Synthesis and structure of azole-fused indeno[2,1-*c*]quinolines and their anti-mycobacterial properties†

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Prompted by our discovery of a new class of conformationally-locked indeno[2,1-*c*]quinolines as anti-mycobacterials, compounds **2a** and **3a** (Fig. 1; MIC < 0.39 μg mL^{-1} and 0.78 μg mL^{-1}, respectively)[14] with a freely rotating C2-imidazolo substituent, we herein describe the synthesis of pentacyclic azole-fused quinoline derivatives **4** and **5**, in which we have restricted the rotation of the C2-imidazolo moiety by fusing it to the adjacent quinoline-nitrogen to give a five-membered fused azole heterocycle. The idea of locking the flexibility of the system by conformational constraint was simply to reduce its entropy, thereby reducing the overall free-energy of its binding to the target receptor. Out of 22 different azole-fused indeno[2,1-*c*]quinoline derivatives, seven structurally distinct compounds, **9**, **15**, **17**, **25**, **27**, **28** and **29**, have shown 79–99% growth inhibition of *Mycobacterium tuberculosis* H37Rv at a fixed dose of 6.25 μg mL^{-1}. The efficacies of these compounds were evaluated *in vitro* for 8/9 consecutive days using the BACTEC radiometric assay upon administration of single dose on day one. Of these, two compounds, **9** and **28**, inhibited growth of *M. tuberculosis* very effectively at MIC < 0.39 μg mL^{-1} (0.89 μM and 1 μM, respectively). These active compounds **9**, **15**, **17**, **25**, **27**, **28** and **29** were screened for their cytotoxic effect on mammalian cells (human monocytic cell line U937), which showed that the human cell survival is almost unperturbed (100% survival), except for compound **25**, hence these new compounds with new scaffolds have been identified as potent anti-mycobacterials, virtually with no toxicity. Thus these "hit" molecules constitute our important "leads" for further optimization by structure–activity relationship against TB.

Introduction

Many natural and synthetic biologically active compounds are found to be nitrogen containing heterocycles and they constitute an important class of pharmacophores in medicinal chemistry.[1–4] Within this group of heterocycles, quinoline derivatives have been well known in medicinal chemistry as anti-malarials,[5] anti-bacterials,[6] anti-cancer[7] as well as anti-mycobacterials.[8–10] Quinoline-based anti-TB compound TMC207[11] (Fig. 1) bearing a bulky biaryl side chain at position C3, is a highly potent anti-TB agent, has novel mode of action and is currently in phase II clinical trials with very promising activity against MDR-TB.[12]

Based on molecular dissection of TMC207, we have recently reported the design, synthesis and biological activity of relatively less complex molecules possessing potent anti-TB activity,[13,14] among which conformationally-locked indeno[2,1-*c*]quinolines[14] **2a** and **3a** showed effective inhibition of *Mycobacterium tuberculosis* H37Rv with MIC_{99} < 0.39 μg mL^{-1} (1 μM) for the former and MIC_{99} < 0.78 μg mL^{-1} (2 μM) for the latter in the whole cell assay. We assumed that by covalently restricting the rotation of the C2-imidazolo moiety in **2a** and **3a**, by fusing to the adjacent quinoline-nitrogen in the form of pentacyclic azole-fused quinoline derivatives **4** and **5**, we might be able to reduce the entropy of the system without imposing enthalpy penalty, hence directly contributing to the reduction of the overall free-energy of binding to the target receptor. We also argued that this would give us scope to explore the pharmacological role of the free-rotating C2-imidazolo substituent in compounds **2a** and **3a** for the anti-tuberculotic activity (Fig. 1).

Literature survey revealed that the tetrazolo-, 1,2,4-triazole- and dihydroimidazole-fused quinolines were found to posses important biological activities. Tetrazolo-fused quinolines have anti-inflammatory, anti-bacterial properties[15] and platinum(II) complexes of tetrazolo-quinolones were found to possess anti-tumor properties,[16,17] whereas condensed 1,2,4-traizoles are found to be excellent anti-depressants.[18a–g] Synthesis of azole-fused quinolines[19] and isoquinolines[20] is reported in literature and these compounds have been studied for the spectral characteristics like proton-magnetic resonance[19] and photochemical properties,[21] but no conclusive NMR data that unambiguously substantiates the ring-closure to the fused heterocycles has been presented so far.[22–26]

Inspired by the interesting biological activities of fused quinolines and the potent anti-TB activity displayed by our conformationally locked indeno[2,1-*c*] quinolines **2a** and **3a**, in which the imidazolo group at the C2 position of the quinoline ring is important for biological activity. In order to examine the role of the

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† Electronic supplementary information (ESI) available: Spectral data (1D-NMR, 2D-NMR, LCMS, Mass, HPLC and IR) for all new compounds is included. See DOI: 10.1039/c0ob00445f

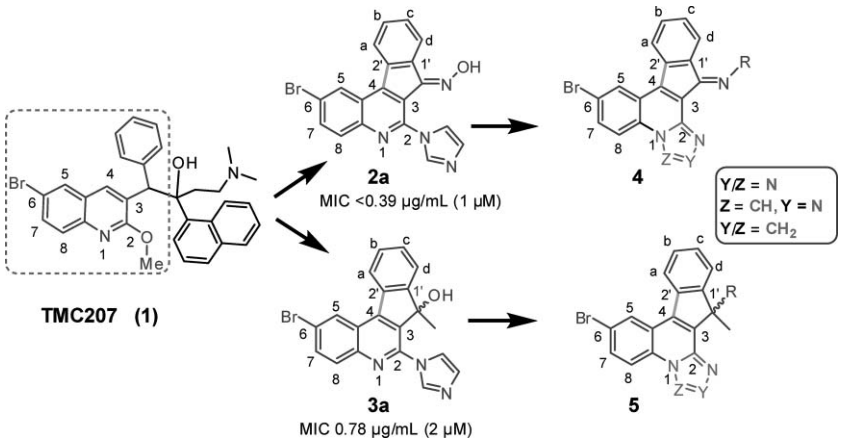


Fig. 1 Structures of conformationally-locked indeno[2,1-*c*]quinoline **2a**, **3a**, **4**, **5** and **TMC207**.[11] The left-half of TMC207 (**1**) (shown in a dotted box) is conformationally-locked at C4 of the quinoline system to C2′ of the phenyl ring to give relatively simple molecules **2a** and **3a**, which have been shown to successfully inhibit the growth of *Mycobacterium tuberculosis* H37Rv with minimum inhibitory concentration (MIC) of <0.39 μg mL^{-1} and 0.78 μg mL^{-1}.[14] In order to examine the role of the free-rotating imidazolo ring at C2, we have conformationally-locked the C2-imidazolo ring by heteroannulation with the quinoline-nitrogen to give the **double-locked** indeno[2,1-*c*]quinoline derivatives with general formulae **4** and **5**.

free-rotating imidazolo group at C2, we have conformationally-locked the C2-imidazolo ring by heteroannulation with the quinoline nitrogen to give the pentacyclic double-locked indeno[2,1-*c*]quinoline derivatives **4** and **5**.

We herein report the design, synthesis and anti-mycobacterial activity of the fused tetrazole-, triazole- and dihydroimidazole-indeno[2,1-*c*]quinolines **7–29** with detailed spectroscopic analysis of the ring closure reaction involving the C2 substituent and quinoline nitrogen.

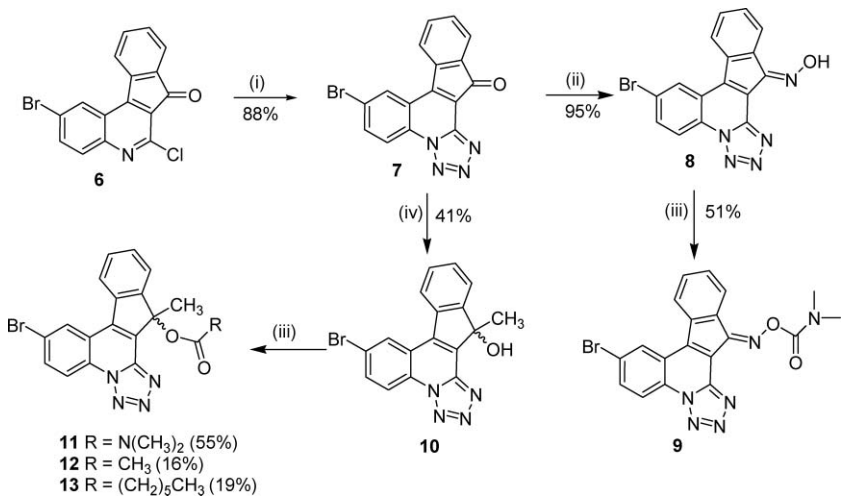
Results

1.0 Synthesis of tetrazole-fused indeno[2,1-*c*]quinolines (9–13)

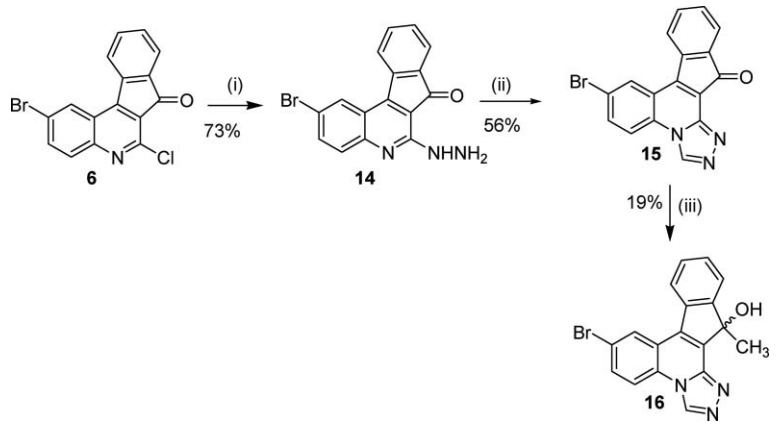
Synthesis of the title compounds **9–13** was started from an easily accessible compound **6**[14] (Scheme 1), which upon treatment with NaN_3 resulted in nucleophilic displacement of the C2-chloro to C2-azido *in situ*, which concomitantly cyclized in a one-pot reaction to give the fused tetrazolo indeno[2,1-*c*]quinoline **7** (88%) in a single step. Subsequently, the oxime derivative **8** was prepared in 95% yield from compound **7** by heating the latter with $NH_2OH{\cdot}HCl$ in DMF at 120 °C. Compound **8** was then converted to *N*,*N*-dimethylcarbamyl oxime **9** (51%) by treatment with *N*,*N*-dimethylcarbamyl chloride and NaH in DMF. Compound **7** was also converted to the racemic C-methyl alcohol **10** (41%) by a Grignard reaction with CH_3MgI under standard conditions. Compound **10** was subsequently transformed to various ester derivatives **11–13** (16–55%) by treating with corresponding acid chlorides in *N*,*N*-dimethylformamide in the presence of NaH.

