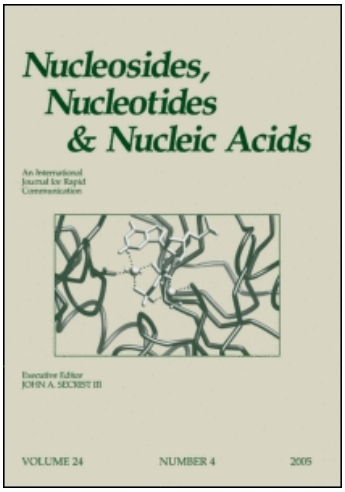

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Synthesis of Zidovudine Derivatives with Anti-HIV-1 and Antibacterial Activities

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SYNTHESIS OF ZIDOVUDINE DERIVATIVES WITH ANTI-HIV-1 AND ANTIBACTERIAL ACTIVITIES

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□ *Twelve novel zidovudine derivatives were prepared by modifying 5′-hydroxyl group of sugar moiety (**1–8**) and 5-methyl group of thymidine nucleus (**9–12**) and characterized spectrally. The compounds were evaluated for anti-HIV-1, antitubercular and antibacterial activities. Compound (3-azido-tetrahydro-5- (3,4-dihydro-5-methyl-2,4-dioxopyrimidin- 1 (2*H*)-yl) furan-2-yl)methyl 7- (4-(2-phenylacetoyloxy) -3,5- dimethylpiperazin-1-yl) -5- (2-phenylacetoyloxyamino) -1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate **(5)** was found to be the most potent anti-HIV-1 agent with EC_{50} of 0.0012 μM against HIV-1_{IIIB} and CC_{50} of 34.05 μM against MT-4 with selectivity index of 28,375. Compound **5** inhibited* Mycobacterium tuberculosis *with MIC of 1.72 μM and inhibited four pathogenic bacteria with MIC of less than 1 μM.*

INTRODUCTION

Acquired immune deficiency syndrome (AIDS) is a collection of symptoms and infections resulting from the specific damage to the immune

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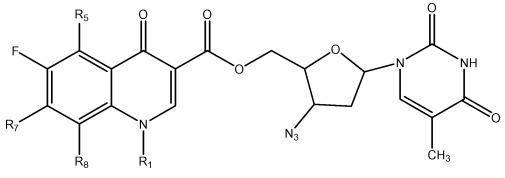
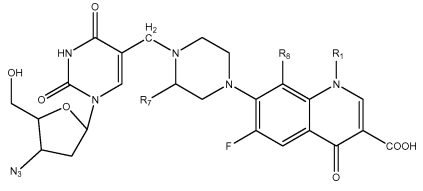
system caused by the human immunodeficiency virus (HIV) in humans.[1] According to the latest figures published in the *UNAIDS/WHO 2006 AIDS Epidemic Update*, an estimated 39.5 million people are living with HIV. There were 4.3 million new infections in 2006 with 2.8 million (65%) of these occurring in sub-Saharan Africa and important increases in Eastern Europe and Central Asia, where there are some indications that infection rates have risen by more than 50% since 2004. In 2006, 2.9 million people died of AIDS-related illnesses. The late stage of the HIV infection leaves individuals prone to opportunistic infections like tuberculosis (TB), bacterial and fungal infections. HIV and TB are lethal combination, each speeding the other's progress. TB is a major cause of death among people living with HIV/AIDS. About 90% of deaths related to HIV infection and AIDS are caused by opportunistic infections. Through logic and orderly thinking, it appears that an ideal drug for HIV/AIDS patients should suppress HIV replication thereby acting as anti-HIV drug and also should treat opportunistic infections like TB and other bacterial infections.[2] To improve antiviral activity and to obtain antibacterial activities we have suggested "dual-drug" strategy that combine an HIV inhibitor zidovudine and an antibacterial agents (fluoroquinolones) integrated into a single molecule. The following advantages were envisaged for this strategy: 1) the undesirable physicochemical property such as low membrane permeability of zidovudine would be improved; 2) and the compounds would treat the tuberculosis and other bacterial infections. Based on these premises, we have developed for the first time many potent hybrid-type anti-HIV and antimycobacterial agents.[3–7] In this article, we described the zidovudine derivatives modified at 5-methyl group of thymidine nucleus and 5'-hydroxyl group of sugar moiety.

