^{1}H NMR spectra of compounds **27**, **28** characteristic for N=CH proton singlets at 8.25 and 8.20 ppm as well as signals in the area of 7.39-7.95 ppm of aromatic protons were observed.

Conclusions

The research once again confirms that the most convenient way to synthesize (pyrimidin-3-yl)acetyl azides is nitrosation of the corresponding acetohydrazides, which in turn are valuable synthons for hydrazone synthesis. Aryl (pyrimidin-3-yl)methyl ureas can be synthesized by two methods − starting with (pyrimidin-3-yl)acetyl azides or from (pyrimidin-3-yl)acetic acids. (Pyrimidin-3-yl)acetyl azides heated in dry benzene undergo rearrangement to isocyanate, which in reaction with aryl amines gave ureas. (Pyrimidin-3-yl)acetic acids reacted with diphenyl phosphoryl azide in the presence of triethylamine in dry benzene to form (pyrimidin-3-yl)acetyl azides following by *in situ* reaction with aryl amines to yield the corresponding ureas, i.e., additional procedure for isolation of azides was not required.

Experimental Section

General. Melting points were determined in open capillaries with a digital melting point IA9100 series apparatus (ThermoFischer Scientific) and are uncorrected. All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F_{254} aluminium plates (Merck). Visualisation was accomplished by UV light. IR spectra were recorded on an FTIR spectrophotometer Spectrum BX II (Perkin Elmer) as potassium bromide pellets. NMR spectra were recorded on a Bruker Ascend 400 (400 and 100 MHz, respectively). ^{1}H and ^{13}C NMR were referenced to residual solvent peaks. High Resolution Mass Spectrometry (HRMS) analyses were carried out on a ESI TOF 6230 (Agilent Technologies) mass spectrometer.

General procedure for the bromination of compound 10 and 14. To a mixture of ester **10** or hydrazide **14** (5 mmol) in glacial acetic acid (7 mL), the bromine (0.58 ml, 10 mmol) was added dropwise under stirring at room temperature. The reaction mixture was stirred at this temperature for 1 h, the precipitate was collected by filtration, washed with water or acetone and dried over sodium sulphate in vacuum.

Ethyl-(5-bromo-6-methyl-2-methylthio-4-oxo-3,4-dihydropyrimidin-3-yl)acetate (11). White solid, yield 1.43 g (89%), mp 128–130 °C. IR, ν, cm^{-1}: 1686, 1741 (C=O). ^{1}H NMR ($CDCl_3$), δ, ppm: 1.31 (t, *J* 7.2 Hz, 3H, $OCH_2\underline{CH_3}$), 2.48 (s, 3H, CH_3), 2.60 (s, 3H, SCH_3), 4.27 (k, *J* 7.2 Hz, 2H, $O\underline{CH_2}CH_3$), 4.85 (s, 2H, NCH_2); ^{13}C NMR ($CDCl_3$), δ, ppm: 14.1 (SCH_3), 15.3 (CH_3), 24.8 (6-CH_3), 46.0 (NCH_2), 62.2 (OCH_2), 107.3 (5-C), 158.3, 159.6, 161.1, 166.2 (2-C, 4-C, 6-C, C=O). HRMS (ES): $[M+H]^+$ calculated for $C_{10}H_{13}BrN_2O_3S$, 322.9883; found 322.9885.

(5-Bromo-6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)acetohydrazide (15). White solid, yield 1.05 g (76%), mp > 300 °C (dec.). IR, ν, cm^{-1}: 1637, 1697, 1737 (C=O); 3203, 3248 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.28 (s, 3H, CH_3), 4.03 (br s, 2H, NH_2), 4.55 (s, 2H, NCH_2), 11.23 (s, 1H, NH), 11.82 (s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 20.0 (CH_3), 42.3

(NCH_2), 94.7 (5-C), 150.4, 151.2, 159.4, 166.9 (2-C, 4-C, 6-C, C=O). HRMS (ES): $[M+Na]^+$ calculated for $C_7H_9BrN_4NaO_3$, 298.9750; found 298.9758.