2.0 Synthesis of triazole-fused indeno[2,1-*c*]quinolines (15 and 16)

These compounds were prepared from chloroketone **6**[14] (Scheme 2). Treatment of compound **6** with $NH_2NH_2{\cdot}H_2O$ in ethanol at reflux temperature gave compound **14** (73%), which



Scheme 1 Synthesis of tetrazole-fused indeno[2,1-*c*]quinolines (**7–13**): *Reagents and Conditions*: (i) NaN_3, DMF, 80 °C, 5 h; (ii) $NH_2OH{\cdot}HCl$, DMF, 120 °C, 5 h; (iii) NaH, RCOCl, DMF; (iv) CH_3MgI, THF, rt, 12 h.



Scheme 2 Synthesis of triazole-fused indeno[2,1-*c*]quinolines (**15** and **16**): *Reagents and Conditions*: (i) $NH_2NH_2{\cdot}H_2O$, C_2H_5OH, reflux, 48 h; (ii) HCOOH, reflux; 24 h; (iii) CH_3MgI, THF, 0 °C–rt.

upon treatment with HCOOH under reflux gave compound **15** (56%). Compound **15** was converted to the racemic C-methyl alcohol **16** (19%) by the Grignard reaction with CH_3MgI under standard conditions.

3.0 Synthesis of substituted triazolo-fused indeno[2,1-*c*]quinolines (17–23)

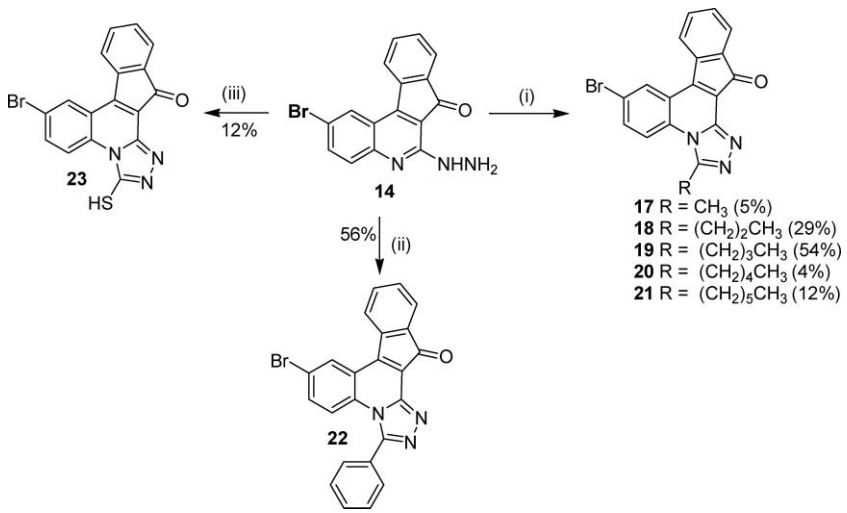
Treatment of hydrazino compound **14**, with various aliphatic acids at 140 °C resulted in the alkyl substituted fused triazoles **17–21** (4–54%) as shown in Scheme 3. Phenyl substituted triazole **22** was prepared in 56% yield by the treatment of C2-hydrazino compound **14** with benzoyl chloride at reflux temperature, whereas mercapto-triazole **23** was prepared in 12% yield by heating compound **14** and CS_2 in pyridine for 20 h (Scheme 3).

4.0 Synthesis of fused-dihydroimidazole indeno[2,1-*c*]quinolines (25–29)

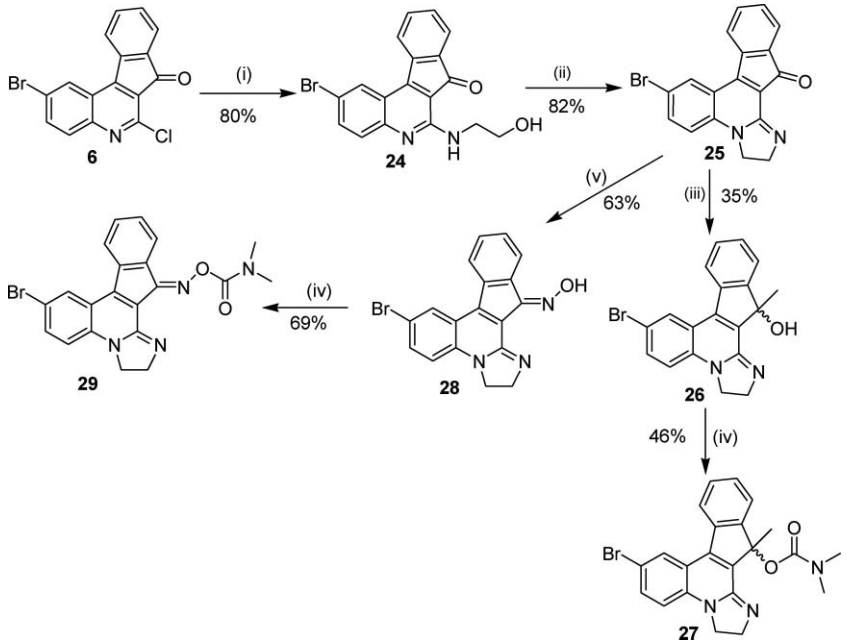
These compounds were prepared by nucleophilic substitution of C2-chloro of compound **6**[14] with 2-aminoethanol to give the corresponding C2-hydroxyethylamino derivative **24** (79%) (Scheme 4), which was cyclized in phosphrous oxychloride to give dihydroimidazole fused quinoline **25** (82%). Grignard reaction of CH_3MgI of compound **25** gave the alcohol **26** (35%), which was further treated with *N*,*N*-dimethylcarbamyl chloride and NaH in DMF to give compound **27** (46%). The oxime derivative of compound **25** was prepared by treating it with $NH_2OH{\cdot}HCl$ and aq. NaOH in ethanol to give compound **28** (63%). Oxime **28** upon treatment with *N*,*N*-dimethylcarbamyl chloride and NaH in DMF afforded derivative **29** (69%).

5.0 Spectroscopic evidence of the ring-closure reaction to give the azole-fused indeno[2,1-*c*]quinoline systems

Formation of ring fused indeno[2,1-*c*]quinolines, tetrazole **7**, triazole **15** and dihydroimidazole **25**, was proved by extensive 1D and 2D NMR studies (see ESI† and Experimental section). The observed chemical shifts of precursor chloroketone **6** and the ring fused tetrazole (compound **7**), triazole (compound **15**) and dihydroimidazole (compound **25**) are given in Table S1 in ESI†. The proton chemical shifts of the quinoline protons in the N1 and



Scheme 3 Synthesis of alkyl/aryl substituted fused triazoloindeno[2,1-*c*]quinolines (**17–23**): *Reagents and Conditions*: (i) RCOOH, 135–140 °C, 20 h; (ii) PhCOCl, 140 °C, reflux, 3 h; (iii) CS_2, pyridine, reflux, 20 h.



Scheme 4 Synthesis of dihydroimidazole-fused indeno[2,1-*c*]quinolines (**25–29**): *Reagents and Conditions*: (i) $NH_2CH_2CH_2OH$, C_2H_5OH, reflux, 48 h; (ii) $POCl_3$, reflux, 3 h; (iii) CH_3MgI, THF, 0 °C–rt; (iv) RCOCl, NaH, DMF; (v) $NH_2OH.HCl$, NaOH, EtOH, H_2O, reflux.

C2 fused quinoline system clearly shows the electronic influence of the **[2,1-*c*]** fused heterocyclic ring. The key structural evidence for the formation of tetrazolo compound **7** came from the comparison of its ^{1}H-NMR spectrum with the precursor chloroketone **6**: Compound **7** showed the expected downfield shift of quinoline ring protons H8 (δ 8.85), H7 (δ 8.48) and H5 (δ 9.15) due to the tetrazole ring-current as compared to that of compound **6** in which protons H8, H7 and H5 appeared at δ 8.12, 8.27 and 9.00 respectively (Table S1 ESI†). The IR spectrum of compound **7** also showed clearly the absence of the azide band[27] at ν_{max} 2100–2270 cm^{-1}.

The ^{1}H-NMR spectrum of compound **15**, showed the expected downfield shift of H8 (δ 8.65) and H7 (δ 8.31) protons due to the triazole ring-current as compared to compound **6**, in which protons H8 and H7 appeared at δ 8.12 and 8.27 respectively (Table S1 ESI† and Experimental section). The isolated signal at δ 10.17 was unambiguously assigned to the triazole ring proton (H9), since it disappears upon substitution at that position (see NMR data of compounds **17–22** in Experimental section). The ^{1}H-NMR spectrum of compound **23** showed a downfield singlet at δ 14.93 which was assigned to –SH protons as it is D_2O exchangeable. The downfield doublet at δ 10.98 was assigned to the H8 proton of the quinoline ring which may be due to the local anisotropy of C═S. In COSY the proton–proton coupling of H8 proton at δ 10.98 with the H7 proton at 8.23 also proves the assignment of the H8 proton. Our *ab initio* studies and comparison of theoretical proton chemical shifts of compound **23** with that of experimental showed that the thione tautomeric form of compound **23** is more stable than the thiol form (Table S2 in ESI†).