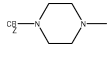
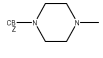
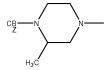
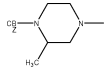
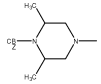
RESULTS AND DISCUSSION

The general preparation of various ester derivatives of zidovudine **1–8** (Table 1) are described in (series 1) Scheme 1. N-Protected fluoroquinolones like norfloxacin, ciprofloxacin, lomefloxacin, gatifloxacin and sparfloxacin and non-protected fluoroquinolones like enrofloxacin, levofloxacin and ofloxacin reacted with thionyl chloride to activate its C-3 carboxylic acid followed by reaction with zidovudine in presence of pyridine under microwave irradiation yielded 37–59% of esters **1–8**. When compared to conventional method of 1–2 hours process, microwave assisted synthesis was performed with short reaction times (1–3 minutes), with ease and was environment friendly. In the second series zidovudine was stirred with sulfuryl chloride for 48 hours followed by reaction with fluoroquinolones like norfloxacin, ciprofloxacin, lomefloxacin, gatifloxacin under microwave irradiation yielded 40–54% of **9–12**. The purity of the synthesized

TABLE 1 Physical constants, anti-HIV-1, and antimycobacterial activities of zidovudine derivatives

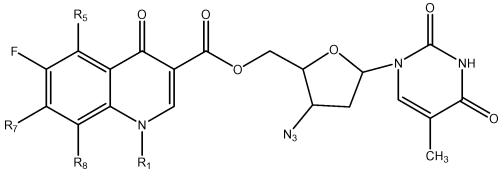


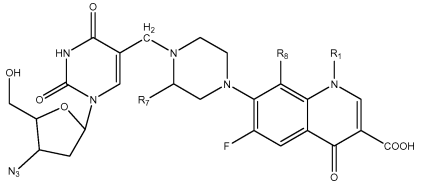


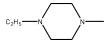
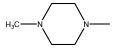
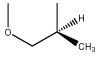
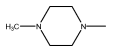
								Anti-HIV-1					
No.	R_1	R_8	R_7	R_5	Yield (%)	m.p. (°C)	C8166 CC_{50} (μM)	Syn form EC_{50} (μM)	MT-4 CC_{50} (μM)	HIV-1 $_{IIIB}$ EC_{50} (μM)	ClogP	MIC MTB (μM)	MC^2 MIC (μM)
1	C_2H_5	H		H	50	152	> 284.62	0.016	NT	NT	3.72	4.45	17.79
2	△	H		H	45	157	130.31	0.0070	131.48	0.0071	4.13	0.55	2.18
3	C_2H_5	F		H	27	107	> 272.22	0.0018	45.04	0.0018	2.65	8.51	68.05
4	△	OCH_3		H	48	103	25.11	0.0062	27.27	0.0069	3.23	2.06	8.24
5	△	F		NH-CBZ	50	107	> 219.81	0.0093	34.05	0.0012	4.64	3.44	13.74

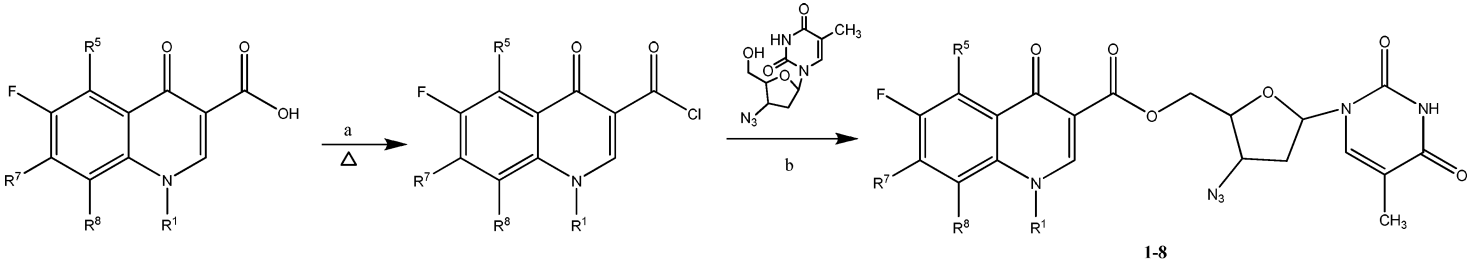
(Continued on next page)

TABLE 1 Physical constants, anti-HIV-1, and antimycobacterial activities of zidovudine derivatives *(Continued)*





No.	R_1	R_8	R_7	R_5	Yield (%)	m.p. (°C)	C8166 CC_{50} (μM)	Anti-HIV-1 Syn form EC_{50} (μM)	Anti-HIV-1 MT-4 CC_{50} (μM)	Anti-HIV-1 HIV-1 $_{IIIB}$ EC_{50} (μM)	ClogP	MIC MTB (μM)	MC^2 MIC (μM)
6		H		H	42	105	> 328.61	0.034	164.57	0.033	1.39	2.56	5.14
7				H	59	110	>327.55	0.010	105.16	0.0085	0.70	5.13	5.13
8				H	55	130	145.97	0.00098	41.71	0.0066	0.91	2.55	20.47
9	C_2H_5	H	H	-	50	163	> 342.14	142.29	NT	NT	0.16	2.67	10.69
10		H	H	-	40	178	> 335.22	139.42	NT	NT	−0.15	2.61	2.61
11	C_2H_5	F	CH_3	-	54	167	> 324.38	6.93	> 324.38	9.31	−0.33	2.53	20.27
12		OCH_3	CH_3	-	46	173	250.88	13.99	190.18	3.87	−0.38	2.44	< 1.22
AZT	—	—	—	—	—	—	4892.2	0.015	325.92	0.027	0.24	—	—



SCHEME 1 Synthetic protocol of zidovudine derivatives.

compounds was monitored by thin layer chromatography (TLC) and elemental analyses and the structures were identified by spectral data.

