# PYRIMIDINE AND FURO[2,3-*d*]PYRIMIDINE DERIVATIVES: SYNTHESIS, CYTOSTATIC AND ANTIBACTERIAL EVALUATIONS


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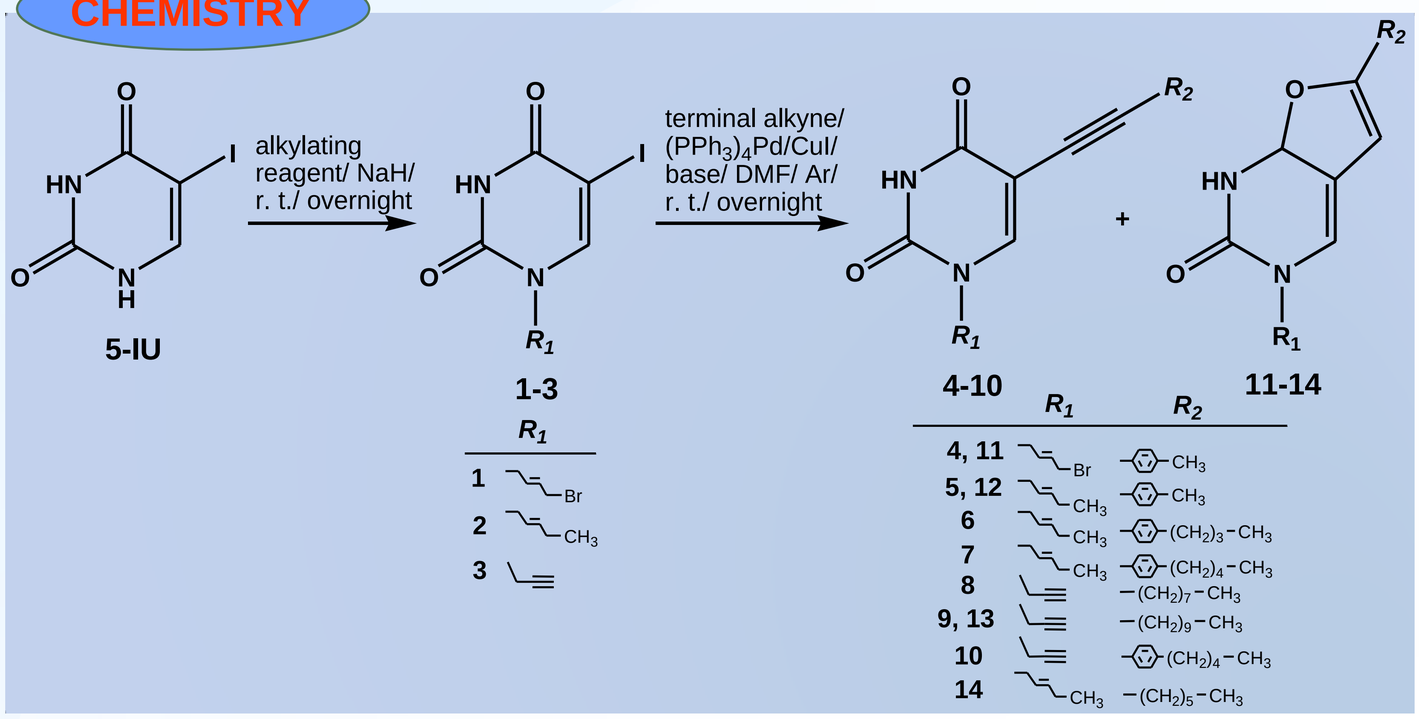
## INTRODUCTION

Furo[2,3-*d*]pyrimidines are purinomimetics which were subjected to biological investigations to assess their potential therapeutic usefulness. Furopyrimidines attract considerable attention due to their great practical significance through exerting pharmacological potential as antiviral, antimicrobial, and antitumor agents, and is one of the most recently explored scaffolds to have potential anticancer activity through inhibition of various protein kinases.[1] Furthermore, it was found that some 1,2,3-triazole tethered pyrimidines and furopyrimidines showed pronounced antiviral and cytostatic activity.[2] In continuation of our efforts towards the fused pyrimidines [3,4] we prepared C-5 alkynylated pyrimidines and C-6-alkylated furo[2,3-*d*]pyrimidines substituted at *N*-1 or *N*-3 with butenyl, propargyl and 1,2,3-triazolyl substituents.

