Novel 2-Hydrazino-pyrimidin-4(3*H*)-One Derivatives as Potential Dihydrofolate Reductase Inhibitors

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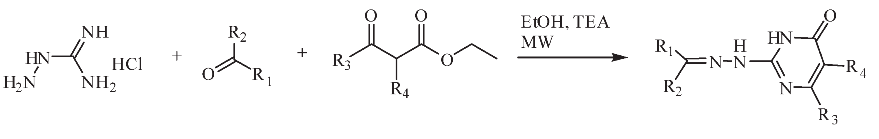

Novel substituted 2-hydrazino-pyrimidin-4(3*H*)-one derivatives were synthesized and examined for their antifolate activity against DHFR from *Pneumocystis carinii* (pc), *Toxoplasma gondii* (tg), *Mycobacterium avium* (ma), and rat liver (rl). A novel, simple, and feasible methodology was developed for the synthesis of the titled compounds. Amongst these, compound **8** 6-phenyl-2-(2-(1-(thiophen-2-yl) ethylidene)hydrazinyl) pyrimidin-4(3*H*)-one exhibited 17.74 μ*M* activity against pcDHFR.

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INTRODUCTION

Dihydrofolate reductase (DHFR), a crucial enzyme required for the conversion of folic acid to dihydro and tetrahydro folic acid (a cofactor involved in one carbon transfer in purine and pyrimidine *de-novo* synthesis) has been successfully explored as a target for the treatment of various infective diseases. Opportunistic organisms such as *Pneumocystis carinii* (pc), *Toxoplasma gondii* (tg), and *Mycobacterium avium* (ma) cause life threatening infections in immunocompromised hosts. Majority of the DHFR inhibitors explored have a 2,4-diamino moiety on the aromatic/heteroaromatic ring as an important pharmacophoric feature which forms a crucial H-bonding interaction at the bottom of the active site in both microbial and human DHFR [1]. The structural requirements of potential DHFR inhibitors have been summarized in a recent review article [2]. Only few reports are found in literature for DHFR inhibitors lacking 2,4-diamino moiety on the pyrimidine/triazine nucleus.

Gschwend *et al.* screened a library of 50,000 compounds using the program DOCK to develop selective inhibitors towards *P. carinii* [3]. Several novel classes of compounds were identified as potential DHFR inhibitors, providing new avenues for lead optimization. The most potent compound (Threne Red Violet RH, Fig. 1) identified had IC_{50} of 6.9 μ*M* towards the fungal enzyme.

This indicated that novel scaffolds could be designed inhibiting the folate pathway efficiently. In this light, virtual screening of ASINEX database using docking algorithm Glide was undertaken [4]. Crystal structure pcDHFR PDB ID: 1KLK, 2.30 Å resolution [5] was used for the docking studies. Initially, all compounds were docked using HTVS mode in Glide, top 10% hits from this study were again docked using SP (Standard precision mode). Finally, top 1% hits emerged from this study were redocked using XP (Extra precision mode). The scaffolds obtained from XP docking were used for novel inhibitor design.

Interestingly, in these virtual screening studies some of the new scaffolds lacking conventional 2,4-diamino pharmacophore, were also identified as hits but have not yet been reported as DHFR inhibitors. On the basis of the structural features of the new scaffolds obtained from virtual screening, 2-hydrazino-pyrimidin-4(3*H*)-one as the basic nucleus was chosen as a potential part of designed DHFR inhibitors.

The designed analogs were studied computationally to get an insight into the binding pattern of these compounds. When a 2-hydrazino-pyrimidin-4(3*H*)-one analog was superimposed on trimethoprim, in the active site of pcDHFR, conserved interactions were observed. It was also observed that the –NH of the pyrimidinone part forms hydrogen bonding with Ile123 in the active site of pcDHFR. The docking studies revealed that pyrimidinone part of the molecule is stabilized using van der Waals interactions with residues like Ile123, Ile10, Val11, Phe36, Glu32, Ile33, and Leu25. The bridge portion of the designed analogs are shown to form

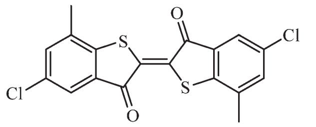


Figure 1. Hit identified from the study of Gschwend *et al.*

favorable interactions with Ile123, Thr61, whereas the distal part forms van der Waals interactions with Asn23, Ser64, Pro66, Ile65, Phe69, Leu72, and Phe36 in the active site of the enzyme. Pyrimidinone ring forms π-π stacking interactions with Phe36 (4.470 Å) at the bottom of the active site.