In the initial phase of screening, the synthesized compounds were evaluated for inhibitory activity against HIV-1 replication in acutely infected C8166 cells (inhibition of syncytium formation).[8] The cellular toxicity of compounds on C8166 cells was assessed by MTT colorimetric assay.[9] The minimum toxic concentration that caused the reduction of viable cells by 50% (CC_{50}) was determined from dose-response curve. The effect of samples on acute HIV-1 infectivity was measured by the syncytia formation assay. The inhibitory percentage of syncytial cell formation was calculated by the percentage of syncytial cell number in sample-treated culture compared to that in infected control culture.[10] EC_{50} is the concentration of drug that reduces syncytia formation by 50%. Zidovudine was used as a positive control. The CC_{50} and EC_{50} were reported in Table 1. Rapid glance of the results revealed compounds **1–8,** which modified at 5' hydroxyl group of sugar moiety of zidovudine showed very good activity with EC_{50} ranging from 0.00098–0.034 μM and seven compounds were found to be more active (1–15 folds) than zidovudine (EC_{50} of 0.015 μM). Compound [3-azido-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)tetrahydro-2-furanyl]methyl 9-fluoro-3-methyl-10-(4-methylpiperazino)-7-oxo-2,3-dihydro-7*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylate (**8**) was found to be the most active compound with EC_{50} of 0.00098 μM and fifteen times more active than zidovudine. Compound **8** showed the selectivity index of (CC_{50}/EC_{50}) 148,949. Compounds **9–12** which were modified at 5-methyl group of thymidine nucleus of zidovudine do not show any promising activity. Compounds **1**, **3**, **5**, **6**, **7**, **9–11** did not show any toxicity till 200 μg/mL.

The compounds exhibited good activity or low toxicity were further evaluated for their inhibitory effect on the replication of HIV-1_{IIIB} in MT-4 cell lines by MTT assay method[8] and their EC_{50} (effective concentration of compound (μM) achieving 50% protection in MT-4 cell lines against the cytopathic effect of HIV-1), and CC_{50} (cytotoxic concentration of compound (μM) required to reduce the viability of mock infected MT-4 cells by 50%), are reported in the Table 1 with zidovudine as standard drug for comparison. Rapid glance to the obtained results revealed that the compounds **2–9** exhibited good anti-HIV activity with EC_{50} ranging from 0.0012–0.033 μM. Six compounds (**2–5, 7–8**), (EC_{50} ranging from 0.0012 to 0.0085 μM) were found to be more potent than zidovudine (EC_{50} of 0.027 μM). Among the synthesized compounds, compound [3-azido-5-(5-methyl-2,4-dioxo-1,2,3,4-tetrahydro-1-pyrimidinyl)tetrahydro-2-furanyl]methyl 5-[(benzyloxy)carbonyl]amino-7–4-[(benzyloxy)carbonyl]-3,5-dimethylpiperazino-1-cyclopropyl-6-fluoro-4-oxo-1,4-dihydro-3-quinolinecarboxylate (**5**) was found to be the most potent compound with EC_{50} of 0.0012 μM against HIV-1 replication and

CC_{50} of 34.05 μM against MT-4 cell lines with selectivity index (CC_{50} /EC_{50}) of >28375. Compound **5** was 22 times more active than parent zidovudine. Compounds **9–12** which modified at 5-methyl group of thymidine nucleus of zidovudine not showed any promising activity in this study also. When compared to zidovudine all the compounds (except **11**) were cytotoxic to MT-4 cell lines.

With respect to the structure-activity relationship, compounds which were modified at 5′ -hydroxyl group of sugar moiety of zidovudine showed very good activities and compounds modified at 5-methyl group of thymidine nucleus of zidovudine does not show any promising activities. These results have revealed that ester derivatives **1–8** are easily hydrolyzed by esterases to zidovudine, which gets tri-phosphorylated and act as a competitive inhibitor for HIV reverse transcriptase (RT) enzymes, whereas 5-aminomethylated compounds **9–12** were unable to bind to the active site pocket of HIV-RT enzyme.

The lipophilicity (ClogP) of the synthesized compounds increased remarkably compared with the parent drug, zidovudine (Table 1). This may render them more capable of penetrating various biomembranes,[11] consequently improving their permeation properties through viral cell membranes. The results showed that there was an improvement in anti-HIV activity compared to the parent drug.

