Conformationally-constrained indeno[2,1-*c*]quinolines – a new class of anti-mycobacterial agents†

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The design, synthesis and anti-mycobacterial activities of 23 conformationally-constrained indeno[2,1-*c*]quinolines against *Mycobacterium tuberculosis* H37Rv is reported. Based on a structural comparison with the anti-TB TMC207 we have devised a synthetic methodology for making new conformationally-constrained indeno[2,1-*c*]quinoline analogs (Fig. 1), by retaining the biologically significant quinoline and the phenyl rings in the SW and NW hemispheres, respectively. This new class of conformationally-constrained compounds has been designed such that their conformational flexibility across C4-C2′ is diminished to nil by covalently locking the C4 center of the quinoline moiety in the SW hemisphere with the C2′ center of the phenyl ring in the NW hemisphere, thereby decreasing the entropic penalty for their complex formation within the target protein, which will in turn give improved free-energy of stabilization of the complex. The efficacies of these anti-TB compounds were evaluated *in vitro* for 8/9 consecutive days using the BACTEC radiometric assay upon administration of a single-dose on day one. Compounds **11**, **13**, **16**, **24**, **30**, **32** and **34** showed 85-99% growth inhibition of *Mycobacterium tuberculosis*. Compounds **13** and **34** however have inhibited the mycobacterial growth more effectively than others in the series, with minimum inhibitory concentrations (MIC) of 0.39 μg mL^{-1} (1 μM) and 0.78 μg mL^{-1} (2 μM) respectively.

Introduction

Tuberculosis (TB) is a contagious, deadly disease that spreads through air and has become a serious worldwide health problem.[1] It is the greatest cause of mortality and morbidity worldwide.[2] The WHO has reported that 1/3 (nearly 2 billion) of the world's population is already infected with TB bacilli and every second a new case of TB infection is reported.[3] The WHO report also reveals that 22 countries have the highest TB burden, among them India, China, Indonesia, South Africa and Nigeria rank 1st to 5th respectively in terms of absolute number of TB cases.[4] In 2004, 14.6 million chronic active cases, 8.9 million new cases, and 1.6 million deaths were reported worldwide.[3,4] According to the WHO, the increase in the cases of TB during recent years was largely due to the pathogenic synergy with HIV infection.[3,4] The situation has worsened very seriously with the spread of HIV-1, which allows the latent TB to become active and makes the patient more susceptible to re-infection with either drug-susceptible or drug-resistant strains. Moreover, the increasing emergence of drug-resistant TB, particularly multi-drug resistant TB (MDR-TB),[5] extensive-drug resistant TB (XDR-TB)[6] and the latent form of TB is a great threat to mankind and has already caused several fatal outbreaks.[7] This justifies an urgent need to discover and develop new and effective anti-TB drugs to treat this deadly disease. Focusing on the existing drugs and drug targets for anti-TB drug development[8] may have limitations because of potential cross-resistance of *M. tuberculosis*.[9]

Among the new anti-TB drugs,[10] the quinoline class of compounds[11,12] has shown promising activity against resistant TB. Amongst these, diarylquinoline based molecule R207910 (TMC207) inhibits TB with very high potency.[13] The MIC of TMC207 against *M. tuberculosis* H37Rv is 0.060 μg mL^{-1}, (0.1 μM).[13] Insights from both experimental and theoretical investigations[13] reveal that ATP synthase subunit C is the target of this drug and a mode of action has been discussed.[14,15]

In order to elaborate on the SAR and to develop synthetically more accessible analogs of TMC207, we have systematically altered the functional groups in the four hemispheres of the TMC207 molecule: North-East (NE),[16,17] North-West (NW),[17] South-East (SE)[16,17] and South-West (SW)[17,18] (Fig. 1). One of our primary aims is to develop highly potent molecules with minimal structural complexity, in high yield and through easier routes leading to their chemical synthesis. We have reported the functional importance of the phenyl, naphthyl and bromine moieties of TMC207, based on ATP synthase-ligand docking calculations.[16-18] These studies also revealed the critical role of electrostatic interactions, van der Waals interactions in determining the biological activity.[16-18]

Herein we have explored a novel class of 23 new conformationally-constrained indeno[2,1-*c*]quinolines by covalently locking the C4 center of the quinoline moiety in the SW hemisphere with the C2′ center of the phenyl ring in the NW hemisphere (shown in green dotted line in Fig. 1(A)) based on

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† Electronic supplementary information (ESI) available: Spectral data (^{1}H, ^{13}C NMR, DEPT, LCMS, Mass, HPLC and IR) for all new compounds. See DOI: 10.1039/b924102g

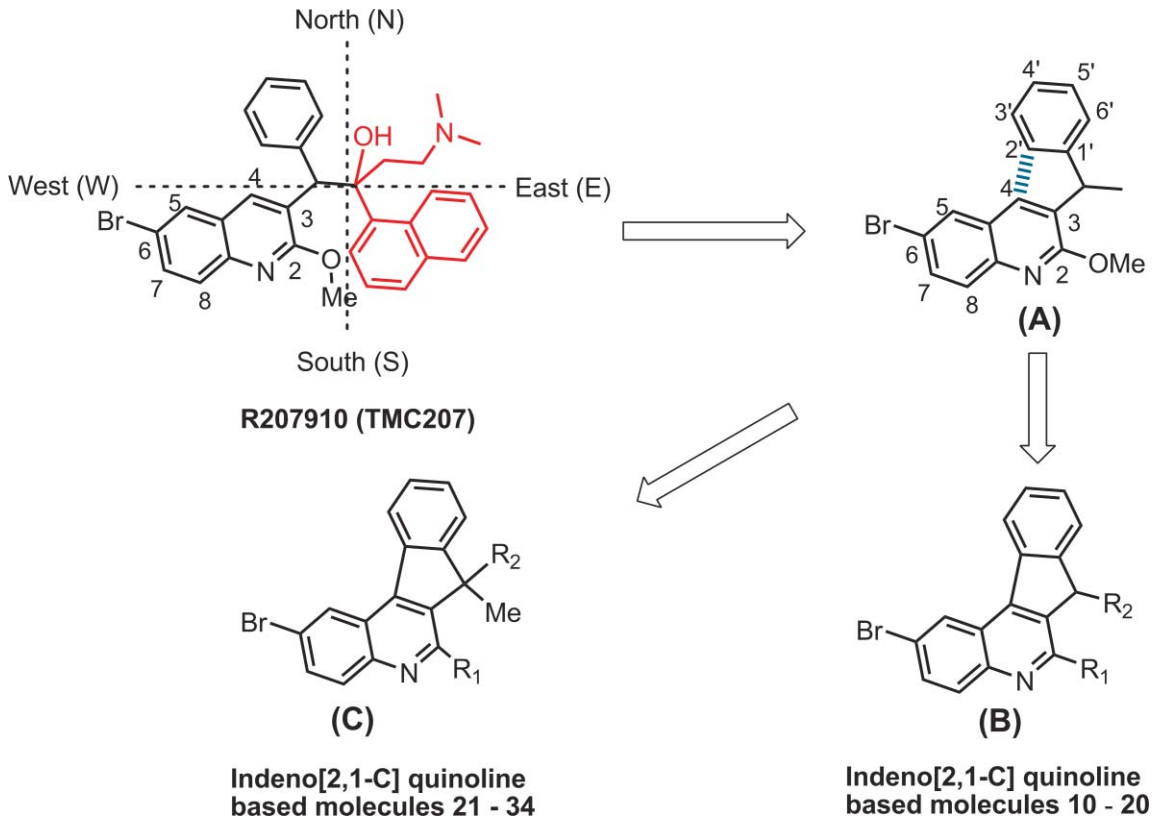


Fig. 1 Four structural hemispheres of R207910 (TMC207). The variable part is shown in red. C4-C2′ bond is shown with a green dotted line in the conformationally-constrained core (A). General formulae (B) and (C) represent the series of compounds synthesized.

following considerations: (1) As TMC207 is a unique molecule with a novel mode of action in term of its anti-mycobacterial activity, which has two chiral centres, *i.e.* four diastereomers, out of which only *R*/*S* diastereomer is active, we saw the need to work around this molecule in order to find a less complex molecule ideally without any chiral centers, which should be cost effective/affordable and accessible. (2) Dissection of the TMC207 molecule (Fig. 1) into four hemispheres shows that the phenyl ring is located at the NW hemisphere, and this phenyl has a free rotation (Fig. 1) with respect to quinoline skeleton. The free rotation of this phenyl ring should potentially increase the entropy during the ligand-protein complex formation, which we wanted to minimize by locking the C2′ phenyl at the C4 position of quinoline, thereby increasing the free-energy of stabilization of the ligand-protein complex.

We anticipated that the entropic penalty for complex formation with the target protein would be reduced upon restricting the conformational flexibility, which might enhance the binding affinity. Based on a simple two-dimensional comparison of the TMC207 with our conformationally-constrained molecules (Fig. 1), we have attempted to explore the biological significance of the quinoline moiety and the phenyl ring in the SW and NW hemispheres of TMC207, respectively. This was achieved by constructing the indeno[2,1-*c*]quinoline core system as shown in **A**→ **B**/**C** in Fig. 1. At the same time, the functionally important groups of the NE hemisphere were replaced with different polar groups, which would retain the equivalent polar interactions with the binding site.

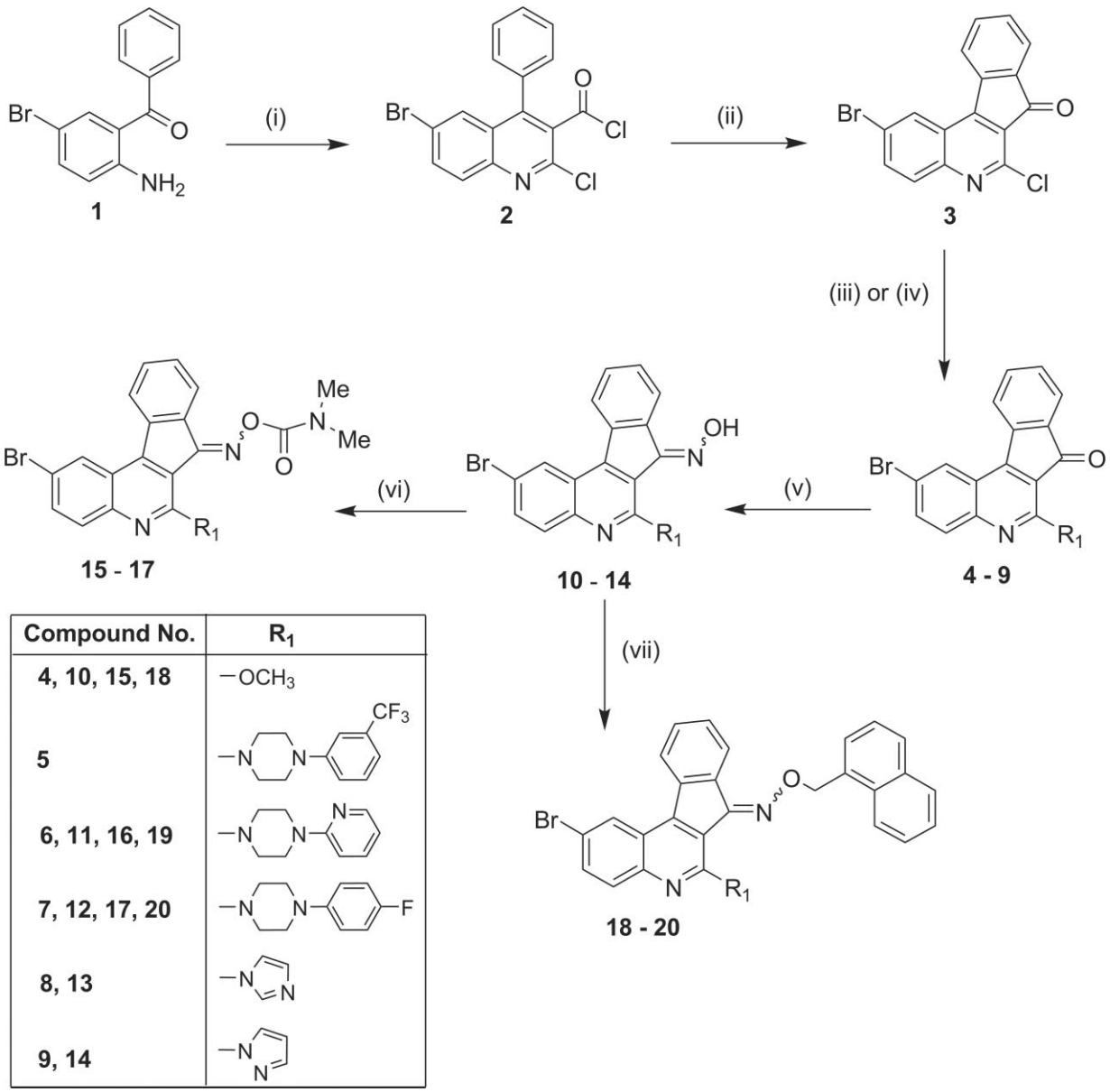
We herein report that the new indeno[2,1-*c*]quinoline based molecules exhibited very good activity toward *M. tuberculosis* H37Rv, showing up to 99% inhibition *in vitro* by BACTEC 460 radiometric assay[19,20] at MIC of <0.39-6.25 μg mL^{-1} (<0.99-14.63 μM mL^{-1}).

Results

Synthesis

Synthesis of the conformationally-constrained indeno[2,1-*c*]quinoline molecules started with 2-amino-5-bromo-benzophenone[21] (**1**, Scheme 1). Treatment of benzophenone **1**[21] with malonic acid in $POCl_3$ gave quinoline **2** (<20%) and unreacted benzophenone **1**. Optimization of reaction conditions however improved the yield of quinoline **2** (53%) along with the desired conformationally-locked indeno[2,1-*c*]quinoline **3** (16%) as a result of Friedel-Crafts cyclization of **2**. The yield of indeno[2,1-*c*]quinoline **3** (84%) was however improved by intramolecular Friedel-Crafts acylation ($AlCl_3$)[21] of quinoline **2**. Nucleophilic displacement at the C2 center of 2-chloro-indeno[2,1-*c*]quinoline **3** by an appropriate nucleophile furnished 2-substituted indeno[2,1-*c*]quinolines **4-9** (71-97%) (Scheme 1 and experimental section).

