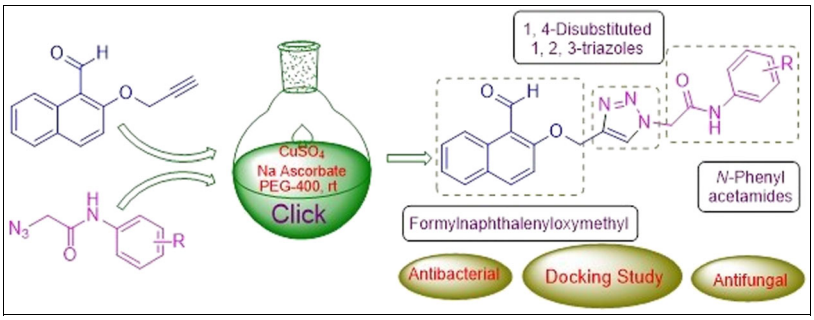
Synthesis, antimicrobial activity, and molecular docking study of formylnaphthalenyloxymethyl-triazolyl-*N*-phenylacetamides

Mahesh B. Muluk,[a] Sambhaji T. Dhumal,[b] Pramod S. Phatak,[a] Naziya N. M. A. Rehman,[c] Prashant P. Dixit,[c] Prafulla B. Choudhari,[d] Ramrao A. Mane,[b] and Kishan P. Haval[a]*

[a]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University Sub-Campus, Osmanabad 413501, Maharashtra, India
[b]Department of Chemistry, Dr. Babasaheb Ambedkar Marathwada University, Aurangabad 431004, Maharashtra, India
[c]Department of Microbiology, Dr. Babasaheb Ambedkar Marathwada University, Sub-Campus, Osmanabad 413501, Maharashtra, India
[d]Department of Pharmaceutical Chemistry, Bharati Vidhyapeeth College of Pharmacy, Kolhapur 416013, Maharashtra, India
*E-mail: havalkp@gmail.com

Received December 15, 2018
DOI 10.1002/jhet.3628
Published online 00 Month 2019 in Wiley Online Library (wileyonlinelibrary.com).



In the present study, substituted formylnaphthalenyloxymethyl-triazolyl-*N*-phenylacetamide derivatives (**6a**–**k**) have been designed and synthesized employing click chemistry approach and evaluated for their *in vitro* antifungal and antibacterial activities. All the newly synthesized compounds were thoroughly characterized by ^{1}H NMR, ^{13}C NMR, and HRMS spectral techniques. Among the screened compounds, **6d**, **6e**, **6j**, and **6k** have shown good antifungal and antibacterial activities. Compound **6k** has shown very effective antimicrobial activity. We further performed exploratory docking studies on microbial DNA gyrase to rationalize the *in vitro* biological data and to demonstrate the mechanism of antimicrobial activity. This is the first report to demonstrate the formylnaphthalenyloxymethyl, triazole, and *N*-phenylacetamide hybrids as potential antimicrobial agents.

J. Heterocyclic Chem., **00,** 00 (2019).

INTRODUCTION

The microbial resistance is an important public health concern worldwide, despite of growing knowledge about infectious diseases and availability of various antibiotics and chemotherapeutics [1]. In the USA alone, antibiotic-resistant bacteria cause at least 2 million infections and 23,000 deaths a year [2]. Therefore, the innovation and development of new effective antimicrobial agents with novel chemical structures and mechanisms to address the drug resistance and improve the antimicrobial potency is of prime interest [3]. The molecular hybridization has emerged as one of the best synthetic strategies to synthesize effective lead compounds with novel mechanism of action and structural modification to improve their binding affinity and activity [4]. Literature revealed that some molecular hybrid compounds having broad spectrum of biological activities (Fig. 1) [5–8].

Compounds bearing *N*-phenylacetamide unit have been identified as significant anticancer [9], antimicrobial [10], human sirtuin 2 inhibitor [11], and other biological activities [12]. 1,4-Disubstituted 1,2,3-triazoles have received significant attention due to their broad range of biological activities such as antitubercular [13], antimicrobial [14], anticancer [15], anti-inflammatory [16], antimalarial [17], anti-HIV [18], anti-diabetic [19], and anti-oxidant [20]. These can be synthesized by copper(I) catalyzed azide-alkyne cyloaddition "click" reaction [21].

Recently, Lal *et al*. have reported molecular hybrid triazolyl-naphthaldehye oxime derivatives possessing antimicrobial activity [22]. In view of these findings and in our continuing efforts on the synthesis of bioactive organic compounds [23], herein, we have reported the synthesis and antimicrobial activity of the substituted formylnaphthalenyloxymethyl-triazolyl-*N*-phenylacetamide derivatives (**6a**–**k**) *via* click chemistry approach.

RESULTS AND DISCUSSIONS

Chemistry. The title compounds, new substituted for mylnaphthalenyloxymethyl-triazolyl-*N*-phenylacetamide derivatives (**6a**–**k**), have been synthesized starting from

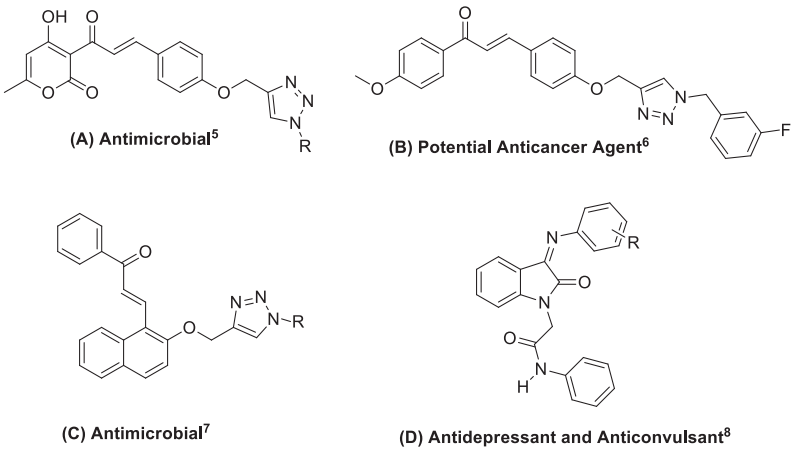
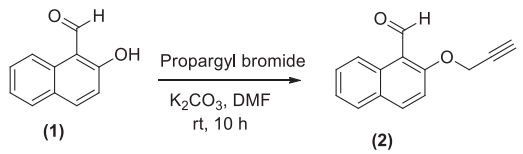