## CHEMISTRY




| | $R_1$ |
|---|---|
| 1 | $CH_2$–C≡C–Br |
| 2 | $CH_2$–C≡C–$CH_3$ |
| 3 | $CH_2$–C≡CH |

| | $R_1$ | $R_2$ |
|---|---|---|
| 4, 11 | $CH_2$–C≡C–Br | $C_6H_4$–$CH_3$ |
| 5, 12 | $CH_2$–C≡C–$CH_3$ | $C_6H_4$–$CH_3$ |
| 6 | $CH_2$–C≡C–$CH_3$ | $C_6H_4$–$(CH_2)_3$–$CH_3$ |
| 7 | $CH_2$–C≡C–$CH_3$ | $C_6H_4$–$(CH_2)_4$–$CH_3$ |
| 8 | $CH_2$–C≡CH | –$(CH_2)_7$–$CH_3$ |
| 9, 13 | $CH_2$–C≡CH | –$(CH_2)_9$–$CH_3$ |
| 10 | $CH_2$–C≡CH | $C_6H_4$–$(CH_2)_4$–$CH_3$ |
| 14 | $CH_2$–CH=CH–$CH_3$ | –$(CH_2)_5$–$CH_3$ |

| | $R_1$ |
|---|---|
| 15 | H |
| 16 | $CH_2$–$C_6H_5$ |
| 17 | $C_6H_4$–F |
| 18 | $C_6H_4$–Cl |
| 19 | $C_6H_4$–$CF_3$ |

| | $R_1$ | $R_2$ |
|---|---|---|
| 20 | $CH_2$–$C_6H_5$ | $C_6H_4$–$CH_3$ |
| 21 | $CH_2$–$C_6H_5$ | $C_6H_4$–$(CH_2)_4$–$CH_3$ |
| 22, 26 | $C_6H_4$–F | –$(CH_2)_9$–$CH_3$ |
| 23, 27 | $C_6H_4$–Cl | $C_6H_4$–$CH_3$ |
| 24 | $C_6H_4$–$CF_3$ | $C_6H_4$–$CH_3$ |
| 25, 28 | $C_6H_4$–$CF_3$ | 3,5-difluorophenyl |

## CYTOSTATIC EVALUATION

Cytostatic evaluations of *N*-1-butenyl, propargy or 1,2,3-triazolyl and/or C-5 substituted uracil and C-6 alkylated furo[2,3-*d*]pyrimidine derivatives were performed on the growth of human cervix adenocarcinoma (HeLa), colon adenocarcinoma (CaCo-2), chronic myeloid leukemia in blast crisis (K562), Burkitt lymphoma (Raji), and on the normal Madin Darby canine kidney (MDCK I) cells as well.

| *compd.* | $^{a}IC_{50}$(μmol dm$^{-3}$) | | | | |
|---|---|---|---|---|---|
| | HeLa | CaCo-2 | MDCK1 | K562 | Raji |
| **1** | > 100 | > 100 | > 100 | > 100 | > 100 |
| **2** | > 100 | > 100 | > 100 | > 100 | 77 |
| **8** | > 100 | > 100 | > 100 | 100 | 72 |
| **9** | > 100 | > 100 | > 100 | > 100 | 95 |
| **10** | > 100 | > 100 | > 100 | > 100 | 81 |
| **11** | > 100 | > 100 | 100 | 100 | 100 |
| **12** | > 100 | > 100 | > 100 | > 100 | 71 |
| **15** | > 100 | > 100 | - | 42 | 100 |
| **16** | > 100 | > 100 | - | 100 | > 100 |
| **20** | 37 | - | - | - | 39 |
| **21** | 100 | > 100 | > 100 | 13 | 15 |
| **23** | > 100 | > 100 | - | > 100 | >100 |
| **24** | > 100 | > 100 | 99 | 46 | 85 |
| **25** | > 100 | > 100 | > 100 | **8.4** | 61 |
| **26** | > 100 | > 100 | - | 65 | 87 |
| **27** | > 100 | > 100 | - | 100 | >100 |
| **28** | > 100 | > 100 | > 100 | 64 | **7.9** |

$^{a}IC_{50}$ –Concentration that inhibited cell growth by 50%. Exponentially growing cells were treated with substances during 72-hrs period. Cytotoxicity was analysed using MTT survival assay.

