Synthesis of 6-oxopyrimidin-1(6H)-yl benzamide derivatives and evaluation of their antibacterial and cytotoxic activity

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ABSTRACT
A series of novel 2-alkylamino and 2, 4-dialkyl amino 6-oxopyrimidin-1(6H)-yl) benzamide derivatives were prepared in good yields from a base-catalyzed ring opening of oxadiazolo[3,2-a]pyrimidin-5-one and evaluated for their antibacterial and cytotoxicity. Most of the compounds exhibited antibacterial activity. In particular, compounds 5b and 5k exhibited considerable antibiotic activity against Klebsiella pneumoniae and Bacillus cereus. In addition, compounds 5g and 5i also inhibited the growth of two human tumor cell lines (A549 and H460) at micromolar concentrations.

GRAPHICAL ABSTRACT

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Introduction
Pyrimidine is a prominent pharmacophore prevailing in many heterocyclic natural products.[1] Pyrimidines and their derivatives have a long and distinguished history extending from the days of their discovery as important constituents of nucleic acids (like uracil, cytocine, and thymine) to their current use in the chemotherapy of AIDS. During the past two decades, several pyrimidine derivatives were found to have widespread clinical applications including chemotherapy. There are a large number of pyrimidine-based antimetabolites, which act as antagonists of endogenous substrates. The structural modification may be either on the pyrimidine ring or on the pendant sugar group. Lamivudine[2] is one of the examples which acts as an effective anti-AIDS drug when used in combination with zidovudine (Fig. 1).
Likewise, there are several pyrimidone-based marketed drugs such as Uramustine,[3] Tegafur,[4] Fluorouracil[5] (antineoplastic), Flucytosine[6] (antifungal), and Idoxuridine[7] (antiviral) (Fig. 2). In addition, analgesic,[8] anticancer,[9] antioxidant,[10] antibacterial,[11] antiviral,[12] anti-inflammatory,[13] antiplatelet,[14] antiproliferative,[15] and antitumor[16] activities were reported for pyrimidine-based derivatives.

In the course of our research devoted to the development of a new class of pyrimidine and condensed pyrimidine moieties, we have focused on the synthesis and biological evaluation of several 6-oxopyrimidin-1(6H)-yl benzamide derivatives, which may show promising antibacterial and cytotoxic activities. In particular, condensed pyrimidine[17] derivatives possessing anti-inflammatory and analgesic activities are well documented in the literature.[18] This background of pyrimidine-based derivatives motivated us to synthesize the titled derivatives for their biological evaluation.

There is an extensive work reported on nucleophilic displacement followed by rearrangement of electron-poor five-membered systems such as 1,3,4-oxadiazoles,[19] 1,3,4-thiadiazoles,[20] nitroimidazoles,[19,21] bis(1,3,4-thiadiazol-2-yl)-1,3,5-triazinium halides,[22] isothiazole,[23] and isoxazoles.[24] Pace et al.[25] studied the addition of nucleophile, ring-opening, and ring-closure (ANORC) rearrangements of 1,2,4-oxadiazoles as a valid approach for the obtaining heterocycles such as 1,2,4-triazoles,[25] 1,2,4-oxadiazoles,[26] 1,2,4-triazines,[25b,27] 1,2,4-oxadiazinones,[28] indazoles,[29] and amino-1,2,4-triazoles.[25]
Taking advantage of the literature precedence, we intended to derive 2-alkylamino 6-oxopyrimidin-1(6H)-yl benzamide derivatives (6a–k) by nucleophilic displacement on oxadiazolo[3,2-a]pyrimidin-5-one (2).

In this article, we report the synthesis of a new class of 2-alkylamino and 2, 4-dialkyl amino 6-oxopyrimidin-1(6H)-yl benzamide derivatives by using base-mediated ring opening of oxadiazolo[3,2-a]pyrimidin-5-one using dimethylformamide (DMF) as solvent. The title compounds were subjected to in vitro antibacterial and cytotoxicity studies to examine the relationship between structural modifications and biological activity. Compounds 5a–k and 6a–k showed significant antibacterial activity in comparison to streptomycin, a first-line antibiotic drug. In addition, compounds 5g, 5i, and 5k showed significant cytotoxicity activity in comparison to puromycin, an amino-nucleoside antibiotic derived from the Streptomyces alboniger bacterium.

