Med Chem Res
DOI 10.1007/s00044-013-0555-y

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antimicrobial activity of pyrimidine chalcones

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Received: 30 November 2012 / Accepted: 18 February 2013

Abstract In the realm of biochemical research, chalcones have been efficiently explored as antimicrobial agents. The present study focuses on the synthesis of pyrimidine chalcones, i.e. (*E*)-1-(6′-hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2′,4′-dioxopyrimidin-5′-yl)-3-[-*p*-{(1″-aryl-1*H*-1″,2″,3″-triazol-4″-yl) methoxy}phenyl]-prop-2-ene-1-ones (**7a–7i**) by the reaction of 4-triazolomethoxybenzaldehyde, *i.e.* 4-{(1-aryl-1*H*-1,2,3-triazol-4-yl)methoxy}benzaldehyde (**4a–4i**) and 5-acetyl-1,3-dimethylbarbituric acid in (**6**) 50–80 % yields. The structures of these compounds were established on the basis of their FT-IR, ^{1}H NMR, ^{13}C NMR and mass spectral analysis. Compounds **7b–7i** were screened for their in vitro antibacterial activity against *Rhodococcus rhodochrous* MTCC 265, a gram +ve bacteria and *Escherichia coli*, a gram −ve bacteria by the agar disc diffusion method.

Keywords Barbituric acid · Triazole · Chalcone · Antimicrobial activity

Introduction

Development of new antibacterial agents with novel structure and mode of action remains the primary goal of scientists due to the development of increasing bacterial resistance against classical antibacterial agents. Chalcones and pyrimidine derivatives are known to be good antibacterial agents (Swamy and Agasimundin, 2008; Liu *et al*., 2008). Apart from this, a number of chalcones having hydroxyl and alkoxy groups at different positions have been reported to possess antiulcer (Jeffrey *et al*., 1996), antifungal (Lahtchev *et al*., 2008), antioxidant (Detsi *et al*., 2009), vasodilatory (Dong *et al*., 2009), antimitotic (Rao *et al*., 2009), antimalarial (Ram *et al*., 2000), antileishmanial (Liu *et al*., 2003), inhibition of chemical mediators release, inhibition of leukotriene B_4, (Horng *et al*., 2003) inhibition of tyrosinase (Khatib *et al*., 2005; Te, 2009) and inhibition of aldose reductase (Fabio *et al*., 1998) activities. Appreciation of these findings motivated us to synthesize chalcones as a potential template for the discovery of antimicrobial agents. Most widely used method for the synthesis of chalcones is the condensation of aromatic aldehydes with acetophenones in the presence of alkali.

In the last few decades, the chemistry of 1,2,3-triazoles has received considerable attention owing to their synthetic and effective biological importance. Although 1,2,3-triazole moiety itself does not occur in nature, there are numerous examples in literature that show diverse biological activities associated with this system, such as anti-HIV activity (Alvarez *et al*., 1994; Velazquez *et al*., 1998; Whiting *et al*., 2006; Brik *et al*., 2003), antimicrobial activity (Genin *et al*., 2000), β_3-selective adrenergic agonism (Brockunier *et al*., 2000), kinase inhibitory (Pande and Ramos, 2005; Olesen *et al*., 2003) and other enzyme inhibitory activities (Krasinski *et al*., 2005; Mocharla *et al*., 2005). 1,2,3-Triazole moieties have been incorporated into a wide variety of therapeutically interesting drug candidates; for example, antibacterial agents linezolid (Zyvox), β-lactam (tazobactam) (Reck *et al*., 2005) and anticancer agents (carboxyamidotriazole CAI) (Agalave *et al*., 2011).

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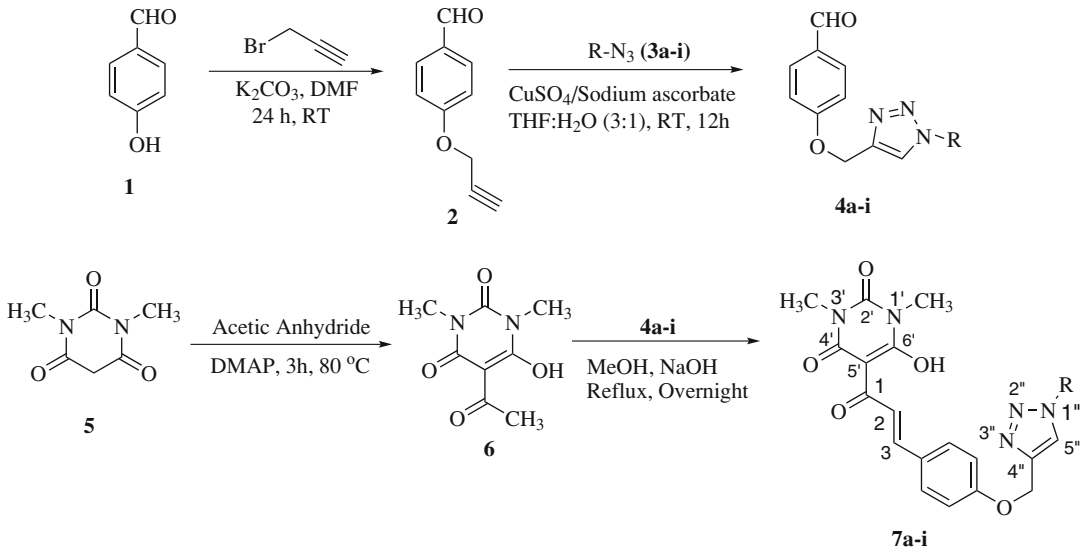
Published online: 06 March 2013



