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Synthesis and evaluation of some new spiro indoline-based heterocycles as potentially active antimicrobial agents

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Abstract—Several new spiro indoline-based heterocycles were synthesized by prior preparation of the 4-(2′-oxo-indol-3′-ylidene)-oxazol-5-one derivatives and subsequent reaction of the produced indol-3-ylidene based heterocycles with activated nitrile reagents. The obtained products were allowed to react with hydrazine hydrate in alcoholic basic to give the target compounds. Structure of these products was confirmed on the bases of elemental as well as spectral data. Representative compounds of the hitherto synthesized products were tested and evaluated as antimicrobial agents.

1. Introduction

Long time ago, several patents and reports that, deal with pharmacological studies on various heterocyclic systems, have been published. Of these various heterocycles, the indole nucleus has been reported to possess great importance in the field of medicine and biochemistry.[1–5]

On the other hand, pyran nucleus has been found to be associated with a group of biological activities.[6,7] Furthermore, it has been reported that sharing of the indole 3-carbon atom in the formation of spiro indoline derivatives highly enhances biological activity.[8]

Prompted by these findings and the reported[9] importance of reactions of arylidene azolones with activated nitriles to form polycyclic products, we report herein in this thesis about the behavior of 4-(3′-indol-3′-ylidene)-3-substituted 1,2-oxazoline-5-one derivatives **4** toward the same reagents.

2. Results and Discussion

The hitherto synthesized compounds were prepared according to the sequence of reactions that are illustrated in Charts 1–3. Thus, refluxing an ethanolic solution of the previously unreported 1,2-oxazolone derivatives with ethyl cyanoacetate in presence of few drops of piperidine afforded pure colored products in an average good yield. The latter products might be formulated as the intermediate adducts **5a**,**b** or their spiro (3′*H*) indol-3′,4-(4*H*)-pyrano(3,2-*d*)-1,2-oxazole end products **6a**,**b**.

Analytical data of the synthesized compounds indicated a molecular formulae of $C_{17}H_{15}N_3O_5$ and $C_{22}H_{17}N_3O_5$, respectively, which are in accordance with the latter structure **6**. ^{1}H NMR spectrum of compound **6b** revealed no singlet signals in the region of 4.40–4.00 ppm. If the obtained products are the acyclic oxazole derivatives **5**, at least two singlet signals in this range, which corresponds to the activated methine protons, should have been expected to appear for each product in its ^{1}H NMR spectrum. The latter observation confirms the conversion of the intermediate Michael adducts **5a**,**b** into the corresponding spiro end products **6a** and **6b**, respectively.

Reaction of **4a**,**b** with malononitrile in alcoholic basic medium yielded pure yellow-colored products **6c**,**d**. IR spectra of these products exhibited five characteristic absorption bands at 3480–3210, 2220–2200, 1675,

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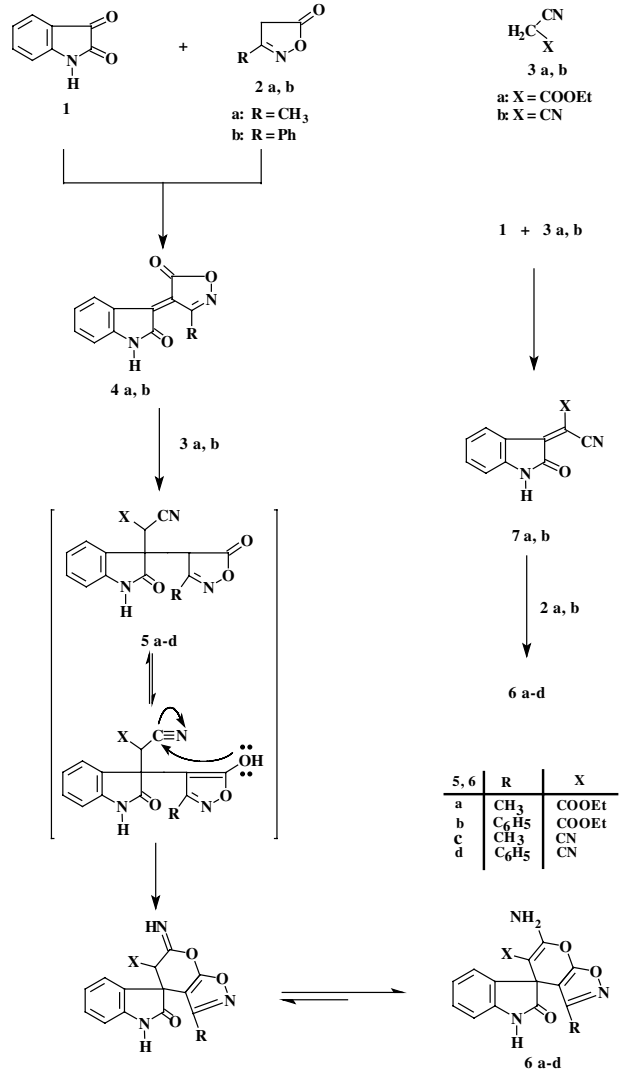

