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Original article

Synthesis and antimycobacterial activity of prodrugs of indeno[2,1-*c*]quinoline derivatives

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ABSTRACT

Recently we have reported anti-TB properties of a new class of conformationally-constrained indeno[2,1-*c*]quinolines, which are although considerably active (MIC 0.39–0.78 μg/mL) suffered from intense solubility problems. We thought of improving their bioavailability by prodrugs approach. Accordingly esters of the "Lead" indeno[2,1-*c*]quinolines **1**, **15** and **27** derivatives were synthesized and their prodrug nature at the physiological pH were confirmed. Prodrugs were evaluated for their antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv by MABA assay to show that they have 2- to 4-fold improved anti-TB activities, increased aqueous solubility and superior selectivity index over their respective parent compounds. MIC of these prodrugs was in the range of <0.20–6.0 μg/mL, and in general, no cytotoxicity was observed in VERO cells.

1. Introduction

Mycobacterium tuberculosis (M. TB) is the leading bacterial infectious agent in humans, and is responsible for death of almost 3 million people each year [1], which has been a major global health problem for decades. The resurgence of TB is associated with the emergence of HIV/AIDS epidemic [2] and the fast development of multidrug resistant TB bacterial strains [3,4]. A current first-line TB drug regimen is more than 40 years old, and consists primarily of rifampicin and isoniazid. Single drug therapy is now known to result in the rapid emergence of drug resistant *M. tuberculosis bacilli* [5] due to the sequential accumulation of spontaneous genetic mutations [6–8]. Current conventional directly observed treatment short course (DOTS) therapy, which has been used for decades, is a multiple drug regimen given over a long duration of time (6–12 months). It combines isoniazid (INH), rifampin (RIF), pyrazinamide (PZA), and ethambutol (EMB). These antibiotics are effective in active, drug-susceptible TB, provided that patients complete the course. Non-compliance of patients has contributed to the appearance of multidrug resistant (MDR) and extensively drug resistant TB (XDR-TB) strains. These suggest that there is an urgent need for new anti-TB drugs with novel mechanism of action, which are synthetically feasible, with minimal side effects, and have required physicochemical properties allowing oral administration with reduced treatment time. Recently, many novel inhibitors such as those for ATP synthase [9,10], cell wall assembly [11], isocitrate lyase [12] and protein synthesis [13] have emerged as anti-TB targets. Quinoline-based anti-TB compound TMC207 bearing a bulky biaryl side chain at position C3, is a highly potent anti-TB agent, has novel mode of action, with very promising activity against MDR-TB [9,14].

Based on molecular dissection of TMC207 (Fig. 1), we have recently reported design, synthesis and biological activity of relatively less complex quinoline derivatives, which show potent anti-TB activity [15–19]. In these efforts, we have discovered a new class of conformationally-locked indeno[2,1-*c*]quinoline compounds which posses excellent antimycobacterial activity, such as those of compounds **1**, **15** and **27** (Fig. 1) which, respectively, showed 91, 99,

Abbreviations: DCM, dichloromethane; DMF, *N*,*N*-dimethylformamide; DMAP, 4-dimethylaminopyridine; DMSO, dimethyl sulfoxide; EDC.HCl, *N*-Ethyl-*N*′-(3-Dimethylaminopropyl) carbodiimide hydrochloride; MDR, multidrug resistance; MIC, minimum inhibitory concentration; mp, melting point; MeOH, methanol; NMR, nuclear magnetic resonance; SI, selectivity index; SAR, structure–activity relationship; TB, tuberculosis; THF, tetrahydrofuran; TLC, thin layer chromatography; XDR, extensive drug resistance.

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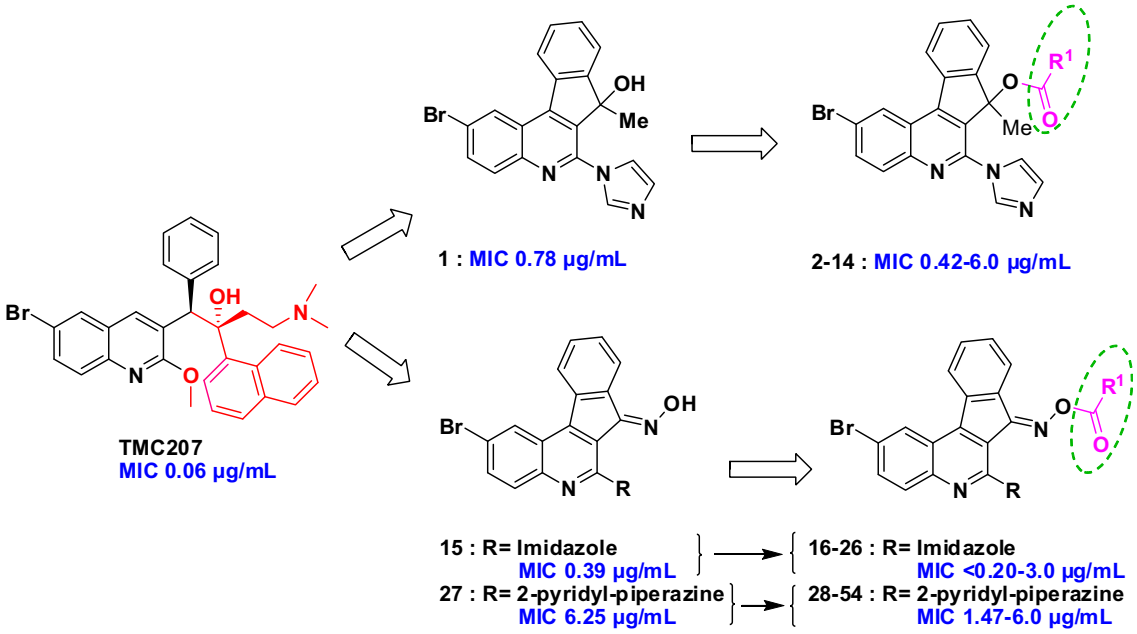


Fig. 1. Conformationally-constrained compounds **1**, **15** and **27**, which are relatively structurally simpler than the parent TMC207, have shown to be considerably active against *Mycobacterium tuberculosis* in our lab, see Refs [14–18]; they have been transformed to their corresponding ester derivatives **2**–**14**, **16**–**26** and **28**–**54**, respectively, as prodrugs, which are more potent (compare MICs) than their parents.

and 90% growth inhibition of *M. tuberculosis* H37Rv with minimum inhibitory concentration (MIC) of 0.78 μg/mL (2 μM), <0.39 μg/mL (1 μM), and 6.25 μg/mL (12.8 μM) [18].

Antimycobacterial activity of these molecules is comparable to the standard drug isoniazid. However these molecules are facing the problem of poor aqueous solubility, as inadequate aqueous solubility is an important factor limiting parenteral, percutaneous, and oral bioavailability. To overcome the problem of aqueous solubility we herein report the preparation of the ester derivatives (prodrugs) of these molecules, which are deemed to have optimum balance between hydrophilicity and lipophilicity thereby enhancing bioavailability and, consequently, improving anti-mycobacterial activity. Among the three series of 51 different ester derivatives of indeno[2,1-*c*]quinolines **1**, **15** and **27**, 33 esters were found to have anti-TB activity with MIC [up to 99% inhibition *in vitro* determined by Microplate Alamar Blue Assay (MABA)] varying in the range of <0.20–6.0 μg/mL. Their partition coefficients in octanol–water mixture at pH 7.4 were determined. The ester derivatives of compound **15** however displayed superior anti-TB activity and the selectivity index (SI), in that compound **16** (MIC <0.20 μg/mL, SI >71.52) and **18** (MIC <0.20 μg/mL, SI > 200) were the most active. In general, ester derivatives of compounds **1** and **15** showed more improved aqueous solubility and lipophilicity than the parent compounds. Hence, the ester derivatives of these conformationally-constrained indeno[2,1-*c*]quinolines, compounds **1, 15** and **27**, represent highly potent, selective and non-toxic anti-TB compounds which are attractive leads for further anti-TB drug development.

2. Results

2.1. Chemistry

Compounds **1**, **15** and **27** (Scheme 1) that served as starting materials were prepared according to published method [18]. Compounds **2**–**13** were synthesized by treatment of compound **1** with sodium hydride (3 eq) and corresponding acid chlorides (3 eq) in dry DMF at 0 °C to room temperature for 15 h. The ester derivatives **2**–**13** were obtained in moderate to good yields (12–67%). Various conditions were employed to prepare amino esters derivatives of compound **1**, but we succeeded to prepare only ester of Boc-glycine, *i.e.* compound **14** which was prepared by treating compound **1** with *n*-BuLi and Boc-glycine-*N*-hydroxysuccinimide ester in dry THF at −78 °C in 28% yield.

Esters **16**, **17** and **26** were prepared by treating oxime **15** with NaH (3 eq) in dry DMF and corresponding acid chlorides (3 eq) in moderate yield (40–49%). Other esters derivatives, compounds **18**–**25** were prepared by treating corresponding acids with oxime **15** using EDC.HCl, DMAP in DMF in good yields (26–76%) [20]. Esters of compound **15** were unstable, and hydrolyzed to their parent oxime **15** during aqueous work-up. By quenching reaction with phosphate buffer (pH = 6.5–7.0) and extracting it with ethyl acetate avoided the problem of ester hydrolysis (40–50%).

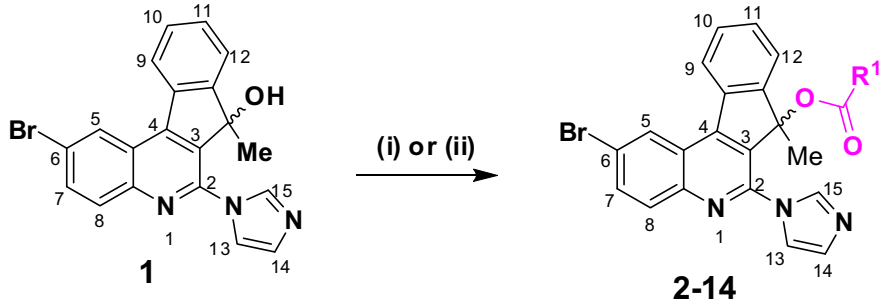
Aliphatic esters **28**, **29** and **39** [18] were prepared by treating oxime **27** with NaH (3 eq) in dry DMF and corresponding acid chlorides, in moderate yields (60%). Other aliphatic ester derivatives, compound **30**–**38** and **40**–**42** and all amino esters, compound **43**–**54** were prepared by treating corresponding aliphatic acids, Boc/Fmoc-amino acids with oxime **27** using EDC.HCl, DMAP in dry DMF in good yields (27–96%) [20].

2.2. Biology

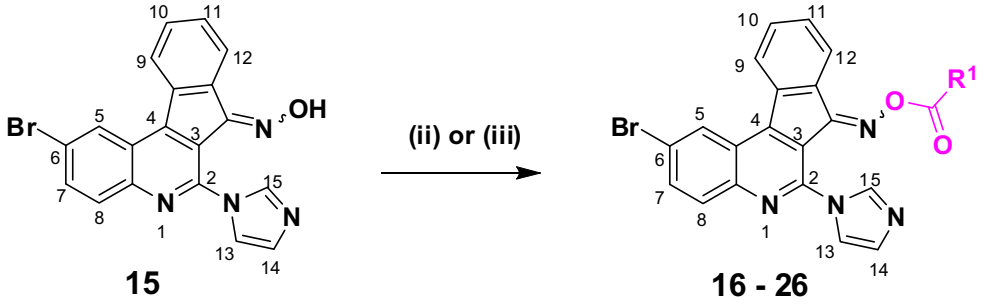
All synthesized ester derivatives of compounds **1**, **15** and **27** (Scheme 1) were evaluated against *M. tuberculosis* H37Rv in a Microplate Alamar Blue Assay (MABA) method [21]. Cell viability in the presence or in the absence of test compounds was determined by Mosmans's MTT assay [22] for the most active compounds.

2.2.1. Esters of compound *1*

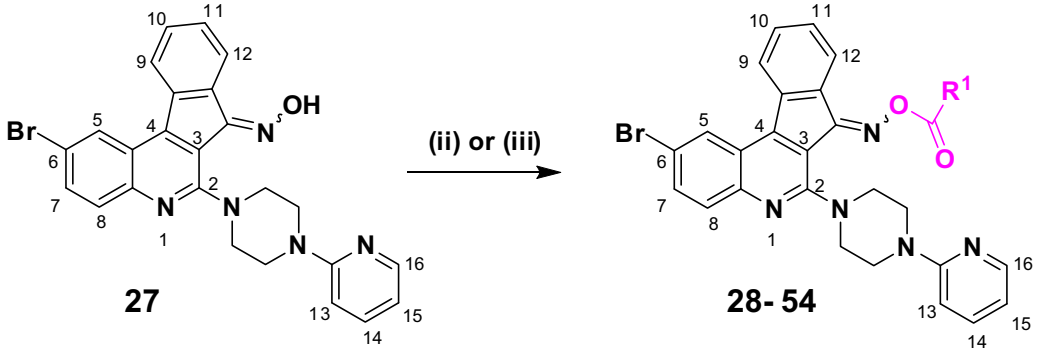
The results of growth inhibition of ester derivatives **2**–**14** of compound **1** (Scheme 1) against *M. tuberculosis* H37Rv are shown in Table 1. Out of 13 esters, 9 esters displayed good to excellent activity



2: R^1 = -CH_3; **3**: R^1 = -CH_2CH_3; **4**: R^1 = -$(CH_2)_2CH_3$; **5**: R^1 = -$(CH_2)_3CH_3$; **6**: R^1 = -$(CH_2)_4CH_3$;
7: R^1 = -$(CH_2)_5CH_3$; **8**: R^1 = -$(CH_2)_6CH_3$; **9**: R^1 = -$(CH_2)_7CH_3$; **10** R^1 = -$(CH_2)_{12}CH_3$;
11: R^1 = -$(CH_2)_{13}CH_3$;**12**: R^1 = -$N(CH_3)_2$; **13**: R^1 = -CH_2CF_3; **14**: R^1 = -CH_2NHBoc



16: R^1 = -CH_3; **17**: R^1 = -CH_2CH_3; **18**: R^1 = -$(CH_2)_2CH_3$; **19**: R^1 = -$(CH_2)_3CH_3$;
20: R^1 = -$(CH_2)_4CH_3$; **21**: R^1 = -$(CH_2)_5CH_3$; **22**: R^1 = -$(CH_2)_7CH_3$; **23**: R^1 = -$(CH_2)_8CH_3$;
24: R^1 = -$(CH_2)_{12}CH_3$; **25**: R^1 = Boc-proline; **26**: R^1 = -$N(CH_3)_2$



28: R^1 = -CH_3; **29**: R^1 = -CH_2CH_3; **30**: R^1 = -$(CH_2)_2CH_3$; **31**: R^1 = -$(CH_2)_3CH_3$; **32**: R^1 = -$(CH_2)_4CH_3$;
33: R^1 = -$(CH_2)_5CH_3$; **34**: R^1 = -$(CH_2)_7CH_3$; **35**: R^1 = -$(CH_2)_8CH_3$; **36**: R^1 = -$(CH_2)_{10}CH_3$;
37: R^1 = -$(CH_2)_{13}CH_3$; **38**: R^1 = -$(CH_2)_3CH_2$Br; **39**: R^1 = -$N(CH_3)_2$; **40**: R^1 = -Cyclopropyl;
41: R^1 = (*E*)-3-(furan-2-yl)acryloyl; **42**: R^1 = -CH_2NHAc; **43**: R^1 = Boc-proline; **44**: R^1 = *tert*-butyl 1-methylcyclopentylcarbamate-1yl; **45**: R^1 = -CH_2NHBoc; **46**: R^1 = Boc-alanine; **47**: R^1 = Boc-leucine;
48: R^1 = Boc-tert-leucine; **49**: R^1 = Boc-methionine; **50**: R^1 = *tert*-butyl-2-(3-fluorophenyl) ethylcarbamate-1-yl; **51**: R^1 = *tert*-butyl 2-phenylethylcarbamate-1-yl; **52**: R^1 = -CH_2NHFmoc;
53: R^1 = Fmoc-leucine; **54**: R^1 = Fmoc-valine

Scheme 1. Reagents and conditions: (i) dry THF, *n*-BuLi, Boc-glycine-*N*-hydroxysuccinimide ester, −78 °C, 2 h then room temperature. 1 h. (for compound **14**) (ii) dry DMF, NaH (3 eq), R^1COCl (3 eq), 0 °C to room temperature, 15 h. (iii) dry DMF, EDC.HCl (1.5 eq), DMAP, R^1COOH, room temperature, 4 h. Note that we have used arbitrary systematic position numbering of protons for the sake of easier comparison within the same structural scaffold. The IUPAC nomenclature of compounds is used throughout the text in the experimental section.

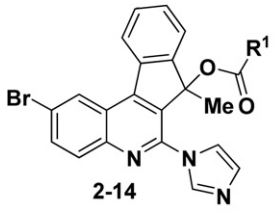
against *M. tuberculosis* H37Rv, MIC in the range of 0.42 (**7**, R^1 = hexyl)–6.0 (**12**, R^1 = dimethylamino) μg/mL. Compounds **7** and **13** (R^1 = 2,2,2-trifluoroethyl) are almost 2-fold more potent than parent alcohol **1**. It was found that compounds having aliphatic side chain (R^1-group in **1**, Scheme 1) from C-4 to C-8 gave most potent compounds. The heptanoic ester derivative **7**, showed excellent activity (MIC = 0.42 μg/mL). By increasing the chain length from C-7 (as in compound **7**) to C-8 (as in compound **8**) resulted in 8-fold decrease in the antimycobacterial activity. Compounds **10** and **11** having long aliphatic chain (R^1-group) C-13 and C-14, respectively, were found to be inactive. Compound **13** having $-CH_2CF_3$ group was found to be 1.5-fold more potent than the parent compound **1**. Table 1 shows that compound **7** and **13** have better SI than other active compounds, as well as that of the parent alcohol **1**. Hydrolysis study of ester derivatives of compound **1** suggests that they are not being hydrolyzed in blood serum (pH 7.4) except ester **13**. While in aqueous ammonia (pH 8.0) all ester derivatives hydrolyzed to compound **1** except compound **12** (R^1 = dimethylamino, least active in the series with MIC of 6.0 μg/mL) which perhaps may be owing to the stable chemical nature of the amide bond. Compounds **13** and **14** are hydrolyzed almost completely to parent compound **1** in aqueous ammonia (pH 8.0). Cytotoxicity data of active prodrugs of compound **1** suggest that these compounds are non-toxic to normal human cell lines (Table 1).

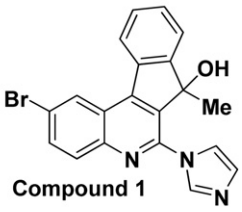
2.2.2. Esters of compound *15*

Table 2 presents the results of growth inhibition of ester derivatives **16**–**26** vis-à-vis their parent **15** against *M. tuberculosis* H37Rv by MABA assay [21]. Out of 11 ester derivatives of compound **15**, 10 compounds were found to be active, having MIC between <0.20 (**16**: R^1 = methyl and **18**: R^1 = propyl)–3.0 (**23**: R^1 = nonyl) μg/mL. Compounds **16**–**22** having chain length (R^1-group) C-1–C-9 were found to be active. Compounds having C-1–C-8 (shorter) aliphatic chains showed more impressive activity (Table 2, Compounds **16**–**22**), whereas further increase in the chain length of R^1-group resulted in decrease (C-9, **23**) or loss (C-13, **24**) of activity. Moving from aliphatic acid esters to amino acid ester (**25**) or carbamoyl derivative (**26**) regains the activity.

All the ester derivatives of compound **15** are being hydrolyzed to parent compound in blood serum (pH 7.4) as well as in aqueous ammonia (pH 8.0), with half-lives ($t_{1/2}$) in the range of 1–10 h, except compound **26**. With increase in the aliphatic chain length **17**, **18**, **19** and **20** there is a gradual increase in $t_{1/2}$ values 3.5 h, 4.0 h, 6.0 h, 10 h. The difference in the stability of these compounds must be attributed to the structural variation in the side chain, leading to steric, electronic as well as the solubility effects in compounds **16**–**22**. These data suggest that compounds having $t_{1/2}$ in the range of (1–4 h) are more active (*i.e.* compounds **16** and **18**) compared to other analogs. Compound **15** was thus proven to be an attractive candidate to synthesize prodrugs, by improvement of aqueous solubility, lipophilicity in order to steer to the better activity with good selectivity index. Cytotoxicity data (Table 2) of these compounds suggest that these compounds are non-toxic to normal human cell lines compared to compound **15**.