## ANTIBACTERIAL EVALUATION

Inhibitory effects of uracil and furo[2,3-*d*]pyrimidine derivatives were investigated on the growth of gram positive and gram negative bacterial strains.

| *compd.* | MIC (μg/ ml) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Gram positive bacterial strains | | | | Gram negative bacterial strains | | | |
| | *Staphylococcus aureus* ATCC 25923 | *Enterococcus faecalis* | *Staphylococcus aureus* | VRE[a] | *Pseudomonas aeurigonsa* ATCC 27853 | *Escherichia coli* ATCC 25925 | *Acinetobacter baumannii* ATCC 19606 | *Klebsiella pneumoniae* ESBL strain[b] |
| **2** | >256 | >256 | >256 | >256 | >256 | >256 | >256 | >256 |
| **8** | 256 | 128 | 256 | 256 | 256 | >256 | 128 | >256 |
| **9** | 256 | 128 | 256 | 128 | 256 | >256 | 128 | >256 |
| **12** | >256 | 256 | >256 | >256 | >256 | >256 | >256 | >256 |
| **20** | >256 | **8** | >256 | >256 | >256 | >256 | >256 | >256 |
| **21** | >256 | >256 | >256 | >256 | >256 | >256 | >256 | >256 |
| **23** | >256 | 128 | >256 | 256 | >256 | >256 | 256 | >256 |
| **24** | >256 | 128 | >256 | >256 | >256 | >256 | 256 | >256 |
| **25** | >256 | >256 | >256 | >256 | >256 | >256 | >256 | >256 |
| **26** | >256 | 256 | >256 | 256 | >256 | >256 | 256 | >256 |
| **27** | >256 | 256 | 256 | >256 | >256 | >256 | 256 | >256 |
| **28** | >256 | 128 | >256 | >256 | 256 | >256 | 256 | >256 |
| **CAZ[c]** | 1 | 1 | 1 | 1 | 1 | - | - | - |
| **CIP[d]** | 0.125 | 0.125 | 0.125 | 0.125 | 0.125 | - | - | - |

*Minimal inhibitory concentration; [a]VRE – vancomycin-resistant *Enterococcus faecium;* [b]ESBL – extended spectrum beta-lactamase = resistant strains; [c]CAZ – ceftazidime; [d]CIP – ciprofloxacin.

## CONCLUSION

C-5 alkynylated pyrimidines (4-10) substituted at *N*-1 with butenyl or propargyl were synthesised by Sonogashira cross-coupling reaction of *N*-1 substituted pyrimidines (1-3) with corresponding alkynes under both conventional and microwave conditions, in good to excellent yields. The 5-*endo-dig* cyclisation of C-5-alkynylpyrimidine derivatives (4-10) afforded the corresponding furo[2,3-*d*]pyrimidines (11-14) in good yields. Cu(I)-catalyzed 'click' reaction under microwave irradiation was adopted in the synthesis of regioselective 1,4- disubstituted 1,2,3-triazole pyrimidine derivatives (15-19) while post-Sonogashira reaction with terminal alkynes afforded both C-5 alkynylated (20-25) and furo[2,3-*d*]pyrimidine (26-28) derivatives. Of all evaluated compounds pyrimidine (25) and furo[2,3-d]pyrimidine (28) derivatives with 3,5-difluorophenyl at C-5 and *p*-trifluoromethylphenyl at 1,2,3-triazole showed the strongest effect at micromolar concentrations on the growth of K562 and Raji tumor cells, respectively.

## References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