Chart 1.

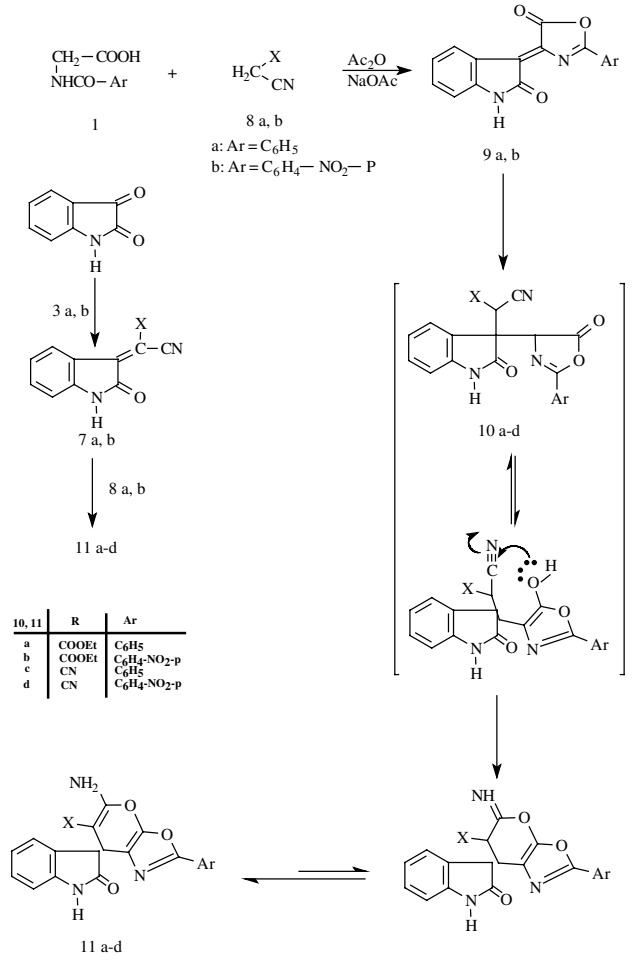

Chart 2.

1625–1620, and 1180 cm^{-1} that correspond to NH_2 and NH, cyano, cyclic secondary amidic, C=N and cyclic ether linkage, respectively. ^1H NMR spectra also revealed the absence of any singlet signals that might correspond to the previously mentioned methine protons.

Besides the normal signals that correspond to the different protons of aromatic and alkyl moieties in ^1H NMR spectrum of compound **6c**, there were appeared two other broad signals at 11.30 and 7.55 ppm that disappeared on adding deuterium oxide. The latter signal might be ascribed to the two exchangeable protons of the amino function. The presence of the latter amino protons signal and the absence of any methine signal in ^1H NMR spectrum of compound **6c** highly substantiate the suggested enamino nitrile structure **6** for this product.

The formation of products **6** from the reaction of **4** with malononitrile or ethyl cyanoacetate is assumed to proceed via addition of the active methylene reagents (Michael donors) to the activated double bond in **4** (Michael acceptors) to yield the intermediate Michael adducts **5**, which then cyclize under the reaction conditions to the isolable end products (Chart 1).

Further confirmation for the suggested structures was obtained from an independent synthesis via prior preparation of the arylidene derivatives **7a**,**b** and subsequent reaction of the latter products with the oxazolone derivatives **2a**,**b** to give the end products **6** in good yield. No depression in melting points was observed on admixing a sample of any of the latter end products with authentic samples that were prepared via the previously mentioned first pathway (Chart 1).