Figure 1. Some bioactive molecular hybrid compounds.

commercially available 2-hydroxy-1-naphthaldehyde (**1**). The key intermediate, 2-(prop-2-yn-1-yloxy)-1-naphthaldehyde (**2**) was prepared from 2-hydroxy-1-naphthaldehyde (**1**) and propargyl bromide in the presence of anhydrous K_2CO_3 in DMF at room temperature for 10 h (Scheme 1). In the second step, substituted 2-azido-*N*-phenylacetamides (**5a–k**) were obtained from the corresponding substituted amines (**3a–k**) on reaction with acetyl chloride followed by sodium azide (Scheme 2). The copper(I) catalyzed cycloaddition reaction of 2-(prop-2-yn-1-yloxy)-1-naphthaldehyde (**2**) with substituted 2-azido-*N*-phenylacetamides (**5a–k**) furnished the corresponding substituted formylnaphtha lenyloxymethyl-triazolyl-*N*-phenylacetamides (**6a–k**) with 82–90% yields (Scheme 3).

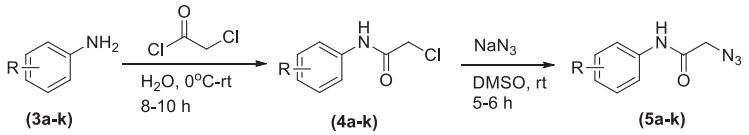
The structures of all the synthesized products were established by using ^{1}H NMR, ^{13}C NMR, and HRMS data. The ^{1}H NMR spectrum of compound (**6a**) that displays two characteristic peaks at δ 5.35 and 5.54 ppm as singlets confirms the presence of OCH_2 and NCH_2, respectively. The amido-NH appeared as a singlet at δ 10.42 confirming the presence of 1,2,3-triazole ring in compound (**6a**). The characteristic peak of aldehyde (CHO) is observed at 10.79 ppm. In ^{13}C NMR spectrum of (**6a**), the peaks appeared at δ 51.2 and 62.9 confirm the presence of OCH_2 and NCH_2 methylene carbons, respectively. Whereas the signals at 162.42 and 190.43 ppm due to the amide and aldehyde carbon, respectively. The HRMS spectrum further strengthens the structure assigned to 2-(4-(((1-formylnaphthalen-2-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-*N*-phenylacetamide (**6a**) as it displays $[M-H]^-$ ion peak at *m/z* 385.1302 for its molecular formula $C_{22}H_{18}N_4O_3$.

Scheme 1. Synthesis of 2-(prop-2-yn-1-yloxy)-1-naphthaldehyde (**2**).

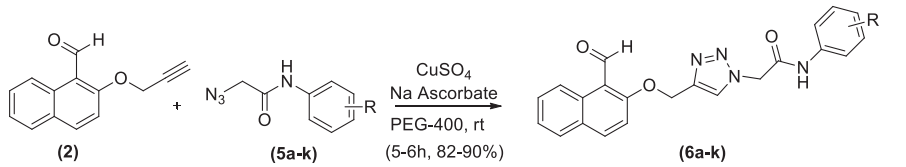


Antibacterial and antifungal activities. The *in vitro* antimicrobial activity of the synthesized compounds (**6a–k**) was evaluated by using agar well diffusion method [24]. Various potent microbial pathogens were used for this study. For assessing antibacterial activity, Gram-positive bacterial pathogens, *Staphylococcus aureus*, *Bacillus cereus*, *Bacillus megaterium*, *Micrococcus glutamicum*, and *Bacillus subtilis* and Gram-negative pathogens, *Escherichia coli*, *Salmonella typhi*, *Shigella boydii*, *Enterobacter aerogenes*, *Pseudomonas aerogenosa*, and *Salmonella abony* were used. Furthermore, antifungal activity of synthesized compounds was determined against *Aspergillus niger*, *Saccharomyces cerevisiae*, and *Candida albicans*. Tetracyclin and Nystatin were used as standard antibacterial and antifungal reference compounds, respectively. The inoculums of each bacterial and fungal pathogen were developed by growing them overnight in a nutrient broth medium at 37°C, and then this broth was used for the study. The bacterial suspension was diluted by using sterile saline to adjust the turbidity to the 0.5 McFarland standards. The Mueller Hinton agar plates were inoculated with 200-μL diluted suspension of each pathogen. Wells were punched in the agar medium. All synthesized compounds (**6a–k**) were dissolved to get final concentration of 2 mg/mL in DMSO; 100 μL of each compound solution was placed in a well; 100 μL of DMSO solution without any compound was also placed in a well to check its activity against the pathogenic culture. Petri dishes were incubated for 24 h at 37°C. After complete incubation, the antimicrobial activity of

Scheme 2. Synthesis of substituted 2-azido-*N*-phenylacetamides (**5a**–**k**).



Scheme 3. Synthesis of substituted formylnaphthalenyloxymethyl-triazolyl-*N*-phenylacetamides (**6a**–**k**).



6a : R = H, **6b** : R = 3-OCH_3, **6c** : R = 4-NO_2,
6d : R = 3-CH_3, **6e** : R = 2-CH_3, **6f** : R = 3-NO_2,
6g : R = 4-CH_3, **6h** : R = 4-OCH_3, **6i** : R = 2-Cl,
6j : R = 3-Cl, **6k** : R = 4-Cl

the synthesized compounds (**6a**–**k**) was measured by the zone of inhibition around wells as bacterial growth inhibition.

Out of 11 synthesized compounds, compound **6k** with a 4-chloro substituted benzene ring displayed notable activity against all the pathogens. The maximum zone of inhibition, that is, 19 and 17 mm, was observed against bacterial pathogens, *B. cereus* and *S. aureus*, respectively. Compound **6j** having a 3-chloro substituted benzene ring was also found to have good antimicrobial activity. The maximum inhibition activity of **6j** was observed against pathogen *E. coli*, whereas compounds **6d** and **6e** with 3-methyl and 2-methyl substituted benzene rings, respectively, have also shown good antimicrobial activity (Table 1).

