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Efficient synthesis of antifungal pyrimidines via palladium catalyzed Suzuki/Sonogashira cross-coupling reaction from Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones

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ABSTRACT

An efficient regioselective approach to the synthesis of tetrasubstituted pyrimidines was developed by sequential functionalization of easily available Biginelli 3,4-dihydropyrimidine-2(1*H*)-ones via dehydrogenation, chlorination followed by palladium catalyzed C–C Suzuki/Sonogashira coupling reaction. All the synthesized compounds were evaluated in vitro for their antifungal activities against *Candida albicans*, *Cryptococcus neoformans*, *Benjaminiella poitrasii*, *Yarrowia lipolytica*, and *Fusarium oxysporum*, and antibacterial activities against Gram-negative *Escherichia coli* and Gram-positive *Staphylococcus aureus*.

1. Introduction

Fungal infections have emerged as a growing threat over the past two decades, particularly those caused by opportunistic pathogens in immune-compromised patients suffering from HIV infection, transplant recipients, and patients receiving cancer therapy.[1–8] The majority of these infections is caused by the most dreadful human pathogen *Candida albicans*. Infection rates by *Candida* species have increased by over a factor of 20 during the last couple of decades. The commercially available antifungal drug amphotericin B remains the standard therapy for life-threatening mycoses. However, this drug is associated with significant toxicity, including fever, headache, nausea, and vomiting, and dose-limiting nephrotoxicity.[9,10] Moreover, recent studies have documented resistance of *Candida* species to fluconazole[11] and other azole and triazole drugs,[12,13] which have been used widely. A potential approach to overcome this resistance problem is to design new and innovative agents with a completely different mode of action so that no cross-resistance with the present therapeuticals can occur.

Among the various nitrogen heterocycles, pyrimidine derivative have not been exploited as antifungal agents to a large extent. Except for a few pyrimidine derivatives such as trimethoprim and 5-fluorocytosine[14] no other compound has been found clinically successful.

The Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) are known for more than a century.[15] These non-planar heterocyclic compounds have interesting multifaceted pharmacological profiles such as calcium channel modulators, α_{1a}-adrenergic receptor antagonists, mitotic kinesin inhibitors, and hepatitis B virus replication inhibitors.[16–18] We were particularly interested in exploiting the versatility of the Suzuki cross-coupling procedure to prepare ethyl 4-methyl-2,6-diphenylpyrimidine-5-carboxylate **4**, starting from the easily available Biginelli DHPM. There are only a few reports in the literature for the synthesis of tetrasubstituted pyrimidines.[19–22] However, analogues of compound **4** have been previously synthesized by the reaction of nitrobenzylidene acetoacetic ester with nitrobenzaldehyde and ammonium acetate followed by dehydrogenation.[23] But the reported synthetic route can be applied only if an electron withdrawing nitro group is present in the aromatic ring of the benzylidene acetoacetic ester. Indeed, it would be advantageous to develop efficient synthesis of tetrasubstituted pyrimidines from Biginelli DHPMs. Recently, Kang et al.[24] developed a novel and efficient synthesis of multifunctionalized

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pyrimidines through Kappe dehydrogenation and PyBroP-mediated coupling with nucleophiles. However, there is no methodology reported for the direct arylation of the oxidized products of DHPMs, the corresponding 2-halopyrimidines. Herein, we report for the first time a short and efficient conversion of Biginelli DHPMs to multifunctionalized pyrimidines via oxidation, halogenation followed by Suzuki/Sonogashira cross-coupling reactions and the preliminary biological evaluation of all the synthesized compounds for their antifungal activities.

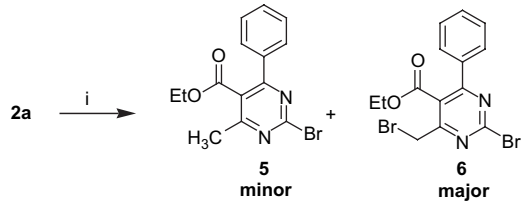
2. Chemistry

2.1. Biginelli reaction and oxidation of DHPM

The easily available Biginelli 3,4-dihydropyrimidine-2(1*H*)-ones were used as a starting material for the preparation of the new multifunctionalized pyrimidines. The overall synthetic protocol along with the target molecules synthesized, reagents and conditions are shown in Scheme 1. A series of DHPM libraries were synthesized using the method reported earlier.[25] For the second reaction step, we initially attempted oxidation of DHPMs using 60% nitric acid as reported in the literature.[26] The method in general provides moderate to good yields of oxidized products. However, factors such as steric hindrance, the presence of electron withdrawing substituents on phenyl ring, and solubility of DHPMs affected the yield and rate of reaction. Therefore, fine-tuning of conditions with respect to HNO_3 concentration and the reaction time was necessary in every case. In the light of the recent method reported by Shanmugam and Perumal[27] avoiding the said limitations, oxidation of DHPMs was carried out by the addition of CAN (Ceric Ammonium Nitrate) solution in water (3 equiv) to a mixture of **1a**–**h** and $NaHCO_3$ (5 equiv) suspended in acetone at ice–salt bath temperature, followed by stirring the reaction mixture at ambient temperature for 12 h (Scheme 1).

2.2. Halogenation reaction

To achieve better yields in Suzuki cross-coupling reaction and keeping in mind the low dissociation energy of carbon bromine bond, ethyl 1,2-dihydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate **2a** was heated with $POBr_3$ at 175 °C (Scheme 2) to obtain 2-bromopyrimidine derivative **5** as reported by Blachut et al.[28]



Scheme 2. Bromination reaction of **2a**: (i) $POBr_3$, 170 °C, 1 h, 85% (**6**).

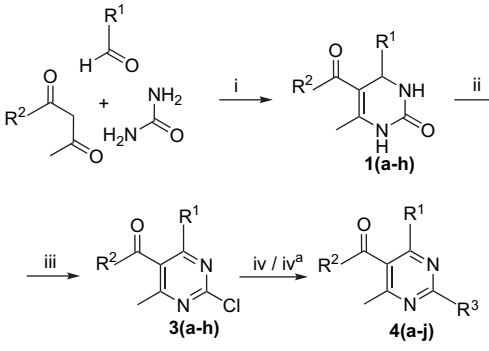
However, contrary to the literature report, we obtained the dibrominated ethyl 2-bromo-4-(bromomethyl)-6-phenylpyrimidine-5-carboxylate **6** as a major product and the expected monobrominated compound **5** was detected as a minor product (5%) by GC analysis.

The formation of dibrominated product was unambiguously supported by spectroscopic and analytical data. In the ^{1}H NMR spectra of compound **6**, the methylene protons attached to C_6 carbon can be readily assigned as a singlet at δ 4.63 ppm with an integration of two protons confirming the presence of methylene group. Accordingly, in the ^{13}C NMR spectra of compound **6**, the signal at δ 28.2 ppm can be assigned to methylene carbon attached to the C_6 carbon of pyrimidine ring system. In addition, the mass spectrum showed a peak for the molecular ion at *m*/*z* 397, 399, and 402 confirming the dibrominated product **6**. Thus, compound **6** was well characterized by IR and NMR spectral analyses; additionally the mass spectrum and elemental analysis are in conformity with the structure **6** (Scheme 2).

In order to avoid the above complication, a mixture of compound **2a** and *N*,*N*-dimethylaniline was refluxed in $POCl_3$ as chlorinating agent for 12 h to obtain ethyl 2-chloro-4-methyl-6-phenylpyrimidine-5-carboxylate **3a** in 82% yield as shown in Scheme 1.

