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ORIGINAL PAPER

New class of antitubercular compounds: synthesis and anti-tubercular activity of 4-substituted pyrrolo[2,3-*c*]quinolines

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Abstract Modified synthesis and antitubercular activity of 4-substituted pyrrolo[2,3-*c*]quinolines are reported. Some of the compounds showed significant antitubercular activity, when compared to some of the existing antitubercular drugs. A compound with an imidazole moiety at position 4 shows the highest activity and least toxicity.

Keywords Heterocycles · Strained molecules · Aldehydes · Mannich reaction · Antitubercular

Introduction

Increasing drug resistance along with emergence of multidrug-resistant tuberculosis (MDR-TB) has made TB a global epidemic with 8.5 million new cases in 2011 [1]. Newer chemical entities are thus required to solve this problem. Although new chemical entities far removed structurally from the existing drugs might provide an answer to this problem, the inherent structural difference means that the systematic study of a drug candidate's efficacy or mode of action is much more difficult. Thus molecules bearing some resemblance to the existing drugs are a reasonable starting point for the rational development of newer entities to combat tuberculosis.

Isoniazid, the most well-known antitubercular drug, and ethionamide, a drug used for treatment of MDR-TB, were the starting points for our exploration in this area. Attempts in our lab to synthesize 4-substituted pyrrolo[2,3-*c*]quinolines has been going on for some time. These molecules have similar structures to isoniazid and ethionamide (Fig. 1). The presence of a quinoline system is also an important feature of 4-substituted pyrrolo[2,3-*c*]quinolines because many antitubercular compounds possess this skeleton [2–5]. Structural correlation also led us to another interesting observation: pyrrolnitrin, a natural product isolated form *Pseudomonas* species, shows moderate antitubercular activity [6]. After comparing 4-substituted pyrrolo[2,3-*c*]quinolines with respect to the pyrrolnitrin skeleton, one can clearly see that pyrrolo[2,3-*c*]quinolines can be treated as a modified pyrrolnitrin system having substantial structural rigidity (Fig. 1).

Results and discussion

Fused pyrroloquinolines exhibit numerous biological activities [7–16]. Synthetic methods for these molecules generally preclude any universal strategy, as pyrrole can be linked to either the benzene or pyridine half of the quinoline skeleton [17–25]. Only few reports pertaining to the synthesis of 4-substituted pyrrolo[2,3-*c*]quinolines are known in the literature [26–30]. These methods, though successful in the synthesis of the desired molecules, are not truly robust in allowing diverse substitutions at position 4 of pyrrolo[2,3-*c*]quinoline. There was therefore the need

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for an improvised strategy to overcome the aforementioned shortcoming.

In our attempt to devise a general method for the synthesis of 4-substituted pyrrolo[2,3-*c*]quinolines, we decided to use the synthesis of aplidiopsamine A (9-[(3*H*-pyrrolo[2,3-*c*]quinolin-4-yl)methyl]-9*H*-purin-6-amine, **1a**) as a model reaction owing to its relative structural complexity; it was felt that any method that can successfully synthesize aplidiopsamine A can be used as a general method for the synthesis of other 4-substituted pyrrolo[2,3-*c*]quinolines. The synthetic route devised was partially based on the most probable biochemical route for aplidiopsamine A, as suggested by Carroll et al. [12]. It was planned in two parts, first involving the synthesis of *o*-nitrophenylpyrrole and 2-(6-amino-9*H*-purine-9-yl)acetaldehyde and then coupling the two units, first by reduction of *o*-nitrophenylpyrrole to *o*-aminophenylpyrrole followed by a Mannich-type reaction [31, 32] between *o*-aminophenylpyrrole and 2-(6-amino-9*H*-purine-9-yl)acetaldehyde to generate the target molecule. The source of *o*-nitrophenylpyrrole was envisioned to be the reaction between *o*-nitrostyrene and TosMIC [33–37]. 2-(6-Amino-9*H*-purine-9-yl)acetaldehyde was to be obtained from the reaction between adenine and commercially available 2-bromo-1,1-diethoxyethane, followed by acetal deprotection [38]. It is important to note here that using other aliphatic or aromatic aldehydes in place of 2-(6-amino-9*H*-purine-9-yl)acetaldehyde will give different 4-substituted[2,3-*c*]quinolines.