The ^{1}H-NMR spectrum of dihyroimidazole compound **25** showed the expected upfield shift of the quinoline ring protons H8, H7 and H5 which appeared at δ 6.68, 7.57 and 8.19 respectively as compared with compound **6** (Table S1 ESI†). The ^{1}H NMR shifts of the protons in the dihydroimidazolo system and the fused quinoline protons, upon addition of a drop of CF_3COOH (TFA), in compound **25** showed the expected downfield shift of all ring protons (See Table S1 ESI†). When TFA was added in a similar way to the NMR sample of the C2 imidazolo compound **2d** (Table Sl ESI†), the ^{1}H chemical shifts of the quinoline protons moved downfield by ~0.1 ppm, whereas a much larger downfield shift was observed for the imidazole protons (1.41–0.46 ppm, Table S1 and Fig S2 ESI†).

Detailed NMR characterization by 1D and 2D NMR spectra, such as COSY to show proton–proton connectivity, HSQC to show proton–carbon connectivity and finally HMBC to establish long-range proton–carbon proved the structures of the azole-fused indeno[2,1-*c*] quinolines (see ESI† and experimental section).

A plot of experimental ^{1}H NMR chemicals shifts *versus* aromatic proton positions is shown in Fig. S1 (ESI†). It clearly shows that the quinoline ring protons H5, H7 and H8 have a dramatic change in chemical shifts after formation of ring fused compounds as compared to precursor compound **6**.

6.0 Anti-mycobacterial activity

Compounds **7–13**, **15–29** and standard drug isoniazid[28] were tested against *M. tuberculosis* H37Rv (ATCC 27294) at a fixed concentration of 6.25 μg mL^{-1} by the BACTEC 460 radiometric method[29,30] 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. Compounds **9**, **15**, **17**, **25**, **27**, **28** and **29** were found to inhibit the *M. tb* H37Rv growth successfully by 97%, 99%, 99%, 81%, 79%, 97% and 99% respectively. Fig. 2 shows the bar graph of % TB growth for the compounds **9**, **15**, **17**, **25**, **27**, **28** and **29** along with isoniazid[28] for the comparison under identical experimental conditions.

Table 1 % Growth 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]

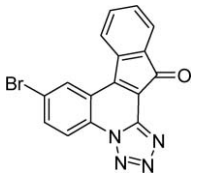
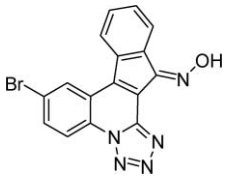
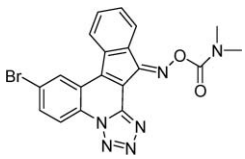
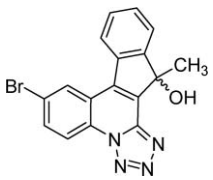
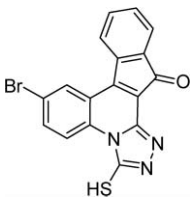
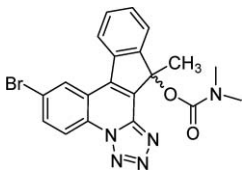
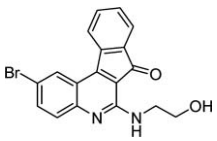
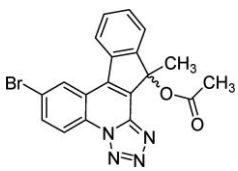
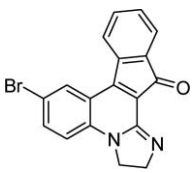
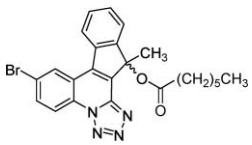
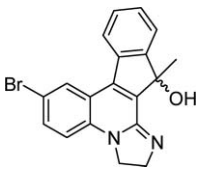
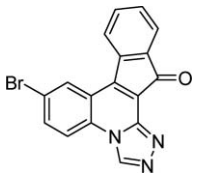
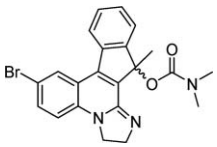
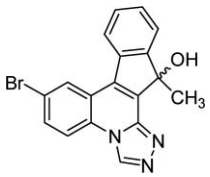
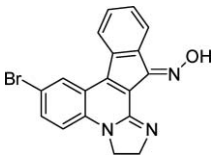
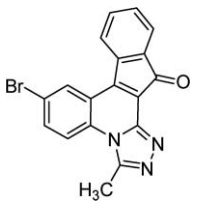
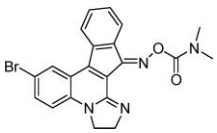
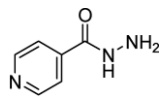
Comp. No.	Structure	% Growth Inhibition[b]	clogP	Comp. No.	Structure	% Growth Inhibition[b]	clogP
7		46	4.35	**20**		55	6.26
8		43	4.52	**21**		47	6.79
9		97	4.13	**22**		15	5.97
10		51	3.49	**23**		55	4.82
11		29	4.59	**24**		25	4.45
12		45	4.35	**25**		81	3.82
13		39	6.99	**26**		52	4.12

Table 1 *(Contd.)*

Comp. No.	Structure	% Growth Inhibition[b]	clogP	Comp. No.	Structure	% Growth Inhibition[b]	clogP
15		99	3.87	**27**		79	5.31
16		66	3.02	**28**		97	3.87
17		99	4.14	**29**		99	5.34
18		72	5.20		 Isoniazid	99	0.67[c]
19		69	5.73				

[a] Values are means of triplicate measurement of % growth inhibition (GI). Assays are performed by the BACTEC 460 radiometric method.[29,30] [b] Estimated with reference to Growth Inhibition of the first front-line inhibitor, Isoniazid. [c] From PubChem (http://pubchem.ncbi.nlm.nih.gov).

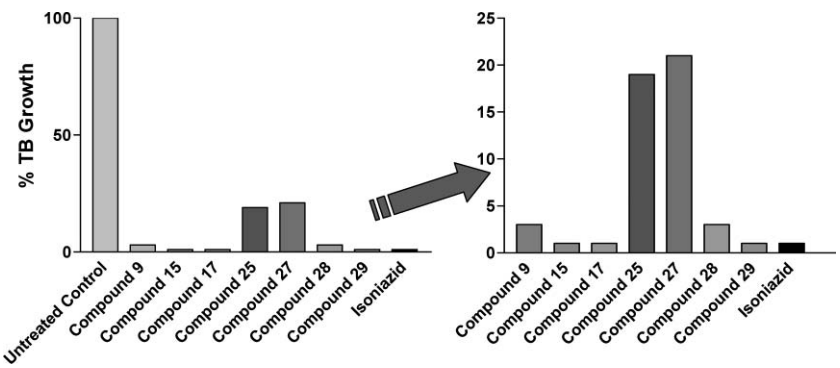


Fig. 2 % TB growth inhibition for compounds **9**, **15**, **17**, **25**, **27**, **28** and **29** along with standard drug Isoniazid and untreated control.

7.0 MIC and Cytotoxicity

The MIC of the most active compounds **9**, **15**, **17**, **25**, **27**, **28**, and **29** are given in Table 2. These seven compounds have an MIC in the range of 0.89–17.86 μM. Compounds **9** and **28** inhibited the mycobacterial growth very effectively compared to others in the series, with minimum inhibitory concentrations (MIC) of 0.39 μg mL^{-1} (0.89 μM) and 0.39 μg mL^{-1} (1.0 μM) respectively.

Certain therapeutic properties are required to identify if an anti-mycobacterial compound has the potential to be a drug. Toxicity is one of those important criteria. Hence, we have investigated the potential toxicity of our fused quinolines towards mammalian cells (human monocytic cell line U937). Compounds **9**, **15**, **17**, **25**, **27**, **28** and **29** were screened for cytotoxicity against human monocytic cell line U937 (Mossman's MTT assay).[31–33] This preliminary evaluation of cytotoxicity revealed that compounds **9**, **15**, **17** and **28** were non cytotoxic to host cells (human monocytic cells) at given concentration (Table 2), while compounds **25**, **27** and **29** are least safe at a higher concentration (10 μg mL^{-1}).

8.0 Discussion

Most of the synthesized compounds were found to have good anti-mycobacterial activity. Seven molecules of three different classes, *i.e.* tetrazolo-, triazolo-, and dihydroimidazolo-fused indeno[2,1-*c*]quinolines (compounds **9**, **15**, **17**, **25**, **27**, **28** and **29**) showed good to excellent anti-*TB* activity (Table 1).

Compounds **9**, **15**, **17**, **28** and **29** of three different series showed most impressive TB growth inhibition in the range of 97–99%. Two compounds, compound **9** (97% GI, Table 1; MIC (0.39 μg mL^{-1}, 0.89 μM)) and compound **28** (97% GI, Table 1; MIC (0.39 μg mL^{-1}, 1.0 μM)) were found to have excellent anti-mycobacterial activity against H37Rv. Compound **28**, the oxime derivative of a fused dihydroimidazole, and compound **2a**, having a freely rotating imidazolo substituent at C2, have comparable TB growth inhibition and MIC values, whereas compound **9** (0.39 μg mL^{-1}, 0.89 μM), a carbamoyl ester of a fused tetrazole, is having slightly better MIC than compound **2a** (0.39 μg mL^{-1}, 1.0 μM).

The oxime carbamoyl esters, compound **9** (97% GI) and fused dihydroimidazole compound **29** (99% GI), were found to have excellent percentage growth inhibition whereas their parent oximes, compound **8** (43% GI) and compound **25** (81% GI), were found to be relatively less active. The Grignard reaction generated alcohols of three different series, *i.e.* molecules **10**, **16** and **26** have been found to inhibit the *M. tb* growth by 51%, 66% and 52% respectively. In general, derivatives carrying a tertiary hydroxyl group were found to have moderated anti-mycobacterial activity. Ester derivatives of tertiary alcohol **10** (51% GI), compounds **11**, **12** and **13**, were found to be less active, which suggests that increase in steric bulk at the tertiary position shows gradual decrease in activity.