Compounds 4 and 7	R	Compounds 4 and 7	R
a	4-$CH_3C_6H_4$	f	3-$CH_3C_6H_4$
b	4-$OCH_3C_6H_4$	g	4-BrC_6H_4
c	4-FC_6H_4	h	4-ClC_6H_4
d	C_6H_5	i	Benzyl
e	3-$OCH_3C_6H_4$		

Scheme 1 Synthesis of the compounds **7a–i**

In view of the pharmacological properties associated with chalcones, pyrimidines, triazoles and their derivatives, we were prompted to combine these heterocyclic moieties in order to arrive at more discernable results. Herein, we report the synthesis of pyrimidine chalcones **7a–7i** and evaluation of their antimicrobial activity against gram +ve and gram −ve bacteria.

Results and discussion

Chemistry

In the present work, the synthesis of (*E*)-1-(6′-hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2′,4′-dioxopyrimidin-5′-yl)-3-[-*p*-{(1″-aryl-1*H*-1″,2″,3″-triazol-4″-yl)methoxy}phenyl]-prop-2-ene-1-ones **7a–7i** was accomplished by the reaction of 4-{(1-aryl-1*H*-1,2,3-triazol-4-yl)methoxy}benzaldehyde **4a–4i** and 5-acetyl-1,3-dimethylbarbituric acid (**6**) (Sivakumar Malliappan, 2009). The compounds **4a–4i** are synthesised by the reaction of different azide derivatives **3a–3i** and *p*-(prop-2-ynyloxy)benzaldehyde (**2**) in the presence of $CuSO_4$/sodium ascorbate at room temperature in good yields (Frank and Venkata, 2007). Compound **2** was prepared from *p*-hydroxy benzaldehyde (**1**) and propargyl bromide in the presence of K_2CO_3 by known method (Guantai *et al.*, 2010). The 5-acetyl-1, 3-dimethylbarbituric acid (**6**) was also prepared by the known method from 1,3-dimethylbarbituric acid (**5**) and acetic anhydride (Jursic and Neumann, 2001). The synthetic route for the synthesis of above compounds is outlined in Scheme 1.

On a trial basis, condensation of **4a** with 5-acetyl-1,3-dimethylbarbituric acid (**6**) in methanol in the presence of sodium hydroxide gave chalcone **7a**. The IR spectrum of compound **7a** showed peaks at 1,172, 1,590, 1,673, 1,718 and 3,420 cm^{-1} which corresponds to ether group, three carbonyl groups and OH group, respectively. The ^1H NMR of pyrimidine chalcone **7a** showed a singlet of $-CH_3$ at δ 2.37. A sharp singlet at δ 3.20 integrating for six protons of barbituric acid was assigned to two N–CH_3 groups. A singlet at δ 5.32 of two protons was assigned to OCH_2 group. Two doublets at δ 7.98 ($J = 16.1$ Hz) and 8.39 ($J = 15.4$ Hz) indicate that the double bond in the enone linkage is in *trans* confirmation. The remaining aromatic protons of chalcone appeared at δ 6.97–8.92. The ^{13}C NMR spectra of chalcone derivatives were recorded in DMSO-d_6 and spectral signals were in good agreement

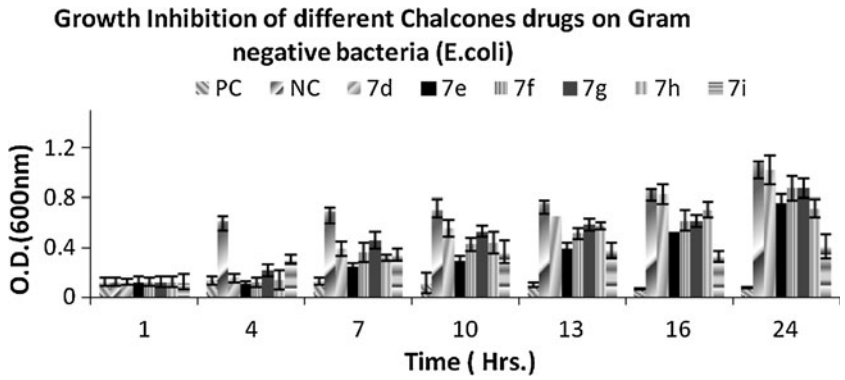


Fig. 1 Time-dependent growth inhibition studies of various derivatives of chalcones on *E.coli*. All the derivatives were effective in inhibiting the growth, **7e** was found to be most efficacious with ~70 % growth inhibition followed by **7d**, **7f**, **7g** and **7h** showed ~60 % killing within 4 h. Even after 7 h, ~50 % killing was observed by the above mentioned derivatives and 7e showed ~65 % killing in the same time period. *(PC Positive Control, NC Negative Control)*

with proposed structure. Details of ^{1}H NMR and ^{13}C NMR spectra of **7a** are given in experimental section. Characteristic molecular ion peak, $[M-H]^{+}$ peak, at *m/z* 474.4 was observed in the mass spectra of **7a**. Similarly, compounds **7b–7i** were prepared by condensing 5-acetyl-1,3-dimethylbarbituric acid **(6)** with corresponding **4b–4i**. The chemical structures of all the synthesised compounds **7b–7i** were also established on the basis of their spectroscopic data (FT-IR, ^{1}H NMR, ^{13}C NMR and Mass) and elemental analysis.