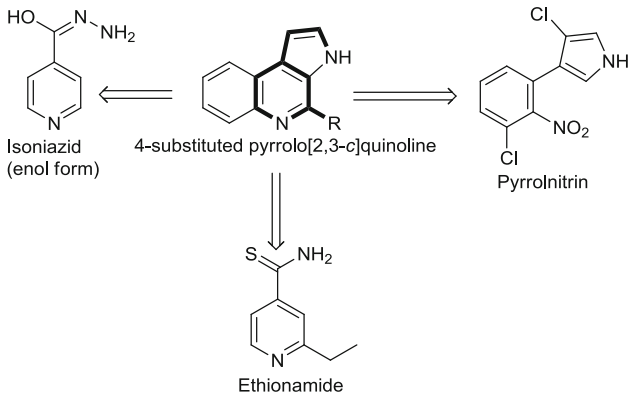


Fig. 1 Structural similarities between isoniazid, 4-substituted pyrrolo[2,3-*c*]quinoline, pyrrolnitrin, and ethionamide

Synthesis of aplidiopsamine A started with the reaction between TosMIC and *o*-nitrostyrene [39] in the presence of potassium *tert*-butoxide to generate *o*-nitrophenylpyrrole (**2**), followed by reduction in the presence of iron and hydrochloric acid to *o*-aminophenylpyrrole **3** (Scheme 1).

2-(6-Amino-9*H*-purine-9-yl)acetaldehyde (**4a**) was obtained in acetal protected form by reaction of adenine with 2-bromo-1,1-diethoxyethane, followed by deprotection. After required amine **3** and aldehyde **4a** were prepared, reactions were carried out in DMF using various acids in order to optimize the reaction conditions. Formation of 4-methyl-3*H*-pyrrolo[2,3-*c*]quinoline as a by-product along with the desired compound was observed when HCl, $ZnCl_2$, and *p*-toluenesulfonic acid (PTSA) were used as catalyst. No by-product formation happened while using acetic acid and under neat reaction conditions. The better yield (62 %) obtained while using acetic acid compared to neat reaction (32 %) prompted us to use acetic acid in DMF to carry out the final step for the synthesis of aplidiopsamine A. Thus the successful synthesis of aplidiopsamine A was accomplished (Scheme 1) in 22.8 % overall yield.

In order to establish the generality of the developed procedure, reactions were carried out with aldehydes containing natural bases like uracil, thymine, and cytosine, as well as several aromatic and aliphatic aldehydes (Table 1).

Scheme 1

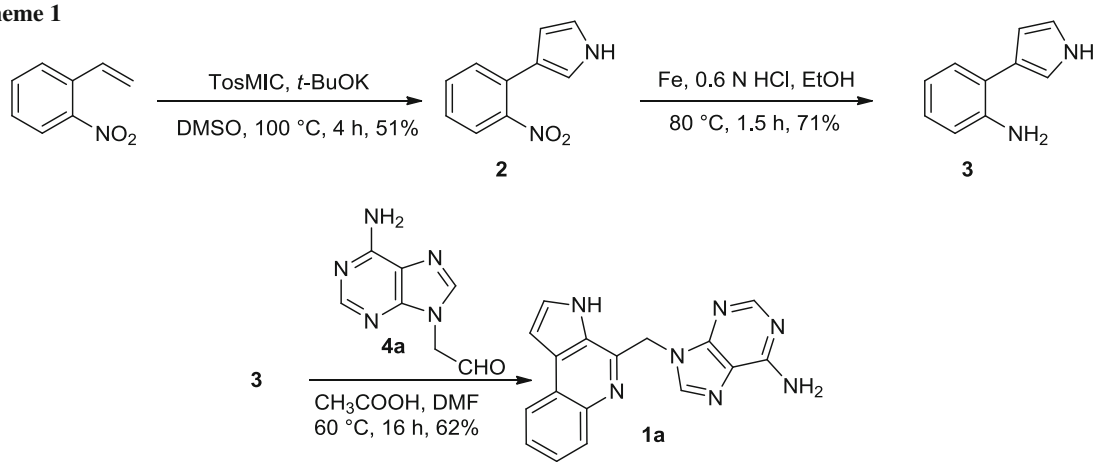
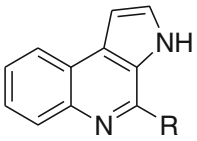


Table 1 Yield, antitubercular activity, and cytotoxicity of 4-substituted pyrrolo[2,3-*c*]quinolines



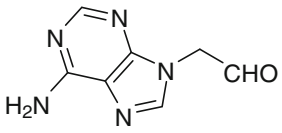
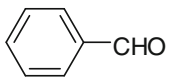
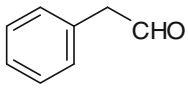
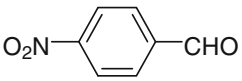
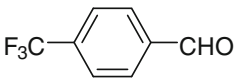
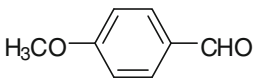
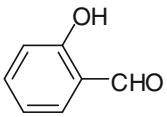
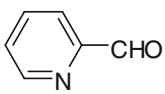
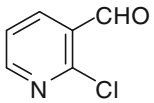
Compound	RCHO **4a-u**	Yield/%	Antitubercular activity: MIC/μM	Cytotoxicity: % inhibition[a]
1a		62	158.7	n.d.
1b		82	12.9	22.1
1c		63	12.2	22.6
1d		68	6.0	16.4
1e		79	5.6	18
1f		67	45.6	12.6
1g		53	48.0	n.d.
1h		85	>160	n.d.
1i		72	5.5	15.6

