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Original scientific paper

Synthesis and biological activities of some indoline derivatives

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Abstract: The reaction of indoline with a substituted benzoyl chloride in the presence of K_2CO_3 in THF gave compound **4**. Compound **4** was subjected to chlorosulphonation to obtain compound **5**. Condensation of aromatic amines with compound **5** led to the synthesis of indoline derivatives **6(a–f)**. Similarly, 5-nitroindoline was treated with a substituted benzoyl chloride to obtain the nitro compound **9**, which was reduced using stannous chloride and reacted further with aromatic sulphonyl chloride to obtain the indoline derivatives **11(a–e)**. These compounds were tested for antibacterial, anti-tuberculosis and antifungal activity. Some of them showed very good activity against some gram-positive and gram negative bacteria, fungal strains and also *Mycobacterium tuberculosis*. All of the synthesized compounds were subjected to antioxidant activity testing using the *in vitro* DPPH assay and most of them showed very good activity.

Keywords: indoline; antioxidant activity; antifungal; anti-tuberculosis and antibacterial activity.

INTRODUCTION

Indoline and other related ring systems possess several interesting biological activities. The indolines are also interesting structural scaffolds and have, for example, been evaluated as 5-HT_{2C} receptor agonists for the treatment of obesity.[1] Factor Xa (FXa) is well known to play a pivotal role in blood coagulation; hence, an FXa inhibitor is a promising drug candidate for prophylaxis and treatment of thromboembolic diseases. Some indoline derivatives have been found to show very good FXa inhibitory activities.[2] Indoline derivatives have also been found to show an antagonistic effect on progesterone receptors.[3] In addition, indolines have been evaluated for antimicrobial activity.[4] Owing to the biological importance of indolines and in continuation of our work on the synthesis of biologically important heterocyclic compounds, the synthesis of some indolines is reported herein.

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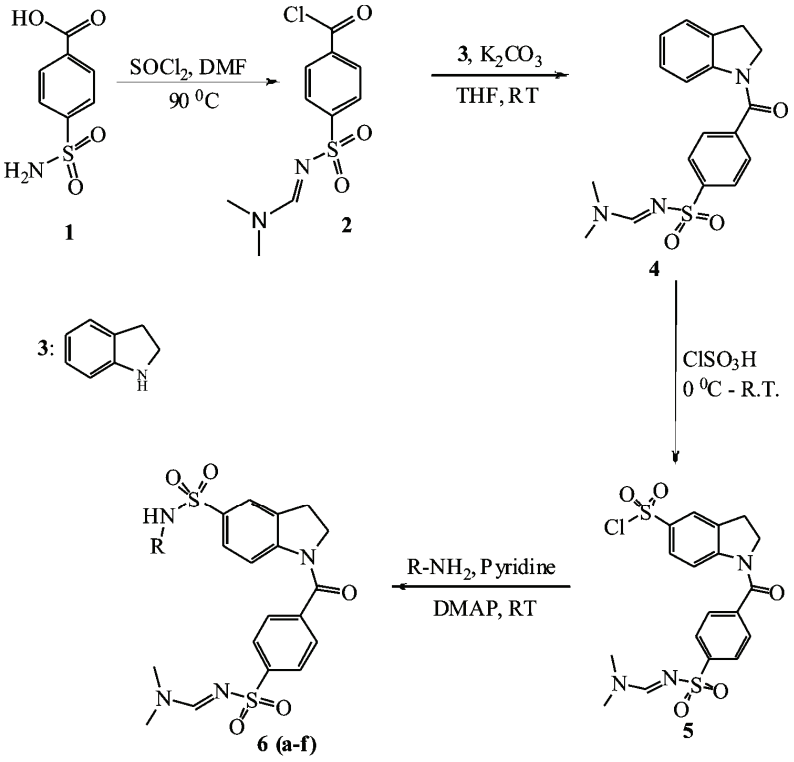
RESULTS AND DISCUSSION

In present work, the synthesis of novel indoline derivatives is reported starting with the substituted benzoyl chloride **2**, which was prepared by the reaction of 4-(aminosulfonyl)benzoic acid with $SOCl_2$ and DMF. Treatment of **2** with indoline **3** in the presence of K_2CO_3 in THF afforded compound **4**. Compound **4** was subjected to chlorosulphonation to obtain compound **5**, which on reaction with aromatic amines in presence of pyridine and a catalytic amount of DMAP using THF as the solvent yielded the indoline derivatives **6(a–f)**. The synthetic scheme to **6(a–f)** is shown in Scheme 1 and the structural data of **6(a–f)** are given in Table I.