General procedure for the synthesis of acetic acids 12 and 13. A mixture of compound **10** or **11** (5 mmol) and solution of 20% sodium hydroxide (3.2 mL) was heated at reflux for 2 h, then cooled to room temperature. The reaction mixture was acidified with conc. hydrochloric acid to pH 2 and kept at temperature 5–10 °C for 2 h. The resultant precipitate was collected by filtration, washed with cold water and dried.

(6-Methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)acetic acid (12). White powder, yield 0.58 g (63%), mp 245–246 °C; (mp 244–246 °C, ref[30]).

(5-Bromo-6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)acetic acid (13). White powder, yield 0.92 g (70%), mp 229–230 °C; (mp 235–236 °C, ref[31]).

General procedure for the synthesis of acetyl azides 1 and 16.

Method A. To a cooled (0−5 °C) suspension of hydrazide **14** or **15** (5 mmol), water (15 mL) and conc. hydrochloric acid (4 mL), a solution of sodium nitrite (1.21 g, 17.5 mmol) in water (5 mL) was added dropwise under stirring. The reaction mixture was stirred at this temperature for 30 min., the precipitate was collected by filtration, washed with cold water and dried over sodium sulphate in vacuum.

(6-Methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)acetyl azide (1). White solid, yield 0.76 g (73%), mp 134–136 °C; (mp135–137 °C, ref[17]).

(5-Bromo-6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)acetyl azide (16). White solid, yield 0.88 g (61%), mp 248–250 °C (dec.). IR, ν, cm^{-1}: 1655, 1709, 1733 (C=O), 2158 (N_3), 3215 (NH). ^{1}H NMR ($CDCl_3$), δ, ppm: 2.40 (s, 3H, CH_3), 4.75 (s, 2H, NCH_2), 10.48 (s, 1H, NH); ^{13}C NMR ($CDCl_3$), δ, ppm: 20.3 (CH_3), 44.4 (CH_2), 96.8 (5-C), 149.0, 151.5, 158.7 (2-C, 4-C, 6-C), 174.2 (C=O). HRMS (ES): $[MH-CH_2CON_3]^+$ calculated for $C_5H_5BrN_2O_2$, 206.9600; found 206.9600.

Method B (only for azide **1**). To a cooled to -5 °C temperature suspension of acid **3** (0.184 g, 1 mmol) in abs. acetone (2 mL), triethylamine (0.28 mL, 2 mmol), then ethyl chloroformate (0.19 mL, 2 mmol)) was added dropwise under stirring. The reaction mixture was stirred at this temperature for 30 min, then a solution of sodium nitrite (0.083 g, 1.2 mmol) in water (0.5 mL) was added dropwise under stirring. The reaction mixture was stirred at -5–5 °C temperature for 7 h and was kept at temperature 5–10 °C overnight. Then the reaction mixture was diluted with water (15 mL), saturated with sodium chloride and extracted with dichloromethane (3 × 10 mL). The extracts were combined, dried over sodium sulphate and filtered. After removal of the solvent 0.073g (35%) of azide **1**, mp 135–137 °C was obtained.

General procedure for the synthesis of ureas 8, 17–23

Method A. A mixture of azide **1** or **16** (0.5 mmol) and corresponding aniline (0.75 mmol) in dry benzene (5 mL) was heated at reflux for 2–4 h. The reaction mixture was evaporated under reduced pressure to dryness. The residue was worked up with methanol to give a solid, which

was collected by filtration, washed with methanol and crystallized from a mixture of dimethyl formamide and water.

***N*-(2,4-Dichlorophenyl)-*N*'-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]urea (8).** White powder, yield 0.123 g (72%), mp 221–223 °C; (mp 223–225 °C, ref[17]).