Table 1
Esters of compound **1** – MIC, toxicity, hydrolysis and partition coefficient study.

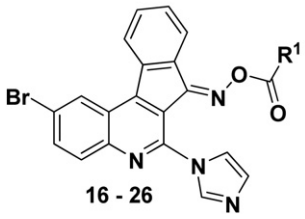


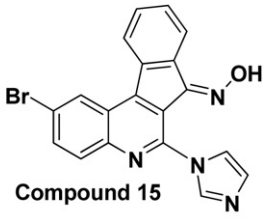


Comp No.	R^1	MIC,[a] μg/mL	% Cell viability[b] after 72 h				SI	Hydrolyzed compound (1) formed in 12 days, at 37 °C		$t_{½}$ in days		Partition coefficient		
			Concentration (μg/mL)					Blood serum[c] (%)	Aq. NH_3[d] (%)	Blood serum	Aq. NH_3	P^c	*log P*	ClogP
			1.25	5.0	10	20								
1	–	0.78	93	64	64	37	4.3	–	–	–	–	54.25	1.7	3.77
2	$-CH_3$	1.88	94	90	63	35	7.5	Nd	90	–	10	481.5	2.7	4.62
3	$-CH_2CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
4	$-(CH_2)_2CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
5	$-(CH_2)_3CH_3$	1.53	91	75	48	4	5.6	Nd	90	–	12	42.8	1.7	6.21
6	$-(CH_2)_4CH_3$	1.60	85	77	54	15	6.1	Nd	90	–	12	25.7	1.4	6.74
7	$-(CH_2)_5CH_3$	0.42	85	83	68	54	40.2	Nd	86	–	13	50.7	1.7	7.27
8	$-(CH_2)_6CH_3$	3.42	87	72	52	17	2.5	Nd	90	–	11	63.1	1.8	7.80
9	$-(CH_2)_7CH_3$	1.56	86	75	71	50	11.4	Nd	90	–	12	39.3	1.6	8.33
10	$-(CH_2)_{12}CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
11	$-(CH_2)_{13}CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
12	$-N(CH_3)_2$	6.0	63	–	69	–	–	Nd	Nd	–	–	80.3	1.9	4.87
13	$-CH_2CF_3$	0.50	92	80	62	26	22.4	50	96	20	1	67.6	1.8	4.92
14	$-CH_2NHBoc$	2.03	90	83	62	28	6.0	Nd	97	–	1	61.1	1.8	5.45

$t_{½}$ is the time required for 50% hydrolysis at 37 °C.
P^c is the apparent partition coefficient between 1-octanol and water at room temperature (25 °C). SI, Selectivity Index of compound.
[a] MIC Minimum Inhibitory Concentration, determined by Microplate Alamar Blue Assay (MABA) [21] (see Experimental section for details)
[b] Determined by Mosmans's MTT assay [22] (see Experimental section for details)
[c] The enzymatic hydrolysis of each compound (1 mg) was carried out in 80% human blood serum/phosphate buffer (pH 7.4) incubated at 37 °C. The rate of enzymatic hydrolysis was determined by LC-MS/TLC following the literature procedure [23].
[d] The rates of chemical hydrolysis of compounds were studied in aqueous ammonia solution (10 % aqueous ammonia in methanol, pH 8) at 37 °C determined by LC-MS. Nd represents for those molecules which have not been hydrolyzed.

Table 2
Esters of compound **15** – MIC, toxicity, hydrolysis and partition coefficient study.





Comp No.	R^1	MIC,[a] μg/mL	% Cell viability[b] after 72 h				SI	Hydrolyzed compound (**15**) formed in 24 h, 37 °C		$t_{½}$ in hours		Partition coefficient		
			Concentration (μg/mL)					Blood serum[c] (%)	Aq. NH_3[d] (%)	Blood serum	Aq. NH_3	*P*[c]	*log P*	ClogP
			1.25	5.0	10	20								
15	–	<0.39	100	91	77	77	>5	–	–	–	–	1.7	0.2	4.90
16	$-CH_3$	<0.2	87	78	59	42	>71	94	95	3.5	2.0	13.0	1.1	4.34
17	$-CH_2CH_3$	0.29	84	86	75	67	>137	90	95	3.5	2.0	17.4	1.2	4.87
18	$-(CH_2)_2CH_3$	<0.2	85	88	69	70	>200	90	95	4.0	1.5	30.9	1.5	5.40
19	$-(CH_2)_3CH_3$	0.28	85	82	75	51	60	90	90	6.0	3.0	43.8	1.6	5.93
20	$-(CH_2)_4CH_3$	1.5	81	–	100	–	–	85	90	10	6.0	129.9	2.1	6.46
21	$-(CH_2)_5CH_3$	0.36	85	80	67	60	>111	85	95	8.0	2.0	33.0	1.5	6.99
22	$-(CH_2)_7CH_3$	0.39	87	85	77	72	>102	95	95	3.0	1.0	83.8	1.9	8.05
23	$-(CH_2)_8CH_3$	3.0	100	–	81	–	–	90	90	6.0	1.0	28.2	1.4	8.57
24	$-(CH_2)_{12}CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
25	Boc-proline	0.39	87	86	74	78	>102	95	90	1.0	0.5	19.0	1.3	6.25
26	$-N(CH_3)_2$	0.27	77	82	61	50	49	Nd	Nd	Nd	Nd	14.7	1.1	4.40

$t_{½}$ is the time required for 50% hydrolysis at 37 °C.
P[c] is the apparent partition coefficient between 1-octanol and water at room temperature (25 °C). SI is Selectivity Index.
[a] MIC Minimum Inhibitory Concentration determined by Microplate Alamar Blue Assay (MABA) [21] (see Experimental section for details)
[b] Determined by Mosmans's MTT assay [22] (see Experimental section for details)
[c] The enzymatic hydrolysis of each compound (1 mg) was carried out in 80% human blood serum / phosphate buffer (pH 7.4) incubated at 37 °C. The rate of enzymatic hydrolysis was determined by LC-MS/TLC following the literature procedure [23].
[d] The rates of chemical hydrolysis of compounds were studied in aqueous ammonia solution (10 % aqueous ammonia in methanol, pH 8) at 37 °C determined by LC-MS. Nd represents for those molecules which have not been hydrolyzed.

2.2.3. Esters of compound *27*

13 Aliphatic ester derivatives of compound **27** have been prepared (Table 3) and evaluated for their antimycobacterial activity against M. TB H37Rv. Four ester derivatives (**29**, **32**, **38** and **41**) having small aliphatic chain (R^1 = ethyl, pentyl, 4-bromobutyl and *E*-2-(furan-2-yl)ethenyl, respectively) were found active, whereas compounds possessing long aliphatic chain from C6 to C14 (**33**–**37**) were found to be inactive as they became hydrophobic in nature. Compound **39** with carbamoyl group ($R^1 = -N(CH_3)_2$) was found to be equipotent as to the parent oxime **27**.

2.2.4. Amino acid esters of compound *27*

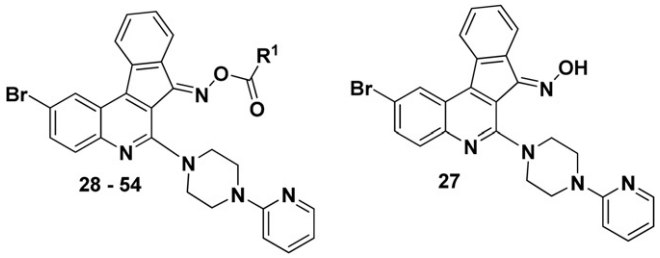
The amino acids used to prepare chemically diverse ester derivatives of compound **27** are aliphatic amino acids: Boc-alanine, Fmoc-valine, Boc-leucine, Boc-glycine, Boc-methionine, aromatic amino acids, Boc-phenylalanine, Boc-3-fluorophenylalanine, secondary amino acids such as Boc-proline, and some unnatural amino acids like 1-(Boc-amino)cyclopentanecarboxylic acid, Boc-*tert*-leucine etc. Accordingly, various *N*-protected amino acids (with *N*-acetylglycine (**42**), Boc-proline (**43**), Boc-glycine (**45**), Boc-alanine (**46**), Boc-leucine (**47**), Boc-*tert*-leucine (**48**), Boc-methionine (**49**), Boc-3-fluorophenylalanine (**50**), Boc-phenylalanine (**51**), Fmoc-glycine (**52**), Fmoc-leucine (**53**) and Fmoc-valine (**54**)) esters were synthesized.

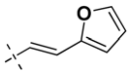
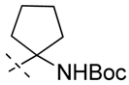
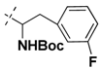
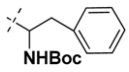
Four amino ester derivatives, compound **43** (MIC = 1.53 μg/mL), **45** (MIC = 1.55 μg/mL), **48** (MIC = 1.52 μg/mL) and **54** (MIC = 1.47 μg/mL) exhibited better antimycobacterial activity than parent compound **27**. Esters of aromatic amino acid like compound **50** (MIC = 2.98 μg/mL) and **51** (MIC = 3.47 μg/mL) also have comparable antimycobacterial activity. Compound **50** having 3-fluoro group on the phenyl ring is more potent than **51** (Table 3), suggesting that fluoro group is imparting in biological activity. It was found that the aliphatic ester derivatives of compound **27** exhibited excellent antimycobacterial activity than the amino ester derivatives (Table 3).

Hydrolysis study of esters of compound **27** shows that in blood serum (pH 7.4) the rate of hydrolysis of these esters is slow. Only Boc-amino acid esters **42**, **45** and **50** are being hydrolyzed upto 95% over 24 h. Compound **50** having Boc-3-fluorophenylalanine (MIC = 2.98 μg/mL) was more susceptible to hydrolysis in blood serum (pH 7.4) as compared to **51** having ester of Boc-phenylalanine (MIC = 6.0 μg/mL). This suggests that the fluoro group is contributing to hydrolysis as well as imparting in biological activity. Cytotoxicity data of these compounds showed that they are not toxic to human cells (Table 3).

Table 4 represents the MIC and structures of active compounds from three different series *i.e.* esters of compound **1**, **15** and **27**. In total 33 ester derivatives were found active against *M. tuberculosis* H37Rv which are having MIC in the range of 0.2–6.0 μg/mL. Two ester derivatives of compound **1**, *i.e.* heptanoic acid ester **7** (MIC = 0.42 μg/mL) and 3,3,3-trifluoropropanoate **13** (MIC = 0.50 μg/mL) were found to exhibit improved activity, whereas eight ester derivatives (R^1 = methyl (**16**), ethyl (**17**), propyl (**18**), butyl (**19**), hexyl (**21**), octyl (**22**), *N*-Boc-pyrrolidin-2-yl (**25**), dimethylamino (**26**)) of compound **15**, were found to possess better to comparable activity as that of **15**. Ten ester derivatives (R^1 = ethyl (**29**), pentyl (**32**), 4-bromobutyl (**38**), dimethylamino (**39**), *N*-Boc-pyrrolidin-2-yl (**43**), *N*-Boc-aminomethyl (**45**), (**48**), 1-(*N*-Boc-

Table 3
Esters of Compound **27** – MIC, toxicity, hydrolysis and partition coefficient study.



Comp No.	R^1	MIC,[a] μg/mL	% Cell viability[b] after 72 h				SI	Hydrolyzed compound (**27**) formed in 24 h, 37 °C		$t_{½}$ in hours		Partition coefficient		
			Concentration (μg/mL)					Blood serum[c] (%)	Aq. NH_3[d] (%)	Blood serum	Aq. NH_3	P^c	*log P*	ClogP
			1.25	5.0	10	20								
27	–	6.25	100	100	56	49	71	–	–	–	–	2053	3.3	5.95
28	$-CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
29	$-CH_2CH_3$	3.13	83	88	81	83	>13	13	95	Nd	6	447.4	2.7	5.92
30	$-(CH_2)_2CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
31	$-(CH_2)_3CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
32	$-(CH_2)_4CH_3$	3.16	96	86	85	87	>13	5	95	Nd	24	115.1	2.1	7.51
33	$-(CH_2)_5CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
34	$-(CH_2)_7CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
35	$-(CH_2)_8CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
36	$-(CH_2)_{10}CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
37	$-(CH_2)_{13}CH_3$	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
38	$-(CH_2)_3CH_2Br$	2.03	99	94	79	80	>20	10	95	Nd	4	29.3	1.5	6.83
39	$-N(CH_3)_2$	1.56	100	100	68	47	88	Nd	Nd	Nd	–	216.8	2.3	5.45
40		Inactive	–	–	–	–	–	–	–	–	–	–	–	–
41		6.0	100	–	85	–	–	Nd	95	Nd	4	27.1	1.4	6.96
42	CH_2NHAc	6.0	83	–	77	–	–	95	95	8	6	15.0	1.2	4.25
43	Boc-proline	1.53	86	75	61	69	>26	13	95	Nd	1	198	2.3	7.29
44		Inactive	–	–	–	–	–	–	–	–	–	–	–	–
45	$-CH_2NHBoc$	1.55	87	82	63	49	22	95	95	1	0.15	5.0	0.7	6.11
46	Boc-alanine	6.0	100		100	–	–	66	95	20	2	49.1	1.7	6.42
47	Boc-leucine	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
48	Boc-*tert*-leucine	1.52	92	86	87	82	>26	11	95	Nd	2	31.9	1.5	7.75
49	Boc-methionine	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
50		2.98	92	90	79	84	>13	95	95	6	3	13.8	1.1	7.98
51		3.47	87	87	71	73	>12	70	98	18	3	16.0	1.2	7.84
52	$-CH_2NHFmoc$	6.0	68		73	–		29	90	Nd	1.5	24.1	1.4	8.40
53	Fmoc-leucine	Inactive	–	–	–	–	–	–	–	–	–	–	–	–
54	Fmoc-valine	1.47	85	89	81	80	>27	7	96	Nd	1	66.0	1.8	9.63

$t_{½}$ is the time required for 50% hydrolysis at 37 °C.
P^c is the apparent partition coefficient between 1-octanol and water at room temperature (25 °C). SI, Selectivity Index of compound.
[a] MIC Minimum Inhibitory Concentration determined by Microplate Alamar Blue Assay (MABA) [21] (see Experimental section for details)
[b] determined by Mosmans's MTT assay [22] (see Experimental section for details)
[c] The enzymatic hydrolysis of each compound (1 mg) was carried out in 80% human blood serum/phosphate buffer (pH 7.4) incubated at 37 °C. The rate of enzymatic hydrolysis was determined by LC-MS/TLC following the literature procedure [23].
[d] The rates of chemical hydrolysis of compounds were studied in aqueous ammonia solution (10% aqueous ammonia in methanol, pH 8) at 37 °C determined by LC-MS. Nd represents for those molecules which have not been hydrolyzed.

Table 4
MICs[a] of active ester derivatives of compound **1**, **15** and **27**.

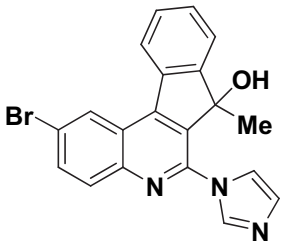
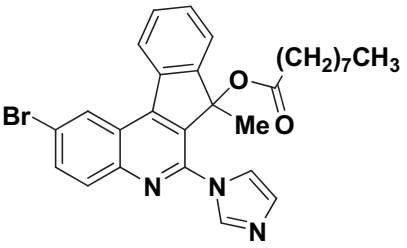
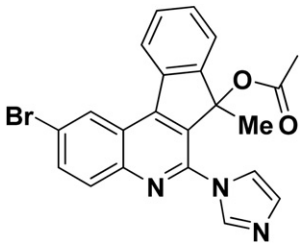
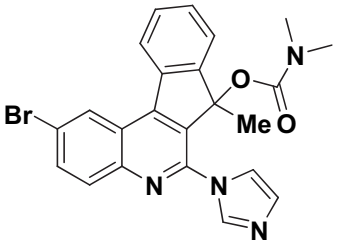
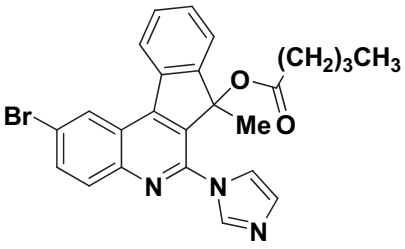
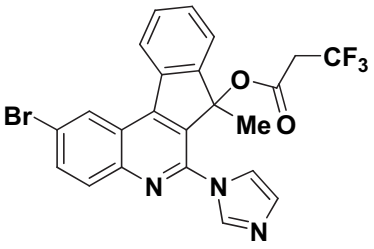
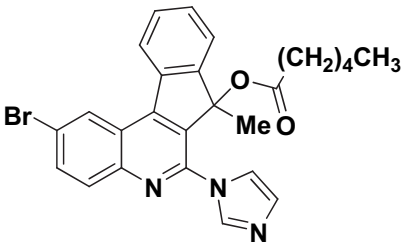
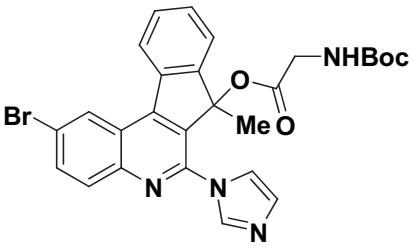
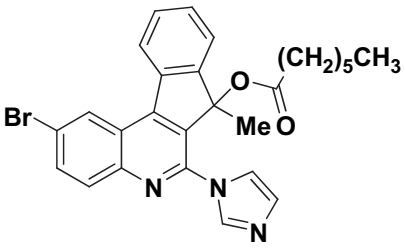
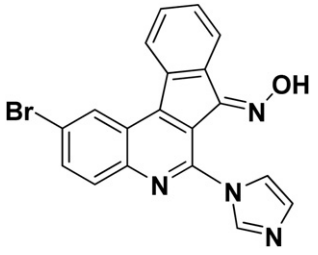
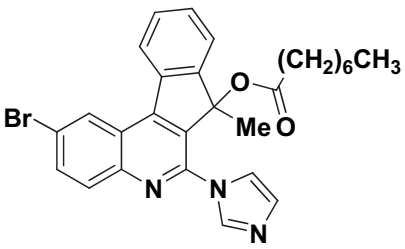
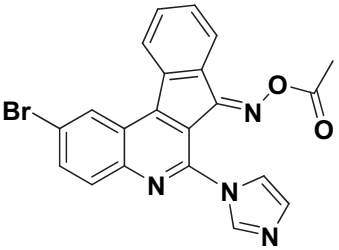
Comp no.	Structure	MIC μg/mL	Comp no.	Structure	MIC μg/mL
1		0.78	**9**		1.56
2		1.88	**12**		6.0
5		1.53	**13**		0.50
6		1.60	**14**		2.03
7		0.42	**15**		0.39
8		3.42	**16**		0.2

Table 4 (*continued*).