Similarly, 4-(2′-oxo-indol-3′-ylidene)-1,3-oxazol-5-one derivatives **9a**,**b** showed the same behavior, when subjected to react, under similar reaction conditions, with the same reagents. Thus, prior preparation of compounds **9**, by reaction of 2,3-dioxoindole with hippuric acid derivatives **8** and subsequent treatment of the prepared compounds with active nitrile reagents afforded the intermediate Michael adducts **10** that cyclize simultaneously to the spiro (3′*H*)-indol-3′,4-(4*H*) pyrano(3,2-*d*)-1,3-oxazole end products **11a**–**d** (Chart 2).

Besides correct elemental analysis, structure of the hitherto synthesized spiro compounds **11** was confirmed on the basis of spectral data and whenever possible, by

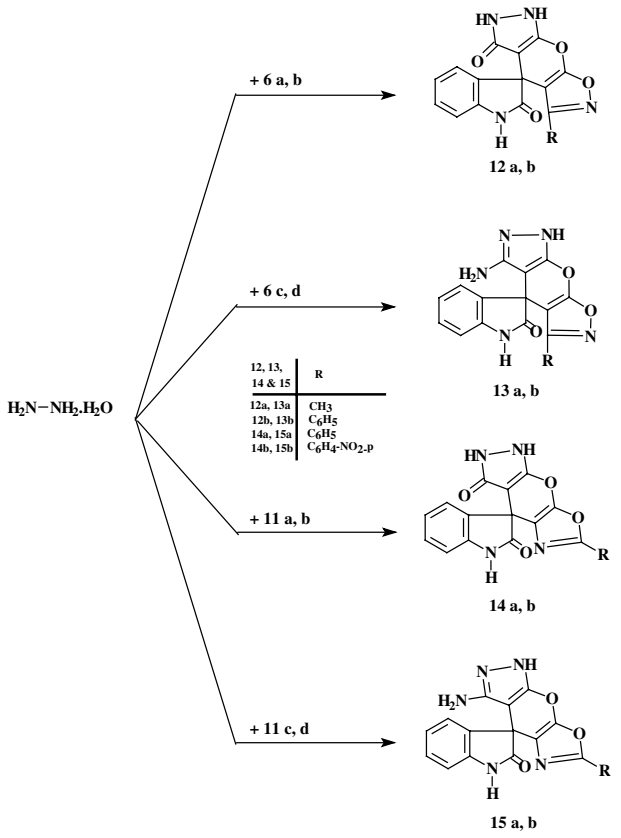

Chart 3.

an independent synthetic pathways. Thus, compounds **11a**,**b** were independently synthesized by refluxing the arylidene derivatives **7a**,**b** with hippuric acid derivatives in acetic anhydride in the presence of a catalytic amount of fused sodium acetate. IR spectrum of compound **11c** showed absorption bands at 3460–3240, 2220, 1675, 1625, and 1180 cm^{-1} that might be ascribed to the amino and NH, cyano, cyclic secondary amidic C=N and pyran ether moieties, respectively.

Besides, the multiplet aromatic signals that appeared in the range of 7.15–6.65 ppm in ^1H NMR of the cyano derivative **11d**, there were appeared, as for compound **6c**, two other exchangeable broad signals that were centered near 10.25 and 7.35 ppm and might be attributed to the cyclic amidic and primary amino protons, respectively.

In this aspect, it is also interesting to mention that the amino signal of structure **6b** is deshielded by 0.50–0.70 ppm as compared to that in compounds **6c** and **11d**. This low field shift is due to the anisotropic effect of the ethoxycarbonyl function in **6b**.

In view of literature reports[11,12] about the reaction of acyclic and cyclic β-enamino esters and β-enamino nitriles with hydrazines and amines to yield Michael adducts, which then undergo further reactions depending on the nature of the reacting enamino ester or nitrile, It seems worthy to investigate and rationalize this behavior on the hitherto prepared enamino nitriles and esters **6** and **11**, respectively.