***N*-(2-Chlorophenyl)-*N*'-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]urea (17).** White powder, yield 0.099 g (64%), mp 205–207 °C. IR, ν, cm^{-1}: 1644, 1662, 1715 (C=O), 3293, 3346 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.05 (s, 3H, CH_3), 5.23 (d, *J* 6.4 Hz, 2H, NCH_2), 5.51 (s, 1H, 5-CH), 6.98 (t, *J* 8.0 Hz, 1H, 4'-ArH), 7.25 (t, *J* 8.0 Hz, 1H, 5'-ArH), 7.39 (d, *J* 8.0 Hz, 1H, 3'-ArH), 7.77 (t, *J* 6.4 Hz, 1H, NCH_2NH), 8.06 (d, *J* 8.0 Hz, 1H, 6'-ArH), 8.36 (s, 1H, CONH), 11.21 (br s, 1H, 1-NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8 (CH_3), 45.6 (CH_2), 99.0 (5-C), 122.0, 122.4, 123.8, 128.1, 129.9, 136.9 (Ar-C), 151.9, 153.1, 154.6, 163.6 (2-C, 4-C, 6-C, C=O). HRMS (ES): $[M+Na]^+$ calculated for $C_{13}H_{13}ClN_4NaO_3$, 331.0568; found 331.0580.

***N*-(4-Chlorophenyl)-*N*'-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]urea (18).** White powder, yield 0.117 g (76%), mp 245–247 °C. IR, ν, cm^{-1}: 1642, 1682, 1732 (C=O), 3265, 3415 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.04 (s, 3H, CH_3), 5.21 (d, *J* 6.4 Hz, 2H, NCH_2), 5.50 (s, 1H, 5-CH), 6.91 (t, *J* 6.4 Hz, 1H, NCH_2NH), 7.27 (d, *J* 8.8 Hz, 2H, 3',5'-ArH), 7.38 (d, *J* 8.8 Hz, 2H, 2',6'-ArH), 8.90 (s, 1H, CONH), 11.25 (br s, 1H, 1-NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8 (CH_3), 45.7 (CH_2), 99.1 (5-C), 119.9, 125.8, 129.3, 139.6 (Ar-C), 151.9, 153.1, 154.6, 163.6 (2-C, 4-C, 6-C, C=O). HRMS (ES): $[M+Na]^+$ calculated for $C_{13}H_{13}ClN_4NaO_3$, 331.0568; found 331.0579.

***N*-(2,6-Dichlorophenyl)-*N*'-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]urea (19).** White powder, yield 0.091 g (53%), mp 224–226 °C. IR, ν, cm^{-1}: 1648, 1660, 1724 (C=O), 3249, 3351 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.06 (s, 3H, CH_3), 5.21 (d, *J* 6.4 Hz, 2H, NCH_2), 5.51 (s, 1H, 5-CH), 7.08 (t, *J* 6.4 Hz, 1H, NCH_2NH), 7.27 (t, *J* 8.0 Hz, 1H, 4'-ArH), 7.48 (d, *J* 8.0 Hz, 2H, 3',5'-ArH), 8.31 (s, 1H, CONH), 11.21 (s, 1H, 1-NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.6 (CH_3), 46.0 (CH_2), 98.8 (5-C), 128.5, 128.8, 134.0 (2) (Ar-C), 151.7, 152.7, 154.3, 163.2 (2-C, 4-C, 6-C, C=O). HRMS (ES): $[M+H]^+$ calculated for $C_{13}H_{12}Cl_2N_4O_3$, 343.0359; found 343.0361.

***N*-(4-Bromophenyl)-*N*'-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]urea (20).** White powder, yield 0.115 g (65%), mp 240–242 °C. IR, ν, cm^{-1}: 1643, 1733 (C=O), 3266, 3414 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.04 (s, 3H, CH_3), 5.20 (d, *J* 6.4 Hz, 2H, NCH_2), 5.49 (s, 1H, 5-CH), 6.90 (t, *J* 6.4 Hz, 1H, NCH_2NH), 7.32 (d, *J* 8.8 Hz, 2H, 3',5'-ArH), 7.39 (d, *J* 8.8 Hz, 2H, 2',6'-ArH), 8.89 (s, 1H, CONH), 11.17 (br s, 1H, 1-NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.8 (CH_3), 45.8 (CH_2), 99.1 (5-C), 113.7, 120.4, 132.2, 139.9 (Ar-C), 151.9, 153.2, 154.6, 163.6 (2-C, 4-C, 6-C, C=O). HRMS (ES): $[M+H]^+$ calculated for $C_{13}H_{13}BrN_4O_3$, 353.0244; found 353.0255.