2.3. Palladium catalyzed Suzuki–Miyaura/Sonogashira C–C bond formation reaction

The palladium catalyzed Suzuki–Miyaura cross-coupling reaction offers an attractive methodology for the introduction of aryl, alkenyl, and alkyl substituents into the electrophilic aromatic ring (Ar–X, where X=Cl, Br, I, OTf). From a survey of the literature, it was found that carbon–carbon bond formation on 2-halopyrimidines via transition-metal catalyzed cross-coupling reaction is well documented.[29–33] A wide variety of solvents and bases are commonly used in the Suzuki–Miyaura coupling reaction. Depending



	R1	R2	R3
a	C_6H_5	OEt	C_6H_5-4-$N(CH_3)_2$
b	4-$CH_3C_6H_4$	OEt	C_6H_5-4-$N(CH_3)_2$
c	3-$NO_2C_6H_4$	OEt	C_6H_5-4-$N(CH_3)_2$
d	3-ClC_6H_4	OEt	C_6H_5-4-$N(CH_3)_2$
e	2,5-$(OCH_3)_2C_6H_3$	OEt	C_6H_5-4-$N(CH_3)_2$
f	3,4,5-$(OCH_3)_3C_6H_2$	OEt	C_6H_5-4-$N(CH_3)_2$
g	4-$OCH_3C_6H_4$	OEt	C_6H_5-4-$N(CH_3)_2$
h	2,5-$(OCH_3)_2C_6H_3$	C_6H_5	1-$C_{10}H_7$
i	3,4,5-$(OCH_3)_3C_6H_2$	OEt	C≡C-C_6H_5
j	3,4,5-$(OCH_3)_3C_6H_2$	OEt	C≡C-C_6H_4-4-OCH_3

Scheme 1. Reagents and conditions: (i) Ref. 25, 80–92%; (ii) ceric ammonium nitrate (CAN), acetone, $NaHCO_3$, −5 °C to rt, 12 h, 70–92%; (iii) *N*,*N*-dimethylaniline, $POCl_3$, reflux, 12 h, 68–82%; (iv) (**4a**–**4h**) Boronic acid, $Pd(OAc)_2$, PPh_3, satd aqueous solution of Na_2CO_3–dioxane (4:6 v/v), 110 °C, 3–5 h, 78–95%; (iv[a]) (**4i** and **4j**) $Pd(PPh_3)_4$, acetonitrile, alkyne, triethyl amine, CuI, reflux, 4 h, 85–90%.

upon the position of the chloro substituents in the pyrimidine ring, the choice of solvent, base, and catalyst varies.

Initially, we attempted to use the reaction conditions reported earlier for Suzuki–Miyaura with 2-chloropyrimidine. However, this resulted in affording the cross-coupled product in moderate yields only. Then, we proceeded to optimize conditions to improve the yields. The results obtained are reported in Table 1.

In method A, the Suzuki coupling was carried out using the classical terakis(triphenylphosphine)palladium(0) as a catalyst in DME–H_2O (8:2) and Na_2CO_3 as base to achieve the cross-coupled product **4a** in 65% isolated yield.

Likewise, in method B 1,2-bis(diphenylphosphino)ethane palladium(II) chloride in dioxane and Na_2CO_3 as base gave the product ethyl 2-(4-(dimethylamino)phenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate **4a** in 60% yield. When we used a mixture of saturated aqueous solution of Na_2CO_3 as a base with dioxane (4:6 v/v) as a solvent in the presence of 0.2 equiv of PPh_3 and 0.04 equiv of $Pd(OAc)_2$ cross-coupled product **4a** was isolated in 85% yield after column chromatography (method C). Encouraged by the results obtained from CAN mediated oxidation of DHPMs followed by chlorination and the Suzuki–Miyaura sequence, it was obvious to extend this concept to the synthesis of various 2,4,5,6-tertasubstituted pyrimidines (Scheme 1). As a result various DHPMs were synthesized by using multicomponent approach from a variety of aromatic aldehydes, 1,3-diketones and urea and subjected to oxidation, chlorination followed by Suzuki coupling to obtain the various tetrasubstituted pyrimidines as crystalline solid (**4a**–**e** and **4h**) or as yellow oils (**4f**, **4g**) in excellent yields as shown in Table 2.

The alkynyl group introduction into ethyl 2-chloro-4-(3,4,5-trimethoxyphenyl)-6-methylpyrimidine-5-carboxylate **3f** was carried out by using standard Sonogashira reaction conditions. 2-Chloropyrimidine **3f** reacted with aryl acetylene (Table 2) at reflux temperature of acetonitrile in the presence of $Pd(PPh_3)_4$ (0.04 equiv) and CuI to form the corresponding 2-(arylethynyl) pyrimidines **4i** and **4j** in 85% and 90% isolated yields, respectively, as yellow oils.

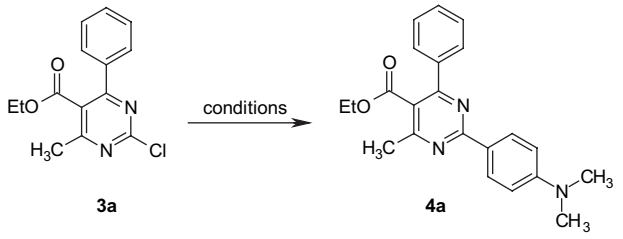
Moreover, X-ray crystallographic analysis of compound **4b** confirmed its structure as a tetrasubstituted pyrimidine derivative as shown by its ORTEP diagram (Fig. 1).

In vitro antimicrobial activities of the newly synthesized compounds were evaluated against the fungal strains viz., *C. albicans* 1 and 2, *Cryptococcus neoformans*, *Benjaminiella poitrasii*, *Yarrowia lipolytica*, *Fusarium oxysporum* 1 and 2 strains, and bacterial strains *Escherichia coli* (NCIM 2574) and *Staphylococcus aureus* (NCIM 2122) by microbroth dilution assay.

All the newly synthesized compounds exhibited comparable activities against the tested fungal strains to the reference drugs within MIC range 8–128 μg/ml (Table 3). Amongst all the screened compounds, **4c**, **4d**, **4e**, and **4j** displayed good activities against *C. albicans* 1 and 2. Among these, compound **4e** having methoxy substituents present at 2 and 5 positions on aryl ring was the most potent compound displaying significant activities at 8 μg/ml concentration. However, compounds **4d** and **4**(**f**–**j**) were significantly active against *C. neoformans* whereas compounds **4g** and **4i** having methoxy substituents present on aryl ring were found to be more potent against *B. poitrasii* at 16 μg/ml concentration. Compounds **4b**, **4d**, **4f**, and **4g** showed only moderate activities against *Y. lipolytica*. The best results were obtained with compound **4h** having naphthalene ring at the 2 position and activities of which was comparable to that of amphotericin B. Compounds **4c**, **4d**, **4g**, and **4j** showed good activities against *F. oxysporum* 1 and 2, a plant pathogen.

In vitro antibacterial activities of the newly synthesized compounds were also evaluated against the bacterial strains *E. coli* (NCIM 2574) and *S. aureus* (NCIM 2122) (Table 4). All the synthesized compounds **4**(**a**–**j**) showed comparable or better activities against the strain of *E. coli* with reference to erythromycin. Compounds **4d**, **4g**, and **4i** showed comparable activities with the standard drug erythromycin, whereas compounds **4a**–**4c**, **4e**, **4f**, **4h**, and **4j** showed higher activities than erythromycin. It was compound **4a** with no substituents present in the phenyl ring showed the more potent activities (MIC_{90}=16 μg/ml) as compared to the rest of the compounds tested. Compounds **4a**, **4b**, and **4g** were found to be potent against the strains of *S. aureus* and activities of these compounds were comparable to that of the standard erythromycin. Compound **4f** exhibited lowest MIC (16 μg/ml) against *S. aureus*, which were comparable to tetracycline (Table 4).

Table 1
Conditions for Suzuki coupling reaction on **3a**



3a **4a**

Entry	Pd catalyst	Method[a]	Product	Yield (%)
1	$Pd(PPh_3)_4$	A	**4a**	65
2	$Pd(dppe)Cl_2$	B	**4a**	60
3	$Pd(OAc)_2$	C	**4a**	85

[a] Condition A: **3a** (1.0 equiv), 4-(*N*,*N*-dimethylamino)phenylboronic acid (1.2 equiv), $Pd(PPh_3)_4$ (0.04 equiv), Na_2CO_3 (3.0 equiv), DME–H_2O (8:2), reflux, 5 h. Condition B: **3a** (1.0 equiv), 4-(*N*,*N*-dimethylamino)phenylboronic acid (1.2 equiv), $Pd(dppe)Cl_2$ (0.04 equiv), Na_2CO_3 (3.0 equiv), dioxane, reflux, 5 h. Comdition C: **3a** (1.0 equiv), 4-(*N*,*N*-dimethylamino)phenylboronic acid (1.2 equiv), $Pd(OAc)_2$ (0.04 equiv), PPh_3 (0.2 equiv), satd aqueous solution of Na_2CO_3–dioxane (4:6 v/v), reflux, 5 h.