Thus, reaction of each of products **6** and **11** with hydrazine hydrate in absolute ethanol in presence of few drops of piperidine or triethyl amine yielded a group of spiro indoline-based fused tricyclic products that were formulated as the spiro (3′*H*)-indol-3′,4-(4*H*)pyrazolo-(3,4-*b*)pyrano(3,2-*d*)-1,2-oxazole derivatives **12** and **13** and spiro (3′*H*)-indol-3′,4-(4*H*)pyrazolo-(3,4-*b*)pyrano(3,2-*d*)-1,3-oxazole derivatives **14** and **15**, respectively (Chart 3). Structure of the latter pyrazolo derivatives was established on the basis of correct elemental and spectral data (see Experimental). Besides, the characteristic absorption bands for the cyclic amidic functions in the hitherto prepared indolene-based spiro pyrazolo(3,4-*b*)pyrano(3,2-*d*)oxazole derivatives **12**–**15**, IR spectra of compounds **12** revealed their NH stretching vibrations in the region of 3240–3200 cm^{-1}.

The synthesized spiro tricyclic compounds might exhibit enhanced and/or altered biological activities as a result of the presence of an extended fused pyrazole moiety in their structure.

3. Antimicrobial screening

The antibacterial as well as antifungal activities of a solution of the hitherto synthesized compounds in dimethyl formamide (DMF) were tested and evaluated against some gram positive (*Bacillus subtilis* and *Bacillus megatherium*, gram negative (*Escherichia coli*) and fungi (*Aspergillus niger* and *Aspergillus oryzae*) and compared with respect to some reference antibiotics that were purchased from Egyptian market. The obtained results (Table 4) revealed that while most of the prepared spiro 3*H*-indole-3,4′-pyrano(3′,2′-*d*)oxazole derivatives (**6a**–**d** and **11a**–**d**) showed comparable activity, the spiro 3*H*-indole-3,4′-pyrazolo(3′,4′-*b*)pyrano(3′,2′-*d*)oxazole derivatives (**12a**,**b**, **13a**,**b**, **14a**,**b**, and **15a**,**b**) revealed very high activity with respect to the used references. On the other hand, nearly all of the prepared compounds exhibited an interesting high antifungal activity against the reference chemotherapeutics.

4. Experimental

The homogeneity and purity of the prepared compounds were checked by TLC. Melting points are uncorrected and measured on a Fisher–Johns apparatus. Recorded yields correspond to the pure products. IR (KBr) spectra were recorded on a Perkin Elmer SP-880 spectrophotometer and ^1H NMR spectra were measured on a Varian 270 MHz spectrometer using $CDCl_3$ solvent and tetramethylsilane (TMS) as in internal standard (chemical shifts are given as in ppm). Microanalyses were carried out in the Microanalytical data unit in Cairo and at University of Mansoura. Nomenclature of the hitherto prepared compounds is given in accordance with IUPAC rules for nomenclature of organic compounds.

Table 1. Physical and spectral data of the newly synthesized compounds (**4a**,**b**) and (**6a–d**)