Minimum inhibitory concentration. Minimum inhibitory concentration (MIC) is the lowest concentration of an antimicrobial (compounds) drug that will inhibit the visible growth of a microorganism after overnight incubation. The MIC was determined for the most potent selected antimicrobial compounds **6j** and **6k**. The MIC was determined against *S. aureus*, *E. coli*, and *B. cereus*. The MIC was determined by following the method and guidelines of Clinical and Laboratory Standard Institute. The results are shown in Table 2.

Molecular docking study. Molecular docking analysis was utilized to predict the mechanism of action of the synthesized derivatives for antimicrobial potential [25]. All the molecules exhibited binding energies in the

Table 1

Antibacterial and antifungal activity in zone of inhibition (mm) of compounds **6a**–**k**.

	Compounds											
Pathogens	**6a**	**6b**	**6c**	**6d**	**6e**	**6f**	**6g**	**6h**	**6i**	**6j**	**6k**	Standard[a]
Salmonella typhi	—	—	12	—	12	—	—	—	—	13	14	27
Enterobacter aerogenes	—	08	—	11	—	—	—	13	—	14	15	33
Bacillus subtilis	08	—	12	14	14	—	—	—	—	10	16	34
Candida albicans	—	—	—	12	10	—	—	—	—	09	15	25
Pseudomonas aerogenosa	—	—	—	13	—	—	—	—	—	12	14	30
Salmonella abony	—	—	—	—	16	—	—	—	—	13	13	30
Bacillus megaterium	—	—	—	15	—	—	—	12	—	—	11	27
Escherichia coli	09	08	13	11	08	09	10	—	—	17	16	29
Staphylococcus aureus	—	—	—	16	12	—	—	—	—	14	17	25
Shigella boydii	—	—	—	—	14	—	—	—	07	12	14	27
Saccharomyces cerevisiae	—	06	—	10	—	—	—	—	—	11	16	24
Aspergillus niger	—	—	—	—	—	—	—	—	—	11	12	26
Bacillus cereus	07	—	—	13	16	—	—	15	—	14	19	33
Micrococcus glutamicum	—	—	—	14	—	—	—	—	—	—	11	31

Diameter of zone of inhibition is given in millimeter (mm).
[a]Tetracyclin and Nystatin were used as standard antibacterial and antifungal reference compounds, respectively.

Table 2

MIC in μg/mL of compounds **6j** and **6k**.

Pathogens	Compounds		
	6j	**6k**	Standard
Staphylococcus aureus	180	40	6.5
Escherichia coli	70	120	4.5
Bacillus cereus	90	35	5

MIC, minimum inhibitory concentration.

range of −33.62 to −60.10 kcal/mol. Compound **6j** showed aromatic interaction with HIS99, hydrophobic interaction with PRO79, ILE94, and Van der Waal interactions with ARG136, GLY119, HIS99, ILE94, HIS55, and GLU50 (Fig. 2). Compound **6k** showed aromatic interaction with HIS99, hydrophobic interaction with PRO79, ILE94, and Van der Waal interactions with HIS99, ILE94, HIS55, and GLU50 (Fig. 3). Compound **6d** showed aromatic interaction with HIS99, hydrophobic interaction with PRO79, ILE94, LEU98, HIS99, GLY119, and Van der Waal interactions with ARG136, GLY119, HIS99, ILE94, PRO79, ARG76, HIS55, and GLU50 (Fig. 4).

Absorption, distribution, metabolism, and excretion prediction. Good efficacy and acceptable absorption, distribution, metabolism, and excretion (ADME) profile are the most important properties of any successful drugs. All the synthesized derivatives (**6a–k**) were scrutinized for ADME prediction using Swiss ADME portal [26]. All the molecules showed excellent ADME parameters with low Lipinski violation, which is desirable for the oral absorption of drug candidates, and the results are shown in Table 3.

Docking analysis. Molecular docking analysis was performed to predict possible mode of action of the synthesized triazole derivatives. Crystal structure of the DNA gyrase of *E. coli* was utilized for docking analysis. Crystal structure of DNA gyrase (PDB ID: 5l3j) was downloaded from the free protein database www.rcsb.org Crystal structure of the downloaded DNA gyrase was refined prior to the docking analysis *via* removal of the water and addition of the hydrogen atoms so that native geometry of the protein will be retained. Ligands were prepared in Vlife engine module and optimized *via* Merck molecular force field. Biopredicta module of the Vlife MDS was utilized for docking analysis.

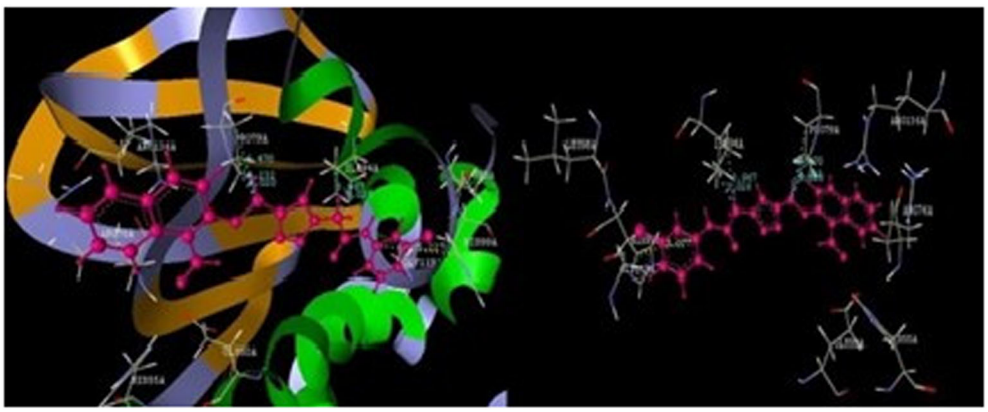


Figure 2. Binding mode of **6j** into the active site of DNA gyrase. [Color figure can be viewed at wileyonlinelibrary.com]