Scheme 1.

Similarly, 5-nitroindoline (**8**) on treatment with compound **7** gave the nitro derivative **9**, which was further reduced by stannous chloride to the amino derivative **10**. The amino derivative on treatment with aromatic sulphonyl chlorides gave the indoline derivatives **11(a–e)**. The synthetic scheme to **11(a–e)** is shown in Scheme 2 and the structural data of **11(a–e)** are given in Table II.

The compounds **6(a–f)** and **11(a–e)** were characterized by FTIR, ^{1}H-NMR and mass spectroscopy.

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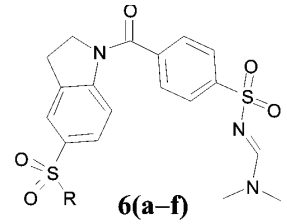
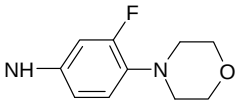
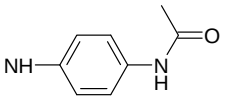
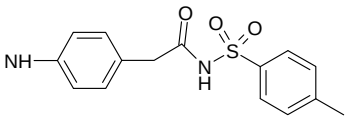
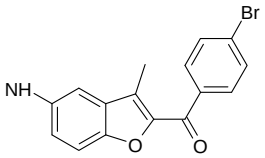
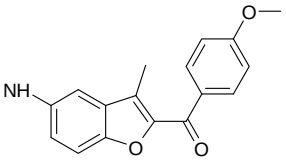
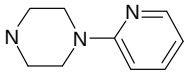
TABLE I. Structure of the synthesized compounds **6(a–f)**



6(a–f)

Compound	R
6a	
6b	
6c	
6d	
6e	
6f	

Compound ***6a***. Yield: 89 %; white crystalline; m.p. 119 °C; Anal. Calcd. for $C_{28}H_{30}FN_5O_6S_2$: C, 54.62; H, 4.91; N, 11.37 %. Found: C, 54.61; H, 4.90; N, 11.36 %. IR (KBr, cm^{-1}): 3452 (stretching of NH), 3047 (stretching of N=C–H), 2937, 2840 (stretching of C–H), 1634 (stretching of amide C=O), 1246 (stretching of C–F), 1050 (stretching of C–O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ ppm) 2.85 (4H, *t*, morpholine CH_2), 2.90 (3H, *s*, NCH_3), 3.09 (2H, *t*, indoline CH_2), 3.16 (3H, *s*, NCH_3), 3.68 (4H, *t*, morpholine CH_2), 4.01 (2H, *t*, indoline CH_2), 6.53–7.88 (10H, *m*, aromatic protons), 8.26 (1H, *s*, N=CH), 10.52 (1H, *s*, NH). MS (*m*/*z*): 615 (M^+) with all isotopic and other peaks.