The indeno[2,1-*c*]quinoline-7-oximes **10-14** (72-96%) were synthesized by heating $NH_2OH{\cdot}HCl$ and NaOH with the appropriate indeno[2,1-*c*]quinoline-7-ketones (**4**, **6-9**, respectively) in an ethanol-water (2 : 1, v/v) mixture. The oximes **10-12** were

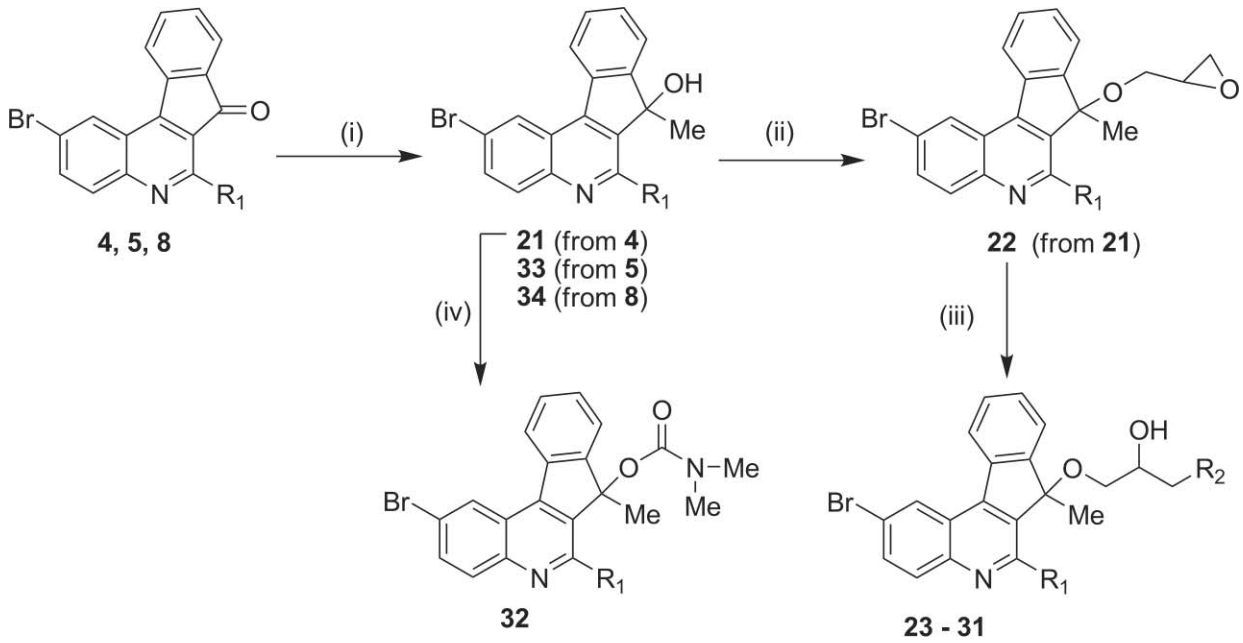


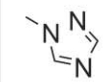
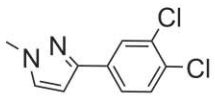
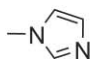
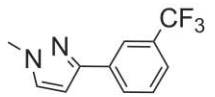
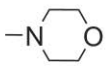
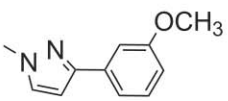
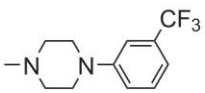
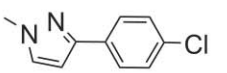
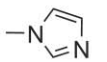
Compound No.	R_1
4, 10, 15, 18	$-OCH_3$
5	
6, 11, 16, 19	
7, 12, 17, 20	
8, 13	
9, 14	

Scheme 1 Synthesis of conformationally-constrained indeno[2,1-*c*]quinolines (**3-20**). *Reagents and conditions*: (i) malonic acid (1.5 eq), $POCl_3$, 105 °C, 3 h; 53%; (ii) $AlCl_3$ (2.5 eq), DCM, rt, 3 h; 84%; (iii) NaOMe (10 eq), dry THF : dry MeOH (2 : 1), reflux, 3 h; **4** (97%); (iv) R_1H (5 eq), pyridine, 105 °C, 12 h; **5** (90%), **6** (92%), **7** (71%), **8** (87%), **9** (76%); (v) $NH_2OH{\cdot}HCl$ (3 eq), NaOH (5 eq), EtOH-water (2 : 1), 0 °C, 15 min followed by 80-90 °C, 3-8 h; **10** (91%), **11** (96%), **12** (95%), **13** (72%), **14** (94%); (vi) NaH (1.1 eq), *N*,*N*-dimethylcarbamyl chloride (2 eq), dry DMF, rt, 12 h; **15** (66%), **16** (63%), **17** (62%); (vii) NaH (1.1 eq), 1-chloromethyl naphthalene (1.5 eq), dry DMF, rt, 3-12 h; **18** (48%), **19** (54%), **20** (50%).

subsequently acylated with *N*,*N*-dimethylcarbamoyl chloride and NaH in dry DMF to give the corresponding *N*,*N*-dimethylcarbamoyl oximes **15-17** (62-66%). The second set of molecules was prepared from indeno[2,1-*c*]quinoline-7-oximes **10-12** to give *O*-naphthalene-1-yl methyl-oximes **18-20** (48-54%) by alkylation with 1-chloromethyl-naphthalene using NaH (Scheme 1 and experimental section).

The third set of molecules (Scheme 2) were based on the conversion of 2-methoxyindeno[2,1-*c*]quinoline-7-ketone **4** to the corresponding 7-methyl-7-ol **21** (77%) as an inseparable enantiomeric mixture by Grignard reagent (MeMgI). The key intermediate oxirane **22** (69%) was then synthesized by treatment of alcohol **21** with *epi*-chlorohydrin and NaH. Oxirane **22** was subsequently reacted with appropriate amines (R_2H) and K_2CO_3 to give **23-31** (40-77%, respectively) as a diastereomeric mixture. From these, only the diastereomeric mixture of compounds **23** and **24** could be separated as pure **23** and **24** (compound **23** is relatively less polar then **24**) by flash column chromatography. Compound **32** was synthesized by acylation of the alcohol **21** with *N*,*N*-dimethyl carbamoyl chloride in dry DMF using NaH. Grignard reaction of MeMgI on ketones **5** and **8** gave target compounds **33** (82%) and **34** (56%) respectively.



Compd No.	R_1	R_2	Compd No.	R_1	R_2
4, 21, 22, 32	$-OCH_3$		**29**	$-OCH_3$	
23, 24	$-OCH_3$		**30**	$-OCH_3$	
25	$-OCH_3$		**31**	$-OCH_3$	
26	$-OCH_3$		**5, 33**		
27	$-OCH_3$		**8, 34**		
28	$-OCH_3$				

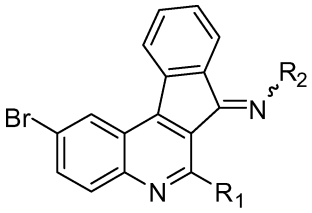
Scheme 2 Synthesis of compounds **21-34**. *Reagents and conditions*: (i) MeMgI (1.2-6 eq), dry THF, **21**, 15 °C-rt, 6 h, (77%); **33**, rt, 6 h, (82%); **34**, 0 °C, 15 min (56%); (ii) NaH (2.1 eq), *epi*-chlorohydrin (2.1 eq), dry DMF, rt, 48 h; 69%; (iii) K_2CO_3 (5 eq), R_2H (1-5 eq), dry DMF, 65-70 °C, 15 h; **23** (22%), **24** (28%), **25** (50%), **26** (70%), **27** (40%), **28** (77%), **29** (77%), **30** (70%), **31** (41%); (iv) dry DMF, *N*,*N*-dimethylcarbamoyl chloride (2.5 eq), NaH (2.1 eq), rt, 15 h; **32** (25%).

Anti-mycobacterial activity

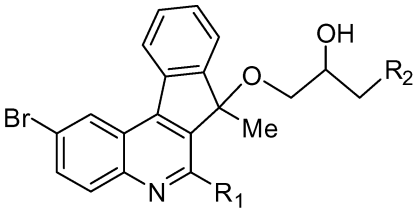
Compounds **10-34** and standard drug Isoniazid[22] were tested against *M. tuberculosis* H37Rv (ATCC 27294) at a fixed concentration of 6.25 μg mL^{-1} by BACTEC 460 radiometric method[19,20] upon administration of a single-dose on day-one and then the TB growth was monitored for 8/9 consecutive days. The results are summarized in Table 1. On the basis of the calculated values of growth index (GI) and growth inhibition (%) (Figure S1, Supplementary information), seven compounds **11**, **13**, **16**, **24**, **30**, **32** and **34** were found to show excellent anti-mycobacterial activity. Fig. 2 shows the bar graph of % TB growth inhibition for the compounds **11**, **13**, **16**, **24**, **30**, **32** and **34** along with Isoniazid[22] for the sake of comparison under identical experimental conditions.

Fig. 2 shows comparison of the inhibition ability of compounds **11**, **13**, **16**, **24**, **30**, **32** and **34** with respect to Isoniazid, and suggests

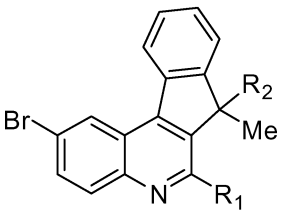
Table 1 % GI inhibition of *M. tuberculosis* H37Rv at a fixed dose 6.25 μg mL^{-1}, administered on day-one, and effect observed for 8/9 consecutive days and clogP values[a]



10 - 20



23 - 31



32 - 34

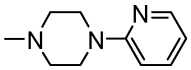
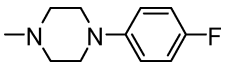
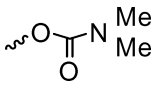
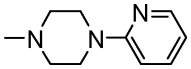
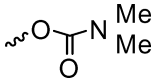
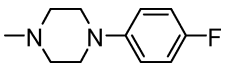
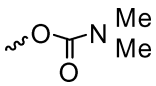
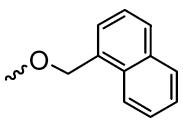
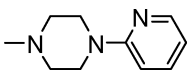
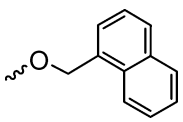
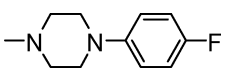
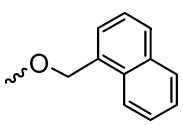
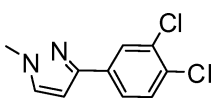
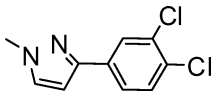
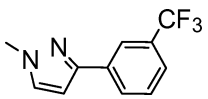
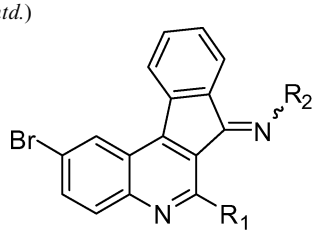
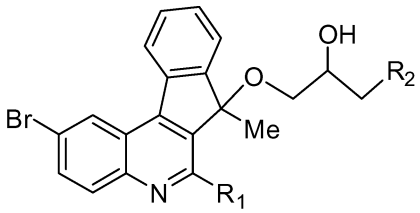
Compd. no.	R_1	R_2	% GI Inhibition[b]	clogP
10	-OCH_3	-OH	22	5.67
11		-OH	90	5.95
12		-OH	16	7.22
13		-OH	99	4.90
14		-OH	29	5.29
15	-OCH_3		58	5.18
16			85	5.45
17			50	6.71
18	-OCH_3		13	9.36
19			29	9.66
20			8	10.92
23	-OCH_3		43	8.11
24	-OCH_3		88	8.11
25	-OCH_3		77	7.70

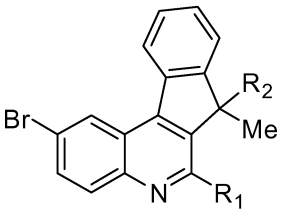
Table 1 (*Contd.*)



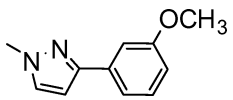
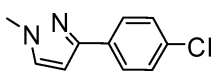
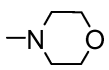
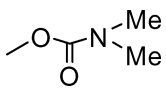
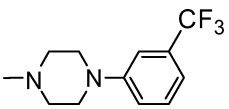
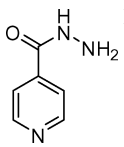
10 - 20



23 - 31



32 - 34

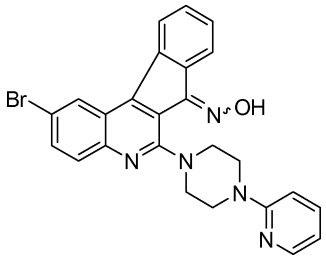
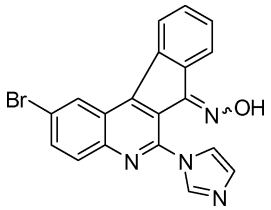
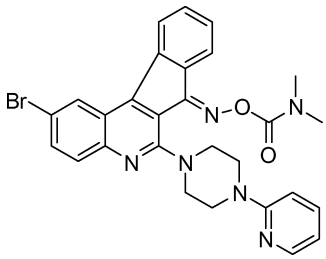
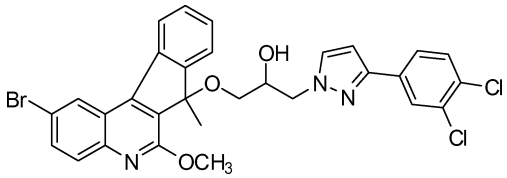
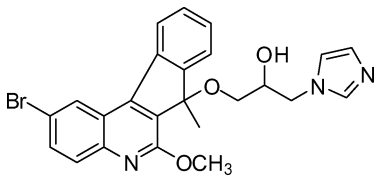
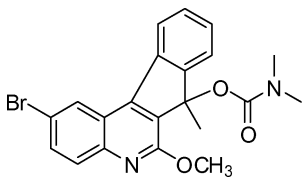
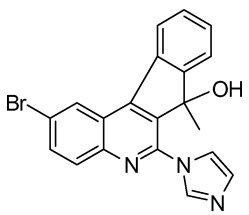
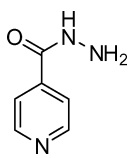
Compd. no.	R_1	R_2	% GI Inhibition[b]	clogP
26	-OCH_3		66	6.75
27	-OCH_3		40	7.51
28	-OCH_3		77	4.68
29	-OCH_3		79	3.68
30	-OCH_3		98	4.27
31	-OCH_3		68	4.71
32	-OCH_3		92	5.65
33		-OH	34	6.94
34		-OH	91	3.77
 **Isoniazid**			99	–0.8[c]

[a] Values are means of triplicate measurement of % GI inhibition. Assays are performed by BACTEC 460 radiometric method.[19,20] [b] Estimated with reference to Growth Inhibition of the first front-line inhibitor, Isoniazid. [c] From PubChem (http://pubchem.ncbi.nlm.nih.gov).

that these compounds can successfully inhibit the *M. tuberculosis* H37Rv growth by 90% (±4.54), 99% (±0.29), 85% (±3.54), 88% (±3.11), 98% (±0.98), 92% (±0.96) and 91% (±3.15), respectively under identical experimental condition. These compounds are comparable to Isoniazid (Table 1, Figure S1). Based on the GI plots, it was observed that Isoniazid did not show zero growth of *M. tuberculosis* (Figure S1), which was not the case with the highly active compound **13**. The anti-mycobacterial activity profiles of compounds **13** and **30** suggest that they may have a bactericidal effect, as there was no growth in the treated control over 8/9 consecutive days. MIC of the most active compounds **11**, **13**, **16**, **24**, **30**, **32** and **34** are given in Table 2.

Diastereomers **23** and **24** displayed different biological activities. We found that more the polar diastereomer **24** is more active (88% inhibition) than the relatively less polar diastereomer **23** (43% inhibition). The high-inhibition capacity of compound **30** (98% inhibition) is likely because of its relatively smaller size, hence better induced fitting in the binding site (lower van der Waals energy as described by docking and scoring calculations, Table S3 in SI).