***N*-(2,4-Dibromophenyl)-*N*'-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]urea (21).** White powder, yield 0.156 g (72%), mp 236–237 °C. IR, ν, cm^{-1}: 1656, 1718 (C=O), 3327 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.05 (s, 3H, CH_3), 5.22 (d, *J* 6.0 Hz, 2H,

NCH_2), 5.50 (s, 1H, 5-CH), 7.47 (d, *J* 8.8 Hz, 1H, 5'-ArH), 7.77 (s, 1H, 3'-ArH), 7.89 (t, *J* 6.0 Hz, 1H, NCH_2NH), 8.01 (d, *J* 8.8 Hz, 1H, 6'-ArH), 8.25 (s, 1H, CONH), 11.19 (br s, 1H, 1-NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.6 (CH_3), 45.3 (CH_2), 98.8 (5-C), 113.5, 114.2, 123.6, 131.2, 134.5, 137.7 (Ar-C), 151.6, 152.7, 154.2, 163.0 (2-C, 4-C, 6-C, C=O. HRMS (ES): $[M+H]^+$ calculated for $C_{13}H_{12}Br_2N_4O_3$, 432.9329; found 432.9340.

***N*-[(5-Bromo-6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]-*N'*-(2,4-dichlorophenyl)urea (22).** White powder, yield 0.15 g (71%), mp 247–249 °C. IR, ν, cm^{-1}: 1659, 1717 (C=O), 3319 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.24 (s, 3H, CH_3), 5.28 (d, *J* 6.4 Hz, 2H, NCH_2), 7.32 (d, *J* 9.2 Hz, 1H, 5'-ArH), 7.54 (s, 1H, 3'-ArH), 7.93 (t, *J* 6.4 Hz, 1H, NCH_2NH), 8.16 (d, *J* 9.2 Hz, 1H, 6'-ArH), 8.44 (s, 1H, CONH), 11.67 (s, 1H, 1-NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 20.0 (CH_3), 46.8 (CH_2), 95.0 (5-C), 122.4, 122.6, 126.1, 127.9, 128.9, 136.1 (Ar-C), 150.3, 151.3, 154.2, 159.4 (2-C, 4-C, 6-C, C=O). HRMS (ES): $[M+H]^+$ calculated for $C_{13}H_{11}BrCl_2N_4O_3$, 422.9441; found 422.9439.

***N*-[(5-Bromo-6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]-*N'*-(2,4-dibromophenyl)urea (23).** White powder, yield 0.176 g (69%), mp 247–248 °C. IR, ν, cm^{-1}: 1661, 1718 (C=O), 3325 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.24 (s, 3H, CH_3), 5.28 (d, *J* 4.8 Hz, 2H, NCH_2), 7.47 (d, *J* 8.4 Hz, 1H, 5'-ArH), 7.78 (s, 1H, 3'-ArH), 8.0 (br s, 1H, NCH_2NH), 8.02 (br s, 1H, 6'-ArH), 8.26 (s, 1H, CONH), 11.67 (s, 1H, 1-NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 20.0 (CH_3), 46.8 (CH_2), 95.0 (5-C), 113.5, 114.2, 123.5, 131.2, 134.5, 137.6 (Ar-C), 150.3, 151.3, 154.2, 159.4 (2-C, 4-C, 6-C, C=O). HRMS (ES): $[M+H]^+$ calculated for $C_{13}H_{11}Br_3N_4O_3$, 510.8434; found 510.8440.

Method B. To a stirred mixture of acid **12** or **13** (0.5 mmol) in dry benzene (5 mL) triethylamine (0.28 mL, 2 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 10 min., then diphenyl phosphoryl azide (0.44 mL, 2 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 24 h, then the corresponding aniline (0.75 mmol) was added. The reaction mixture was heated at reflux for 3 h and evaporated under reduced pressure to dryness. The residue was worked up with methanol to give a solid, which was collected by filtration, washed with methanol and dried to yield 0.067 g (39%) of **8**, 0.014 g (8%) of **19**, 0.11 g (52%) of **21**, 0.072 g (34%) of **22** or 0.061 g (24%) of **23**.