Ketones **15** (99% GI) and **17** (99% GI) from the triazolo series have comparable steric bulk at the C9 position and were found to show excellent growth inhibition of *M. tb*. While increasing the chain length or steric bulk on the triazole ring, as in compounds **18** (72% GI), **19** (69% GI), and **22** (15% GI), showed the gradual decrease in their *M. tb* growth inhibition.

The parent keto-compounds from tetrazole, triazole and dihydroimidazole, *i.e.* compounds **7**, **15** and **25**, showed 46%, 99% and 81% growth inhibition respectively. This shows that triazole-fused indeno[2,1-*c*]quinolines have great potential to develop as effective anti-mycobacterial agents.

Compounds **9** and **28** inhibited growth of *M. tuberculosis* very effectively at MIC < 0.39 μg mL^{-1} (0.89 μM and 1 μM, respectively). These active compounds were screened for cytotoxic effect on mammalian cells (human monocytic cell line U937), which showed that the human cell survival is almost unperturbed (97–99% survival, Table 2) when they were treated with compounds **9**, **15**, **17** or **28**, hence identified as potent anti-mycobacterials, virtually with no toxicity.

Conclusion

We have designed and synthesized a novel class of tetrazole-, triazole- and dihydroimidazole-fused indeno[2,1-*c*]quinoline molecules as anti-mycobacterial agents. Molecules **9**, **15**, **17**, **25**, **27**, **28** and **29** inhibited the growth of *M. tb* effectively at the concentration of 6.25 μg mL^{-1}. Compound **9** and **28** inhibited growth of *M. tuberculosis* very effectively at minimum inhibitory concentration (MIC) < 0.39 μg mL^{-1} (0.89 μM) and (1 μM) respectively, which is comparable to that of the existing front-line drug isonaizid (MIC 0.25 μg mL^{-1}). Thus these "hit" molecules constitute our important "leads" for further optimization by structure–activity relationship to develop as effective anti-mycobacterial agents which can help to shorten the duration of current anti-TB therapy.

Experimental section

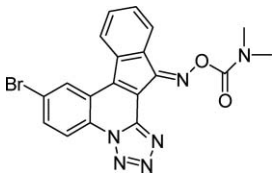
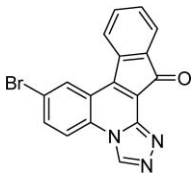
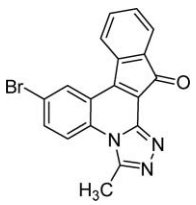
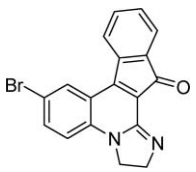
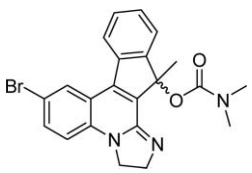
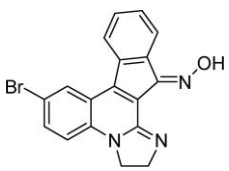
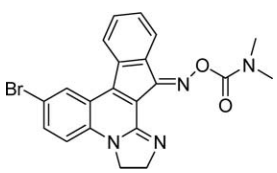
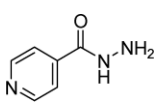
Chemistry – General experimental methods

Purification and drying of reagents and solvents were carried out according to literature procedure.[34]

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 up to 2 decimal places. IR spectra were recorded on Perkin–Elmer Spectrum RX1.

Preparation of 7-bromo-13*H*-indeno[2,1-*c*]tetrazolo[1,5-*a*]quinolin-13-one (7). A mixture of 2-bromo-6-chloro-indeno[2,1-*c*]quinolin-7-one **6**[14] (5.0 g, 14.53 mmol), sodium azide (1.88 g, 29.06 mmol) in *N*,*N*-dimethyformamide (100 mL) was heated at 80 °C under nitrogen atmosphere for 5 h. The reaction mixture was cooled and then quenched with water, light green solid obtained was filtered. The solid was washed with water (3 × 200 mL) and further purified by giving ethyl acetate washings, dried under reduced pressure to obtain 7-bromo-13*H*-indeno[2,1-*c*]tetrazolo[1,5-a]quinolin-13-one **7** (4.5 g, 88%) as a light green solid. mp 300–301 °C; IR ν_{max}(KBr, cm^{-1}) 1713.77; ^{1}H-NMR (600 MHz, DMSO-d_6): δ 7.76 (t, *J* = 7.2 Hz, 1 H, Hc), 7.85–7.90 (m, 1 H, Hb), 7.92 (d, *J* = 7.2 Hz, 1 H, Hd), 8.48 (d, *J* = 8.7 Hz, 1 H, H7), 8.66 (d, *J* = 7.6 Hz, 1 H, Ha), 8.85 (d, *J* =

Table 2 MIC[a] of compounds **9**, **15**, **17**, **25**, **27**, **28** and **29** against *M. tuberculosis* H37Rv and cytotoxic effects on human monocytic cell line U937 after 72 h

Compd. No.	Structure	MIC (μg mL^{-1})	MIC$_{99}$/μM	% Cell Viability after 72 h	
				Conc. (1 μg mL^{-1})	Conc. (10 μg mL^{-1})
9		<0.39	0.89	100	100
15		6.25	17.86	100	100
17		6.25	17.17	100	100
25		3.125	8.90	38	39
27		6.25	14.27	96	10
28		<0.39	1.06	100	76
29		1.56	3.56	79	8
Isoniazid		0.256	1.86		

[a] MIC determined by BACTEC 460 radiometric method.[29,30] MIC was the lowest concentration inhibiting 99% of growth.

8.7 Hz, 1 H, H8), 9.15 (s, 1 H, H5). ESI-MS *m/z* of 350.90, 352.90 $[M+H]^+$ was obtained for a calculated mass of 350.98, 352.98.

Preparation of 7-bromo-13*H*-indeno[2,1-*c*]tetrazolo[1,5-*a*]quinolin-13-one oxime (8). A mixture of compound **7** (5.00 g, 14.24 mmol), hydroxylamine hydrochloride (6.92 g, 99.71 mmol) and anhydrous DMF (200 mL) was heated at 120 °C for 5 h. The reaction mixture was poured into water and filtered; crude product was washed with ethyl acetate, methanol and hexane, dried under reduced pressure to get desired product **8** (5.0 g, 95%) as yellow solid; mp 295–296 °C. IR ν_{max} (KBr, cm^{-1}) 3148.25; ^{1}H NMR (600 MHz, DMSO-d_6): δ 7.72–7.77 (m, 1 H, Hc), 7.78–7.84 (m, 1 H, Hb), 8.65 (d, J = 6.4 Hz, 1 H, Hd), 8.65–8.70 (m, 1 H, Ha), 8.33 (d, J = 8.7 Hz, 1 H, H7), 8.82 (d, J = 8.4 Hz, 1 H, H8), 9.11 (s, 1 H, H5), 13.82 (brs, 1 H, =N–OH). ^{13}C NMR (150.9 MHz, DMSO-d_6): δ 120.1 (C8), 122.2, 124.6 (Ca), 128.2 (Ar–C), 128.5 (Cd), 130.6 (Cc), 130.9, 131.7, 131.9 (Cb), 134.1, 134.6 (C7), 137.5, 138.7 (Ar–C). ESI-MS *m/z* of 365.80, 367.60 $[M+H]^+$ was obtained for a calculated mass of 365.99, 367.99.

General procedure A: Preparation of compounds 9, 11, 27 and 29. The appropriate oximes or alcohols **8**, **10**, **26** and **28** (1 eq) and sodium hydride (3 eq) in anhydrous DMF at 0 °C were stirred for 15–30 min, to this reaction mixture *N*,*N*-dimethylcarbamyl chloride (3 eq) was added dropwise, and stirred for 3 h at room temperature. The reaction mixture was poured into water, extracted with DCM or ethyl acetate. The organic extract was dried over anhydrous sodium sulfate, filtered and solvents were evaporated under reduced pressure to obtain the corresponding acylated crude products **9**, **11**, **27** and **29**.

General procedure B: Preparation of compounds 10, 16, and 26. A freshly prepared solution of methyl magnesium iodide (3 M solution in dry diethyl ether, 6 eq) was added to ketones **7**, **15** and **25** (1 eq) in dry THF at 0 °C, and stirred for 1–5 h at room temperature. The reaction was quenched with saturated ammonium chloride solution and extracted with ethyl acetate, organic layer washed with brine, dried over anhydrous sodium sulfate, filtered and evaporated under reduced pressure to obtain the crude product. Crude product was purified by column chromatography eluting with 2–5% methanol and DCM.

General procedure C: Preparation of compounds 12 and 13. Sodium hydride (3 eq) was added to compound **10** (1 eq) in dry DMF at 0 °C (ice bath) under nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 30 min. The appropriate acid chloride (3 eq) was added to the reaction mixture and stirred for 3 h at room temperature. The reaction mixture was quenched with ice and extracted with DCM. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to obtain crude product. This crude product was purified by column chromatography (silica gel 100–200 mesh, gradual elution with ethyl acetate–hexane in 5–10%) to get the corresponding derivatives **12** and **13**.

7-Bromo-13*H*-indeno[2,1-*c*]tetrazolo[1,5-*a*]quinolin-13-one-*O*-dimethylcarbamoyl oxime (9). Procedure A. The crude product was purified by column chromatography eluting with 5% methanol and DCM to get the desired product **9** (51%) as yellow solid; mp 227–228 °C. IR ν_{max} (KBr, cm^{-1}) 1756.85; ^{1}H NMR (600 MHz, DMSO-d_6): δ 3.07 (s, 3 H, NCH_3), 3.22 (s, 3 H, NCH_3), 7.70 (d, J = 7.6 Hz, 1H, Hc), 7.76 (t, J = 7.6 Hz, 1 H, Hb), 8.27 (dd, J = 1.9, 9.1 Hz, 1 H, H7), 8.40 (d, J = 7.6 Hz, 1 H, Hd), 8.61 (d, J = 7.6 Hz, 1 H, Ha), 8.73 (d, J = 9.1 Hz, 1 H, H8), 9.01 (d, J = 1.9 Hz, 1 H, H5). ESI-MS *m/z* of 436.70, 438.80 $[M+H]^+$ was obtained for a calculated mass of 437.03, 439.03.