3. Conclusion

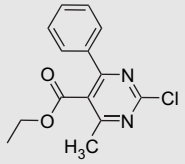
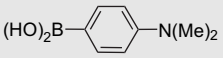
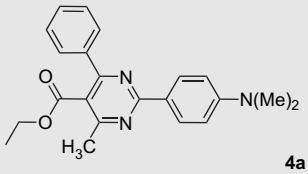
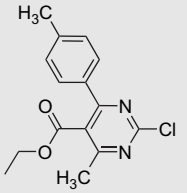
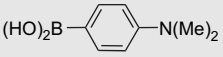
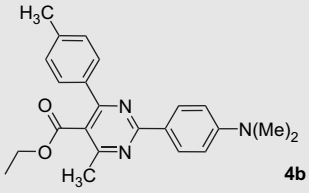
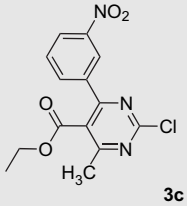
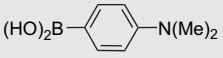
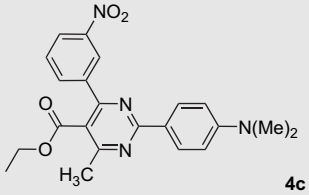
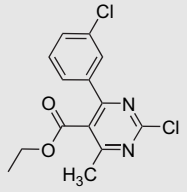
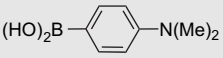
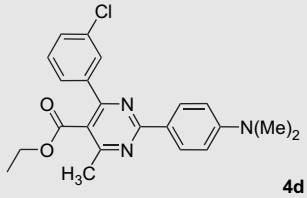
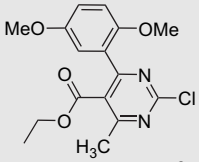
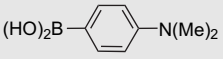
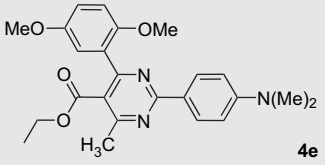
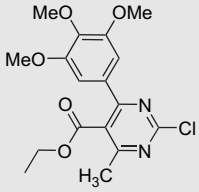
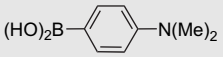
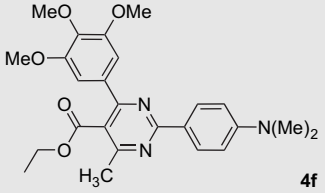
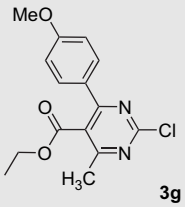
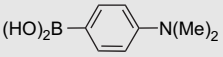
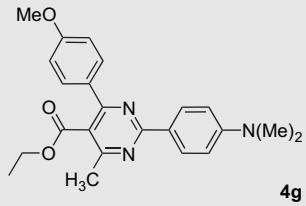
In conclusion, we have developed a four step protocol for the synthesis of diversely substituted novel pyrimidines. A series of chlorinated pyrimidines were synthesized from easily available Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones. The chlorinated pyrimidines were subjected to the conditions normally employed for Suzuki/Sonogashira coupling reactions to obtain *C*-phenyl pyrimidines. All the new molecules exhibited excellent in vitro antifungal and antibacterial profiles. The potency of most of the active compounds was greater than or comparable to standard drug fluconazole. We observed a qualitative correlation between antifungal activities and structure of pyrimidines. It can be concluded that the antifungal activities of pyrimidine are governed by the presence of strongly electron donating methoxy or electron withdrawing nitro substituents present at aryl ring. These compounds also possess significant activities against bacterial strains. Furthermore, since chloro compounds tend to be more easily available commercially, as well as less expensive, this pathway is quite desirable. A variety of commercially available 1,3-diketones and various substituted aldehydes and boronic acids can be used as building blocks to generate diversity on the core pyrimidine ring to obtain more potent antifungal and antibacterial compounds.

4. Experimental

4.1. General

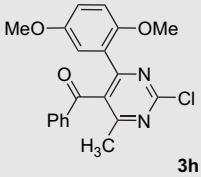
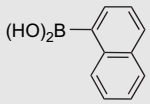
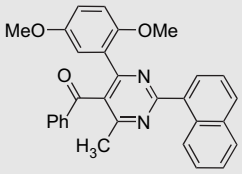
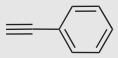
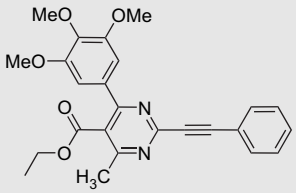
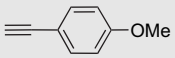
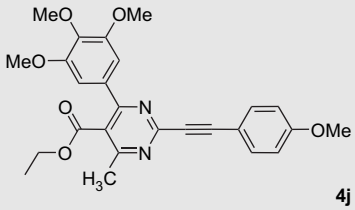
All chemicals were of research grade, obtained from Sigma–Aldrich, and were used without any further purification. Infrared spectra were recorded on an ATI MATT-SON RS-1 Research Series

Table 2
Synthesis of tetrasubstituted pyrimidines

Entry	Chloropyrimidine **3**(**a–h**)	Boronic acid/alkyne	Time (h)	Product **4**(**a–j**)	Yield[a] (%)
a	 **3a**		3	 **4a**	85
b	 **3b**		3	 **4b**	80
c	 **3c**		2	 **4c**	95
d	 **3d**		3	 **4d**	82
e	 **3e**		4	 **4e**	85
f	 **3f**		5	 **4f**	88
g	 **3g**		3.5	 **4g**	82

(*continued on next page*)

Table 2 (*continued*)

Entry	Chloropyrimidine **3**(**a–h**)	Boronic acid/alkyne	Time (h)	Product **4**(**a–j**)	Yield[a] (%)
h	 **3h**		4	 **4h**	78
i	**3f**		4	 **4i**	85
j	**3f**		4	 **4j**	90

[a] Isolated yields after column chromatography. Compounds **4i** and **4j** were synthesized by the classical Sonogashira reaction (see Section 4).

FT-IR spectrometer. NMR spectra were recorded on Bruker Avance DPX-200 spectrometer in $CDCl_3$. The melting points were uncorrected and recorded on the BUCHI melting point instrument model B-540. Elemental analyses were obtained from Flash EA 1112 Thermo Finnigan instrument at Microanalysis Laboratory, National Chemical Laboratory, Pune. Column chromatography was performed using silica gel (60–120 mesh size) purchased from Thomas Baker and TLC was carried out using aluminum sheets pre-coated with silica gel $60F_{254}$ purchased from Merck.

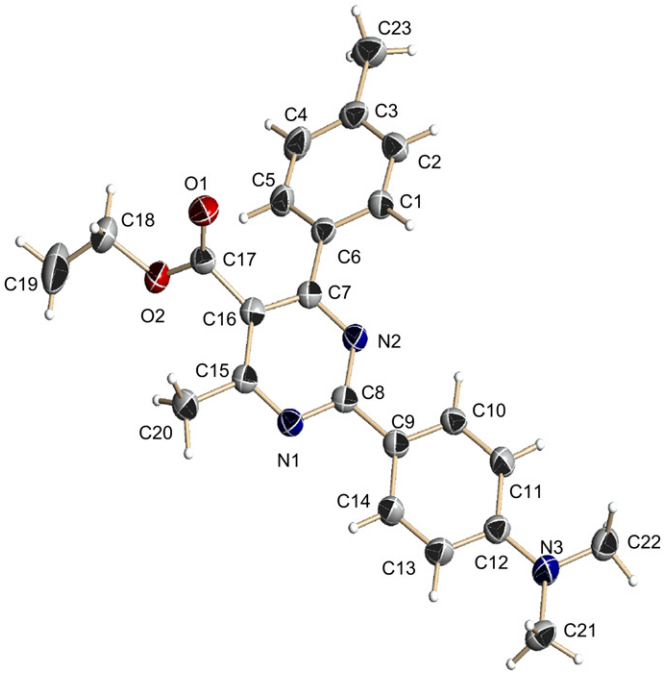


Figure 1. X-ray crystal structure of compound **4b**.

4.2. Ethyl 1,2-dihydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate 2a

A mixture of 5-ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidine-2(1*H*)-one **1a** (1.0 g, 3.84 mmol) and $NaHCO_3$ (1.61 g, 19.23 mmol) in 50 ml of acetone was cooled to −5 °C using ice–salt mixture. To this stirred suspension CAN (6.32 g, 11.53 mmol) in water (25 ml) was added for 1 h at −5 °C under argon atmosphere. The stirring was continued overnight at room temperature, and the reaction mixture was diluted with $CHCl_3$ (50 ml) and decanted. The residue was washed with $CHCl_3$ (2×40 ml). The combined $CHCl_3$ layer was washed with brine solution, dried over anhydrous Na_2SO_4, and purified by column chromatography using EtOAc–pet. ether (1:1) to afford pure product **2a** (0.793 g, 80%) as a white solid. R_f (EtOAc) 0.55; mp 191–193 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.92 (t, J=7.1 Hz, 3H), 2.61 (s, 3H), 4.04 (q, J=7.1 Hz, 2H), 7.37–7.48 (m, 3H), 7.57–7.62 (m, 2H), 13.73 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.3, 61.5, 111.4, 127.9, 128.2, 130.7, 158.2, 166.0; IR ($CHCl_3$, cm^{-1}): 3150, 2600, 1723, 1654, 1603, 1465, 1424, 1280, 1105, 755. Anal. Calcd for $C_{14}H_{14}N_2O_3$: C, 65.11; H, 5.46; N, 10.85. Found: C, 64.97; H, 5.58; N, 10.62.