Table 2 MIC [a] of compounds against *M. tuberculosis* H37Rv

Compd. no.	Structure	MIC/μg mL^{-1}	MIC/μM
11		6.25	12.8
13		< 0.39	< 0.99
16		1.56	2.79
24		3.125	5.0
30		3.125	6.51
32		6.25	14.63
34		0.78	1.98
Isoniazid		0.256	1.86

[a] MIC determined by BACTEC 460 radiometric method.[19,20]

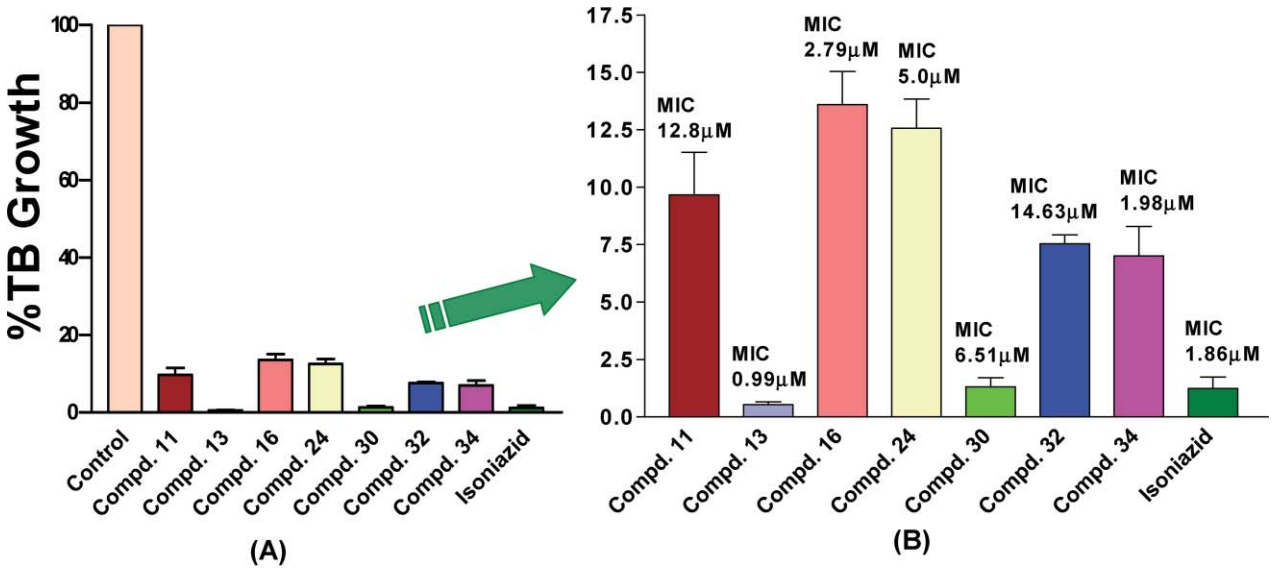


Fig. 2 % TB growth inhibition shown for compounds **11**, **13**, **16**, **24**, **30**, **32** and **34** along with standard drug Isoniazid. Negative control is shown in error bar graph (**A**). MIC_{99} in μM of individual compounds is represented on the top of bar in (**B**). The daywise %GI curve upon single dose at day one is given in supporting information Figure S1.

Cytotoxicity

Cytotoxicity results of **11**, **13**, **16**, **24**, **32** and **34** (Table 3) suggest that these compounds are not cytotoxic to host cells at the given concentrations, except compound **30**, which is the least safe (cell viability 65%) to human monocytic cells.

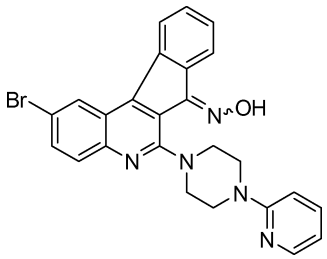
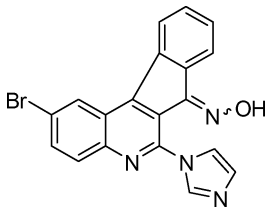
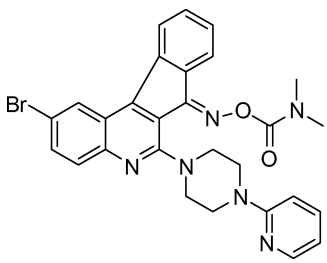
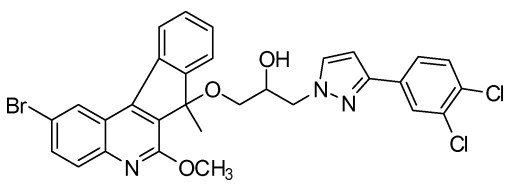
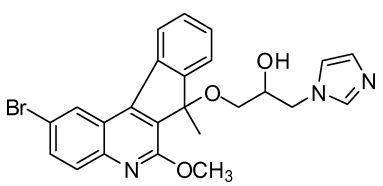
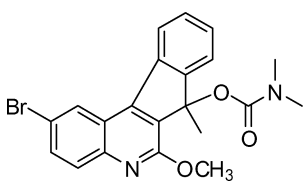
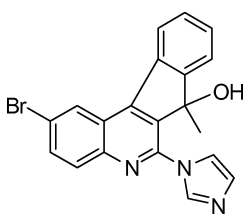
Discussion

The bulky naphthalene group of the SE hemisphere of TMC207 was replaced by a methyl group in compounds **33** and **34** while the tertiary hydroxyl group of the NE hemisphere was retained, which would enable polar interactions with the binding site and maintain both polar and non-polar interactions with the target protein. Compound **34** displayed good biological activity; presumably the imidazole ring enhanced the cell-membrane permeability[23,24] while the hydroxyl group may form polar interactions with the target site. The low biological activity of compound **33** as compared to **34** may be due to steric hindrance caused by the bulky trifluoromethyl-phenyl-piperazine group at the C2 position. Also docking calculations (SI) with putative target ATP-synthase subunit C (since these compounds are derivatives of DARQ[12,13]) reveal that compound **33** had high van der Waals docking energies (Table S3).

In general, derivatives carrying a tertiary hydroxyl group (compound **34**) or an oxime group (compound **11** and **13**) along with imidazole (compound **34** and **13**) or 2-pyridyl-piperizine groups (compound **11** and **16**) at the C2 position showed good anti-mycobacterial activity (Table 1). Replacing the tertiary hydroxyl group with an oxime resulted in more polar compounds (**10-14**), which we assumed would bind relatively more tightly with the target binding site. In addition, loss of the methyl group would allow less hindered interactions of the hydroxyl group with the binding site. Both imidazole and 2-pyridyl piperazine are potential proton-acceptors as with DARQ, which could block the proton-transfer of ATP-synthase, when bound to its subunit C.[12,13]

Compound **13** showed most impressive TB inhibition (99%, Table 1) and lowest MIC (<0.39 μg mL^{-1}, 0.99 μM, Table 2) amongst all the compounds tested. Compound **13** has an imidazole ring at C2 which besides being a good protonable group at physiological pH, could also act as a binding region by proton bridge, and at the same time may be helping in enhancing membrane permeability.[23,24] It is likely that the highly polar oxime group of compound **13** can act as a main binding motif to the protein. The relatively smaller size of compound **13** could potentially improve induced fitting in the binding site (low van der Waals energy, Table S3), as was observed with docking calculations (Table S3). Compound **13** has a smaller imidazole group at the C2 position (99% GI), relative to compound **11** with a 2-pyridyl piperazine group (90% GI), and inhibits *Mycobacterium* TB effectively. Apparently, the oxime analogue; compound **13** with an imidazole group (MIC <0.39 μg mL^{-1}) is likely to be the reason for its enhanced potency compared to compound **34** (MIC 0.78 μg mL^{-1}), which possesses a relatively less polar hydroxyl group. However, both compounds **34** (91% GI) and **13** (99% GI) have a smaller and similar imidazole moiety at the C2 position and they showed very similar and effective TB inhibition, suggesting a critical role for the imidazole ring, as discussed above. A slight change of the aromatic character of the nitrogen *i.e.* from imidazole in **13** (99% GI) to pyrazole in **14** (29% GI) resulted in a drastic reduction in biological activity for the latter. A possible reason could be a difference in pK_a values of imidazole and pyrazole. The pK_a of the imidazole group is ~6.3 and the pK_a of the pyrazole group is ~2.1, and hence there is a considerable concentration (~10%) of protonated **13** at neutral pH compared to that of **14**. Perhaps, this charged species of **13** is the active form and makes compound **13** highly active against *M. tuberculosis*. Similarly activity of compound **28** and compound **30** can be compared. Compound **30** (98% GI) is also an imidazole

Table 3 Cytotoxic effects of tested compounds on human monocytic cell line U937 at 24 h and 72 h after the treatment (See experimental section for cytotoxicity protocol)

		Human monocytic U937 cell viability (%)							
Compd. No.	Structure	24 h	Conc./ μg mL^{-1}	72 h	Conc./ μg mL^{-1}	24 h	Conc./ μg mL^{-1}	72 h	Conc./ μg mL^{-1}
11		100	4	100	4	100	1	100	1
13		89	3	91	3	100	1	100	1
16		100	5	100	5	100	1	100	1
24		79	5	82	5	100	1	100	1
30		80	10	68	10	78	1	65	1
32		90	10	74	10	100	1	100	1
34		48	5	64	5	85	1	93	1

containing analogue with a similar pK_a and displays excellent activity as compared to pyrazole containing compound **28** (77% GI). Comparison of compound **13** (imidazole at C2) (99% GI) and **30** (imidazole at side chain) (98% GI), both displaying the highest TB inhibition, allows us to conclude that besides the common core (conformationally constrained system), the imidazole ring may have a crucial functional role in modulating the binding to the target protein. We suggest that the polar groups on these two compounds could form stabilizing interactions with the putative target receptor ATP-synthase.

Comparison of compound **16** (85% GI) and compound **11** (90% GI) suggest that the 2-pyridyl-piperizine moiety at the C2 position is critical, and presumably the adverse bulkiness of the functional 2-pyridyl-piperizine group is compensated by the high proton-affinity or hydrogen-bonding capability of the pyridyl-piperazine group. Compounds **10** (22% GI), **15** (58% GI) and **18** (13% GI) were found to be less active as compared to the compounds **11** (90% GI), **13** (99% GI), **16** (85% GI) and **34** (91% GI) (Table 1), which suggests that the C2 position should not have electron donating group like methoxy group. Compounds **18-20** showed very low (<29% GI) anti-mycobacterial activities, possibly due to the bulky naphthalene group, making it hydrophobic (clogP values for compound **18**, **19** and **20** are 9.36, 9.66 and 10.92 respectively) which may be preventing the interaction of the oxime group with the target protein.

Our preliminary docking studies for compounds **10-20** (data set I in Table S3) have been analyzed by AutoDock scoring, potential of mean force (PMF) scoring, X-scoring and by electrostatic energies in comparison with their respective biological activity data (Table S3). It has been found that biologically active molecules show lower docking scores (Table S3).

The compounds presented here possess a conformationally constrained indeno[2,1-*c*]quinoline core, which has analogy to the well-known TMC207.[12,13] Besides, the replacement of polar groups of the NE hemisphere of TMC207 with oxime and hydroxyl, we foresee that further SAR studies with more analogs might shed more light to further explore and modulate the synergistic effects of both the indeno[2,1-*c*]quinoline core as well as the substituents at C2 position of the ring, as observed for compounds **11**, **13** and **34**.

Conclusion

In conclusion, we have designed and synthesized a novel class of conformationally constrained anti-mycobacterial molecules based on the combination of the indeno[2,1-*c*]quinoline backbone with various polar groups. The effects of various substituents on the indeno[2,1-*c*]quinoline skeleton on the relative activity of the molecules synthesized are described. The activity of seven molecules, **11** (MIC 6.25 μg mL^{-1}), **13** (MIC 0.39 μg mL^{-1}), **16** (MIC 1.56 μg mL^{-1}), **24** (MIC 3.125 μg mL^{-1}), **30** (MIC 3.125 μg mL^{-1}), **32** (MIC 6.25 μg mL^{-1}) and **34** (MIC 0.78 μg mL^{-1}) were comparable to that of the existing front-line drug, Isoniazid (MIC 0.25 μg mL^{-1}) under identical conditions. This is the first report on indeno[2,1-*c*]quinoline derivatives as active anti-mycobacterial agents. This class of molecules has shown a great potential to develop as effective, easily accessible anti-mycobacterial agents, which can help to shorten the duration of anti-TB therapy.

Experimental section

Chemistry – general experimental methods

2-Amino-5-bromo-benzophenone (**1**) was prepared according to the literature procedure.[21] Purification and drying of reagents and solvents were carried out according to literature procedures.[25] 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, ^{13}C NMR spectra were recorded on a Bruker Biospin 400 MHz spectrometer with TMS as an internal standard. The values of chemical shifts are expressed in δ ppm and the coupling constants (J) in Hertz (Hz). Mass spectra were recorded on an API 2000 LC/MS/MS system spectrometer up to 2 decimal places. IR spectra were recorded on a Perkin-Elmer Spectrum RX1.

6-Bromo-2-chloro-4-phenyl-quinoline-3-carbonyl chloride (2)

2-Amino-5-bromo-benzophenone[21] (**1**, 10.0 g, 36.23 mmol) and malonic acid (5.65 g, 54.30 mmol) were mixed, dried under reduced pressure, dissolved in freshly distilled $POCl_3$ (200 mL) and heated at 105 °C for 3 h. The reaction mixture was cooled, poured in crushed ice in portions with constant stirring and extracted with DCM (2 × 500 mL). A DCM insoluble yellow solid was formed. The DCM extract was washed with water until the aqueous washes became neutral to pH paper, followed by brine (1 × 100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to obtain a brown gum. This crude gum was purified by column chromatography (silica gel 100-200 mesh, eluent: gradient elution with n-hexane to 3% ethyl acetate in n-hexane) to give compound **2** (7.33 g, 53%) as a yellow solid; mp 166-170 °C. ν_{max} (KBr, cm^{-1}): 1773. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.40 (m, 2 H, Ar-H), 7.53-7.61 (m, 3 H, Ar-H), 7.74 (d, J = 2.0 Hz, 1 H, Ar-H), 7.88 (dd, J = 9.0, 2.0 Hz, 1 H, Ar-H), 7.96 (d, J = 9.0 Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 122.5 (Ar-C), 126.6 (Ar-C), 129.0 (Ar-C), 129.1 (Ar-C), 129.4 (Ar-C), 130.1 (Ar-C), 130.5 (Ar-C), 131.9 (Ar-C), 132.1 (Ar-C), 135.7 (Ar-C), 143.4 (Ar-C), 146.3 (Ar-C), 146.8 (Ar-C), 165.9 (C=O). ESI-MS m/z of 380.00, 381.90 [M+H]$^+$ was obtained for a calculated mass of 379.92, 381.92.

The yellow solid obtained was washed with DCM, dried and characterized by mp and ^{1}H-NMR, which matched with compound **3** (2.0 g, 16%) [See below for the spectroscopic properties of compound **3**].