Table 1 continued

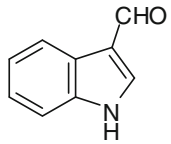
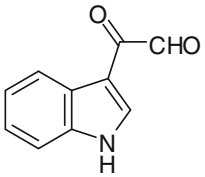
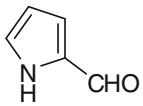
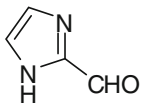
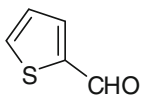
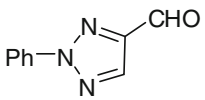
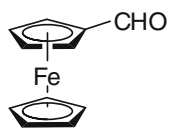
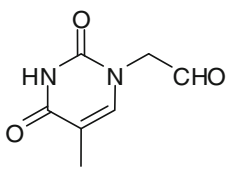
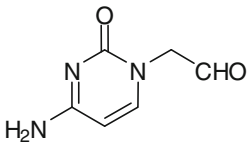
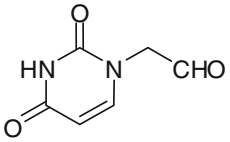
Compound	RCHO **4a-u**	Yield/%	Antitubercular activity: MIC/μM	Cytotoxicity: % inhibition[a]
1j		78	176	n.d.
1k		61[b]	80.2	n.d.
1l		65	3.3	24.6
1m		86	3.3	8.6
1n		72	44	18.4
1o		74	>160	n.d.
1p		69	32.8	30.4
1q		52	81.6	n.d.

Table 1 continued

Compound	RCHO **4a-u**	Yield/%	Antitubercular activity: MIC/μM	Cytotoxicity: % inhibition[a]
1r		32	85.9	n.d.
1s		49	21.4	21.2
1t	$(CH_3)_2CHCH_2CHO$	57	6.9	17.6
1u	CH_3CHO	48	137	n.d.
	Isoniazid	–	0.7	–
	Ciprofloxacin	–	4.7	–
	Ethambutol	–	7.6	–

n.d. not determined

[a] Cytotoxicity at 50 μM; only for compounds with MIC values <48 μM

[b] Solvent used for this reaction was ethanol instead of DMF

While choosing the aldehydes **4b–4u** we have ensured that some of the examples contain either a free amino group (modified cytosine aldehyde) or nitrogen with a relatively free lone pair of electrons (pyridine-2-carbaldehyde, imidazole-2-carbaldehyde, and 2-phenyl-1,2,3-triazole-4-carbaldehyde). The main motivation was to demonstrate the advantage of aldehydes over acid chlorides in such substrates with reactive nitrogen, which we suggest is a major disadvantage in the existing methodology by Ni et al. [26]. The yields obtained for the final step leading to formation of various 4-substituted pyrrolo[2,3-*c*]quinolines were between 32 and 86 % (Table 1).

The products were characterized by ^{1}H and ^{13}C NMR and mass spectrometry and were assayed for antitubercular activity [40]. The best results were obtained when the substituents at position 4 of pyrrolo[2,3-*c*]quinoline skeleton were pyrrol-2-yl (**1l**), imidazol-2-yl (**1m**), 2-chloropyridin-3-yl (**1i**), isobutyl (**1t**), *p*-nitrophenyl (**1d**), and *p*-(trifluoromethyl)phenyl (**1e**). The compounds exhibited better minimum inhibitory concentration (MIC) values than ethambutol and similar values to ciprofloxacin. Comparison of the activity shown by compound **1b** with that of compounds **1d**, **1e**, **1f**, and **1g** clearly indicates that the presence of an electron-withdrawing group increases the antitubercular activity of pyrrolo[2,3-*c*]quinolines. Introduction of an extra methylene group in compound **1c** with respect to that of compound **1b** has no impact on the activity of the molecule as the MIC values are comparable. However with aliphatic substituents at position 4, increase in the chain length in **1t** compared to **1u** does increase the activity of the molecule as clearly indicated by the MIC values. Isoniazid, however, showed better activity compared to 4-substituted pyrrolo[2,3-*c*]quinolines.

Further cytotoxicity assays carried out in order to ascertain the effect of compounds on healthy cells revealed that compound **1m**, which along with compound **1l** shows the highest activity, is least toxic to healthy cells. Other active compounds (MIC values <10 μM) showed percentage inhibition of RAW 264.7 cells in the range 15–24 %. Thus compound **1m** can be modified further in order to improve its efficacy as well as to reduce its cytotoxicity.