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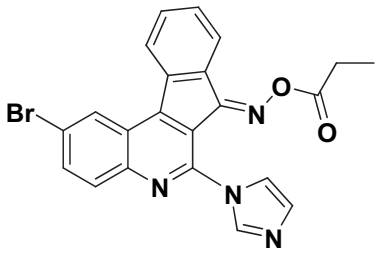
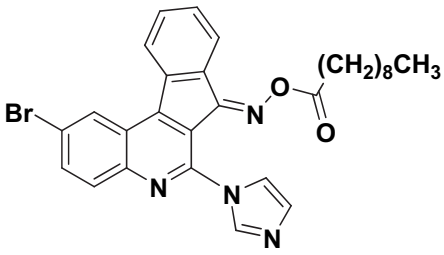
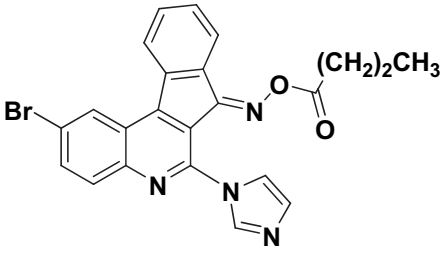
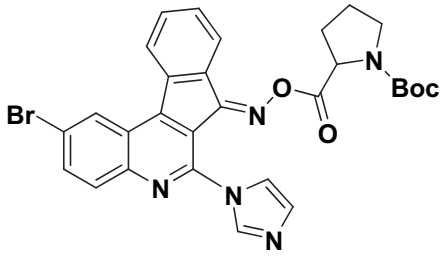
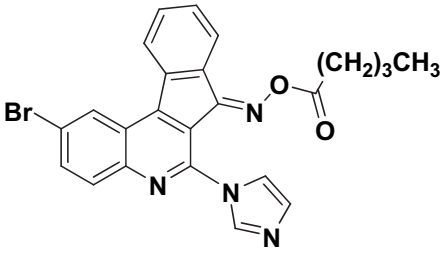
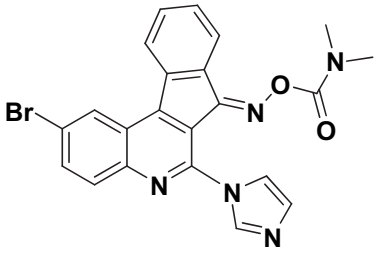
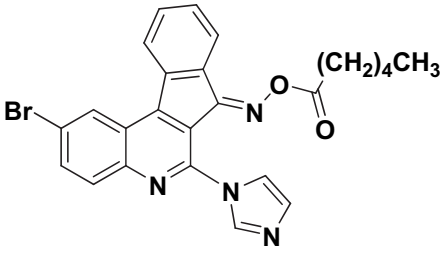
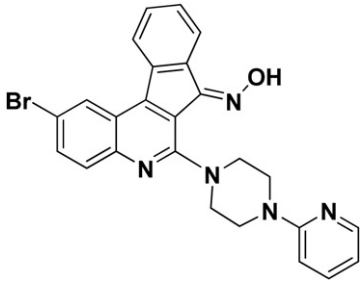
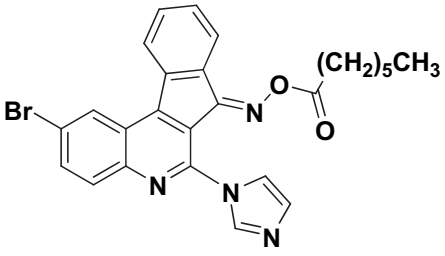
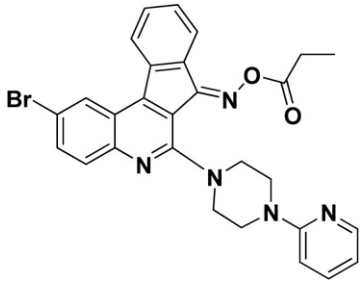
17		0.29	**23**		3.0
18		0.2	**25**		0.39
19		0.28	**26**		0.27
20		1.5	**27**		6.25
21		0.36	**29**		3.13

(*continued on next page*)

Table 4 (*continued*).

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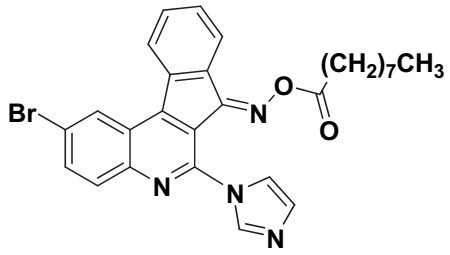
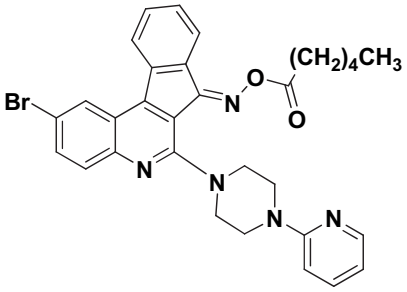
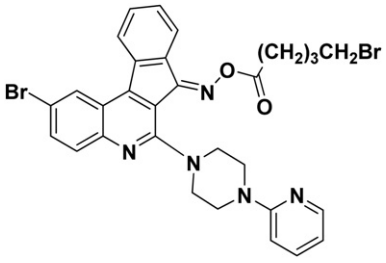
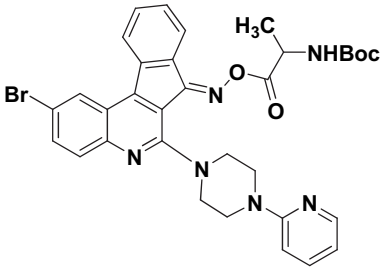
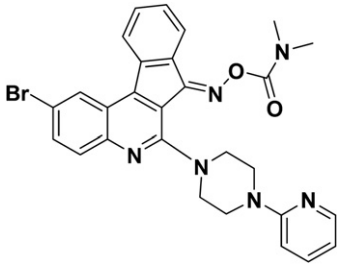
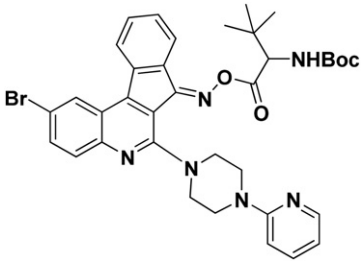
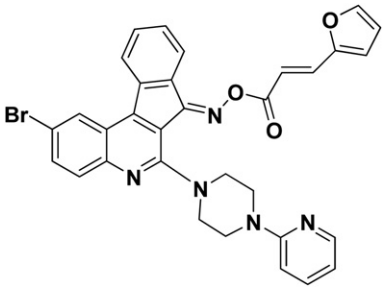
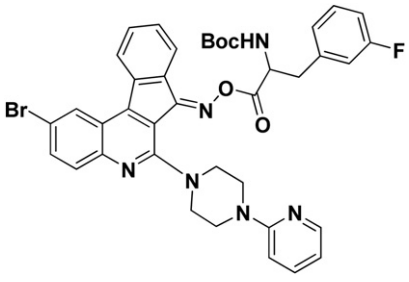
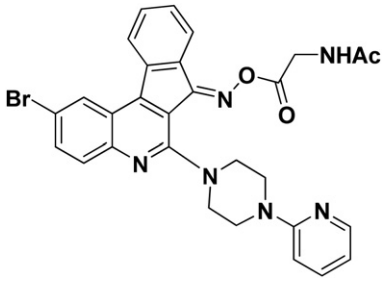
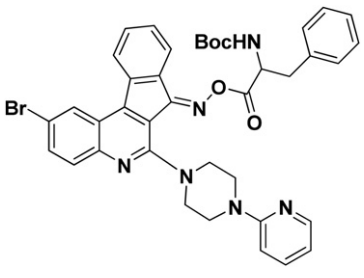
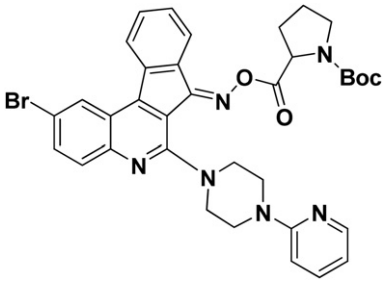
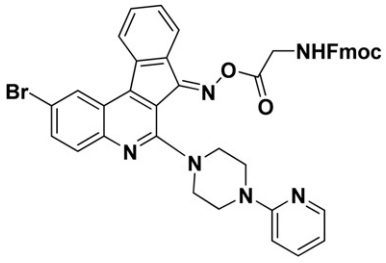
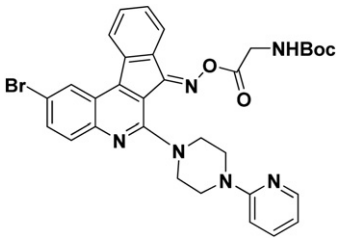
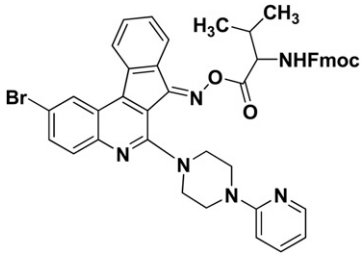
22		0.39	**32**		3.16
38		2.03	**46**		6.0
39		1.56	**48**		1.52
41		6.0	**50**		2.98
42		6.0	**51**		3.47

Table 4 (*continued*).

Comp no.	Structure	MIC μg/mL	Comp no.	Structure	MIC μg/mL
43		1.53	**52**		6.0
45		1.55	**54**		1.47

[a] MIC Minimum Inhibitory Concentration determined by Microplate Alamar Blue Assay (MABA) [21] (see Experimental section for details).

amino)-2-(3-fluorophenyl)ethyl (**50**), 1-(Boc-amino)-2-(phenyl) ethyl (**51**), 1-(Fmoc-amino)-2-methylpropyl (**54**)) were found to exhibit better activity, than their parent compound **27**. In general, the esters (as prodrugs) of compound **15** exhibited excellent antimicrobial activity and selectivity index because of improved solubility.

3. Measurement of the partition coefficient of all ester derivatives

All the active ester derivatives were studied for their aqueous solubility, by measuring the partition coefficient values in 1-octanol/water mixture. The prodrug nature of these active esters was determined from their efficient prodrug to drug (parent compound) conversion at physiological pH.

4. Aqueous solubility and lipophilicity

Drug lipophilicity is a very important factor that influences the pharmacokinetic and pharmaco-dynamic behavior of compounds. Partitioning within a biological system and biological activity are governed by recognition forces that are, among others, defined by hydrophobic interactions. High lipophilicity often goes with poor aqueous solubility. This can bring with it many challenges often making development of a seemingly promising drug candidate very difficult. Thus drug molecule should possess optimum balance between hydrophilic and lipophilic properties.

Partition coefficient (*P*) was determined [24] for all the active ester derivatives of compound **1**, compound **15** and **27** using mixture of octanol and phosphate buffer solution (pH 7.4) at room temperature. The *P* values for the esters of compound **1** ranged from 25.7 to 481.5. The most lipophilic compound in this series is acetate **2** (481.5) which is 9 times more lipophilic than the parent alcohol **1** (54.25). The most active compounds in this series are compound **7** (R^1 = hexyl, MIC 0.42 μg/mL) and **13** (R^1 = 2,2,2-Trifluoroethyl, MIC 0.50 μg/mL). Active ester derivatives of compound **1** are having log *P* values in the range of 1.4–2.7. Compound **7** is having log *P* 1.7, MIC = 0.42 μg/mL, and log *P* 1.8, MIC = 0.50 μg/mL for compound **13** while compound **1** is having log *P* 1.7 and MIC = 0.78 μg/mL.

P values for the esters of compound **15** ranged from 13.0 for the least lipophilic compound **16** (R^1 = methyl) to 129.9 for the most lipophilic compound **19** (pentanoic ester derivative). Thus the increase in lipophilicity of 5–76 times that of the parent compound **15** (*P* = 1.7) was achieved through conversion to the ester derivatives. The log *P* value for the compound **15** is 0.2, while all the active esters of compound **15** are having log *P* values in the range of 1.1–2.1. Thus the 5–10 times improvement in the lipophilicity of molecules was achieved, which enhanced biological activity of compounds by 2-fold, compound **15** (MIC = 0.39 μg/mL, log *P* = 0.2), while compound **16** (MIC = 0.2 μg/mL, log *P* = 1.1), **17** (R^1 = ethyl, MIC = 0.29 μg/mL, log *P* = 1.2), **18** (R^1 = propyl, MIC = 0.2 μg/mL, log *P* = 1.5), **19** (R^1 = butyl, MIC = 0.28 μg/mL, log *P* = 1.6) and **26** (R^1 = dimethylamino, MIC = 0.27 μg/mL, log *P* = 1.1). It was suggested, in the design of drug, compounds having log *P* values in the range of 1–3 are appropriate [25].

P values for the esters of compound **27** ranged from 5.0 for the least lipophilic Boc-glycine ester **45** to 447.4 for the most lipophilic propionic ester **29**. The log *P* value for compound **27** is 3.3 (MIC = 6.25 μg/mL) which is slightly higher, while its prodrugs are having log *P* values in the range of 0.7–2.7, all the esters are having better MIC values in the range of 1.47–6.0 μg/mL. Among the amino ester derivatives, compound **43** esterified with Boc-proline is having higher *P* value (198).

5. Hydrolysis in human serum/aqueous solution

Rates of hydrolysis for active esters were studied in human blood serum at 37 °C which was diluted to 80% with 0.16 M phosphate buffer (pH 7.4) as human serum or plasma is a commonly used medium to determine the ester hydrolysis of prodrugs for topical drug delivery [26,27]. The ester derivatives of compound **1**

were stable in blood serum, they did not hydrolyze at pH 7.4 in 24 h. Only compound **13**, having trifluoro propionic group was being hydrolyzed (4%) to parent alcohol **1** after 24 h. In order to test the stability/hydrolyzeability of these compounds within the time-frame of a typical screening assay, we have further incubated these compounds (active esters) with blood serum for 12 consecutive days at 37 °C, but these compounds were not hydrolyzed, except compound **13** which was hydrolyzed up to 50%. The rates of chemical hydrolysis of these compounds were also studied in 10% aqueous ammonia solution (pH 8) at 37 °C for 24 h, ester derivatives **13** and **14** (R^1 = *N*-Boc-aminomethyl) were hydrolyzed to the parent compound **1**, whereas the ester derivatives **5**–**9** (R^1 = from butyl to octyl) were hydrolyzed only in the range of 11–13%. Compound **2** with acetyl ester and compound **13**, with dimethylcarbamoyl group, were stable even in 10% aqueous ammonia solution (pH 8).

With an increase in the esters aliphatic chain length (C2–C5), as in **17** (MIC 0.29 μg/mL) to **18** (MIC 0.20 μg/mL) to **19** (MIC 0.28 μg/mL), and to **20** (MIC 1.50 μg/mL), there is gradual increase in the stability of the corresponding ester group as seen in their respective $t_{1/2}$ values of 3.5 h, 4.0 h, 6.0 h and 10.0 h. Thus, the comparison of MIC with the $t_{1/2}$ shows that the MIC of **17**–**19** is clearly associated with their bioavailability. In addition to that, Boc-proline ester **25** (MIC 0.39 μg/mL) having $t_{1/2}$ (1 h) further indicates that $t_{1/2}$ of ester hydrolysis is a critical factor for biological activity of prodrugs. Above data suggest that the molecules with short $t_{1/2}$ are more active than compounds with higher (longer) $t_{1/2}$.

The rates of chemical hydrolysis of esters of compound **15** were studied in aqueous ammonia solution at pH 8.0 at 37 °C for 24 h. All ester derivatives except compound **26** (R^1 = dimethylamino) were getting hydrolyzed to parent compound **15**, having the half-lives ($t_{1/2}$) from 0.5 to 6 h.

Similarly hydrolysis studies of esters of compound **27** were carried out in blood serum at pH 7.4 and in aqueous ammonia at pH 8.0. In blood serum the rate of hydrolysis of these esters was rather slow. Only Boc-amino ester derivatives **42** (*N*-acetylglycine ester, MIC 6.0 μg/mL), **45** (*N*-Boc-glycine ester, MIC 1.55 μg/mL) and **50** (*N*-Boc-3-fluorophenylalanine ester, MIC 2.98 μg/mL) were hydrolyzed up to 95% within 24 h. Compounds **42**, **45** and **50** are having half life ($t_{1/2}$) of 8, 1 and 6 h respectively. Interestingly compound **50** (MIC 2.98 μg/mL, $t_{1/2}$ 6 h, Boc-3-fluorophenylalanine) is more active than **51** (MIC 3.47 μg/mL, $t_{1/2}$ 18 h, Boc-phenylalanine), which is having fluoro substitution on meta-position of the phenyl ring. These results clearly indicate that fluoro group contributes to hydrophilic and electrostatic interactions which lead to superior biological activity over compound **51**. These data also suggest that the molecules with short $t_{1/2}$ are more active than other compounds with higher $t_{1/2}$.

All the ester derivatives of compound **27** are getting hydrolyzed in aqueous ammonia (pH 8.0) except compound **39**, which is having dimethylcarbamoyl group. It is remarkable that compounds having dimethylcarbamoyl ester group are stable in blood serum (pH 7.4) as well in aqueous ammonia (pH 8.0) in all three series of compounds.

6. Conclusion

In conclusion the prodrugs of parent compound **1**, i.e. **7** (MIC = 0.42 μg/mL) and **13** (MIC = 0.50 μg/mL) are having better antimycobacterial activity, selectivity index and improved solubility. Similarly prodrugs **16**–**22** and **25**–**26** are showing better antimycobacterial activity (MIC 0.2–1.5 μg/mL) and excellent selectivity index as compared to parent compound **15**. Biological results of these prodrugs further suggest that parent compounds **1** and **15** are scaffolds of considerable promise as targets to make other suitable prodrugs which will have required pharmacokinetic properties for animal studies to explore new anti-TB agents.

7. Experimental section

7.1. Biology

The MICs were determined by using M. TB H37Rv ATCC 27294 in MABA [20] according to published procedure. Reported MICs are an average of three individual measurements.

7.1.1. Microplate Alamar Blue Assay (MABA) [21]

The test compound MICs against M. TB H37Rv (ATCC# 27294) were assessed by the MABA using rifampin and isoniazid as positive controls. Compound stock solutions were prepared in DMSO at a concentration of 12.8 mM, and the final test concentrations ranged from 128 μM to 0.5 μM. Two fold dilutions of compounds were prepared in Middlebrook 7H12 medium (7H9 broth containing 0.1% w/v casitone, 5.6 μg/mL palmitic acid, 5 mg/mL bovine serum albumin, 4 mg/mL catalase, filter sterilized) in a volume of 100 μL in 96-well microplates (BD Optilux™, 96-well Microplates, black/clear flat bottom). TB cultures (100 μL inoculum of 2×10^5 cfu/mL) were added, yielding a final testing volume of 200 μL. The plates were incubated at 37 °C. On the seventh day of incubation 12.5 μL of 20% Tween 80, and 20 μL of Alamar Blue (Invitrogen BioSource™) were added to the wells of test plate. After incubation at 37 °C for 16–24 h, fluorescence of the wells was measured (ex 530, em 590 nm). The MICs were defined as the lowest concentration effecting a reduction in fluorescence of ≥90% relative to the mean of replicate bacteria-only controls.

7.1.2. Cytotoxicity assay

Cell viability in the presence and absence of test compounds was determined by Mosmans's MTT assay [22] for the most active compounds from our data set. The cells (human monocytic cell line U937) were plated in flat-bottomed 96-well plates (1×10^5 cells/mL), cultured for 1 h in controlled atmosphere (CO_2 5% at 37 °C), and non-adherent cells were washed by gentle flushing with RPMI 1640. Adherent cells were cultured in the presence of medium alone, Tween 20 (3%) (live and dead controls, respectively) or different concentration of compounds (depending upon the solubility) in a triplicate assay. After completion of the experiment protocol 10 μL of MTT solution (5 mg/mL solution in Phosphate Buffer Saline) was added in each well. Plates were incubated for 3 h in CO_2 incubator at 37 °C. Then 100 μL solubilizing solution (0.4 M HCl in isopropanol) was added to solubilize the formazan crystals formed by the surviving cells. Finally the absorbance was read at 600 nm in a microplate reader (Bio-Rad-i Mark) using acidified isopropanol as blank. The results were presented as percentage cell viability.

7.1.3. Experimental procedure for partition coefficient measurements [24]

1-Octanol/aqueous phase partition coefficients were determined at room temperature using the shake flask method. The standard solution of water saturated with 1-octanol prepared by shaking them for 24 h. Solution of compound (10^{-4} M concentration) in the equal amounts of 1-octanol and water was prepared from previously saturated solution of 1-octanol/aqueous phase and shaken vigorously for 1 h, and the contents were allowed to stand for 15 min. Sample was centrifuged for 10 min with 10,000 rpm to avoid emulsions. Recorded the blank readings and the UV absorbance for both the phases at 280 nm. The partition coefficients were calculated from the ratio of the absorbance between the octanol and water phases.

7.1.4. Hydrolysis study

7.1.4.1. Hydrolysis in aqueous solution. The rates of chemical hydrolysis of prodrugs were studied in aqueous ammonia solution at pH 8 at 37 °C. An appropriate amount (1 mg) of prodrugs was dissolved (1 mL, 10% aqueous ammonia in methanol). The solutions were placed in a thermostatically controlled water bath at 37 °C. Hydrolysis rate was monitored by TLC as well as LC-MS.

7.1.4.2. Hydrolysis in human serum. The rates of hydrolysis for prodrugs were studied in human serum at 37 °C which was diluted to 80% with 0.16 M phosphate buffer of pH 7.4. The reactions were initiated by dissolving an appropriate amount (1 mg) of prodrugs in 1 mL ethanol, and preheated human blood serum in phosphate buffer (200 μL) was added. The solutions were kept in a water bath at 37 °C, sample centrifuged for 10 min at 10,000 rpm, the supernatant was analyzed for remaining prodrugs, monitored by TLC as well as LC-MS.

7.2. Chemistry

Purification and drying of reagents and solvents were carried out according to literature procedures [28]. Thin layer chromatographic analysis was performed on E-Merck 60 F 254 precoated aluminium thin layer chromatographic plates. All air-sensitive reactions were carried out under nitrogen atmosphere. Melting points were determined on a Büchi melting point B-540 instrument and are uncorrected. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Bruker Biospin 400 MHz, Bruker Avance DRX500 and DRX600 spectrometers with TMS as an internal standard. The values of chemical shifts are expressed in ppm and the coupling constants (J) in Hertz (Hz). Mass spectra were recorded on API 2000 LC/MS/MS system spectrometer upto 2 decimals. IR spectra were recorded on Perkin–Elmer Spectrum RX1 instrument.