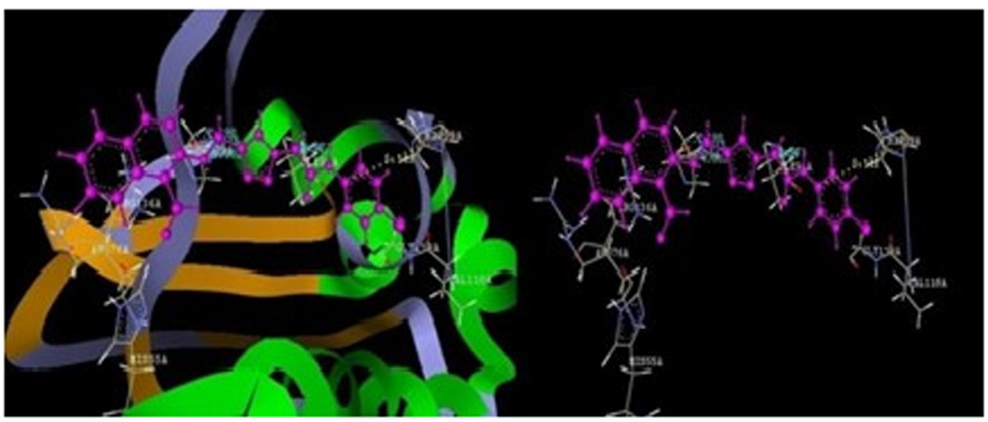


Figure 3. Binding mode of **6k** into the active site of DNA gyrase. [Color figure can be viewed at wileyonlinelibrary.com]

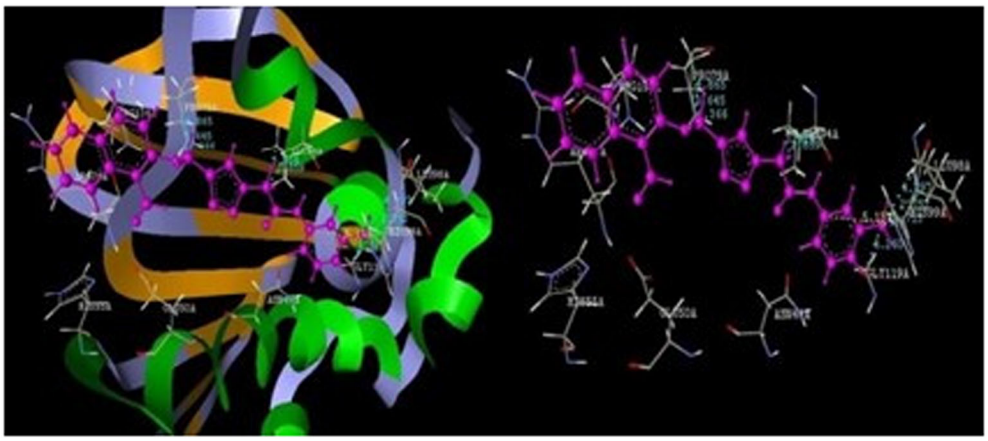


Figure 4. Binding mode of **6d** into the active site of DNA gyrase. [Color figure can be viewed at wileyonlinelibrary.com]

Table 3

ADME prediction and bioavailability score.

Entry	MW	Rotatable bonds	H-bond acceptors	H-bond donors	MR	Log *P*	Bioavailability score
6a	372.38	7	5	1	104.57	2.69	0.55
6b	402.4	8	6	1	111.06	3	0.55
6c	417.37	8	7	1	113.39	2.4	0.55
6d	386.4	7	5	1	109.54	2.99	0.55
6e	386.4	7	5	1	109.54	2.99	0.55
6f	417.37	8	7	1	113.39	2.45	0.55
6g	386.4	7	5	1	109.54	2.81	0.55
6h	402.4	8	6	1	111.06	2.36	0.55
6i	406.82	7	5	1	109.58	3.09	0.55
6j	406.82	7	5	1	109.58	3.09	0.55
6k	406.82	7	5	1	109.58	3.04	0.55

ADME, acceptable absorption, distribution, metabolism, and excretion.

EXPERIMENTAL

All reagents were purchased from Merck and Aldrich and used without further purification. Melting points were determined in open capillaries and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker DRX-300 and 400 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard and chemical shifts are in δ (ppm). ^{13}C NMR spectra were recorded on a Bruker DRX-75 and 100-MHz NMR in $CDCl_3$/DMSO-d_6. High-resolution mass spectra (HRMS) were obtained using Agilent 6520 (Q-TOF) ESI-HRMS instrument. The purity of the titled and intermediate compounds was checked by thin-layer chromatography (TLC) using silica-gel, $60F_{254}$ aluminum sheets as an adsorbent, and visualization was accomplished by iodine/ultraviolet light.

Procedure for the synthesis of 2-(prop-2-yn-1-yloxy)-1-naphthaldehyde (2). To a mixture of 2-hydroxy-1-naphthaldhyde (1.0 mmol) and anhydrous potassium carbonate (1.5 mmol) in dimethyformamide (DMF) (10 mL), propargyl bromide (80% in toluene, 1.5 mmol) was added slowly at 0°C and stirred for 10 h. After the completion of the reaction as monitored by TLC, ice-cold water was added to it. The obtained solid compound was filtered and crystallized from ethanol. The melting point was in good agreement with the reported [7]. Yield: 72%, mp 108–112°C.

General procedure for the synthesis of substituted 2-azido-*N*-phenylacetamides (5a–k). The chloroacetyl chloride (1.5 mmol) was added dropwise in aqueous solution of substituted anilines (**3a–k**) (1.0 mmol) at 0°C and stirred for 8–10 h at room temperature. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured on crushed ice. The solid obtained were filtered and recrystallized from ethanol to furnish the corresponding substituted 2-chloro-*N*-phenylacetamides (**4a–k**). Then, the obtained substituted 2-chloro-*N*-phenylacetamides (**4a–k**) (1.0 mmol) and sodium azide (1.0 mmol) were stirred in DMSO for 5–6 h at room temperature. After completion of reaction, the water was added in reaction mixture and extracted with ethyl acetate to give the corresponding substituted 2-azido-*N*-phenylacetamides (**5a–k**).

