Synthesis of new peptidyl- and glycosylpyrimidine derivatives

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A new series of 2-*N*-(phthalyl- or tosylamino acid)pyrimidines have been synthesised from the coupling of pyrimidine derivatives with phthalyl- or tosylamino acids. Hydrazinolysis of 2-*N*-phthalyl derivatives afforded unprotected amino acid derivatives. New derivatives of peptidylpyrimidines have been synthesised from the reaction of pyrimidine derivatives with α-amino acids methyl ester hydrochloride *viz* different routes. Also, new glycosides have been prepared from the reaction of pyrimidine derivatives with α-D-glucopyranosyl bromide. Most of the synthesised compounds showed a significant antimicrobial activity.

Keywords: pyrimidines, α-amino acids, peptidylpyrimidines, glycosides, antimicrobial activity

Nitrogen-containing heterocyclic compounds have displayed a broad spectrum of biological effects. Within the synthesis of heterocyclic *N*-containing compounds, pyrimidine and its derivatives attracted considerable attention as they are often present in biologically active compounds and there are many examples of biological activities found for small molecules based on pyrimidine moiety.[1–5] They are of great importance in the fundamental metabolism for uracil, thiamine and cytosine, which are three bases found in the nucleotide. Hence pyrimidine bases play significant role in vital biochemical process for humans and animals.[6–10]

α-Amino acids and their esters have been reported to be biologically active as anticancer agents,[11] pseudo analogues of the naturally occurring antibiotic sparsomycin,[12] chromogenic substrates of proteolytic enzymes,[13] rat kidney enzyme inhibitors,[14] and inhibitors of mammalian collagenase.[15] Also, it is used as intermediate in the synthesis of prodrugs for cancer treatment,[16] the antibiotic reutericyclin[17] and cell adhesive agents used for the synthesis of cyclic peptides.[18] Glycosides extensively exist in animals and plants and take on an important biological function.[19] Significant antibacterial and anticancer activities of glycosides have attracted many workers to attempt to improve the biological activity of these compounds by the glycosylation in order to increase their solubility in water and guidance quality.[20–22] Guided by the above observations, and in continuation of our interest in the synthesis of heterocycles of medical applications,[23–25] we report here a convenient synthesis of new pyrimidine derivatives conjugated with flexible amino acids and glycosyl moiety as side chains hoping that the produced compounds will have improved biological potential.

Results and discussion

The reaction of 3-(3-nitrophenyl)-1-(phenoxathiin-2-yl)-propenone (**1**) with urea and/or thiourea in ethanolic sodium ethoxide solution, afforded the key precursor pyrimidine derivatives **2a,b**. The structures of compounds **2a,b** were established on the basis of its elemental analysis and spectral data (Scheme 1).

The coupling of compounds **2a** and/or **2b** with N-phthalyamino acids and N-tosylamino acids *viz* glycine, DL-alanine and DL-phenylalanine in the presence of *N,N′*-dicyclohexylcarbodiimide (DCC) as the condensing agent[26,27] in a one-step reaction at room temperature, yielded 2-*N*-(phthalyl- glycyl, DL-alanyl or DL-phenylalanyl)pyrimidines **3a–f** and 2-*N*-(tosyl-glycyl, DL-alanyl or DL-phenylalanyl) pyrimidines **4a–f**, respectively.

Hydrazinolysis of *N*-phthalyl derivatives **3a–f** with an ethanolic solution of hydrazine hydrate furnished 4-(3-nitrophenyl)-6-(phenoxathiin-2-yl)-2-(glycyl-, DL-alanyl- or DL-phenylalanyl)oxy- or mercaptopyrimidines (**5a–f**), Scheme 1. On the other hand, the reaction of pyrimidine derivative **2a** and chloroacetic acid in methanolic sodium methoxide solution gave [4-(3-nitrophenyl)-6-(phenoxathiin-2-yl)pyrimidin-2-yloxy]acetic acid (**6**), Scheme 2.

Refluxing of compound **6** with thionyl chloride on a water bath for 2h gave pyrimidinyloxyacetyl chloride **7a**, which was *in situ* treated with sodium azide[28] to yield the corresponding pyrimidinyloxyacetyl azide **7b**. Recently, there has been a growing interest in the synthesis of peptides for medicinal applications.[29–31] Promoted by this fact, we report here the synthesis of new peptidylpyrimidine derivatives for increasing the bioactivity of the synthesised compounds. Thus, the condensation of compound **6** with α-amino acids methyl ester hydrochloride in presence of tetrahydrofuran containing DCC afforded the corresponding pyrimidinylamino acid derivatives **8a–c**, which can also be obtained *viz* two other routes:

(1) Condensation of pyrimidinyloxyacetyl chloride **7a** with the same α-amino acids methyl ester hydrochloride in dioxane containing triethylamine.
(2) Condensation of pyrimidinyloxyacetyl azide **7b** with the same α-amino acids methyl ester hydrochloride.[32]