The compounds were screened for their *in vitro* antimycobacterial activity against *Mycobacterium tuberculosis* (MTB) and *M. smegmatis* ATCC 14468 (MC^2) by agar dilution method for the determination of MIC in duplicate.[12] The minimum inhibitory concentration (MIC) is defined as the minimum concentration of compound required to give complete inhibition of bacterial growth and MICs of the synthesized compounds are reported in Table 1. All the compounds inhibited MTB with MICs ranging from 0.55–8.51 μM and when compared ofloxacin (MIC of 2.16 μM) two compounds (**2** and **4**) were found to be more active. Compound **2** was found to be the most active compound with MIC of 0.55 μM and was four time more potent than ofloxacin.

All the compounds were evaluated for their in vitro antibacterial activity against 21 pathogenic bacteria by conventional agar dilution procedures[13] and the results of these assays are summarized in Table 2. The data for norfloxacin, ciprofloxacin, and gatifloxacin were included for comparison. The antibacterial activity data revealed that all the test compounds showed mild to moderate activity against tested bacteria.

EXPERIMENTAL SECTION

Melting points were taken on an electrothermal melting point apparatus (Buchi BM530) in open capillary tubes and are uncorrected. ^{1}H-NMR

TABLE 2 Antibacterial activities of zidovudine derivatives

Micro-organisms	Minimum inhibitory concentration in μM														
	Nor	Cipro	Gati	1	2	3	4	5	6	7	8	9	10	11	12
E. Coli ATCC	0.59	0.27	1.04	8.89	2.18	4.26	1.03	0.64	2.55	0.64	27.48	2.67	0.32	9.57	0.58
S. arizono	0.59	0.27	0.51	17.79	4.38	17.01	1.03	0.64	2.55	0.64	27.48	2.67	0.32	9.57	0.58
A. baumanii	2505.2	1207.2	133.2	284.6	279.8	272.2	263.59	164.3	163.8	163.8	219.8	342.1	167.6	306.3	149.8
S. dysnteriae	1.22	0.27	0.24	4.45	0.55	0.12	< 0.12	5.14	40.94	81.89	27.48	1.33	0.32	4.79	0.58
S. boydii	1.22	0.27	1.04	4.45	4.38	4.26	1.03	0.64	5.13	81.89	27.48	5.35	0.65	19.14	0.58
K. pneumoniae	39.14	4.71	4.16	142.3	34.98	68.05	16.47	2.56	10.24	81.89	54.95	42.76	2.61	76.56	74.89
P. reltgerii	1.22	0.27	1.04	142.3	17.49	68.05	16.47	82.15	81.89	5.13	54.95	5.35	2.61	76.56	4.69
E. Coli	1252.6	1207.2	133.2	142.3	139.9	4.26	32.95	10.27	5.13	10.24	27.48	171.1	83.80	76.56	74.89
S. aureus ATCC	626.3	301.8	133.2	284.6	17.49	272.2	4.13	5.14	40.94	20.47	219.8	85.53	83.80	76.56	74.89
P. mirabilis	1252.6	603.6	266.4	284.6	69.96	34.03	32.95	41.08	40.94	81.89	54.95	171.1	167.6	153.1	149.8
MRSA	313.2	603.6	33.3	284.6	34.98	272.2	131.79	164.3	163.8	163.8	219.8	171.1	167.6	153.1	18.72
S. aureus	313.2	150.9	66.6	284.6	2.18	272.2	8.24	5.14	40.94	40.94	219.8	21.38	5.25	19.14	9.36
V. cholera	313.2	150.9	133.2	17.79	2.18	68.05	2.06	< 0.15	1.28	< 0.15	54.95	0.67	0.15	4.79	< 0.13
S. sonnei	2.44	0.27	0.51	17.79	34.98	136.1	0.51	20.54	20.47	0.64	54.95	2.67	0.65	4.79	0.28
S. paratyphi A	19.57	2.35	2.08	17.79	34.98	4.26	8.24	5.14	20.47	10.24	54.95	85.53	83.80	153.1	37.44
Salmonella enteritidis	0.28	18.86	0.51	8.89	2.18	34.03	16.47	5.14	10.24	1.28	27.48	85.53	167.6	19.14	9.36
P. aerogenosa	313.2	150.9	133.2	142.3	139.9	136.1	131.79	164.3	163.8	163.8	109.9	171.1	167.6	153.1	149.8
S. typhi	2.44	1.18	1.04	142.3	139.9	136.1	2.06	2.56	5.13	81.89	27.48	42.76	5.25	76.56	74.89
Serratia	2.44	0.27	0.51	142.3	69.96	136.1	65.89	5.14	40.94	20.47	109.9	21.38	5.25	76.56	9.36
Morgenella morganii	156.58	75.45	16.65	142.3	139.9	68.05	65.89	82.15	81.89	81.89	54.95	171.1	167.6	153.1	37.44
S. Ty-phimurium	2.44	0.57	0.51	142.31	17.49	68.05	1.03	5.14	40.94	20.47	54.95	171.05	167.61	76.56	2.34

