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An efficient one-pot synthesis, structure, antimicrobial and antioxidant investigations of some novel quinolyldibenzo[*b*,*e*][1,4]diazepinones

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ABSTRACT

A highly improved one-pot procedure for the synthesis of diazepinones, which incorporate a bioactive quinoline nucleus, under catalyst-, and solvent-free environment has been developed. The method allowed us to achieve the products in high yields without requiring a chromatographic separation. All new quinolyldibenzo[*b*,*e*][1,4]diazepinones **6a**–**h** thus obtained were further treated to achieve N10–allylated products **7a**–**h** by a simple allylation. The structure of all new synthesized compounds was established based on elemental analysis, mass, ^{1}H NMR, ^{13}C NMR, IR spectral data, 2D NMR experiments, and single crystal X-ray study. From in vitro antimicrobial activity studies it revealed all are active against Gram positive (*Streptococcus pneumoniae*, *Clostridium tetani*, and *Bacillus subtilis*), Gram negative (*Salmonella typhi*, *Vibrio chlolerae* and *Escherichia coli*), *M. Tuberculosis H37RV* bacteria, and fungus like *Candia albicans* and *Aspergillus fumigatus*. All were also found to display good antioxidant activity of a ferric reducing power.

1,4-Diazepines continue to receive an overwhelming importance in medicinal chemistry due to their promising and potential pharmaceutical properties.[1] Examples include chlorodiazepoxide and diazepam in the treatment of anxiety,[2] clozapines from the piperidinyldibenzodiazepine family in schizophrenia, as well as the muscarinic receptor (M1) antagonist pirenzepines, and the platelet activating factor inhibitor apafant.[3] After their entry as a tranquilizer in 1970's, there has been increasing therapeutic use and demand of class of these compounds, which broadened their scope such as sedative, hypnotic, muscular relaxant and anticonvulsant. Moreover, as antipsychotic drugs[4a,b] in the treatment of schizophrenia, and possessing antianaphylactic activity,[4c] these compounds have attracted interest of many researchers. According to the criterion of pharmacological value, tricyclic systems incorporating a 1,4-diazepine unit into their structure is a key derivative.[5]

Acid catalyzed cyclization of an enaminone with an aldehyde is a key step to afford these heterocycles. Various aldehydes such as benzaldehyde, 2,3,4-pyridinecarbaldehydes, and 2-thiophene carbaldehydes have been employed.[6] To the best of our knowledge however; there is no report on quinoline-3-carbaldehydes. Incorporation of this biologically potential unit[7] into the diazepine skeleton would generate a novel molecular template which likely to exhibit interesting properties. Both benzodiazepine and quinoline units have promising pharmaceutical properties. Diazepine substructure has been evaluated as antioxidants and lipid peroxidation inhibitors in vitro.[8] In the same way, quinoline as antioxidant, anti-inflammatory and anticancer activities, as a key structure feature.[9,10] The presence of 3,4-double bond and 2-oxo functionality in quinolone is known to exhibit hydroxyl radical scavenging properties.[10a] For example, rebamipide is an effective antioxidant and antiulcer agent.[10b] Therefore, we planned the synthesis and biological investigations of quinolyldiazepines, which is not only desirable but may open interesting new area in medicinal research. Furthermore, an alkylation in general, and allylation in particular, at benzodiazepine nitrogen reported to improve the affinity towards the cholecystokinin (CCK2) receptor that is involved in many pathological situations.[11] Those, which include anxiety[12a] and panic[12b] particularly are relevant targets to therapeutic interventions.

Various routes have been intentional for the synthesis of class of these compounds.[6,13] Common one is a cyclization of an enaminone derived from diketones and *o*-phenylenediamine, with an aldehyde. Raboisson et al. and Eduardo et al. used a two-step procedure wherein, an enaminone formed in the first step undergoes cyclization with an aldehyde in the presence of acetic acid under ethanol reflux.[6a,b] Formation of intermediate Michael adduct from aldehyde and diketone, and its subsequent reaction with diamines

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is another way to assess these compounds, well studied by Orlov et al. A rarely existing route so far is the in situ cyclization of enaminone with aldehyde.[6c] This approach however, suffers from a longer reaction time, usage of excess organic solvents, and lower yields. Even, an enaminone sometime requires a chromatographic separation.[6f] So, it would be much more efficient and green approach, if one could design a new synthetic approach which eliminate an intermediate isolation step, and the use of solvents, and of course taking less reaction time.