Hydrazinolysis of methyl {2-[4-(3-nitrophenyl)-6-(phenoxathiin-2-yl)pyrimidin-2-yloxy]acetylamino}acetate (**8a**) in ethanol gave the corresponding acid hydrazide **9**. The diazotisation of **9** in acidic medium afforded the corresponding acid azide **10**, which coupled with the same α-amino acids methyl ester hydrochloride to give the corresponding dipeptide derivatives **11a–c**. Finally, the reaction of pyrimidine derivatives **2a,b** with 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl bromide in ethanol containing potassium hydroxide afforded the corresponding glycoside derivatives **12a,b** (Scheme 2). The structures of the synthesised compounds were assigned on the basis of elemental analysis and spectral data. (*cf*. experimental)

Antimicrobial activity

The antimicrobial activity of the synthesised compounds was determined *in vitro* using the hole plate and filter paper methods [33] against a variety of bacteria and fungi.

Comparative studies of our prepared compounds and standard drug were also carried out. The Gram+ve bacteria were *Bacillus subtilis*, *Rhodococcus equi*; the Gram–ve bacteria were *Escherichia coli*, *Pseudomonas aeruginosa* and the fungi were *Penicillium notatum* and *Aspergillus niger*. Ampicillin and Mycostatin were used as standard drugs for antibacterial and antifungal activity respectively. The results are illustrated in Table 1. The investigation of antibacterial and antifungal screening data revealed that all tested compounds showed moderate to good activity compared to standard drugs used. Also, the presence of tosyl group in the amino acids moiety of synthesised compounds enhanced their activities compared

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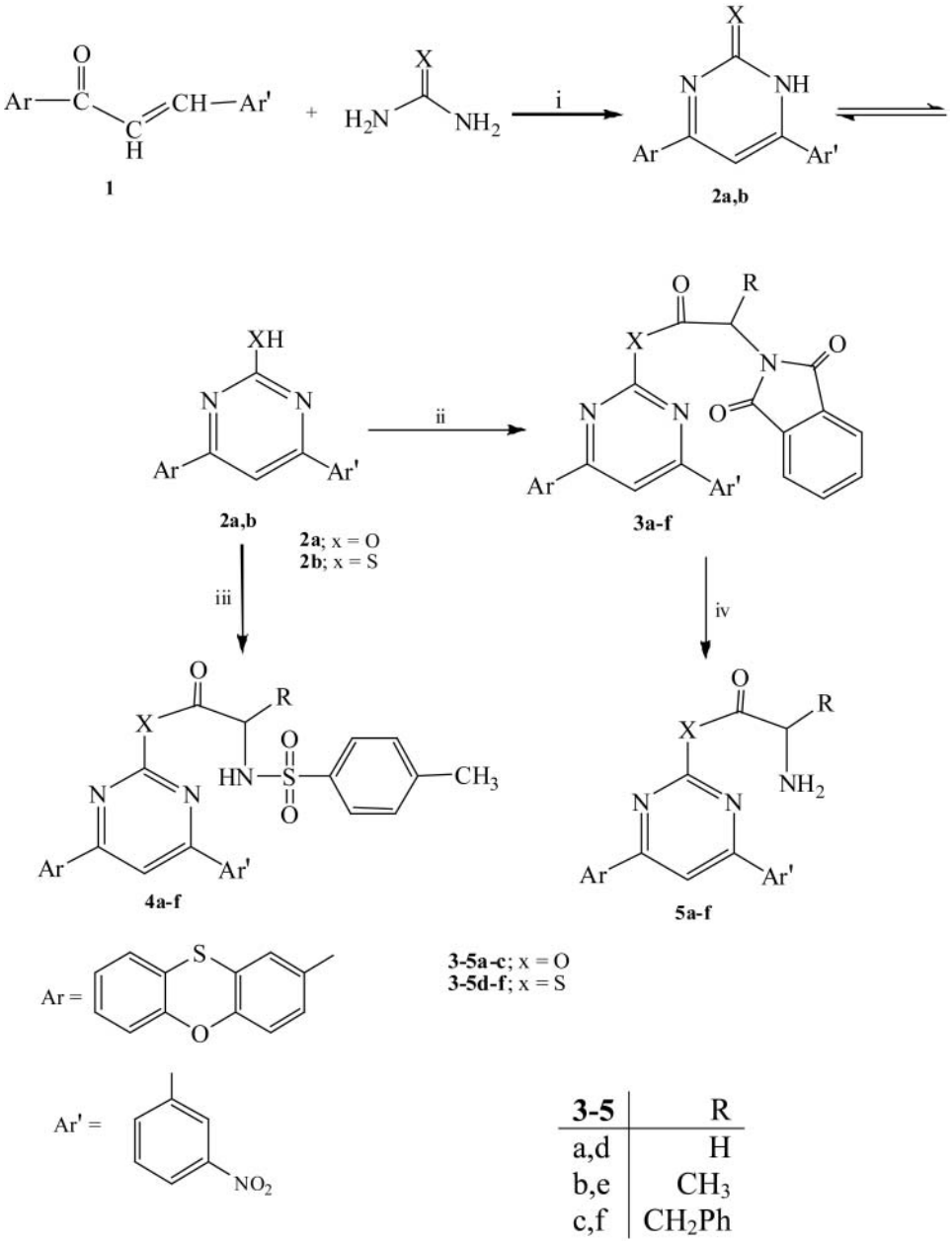


Scheme 1 (i) EtONa, reflux 8h; (ii) *N*-phthalylamino acids, DCC, THF; (iii) *N*-tosylamino acids; DCC, THF; (iv) $N_2H_4.H_2O$, EtOH.

with phthalyl group. Furthermore, the removal of the phthalyl group from compounds decreased the activities.