**Results and discussion**

**Chemistry**

In this study previously reported oxadiazole\(^{[30]}\) was converted into new 2-alkylamino and 2,4-dialkyl amino 6-oxopyrimidin-1(6H)-yl benzamide derivatives (5a–k and 6a–k). The synthesis of oxadiazole (1) was achieved by reaction of ethyl 4-bromobenzoate with hydrazine hydrate in ethanol to give hydrazide, which upon subsequent reaction with cyanogen bromide in ethanol furnished oxadiazole (1) in 72% yield (over two steps). For conversion of oxadiazole (1) into pyrimidin-5-one (2), the required bis(1,3,5-trichloro phenyl) malonate reagent was prepared in 85% yield using a literature protocol by treating malonic acid with 2,4,6-trichlorophenol in phosphorous oxychloride. Oxadiazole (1) on reaction with bis (1,3,5-trichloro phenyl) malonate in chlorobenzene under reflux provided 2-(4-bromophenyl)-7-hydroxy-5H-[1,3,4]oxadiazolo[3,2-a]pyrimidin-5-one (2) in 92% yield.\(^{[31]}\) The pyrimidin-5-one 2 was subjected to chlorination using phosphorous oxychloride to obtain chloro derivative 3 in 94% yield (Scheme 1), which served as a synthetic precursor for the preparation of titled derivatives.

We wanted to evaluate the feasibility of ring opening of chloro derivative 3 by a reactive secondary amine such as morpholine by screening different bases (triethyl amine [TEA], diisopropylethyl amine [DIPEA], and 1,8-diazabicyclo[5.4.0]undec-7-ene [DBU]) in combination with different solvent systems at different temperature conditions. In an ethanolic solvent system, room temperature reaction with TEA (Table 1, entry 1) and reflux condition with DIPEA (entry 2) gave poor yields (entries 1 and 2). A dichloromethane (DCM) solvent system with DBU provided moderate yield (entry 3), whereas

![Scheme 1. Synthesis of key intermediate 3.](image-url)
in the DMF solvent system, room-temperature reaction with K₂CO₃ (entry 4) (Scheme 2) gave good yields in a relatively shorter time (2 h).

Based on optimized conditions (Table 1, entry 4) for ring-opening reaction of chloro derivative (3) with morpholine (4a), similar reaction was attempted with different amines (4b–k) (Table 2).

In addition, ring opening of chloro derivative (3) was attempted with excess amines (4a–k) in dimethylsulfoxide (DMSO) at 90 °C for 16 h to get 2,4-dialkyl amino 6-oxopyrimidin-1(6H)-yl) benzamide derivatives (6a–k) (Scheme 3, Table 3).

### Biological activity

**Antibacterial activity**
The antibacterial activities of compounds 5a–i and 6a–i were assessed and compared against Streptomycin using the agar well diffusion method. The antibacterial activity was assayed by measuring the diameter of the inhibition zone. About 1 mg ml⁻¹ of the test compounds (5a–k and 6a–k) and 1 mg ml⁻¹ of Streptomycin (control) were dispensed into the wells. The plates were incubated at 37 °C for 24 h. The sensitivity of the test organisms to the compounds (5a–k and 6a–k) was determined by measuring the diameters of the zone of inhibition surrounding the wells. The diameters of the zones of inhibition were measured with a ruler and indicated in Table 4.

**Cytotoxicity assay**
The synthesized compounds were tested for cytotoxicity by measuring their effect on the percentage viability of two different cell lines, adenocarcinomic human alveolar basal epithelial cells (A549) and human lung cancer cells (H460), by applying the XTT reagent. Compounds were tested over a range of concentrations from 1 mM to 0.051 μM, and the

### Table 1. Optimization of ring-opening<sup>a</sup> reaction.

| Entry | Base | Solvent | Time | Temp. (°C) | Yield<sup>b</sup> (%) |
|-------|------|---------|------|------------|------------------------|
| 1     | TEA  | EtOH    | 20 h, 16 h<sup>c</sup> | RT         | 10                     |
| 2     | DIEA | EtOH    | 16 h | Reflux     | 22                     |
| 3     | DBU  | DCM     | 16 h | RT         | 47.2                   |
| 4     | K₂CO₃| DMF     | 2 h  | RT         | 78                     |

<sup>a</sup>Reactions were carried out with 2.59 mmol of chloro derivative 3, 7.77 mmol of base and 5 mL of solvent, for the specified time period and temperature.