General procedure for the synthesis of substituted formylnaphthalenyloxymethyl-triazolyl-*N*-phenylacetamides (6a–k). 2-(Prop-2-yn-1-yloxy)-1-naphthaldehyde (**2**) (1.0 mmol) and substituted 2-azido-*N*-phenylacetamides (**5a–k**) (1.0 mmol) were stirred in the presence of $CuSO_4.5H_2O$ (20 mol%) and sodium ascorbate (20 mol%) in PEG-400 at

room temperature. The progress of the reaction was monitored by TLC. After completion of the reaction, the reaction mixture was poured on ice. The white solid obtained was filtered, washed with water, and crystallized in ethanol to furnish the corresponding substituted formylnaphthalenyloxymethyl-triazolyl-*N*-phenylacetamides (**6a**–**k**) with 82–90% yields.

2-(4-(((1-Formylnaphthalen-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-N-phenylacetamide (6a). Yield: 86%; mp 150–152°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.35 (s, 2H, OCH_2), 5.54 (s, 2H, NCH_2), 7.07 (t, *J* = 7.2 Hz, 1H, Ar—H), 7.29 (t, *J* = 7.6 Hz, 2H, Ar—H), 7.44 (t, *J* = 7.6 Hz, 1H, Ar—H), 7.58–7.62 (m, 3H, Ar—H), 7.75 (d, *J* = 9.2 Hz, 1H, Ar—H), 7.88 (d, *J* = 8.0 Hz, 1H, Ar—H), 8.22 (d, *J* = 8.8 Hz, 1H, Ar—H), 8.31 (s, 1H, Triazolyl-H), 9.14 (d, *J* = 8.8 Hz, 1H, Ar—H), 10.42 (s, 1H, Amido-NH), 10.79 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ = 51.2, 62.9, 113.6, 114.9, 118.1, 122.4, 122.8, 122.9, 123.6, 126.9, 127.2, 127.5, 128.50, 129.1, 136.4, 136.7, 160.1, 161.5, 162.4, 190.4; HRMS: *m/z* Calcd for $C_{22}H_{18}N_4O_3$ [M-H]$^-$: 385.1298 and found 385.1302.

2-(4-(((1-Formylnaphthalen-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-methoxyphenyl)acetamide (6b). Yield: 90%; mp 220–221°C; ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO-d_6) δ = 3.71 (s, 3H, OCH_3), 5.32 (s, 2H, OCH_2), 5.52 (s, 2H, NCH_2), 6.61 (d, *J* = 6.0 Hz, 1H, Ar—H), 7.07–7.08 (m, 1H, Ar—H), 7.15–7.17 (m, 1H, Ar—H), 7.27–7.93 (m, 5H, Ar—H), 8.17–8.32 (m, 2H, merged signals, Triazolyl-H & Ar—H), 9.10 (d, *J* = 8.4 Hz, 1H, Ar—H), 10.41 (s, 1H, Amido-NH), 10.75 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ = 52.8, 55.6, 63.3, 105.8, 110.1, 112.2, 112.30, 115.6, 115.6, 116.8, 124.4, 125.6, 128.9, 129.1, 129.2, 130.5, 131.1, 138.6, 139.7, 160.1, 163.5, 164.7, 192.4; HRMS: *m/z* Calcd for $C_{23}H_{20}N_4O_4$ [M-H]$^-$: 415.1407 and found 415.1407.

2-(4-(((1-Formylnaphthalen-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-nitrophenyl)acetamide (6c). Yield: 83%; mp 162–164°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.43 (s, 2H, OCH_2), 5.55 (s, 2H, NCH_2), 7.45 (bs, 1H, Ar—H), 7.61–7.71 (m, 2H, Ar—H), 7.84 (bs, 3H, Ar—H), 8.07–8.29 (m, 4H, merged signals, Triazolyl-H & Ar—H), 9.15 (bs, 1H, Ar—H), 10.81 (s, 1H, CHO), 11.06 (s, 1H, Amido-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 52.8, 63.4, 115.8, 116.7, 119.5, 124.3, 125.3, 125.6, 127.1, 128.8, 129.1, 130.3, 131.1, 138.3, 143.1, 144.9, 163.4, 165.7, 191.8; HRMS: *m/z* Calcd for $C_{22}H_{17}N_5O_5$ [M-H]$^-$: 430.1152 and found 430.1153.

2-(4-(((1-Formylnaphthalen-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(m-tolyl)acetamide (6d). Yield: 87%; mp 160–163°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.24 (s, 3H, CH_3), 5.26 (s, 2H, OCH_2), 5.45 (s, 2H, NCH_2), 6.82 (d, *J* = 5.2 Hz, 1H, Ar—H), 7.08–7.12 (m, 1H, Ar—H), 7.29–7.37 (m, 2H, Ar—H), 7.53–7.63 (m, 2H, Ar—H), 7.78–7.87 (m, 2H, Ar—H), 8.10–8.18 (m, 2H, merged signals, Triazolyl-H & Ar—H), 9.09 (d, *J* = 7.2 Hz, 1H, Ar—H), 10.29 (s, 1H, Amido-NH), 10.74 (s, 1H, CHO); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 21.5, 52.7, 63.8, 115.8, 116.7, 116.8, 119.7, 120.1, 124.9, 124.9, 125.2, 126.6, 127.1, 129.1, 129.1, 129.9, 130.1, 138.3, 138.6, 139.1, 163.1, 164.5, 191.5; HRMS: *m/z* Calcd for $C_{23}H_{20}N_4O_3$ [M-H]$^-$: 399.1457 and found 399.1456.

2-(4-(((1-Formylnaphthalen-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(o-tolyl)acetamide (6e). Yield: 85%; mp 200–202°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.22 (s, 3H, CH_3), 5.38 (s, 2H, OCH_2), 5.52 (s, 2H, NCH_2), 7.06–7.17 (m, 3H, Ar—H), 7.42 (bs, 2H, Ar—H), 7.55–7.65 (m, 1H, Ar—H), 7.75 (d, *J* = 8.4 Hz, 1H, Ar—H), 7.87–7.88 (m, 1H, Ar—H), 8.17–8.31 (m, 2H, merged signals, Triazolyl-H & Ar—H), 9.10 (d, *J* = 7.6 Hz, 1H, Ar—H), 9.75 (s, 1H, Amido-NH), 10.75 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6) δ = 18.2, 63.3, 70.3, 115.7, 115.8, 116.8, 124.4, 125.5, 125.6, 126.5, 126.7, 128.9, 129.2, 130.4, 131.1, 131.1, 132.5, 135.7, 138.6, 163.5, 163.5, 164.9, 192.3; HRMS: *m/z* Calcd for $C_{23}H_{20}N_4O_3$ [M-H]$^-$: 399.1457 and found 399.1451.