Keeping in mind so-called synthetic and biological, we report here more efficient solvent- and catalyst-free method for the synthesis of new quinolyldibenzodiazepinones. Besides affording new biologically active scaffolds, this new approach also promised advantages like less reaction time, no isolation step, no chromatographic separation, and no use of toxic solvent.

In present work, we describe a catalyst-, and solvent-free procedure for one-pot synthesis of novel N_1-allylated quinolyldibenzo[*b*,*e*][1,4]diazepin-1-ones from qunoline-3-carbaldehydes, 1,3-cyclohexadione and *o*-phenylenediamine. The method[14] is simple and highly efficient one.

Quinolines **2a**–**d**, obtained by Vilsmeier–Haack reaction,[15] when treated with AcOH[16] or HCl[17] followed by allylation[16–18] they gave corresponding quinolones **3a**–**d** as shown in Scheme 1.

In our first attempt, we examined an acetic acid catalyzed reaction taking a mixture of an equimolar *o*-phenylenediamine **4**, 1,3-cyclohexadione **5a** and quinolone aldehyde **3a** in refluxing ethanol for 14 h to effect dibenzodiazepine **6a**. However, it gave no good yield (Table 1, entry 1). Instead, it proceeded via different possibilities as confirmed by TLC. Next, we tested the reaction in absence and presence of ethanol under microwave irradiation. Again, there was no improvement in the yield of **6a** (Table 1, entries 2, 3). Finally, we employed a solvent-free thermally induced reaction. Initially, we could not succeed but upon increasing temperature with an increment of 20 °C, raising it up to 100 °C, we found a very low yield due to incomplete reaction (Table 1, entries 4–5). But rising to 120 °C, surprisingly, we got desired product **6a** in 90% yield with an excellent purity. There was no chromatographic separation needed to purify the product. Simply upon washing the crude reaction mass by ethanol, we could get almost pure products. Further increase in the temperature could not improve the yield. Thus, other products were prepared by this same optimal condition.

Accordingly, we have synthesized a series of compounds **6a**–**h**[19] (Scheme 2, Table 2).

Allylated products **7a**–**h** were obtained by allylating compounds **6a**–**h** with allyl bromide in DMF in the presence of K_2CO_3 for 12 h (Table 3). Out of three possibilities of allylation i.e. either at N-5 and/or N-10 positions, a close examination of spectroscopic data showed that an allylation took place at N-10. The same was also supported by a literature.[13c,20] Thus, the present method exclusively give a single allylated product.

Structures of the compounds; **6a**–**h** and **7a**–**h**, were established by spectral data (^{1}H NMR, ^{13}C NMR, DEPT-135, IR and mass spectrometry) that are summarized in the experimental section.[21] ^{1}H NMR of **6a** showed two signals (2 × 3H); one singlet at δ 1.12 and second one at δ 1.14 assigned to methyl protons attached to C-3. A singlet appeared at δ 2.20 was consistent with C-2 methylene protons. A C-4 methylene protons gave two doublet signals; one at δ 2.58 (J = 16.0 Hz) and second one at δ 2.76 (J = 16.0 Hz). A doublet that appeared at δ 5.56 with coupling constant, J = 5.2 Hz, is assigned to N-10 proton. In the allylated product **7a**, its disappearance showed that N-10 nitrogen is involved in the allylation. Another doublet that appeared at δ 5.76 with J = 5.6 Hz, is due to C-11 methine proton. N-5 proton gave a singlet at δ 8.93. Methyl protons at C-3 in **7a** resonate as a two singlet; one at δ 1.10 and second at δ 1.12. A C-11 methine proton gave singlet at δ 5.88. A singlet that appeared at δ 8.88 is due to N-5 proton.