spectra were scanned on a JEOL Fx 300MHz NMR spectrometer using DMSO-d_6 as solvent. Chemical shifts are expressed in δ (ppm) relative to tetramethylsilane. Elemental analyses (C, H, and N) were performed on Perkin Elmer (Waltham, MA, USA) model 240C analyzer and the data were within $\pm 0.4\%$ of the theoretical values. The progress of the reactions and homogeneity of the compounds were monitored by ascending thin-layer chromatography (TLC) on silica gel G (precoated silica gel plate 60 F_{254}; Merck, Whitehouse Station, NJ, USA) and visualized by using UV radiation. Some of the reactions were carried out using microwave oven from Catalyst, India (Pune, India). The log P values were determined using ChemDraw 8.0 software.

General Procedure for the Synthesis of Compounds 1–8

To N-protected fluoroquinolone (1.00 equiv.) was added thionyl chloride (10.00 equiv.) and the mixture was refluxed at 75°C for 10 hrs. The excess thionyl chloride was distilled under pressure and further used without any purification. The resultant was reacted with zidovudine (1.00 equiv.) in dichloromethane and pyridine to yield the titled ester compounds (**1–8**).

(3-Azido-tetrahydro-5-(3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl)furan-2-yl)methyl 7-(4-(2-phenylacetoyloxy)piperazin-1-yl)-1-ethyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (1): Yield: 50%; m.p.: 152°C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.13 (t, 3H, CH_2CH_3), 1.4 (s, 3H, CH_3 of pyrimidinyl ring), 2.13 (m, 1H, CH-N_3), 3.15 (d, 2H, CH_2CH_3), 3.22 (dd, 4H, 2CH_2-), 3.58 (dd, 4H, 2CH_2-), 4.54 (d, 1H, CH of furyl ring), 4.85 (s, 2H, CH_2), 4.88 (s, 2H, CH_2 of benzyloxy), 5.62 (t, 1H, CH of furyl ring), 5.64 (s, 2H, CH_2), 7.00–7.20 (m, 5H, ArH), 8.34 (s, 1H, C_8-H), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.00 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.32 (s, 1H, C_5-H), 9.56 (s, 1H, C_2-H); m/z: 702.26 (100.0%), 703.26 (37.5%), 704.26 (9.4%), 703.25 (3.0%). Anal calc for ($C_{34}H_{35}FN_8O_8$) C, 58.11, H, 5.02, N, 15.95. Found: C, 58.22, H, 5.09, N, 15.98.

(3-Azido-tetrahydro-5-(3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl) furan-2-yl)methyl 7-(4-(2-phenylacetoyloxy)piperazin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro -4-oxoquinoline-3-carboxylate (2): Yield: 45%; m.p.: 157°C; ^{1}H NMR (DMSO-d_6) δ ppm: 0.28–0.52 (m, 4H, cyclopropyl), 1.38 (m, 1H, cyclopropyl), 1.4 (s, 3H, CH_3 of pyrimidinyl ring), 2.13 (m, 1H, CH-N_3), 3.22 (dd, 4H, 2CH_2-), 3.58 (dd, 4H, 2CH_2-), 4.54 (d, 1H, CH of furyl ring), 4.85 (s, 2H, CH_2), 4.88 (s, 2H, CH_2 of benzyloxy), 5.62 (t, 1H, CH of furyl ring), 5.64 (s, 2H, CH_2), 7.00–7.20 (m, 5H, ArH), 8.34 (s, 1H, C_8-H), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.00 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.32 (s, 1H, C_5-H), 9.56 (s, 1H, C_2-H); m/z: 714.26 (100.0%), 715.26 (38.6%), 716.26 (9.9%), 715.25 (3.0%). Anal calc

for ($C_{35}H_{35}FN_8O_8$) C, 58.82, H, 4.94, N, 15.68. Found: C, 58.22, H, 4.99, N, 15.68.