Antimicrobial activity

As part of the search for novel antimicrobial agents, the efficacy of the synthetic chalcone derivatives was done by a modified AATCC-100-1998 method on *Rhodococcus rhodochrous* MTCC 265, gram +ve and gram −ve strain of bacteria *Esherichia coli* spp, respectively (Saisivam and Kishan, 2006; Wadher *et al*., 2006). Antimicrobial activity of the sample was done by assessed qualitative and quantitative analysis. Nutrient broth, nutrient agar and agar (HiMedia Lab) were purchased from Difco. The growth inhibition zone present after 24 h of incubation at 37 °C determines the *antibacterial effect* of the sample. Briefly, the chalcones (5 mg/ml) containing bacterial cultures in a nutrient broth were incubated in an orbital shaker (Gallenkamp) at a speed of 100 rpm at 30 °C for 24 h. The readings were noted after every hour. All the experiments were done in triplicates along with controls. The percentage growth inhibition was calculated by

$$\text{Growth inhibition } (\%) = \left(\text{OD}_{\text{control}} - \text{OD}_{\text{sample}}\right) / \text{OD}_{\text{control}} \times 100$$

OD = Optical Density of the culture.

Growth inhibition data of different chalcones on gram −ve bacteria are summarized in Fig. 1.

The antimicrobial activity was also performed by filter paper disc plate method (Loo *et al*., 1945). Known antibiotic, such as gentamycin was used as standard antibacterial agent for comparison purposes. Solutions of the test compounds and gentamycin were dissolved in DMSO at concentrations of 5 mg/ml. The twofold dilution of the compounds and gentamycin were prepared. The antimicrobial screening data were recorded in Table 1.

Experimental protocol

All the reagents purchased were of commercial grade and used without further purification. Solvents were dried and purified by standard techniques. ^{1}H NMR (400 MHz) and ^{13}C NMR (100.5 MHz) were recorded on JNM ECX- 400P (Jeol, USA) spectrometer using TMS as an internal standard. Chemical shifts were reported in parts per million (ppm). Mass spectra were recorded on API-2000 mass spectrometer in negative mode. IR absorption spectra were recorded in the 400–4000 cm^{-1} range on a Perkin–Elmer FT-IR spectrometer using KBr pallets. Melting points were determined using Buchi M-560 and are uncorrected. Elemental analysis was done on Vario EL III. The reactions were monitored by thin layer chromatography (TLC), on aluminium plates coated with silica gel 60 F_{254} (Merck). UV radiation and iodine were used as the visualizing agents. Column chromatography was performed on silica gel (100–200 mesh).

General procedure for the preparation of *p*-{(1-aryl-1*H*-1,2,3-triazol-4-yl)methoxy}benzaldehyde (**4a–4i**)

4-(Prop-2-ynyloxy) benzaldehyde (**2**) (1 mmol) and aryl azides (**3a–3i**) (1.5 mmol) were dissolved in THF:H_2O

Table 1 Antimicrobial activity of chalcones, positive control gentamycin and negative control (DMSO) by the Kirby–Bauer single disc susceptibility test (Diameter of zone of inhibition, mm)

Compounds	Gram +ve (Cocci)			Gram −ve (*E. coli* DH5α)		
	+ve control	2.5 mg/ml	5 mg/ml	+ve control	2.5 mg/ml	5 mg/ml
7a	–	–	–	–	–	–
7b	8 ± 0.02	2 ± 0.10	2 ± 0.12	9 ± 0.03	0 ± 0.00	0 ± 0.00
7c	8 ± 0.12	0 ± 0.00	0 ± 0.00	10 ± 0.05	0 ± 0.00	0 ± 0.00
7d	9 ± 0.03	4 ± 0.04	3 ± 0.03	7 ± 0.02	4 ± 0.07	3 ± 0.03
7e	8 ± 0.02	3 ± 0.02	2 ± 0.18	5 ± 0.03	3 ± 0.03	3.5 ± 0.13
7f	7 ± 0.14	3 ± 0.06	2 ± 0.07	9 ± 0.13	2 ± 0.06	2 ± 0.12
7g	8 ± 0.13	3 ± 0.03	2 ± 0.05	9 ± 0.03	0 ± 0.00	0 ± 0.00
7h	5 ± 0.14	0 ± 0.0	0 ± 0.00	11 ± 0.16	0 ± 0.00	0 ± 0.00
7i	7 ± 0.12	2 ± 0.12	2 ± 0.02	7 ± 0.04	0 ± 0.00	0 ± 0.00

+ve control gentamycin, ***7a*** owing to its non-solubility in any solvent, this compound could not be tested

(3:1) in a round bottom flask. To the solution copper sulphate (0.2 mmol) and sodium ascorbate (0.4 mmol) were added and stirred at room temperature for 12 h. The mixture was concentrated under reduced pressure and diluted with ethyl acetate and washed with water. The combined organic extract was dried over anhydrous sodium sulphate and concentrated under reduced pressure. The crude product was purified by column chromatography (5 % MeOH:$CHCl_3$).