4.3. Ethyl 2-chloro-4-methyl-6-phenylpyrimidine-5-carboxylate 3a

N,*N*-Dimethylaniline (0.515 ml, 4.06 mmol) was added to a stirred solution of ethyl 1,2-dihydro-6-methyl-2-oxo-4-phenylpyrimidine-5-carboxylate **2a** (0.750 g, 2.90 mmol) in $POCl_3$ (20 ml) and the reaction mixture was refluxed overnight. Excess of $POCl_3$ was removed under reduced pressure and the residue poured into ice water and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and

Table 3
In vitro antifungal activities for compounds **4**(**a**–**j**)

Compound	Inhibitory concentration in μg/ml													
	1		**2**		**3**		**4**		**5**		**6**		**7**	
	MIC[a]	IC_{50}[b]	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}	MIC	IC_{50}
4a	>128	128	>128	128	128	64	>128	128	128	64	>128	64	>128	64
4b	128	64	128	64	128	64	64	32	64	32	128	64	>128	64
4c	16	8	16	8	>128	64	32	16	128	64	32	16	32	16
4d	32	16	32	16	64	32	32	16	64	32	32	16	32	16
4e	8	4	8	4	128	32	64	32	>128	64	>128	64	>128	64
4f	>128	64	>128	64	32	16	32	16	64	32	64	32	64	32
4g	64	32	64	32	64	32	16	8	64	16	32	16	32	16
4h	128	64	128	64	64	16	32	16	32	16	64	32	64	32
4i	128	64	128	64	64	32	16	8	>128	128	128	64	128	64
4j	32	16	32	16	64	16	64	32	>128	128	32	16	32	16
Amphotericin-B	4	0.5	4	0.5	64	8	8	2	32	8	16	8	16	8
Fluconazole	32	16	32	16	32	16	64	8	31	16	8	4	8	4

Compound **1**: *C. albicans* 1; compound **2**: *C. albicans* 2; compound **3**: *C. Neoformans*; compound **4**: *B. poitrasii*; compound **5**: *Y. lipolytica*; compound **6**: *F. oxysporum* 1; compound **7**: *F. oxysporum* 2.
Negative control, DMSO, No inhibition.
[a] MIC_{90} (Minimum inhibitory concentration) was determined as 90% inhibition of growth with respect to the growth control.
[b] IC_{50} was the concentration at which 50% growth inhibition was observed.

Table 4
In vitro antibacterial activities for compounds **4**(**a**–**j**)

compound	Inhibitory concentration in μg/ml			
	E. coli		*S. aureus*	
	MIC	IC_{50}	MIC	IC_{50}
4a	16	8	32	16
4b	32	16	32	16
4c	32	16	64	32
4d	64	32	128	32
4e	32	16	64	32
4f	32	16	16	8
4g	64	32	32	16
4h	32	16	64	32
4i	64	32	128	64
4j	32	16	64	32
Tetracycline	8	4	16	8
Erythromycin	64	32	32	16

evaporated in vacuo. The crude product was purified by column chromatography using EtOAc–pet. ether (0.5:9.5) to afford colorless thick liquid **3a** (0.670 g, 82%). R_f (10% EtOAc–pet. ether) 0.62; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.07 (t, J=7.2 Hz, 3H), 2.62 (s, 3H), 4.20 (q, J=7.2 Hz, 2H), 7.40–7.50 (m, 3H), 7.63–7.67 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.5, 22.4, 62.1, 124.3, 128.3, 128.5, 130.6, 136.1, 160.4, 166.1, 166.9, 168.5; IR ($CHCl_3$, cm^{-1}): 3062, 2983, 1728, 1538, 1446, 1380, 1306, 1207, 1185, 937, 863, 768, 793, 698. Anal. Calcd for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.74; N, 10.12. Found: C, 60.92; H, 4.51; N, 9.95.

4.4. Ethyl 2-(4-(dimethylamino)phenyl)-4-methyl-6-phenylpyrimidine-5-carboxylate 4a

A mixture of ethyl 2-chloro-4-methyl-6-phenylpyrimidine-5-carboxylate **3a** (0.5 g, 1.81 mmol) and 4-(*N*,*N*-dimethylamino)phenylboronic acid (0.358 g, 2.17 mmol) was dissolved in dioxane (12 ml) and stirred for 5 min at room temperature. To this mixture saturated solution of Na_2CO_3 (8 ml) was added followed by palladium acetate (0.016 g, 0.072 mmol) and triphenylphosphine (0.094 g, 0.36 mmol). The reaction mixture was heated to 110 °C for 3 h. The cooled mixture was diluted with ethyl acetate, filtered over a plug of Celite bed, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography using EtOAc–pet. ether (0.5:9.5) to afford **4a** as pale yellow solid (0.560 g, 85%). R_f (10% EtOAc–pet. ether) 0.58, blue fluorescent spot; mp 122–124 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.05 (t, J=7.2 Hz, 3H), 2.65 (s, 3H), 3.06 (s, 6H), 4.17 (q, J=7.2 Hz, 2H), 6.76 (d, J=9.1 Hz, 2H), 7.44–7.48 (m, 3H), 7.71–7.75 (m, 2H), 8.45 (d, J=9.1 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.5, 22.9, 40.1, 61.4, 111.3, 121.4, 124.6, 128.2, 128.3, 129.6, 130.0, 138.7, 152.3, 163.4, 163.9, 165.0, 168.8; IR ($CHCl_3$, cm^{-1}): 3017, 2984, 1718, 1608, 1535, 1402, 1364, 1265, 1188, 1080, 810, 757, 700, 667. Anal. Calcd for $C_{22}H_{23}N_3O_2$: C, 73.11; H, 6.41; N, 11.63. Found: C, 73.32; H, 6.54; N, 11.75.

4.5. Ethyl 1,2-dihydro-6-methyl-2-oxo-4-*p*-tolylpyrimidine-5-carboxylate 2b

Compound **1b** (1 g, 3.64 mmol) was reacted as described in Section 4.2 to give **2b** as white solid (0.812 g, 82%). R_f (EtOAc) 0.55; mp 167–169 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.99 (t, J=7.0 Hz, 3H), 2.39 (s, 3H), 2.58 (s, 3H), 4.08 (q, J=7.0 Hz, 2H), 7.23 (d, J=8.2 Hz, 2H), 7.51 (d, J=8.2 Hz, 2H), 13.64 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.4, 21.3, 61.5, 111.3, 128.0, 129.0, 141.3, 158.3, 166.2; IR ($CHCl_3$, cm^{-1}): 3150, 2600, 1730, 1545, 1645, 1600, 1524, 1424, 1250, 1180, 820, 756. Anal. Calcd for $C_{15}H_{16}N_2O_3$: C, 66.16; H, 5.92; N, 10.29. Found: C, 66.04; H, 5.75; N, 10.41.

4.6. Ethyl 2-chloro-4-methyl-6-*p*-tolylpyrimidine-5-carboxylate 3b

Compound **2b** (0.8 g, 2.94 mmol) was reacted as described in Section 4.3 to give **3b** as colorless liquid (0.664 g, 78%). R_f (10% EtOAc–pet. ether) 0.65; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.13 (t, J=7.2 Hz, 3H), 2.40 (s, 3H), 2.60 (s, 3H), 4.23 (q, J=7.2 Hz, 2H), 7.25 (d, J=8.0 Hz, 2H), 7.57 (d, J=8.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.6, 21.3, 22.4, 62.1, 124.1, 128.3, 129.3, 133.3, 141.3, 160.4, 166.0, 167.2, 168.3; IR ($CHCl_3$, cm^{-1}): 3058, 2982, 1728, 1612, 1540, 1445, 1378, 1306, 1207, 1185, 1081, 934. Anal. Calcd for $C_{15}H_{15}ClN_2O_2$: C, 61.97; H, 5.20; N, 9.63. Found: C, 61.84; H, 5.25; N, 9.79.

4.7. Ethyl 2-(4-(dimethylamino)phenyl)-4-methyl-6-*p*-tolylpyrimidine-5-carboxylate 4b

Compound **3b** (0.4 g, 1.37 mmol) was reacted as described in Section 4.4 to give **4b** as pale yellow solid (0.413 g, 80%). R_f (10% EtOAc–pet. ether) 0.57, blue fluorescent spot; mp 117–119 °C; ^{1}H

NMR (200 MHz, $CDCl_3$) δ: 1.11 (t, J=7.2 Hz, 3H), 2.42 (s, 3H), 2.64 (s, 3H), 3.05 (s, 6H), 4.20 (q, J=7.2 Hz, 2H), 6.76 (d, J=9.2 Hz, 2H), 7.26 (d, J=8.0 Hz, 2H), 7.65 (d, J=8.0 Hz, 2H), 8.44 (d, J=9.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.6, 21.3, 22.8, 40.0, 61.4, 111.3, 121.3, 124.8, 128.3, 129.0, 129.9, 135.8, 139.7, 152.2, 163.1, 163.8, 164.7, 169.0; IR ($CHCl_3$, cm^{-1}): 3020, 1717, 1605, 1530, 1462, 1376, 1360, 1266, 1185, 1076, 861. Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.58; H, 6.71; N, 11.19. Found: C, 73.64; H, 6.55; N, 11.28.