7-Bromo-13-methyl-13*H*-indeno[2,1-*c*]tetrazolo[1,5-*a*]quinolin-13-ol (10). Procedure B. The crude product was purified by column chromatography eluting with 2–5% methanol and DCM to get the desired product **10** (41%) as off-white solid; mp 254–255 °C. IR ν_{max} (KBr, cm^{-1}) 3432.59; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86 (s, 3 H, CH_3), 5.99 (s, 1 H, D_2O exchangeable, CHO*H*), 7.57–7.62 (m, 2 H, Ar–H), 7.76–7.82 (m, 1 H, Ar–H), 8.22 (dd, J = 1.84, 8.88 Hz, 1 H, H7), 8.45–8.48 (m, 1 H, Ar–H), 8.73 (d, J = 8.96 Hz, 1 H, H8), 9.02 (d, J = 1.88 Hz, 1 H, H5). ^{13}C NMR (100.6 MHz, DMSO-d_6) δ 24.0 (CH_3), 77.8 (OH–*C*), 118.9 (Ar–C), 121.2 (Ar–C), 121.3 (Ar–C), 122.8 (Ar–C), 123.5 (Ar–C), 127.3 (Ar–C), 128.6 (Ar–C), 129.0 (Ar–C), 133.5 (Ar–C), 134.00 (Ar–C), 134.9 (Ar–C), 136.3 (Ar–C), 143.6 (Ar–C), 152.3 (Ar–C). ESI-MS *m/z* of 366.90, 369.10 $[M+H]^+$ was obtained for a calculated mass of 367.01, 369.01.

7-Bromo-13-methyl-13*H*-indeno[2,1-*c*]tetrazolo[1,5-*a*]quinolin-13-yl dimethylcarbamate (11). Procedure A. The crude product was purified by column chromatography eluting with 2% methanol and DCM to get the desired product **11** (55%) as off-white solid; mp 256–257 °C. IR ν_{max} (KBr, cm^{-1}) 1705.86; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.0 (s, 3 H, CH_3), 2.62 (s, 3 H, NCH_3), 3.11 (s, 3 H, NCH_3), 7.54–7.58 (m, 2 H, Ar–H), 7.65 (d, J = 7.12 Hz, 1 H, Ar–H), 7.98 (dd, J = 1.92, 8.72 Hz, 1 H, H7), 8.22 (d, J = 7.6 Hz, 1 H, Ar–H), 8.70 (d, J = 8.88 Hz, 1 H, H8), 8.89 (d, J = 1.92 Hz, 1 H, H5). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.3 (CH_3), 36.2 (NCH_3), 36.5 (NCH_3), 83.2 (–O–C–CH_3), 119.4 (Ar–C), 121.9 (Ar–C), 122.4 (Ar–C), 123.8 (Ar–C), 128.4 (Ar–C), 129.3 (Ar–C), 129.7 (Ar–C), 130.1 (Ar–C), 132.3 (Ar–C), 133.6 (Ar–C), 136.6 (Ar–C), 137.7 (Ar–C), 143.8 (Ar–C), 149.7 (Ar–C), 153.9 (N–CO). ESI-MS *m/z* of 437.90, 440.00 $[M+H]^+$ was obtained for a calculated mass of 438.05, 440.05.

7-Bromo-13-methyl-13*H*-indeno[2,1-*c*]tetrazolo[1,5-*a*]quinolin-13-yl acetate (12). Procedure C. The crude product was purified by column chromatography eluting with 5–10% ethyl acetate in hexane to get the desired product **12** (16%) as off-white solid; mp 266–268 °C. IR ν_{max} (KBr, cm^{-1}) 1740.94; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99 (s, 3 H, CH_3), 2.02 (s, 3 H, $COCH_3$), 7.46–7.62 (m, 2 H, Ar–H), 7.64 (d, J = 8.04 Hz, 1 H, H8), 8.01 (dd, J = 1.96, 8.88 Hz, 1 H, H7), 8.24 (d, J = 7.52 Hz, 1 H, Ar–H), 8.71 (d, J = 8.84 Hz, 1 H, Ar–H), 8.90 (d, J = 1.92 Hz, 1 H, H5). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 21.2 (CH_3), 24.6 ($COCH_3$), 83.3 (–O–C–CH_3), 119.4 (Ar–C), 122.1 (Ar–C), 122.4 (Ar–C), 123.8 (Ar–C), 128.4 (Ar–C), 129.5 (Ar–C), 129.8 (Ar–C), 130.1 (Ar–C), 131.3 (Ar–C), 133.8 (Ar–C), 136.7 (Ar–C), 137.9 (Ar–C), 143.6 (Ar–C), 148.8 (Ar–C), 169.1 (CO). ESI-MS *m/z* of 409.00, 411.10 $[M+H]^+$ was obtained for a calculated mass of 409.03, 411.02.

7-Bromo-13-methyl-13*H*-indeno[2,1-*c*]tetrazolo[1,5-*a*]quinolin-13-ylheptanoate (13). Procedure C. The crude product was purified by column chromatography eluting with 5–10% ethyl acetate in hexane to get the desired product **13** (19%) as off-white solid; mp 159–161 °C. IR$_{\nu max}$ (KBr, cm^{-1}) 1733.97; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.90 (t, J = 7.1 Hz, 3 H, CH_2CH_3),

1.18–1.35 (m, 6 H,–CH_2–(CH_2)$_3$$CH_3$), 1.49 (quint, J = 6.9 Hz, 2 H, CH_2– (CH_2)$_3$ CH_3), 2.04 (s, 3 H, CH_3), 2.39 (t, 2 H, J = 7.3 Hz, COCH_2), 7.69–7.76 (m, 2 H, Hb, Hc), 7.87 (m, 1 H, Hd), 8.38 (dd, J = 2, 9.1 Hz, 1 H, H7), 8.68 (d, J = 7.6 Hz, 1 H, Ha), 8.86 (d, J = 9.1 Hz, 1 H, H8), 9.18 (d, J = 2.0 Hz, 1H, H5). ^{13}C-NMR (125.8 MHz, DMSO-d_6): δ 13.9 ($CH_3$$CH_2$), 21.9 ($CH_3$$CH_2$), 24.3 (O–C–$CH_3$), 24.4 (–$CH_2$–), 27.9 (–$CH_2$–), 30.8 (–$CH_2$–), 33.7 (CO$CH_2$–), 82.9 (C–O), 119.6 (C8), 121.8 (Ar–C), 122.0 (Ar–C), 122.4 (Ar–C), 124.6 (Ar–C), 128.0 (C5), 129.7 (Cb), 129.73 (Ar–C), 129.8 (Cc), 131.0 (C3), 134.4 (C7), 136.3 (Ar–C), 137.6 (C4), 143.5 (C2), 148.4 (Ar–C), 171.2 (C═O). ESI-MS m/z of 478.70, 481.00 [M+H]$^+$ was obtained for a calculated mass of 479.10, 481.10.

2-Bromo-6-hydrazinyl-7*H*-indeno[2,1-*c*]quinolin-7-one (14). A mixture of 2-bromo-6-chloro-indeno[2,1-*c*]quinolin-7-one[14] (2.0 g, 5.8 mmol), hydrazine hydrate (1.45 g, 29.06 mmol) in ethanol (20 mL) was refluxed under nitrogen atmosphere for 24 h. The solvents were removed under reduced pressure; the red solid obtained was quenched in water (500 mL) and filtered. The solid was washed with water (3 × 200 mL) and dried under reduced pressure to obtain *2*-bromo-6-hydrazinyl-7*H*-indeno[2,1-*c*]quinolin-7-one **14** as a red solid. The red solid obtained was heated with conc. HCl at 60 °C for 24 h. The reaction mixture cooled, diluted with water and filtered to get the red solid as pure compound **14** (1.2 g, 73%). mp decomposes at 250 °C. IR$_{vmax}$ (KBr, cm^{-1}); 1702, 3273, 3314, ^{1}H NMR (400 MHz, DMSO-d_6): δ 4.19 (s, 2 H, D_2O exchangable), 7.43–7.8 (m, 1 H, Ar–H), 7.54–7.74 (m, 3 H, Ar–H and 1 H, D_2O exchangable), 7.92–7.96 (m, 1 H, Ar–H), 7.99 (d, J = 7.76 Hz, 1 H, Ar–H), 8.37 (s, 1 H, Ar–H). ESI-MS m/z of 339.80, 341.80 [M+H]$^+$ was obtained for a calculated mass of 340.00, 342.00.

7-Bromo-13*H*-indeno[2,1-*c*][1,2,4]triazolo[4,3-*a*]quinolin-13-one (15). A mixture of 2-bromo-6-hydrazinyl-7*H*-indeno[2,1-*c*]quinolin-7-one **14** (4.0 g, 11.79 mmol) in formic acid (50 mL) was refluxed under nitrogen atmosphere for 24 h. The reaction was quenched with aqueous sodium bicarbonate (500 mL) and filtered. The solid obtained was washed with water (3 × 200 mL) and dried under reduced pressure to obtain 7-bromo-13*H*-indeno[2,1-*c*][1,2,4]triazolo[4,3-*a*]quinolin-13-one **15** (2.3 g, 56%) as a brown solid. mp >300 °C. IR$_{vmax}$ (KBr, cm^{-1}) 1724.27; ^{1}H-NMR (600 MHz, DMSO-d_6): δ 7.64 (t, J = 7.2 Hz, 1 H, Hc), 7.77 (t, J = 7.6 Hz, 1 H, Hb), 7.78 (d, J = 7.6 Hz, 1 H, Hd), 8.31 (d, J = 9.1 Hz, 1 H, H7), 8.39 (d, J = 7.6 Hz, 1 H, Ha), 8.65 (d, J = 9.1 Hz, 1 H, H8), 8.84 (d, J = 1.2 Hz, 1 H, H5), 10.17 (s, 1 H, H9). ^{13}C-NMR (150.9 MHz, DMSO-d_6): δ 118.4 (C3), 120.3 (C8 & C6), 120.9 (Ar–C), 124.1 (Cd), 125.1 (Ca), 129.1 (C5), 131.1 (Cc), 132.4 (Ar–C), 132.5(Ar–C), 135.4 (Cb), 136.0 (C7), 137.1 (Ar–C), 140.8 (Ar–C), 142.5 (C2), 146.3 (C4), 189.8 (C═O). ESI-MS m/z of 349.90, 351.70 [M+H]$^+$ was obtained for a calculated mass of 349.99, 351.99.