p-{(1-(*p*-Tolyl)-1*H*-1,2,3-triazol-4-yl)methoxy}benzaldehyde (**4a**)

The product was obtained as mentioned in general procedure from **2** (200 mg, 1 mmol) and **3a** (199 mg, 1.2 mmol). It was obtained as a light yellow solid. Yield = 60.1 %; m.p. = 134–135 °C; IR ν_{max} (cm^{-1}) = 1,165 (O–C), 1,683 (C=O), 2,756, 2,839 (2 × aldehyde C–H) and 2,930 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.39 (3H, s, $–CH_3$), 5.35 (2H, s, $–OCH_2$), 7.12 (2H, d, J = 6.6 Hz, ArH), 7.29 (2H, d, J = 7.32 Hz, ArH), 7.58 (2H, d, J = 8.04 Hz, ArH), 7.83 (2H, d, J = 6.6 Hz, ArH), 8.02 (1H, s) and 9.87 (1H, s –C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.06, 62.07, 115.04, 120.46, 121.16, 130.34, 131.98, 134.50, 139.15, 144.14, 163.04 and 190.72.

p-{(1-(*p*-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy}benzaldehyde (**4b**)

The product was obtained as mentioned in general procedure from **2** (400 mg, 1 mmol) and **3b** (447 mg, 1.2 mmol). It was obtained as crystalline light brown solid. Yield = 58.2 %; m.p. = 126–127 °C; IR ν_{max} (cm^{-1}) = 1,162 (O–C), 1,692 (C = O), 2,734, 2,796 (2 × aldehyde C–H) and 2,925 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (3H, s, OCH_3), 5.34 (2H, s, $–OCH_2$), 7.00 (2H, d, J = 8.76 Hz, ArH), 7.13 (2H, d, J = 8.00 Hz, ArH), 7.62 (2H, d, J = 8.8 Hz, ArH), 7.83 (2H, d, J = 6.08 Hz, ArH), 8.10 (1H, s) and 9.87 (1H, s, –C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.61, 62.11, 114.79, 115.06, 122.25, 122.35, 130.36, 132.01, 159.97, 163.05 and 190.75.

p-{(1-(*p*-Flourophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy}benzaldehyde (**4c**)

The product was obtained as mentioned in general procedure from **2** (300 mg, 1 mmol) and **3c** (308 mg, 1.2 mmol). It was obtained as a light orange solid. Yield = 61.1 %; m.p. = 138–140 °C; IR ν_{max} (cm^{-1}) = 1,162 (O–C), 1,688 (C=O), 2,755, 2,837 (2 × aldehyde C–H) and 3,090 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.37 (2H, s, $–OCH_2$), 7.13 (2H, d, J = 8.08 Hz, ArH), 7.20–7.25 (2H, m, ArH), 7.69–7.72 (2H, m, ArH), 7.85 (2H, d, J = 8.76 Hz, ArH), 8.05 (1H, s) and 9.89 (1H, s, –C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.99, 115.03, 116.68, 116.91, 122.56, 130.41, 132.00, 133.13, 161.27, 162.96, 163.75 and 190.71.

p-{(1-(Phenyl)-1*H*-1,2,3-triazol-4-yl)methoxy}benzaldehyde (**4d**)

The product was obtained as mentioned in general procedure from **2** (100 mg, 1 mmol) and **3d** (89 mg, 1.2 mmol). It was obtained as a yellow solid. Yield = 61.1 %; m.p. = 101–103 °C; IR ν_{max} (cm^{-1}) = 1,164 (O–C), 1,690 (C=O), 2,735, 2,801 (2 × aldehyde C–H) and 2,860 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.36 (2H, s, $–OCH_2$), 7.14 (2H, d, J = 8.08 Hz, ArH), 7.44 (1H, t, J = 7.39 Hz, ArH), 7.50–7.54 (2H, m, ArH), 7.73 (2H, d, J = 8.04 Hz, ArH), 7.84 (2H, d, J = 8.08 Hz, ArH), 8.28 (1H, s) and

9.88 (1H, s, –C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.03, 115.06, 120.63, 129.02, 129.83, 130.40, 132.00, 136.95, 163.01 and 190.72.

p-{(1-(m-Methoxyphenyl)-1*H*-1,2,3-triazol-4-yl)methoxy} benzaldehyde (**4e**)

The product was obtained as mentioned in general procedure from **2** (200 mg, 1 mmol) and **3e** (223 mg, 1.2 mmol). It was obtained as a light brown solid. Yield = 54.4 %; m.p. = 92–93 °C; IR ν_{max} (cm^{-1}) = 1,164 (O–C), 1,684 (C=O), 2,747, 2,830 (2 × aldehyde C–H) and 2,934 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.86 (3H, s, $–OCH_3$), 5.35 (2H, s, $–OCH_2$), 6.97 (1H, dd, J = 5.88, J = 8.76 Hz, ArH), 7.13 (2H, d, J = 8.8 Hz, ArH), 7.25 (1H, d, J = 8.00 Hz, ArH), 7.34 (1H, s, ArH), 7.41 (1H, t, J = 8.08 Hz, ArH), 7.84 (2H, d, J = 8.05 Hz, ArH), 8.13 (1H, s) and 9.88 (1H, s, –C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 55.62, 61.84, 106.51, 112.52, 114.78, 115.06, 130.40, 130.65, 132.01, 138.10, 160.66, 163.01 and 190.75.