2-(4-(((1-Formylnaphthalen-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(3-nitrophenyl)acetamide (6f). Yield: 90%; mp 174–175°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.31 (s, 2H, OCH_2), 5.45 (s, 2H, NCH_2), 7.33–7.38 (m, 1H, Ar—H), 7.41–7.46 (m, 1H, Ar—H), 7.50–7.58 (m, 1H, Ar—H), 7.70–7.75 (m, 1H, Ar—H), 7.82–7.88 (m, 1H, Ar—H), 8.06–8.14 (m, 2H, Ar—H), 8.51 (bs, 1H, Triazolyl-H), 9.10 (d, *J* = 6.4 Hz, 1H), 10.75 (s, 1H, CHO), 10.83 (s, 1H, Amido-NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 52.3, 63.1, 113.4, 115.3, 116.3, 118.3, 123.9, 124.8, 125.2, 126.8, 128.4, 128.6, 129.7, 130.4, 130.6, 137.5, 139.5, 147.9, 162.9, 165.1, 191.3; HRMS: *m/z* Calcd for $C_{22}H_{17}N_5O_5$ [M-H]$^-$: 430.1152 and found 430.0980.

2-(4-(((1-Formylnaphthalen-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(p-tolyl)acetamide (6g). Yield: 88%; mp 180–181°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 2.21 (s, 3H, CH_3), 5.20 (s, 2H, OCH_2), 5.42 (s, 2H, NCH_2), 7.01 (bs, 1H, Ar—H), 7.36 (bs, 1H, Ar—H), 7.53–7.57 (m, 3H, Ar—H), 7.70–7.77 (m, 1H, Ar—H), 8.04 (bs, 2H, merged signals, Triazolyl-H & Ar—H), 9.10 (bs, 1H, Ar—H), 10.11 (s, 1H, Amido-NH), 10.75 (s, 1H, CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.1, 52.9, 63.7, 116.0, 116.9, 119.8, 124.5, 125.5, 127.1, 128.2, 128.6, 129.9, 130.4, 131.2, 133.38, 136.5, 138.5, 163.6, 164.5, 191.9; HRMS: *m/z* Calcd for $C_{23}H_{20}N_4O_3$ [M-H]$^-$: 399.1457 and found 399.1281.

2-(4-(((1-Formylnaphthalen-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)-N-(4-methoxyphenyl)acetamide (6h). Yield: 89%; mp 230–232°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 3.70 (s, 3H, OCH_3), 5.26 (s, 2H, OCH_2), 5.49 (s, 2H, NCH_2), 6.80 (d, *J* = 8.8 Hz, 2H, Ar—H), 7.40 (t, *J* = 8.6 Hz, 1H, Ar—H), 7.45 (d, *J* = 8.8 Hz, 2H, Ar—H), 7.56 (t, *J* = 8.6 Hz, 1H, Ar—H), 7.70 (d, *J* = 9.2 Hz, 1H, Ar—H), 7.84 (d, *J* = 8.0 Hz, 1H, Ar—H), 8.17 (d, *J* = 9.2 Hz, 1H, Ar—H), 8.26 (bs, 1H, Triazolyl-H), 9.10 (d, *J* = 8.4 Hz, 1H, Ar—H), 10.28 (s, 1H, Amido-NH), 10.74 (s, 1H, CHO); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.3, 63.1, 113.4, 115.3, 116.3, 118.3, 123.9, 124.8, 125.2, 127.1, 127.4, 128.4, 128.6, 129.8, 130.4, 130.6, 137.9, 139.5, 147.9, 162.9, 165.1, 191.3; HRMS: *m/z* Calcd for $C_{23}H_{20}N_4O_4$ [M + H]$^+$: 417.1563 and found 417.0943.

N-(2-Chlorophenyl)-2-(4-(((1-formylnaphthalen-2-yl)oxy)methyl)-1H-1,2,3-triazol-1-yl)acetamide (6i). Yield: 84%; mp 138–139°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.42 (s, 2H, OCH_2), 5.48 (s, 2H, NCH_2), 7.12 (t, *J* = 8.4 Hz, 1H, Ar—H), 7.24 (t, *J* = 8.4 Hz, 1H, Ar—H), 7.37–7.40 (m, 2H, Ar—H), 7.53–7.57 (m, 1H, Ar—H), 7.66–7.69 (m, 1H, Ar—H), 7.76–7.82 (m, 2H, Ar—H), 7.90 (bs, 1H, Ar—H), 8.16 (d, *J* = 8.8 Hz, 1H, Triazolyl-H), 9.08 (d, *J* = 8.4 Hz, 1H, Ar—H), 9.95 (s, 1H, Amido-NH), 10.73 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO-d_6): δ = 52.6, 63.3, 114.8, 116.9, 124.6, 125.0, 125.3, 126.1, 126.3, 126.4, 127.5, 128.6, 128.7, 129.7, 129.8, 131.2, 134.4, 137.8, 162.3, 163.1, 164.8, 191.6; HRMS: *m/z* Calcd for $C_{22}H_{17}ClN_4O_3$ [M-H]$^-$: 419.0911 and found 419.0910.

N-(3-Chlorophenyl)-2-(4-(((1-formylnaphthalen-2-yl)oxy) methyl)-1H-1,2,3-triazol-1-yl)acetamide (6j). Yield: 82%; mp 146–147°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.28 (s, 2H, OCH_2), 5.46 (s, 2H, NCH_2), 6.99 (d, J = 6.0 Hz, 1H, Ar—H), 7.20 (t, J = 8.4 Hz, 1H, Ar—H), 7.37 (bs, 2H, Ar—H), 7.53 (t, J = 8.4 Hz, 1H, Ar—H), 7.61 (d, J = 8.0 Hz, 1H, Ar—H), 7.70–7.79 (m, 2H, Ar—H), 8.10–8.18 (m, 2H, merged signals, Triazolyl-H & Ar—H), 9.09 (d, J = 8.4 Hz, 1H, Ar—H), 10.54 (s, 1H, Amido-NH), 10.74 (s, 1H, CHO); ^{13}C NMR (100 MHz, DMSO-d_6) δ = 52.4, 63.3, 115.6, 116.5, 117.9, 118.9, 123.7, 124.1, 125.1, 126.7, 128.6, 128.8, 129.9, 130.8, 130.9, 133.3, 133.4, 138.1, 140.1, 142.5, 163.2, 164.8, 191.2; HRMS: *m/z* Calcd for $C_{22}H_{17}ClN_4O_3$ [M-H]$^-$: 419.0911 and found 419.0911.