Conclusions

We have described a general synthesis of 4-substituted pyrrolo[2,3-*c*]quinolines showing antitubercular activity. To the best of our knowledge this is the first report on antitubercular activity exhibited by a fused pyrroloquinoline system. The approach described herein gives a similar overall yield for aplidiopsamine A as that reported by Mahajan et al. and Panarese et al. it is also a more flexible method as diverse aldehydes can be exploited to prepare 4-substituted pyrrolo[2,3-*c*]quinolines. The synthetic route

utilized is shorter and more efficient compared to the existing ones. By choosing aldehydes over acid chlorides [26] (as reported previously) we have shown that the reaction is now compatible with substrates containing reactive nitrogen, and reactivity normally associated with acid chlorides does not hamper the synthesis of diverse compounds. Work is currently underway to synthesize modified analogues of these compounds to improve the antitubercular activity as well as to carry out the enzyme binding studies.

Experimental

All starting materials were purchased from Aldrich, Spectrochem, SRL, and Sd Fine (India) and used directly without further purification. Solvents were dried using standard methods and distilled before use. Visualization of TLC plates was achieved by use of UV light (254 nm) or iodine. Melting points were recorded on a Stuart SMP 30 melting point apparatus. ^{1}H (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were recorded in $CDCl_3$ and DMSO-d_6 solution with TMS as internal standard. IR spectra were recorded as KBr plates on a Jasco FT/IR-4200 instrument. High resolution mass spectra were recorded on a Bruker microTOF QII instrument. Column chromatography was performed on silica gel (100–200 mesh, SRL, India).

*3-(o-Nitrophenyl)pyrrole (**2**)*
To a solution of 2.4 g *o*-nitrostyrene (16.09 mmol) in 30 cm^3 DMSO 4 g TosMIC (20.5 mmol) and 3.611 g *t*-BuOK (32.2 mmol) were added, and the reaction mixture was stirred for 4 h at 100 °C. After completion of the reaction as indicated by TLC, 30 cm^3 brine solution was added and the reaction mixture was extracted with ethyl acetate (3 × 50 cm^3), and the combined organic layer was dried over anhydrous Na_2SO_4. Ethyl acetate was removed under vacuum. The crude product was subjected to column chromatography (silica gel, 8–10 % EtOAc/ *n*-hexane) to provide the pure compound as a yellow oil. Yield: 1.52 g (51 %). The structure was confirmed by IR, ^{1}H, ^{13}C NMR, and MS, which were consistent with those described in the literature [Ref. 27].

*3-(o-Aminophenyl)pyrrole (**3**)*
To a solution of 1.3 g *o*-nitrophenylpyrrole (6.91 mmol) in 20 cm^3 ethanol 3.858 g Fe (69.08 mmol) and 1.5 cm^3 0.6 N HCl were added and the reaction mixture was stirred at 80 °C for 1.5 h. The reaction mixture was cooled to room temperature and passed through a Celite pad and the solvent was evaporated. HCl was neutralized with $NaHCO_3$ and the aqueous solution was extracted with EtOAc (3 × 50 cm^3); the combined organic layer was washed with brine (2 × 20 cm^3) and dried with Na_2SO_4. Ethyl acetate was removed under vacuum. The crude product thus obtained was subjected to column chromatography (silica gel, 30–40 % EtOAc/ *n*-hexane) to afford the desired compound as a brown liquid. Yield: 0.780 g (71 %). The structure was confirmed by IR, ^{1}H, ^{13}C NMR, and MS, which were consistent with those described in the literature [Ref. 27].

*General procedure for the preparation of 4-substituted pyrrolo[2,3-c]quinolones **1a–1u***

To a solution of aminophenylpyrrole (1.89 mmol) and aldehyde (1.89 mmol) in 15 cm^3 DMF was added acetic acid (20 mol%). The solution was stirred for 12 h at 60 °C. After completion of the reaction as indicated by TLC, the reaction mixture was cooled to room temperature. Brine (10 cm^3) and 5 cm^3 $NaHCO_3$ were added to the reaction mixture and it was extracted with ethyl acetate (3 × 30 cm^3). The combined organic layer was washed with 30 cm^3 brine and dried over sodium sulfate. Removal of ethyl acetate under reduced pressure gave the crude product, which was chromatographed over silica gel to afford the desired compounds **1a**–**1u** in 32–86 % yields (Table 1).