2-Bromo-6-chloro-indeno[2,1-*c*]quinolin-7-one (3)

To a cooled (0 °C) solution of compound **2** (8.15 g, 21.39 mmol) in DCM (150 mL), aluminium chloride (7.11 g, 53.5 mmol) was added portion wise and then the mixture was stirred at room temperature for 3 h. The color of the reaction turned brown. The reaction mixture was again cooled to 0 °C, quenched by adding ice and stirred vigorously for 1 h. The desired product precipitated as a yellow solid which was extracted with DCM (4 × 500 mL). The organic layer was evaporated under reduced pressure to obtain a yellow solid which was washed with methanol (3 × 100 mL), ethyl acetate (2 × 50 mL), n-hexane (2 × 50 mL) and dried under reduced

pressure to obtain pure compound **3** (6.20 g, 84%); mp 304-306 °C. ν_{max} (KBr, cm^{-1}): 1714. ^1H NMR (400 MHz, CF_3COOD): δ 8.06-8.13 (m, 1 H, Ar-H), 8.14-8.20 (m, 1 H, Ar-H), 8.26 (d, $J = 7.2$ Hz, 1 H, Ar-H), 8.35 (d, $J = 9.0$ Hz, 1 H, Ar-H), 8.60 (d, $J = 9.0$ Hz, 1 H, Ar-H), 8.72 (d, $J = 7.5$ Hz, 1 H, Ar-H), 9.33 (s, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, CF_3COOD): δ 124.8 (Ar-C), 125.8 (Ar-C), 126.5 (Ar-C), 129.4 (Ar-C), 129.8 (Ar-C), 130.8 (Ar-C), 131.8 (Ar-C), 137.5 (Ar-C), 139.1 (Ar-C), 140.1 (Ar-C), 140.8 (Ar-C), 144.1 (Ar-C), 145.7 (Ar-C), 146.2 (Ar-C), 190.2 (C=O). ESI-MS m/z of 344.00, 345.90 $[M+H]^+$ was obtained for a calculated mass of 343.95, 345.95.

2-Bromo-6-methoxy-indeno[2,1-*c*]quinolin-7-one (4)

To a suspension of compound **3** (5.00 g, 14.51 mmol) in dry THF : dry MeOH (2 : 1, 450 mL), sodium methoxide (30% w/v in MeOH, 26.1 mL, 145.1 mmol) was added and refluxed under nitrogen atmosphere for 3 h. The reaction mixture was concentrated under reduced pressure to obtain a brown solid. The brown solid obtained was extracted with DCM (500 mL), washed with water (3×200 mL) and brine (1×100 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to obtain compound **4** (4.80 g, 97%) as a yellow solid; mp 208-210 °C. ν_{max} (KBr, cm^{-1}): 1719. ^1H NMR (400 MHz, $CDCl_3$): δ 4.19 (s, 3 H, OCH_3), 7.44-7.52 (m, 1 H, Ar-H), 7.60 (td, $J = 7.6$, 1.2 Hz, 1 H, Ar-H), 7.74 (d, $J = 8.8$ Hz, 2 H, Ar-H), 7.79 (dd, $J = 9.0$, 2.0 Hz, 1 H, Ar-H), 8.01 (d, $J = 7.6$ Hz, 1 H, Ar-H), 8.50 (d, $J = 2.0$ Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 54.0 (OCH_3), 114.9 (Ar-C), 118.9 (Ar-C), 122.1 (Ar-C), 123.9 (Ar-C), 124.2 (Ar-C), 126.9 (Ar-C), 130.1 (Ar-C), 131.2 (Ar-C), 133.4 (Ar-C), 134.1 (Ar-C), 135.5 (Ar-C), 140.7 (Ar-C), 150.0 (Ar-C), 154.2 (Ar-C), 158.6 (Ar-C), 190.7 (C=O). ESI-MS m/z of 340.10, 342.10 $[M+H]^+$ was obtained for a calculated mass of 340.00, 342.00.

General procedure A for 5-9: 6-amino-2-bromo-indeno[2,1-*c*]quinolin-7-ones

A mixture of compound **3** (1 eq) and the appropriate amine (R_1H, 5 eq) was heated in dry pyridine at 105 °C for 12 h. The reaction mixture was cooled to room temperature and poured into water. The precipitate obtained was filtered, washed with water and dried under reduced pressure to obtain the corresponding 2-bromo-indeno[2,1-*c*]quinolin-7-ones **5-9** in good yield (71-92%).

2-Bromo-6-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-indeno[2,1-*c*]quinolin-7-one (5)

Procedure A, yield 90%. Red solid; mp 177-179 °C. ν_{max} (KBr, cm^{-1}): 1702. ^1H NMR (400 MHz, $CDCl_3$): δ 3.31-3.38 (m, 4 H, Ar-N-CH_2-CH_2), 3.79-3.86 (m, 4 H, Ar-N-CH_2-CH_2), 6.94-7.02 (m, 4 H, Ar-H), 7.42-7.50 (m, 1 H, Ar-H), 7.55-7.62 (m, 1 H, Ar-H), 7.63-7.70 (m, 2 H, Ar-H), 7.73 (dd, $J = 9.0$, 2.0 Hz, 1 H, Ar-H), 8.03 (d, $J = 7.5$ Hz, 1 H, Ar-H), 8.47 (d, $J = 2.0$ Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.0 (Ar-N-CH_2-CH_2), 50.4 (Ar-N-CH_2-CH_2), 115.5 (Ar-C), 115.7 (Ar-C), 116.0 (Ar-C), 117.99 (Ar-C), 118.0 (Ar-C), 118.1 (Ar-C), 121.3 (Ar-C), 123.9 (Ar-C), 124.0 (Ar-C), 126.9 (Ar-C), 130.2 (Ar-C), 131.0 (Ar-C), 133.5 (Ar-C), 134.1 (Ar-C), 135.7 (Ar-C), 141.1 (Ar-C), 148.0 (Ar-C), 149.8 (Ar-C), 151.0 (Ar-C), 154.7 (Ar-C), 155.5 (Ar-C), 156.1 (Ar-C), 158.5 (Ar-C), 191.9 (C=O). ESI-MS m/z of 538.00, 539.90 $[M+H]^+$ was obtained for a calculated mass of 538.07, 540.07.

2-Bromo-6-(4-pyridin-2-yl-piperazin-1-yl)-indeno[2,1-*c*]quinolin-7-one (6)

Procedure A, yield 92%. Red solid; mp 186-188 °C. ν_{max} (KBr, cm^{-1}): 1699. ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 8 H, piperazine-CH_2), 6.65 (dd, $J = 7.0$, 5.1 Hz, 1 H, Ar-H), 6.71 (d, $J = 8.5$ Hz, 1 H, Ar-H), 7.43-7.54 (m, 2 H, Ar-H), 7.58 (td, $J = 7.5$, 1.1 Hz, 1 H, Ar-H), 7.63-7.76 (m, 3 H, Ar-H), 8.01 (d, $J = 7.5$ Hz, 1 H, Ar-H), 8.18-8.25 (m, 1 H, Ar-H), 8.45 (d, $J = 2.0$ Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 45.3 (Ar-N-CH_2-CH_2), 48.7 (Ar-N-CH_2-CH_2), 107.1 (Ar-C), 113.4 (Ar-C), 115.8 (Ar-C), 117.8 (Ar-C), 121.1 (Ar-C), 123.77 (Ar-C), 123.81 (Ar-C), 126.7 (Ar-C), 130.0 (Ar-C), 130.8 (Ar-C), 133.4 (Ar-C), 133.9 (Ar-C), 135.5 (Ar-C), 137.5 (Ar-C), 140.9 (Ar-C), 147.9 (Ar-C), 150.8 (Ar-C), 154.4 (Ar-C), 155.4 (Ar-C), 159.6 (Ar-C), 191.6 (C=O). ESI-MS m/z of 471.00, 473.10 $[M+H]^+$ was obtained for a calculated mass of 471.08, 473.08.

2-Bromo-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-indeno[2,1-*c*]quinolin-7-one (7)

Procedure A, yield 71%. Red solid; mp 192-194 °C. ν_{max} (KBr, cm^{-1}): 1703. ^1H NMR (400 MHz, $CDCl_3$): δ 3.22-3.46 (m, 4 H, Ar-N-CH_2-CH_2), 3.72-3.90 (m, 4 H, Ar-N-CH_2-CH_2), 6.94-7.02 (m, 4 H, Ar-H), 7.46 (t, $J = 7.4$ Hz, 1 H, Ar-H), 7.59 (t, $J = 7.5$ Hz, 1 H, Ar-H), 7.64-7.76 (m, 3 H, Ar-H), 8.01 (d, $J = 7.5$ Hz, 1 H, Ar-H), 8.46 (d, $J = 1.8$ Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 49.0 (Ar-N-CH_2-CH_2), 50.4 (Ar-N-CH_2-CH_2), 115.5 (Ar-C), 115.7 (Ar-C), 116.0 (Ar-C), 117.98 (Ar-C), 118.03 (Ar-C), 118.11 (Ar-C), 121.3 (Ar-C), 123.9 (Ar-C), 124.0 (Ar-C), 127.0 (Ar-C), 130.2 (Ar-C), 131.0 (Ar-C), 133.5 (Ar-C), 134.1 (Ar-C), 135.7 (Ar-C), 141.1 (Ar-C), 148.1 (Ar-C), 151.0 (Ar-C), 154.7 (Ar-C), 155.5 (Ar-C), 156.1 (Ar-C), 158.5 (Ar-C), 191.9 (C=O). ESI-MS m/z of 488.00, 490.10 $[M+H]^+$ was obtained for a calculated mass of 488.08, 490.08.

2-Bromo-6-imidazol-1-yl-indeno[2,1-*c*]quinolin-7-one (8)

Procedure A, yield 87%. Red solid; mp 284-286 °C. ν_{max} (KBr, cm^{-1}): 1712. ^1H NMR (400 MHz, DMSO-d_6): δ 7.13 (s, 1 H, Ar-H), 7.65 (t, $J = 7.2$ Hz, 1 H, Ar-H), 7.73-7.82 (m, 2 H, Ar-H), 7.88 (s, 1 H, Ar-H), 7.98 (d, $J = 9.0$ Hz, 1 H, Ar-H), 8.12 (d, $J = 9.0$ Hz, 1 H, Ar-H), 8.43 (s, 1 H, Ar-H), 8.54 (d, $J = 7.5$ Hz, 1 H, Ar-H), 8.87 (s, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, CF_3COOD): δ 120.1 (Ar-C), 121.9 (Ar-C), 124.3 (Ar-C), 127.4 (Ar-C), 128.35 (Ar-C), 128.37 (Ar-C), 128.5 (Ar-C), 130.0 (Ar-C), 132.6 (Ar-C), 135.2 (Ar-C), 136.0 (Ar-C), 138.9 (Ar-C), 139.4 (Ar-C), 141.9 (Ar-C), 142.7 (Ar-C), 143.0 (Ar-C), 151.3 (Ar-C), 160.0 (Ar-C), 194.0 (C=O). ESI-MS m/z of 376.03, 378.05 $[M+H]^+$ was obtained for a calculated mass of 376.01, 378.01.

2-Bromo-6-pyrazol-1-yl-indeno[2,1-*c*]quinolin-7-one (9)

Procedure A, yield 76%. Red solid; mp 289-290 °C. ν_{max} (KBr, cm^{-1}): 1711. ^1H NMR (400 MHz, DMSO-d_6): δ 6.56-6.60 (m, 1 H, Pyrazole-CH), 7.59 (t, $J = 7.2$ Hz, 1 H, Ar-H), 7.66 (d, $J = 7.0$ Hz, 1 H, Ar-H), 7.69-7.76 (m, 1 H, Ar-H),

7.85 (d, $J = 1.0$ Hz, 1 H, Ar-H), 7.92 (d, $J = 9.0$ Hz, 1 H, Ar-H), 8.05 (d, $J = 8.7$ Hz, 1 H, Ar-H), 8.41 (d, $J = 2.4$ Hz, 1 H, Ar-H), 8.43 (d, $J = 7.6$ Hz, 1 H, Ar-H), 8.77 (s, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 107.6 (Ar-C), 117.3 (Ar-C), 122.2 (Ar-C), 123.6 (Ar-C), 124.2 (Ar-C), 124.7 (Ar-C), 126.7 (Ar-C), 131.4 (Ar-C), 131.75 (Ar-C), 131.79 (Ar-C), 133.0 (Ar-C), 134.7 (Ar-C), 136.4 (Ar-C), 140.1 (Ar-C), 142.6 (Ar-C), 146.6 (Ar-C), 149.6 (Ar-C), 154.4 (Ar-C), 188.9 (C=O). ESI-MS *m/z* of 375.90, 377.70 $[M+H]^+$ was obtained for a calculated mass of 376.01, 378.01.

General procedure B for 10-14: 6-amino-2-bromo-indeno[2,1-*c*]quinolin-7-one oximes

To a cooled (0 °C) suspension of the appropriate ketone **4**, **6**, **7**, **8** and **9** (1 eq) and hydroxylamine hydrochloride (3 eq) in ethanol-water (2 : 1) mixture, sodium hydroxide pellets (5 eq) were added in portions. The reaction was stirred at 0 °C for 15 min and then heated up to 80-90 °C for 3-8 h. The reaction mixture was cooled to room temperature and poured into 15% aq. hydrochloric acid. The precipitate obtained was filtered, washed with water and dried under reduced pressure to obtain the corresponding oximes **10-14** in good yield (72-96%).

2-Bromo-6-methoxy-indeno[2,1-*c*]quinolin-7-one oxime (10)

Procedure B, yield 91%. Yellow solid; mp 270-275 °C. ν_{max} (KBr, cm^{-1}): 3176, 1640. ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.08 (s, 3 H, OCH_3), 7.54-7.69 (m, 2 H, Ar-H), 7.77 (d, $J = 9.0$ Hz, 1 H, Ar-H), 7.83 (d, $J = 8.6$ Hz, 1 H, Ar-H), 8.41 (d, $J = 6.8$ Hz, 1 H, Ar-H), 8.51 (d, $J = 7.3$ Hz, 1 H, Ar-H), 8.67 (s, 1 H, Ar-H), 13.38 (s, 1 H, C=N-O*H*). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 53.4 (OCH_3), 117.8 (Ar-C), 118.0 (Ar-C), 122.2 (Ar-C), 124.2 (Ar-C), 125.9 (Ar-C), 128.5 (Ar-C), 129.4 (Ar-C), 129.9 (Ar-C), 130.4 (Ar-C), 130.8 (Ar-C), 133.0 (Ar-C), 137.0 (Ar-C), 144.7 (Ar-C), 145.7 (Ar-C), 150.1 (Ar-C), 157.9 (C=N-OH). ESI-MS *m/z* of 355.10, 357.00 $[M+H]^+$ was obtained for a calculated mass of 355.01, 357.01.

2-Bromo-6-(4-pyridin-2-yl-piperazin-1-yl)-indeno[2,1-*c*]quinolin-7-one-oxime (11)

Procedure B, yield 96%. Greenish solid; mp 235-237 °C. ν_{max} (KBr, cm^{-1}): 3014, 1603. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.57-3.70 (m, 4 H, Ar-N-CH_2-CH_2), 3.77-3.90 (m, 4 H, Ar-N-CH_2-CH_2), 6.97 (t, $J = 6.5$ Hz, 1 H, Ar-H), 7.46 (d, $J = 9.0$ Hz, 1 H, Ar-H), 7.53-7.69 (m, 2 H, Ar-H), 7.78 (d, $J = 9.0$ Hz, 1 H, Ar-H), 7.82 (dd, $J = 9.0$, 1.4 Hz, 1 H, Ar-H), 7.98-8.11 (m, 2 H, Ar-H), 8.45 (d, $J = 7.5$ Hz, 1 H, Ar-H), 8.56 (d, $J = 7.0$ Hz, 1 H, Ar-H), 8.70 (d, $J = 1.0$ Hz, 1 H, Ar-H), 13.30 (s, 1 H, D_2O exchangeable, C=N-O*H*). ^{13}C NMR (100.6 MHz, THF-d_8): δ 45.9 (Ar-N-CH_2-CH_2), 50.49 (Ar-N-CH_2-CH_2), 107.6 (Ar-C), 113.4 (Ar-C), 118.1 (Ar-C), 122.6 (Ar-C), 123.7 (Ar-C), 124.0 (Ar-C), 126.7 (Ar-C), 128.5 (Ar-C), 129.3 (Ar-C), 130.1 (Ar-C), 130.6 (Ar-C), 131.1 (Ar-C), 132.1 (Ar-C), 137.66 (Ar-C), 137.72 (Ar-C), 147.0 (Ar-C), 148.6 (Ar-C), 152.9 (Ar-C), 157.6 (Ar-C), 160.9 (C=N-OH). ESI-MS *m/z* of 486.40, 488.30 $[M+H]^+$ was obtained for a calculated mass of 486.09, 488.09.