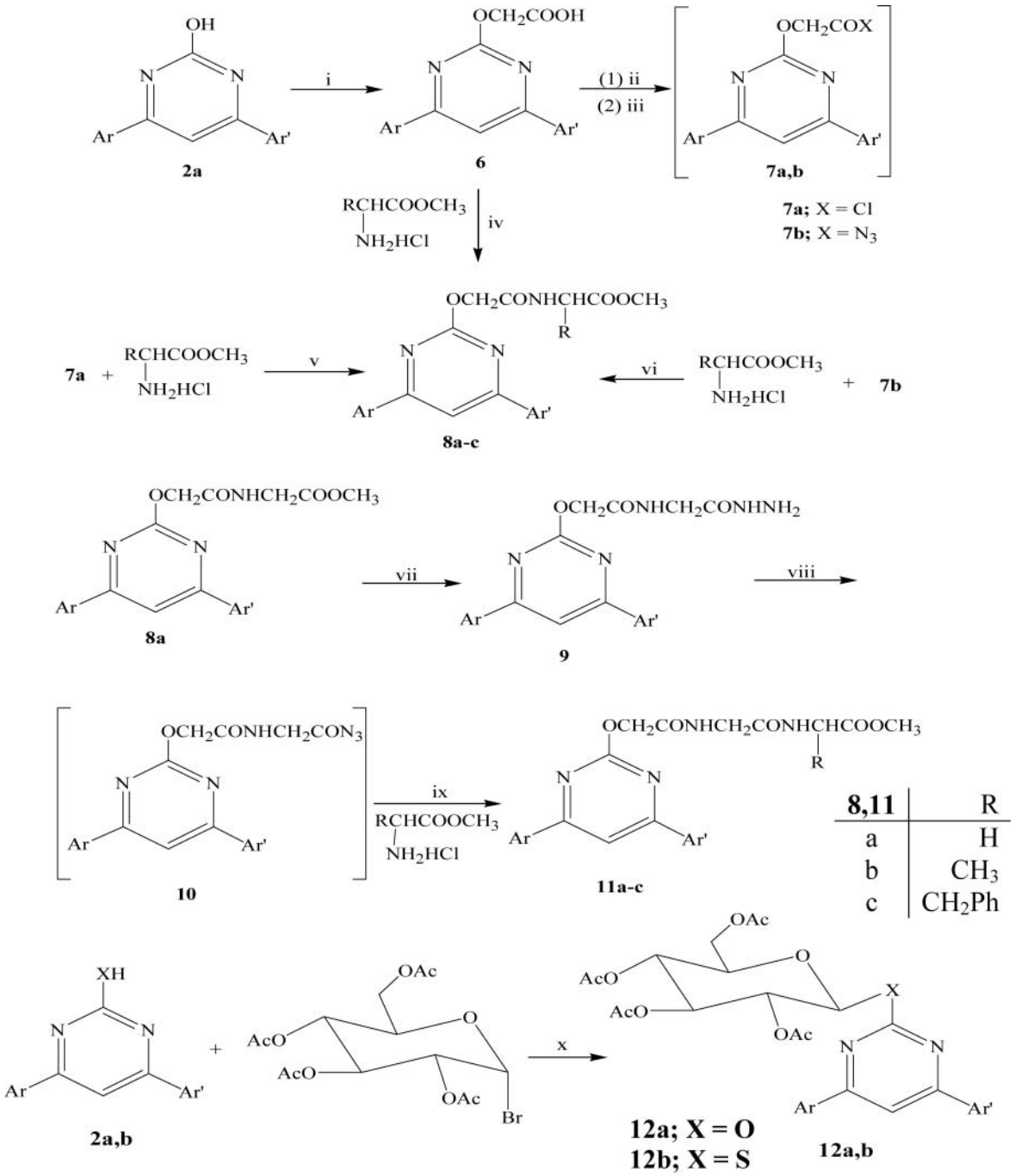
In conclusion, we have demonstrates the scope for the utility of pyrimidine derivatives for construction of novel pyimidinyl-amino acid derivatives, dipeptidylpyrimidines and glycoside derivatives of valuable antimicrobial activity.