General procedure for the synthesis of hydrazones 24 and 25. A mixture of hydrazide **14** (0.099 g, 0.5 mmol) and 2-propanol (10 mL) was heated at reflux for 3 min., then cooled to 70–75 °C temperature and the corresponding benzaldehyde was added. The reaction mixture was cooled to room temperature, the resultant precipitate was collected by filtration, washed with methanol and dried.

***N*'-[(2-Chlorophenyl)methylene]-(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)acetohydrazide (24).** White solid, yield 0.138 g (86%), mp 311–312 °C. IR, ν, cm^{-1}: 1657, 1682, 1714 (C=O), 3189, 3233, 3436 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.09 (s, 3H, CH_3), 4.47, 4.88 (2s, 2H, NCH_2), 5.54 (s, 1H, 5-CH), 7.40–7.47 (m, 2H, 4',5'-ArH), 7.53 (d, *J* 7.2 Hz, 1H, 3'-ArH), 7.93, 8.01 (2d, *J* 7.2 Hz, 1H, 6'-ArH), 8.40, 8.58 (2s, 1H, N=CH), 11.24, 11.27 (2s, 1H, CONH), 11.81, 11.89 (2s, 1H, 1-NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.6 (CH_3), 41.2

(CH_2), 98.6 (5-C), 127.3, 128.1, 130.4, 131.7, 131.8, 133.4 (Ar-C), 140.4, 151.8, 152.2, 163.1, 168.7 (2-C, 4-C, 6-C, N=CH, C=O). HRMS (ES): $[M+H]^+$ calculated for $C_{14}H_{13}ClN_4O_3$, 321.0758; found 321.0749.

***N*'-[(2,4-Dichlorophenyl)methylene]-(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)acetohydrazide (25)**. White solid, yield 0.137 g (77%), mp 318–320 °C. IR, ν, cm^{-1}: 1652, 1660, 1714 (C=O), 3190, 3436 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.08 (s, 3H, CH_3), 4.47, 4.87 (2s, 2H, NCH_2), 5.53 (s, 1H, 5-CH), 7.49 (d, *J* 8.4 Hz, 1H, 5'-ArH), 7.72 (s, 1H, 3'-ArH), 7.93, 8.02 (2d, *J* 8.4 Hz, 1H, 6'-ArH), 8.34, 8.53 (2s, 1H, N=CH), 11.25, 11.27 (2s, 1H, CONH), 11.86, 11.94 (2s, 1H, 1-NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.6 (CH_3), 41.2 (CH_2), 98.6 (5-C), 128.4, 128.6, 129.8, 130.8, 134.1, 135.4 (Ar-C), 139.3, 151.8, 152.2, 163.0, 168.8 (2-C, 4-C, 6-C, N=CH, C=O). HRMS (ES): $[M+Na]^+$ calculated for $C_{14}H_{12}Cl_2N_4NaO_3$, 377.0179; found 377.0171.

***N*-[(6-Methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]hydrazinecarboxamide (26)**. A mixture of azide **1** (0.209 g, 1 mmol) and dry benzene (20 mL) was heated at reflux for 2 h, then the solvent was removed under reduced pressure. The residue was dissolved in dry diethyl ether (40 mL) and 100% hydrazine hydrate (0.06 mL, 1.2 mmol) was added. The reaction mixture was kept at room temperature for 1 h, the resultant precipitate was collected by filtration, washed with methanol and dried to yield 0.141 g (66%) of compound **26**, mp 198–200 °C. IR, ν, cm^{-1}: 1644, 1683, 1734 (C=O); 3223, 3364 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.03 (s, 3H, CH_3), 4.19 (br s, 2H, NH_2), 5.16 (d, *J* 6.8 Hz, 2H, NCH_2), 5.46 (s, 1H, 5-CH), 6.96 (br s, 1H, $NCH_2\underline{NH}$), 7.23 (s, 1H, CONH), 10.75 (br s, 1H, NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.6 (CH_3), 45.5 (CH_2), 98.8 (5-C), 151.7, 152.4, 159.1, 163.1 (2-C, 4-C, 6-C, C=O). HRMS (ES): $[M+H]^+$ calculated for $C_7H_{11}N_5O_3$, 214.0935; found 214.0929.