Substituted pyrimidin-4(3*H*)-one compounds have widespread biological activities [6]. However, to the best of our knowledge these types of molecules are not yet explored as DHFR inhibitors. Therefore, based on virtual screening and new scaffold design, synthesis and evaluation of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives against DHFR from various opportunistic microorganisms were undertaken.

RESULTS AND DISCUSSION

The reported methods for the synthesis of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives involve acetic acid catalyzed condensation reaction of aromatic aldehydes with a cyclic intermediate of ethyl acetoacetate and semicarbazide [6,7]. Formic acid catalyzed condensation reaction of ketone with semicarbazide has also been reported [8].

However, reported methods for the synthesis of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives suffer from several disadvantages such as use of commercially unavailable cyclic intermediates as starting material, multi-step reactions which in turn make the process costly, lengthy, time consuming and also affect the yield and quality of the final products. Moreover, the use of acetic acid or formic acid [8], makes the workup cumbersome. Therefore, designing an efficient protocol using commercially available starting materials, involving easy workup procedure for the synthesis of these compounds was taken into consideration.

In the present work, initially a two step process was developed using conventional heating (Method 1). The first step involves condensation of ethanolic solution of substituted ketones with semicarbazide hydrochloride to yield a substituted semicarbazone using absolute ethanol as solvent.

In step II, the ethanolic solution of semicarbazone was treated with various β- ketoesters in presence of a base to yield the desired analogs as shown in Scheme 1. Various bases such as triethylamine, pyridine and ammonium acetate were explored for this step. Triethylamine was found to give good yields, in less time than other bases.

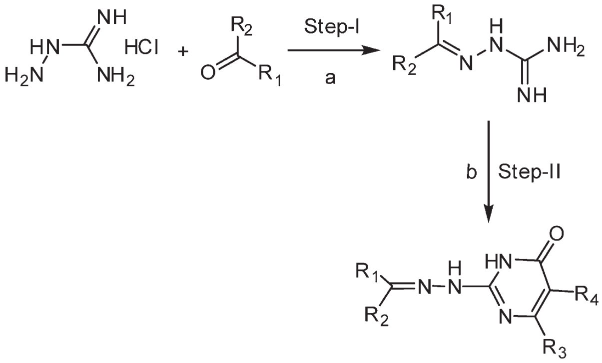
Microwave (MW) assisted synthesis is known to be advantageous over conventional reaction reported in literature; with respect to time, yield and workup procedures [9].

In this light, the above synthetic scheme was carried out using microwave irradiation (Method 2). Although steps I and II took many hours to complete under conventional heating (Method 1) no more starting materials could be detected after 10–20 min under microwave irradiation.

Encouraged by the results obtained using microwave method, a one pot microwave assisted method was also investigated.

In case of one pot microwave assisted reaction, an ethanolic solution of β-ketoester, semicarbazide hydrochloride and substituted ketone was subjected to microwave irradiation with intermittent addition of triethylamine. Appropriate workup procedures followed by column purification led to the isolation of the desired compound as shown in Scheme 2. Thus, a one step process using microwave irradiation without isolating the intermediate was developed (Method 3). Thereafter, all

Scheme 1. Method for the synthesis of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives. A, EtOH, reflux; b, TEA, EtOH, reflux.



Scheme 2. Microwave assisted one pot method for the synthesis of 2-hydrazino-pyrimidin-4(3*H*)-ones.