4.8. Ethyl 1,2-dihydro-6-methyl-4-(3-nitrophenyl)-2-oxopyrimidine-5-carboxylate 2c

Compound **1c** (0.850 g, 2.78 mmol) was reacted as described in Section 4.2 to give **2c** as yellow solid (0.607 g, 72%). R_f (EtOAc) 0.38; mp 213–215 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.89 (t, J=7.2 Hz, 3H), 2.76 (s, 3H), 3.98 (q, J=7.2 Hz, 2H), 7.33–7.38 (m, 1H), 7.56–7.76 (m, 2H), 8.21–8.26 (m, 1H), 13.70 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.3, 20.3, 61.2, 109.6, 124.1, 128.9, 129.6, 133.6, 146.2, 157.6, 163.5; IR ($CHCl_3$, cm^{-1}): 3362, 1715, 1659, 1592, 1532, 1460, 1376, 1353, 1287,1272, 1206, 1093, 1032, 924. Anal. Calcd for $C_{14}H_{13}N_3O_5$: C, 55.45; H, 4.32; N, 13.86. Found: C, 55.34; H, 4.15; N, 13.97.

4.9. Ethyl 2-chloro-4-methyl-6-(3-nitrophenyl)pyrimidine-5-carboxylate 3c

Compound **2c** (0.720 g, 2.37 mmol) was reacted as described in Section 4.3 to give **3c** as yellow solid (0.533 g, 70%). R_f (20% EtOAc–pet. ether) 0.48; mp 98–100 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.19 (t, J=7.2 Hz, 3H), 2.66 (s, 3H), 4.30 (q, J=7.2 Hz, 2H), 7.68 (t, J=8.0 Hz, 1H), 8.01–8.06 (m, 1H), 8.34–8.40 (m, 1H), 8.55 (t, J=2.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.6, 22.6, 62.6, 123.4, 124.5, 125.2, 129.8, 134.3, 137.6, 148.2, 160.7, 163.3, 166.3, 169.3; IR ($CHCl_3$, cm^{-1}): 3008, 2925, 1726, 1614, 1535, 1462, 1376, 1309, 1280, 1232, 1083, 1012, 907, 862. Anal. Calcd for $C_{14}H_{12}ClN_3O_4$: C, 52.27; H, 3.76; N, 13.06. Found: C, 52.34; H, 3.62; N, 13.22.

4.10. Ethyl 2-(4-(dimethylamino)phenyl)-4-methyl-6-(3-nitrophenyl)pyrimidine-5-carboxylate 4c

Compound **3c** (0.450 g, 1.40 mmol) was reacted as described in Section 4.4 to give **4c** as light yellow solid (0.540 g, 95%). R_f (20% EtOAc–pet. ether) 0.45, blue fluorescent spot; mp 138–140 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.15 (t, J=7.1 Hz, 3H), 2.68 (s, 3H), 3.07 (s, 6H), 4.24 (q, J=7.1 Hz, 2H), 6.76 (d, J=9.2 Hz, 2H), 7.65 (t, J=8.0 Hz, 1H), 8.04–8.09 (m, 1H), 8.31–8.37 (m, 1H), 8.43 (d, J=9.2 Hz, 2H), 8.63 (t, J=2.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.7, 23.1, 40.1, 61.8, 111.4, 121.3, 123.5, 124.0, 124.24, 129.3, 130.1, 134.4, 140.3, 148.2, 152.5, 160.9, 164.2, 165.7, 168.1; IR ($CHCl_3$, cm^{-1}): 2940, 1701, 1608, 1533, 1462, 1377, 1271, 1192, 1117, 1082, 945, 862. Anal. Calcd for $C_{22}H_{22}N_4O_4$: C, 65.01; H, 5.46; N, 13.78. Found: C, 65.20; H, 5.58; N, 13.62.

4.11. Ethyl 4-(3-chlorophenyl)-1,2-dihydro-6-methyl-2-oxopyrimidine-5-carboxylate 2d

Compound **1d** (0.8 g, 2.72 mmol) was reacted as described in Section 4.2 to give **2d** as white solid (0.603 g, 76%). R_f (EtOAc) 0.58; mp 153–155 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.01 (t, J=7.2 Hz, 3H), 2.64 (s, 3H), 4.11 (q, J=7.2 Hz, 2H), 7.33–7.65 (m, 4H), 13.82 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.4, 18.8, 61.6, 111.2, 126.0, 128.1, 129.4, 130.5, 134.3, 139.1, 158.1, 165.4; IR ($CHCl_3$, cm^{-1}): 3325, 3090, 1719, 1655, 1603, 1571, 1474, 1445, 1369, 1280, 1266, 1215, 1108, 1015, 971. Anal. Calcd for $C_{14}H_{13}ClN_2O_3$: C, 57.45; H, 4.48; N, 9.57. Found: C, 57.58; H, 4.55; N, 9.40.

4.12. Ethyl 2-chloro-4-(3-chlorophenyl)pyrimidine-5-carboxylate 3d

Compound **2d** (0.550 g, 1.88 mmol) was reacted as described in Section 4.3 to give **3d** as colorless solid (0.460 g, 79%). R_f (10% EtOAc–pet. ether) 0.62; mp 62–64 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.14 (t, J=7.2 Hz, 3H), 2.63 (s, 3H), 4.25 (q, J=7.2 Hz, 2H), 7.35–7.68 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.6, 22.5, 62.3, 124.4, 126.5, 128.4, 129.9, 130.7, 134.7, 137.8, 160.5, 164.5, 166.6, 168.9; IR ($CHCl_3$, cm^{-1}): 3070, 2984, 1731, 1537, 1478, 1431, 1374, 1308, 1268, 1226, 1186, 1144, 1081, 1012, 939, 892. Anal. Calcd for $C_{14}H_{12}Cl_2N_2O_2$: C, 54.04; H, 3.89; N, 9.00. Found: C, 54.20; H, 3.71; N, 9.14.

4.13. Ethyl 4-(3-chlorophenyl)-2-(4-(dimethylamino)phenyl)-6-methylpyrimidine-5-carboxylate 4d

Compound **3d** (0.4 g, 1.29 mmol) was reacted as described in Section 4.4 to give **4d** as yellow solid (0.417 g, 82%); R_f (10% EtOAc–pet. ether) 0.60, blue fluorescent spot; mp 124–126 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.12 (t, J=7.2 Hz, 3H), 2.66 (s, 3H), 3.06 (s, 6H), 4.21 (q, J=7.2 Hz, 2H), 6.76 (d, J=9.2 Hz, 2H), 7.34–7.48 (m, 2H), 7.56–7.61 (m, 1H), 7.74–7.76 (m, 1H), 8.44 (d, J=9.2 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.6, 22.9, 40.0, 61.6, 111.3, 121.3, 124.3, 126.5, 128.5, 129.5, 129.6, 130.0, 134.3, 140.4, 152.4, 161.9, 164.0, 165.3, 168.3; IR ($CHCl_3$, cm^{-1}): 2981, 2902, 1721, 1608, 1583, 0478, 1401, 1364, 1262, 1188. Anal. Calcd for $C_{22}H_{22}ClN_3O_2$: C, 66.75; H, 5.60; N, 10.61. Found: C, 66.70; H, 5.42; N, 10.49.

4.14. Ethyl 1,2-dihydro-4-(2,5-dimethoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate 2e

Compound **1e** (0.7 g, 2.18 mmol) was reacted as described in Section 4.2 to give **2e** (0.612 g, 88%) as light brown solid. R_f (EtOAc) 0.48; mp 171–173 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.97 (t, J=7.2 Hz, 3H), 2.66 (s, 3H), 3.71 (s, 3H), 3.81 (s, 3H), 4.03 (q, J=7.2 Hz, 2H), 6.80 (d, J=8.9 Hz, 1H), 6.96 (dd, J=3.0, 8.9 Hz, 1H), 7.12 (d, J=3.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.5, 55.6, 55.8, 60.8, 111.3, 112.3, 115.0, 117.5, 150.5, 153.6, 158.3, 165.1; IR ($CHCl_3$, cm^{-1}): 3311, 3073, 1717, 1657, 1594, 1494, 1456, 1436, 1365, 1322, 1284, 1267, 1223, 1130. Anal. Calcd for $C_{16}H_{18}N_2O_5$: C, 60.37; H, 5.70; N, 8.80. Found: C, 60.48; H, 5.92; N, 8.95.