Experimental

Melting points are uncorrected. IR spectra in KBr were recorded on a Perkin–Elmer 298 spectrophotometer. ^{1}H NMR spectra were obtained on an Varian Gemini 200 MHz instrument using TMS as internal reference with chemical shifts expressed as δ ppm. Mass spectra were recorded on a Shimadzu GCMS-QP 1000 instrument (70 eV EI mode). Microanalytical data was carried out in the Microanalytical Center, Cairo university, Egypt. Analytical TLC was carried out using Merk 60 F254 aluminium sheets and visualised by UV light (254 nm).

4-(3-Nitrophenyl)-6-phenoxathiin-2-ylpyrimidin-2-ol(thiol) (**2a,b**): To a mixture of 3-(3-nitrophenyl)-1-phenoxathiin-2-ylpropenone (**1**) (3.75 g, 10 mmol), urea (0.6 g, 10 mmol) and/or thiourea (0.76 g, 10 mmol) in ethanol (40 mL) was added an ethanolic sodium ethoxide solution [prepared from sodium (0.28 g) and absolute ethanol (20 mL)]. The reaction mixture was heated under reflux for 8 h, then cooled, added to ice-cold water (50 mL) and acidified with HCl (20 mL). The precipitate formed was filtered off and recrystallised to give **2a** and **2b**; IR for **2a**; ν = 3390–3200 (OH, NH), 1670 cm^{-1} (CO); IR for **2b**; ν = 2280 (SH), 1605 (CN), 1260 cm^{-1} (CS); ^{1}H NMR (DMSO-d_6) for **2a**: 7.12–8.20 (m, 12H, ArH), 8.50 (brs, 1H, NH, exchangeable); ^{1}H NMR (DMSO-d_6) for **2b**: 7.10–8.15 (m, 12H, ArH), 8.52 (brs, 1H, NH, exchangeable).

*4-(3-Nitrophenyl)-6-(phenoxathiin-2-yl)-2-*N*-(phthalyl- or tosylglycyl-, DL-alanyl or DL-phenylalanyl)oxy- or mercaptopyrimidines* (**3,4)a–f**: An *N*-phthayl- or *N*-tosylamino acids (4 mmol) *viz* (glycine, DL-alanine and DL-phenylalanine) and pyrimidine derivatives **2a** and/or **2b** (4 mmol) were dissolved in tetrahydrofuran (30 mL). The reaction mixture was cooled to 0 °C, then *N,N'*-dicyclohexylcarbodiimide (1.03 g, 5 mmol) was added and the reaction mixture was stirred for 24 h at 0 °C, and for another 24 h at room temperature. The precipitated dicyclohexylurea was filtered off and the filtrate was washed with 1N HCl (10 mL), 5% $NaHCO_3$ (10 mL), dried on anhydrous sodium sulfate and left overnight. It was then filtered off, then the filtrate was evaporated *in vacuo* and the solid residue was recrystallised from proper solvents to give (**3,4)a–f**. IR of **3a–f**: ν = 2960–2850 (aliphatic CH), 1765–1740, 1720–1710 cm^{-1} (CO); IR of **4a–f**:



Scheme 2 i) $ClCH_2COOH$, MeONa, reflux 3h; ii) $SOCl_2$, reflux 2h; iii) NaN_3, dry acetone, stirring 1h; iv) DCC, THF; v) dioxane, Et_3N; vi) EtOAc, Et_3N; vii) $N_2H_4.H_2O$, EtOH; viii) $NaNO_2$ /AcOH; ix) EtOAc, Et_3N; x) EtOH, KOH.

ν = 3230–3100 (NH), 1725–1710 (CO), 1360–1320, 1150–1125 cm^{-1} (SO_2). ^1H NMR (DMSO-d_6) for **3a**: 4.15 (s, 2H, CH_2), 6.95–7.90 (m, 16H, ArH); ^1H NMR (DMSO-d_6) for **3b**: 1.4 (d, 3H, CH_3), 4.55 (q, 1H, CH), 7.10–8.05 (m, 16H, ArH); ^1H NMR (DMSO-d_6) for **3e**: 1.15 (d, 3H, CH_3), 4.85 (q, 1H, CH), 7.12–8.10 (m, 16H, ArH); ^1H NMR (DMSO-d_6) for **4a**: 2.25 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 7.11–8.20 (m, 16H, ArH), 8.40 (s, 1H, NH, exchangeable); ^1H NMR ($CDCl_3$) for **4b**: 1.10 (d, 3H, CH_3), 2.20 (s, 3H, CH_3), 5.2 (q, 1H, CH), 6.95–8.10 (m, 16H, ArH), 8.35 (s, 1H, NH, exchangeable); ^1H NMR (DMSO-d_6) for **4f**: 2.23 (s, 3H, CH_3), 2.60 (d, 2H, CH_2), 4.80 (t, 1H, CH), 7.15–8.10 (m, 21H, ArH), 8.50 (s, 1H, NH, exchangeable).