7.2.1. General procedure A

Oxime compounds **15** or compound **27** (1 eq), EDC.HCl (1.5 eq) and DMAP (1.5 eq) were stirred in dry DMF for 20 min at room temperature. Corresponding acid (1.5 eq) was added and reaction was further stirred for 4 h. Reaction was quenched with water and extracted with DCM. Organic layer was washed with brine, dried over sodium sulfate; filtered and solvents were evaporated under reduced pressure. Crude product was washed with pentane to obtain pure compound.

7.2.2. General procedure B

To a cooled (0 °C) solution of oxime compound **15** or compound **27** (1 eq) in dry DMF, sodium hydride (3 eq) was added under nitrogen atmosphere and stirred for 30 min. Reaction mixture color changed from yellow to dark red with evolution of hydrogen gas. Corresponding acid chloride (3 eq) was added and reaction was stirred for 15 h at room temperature after which reaction was quenched with ice. Reaction mixture was extracted with DCM, washed by brine. Organic layer was dried over sodium sulfate, filtered and solvents were evaporated under reduced pressure to get crude product. Crude product was washed with pentane several times to get pure compound.

*7.2.2.1. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl acetate **(2)** Procedure B, yield 23%.* Light-brown solid; mp 237–238 °C, IR$_{\nu max}$ (KBr, cm^{-1}) 1742.69; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.62 (s, 3 H, $C\underline{H}_3$), 2.05 (s, 3 H, $OCOC\underline{H}_3$), 7.30 (s, 1 H, H14), 7.51–7.62 (m, 4 H, H10, H11, H15 and H12), 7.88 (dd, J = 2.0, 9.0 Hz, 1 H, H7), 8.00 (d, J = 9.0 Hz, 1 H, H8), 8.15 (s, 1 H, H13), 8.31 (d, J = 7.5 Hz, 1 H, H9), 8.85 (d, J = 2.0 Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 21.8 ($\underline{C}H_3COO$), 23.7 ($\underline{C}H_3C$), 83.9 ($CH_3-\underline{C}$), 119.8 (C15), 122.2 (Ar-C), 122.4 (C12), 124.6 (C9), 125.2 (C4a), 126.6 (C5), 129.7 (C10, C14), 130.8 (C11), 131.7 (C8), 132.9 (C3), 134.1 (C7), 136.7 (Ar-C), 145.2 (C9a), 146.9 (C4), 147.0 (C8a), 148.5 (C12a), 168.7 (C=O). **ESI-MS** m/z of $[M+H]^+$ 434.00, 436.00 was obtained for a calculated mass of 434.05, 436.05.

*7.2.2.2. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl propionate **(3)** Procedure B, yield 22%.* Light-brown solid; mp 244–245 °C, ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.02 (t, J = 7.2 Hz, 3 H, $CH_2C\underline{H}_3$), 1.62 (s, 3 H, $CC\underline{H}_3$), 2.34 (q, J = 7.2 Hz, 2 H, $C\underline{H}_2CH_3$), 7.29 (s, 1 H, H14), 7.56–7.61 (m, 4 H, H10, H11, H12 and H15), 7.88 (dd, J = 1.8, 9.0 Hz, 1H, H7), 8.00 (d, J = 9.0 Hz, 1 H, H8), 8.14 (s, 1 H, H13), 8.31 (d, J = 7.2 Hz, 1 H, H9), 8.85 (d, J = 2.4 Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 8.7 ($CH_2\underline{C}H_3$), 23.7 (CCH_3), 28.1 ($\underline{C}H_2CH_3$), 83. 7 ($CH_3\underline{C}$), 119.8 (C15), 122.2 (Ar-C), 122.3 (C12), 124.6 (C9), 125.2 (C4a), 126.6 (C5), 129.7 (C10 and C14), 130.8 (C11), 131.7 (C8), 133.0 (C3), 134.1 (C7), 136.7 (Ar-C), 137.5 (C13), 145.2 (C9a), 146.9 (C4), 146.95 (C8a), 148.7 (C12a), 172.2 (C=O). **ESI-MS** m/z of $[M+H]^+$ 448.20, 450.20 was obtained for a calculated mass of 448.06, 450.06.

*7.2.2.3. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl butyrate **(4)** Procedure B, yield 19%.* White solid; mp 214–215 °C, ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.86 (t, J = 7.2 Hz, 3 H, $C\underline{H}_3CH_2$), 1.49–1.56 (m, 2 H, $CH_3C\underline{H}_2$), 1.62 (s, 3 H, $C\underline{H}_3C$), 2.24–2.37 (m, 2 H, $COC\underline{H}_2$), 7.29 (s, 1 H, H14), 7.51–7.63 (m, 4 H, H10, H11, H12 and H15), 7.87 (dd, J = 1.8, 9.0 Hz, 1 H, H7), 8.00 (d, J = 9 Hz, 1 H, H8), 8.17 (s, 1 H, H13), 8.30 (d, J = 7.8 Hz, 1 H, H9), 8.85 (d, J = 1.8 Hz, 1 H, H-5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 13.5 ($\underline{C}H_3CH_2$), 18.0 ($CH_3\underline{C}H_2$), 23.7 ($\underline{C}H_3C$), 36.6 ($CO\underline{C}H_2$), 83.6 ($CH_3\underline{C}$), 119.8 (C15), 122.1 (Ar-C), 122.3 (C12), 124.6 (C9), 125.2 (C4a), 126.6 (C5), 129.6 (C10), 129.7 (C14), 130.8 (C11), 131.7 (C8), 132.9 (C3), 134.1 (C7), 136.7 (Ar-C), 137.5 (C13), 145.1 (C9a), 146.9 (C4), 147.0 (C8a), 148.7 (C12a), 171.4 (C=O). **ESI-MS** m/z of $[M+H]^+$ 462.30, 464.30 was obtained for a calculated mass of 462.08, 464.08.

*7.2.2.4. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl pentanoate **(5)** Procedure B, yield 21%.* Gray solid; mp 140–143 °C, ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.85 (t, J = 7.5 Hz, 3 H, $C\underline{H}_3CH_2$), 1.21–1.30 (m, 2 H, $CH_3C\underline{H}_2$), 1.43–1.52 (m, 2 H, $OCOCH_2C\underline{H}_2$), 1.61 (s, 3 H, $CC\underline{H}_3$), 2.26–2.39 (m, 2 H, $OCOC\underline{H}_2$), 7.29 (s, 1 H, H14), 7.51–7.62 (m, 4 H, H10, H11, H12 and H15), 7.88 (dd, J = 2.5, 9.5 Hz, 1 H, H7), 8.00 (d, J = 9.0 Hz, 1 H, H8), 8.16 (s, 1 H, H13), 8.31 (d, J = 8.0 Hz, 1 H, H9), 8.84 (d, J = 2.0 Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 13.6 ($\underline{C}H_3CH_2$), 22.1 ($CH_3\underline{C}H_2CH_2$), 23.6 ($C\underline{C}H_3$), 26.5 ($CH_3CH_2\underline{C}H_2$), 34.4 ($CO\underline{C}H_2$), 83.6 ($\underline{C}CH_3$), 119.8 (C15), 122.1 (Ar-C), 122.2 (C12), 124.6 (C9), 125.2 (C4a), 126.6 (C5), 129.7 (C15), 130.8 (C11), 131.7 (C8), 132.9 (C3), 134.1 (C7), 136.7 (Ar-C), 137.5 (C13), 145.2 (C9a), 146.9 (C4), 147.0 (C8a), 148.7 (C12a), 171.6 (C=O). **ESI-MS** m/z of $[M+H]^+$ 475.80, 477.80 was obtained for a calculated mass of 476.09, 478.09.

*7.2.2.5. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl hexanoate **(6)** Procedure B, yield 56%.* Off-white solid; mp 108–110 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1744.48; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.83 (t, J = 7.0 Hz, 3 H, $C\underline{H}_3CH_2$), 1.18–1.30 (m, 4 H, $(C\underline{H}_2)_2$), 1.44–1.52 (m, 2 H, $OCOCH_2C\underline{H}_2$), 1.61 (s, 3 H, $CC\underline{H}_3$), 2.23–2.39 (m, 2 H, $OCOC\underline{H}_2$), 7.29 (s, 1 H, H14), 7.50–7.63 (m, 4 H, H10, H11, H12 and H15), 7.88 (dd, J = 2.4, 9.0 Hz, 1 H, H7), 8.00 (d, J = 9.0 Hz, 1 H, H8), 8.16 (s, 1 H, H13), 8.31 (d, J = 7.5 Hz, 1 H, H9), 8.85 (d, J = 2.0 Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 13.8 ($\underline{C}H_3CH_2$), 22.2 ($CH_3\underline{C}H_2CH_2$), 23.6 ($C\underline{C}H_3$), 24.2 ($CH_3CH_2CH_2\underline{C}H_2$), 31.0 ($CH_3\underline{C}H_2CH_2$), 34.7 ($CO\underline{C}H_2$), 83.7 ($\underline{C}CH_3$), 119.8 (C15), 122.1 (Ar-C), 122.2 (C12), 124.6 (C9), 125.2 (C4a), 126.6 (C5), 129.6 (C10), 129.7 (C14), 130.8 (C11), 131.7 (C8), 132.9 (C3), 134.1 (C7), 136.5 (Ar-C),

137.5 (C13), 145.1 (C9a), 146.9 (C4), 147.0 (C8a), 148.7 (C12a), 171.6 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 489.90, 491.90 was obtained for a calculated mass of 490.11, 492.11.

7.2.2.6. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl heptanoate ***(7)*** *Procedure B, yield 40%.* Off-white solid; mp 120–122 °C, ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.84 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2), 1.18–1.28 (m, 6 H, $(CH_2)_3$), 1.44–1.53 (m, 2 H, $OCOCH_2CH_2$), 1.61 (s, 3 H, CCH_3), 2.25–2.39 (m, 2 H, $OCOCH_2$), 7.29 (s, 1 H, H14), 7.51–7.63 (m, 4 H, H10, H11, H12 and H15), 7.88 (dd, *J* = 1.8, 9.0 Hz, 1 H, H7), 8.00 (d, *J* = 9.0 Hz, 1 H, H8), 8.16 (s, 1 H, H13), 8.31 (d, *J* = 7.8 Hz, 1 H, H9), 8.85 (d, *J* = 2.4 Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 14.0 (CH_2CH_3), 22.4 (CH_2), 23.6 (CCH_3), 24.5 (CH_2), 28.7 (CH_2), 31.4 (CH_2), 34.8 ($COCH_2$), 83.7 (CCH_3), 119.8 (C15), 122.1 (Ar-C), 122.3 (C12), 124.6 (C9), 125.2 (C4a), 126.6 (C5), 129.7 (C10 and C14), 130.8 (C11), 131.7 (C8), 132.9 (C3), 134.1 (C7), 136.8, 145.2 (C9a), 146.9 (C4), 147.0 (C8a), 148.7 (C12a), 171.6 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 504.00, 505.90 was obtained for a calculated mass of 504.12, 506.12.

7.2.2.7. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl octanoate ***(8)*** *Procedure B, yield 45%.* Off-white solid, mp 121–123 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1743.95; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.82 (t, *J* = 7.5 Hz, 3 H, CH_3CH_2), 1.14–1.31 (m, 8 H, $(CH_2)_4$), 1.44–1.54 (m, 2 H, $OCOCH_2CH_2$), 1.61 (s, 3 H, CCH_3), 2.24–2.38 (m, 2 H, $OCOCH_2$), 7.29 (s, 1 H, H14), 7.51–7.62 (m, 4 H, H10, H11, H12 and H15), 7.88 (dd, *J* = 2.0, 9.0 Hz, 1 H, H7), 8.00 (d, *J* = 9.0 Hz, 1 H, H8), 8.15 (s, 1 H, H13), 8.31 (d, *J* = 8.0 Hz, 1 H, H9), 8.84 (d, *J* = 2.0 Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 14.0 (CH_3CH_2), 22.5 ($CH_3CH_2CH_2$), 23.6 (CCH_3), 24.5 (CH_3CH_2), 28.8 ($COCH_2CH_2$), 28.9 ($COCH_2CH_2$), 31.6 (CH_2), 34.7 (CH_2), 83.7 (CCH_3), 119.7 (C15), 122.1 (Ar-C), 122.2 (C12), 124.6 (C9), 125.2 (C4a) , 126.6 (C5), 129.68 (C10), 129.69 (C14), 130.7 (C11), 131.7 (C8), 132.9 (C3), 134.1 (C7), 136.7 (Ar-C), 137.5 (C13), 145.1 (C9a), 146.9 (C4), 147.0 (C8a), 148.7 (Ar-C), 171.6 (C=O). **ESI-MS** *m/z* of $[M]^+$ 517.70, 519.70 was obtained for a calculated mass of 517.13, 519.13.

7.2.2.8. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl nonanoate ***(9)*** *Procedure B, yield 67%.* Off-white solid, mp 81–82 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1745.73; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.85 (m, 3 H, CH_3CH_2), 1.16–1.28 (m, 10 H, $(CH_2)_5$), 1.44–1.52 (m, 2 H, $OCOCH_2CH_2$), 1.60 (s, 3 H, CCH_3), 2.26–2.40 (m, 2 H, $OCOCH_2$), 7.30 (t, *J* = 1.2 Hz, 1 H, H14), 7.51–7.63 (m, 4 H, H10, H11, H12 and H15), 7.88 (dd, *J* = 1.8, 9.0 Hz, 1 H, H7), 8.00 (d, *J* = 9.0 Hz, 1 H, H8), 8.16 (d, *J* = 1.2 Hz, 1 H, H13), 8.32 (d, *J* = 7.8 Hz, 1 H, H9), 8.85 (d, *J* = 2.4 Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 14.1 (CH_3CH_2), 22.6 (CH_3CH_2), 23.5 (CH_3C), 24.5 (CH_2), 28.9 (CH_2), 29.0 (CH_2), 29.1 (CH_2), 31.7 ($CH_3CH_2CH_2$), 34.7 ($COCH_2$), 83.5 (CCH_3), 119.7 (C15), 122.1 (Ar-C), 122.2 (C12), 124.6 (C9), 125.1 (C4a), 126.5 (C10), 129.5 (C15), 129.7 (C10, C14), 130.8 (C11), 131.6 (C8), 132.7 (C3), 134.1 (C7), 136.6 (Ar-C), 137.4 (C13), 145.0 (C9a), 146.8 (C4), 146.9 (C8a), 148.5 (C12a), 171.7 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 531.60, 533.60 was obtained for a calculated mass of 531.15, 533.15.

7.2.2.9. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl tetradecanoate ***(10)*** *Procedure B, yield 33%.* Off-white solid, mp 77–79 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.82–0.88 (m, 3 H, CH_3CH_2), 1.15–1.38 (m, 20 H, $CH_3(CH_2)_{10}$), 1.40–1.52 (m, 2 H, CH_2CH_2CO), 1.59 (s, 3 H, CCH_3), 2.25–2.38 (m, 2 H, $COCH_2$), 7.29 (s, 1 H, Ar-H), 7.40–7.68 (m, 4 H, Ar-H), 7.87 (dd, *J* = 2.0, 9.0 Hz, 1 H, Ar-H), 7.99 (d, *J* = 9.0 Hz, 1 H, Ar-H), 8.18 (s, 1 H, Ar-H), 8.30 (d, *J* = 7.5 Hz, 1 H, Ar-H), 8.83 (d, *J* = 1.9 Hz, 1 H, Ar-H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 14.1 (CH_3CH_2), 22.7 (CH_3CH_2), 23.6 (CH_3C), 24.5 (CH_2), 28.9 (CH_2), 29.2 (CH_2), 29.33 (CH_2), 29.37 (CH_2), 29.47 (CH_2), 29.53 (CH_2), 29.60 (CH_2), 29.63 (CH_2), 31.9 (CH_2), 34.7 (CH_2), 83.6 (CH_3C), 119.8 (Ar-C), 122.13 (Ar-C), 122.19 (Ar-C), 124.6 (Ar-C), 125.1 (Ar-C), 126.5 (Ar-C), 129.36 (Ar-C), 129.67 (Ar-C), 130.7 (Ar-C), 131.6 (Ar-C), 132.8 (Ar-C), 134.1 (Ar-C), 134.6 (Ar-C), 145.0 (Ar-C), 146.8 (Ar-C), 147.0 (Ar-C), 148.6 (Ar-C), 171.7 (CaO). **ESI-MS** *m/z* of $[M+H]^+$ 602.10, 603.90 was obtained for a calculated mass of 602.23, 604.23.

7.2.2.10. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl pentadecanoate ***(11)*** *Procedure B, yield 12%.* White solid; mp 67–69 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.87 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2), 1.16–1.33 (m, 22 H, CH_2), 1.43–1.52 (m, 2 H, $COCH_2CH_2$), 1.60 (s, 3 H, CCH_3), 2.27–2.40 (m, 2 H, $COCH_2$), 7.30 (s, 1 H, H14), 7.52–7.63 (m, 4 H, H10, H11, H12 and H15), 7.88 (dd, *J* = 1.8, 9.0, Hz, 1 H, H7), 8.00 (d, *J* = 9.0 Hz, 1 H, H8), 8.16 (s, 1 H, H13), 8.32 (d, *J* = 9.0 Hz, 1 H, H9), 8.85 (d, *J* = 2.0 Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 14.0 (CH_3CH_2), 22.7 (CH_3CH_2), 23.5 (CH_2), 24.5 (CH_3C), 28.9 (CH_2), 29.2 (CH_2), 29.3 (CH_2), 29.4 (CH_2), 29.5 (CH_2), 29.61 (CH_2), 29.64 (CH_2), 29.7 (CH_2), 31.9 ($COCH_2CH_2$), 34.7 ($COCH_2CH_2$), 83.5 (CH_3C), 119.7 (C15), 122.1 (Ar-C), 122.2 (C12), 124.6 (C9), 125.1 (C4a), 126.5 (C5), 129.64 (C10), 129.68 (C14), 130.8 (C11), 131.6 (C8), 132.8 (C3), 134.1 (C7), 136.6 (Ar-C), 137.5 (C13), 145.0 (C9a), 146.8 (C4), 146.9 (C8a), 148.5 (C12a), 171.7 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 616.40, 618.50 was obtained for a calculated mass of 616.25, 618.25.

7.2.2.11. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl dimethylcarbamate ***(12)*** *Procedure B, yield 55%.* white solid, mp 241–243 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.53 (s, 3 H, CCH_3), 2.73 (s, 3 H, CH_3N), 3.03 (s, 3 H, CH_3N), 7.26 (s, 1 H, Ar-H). 7.45–7.62 (m, 4 H, Ar-H), 7.85 (dd, *J* = 2.0, 9.0 Hz, 1 H, Ar-H), 7.98 (s, 1 H, Ar-H), 8.0 (d, *J* = 2.5 Hz, 1 H, Ar-H), 8.29 (d, *J* = 7.1 Hz, 1 H, Ar-H), 8.83 (d, *J* = 2.0 Hz, 1 H, Ar-H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 24.11 (CH_3C), 36.3 (NCH_3), 83.3 (CH_3C), 119.8 (Ar-C), 121.9 (Ar-C), 122.0 (Ar-C), 124.6 (Ar-C), 125.3 (Ar-C), 126.5 (Ar-C), 129.3 (Ar-C), 129.5 (Ar-C), 130.6 (Ar-C), 131.6 (Ar-C), 133.8 (Ar-C), 134.5 (Ar-C), 136.4 (Ar-C), 137.4 (Ar-C), 144.1 (Ar-C), 146.5 (Ar-C), 146.8 (Ar-C), 149.2 (Ar-C), 153.5 (C=O). **ESI-MS** *m/z of* $[M+H]^+$ 462.90, 464.70 was obtained for a calculated mass of 463.07, 465.07.

7.2.2.12. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl 3,3,3-trifluoropropanoate ***(13)*** *Procedure B, yield 27%.* Off-white solid; mp 195–206 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1766.03; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.67 (s, 3 H, CCH_3), 3.05–3.25 (m, 2 H, CH_2CF_3), 7.31 (s, 1 H, H14), 7.49–7.64 (m, 4 H, H10, H11, H12 and H15), 7.90 (dd, *J* = 2.0, 9.0 Hz, 1 H, H7), 8.01 (d, *J* = 9.0 Hz, 1 H, H8), 8.06 (s, 1 H, H13), 8.31 (d, *J* = 8.0 Hz, 1 H, H9), 8.84 (d, *J* = 2.0 Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 23.9 (CH_3), 39.8 (CF_3CH_2), 40.0 (CF_3CH_2), 40.3 (CF_3CH_2), 40.5 (CF_3CH_2), 85.5 (CH_3C), 119.7 (C15), 121.9 (Ar-C), 122.4 (C12), 122.5 (Ar-C), 124.0 (Ar-C), 124.8 (C9), 125.2 (C4a), 126.6 (C5), 129.8 (C10, C14), 130.2 (C10), 131.0 (C11), 131.8 (C8), 132.2 (Ar-C), 134.5 (C7), 136.7 (Ar-C), 137.3 (C13), 145.0 (C9a), 147.1 (Ar-C), 147.14 (Ar-C), 147.4 (Ar-C), 161.9 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 501.80, 503.70 was obtained for a calculated mass of 502.03, 504.03.