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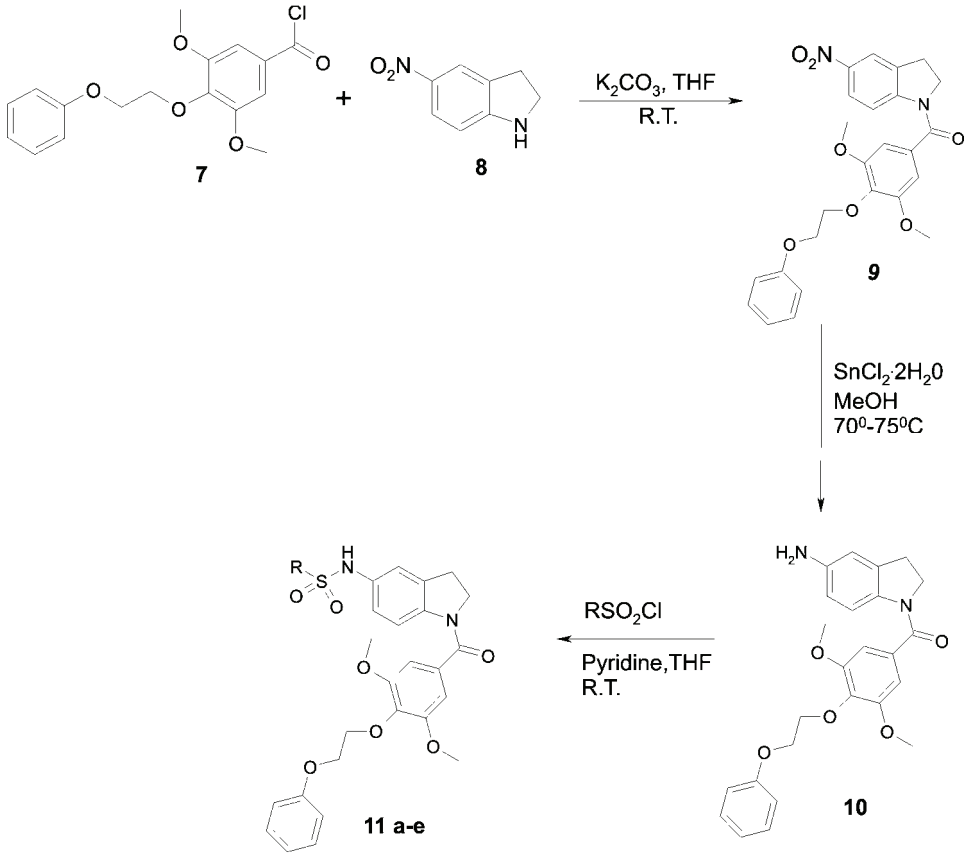

Scheme 2.

Compound ***6b***. Yield: 76 %; grey microcrystalline; m.p; 146 °C. Anal. Calcd. for $C_{26}H_{27}N_5O_6S_2$: C, 54.82; H, 4.78; N, 12.29 %. Found: C, 54.81; H, 4.77; N, 12.28 %. IR (KBr, cm^{-1}): 3455 (stretching of NH), 3050 (stretching of N=C–H), 2927, 2830 (stretching of C–H), 1632 (stretching of amide C=O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ ppm): 2.67 (3H, *s*, NHCOC**H**$_3$), 2.71 (2H, *t*, indoline CH_2), 2.90 (3H, *s*, NCH_3), 3.16 (3H, *s*, NCH_3), 3.90 (2H, *t*, indoline CH_2), 6.83–8.25 (11H, *m*, aromatic protons), 8.28 (1H, *s*, N=CH), 8.72 (1H, *s*, NHCO), 10.25 (1H, *s*, $NHSO_2$). MS (*m*/*z*): 569 (M^+) with all isotopic and other peaks.

Compound ***6c***. Yield: 90 %; red powder; m.p. 132 °C; Anal. Calcd. for $C_{33}H_{33}N_5O_8S_3$: C, 54.76; H, 4.60; N, 9.68 %. Found: C, 54.75; H, 4.61; N, 9.67 %. IR (KBr, cm^{-1}): 3450 (stretching of NH), 3048 (stretching of N=C–H), 2929, 2832 (stretching of C–H), 1633 (stretching of amide C=O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ/ ppm): 2.37 (3H, *s*, $ArCH_3$), 2.92 (3H, *s*, NCH_3), 3.09 (2H, *t*, indoline CH_2), 3.16 (3H, *t*, NCH_3), 3.42 (2H, *s*, CH_2CO), 3.98 (2H, *t*, indoline CH_2),

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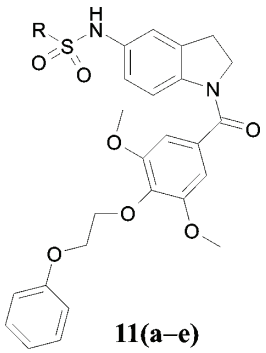
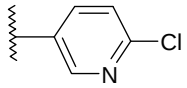
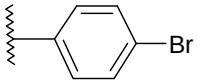
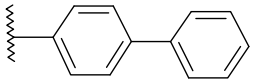
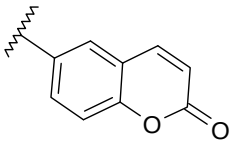
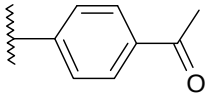
6.99–8.25 (15H, *m*, aromatic protons), 8.26 (1H, *s*, N=CH), 8.57 (1H, *s*, $NHSO_2$), 10.52 (1H, *s*, $CONHSO_2$). MS (*m*/*z*): 723 (M^+) with all isotopic and other peaks.