Table 1
Optimization of the reaction conditions

Entry	Solvent	Catalyst	Temp (°C)	Time (h)	Yield (%)
1	Ethanol	AcOH	Reflux	14	62
2	Ethanol	AcOH	Reflux[a]	4[b]	75
3	None	—	50[a]	4[b]	—
4	None	—	80	10	55
5	None	—	100	6	69
6	None	—	120	2.5	90

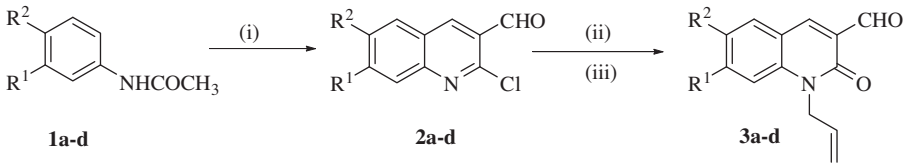
[a] Microwave irradiation.
[b] Time in minute.

The stereochemistry of the compounds were confirmed by 2D NMR experiments; COSY (double quantum filtered correlation spectroscopy) and NOESY (nuclear Overhauser effect spectroscopy) of representative **6a** (Fig. 1) and a single crystal X-ray data[22] of representative **7c** (Figs. 2 and 3). The data are fully agreed with their proposed structures.

All new mono **6a**–**h**, and diallylated **7a**–**h** quinolyldibenzo [*b*,*e*][1,4]diazepin-1-ones were screened in vitro for their antibacterial and antifungal activity by the macro-broth dilution assay.[23,24] Table 4 summarizes the test results.

Ampicillin, norfloxacin, chloramphenicol, ciprofloxacin, griseofulvin and nystatin were used as standard reference drugs to compare the present tests results. Besides, we have determined ferric-reducing antioxidant power (FRAP) and antitubercular activity of the compounds employing Benzie and Strain's modified method[25] and L.J. Medium respectively. FRAP values are expressed as ascorbic acid equivalent (mmol/100 g) (Table 5). Percent growth inhibition of *M. Tuberculosis H37RV* bacteria was measured by a test solution containing 250 μg/mL of respective compounds in DMSO (Table 5).

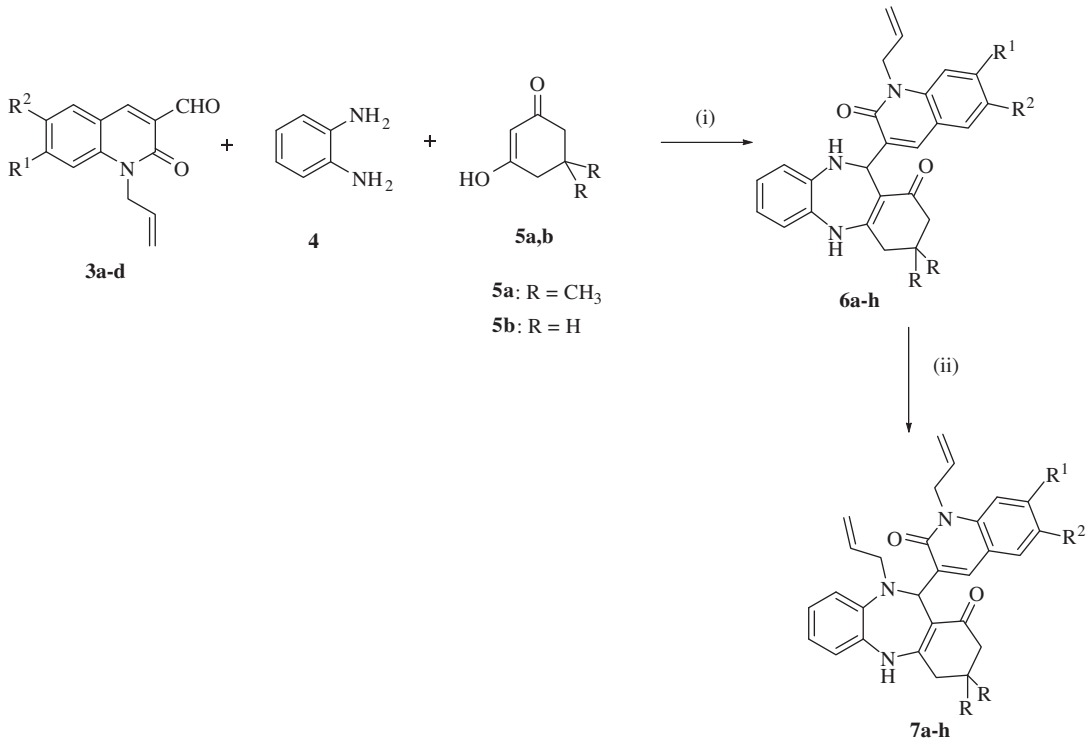
From antimicrobial test results, it follows that compounds are active against Gram-positive (*Clostridium tetani* and *Bacillus subtilis*) bacteria, and fungi *Candia albicans*, with their MICs values close to reference drug ampicillin (100 μg/mL), and an antifungal drug griseofulvin (500 μg/mL) respectively. While compounds **6c**, **6h** and **7d** are relatively more potent than ampicillin against *Cl. tetani*, others **6a**, **6b**, **6d**, **6e**, **7e**, **7g**, and **7h** have similar effect against these bacteria. However, majority of compounds are active against *B. subtilis*. It includes **6a**, **6b**, **6d**, **6e**, and **7e**. Though the results are not so impressive against *Streptococcus pneumonia*, there exist only



