Bioorganic & Medicinal Chemistry Letters 21 (2011) 3966–3969

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

1-Chloro-2-formyl indenes and tetralenes as antitubercular agents

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ARTICLE INFO

Article history:
Received 12 February 2011
Revised 30 April 2011
Accepted 6 May 2011
Available online 14 May 2011

Keywords:
Tetralene
Indene
Antitubercular
Vilsmeier–Haack–Arnold reaction
Acute oral toxicity

ABSTRACT

1-Chloro-2-formyl indenes and tetralenes have been synthesized using Vilsmeier–Haack–Arnold reaction onto indanones and tetralones. Most of these analogues exhibited antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain with MICs ranging from 30 to 500 μg/mL. Analogue **13** was further modified to some derivatives. The most active analogue **23** showing MIC at 30 μg/mL was further evaluated for acute oral toxicity in Swiss albino mice and was found to be safe up to 300 mg/kg dose.

Tuberculosis is one of the largest killers in the world from any single infectious disease.[1] One third of the world's population is thought to be infected by this pathogen. In 2007, there were an estimated 13.7 million chronic active cases and in 2008, about 1.3 million were died of this disease.[2,3] Although per capita TB incidence is stable or declining in all the six WHO regions, number of patients every year is increasing continuously. Due to the development of multidrug resistance and extensive drug resistance of *Mycobacterium* against various antimycobacterial drugs and also a high prevalence of it in AIDS patients, the problem has become fiercer. WHO has targeted the elimination of tuberculosis by 2050 as a public health problem. The development of resistance to present antitubercular drugs has posed a serious threat to the treatment and management of the disease. Hence, there is an urgent need to develop a new, effective and affordable antiTB drug.

In the recent past, two naturally occurring tetralones, that is, shinanolone and hydroxymethoxy tetralone have been reported as potent antimycobacterial agents.[1,4,5] Shinanolone was obtained through bioactivity guided isolation from the chloroform extract of roots of *Euclea natalensis* (Family: *Ebenaceae*), exhibiting antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain with MIC at 100 μg/mL. Hydroxymethoxy tetralone showed better potency having MIC at 6.25 μg/mL against the same strain of *M. tuberculosis*. Hydroxymethoxy tetralone was isolated from the chloroform extract of *Engelhardia roxburghiana* Hay (Family: *Juglandaceae*) roots. Encouraged by the efficacy of these tetralone derivatives, we synthesized several tetralone and indanone derivatives as antimycobacterial agents (Fig. 1), using Vilsmeier–Haack–Arnold reaction to formylate activated aromatic ring systems.[6] The reaction has got a wide application in synthesizing many heterocyclic compounds.[7–12] Vilsmeier–Haack–Arnold reaction of 1-indanones and 1-tetralones yield unusual 1-chloro-2-formyl indenes and tetralenes under mild reaction conditions.[13] All the synthesized analogues were evaluated against *M. tuberculosis* H37Rv strain by BACTEC method. Analogue, **23** was further evaluated for acute oral toxicity in Swiss albino mice.

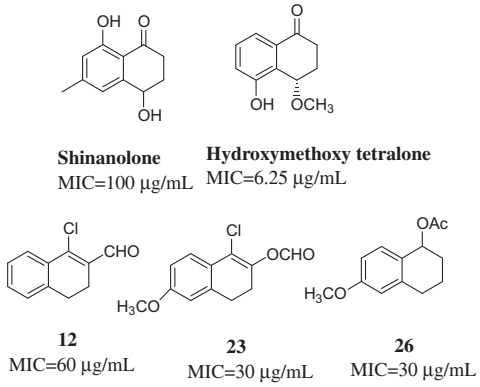

Figure 1. Shinanolone, hydroxymethoxy tetralone and some of the active analogues as antitubercular agents.