7.2.2.13. 2-Bromo-6-(1H-imidazol-1-yl)-7-methyl-7H-indeno[2,1-c] quinolin-7-yl 2-(tert butoxycarbonylamino)acetate ***(14)***. A mixture of compound **1** (1.0 g, 2.55 mmol), Boc-glycine-*N*-hydroxysuccinimide ester (2.08 g, 7.66 mmol) in dry THF (80 mL) was cooled to −78 °C then *n*-BuLi (4.5 mL, 3.82 mmol) was added, reaction mixture stirred for 30 min at same temperature and then allowed to warm at room temperature and stirred for 1 h, color of the reaction changed from yellow to dark red. Reaction was quenched with aqueous ammonium chloride. Reaction mixture was diluted with ethyl acetate (100 mL), washed with brine (3 × 50 mL) and dried over anhydrous sodium sulfate. Organic layer

was filtered and solvents were evaporated under reduced pressure to obtain a gum as a crude product. Crude product was purified by column chromatography (silica gel 100–200 mesh, eluent: 2% methanol in DCM) to give pure compound **14** (0.38 g, 28%) as an off-white solid; mp 197–198 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1770.99; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.37 (s, 9 H, Boc), 1.63 (s, 3 H, CCH_3), 3.83 (dd, J = 6.0, 18.5 Hz, 1 H, CH_2NHBoc), 3.93 (dd, J = 6.0, 18.5 Hz, 1 H, CH_2NHBoc), 4.84 (bs, 1 H, NH, D_2O exchangeable), 7.30 (s, 1 H, H14), 7.52–7.63 (m, 4 H, H10, H11, H12 and H15), 7.89 (dd, J = 2.0, 9.0 Hz, 1 H, H7), 8.00 (d, J = 9.0 Hz, 1 H, H8), 8.10 (s, 1 H, H13), 8.30 (d, J = 7.5 Hz, 1 H, H9), 8.84 (d, J = 2.0 Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 23.7 (CH_3C), 28.2 (NHBoc), 43.0 ($COCH_2$), 80.1 ($(CH_3)_3C$), 84.8 (CH_3C), 119.9 (C15), 122.4 (Ar-C), 122.7 (C12), 124.7 (C9), 125.2 (C4a) , 126.6 (C5), 129.8 (C10), 129.9 (C15), 131.9 (C8), 132.7 (C3), 134.3 (C7), 136.7 (Ar-C), 137.6 (C13), 145.2(C9a), 147.1 (C8a), 147.9 (C12a), 155.5 ($CO(CH_3)_3$), 168.4 (C=O). **ESI-MS** m/z of $[M + H]^+$ 548.70, 550.70 was obtained for a calculated mass of 549.11, 551.11.

*7.2.2.14. 2-Bromo-6-(1H-imidazol-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-acetyl oxime **(16)** Procedure B, yield 47%.* Light-brown solid; mp 243–245 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1783.56; ^{1}H-NMR (600 MHz, DMSO-d_6): δ 2.26 (s, 3 H, CH_3CO), 7.08 (s, 1 H, H14), 7.71 (t, J = 7.6 Hz, 1 H, H10), 7.75–7.81 (m, 2 H, H11 and H15), 8.00 (d, J = 9.0 Hz, 1 H, H8), 8.07 (dd, J = 1.8, 9.0 Hz, 1 H, H7), 8.32 (s, 1 H, H13), 8.45 (d, J = 7.5 Hz, 1 H, H12), 8.62 (d, J = 7.8 Hz, 1 H, H9), 8.88 (d, J = 1.8 Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, DMSO-d_6): δ 19.1 (CH_3CO), 119.9 (C15), 120.7 (Ar-C), 122.1 (Ar-C), 123.4 (Ar-C), 125.5 (C9), 126.2 (C5), 128.0 (C14), 128.9 (C12a), 130.1 (C12), 131.6 (C8 and C11), 133.3 (C10), 135.2 (C7), 137.8 (C9a), 137.9 (C13), 144.2 (Ar-C), 146.9 (C8a), 148.3 (C4), 154.5 (C3a), 169.2 (C=O). **ESI-MS** m/z of $[M + H]^+$ 432.70, 434.80 was obtained for a calculated mass of 433.03, 435.03.

*7.2.2.15. 2-Bromo-6-(1H-imidazol-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-propionyl oxime **(17)** Procedure B, yield 40%.* Light-brown solid; mp 246–248 °C. ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.11 (t, J = 7.4 Hz, 3 H, CH_3CH_2), 2.62 (q, J = 7.4 Hz, 2 H, CH_3CH_2), 7.09 (s, 1 H, H14), 7.54–7.52 (m, 1 H, H11), 7.73–7.82 (m, 2 H, H10 and H15), 7.99 (d, J = 9.0 Hz, 1 H, H8), 8.06 (dd, J = 1.4, 10.5 Hz, 1 H, H7), 8.32 (s, 1 H, H13), 8.43 (d, J = 7.4 Hz, 1 H, H9), 8.61 (d, J = 7.7 Hz, 1 H, H12), 8.86 (s, 1 H, H5). ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ 8.2 (CH_3CH_2), 24.6 (CH_3CH_2), 119.6 (Ar-C), 120.1 (Ar-C), 121.7 (Ar-C), 122.9 (Ar-C), 125.0 (Ar-C), 125.8 (Ar-C), 127.6 (Ar-C), 128.4 (Ar-C), 129.7 (Ar-C), 131.1 (Ar-C), 131.2 (Ar-C), 132.9 (Ar-C), 134.8 (Ar-C), 137.42 (Ar-C), 137.44 (Ar-C), 143.8 (Ar-C), 146.4 (Ar-C), 147.8 (Ar-C), 154.1 (Ar-C), 171.8 (C=O). **ESI-MS** m/z of $[M + H]^+$ 446.70, 448.80 was obtained for a calculated mass of 447.04, 449.04.

*7.2.2.16. 2-Bromo-6-(1H-imidazol-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-butyryl oxime **(18)** Procedure A, yield 43%.* Yellow solid; mp 190–191 °C, ^{1}H-NMR (600 MHz, DMSO-d_6): δ 0.96 (t, J = 7.2 Hz, 3 H, CH_3CH_2), 1.58–1.67 (m, 2 H, CH_3CH_2), 2.58 (t, J = 7.2 Hz, 2 H, $COCH_2CH_2$), 7.08 (t, J = 1.2 Hz, 1 H, H14), 7.68 (t, J = 7.8 Hz, 1 H, H11), 7.74 (dt, J = 1.2, 7.8 Hz, 1 H, H10), 7.77 (t, J = 1.2 Hz, 1 H, H15), 7.97 (d, J = 9.0 Hz, 1 H, H8), 8.03 (dd, J = 1.8, 9.0 Hz, 1 H, H7), 8.30 (d, J = 1.2 Hz, 1 H, H13), 8.39 (dd, J = 0.6, 7.2 Hz, 1 H, H9), 8.54 (d, J = 7.8 Hz, 1 H, H12), 8.80 (d, J = 1.8 Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, DMSO-d_6): δ 13.9 (CH_3CH_2), 18.1 (CH_3CH_2), 33.8 ($COCH_2$), 120.5 (C15), 121.3 (Ar-C), 122.7 (Ar-C), 124.0 (Ar-C), 126.1 (C9), 126.6 (C5), 128.7 (C14), 129.6 (C12a), 130.7 (C12), 132.2 (C8 and C11), 134.0 (C10), 135.1 (Ar-C), 135.9 (C7), 138.4 (C13), 138.5 (C9a), 144.9 (Ar-C), 147.6 (C8a), 148.9 (Ar-C), 155.3 (C3a), 171.8 (C=O). **ESI-MS** m/z of $[M + H]^+$460.80, 462.70 was obtained for a calculated mass of 461.06, 463.06.

*7.2.2.17. 2-Bromo-6-(1H-imidazol-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-pentanoyl oxime **(19)** Procedure A, yield 60%.* Light-brown solid; mp 230–232 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1765.72; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.94 (t, J = 7.3 Hz, 3 H, CH_3CH_2), 1.39–1.44 (m, 2 H, CH_3CH_2), 1.63–1.72 (m, 2 H, $CH_3CH_2CH_2$), 2.57 (t, J = 7.5 Hz, 2 H, $COCH_2$), 7.22 (d, J = 0.9 Hz, 1 H, H14), 7.59–7.71 (m, 3 H, H10, H11 and H15), 7.90 (dd, J = 2.0, 9.0 Hz, 1 H, H7), 7.99 (d, J = 9.0 Hz, 1H, H8), 8.23 (s, 1 H, H13), 8.29 (d, J = 7.7 Hz, 1 H, H9), 8.55 (d, J = 7.4 Hz, 1 H, H12), 8.74 (d, J = 2.0 Hz, 1 H, H5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 13.7 (CH_3CH_2), 22.1 (CH_3CH_2), 26.4 ($CH_3CH_2CH_2$), 31.9 ($COCH_2$), 119.6 (Ar-C), 120.4 (Ar-C), 122.5 (Ar-C), 123.8 (Ar-C), 124.3 (Ar-C), 126.1 (Ar-C), 128.8 (Ar-C), 129.5 (Ar-C), 130.7 (Ar-C), 131.4 (Ar-C), 131.8 (Ar-C), 132.8 (Ar-C), 135.0 (Ar-C), 137.9 (Ar-C), 138.6 (Ar-C), 144.3 (Ar-C), 147.4 (Ar-C), 148.6 (Ar-C), 154.4 (Ar-C), 172.1 (C=O). **ESI-MS** m/z of $[M + H]^+$ 474.90, 476.90 was obtained for a calculated mass of 475.07, 477.07.

*7.2.2.18. 2-Bromo-6-(1H-imidazol-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-hexanoyl oxime **(20)** Procedure A, yield 46%.* Yellow solid; mp, compound decomposed above 151 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.92 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.33–1.43 (m, 4 H, 2 × CH_2), 1.68–1.75 (m, 2 H, $COCH_2CH_2$), 2.57 (t, J = 7.5 Hz, 2 H, $COCH_2$), 7.25 (s, 1 H, H14), 7.59–7.63 (m, 1 H, H11), 7.68–7.73 (m, 2 H, H10 and H15), 7.90 (dd, J = 2.0, 9.0 Hz, 1 H, H7), 7.99 (d, J = 9.0 Hz, 1 H, H8), 8.26–8.32 (m, 2 H, H9 and H13), 8.54 (d, J = 7.5 Hz, 1 H, H12), 8.73 (d, J = 2.0 Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 13.9 (CH_3), 22.4 (CH_2), 24.1 (CH_2), 31.1 (CH_2), 32.2 ($COCH_2$), 119.7 (C15), 120.7 (Ar-C), 122.7 (Ar-C), 124.2 (Ar-C), 124.6 (C9), 126.3 (C5), 128.5 (C14), 129.8 (C12a), 130.9 (C12), 131.5 (C11), 132.0 (C8), 132.9 (C10), 135.2 (C7), 137.8 (C13), 138.9 (C9a), 144.6 (Ar-C), 147.7 (C8a), 148.9 (C4), 154.6 (C3a), 172.1 (C=O). **ESI-MS** m/z of $[M + H]^+$ 489.00, 490.90 was obtained for a calculated mass of 489.09, 491.09.

*7.2.2.19. 2-Bromo-6-(1H-imidazol-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-heptanoyl oxime **(21)** Procedure A, yield 58%.* Yellow solid; mp, compound decomposed above 153 °C. ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 0.89 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.24–1.45 (m, 6 H, $(CH_2)_3$), 1.62–1.75 (m, 2 H, $COCH_2CH_2$), 2.56 (t, J = 7.5 Hz, 2 H, $COCH_2CH_2$), 7.22 (s, 1 H, Ar-H), 7.57–7.64 (m, 1 H, Ar-H), 7.65–7.75 (m, 2 H, Ar-H), 7.90 (dd, J = 2.0, 9.0 Hz, 1 H, H7), 7.80 (d, J = 9.0 Hz, 1 H, H8), 8.24 (s, 1 H, Ar-H), 8.31 (d, J = 7.6 Hz, 1 H, Ar-H), 8.55 (d, J = 7.4 Hz, 1 H, Ar-H), 8.75 (d, J = 2.0 Hz, 1 H, H5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 14.0 (CH_3), 22.5 (CH_2), 24.4 (CH_2), 28.6 (CH_2), 31.4 (CH_2), 32.2 ($COCH_2$), 119.6 (Ar-C), 120.6 (Ar-C), 122.6 (Ar-C), 124.1 (Ar-C), 124.5 (Ar-C), 126.3 (Ar-C), 128.9 (Ar-C), 129.7 (Ar-C), 130.8 (Ar-C), 131.5 (Ar-C), 131.9 (Ar-C), 132.9 (Ar-C), 135.2 (Ar-C), 137.9 (Ar-C), 138.8 (Ar-C), 144.5 (Ar-C), 147.6 (Ar-C), 148.8 (Ar-C), 154.6 (Ar-C), 172.2 (C=O). **ESI-MS** m/z of $[M + H]^+$ 503.10, 505.00 was obtained for a calculated mass of 503.10, 505.10.

*7.2.2.20. 2-Bromo-6-(1H-imidazol-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-nonanoyl oxime **(22)** Procedure A, yield 55%.* Yellow solid; mp 147–149 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.87 (t, J = 7.0 Hz, 3 H, CH_3CH_2), 1.20–1.35 (m, 10 H, $CH_3(CH_2)_5$), 1.68–1.75 (m, 2 H, CH_2CH_2), 2.58 (t, J = 7.4 Hz, 2 H, $COCH_2CH_2$), 7.27 (s, 1 H, H14), 7.60–7.65 (m, 1 H, H11), 7.70–7.75 (m, 2 H, H15 and H10), 7.92 (dd, J = 2.0, 9.0 Hz, 1 H, H7), 8.00 (d, J = 9.0 Hz, 1 H, H8), 8.31 (s, 1 H, H9), 8.37 (s, 1 H, H13), 8.55 (d, J = 7.4 Hz, 1 H, H12), 8.76 (d, J = 2.0 Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 14.1 (CH_3CH_2), 22.6 (CH_2), 24.5 (CH_2), 29.0 (CH_2), 29.09 (CH_2), 29.25 (CH_2), 31.8 (CH_2), 32.2 ($COCH_2$), 120.0 (C15), 120.6 (Ar-C), 122.9 (Ar-C), 124.31 (Ar-C), 124.65 (C9), 126.2 (C5), 129.7 (C12a), 130.9 (C12), 131.5 (C11), 132.0 (C8), 132.9 (C10), 135.2 (C7), 137.5 (C13), 138.8 (C9a), 147.6 (C8a), 149.0 (C4), 154.6 (C3a), 172.2 (C=O). **ESI-MS** m/z of $[M + H]^+$ 531.10, 533.10 was obtained for a calculated mass of 531.13, 533.13.

7.2.2.21. 2-Bromo-6-(1H-imidazol-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-decanoyl oxime ***(23)*** *Procedure A, yield 47%.* Yellow solid; mp 147–148 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.86 (t, $J = 6.7$ Hz, 3 H, $C\underline{H}_3CH_2$), 1.17–1.42 (m, 12 H, $CH_3(C\underline{H}_2)_6$), 1.61–1.77 (m, 2 H, $CH_2C\underline{H}_2$), 2.56 (t, $J = 7.5$ Hz, 2 H, $COC\underline{H}_2CH_2$), 7.22 (s, 1 H, H14), 7.58–7.65 (m, 1 H, H11), 7.69 (d, $J = 1.0$ Hz, 1 H, H15), 7.70–7.74 (m, 1 H, H10), 7.91 (dd, $J = 2.0$, 9.0 Hz, 1 H, H7), 7.99 (d, $J = 9.0$ Hz, 1 H, H8), 8.24 (s, 1 H, H13), 8.31 (d, $J = 7.8$ Hz, 1 H, H9), 8.55 (d, $J = 7.4$ Hz, 1 H, H12), 8.75 (d, $J = 2.0$ Hz, 1 H, H5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 14.1 ($\underline{C}H_3CH_2$), 22.7 ($CH_3\underline{C}H_2$), 24.4 ($\underline{C}H_2$), 28.95 ($\underline{C}H_2$), 29.28 ($\underline{C}H_2$), 31.85 ($\underline{C}H_2$), 32.24 ($CO\underline{C}H_2$), 119.6 (Ar-C), 120.7 (Ar-C), 122.6 (Ar-C), 124.1 (Ar-C), 125.6 (Ar-C), 126.3 (Ar-C), 129.0 (Ar-C), 129.7 (Ar-C), 130.9 (Ar-C), 131.4 (Ar-C), 131.9 (Ar-C), 132.9 (Ar-C), 135.2 (Ar-C), 137.9 (Ar-C), 138.8 (Ar-C), 144.6 (Ar-C), 147.7 (Ar-C), 148.9 (Ar-C), 154.6 (Ar-C), 172.2 (C=O). **ESI-MS** *m/z* of $[M + H]^+$ 544.70, 546.70 was obtained for a calculated mass of 545.15, 547.15.

7.2.2.22. 2-Bromo-6-(1H-imidazol-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-tetradecanoyl oxime ***(24)*** *Procedure A, yield 26%.* Yellow solid; mp 240–242 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1769.50; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.86 (t, $J = 6.6$ Hz, 3 H, $C\underline{H}_3CH_2$), 1.20–1.31 (m, 18 H, $CH_3(C\underline{H}_2)_9$), 1.34–1.41 (m, 2 H, $COCH_2CH_2C\underline{H}_2$), 1.65–1.70 (m, 2 H, $COCH_2C\underline{H}_2$), 2.56 (t, $J = 7.5$ Hz, 2 H, $COC\underline{H}_2$), 7.22 (s, 1 H, H14), 7.61 (t, $J = 7.6$ Hz, 1 H, H11), 7.67 (d, $J = 1.2$ Hz, 1 H, H15), 7.72 (dd, $J = 0.8$, 7.56 Hz, 1 H, H10), 7.90 (dd, $J = 2.0$, 9.0 Hz, 1 H, H7), 7.99 (d, $J = 9.0$ Hz, 1 H, H8), 8.24 (s, 1 H, H13), 8.30 (d, $J = 7.8$ Hz, 1 H, H9), 8.55 (d, $J = 7.5$ Hz, 1 H, H12), 8.74 (d, $J = 2.0$ Hz, 1 H, H5). ^{13}C-NMR (126.8 MHz, $CDCl_3$): δ 13.5 ($\underline{C}H_3CH_2$), 24.6 ($CH_3\underline{C}H_2$), 24.9 ($\underline{C}H_2$), 29.0 ($\underline{C}H_2$), 29.2 ($\underline{C}H_2$), 29.3 ($\underline{C}H_2$), 29.35 ($\underline{C}H_2$), 29.4 ($\underline{C}H_2$), 29.5 ($\underline{C}H_2$), 29.69 ($\underline{C}H_2$), 29.70 ($\underline{C}H_2$), 32.0 ($COCH_2\underline{C}H_2$), 32.3 ($CO\underline{C}H_2CH_2$), 119.7 (C15), 120.9 (Ar-C), 122.7 (Ar-C), 124.2 (Ar-C), 124.6 (C9), 126.4 (C5), 128.9 (C14), 129.9 (Ar-C), 130.9 (C12), 131.5 (C11), 132.1 (C8), 132.9 (C10), 135.2 (C7), 138.0 (C13), 139.0 (Ar-C), 144.8 (Ar-C), 147.9 (Ar-C), 148.9 (Ar-C), 154.8 (Ar-C), 172.19 (C=O). **ESI-MS** *m/z* of $[M + H]^+$ 601.20, 603.10 was obtained for a calculated mass of 601.21, 603.21.