General procedure for the synthesis of semicarbazones 27 and 28. A mixture of semicarbazide **26** (0.107 g, 0.5 mmol), the corresponding benzaldehyde (0.6 mmol) and abs. ethanol (25 mL) was stirred at room temperature for 24 h. Then the solid formed was collected by filtration, washed with ethanol and dried.

(2-Chlorobenzylidene)-*N*-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]hydrazinecarboxamide (27). White solid, yield 0.086 g (51%), mp 241–242 °C. IR, ν, cm^{-1}: 1642, 1687, 1714 (C=O), 3211, 3341, 3425 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.04 (s, 3H, CH_3), 5.29 (d, *J* 6.4 Hz, 2H, NCH_2), 5.49 (s, 1H, 5-CH), 7.32 (t, *J* 6.4 Hz, 1H, $NCH_2\underline{NH}$), 7.39–7.41 (m, 2H, 4',5'-ArH), 7.49 (d, *J* 6.0 Hz, 1H, 3'-ArH), 7.93 (d, *J* 6.0 Hz, 1H, 6'-ArH), 8.25 (s, 1H, N=CH), 10.83 (s, 1H, CONH), 11.19 (s, 1H, 1-NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.6 (CH_3), 45.6 (CH_2), 98.9 (5-C), 127.0, 127.9, 130.4, 131.2, 132.0, 132.9 (Ar-C), 136.9, 151.7, 152.6, 154.5, 163.1 (2-C, 4-C, 6-C, N=CH, C=O). HRMS (ES): $[M+H]^+$ calculated for $C_{14}H_{14}ClN_5O_3$, 336.0858; found 336.0868.

(2,4-Dichlorobenzylidene)-*N*-[(6-methyl-2,4-dioxo-1,2-dihydropyrimidin-3(4*H*)-yl)methyl]hydrazinecarboxamide (28). White solid, yield 0.126 g (68%), mp 255–260 °C. IR, ν, cm^{-1}: 1645, 1714 (C=O), 3212, 3359, 3407 (NH). ^{1}H NMR (DMSO-d_6), δ, ppm: 2.04 (s, 3H,

CH_3), 5.29 (s, 2H, NCH_2), 5.48 (s, 1H, 5-CH), 7.31 (s, 1H, NCH_2NH), 7.49 (d, *J* 6.8 Hz, 1H, 5'-ArH), 7.67 (s, 1H, 3'-ArH), 7.95 (d, *J* 6.8 Hz, 1H, 6'-ArH), 8.20 (s, 1H, N=CH), 10.84 (s, 1H, CONH), 11.09 (s, 1H, 1-NH); ^{13}C NMR (DMSO-d_6), δ, ppm: 18.6 (CH_3), 45.6 (CH_2), 98.9 (5-C), 128.2, 128.3, 129.8, 131.2, 133.6, 134.7 (Ar-C), 135.9, 151.7, 152.4, 154.5, 163.1 (2-C, 4-C, 6-C, N=CH, C=O). HRMS (ES): $[M+H]^+$ calculated for $C_{14}H_{13}Cl_2N_5O_3$, 370.0468; found 370.0479.