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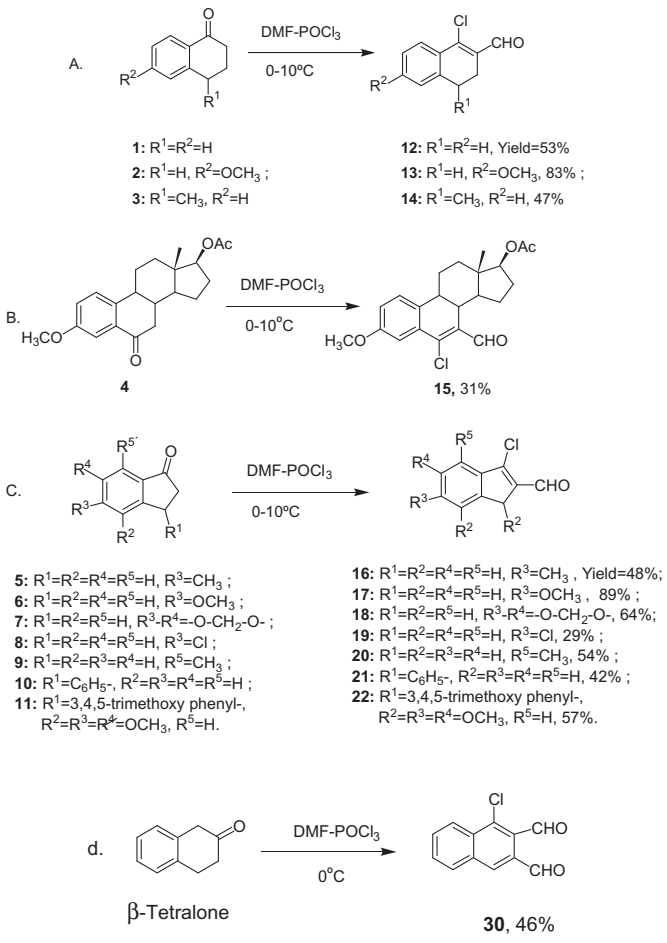
doi:10.1016/j.bmcl.2011.05.016



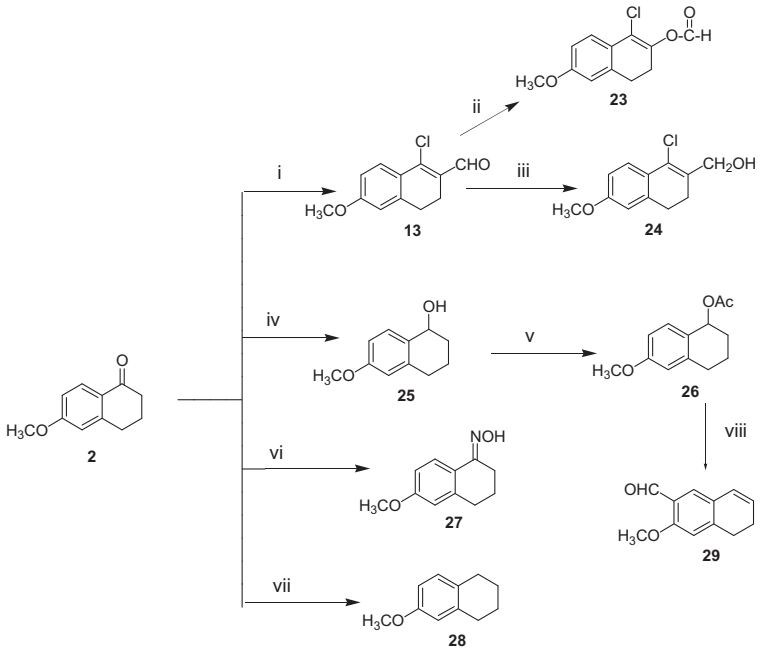
Scheme 1. Vilsmeier–Haack–Arnold reaction of indanones and tetralones.