7-Bromo-13-methyl-13*H*-indeno[2,1-*c*][1,2,4]triazolo[4,3-*a*]quinolin-13-ol (16). Procedure B. The crude product was purified by column chromatography eluting with 2–5% methanol and DCM to get the desired product **16** (19%) as a pale yellow solid; mp 262–263 °C. IR$_{vmax}$ (KBr, cm^{-1}) 3246.08; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90 (s, 3 H, CH_3), 5.85 (s, 1 H, D_2O exchangeable, CHO*H*), 7.49–7.57 (m, 2 H, Ar–H), 7.70–7.76 (m, 1 H, Ar–H), 8.09 (d, J = 8.88 Hz, 1 H, Ar–H), 8.33 (d, J = 7.2 Hz, 1 H, Ar–H), 8.59 (d, J = 8.8 Hz, 1 H, Ar–H), 8.84 (s, 1 H, Ar–H), 10.13 (s, 1 H, Ar–H). ^{13}C NMR (100.6 MHz, DMSO-d_6): δ 24.7 (CH_3), 78.4 (*C*–OH), 119.5 (Ar–C), 119.7 (Ar–C), 121.7 (Ar–C), 123.1 (Ar–C), 123.3 (Ar–C), 127.5 (Ar–C), 128.5 (Ar–C), 128.9 (Ar–C), 130.0 (Ar–C), 132.0 (Ar–C), 132.4 (Ar–C), 136.1 (Ar–C), 136.3 (Ar–C), 136.8 (Ar–C), 144.2 (Ar–C), 152.5 (Ar–C). ESI-MS m/z of 365.80, 367.80 [M+H]$^+$ was obtained for a calculated mass of 366.02, 368.02.

7-Bromo-3-methyl-13*H*-indeno[2,1-*c*][1,2,4]triazolo[4,3-*a*]quinolin-13-one (17). A mixture of compound **14** (2.0 g, 5.89 mmol) and acetic acid (15 ml) was refluxed at 135 °C for 20 h. The reaction mixture was cooled to room temperature and then poured on sodium bicarbonate solution. It was then extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and filtered, evaporated under reduced pressure to obtain a crude solid. The crude product was purified by column chromatography (silica 100–200 mesh) eluting with 1.5% methanol and DCM to give **17** (0.10 g, 5%) as red solid; mp >300 °C. IR$_{vmax}$ (KBr, cm^{-1}) 1717.29; ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.06 (s, 3 H, CH_3), 7.52 (t, J = 7.3 Hz, 1H, Hc), 7.64 (d, J = 7.3 Hz, 1 H, Hd), 7.65 (t, J = 7.6 Hz, 1 H, Hb), 8.08 (dd, J = 2.1, 9.1 Hz, 1 H, H7), 8.22 (d, J = 7.6 Hz, 1 H, Ha), 8.37 (d, J = 9.1 Hz, 1 H, H8), 8.68 (d, J = 2.1 Hz, 1 H, H5). ^{13}C NMR (125.8 MHz, DMSO-d_6): δ 15.3 (CH_3), 118.0 (C3), 119.2 (C6), 119.6 (C8), 121.3 (Ar–C), 123.6 (Cd), 124.4 (Ca), 128.4 (C5), 130.5 (Cc), 132.1 (Ar–C), 133.3 (Ar–C), 134.8 (Cb), 134.9 (C7), 140.1 (Ar–C), 143.5 (C2), 145.0 (C4), 146.6 (Ar–C), 189.1 (C═O). ESI-MS m/z of 364.00, 365.90 [M+H]$^+$ was obtained for a calculated mass of 364.00, 366.00.

7-Bromo-3-propyl-13*H*-indeno[2,1-*c*][1,2,4]triazolo[4,3-*a*]quinolin-13-one (18). A mixture of compound **14** (0.3 g, 0.88 mmol) and butyric acid (10 ml) was refluxed at 140 °C for 20 h. The reaction mixture was cooled and then poured on sodium bicarbonate solution. It was then extracted with DCM. The organic layer was dried over anhydrous sodium sulfate and filtered, evaporated under reduced pressure to obtain a crude solid. The crude product was purified by column chromatography (silica 230–400 mesh) eluting with 5% methanol and DCM to give compound **18** (0.1 g; 29%) as brown solid; mp 225–226 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.16 (t, J = 7.4 Hz, 3 H, CH_3), 1.99–2.15 (m, 2 H, CH_2CH$_3$), 3.43 (t, J = 7.56 Hz, 2 H, –CCH_2), 7.47 (t, J = 7.48 Hz, 1 H, Ar–H), 7.61 (t, J = 7.6 Hz, 1 H, Ar–H), 7.80 (d, J = 7.2 Hz, 1 H, Ar–H), 7.94–7.98 (m, 2 H, Ar–H), 8.15 (d, J = 9.12 Hz, 1 H, Ar–H), 8.71 (d, J = 2.12 Hz, 1 H, Ar–H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 13.9 ($CH_3$$CH_2$), 20.1 ($CH_3$$CH_2$), 31.3 ($CH_3CH_2CH_2$), 118.6 (Ar–C), 119.2 (Ar–C), 119.9 (Ar–C), 122.4 (Ar–C), 123.4 (Ar–C), 124.8 (Ar–C), 129.5 (Ar–C), 130.7 (Ar–C), 133.0 (Ar–C), 133.5 (Ar–C), 134.3 (Ar–C), 134.7 (Ar–C), 140.8 (Ar–C), 144.5 (Ar–C), 145.1 (Ar–C), 149.9 (Ar–C), 189.3 (C═O). ESI-MS m/z of 392.00, 394.00 [M+H]$^+$ was obtained for a calculated mass of 392.03, 394.03.

7-Bromo-3-butyl-13*H*-indeno[2,1-*c*][1,2,4]triazolo[4,3-*a*]quinolin-13-one (19). A mixture of compound **14** (0.2 g, 0.58 mmol) and pentanoic acid (8 ml) was refluxed at 140 °C for 20 h. Reaction mixture was cooled and then poured on sodium bicarbonate solution. It was then extracted with DCM, the organic layer was dried over anhydrous sodium sulfate and filtered, evaporated under reduced pressure to obtain a crude solid. Crude product

was purified by column chromatography (silica 230–400 mesh) eluting with 5% methanol and DCM to give **19** (0.13 g; 54%) as brown solid; mp 281–282 °C. IR$_{vmax}$ (KBr, cm^{-1}) 1719.31; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.02 (t, J = 7.4 Hz, 3 H, CH_3), 1.54–1.65 (m, 2 H, CH_2CH$_3$), 1.94–2.20 (m, 2 H, CH_2CH$_2$CH$_3$), 3.45 (t, J = 9.52 Hz, 2 H, –CCH_2CH$_2$), 7.43–7.50 (m, 1 H, Ar–H), 7.60 (t, J = 8.28 Hz, 1 H, Ar–H), 7.80 (d, J = 8.32 Hz, 1 H, Ar–H), 7.93–7.99 (m, 2 H, Ar–H), 8.15 (d, J = 8.32 Hz, 1 H, Ar–H), 8.71 (d, J = 1.8 Hz, 1 H, Ar–H). ^{13}C NMR (100.6 MHz, $CDCl_3$ + DMSO-d_6): δ 13.8 (*C*H$_3$CH$_2$), 22.4 (CH$_3$*C*H$_2$), 28.6 (CH$_3$CH$_2$*C*H$_2$CH$_2$), 29.0 (CH$_3$CH$_2$CH$_2$*C*H$_2$), 118.6 (Ar–C), 119.0 (Ar–C), 119.9 (Ar–C), 122.3 (Ar–C), 123.4 (Ar–C), 124.7 (Ar–C), 129.4 (Ar–C), 130.7 (Ar–C), 132.9 (Ar–C), 133.4 (Ar–C), 134.3 (Ar–C), 134.7 (Ar–C), 140.7 (Ar–C), 144.4 (Ar–C), 145.1 (Ar–C), 150.1 (Ar–C), 189.2 (C═O). ESI-MS m/z of 405.80, 407.90 [M+H]$^+$ was obtained for a calculated mass of 406.05, 408.05.

7-Bromo-3-pentyl-13*H*-indeno[2,1-*c*][1,2,4]triazolo[4,3-*a*]quinolin-13-one (20). A mixture of compound **14** (1.5 g, 5.89 mmol) and hexanoic acid (15 ml) was refluxed at 135 °C for 20 h. The reaction mixture was cooled and then poured on sodium bicarbonate solution. It was then extracted with DCM, the organic layer was dried over anhydrous sodium sulfate and filtered, evaporated under reduced pressure to obtain a crude solid. The crude product was purified by column chromatography (silica 230–400 mesh) eluting with 5% methanol and DCM to give **20** (0.10 g, 4%) as red solid; mp 272–273 °C. IR$_{vmax}$ (KBr, cm^{-1}) 1720.31; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.93 (t, J = 7.28 Hz, 3 H, CH_3), 1.37–1.44 (m, 2 H, CH$_2$*C*H$_2$CH$_3$), 1.48–1.55 (m, 2 H, CH_2CH$_2$CH$_3$), 1.97–2.03 (m, 2 H, –CCH$_2$CH_2) 3.40 (m, 2 H, –CCH_2CH$_2$), 7.48 (t, J = 7.32 Hz, 1 H, Ar–H), 7.60 (t, J = 7.56 Hz, 1 H, Ar–H), 7.80 (d, J = 7.12 Hz, 1 H, Ar–H), 7.93–7.99 (m, 2 H, Ar–H), 8.14 (d, J = 9.16 Hz, 1 H, Ar–H), 8.70 (d, J = 2.0 Hz, 1 H, Ar–H). ^{13}C NMR (100.6 MHz, CF_3COOD): δ 14.4 (CH$_2$*C*H$_3$), 24.0 (CH$_2$*C*H$_2$CH$_3$), 27.4 (CH$_2$*C*H$_2$CH$_2$CH$_2$CH$_3$), 31.4 (CH$_2$*C*H$_2$CH$_2$CH$_3$), 33.0 (*C*H$_2$CH$_2$CH$_2$CH$_2$CH$_3$), 115.0 (Ar–C), 122.1 (Ar–C), 124.7 (Ar–C), 126.9 (Ar–C), 128.7 (Ar–C), 128.9 (Ar–C), 134.4 (Ar–C), 134.9 (Ar–C), 135.2 (Ar–C), 136.3 (Ar–C), 139.0 (Ar–C), 141.6 (Ar–C), 142.2 (Ar–C), 154.2 (Ar–C), 158.5 (Ar–C), 192.8 (C═O). ESI-MS m/z of 420.00, 422.20 [M+H]$^+$ was obtained for a calculated mass of 420.07, 422.06.