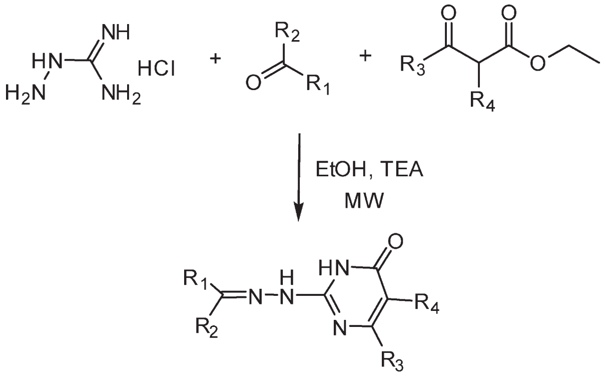
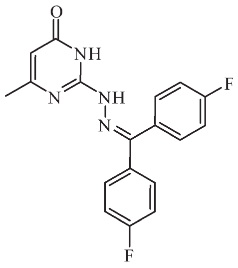
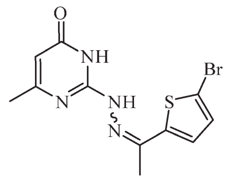
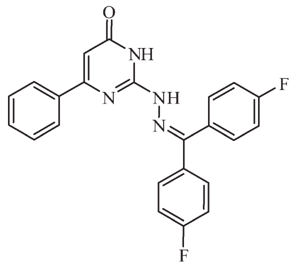
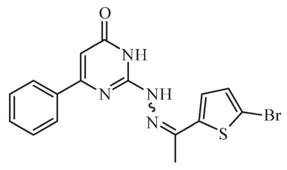
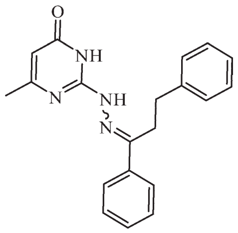
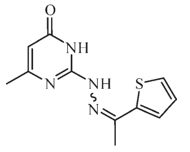
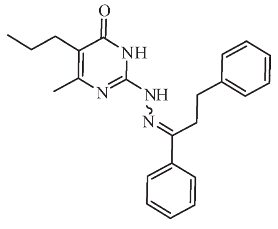
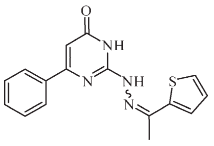


Table 1

List of synthesized 2-hydrazino-pyrimidin-4(3*H*)-one derivatives.

No.	Structure	Mol. formula	No.	Structure	Mol. formula
1		$C_{18}H_{14}F_2N_4O$	5		$C_{11}H_{11}BrN_4OS$
2		$C_{23}H_{16}F_2N_4O$	6		$C_{16}H_{13}BrN_4OS$
3		$C_{20}H_{20}N_4O$	7		$C_{11}H_{12}N_4OS$
4		$C_{23}H_{26}N_4O$	8		$C_{16}H_{14}N_4OS$

the compounds were synthesized using one pot microwave assisted method (Method 3).

The processes developed in this present work are feasible, simple, cost-effective and time saving.

The course of the reaction was monitored by thin layer chromatography (TLC) and the structures were confirmed by spectral data. The MS of all the compounds exhibited the molecular ion peak. ^{1}H NMR spectra of 2-hydrazino-pyrimidin-4(3H)-one showed the presence of characteristic, D_2O exchangeable –NH peaks at δ ranging from 7.0 to 8.0. All the other spectral data was found to be satisfactory. The list of synthesized compounds is given Table 1.

The synthesized compounds were evaluated for their ability to inhibit DHFR from pc, tg, ma, and rl using a continuous spectrophotometric assay measuring oxidation at 340 n*M* of NADPH at 37°C under conditions of saturating substrate and cofactor as previously described [10,11]. The results of this assay are given in Table 2, along with previously reported data for reference compounds [12].

The compound **5** showed 51.38 μ*M* activity against pcDHFR and 60.54 μ*M* activity against maDHFR. The Compound **8** also exhibited comparable potency as that of trimethoprim against pcDHFR. The Compound **6** exhibited micromolar potency against pc DHFR. However, the synthesized molecules were not selective.

In summary based on virtual screening experiments, 2-hydrazino-pyrimidin-4(3*H*)-one was designed as novel antifolate scaffold. An efficient, simple protocol was

Table 2

Dihydrofolate reductase inhibition by synthesized compounds.