The synthesis of these analogues is depicted in Scheme 1. Various tetralones (**1**–**4**) and indanones (**5**–**11**) were treated with Vilsmeier reagent to get corresponding 1-chloro-2-formyl tetralene (**12**–**15**) and indene (**16**–**22**) derivatives. Substrate **11** was synthesized as per our previously reported method.[14] For Vilsmeier reagent, a mixture of dry dimethylformamide–phosphorus oxychloride (DMF–$POCl_3$) was used.[15] However, 2-tetralone (β-tetralone) unexpectedly yielded a fully aromatized product, that is, 1-chloro-2, 3-diformyl naphthalene (**30**) under the similar reaction conditions. All the compounds were characterized by spectroscopy.[16]

Further, in order to establish structure activity relationship of these compounds, **13** and **2** were further modified to various analogues as shown in Scheme 2. Aldehyde **13** underwent Baeyer–Villiger oxidation in presence of *m*-chloroperbenzoic acid to afford a formate ester **23**. On sodium borohydride reduction compound **2** yielded a corresponding alcohol **25**. Its subsequent acetylation gave **26** in good yield.[17] The oxime derivative (**27**) was obtained by treating it with hydroxylamine hydrochloride.[18] While, a fully reduced tetralin analogue (**28**) was obtained by treating it with sodium borohydride in trifluoroacetic acid in good yield.[19]

Recently, NMR spectroscopy has been used for monitoring the chemical reactions in real.[20] The ^{1}H NMR experiment was run at 2–5 min intervals for substrate **2** after dissolving it in deuterated chloroform and adding the reagents ($POCl_3$ + DMF). From the proton spectra it was evident that over the period of time some of the tetralone **2**, resonances at δ 2.0, 2.5, 6.7, and 7.8 ppm were disappeared and appearance of new peaks at δ 2.7, 3.2, 3.8, 5.8, 7.6, 8.2, and 10.2 ppm just after one minute of reaction indicated the spontaneity of the reaction. The complete transformation of starting tetralone was observed after 15–20 min. Then final product **13**, was obtained after pouring this reaction mixture in cold water.

All these analogues were evaluated[21] for antitubercular activity against *M. tuberculosis* H37Rv strain radiometrically by BACTEC 460 and their minimum inhibitory concentrations (MICs) are presented in Table 1. Most of the compounds of this series exhibited antitubercular activity with MICs ranging from 30 to 500 μg/mL. Compounds **16**, **21**, **24**, **27**, **29**, and **30** possessed low level of activity showing MIC value of 500–250 μg/mL,



Scheme 2. Reagents and conditions: (i) DMF–$POCl_3$, 0 °C to rt, 1 h, 83%; (ii) DCM, *m*-CPBA, 0–10 °C for 1 h then rt for overnight, 39%; (iii) $NaBH_4$, MeOH, RT, 89%; (iv) $NaBH_4$, MeOH, rt, 91%; (v) Ac_2O, dry pyridine, rt, overnight, 89%; (vi) $NH_2OH.HCl$, ethanol, reflux, 1 h, 79%; (vii) $NaBH_4$–TFA, 0–10 °C, 83%; (viii) DMF–$POCl_3$, 80 °C, 3 h, 76%.

Table 1
Antimycobacterial activity of tetralene and indene analogues against *M. tuberculosis* $H_{37}Rv$ strain by BACTEC assay

S. No.	Compd No.	MIC (μg/mL)	S. No.	Compd no.	MIC (μg/mL)
1	**12**	60	12	**23**	30
2	**13**	125	13	**24**	500
3	**14**	125	14	**25**	na[a]
4	**15**	na[a]	15	**26**	30
5	**16**	250	16	**27**	500
6	**17**	125	17	**28**	125
7	**18**	125	18	**29**	500
8	**19**	125	19	**30**	500
9	**20**	125	20	Rifampicin	2.0
10	**21**	250	21	Streptomycin	2.0
11	**22**	na[a]	—	—	—

[a] na = Inactive at 500 μg/mL.

Compounds **13**, **14**, **17**–**20**, and **28** exhibited moderate level of activity (MIC = 125 μg/mL), while compounds **12**, **23**, and **26** possessed higher level of activity (MIC range 60–30 μg/mL). Rest of the compounds, that is, **15**, **22**, and **25** were found inactive at 500 μg/mL concentration.