2-Bromo-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-indeno[2,1-*c*]quinolin-7-one oxime (12)

Procedure B, yield 95%. Yellow solid; mp 241-243 °C. ν_{max} (KBr, cm^{-1}): 3167, 1699. ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.10-3.38 (m, 4 H, Ar-N-CH_2-CH_2), 3.50-3.74 (m, 4 H, Ar-N-CH_2-CH_2), 6.95-7.14 (m, 4 H, Ar-H), 7.54-7.70 (m, 2 H, Ar-H), 7.76 (d, $J = 7.0$ Hz, 1 H, Ar-H), 7.81 (d, $J = 9.5$ Hz, 1 H, Ar-H), 8.47 (d, $J = 7.2$ Hz, 1 H, Ar-H), 8.57 (d, $J = 7.2$ Hz, 1 H, Ar-H), 8.71 (s, 1 H, Ar-H), 13.21 (s, 1 H, D_2O exchangeable, C=N-O*H*). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 48.9 (Ar-N-CH_2-CH_2), 49.1 (Ar-N-CH_2-CH_2), 115.2 (Ar-C), 115.5 (Ar-C), 117.2 (Ar-C), 117.3 (Ar-C), 117.5 (Ar-C), 119.9 (Ar-C), 121.8 (Ar-C), 124.1 (Ar-C), 125.8 (Ar-C), 128.6 (Ar-C), 129.4 (Ar-C), 130.17 (Ar-C), 130.23 (Ar-C), 130.8 (Ar-C), 133.0 (Ar-C), 137.4 (Ar-C), 144.4 (Ar-C), 146.4 (Ar-C), 148.2 (Ar-C), 150.8 (Ar-C), 154.9 (Ar-C), 155.8 (Ar-C). ESI-MS *m/z* of 503.40, 505.40 $[M+H]^+$ was obtained for a calculated mass of 503.09, 505.09.

2-Bromo-6-imidazol-1-yl-indeno[2,1-*c*]quinolin-7-one oxime (13)

Procedure B, yield 72%. Brown solid; mp 268-271 °C. ν_{max} (KBr, cm^{-1}): 3402, 1710. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.68-7.84 (m, 2 H, Ar-H), 7.96 (s, 1 H, Ar-H), 8.13 (s, 2 H, Ar-H), 8.28 (s, 1 H, Ar-H), 8.55 (d, $J = 7.1$ Hz, 1 H, Ar-H), 8.73 (d, $J = 7.1$ Hz, 1 H, Ar-H), 9.0 (s, 1 H, Ar-H), 9.79 (s, 1 H, Ar-H), 13.44 (s, 1 H, D_2O exchangeable, C=N-O*H*). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 119.7 (Ar-C), 122.60 (Ar-C), 122.64 (Ar-C), 123.4 (Ar-C), 124.7 (Ar-C), 125.3 (Ar-C), 126.4 (Ar-C), 128.9 (Ar-C), 129.6 (Ar-C), 131.7 (Ar-C), 131.8 (Ar-C), 132.0 (Ar-C), 134.9 (Ar-C), 136.2 (Ar-C), 137.0 (Ar-C), 141.6 (Ar-C), 145.4 (Ar-C), 146.0 (Ar-C), 149.0 (Ar-C). ESI-MS *m/z* of 390.90, 393.00 $[M+H]^+$ was obtained for a calculated mass of 391.02, 393.02.

2-Bromo-6-pyarazol-1-yl-indeno[2,1-*c*]quinolin-7-one oxime (14)

Procedure B, yield 94%. Light brown solid; mp 195-198 °C. ν_{max} (KBr, cm^{-1}): 3453, 1660. ^{1}H NMR (400 MHz, CF_3COOD): δ 7.04-7.12 (m, 1 H, Ar-H), 7.68-7.82 (m, 2 H, Ar-H), 8.01-8.11 (m, 2 H, Ar-H), 8.29 (d, $J = 7.2$ Hz, 1 H, Ar-H), 8.44 (s, 1 H, Ar-H), 8.66 (d, $J = 7.2$ Hz, 1 H, Ar-H), 8.77 (s, 1 H, Ar-H), 9.34 (s, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, CF_3COOD): δ 110.0 (Ar-C), 115.6 (Ar-C), 123.7 (Ar-C), 124.8 (Ar-C), 125.1 (Ar-C), 126.2 (Ar-C), 128.7 (Ar-C), 130.3 (Ar-C), 130.6 (Ar-C), 132.9 (Ar-C), 133.7 (Ar-C), 134.1 (Ar-C), 137.4 (Ar-C), 138.6 (Ar-C), 139.6 (Ar-C), 145.0 (Ar-C), 150.2 (C=N-OH), 150.7 (C=N-OH). ESI-MS *m/z* of 390.90, 392.90 $[M+H]^+$ was obtained for a calculated mass of 391.02, 393.02.

General procedure C for 15-17: acylation of the oximes

The appropriate oximes **10-12** (1 eq) and *N*,*N*-dimethylamine carbamyl chloride (2 eq) were stirred at room temperature in anhydrous DMF for 12 h in presence of sodium hydride (1.1 eq). The reaction mixture was poured into water; the precipitate obtained was filtered, washed with cold water and dried under reduced pressure to obtain the corresponding acylated products **15-17**.

2-Bromo-6-methoxy-indeno[2,1-*c*]quinolin-7-one *N*,*N*-dimethyl carbamoyl oxime (15)

Procedure C, yield 66%. Yellow solid; mp 238-240 °C. ν_{max} (KBr, cm^{-1}): 1748. ^1H NMR (400 MHz, $CDCl_3$): δ 3.13 (s, 3 H, -NCH_3), 3.21 (s, 3 H, -NCH_3), 4.23 (s, 3 H, OCH_3), 7.49 (t, J = 7.6 Hz, 1 H, Ar-H), 7.56-7.64 (m, 1 H, Ar-H), 7.70-7.76 (m, 1 H, Ar-H), 7.78 (d, J = 8.9 Hz, 1 H, Ar-H), 8.18 (d, J = 7.7 Hz, 1 H, Ar-H), 8.35 (d, J = 7.6 Hz, 1 H, Ar-H), 8.54 (d, J = 1.8 Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, CF_3COOD): δ 38.1 (-NCH_3), 39.2 (-NCH_3), 61.0 (OCH_3), 119.4 (Ar-C), 123.3 (Ar-C), 123.5 (Ar-C), 126.1 (Ar-C), 129.1 (Ar-C), 130.6 (Ar-C), 132.5 (Ar-C), 132.9 (Ar-C), 136.3 (Ar-C), 136.6 (Ar-C), 138.6 (Ar-C), 139.1 (Ar-C), 141.5 (Ar-C), 157.1 (Ar-C), 158.9 (Ar-C), 159.4 (Ar-C), 159.9 (C=N-OH). ESI-MS m/z of 426.00, 428.10 $[M+H]^+$ was obtained for a calculated mass of 426.05, 428.04.

2-Bromo-6-(4-pyridin-2-yl-piperazin-1-yl)-indeno[2,1-*c*]quinolin-7-one *N*,*N*-dimethyl carbamoyl oxime (16)

Procedure C, yield 63%. Brownish-yellow solid; mp 215-217 °C. ν_{max} (KBr, cm^{-1}): 1752. ^1H NMR (400 MHz, $CDCl_3$): δ 3.11 (s, 3 H, -NCH_3), 3.20 (s, 3 H, -NCH_3), 3.69-3.80 (m, 4 H, Ar-N-CH_2-CH_2), 3.84-3.93 (m, 4 H, Ar-N-CH_2-CH_2), 6.56-6.66 (m, 1 H, Ar-H), 6.74 (d, J = 8.5 Hz, 1 H, Ar-H), 7.43-7.56 (m, 2 H, Ar-H), 7.61 (t, J = 7.6 Hz, 1 H, Ar-H), 7.71 (dd, J = 9.0, 2.0 Hz, 1 H, Ar-H), 7.78 (d, J = 9.0 Hz, 1 H, Ar-H), 8.17-8.28 (m, 2 H, Ar-H), 8.37 (d, J = 7.5 Hz, 1 H, Ar-H), 8.57 (d, J = 2.0 Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 36.7 (-NCH_3), 37.5 (-NCH_3), 45.1 (Ar-N-*C*H_2-CH_2), 49.5 (Ar-N-CH_2-*C*H_2), 107.3 (Ar-C), 112.9 (Ar-C), 118.2 (Ar-C), 119.4 (Ar-C), 121.9 (Ar-C), 124.1 (Ar-C), 126.0 (Ar-C), 129.0 (Ar-C), 129.9 (Ar-C), 130.0 (Ar-C), 130.5 (Ar-C), 131.9 (Ar-C), 133.7 (Ar-C), 137.3 (Ar-C), 140.0 (Ar-C), 147.1 (Ar-C), 147.8 (Ar-C), 148.2 (Ar-C), 154.4 (*O*-*C*O-N), 156.2 (Ar-C), 156.6 (Ar-C), 159.7 (C=N-OH). ESI-MS m/z of 557.40, 559.20 $[M+H]^+$ was obtained for a calculated mass of 557.13, 559.13.

2-Bromo-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-indeno[2,1-*c*]quinolin-7-one *N*,*N*-dimethyl carbamoyl oxime (17)

Procedure C, yield 62%. Yellow solid; mp 192-194 °C. ν_{max} (KBr, cm^{-1}): 1752. ^1H NMR (400 MHz, $CDCl_3$): δ 3.11 (s, 3 H, -NCH_3), 3.19 (s, 3 H, -NCH_3), 3.40-3.49 (m, 4 H, Ar-N-CH_2-CH_2), 3.75-3.83 (m, 4 H, Ar-N-CH_2-CH_2), 6.97 (d, J = 6.4 Hz, 4 H, Ar-H), 7.49 (t, J = 7.6 Hz, 1 H, Ar-H), 7.60 (t, J = 7.6 Hz, 1 H, Ar-H), 7.72 (dd, J = 9.0, 2.0 Hz, 1 H, Ar-H), 7.78 (d, J = 9.0 Hz, 1 H, Ar-H), 8.22 (d, J = 7.8 Hz, 1 H, Ar-H), 8.37 (d, J = 7.4 Hz, 1 H, Ar-H), 8.57 (d, J = 1.7 Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, CF_3COOD): δ 38.3 (-NCH_3), 39.1 (-NCH_3), 50.4 (Ar-N-*C*H_2-CH_2), 58.1 (Ar-N-CH_2-*C*H_2), 120.4 (Ar-C), 120.6 (Ar-C), 121.5 (Ar-C), 123.3 (Ar-C), 123.4 (Ar-C), 125.0 (Ar-C), 125.1 (Ar-C), 126.0 (Ar-C), 129.1 (Ar-C), 130.5 (Ar-C), 132.4 (Ar-C), 132.6 (Ar-C), 136.4 (Ar-C), 136.6 (Ar-C), 138.1 (Ar-C), 139.3 (Ar-C), 139.7 (Ar-C), 141.9 (Ar-C), 152.7 (Ar-C), 157.8 (*O*-*C*O-N), 159.4 (Ar-C), 159.6 (Ar-C), 167.9 (C=N-OH). ESI-MS m/z of 574.40, 576.20 $[M+H]^+$ was obtained for a calculated mass of 574.13, 576.12.

General procedure D for 18-20: 6-amino-2-bromo-indeno[2,1-*c*]quinolin-7-one-*O*-naphthalen-1-ylmethyl-oximes

Sodium hydride (1.1 eq) was added to the appropriate oxime **10-12** (1 eq) in dry DMF at 0 °C (ice bath) under nitrogen atmosphere. The reaction mixture was stirred at room temperature for 30 min. 1-Chloromethyl naphthalene (1.5 eq) was added to the reaction mixture and stirred for 3-12 h. The reaction was quenched with ice, diluted with ethyl acetate and washed with brine several times. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to obtain a gum as a crude product. This crude product was purified by column chromatography (silica gel 100-200 mesh, gradual elution with ethyl acetate, n-hexane mixture) to give the corresponding oximes **18-20**.

2-Bromo-6-methoxy-indeno[2,1-*c*]quinolin-7-one-*O*-naphthalen-1-ylmethyl-oxime (18)

Procedure D, yield 48%. Pale-yellow solid; mp 188-192 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 4.24 (s, 3 H, OCH_3), 6.01 (s, 2 H, C=NOCH_2Ar), 7.29 (t, J = 7.6 Hz, 1 H, Ar-H), 7.45 (t, J = 7.6 Hz, 1 H, Ar-H), 7.50-7.60 (m, 3 H, Ar-H), 7.64-7.72 (m, 2 H, Ar-H), 7.76 (d, J = 9.0 Hz, 1 H, Ar-H), 7.86-7.96 (m, 2 H, Ar-H), 8.11 (d, J = 7.7 Hz, 1 H, Ar-H), 8.25-8.34 (m, 2 H, Ar-H), 8.54 (d, J = 2.0 Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$+DMSO-d_6): δ 53.7 (OCH_3), 76.8 (C=NO*C*H_2Ar), 117.5 (Ar-C), 117.9 (Ar-C), 122.4 (Ar-C), 123.1 (Ar-C), 123.9 (Ar-C), 125.1 (Ar-C), 125.7 (Ar-C), 125.8 (Ar-C), 126.2 (Ar-C), 127.6 (Ar-C), 128.3 (Ar-C), 129.1 (Ar-C), 129.3 (Ar-C), 129.7 (Ar-C), 129.8 (Ar-C), 130.0 (Ar-C), 130.5 (Ar-C), 131.7 (Ar-C), 132.0 (Ar-C), 132.7 (Ar-C), 133.5 (Ar-C), 138.2 (Ar-C), 145.6 (Ar-C), 146.4 (Ar-C), 151.5 (Ar-C), 158.0 (C=N-OH). ESI-MS m/z of 494.90, 497.00 $[M+H]^+$ was obtained for a calculated mass of 495.07, 497.07.