*9-[(3H-Pyrrolo[2,3-c]quinolin-4-yl)methyl]-9H-purin-6-amine (aplidiopsamine A, **1a**)*
Starting from aldehyde **4a**, 473 mg **1a** (62 %) was isolated as a yellow oil, which solidifies under cooling. The structure was confirmed by ^{1}H, ^{13}C NMR, and MS data, which were consistent with those described in the literature [Ref. 12].

*4-Phenyl-3H-pyrrolo[2,3-c]quinoline (**1b**)*
Starting from aldehyde **4b**, 187 mg **1b** (82 %) was isolated as a yellow solid. M.p.: 209 °C ([27] 212–214 °C). The structure was confirmed by IR, ^{1}H, ^{13}C NMR, and MS data, which were consistent with those described in the literature [Ref. 27].

*4-Benzyl-3H-pyrrolo[2,3-c]quinoline (**1c**)*
Starting from aldehyde **4c**, 91 mg **1c** (63 %) was isolated as a white solid. M.p.: 172–174 °C ([27] 179–181 °C). The structure was confirmed by IR, ^{1}H, ^{13}C NMR, and MS data, which were consistent with those described in the literature [Ref. 27].

*4-(4-Nitrophenyl)-3H-pyrrolo[2,3-c]quinoline (**1d**)*
Starting from aldehyde **4d**, 305 mg **1d** (68 %) was isolated as a light yellow solid. M.p.: 215 °C ([27] 220–221 °C). The structure was confirmed by IR, ^{1}H, ^{13}C NMR, and MS data, which were consistent with those described in the literature [Ref. 27].

4-[4-(Trifluoromethyl)phenyl]-3H-pyrrolo[2,3-c]quinoline (**1e**, $C_{18}H_{11}F_3N_2$)
Starting from aldehyde **4e**, 572 mg **1e** (69 %) was isolated as a white solid. M.p.: 165–167 °C; R_f = 0.65 (*n*-hexane/ethyl acetate = 7:3); ^{1}H NMR (400 MHz, $CDCl_3$):

δ = 7.12–7.16 (m, 1H), 7.44 (t, J = 2.8 Hz, 1H), 7.54–7.62 (m, 4H), 7.88 (d, J = 8.1 Hz, 2H), 8.14–8.19 (m, 1H), 8.21–8.26 (m, 1H), 9.66 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 102.33, 123.09, 123.36, 123.9 (CF_3, J = 273 Hz), 125.85, 126.37, 126.57, 126.86, 127.19, 128.6, 129.55, 129.80, 130.50, 130.83, 131.15, 131.47, 141.70, 142.84, 145.16 ppm; IR (KBr): $\bar{\nu}$ = 3,092, 1,475, 1,323, 1,131, 1,012, 754 cm^{-1}; HRMS: calcd for $C_{18}H_{12}F_3N_2$ [M + H$^+$] 313.0947, found 313.0938.

*4-(4-Methoxyphenyl)-3H-pyrrolo[2,3-c]quinoline (**1f**)*
Starting from aldehyde **4f**, 104 mg **1f** (67 %) was isolated as a pale brown solid. M.p.: 168–170 °C ([13] 173–174 °C). The structure was confirmed by IR, ^{1}H, ^{13}C NMR, and MS data, which were consistent with those described in the literature [Ref. 27].

2-(3H-Pyrrolo[2,3-c]quinolin-4-yl)phenol
(**1g**, $C_{17}H_{12}N_2O$)
Starting from aldehyde **4g**, 178 mg **1g** (53 %) was isolated as a yellow solid. M.p.: 208–210 °C; R_f = 0.4 (*n*-hexane/ethyl acetate = 6:4); ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.00–7.14 (m, 2H), 7.32 (d, J = 2.9 Hz, 1H), 7.37–7.46 (m, 1H), 7.58–7.70 (m, 2H), 7.76 (d, J = 2.9 Hz, 1H), 8.02–8.07 (m, 1H), 8.09 (dd, J = 8.1, 1.5 Hz, 1H), 8.33–8.45 (m, 1H), 12.11 (s, 1H), 14.05 (s, 1H) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): δ = 101.99, 117.93, 119.43, 120.45, 123.07, 123.64, 125.82, 126.52, 127.04, 127.86, 129.83, 130.04, 130.61, 131.67, 139.65, 146.48, 159.30 ppm; IR (KBr): $\bar{\nu}$ = 3,309, 3,051, 1,585, 1,503, 1,378, 1,160, 737 cm^{-1}; HRMS: calcd for $C_{17}H_{13}N_2O$ [M + H$^+$] 261.1022, found 261.1058.