<sup>b</sup>Yields are calculated after purification by column chromatography.

<sup>c</sup>The reaction was carried out under reflux temperature.

**Scheme 2.** Synthesis of 2-alkylamino 6-oxopyrimidin-1(6H)-yl) benzamide derivative (5a).
Table 2. Synthesis of 2-alkylamino 6-oxopyrimidin-1(6H)-yl-benzamide derivatives using Scheme 2.

| Entry | Amine            | Product | Yield (%)<sup>a</sup> | Entry | Amine            | Product | Yield (%)<sup>a</sup> |
|-------|------------------|---------|-----------------------|-------|------------------|---------|-----------------------|
| 1     | F₃C-CH₂-NH₂      | 4b      | 76                    | 6     | CH₃-CH₂-NH₂      | 4g      | 81                    |
|       |                  |         |                       |       |                  |         |                       |
| 2     | H₂N-CH=CH₂       | 4c      | 71                    | 7     | H₂N-CH=CH₂       | 4h      | 76                    |
|       |                  |         |                       |       |                  |         |                       |
| 3     | H₂N-CH₃          | 4d      | 72                    | 8     | CH₃              | 4i      | 78                    |
|       |                  |         |                       |       |                  |         |                       |
| 4     | H₂N=CH₂          | 4e      | 82                    | 9     | CH₂-CH₂-NH₂      | 4j      | 79                    |
|       |                  |         |                       |       |                  |         |                       |
| 5     | H₂N=cyclohexyl   | 4f      | 74                    | 10    | CH₂-CH₂-NHBoc    | 4k      | 85<sup>b</sup>        |

<sup>a</sup>Yields are calculated after purification by column chromatography.
<sup>b</sup>See Ref 34.
calculated IC_{50} values (i.e., the concentration (μM) of compounds able to cause 50% of cell death with respect to the control culture) are reported in Table 5. Result shows that few compounds inhibited the growth of human cancer cell lines with IC_{50} values in the micro-molar range. Compound 5g with longer and bulky side chain showed significant activity (IC_{50} 0.4 μM) against the A549 cell line, the lipophilic group containing 5i and 5k showed moderate inhibition against the A549 cell line, and 5k, 5g, and 5i showed moderate activity against the H460 cell line compared to puromycin. Compounds with apolar and shorter side chains were less active (IC_{50} about 10-fold higher).

From the cytotoxic activity results of 2-alkylamino 6-oxopyrimidin-1(6H)-yl benzamide derivatives (5) on human lung carcinoma cell sublines, it was observed that the better results were shown by 5g and 5i. Thus the compounds 5g and 5i were assayed for cytotoxic activity against nontumoral mammalian cell lines MDCK and Vero cells. Compound 5g has shown IC_{50} values of 29.4 μM on MDCK and 38.3 μM on Vero cells when compared with standard Puromycin, having IC_{50} values of 0.29 μM for MDCK and 0.57 μM for Vero cells, whereas 5i did not show any cytotoxicity on both the tested cell lines. The results were analyzed using the Graph Pad Prism4 program (Fig. 3).

The A549 and H460 cell lines were maintained in Ham’s F12k and RPMI media supplemented with 10% FBS and 1% antibiotics (100 U/mL penicillin, 100 μg/mL streptomycin) respectively. The cells were grown at 37 °C in a humidified incubator with 5% CO_{2}. Cells were subcultured by treating them with cell dissociation buffer. Both cell lines were seeded in a 96-well microtiter plate at a concentration of 7500 cells per well. Cells were allowed to attach for 24 h at 37 °C, 5% CO_{2}. The cells were exposed to the test compounds and positive drug control, Puromycin (SIGMA). The microtiter plate was incubated for further 72 h and thereafter cytotoxicity was measured using the XTT (Invitrogen) reagent (1 mg/ml XTT and 7.7 μg/ml phenazine methosulfate in PBS). The plates were incubated for 2 to 4 h and absorbance was read at 450 nm using a Spectra Max multimode microplate reader (Molecular Devices). The results were analyzed using the Graph Pad Prism4 program (Fig. 3).