1a-d **2a-d** **3a-d**

1a, R^1=Cl, R^2=H; **1b**, R^1=Me, R^2=H; **1c**, R^1,R^2 = H; **1d**, R^1=H, R^2=Me

Scheme 1. Reagents and conditions: (i) DMF, $POCl_3$, 75–80 °C, 8 h; (ii) aq AcOH, reflux, 4 h; (iii) allyl bromide, K_2CO_3, DMF, 12h, room temperature.



Scheme 2. Reagents and conditions: (i) 120 °C, 2.5–3.0 h; (ii) allyl bromide, K_2CO_3, DMF, 12 h, room temperature.

Table 2
Synthesis of dibenzodiazepinones **6a–h**

Product	R	R^1	R^2	Time (h)	Yield (%)	Mp[a] (°C)
6a	Me	Cl	H	2.5	90	270–272
6b	H	Cl	H	2.7	90	276–278
6c	Me	H	H	2.6	83	214–215
6d	H	H	H	2.8	88	173–175
6e	Me	Me	H	2.6	80	175–177
6f	H	Me	H	3.0	80	274–276
6g	Me	H	Me	2.5	92	175–177
6h	H	H	Me	3.0	75	270–273

[a] Uncorrected.

Table 3
Synthesis of N10-allylated dibenzodiazepinones **7a–h**

Product	R	R^1	R^2	Yield (%)	Mp[a] (°C)
7a	Me	Cl	H	95	150–152
7b	H	Cl	H	92	118–121
7c	Me	H	H	93	192–194
7d	H	H	H	90	151–153
7e	Me	Me	H	91	160–163
7f	H	Me	H	87	140–142
7g	Me	H	Me	90	148–150
7h	H	H	Me	92	156–158

[a] Uncorrected.

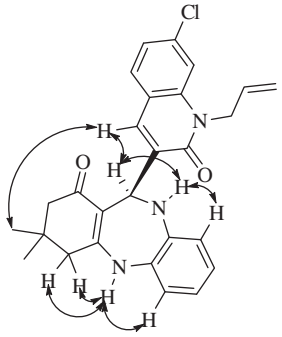


Figure 1. Characteristic NOE's of **6a**.