7.2.2.23. tert-Butyl 2-((2-bromo-6-(1H-imidazol-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)carbonyl)pyrrolidine-1-carboxylate ***(25)*** *Procedure A, yield 76%.* Light-brown solid; mp 219–222 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1784.66; Rotamers in the ratio of (1:1), ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.24 (s, 4.5 H, $(C\underline{H}_3)_3C$), 1.38 (s, 4.5 H, $(C\underline{H}_3)_3C$), 1.83–1.93 (m, 3 H, $CH_2C\underline{H}_2CH_2$), 2.10–2.30 (m, 1 H, $CHC\underline{H}_2C\underline{H}_2$), 3.36–3.42 (m, 2 H, $CH_2C\underline{H}_2N$), 4.50–4.65 (m, 1 H, $NC\underline{H}CO$), 7.08 (s, 1 H, Ar-H), 7.72 (d, $J = 6.4$ Hz, 1 H, Ar-H), 7.75–7.79 (m, 2 H, Ar-H), 7.95–8.03 (m, 1 H, Ar-H), 8.04–8.10 (m, 1 H, Ar-H), 8.29–8.34 (m, 1 H, Ar-H), 8.39–8.45 (m, 1 H, Ar-H), 8.66 (d, $J = 7.6$ Hz, 1 H, Ar-H), 8.91 (s, 1 H, H5). ^{13}C-NMR (100.6 MHz, DMSO-d_6): δ 22.8, 24.0, 27.3, 27.5, 29.1, 29.8, 29.4, 45.8, 46.1, 56.9 ($N\underline{C}HCO$), 78.8 ($(CH_3)_3\underline{C}$), 119.5 (Ar-C), 120.1 (Ar-C), 121.7 (Ar-C), 122.9 (Ar-C), 125.2 (Ar-C), 125.8 (Ar-C), 127.6 (Ar-C), 128.5 (Ar-C), 129.8 (Ar-C), 131.2 (Ar-C), 133.2 (Ar-C), 134.9 (Ar-C), 137.3 (Ar-C), 137.6 (Ar-C), 143.8 (Ar-C), 146.5 (Ar-C), 148.0 (Ar-C), 152.2 (Ar-C), 153.0 (Ar-C), 155.4 (Ar-C), 161.8 (N–C=O), 170.0 (CH–$\underline{C}$=O). **ESI-MS** *m/z* of $[M + H]^+$ 587.90, 589.70 was obtained for a calculated mass of 588.12, 590.12.

7.2.2.24. 2-Bromo-6-(1H-imidazol-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-dimethylcarbamoyl oxime ***(26)*** *Procedure B, yield 49%.* Light-brown solid; mp 270–272 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1750.47; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.10 (s, 3 H, $NC\underline{H}_3$), 3.20 (s, 3 H, $NC\underline{H}_3$), 7.25 (s, 1 H, H14), 7.59 (t, $J = 7.8$ Hz, 1 H, H10), 7.67–7.73 (m, 1 H, H11), 7.84–7.91 (m, 2 H, H7 and H15), 7.99 (d, $J = 8.4$ Hz, 1 H, H8), 8.31 (d, $J = 7.8$ Hz, 1 H, H9), 8.40 (d, $J = 7.2$ Hz, 1 H, H12), 8.46 (s, 1 H, H13), 8.73 (d, $J = 1.8$ Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 36.6 ($NC\underline{H}_3$), 37.5 ($NC\underline{H}_3$), 120.1 (C15), 120.3 (Ar-C), 122.2 (Ar-C), 123.7 (Ar-C), 124.4 (C9), 126.0 (C5), 128.7 (C14), 129.3 (C12), 129.5 (C12a), 131.0 (C11), 131.7 (C8), 132.5 (C10), 134.8 (C7), 138.5 (C13), 131.1 (C9a), 144.9 (Ar-C), 147.6 (C8a), 148.3 (C4), 153.8 (C=O), 154.6 (C3a), (C=O). **ESI-MS** *m/z* of $[M + H]^+$ 461.80, 463.90 was obtained for a calculated mass of 462.05, 464.05.

7.2.2.25. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-acetyl oxime ***(28)*** *Procedure B, yield 60%.* Brown solid; mp 213–214 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1785.38; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 2.42 (s, 3 H, $C\underline{H}_3$), 3.70–3.95 (m, 8 H, piperizine-$C\underline{H}_2$), 6.64 (dd, $J = 5.5$, 7.0 Hz, 1 H, H15), 6.76 (d, $J = 8.5$ Hz, 1 H, H13), 7.48–7.56 (m, 2 H, H11 and H14), 7.58–7.65 (m, 1 H, H10), 7.73 (dd, $J = 2.0$, 9.0 Hz, 1 H, H7), 7.78 (d, $J = 9.0$ Hz, 1 H, H8), 8.20 (d, $J = 7.5$ Hz, 2 H, H9, H16), 8.22–8.26 (m, 1 H, H16), 8.40 (d, $J = 7.5$ Hz, 1 H, H12), 8.56 (d, $J = 2.0$ Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 19.6 ($CO\underline{C}H_3$), 45.4 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 113.1 (C15), 118.4 (Ar-C), 118.9 (Ar-C), 121.9 (Ar-C), 124.2 (C9), 126.1 (C5), 130.1 (C12), 130.2 (C14), 130.6 (C8), 132.3 (C10), 134.1 (C7), 140.1 (Ar-C), 148.0 (C16), 148.6 (Ar-C), 156.5 (Ar-C), 157.5 (Ar-C), 167.2 (C=O). **ESI-MS** *m/z* of $[M + H]^+$ 528.5, 530.5 was obtained for a calculated mass of 528.10, 530.10.

7.2.2.26. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-propionyl oxime ***(29)*** *Procedure B, yield 60%.* Yellow solid; mp 196–199 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1789.32; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.35 (t, $J = 7.5$ Hz, 3 H, $C\underline{H}_3$), 2.69 (q, $J = 7.5$ Hz, 2 H, $CH_3C\underline{H}_2$), 3.67–3.76 (m, 4 H, piperizine-CH_2), 3.83–3.96 (m, 4 H, piperizine-$C\underline{H}_2$), 6.62 (dd, $J = 5.0$, 7.0 Hz, 1 H, H15), 6.76 (d, $J = 8.5$ Hz, 1 H, H13), 7.47–7.55 (m, 2 H, H11 and H14), 7.60 (t, $J = 7.5$ Hz, 1 H, H10), 7.72 (dd, $J = 2.0$, 9.0 Hz, 1 H, H7), 7.78 (d, $J = 9.0$ Hz, 1 H, H8), 8.19 (d, $J = 7.5$ Hz, 1 H, H9), 8.22 (dd, $J = 1.5$, 5.0 Hz, 1 H, H16), 8.41 (d, $J = 8.0$ Hz, 1 H, H12), 8.56 (d, $J = 2.0$ Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 9.1 ($\underline{C}H_3$), 26.2 ($CO\underline{C}H_2CH_3$), 45.1 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 107.4 (C13), 113.0 (C15), 118.4 (Ar-C), 119.0 (Ar-C), 121.9 (Ar-C), 124.1 (C9), 126.1 (C5), 130.1 (C12), 130.2 (C11), 130.6 (C8), 132.2 (C10), 134.0 (C7), 137.8 (C14), 140.1 (Ar-C), 147.9 (C16 and C4), 148.5 (C8a), 156.6 (C2), 157.5 (C3a), 170.8 (C=O). **ESI-MS** *m/z* of $[M + H]^+$ 542.10, 544.10 was obtained for a calculated mass of 542.11, 544.1.

7.2.2.27. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-butyryl oxime ***(30)*** *Procedure A, yield 52%.* Brown solid; mp 190–191 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.09 (t, $J = 7.5$ Hz, 3 H, $C\underline{H}_3$), 1.82–1.95 (m, 2 H, $C\underline{H}_2CH_3$), 2.65 (t, $J = 7.5$ Hz, 2 H, $COC\underline{H}_2$), 3.67–3.78 (m, 4 H, piperizine-CH_2), 3.85–3.97 (m, 4 H, piperizine-CH_2), 6.58–6.67 (m, 1 H, H15), 6.76 (d, $J = 7.5$ Hz, 1 H, H13), 7.46–7.56 (m, 2 H, H11 and H14), 7.58–7.65 (m, 1 H, H10), 7.73 (dd, $J = 2.0$, 9.0 Hz, 1 H, H7), 7.78 (d, $J = 9.0$ Hz, 1 H, H8), 8.18–8.26 (m, 2 H, H9 and H16), 8.41 (d, $J = 7.5$ Hz, 1 H, H12), 8.57 (d, $J = 2.0$ Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 13.8 ($CH_2\underline{C}H_3$), 18.4 ($\underline{C}H_2CH_3$), 34.7 ($CO\underline{C}H_2$), 45.3 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 113.0 (C15), 118.4 (Ar-C), 119.0 (Ar-C), 122.0 (Ar-C), 124.1 (C9), 126.1 (C5), 130.1 (C12), 130.2 (C11), 130.6 (C8), 132.2 (C10), 134.0 (C7), 140.1 (Ar-C), 147.9 (Ar-C), 148.5 (C16), 157.5 (Ar-C), 169.8 (C=O). **ESI-MS** *m/z* of $[M + H]^+$ 556.10, 558.10 was obtained for a calculated mass of 556.13, 558.13.

7.2.2.28. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-pentanoyl oxime ***(31)*** *Procedure A, yield 76%.* Yellow solid; mp 167–169 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.99 (t, $J = 7.2$ Hz, 3 H, $CH_2C\underline{H}_3$), 1.45–1.55 (m, 2 H, $C\underline{H}_2CH_3$), 1.76–1.87 (m, 2 H, $C\underline{H}_2CH_2CH_3$), 2.67 (t, $J = 7.2$ Hz, 2 H, $COC\underline{H}_2$), 3.70–3.76 (m, 4 H, piperazine-$C\underline{H}_2$), 3.85–3.94 (m, 4 H, piperazine-$C\underline{H}_2$), 6.60–6.65 (m, 1 H, H15), 6.76 (d, $J = 7.8$ Hz, 1 H, H13),

7.47–7.54 (m, 2 H, H11 and H14), 7.59–7.64 (m, 1 H, H10), 7.73 (dd, $J = 1.8$, 9.0 Hz, 1 H, H7), 7.78 (d, $J = 9.0$ Hz, 1 H, H8), 8.20 (d, $J = 7.8$ Hz, 1 H, H9), 8.22–8.50 (m, 1 H, H16), 8.41 (d, $J = 7.2$ Hz, 1 H, H12), 8.56 (d, $J = 2.4$ Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 13.7 ($CH_2\underline{C}H_3$), 22.3 ($CH_2\underline{C}H_2CH_3$), 26.9 ($\underline{C}H_2CH_2CH_3$), 32.5 ($CO\underline{C}H_2CH_2$), 45.3 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 113.0 (C13), 118.4 (Ar-C), 119.1 (Ar-C), 122.0 (Ar-C), 124.1 (C9), 126.1 (C5), 130.05 (C12), 130.17 (Ar-C), 130.19 (C11), 130.6 (C8), 132.2 (C10), 134.0 (C7), 137.9 (Ar-C), 140.1 (Ar-C), 147.9 (C16), 148.5 (Ar-C), 156.6 (Ar-C), 157.5 (Ar-C), 170.0 (C=O). **ESI-MS** m/z of $[M + H]^+$ 570.60, 572.50 was obtained for a calculated mass of 570.15, 572.14.

*7.2.2.29. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno [2,1-c]quinolin-7-one O-hexanoyl oxime **(32)** Procedure A, yield 58%.* Green solid; mp 171–172 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1780.38; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.93 (t, $J = 7.2$ Hz, 3 H, $CH_2\underline{C}H_3$), 1.35–1.49 (m, 4 H, $CH_2\underline{C}H_2\underline{C}H_2CH_3$), 1.80–1.87 (m, 2 H, $COCH_2\underline{C}H_2\underline{C}H_2$), 2.65 (t, $J = 7.2$ Hz, 2 H, $CO\underline{C}H_2CH_2$), 3.68–3.78 (m, 4 H, piperazine-$\underline{C}H_2$), 3.85–3.94 (m, 4 H, piperazine-$\underline{C}H_2$), 6.59–6.65 (m, 1 H, H15), 6.74 (d, $J = 8.4$ Hz, 1 H, H13), 7.47–7.55 (m, 2 H, H11 and H14), 7.59–7.64 (m, 1 H, H10), 7.72 (dd, $J = 2.0$, 9.0 Hz, 1 H, H7), 7.78 (d, $J = 9.0$ Hz, 1 H, H8), 8.20 (d, $J = 7.8$ Hz, 1 H, H9), 8.21–8.24 (m, 1 H, H16), 8.40 (d, $J = 7.2$ Hz, 1 H, H12), 8.56 (d, $J = 2.4$ Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 13.9 ($CH_2\underline{C}H_3$), 22.3 ($\underline{C}H_2CH_3$), 24.6 ($\underline{C}H_2CH_2CH_3$), 31.3 ($\underline{C}H_2\underline{C}H_2$), 32.8 ($CO\underline{C}H_2$), 45.3 (piperizine-$\underline{C}H_2$), 49.5 (piperizine-$\underline{C}H_2$), 113.0 (C15), 118.4 (Ar-C), 119.1 (Ar-C), 121.9 (Ar-C), 124.1 (C9), 126.1 (C5), 130.05 (C12), 130.16 (Ar-C), 130.19 (C10), 130.6 (C8), 132.2 (C11), 134.0 (C7), 137.5 (C14), 140.1 (Ar-C), 147.8 (C16), 148.5 (Ar-C), 156.6 (Ar-C), 157.5 (Ar-C), 159.9 (Ar-C), 170.0 (C=O). **ESI-MS** m/z of $[M + H]^+$ 583.90, 585.90 was obtained for a calculated mass of 584.16, 586.16.

*7.2.2.30. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno [2,1-c]quinolin-7-one O-heptanoyl oxime **(33)** Procedure A, yield 96%.* Yellow solid; mp, compound decomposed above 300 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1778.28; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.0$ Hz, 3 H, $CH_2\underline{C}H_3$), 1.14–1.42 (m, 4 H, $\underline{C}H_2\underline{C}H_2CH_3$), 1.43–1.48 (m, 2 H, $\underline{C}H_2CH_2CH_2CH_3$), 1.50–1.84 (m, 2 H, $COCH_2\underline{C}H_2CH_2$), 2.65 (t, $J = 7.5$ Hz, 2 H, $CO\underline{C}H_2CH_2$), 3.68–3.74 (m, 4 H, piperizine-CH_2), 3.84–3.90 (m, 4 H, piperizine-CH_2), 6.00–6.64 (m, 1 H, Ar-H), 6.74 (d, $J = 8.6$ Hz, 1 H, Ar-H), 7.45–7.56 (m, 2 H, Ar-H), 7.58–7.65 (m, 1 H, Ar-H), 7.73 (dd, $J = 2.0$, 9.0 Hz, 1 H, H7), 7.78 (d, $J = 9.0$ Hz, 1 H, H8), 8.21 (d, $J = 7.2$ Hz, 2 H, Ar-H), 8.41 (d, $J = 7.8$ Hz, 1 H, Ar-H), 8.57 (d, $J = 2.0$ Hz, 1 H, H5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 14.0 ($\underline{C}H_3$), 22.5 ($\underline{C}H_2$), 24.8 ($\underline{C}H_2$), 28.8 ($\underline{C}H_2$), 31.4 ($\underline{C}H_2$), 32.8 ($CO\underline{C}H_2$), 45.2 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 107.2 (Ar-C), 113.1 (Ar-C), 118.3 (Ar-C), 119.0 (Ar-C), 121.9 (Ar-C), 124.1 (Ar-C), 126.1 (Ar-C), 130.03 (Ar-C), 130.14 (Ar-C), 130.53 (Ar-C), 132.2 (Ar-C), 134.0 (Ar-C), 137.4 (Ar-C), 140.1 (Ar-C), 147.81 (Ar-C), 147.93 (Ar-C), 148.5 (Ar-C), 156.6 (Ar-C), 157.4 (Ar-C), 159.8 (Ar-C), 170.0 (C=O). **ESI-MS** m/z of $[M + H]^+$ of 598.50, 600.50 was obtained for calculated mass of 598.18, 600.18.

*7.2.2.31. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-one O-nonanoyl oxime **(34)** Procedure A, yield 65%.* Green solid; mp 159–160 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1776.52; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.5$ Hz, 3 H, $CH_2\underline{C}H_3$), 1.22–1.50 (m, 10 H), 1.79–1.88 (m, 2 H), 2.66 (t, $J = 7.5$, 2 H, $CO\underline{C}H_2$), 3.70–3.80 (m, 4 H, piperizine-CH_2), 3.83–3.95 (m, 4 H, piperizine-CH_2), 6.60–6.67 (m, 1 H, H15), 6.75 (d, $J = 8.0$ Hz, 1 H, H13), 7.48–7.55 (m, 2 H, H11 and H14), 7.58–7.65 (m, 1 H, H10), 7.72 (dd, $J = 2.5$, 8.5 Hz, 1 H, H7), 7.78 (d, $J = 9.0$ Hz, 1 H, H8), 8.18–8.25 (m, 2 H, H9 and H16), 8.41 (d, $J = 8.0$ Hz, 1 H, H12), 8.56 (d, $J = 2.0$ Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.6 ($\underline{C}H_2CH_3$), 24.9 ($\underline{C}H_2$), 29.10 ($\underline{C}H_2$), 29.17 ($\underline{C}H_2$), 29.23 ($\underline{C}H_2$), 31.8 ($\underline{C}H_2$), 32.8 ($CO\underline{C}H_2$), 45.3 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 113.0 (C15), 118.3 (Ar-C), 119.0 (Ar-C), 121.9 (Ar-C), 124.1 (C9), 126.1(C5), 130.05 (C10), 130.16 (C11), 130.6 (C8), 132.2 (C10), 134.0 (C7), 140.1 (Ar-C), 147.8 (C16), 148.5 (Ar-C), 156.6 (Ar-C), 157.4 (Ar-C), 170.0 (C=O). **ESI-MS** m/z of $[M + H]^+$ 626.00, 628.10 was obtained for a calculated mass of 626.21, 628.21.

*7.2.2.32. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno [2,1-c]quinolin-7-one O-decanoyl oxime **(35)** Procedure A, yield 60%.* Green solid; mp 138–140 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1777.24; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.88 (t, $J = 7.0$ Hz, 3 H, $CH_2\underline{C}H_3$), 1.18–1.50 (m, 12 H, CH_2), 1.78–1.88 (m, 2 H, $COCH_2\underline{C}H_2$), 2.66 (t, $J = 7.0$ Hz, 2 H, $CO\underline{C}H_2CH_2$), 3.66–3.75 (m, 4 H, piperizine-CH_2), 3.84–3.92 (m, 4 H, piperizine-CH_2), 6.59–6.65 (m, 1 H, H15), 6.74 (d, $J = 8.5$ Hz, 1 H, H13), 7.45–7.54 (m, 2 H, H11 and H14), 7.58–7.63 (m, 1 H, H10), 7.72 (dd, $J = 2.0$, 9.0 Hz, 1 H, H7), 7.77 (d, $J = 9.0$ Hz, 1 H, H8), 8.18 (d, $J = 8.0$ Hz, 1 H, H9), 8.22 (dd, $J = 1.5$, 5.0 Hz, 1 H, H16), 8.40 (d, $J = 7.5$ Hz, 1 H, H12), 8.55 (d, $J = 2.0$ Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 14.1 (CH_3), 22.7 ($CH_3\underline{C}H_2$), 24.9 ($\underline{C}H_2$), 29.2 ($\underline{C}H_2$), 29.26 ($\underline{C}H_2$), 29.27 ($\underline{C}H_2$), 29.40 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 32.8 ($CO\underline{C}H_2CH_2CH_2$), 45.2 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 107.3 (C13), 113.1 (C15), 118.4 (Ar-C), 119.0 (Ar-C), 121.9 (Ar-C), 124.1 (C9), 126.1 (C5), 130.0 (C12), 130.1 (C11), 130.6 (C8), 132.2 (C10), 134.0 (C7), 137.5 (C14), 140.1 (Ar-C), 147.8 (C16), 147.9 (Ar-C), 148.5 (Ar-C), 156.6 (Ar-C), 157.5 (Ar-C), 159.8 (Ar-C), 170.0 (C=O). **ESI-MS** m/z of $[M + H]^+$ 639.70, 641.70 was obtained for a calculated mass of 640.22, 642.22.