4-(Pyridin-2-yl)-3H-pyrrolo[2,3-c]quinoline
(**1h**, $C_{16}H_{11}N_3$)
Starting from aldehyde **4h**, 78 mg **1h** (85 %) was isolated as yellow solid. M.p.: 155 °C; R_f = 0.5 (*n*-hexane/ethyl acetate = 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.11 (s, 1H), 7.35 (s, 1H), 7.49 (t, 1H, J = 8 Hz), 7.55–7.59 (m, 3H), 7.64 (d, 1H, J = 4 Hz), 8.00 (d, 1H, J = 8 Hz), 8.07 (d, 1H, J = 8 Hz), 8.22 (d, 1H, J = 8 Hz), 9.14 (s, 1H, NH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 102.2, 123.1, 123.4, 124.9, 126.5, 127.0, 127.5, 129.5, 129.9, 131.4, 132.7, 133.2, 142.5, 143.4, 149.0 ppm; IR (KBr): $\bar{\nu}$ = 3,373, 3,061, 1,576, 1,156, 1,063, 743 cm^{-1}; HRMS: calcd for $C_{16}H_{12}N_3$ [M + H$^+$] 246.1026, found 246.1045.

4-(2-Chloropyridin-3-yl)-3H-pyrrolo[2,3-c]quinoline
(**1i**, $C_{16}H_{10}ClN_3$)
Starting from aldehyde **4i**, 178 mg **1i** (72 %) was isolated as a brown solid. M.p.: 206–209 °C; R_f = 0.5 (*n*-hexane/ethyl acetate = 5:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, 1H, J = 8 Hz), 7.27 (d, 1H, J = 8 Hz), 7.52–7.53 (t, 1H, J = 4 Hz), 7.61–7.64 (m, 2H), 7.97 (d, 1H, J = 8 Hz), 8.17 (d, 2H, J = 8 Hz), 8.26–8.29 (m, 1H), 10.31 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 101.8, 122.9, 123.2, 123.6, 126.6, 126.6, 127.6, 127.7, 129.5, 129.6, 134.1, 140.9, 142.4, 143.0, 149.8, 149.9 ppm; IR (KBr): $\bar{\nu}$ = 3,082, 1,588, 1,480, 1,125, 1,027, 728 cm^{-1}; HRMS: calcd for $C_{16}H_{11}ClN_3$ [M + H$^+$] 280.0636, found 280.0651.

*4-(1H-Indol-3-yl)-3H-pyrrolo[2,3-c]quinoline (**1j**)*
Starting from aldehyde **4j**, 115 mg **1j** (78 %) was isolated as a yellow solid. M.p.: 266–268 °C ([27] 264–266 °C). The structure was confirmed by IR, ^{1}H, ^{13}C NMR, and MS data, which were consistent with those described in the literature [Ref. 27].

*(1H-Indol-3-yl)(3H-pyrrolo[2,3-c]quinolin-4-yl)-methanone (**1k**)*
Starting from aldehyde **4k**, 437 mg **1k** (61 %) was isolated as a yellow solid. M.p.: 201 °C. The structure was confirmed by ^{1}H, ^{13}C NMR, and MS data, which were consistent with those described in the literature [Ref. 13].

4-(1H-Pyrrol-2-yl)-3H-pyrrolo[2,3-c]quinoline
(**1l**, $C_{15}H_{11}N_3$)
Starting from aldehyde **4l**, 75 mg **1l** (65 %) was isolated as a brown oil. R_f = 0.5 (*n*-hexane/ethyl acetate = 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.40 (t, 1H, J = 3.6 Hz), 6.91 (d, 1H, J = 4 Hz), 7.01 (t, 1H, J = 1.6 Hz), 7.06 (d, 1H, J = 3.2 Hz), 7.44 (d, 1H, J = 4 Hz), 7.48–7.56 (m, 2H), 8.09 (d, 1H, J = 8 Hz), 8.14 (d, 1H, J = 8 Hz), 9.53 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 102.2, 109.6, 110.5, 111.4, 121.26, 122.7, 122.9, 125.3, 126.5, 126.7, 128.1, 129.6, 138.1, 142.0 ppm; IR (KBr): $\bar{\nu}$ = 2,932, 1,662, 1,583, 1,483, 1,098, 757 cm^{-1}; HRMS: calcd for $C_{15}H_{12}N_3$ [M + H$^+$] 234.1026, found 234.1016.

4-(1H-Imidazol-2-yl)-3H-pyrrolo[2,3-c]quinoline
(**1m**, $C_{14}H_{10}N_4$)
Starting from aldehyde **4m**, 58 mg **1m** (86 %) was isolated as a yellow solid. M.p.: 173–176 °C; R_f = 0.5 (*n*-hexane/ethyl acetate = 5:5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.02 (s, 1H), 7.10 (d, 1H, J = 4 Hz), 7.31 (s, 1H), 7.50–7.58 (m, 3H), 8.10 (d, 1H, J = 8 Hz), 8.25 (d, 1H, J = 8 Hz), 11.44 (s, 1H, NH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): δ = 101.4, 118.3, 123.3, 123.9, 126.1, 126.4, 126.8, 127.6, 128.4, 129.6, 130.3, 135.7, 141.9, 146.0 ppm; IR (KBr): $\bar{\nu}$ = 3,380, 3,343, 3,048, 1,523, 1,384, 1,108, 751 cm^{-1}; HRMS: calcd for $C_{14}H_{11}N_4$ [M + H$^+$] 235.0978, found 235.1003.