TABLE II. Structure of the synthesized compounds **11(a–e)**



11(a–e)

Compound	R
11a	
11b	
11c	
11d	
11e	

Compound ***6d***. Yield: 85 %; brown crystalline; m.p. 124 °C. Anal. Calcd. for $C_{34}H_{29}BrN_4O_7S_2$: C, 54.47; H, 3.90; N, 7.47 %. Found: C, 54.46; H, 3.89; N, 7.46 %. IR (KBr, cm^{-1}): 3450 (stretching of NH), 3048 (stretching of N=C–H), 2929, 2832 (stretching of C–H), 1682 (stretching of Ar–C=O), 1633 (stretching of amide C=O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.51 (3H, *s*, $ArCH_3$), 2.76 (2H, *t*, indoline CH_2), 3.07 (3H, *s*, NCH_3), 3.15 (3H, *s*, NCH_3), 4.00 (2H, *t*, indoline CH_2), 7.41–8.01 (14H, *m*, aromatic protons), 8.26 (1H, *s*, N=CH), 10.52 (1H, *s*, NH). MS (*m*/*z*): 749 (M^+) with all isotopic and other peaks.

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Compound ***6e***. Yield: 88 %; brown microcrystalline; m.p. 132 °C. Anal. Calcd. for $C_{35}H_{32}N_4O_8S_2$: C, 59.99; H, 4.60; N, 7.99 %. Found: C, 59.98; H, 4.59; N, 7.99 %. IR (KBr, cm^{-1}): 3438 (stretching of NH), 3052 (stretching of N=C–H), 2928, 2842 (stretching of C-H), 1685 (stretching of Ar–C=O), 1635 (stretching of amide C=O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.53 (3H, *s*, $ArCH_3$), 3.08 (2H, *t*, indoline CH_2), 3.15 (6H, *s*, $N(CH_3)_2$), 3.88 (3H, *s*, OCH_3), 4.03 (2H, *t*, indoline CH_2), 7.10–8.05 (14H, *m*, aromatic protons), 8.26 (1H, *s*, N=CH), 10.52 (1H, *s*, NH). MS (*m*/*z*): 700 (M^+) with all isotopic and other peaks.

Compound ***6f***. Yield: 95 %; white needles; m.p. 160 °C; Anal. Calcd. for $C_{27}H_{30}N_6O_5S_2$: C, 55.65; H, 5.19; N, 14.42 %. Found: C, 55.64; H, 5.18; N, 14.42 %. IR (KBr, cm^{-1}): 3434 (stretching of NH), 3050 (stretching of N=C–H), 2927, 2852 (stretching of C–H), 1631 (stretching of amide C=O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.94 (6H, *s*, $N(CH_3)_2$), 3.05 (2H, *t*, indoline CH_2), 3.19 (4H, *t*, piperazine CH_2), 3.63 (4H, *t*, piperazine CH_2), 4.06 (2H, *s*, indoline CH_2), 6.89–8.45 (11H, *m*, aromatic protons), 8.26 (1H, *s*, N=CH). MS (*m*/*z*): 582 (M^+) with all isotopic and other peaks.

Compound ***11a***. Yield: 76 %; red crystals; m.p. 155 °C; Anal. Calcd. for $C_{30}H_{28}ClN_3O_7S$: C, 59.06; H, 4.63; N, 6.89 %. Found: C, 59.05; H, 4.62; N, 6.88 %. IR (KBr, cm^{-1}): 3486 (stretching of NH), 2902, 2852 (stretching of C–H), 1632 (stretching of amide C=O), 1240 (stretching of C–O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.98 (2H, *t*, indoline CH_2), 3.73 (6H, *s*, OCH_3), 3.97 (2H, *t*, indoline CH_2), 4.22 (4H, *m*, OCH_2), 6.83–9.03 (13H, *m*, aromatic protons), 10.52 (1H, *s*, NH). MS (*m*/*z*): 609 (M^+) with all isotopic and other peaks.