	Activity IC_{50} (μM)			
S. N.	pc	tg	ma	rl
1	138.102 (32)	138.102 (28)	138.102 (22)	138.102 (35)
2	10.313 (3)	10.313 (0)	10.313 (0)	10.313 (9)
3	12.515 (7)	12.515 (4)	12.515 (8)	12.515 (0)
4	126.036	12.401 (26)	12.401 (22)	20.208
5	13.294 (5)	51.375	60.544	13.294 (58)
6	88.833	95.949	126.981	58.674
7	19.130 (8)	173.499	93.153	19.130 (58)
8	17.740	14.209 (20)	14.209 (19)	14.766
Trimethprim[a]	12	2.80	0.30	180
Piritrexim[a]	0.013	0.0043	0.00061	0.0033
Trimetrexate[a]	0.042	0.01	0.0015	0.003

Inhibitory concentration (IC_{50}, μM) against rlDHFR, pcDHFR, tgDHFR and maDHFR by target compounds. Triplicate assays were performed as previously described [10,11].

Because of lack of solubility the exact IC_{50} could not be determined for some compounds; hence maximum soluble concentration was used to determine % inhibition. Number in parentheses indicates percent inhibition obtained at that concentration. For e.g., 138.102 (32) indicates 32% inhibition at 138.102 μM concentration.

[a] Data taken from reference [12].

developed for synthesis of these molecules. The synthesized compounds were evaluated against DHFR of opportunistic organisms. Some of the evaluated compounds showed appreciable antifolate activity, thus validating our methodology. Therefore, these compounds could act as good leads for novel antifolates. The results would be used for design and synthesis of analogs with improved potency and selectivity.

EXPERIMENTAL

Melting points (mp) were recorded on Thermomik Compbell electronics, having oil-heating system and were uncorrected. The microwave reactions were carried out using CEM Focused Microwave System in monomode, Model Discover. Analytical thin-layer chromatography (TLC) was carried out on precoated plates SiO_2 (silica gel 60, F 254, Merck). SiO_2 (Silica gel 420, Merck) was used for column chromatography using CombiFlash® RETRIEVE® system. FTIR spectra were recorded on ''Buck scientific infrared spectroscopy M500 spectrophotometer'' using KBr pellets. All the NMR spectra were recorded on FT-NMR JEOL, 60 MHz or JEOL AL 300 MHz spectrometer with DMSO-*d6* or $CDCl_3$ as solvent using tetramethyl silane (TMS) as internal reference: s = singlet, d = doublet, t = triplet, q = quartet, m = mutiplet, bs = broad singlet. The mass spectrum was recorded on a Waters Q/TOF Micromass spectrometer.

General procedure method 1 (method using conventional reflux) Step I: synthesis of semicarbazone. Substituted ketone (13.7 mmol) and semicarbazide hydrochloride (13.7 mmol) were stirred in 30 mL absolute ethanol in a round bottom flask and the mixture was refluxed on a sand bath with vigorous stirring for 14–18 hrs. After the reaction commenced, ketones reacted with semicarbazide hydrochloride giving a base spot on TLC (in solvent system EtOAc:Hexanes = 9:1). The reaction mixture was then concentrated under reduced pressure and the obtained solid residue was partitioned between 50 mL water and 50 mL EtOAc:hexanes (1:9) to extract unreacted starting materials in organic layer. Aqueous layer was stirred for 5 min with solid sodium bicarbonate (3 g) leading to precipitation of solid semicarbazone which was then filtered and washed with water (3 × 50 mL). The obtained solid was recrystallized from 40 mL of MeOH. This gave pure semicarbazone in free base form which was used for the cyclization with β-ketoester.

Representative example. 2-(bis(4-fluorophenyl)methylene) hydrazinecarboximidamide: To the ethanolic solution of bis(4-fluorophenyl)methanone (3g, 13.7 mmol); semicarbazide hydrochloride (1.51 g, 13.7 mmol) was added according to step 1, to yield 2.87g (yield: 76.12%) of pure yellow colored semicarbazone product ((2-(bis(4-fluorophenyl)methylene) hydrazinecarboximidamide).

Step II: Synthesis of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives. The semicarbazone (6.16 mmol), the β-ketoester derivative (6.16 mmol) and triethylamine (3.08 mmol) as a catalyst were suspended in 30 mL absolute ethanol and the mixture was refluxed on a sand bath with stirring for 18–22 hrs. TLC showed a product spot (R_f of 0.4–0.6 in the solvent system EtOAc:Hexanes (7:3)). The reaction mixture was concentrated under vacuum and was partitioned between EtOAc (25 mL) and water (25 mL). The organic layer was separated, and the aqueous layer was extracted further with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (75 mL), dried ($NaSO_4$), and concentrated in vacuo. Column purification using flash chromatography (SiO_2, 5 g, 15% EtOAc/hexanes) of the crude product yielded pure 2-hydrazino-pyrimidin-4(3H)-one derivatives.