7-Bromo-3-hexyl-13*H*-indeno[2,1-*c*][1,2,4]triazolo[4,3-*a*]quinolin-13-one (21). A mixture of compound **14** (2.0 g, 5.89 mmol) and heptanoic acid (15 ml) was refluxed at 135 °C for 20 h. The reaction mixture was cooled and then poured on sodium bicarbonate solution. It was then extracted with DCM, the organic layer was dried over anhydrous sodium sulfate and filtered, evaporated under reduced pressure to obtain a crude solid. The crude product was purified by column chromatography (silica 230–400 mesh) eluting with 5% methanol and DCM to give **21** (0.3 g, 12%) as brown solid; mp 279–280 °C. IR$_{vmax}$ (KBr, cm^{-1}) 1720.12; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.90 (t, J = 6.88 Hz, 3 H, CH_3), 1.1.34–1.37 (m, 4 H, *C*H$_2$*C*H$_2$CH$_3$), 1.50–1.54 (m, 2 H, CH_2CH$_2$CH$_2$CH$_3$), 1.95–2.02 (m, 2 H, –CCH$_2$CH_2) 3.45 (t, J = 9.52 Hz, 2 H, –CCH_2CH$_2$), 7.43–7.50 (m, 1 H, Ar–H), 7.61 (t, J = 8.44 Hz, 1 H, Ar–H), 7.81 (d, J = 7.0 Hz, 1 H, Ar–H), 7.95–7.99 (m, 2 H, Ar–H), 8.16 (d, J = 8.76 Hz, 1 H, Ar–H), 8.72 (d, J = 2.12 Hz, 1 H, Ar–H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 14.0 (–CH$_2$*C*H$_3$), 22.5 (–CH$_2$–), 26.4 (–CH$_2$–), 29.0 (–CH$_2$–), 29.37 (–CH$_2$–), 31.4 (–CH$_2$–), 118.6 (Ar–C), 118.7 (Ar–C), 119.8 (Ar–C), 121.9 (Ar–C), 123.2 (Ar–C), 124.4 (Ar–C), 129.0 (Ar–C), 130.6 (Ar–C), 132.6 (Ar–C), 133.1 (Ar–C), 134.2 (Ar–C), 134.7 (Ar–C), 140.4 (Ar–C), 144.0 (Ar–C), 144.6 (Ar–C), 150.0 (Ar–C), 188.8 (*C*═O). ESI-MS m/z of 433.50, 435.70 [M+H]$^+$ was obtained for a calculated mass of 434.08, 436.08.

7-Bromo-3-phenyl-13*H*-indeno[2,1-*c*][1,2,4]triazolo[4,3-*a*]quinolin-13-one (22). A mixture of compound **14** (1.0 g, 2.94 mmol) and benzoyl chloride (15 ml) was refluxed at 140 °C for 24 h. Reaction mixture was cooled and then poured on sodium bicarbonate solution. It was then extracted with DCM, the organic layer was dried over anhydrous sodium sulfate and filtered, evaporated under reduced pressure to obtain an oily residue, which upon trituration with n-hexane gave a solid. The solid was filtered, washed with n-hexane to give **22** (0.7 g; 56%) as red solid; mp >300 °C. IR$_{vmax}$ (KBr, cm^{-1}) 1716.45; ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.47 (d, J = 9.08 Hz, 1 H), 7.58 (t, J = 7.36 Hz, 1 H, Ar–H), 7.64–7.76 (m, 6 H, Ar–H), 7.84 (d, J = 7.72, 1 H, Ar–H), 7.91 (d, J = 9.04 Hz, 1 H, Ar–H), 8.35 (d, J = 7.52 Hz, 1 H, Ar–H), 8.78 (s, 1 H, Ar–H). ^{13}C NMR (100.6 MHz, CF_3COOD): δ 114.6 (Ar–C), 122.1 (Ar–C), 124.6 (Ar–C), 125.3 (Ar–C), 127.0 (Ar–C), 128.6 (Ar–C), 128.8 (Ar–C), 130.2 (Ar–C), 131.6 (Ar–C), 132.2 (Ar–C), 133.0 (Ar–C), 134.7 (Ar–C), 134.8 (Ar–C), 135.7 (Ar–C), 136.2 (Ar–C), 138.9 (Ar–C), 140.9 (Ar–C), 141.6 (Ar–C), 142.0 (Ar–C), 151.8 (Ar–C), 158.8 (Ar–C), 192.5 (C═O). ESI-MS m/z of 426.00, 428.00 [M+H]$^+$ was obtained for a calculated mass of 426.02, 428.02.

7-Bromo-3-mercapto-13*H*-indeno[2,1-*c*][1,2,4]triazolo[4,3-*a*]-quinolin-13-one (23). To a solution of compound **14** (0.3 g, 0.884 mmol) in pyridine (6 ml) was added carbon disulfide (0.8 ml) and heated to 40 °C for 1 h. It was then refluxed at 115 °C for 20 h. The reaction mixture was cooled and poured in water, solid separated was filtered and washed with water. This crude product was dried under reduced pressure and purified by column chromatography (silica gel 100–200 mesh, gradual elution with 1–3% of methanol, DCM mixture) to get the corresponding compound **23** (40.0 mg; 12%) as dark violet solid; mp >300 °C. IR$_{vmax}$ (KBr, cm^{-1}) 1715.55; ^{1}H-NMR (500 MHz, DMSO-d_6): δ 7.67 (t, J = 7.5 Hz, 1 H, Hc), 7.78 (d, J = 6.6, 1 H, Hd), 7.80 (t, J = 7.6 Hz, 1 H, Hb), 8.23 (d, J = 9.1 Hz, 1 H, H7), 8.39 (d, J = 7.6 Hz, 1 H, Ha), 8.76 (s, 1 H, H5), 10.98 (d, J = 9.1 Hz, 1 H, H8), 14.93 (s, 1H, SH). ^{13}C-NMR (125.8 MHz, DMSO-d_6): δ 117.8 (C3), 118.6 (C8), 119.9 (C6), 122.0 (Ar–C), 123.9 (Cd), 124.9 (Ca), 128.3 (C5), 131.2 (Cc), 132.1 (Ar–C), 134.4 (C7), 135.1 (Cb), 135.9 (Ar–C), 139.8 (Ar–C), 140.8 (C2), 148.4 (C4), 161.9 (C-SH), 188.6 (C═O). ESI-MS m/z of 381.70, 383.80 [M+H]$^+$ was obtained for a calculated mass of 381.96, 383.96.

2-Bromo-6-(2-hydroxyethylamino)-7*H*-indeno[2,1-*c*]quinolin-7-one (24). A mixture of 2-bromo-6-chloro-indeno[2,1-*c*]quinolin-7-one **6**[14] (1.0 g, 2.90 mmol) and 2-aminoethanol (4.2 mL, 69.7 mmol) in ethanol (40 mL) was refluxed for 24 h. The reaction was quenched with water. The red solid obtained was filtered. The solid was washed with water (2 × 100 mL), and further purified by giving methanol and ethyl acetate washings, dried under reduced pressure to obtain 2-bromo-6-(2-hydroxyethylamino)-7*H*-indeno[2,1-*c*]quinolin-7-one **24** (0.850 g, 79%) as a red solid. mp 226–228 °C. IR ν_{max} (KBr, cm^{-1}) 3362.16, 1697.53; ^{1}H NMR

(400 MHz, $CDCl_3$): δ 3.75–3.84 (m, 2 H, –NHCH_2), 3.86–3.94 (m, 2 H, CH_2OH), 5.29 (s, 1 H, D_2O exchangeable, NH or OH) 7.35–7.42 (m, 1 H, D_2O exchangeable, NH or OH), 7.45 (dd, J = 7.36, 7.20 Hz, 1 H, Ar–H), 7.53 (d, J = 9.04 Hz, 1 H, Ar–H), 7.56–7.63 (m, 1 H, Ar–H), 7.65–7.73 (m, 2 H, Ar–H), 7.97 (d, J = 7.48 Hz, 1 H, Ar–H), 8.32 (d, J = 2.08 Hz, 1 H, Ar–H).^{13}C NMR (100.6 MHz, DMSO-d_6): δ 41.9 (NCH_2), 59.0 (OCH_2), 110.9 (Ar–C), 115.3 (Ar–C), 118.2 (Ar–C), 119.1 (Ar–C), 131.1 (Ar–C), 132.3 (Ar–C), 139.8 (Ar–C), 151.2 (Ar–C), 151.4 (Ar–C), 152.6 (Ar–C), 192.5 (C═O). ESI-MS m/z of 369.00, 370.80 $[M+H]^+$ was obtained for a calculated mass of 369.02, 371.02.