Compound ***11b***. Yield: 65 %; white needles; m.p. 99 °C; Anal. Calcd. for $C_{31}H_{29}BrN_2O_7S$: C, 56.97; H, 4.47; N, 4.29 %. Found: C, 56.96; H, 4.46; N, 4.28 %. IR (KBr, cm^{-1}): 3488 (stretching of NH), 2922, 2852 (stretching of C–H), 1632 (stretching of amide C=O), 1246 (stretching of C–O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 3.00 (2H, *t*, indoline CH_2), 3.73 (6H, s, OCH_3), 3.98 (2H, *t*, indoline CH_2), 4.22 (4H, *m*, OCH_2), 6.84–7.79 (14H, *m*, aromatic protons), 10.25 (1H, *s*, NH). MS (*m*/*z*): 653 (M^+) with all isotopic and other peaks.

Compound ***11c***. Yield: 78 %; grey crystals; m.p. 106 °C; Anal. Calcd. for $C_{37}H_{34}N_2O_7S$: C, 68.29; H, 5.27; N, 4.30 %. Found: C, 68.28; H, 5.26; N, 4.29 %. IR (KBr, cm^{-1}): 3488 (stretching of NH), 2922, 2852 (stretching of C–H), 1632 (stretching of amide C=O), 1246 (stretching of C–O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 3.00 (2H, *t*, indoline CH_2), 3.71 (6H, *s*, OCH_3), 3.97 (2H, *t*, indoline CH_2), 4.22 (4H, *m*, OCH_2), 6.82–7.85 (19H, *m*, aromatic protons), 10.52 (1H, *s*, NH). MS (*m*/*z*): 650 (M^+) with all isotopic and other peaks.

Compound ***11d***. Yield: 80 %; yellow crystals; m.p. 105 °C; Anal. Calcd. for $C_{34}H_{30}N_2O_9S$: C, 63.54; H, 4.71; N, 4.36 %. Found: C, 63.54; H, 4.71; N, 4.35 %. IR (KBr, cm^{-1}): 3486 (stretching of NH), 2902, 2852 (stretching of C–H), 1690 (stretching of coumarin CO), 1633 (stretching of amide C=O), 1245 (stretching

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of C–O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 3.00 (2H, *t*, indoline CH_2), 3.80 (6H, *s*, OCH_3), 3.98 (2H, *t*, indoline CH_2), 4.41 (4H, *m*, OCH_2), 6.60–8.21 (15H, *m*, aromatic protons), 10.52 (1H, *s*, NH). MS (*m*/*z*): 642 (M^+) with all isotopic and other peaks.

*Compound **11e***. Yield: 81 %; yellow crystals; m.p. 111 °C; Anal. Calcd. for $C_{33}H_{32}N_2O_8S$: C, 64.27; H, 5.23; N, 4.54 %. Found: C, 64.27; H, 5.22; N, 4.53 %. IR (KBr, cm^{-1}): 3445 (stretching of NH), 3198, 2935, 2842 (stretching of C–H), 1720 (stretching of $COCH_3$), 1632 (stretching of amide C=O), 1250 (stretching of C–O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.04 (3H, *s*, $COCH_3$), 3.00 (2H, *t*, indoline CH_2), 3.77 (6H, *s*, OCH_3), 4.02 (2H, *t*, indoline CH_2), 4.24 (4H, *m*, OCH_2), 6.81–7.71 (14H, *m*, aromatic protons), 10.17 (1H, *s*, NH); MS (*m*/*z*): 616 (M^+) with all isotopic and other peaks.

The compounds **6(a–f)** and **11(a–e)** were tested for their antioxidant, antibacterial, antifungal and anti-tuberculosis activities.

Amongst the compounds screened for antioxidant activity, **6a**, **6b**, **6e**, **6f** and **11 (a–e)** showed very good antioxidant activities, as shown in Table III.

All the screened compounds, except **6b**, **6c**, **11d** and **11e**, exhibited very good antifungal and antibacterial activities, as shown in Tables IV and V, respectively.