Representative example. 2-(2-(bis(4-fluorophenyl) methylene) hydrazinyl)-6-methylpyrimidin-4(3H)-one (**1**): The ethanolic solution of 2-(bis(4-fluorophenyl) methylene) hydrazinecarboximidamide (1 g, 3.6 mmol) was treated with ethylacetoacetate (0.47 g, 3.6 mmol) and triethyl amine (0.18 g, 1.8 mmol) according to step 2, to yield 0.521 g (yield: 42%) of 2-(2-(bis(4-fluorophenyl)methylene)hydrazinyl)-6-methyl pyrimidin-4(3H)-one as buff colored solid.

Method 2: (method using microwave assisted reaction) Step I: Synthesis of semicarbazone. A mixture of the ketone (13.7 mmol) and semicarbazide hydrochloride (13.7 mmol) suspended in 30 mL absolute ethanol. This reaction mixture was subjected to microwave irradiation at a power of 60 W, for 15 min (target temperature 100°C). After the completion of reaction the compounds were isolated and purified as described in step I of method 1.

Representative example. 2-(2-(bis(4-fluorophenyl) methylene) hydrazinyl)-6-methylpyrimidin-4(3H)-one: To the ethanolic solution of bis(4-fluorophenyl)methanone (3 g, 13.7 mmol); semicarbazide hydrochloride (1.51 g, 13.7 mmol) was added according to step 1, to yield 3.2 g (yield: 85.13%) of pure yellow colored semicarbazone product ((2-(bis(4-fluorophenyl)methylene) hydrazinecarboximidamide).

Step II: Synthesis of 2-hydrazino-pyrimidin-4(3*H*)-one derivatives. The semicarbazone (3.6 mmol), the β-ketoester derivative (3.6 mmol) and triethylamine (1.8 mmol) as a catalyst were suspended in 30 mL absolute ethanol. This reaction mixture was subjected to microwave irradiation at a power of 60 W, for 20 min (target temperature of 100°C). After the completion of reaction the compounds were isolated and purified as described in step II of method 1.

Representative example. 2-(2-(bis(4-fluorophenyl) methylene) hydrazinyl)-6-methylpyrimidin-4(3H)-one (**1**): The ethanolic solution of 2-(bis(4-fluorophenyl) methylene) hydrazinecarboximidamide (1 g, 3.6 mmol) was treated with ethylacetoacetate (0.47 g, 3.6 mmol) and triethyl amine (0.18 g, 1.8 mmol) according to step 2, to yield 0.583 g (yield: 47%) of 2-(2-(bis(4-fluorophenyl)methylene)hydrazinyl)-6-methyl pyrimidin-4(3H)-one as buff colored solid.

Method 3: (One pot microwave assisted method). A mixture of ketone (27.5 mmol), semicarbazide hydrochloride (27.5 mmol) and β-ketoester (27.5 mmol) were suspended in 30 mL absolute ethanol. This reaction mixture was subjected to microwave irradiation with power of 60 W, for 10 min (target temperature 100°C). After 10 min triethylamine (13.75 mmol) was added in and reaction mixture was subjected to microwave irradiation at the power range of 100 W, for 15–20 min (target temperature 100°C). Most of the starting material consumed after this time, the reaction mixture was then concentrated under reduced pressure and partitioned between water (50 mL) and EtOAc (50 mL). The organic layer was separated, and the aqueous layer was extracted further with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (75 mL), dried (NaSO$_4$), and concentrated *in vacuo*. Column purification using flash chromatography (SiO$_2$, 5 g, 15% EtOAc/hexanes) of the crude product yielded pure 2-hydrazino-pyrimidin-4(3H)-one derivatives.