7-Bromo-2*H*-imidazo[1,2-*a*]indeno[2,1-*c*]quinolin-13(3H)-one (25). 2-Bromo-6-(2-hydroxyethylamino)-7*H*-indeno[2,1-*c*] quinolin-7-one **24** (4.0 g, 10.83 mmol) in phosphorusoxychloride (50 mL) was refluxed for 7 h. The reaction was quenched with ice, the reaction mixture was neutralized with 10% NaOH solution, extracted with dichloromethane (500 mL) and washed with water (2 × 200 mL) and brine (100 mL). The organic extract was dried over anhydrous sodium sulfate, the solvents were evaporated under reduced pressure to obtain blue solid. The solid was further purified by giving ethyl acetate and hexane washings, dried under reduced pressure to obtain 7-bromo-2*H*-imidazo[1,2-*a*]indeno[2,1-*c*]quinolin-13(3*H*)-one **25** (3.1 g, 82%) as a blue solid. mp 276–279 °C. IR ν_{max} (KBr, cm^{-1}) 1716.68; ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.92 (t, J = 10.2 Hz, 2 H, CH_2–N), 4.25 (t, J = 10.2 Hz, 2 H, CH_2–N═), 6.68 (d, J = 9.1 Hz, 1 H, H8), 7.48 (t, J = 7.6 Hz, 1 H, Hc), 7.58–7.56 (m, 2 H, H7&Hb), 7.73 (d, J = 7.2 Hz, 1 H, Hd), 7.89 (d, J = 7.6 Hz, 1 H, Ha), 8.17 (d, J = 1.9 Hz, 1 H, H5).^{13}C NMR (150.9 MHz, $CDCl_3$): δ 45.7 (–CH_2–), 54.3 (–CH_2–), 112.8 (C6), 114.7 (C8), 118.4 (Ar–C), 118.8 (C3), 123.7 (Ca), 123.9 (Cd), 128.9 (C5), 131.1 (Cc), 133.2 (Ar–C), 133.6 (Ar–C), 136.5 (Ar–C), 139.9 (Ar–C), 141.3 (Ar–C), 150.4 (C2), 154.3 (C4), 190.2 (C═O). ESI-MS m/z of 350.80, 352.90 $[M+H]^+$ was obtained for a calculated mass of 351.01, 353.01.

7-Bromo-13-methyl-3,13-dihydro-2*H*-imidazo[1,2-*a*]indeno[2,1-*c*]quinolin-13-ol (26). Procedure B. The crude product was purified by column chromatography eluting with 5–10% methanol and DCM to get desired product **26** (35%) as green solid; mp 146–148 °C. IR ν_{max} (KBr, cm^{-1}) 3438.40; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.8 (s, 3 H, CH_3), 3.47 (s, 1 H, D_2O exchangeable, CHO*H*), 3.86–4.16 (m, 4 H, CH_2CH_2), 6.66 (d, J = 8.68 Hz, 1 H, Ar–H), 7.42–7.49 (m, 3 H, Ar–H), 7.65–7.67 (m, 1 H, Ar–H), 7.97–7.99 (m, 1 H, Ar–H), 8.24 (d, J = 2.04 Hz, 1 H, Ar–H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 24.5 (CH_3), 45.7 (N$CH_2$$CH_2$), 53.3 ($NCH_2CH_2$═N), 79.2 (C–OH), 112.4 (Ar–C), 113.7 (Ar–C), 119.8 (Ar–C), 123.1 (Ar–C), 127.4 (Ar–C), 128.6 (Ar–C), 128.8 (Ar–C), 132.6 (Ar–C), 136.0 (Ar–C), 136.7 (Ar–C), 138.5 (Ar–C), 139.4 (Ar–C), 151.7 (Ar–C), 153.0 (Ar–C). ESI-MS m/z of 366.90, 368.90 $[M+H]^+$ was obtained for a calculated mass of 367.04, 369.04.

7-Bromo-13-methyl-3,13-dihydro-2*H*-imidazo[1,2-*a*]indeno[2,1-*c*]quinolin-13-yl dimethylcarbamate (27). Procedure A. The crude product was purified by washing with n-hexane to get the desired product **27** (46%) as green solid; mp 179–181 °C. IR ν_{max} (KBr, cm^{-1}) 1630.99, 1706.17; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.82 (s, 3 H, CH_3), 2.70 (s, 3 H, NCH_3), 2.94 (s, 3 H, NCH_3), 3.92–398 (m, 2 H, ═NCH_2), 4.15–4.21 (m, 2 H, –NCH_2), 6.66 (d, J = 8.72 Hz, 1 H, Ar–H) 7.38–7.49 (m, 4 H, Ar-H),, 8.04 (d, J = 7.6 Hz, 1 H, Ar–H), 8.28 (d, J = 2.04 Hz, 1 H, Ar–H). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 23.3 (CH_3), 36.2 (NCH_3), 36.5 (NCH_3), 45.7 (CH_2), 53.8 (CH_2), 83.6 (CH_3–*C*–O), 112.0 (Ar–C), 113.6 (Ar–C), 120.0 (Ar–C), 121.6 (Ar–C), 123.4 (Ar–C), 127.5 (Ar–C), 128.6 (Ar–C), 128.7 (Ar–C), 132.4 (Ar–C), 134.5 (Ar–C), 137.2 (Ar–C), 138.9 (Ar–C), 139.7 (Ar–C), 149.8 (Ar–C), 152.1 (Ar–C), 154.3 (Ar–C). ESI-MS m/z of 438.00, 440.00 $[M+H]^+$ was obtained for a calculated mass of 438.08, 440.07.

7-Bromo-2*H*-imidazo[1,2-*a*]indeno[2,1-*c*]quinolin-13(3*H*)-one oxime (28). To a cooled (0 °C) suspension of the compound **26** (1.0 g, 2.85 mmol) in ethanol (30 ml), hydroxylamine hydrochloride (0.59 g, 8.54 mmol) and sodium hydroxide (0.45 g, 11.39 mmol) in water (10 ml) was added. The reaction mixture was stirred for 15 min, and further refluxed for 20 h. The reaction mixture was cooled to room temperature and poured into water. The precipitate obtained was filtered, washed with water, ethyl acetate and hexane, and dried under reduced pressure to obtain the oxime **28** (63%) as red solid; mp 273–275 °C. IR ν_{max} (KBr, cm^{-1}) 1621.97, 3421.82; ^{1}H NMR (400 MHz, CF_3COOD): δ 4.32 (t, J = 10.08 Hz, 2 H, –NCH_2), 4.77 (t, J = 10.0 Hz, 2 H, ═NCH_2), 7.37 (d, J = 9.08 Hz, 1 H, Ar–H), 7.59–7.60 (m, 2 H, Ar–H), 7.94 (d, J = 8.68 Hz, 1 H, Ar–H), 8.14–8.20 (m, 1 H, Ar–H), 8.41 (d, J = 3.08, 1 H, Ar–H), 8.67 (s, 1 H, Ar–H). ^{13}C NMR (100.6 MHz, CF_3COOD): δ 43.3 (–NCH_2), 47.0 (═NCH_2), 116.7 (Ar–C), 119.9 (Ar–C), 124.5 (Ar–C), 128.8 (Ar–C), 128.9 (Ar–C), 129.5 (Ar–C), 131.6 (Ar–C), 132.6 (Ar–C), 134.6 (Ar–C), 135.7 (Ar–C), 136.9 (Ar–C), 149.3 (Ar–C), 149.9 (C═N–OH). ESI-MS m/z of 365.80, 367.90 $[M+H]^+$ was obtained for a calculated mass of 366.02, 368.02

7-Bromo-2*H*-imidazo[1,2-*a*]indeno[2,1-*c*]quinolin-13(3*H*)-one O-dimethylcarbamoyl oxime (29). Procedure A. The crude product was purified by washing with n-hexane to get desired product **29** (69%) as violet solid; mp 160–162 °C. IR ν_{max} (KBr, cm^{-1}) 1640.53, 1735.80; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.10 (s, 3 H, NCH_3), 3.18 (s, 3 H, NCH_3), 3.99 (t, J = 10 Hz, 2 H, ═NCH_2), 4.25 (t, J = 10 Hz, 2 H, –NCH_2), 6.72 (d, J = 8.76 Hz, 1 H, Ar–H), 7.42–7.58 (m, 3 H, Ar–H), 7.99 (d, J = 7.68 Hz, 1 H, Ar–H), 8.18 (d, J = 2.04 Hz, 1 H, Ar–H), 8.26 (d, J = 7.48 Hz, 1 H, Ar–H). ^{13}C NMR (100.6 MHz, $CDCl_3$ + DMSO-d_6): δ 36.7 (CONCH_3), 37.5 (CONCH_3), 46.0 (CH_2CH_2═N), 53.3 (CH_2CH_2═N), 112.5 (Ar–C), 114.4 (Ar–C), 118.4 (Ar–C), 123.6 (Ar–C), 127.5 (Ar–C), 128.6 (Ar–C), 129.6 (Ar–C), 129.8 (Ar–C), 131.3 (Ar–C), 131.6 (Ar–C), 134.4 (Ar–C), 138.6 (Ar–C), 139.3 (Ar–C), 145.3 (Ar–C), 150.3 (Ar–C), 154.5 (Ar–C), 155.7 (O*CO*N$(CH_3)_2$). ESI-MS m/z of 437.00, 439.20 $[M+H]^+$ was obtained for a calculated mass of 437.06, 439.05.

Biological Activity – Methods

Anti-mycobacterial activity. Compounds **7–13**, **15–29** and the first front-line drug isoniazid[28] (employed 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[31–33] for the most active compounds (**9**, **15**, **17**, **25**, **27**, **28**, and **29**) 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 (5% CO_2 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 2). After completion of the experiment protocol 10 µL of MTT solution (5 mg mL^{-1} solution in Phosphate Buffer Saline) was added to each well. Plates were incubated for three hours in a 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 2).

Abbreviations

DCM	dichloromethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
GI	growth index
MDR	multi-drug resistance
MIC	minimum inhibitory concentration
mp	melting point
MeOH	methanol
NMR	nuclear magnetic resonance
SAR	structure–activity relationship
NaH	sodium hydride
TB	tuberculosis
TLC	thin layer chromatography
THF	tetrahydrofuran

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