Compound **12** having a 1-chloro-2-formyl arrangement in the tetralin system exhibited antitubercular activity (MIC at 60 μg/mL). On introducing a methoxy group in the aromatic ring at 6-position (i.e., **13**), antitubercular activity was reduced (MIC at 125 μg/mL). Similarly, on attaching a methyl group at 4-position of aliphatic ring (i.e., **14**) antitubercular activity was reduced (MIC at 125 μg/mL). The five membered 1-chloro-2-formyl indene derivatives exhibited moderate level of antitubercular activity. When the 5-methyl derivative (**16**) was replaced with a methoxy group (**17**), activity was enhanced by two fold. Similarly, 5,6-methylenedioxy indene analogue (**18**) exhibited better activity than the analogue **16**. Replacement of 5-methyl group with a chloro substituent (**19**, MIC = 125 μg/mL) doubled the activity. However, introduction of a phenyl unit at 3-position of the indene unit did not improve the activity (compounds **21** and **22**). Further modifications of compound **13** were not found beneficial, as most of the analogues exhibited lower activity than the parent compound. However, modification of 2-aldehyde of analogue **13** to its corresponding 2-formate ester **23**, activity was increased by four folds (MIC = 30 μg/mL). Thus, although most of the indene analogues possessed moderate level of antitubercular activity, tetralene analogues were better candidates for higher potency.

The most active analogue of **13**, that is, 2-formyl ester **23** was further evaluated for in vivo acute oral toxicity in Swiss albino mice at 5, 50 and 300 mg/kg single oral dose.[22] No observational changes, morbidity and mortality were observed throughout the experimental period. Blood and serum samples upon analysis showed nonsignificant changes in all the parameters studied like total RBC, WBC count, differential leukocyte count, hemoglobin, serum total cholesterol, triglycerides, creatinine level, SGPT and SGOT activity. Similarly, animals on gross pathological study showed no changes in any of the organs studied including their absolute and relative weights. Thus, the experiment showed that compound **23** was well tolerated by the Swiss albino mice up to the dose level of 300 mg/kg body weight as a single acute oral dose. However, sub-acute and chronic experiments with the test drug need to be carried out to look for any adverse effect on repeated exposure to the test drug compound **23** for its future development.

In conclusion, both tetralone and indanone based 1-chloro-2-formyl analogues have exhibited antimycobacterial activity against M. tuberculosis H37Rv strain. The most active analogue **23** was found to be safe up to 300 mg/kg dose in Swiss albino mice in acute oral toxicity. A detailed structure activity relationship study is needed for this class of compounds to get a better candidate in future.

Acknowledgments

The authors are thankful to the Director, CIMAP for constant encouragement and providing necessary facilities and also to the Director, National JALMA Institute for Leprosy and other Mycobacterial Diseases (ICMR), Agra, India for providing the Mycobacterial strain. The financial support from CSIR is duly acknowledged.