Compd no.	Mp (°C) yield (%)	Molecular formula (M. wt.)	% Analysis Calcd/(Found)			IR (v, cm^{-1}) and ^1H NMR ($CDCl_3$, ppm)
			C	H	N	
4a	205 (70)	$C_{12}H_8N_2O_3$ (228.22)	63.15 (63.26)	3.54 (3.32)	12.2 (12.39)	IR: 3210 (NH), 1695 (C=O), 1680 (*sec*-amidic C=O), 1630 (C=N)
4b	245 (75)	$C_{17}H_{10}N_2O_3$ (290.29)	70.33 (70.23)	3.48 (3.37)	9.65 (9.56)	IR: 3200 (NH), 1695 (C=O), 1680 (*sec*-amidic C=O), 1625 (C=N)
6a	230 (70)	$C_{17}H_{15}N_3O_5$ (341.35)	59.81 (59.73)	4.44 (4.67)	12.31 (12.51)	IR: 3460 (NH_2), 3240 (NH), 1725 ($COOC_2H_5$), 1680 (*sec*-amidic C=O), 1625 (C=N), 1175 (ether linkage of pyran moiety)
6b	265 (80)	$C_{22}H_{17}N_3O_5$ (403.42)	65.50 (65.33)	4.26 (4.16)	10.42 (10.33)	IR: 3480 (NH_2), 3220 (NH), 1725 ($COOC_2H_5$), 1680 (*sec*-amidic C=O), 1620 (C=N), 1175 (ether linkage of pyran moiety). H NMR: 11.35 (br, 1H, amidic N*H*, ex.), 8.05 (br, 2H, NH_2, ex.), 7.45-6.90 (m, 9H, Ar–H) 4.15 (q, 2H, CH_2–CH_3), 1.10 (t, 3H, CH_2–CH_3)
6c	250 (80)	$C_{15}H_{10}N_4O_3$ (294.29)	61.22 (61.09)	3.43 (3.55)	19.04 (18.86)	IR: 3460 (NH_2), 3210 (NH),2200 (C≡N), 1675 (*sec*-amidic C=O), 1625 (C=N) 1180 (ether linkage of pyran moiety) H NMR: 11.30 (br, 1H, amidic N*H*), 7.55 (br, 2H, NH_2, ex.) 7.35-6.95 (m, 4H, Ar–H), 0.95 (s, 3H, oxazolyl CH_3 protons)
6d	281 (75)	$C_{20}H_{12}N_4O_3$ (356.36)	67.40 (67.33)	3.40 (3.28)	15.73 (15.64)	IR: 3480 (NH_2), 3240 (NH), 2220 (C≡N), 1675 (*sec*-amidic C=O), 1620 (C=N),1180 (ether linkage of pyran moiety)

4.1. Synthesis of 4-(2′-oxo-indol-3′-ylidene)-1,2-oxazol-5-one derivatives (4a,b)

A mixture of isatin (10 mmol) and 3-substituted isoxazolone derivatives **2a**,**b** (10 mmol in each case) in absolute ethanol (20 mL) containing 3 drops of piperidine was refluxed for 6 h. The solid that separated was filtered off and recrystallized from ethanol to give pure orange to red products **4a**,**b** (cf. Table 1).

4.2. Synthesis of 6-amino spiro [3′*H*-indol-3′,4-(4*H*)-pyrano (3,2-*d*)-1,2-oxazol] (1′*H*)-2′-one derivatives (6a–d)

To a solution of **4a**,**b** (10 mmol in each case) in absolute ethanol (20 mL) containing 3 drops of piperidine, ethyl cyanoacetate **3a** or malono nitrile **3b** (10 mmol in each case) was added and the whole reaction mixture was refluxed for 6 h, Following up the reaction as in 4.1 gave pure pale to deep red products **6a**–**d** (cf. Table 1).

4.3. Synthesis of 2-oxo-(3*H*)-indol-3-ylidene malononitrile and 2-oxo-(3*H*)-indol-3-ylidene ethyl cyanoacetate (7a,b)

To a solution of isatin (10 mmol) in absolute ethanol (20 mL) containing 3 drops of piperidine, ethyl cyanoacetate **3a** or malononitrile **3b** (10 mmol in each case) was added. The reaction mixture was heated for 5 min, then left to cool. Following up the reaction as in 4.1 gave pure pale to deep red products **7a**,**b.**

4.4. Alternative synthetic route for preparation of compounds 6a–d

A mixture of **2a**,**b** (10 mmol in each case) and **7a**,**b**[10] (10 mmol in each case) in absolute ethanol (20 mL) containing 3 drops of piperidine, was refluxed for 6 h, then left to cool. Following up the reaction as in 4.1 gave pure, pale to deep red products **6a**–**d** (cf. Table 1).

4.5. Synthesis of 4-(2′-oxo-indol-3′-ylidene)-1,3-oxazol-5-one derivatives (9a,b)

A mixture of isatin (10 mmol) and hippuric acid derivatives **8a**,**b** (10 mmol in each case) in acetic acid anhydride (15 mL) containing fused sodium acetate (1 g) was refluxed in water bath for 3 h, then left to cool. Ethanol (15 mL) was added to the mixture and left it overnight. Following up the reaction as in 4.1 yielded pure gray to black products **9a**,**b** (cf. Table 2).