2-Bromo-6-(4-pyridin-2-yl-piperazin-1-yl)-indeno[2,1-*c*]quinolin-7-one-*O*-naphthalen-1-ylmethyl-oxime (19)

Procedure D, yield 54%. Orange-red solid; mp 98-100 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 3.58-3.67 (m, 8 H, Ar-N-CH_2-CH_2), 6.00 (s, 2 H, C=NOCH_2Ar), 6.36 (d, J = 8.5 Hz, 1 H, Ar-H), 6.61 (dd, J = 6.8, 1.6 Hz, 1 H, Ar-H), 7.36 (t, J = 7.5 Hz, 1 H, Ar-H), 7.40-7.47 (m, 1 H, Ar-H), 7.48-7.57 (m, 4 H, Ar-H), 7.65 (d, J = 7.0 Hz, 1 H, Ar-H), 7.69 (dd, J = 9.0, 1.8 Hz, 1 H, Ar-H), 7.78 (d, J = 8.9 Hz, 1 H, Ar-H), 7.89 (d, J = 8.2 Hz, 1 H, Ar-H), 7.91-7.96 (m, 1 H, Ar-H), 8.15-8.22 (m, 3 H, Ar-H), 8.40 (d, J = 7.6 Hz, 1 H, Ar-H), 8.60 (d, J = 1.7 Hz, 1 H, Ar-H).^{13}C NMR (100.6 MHz, $CDCl_3$): δ 45.2 (Ar-N-*C*H_2-CH_2), 49.2 (Ar-N-CH_2-*C*H_2), 106.9 (Ar-C), 113.3 (Ar-C), 118.1 (Ar-C), 119.5 (Ar-C), 122.2 (Ar-C), 123.4 (Ar-C), 123.7 (Ar-C), 125.3 (Ar-C), 125.95 (Ar-C), 125.97 (Ar-C), 126.0 (Ar-C), 126.5 (Ar-C), 126.7 (Ar-C), 128.7 (Ar-C), 129.1 (Ar-C), 129.4 (Ar-C), 129.9 (Ar-C), 130.20 (Ar-C), 130.24 (Ar-C), 130.7 (Ar-C), 131.5 (Ar-C), 132.5 (Ar-C), 133.0 (Ar-C), 133.6 (Ar-C), 137.3 (Ar-C), 138.9 (Ar-C), 145.9 (Ar-C), 147.3 (Ar-C), 147.9 (Ar-C), 152.4 (Ar-C), 156.1 (Ar-C), 159.7 (C=N-OH). ESI-MS m/z of 626.20, 628.10 $[M+H]^+$ was obtained for a calculated mass of 626.16, 628.15.

2-Bromo-6-[4-(4-fluoro-phenyl)-piperazin-1-yl]-indeno[2,1-*c*]quinolin-7-one-*O*-naphthalen-1-ylmethyl-oxime (20)

Procedure D, yield 50%. Brownish-red solid; mp 203-206 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.97-3.06 (m, 4 H, Ar-N-CH_2-CH$_2$), 3.57-3.64 (m, 4 H, Ar-N-CH$_2$-CH_2), 6.02 (s, 2 H, C=NOCH_2Ar), 6.48-6.58 (m, 2 H, Ar-H), 6.85 (t, $J = 8.7$ Hz, 2 H, Ar-H), 7.40-7.48 (m, 2 H, Ar-H), 7.53-7.61 (m, 3 H, Ar-H), 7.64 (d, $J = 6.5$ Hz, 1 H, Ar-H), 7.70 (dd, $J = 9.0$, 2.0 Hz, 1 H, Ar-H), 7.77 (d, $J = 9.0$ Hz, 1 H, Ar-H), 7.86 (d, $J = 8.3$ Hz, 1 H, Ar-H), 7.91-7.98 (m, 1 H, Ar-H), 8.12-8.18 (m, 1 H, Ar-H), 8.21 (d, $J = 7.8$ Hz, 1 H, Ar-H), 8.49 (d, $J = 7.3$ Hz, 1 H, Ar-H), 8.60 (d, $J = 2.0$ Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, THF-d$_8$): δ 50.3 (Ar-N-*C*H$_2$-CH$_2$), 50.8 (Ar-N-CH$_2$-*C*H$_2$), 77.3 (C=NO*C*H$_2$Ar), 115.7 (Ar-C), 116.0 (Ar-C), 118.3 (Ar-C), 118.4 (Ar-C), 118.7 (Ar-C), 120.6 (Ar-C), 123.1 (Ar-C), 124.6 (Ar-C), 124.8 (Ar-C), 126.2 (Ar-C), 126.9 (Ar-C), 126.95 (Ar-C), 127.1 (Ar-C), 127.4 (Ar-C), 129.6 (Ar-C), 129.7 (Ar-C), 130.2 (Ar-C), 130.9 (Ar-C), 131.2 (Ar-C), 131.3 (Ar-C), 131.9 (Ar-C), 132.5 (Ar-C), 133.9 (Ar-C), 134.3 (Ar-C), 135.0 (Ar-C), 140.0 (Ar-C), 146.7 (Ar-C), 148.6 (Ar-C), 149.5 (Ar-C), 153.1 (Ar-C), 156.7 (Ar-C), 157.1 (Ar-C), 159.0 (Ar-C). ESI-MS *m/z* of 643.60, 645.50 [M+H]$^+$ was obtained for a calculated mass of 643.15, 645.15.

2-Bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-ol (21)

Compound **4** (2.0 g, 5.91 mmol) was dissolved in dry THF (130 mL), to this freshly prepared methyl magnesium iodide (1 M solution in diethyl ether, 7.1 mL, 7.1 mmol) was added in one portion at 15 °C under nitrogen atmosphere. The reaction was stirred for 3 h allowing it to gradually warm up to room temperature during which the color of reaction mixture changed from yellow to dark brown. Reaction was quenched by adding ice and reaction mixture was extracted with ethyl acetate (150 mL), washed with saturated ammonium chloride solution (60 mL), water (100 mL) and brine (50 mL). The organic extract was dried over anhydrous sodium sulfate, filtered and the solvents were evaporated under reduced pressure to obtain a brown sticky mass as a crude product. Crude product was purified by column chromatography (silica gel 100-200 mesh, eluent: 7% ethyl acetate in n-hexane) to give **21** (1.6 g, 77%) as an off white solid; mp 159-160 °C. ν_{max} (KBr, cm^{-1}): 3338. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.80 (s, 3 H, CH$_3$), 3.10 (s, 1 H, D$_2$O exchangeable, CHO*H*), 4.19 (s, 3 H, OCH$_3$), 7.45-7.53 (m, 3 H, Ar-H), 7.58 (d, $J = 8.9$ Hz, 1 H, Ar-H), 7.62-7.70 (m, 1 H, Ar-H), 7.95-8.04 (m, 1 H, Ar-H), 8.46 (s, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.9 (CH$_3$), 53.3 (OCH$_3$), 78.5 (*C*HOH), 117.9 (Ar-C), 122.5 (Ar-C), 122.9 (Ar-C), 123.7 (Ar-C), 125.6 (Ar-C), 128.3 (Ar-C), 128.5 (Ar-C), 129.5 (Ar-C), 130.6 (Ar-C), 131.5 (Ar-C), 135.6 (Ar-C), 143.9 (Ar-C), 145.3 (Ar-C), 151.8 (Ar-C), 159.3 (Ar-C). ESI-MS *m/z* of 355.80, 357.90 [M+H]$^+$ was obtained for a calculated mass of 356.03, 358.03.

2-Bromo-6-methoxy-7-methyl-7-oxiranylmethoxy-7*H*-indeno[2,1-*c*]quinoline (22)

Compound **21** (2.0 g, 5.62 mmol) was dissolved in dry DMF (7 mL) and cooled to 0 °C, under nitrogen atmosphere. Sodium hydride (0.28 g, 11.8 mmol) was added to it and stirred for 30 min. During this period, the color of the reaction changed from yellow to dark red. *epi*-Chlorohydrin (1.1 g, 11.8 mmol) was added to the reaction mixture and stirred for 48 h at room temperature and quenched with ice. The reaction mixture was extracted with ethyl acetate (150 mL), washed with brine (3 × 50 mL), dried over anhydrous sodium sulfate, filtered and the solvents were evaporated under reduced pressure to obtain a gum as a crude product. The crude product was purified by column chromatography (silica gel 100-200 mesh, eluent: 8% ethyl acetate in n-hexane) to give **22** as (1 : 1 diastereomeric mixture) (1.60 g, 69%) a light yellowish green solid along with starting alcohol (0.40 g, 20%); mp 159-160 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83 (s, 1.5 H, CH$_3$), 1.84 (s, 1.5 H, CH$_3$), 2.26 (dd, $J = 5.0$, 2.6 Hz, 0.5 H, Epoxy-CH_2), 2.35 (dd, $J = 5.0$, 2.3 Hz, 0.5 H, Epoxy-CH_2), 2.62 (dd, $J = 9.3$, 5.3 Hz, 1 H, Epoxy-CH_2), 2.79 (dd, $J = 10.6$, 5.7 Hz, 0.5 H, OCH$_2$C*H*), 2.87 (dd, $J = 11.6$, 6.2 Hz, 0.5 H, OCH$_2$C*H*), 2.90-3.04 (m, 2 H, OCH_2CH), 4.18 (s, 3 H, OCH$_3$), 7.45-7.56 (m, 2 H, Ar-H), 7.59-7.66 (m, 1 H, Ar-H), 7.73 (dd, $J = 8.9$, 1.6 Hz, 1 H, Ar-H), 7.82 (dd, $J = 8.9$, 1.6 Hz, 1 H, Ar-H), 8.17 (d, $J = 7.0$ Hz, 1 H, Ar-H), 8.62 (s, 1 H, Ar-H).^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.4 (CH$_3$), 23.5 (CH$_3$), 44.7 (OCH$_2$), 44.9 (OCH$_2$), 50.64 (OCH$_2$*C*H), 50.68 (OCH$_2$*C*H), 53.53 (OCH$_3$), 53.56 (OCH$_3$), 65.3 (Epoxy-CH_2), 65.9 (Epoxy-CH_2), 84.48 (*C*HOH), 84.53 (*C*HOH), 117.93 (Ar-C), 117.97 (Ar-C), 123.09 (Ar-C), 123.10 (Ar-C), 123.65 (Ar-C), 123.71 (Ar-C), 123.82 (Ar-C), 123.86 (Ar-C), 126.27 (Ar-C), 126.30 (Ar-C), 128.68 (Ar-C), 128.70 (Ar-C), 129.3 (Ar-C), 129.6 (Ar-C), 129.7 (Ar-C), 129.79 (Ar-C), 129.80 (Ar-C), 132.69 (Ar-C), 132.72 (Ar-C), 137.7 (Ar-C), 137.8 (Ar-C), 145.6 (Ar-C), 145.7 (Ar-C), 147.03 (Ar-C), 147.05 (Ar-C), 148.8 (Ar-C), 148.9 (Ar-C), 159.67 (Ar-C), 159.71 (Ar-C). ESI-MS *m/z* of 412.10, 414.10 [M+H]$^+$ was obtained for a calculated mass of 412.05, 414.05.

General procedure E for 23-31: 1-(2-bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-yloxy)-3-amino-propan-2-ol derivatives

To a mixture of activated potassium carbonate (5 eq) and compound **3** (1 eq) in dry DMF, the appropriate amine (R_2H, 1~5 eq) was added under nitrogen atmosphere. The reaction was stirred at 65-70 °C for 15 h and quenched with ice. The reaction mixture was diluted with ethyl acetate and washed thrice with brine. The organic extract was dried over anhydrous sodium sulfate, filtered and the solvents were evaporated under reduced pressure to obtain an oily compound as a crude product. The crude product was purified by flash column chromatography (on silica gel 230-400 mesh) to obtain the corresponding 3-amino-propan-2-ol derivatives **23-31** in reasonable yields (22~77%). Compounds **23** and **24** were obtained in a 4 : 6 diastereomeric ratio and were separated by column chromatography to give two pair of diastereomers, as compound **23** and compound **24**. Analytical data of, compound **23** and compound **24** represent data of racemic diastereomer respectively.

1-(2-Bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-yloxy)-3-[3-(3,4-dichloro-phenyl)-pyrazol-1-yl]-propan-2-ol (23)

Procedure E, Yield 22% as a racemic diastereomer. Sticky solid. ν_{max} (KBr, cm^{-1}): 3391. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (s, 3 H, CH$_3$), 2.44 (dd, $J = 9.6$, 7.5 Hz, 1 H, OCH$_2$), 3.01 (dd, $J = 9.7$, 4.4 Hz, 1 H, OCH$_2$), 3.50 (d, $J = 2.4$ Hz, 1 H, D$_2$O exchangeable, CHO*H*), 3.97 (dd, $J = 13.5$, 5.7 Hz, 1 H, NCH_2CHOH), 4.01-4.09

(m, 1 H, C*H*OH), 4.10-4.13 (m, 1 H, NCH_2CHOH), 4.14 (s, 3 H, OCH_3), 6.23 (d, $J = 2.2$ Hz, 1 H, Pyrazole-CH), 7.29 (dd, $J = 8.3$, 1.9 Hz, 1 H, Ar-H), 7.33-7.39 (m, 2 H, Ar-H), 7.46-7.58 (m, 3 H, Ar-H), 7.61 (d, $J = 1.8$ Hz, 1 H, Ar-H), 7.70 (dd, $J = 9.0$, 2.0 Hz, 1 H, Ar-H), 7.76 (d, $J = 8.9$ Hz, 1 H, Ar-H), 8.10 (d, $J = 7.2$ Hz, 1 H, Ar-H), 8.49 (d, $J = 1.9$ Hz, 1 H, Ar-H).^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.3 (CH_3), 53.5 (OCH_3), 54.1 (N*C*H_2CHOH), 65.3 (OCH_2), 69.1 (*C*HOH), 84.7 (CH_3*C*O-), 102.6 (Ar-C), 118.1 (Ar-C), 123.0 (Ar-C), 123.5 (Ar-C), 124.1 (Ar-C), 124.5 (Ar-C), 126.2 (Ar-C), 127.0 (Ar-C), 128.1 (Ar-C), 129.5 (Ar-C), 129.6 (Ar-C), 129.7 (Ar-C), 130.4 (Ar-C), 131.2 (Ar-C), 132.4 (Ar-C), 132.5 (Ar-C), 132.7 (Ar-C), 133.2 (Ar-C), 137.7 (Ar-C), 145.9 (Ar-C), 146.9 (Ar-C), 148.3 (Ar-C), 149.0 (Ar-C), 159.1 (Ar-C). ESI-MS m/z of 624.10, 626.30 $[M+H]^+$ was obtained for a calculated mass of 624.05, 626.04.

1-(2-Bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-yloxy)-3-[3-(3,4-dichloro-phenyl)-pyrazol-1-yl]-propan-2-ol (24)

Procedure E, Yield 28% as a racemic diastereomer. Sticky solid. ν_{max} (KBr, cm^{-1}): 3294. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83 (s, 3 H, CH_3), 2.73 (dd, $J = 9.6$, 5.4 Hz, 1 H, OCH_2), 2.92 (dd, $J = 9.6$, 4.2 Hz, 1 H, OCH_2), 3.43 (br-s, 1 H, D_2O exchangeable, CHO*H*), 3.88-3.98 (m, 1 H, C*H*OH), 4.10-4.16 (m, 1H, NCH_2), 4.18 (s, 3 H, OCH_3), 4.29 (dd, $J = 13.8$, 4.4 Hz, 1 H, NCH_2), 6.45 (d, $J = 2.2$ Hz, 1 H, Ar-H), 7.39 (d, $J = 8.3$ Hz, 1 H, Ar-H), 7.45 (d, $J = 2.2$ Hz, 1 H, Ar-H), 7.47-7.59 (m, 4 H, Ar-H), 7.73 (d, $J = 8.9$, 2.0 Hz, 1 H, Ar-H), 7.77 (d, $J = 2.0$ Hz, 1 H, Ar-H), 7.81 (d, $J = 8.9$ Hz, 1 H, Ar-H), 8.15 (d, $J = 7.0$ Hz, 1 H, Ar-H), 8.60 (d, $J = 2.0$ Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.5 (CH_3), 53.6 (OCH_3), 54.5 (NCH_2), 64.7 (OCH_2), 69.5 (*C*HOH), 84.5 (CH_3*C*O-), 102.8 (Ar-C), 118.2 (Ar-C), 123.1 (Ar-C), 123.4 (Ar-C), 124.1 (Ar-C), 124.7 (Ar-C), 126.3 (Ar-C), 127.2 (Ar-C), 128.3 (Ar-C), 129.5 (Ar-C), 129.7 (Ar-C), 129.9 (Ar-C), 130.5 (Ar-C), 131.3 (Ar-C), 132.1 (Ar-C), 132.6 (Ar-C), 132.9 (Ar-C), 133.3 (Ar-C), 137.7 (Ar-C), 145.9 (Ar-C), 147.0 (Ar-C), 148.4 (Ar-C), 149.4 (Ar-C), 159.3 (Ar-C). ESI-MS m/z of 624.30, 626.40 $[M+H]^+$ was obtained for a calculated mass of 624.05, 626.04.