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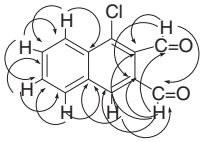
15. *General procedure for the synthesis of 1-chloro-2-formyl indenes and tetralenes:* Indanone Or tetralone (2 mmol) was taken in dry dimethylformamide (1 mL) and stirred at 0–10 °C in an ice bath. To this phosphorus oxychloride (0.5 mL, 836 mg, 5.43 mmol) was added and further stirred for 1 h. On completion, the reaction mixture was poured in crushed ice, extracted with ethyl acetate, washed with water. The organic layer was dried over anhydrous sodium sulphate and evaporated in vacuo. The desired 1-chloro-2-formyl indenes/tetralenes were obtained either solid or oil. In some of the cases chromatographic purification was done through silica gel column and hexane–ethyl acetate as eluents.
16. *Selected physical data*: **13:** Yield = 83%, mp = 76–78 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.56(t, 2H, 4-CH_2, J = 7.78 Hz), 2.76 (t, 2H, 3-CH_2, J = 7.86 Hz), 3.79 (s, 3H, OCH_3), 6.68 (d, 1H, 5-CH, J = 2.25 Hz), 6.77 (dd, 1H,7-CH, J = 8.7 Hz, 2.5 Hz), 7.74 (d, 1H, 8-CH, J = 8.7 Hz), 10.27 (s, 1H, CHO). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.99, 27.94, 55.76, 112.55, 114.01, 125.31, 128.62, 130.28, 141.59, 146.02, 162.68, 190.34; EI mass (MeOH): 223 [M$^+$], 208[M-CH_3]$^+$, 180 [M-CO-CH_3]$^+$; IR (KBr, cm^{-1}): 2932, 1655, 1606, 1486, 1180. Compound **23:** Yield = 39%, mp = oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.86 (br s, 2H, 4-CH_2), 3.13 (br s, 2H, 3-CH_2), 3.91(s, 3H, OCH_3), 6.62 (s, 1H, 5-CH), 6.83 (dd, 1H, 8-CH), 7.32 (br s, 1H, 7-CH), 8.05 (s, 1H, OCHO); ESI mass (MeOH): 247 [M+H]$^+$, 262 [M+Na]$^+$, 285 [M+K]$^+$. IR (KBr, cm^{-1}): 2925, 1727, 1632, 1504, 1257. Compound **26:** Yield = 89%, oil, ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.78–1.80 (m, 2H, 3-CH_2), 1.90–1.93 (m, 2H, 2-CH_2), 2.06 (s, 3H, $OCOCH_3$), 2.73–2.79 (m, 2H, 4-CH_2), 3.78 (s, 3H, OCH_3), 5.95 (t, 1H, 1-CH, J = 3.52 Hz), 6.63(d, 1H, 5-CH, J = 2.14 Hz), 6.72–6.76 (dd, 1H, 7-CH, J = 8.49 and 2.51 Hz), 7.22–7.86 (d, 1H, 8-CH, J = 8.51 Hz); ESI mass (MeOH): 191.9 [M+H]$^+$, 213.8 [M+Na]$^+$, 381.1[2 M–H]$^+$.
The structure of ***30***: In ^{1}H NMR, two distinct singlets at δ 10.6 and 10.87 ppm for two aldehydic protons were further supported in ^{13}C NMR. Further, one singlet, two doublets and two triplets in aromatic region each integrating for one proton clearly indicated that the second aldehyde was also present in the A ring. ^{13}C NMR and DEPT 135 spectra confirmed presence of seven methines (two aldehydic) and five quaternary carbons and hence, total 12 carbons. HR-MS indicated its molecular formulae as $C_{12}H_7ClO_2$. Further, in HMBC experiment, both the aldehydic protons showed long range correlations with the carbonyl carbons of each other. Further, one of the aldehydes showed strong correlation with an aromatic CH, while another aldehyde showed correlations with two quaternary carbons. Thus, suggesting both the aldehydes *ortho* to each other. All this confirmed the structure of **30** as 1-chloro-naphthalene 2,3-dicarboxaldehyde. Compound **30**: Yield = 46%; mp = 129-131 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.57–7.62 (t, 1H, –CH), 7.71–7.77 (t, 1H, –CH), 7.91–7.93 (d, 1H, –CH), 8.50 (s,1H, –CH), 8.92–8.95 (d, 1H, –CH), 10.60 (s, 1H, CHO), 10.87 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 125.30, 128.39, 128.58, 129.73, 130.95, 131.57, 132.92, 133.82, 137.01, 140.09, 188.94, 192.02; DEPT 135: ^{13}C NMR ($CDCl_3$, 75 MHz): δ 125.30 (CH aromatic), 128.39 (CH aromatic), 130.95 (CH aromatic), 132.92 (CH aromatic),

137.01 (CH aromatic), 188.94 (CH aldehyde), 192.02 (CH aldehyde); ESI mass (MeOH): 258 $[M+K]^+$.



HMBC correlations of compound **30**.

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