(3-Azido-tetrahydro-5-(3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl)furan-2-yl)methyl 7-(4-(2-phenylacetoyloxy)-3-methylpiperazin-1-yl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (3): Yield: 27%; m.p.: 107°C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.13 (t, 3H, CH_2CH_3), 1.3 (3H, CH_3 of piperazine), 1.4 (s, 3H, CH_3 of pyrimidinyl ring), 2.13 (m, 1H, CH-N_3), 3.15 (d, 2H, CH_2CH_3), 3.22 (dd, 4H, $2CH_2$-), 3.58 (dd, 4H, $2CH_2$–), 4.54 (d, 1H, CH of furyl ring), 4.85 (s, 2H, CH_2), 4.88 (s, 2H, CH_2 of benzyloxy), 5.62 (t, 1H, CH of furyl ring), 5.64 (s, 2H, CH_2), 7.00–7.20 (m, 5H, ArH), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.00 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.32 (s, 1H, C_5-H), 9.56 (s, 1H, C_2-H); m/z: 734.26 (100.0%), 735.27 (38.6%), 736.27 (8.9%), 735.26 (3.0%), 737.27 (1.7%), 736.26 (1.2%). Anal calc for ($C_{35}H_{36}F_2N_8O_8$) C, 57.22, H, 4.94, N, 15.25. Found: C, 57.62, H, 4.99, N, 15.28.

(3-Azido-tetrahydro-5-(3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl)furan-2-yl)methyl 7-(4-(2-phenylacetoyloxy)-3-methylpiperazin-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylate (4): Yield: 48%; m.p.: 103°C; ^{1}H NMR (DMSO-d_6) δ ppm: 0.28–0.52 (m, 4H, cyclopropyl), 1.3 (3H, CH_3 of piperazine), 1.38 (m, 1H, cyclopropyl), 1.4 (s, 3H, CH_3 of pyrimidinyl ring), 2.13 (m, 1H, CH-N_3), 3.02 (t, 1H, CH–), 3.22 (dd, 2H, $2CH_2$–), 3.4 (s, 3H, –OCH_3), 3.58 (dd, 4H, $2CH_2$–), 4.54 (d, 1H, CH of furyl ring), 4.85 (s, 2H, CH_2), 4.88 (s, 2H, CH_2 of benzyloxy), 5.62 (t, 1H, CH of furyl ring), 5.64 (s, 2H, CH_2), 7.00–7.20 (m, 5H, ArH), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.00 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.32 (s, 1H, C_5–H), 9.56 (s, 1H, C_2–H); m/z: 758.28 (100.0%), 759.29 (40.8%), 760.29 (10.0%), 759.28 (3.0%), 761.29 (2.0%), 760.28 (1.2%). Anal calc for ($C_{37}H_{39}FN_8O_9$) C, 58.57, H, 5.18, N, 14.77. Found: C, 58.02, H, 5.11, N, 14.78.

(3-Azido-tetrahydro-5-(3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl)furan-2-yl)methyl 7-(4-(2-phenylacetoyloxy)-3,5-dimethylpiperazin-1-yl)-5-(2-phenylacetoyloxyamino)-1-cyclopropyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylate (5): Yield: 50%; m.p.: 107°C; ^{1}H NMR (DMSO-d_6) δ ppm: 0.28–0.52 (m, 4H, cyclopropyl), 1.3 (6H, $2CH_3$ of piperazine), 1.38 (m, 1H, cyclopropyl), 1.4 (s, 3H, CH_3 of pyrimidinyl ring), 2.13 (m, 1H, CH-N_3), 3.01 (dd, 2H, 2CH-), 3.58 (dd, 4H, $2CH_2$–), 4.54 (d, 1H, CH of furyl ring), 4.85 (s, 2H, CH_2), 4.88 (s, 2H, CH_2 of benzyloxy), 5.62 (t, 1H, CH of furyl ring), 5.64 (s, 4H, $2CH_2$), 7.00–7.20 (m, 10H, ArH), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.00 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.56 (s, 1H, C_2-H); Anal calc for ($C_{45}H_{45}F_2N_9O_{10}$) C, 59.40, H, 4.98, N, 13.85. Found: C, 59.02, H, 4.91, N, 13.88.

(3-Azido-tetrahydro-5-(3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl)furan-2-yl)methyl 1-cyclopropyl-7-(4-ethylpiperazin-1-yl)-6-fluoro-1,4-dihy-

dro-4-oxoquinoline-3-carboxylate (6): Yield: 42%; m.p.: 105°C; ^{1}H NMR (DMSO-d_6) δ ppm: 0.28–0.52 (m, 4H, cyclopropyl), 1.13 (t, 3H, CH_2CH_3), 1.38 (m, 1H, cyclopropyl), 1.4 (s, 3H, CH_3 of pyrimidinyl ring), 2.13 (m, 1H, CH-N_3), 3.15 (d, 2H, CH_2CH_3), 3.22 (dd, 4H, $2CH_2$-), 3.58 (dd, 4H, $2CH_2$-), 4.54 (d, 1H, CH of furyl ring), 4.85 (s, 2H, CH_2), 5.62 (t, 1H, CH of furyl ring), 5.64 (s, 2H, CH_2), 8.34 (s, 1H, C_8-H), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.00 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.32 (s, 1H, C_5-H), 9.56 (s, 1H, C_2-H); m/z: 608.25 (100.0%), 609.25 (34.5%), 610.26 (4.9%), 610.25 (2.2%). Anal calc for ($C_{29}H_{33}FN_8O_6$) C, 57.23, H, 5.47, N, 18.41. Found: C, 57.52, H, 5.48, N, 18.48.