*7.2.2.33. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno [2,1-c]quinolin-7-one O-dodecanoyl oxime **(36)** Procedure A, yield 47%.* Yellow solid; mp 175–176 °C. ^{1}H-NMR (600 MHz, $CDCl_3$): δ 0.87 (t, $J = 7.2$ Hz, 3 H, $CH_2\underline{C}H_3$), 1.19–1.50 (m, 16 H), 1.79–1.88 (m, 2 H, $COCH_2\underline{C}H_2$), 2.66 (t, $J = 7.2$ Hz, 2 H, $CO\underline{C}H_2$), 3.68–3.78 (m, 4 H, piperizine-CH_2), 3.82–3.98 (m, 4 H, piperizine-CH_2), 6.60–6.66 (m, 1 H, H15), 6.75 (d, $J = 6.0$ Hz, 1 H, H13), 7.47–7.55 (m, 2 H, H11 and H14), 7.61 (t, $J = 7.8$ Hz, 1 H, H10), 7.73 (d, $J = 8.4$ Hz, 1 H, H7), 7.78 (d, $J = 9.0$ Hz, 1 H, H8), 8.18–8.25 (m, 2 H, H9 and H16), 8.41 (d, $J = 7.2$ Hz, 1 H, H12), 8.57 (bs, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 14.1 ($CH_2\underline{C}H_3$), 22.7 ($\underline{C}H_2$), 24.9 ($\underline{C}H_2$), 29.2 ($\underline{C}H_2$), 29.28 ($\underline{C}H_2$), 29.33 ($\underline{C}H_2$), 29.45 ($\underline{C}H_2$), 29.6 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 32.8 ($CO\underline{C}H_2$), 45.3 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 113.0 (C13), 118.4 (Ar-C), 119.1 (Ar-C), 122.0 (Ar-C), 124.1 (C9), 126.1 (C5), 130.06 (C12), 130.16 (Ar-C), 130.20 (C11), 130.60 (C8), 132.2 (C10), 134.0 (C7), 140.2 (Ar-C), 147.9 (C16), 148.6 (Ar-C), 156.6 (Ar-C), 157.5 (Ar-C), 170.0 (C=O). **ESI-MS** m/z of $[M + H]^+$ 668.50, 670.60 was obtained for a calculated mass of 668.26, 670.25.

*7.2.2.34. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno [2,1-c]quinolin-7-one O-pentadecanoyl oxime **(37)** Procedure A, yield 34%.* Green solid; mp 115–116 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.87 (t, $J = 7.0$ Hz, 3 H, $CH_2\underline{C}H_3$), 1.17–1.50 (m, 22 H, $(CH_2)_{11}$), 1.78–1.88 (m, 2 H, $COCH_2\underline{C}H_2$), 2.66 (t, $J = 7.5$ Hz, 2 H, $CO\underline{C}H_2$), 3.68–3.76 (m, 4 H, piperizine-$\underline{C}H_2$), 3.84–3.93 (m, 4 H, piperizine-$\underline{C}H_2$), 6.59–6.65 (m, 1 H, H15), 6.74 (d, $J = 8.5$ Hz, 1 H, H13), 7.47–7.55 (m, 2 H, H10 and H14), 7.58–7.65 (m, 1 H, H11), 7.73 (dd, $J = 2.5$, 9.0 Hz, 1 H, H7), 7.78 (d, $J = 9.0$ Hz, 1 H, H8), 8.18- 8.25 (m, 2 H, H12 and H16), 8.41 (d, $J = 7.5$ Hz, 1 H, H9), 8.56 (d, $J = 2.0$ Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 14.1 ($CH_2\underline{C}H_3$), 22.7 ($\underline{C}H_2$), 24.9 ($\underline{C}H_2$), 29.17 ($\underline{C}H_2$), 29.28 ($\underline{C}H_2$), 29.36 ($\underline{C}H_2$), 29.45 ($\underline{C}H_2$), 29.61 ($\underline{C}H_2$), 29.65 ($\underline{C}H_2$), 29.67 ($\underline{C}H_2$), 29.69 ($\underline{C}H_2$), 31.9 ($\underline{C}H_2$), 32.8 ($CO\underline{C}H_2$), 45.2 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 107.3 (C13), 113.1 (C15), 118.4 (Ar-C), 119.1 (Ar-C), 121.9 (Ar-C), 124.1 (C9), 126.1 (C5), 130.05 (C12), 130.15 (Ar-C), 130.17 (C11), 130.6 (C8), 132.1 (C10), 134.0 (C7), 140.1 (Ar-C), 147.8 (C16), 148.5 (Ar-C), 156.6 (Ar-C), 157.5 (Ar-C),

170.0 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 709.90, 712.00 was obtained for a calculated mass of 710.30, 712.30.

7.2.2.35. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno [2,1-c]quinolin-7-one O-5-bromopentanoyl oxime ***(38)*** *Procedure A, yield 66%.* Yellow solid; mp 195–196 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1778.47; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.94–2.08 (m, 4 H, CH_2CH_2), 2.69–2.75 (m, 2 H, $COCH_2$), 3.47 (t, *J* = 6.6 Hz, 2 H, CH_2CH_2Br), 3.68–3.77 (m, 4 H, piperizine-CH_2), 3.85–3.94 (m, 4 H, piperizine-CH_2), 6.62–6.68 (m, 1 H, H15), 6.75 (d, *J* = 8.4 Hz, 1 H, H13), 7.48–7.54 (m, 2 H, H11 and H14), 7.59–7.64 (m, 1 H, H10), 7.72 (dd, *J* = 2.4, 9.0 Hz, 1 H, H7), 7.77 (d, *J* = 8.4 Hz, 1 H, H8), 8.19 (d, *J* = 7.8 Hz, 1 H, H9), 8.22–8.25 (m, 1 H, H16), 8.39 (d, *J* = 7.2 Hz, 1 H, H12), 8.55 (d, *J* = 2.4 Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 23.4 (CH_2), 31.79 (CH_2), 31.82 ($COCH_2$), 32.9 (CH_2Br), 45.3 (piperazine-CH_2), 49.5 (piperazine-CH_2), 113.0 (Ar-C) 118.4 (Ar-C), 118.9 (Ar-C), 121.9 (Ar-C), 124.2 (C9), 126.1 (C5), 130.08 (C12), 130.13 (Ar-C), 130.22 (C11), 130.6 (C8), 132.3 (C10), 134.1 (C7), 140.2 (Ar-C), 147.9 (Ar-C), 148.6 (Ar-C), 156.5 (Ar-C), 157.7 (Ar-C), 169.4 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 647.80, 649.70 was obtained for a calculated mass of 648.06, 650.05.

7.2.2.36. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno [2,1-c]quinolin-7-one O-cyclopropanecarbonyl oxime ***(40)*** *Procedure A, yield 55%.* Brown solid; mp 217–219 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1765.10; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.08–1.14 (m, 2 H, CH_2), 1.25–1.30 (m, 2 H, CH_2), 1.93–2.00 (m, 1 H, CH), 3.69–3.74 (m, 4 H, piperizine-CH_2), 3.85–3.93 (m, 4 H, piperizine-CH_2), 6.61–6.65 (m, 1 H, H15), 6.73 (d, *J* = 8.4 Hz, 1 H, H13), 7.48–7.55 (m, 2 H, H11 and H14), 7.59–7.64 (m, 1 H, H10), 7.71 (dd, *J* = 2.4, 9.0 Hz, 1 H, H7), 7.77 (d, *J* = 9.0 Hz, 1 H, H8), 8.18–8.24 (m, 2 H, H9 and H16), 8.48 (d, *J* = 7.2 Hz, 1 H, H12), 8.55 (d, *J* = 2.4 Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 9.6 (cyclopropyl-CH_2), 11.6 (CH), 45.3 (piperazine-CH_2), 49.5 (piperazine-CH_2), 113.0 (C15), 118.4 (Ar-C), 119.1 (Ar-C), 121.9 (Ar-C), 124.1 (C9), 126.1 (C5), 130.2 (C12), 130.6 (C11), 132.2 (C8), 134.0 (C7), 140.1 (Ar-C), 147.8 (Ar-C), 148.4 (Ar-C), 156.6 (Ar-C), 157.3 (Ar-C), 159.7 (Ar-C), 171.6 (C=O). **ESI-MS** *m/z* of $[M]^+$ 554.60, 556.50 was obtained for a calculated mass of 554.12, 556.12.

7.2.2.37. 2-Bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno [2,1-c]quinolin-7-one O-(E)-3-(furan-2-yl)acryloyl oxime ***(41)*** *Procedure A, yield 46%.* Brown solid; mp 224–225 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1747.42; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.72–3.80 (m, 4 H, piperizine-CH_2), 3.89–4.00 (m, 4 H, piperizine-CH_2), 6.50–6.55 (m, 1 H, Ar-H), 6.61–6.70 (m, 2 H, H15 and COCH=CH), 6.71–6.81 (m, 2 H, H13 and Ar-H), 7.48–7.57 (m, 3 H, H11, H14 and Ar-H), 7.59–7.65 (m, 1 H, H10), 7.68–7.75 (m, 2 H, H7 and COCH=CH), 7.78 (d, *J* = 9.0 Hz, 1 H, H8), 8.18–8.26 (m, 2 H, H9 and H16), 8.50 (d, *J* = 7.5 Hz, 1 H, H12), 8.56 (d, *J* = 2.0 Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 45.3 (piperazine-CH_2), 49.5 (piperazine-CH_2), 112.0 (Ar-C), 112.7 (Ar-C), 113.0 (Ar-C), 116.5 (Ar-C), 118.4 (Ar-C), 119.1 (Ar-C), 121.9 (Ar-C), 124.1 (C9), 126.1 (C5), 130.16 (C12), 130.21 (Ar-C), 130.25 (C11), 130.58 (C8), 132.2 (C10), 133.5 (C7), 134.0 (Ar-C), 140.1 (Ar-C), 145.4 (Ar-C), 147.8 (C16), 148.5 (Ar-C), 150.8 (Ar-C), 157.6 (Ar-C), 164.3 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 606.00, 608.00 was obtained for a calculated mass of 606.11, 608.11.

7.2.2.38. N-(2-(2-Bromo-6-(4-phenylpiperazin-1-yl)-7H- indeno [2,1-c]quinolin-7-ylideneaminooxy)-2-oxoethyl)acetamide ***(42)*** *Procedure A, yield 70%.* Red solid; mp 174–176 °C. ^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.10 (s, 3 H, $NHCOCH_3$), 3.64–3.74 (m, 4 H, piperizine-CH_2), 3.77–3.87 (m, 4 H, piperizine-CH_2), 4.42 (d, *J* = 5.0 Hz, 2 H, $COCH_2NHAc$), 6.35–6.42 (m, 1 H, Ar-H), 6.60–6.66 (m, 1 H, Ar-H), 6.74 (d, *J* = 8.56 Hz, 1 H, Ar-H), 7.45–7.65 (m, 3 H, Ar-H), 7.65–7.80 (m, 2 H, Ar-H), 8.14 (d, *J* = 7.8 Hz, 1 H, Ar-H), 8.20–8.30 (m, 1 H, Ar-H), 8.32 (d, *J* = 7.6 Hz, 1 H, Ar-H), 8.51 (d, *J* = 1.5 Hz, 1 H, H5). ^{13}C-NMR (126.8 MHz, $CDCl_3$): δ 23.0 ($COCH_3$), 40.5 ($COCH_2$), 45.4 (piperazine-CH_2), 49.5 (piperazine-CH_2), 107.7 (Ar-C), 113.2 (Ar-C), 118.6 (Ar-C), 121.9 (Ar-C), 124.2 (Ar-C), 126.2 (Ar-C), 129.9 (Ar-C), 130.4 (Ar-C), 130.6 (Ar-C), 132.5 (Ar-C), 132.8 (Ar-C), 134.3 (Ar-C), 137.8 (Ar-C), 140.1 (Ar-C), 147.5 (Ar-C), 148.2 (Ar-C), 148.7 (Ar-C), 156.4 (Ar-C), 158.6 (Ar-C), 167.2 (Ar-C), 170.6 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 585.00, 587.10 was obtained for a calculated mass of 585.13, 587.13.

7.2.2.39. tert-Butyl 2-((2-bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)carbonyl)pyrrolidine-1-carboxylate ***(43)****.* Rotamers in the ratio of 6:4. Procedure A, yield 41%. Brown solid; mp 172–174 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1779.38; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.39 (s, 5 H, N-Boc), 1.49 (s, 4 H, N-Boc), 1.90–2.50 (m, 4 H, proline-CH_2), 3.50–4.00 (m, 10 H, piperazine-CH_2CH_2, proline-CH_2), 4.52–4.60 (m, 0.6 H, proline-CH), 4.69–4.72 (m, 0.4 H, proline-CH), 6.59–6.66 (m, 1 H, Ar-H), 6.70–6.75 (m, 1 H, Ar-H), 7.45–7.55 (m, 2 H, Ar-H), 7.56–7.64 (m, 1 H, Ar-H), 7.69–7.80 (m, 2 H, Ar-H), 8.10–8.22 (m, 2 H, Ar-H), 8.35 (d, *J* = 7.8 Hz, 0.6 H, Ar-H), 8.44 (d, *J* = 7.8 Hz, 0.4 H, Ar-H), 8.56 (bs, 1 H, Ar-H). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 23.9, 24.6, 26.9, 28.4, 28.5, 30.2, 31.3, 34.7, 45.2, 45.3, 46.49, 46.6, 46.8, 49.5, 58.2, 58.7, 80.4, 80.7, 107.3 (Ar-C), 112.9 (Ar-C), 113.2 (Ar-C), 118.5 (Ar-C), 118.8 (Ar-C), 118.9 (Ar-C), 121.9 (Ar-C), 124.1 (Ar-C), 124.2 (Ar-C), 126.2 (Ar-C), 130.12 (Ar-C), 130.21 (Ar-C), 130.37 (Ar-C), 130.44 (Ar-C), 130.59 (Ar-C), 132.21 (Ar-C), 132.42 (Ar-C), 134.04 (Ar-C), 134.16 (Ar-C), 137.58 (Ar-C), 140.12 (Ar-C), 148.0 (Ar-C), 148.11 (Ar-C), 148.68 (Ar-C), 153.6 (Ar-C), 154.5 (Ar-C), 156.5 (Ar-C), 158.3 (Ar-C), 158.4 (Ar-C), 159.5 (Ar-C), 169.5 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 682.90, 684.90 was obtained for a calculated mass of 683.19, 685.19.

7.2.2.40. tert-Butyl 1-((2-bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)carbonyl)cyclopentylcarbamate ***(44)*** *Procedure A, yield 49%.* Yellow solid; mp 200–201 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1778.12; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.38 (s, 9 H, N-Boc), 1.80–1.95 (m, 4 H, cyclopentane-CH_2), 1.96–2.16 (m, 2 H, cyclopentane-CH_2), 2.41–2.52 (m, 2 H, cyclopentane-CH_2), 3.69–3.77 (m, 4 H, piperizine-CH_2), 3.88–3.96 (m, 4 H, piperizine-CH_2), 5.10 (s, 1 H), 6.58–6.65 (m, 1 H, H15), 6.74 (d, *J* = 8.5 Hz, 1 H, H13), 7.47–7.55 (m, 2 H, H11 and H14), 7.57–7.64 (m, 1 H, H10), 7.72 (dd, *J* = 2.0, 9.0 Hz, 1 H, H7), 7.78 (d, *J* = 9.0 Hz, 1 H, H8), 8.16–8.25 (m, 2 H, H9 and H16), 8.46 (d, *J* = 8.0 Hz, 1 H, H12), 8.56 (d, *J* = 2.0 Hz, 1 H, H5). ^{13}C-NMR (125.6 MHz, $CDCl_3$): δ 24.3 (cyclopentane-CH_2), 28.3 (Boc-CH_3), 38.0 (cyclopentane-CH_2), 45.2 (piperizine-CH_2), 49.5 (piperizine-CH_2), 107.4 (C13), 113.0 (Ar-C), 118.3 (Ar-C), 119.1 (Ar-C), 121.9 (C15), 124.1 (C9), 126.1 (C15), 130.1 (C12 and C11), 130.6 (C8), 132.2 (C10), 134.0 (C7), 140.1 (Ar-C), 147.8 (Ar-C), 148.5 (Ar-C), 154.7 (Ar-C), 156.6 (Ar-C), 170.8 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 696.90, 698.70 was obtained for a calculated mass of 697.21, 699.21.

7.2.2.41. tert-Butyl 2-(2-bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)-2-oxoethylcarbamate ***(45)*** *Procedure A, yield 53%.* Brown solid; mp 173–175 °C. $IR_{\nu max}$ (KBr, cm^{-1}) 1703.00; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.45 (s, 9 H, N-Boc), 3.65–3.70 (m, 4 H, piperizine-CH_2), 3.75–3.80 (m, 4 H, piperizine-CH_2), 4.30 (d, *J* = 5.7 Hz, 2 H, $COCH_2NH$), 5.20 (d, *J* = 4.7 Hz, 1 H, NH), 6.62 (dd, *J* = 5.7, 6.7 Hz, 1 H, H15), 6.73 (d, *J* = 8.6 Hz, 1 H, H13), 7.45–7.55 (m, 2 H, H11 and H14), 7.57–7.65 (m, 1 H, H10), 7.72 (dd, *J* = 2.0, 8.9 Hz, 1 H, H7), 7.77 (d, *J* = 9.0 Hz, 1 H, H8), 8.15–8.25 (m, 2 H, H9 and H16), 8.36 (d, *J* = 7.6 Hz, 1 H, H12), 8.55 (d, *J* = 2.0 Hz, 1 H, H5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 28.3 (Boc), 31.4 (CCH_3), 41.6 ($COCH_2NH$), 45.1 (piperazine-CH_2), 49.5

(piperazine-$\underline{C}H_2$), 80.4 ($\underline{C}(CH_3)_3$), 106.3 (Ar-C), 107.3 (Ar-C), 113.2 (Ar-C), 118.4 (Ar-C), 121.7 (Ar-C), 123.9 (Ar-C), 126.0 (Ar-C), 129.7 (Ar-C), 130.2 (Ar-C), 130.4 (Ar-C), 132.2 (Ar-C), 134.0 (Ar-C), 137.4 (Ar-C), 139.8 (Ar-C), 147.8 (Ar-C), 147.9 (Ar-C), 148.4 (Ar-C), 155.7 (Ar-C), 156.3 (Ar-C), 158.2 (C=O), 159.6 (Ar-C), 162.5 (Ar-C), 167.4 (CO). **ESI-MS** *m/z* of $[M+H]^+$ 643.00, 645.00 was obtained for a calculated mass of 643.16, 645.16.

7.2.2.42. tert-Butyl 1-(2-bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)-1-oxopropan-2-ylcarbamate ***(46)*** *Procedure A, yield 86%.* Yellow solid; mp 186–187 °C. ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.45 (s, 9 H, N-Boc), 1.58 (d, $J = 7.0$ Hz, 3 H, CHC$\underline{H}_3$), 3.62–3.90 (m, 8 H, piperazine-C$\underline{H}_2$), 4.70–4.80 (m, 1 H, C$\underline{H}$CH$_3$), 5.19 (d, $J = 7.5$ Hz, 1 H, NH), 6.63 (dd, $J = 1.5$, 5.0 Hz, 1 H, H15), 6.75 (d, $J = 8.5$ Hz, 1 H, H13), 7.48–7.54 (m, 2 H, H11 and H14), 7.58–7.64 (m, 1 H, H10), 7.72 (dd, $J = 2.0$, 9.0 Hz, 1 H, H7), 7.77 (d, $J = 9.0$ Hz, 1 H, H8), 8.18 (d, $J = 8.0$ Hz, 1 H, H9), 8.22 (dd, $J = 1.5$, 5.0 Hz, 1 H, H16), 8.41 (d, $J = 7.5$ Hz, 1 H, H12), 8.54 (d, $J = 2.0$ Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 19.0 (CH$\underline{C}H_3$), 28.3 (Boc-$\underline{C}H_3$), 45.3 (piperazine-$\underline{C}H_2$), 48.4 (CH–$\underline{C}H_3$), 49.5 (piperazine-$\underline{C}H_2$), 80.4 ($\underline{C}(CH_3)_3$), 107.4 (C13), 113.0 (C15), 118.4 (Ar-C), 118.7 (Ar-C), 121.9 (Ar-C), 124.2 (C9), 126.1 (C5), 130.04 (Ar-C), 130.33 (C12), 130.39 (C11), 130.59 (C8), 132.4 (C10), 134.2 (Ar-C), 140.1 (Ar-C), 148.1 (C16), 148.7 (Ar-C), 155.0 (Ar-C), 156.5 (Ar-C), 158.5 (Ar-C), 170.0 (C=O). **ESI-MS** *m/z* of $[M]^+$ 656.60, 658.60 was obtained for a calculated mass of 656.17, 658.17.