7d which is more potent against all three Gram-positive bacteria. Similarly, **6f** has good activity against all three Gram-negative bacteria with a lower MIC particularly in case of *Escherichia coli*, against which MICs of **7b** and **6f** were recorded less than standard while similar in case of others **7b** and **7g**. From the antifungal test results, it revealed that a major span of compounds is active against fungi particularly *C. albicans*. Surprisingly, none of the compounds found active against *Aspergillus fumigatus*. Comparison of these results with a standard drug griseofulvin makes compounds **7c**, and **7f** more active against *C. albicans*. MICs of others **6c**, **6b**, **6d**, **7d**, **6e** and **7e**, were observed in the same range. As shown in Table 4, none of the compounds except **6f** and **7b** have inhibitory effect against *E. coli*. However, compounds **7b** and **6f** with a MIC value 62.5 μg/mL showed a good activity which is very near to that exhibited by a standard drug ampicillin. While compound **7d** having an MIC of 100 μg/mL, was active against Gram positive bacteria *B. subtilis*, compound **6h** with MIC of 100 μg/mL was relatively active against Gram positive bacteria *C. tetani* compared to ampicillin. Similarly compounds **6g** and **7h** (MIC-200 μg/mL) showed good activity against Gram positive bacteria *B. subtilis*. Compounds **6c** and **7d** (MIC-200 μg/mL) remained excellent against *C. tetani*. Also compounds **7b**, **7d**, **6f**, **6g**, **7g** and **7h** (MIC-250 μg/mL) showed an excellent activity against fungal pathogen *C. albicans* as compared to griseofulvin. The MIC of **6d** (200 μg/mL) against *Vibrio cholera* showed a moderate activity as compared to Ampicillin. When tested against *M. tuberculosis H37RV* bacteria following a conventional L.J. Medium method, it was found that compounds **6a**, **6e**, **6f**, **6g**, **6h**, **7b**, **7f** and **7d** showed more than 50% growth inhibition. Among them **6e** and **6g** have a better performance than

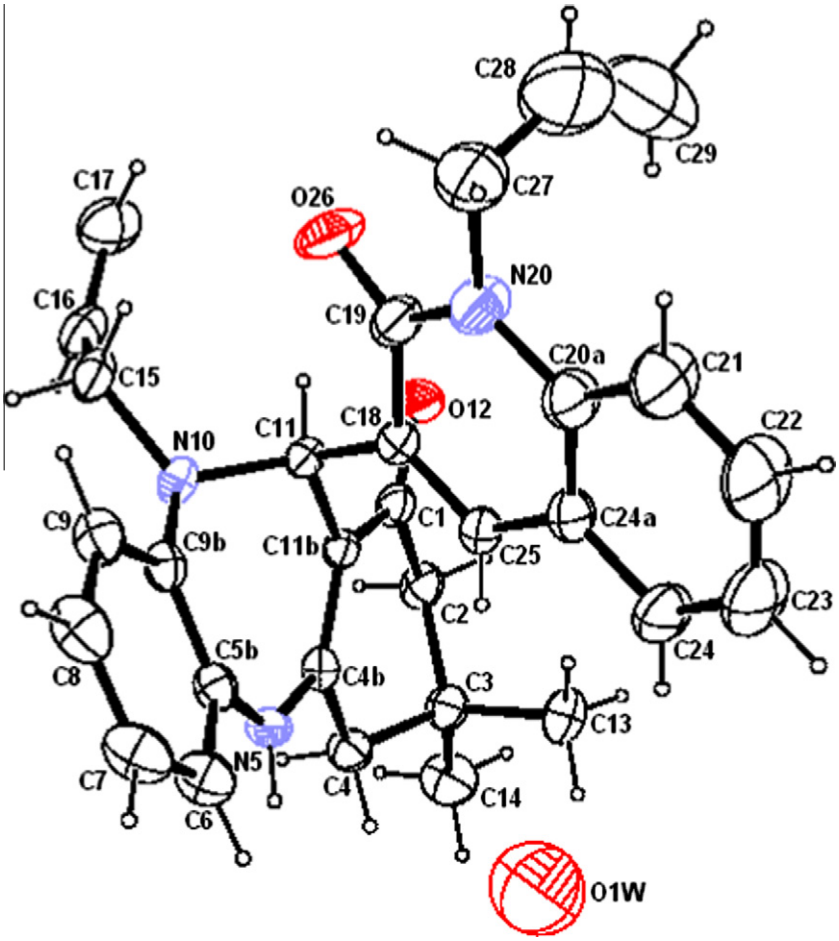


Figure 2. ORTEP view of the compound **7c**.