4.6. Synthesis of 6-amino spiro [3′*H*-indol-3′,4-(4*H*)-pyrano(3,2-*d*)-1,3-oxazol] (1′H)-2′-one derivatives (11a–d)

To a suspension of **9a**,**b** (10 mmol in each case) in absolute ethanol (20 mL) containing 3 drops of piperidine, **3a**,**b** (10 mmol in each case) was added. After refluxing for 4 h, the reaction mixture was poured onto ice water and the resulting precipitate filtered off. Recrystallization of the latter crude product, from methanol, afforded pure orange to brown products (cf. Table 2).

4.7. Alternative synthetic route for preparation of compounds 11a–d

A mixture of **8a**,**b** (5 mmol in each case) and fused sodium acetate (0.3 g) in acetic anhydride (10 mL) was refluxed in water bath for 40 min. Then **7a**,**b** (5 mmol in each case) was added to the reaction mixture and ref-

Table 2. Physical and spectral data of the newly synthesized compounds (**9a**,**b**) and (**11a**–**d**)

Compd no.	Mp (°C), yield (%)	Molecular formula (M. wt.)	% Analysis calcd/(found)			IR (ν, cm^{-1}) and ^1H NMR ($CDCl_3$, δ/ppm)
			C	H	N	
9a	160 (90)	$C_{17}H_{10}N_2O_3$ (290.29)	70.33 (70.45)	3.48 (3.52)	9.65 (9.69)	IR: 3210 (NH), 1695 (C=O), 1680 (*sec*-amidic C=O), 1620 (C=N)
9b	80 (220)	$C_{17}H_9N_3O_5$ (335.29)	60.89 (60.73)	2.71 (2.89)	12.54 (12.62)	IR: 3200 (NH), 1695 (C=O), 1680 (*sec*-amidic C=O), 1625 (C=N)
11a	195 (70)	$C_{22}H_{17}N_3O_5$ (403.42)	65.50 (65.35)	4.26 (4.33)	10.42 (10.53)	IR: 3450 (NH_2), 3220 (NH), 1720 ($COOC_2H_5$), 1680 (*sec*-amidic C=O) 1620 (C=N), 1170 (ether linkage of pyran moiety)
11b	220 (80)	$C_{22}H_{16}N_4O_7$ (448.42)	58.92 (58.80)	3.60 (3.71)	12.50 (12.55)	IR: 3470 (NH_2), 3210 (NH), 1725 ($COOC_2H_5$), 1680 (*sec*-amidic C=O), 1625 C=N), 1170 (ether linkage of pyran moiety)
11c	230 (85)	$C_{20}H_{12}N_4O_3$ (356.36)	67.40 (67.64)	3.40 (3.21)	15.73 (15.84)	IR: 3460 (NH_2), 3240 (NH), 2220 (C≡N), 1675 (*sec*-amidic C=O), 1625 (C=N), 1180 (ether linkage of pyran moiety)
11d	258 (80)	$C_{20}H_{11}N_5O_5$ (401.36)	59.85 (59.71)	2.77 (2.68)	17.45 (17.52)	IR: 3480 (NH_2), 3200 (NH), 2220 (C≡N), 1675 (*sec*-amidic C=O), 1620 (C=N), 1180 (ether linkage of pyran moiety) H NMR: 10.25 (br, 1H, amidic N*H*, ex.), 7.35 (br, 2H, NH_2, ex.), 7.15-6.65 (m, 8H, Ar–H)

luxed for 6 h, then left to cool. Ethanol (15 mL) was added to the mixture and poured onto ice water. The resulting precipitate filtered off and recrystallized from ethanol to give pure orange to brown products **11a**–**d** (cf. Table 2).

4.8. Synthesis of spiro [(3*H*)-indol-3,4′-(4′*H*)-pyrazolo-(3,4-*b*)pyrano(3,2-*d*)-1′,2′-oxazol] 2-(1*H*)-one derivatives (12, 13)

Using a solution of **6a**–**d** (10 mmol in each case) and hydrazine hydrate (10 mmol) and following up the reaction conditions as in 4.1, pure yellow to brown products **12a**,**b** and **13a**,**b** were obtained (cf. Table 3).

4.9. Synthesis of spiro [(3*H*)-indol-3,4′-(4′*H*)-pyrazolo-(3,4-*b*)pyrano(3,2-*d*)-1′,3′-oxazol]2-(1*H*)-one derivatives (14 and 15)

The reactants, **11a**–**d** (10 mmol in each case) and hydrazine hydrate (10 mmol), were mixed as described above. Following up the reaction yielded pure gray to black products **14a**,**b** and **15a**,**b** (cf. Table 3).