(3-Azido-tetrahydro-5-(3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl)furan-2-yl)methyl 9-fluoro-3,7-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylate (7): Yield: 59%; m.p.: 110°C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.35 (s, 3H, CH_3), 1.4 (s, 3H, CH_3 of pyrimidinyl ring), 2.13 (m, 1H, CH-N_3), 3.22 (dd, 4H, $2CH_2$-), 3.58 (dd, 4H, $2CH_2$-), 4.12 (m, 1H, -$CHCH_3$), 4.54 (d, 1H, CH of furyl ring), 4.85 (s, 2H, CH_2), 5.32 (d, 1H, CH of CH_2 of oxazino ring), 5.46 (d, 1H, CH of CH_2 of oxazino ring), 5.62 (t, 1H, CH of furyl ring), 5.64 (s, 2H, CH_2), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.00 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.32 (s, 1H, C_5-H), 9.56 (s, 1H, C_2-H); m/z: 610.23 (100.0%), 611.23 (33.5%), 612.24 (4.6%), 612.23 (2.4%). Anal calc for ($C_{28}H_{31}FN_8O_7$) C, 55.08, H, 5.12, N, 18.35. Found: C, 54.98, H, 5.11, N, 18.38.

(3*S*)-(3-Azido-tetrahydro-5-(3,4-dihydro-5-methyl-2,4-dioxopyrimidin-1(2*H*)-yl)furan-2-yl)methyl 9-fluoro-3,7-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylate (8): Yield: 55%; m.p.: 130°C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.36 (s, 3H, CH_3), 1.42 (s, 3H, CH_3 of pyrimidinyl ring), 2.13 (m, 1H, CH-N_3), 3.25 (dd, 4H, $2CH_2$-), 3.63 (dd, 4H, $2CH_2$-), 4.12 (m, 1H, -$CHCH_3$), 4.54 (d, 1H, CH of furyl ring), 4.88 (s, 2H, CH_2), 5.31 (d, 1H, CH of CH_2 of oxazino ring), 5.46 (d, 1H, CH of CH_2 of oxazino ring), 5.62 (t, 1H, CH of furyl ring), 5.64 (s, 2H, CH_2), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.15 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.42 (s, 1H, C_5-H), 9.66 (s, 1H, C_2-H); m/z: 610.23 (100.0%), 611.23 (33.5%), 612.24 (4.6%), 612.23 (2.4%). Anal calc for ($C_{28}H_{31}FN_8O_7$) C, 55.08, H, 5.12, N, 18.35. Found: C, 54.98, H, 5.11, N, 18.38.

General Procedure for the Synthesis of Compounds 9–12

To zidovudine (1.00 equiv.) in dichloromethane added sulfuryl chloride (5.00 equiv.) and stirred at room temperature for 48 hours. After the completion of reaction the dichloromethane and excess of sulfuryl chloride were distilled off under reduced pressure. This was further treated with fluoroquinolones (1.00 equiv.) like norfloxacin, ciprofloxacin, lomefloxacin,

gatifloxacin in dichloromethane and pyridine to yield the titled compounds (**9–12**).

7-(4-((1-(4-azido-tetrahydro-5-(hydroxymethyl)furan-2-yl)-1,2,3,4-tetrahydro-2,4-dioxopyrimidin-5-yl)methyl)piperazine-1-yl)-1-ethyl-6-fluoro-1,-4-dihydro-4-oxoquinoline-3-carboxylic acid (9): Yield: 50%; m.p.: 163°C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.13 (t, 3H, CH_2CH_3), 3.4 (s, 2H, CH_2), 2.13 (m, 1H, CH-N_3), 3.15 (d, 2H, CH_2CH_3), 3.22 (dd, 4H, $2CH_2$-), 3.58 (dd, 4H, $2CH_2$-), 4.62 (s, 1H, OH), 5.62 (t, 1H, CH of furyl ring), 3.94 (s, 2H, CH_2), 6.54 (d, 1H, CH, -O-CH-O- of furyl ring), 8.34 (s, 1H, C_8-H), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.00 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.32 (s, 1H, C_5-H), 9.56 (s, 1H, C_2-H), 14.4 (1H, COOH); m/z: 584.21 (100.0%), 585.22 (28.7%), 586.22 (5.4%), 585.21 (3.0%). Anal calc for ($C_{26}H_{29}FN_8O_7$) C, 53.42, H, 5.00, N, 19.17. Found: C, 53.52, H, 4.99, N, 19.18.