7.2.2.43. tert-Butyl 1-(2-bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)-4-methyl-1-oxopentan-2-ylcarbamate ***(47)*** *Procedure A, yield 80%.* Brown solid; mp 122–123 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1774.21; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.99 (d, $J = 6.32$ Hz, 3 H, C$\underline{H}_3$), 1.02 (d, $J = 6.08$ Hz, 3 H, C$\underline{H}_3$), 1.45 (s, 9 H, N-Boc), 1.65–1.85 (m, 3 H, $\underline{C}H_2\underline{C}H(CH_3)_2$), 3.60–3.90 (m, 8 H, piperizine-CH_2), 4.65–4.75 (m, 1 H, C$\underline{H}$NH), 5.02 (d, $J = 8.64$ Hz, 1 H), 6.60–6.65 (m, 1 H, H15), 6.73 (d, $J = 8.6$ Hz, 1 H, H13), 7.45–7.55 (m, 2 H, H11 and H14), 7.61 (t, $J = 8.1$ Hz, 1 H, H10), 7.72 (dd, $J = 1.9$, 8.8 Hz, 1 H, H7), 7.78 (d, $J = 9.0$ Hz, 1 H, H8), 8.15–8.30 (m, 2 H, H9 and H16), 8.45 (d, $J = 7.8$ Hz, 1 H, H12), 8.56 (d, $J = 1.9$ Hz, 1 H, H5). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 21.9 (CH$\underline{C}H_3$), 22.9 (CH$\underline{C}H_3$), 24.8 ($\underline{C}H(CH_3)_2$), 28.3, 28.4, 42.0 ($CHCH_2$), 45.1 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 51.1 (CO$\underline{C}$H), 80.3 ($\underline{C}(CH_3)_3$), 107.3 (Ar-C), 113.0 (Ar-C), 118.4 (Ar-C), 118.7 (Ar-C), 121.8 (Ar-C), 124.1 (Ar-C), 126.1 (Ar-C), 130.0 (Ar-C), 130.3 (Ar-C), 130.5 (Ar-C), 132.3 (Ar-C), 134.1 (Ar-C), 137.4 (Ar-C), 140.0 (Ar-C), 147.9 (Ar-C), 148.0 (Ar-C), 148.6 (Ar-C), 155.4 (Ar-C), 156.5 (C=O), 158.5 (Ar-C), 159.7 (Ar-C), 170.1 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 699.40, 701.20 was obtained for a calculated mass of 699.20, 701.22.

7.2.2.44. tert-Butyl 1-(2-bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)-3,3-dimethyl-1-oxobutan-2-ylcarbamate ***(48)*** *Procedure A, yield 53%.* Yellow solid; mp 156–157 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1776.47; ^{1}H-NMR (500 MHz, $CDCl_3$): δ 1.11 (s, 9 H, ($C\underline{H}_3$)$_3$C), 1.46 (s, 9 H, NHBoc), 3.60–3.95 (m, 8 H, piperizine-CH_2), 4.45 (d, $J = 9.5$ Hz, 1 H, NHC$\underline{H}$), 5.25–5.35 (m, 1 H, N$\underline{H}$), 6.23 (dd, $J = 5.0$, 6.5 Hz, 1 H, H15), 6.73 (d, $J = 8.5$ Hz, 1 H, H13), 7.45–7.55 (m, 2 H, H11 and H14), 7.57–7.63 (m, 1 H, H10), 7.72 (dd, $J = 2.5$, 9.0 Hz, 1 H, H7), 7.77 (d, $J = 9.0$ Hz, 1 H, H8), 8.19 (d, $J = 7.5$ Hz, 1 H, H9), 8.21 (dd, $J = 1.5$, 5.0 Hz, 1 H, H16), 8.45 (d, $J = 7.0$ Hz, 1 H, H12), 8.55 (d, $J = 1.5$ Hz, 1 H, H5). ^{13}C-NMR (125.8 MHz, $CDCl_3$): δ 26.5 ($\underline{C}H_3$)$_3$C), 28.3 (Boc), 35.0 ($\underline{C}(CH_3)_3$), 45.1 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 60.8 (NH$\underline{C}$H), 80.3 ((CH$_3$)$_3\underline{C}$O), 107.2 (C13), 113.0 (C15), 118.4 (Ar-C), 118.8 (Ar-C), 121.9 (Ar-C), 124.1 (C9), 126.2 (C5), 130.0 (C11), 130.4 (C12), 130.5 (C8), 132.4 (C10), 134.1 (C7), 137.4 (C14), 140.1 (Ar-C), 148.0 (C16), 148.1 (Ar-C), 148.7 (Ar-C), 155.5 (Ar-C), 156.5 (Ar-C), 158.5 (Ar-C), 159.8 (Ar-C), 168.9 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 699.50, 701.40 was obtained for a calculated mass of 699.22, 701.22.

7.2.2.45. tert-Butyl 1-(2-bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2, 1-c]quinolin-7-ylideneaminooxy)-4-(methylthio)-1-oxobutan-2-ylcarbamate ***(49)*** *Procedure A, yield 27%.* Yellow solid; mp 162–163 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1772.03; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.46 (s, 9 H, N-Boc), 2.05–2.10 (m, 1 H), 2.11 (s, 3 H, SC$\underline{H}_3$), 2.25–2.31 (m, 1 H), 2.60–2.70 (m, 2 H), 3.62–4.0 (m, 8 H, piperizine-CH_2), 4.84–4.90 (m, 1 H), 5.30 (d, $J = 8.4$ Hz, 1 H), 6.64 (t, $J = 5.4$ Hz, 1 H, H15), 6.76 (d, $J = 9.0$ Hz, 1 H, H13), 7.46–7.56 (m, 2 H, H11 and H14), 7.62 (t, $J = 7.8$ Hz, 1 H, H10), 7.72 (dd, $J = 1.8$, 9.0 Hz, 1 H, H7), 7.77 (d, $J = 9.0$ Hz, 1 H, H8), 8.18 (d, $J = 7.8$ Hz, 1 H, H9), 8.22 (dd, $J = 1.2$, 4.8 Hz, 1 H, H16), 8.45 (d, $J = 7.8$ Hz, 1 H, H12), 8.54 (d, $J = 1.8$ Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 15.6 (S$\underline{C}H_3$), 28.4 (OC($\underline{C}H_3$)$_3$), 30.2 (S$\underline{C}H_2$), 32.4 ($\underline{C}H_2$), 45.4 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 51.7 (NH$\underline{C}$H), 80.6 (O$\underline{C}$(CH$_3$)$_3$), 113.0 (C15), 118.5 (Ar-C), 118.7 (Ar-C), 121.9 (Ar-C), 124.2 (C9), 126.2 (C5), 130.0 (C12), 130.5 (C11), 130.6 (C8), 132.5 (C10), 134.2 (C7), 140.2 (Ar-C), 148.2 (Ar-C), 148.7 (Ar-C), 155.3 (Ar-C), 156.5 (CO), 158.7 (Ar-C), 169.2 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 717.10, 719.10 was obtained for a calculated mass of 717.18, 719.18.

7.2.2.46. tert-Butyl 1-(2-bromo-6-(4-(pyridin-2-yl)piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)-3-(3-fluorophenyl)-1-oxopropan-2-ylcarbamate ***(50)*** *Procedure A, yield 89%.* Brown solid; mp 164–165 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1771.63; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.43 (s, 9 H, NHBoc), 3.15–3.33 (m, 2 H, $\underline{C}H_2$Ph), 3.65–3.75 (m, 4 H, piperizine-CH_2), 3.80–3.90 (m, 4 H, piperizine-CH_2), 4.92 (d, $J = 7.2$ Hz, 1 H, C$\underline{H}$NH), 5.23 (d, $J = 8.4$ Hz, 1 H, N$\underline{H}$), 6.62–6.66 (m, 1 H, Ar-H), 6.73 (d, $J = 8.4$ Hz, 1 H, Ar-H), 6.83–6.88 (m, 1 H, Ar-H), 6.90–7.05 (m, 2 H, Ar-H), 7.19–7.25 (m, 1 H, Ar-H), 7.40–7.44 (m, 1 H, Ar-H), 7.49–7.53 (m, 1 H, Ar-H), 7.55–7.62 (m, 1 H, Ar-H), 7.72 (dd, $J = 2.4$, 9.0 Hz, 1 H, H7), 7.76 (d, $J = 9.0$ Hz, 1 H, H7), 8.11–8.21 (m, 2 H, Ar-H), 8.22 (dd, $J = 1.8$, 4.8 Hz, 1 H, Ar-H), 8.52 (d, $J = 1.8$ Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 28.3 (OC($\underline{C}H_3$)$_3$), 38.8 ($\underline{C}H_2$Ph), 45.3 (piperazine-$\underline{C}H_2$), 49.5 (piperazine-$\underline{C}H_2$), 53.8 (NH$\underline{C}$H), 80.6 (O$\underline{C}$(CH$_3$)$_3$), 107.4 (Ar-C), 113.1 (Ar-C), 114.2 (Ar-C), 114.3 (Ar-C), 116.3 (Ar-C), 116.5 (Ar-C), 118.4 (Ar-C), 118.7 (Ar-C), 121.9 (Ar-C), 124.1 (Ar-C), 125.1 (Ar-C), 125.2 (Ar-C), 126.2 (Ar-C), 129.7 (Ar-C), 129.9 (Ar-C), 130.2 (Ar-C), 130.3 (Ar-C), 130.6 (Ar-C), 132.4 (Ar-C), 132.8 (Ar-C), 134.2 (Ar-C), 137.6 (Ar-C), 138.1 (Ar-C), 138.2 (Ar-C), 140.1 (Ar-C), 147.7 (Ar-C), 148.2 (Ar-C), 148.8 (Ar-C), 155.0 (Ar-C), 156.1 (Ar-C), 156.5 (Ar-C), 158.8 (Ar-C), 159.7 (Ar-C), 162.1 (Ar-C), 163.7 (Ar-C), 168.8 (C=O). **ESI-MS** *m/z* of $[M+H]^+$ 751.60, 753.60 was obtained for a calculated mass of 751.20, 753.20.

7.2.2.47. tert-Butyl 1-(2-bromo-6-(4-(pyridin-2-yl) piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)-1-oxo-3-phenylpropan-2-ylcarbamate ***(51)*** *Procedure A, yield 37%.* Yellow solid; mp 167–168 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1776.25; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 1.42 (s, 9 H, NHBoc), 3.15–3.30 (m, 2 H, $\underline{C}H_2$Ph), 3.60–3.75 (m, 4 H, piperizine-CH_2), 3.75–3.93 (m, 4 H, piperizine-CH_2), 4.92 (d, $J = 7.2$ Hz, 1 H, CHNH), 5.17 (d, $J = 8.2$ Hz, 1 H, N$\underline{H}$), 6.60–6.64 (m, 2 H, Ar-H), 7.10–7.33 (m, 5 H, Ar-H), 7.34–7.67 (m, 3 H, Ar-H), 7.70–7.80 (m, 2 H, Ar-H), 8.09 (d, $J = 7.5$ Hz, 1 H, Ar-H), 8.15 (d, $J = 7.6$ Hz, 1 H, Ar-H), 8.17–8.24 (m, 1 H, Ar-H), 8.53 (s, 1 H, Ar-H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 28.2 (OC($\underline{C}H_3$)$_3$), 38.9 (CH_2Ph), 45.1 (piperazine-$\underline{C}H_2$), 49.4 (piperazine-$\underline{C}H_2$), 53.8 (NH$\underline{C}$H), 80.3 (O$\underline{C}$(CH$_3$)$_3$), 107.2 (Ar-C), 113.0 (Ar-C), 118.3 (Ar-C), 118.6 (Ar-C), 121.7 (Ar-C), 123.9 (Ar-C), 126.0 (Ar-C), 127.2 (Ar-C), 127.9 (Ar-C), 128.6 (Ar-C), 129.3 (Ar-C), 129.7 (Ar-C), 130.2 (Ar-C), 130.4 (Ar-C), 132.2 (Ar-C), 132.5 (Ar-C), 134.0 (Ar-C), 135.4 (Ar-C), 137.4 (Ar-C), 137.6 (Ar-C), 139.8 (Ar-C), 147.8 (Ar-C), 147.98 (Ar-C), 148.5 (Ar-C), 154.9 (Ar-C), 156.4 (Ar-C), 158.5 (Ar-C), 159.7 (Ar-C), 168.9 (C=O). **ESI-MS** *m/z* of

$[M+H]^+$ 733.40, 735.30 was obtained for a calculated mass of 733.21, 735.21.

7.2.2.48. (9H-Fluoren-9-yl)methyl 2-(2-bromo-6-(4-(pyridin-2-yl) piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)-2-oxoethylcarbamate ***(52)*** *Procedure A, yield 40%.* Brown solid; mp 185–186 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1719.12, 1776.16; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 3.75–3.82 (m, 4 H, piperizine-CH_2), 3.85–3.92 (m, 4 H, piperizine-CH_2), 4.23 (t, $J = 8.4$ Hz, 1 H, Fmoc-CH), 4.32–4.40 (m, 2 H, Fmoc-CH_2), 4.44 (d, $J = 7.0$ Hz, 2 H, $COCH_2$), 5.60–5.70 (m, 1 H, NH), 6.60–6.68 (m, 1 H, Ar-H), 6.72–6.79 (m, 1 H, Ar-H), 7.20–7.30 (m, 2 H, Ar-H), 7.35–7.41 (m, 2 H, Ar-H), 7.42–7.48 (m, 1 H, Ar-H), 7.49–7.52 (m, 1 H, Ar-H), 7.55–7.64 (m, 3 H, Ar-H), 7.66–7.80 (m, 4 H, Ar-H), 8.13 (d, $J = 7.5$ Hz, 1 H, Ar-H), 8.22 (d, $J = 3.5$ Hz, 1 H, Ar-H), 8.32 (d, $J = 7.5$ Hz, 1 H, Ar-H), 8.51 (s, 1 H, Ar-H). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 42.0 ($COCH_2$), 45.4 (piperazine-CH_2), 47.1 (Fmoc-CH), 49.5 (piperazine-CH_2), 67.5 (Fmoc-CH_2), 107.8 (Ar-C), 113.1 (Ar-C), 118.6 (Ar-C), 119.9 (Ar-C), 120.0 (Ar-C), 121.8 (Ar-C), 124.2 (Ar-C), 125.1 (Ar-C), 126.1 (Ar-C), 127.05 (Ar-C), 127.12 (Ar-C), 127.66 (Ar-C), 127.77 (Ar-C), 129.9 (Ar-C), 130.4 (Ar-C), 130.6 (Ar-C), 132.5 (Ar-C), 134.2 (Ar-C), 140.1 (Ar-C), 141.3 (Ar-C), 143.7 (Ar-C), 148.2 (Ar-C), 148.6 (Ar-C), 156.3 (Ar-C), 156.4 (Ar-C), 158.6 (Ar-C), 167.2 (C=O). **ESI-MS** m/z of $[M+H]^+$ 765.30, 767.20 was obtained for a calculated mass of 765.18, 767.18.

7.2.2.49. (9H-Fluoren-9-yl)methyl 1-(2-bromo-6-(4-(pyridin-2-yl) piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)-4-methyl-1-oxopentan-2-ylcarbamate ***(53)*** *Procedure A, yield 34%.* Brown solid; mp 125–126 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1774.12; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 0.92–1.10 (m, 6 H, CH_3), 1.72–1.82 (m, 3 H, $CHCH_2CH$), 3.60–3.40 (m, 8 H, piperizine-CH_2), 4.23 (t, $J = 6.72$ Hz, 1 H, $ArCHCH_2$), 4.40–4.50 (m, 2 H, $ArCHCH_2$), 4.70–4.83 (m, 1 H, CHNH), 5.32 (d, $J = 8.8$ Hz, 1 H, NHCH), 6.61 (t, $J = 6.0$ Hz, 1 H, Ar-H), 6.73 (d, $J = 8.5$ Hz, 1 H, Ar-H), 7.26–7.34 (m, 2 H, Ar-H), 7.38 (t, $J = 7.4$ Hz, 2 H, Ar-H), 7.47 (q, $J = 7.1$ Hz, 2 H, Ar-H), 7.52–7.68 (m, 3 H, Ar-H), 7.69–7.85 (m, 4 H, Ar-H), 8.16–8.27 (m, 2 H, Ar-H), 8.41 (d, $J = 7.6$ Hz, 1 H, Ar-H), 8.55 (s, 1 H, Ar-H). ^{13}C-NMR (100.6 MHz, $CDCl_3$): δ 21.8 ($CHCH_3$), 22.9 ($CHCH_3$), 24.7 ($CHCH_3$), 41.9 ($CHCH_2$), 45.1 (piperazine-CH_2), 47.1 (Ar-CH), 49.4 (piperazine-CH_2), 51.5, 67.2 (OCH_2), 107.2 (Ar-C), 113.1 (Ar-C), 118.4 (Ar-C), 118.6 (Ar-C), 119.9 (Ar-C), 121.7 (Ar-C), 124.1 (Ar-C), 125.0 (Ar-C), 126.0 (Ar-C), 127.0 (Ar-C), 127.7 (Ar-C), 129.9 (Ar-C), 130.1 (Ar-C), 130.3 (Ar-C), 130.5 (Ar-C), 132.4 (Ar-C), 134.4 (Ar-C), 137.4 (Ar-C), 140.0 (Ar-C), 141.2 (Ar-C), 143.5 (Ar-C), 143.7 (Ar-C), 147.9 (Ar-C), 148.0 (Ar-C), 148.5 (Ar-C), 156.0 (Ar-C), 156.4 (Ar-C), 158.6 (Ar-C), 159.7 (N–C=O), 169.8 (C=O). **ESI-MS** m/z of $[M+H]^+$ 821.20, 823.30 was obtained for a calculated mass of 821.24, 823.24.

7.2.2.50. (9H-Fluoren-9-yl)methyl 1-(2-bromo-6-(4-(pyridin-2-yl) piperazin-1-yl)-7H-indeno[2,1-c]quinolin-7-ylideneaminooxy)-3-methyl-1-oxobutan-2-ylcarbamate ***(54)*** *Procedure A, yield 70%.* Brown solid; mp 127–128 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1772.28; ^{1}H-NMR (600 MHz, $CDCl_3$): δ 1.06 (d, $J = 6.6$ Hz, 3 H, CH_3), 1.11 (d, $J = 6.6$ Hz, 3 H, CH_3), 2.27–2.35 (m, 1 H, $CH(CH_3)_2$), 3.60–3.98 (m, 8 H, piperazine-CH_2), 4.21–4.27 (m, 1 H, Fmoc-CH), 4.40–4.56 (m, 2 H, Fmoc-CH_2), 4.64 (dd, $J = 6.0, 9.0$ Hz, 1 H, NCH), 5.45 (d, $J = 9.0$ Hz, 1 H, NH), 6.61–6.66 (m, 1 H, H15), 6.74 (d, $J = 8.4$ Hz, 1 H, H13), 7.26–7.33 (m, 2 H, Ar-H), 7.36–7.41 (m, 2 H, Ar-H), 7.47–7.52 (m, 2 H, H11 and H14), 7.58–7.62 (m, 3 H, Ar-H), 7.72 (dd, $J = 1.8, 9.0$ Hz, 1 H, H7), 7.77 (d, $J = 9.0$ Hz, 1 H, Ar-H), 8.18 (d, $J = 7.8$ Hz, 1 H, H9), 8.22 (d, $J = 4.2$ Hz, 1 H, H16), 8.40 (d, $J = 7.8$ Hz, 1 H, H12), 8.54 (d, $J = 1.8$ Hz, 1 H, H5). ^{13}C-NMR (150.9 MHz, $CDCl_3$): δ 17.9 (CH_3), 19.2 (CH_3), 31.7 ($CH(CH_3)_2$), 45.3 (piperazine-CH_2), 47.2 (Fmoc-CH), 49.5 (piperazine-CH_2), 58.4 (NCH), 67.3 (Fmoc-CH_2), 113.0 (C15), 118.5 (Ar-C), 118.7 (Ar-C), 120.0 (Ar-C), 121.9 (Ar-C), 124.2 (C9), 125.1 (Ar-C), 126.1 (C5), 127.1 (Ar-C), 127.8 (Ar-C), 130.0 (C12), 130.2 (C11), 130.5 (Ar-C), 130.6 (Ar-C), 132.5 (Ar-C), 134.2 (C7), 140.2 (Ar-C), 141.3 (Ar-C), 143.68 (Ar-C), 143.81 (Ar-C), 148.2 (Ar-C), 148.7 (Ar-C), 156.3 (Ar-C), 156.5 (Ar-C), 158.8 (Ar-C), 169.1 (C=O). **ESI-MS** m/z of $[M+H]^+$ 806.90, 808.80 was obtained for a calculated mass of 807.22, 809.22.

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Appendix. Supplementary information

Supplementary data related to this article can be found online at doi:10.1016/j.ejmech.2011.01.053.

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