**Experimental**

Analytical grade solvents and commercially available reagents were used without further purification. The column chromatography was carried over silica gel (60–120 mesh), purchased from Sisco Research Laboratories Pvt. Ltd. Melting points were determined in open capillaries in an electrical melting-point apparatus and are uncorrected. 1H NMR and 13C NMR spectra were recorded on a 400-MHz Varian spectrometer in dimethylsulfoxide (DMSO-d_6) or CDCl_3 using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in δ relative to TMS; the coupling constants are given in Hz. Infrared
| Entry | Amine | Product | Yield (%)<sup>a</sup> | Entry | Amine | Product | Yield (%)<sup>a</sup> |
|-------|-------|---------|----------------------|-------|-------|---------|----------------------|
| 1     | ![4a](image) | ![6a](image) | 77                   | 7     | ![4g](image) | ![6g](image) | 62                   |
| 2     | ![4b](image) | ![6b](image) | 76                   | 8     | ![4h](image) | ![6h](image) | 75                   |
| 3     | ![4c](image) | ![6c](image) | 70                   | 9     | ![4i](image) | ![6i](image) | 73                   |
| 4     | ![4j](image) | ![6d](image) | 69                   | 10    | ![4j](image) | ![6j](image) | 73                   |

(Continued)
| Entry | Amine | Product      | Yield (%)<sup>a</sup> | Entry | Amine | Product      | Yield (%)<sup>a</sup> |
|-------|-------|--------------|------------------------|-------|-------|--------------|------------------------|
| 5     | ![Image](image1.png) | ![Image](image2.png) | 82                     | 11    | ![Image](image3.png) | ![Image](image4.png) | 83<sup>b</sup>         |
| 6     | ![Image](image5.png) | ![Image](image6.png) | 79                     |       |       |              |                        |

<sup>a</sup>Yields are calculated after purification by column chromatography.

<sup>b</sup>See Ref 34.
(IR) spectra in KBr disk were recorded from 4000 to 400 cm\(^{-1}\) on an Avatar 330 FT-IR spectrometer equipped with DTGS detector. Mass spectra were recorded using an Agilent 1100 MSD spectrometer in electrospray mode. The starting compound 1 was prepared by previously reported direct cyclization of 4-bromobenzohydrazide and cyanogen bromide.

**General procedure for the preparation of 5-substituted 2-(4-bromophenyl)-7-chloro-5H-[1,3,4]oxadiazolo[3,2-a]pyrimidin-5-ol (5a–i)**

The mixture of 2-(4-bromophenyl)-7-chloro-5H-[1,3,4]oxadiazolo[3,2-a]pyrimidin-5-one 3 (0.5 g, 1.53 mmol), potassium carbonate (0.63 g, 4.59 mmol) and the appropriate amine 4 (1.53 mmol) in dimethylformamide (5 mL) was stirred at room temperature for 2–16 h. The completion of the reaction was indicated by thin-layer chromatography (TLC), the

| Compound | Escherichia coli | Proteeus vulgaris | Salmonella paratyphi | Klebsiella pneumonia | Staphylococcus aureus | Bacillus cereus |
|----------|-----------------|------------------|---------------------|---------------------|----------------------|----------------|
| 5a       | 7               | 2                | 5                   | 4                   | 3                    | 6              |
| 5b       | 3               | 8                | 7                   | 14                  | 8                    | 14             |
| 5c       | 2               | 4                | 6                   | 11                  | 6                    | 12             |
| 5d       | 2               | 5                | 5                   | 8                   | 4                    | 10             |
| 5e       | 2               | 3                | 3                   | 2                   | 6                    | 8              |
| 5f       | 2               | 4                | 4                   | 2                   | 6                    | 8              |
| 5g       | 2               | 3                | 2                   | 2                   | 4                    | 2              |
| 5h       | 2               | 2                | 2                   | 10                  | 3                    | 5              |
| 5i       | 5               | 7                | 4                   | 6                   | 2                    | 6              |
| 5j       | 1               | 2                | 2                   | 12                  | 1                    | 10             |
| 5k       | 7               | 2                | 15                  | 13                  | 7                    | 10             |
| 6a       | 3               | 7                | 9                   | 10                  | 7                    | 10             |
| 6b       | 2               | 2                | 1                   | 4                   | 3                    | 5              |
| 6c       | 1               | 4                | 3                   | 5                   | 3                    | 5              |
| 6d       | 1               | 2                | 2                   | 4                   | 4                    | 8              |
| 6e       | 5               | 4                | 3                   | 10                  | 4                    | 8              |
| 6f       | 4               | 7                | 4                   | 6                   | 3                    | 10             |
| 6g       | 2               | 5                | 4                   | 7                   | 4                    | 10             |
| 6h       | 5               | 3                | 2                   | 12                  | 3                    | 9              |
| 6i       | 2               | 4                | 6                   | 10                  | 4                    | 11             |
| 6j       | 2               | 5                | 2                   | 9                   | 2                    | 7              |
| 6k       | 8               | 2                | 5                   | 10                  | 5                    | 6              |