TABLE III. Antioxidant activity (%) of the compounds

Compound	Concentration / μg ml^{-1}		
	200	100	50
L-Ascorbic acid	99.2	99	98.8
6a	93.5	92.00	88.05
6b	90.00	88.05	85.00
6c	28.05	24.36	20.7
6d	57.9	48.0	28.2
6e	98.6	98.5	89.8
6f	98.4	98.0	85.8
11a	99.00	97.2	93.6
11b	94.2	93.2	92.6
11c	95.00	92.40	78.05
11d	94.55	92.40	85.05
11e	91.70	83.25	70.22

TABLE IV. Antifungal activity of the compounds

Compound	Concentration / μg ml^{-1}														
	5	25	50	100	250	5	25	50	100	250	5	25	50	100	250
	A. niger					*A. clavatus*					*C. albicans*				
Griseofulvin	19	23	25	25	28	18	21	22	22	24	–	–	–	–	–
Nystatin	18	19	24	29	29	18	21	24	25	26	–	–	–	–	–
6a	–	10	15	17	19	–	11	16	17	19	–	14	16	17	20
6d	–	12	16	19	21	–	12	15	19	22	–	12	15	20	22
6e	–	13	17	19	22	–	13	17	18	20	–	15	17	19	21

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TABLE IV. Continued

Compound	Concentration / μg ml^{-1}														
	5	25	50	100	250	5	25	50	100	250	5	25	50	100	250
	A. niger					*A. clavatus*					*C. albicans*				
6f	–	14	16	18	19	–	13	15	18	19	–	15	17	19	20
11a	–	14	16	19	20	–	11	17	18	19	–	12	17	18	21
11b	–	12	15	18	20	–	12	15	18	19	–	13	15	18	19
11c	–	13	16	20	21	–	13	16	18	20	–	15	16	19	20

TABLE V. Antibacterial activity of the compounds

Compound	Concentration / μg ml^{-1}															
	25	50	100	250	25	50	100	250	25	50	100	250	25	50	100	250
	E. coli				*P. aeruginosa*				*S. aureus*				*S. pyogenes*			
Ampicillin	15	16	19	20	15	15	18	20	14	16	18	19	13	14	16	20
Ciprofloxacin	23	28	28	28	23	24	26	27	19	21	21	22	19	21	22	22
Norfloxacin	25	26	27	29	19	21	23	23	19	20	21	21	22	25	26	28
6a	13	15	17	21	12	14	18	21	12	14	17	19	11	12	15	17
6d	16	18	20	22	15	17	19	22	11	12	15	17	12	14	17	20
6e	13	13	15	17	11	12	15	16	15	18	20	22	11	14	16	18
6f	11	11	14	15	11	12	13	15	12	14	15	17	11	13	15	17
11a	11	14	16	17	11	14	17	19	12	14	15	15	11	13	14	15
11b	11	13	17	17	10	12	15	18	14	16	19	23	12	14	16	17
11c	11	13	15	15	10	13	14	16	17	19	19	24	12	15	17	19

Compounds **6a** (*MIC* = 100 μg/ml) and **6f** (*MIC* = 62.5 μg/ml) showed promising anti-tuberculosis activity, as shown in Table VI.

TABLE VI. Anti-tuberculosis activity of the compounds

Compound	*MIC* / μg ml^{-1}
Steptomycin	4
Isoniazid	0.2
Rifampicin	40
Ethambutol	2
6a	100
6d	250
6e	250
6f	62.5
11a	500
11b	1000
11c	>1000

EXPERIMENTAL

All the recorded melting points were determined in an open capillary and are uncorrected. The IR spectra were recorded on a Perkin-Elmer FTIR spectrophotometer in KBr discs. The ^{1}H-NMR spectra were recorded on a 400 MHz spectrophotometer in DMSO-d_6 as solvent and TMS as the internal standard. The mass spectra were obtained using a Waters mass spectrometer.

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*4-(2,3-Dihydro-1*H*-indol-1-ylcarbonyl)*-N-*[(1*E*)-(dimethylamino)methylene]-benzenesulphonamide (**4**)*

Compounds **2** (0.010 mol) and **3** (0.010 mol) were dissolved in THF together with K_2CO_3. The reaction mixture was stirred at room temperature for 4 h. The reaction mixture was then poured into water and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4 and concentrated under vacuum.

*Compound **4***. Yield: 85 %, red crystalline, m.p. 161 °C. Anal. Calcd. for $C_{18}H_{19}N_3O_3S$: C, 60.49; H, 5.36; N, 11.76 %. Found: C, 60.48; H, 5.35; N, 11.76 %. IR (KBr, cm^{-1}): 3047 (stretching of N=C–H), 2937, 2840 (stretching of C–H), 1634 (stretching of amide C=O). ^{1}H--NMR (400 MHz, DMSO-d_6, δ / ppm): 2.94 (3H, *s*, NCH_3), 3.09 (2H, *t*, indoline CH_2), 3.17 (3H, *s*, NCH_3), 3.98 (2H, *t*, indoline CH_2), 7.07–7.87 (8H, *m*, aromatic protons), 8.27 (1H, *s*, N=CH). MS (*m*/*z*): 357 (M^+) with all isotopic and other peaks.