4.15. Ethyl 2-chloro-4-(2,5-dimethoxyphenyl)-6-methyl pyrimidine-5-carboxylate 3e

Compound **2e** (0.5 g, 1.57 mmol) was reacted as described in Section 4.3 to give **3e** (0.406 g, 77%) as light brown solid. R_f (30% EtOAc–pet. ether) 0.49; mp 90–92 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.03 (t, J=7.2 Hz, 3H), 2.69 (s, 3H), 3.69 (s, 3H), 3.81 (s, 3H), 4.11 (q, J=7.2 Hz, 2H), 6.82 (d, J=9.0 Hz, 1H), 6.97 (dd, J=3.0, 9.0 Hz, 1H), 7.08 (d, J=3.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.5, 23.2, 55.5, 55.8, 61.3, 111.5, 115.6, 117.2, 125.1, 126.6, 150.4, 153.7, 160.5, 165.5, 165.8, 168.9; IR ($CHCl_3$, cm^{-1}): 3017, 2907, 1728, 1587, 1538, 1502, 1464, 1424, 1310, 1273, 1215, 1183, 1086, 1045, 1024, 946, 923, 864, 812, 759, 667. Anal. Calcd for $C_{16}H_{17}ClN_2O_4$: C, 57.06; H, 5.09; N, 8.32. Found: C, 56.88; H, 5.25; N, 8.45.

4.16. Ethyl 2-(4-(dimethylamino)phenyl)-4-(2,5-dimethoxyphenyl)-6-methylpyrimidine-5-carboxylate 4e

Compound **3e** (0.380 g, 1.13 mmol) was reacted as described in Section 4.4 to give **4e** (0.404 g, 85%) as light yellow solid. R_f (30% EtOAc–pet. ether) 0.46, blue fluorescent spot; mp 133–136 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 0.97 (t, J=7.2 Hz, 3H), 2.65 (s, 3H), 2.97 (s, 6H), 3.63 (s, 3H), 3.76 (s, 3H), 4.03 (q, J=7.2 Hz, 2H), 6.67 (d, J=9.0 Hz, 2H), 6.75 (d, J=9.1 Hz, 1H), 6.89 (dd, J=3.0, 9.1 Hz, 1H), 7.16

(d, J=3.0 Hz, 1H), 8.36 (d, J=9.0 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.5, 23.7, 40.0, 55.6, 55.7, 60.6, 111.3, 111.4, 115.7, 116.2, 122.1, 124.7, 129.3, 130.0, 150.7, 152.2, 153.6, 162.4, 164.2, 165.3, 167.4; IR ($CHCl_3$, cm^{-1}): 2934, 1723, 1609, 1537, 1500, 1428, 1402, 1363, 1260, 1224, 1189, 1077, 1047, 1023, 982, 945, 753. Anal. Calcd for $C_{24}H_{27}N_3O_4$: C, 68.39; H, 6.46; N, 9.97. Found: C, 68.44; H, 6.55; N, 10.14.

4.17. Ethyl 1,2-dihydro-4-(3,4,5-trimethoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate 2f

Compound **1f** (0.750 g, 2.14 mmol) was reacted as described in Section 4.2 to give **2f** (0.685 g, 92%) as yellow solid. R_f (EtOAc) 0.50; mp 137–139 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.03 (t, J=7.2 Hz, 3H), 2.60 (s, 3H), 3.89 (s, 6H), 3.90 (s, 3H), 4.11 (q, J=7.2 Hz, 2H), 6.88 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.5, 56.1, 60.8, 61.6, 105.3, 111.5, 140.3, 153.0, 158.2, 166.3; IR ($CHCl_3$, cm^{-1}): 3052, 1720, 1699, 1604, 1506, 1463, 1433, 1385, 1321, 1265, 1241, 1128, 1005, 855. Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.74; H, 5.68; N, 7.95.

4.18. Ethyl 2-chloro-4-(3,4,5-trimethoxyphenyl)-6-methylpyrimidine-5-carboxylate 3f

Compound **2f** (0.6 g, 1.72 mmol) was reacted as described in Section 4.3 to give **3f** (0.473 g, 75%) as colorless solid. R_f (30% EtOAc–pet. ether) 0.51; mp 74–77 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.15 (t, J=7.1 Hz, 3H), 2.61 (s, 3H), 3.90 (s, 9H), 4.25 (q, J=7.1 Hz, 2H), 6.91 (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.7, 22.3, 56.2, 60.9, 62.2, 105.7, 124.3, 131.4, 140.3, 153.3, 160.3, 165.6, 167.3, 168.3; IR ($CHCl_3$, cm^{-1}): 3002, 2907, 1736, 1586, 1544, 1506, 1464, 1417, 1380, 1279, 1226, 1187, 1122, 1089, 1001, 929, 861, 713. Anal. Calcd for $C_{17}H_{19}ClN_2O_5$: C, 55.67; H, 5.22; N, 7.64. Found: C, 55.53; H, 5.32; N, 7.45.

4.19. Ethyl 2-(4-(dimethylamino)phenyl)-4-(3,4,5-trimethoxyphenyl)-6-methylpyrimidine-5-carboxylate 4f

Compound **3f** (0.450 g, 1.22 mmol) was reacted as described in Section 4.4 to give **4f** (0.487 g, 88%) as thick yellow liquid. R_f (30% EtOAc–pet. ether) 0.48, blue fluorescent spot; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.12 (t, J=7.0 Hz, 3H), 2.63 (s, 3H), 3.06 (s, 6H), 3.90 (s, 3H), 3.91 (s, 6H), 4.21 (q, J=7.0 Hz, 2H), 6.77 (d, J=9.0 Hz, 2H), 6.99 (s, 2H), 8.43 (d, J=9.0 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.6, 22.6, 39.9, 56.0, 60.7, 61.4, 105.5, 111.2, 121.3, 124.4, 129.9, 134.0, 139.3, 152.2, 153.0, 162.7, 163.7, 164.7, 168.9; IR ($CHCl_3$, cm^{-1}): 2937, 1717, 1609, 1588, 1538, 1504, 1400, 1363, 1301, 1259, 1188, 1127, 1076, 1006, 946, 911, 853, 834, 804, 758, 732, 708. Anal. Calcd for $C_{25}H_{29}N_3O_5$: C, 66.50; H, 6.47; N, 9.31. Found: C, 66.42; H, 6.59; N, 9.22.

4.20. Ethyl 1,2-dihydro-4-(4-methoxyphenyl)-6-methyl-2-oxopyrimidine-5-carboxylate 2g

Compound **1g** (0.780 g, 2.68 mmol) was reacted as described in Section 4.2 to give **2g** (0.657 g, 85%) as white solid. R_f (EtOAc) 0.52; mp 163–165 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.06 (t, J=7.2 Hz, 3H), 2.59 (s, 3H), 3.86 (s, 3H), 4.12 (q, J=7.2 Hz, 2H), 6.94 (d, J=8.8 Hz, 2H), 7.62 (d, J=8.8 Hz, 2H), 13.64 (br s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.5, 52.2, 55.2, 61.5, 111.0, 113.7, 130.0, 158.3, 161.9, 166.4; IR ($CHCl_3$, cm^{-1}): 3357, 1713, 1667, 1592, 1449, 1377, 1881, 1262, 1213, 1168, 1109, 1019, 842, 797, 686. Anal. Calcd for $C_{15}H_{16}N_2O_4$: C, 62.49; H, 5.59; N, 9.72. Found: C, 62.64; H, 5.48; N, 9.90.

4.21. Ethyl 2-chloro-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate 3g

Compound **2g** (0.6 g, 2.08 mmol) was reacted as described in Section 4.3 to give **3g** (0.496 g, 78%) as colorless liquid. R_f (25% EtOAc–pet. ether) 0.55; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.18 (t, J=7.2 Hz, 3H), 2.59 (s, 3H), 3.87 (s, 3H), 4.27 (q, J=7.2 Hz, 2H), 6.97 (d, J=8.9 Hz, 2H), 7.67 (d, J=8.9 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.7, 22.4, 55.3, 62.1, 114.1, 123.7, 128.4, 130.2, 160.3, 161.9, 165.3, 167.5, 168.1; IR ($CHCl_3$, cm^{-1}): 3003, 2937, 1727, 1608, 1530, 1514, 1380, 1301, 1258, 1207, 1181, 1133, 1082, 1031, 934, 868. Anal. Calcd for $C_{15}H_{15}ClN_2O_3$: C, 58.73; H, 4.93; N, 9.13. Found: C, 58.65; H, 4.65; N, 9.22.