7-(4-((1-(4-azido-tetrahydro-5-(hydroxymethyl)furan-2-yl)-1,2,3,4-tetrahydro-2,4-dioxopyrimidin-5-yl)methyl)piperazine-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (10): Yield: 40%; m.p.: 178°C; ^{1}H NMR (DMSO-d_6) δ ppm: : 0.28–0.52 (m, 4H, cyclopropyl), 1.38 (m, 1H, cyclopropyl), 3.4 (s, 2H, CH_2), 2.13 (m, 1H, CH-N_3), 3.22 (dd, 4H, $2CH_2$-), 3.58 (dd, 4H, $2CH_2$-), 4.62 (s, 1H, OH), 5.62 (t, 1H, CH of furyl ring), 3.94 (s, 2H, CH_2), 6.54 (d, 1H, CH, -O-CH-O- of furyl ring), 8.34 (s, 1H, C_8-H), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.00 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.32 (s, 1H, C_5-H), 9.56 (s, 1H, C_2-H), 14.4 (1H, COOH); m/z: 596.21 (100.0%), 597.22 (29.8%), 598.22 (5.7%), 597.21 (3.0%). Anal calc for ($C_{27}H_{29}FN_8O_7$) C, 54.36, H, 4.90, N, 18.78. Found: C, 54.32, H, 4.91, N, 18.78.

7-(4-((1-(4-azido-tetrahydro-5-(hydroxymethyl)furan-2-yl)-1,2,3,4-tetrahydro-2,4-dioxopyrimidin-5-yl)methyl)-3-methylpiperazine-1-yl)-1-ethyl-6,8-difluoro-1,4-dihydro-4-oxoquinoline-3-carboxylic acid (11): Yield: 54%; m.p.: 167°C; ^{1}H NMR (DMSO-d_6) δ ppm: 1.09 (d, 3H, CH_3), 1.13 (t, 3H, CH_2CH_3), 3.4 (s, 2H, CH_2), 2.13 (m, 1H, CH-N_3), 3.15 (d, 2H, CH_2CH_3), 3.22 (dd, 2H, CH_2-), 3.35 (m, 1H, CH_2-), 3.58 (dd, 4H, $2CH_2$-), 4.62 (s, 1H, OH), 5.62 (t, 1H, CH of furyl ring), 3.94 (s, 2H, CH_2), 6.54 (d, 1H, CH, -O-CH-O- of furyl ring), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.00 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.32 (s, 1H, C_5-H), 9.56 (s, 1H, C_2-H), 14.4 (1H, COOH); m/z: 616.22 (100.0%), 617.22 (32.4%), 618.23 (4.3%), 618.22 (2.3%). Anal calc for ($C_{27}H_{30}F_2N_8O_7$) C, 52.60, H, 4.90, N, 18.17. Found: C, 52.50, H, 4.90, N, 18.18.

7-(4-((1-(4-azido-tetrahydro-5-(hydroxymethyl)furan-2-yl)-1,2,3,4-tetrahydro-2,4-dioxopyrimidin-5-yl)methyl)-3-methylpiperazine-1-yl)-1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-4-oxoquinoline-3-carboxylic acid (12): Yield: 46%; m.p.: 173°C; ^{1}H NMR (DMSO-d_6) δ ppm: : 0.28–0.52 (m, 4H, cyclopropyl), 1.09 (d, 3H, CH_3), 1.38 (m, 1H, cyclopropyl), 3.4 (s, 3H,

-OCH_3), 3.15 (s, 2H, CH_2), 2.13 (m, 1H, CH-N_3), 3.22 (dd, 2H, CH_2-), 3.35 (m, 1H, CH_2-), 3.58 (dd, 4H, $2CH_2$-), 4.62 (s, 1H, OH), 5.62 (t, 1H, CH of furyl ring), 3.94 (s, 2H, CH_2), 6.54 (d, 1H, CH, -O-CH-O- of furyl ring), 8.54 (s, 1H, CH of pyrimidinyl ring), 9.00 (s, 1H, NH of pyrimidinyl ring, D_2O exchangeable), 9.32 (s, 1H, C_5-H), 9.56 (s, 1H, C_2-H), 14.4 (1H, COOH); m/z: 640.24 (100.0%), 641.24 (34.6%), 642.25 (5.0%), 642.24 (2.6%), 643.25 (1.0%). Anal calc for ($C_{29}H_{33}FN_8O_8$) C, 54.37, H, 5.19, N, 17.49. Found: C, 54.32, H, 5.19, N, 17.48.

CONCLUSION

In the present study we identified that zidovudine ester derivative (**5**) was found to show twenty two times more anti-HIV-1 activity to parent compound. Many compounds inhibited HIV- 1 replication, *M. tuberculosis*, and pathogenic bacteria. Thus these derivatives would be beneficial for the effective treatment of HIV/AIDS. This is another milestone in continuation to our dual-acting hybrid molecular approach.

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