1-(2-Bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-yloxy)-3-[3-(3-trifluoromethyl-phenyl)-pyrazol-1-yl]-propan-2-ol (25)

Procedure E, Yield 50%. Off-white fluffy-solid; mp 75-76 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (s, 1.5 H, CH_3), 1.84 (s, 1.5 H, CH_3), 2.49 (dd, $J = 9.6$, 7.0 Hz, 0.5 H, OCH_2), 2.75 (dd, $J = 9.6$, 5.3 Hz, 0.5 H, OCH_2), 2.94 (dd, $J = 11.4$, 4.1 Hz, 0.5 H, OCH_2), 3.02 (dd, $J = 9.6$, 4.2 Hz, 0.5 H, OCH_2), 3.93-4.11 (m, 2 H, C*H*OH and NCH_2), 4.02-4.24 (m, 4 H, NCH_2 and OCH_3), 4.33 (dd, $J = 13.9$, 4.3 Hz, 0.5 H, NCH_2), 4.62 (br-s, 1 H, D_2O exchangeable, CHO*H*), 6.36 (d, $J = 2.4$ Hz, 0.5 H, Ar-H), 6.53 (d, $J = 2.4$ Hz, 0.5 H, Ar-H), 7.38-7.59 (m, 6 H, Ar-H), 7.62-7.98 (m, 4 H, Ar-H), 8.07-8.19 (m, 1 H, Ar-H), 8.51 (d, $J = 2.0$ Hz, 0.5 H, Ar-H), 8.60 (d, $J = 2.0$ Hz, 0.5 H, Ar-H) for total 25 H in diastereomeric ratio 1 : 1. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.3 (CH_3), 23.5 (CH_3), 53.60 (OCH_3), 53.63 (OCH_3), 54.0 (NCH_2), 54.5 (NCH_2), 64.7 (OCH_2), 65.3 (OCH_2), 69.3 (*C*HOH), 69.6 (*C*HOH), 84.6 (CH_3*C*O-), 84.7 (CH_3*C*O-), 102.8 (Ar-C), 102.9 (Ar-C), 118.16 (Ar-C), 118.21 (Ar-C), 122.13 (Ar-C), 122.17 (Ar-C), 122.21 (Ar-C), 122.28 (Ar-C), 122.31 (Ar-C), 122.35 (Ar-C), 122.39 (Ar-C), 122.76 (Ar-C), 123.0 (Ar-C), 123.1 (Ar-C), 123.44 (Ar-C), 123.48 (Ar-C), 124.07 (Ar-C), 124.16 (Ar-C), 124.20 (Ar-C), 124.24 (Ar-C), 124.27 (Ar-C), 124.3 (Ar-C), 125.5 (Ar-C), 126.27 (Ar-C), 126.3 (Ar-C), 128.2 (Ar-C), 128.3 (Ar-C), 128.6 (Ar-C), 128.7 (Ar-C), 128.98 (Ar-C), 129.02 (Ar-C), 129.5 (Ar-C), 129.7 (Ar-C), 129.8 (Ar-C), 130.3 (Ar-C), 130.4 (Ar-C), 130.7 (Ar-C), 130.8 (Ar-C), 131.0 (Ar-C), 131.1 (Ar-C), 131.3 (Ar-C), 131.4 (Ar-C), 132.2 (Ar-C), 132.4 (Ar-C), 132.83 (Ar-C), 132.88 (Ar-C), 133.6 (Ar-C), 133.7 (Ar-C), 137.61 (Ar-C), 137.63 (Ar-C), 145.95 (Ar-C), 145.97 (Ar-C), 146.87 (Ar-C), 146.93 (Ar-C), 148.3 (Ar-C), 148.4 (Ar-C), 150.0 (Ar-C), 150.3 (Ar-C), 159.1 (Ar-C), 159.2 (Ar-C). ESI-MS m/z of 624.30, 626.30 $[M+H]^+$ was obtained for a calculated mass of 624.11, 626.11.

1-(2-Bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-yloxy)-3-[3-(3-methoxy-phenyl)-pyrazol-1-yl]-propan-2-ol (26)

Procedure E, Yield 70%. Reddish solid; mp 98-100 °C. ν_{max} (KBr, cm^{-1}): 3370. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (s, 1.5 H, CH_3), 1.83 (s, 1.5 H, CH_3), 2.58 (dd, $J = 9.5$, 6.5 Hz, 0.6 H, OCH_2), 2.71 (dd, $J = 9.4$, 5.8 Hz, 0.4 H, OCH_2), 2.85-3.04 (m, 1 H, OCH_2), 3.60 (br-s, 1 H, D_2O Exchangeable, CHO*H*), 3.81 (s, 1.5 H, Ph-OCH_3), 3.82 (s, 1.5 H, Ph-OCH_3), 3.91-4.0 (m, 0.5 H, C*H*OH), 4.01-4.15 (m, 2 H, C*H*OH and NCH_2), 4.16 (s, 1.5 H, OCH_3), 4.19 (s, 1.5 H, OCH_3), 4.33 (dd, $J = 13.7$, 4.0 Hz, 0.5 H, - NCH_2), 6.35 (d, $J = 2.0$ Hz, 0.5 H, Ar-H), 6.48 (d, $J = 2.0$ Hz, 0.5 H, Ar-H), 6.76-6.89 (m, 1 H, Ar-H), 7.12-7.19 (m, 1 H, Ar-H), 7.20-7.30 (m, 2 H, Ar-H), 7.36-7.46 (m, 1 H, Ar-H), 7.47-7.53 (m, 2 H, Ar-H), 7.54-7.61 (m, 1 H, Ar-H), 7.68-7.76 (m, 1 H, Ar-H), 7.77-7.86 (m, 1 H, Ar-H), 8.13 (dd, $J = 11.5$, 7.4 Hz, 1 H, Ar-H), 8.54 (d, $J = 1.8$ Hz, 0.5 H, Ar-H), 8.61 (d, $J = 1.8$ Hz, 0.5 H, Ar-H) total 28 H in diastereomeric ratio 1 : 1. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.4 (CH_3), 23.5 (CH_3), 53.5 (OCH_3), 54.0 (NCH_2), 54.3 (NCH_2), 55.2 (Ph-OCH_3), 64.7 (OCH_2), 65.4 (OCH_2), 69.5 (*C*HOH), 69.7 (*C*HOH), 84.5 (OCH_3), 84.6 (OCH_3), 102.7 (Ar-C), 102.8 (Ar-C), 110.6 (Ar-C), 110.7 (Ar-C), 113.62 (Ar-C), 113.65 (Ar-C), 118.1 (Ar-C), 118.15 (Ar-C), 123.1 (Ar-C), 123.16 (Ar-C), 123.5 (Ar-C), 124.03 (Ar-C), 124.09 (Ar-C), 126.3 (Ar-C), 128.3 (Ar-C), 128.4 (Ar-C), 129.4 (Ar-C), 129.51 (Ar-C), 129.56 (Ar-C), 129.59 (Ar-C), 129.65 (Ar-C), 129.8 (Ar-C), 129.85 (Ar-C), 131.9 (Ar-C), 132.0 (Ar-C), 132.76 (Ar-C), 132.79 (Ar-C), 134.21 (Ar-C), 134.25 (Ar-C), 137.66 (Ar-C), 137.68 (Ar-C), 145.9 (Ar-C), 146.98 (Ar-C), 147.0 (Ar-C), 148.4 (Ar-C), 148.5 (Ar-C), 151.3 (Ar-C), 151.5 (Ar-C), 159.2 (Ar-C), 159.3 (Ar-C), 159.7 (Ar-C), 159.8 (Ar-C). ESI-MS m/z of 586.00, 588.00 $[M+H]^+$ was obtained for a calculated mass of 586.13, 588.13.

1-(2-Bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-yloxy)-3-[3-(4-chloro-phenyl)-pyrazol-1-yl]-propan-2-ol (27)

Procedure E, Yield 40%. White fluffy-solid; mp 55-57 °C. ν_{max} (KBr, cm^{-1}): 3419. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (s, 1.5 H, CH_3), 1.83 (s, 1.5 H, CH_3), 2.50 (dd, $J = 9.5$, 7.0 Hz, 0.5 H, OCH_2), 2.72 (dd, $J = 9.5$, 5.6 Hz, 0.5 H, OCH_2), 2.92 (dd, $J = 9.5$, 4.2 Hz, 0.4 H, OCH_2), 2.98 (dd, $J = 9.6$, 4.4 Hz, 0.5 H, OCH_2), 3.54 (br s, 1 H, D_2O exchangeable, CHO*H*), 3.87-4.12 (m, 2.5 H, -NCH_2 and C*H*OH), 4.14 (s, 1.5 H, OCH_3), 4.18 (s, 1.5 H, OCH_3), 4.30 (dd, $J = 13.8$, 4.1 Hz, 0.5 H, -NCH_2), 6.27 (d, $J = 2.1$ Hz, 0.5 H, Pyrazole-CH), 6.44 (d, $J = 2.1$ Hz, 0.5 H,

Pyrazole-CH), 7.27 (d, $J = 8.5$ Hz, 1 H, Ar-H), 7.30 (d, $J = 8.5$ Hz, 1 H, Ar-H), 7.35 (d, $J = 2.2$ Hz, 1 H, Ar-H), 7.44-7.51 (m, 3 H, Ar-H), 7.52-7.57 (m, 1 H, Ar-H), 7.60 (d, $J = 8.4$ Hz, 1 H, Ar-H), 7.68-7.85 (m, 2 H, Ar-H), 8.10 (d, $J = 7$ Hz, 0.5 H, Ar-H), 8.14 (d, $J = 7.3$ Hz, 0.5 H, Ar-H), 8.52 (d, $J = 1.7$ Hz, 0.5 H, Ar-H), 8.60 (d, $J = 1.8$ Hz, 0.5 H, Ar-H) total 25 H in diastereomeric ratio 1 : 1. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.3 (CH_3), 23.5 (CH_3), 53.54 (OCH_3), 53.57 (OCH_3), 54.0 (NCH_2), 54.4 (NCH_2), 64.8 (OCH_2), 65.4 (OCH_2), 69.3 (*C*HOH), 69.6 (*C*HOH), 84.5 (CH_3CO-), 84.7 (CH_3CO-), 102.4 (Ar-C), 102.5 (Ar-C), 118.2 (Ar-C), 123.1 (Ar-C), 123.2 (Ar-C), 123.46 (Ar-C), 123.48 (Ar-C), 124.06 (Ar-C), 124.1 (Ar-C), 126.26 (Ar-C), 126.31 (Ar-C), 126.6 (Ar-C), 126.7 (Ar-C), 128.2 (Ar-C), 128.4 (Ar-C), 128.6 (Ar-C), 128.7 (Ar-C), 128.8 (Ar-C), 129.4 (Ar-C), 129.62 (Ar-C), 129.64 (Ar-C), 129.8 (Ar-C), 129.9 (Ar-C), 131.6 (Ar-C), 131.7 (Ar-C), 131.9 (Ar-C), 132.1 (Ar-C), 132.79 (Ar-C), 132.84 (Ar-C), 133.2 (Ar-C), 133.3 (Ar-C), 137.7 (Ar-C), 145.9 (Ar-C), 147.0 (Ar-C), 147.03 (Ar-C), 148.4 (Ar-C), 148.46 (Ar-C), 150.3 (Ar-C), 150.6 (Ar-C), 159.2 (Ar-C), 159.3 (Ar-C). ESI-MS m/z of 589.80, 591.80 $[M+H]^+$ was obtained for a calculated mass of 590.08, 592.08.

1-(2-Bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-yloxy)-3-pyrazol-1-yl-propan-2-ol (28)

Procedure E, Yield 77%. Off-white solid; mp 106-109 °C. ν_{max} (KBr, cm^{-1}): 3436. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (s, 1.5 H, CH_3), 1.82 (s, 1.5 H, CH_3), 2.60 (dd, $J = 9.5$, 6.0 Hz, 0.5 H, OCH_2), 2.66 (dd, $J = 9.4$, 5.8 Hz, 0.5 H, OCH_2), 2.84-2.94 (m, 1 H, OCH_2), 3.87-3.94 (m, 0.5 H, C*H*OH), 3.96-4.06 (m, 1 H, C*H*OH and-NCH_2), 4.08-4.16 (m, 1 H,-NCH_2), 4.17-4.22 (m, 3 H, OCH_3), 4.29 (dd, $J = 13.8$, 4.0 Hz, 0.6 H,-NCH_2), 6.13 (t, $J = 2.0$ Hz, 0.5 H, Pyrazole-CH), 6.19 (t, $J = 2.0$ Hz, 0.5 H, Pyrazole-CH), 6.35 (br-s, 0.5 H, Ar-H), 7.34-7.40 (m, 1 H, Ar-H), 7.41-7.45 (m, 1 H, Ar-H), 7.46-7.58 (m, 3 H, Ar-H), 7.61 (d, $J = 1.7$ Hz, 1 H, Ar-H), 7.72 (t, $J = 2.2$ Hz, 0.5 H, Ar-H), 7.75 (t, $J = 2.2$ Hz, 0.5 H, Ar-H), 7.82 (dd, $J = 9.0$, 2.1 Hz, 1 H, Ar-H), 8.14-8.21 (m, 1 H, Ar-H), 8.62 (d, $J = 1.5$ Hz, 1 H, Ar-H) total 22 H in diastereomeric ratio 1 : 1. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.31 (CH_3), 23.35 (CH_3), 53.4 (OCH_3), 53.9 (OCH_3), 54.3 (NCH_2), 64.9 (OCH_2), 65.4 (OCH_2), 69.4 (*C*HOH), 84.3 (CH_3CO-), 84.37 (CH_3CO-), 105.1 (Ar-C), 117.9 (Ar-C), 122.96 (Ar-C), 122.98 (Ar-C), 123.32 (Ar-C), 123.36 (Ar-C), 123.9 (Ar-C), 126.1 (Ar-C), 128.23 (Ar-C), 128.25 (Ar-C), 129.2 (Ar-C), 129.5 (Ar-C), 129.7 (Ar-C), 130.17 (Ar-C), 130.19 (Ar-C), 132.6 (Ar-C), 133.3 (Ar-C), 137.5 (Ar-C), 139.1 (Ar-C), 139.2 (Ar-C), 145.6 (Ar-C), 146.8 (Ar-C), 148.32 (Ar-C), 148.37 (Ar-C), 159.1 (Ar-C). ESI-MS m/z of 480.10, 482.20 $[M+H]^+$ was obtained for a calculated mass of 480.09, 482.09.