4-(3-Nitrophenyl)-6-(phenoxathiin-2-yl)-2-(glycyl-, DL-alanyl) or DL-phenylalanyl-oxy- or mercaptopyrimidines (**5a–f**): A mixture of *N*-phthalyl derivatives **3a–f** (10 mmol) and hydrazine hydrate (0.7 mL) in ethanol (25 mL) was refluxed for 4 h. The solvent was removed *in vacuo* and (10 mL) of 0.5N hydrochloric acid was added to the dried residue, the suspension was kept in an ice-bath for 2 h, and the insoluble product was removed by filtration. The filtrate was evaporated to dryness *in vacuo* to give the oily residue which was added to acetone (10 mL), followed by addition (20 mL) of ether, and the solution was kept at 0 °C for 8 h. The product formed was collected by filtration, which upon recrystallisation from a proper solvent gave **5a–f**. IR: ν = 3390–3310 (NH_2), 1725–1715 cm^{-1} (CO); ^1H NMR ($CDCl_3$) for **5a**: 4.50 (s, 2H, CH_2), 5.95 (brs, 2H, NH_2), 6.95–7.85 (m, 12H, ArH); ^1H NMR ($CDCl_3$) for **5b**: 1.15 (d, 3H, CH_3), 4.95 (q, 1H, CH), 5.93 (brs, 2H, NH_2), 6.95–7.92 (m, 12H, ArH).

[4-(3-Nitrophenyl)-6-(phenoxathiin-2-yl)pyrimidin-2-yloxy]acetic acid (**6**): A mixture of **2a** (3.32 g, 8 mmol), chloroacetic acid (0.76 g, 8 mmol) and sodium methoxide (0.35 g of sodium in 20 mL of methanol) in methanol (30 mL) was heated under reflux for 3 h. After the evaporation of solvent, the residue was dissolved in ice-cold water and acidified with HCl (20 mL). The formed solid was filtered off and recrystallised from ethanol to give **6**. Yield, 2.7 g (71%); m.p. 234–236 °C; IR: ν = 3400–3200 (OH), 1695 cm^{-1} (CO); ^1H NMR

Table 1 Antimicrobial activity of some synthesised compounds

Compd. No	*Gram +ve bacteria*				*Gram -ve bacteria*				*Fungi*			
	Bacillus subtilis		*Rhodococcus equi*		*Escherichia coli*		*Pseudomonas aeruginosa*		*Penicillium notatum*		*Aspergillus niger*	
	A	MIC	A	MIC	A	MIC	A	MIC	A	MIC	A	MIC
3a	20	125	21	125	14	125	13	125	18	250	17	250
3c	22	250	24	500	20	250	22	250	19	125	18	125
3d	20	250	18	250	17	125	12	250	17	500	16	250
3f	21	500	19	125	18	250	18	125	18	250	17	250
4b	24	125	23	250	22	500	21	250	20	125	19	125
4c	25	125	22	500	23	250	22	125	22	250	20	500
4e	24	250	24	125	20	125	21	250	21	125	21	125
5a	18	500	19	250	18	250	20	500	17	500	15	250
5c	20	250	21	250	17	125	16	125	15	250	15	125
5f	18	250	16	125	16	500	16	250	16	125	15	250
8a	23	125	21	250	23	125	20	250	18	125	19	125
8b	20	125	22	125	22	250	19	125	18	250	18	500
11a	22	125	20	125	21	500	20	500	17	500	17	125
11c	21	500	19	500	20	250	19	250	20	250	20	125
12a	20	125	17	250	16	125	18	125	22	125	20	250
12b	19	125	21	250	22	250	21	125	21	500	19	250
Ampicillin	25	125	24	125	26	250	25	125	--	--	--	--
Mycostatin	--	--	--	--	--	--	--	--	23	125	25	125

A, Antimicrobial activity of tested compounds; MIC, Minimum inhibitory concentration; Numbers in the table represent the inhibition zone diameter (r mm) of either fungal growth or bacterial cell for each compound; r > 20 mm, high active; r > 12 mm, moderately active; r > 6 mm, slightly active; -, no inhibition was observed.