4.22. Ethyl 2-(4-(dimethylamino)phenyl)-4-(4-methoxyphenyl)-6-methylpyrimidine-5-carboxylate 4g

Compound **3g** (0.400 g, 1.30 mmol) was reacted as described in Section 4.4 to give **4g** (0.419 g, 82%) as yellow liquid. R_f (25% EtOAc–pet. ether) 0.52, blue fluorescent spot; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.15 (t, J=7.1 Hz, 3H), 2.63 (s, 3H), 3.06 (s, 6H), 3.87 (s, 3H), 4.23 (q, J=7.1 Hz, 2H), 6.76 (d, J=9.1 Hz, 2H), 6.98 (d, J=8.8 Hz, 2H), 7.73 (d, J=8.8 Hz, 2H), 8.44 (d, J=9.1 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.7, 22.8, 40.1, 55.3, 61.4, 111.3, 113.7, 121.0, 124.8, 129.95, 129.98, 131.0, 152.3, 161.0, 162.5, 163.8, 164.7, 169.2; IR ($CHCl_3$, cm^{-1}): 2981, 2934, 1717, 1608, 1533, 1509, 1432, 1418, 1399, 1363, 1293, 1263, 1187, 1076, 1032, 946, 909, 804, 803, 756, 667. Anal. Calcd for $C_{23}H_{25}N_3O_3$: C, 70.57; H, 6.44; N, 10.73. Found: C, 70.74; H, 6.52; N, 10.94.

4.23. 5-Benzoyl-4-(2,5-dimethoxyphenyl)-6-methylpyrimidin-2(1*H*)-one 2h

Compound **1h** (0.920 g, 2.61 mmol) was reacted as described in Section 4.2 to give **2h** (0.639 g, 70%) as light brown solid. R_f (EtOAc) 0.55; mp 191–193 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 2.40 (s, 3H), 3.41 (s, 3H), 3.71 (s, 3H), 6.55 (d, J=9.0 Hz, 1H), 6.76–6.79 (dd, J=3.2, 9.0 Hz, 1H), 6.97 (br s, 1H), 7.32–7.36 (m, 2H), 7.44–7.49 (m, 1H), 7.69–7.71 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 54.6, 55.7, 111.5, 115.4, 117.8, 118.3, 128.2, 129.1, 133.1, 137.3, 149.9, 153.3, 158.6, 192.7; IR ($CHCl_3$, cm^{-1}): 3330, 1690, 1665, 1639, 1597, 1498, 1461, 1430, 1376, 1269, 1228, 1179, 1043, 814, 762, 743. Anal. Calcd for $C_{20}H_{18}N_2O_4$: C, 68.56; H, 5.18; N, 8.00. Found: C, 68.64; H, 5.02; N, 7.89.

4.24. (2-Chloro-4-(2,5-dimethoxyphenyl)-6-methylpyrimidin-5-yl)(phenyl)methanone 3h

Compound **2h** (0.6 g, 1.71 mmol) was reacted as described in Section 4.3 to give **3h** (0.428 g, 68%) as thick light blue liquid. R_f (30% EtOAc–pet. ether) 0.52; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.42 (s, 3H), 3.26 (s, 3H), 3.74 (s, 3H), 6.59 (d, J=9.0 Hz, 1H), 6.79–6.85 (dd, J=3.2, 9.0 Hz, 1H), 6.96 (d, J=3.2 Hz, 1H), 7.36–7.44 (m, 2H), 7.50–7.57 (m, 1H), 7.70–7.75 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.5, 54.4, 55.7, 111.5, 115.9, 117.6, 125.2, 126.2, 128.5, 129.1, 130.4, 133.6, 136.3, 149.9, 153.5, 160.4, 165.2, 167.6, 193.6; IR ($CHCl_3$, cm^{-1}): 3019, 2920, 1670, 1598, 1582, 1534, 1503, 1449, 1464, 1424, 1274, 1215, 1180, 1045, 950. Anal. Calcd for $C_{20}H_{17}ClN_2O_3$: C, 65.13; H, 4.56; N, 7.60. Found: C, 65.24; H, 4.41; N, 7.74.

4.25. (4-(2,5-Dimethoxyphenyl)-6-methyl-2-(naphthalen-1-yl)pyrimidin-5-yl)(phenyl) methanone 4h

Compound **3h** (0.350 g, 0.95 mmol) was reacted as described in Section 4.4 to give **4h** (0.340 g, 78%) as light gray solid. R_f (30% EtOAc–pet. ether) 0.50, blue fluorescent spot; mp 67–69 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 2.57 (s, 3H), 3.38 (s, 3H), 3.73 (s, 3H), 6.64 (d, J=9.0 Hz, 1H), 6.79–6.85 (dd, J=3.0, 9.0 Hz, 1H), 7.09 (d, J=3.0 Hz, 1H), 7.40–7.59 (m, 6H), 7.83–8.01 (m, 4H), 8.18–8.22 (dd, J=1.2, 7.2 Hz, 4H), 8.81–8.85 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 23.8, 54.5, 55.7, 111.5, 116.2, 116.7, 125.2, 125.8, 125.9, 126.7, 126.8, 128.4,

129.2, 129.4, 129.5, 130.64, 133.4, 133.54, 134.0, 135.5, 136.8, 150.1, 153.4, 162.3, 164.4, 166.3, 195.2; IR ($CHCl_3$, cm^{-1}): 2930, 1666, 1581, 1595, 1530, 1499, 1462, 1377, 1269, 1250, 1223, 1044, 1023, 926. Anal. Calcd for $C_{30}H_{24}N_2O_3$: C, 78.24; H, 5.25; N, 6.08. Found: C, 78.12; H, 5.34; N, 5.89.

4.26. Ethyl 4-(3,4,5-trimethoxyphenyl)-6-methyl-2-(2-phenylethynyl)pyrimidine-5-carboxylate 4i

A mixture of ethyl 2-chloro-4-(3,4,5-trimethoxyphenyl)-6-methylpyrimidine-5-carboxylate **3f** (0.356 g, 0.97 mmol) and $Pd(PPh_3)_4$ (0.044 g, 0.038 mmol) was dissolved in MeCN (10 ml). To this mixture, phenylacetylene (0.119 g, 1.16 mmol), triethyl amine (0.4 ml, 2.91 mmol), and CuI (0.073 g, 0.038 mmol) were added and the mixture was refluxed under argon for 4 h up to complete consumption of starting material as judged by TLC and GC analyses. After the completion of reaction, reaction mixture was filtered and evaporated and the residue was purified by column chromatography by using EtOAc–pet. ether (1.5:8.5) as a eluent to obtain **4i** (0.357 g, 85%) as a thick liquid. R_f (30% EtOAc–pet. ether) 0.56, blue fluorescent spot; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.15 (t, J=7.2 Hz, 3H), 2.65 (s, 3H), 3.89 (s, 3H), 3.91 (s, 6H), 4.24 (q, J=7.2 Hz, 2H), 6.93 (s, 2H), 7.38–7.43 (m, 3H), 7.68–7.73 (dd, J=2, 7.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.6, 22.4, 56.1, 60.8, 62.0, 87.9, 88.5, 105.5, 121.1, 124.0, 128.3, 129.7, 132.3, 132.6, 139.7, 152.1, 153.2, 163.5, 165.4, 167.7; IR ($CHCl_3$, cm^{-1}): 2981, 2223, 1728, 1588, 1538, 1505, 1463, 1384, 1305, 1244, 1211, 1085, 1023, 854. Anal. Calcd for $C_{25}H_{24}N_2O_5$: C, 69.43; H, 5.59; N, 6.48. Found: C, 69.51; H, 5.42; N, 6.39.

4.27. Ethyl 4-(3,4,5-trimethoxyphenyl)-2-(2-(4-methoxyphenyl)ethynyl)-6-methylpyrimidine-5-carboxylate 4j

Compound **3f** (0.210 g, 0.57 mmol) was reacted as described in Section 4.26 to give **4j** (0.238 g, 90%) as a thick liquid. R_f (30% EtOAc–pet. ether) 0.52, blue fluorescent spot; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.14 (t, J=7.1 Hz, 3H), 2.64 (s, 3H), 3.84 (s, 3H), 3.89 (s, 3H), 3.91 (s, 6H), 4.24 (q, J=7.1 Hz, 2H), 6.88–6.95 (m, 4H), 7.65 (d, J=8.5 Hz, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.7, 22.4, 55.2, 56.1, 60.8, 62.0, 87.3, 89.3, 105.5, 113.0, 114.0, 123.7, 132.5, 134.4, 139.7, 152.4, 153.2, 160.7, 163.5, 165.3, 167.8; IR ($CHCl_3$, cm^{-1}): 3013, 2838, 2212, 1725, 1604, 1588, 1528, 1509, 1464, 1383, 1293, 1249, 1211, 1170, 1086, 833. Anal. Calcd for $C_{26}H_{26}N_2O_6$: C, 67.52; H, 5.67; N, 6.06. Found: C, 67.45; H, 5.54; N, 6.22.