p-{(1-(m-Tolyl)-1*H*-1,2,3-triazol-4-yl)methoxy} benzaldehyde (**4f**)

The product was obtained as mentioned in general procedure from **2** (200 mg, 1 mmol) and **3f** (199 mg, 1.2 mmol). It was obtained as a light orange solid. Yield = 60.1 %; m.p. = 85–88 °C; IR ν_{max} (cm^{-1}) = 1,167 (O–C), 1,689 (C = O), 2,727, 2,850 (2 × aldehyde C–H) and 2,923 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (3H, s, $–CH_3$), 5.35 (2H, s, $–OCH_2$), 7.13 (2H, d, J = 8.08 Hz, ArH), 7.25 (1H, d, J = 8.0 Hz, ArH), 7.39 (1H, t, J = 7.32 Hz, ArH), 7.49 (1H, d, J = 8.04 Hz, ArH), 7.56 (1H, s, ArH), 7.84 (d, 2H, J = 8.8 Hz, ArH), 8.15 (1H, s) and 9.88 (1H, s, –C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.38, 62.09, 115.08, 117.69, 121.30, 129.59, 129.77, 130.40, 132.02, 136.96, 140.11, 163.04 and 190.75.

p-{(1-(*p*-Bromophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy} benzaldehyde (**4g**)

The product was obtained as mentioned in general procedure from **2** (300 mg, 1 mmol) and **3g** (443 mg, 1.2 mmol). It was obtained as a yellow solid. Yield = 66.2 %; m.p. = 164–165 °C; IR ν_{max} (cm^{-1}) = 1,170 (O–C), 1,684 (C=O), 2,747, 2,815 (2 × aldehyde C–H) and 3,072 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (2H, s, $–OCH_2$), 7.12 (2H, d, J = 8.04 Hz, ArH), 7.61–7.66 (4H, m, ArH), 7.85 (2H, d, J = 8.08 Hz, ArH), 8.11 (1H, s) and 9.88 (1H, s –C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 62.00, 115.06, 122.02, 122.75, 130.49, 132.05, 133.02, 1662.95 and 190.73.

p-{(1-(*p*-Chlorophenyl)-1*H*-1,2,3-triazol-4-yl)methoxy} benzaldehyde (**4h**)

The product was obtained as mentioned in general procedure from **2** (200 mg, 1 mmol) and **3h** (178 mg, 1.2 mmol). It was obtained as crystalline light yellow solid. Yield = 59.7 %; m.p. = 151–153 °C; IR ν_{max} (cm^{-1}) = 1,164 (O–C), 1,688 (C=O), 2,759, 2,843 (2 × aldehyde C–H) and 3,081 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.35 (2H, s, $–OCH_2$), 7.12 (2H, d, J = 8.8 Hz, ArH), 7.49 (2H, d, J = 8.8 Hz, ArH), 7.68 (2H, d, J = 8.8 Hz, ArH), 7.84 (2H, d, J = 8.8 Hz, ArH), 8.12 (1H, s) and 9.88 (1H, s –C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 61.99, 115.04, 121.77, 130.03, 130.46, 132.03, 134.85, 135.55, 162.94 and 190.71.

p-{(1-(Benzyl)-1*H*-1,2,3-triazol-4-yl)methoxy} benzaldehyde (**4i**)

The product was obtained as mentioned in general procedure from **2** (300 mg, 1 mmol) and **3i** (296 mg, 1.2 mmol). It was obtained as a light yellow solid. Yield = 81.96 %; m.p. = 99–100 °C; IR ν_{max} (cm^{-1}) 1,164 (O–C), 1,682 (C=O), 2,761, 2,811 (2 × aldehyde C–H) and 2,843 (C–H); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.23 (2H, s, $–NCH_2$), 5.52 (2H, s, $–OCH_2$), 7.06 (2H, d, J = 8.8 Hz, ArH), 7.24–7.26 (2H, m, ArH), 7.34–7.36 (3H, m, ArH), 7.61 (1H, s), 7.80 (2H, d, J = 8.8 Hz, ArH) and 9.85 (1H, s, –C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.45, 62.03, 115.02, 128.12, 128.88, 129.14, 130.27, 131.93, 134.16, 163.04 and 190.74.

General procedure for the preparation of (E)-1-(6′-hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2′,4′-dioxopyrimidin-5′-yl)-3-[-p-{(1″-aryl-1H-1″,2″,3″-triazol-4″-yl)methoxy}phenyl]-prop-2-ene-1-ones (**7a**–**7i**)

To a solution of 5-acetyl-1,3-dimethylbarbituric acid (**6**) (1 mmol) in absolute methanol, a pellet of sodium hydroxide was added and stirred for 10 min. To this solution respective triazole-linked benzaldehyde (**4a**–**4i**) (1 mmol) was added and the reaction mixture was refluxed overnight. The solid products obtained were purified by column chromatography (5 % MeOH:$CHCl_3$).