References

1. Keche, A. P.; Hatnapure, G. D.; Tale, R. H.; Rodge, A. H.; Birajdar, S. S.; Kamble, V. M. *Bioorg. Med. Chem. Letters* **2012**, *22*, 3445. http://dx.doi.org/10.1016/j.bmcl.2012.03.092
2. Novikov, M. S.; Valuev-Elliston, V. T.; Babkov, D. A.; Paramonova, M. P.; Ivanov, A. V.; Gavryushov, S. A.; Khandazhinskaya, A. L.; Kochetkow, S. N.; Pannecouque, C.; Andrei, G.; Snoeck, R.; Balzarini, J.; Seley-Radtke, K. L. *Bioorg. Med. Chem*. **2013**, *21*, 1150. http://dx.doi.org/10.1016/j.bmc.2012.12.027
3. Pan, L.; Jiang, Y.; Liu, Z.; Liu, X.-H.; Liu, Z.; Wang G.; Li, Z.-M.; Wang, D. *Eur. J. Med. Chem.* **2012**, 50, 18. http://dx.doi.org/10.1016/j.ejmech.2012.01.011
4. Grillot, A.-L.; Le Tiran, A.; Shannon, D.; Krueger, E.; Liao, Y.; O'Dowd., H.; Tang, Q.; Ronkin, S.; Wang, T.; Waal, N.; Li, P.; Lauffer, D.; Sizensky, E.; Tanoury, J.; Perola, E.; Grossman, T. H.; Doyle, T.; Hanzelka, B.; Jones, S.; Dixit V.; Ewing, N.; Liao, S.; Boucher, B.; Jacobs, M.; Bennani, Y.; Charifson, P. S. *J. Med. Chem.* **2014**, *57,* 8792. http://dx.doi.org/10.1021/jm500563g
5. Tale, R. H.; Rodge, A. H.; Hatnapure, G. D.; Keche, A. P. *Bioorg. Med. Chem. Letters* **2011**, *21*, 4648. http://dx.doi.org/10.1016/j.bmcl.2011.03.062
6. Ding, H. X.; Leverett, C. A.; Kyne (Jr.), R. E.; Lui, K. K.-C.; Fink, S. J.; Flick, A. C.; O'Donnell, C. J. *Bioorg. Med. Chem.* **2015**, *23,* 1895. http://dx.doi.org/10.1016/j.bmc.2015.02.056
7. Saurat, T.; Buron, F.; Rodriques, N.; de Tauzia, M. L.; Colliandre, L.; Bourg, S.; Bonnet, P.; Guillaumet, G.; Akssira, M.; Corlu, A.; Guillouzo, C,; Berthier, P.; Rio, P.; Jourdan, M.-L.; Benedetti, H.; Routier, S. *J. Med. Chem*. **2014**, *57*, 613. http://dx.doi.org/10.1021/jm401138v
8. Duan, Y. C.; Zheng, Y. C.; Li, X. C.; Wang, M. M.; Ye, X. W.; Guan, Y. Y.; Liu, G. Z.; Zheng, J. X.; Liu, H. M. *Eur. J. Med. Chem.* **2013**, *64*, 99. http://dx.doi.org/10.1016/j.ejmech.2013.03.058
9. Wang, A. Y.; Lu, Y,; Zhu, H. L.; Jiao, Q. C. *Oncol. Lett*. **2012**, *3*, 373. http://dx.doi.org/10.3892/ol.2011.474