4.28. Ethyl 2-bromo-4-(bromomethyl)-6-phenylpyrimidine-5-carboxylate 6

A mixture of ethyl 1,2-dihydro-6-methyl-2-oxo-4-phenyl-pyrimidine-5-carboxylate **2a** (0.212 g, 0.82 mmol) and $POBr_3$ (0.707 g, 2.46 mmol) was heated up to 170 °C for 1 h. After 1 h, the reaction mixture was cooled to room temperature and ice water was added slowly. The reaction mixture was further neutralized with $NaHCO_3$ and extracted with ethyl acetate. The organic layer was separated, dried over Na_2SO_4, and concentrated in vacuo to obtain the residual crude product, which was purified by column chromatography by using EtOAc–pet. ether (1:9) as a eluent to obtain **6** (0.278 g, 85%) as a thick liquid. R_f (20% EtOAc–pet. ether) 0.55; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.06 (t, J=7.2 Hz, 3H), 4.21 (q, J=7.2 Hz, 2H), 4.63 (s, 2H), 7.43–7.54 (m, 3H), 7.63–7.68 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ: 13.4, 28.2, 62.5, 123.9, 128.5, 128.6, 131.0, 135.8, 152.5, 165.8, 166.1, 167.5; MS: m/z 402, 399, 397, 371, 292, 128, 77; IR ($CHCl_3$, cm^{-1}): 3016, 2938, 1723, 1537, 1520, 1378, 1238, 1216, 757. Anal. Calcd for $C_{14}H_{12}Br_2N_2O_2$: C, 42.03; H, 3.02; N, 7.00. Found: C, 42.14; H, 2.84; N, 6.82.

4.29. Biological evaluation procedure

Minimum inhibitory concentration of compounds was tested according to standard microbroth dilution technique as per NCCLS guidelines.[34–37] Briefly, testing was performed in flat bottom 96-well tissue culture plates in YPG broth for fungal strains and in NA (nutrient broth) for bacterial strains. The concentration range for standard and tested compounds was 128–0.5 μg/ml. The plates were incubated in 28 °C for fungal strains and 37 °C for bacterial strains, and absorbance at 600 nm was recorded after 48 h for *C. albicans* and *F. oxysporum*, 72 h for *C. neoformans*, 24 h for *B. poitrasii*, *Y. lipolytica*, *E. coli*, and *S. aureus*. MIC was determined as 90% inhibition of growth with respect to the growth control and IC_{50} was the concentration at which 50% growth inhibition was observed.

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Supplementary data

Single-crystal data and CIF file of compound **4b** (CCDC # 665187) have been deposited at the Cambridge Crystallographic Data Centre and can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 1123 336 033; or email: deposit@ccdc.ac.uk).

^1H NMR and ^{13}C NMR spectra for all the synthesized compounds are available as Supplementary data. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.08.033.

References and notes

1. Clark, T. A.; Hajjeh, R. A. *Curr. Opin. Infect. Dis.* **2002**, *15*, 569–574.
2. Hage, C. A.; Goldman, M.; Wheat, L. J. *Eur. J. Med. Res.* **2002**, *7*, 236–241.
3. Brown, J. M. *Curr. Opin. Infect. Dis.* **2004**, *17*, 347–352.
4. Garber, G. *Drugs* **2001**, *61*, 1–12.
5. Walsh, T. J.; Groll, A. H. *Transpl. Infect. Dis.* **1999**, *1*, 247–261.
6. Ampel, N. M. *Emerging Infect. Dis.* **1996**, *2*, 109–116.
7. Anaissie, E. *Clin. Infect. Dis.* **1992**, *14*, S43–53.
8. Eggimann, P.; Garbino, J.; Pittet, D. *Lancet Infect. Dis.* **2003**, *3*, 685–702.
9. Gallis, H. A.; Drew, R. H.; Pickard, W. W. *Rev. Infect. Dis.* **1990**, *12*, 308–329.
10. Fanos, V.; Cataldi, L. J. *Chemotherapy* **2000**, *12*, 463–470.
11. Sobel, J. D.; Zervos, M.; Reed, B. D.; Hooton, T.; Soper, D.; Nyirjesy, P.; Heine, M. W.; Willems, J.; Panzer, H. *J. Antimicrob. Chemother.* **2003**, *47*, 34–38.
12. Lyman, C. A.; Walsh, T. J. *Drugs* **1992**, *44*, 9–35.
13. Sojakova, M.; Liptajova, D.; Borovsky, M. *Mycopathologia* **2004**, *157*, 163–169.
14. Shoichet, B. K.; Stroud, R. M.; Santi, D. U.; Kuntz, I. D.; Perry, K. M. *Science* **1993**, *259*, 1445–1450.
15. Biginelli, P. *Gazz. Chim. Ital.* **1893**, *23*, 360–416.
16. Kappe, C. O. *Eur. J. Med. Chem.* **2000**, *35*, 1043–1052.
17. Deres, K.; Schroder, C. H.; Paessens, A.; Goldmann, S.; Hacker, H. J.; Weber, O.; Kraemer, T.; Niewoehner, U.; Pleiss, U.; Stoltefuss, J.; Graef, E.; Koletzki, D.; Masantschek, R. N. A.; Reimann, A.; Jaeger, R.; Groβ, R.; Beckermann, B.; Schlemmer, K.-H.; Haebich, D.; Rubsamen-Waigmann, H. *Science* **2003**, *299*, 893–896.
18. Lengar, A.; Kappe, C. O. *Org. Lett.* **2004**, *6*, 771–774.
19. Erian, A. W. *Chem. Rev.* **1993**, *93*, 1991–2005.
20. Shibuya, I. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2158–2160.
21. Sakai, N.; Aoki, Y.; Sasada, T.; Konakahara, T. *Org. Lett.* **2005**, *7*, 4705–4708.
22. Mathews, A.; Asokan, C. V. *Tetrahedron* **2007**, *63*, 7845–7849.
23. Görlitzer, K.; Heinrici, C. *Pharmazie* **1998**, *53*, 843–847.
24. Kang, F.-A.; Kodah, J.; Guan, Q.; Li, X.; Murray, W. V. *J. Org. Chem.* **2005**, *70*, 1957–1960.
25. Gholap, A. R.; Venkatesan, K.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *Green Chem.* **2004**, *6*, 147–150.
26. Puchala, A.; Belaj, F.; Bergman, J.; Kappe, C. O. *J. Heterocycl. Chem.* **2001**, *38*, 1345–1352.
27. Shanmugam, P.; Perumal, P. T. *Tetrahedron* **2006**, *62*, 9726–9734.
28. Blachut, D.; Czarnocki, Z.; Wojtasiewicz, K. *Synthesis* **2006**, 2855–2864.
29. Cooke, G.; Cremiers, H. A. D.; Rotello, V. M.; Tarbit, B.; Vanderstraeten, P. E. *Tetrahedron* **2001**, *57*, 2787–2789.
30. Saygili, N.; Batsanov, A. S.; Bryce, M. R. *Org. Biomol. Chem.* **2004**, *2*, 852–857.

31. Large, J. M.; Clarke, M.; Williamson, D. M.; McDonald, E.; Collins, I. *Synlett* **2006**, 861–864.
32. Schomaker, J. M.; Delia, T. J. *J. Org. Chem.* **2001**, *66*, 7125–7128.
33. Hartung, C. G.; Backes, A. C.; Felber, B.; Missio, A.; Philipp, A. *Tetrahedron* **2006**, *62*, 10055–10064.
34. National Committee for Clinical Laboratory Standard. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeast, Approved Standard. Document M27-A*; National Committee for Clinical Laboratory Standards: Wayne, PA, USA, 1997.
35. National Committee for Clinical Laboratory Standard. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Conidium Forming Filamentous Fungi: Proposed Standard. Document M38-P*; National Committee for Clinical Laboratory Standard: Wayne, PA, USA, 1998.
36. National Committee for Clinical Laboratory Standards. *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically. Approved Standard*, 5th ed.; NCCLS: Villanova, PA, 2000; M7–A5.
37. Yamamotoa, N.; Fujita, J.; Shinzato, T.; Higa, F.; Tateyamaa, M.; Tohyamaa, M.; Nakasone, I.; Yamaneb, N. *Int. J. Antimicrob. Agents* **2006**, *27*, 171–173.