N-(4-Chlorophenyl)-2-(4-(((1-formylnaphthalen-2-yl)oxy) methyl)-1H-1,2,3-triazol-1-yl)acetamide (6k). Yield: 87%; mp 158–160°C; ^{1}H NMR (400 MHz, DMSO-d_6) δ = 5.26 (s, 2H, OCH_2), 5.44 (s, 2H, NCH_2), 7.18 (bs, 2H, Ar—H), 7.36 (bs, 1H, Ar—H), 7.51 (m, 3H, Ar—H), 7.75 (m, 2H, Ar—H), 8.07–8.13 (m, 2H, merged signals, Triazolyl-H & Ar—H), 9.09 (d, J = 8.4 Hz, 1H, Ar—H), 10.46 (s, 1H, Amido-NH), 10.73 (s, 1H, CHO); HRMS: *m/z* Calcd for $C_{22}H_{18}N_4O_3$ [M-H]$^-$: 419.9725 and found 419.0739.

CONCLUSIONS

In conclusion, a series of new substituted formylnaphthalenyloxymethyl-triazolyl-*N*-phenylacetamides (**6a–k**) were synthesized and evaluated for their antibacterial and antifungal activities. Compounds **6j** and **6k** having 3-chloro and 4-chloro substituted benzene rings, respectively, have shown very good antibacterial and antifungal activities. However, compounds **6d** and **6e** with methyl substituents at 3-position and 4-position, respectively, also displayed notable antimicrobial activity. In addition, the molecular docking study revealed that synthesized molecules are potent DNA gyrase inhibitors. Thus, these four compounds **6d**, **6e**, **6j**, and **6k** can be considered as competent candidates for further study to invent new broad spectrum antibiotics.

Acknowledgments. The authors are thankful to Dr. Babasaheb Ambedkar Marathwada University, Aurangabad for providing necessary facilities. One of the authors M. B. M. is grateful to UGC New Delhi, India, for financial assistance in the form of NET Senior Research Fellowship.

REFERENCES AND NOTES

[1] (a) Yoneyama, H.; Katsumata, R. Biosci Biotechnol Biochem 2006, 70, 1060; (b) Bollu, R.; Banu, S.; Bantu, R.; Gopi Reddy, A.; Nagarapu, L.; Sirisha, K.; Ganesh Kumar, C.; Gunda, S. K.; Shaik, K. Biorg Med Chem Lett 2017, 27, 5158; (c) Anderson, D. I.; Huges, D. Nat Rev Microbiol 2010, 8, 260; (d) Zheng, X.; Sallum, U. W.; Verma, S.; Athar, H.; Evans, C. L.; Hasan, T. Angew Chem Int Ed 2009, 48, 2148; (e) Lopes, S. M. M.; Novais, J. S.; Costa, D. C. S.; Castro, H. C.; Figueiredo, A. M. S.; Ferreira, V. F.; Pinhoe Melo, T. M.; da Silva, F. Eur J Med Chem 2018, 143, 1010.

[2] (a) Li, B.; Webster, T. J. J Orthop Res 2018, 36, 22; (b) Jasovský, D.; Littmann, J.; Zorzet, A.; Cars, O. Ups J Med Sci 2016, 121, 159.

[3] (a) Hou, W.; Zhang, G.; Luo, Z.; Li, D.; Ruan, H.; Ruan, B. H.; Su, L.; Xu, H. Bioorg Med Chem Lett 2017, 27, 5382; (b) Aufort, M.; Herscovici, J.; Bouhours, P.; Moreau, N.; Girard, C. Bioorg Med Chem Lett 2008, 18, 1195; (c) Pereira, D.; Fernandes, P. Bioorg Med Chem Lett 2011, 21, 510; (d) Kamat, S. R.; Salunkhe, R. S.; Choudhari, P. B.; Dhavale, R. P.; Mane, A. H.; Lohar, T. R. Res Chem Intermed 2018, 44, 1351; (e) Kondhare, D. D.; Gyananath, G.; Tamboli, Y.; Kumbhar, S. S.; Choudhari, P. B.; Bhatia, M. S.; Zubaidha, P. K. Med Chem Res 2017, 26, 987.

[4] (a) Viegas-Junior, C.; Danuello, A.; da Silva Bolzani, V.; Barreiro, E. J.; Carlos Fraga, A. M. Curr Med Chem 2007, 14, 1829; (b) Zhang, S.; Saathoff, J. M.; He, L. Design of Hybrid Molecules for Drug Development; Elsevier, 2017, pp 219–237.

[5] Lal, K.; Yadav, P.; Kumar, A.; Kumar, A.; Paul, A. K. Bioorg Chem 2018, 77, 236.

[6] Yadav, P.; Lal, K.; Kumar, A.; Bhushan, S.; Guru, S. K.; Jaglan, S. Eur J Med Chem 2017, 126, 944.

[7] Yadav, P.; Lal, K.; Kumar, L.; Kumar, A.; Paul, A. K.; Kumar, R. Eur J Med Chem 2018, 155, 263.

[8] Gaun, L. P.; Liu, B. Y.; Quan, Y. C.; Yang, L. Y.; Zhen, X. H.; Wang, S. H. Med Chem 2016, 12, 786.

[9] (a) Kumar, R.; Kuar, M.; Bahia, M. S.; Silkari, O. Eur J Med Chem 2014, 80, 83; (b) Pawar, C. D.; Sarkate, A. P.; Karnik, K. S.; Shinde, D. B. Egyp J Basic Appl Sci 2017, 4, 310; (c) Chahroura, O.; Abdallaa, A.; Lama, F.; Midgley, C.; Wang, S. Bioorg Med Chem Lett 2011, 21, 3066.

[10] Chen, L.; Wang, P.; Li, Z.; Zhou, L.; Wu, Z.; Song, B.; Yang, S. Chin J Chem 2016, 34, 1236.