(E)-1-(6′-Hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2′,4′-dioxopyrimidin-5′-yl)-3-[-p-{(1″-(p-tolyl)-1H-1″,2″,3″-triazol-4″-yl)methoxy}phenyl]-prop-2-ene-1-one (**7a**)

The product **7a** was obtained as described earlier in the general procedure from **4a** (100 mg, 1 mmol) and **5** (67 mg, 1 mmol) as a yellow solid. Yield = 51 %; m.p. = 228–230 °C; IR ν_{max} (cm^{-1}) = 1,172 (C–O), 1,590,

1,673, 1,718 (3 × C=O), 2,925 (C–H) and 3,420 (–OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.37 (3H, s, –CH_3), 3.20 (6H, s, N–CH_3), 5.32 (2H, s, –OCH_2), 6.97 (1H, d, J = 8.8 Hz, ArH), 7.22 (2H, d, J = 8.8 Hz, ArH), 7.39 (2H, d, J = 8.08 Hz, ArH), 7.72–7.79 (3H, m, ArH), 7.98 (1H, d, J = 16.1 Hz), 8.39 (1H, d, J = 15.4 Hz) and 8.92 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.63, 27.47, 61.11, 77.37, 96.04, 113.25, 114.78, 115.73, 117.07, 117.41, 119.90, 128.02, 130.26, 131.03, 134.06, 143.15, 153.72, 161.50, 181.71 and 206.86; Anal. calcd. for $C_{25}H_{23}N_5O_5$: C, 63.42, H, 4.90, N, 14.79, Found: C, 63.32, H, 4.95, N, 14.80; ESI–MS m/z: $[M-H]^+$ = 474.4.

(E)-1-(6′-Hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2′,4′-dioxopyrimidin-5′-yl)-3-[-p-{(1″-(p-methoxy phenyl)-1H-1″,2″,3″-triazol-4″-yl)methoxy}phenyl]-prop-2-ene-1-one (**7b**)

The product **7b** was obtained as described earlier in the general procedure from **4b** (200 mg, 1 mmol) and **5** (122 mg, 1 mmol) as a light green solid. Yield = 51.6 %; m.p. = 298–300 °C; IR v_{max} (cm^{-1}) = 1,172 (C–O), 1,651, 1,690, 1,717 (3 × C=O), 2,936 (C–H) and 3,663 (–OH); ^{1}H NMR (400 MHz, DMDO-d_6): δ 3.09 (6H, s, N–CH_3), 3.81 (3H, s, –OCH_3) 5.24 (2H, s, –OCH_2), 7.07–7.13 (4H, m, ArH), 7.48 (2H, d, J = 8.8 Hz, ArH), 7.79–7.81 (4H, m) and 8.84 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.13, 55.57, 61.30, 77.56, 96.08, 114.89, 115.09, 121.85, 122.92, 128.98, 129.31, 129.99, 134.96, 143.48, 158.53, 159.34, 163.40, 186.85 and 207.42; Anal. calcd. for $C_{25}H_{23}N_5O_6$: C, 61.34, H, 4.74, N, 14.31, Found: C, 61.66, H, 4.41, N, 14.72; ESI–MS m/z: $[M-H]^+$ = 490.4.

(E)-1-(6′-Hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2′,4′-dioxopyrimidin-5′-yl)-3-[-p-{(1″-(p-flourophenyl)-1H-1″,2″,3″-triazol-4″-yl)methoxy}phenyl]-prop-2-ene-1-one (**7c**)

The product **7c** was obtained as described earlier in the general procedure from **4c** (200 mg, 1 mmol) and **5** (133 mg, 1 mmol) as a yellow solid. Yield = 51.1 %; m.p. = 258–259 °C; IR v_{max} (cm^{-1}) = 1,172 (C–O), 1,593, 1,660, 1,714 (3 × C=O), 2,947 (C–H) and 3,674 (–OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.21 (6H, s, N–CH_3), 5.33 (2H, s, –OCH_2), 7.21 (2H, d, J = 8.8 Hz, ArH), 7.47 (2H, d, J = 8.8 Hz, ArH), 7.74 (2H, d, J = 8.7 Hz, ArH), 7.94–8.00 (3H, m), 8.40 (1H, d, J = 16.1 Hz) and 8.97 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.66, 66.77, 79.26, 94.19, 113.48, 115.55, 116.51, 117.08, 122.57, 122.94, 127.66, 130.87, 144.49, 154.13, 161.11, 168.72, 173.45, 188.15 and 205.38; Anal. calcd. for $C_{24}H_{20}FN_5O_5$: C, 60.37, H, 4.22, N, 14.67, Found: C, 60.60, H, 4.36, N, 14.53; ESI–MS m/z: $[M-H]^+$ = 478.4.

(E)-1-(6′-Hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2′,4′-dioxopyrimidin-5′-yl)-3-[-p-{(1″-(phenyl)-1H-1″,2″,3″-triazol-4″-yl)methoxy}phenyl]-prop-2-ene-1-one (**7d**)

The product **7d** was obtained as described earlier in the general procedure from **4d** (200 mg, 1 mmol) and **5** (141 mg, 1 mmol) as a yellow solid. Yield = 56.4 %; m.p. = 238–240 °C; IR v_{max} (cm^{-1}) = 1,173 (C–O), 1,592, 1,660, 1,714 (3 × C=O), 2,945 (C–H) and 3,656 (–OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.27 (6H, s, N–CH_3), 5.30 (2H, s, –OCH_2), 7.17 (2H, d, J = 8.8 Hz, ArH), 7.43–7.51 (1H, m, ArH), 7.55–7.59 (2H, m, ArH), 7.70 (2H, d, J = 8.08 Hz, ArH), 7.87 (2H, d, J = 8.04 Hz, ArH), 7.90 (1H, d, J = 16.11 Hz), 8.35 (1H, d, J = 16.1 Hz) and 8.94 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.30, 61.25, 79.04, 94.74, 119.86, 120.42, 123.07, 124.45, 129.16, 130.29, 131.41, 136.87, 143.32, 152.94, 155.04, 169.79, 188.68 and 210.62; Anal. calcd. for $C_{24}H_{21}N_5O_5$: C, 62.74, H, 4.61, N, 15.24, Found: C, 62.89, H, 4.55, N, 15.78; ESI–MS m/z: $[M-H]^+$ = 458.4.