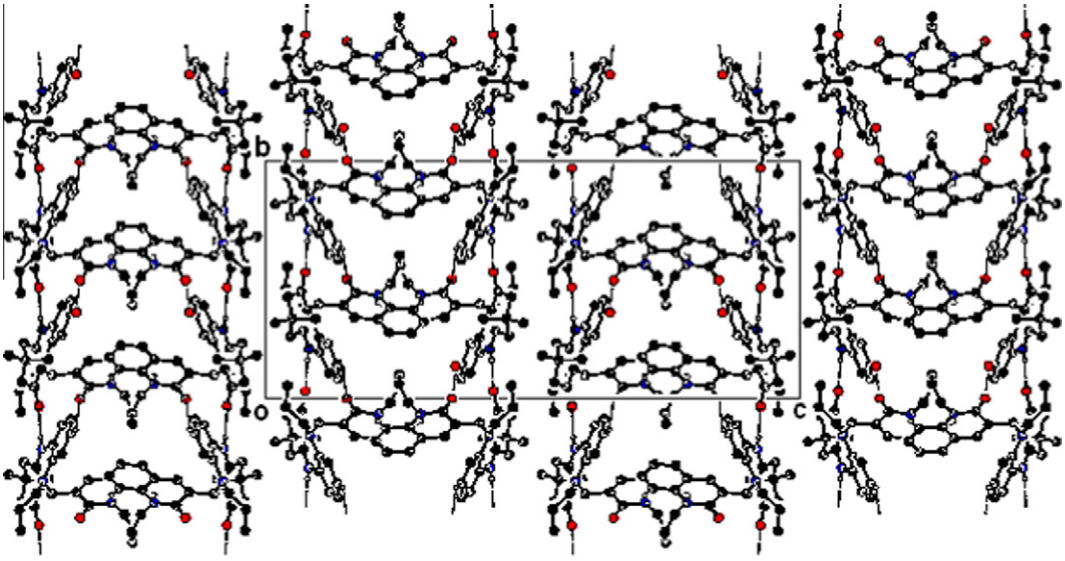


Figure 3. The packing arrangement of compound **7c**.

standard drugs Metronidazole (>256 μg/mL), Fluconazole (>256 μg/mL) and Miconazole (>256 μg/mL). Table 5 summerize the test results. The measurement of ferric reducing power (FRAP value) that ranging from 265 to 499 mmol/100 gm of compound indicates that the compounds are good antioxidant.

In conclusion, the present work demonstrates the synthesis of a series of new quinolyldibenzo[*b*,*e*][1,4]diazepin-1-ones showing good biological activities. While the compounds **6f** and **7b** exhibited good activity against *E. coli.* bacteria, more than half of the compounds showed more than 50% growth inhibition against *M.*

Table 4
Antibacterial and antifungal test results (MIC, μg/mL)

Compound	Gram-positive bacteria			Gram-negative bacteria			Fungi	
	S.p. MTCC 1936	*C.t.* MTCC 449	*B.s.* MTCC 441	*S.t.* MTCC 98	*V.c.* MTCC 3906	*E.c.* MTCC 443	*A.f.* MTCC 3008	*Ca.* MTCC 227
6a	>250	250	250	**100**	>250	250	>250	>250
6b	250	250	250	250	250	**100**	>250	>250
6c	>250	**200**	>250	>250	>250	**200**	>250	>250
6d	200	250	250	250	**200**	**200**	>250	>250
6e	>250	250	250	250	>250	250	>250	>250
6f	>250	500	**200**	**100**	**100**	**62.5**	250	>250
6g	250	500	**200**	250	250	>250	250	>250
6h	>250	**100**	250	250	500	250	>250	>250
7a	>250	500	>250	>250	500	>250	>250	>250
7b	>250	500	250	200	250	**62.5**	>250	>250
7c	>250	500	>250	>250	>250	250	>250	**250**
7d	**100**	**200**	**100**	250	**100**	>250	250	>250
7e	250	250	250	250	>250	200	>250	>250
7f	>250	500	250	**200**	**100**	>250	>250	**250**
7g	250	250	>250	**200**	>250	**100**	250	>250
7h	>250	250	200	250	250	250	250	>250
[A]	100	250	250	100	100	100	—	—
[B]	10	50	100	10	10	10	—	—
[C]	50	50	50	50	50	50	—	—
[D]	50	100	50	25	25	25	—	—
[E]	—	—	—	—	—	—	100	500
[F]	—	—	—	—	—	—	100	100