Table 3. Physical and spectral data of the newly synthesized compounds (**12a**,**b**), (**13a**,**b**), (**14a**,**b**) and (**15a**,**b**)

Compd no.	Mp (°C), yield (%)	Molecular formula (M. wt.)	% Analysis calcd/(found)			IR (ν, cm^{-1}) and ^1H NMR ($CDCl_3$, δ/ppm)
			C	H	N	
12a	>300 (65)	$C_{15}H_{10}N_4O_4$ (310.29)	58.06 (58.31)	3.26 (3.42)	18.06 (18.07)	IR: 3220 (NH), 1675 (*sec*-amidic C=O), 1620 (C=N), 1180 (ether linkage of pyran moiety)
12b	>300 (70)	$C_{20}H_{12}N_4O_4$ (372.36)	64.51 (64.40)	3.26 (3.41)	15.05 (14.98)	IR: 3200 (NH), 1680 (*sec*-amidic C=O), 1625 (C=N), 1170 (ether linkage of pyran moiety)
13a	>300 (75)	$C_{15}H_{11}N_5O_3$ (309.31)	58.24 (58.41)	3.59 (3.72)	22.65 (22.66)	IR: 3460 (NH_2), 3210 (NH),1675 (*sec*-amidic C=O), 1625 (C=N), 1175 (ether linkage of pyran moiety)
13b	>300 (80)	$C_{20}H_{13}N_5O_3$ (371.38)	64.68 (64.51)	3.54 (3.62)	18.86 (18.95)	IR: 3480 (NH2), 3220 (NH),1680 (*sec*-amidic C=O), 1620 (C=N), 1185 (ether linkage of pyran moiety)
14a	>300 (65)	$C_{20}H_{12}N_4O_4$ (372.36)	64.51 (64.63)	3.26 (3.58)	15.05 (14.93)	IR: 3220 (NH), 1675 (*sec*-amidic C=O), 1625 (C=N), 1180 (ether linkage of pyran moiety)
14b	>300 (75)	$C_{20}H_{11}N_5O_6$ (417.36)	57.55 (57.46)	2.66 (2.80)	16.78 (16.85)	IR: 3240(NH),1680 (*sec*-amidic C=O), 1620(C=N), 1180 (ether linkage of pyran moiety)
15a	>300 (70)	$C_{20}H_{13}N_5O_3$ (371.38)	64.68 (64.63)	3.54 (3.36)	18.86 (18.90)	IR: 3465 (NH_2), 3220 (NH),1680 (*sec*-amidic C=O), 1625 (C=N), 1185 (ether linkage of pyran moiety)
15b	>300 (75)	$C_{20}H_{12}N_6O_5$ (416.38)	57.69 (57.81)	2.91 (2.83)	20.19 (20.28)	IR: 3480 (NH_2), 3200 (NH),1675 (*sec*-amidic C=O), 1625 (C=N), 1180 (ether linkage of pyran moiety)

Table 4. Inhibition zone (mean diameter of inhibition in mm) as a criterion of antibacterial and antifungal activities of the newly synthesized spiro indoline-based heterocycles

Compound number	Inhibition zone in mm				
	Bacteria			Fungi	
	Gram positive bacteria		Gram negative bacteria		
	S. subtilis	*B. megatherium*	*E. coli*	*A. niger*	*A. oryzae*
6a	66	55	—	63	71
6b	42	43	—	58	69
6c	35	40	30	66	78
6d	34	34	25	75	74
11a	42	35	—	69	73
11b	—	60	40	72	75
11c	56	63	—	77	79
11d	—	—	—	81	84
12a	65	69	54	85	88
12b	75	65	59	70	80
13a	85	76	60	77	79
13b	81	72	58	84	89
14a	87	86	45	80	86
14b	84	85	40	79	82
15a	76	75	49	90	92
15b	85	70	35	79	86
DMF	18	—	15	11	—
Reference drugs					
Ampicillin	41	29	26	33	—
Chloramphenicol	28	55	48	35	—
Fluconazle	—	—	—	22	16

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