(E)-1-(6′-Hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2′,4′-dioxopyrimidin-5′-yl)-3-[-p-{(1″-(m-methoxy phenyl)-1H-1″,2″,3″-triazol-4″-yl)methoxy}phenyl]-prop-2-ene-1-one (**7e**)

The product **7e** was obtained as described earlier in the general procedure from **4e** (200 mg, 1 mmol) and **5** (122 mg, 1 mmol) as a yellow solid. Yield = 57.9 %; m.p. = 179–180 °C; IR v_{max} (cm^{-1}) = 1,172 (C–O), 1,590, 1,673, 1,710 (3 × C=O), 2,939 (C–H) and 3,418 (–OH); ^{1}H NMR (400 MHz, DMSO-d_6) : δ 3.17 (6H, s, N–CH_3), 3.83 (3H, s, –OCH_3), 5.30 (2H, s, –OCH_2), 7.04 (1H, d, J = 5.84 Hz, ArH), 7.17 (2H, d, J = 8.04 Hz, ArH), 7.42–7.47 (3H, m, ArH), 7.69 (2H, d, J = 8.08 Hz, ArH), 7.93 (1H, d, J = 16.1 Hz), 8.35 (1H, d, J = 15.4 Hz) and 8.98 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.92, 29.24, 56.08, 60.98, 79.34, 94.24, 106.00, 112.21, 114.65, 115.83, 117.91, 122.82, 127.59, 130.99, 132.47, 137.77, 143.63, 145.70, 150.09, 160.27, 163.65, 182.38 and 204.32; Anal. calcd. for $C_{25}H_{23}N_5O_6$: C, 61.34, H, 4.74, N, 14.31, Found: C, 61.61, H, 4.75, N, 14.12; ESI–MS m/z: $[M-H]^+$ = 488.4.

(E)-1-(6′-Hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2′,4′-dioxopyrimidin-5′-yl)-3-[-p-{(1″-(m-tolylphenyl)-1H-1″,2″,3″-triazol-4″-yl)methoxy}phenyl]-prop-2-ene-1-one (**7f**)

The product **7f** was obtained as described earlier in the general procedure from **4f** (100 mg, 1 mmol) and **5** (67 mg, 1 mmol) as a yellow solid. Yield = 51 %; m.p. = 257–259 °C; IR

v_{max} (cm^{-1}) = 1,172 (C–O), 1,590, 1,673, 1,712 (3 × C=O), 2,925 (C–H) and 3,420 (–OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.36 (3H, s, –CH_3), 3.16 (6H, s, N–CH_3), 5.28 (2H, s, –OCH_2), 7.15 (2H, d, J = 8.8 Hz, ArH), 7.27 (1H, d, J = 7.32 Hz, ArH), 7.43 (1H, t, J = 8.00 Hz, ArH), 7.63–7.69 (4H, m, ArH), 7.90 (1H, d, J = 15.4 Hz), 8.35 (1H, d, J = 16.1 Hz) and 8.89 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.64, 27.71, 61.33, 78.93, 94.25, 114.77, 115.70, 117.35, 117.73, 120.68, 122.85, 123.10, 127.58, 129.53, 129.84, 131.13, 136.56, 139.84, 143.43, 145.71, 150.10, 160.88, 182.08 and 202.89; Anal. calcd. for $C_{25}H_{23}N_5O_5$: C, 63.42, H, 4.90, N, 14.79, Found: C, 63.45, H, 4.92, N, 14.47; ESI–MS m/z: $[M-H]^+$ = 472.4.

(E)-1-(6′-Hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2,4-dioxopyrimidin-5-yl)-3-[-p-{(1″-(p-bromophenyl)-1H-1″,2″,3″-triazol-4″-yl)methoxy}phenyl]-prop-2-ene-1-one (**7g**)

The product **7g** was obtained as given in the general procedure from **4g** (200 mg, 1 mmol) and **5** (110 mg, 1 mmol) as a yellow solid. Yield = 70 %; m.p. = 247–250 °C; IR v_{max} (cm^{-1}) = 1,172 (C–O), 1,618, 1,661, 1,716 (3 × C=O) and 3,444 (–OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.17 (6H, s, N–CH_3), 5.29 (2H, s, –OCH_2), 7.16 (2H, d, J = 8.8 Hz, ArH), 7.69 (2H, d, J = 8.8 Hz, ArH), 7.77 (2H, d, J = 8.7 Hz, ArH), 7.85 (2H, d, J = 8.8 Hz, ArH), 7.94 (1H, d, J = 15.4 Hz), 8.35 (1H, d, J = 16.1 Hz), 8.95 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.90, 28.69, 65.72, 71.61, 95.24, 114.93, 115.66, 121.67, 121.89, 122.18, 123.03, 130.97, 132.84, 135.89, 148.69, 150.82, 158.20, 178.04, 185.78 and 210.96; Anal. calcd. for $C_{24}H_{20}BrN_5O_5$: C, 53.54, H, 3.74, N, 13.01, Found: C, 53.60, H, 3.75, N, 13.10; ESI–MS m/z: $[M-H]^+$ = 537.3.