Table 2 Physical data of compounds **2a,b** and **(3–5)a–f**

Compd	Yield /%	M.p./° C (Solvent)*	Mol. formula (MW)	Analysis Calcd / (Found)		
				C	H	N
2a	73	213–215 (EtOH)	$C_{22}H_{13}N_3O_4S$ (415.42)	63.61 (63.93)	3.15 3.41	10.12 (10.01)
2b	70	193–195 (EtOH)	$C_{22}H_{13}N_3O_3S_2$ (431.49)	61.24 (61.43)	3.04 3.29	9.74 (9.50)
3a	74	201–203 (BuOH)	$C_{32}H_{18}N_4O_7S$ (602.57)	63.78 (63.97)	3.01 3.25	9.30 (9.10)
3b	65	225–227 (EtOH)	$C_{33}H_{20}N_4O_7S$ (616.60)	64.28 (64.11)	3.27 3.10	9.09 (9.26)
3c	68	195–197 (EtOH)	$C_{39}H_{24}N_4O_7S$ (692.70)	67.62 (67.40)	3.49 3.23	8.09 (8.24)
3d	70	236–238 (B)	$C_{32}H_{18}N_4O_6S_2$ (618.64)	62.13 (62.01)	2.93 2.71	9.06 (9.23)
3e	76	241–243 (DMF)	$C_{33}H_{20}N_4O_6S_2$ (632.67)	62.65 (62.90)	3.19 3.32	8.86 (8.60)
3f	62	250–252 (DMF)	$C_{39}H_{24}N_4O_6S_2$ (708.76)	66.09 (66.25)	3.41 3.65	7.90 (7.62)
4a	67	210–212 (EtOH)	$C_{31}H_{22}N_4O_7S_2$ (626.66)	59.42 (59.29)	3.54 3.31	8.94 (8.62)
4b	66	185–187 (MeOH)	$C_{32}H_{24}N_4O_7S_2$ (640.69)	59.99 (59.70)	3.78 3.52	8.74 (8.96)
4c	74	197–199 (EtOH)	$C_{38}H_{28}N_4O_7S_2$ (716.78)	63.67 (63.42)	3.94 3.62	7.82 (7.98)
4d	62	213–215 (B)	$C_{31}H_{22}N_4O_6S_3$ (642.73)	57.93 (57.71)	3.45 3.21	8.72 (8.96)
4e	69	226–228 (BuOH)	$C_{32}H_{24}N_4O_6S_3$ (656.75)	58.52 (58.73)	3.68 3.91	8.53 (8.23)
4f	71	236–238 (BuOH)	$C_{38}H_{28}N_4O_6S_3$ (732.85)	62.28 (62.41	3.85 3.98	7.65 (7.41)
5a	62	252–254 (DMF)	$C_{24}H_{16}N_4O_5S$ (472.47)	61.01) (61.23	3.41 3.65	11.86 (11.61)
5b	63	244–246 (BuOH)	$C_{25}H_{18}N_4O_5S$ (486.50)	61.72 (61.49)	3.73 3.45	11.52 (11.76)
5c	60	207–209 (EtOH)	$C_{31}H_{22}N_4O_5S$ (562.60)	66.18 (66.36)	3.94 4.11	9.96 (9.65)
5d	67	232–234 (B)	$C_{24}H_{16}N_4O_4S_2$ (488.54)	59.00 (59.26)	3.30 3.52	11.47 (11.21)
5e	68	260–262 (DMF)	$C_{25}H_{18}N_4O_4S_2$ (502.57)	59.75 (59.93)	3.61 3.93	11.15 (11.32)
5f	73	270–272 (DMF)	$C_{31}H_{22}N_4O_4S_2$ (578.66)	64.34 (64.56)	3.83 3.98	9.68 (9.45)

* EtOH, ethanol; BuOH, *n*-butanol; B, benzene; DMF, *N,N*'-dimethylformamide; MeOH, methanol.

($CDCl_3$): δ = 4.3 (s, 2H, CH_2), 7.10–8.15 (m, 12 H, ArH), 9.60 (s, 1H, OH, exchangeable); Anal. Calcd for $C_{24}H_{15}N_3O_6S$ (473.46): C, 60.88; H, 3.19; N, 8.88. Found: C, 60.61; H, 3.02; N, 8.99%.

[4-(3-Nitrophenyl)-6-(phenoxathiin-2-yl)pyrimidin-2-yloxy]acetyl azide (**7b**): A saturated solution of sodium azide (0.33 g, 5 mmol) in water (5 mL) was added dropwise to a stirred solution of pyrimidinyloxyacetyl chloride **7a** (3 mmol) [prepared from the refluxing of pyrimidinyloxyacetic acid **6** (2 g) and thionyl chloride (8 mL) on a water bath for 2 h, then cooled and added to petroleum ether 40/60 (40 mL). The solid formed was filtered off and dried to give **7a**] at 0–5 °C, then the reaction mixture was stirred for further 1 h at room temperature. The reaction mixture was added to crushed ice (50 g) and the precipitated product was collected by filtration to give **7b** which used *in situ*.

Preparation of compounds (**8a–c**)*; general procedure*

Method a: To a solution of α-amino acids methyl ester hydrochloride *viz* glycine, DL-alanine and DL-phenylalanine (6 mmol) in tetrahydrofuran (40 mL) was added triethylamine (3 mL). The solution was kept for 30 min at 0–5 °C and the precipitated triethylamine hydrochloride was filtered off. To the filtrate at 0 °C was added pyrimidinyloxyacetic acid **6** (4 mmol) and *N,N′*-dicyclohexylcarbodiimide (4 mmol). The reaction was allowed to proceed for 3 h at 0 °C with stirring, for 3 h at 5 °C and for 24 h at room temperature. The precipitated dicyclohexylurea was filtered off, the filtrate was evaporated to dryness under reduced pressure and the residue was recrystallised from tetrahydrofuran to give **8a–c**. Yield for **8a** (74%), **8b** (72%), **8c** (68%).