S.p.: *Streptococcus pneumoniae*, *C.t.*: *Clostridium tetani*, *B.s.*: *Bacillus subtilis*, *S.t.*: *Salmonella typhi*, *V.c.*: *Vibrio cholerae*, *E.c.*: *Escherichia coli*, *A.f.*: *Aspergillus fumigatus*, *C.a.*: *Candida albicans*, [A]: Ampicillin, [B]: Norfloxacin,[C]: Chloramphenicol, [D]: Ciprofloxacin, [E]: Griseofulvin, [F]: Nystatin, MTCC: Microbial Type Culture collection.

Table 5
Antitubercular and antioxidant test results

Compound	Growth of inhibition[a] (%)	Antioxident activity[b]	
		OD (593 nm)	FRAP value[d]
6a	62%	1.628	328.20
6b	<50%	1.338	489.88
6c	<50%	1.609	324.37
6d	<50%	2.291	346.54
6e	91%	1.99	269.75
6f	75%	1.317	498.75
6g	96%	1.775	461.86
6h	58%	1.446	498.75
7a	<50%	2.43	401.18
7b	76%	2.474	361.06
7c	<50%	1.719	265.50
7d	51%	2.474	389.28
7e	67%	1.791	357.83
7f	64%	1.931	382.03
7g	<50%	1.895	291.51
7h	<50%	2.474	498.75
Standard[c]	99%	2.474	–

[a] Concentration of compounds used against *M. Tuberculosis H37RV* bacteria = 250 μg/mL.
[b] Antioxidant activity: Concentration = 200 μg/mL, [c]Standard: Ascorbic Acid (A.A.) = 176 μg/mL.
[c] Standard antimicrobials used: Metronidazole (>256 μg/mL), Fluconazole (>256 μg/mL), Miconazole (>256 μg/mL).
[d] A.A. mm/100 gm sample.

tuberculosis H37RV bacteria. All the compounds except **7f** are active against *C. albicans*. Compound **7f** showed good activity against *A. fumigatus*. All the compounds are comparatively good antimicrobial. Besides this, FRAP values showed a good antioxidant power of the compounds.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.03.100.