Representative example. 2-(2-(bis(4-fluorophenyl) methylene) hydrazinyl)-6-methyl pyrimidin -4(3H)-one (**1**): To the ethanolic solution of bis(4-fluorophenyl)methanone (3 g, 13.7 mmol), aminoguanide hydrochloride (1.51 g, 13.7 mmol) and ethylacetoacetate (1.41 g, 13.7 mmol) triethyl amine (0.69 g, 6.85 mmol) was added according to reaction described above to yield 1.93 g (yield: 40.6%) of buff colored product.

2-(2-(Bis(4-fluorophenyl)methylene)hydrazinyl)-6-methylpyrimidin-4(3*H*)-one (1) IR (KBr) major bands at: 3466, 1654, 1560, 1506, 1384, 1299, 1226, 1157 cm^{-1}; ^{1} H NMR: δ 1.99 (s, 3H, —CH3), 5.78 (s, 1H, Ar —CH), 7.01–7.67 (m, 8H, Ar –H), 9.64 (bs, 2H, ex —NH); ^{13}C NMR: δ 23.01, 103.71, 115.33, 115.62, 116.91, 117.19, 127.80, 129.93, 130.03, 130.78, 130.90, 132.64, 151.93, 161.99, 163.99, 165.13, 165.32, 171.77; *m/z* [M+1]$^+$ 341, [M+2]$^+$ 342, [M+3]$^+$ 343.

2-(2-(Bis(4-fluorophenyl)methylene)hydrazinyl)-6-phenylpyrimidin-4(3*H*)-one (2) This compound was obtained as a yellow colored solid in 20 % yield, mp: 235–237°C; IR (KBr) major bands at: 3473, 1654, 1607, 1498, 1383, 1223, 974, 844 cm^{-1}; ^{1} H NMR: δ 6.37 (s, 1H, Ar –H), 7.04–7.82 (m, 14H, Ar –H and ex —NH), 9.70 (bs, 1H, ex —NH); ^{13}C NMR: δ 109.09, 114026, 115.51, 115.80, 117.25, 117.54, 126.87, 127.15, 128.69, 129.64, 129.75, 129.99, 130.52, 130.70, 130.82, 132.52, 136.79, 149.97, 151.72, 162.37, 163.40, 163.76, 165.31; *m/z* [M+1]$^+$403, [M+2]$^+$ 404, [M+3]$^+$ 405.

2-(2-(1,3-Diphenylpropylidene)hydrazinyl)-6-methylpyrimidin-4(3*H*)-one (3) This compound was obtained as a buff colored solid in 40.24 % yield, mp: 152–154°C; IR (KBr) major bands at: 3468, 1648, 1492, 1378, 1119 cm^{-1};^{1} H NMR: δ 2.09 (s, 3H, —CH3), 2.87 (t, 2H, —CH2), 3.12 (t, 2H, —CH2), 5.73 (s, 1H, Ar-H), 7.26-7.72 (m, 11 H, Ar –H and ex —NH), 9.69 (bs, 1H, —NH); ^{13}C NMR: δ 21.26, 29.41, 32.02, 103.42, 121.86, 126.27, 126.45, 126.64, 128.46, 128.65, 128.82, 128.88, 129.73, 129.88, 129.99, 136.37, 140.30, 162.11, 176.91; *m/z* [M]$^+$ 333, [M+1]$^+$ 334, [M+2]$^+$ 335.

2-(2-(1,3-Diphenylpropylidene)hydrazinyl)-6-methyl-5-propylpyrimidin-4(3*H*)-one (4) This compound was obtained as a buff colored solid in 10 % yield, mp: 213–214°C; ^{1} H NMR: δ 1.90 (s, 3H, —CH$_3$), 2.18 (t, 3H, —CH$_3$), 2.45 (m, 4H, 2—CH$_2$), 2.78 (t, 2H, —CH$_2$), 3.21 (t, 2H, —CH$_2$), 7.20–8.00 (m, 9H, Ar—H), 10.40 (bs, 1H, ex —NH), 11.40 (bs, 1H, ex —NH).

2-(2-(1-(5-Bromothiophen-2-yl)ethylidene)hydrazinyl)-6-methylpyrimidin-4(3*H*)-one (5) This compound was obtained as a light brown solid in 30 % yield, mp: 226–228°C; IR (KBr) major bands at: 3497, 1643, 1560, 1384, 1129, 828 cm^{-1}; ^{1} H NMR: δ 2.17 (s, 3H, —CH$_3$), 2.31 (s, 3H, —CH$_3$), 5.70 (s, 1H, Ar—H), 6.99–7.26 (m, 4H, Ar—H and ex —NH); ^{13}C NMR: δ 21.21, 21.92, 103.18, 113.64, 114.42, 127.24, 130.32, 144.08, 147.18, 152.32, 176.68; *m/z* [M]$^+$ 327.