(E)-1-(6′-Hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2′,4′-dioxopyrimidin-5′-yl)-3-[-p-{(1″-(p-chloro phenyl)-1H-1″,2″,3″-triazol-4″-yl)methoxy}phenyl]-prop-2-ene-1-one (**7h**)

The product **7h** was obtained as described earlier in the general procedure from **4h** (100 mg, 1 mmol) and **5** (63 mg, 1 mmol) as a yellow solid. Yield = 58 %; m.p. = 200–202 °C; IR v_{max} (cm^{-1}) = 1,172 (C–O), 1,620, 1,660, 1,717 (3 × C=O), 2,923 (C–H) and 3,431 (–OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.10 (6H, s, N–CH_3), 5.29 (2H, s, –OCH_2), 7.15 (2H, d, J = 8.79 Hz, ArH), 7.63–7.65 (4H, m, ArH), 7.88–7.91 (3H, d, J = 8.79 Hz), 8.26 (1H, d, J = 16.0 Hz) and 8.96 (1H, s); ^{13}C NMR (100 MHz, DMSO-d_6): δ 25.32, 67.48, 79.24, 97.54, 115.70, 126.08, 127.19, 127.82, 128.91, 129.75, 130.85, 131.99, 135.17, 145.20, 156.54, 158.07, 179.40, 181.08 and 208.15; Anal. calcd. for $C_{24}H_{20}ClN_5O_5$: C, 58.36, H, 4.08, N, 14.18, Found: C, 58.40, H, 4.01, N, 14.20; ESI–MS m/z: $[M-H]^+$ = 492.8.

(E)-1-(6′-Hydroxy-1′,3′-dimethyl-1′,2′,3′,4′-tetrahydro-2′,4′-dioxopyrimidin-5′-yl)-3-[-p-{(1″-(benzyl)-1H-1″,2″,3″-triazol-4″-yl)methoxy}phenyl]-prop-2-ene-1-one (**7i**)

The product **7i** was obtained as described earlier in the general procedure from **4i** (300 mg, 1 mmol) and **5** (203 mg, 1 mmol) as a yellow solid. Yield = 76.6 %; m.p. = 174–176 °C; IR v_{max} (cm^{-1}) = 1,173 (C–O), 1,632, 1,690, 1,716 (3 × C=O), 2,926 (C–H) and 3,433 (–OH); ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.16 (6H, s, N–CH_3), 5.18 (2H, s, NCH_2), 5.56 (2H, s, –OCH_2), 7.10 (2H, d, J = 8.76 Hz, ArH), 7.26–7.35 (5H, m), 7.66 (2H, d, J = 8.08 Hz, ArH), 7.93 (1H, d, J = 16.1 Hz), 8.27 (1H, s) and 8.33 (1H, d, J = 15.38 Hz); ^{13}C NMR (100 MHz, DMSO-d_6): δ 27.88, 53.04, 61.43, 79.24, 94.24, 115.68, 117.72, 125.04, 127.50, 128.08, 128.34, 128.90, 131.18, 135.91, 142.64, 145.74, 150.12, 160.95, 182.15 and 208.32; Anal. calcd. for $C_{25}H_{23}N_5O_5$: C, 63.42, H, 4.90, N, 14.79, Found: C, 63.40, H, 4.92, N, 14.80; ESI–MS m/z: $[M-H]^+$ = 472.4.

Antimicrobial assay

Antimicrobial activity was performed by the Kirby–Bauer single disc susceptibility test. Whatman No. 1 filter paper disc of 6-mm diameter were autoclaved for 15 min at 121 °C. The sterile filter paper discs were impregnated with different concentration of drugs (2.5 mg/ml and 5 mg/ml) were placed on the surface of the agar plates seeded with target test organisms and then kept for incubation at 37 °C over night. The compound diffuses from the filter paper into the agar. For positive control, Gentamycin at a concentration of 2.5 mg/ml was used, while equal amount of solvent (DMSO) was used as a negative control. The antimicrobial activity was assessed by the inhibition of growth of the microorganisms in and around the disc, giving a clear distinct zone called 'Zone of Inhibition'. The results were recorded by measuring the zone of inhibition surrounding the disc (Table 1).

Conclusion

It was concluded after looking at the structure–activity relationship that compounds **7b**, **7d**, **7e**, **7f**, **7g** and **7i** exhibit moderate activity against *Rhodococcus* as compounds **7d**, **7e** and **7f** showed good activity against *E. coli*. The percentage inhibition indicated that activity was bacteriostatic and not bacteriocidal. Though, it can be further anticipated that these

preliminary results could help in designing better molecules with enhanced antibacterial activity.

Acknowledgments The authors would like to thank Council of Scientific and Industrial Research, New Delhi and Defence Research and Development Organisation for the financial support. NI acknowledges Department of Biotechnology for the award of research fellowship.

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