1-(2-Bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-yloxy)-3-[1,2,4]triazol-1-yl-propan-2-ol (29)

Procedure E, Yield 77%. Off-white solid; mp 77-79 °C. ν_{max} (KBr, cm^{-1}): 3385. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.81 (s, 1.5 H, CH_3), 1.82 (s, 1.5 H, CH_3), 2.59 (dd, $J = 9.5$, 6.5 Hz, 0.6 H, OCH_2), 2.74 (dd, $J = 9.8$, 5.0 Hz, 0.6 H, OCH_2), 2.87-2.96 (m, 1 H, OCH_2), 2.99 (dd, $J = 9.5$, 3.6 Hz, 0.6 H, -NCH_2), 3.16-3.23 (m, 1 H, D_2O exchangeable, CHO*H*), 3.85-3.94 (m, 1 H, C*H*OH), 4.00-4.07 (m, 1 H, C*H*OH and -NCH_2), 4.08-4.14 (m, 1 H, -NCH_2), 4.16 (s, 1.5 H, OCH_3), 4.18 (s, 1.5 H, OCH_3), 4.20-4.25 (m, 0.5 H, -NCH_2), 4.31 (dd, $J = 13.8$, 4.2 Hz, 0.6 H, -NCH_2), 7.47-7.58 (m, 3 H, Ar-H), 7.73-7.89 (m, 3 H, Ar-H), 8.07 (s, 0.5 H, Ar-H), 8.15 (s, 0.5 H, Ar-H), 8.16-8.22 (m, 1 H, Ar-H), 8.61-8.66 (m, 1 H, Ar-H) total 21 H in diastereomeric ratio 1 : 1. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.4 (CH_3), 23.5 (CH_3) 51.9 (-NCH_2), 52.4 (-NCH_2), 53.53 (OCH_3), 53.55 (OCH_3), 64.7 (OCH_2), 65.4 (OCH_2), 68.63 (*C*HOH), 68.68 (*C*HOH), 84.5 (CH_3CO-), 84.6 (CH_3CO-), 118.14 (Ar-C), 118.15 (Ar-C), 123.03 (Ar-C), 123.06 (Ar-C), 123.3 (Ar-C), 123.4 (Ar-C), 124.1 (Ar-C), 126.2 (Ar-C), 128.1 (Ar-C), 129.4 (Ar-C), 129.7 (Ar-C), 129.8 (Ar-C), 132.8 (Ar-C), 137.6 (Ar-C), 143.8 (Ar-C), 143.9 (Ar-C), 145.8 (Ar-C), 145.82 (Ar-C), 147.0 (Ar-C), 148.2 (Ar-C), 151.4 (Ar-C), 151.6 (Ar-C), 159.1 (Ar-C). ESI-MS m/z of 481.30, 483.20 $[M+H]^+$ was obtained for a calculated mass of 481.09, 483.09.

1-(2-Bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-yloxy)-3-imidazol-1-yl-propan-2-ol (30)

Procedure E, Yield 70%. Off-white solid; mp 82-84 °C. ν_{max} (KBr, cm^{-1}): 3113. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (s, 3 H, CH_3), 2.60-2.76 (m, 1 H, OCH_2), 2.77-2.94 (m, 1 H, OCH_2), 3.65-3.85 (m, 2 H, NCH_2), 3.92 (dd, $J = 13.5$, 2.8 Hz, 0.5 H, C*H*OH), 4.06 (dd, $J = 13.9$, 3.9 Hz, 0.5 H, C*H*OH), 4.13 (s, 1.5 H, OCH_3), 4.14 (s, 1.5 H, OCH_3), 4.90 (br-s, 1 H, D_2O exchangeable, CHO*H*), 6.64-6.90 (m, 2 H, Ar-H), 7.12-7.29 (m, 1 H, Ar-H), 7.43-7.58 (m, 3 H, Ar-H), 7.68 (dd, $J = 8.9$, 1.3 Hz, 1 H, Ar-H), 7.78 (d, $J = 8.9$ Hz, 1 H, Ar-H), 8.07-8.21 (m, 1 H, Ar-H), 8.59 (s, 1 H, Ar-H). Total 22 H in diastereomeric ratio 1 : 1. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.3 (CH_3), 23.4 (CH_3), 49.9 (-NCH_2), 50.1 (-NCH_2), 53.42 (OCH_3), 53.44 (OCH_3), 64.9 (OCH_2), 65.6 (OCH_2), 69.16 (*C*HOH), 69.22 (*C*HOH), 84.37 (CH_3CO-), 84.42 (CH_3CO-), 118.0 (Ar-C), 119.5 (Ar-C), 123.0 (Ar-C), 123.3 (Ar-C), 123.4 (Ar-C), 123.9 (Ar-C), 126.2 (Ar-C), 128.17 (Ar-C), 128.21 (Ar-C), 128.25 (Ar-C), 129.3 (Ar-C), 129.6 (Ar-C), 129.7 (Ar-C), 132.7 (Ar-C), 137.3 (Ar-C), 137.55 (Ar-C), 137.58 (Ar-C), 145.68 (Ar-C), 145.71 (Ar-C), 146.9 (Ar-C), 148.36 (Ar-C), 148.41 (Ar-C), 159.14 (Ar-C), 159.20 (Ar-C). ESI-MS m/z of 480.16, 482.18 $[M+H]^+$ was obtained for a calculated mass of 480.09, 482.09.

1-(2-Bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-yloxy)-3-morpholin-4-yl-propan-2-ol (31)

Procedure E, Yield 41%. Off-white solid; mp 189-195 °C. ν_{max} (KBr, cm^{-1}): 3394. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.67 (br-s, 1 H, D_2O exchangeable, CHO*H*), 1.77 (s, 1.5 H, CH_3), 1.79 (s, 1.5 H, CH_3), 2.58-2.72 (m, 1 H, Ar-N-CH_2-C*H*$_2$), 2.82-3.10 (m, 4 H, Ar-N-C*H*$_2$-CH_2), 3.25 (d, $J = 13.2$ Hz, 1 H, Ar-N-CH_2-C*H*$_2$), 3.31-3.74 (m, 2 H, Ar-N-CH_2-C*H*$_2$), 3.84-4.09 (m, 2 H, OCH_2), 4.16 (s, 1.5 H, OCH_3), 4.17 (s, 1.5 H, OCH_3), 4.21-4.52 (m, 3 H, NC*H*$_2$C*H*OH), 7.46-7.60 (m, 3 H, Ar-H), 7.74 (dd, $J = 8.9$, 2.0 Hz, 1 H, Ar-H), 7.81 (dd, $J = 8.8$, 1.4 Hz, 1 H, Ar-H), 8.17 (d, $J = 6.9$ Hz, 1 H, Ar-H), 8.61 (d, $J = 1.8$ Hz, 1 H, Ar-H) total 27 H in diastereomeric ratio 1 : 1. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.3 (CH_3), 23.4 (CH_3), 53.50 (OCH_3) 53.55 (OCH_3), 61.4 (Ar-N*C*H$_2$CH$_2$), 62.7 (Ar-N*C*H$_2$CH$_2$), 63.7 (Ar-NCH$_2$*C*H$_2$), 64.4 (Ar-NCH$_2$*C*H$_2$), 64.8 (*C*HOH), 65.4 (OCH_2), 65.7 (OCH_2), 84.5 (CH_3CO-), 84.6 (CH_3CO-), 118.2 (Ar-C), 118.3 (Ar-C), 123.09 (Ar-C), 123.12 (Ar-C), 123.4 (Ar-C), 123.5 (Ar-C), 124.1 (Ar-C), 124.13 (Ar-C), 126.3 (Ar-C), 127.86 (Ar-C), 127.94 (Ar-C), 129.6

(Ar-C), 129.8 (Ar-C), 129.9 (Ar-C), 132.92 (Ar-C), 132.94 (Ar-C), 137.58 (Ar-C), 137.62 (Ar-C), 145.9 (Ar-C), 146.0 (Ar-C), 147.02 (Ar-C), 147.03 (Ar-C), 148.1 (Ar-C), 159.0 (Ar-C), 159.2 (Ar-C). ESI-MS *m/z* of 499.30, 501.30 $[M+H]^+$ was obtained for a calculated mass of 499.12, 501.12.

Dimethyl-carbamic acid 2-bromo-6-methoxy-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-yl ester (32)

To a cooled (0 °C) solution of **21** (0.20 g, 0.56 mmol) in dry DMF (4 mL) sodium hydride (0.030 g, 1.18 mmol) was added under nitrogen atmosphere and stirred for 30 min. During this period, the color of the reaction changed from yellow to dark red. *N*,*N*-Dimethylcarbamyl chloride (0.15 g, 1.40 mmol) was added to the reaction mixture and was stirred for 15 h at room temperature. The reaction was quenched with ice. The reaction mixture was diluted with ethyl acetate (20 mL), washed with brine (3 × 50 mL) and dried over anhydrous sodium sulfate. The organic layer was filtered and solvents were evaporated under reduced pressure to obtain a gum as a crude product. The crude product was purified by column chromatography (silica gel 100-200 mesh, eluent: 10% ethyl acetate in n-hexane) to give **32** (0.060 g; 25%) as a white solid; mp 197-198 °C. ν_{max} (KBr, cm^{-1}): 1711. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.84 (s, 3 H, CH_3), 2.69 (s, 3 H, -NCH_3), 3.03 (s, 3 H, -NCH_3), 4.14 (s, 3 H, OCH_3), 7.40-7.54 (m, 2 H, Ar-H), 7.55-7.61 (m, 1 H, Ar-H), 7.68 (dd, J = 8.9, 2.0 Hz, 1 H, Ar-H), 7.78 (d, J = 8.9 Hz, 1 H, Ar-H), 8.18 (d, J = 7.3 Hz, 1 H, Ar-H), 8.62 (d, J = 2.0 Hz, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.7 (CH_3), 36.1 (NCH_3), 36.2 (NCH_3), 53.3 (OCH_3), 83.3 (*C*HOH), 117.6 (Ar-C), 122.2 (Ar-C), 123.4 (Ar-C), 123.9 (Ar-C), 126.4 (Ar-C), 128.8 (Ar-C), 129.2 (Ar-C), 129.7 (Ar-C), 130.0 (Ar-C), 132.1 (Ar-C), 137.3 (Ar-C), 144.3 (Ar-C), 146.7 (Ar-C), 149.7 (Ar-C), 154.2 (Ar-C), 158.8 (Ar-C). ESI-MS *m/z* of 427.10, 429.20 $[M+H]^+$ was obtained for a calculated mass of 427.07, 429.06.

General procedure F for 33-34: 6-amino-2-bromo-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-ols

A freshly prepared solution of methyl magnesium iodide (3 M solution in dry diethyl ether, 6 eq) was added to the appropriate ketone **5** or **8** (1 eq) in dry THF, at 0 °C, and stirred at 0 °C for 2 h followed by 6 h at room temperature. The reaction was quenched with ice-cold water, diluted with ethyl acetate and washed with saturated ammonium chloride solution followed by brine. The organic layer was dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to obtain the product in good yields.

2-Bromo-7-methyl-6-[4-(3-trifluoromethyl-phenyl)-piperazin-1-yl]-7*H*-indeno[2,1-*c*]quinolin-7-ol (33)

Procedure F. Crude product was purified by column chromatography (100-200 mesh silica gel, eluent: 15% ethyl acetate in hexane) to give pure **33** (82%) as a yellow-orange solid; mp 145-148 °C. ν_{max} (KBr, cm^{-1}): 3441. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.76 (s, 3 H, CH_3), 3.30-3.40 (m, 1 H, -N-CH_2CH_2-N-), 3.46-3.60 (m, 4 H, -N-CH_2CH_2-N-), 4.27-4.36 (m, 2 H, -N-CH_2CH_2-N-), 6.07 (s, 1 H, D_2O exchangeable, CHO*H*), 7.10 (d, J = 7.5 Hz, 1 H, Ar-H), 7.28 (s, 1 H, Ar-H), 7.33 (d, J = 8.6 Hz, 1 H, Ar-H), 7.45 (t, J = 8.0 Hz, 1 H, Ar-H), 7.50-7.58 (m, 2 H, Ar-H), 7.66-7.72 (m, 1 H, Ar-H), 7.74-7.83 (m, 2 H, Ar-H), 8.35 (d, J = 4.7 Hz, 1 H, Ar-H), 8.74 (s, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 23.0 (CH_3), 48.2 (-N-*C*H_2CH$_2$-N-), 49.5 (-N-CH$_2$*C*H_2-N-), 78.9 (*C*HOH), 111.3 (Ar-C), 115.1 (Ar-C), 117.7 (Ar-C), 119.2 (Ar-C), 122.8 (Ar-C), 123.5 (Ar-C), 124.2 (Ar-C), 126.0 (Ar-C), 129.2 (Ar-C), 129.9 (Ar-C), 130.3 (Ar-C), 130.4 (Ar-C), 132.7 (Ar-C), 135.9 (Ar-C), 136.0 (Ar-C), 143.8 (Ar-C), 146.5 (Ar-C), 151.7 (Ar-C), 153.0 (Ar-C), 158.6 (Ar-C). ESI-MS *m/z* of 554.10, 555.90 $[M+H]^+$ was obtained for a calculated mass of 554.11, 556.10.

2-Bromo-6-imidazol-1-yl-7-methyl-7*H*-indeno[2,1-*c*]quinolin-7-ol (34)

Procedure F. The crude reaction mixture was washed with DCM to give desired product **34** (56%) as a pale-yellow solid; mp 175-180 °C. ν_{max} (KBr, cm^{-1}): 3146. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.41 (s, 3 H, CH_3), 6.45 (s, 1 H, D_2O exchangeable, CHO*H*), 7.18 (s, 1 H, Ar-H), 7.55-7.67 (m, 2 H, Ar-H), 7.70-7.78 (m, 1 H, Ar-H), 8.03 (s, 2 H, Ar-H), 8.19 (d, J = 1.2 Hz, 1 H, Ar-H), 8.51 (d, J = 7.0 Hz, 1 H, Ar-H), 8.68 (s, 1 H, Ar-H), 8.95 (s, 1 H, Ar-H). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 22.6 (CH_3), 78.1 (*C*HOH), 120.5 (Ar-C), 121.2 (Ar-C), 123.4 (Ar-C), 124.1 (Ar-C), 124.6 (Ar-C), 126.0 (Ar-C), 128.7 (Ar-C), 129.3 (Ar-C), 130.7 (Ar-C), 131.4 (Ar-C), 133.9 (Ar-C), 134.8 (Ar-C), 135.0 (Ar-C), 138.2 (Ar-C), 145.9 (Ar-C), 146.2 (Ar-C), 152.5 (Ar-C). ESI-MS *m/z* of 392.00, 394.10 $[M+H]^+$ was obtained for a calculated mass of 392.04, 394.04.

Biological activity – methods

Anti-mycobacterial activity

Compounds **10-34** and the first front-line drug Isoniazid[22] (as a reference) were dissolved in DMSO at a concentration of 6.25 μg mL^{-1} and stored at ~4 °C until used.

Cytotoxicity

Cell viability in the presence and absence of test compounds was determined by Mosmans's MTT assay[26-28] for the most active compounds (**11**, **13**, **16**, **24**, **30**, **32** and **34**) from our data set. The cells (human monocytic cell line U937) were plated in flat-bottomed 96 well plates (1×10^5 cells ml^{-1}), 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 (Table 3). After completion of the experiment protocol 10 μL of MTT solution (5 mg mL^{-1} solution in Phosphate Buffer Saline) was added in each well. Plates were incubated for three hours 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 micro plate reader (Bio-Rad-i Mark) using acidified isopropanol as blank. The results were presented as percentage cell viability (Table 3).

NOTE: All amino acid numbering corresponds to *Mycobacterium tuberculosis* ATP synthase subunits A and C. Subunit type shown in superscript.

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