4-(Thiophen-2-yl)-3H-pyrrolo[2,3-c]quinoline
(**1n**, $C_{15}H_{10}N_2S$)
Starting from aldehyde **4n**, 184 mg **1n** (72 %) was isolated as a yellow solid. M.p.: 162–165 °C; R_f = 0.45 (*n*- hexane/ethyl acetate = 7:3); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.10 (d, 1H, J = 4 Hz), 7.14 (t, 1H, J = 4 Hz), 7.43

(t, 1H, $J = 4$ Hz), 7.47 (d, 1H, $J = 8$ Hz), 7.53–7.61 (m, 2H), 7.71 (d, 1H, $J = 8$ Hz), 8.19 (d, 2H, $J = 8$ Hz), 9.38 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 102.4$, 122.9, 123.2, 126.0, 126.4, 126.5, 126.7, 128.0, 128.1, 129.4, 129.8, 140.4, 142.2, 142.7 ppm; IR (KBr): $\overline{\nu} = 3{,}103$, 1,575, 1,528, 1,351, 1,126, 750 cm^{-1}; HRMS: calcd for $C_{15}H_{11}N_2S$ [M + H$^+$] 251.0637, found 251.0644.

4-(2-Phenyl-2H-1,2,3-triazol-4-yl)-3H-pyrrolo[2,3-c]-quinoline (**1o**, $C_{19}H_{13}N_5$)
Starting from aldehyde **4o**, 109 mg **1o** (74 %) was isolated as yellow solid. M.p.: 199 °C; $R_f = 0.5$ (*n*-hexane/ethyl acetate = 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.14$ (t, 1H, $J = 2.0$ Hz), 7.43 (t, 1H, $J = 7.6$ Hz), 7.55–7.66 (m, 5H), 8.19 (d, 2H, $J = 9.6$ Hz), 8.24 (d, 2H, $J = 9.6$ Hz), 8.80 (s, 1H), 10.40 (s, 1H, NH) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 101.8$, 119.1, 123.0, 123.7, 126.4, 126.7, 126.8, 128.0, 129.0, 129.4, 129.5, 129.7, 129.9, 130.0, 132.2, 135.54, 136.0, 139.6, 142.5, 148.9 ppm; IR (KBr): $\overline{\nu} = 3{,}226$, 2,926, 1,592, 1,457, 1,080, 758 cm^{-1}; HRMS: calcd for $C_{19}H_{14}N_5$ [M + H$^+$] 312.1244, found 312.1269.

4-(Ferrocen-1-yl)-3H-pyrrolo[2,3-c]quinoline (**1p**, $C_{21}H_{16}FeN_2$)
Starting from aldehyde **4p**, 540 mg **1p** (69 %) was isolated as a brown solid. M.p.: 177–180 °C; $R_f = 0.4$ (*n*-hexane/ethyl acetate = 8:2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 4.12$ (s, 5H), 4.49 (s, 2H), 5.08 (s, 2H), 7.09 (s, 1H), 7.55 (t, 2H, $J = 8$ Hz), 7.47 (s, 1H), 8.16 (t, 2H, $J = 8$ Hz), 9.45 (s, 1H) ppm; ^{13}C NMR (101 MHz, $CDCl_3$): $\delta = 68.3, 69.4, 70.2, 82.8$, 102.0, 122.8, 123.1, 125.4, 126.2, 128.4, 129.3, 130.1, 143.1, 148.1 ppm; IR (KBr): $\overline{\nu} = 3{,}386$, 2,924, 1,524, 1,090, 880, 751 cm^{-1}; HRMS: calcd for $C_{21}H_{17}FeN_2$ [M + H$^+$] 353.0740, found 353.0777.