*1-[4-({[(1*E*)-(Dimethylamino)methylene]amino}sulphonyl)benzoyl]indoline-5-sulphonyl chloride (**5**)*

Compound **4** (0.010 mol) was added in portions to a solution of chlorosulphonic acid (10 ml) at 0 °C and stirred for 30 min. The reaction mixture was cooled to room temperature and stirred for a further 1 h. The reaction mixture was then poured into cold water and the formed solid was separated by filtration.

*Compound **5***. Yield: 65 %, grey microcrystalline, m.p. 131 °C. Anal. Calcd. for $C_{18}H_{18}ClN_3O_5S_2$: C, 47.42; H, 3.98; N, 9.22 %. Found: C, 47.41; H, 3.97; N, 9.21 %. IR (KBr, cm^{-1}): 3047 (stretching of N=C–H), 2937, 2840 (stretching of C–H), 1634 (stretching of amide C=O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.94 (3H, *s*, NCH_3), 3.09 (2H, *t*, indoline CH_2), 3.17 (3H, *s*, NCH_3), 3.98 (2H, *t*, indoline CH_2), 7.49–8.14 (7H, *m*, aromatic protons), 8.27 (1H, *s*, N=CH). MS (*m*/*z*): 455 (M^+) with all isotopic and other peaks.

*General procedure for the synthesis of **6(a–f)***

Compound **5** (0.010 mol) and the required amine (0.010 mol) were dissolved in THF, together with DMAP and pyridine (0.030 mol). The reaction mixture was stirred at room temperature for 4 h, after which the reaction mixture was poured into dilute HCl and extracted with EtOAc. The organic layer was washed with water, separated, dried over Na_2SO_4 and concentrated under vacuum. The so-obtained crude product was crystallized from a mixture of CH_2Cl_2 and hexane.

*[3,5-Dimethoxy-4-(2-phenoxyethoxy)phenyl](5-nitro-2,3-dihydro-1*H*-indol-1-yl)methanone (**9**)*

Compound **7** (0.010 mol) and **8** (0.010 mol) were dissolved in THF, together with K_2CO_3. The reaction mixture was stirred at room temperature for 4 h and then poured into water and extracted with EtOAc. The separated, organic layer was dried over Na_2SO_4 and concentrated under vacuum.

*Compound **9***. Yield: 80 %; yellow needles; m.p. 93 °C; Anal. Calcd. for $C_{25}H_{24}N_2O_7$: C, 64.65; H, 5.21; N, 6.03 %. Found: C, 64.64; H, 5.20; N, 6.02 %. IR (KBr, cm^{-1}): 2902, 2852 (stretching of C–H), 1632 (stretching of amide C=O), 1515 (stretching of NO_2), 1240 (stretching of C–O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 3.20 (2H, *t*, indoline CH_2), 3.77 (6H, *s*, OCH_3), 4.17 (2H, *t*, indoline CH_2), 4.27 (4H, *m*, OCH_2), 6.92–8.16 (10H, *m*, aromatic protons); MS (*m*/*z*): 464 (M^+) with all isotopic and other peaks.

*(5-Amino-2,3-dihydro-1*H*-indol-1-yl)[3,5-dimethoxy-4-(2-phenoxyethoxy)phenyl]methanone (**10**)*

To a suspension of the nitro derivative **9** (0.10 mol) in methanol (50 ml) were added 5 equivalents $SnCl_2 \cdot 2H_2O$ and the reaction mixture was heated at 70 °C for 4 h. Then the

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mixture was cooled to room temperature, poured into aqueous NH_3 and filtered through celite. The filtrate was extracted with EtOAc. The separated organic layer was dried over Na_2SO_4 and concentrated under vacuum. The product was recrystallized from ethanol.