Method b: Pyrimidinyloxyacetyl chloride **7a** (4 mmol) was dissolved in dioxane (40 mL) and added to a solution of the same α-amino acids methyl ester hydrochloride (6 mmol) in dioxane (20 mL) containing triethylamine (3 mL). The reaction mixture was stirred for 30 min at room temperature followed by refluxing for 3–4 h (TLC). The reaction mixture was cooled, then the precipitated triethylamine hydrochloride was filtered off and the filtrate was washed with 5% $NaHCO_3$ (20 mL), then dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave the solid product which recrystallised to give **8a–c**. Yield for **8a** (69%), **8b** (65%), **8c** (61%).

Method c: To a solution of pyrimidinyloxyacetyl azide **7b** (4 mmol) in ethyl acetate was added the same α-amino acids methyl ester hydrochloride (6 mmol) and triethylamine (3 mL). The reaction mixture was stirred for 5 h at 5 °C and for 10 h at room temperature, then cooled, added to 1N HCl (25 mL), 5% $NaHCO_3$ (25 mL) and dried over anhydrous Na_2SO_4. The solution was evaporated under reduced pressure and the residual material was recrystallised to give **8a–c**. Yield for **8a** (63%), **8b** (61%), **8c** (65%).

Methyl{2-[4-(3-nitrophenyl)-6-(phenoxathiin-2-yl)pyrimidin-2-yloxy]-acetylamino}acetate (**8a**): M.p. 210–212 °C; IR: ν = 3340–3230 (NH), 1725, 1680 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 2.95 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 4.30 (s, 2H, OCH_2), 7.16–8.10 (m, 12H, ArH), 8.95 (s, 1H, NH, exchangeable); Anal. Calcd for $C_{27}H_{20}N_4O_7S$ (544.54): C, 59.55; H, 3.70; N, 10.29. Found: C, 59.68; H, 3.86; N, 10.13%.

Methyl 2-{2-[4-(3-nitrophenyl)-6-(phenoxathiin-2-yl)pyrimidin-2-yloxy]acetylamino}propionate (**8b**): M.p. 236–238 °C; IR: ν = 3350–3220 (NH), 1720, 1675 cm^{-1} (CO); ^1H NMR ($CDCl_3$): δ = 1.60 (d, 3H, CH_3), 2.90 (s, 3H, CH_3), 4.20 (s, 2H, CH_2), 4.80 (q, 1H, CH), 7.10–8.15 (m, 12H, ArH), 8.75 (s, 1H, NH, exchangeable); Anal. Calcd for $C_{28}H_{22}N_4O_7S$ (558.56): C, 60.21; H, 3.97; N, 10.03. Found: C, 60.03; H, 3.62; N, 10.21%.

Methyl 2-{2-[4-(3-nitrophenyl)-6-(phenoxathiin-2-yl)pyrimidin-2-yloxy]acetylamino}-3-phenylpropionate (**8c**): M.p. 205–257 °C; IR: ν = 3330–3190 (NH), 1722, 1670 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.90 (s, 3H, CH_3), 4.10 (s, 2H, OCH_2), 4.25 (d, 2H, CH_2), 4.90 (t, 1H, CH), 7.10–8.15 (m, 17H, ArH), 8.98 (s, 1H, NH); Anal. Calcd for $C_{34}H_{26}N_4O_7S$ (634.66): C, 64.34; H, 4.13; N, 8.83. Found: C, 64.46; H, 4.25; N, 8.62%.

N-Hydrazinocarbonylmethyl-2-[4-(3-nitrophenyl)-6-(phenoxathiin-2-yl)pyrimidin-2-yloxy]acetamide (**9**): Compound **8a** (2.7 g, 5 mmol) was suspended in ethanol (25 mL) and refluxed, until a clear solution was obtained. To this solution, hydrazine hydrate (0.3 mL, 6 mmol) was added and the solution was kept at 0–5 °C for 24 h, the solvent was removed *in vacuo* and to the dried residue was added (10 mL) of 0.5N hydrochloric acid and the solid which separated was recrystallised from ethanol to give **9**. Yield, 1.7 g (63%); M.p. 231–233 °C; IR: ν = 3410–3200 (multiple bands, NH_2 and NH), 1680–1675 cm^{-1} (CO); ^1HNMR (DMSO-d_6): δ = 3.85 (s, 2H, CH_2), 4.20 (s, 2H, OCH_2), 5.85 (brs, 2H, NH_2), 7.10–8.12 (m, 12H, ArH), 8.95, 9.10 (2s, 2H, 2NH, exchangeable); Anal. Calcd for $C_{26}H_{20}N_6O_6S$ (544.54): C, 57.35; H, 3.70; N, 15.43. Found: C, 57.49; H, 3.91; N, 15.21%.