10. Chimenti, F.; Bizzarri, B.; Bolasco, A.; Secci, D.; Chimenti, P.; Carradori, S.; Granese, A.; Rivanera, D.; Frishberg, N.; Bordon, C.; Jones-Brando, L. *J. Med. Chem*. **2009**, *52*, 4574. http://dx.doi.org/10.1021/jm9005862
11. Basarab, G. S.; Manchester, J. I.; Bist, S.; Boriack-Sjodin, P. A.; Dangel, B.; Illingworth, R.; Sherer, B. A.; Sriram, S.; Uria-Nickelsen, M.; Eakin, A. E. *J. Med. Chem*. **2013**, *56*, 8712. http://dx.doi.org/10.1021/jm401208b
12. Boechat, N.; Ferreira, V., F.; Ferreira, S. B.; Ferreira, M. L. G.; da Silva, F. C.; Bastos, M. M.; Costa, M. S.; Lourenco, M. C. S.; Pinto, A. C.; Krettli, A. U.; Aguiar, A. C.; Teixeira, B. M.; da Silva, N. V.; Martins, P. R. C.; Bezerra, F. A. F. M.; Camilo, A. L. S.; da Silva, G., P.; Costa, C. C. P. *J. Med. Chem*. **2011**, *54*, 5988. http://dx.doi.org/10.1021/jm2003624
13. Keche, A. P.; Hatnapure, G. D.; Tale, R. H.; Rodge, A. H.; Kamble, V. M. *Bioorg. Med. Chem. Letters* **2012**, *22*, 6611. http://dx.doi.org/10.1016/j.bmcl.2012.08.118
14. Yang, W.; Wang, Y.; Lai, A.; Qiao, J. X.; Wang, T. C.; Hua, J.; Price, L. A.; Shen, H.; Chen, X.; Wong, P.; Crain, E.; Watson, C.; Huang, C. S.; Seiffert, D. A.; Rehfuss, R.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem*. **2014**, *57*, 6150. http://dx.doi.org/10.1021/jm5006226
15. Voight, E. A.; Gomtsyan, A. R.; Daanen, J. F.; Perner, R. J.; Schmidt, R. G.; Bayburt, E. K.; DiDomenico, S.; McDonald, H. A.; Puttfarchen, P. S.; Chen, J.; Neelands, T. R.; Bianchi, B. R.; Han, P.; Reilly, R. M.; Franklin, P. H.; Segreti, J. A.; Nelson, R. A.; Su, Z.; King, A. J.; Polakowski, J. S.; Baker, S. J.; Gauvin, D. M.; Lewis, L. R.; Mikusa, J. P.; Joshi, S. K.; Faltynek C. R.; Kym, P. R.; Kort, M. E. *J. Med. Chem*. **2014**, *57*, 7412. http://dx.doi.org/10.1021/jm500916t
16. Rineh, A.; Mahmoodi, N.; Abdollahi, M.; Foroumadi, A.; Sorkhi, M.; Shafiee, A. *Arch. Pharm. Chem. Life Sci.* **2007**, *340*, 409. http://dx.doi.org/10.1002/ardp.200700045
17. Jakubkiene, V.; Kacnova, Z.; Burbuliene, M. M.; Vainilavicius, P. *Arkivoc* **2010**, (*xi*), 39.
18. Cabrera-Benitez, N. E.; Perez-Roth, E.; Casula, M.; Ramos-Nuez, A.; Rios-Luci, C.; Rodriguez-Gallego, C.; Sologuren, I.; Jakubkiene, V.; Slutsky, A. S.; Padron, J. M.; Villar, J. *PLOS ONE* **2012**, *7*, e48468. http://dx.doi.org/10.1371/journal.pone.0048468
19. Jakubkiene, V.; Burbuliene, M. M.; Udrenaite, E.; Garaliene V.; Vainilavicius, P. *Pharmazie* **2002**, *57*, 610.
20. Vainilavicius, P.; Smicius, R.; Jakubkiene, V.; Tumkevicius, S. *Monatsh. Chem*. **2001**, *132*, 825.
21. Zanirato, P. *Arkivoc* **2009**, *(i)*, 97.
22. Dogan, S. D.; Demirpolat, E.; Aycan, M .B. Y.; Balci, M. *Tetrahedron* **2015**, *71*, 252. http://dx.doi.org/10.1016/j.tet.2014.11.057
23. Ergun, M.; Dengiz, C.; Ozer, M. S.; Sahin, E.; Balci, M.; *Tetrahedron* **2014**, *70*, 5993.

24. Danielli, F.; Zanirato, P. *Arkivoc* **2000**, *(i)*, 58.
25. Fidesser, E.; Haider, N.; Jbara, R. *Arkivoc* **2001**, *(v)*, 133.
26. Rumi, L.; Pfleger, C.; Spurr, P.; Klinkhammer, U.; Bannwarth. *Org. Process Res. Dev.* **2009**, *13*, 747.
http://dx.doi.org/10.1021/op9000516
27. Koza, G.; Ozcan, Z.; Sahin, E.; Balci, M. *Tetrahedron* **2009**, *65*, 5973.
http://dx.doi.org/10.1016/j.tet.2009.05.090
28. Kuodis, Z.; Rutavičius, A.; Matijoška, A.; Eicher-Lorka, O. *Cent. Eur. J. Chem.* **2007**, *5*, 996.
http://dx.doi.org/10.2478/s11532-007-0043-7
29. Palla, G.; Predieri, G.; Domiano, P.; Vignali, C.; Turner, W. *Tetrahedron* **1986**, *42*, 3649.
http://dx.doi.org/10.1016/S0040-4020(01)87332-4
30. Vainilavicius, P.; Sedereviciute, V. *Khim. Geterotsikl. Soedin.* **1987**, 1520.
31. Jakubkiene, V.; Kacnova, Z.; Burbuliene, M. M.; Vainilavicius, P. *J. Heterocyclic Chem.* **2008**, *45*, 1391.
http://dx.doi.org/10.1002/jhet.5570450522