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19. *General procedure for the synthesis of* ***6a–h***: In a round-bottom flask, a solvent-free equimolar (2 mmol) mixture of *o*-phenylenediamine 4, 1,3-cyclohexadione **5a–b** and quinolone-3-carbaldehyde **3a–d** heated at 120 °C till the completion of the reaction as confirmed by the TLC (2.5–3.0 h). The crude products obtained were purified by washing with ethanol and dried at room temperature. Entire products **6a–h** were received quantitatively with an excellent purity.
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21. *Spectroscopic data of some selected compounds*: Compound **6a**: Yield: 90%, yellow crystals; mp = 270–272 °C; IR (KBr): ν_{max} = 770, 925, 1330, 1375, 1585, 1645, 3245, 3290, 3325 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H = 1.12 (s, 3H, 3-CH_3), 1.14 (s, 3H, 3-CH_3), 2.20 (s, 2H, 2-H), 2.58 (d, 1H, *J* = 16.0 Hz, 4-Ha), 2.76 (d, 1H, *J* = 16.0 Hz, 4-Hb), 4.69 (d, 1H, *J* = 17.2 Hz, 22-Ha), 1.80 (d, 1H, *J* = 16.8 Hz, 22-Hb), 5.09 (d, 2H, *J* = 10.4 Hz, 20-H), 5.56 (d, 1H, *J* = 5.2 Hz, 10-H), 5.76 (d, 1H, *J* = 5.6 Hz, 11-H), 5.89 (m, 1H, 21-H), 6.43–7.51 (m, 8H, Ar-H), 8.93 (s, 1H, 5-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 28.10, 29.02, 32.33, 42.92, 44.23, 44.61, 49.98, 54.08, 107.58, 115.02, 116.37, 118.60, 120.70, 121.10, 122.73, 123.30, 130.84, 131.59, 132.53, 133.55, 134.46, 135.04, 138.45, 139.13, 156.27, 161.14, 192.76 ppm; ESI-MS: *m*/*z*: 459 (M^+); Anal. Calcd for $C_{27}H_{26}ClN_3O_2$: C, 70.55; H, 5.71; N, 9.15. Found: C, 70.25; H, 5.55; N, 9.02. Compound **6e**: Yield: 80%, yellow crystals; mp = 175-177 °C; IR (KBr): ν_{max} = 770, 905, 1400, 1600, 1650, 3175, 3265, 3470 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H = 1.12 (s, 3H, 3-CH_3), 1.15 (s, 3H, 3-CH_3), 2.21 (s, 2H, 2-H), 2.34 (s, 3H, 23-H), 2.60 (d, 1H, *J* = 16.0 Hz, 4-Ha), 2.75 (d, 1H, *J* = 16.4 Hz, 4-Hb), 4.73 (d, 1H, *J* = 16.8 Hz, 22-Hb), 4.80 (d, 1H, *J* = 4 Hz, 22-Ha), 5.08 (d, 2H, *J* = 10.8 Hz, 20-H), 5.58 (d, 1H, *J* = 5.6 Hz, 10-H), 5.78 (d, 1H, *J* = 5.2 Hz, 11-H), 5.9 (m, 1H, 21-H), 6.43-7.32 (m, 8H, Ar-H), 8.92 (s, 1H, 5-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 22.04, 28.31, 28.72, 32.32, 44.08, 44.63, 50.00, 54.19, 107.84, 115.19, 116.36, 117.59, 120.59, 120.98, 121.07, 123.23, 123.75, 128.94, 131.53, 132.75, 132.79, 133.97, 138.34, 138.59, 140.47, 156.20, 161.41, 192.76 ppm; ESI-MS: *m*/*z*: 440.2 ($M+H^+$); Anal. Calcd for $C_{28}H_{29}N_3O_2$: C, 76.51; H, 6.65; N, 9.56. Found: C, 76.59; H, 6.60; N, 9.62. Compound **7a**: Yield: 95%, yellow crystals; mp = 150–152 °C; IR (KBr): ν_{max} = 760, 925, 1350, 1395, 1580, 1650, 3295 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ_H = 1.09 (s, 3H, 3-CH_3), 1.12 (s, 3H, 3-CH_3), 2.13 (s, 2H, 2-H), 2.57 (s, 1H, 4-Ha), 2.74 (d, 1H, *J* = 16.0 Hz, 4-Hb), 3.97 (dd, 1H, *J* = 3.2 Hz & *J* = 3.2 Hz, 22-Ha), 4.24 (dd, 1H, *J* = 6.0 Hz & *J* = 6.0 Hz, 22-Hb), 4.65 (d, 1H, *J* = 17.2 Hz, 25-Hb), 4.73 (d, 1H, *J* = 15.6 Hz, 25-Ha), 4.99 (m, 4H, 20 & 23-H), 5.76 (m, 2H, 21 & 24-H), 5.88 (s, 1H, 11-H), 6.53-7.39 (m, 8H, Ar-H), 8.88 (s, 1H, 5-H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6): δ_C = 27.71, 29.16, 32.42, 44.23, 44.34, 49.98, 56.37, 57.16, 109.27, 114.69, 116.02, 116.87, 118.60, 120.49, 121.31, 122.28, 122.35, 123.54, 130.50, 132.65, 134.21, 134.31, 134.95, 135.93, 137.00, 139.10, 140.39, 156.51, 161.15, 192.20 ppm; ESI-MS: *m*/*z*: 499 (M^+); Anal. Calcd for $C_{30}H_{30}ClN_3O_2$: C, 72.06; H, 6.05; N, 8.40. Found: C, 72.20; H, 5.98; N, 8.52.
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