Preparation of compounds (**11a–c**)*; general procedure*

Compound **9** (2.7 g, 5 mmol) was dissolved in a mixture of [acetic acid (8 mL), HCl (5 mL) and water (10 mL)], the solution was cooled to 0 °C. To this cold solution was added a solution of sodium nitrite (1 g) in water (5 mL) dropwise over 10 min. and the reaction was allowed to proceed for another 15 min at 0 °C. The acid azide **10** was precipitated as a syrup which taken up in cold ethyl acetate (40 mL), then washed with cold 5% $NaHCO_3$ (25 mL) and dried over anhydrous Na_2SO_4. The dried solution of azide **10** was added to α-amino acids methyl ester hydrochloride (6 mmol) *viz* glycine, DL-alanine and DL-phenylalanine in ethyl acetate (25 mL) containing triethylamine (3 mL). The reaction mixture was stirred for 5 h at 5 °C and then for another 10 h at room temperature, then washed with 1N HCl (20 mL), 5% $NaHCO_3$ (20 mL) and dried over anhydrous Na_2SO_4. The dried solution was evaporated *in vacuo* and the residue was recrystallised from *n*-butanol to give **11a–c**.

Methyl (2-{2-[4-(3-nitrophenyl)-6-(phenoxathiin-2-yl)pyrimidin-2-yloxy]acetylamino}acetylamino)acetate (**11a**): Yield, (67%); M.p. 212–214 °C; IR: ν = 3240–3190 (NH), 1725, 1680–1675 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 2.90 (s, 3H, CH_3), 3.95, 4.10 (2s, 4H, $2CH_2$), 4.30 (s, 2H, OCH_2), 7.13–8.10 (m, 12H, ArH), 8.80, 8.90 (2s, 2H, 2NH, exchangeable); Anal. Calcd for $C_{29}H_{23}N_5O_8S$ (601.59): C, 57.90; H, 3.85; N, 11.64. Found: C, 57.70; H, 3.63; N, 11.81%.

Methyl 2-(2-{2-[4-(3-nitrophenyl)-6-(phenoxathiin-2-yl)pyrimidin-2-yloxy]acetylamino}acetylamino)propionate (**11b**): Yield, (60%); M.p. 202–204 °C; IR: ν = 3250–3200 (NH), 1723, 1680–1670 cm^{-1} (CO); ^1H NMR (DMSO-d_6): δ = 1.95 (d, 3H, CH_3), 2.95 (s, 3H, CH_3), 3.90 (s, 2H, CH_2), 4.25 (s, 2H, OCH_2), 4.35 (q, 1H, CH), 7.12–8.15 (m, 12H, ArH), 8.75, 8.80 (2s, 2H, 2NH, exchangeable); Anal. Calcd for $C_{30}H_{25}N_5O_8S$ (615.61): C, 58.53; H, 4.09; N, 11.38. Found: C, 58.72; H, 4.23; N, 11.19%.

Methyl 2-(2-{2-[4-(3-nitrophenyl)-6-(phenoxathiin-2-yl)pyrimidin-2-yloxy]acetylamino}acetylamino)-3-phenylpropionate (**11c**): Yield, (57%); M.p. 197–199 °C; IR: ν = 3245–3185 (NH), 1720, 1680–1675 cm^{-1} (CO); Anal. Calcd for $C_{36}H_{29}N_5O_8S$ (691.71): C, 62.51; H, 4.23; N, 10.12. Found: C, 62.38; H, 4.10; N, 10.26%.

Preparation of compounds (**12a,b**): A mixture of compounds (**2**a or **2b**) (2 mmol) was dissolved in ethanol (20 mL) containing KOH (2 mmol) and stirred at room temperature for 30 min. The tetra-*O*-acetyl-α-D-glucopyranosyl bromide (2 mmol) was then added to the reaction mixture which was stirred at rom temperature for 12 h. The mixture was filtered, washed with water and recrystallised from proper solvent to give the compounds **12a**,**b**; IR for compounds **12a,b**: υ = 1705–1700 cm^{-1} (CO).

4-(3-Nitrophenyl)-6-(phenoxathiin-2-yl)-2-(tetra-O-acetyl-β-D-glucopyranosyloxy)pyrimidine (**12a**): Yield, 56% (*n*-butanol); m.p. 122–124 °C; ^1H NMR ($CDCl_3$): δ = 1.90–2.10 (4s, 12H, 4 CH_3CO), 3.30–4.10 (m, 5H, H-sugar), 4.30 (m, 2H, CH_2), 6.98–8.10 (m, 12H, ArH); Anal. Calcd for $C_{36}H_{31}N_3O_{13}S$ (745.71): C, 57.98; H, 4.19; N, 5.63. Found: C, 57.65; H, 4.25; N, 5.74%.

4-(3-Nitrophenyl)-6-(phenoxathiin-2-yl)-2-(tetra-O-acetyl-β-D-glucopyranosylsulfanyl)pyrimidine (**12b**): Yield, 50% (ethanol); m.p. 131–133 °C; ^1H NMR ($CDCl_3$): δ = 1.92–2.30 (4s, 12H, 4 CH_3CO), 3.20–4.10 (m, 5H, H-sugar), 4.25 (m, 2H, CH_2), 7.10–8.25 (m, 12H, ArH); Anal. Calcd for $C_{36}H_{31}N_3O_{12}S_2$ (761.78): C, 56.76; H, 4.10; N, 5.52. Found: C, 56.51; H, 4.18; N, 5.41%.

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