*Compound **10***. Yield: 66 %; brown powder; m.p. 65 °C; Anal. Calcd. for $C_{25}H_{26}N_2O_5$: C, 69.11; H, 6.03; N, 6.45 %. Found: C, 69.10; H, 6.02; N, 6.44 %. IR (KBr, cm^{-1}): 3445 (stretching of NH_2), 2902, 2852 (stretching of C–H), 1632 (stretching of amide C=O), 1240 (stretching of C–O). ^{1}H-NMR (400 MHz, DMSO-d_6, δ / ppm): 2.94 (2H, *t*, indoline CH_2), 3.75 (6H, *s*, OCH_3), 3.95 (2H, *t*, indoline CH_2), 4.22 (4H, *m*, OCH_2), 4.95 (2H, *bs*, NH_2), 6.40–7.78 (10H, *m*, aromatic protons). MS (*m*/*z*): 434 (M^+) with all isotopic and other peaks.

*General procedure for the synthesis of **11(a–e)***

Compound **10** (0.010 mol) and the required aromatic sulphonyl chloride (0.010 mol) were dissolved in THF, together with DMAP and pyridine (0.030 mol). The reaction mixture was stirred at room temperature for 4 h, after which it was poured into dilute HCl and extracted with EtOAc. The organic layer was washed with water, separated, dried over Na_2SO_4 and concentrated under vacuum. The crude product was crystallized from a mixture of CH_2Cl_2 and hexane mixture.

Anti-oxidant activity

The *in vitro* antioxidant activity of the test compounds was determined by the DPPH method[5]using L-ascorbic acid (an antioxidant agent) as the positive control. The compounds were tested for antioxidant activity at concentrations of 200, 100 and 50 µg/ml.

Antimicrobial activity

The *in vitro* antimicrobial activity of the test compounds was assessed against 24 h cultures of several selected bacteria and fungi. The employed gram positive and gram negative bacteria were *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes* and *Staphylococcus aureus* and the used fungi were *Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*.

The antimicrobial activity of all the compounds was tested using Müller Hinton broth (Hi Media M 391) as the nutrient medium for bacterial and Sabouraud Dextrose broth for fungal growth. The media were prepared using distilled-deionized water and dispensed in 25 ml amounts into 100-mm Petri dishes.The activity was determined by measuring the diameter of inhibition zone in millimetres.

Anti-tuberculosis activity

All the compounds were screened for their in vitro antimycobacterial activity against Mycobacterium tuberculosis by the broth macro dilution method. The activity of the compounds was confirmed by MIC determination against M. tuberculosis. A stock solution of each compound (1 mg/ml) was diluted in sterile distilled water to test the range. Each tube contained 4 ml sterile Middle Brook 7H9 broth containing albumin-dextrose-catalase, Tween 80, glycerol and 4 ml of the compound solution was added to make serial double dilutions. The tubes were incubated at 37 °C for 7 days and then read visually. The MIC was determined as the lowest concentration of the test substance that prevented turbidity. Streptomycin, isoniazid, rifampicin and ethambutol were used as the reference standards.

CONCLUSIONS

In conclusion, a series of novel indoline derivatives were synthesized and subjected to various biological activity tests, *viz*. antioxidant, antifungal, anti-tu-

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berculosis and antibacterial activity. Most of the compounds showed very good antioxidant and anti-infective activities, which suggest that the indoline core has a very high therapeutic value and needs to be explored in further studies.

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ИЗВОД

СИНТЕЗА И БИОЛОШКА АКТИВНОСТ НЕКИХ ДЕРИВАТА ИНДОЛИНА

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Реакцијом индолина са супституисаним бензоил-хлоридом, у присуству K_2CO_3 у THF, добијено је једињење **4** које је, након хлоросулфоновања, преведено у једињење **5**. Кондензацијом ароматичних амина са молекулом **5** добијени су индолински деривати **6(a–f)**. Сличан третман 5-нитроидолина супституисаним бензоил-хлоридом дао је нитро дериват **9**, који је прво редукован калај(II)-хлоридом, а резултујући амин је затим кондензован са ароматичним сулфонил-хлоридом, при чему су добијени индолински деривати **11(a–e)**. Финални производи, **6(a–f)** и **11(a–e)** су тестирани на антибактеријску, антитуберкулозну и антигљивичну активност. Неки од синтетизованих деривата су се показали веома активним према одабраним грам-позитивним и грам-негативним микро-ораганизмима, према одређеним сојевима гљива, као и према *Mycobacterium tuberculosis*. Применом *in vitro* DPPH теста испитане су антиоксидативне особине свих синтетизованих индолина, при чему је код већине деривата детектована запажена антиоксидативна активност.

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