2-(2-(1-(5-Bromothiophen-2-yl)ethylidene)hydrazinyl)-6-phenylpyrimidin-4(3*H*)-one (6) This compound was obtained as a buff colored solid in 43% yield, mp: 225–226°C; ^{1} H NMR: δ 2.12 (s, 3H, —CH$_3$), 6.10 (s, 1H, Ar—H), 6.96–6.97 (d, 1H, Ar—H), 7.091–7.099 (d, 1H, Ar—H), 7.219–7.228 (d, 1H, Ar—H), 7.358–7.365 (d, 1H, Ar—H), 7.477–7.489 (m, 1H, Ar—H), 8.016 (bs, 2H, ex —NH); *m/z* [M]$^+$ 389, [M+2]$^+$ 391.

6-methyl-2-(2-(1-(thiophen-2-yl)ethylidene) hydrazinyl) pyrimidin-4(3*H*)-one (7) This compound was obtained as a light brown solid in 27 % yield, mp: 229–230°C; IR (KBr) major bands at: 3497, 1664, 1633, 1575, 1425, 1384 cm^{-1}; ^{1} H NMR: δ 2.17 (s, 3H, —CH$_3$), 2.37 (s, 3H, —CH$_3$), 5.69 (s, 1H, Ar—H), 7.03–7.34 (m, 3H, Ar—H), 9.24 (bs, 2H, ex —NH); ^{13}C NMR: δ 21.40, 22.20, 103.13, 127.27, 127.43, 128.46, 142.60, 147.78, 152.27, 152.36, 177.02; *m/z* [M+1]$^+$ 249.

6-Phenyl-2-(2-(1-(thiophen-2-yl)ethylidene)hydrazinyl)pyrimidin-4(3*H*)-one (8) This compound was obtained as yellow colored solid in 20% yield, mp: 228–230°C; ^{1} H NMR: δ 2.27 (s, 3H, —CH$_3$), 6.30 (s, 1H, Ar—H), 7.04–7.79 (m, 10H, Ar—H and ex—NH); ^{13}C NMR: δ 17.59, 101.31, 126.77, 126.87, 127.14, 127.23, 127.37, 127.44, 128.52, 128.64, 128.80, 130.44, 151.25, 152.10, 152.24, 167.55; *m/z* [M+1]$^+$ 311.

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REFERENCES AND NOTES

[1] Bag, S.; Tawari, N. R.; Degani, M. S. QSAR & Combi Sci 2008, 28, 296.

[2] Gangjee, A.; Kurup, S.; Namjoshi, O. Curr Pharm Design 2007, 13, 609.

[3] Gschwend, D. A.; Sirawaraporn, W.; Santi, D. V.; Kuntz, I. D. Proteins 1997, 29, 59.

[4] Glide, Version 4.5, Schrödinger, LLC, New York, 2008.

[5] Cody, V.; Galitsky, N.; Luft, J.; Pangborn, W.; Rosowsky, A.; Queener, S. F. Acta Cryst D 2002, 58, 946.

[6] Szilágyi, L.; Illyés, T. Z.; Györgydeák, Z.; Szabó, G.; Karácsony, A. Arkivoc 2004, vii, 243.

[7] Bower, J. D.; Doyle, F. P. J Chem Soc 1957, 727.

[8] Cooper, M. J.; Hull, R.; Wardleworth, M. J Chem Soc Perkin Trans 1 1975, 1433.

[9] Bag, S.; Vaze, V. V.; Degani, M. S. J Chem Res 2006, 4, 267.

[10] Broughton, M. C.; Queener, S. F. Antimicrob Agents Chemother 1991, 35, 1348.

[11] Chio, L.C.; Queener, S. F. Antimicrob Agents Chemother 1993, 37, 1914.

[12] Gangjee, A.; Yang, J.; Queener, S. F. Bioorg Med Chem 2006, 14, 8341.