[11] Yang, L.; Ma, X.; Yuan, C.; He, Y.; Li, L.; Fang, S.; Xia, W.; He, T.; Qian, S.; Xu, Z.; Li, G.; Wang, Z. Eur J Med Chem 2017, 134, 230.

[12] (a) Kulabaş, N.; Tatar, E.; Özakpınar, Ö. B.; Özsavcı, D.; Pannecouque, C.; Clercq, E. D.; Küçükgüzel, İ. E. J Med Chem 2016, 121, 58; (b) Penta, A.; Ganguly, S.; Murugesan, S. Der Pharma Chem 2013, 5, 10.

[13] (a) Yang, P. X.; Wedajo, W.; Yamada, Y.; Dahlroth, S. L.; Neo, J. J. L.; Dick, T. Eur J Med Chem 2018, 144, 262; (b) Nayak, R. J.; Dalimba, N.; Yogeeswari, U.; Sriram, P. D. Bioorg Med Chem Lett 2015, 25, 4169.

[14] (a) Kaushik, C. P.; Luxmi, R.; Singh, D.; Kumar, A. Mol Divers 2017, 21, 137; (b) Kumar, S.; Prasad, S.; Kumar, B.; Gautam, H. K.; Sharma, S. K. Med Chem Res 2016, 25, 1057; (c) Lal, K.; Yadav, P.; Kumar, A. Med Chem Res 2016, 25, 644.

[15] (a) Reddy, V. G.; Bonam, S. R.; Reddy, T. S.; Akunuri, R. K.; Naidu, V. G. M.; Nayak, V. L.; Bhargava, S. K.; Kumar, H. M. S.; Srihari, P.; Kamal, A. Eur J Med Chem 2018, 144, 595; (b) Bollu, R.; Palem, J. D.; Bantu, R.; Guguloth, V.; Nagarapu, L.; Polepalli, S.; Jain, N. Eur J Med Chem 2018, 144, 262; (c) Shaik, S. P.; Nayak, V. L.; Sultana, F.; SubbaRao, A. V.; Shaik, A. B.; Babu, K. S.; Kamal, A. Eur J Med Chem 2017, 126, 36.

[16] Moussa, G.; Alaaeddine, R.; Alaeddine, L. M.; Nassra, R.; Belal, A. S. F.; Ismail, A.; El-Yazbi, A. F.; Abdel-Ghany, Y. S.; Hazzaa, A. Eur J Med Chem 2018, 144, 635.

[17] Brandão, G. C.; Missias, F. C. R.; Arantes, L. M.; Soares, L. F.; Roy, K. K.; Doerksen, R. J.; de Oliveira, A. B.; Pereira, G. R. Eur J Med Chem 2018, 145, 191.

[18] Rai, D.; Chen, W.; Zhan, P.; Liu, H.; Tian, Y.; Liang, X.; de Clercq, E.; Pannecouque, C.; Balzarini, J.; Liu, X. Chem Biol Drug Des 2014, 84, 420.

[19] (a) Wang, G.; Peng, Z.; Wang, J.; Li, X.; Li, J. Eur J Med Chem 2017, 125, 423; (b) Jabeen, F.; Shehzadi, S. A.; Fatmi, M. Q.; Shaheen, S.; Iqbal, L.; Afza, N.; Pandad, S. S.; Ansari, F. L. Bioorg Med Chem Lett 2015, 26, 1029; (c) Rocha, D. R.; Santos, W. C.; Lima, E. S.; Ferreira, V. F. Carbohydr Res 2012, 350, 14.

[20] Dheer, D.; Singh, V.; Shankar, R. Bioorg Chem 2017, 71, 30.

[21] (a) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. Eur J Org Chem 2006, 2006, 51; (b) Binder, W. H.; Kluger, C. Curr Org Chem

2006, 10, 1791; (c) Moses, J. E.; Moorhouse, A. D. Chem Soc Rev 2007, 36, 1249.

[22] Yadav, P.; Lal, K.; Rani, P.; Mor, S.; Kumar, A.; Kumar, A. Med Chem Res 2017, 26, 1469.

[23] (a) Phatak, P. S.; Bakale, R. D.; Dhumal, S. T.; Dahiwade, L. K.; Choudhari, P. B.; Siva Krishna, V.; Sriram, D.; Haval, K. P. Synth Commun 2019, 49, 2017; (b) Kulkarni, R. S.; Haval, N. B.; Kulkarni, J. A.; Dixit, P. P.; Haval, K. P. Eur Chem Bull 2019, 8, 26; (c) Haval, K. P.; Argade, N. P. Synthesis 2007, 2198; (d) Haval, K. P.; Argade, N. P. J Org Chem 2008, 73, 6936; (e) Deore, P. S.; Haval, K. P.; Gadre, S. R.; Argade, N. P. Synthesis 2014, 46, 2683; (f) Shinde, N. V.; Dhake, A. S.; Haval, K. P. Orient J Chem 2016, 32, 515; (g) Shinde, N. V.; Dhake, A. S.; Haval, K. P. Der Pharma Chem 2015, 7, 251; (h) Abhale, Y. K.; Shinde, A. D.; Deshmukh, K. K.; Nawale, L.; Sarkar, D.; Choudhari, P. B.; Kumbhar, S. S.; Mhaske, P. C. Med Chem Res 2017, 26, 2889.

[24] Benakashani, F.; Allafchian, A.; Jalali, S. A. J Karbala Int J Mod Sci 2016, 2, 251.

[25] (a) Gjorgjieva, M.; Tomasic, T.; Barancokova, M.; Katsamakas, S.; Ilas, J.; Tammela, P.; Peterlin Masic, L.; Kikelj, D. J Med Chem 2016, 59, 8941; (b) Deodware, S. A.; Sathe, D. J.; Choudhari, P. B.; Lokhande, T. N.; Gaikwad, S. H. Arab J Chem 2017, 10, 262.

[26] (a) Daina, A.; Michielin, O.; Vincent Zoete, V. J Chem Inf Model 2014, 54, 3284; (b) Daina, A.; Zoete, V. Chem Med Chem 2016, 11, 1117; (c) Daina, A.; Michielin, O.; Zoete, V. Sci Rep 2017, 7, 42717.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.