1-[(3H-Pyrrolo[2,3-c]quinolin-4-yl)methyl]-5-methylpyrimidine-2,4(1H,3H)-dione (**1q**, $C_{17}H_{14}N_4O_2$)
Starting from aldehyde **4q**, 138 mg **1q** (52 %) was isolated as a brown solid, which decomposed when attempting to determine the melting point. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 1.83$ (s, 3H, CH_3), 5.41 (s, 2H, CH_2), 7.18 (s, 1H), 7.48–7.57 (m, 2H), 7.72 (m, 2H), 7.87 (d, 1H, $J = 8$ Hz), 7.98 (s, 1H), 8.27 (d, 1H, $J = 8$ Hz), 11.35 (s, 1H, NH), 12.20 (s, 1H, NH) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 12.5$ (CH_3), 48.6, 101.6, 108.2, 123.5, 125.9, 127.0, 128.0, 128.3, 129.5, 141.8, 143.5, 144.1, 151.7, 162.7, 165.1 ppm; IR (KBr): $\overline{\nu} = 3{,}170$, 1,673, 1,473, 1,364, 1,250, 1,051, 759 cm^{-1}; HRMS: calcd for $C_{17}H_{15}N_4O_2$ [M + H$^+$] 307.1190, found 307.1190.

1-[(3H-Pyrrolo[2,3-c]quinolin-4-yl)methyl]-4-aminopyrimidin-2(1H)-one (**1r**, $C_{16}H_{13}N_5O$)
Starting from aldehyde **4r**, 203 mg **1r** (32 %) was isolated as a white solid, which decomposed when attempting to determine the melting point. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.42$ (s, 2H, CH_2), 5.83 (d, 1H, $J = 6.8$ Hz), 7.17 (s, 1H), 7.50–7.55 (m, 3H), 7.70 (t, 1H, $J = 2.4$ Hz), 7.83 (d, 1H, $J = 8$ Hz), 7.89 (d, 1H, $J = 8$ Hz), 8.27 (d, 1H, $J = 6.5$ Hz), 12.18 (s, 1H, NH) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 50.6$ (CH_2), 93.9, 101.5, 123.5, 125.9, 127.4, 128.0, 128.3, 129.4, 141.9, 144.9, 147.9, 156.2, 166.2 ppm; IR (KBr): $\overline{\nu} = 3{,}177$, 1,663, 1,524, 1,390, 1,272, 1,189, 741 cm^{-1}; HRMS: calcd for $C_{16}H_{14}N_5O$ [M + H$^+$] 292.1193, found 292.1205.

1-[(3H-Pyrrolo[2,3-c]quinolin-4-yl)methyl]pyrimidine-2,4(1H,3H)-dione (**1s**, $C_{16}H_{12}N_4O_2$)
Starting from aldehyde **4s**, 145 mg **1s** (49 %) was isolated as a brown solid, which decomposed when attempting to determine the melting point. ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 5.44$ (s, 2H, CH_2), 5.67 (d, 2H, $J = 8$ Hz), 7.18 (s, 1H), 7.47–7.86 (m, 2H), 7.71 (t, 1H, $J = 2.7$ Hz), 7.82 (d, 2H, $J = 8$ Hz), 8.25 (d, 1H, $J = 7.2$ Hz), 11.31 (s, 1H, NH), 12.21 (s, 1H, NH) ppm; ^{13}C NMR (101 MHz, DMSO-d_6): $\delta = 49.1$ (CH_2), 100.8, 101.6, 123.5, 125.9, 126.9, 129.5, 141.8, 144.0, 147.9, 151.7, 164.5 ppm; IR (KBr): $\overline{\nu} = 3{,}280$, 1,691, 1,464, 1,249, 804, 750 cm^{-1}; HRMS: calcd for $C_{16}H_{13}N_4O_2$ [M + H$^+$] 293.1033, found 293.1023.

*4-Isobutyl-3H-pyrrolo[2,3-c]quinoline (**1t**)*
Starting from aldehyde **4t**, 54 mg **1t** (57 %) was isolated as a yellow solid. M.p.: 201 °C ([27] 205–207 °C). The structure was confirmed by IR, ^{1}H, ^{13}C NMR, and MS data, which were consistent with those described in the literature [Ref. 27].

*4-Methyl-3H-pyrrolo[2,3-c]quinoline (**1u**)*
Starting from aldehyde **4u**, 57.2 mg **1u** (48 %) was isolated as white solid compound. M.p.: 226 °C ([13] 236–237 °C). The structure was confirmed by IR, ^{1}H NMR, and MS data, which were consistent with those described in the literature [Ref. 13].

Biological activity

The in vitro antimycobacterial activity of the compounds against *Mycobacterium tuberculosis* H37Rv was carried out by the microplate Alamar Blue assay method leading to the determination of MIC values in duplicate. MICs of the standard drugs and the synthesized compounds are reported in Table 1 for comparison.

Compounds showing MIC values of less than 48 μM in the antimycobacterial assay were chosen for cytotoxicity determination. Cell line RAW 264.7 (mouse leukemic monocyte macrophage) was used for this purpose and the concentration used was 50 μM. Viability was assessed on the basis of cellular conversion of MTT into a formazan

product, after 72 h of exposure using the Promega Cell Titer 96 non-radioactive cell proliferation assay.

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