Streptomycin
(1 mg / 1 mL)

| Compound | Diameter of inhibition (mm) |
|----------|-----------------------------|
| 5a–i     |                             |
| 6a–i     |                             |

Table 4. Antimicrobial activity of the synthesized compounds 5a–i and 6a–i.

Table 5. Cytotoxic activity of 5a–i and 6a–i against human lung carcinoma cell sublines.

| Compound | A549 | H460 | Compound | A549 | H460 |
|----------|------|------|----------|------|------|
| 5a       | >100 | 91   | 6a       | >100 | 94   |
| 5b       | 88   | 93   | 6b       | 95   | >100 |
| 5c       | >100 | >100 | 6c       | >100 | >100 |
| 5d       | >100 | >100 | 6d       | >100 | >100 |
| 5e       | 84   | 91   | 6e       | 88   | 92   |
| 5f       | >100 | 94   | 6f       | >100 | 95   |
| 5g       | 0.4  | 23   | 6g       | 84   | 88   |
| 5h       | >100 | >100 | 6h       | >100 | >100 |
| 5i       | 82   | >100 | 6i       | 92   | >100 |
| 5k       | >100 | >100 | 6k       | >100 | >100 |
| 5j       | 14   | 15   | 6k       | 86   | 94   |

Puromycin (1 mg / 1 ml) 0.387 0.281
solvent was evaporated, residue was poured into water, and the precipitate that formed was filtered off, washed with water, and then purified by flash column chromatography using hexane and ethyl acetate to give the corresponding oxadiazolo[3,2-a]pyrimidin-5-ol derivative (5).

**General procedure for the preparation of 5,7-disubstituted 2-(4-bromophenyl)-5H-[1,3,4]oxadiazolo[3,2-a]pyrimidin-5-ol (6a–k)**

The mixture of 2-(4-bromophenyl)-7-chloro-5H-[1,3,4]oxadiazolo[3,2-a]pyrimidin-5-one 3 (0.5 g, 1.53 mmol) and the appropriate amine (4) (7.65 mmol) in dimethylsulfoxide (5 mL) was stirred at 90 °C for 16 h. The completion of the reaction was indicated by TLC. The reaction mixture was poured into water, and the precipitate that formed was filtered off, washed with water, and then purified by flash column chromatography using hexane and ethyl acetate to give the corresponding oxadiazolo[3,2-a]pyrimidin-5-ol derivative (6).

**Conclusion**

In conclusion, we have synthesized the 2-alkylamino 6-oxopyrimidin-1(6H)-yl) benzamide (5a–k) and 2, 4-dialkyl amino 6-oxopyrimidin-1(6H)-yl) benzamide derivatives (6a–k).
The compounds 5a–k and 6a–k exhibited very good antibacterial activity against both Gram-positive and Gram-negative bacteria in comparison to Streptomycin, a first-line antibiotic drug (Table 4). Compounds 5g, 5i, and 5k showed potent cytotoxicity activity. The structure and biological activity relationship of title compounds showed that the presence of pyrimidone nuclei and amino guanidine skeleton, as well as biologically active aminoethyl cyclohexane, morpholine, piperidine, 3-aminopyrrolidine, dimethyl amine, and 2,2,2-trifluoroethylamine groups attached to the pyrimidone ring, are responsible for good antibacterial activity and cytotoxic activity. Based on these results, new compounds are being synthesized by keeping pyrimidone nuclei with suitable substituents for their cytotoxicity activity and will be reported in due course.

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For compounds 5 K and 6 K: A solution of Boc compound in 1,4-dioxane (10 vol) was added to 4 N HCl in dioxane (5 vol) at room temperature under N₂ atmosphere and the reaction mixture was stirred at room temperature for 16 h. Solvent was evaporated under reduced pressure and triturated with diethyl ether to afford corresponding amines in quantitative yields.

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