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Full Length Research Paper

Synthesis of Some Indole Derivatives of Antibactericidal Properties

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In this paper, the synthesis of heterylindoles, some selected derivatives have been evaluated for their antibacterial activities. The chemical structure activity relationship was also discussed.

Keywords: Heterylindole synthesis, Antibacterial activity

INTRODUCTION

The importance of indole nucleus (Sridar, 1997; Baudin *et al*., 1996), is well documented in the field of pharmaceutical chemistry as well as in plant and animal biochemistry (Joshi and Chand, 1982). It is reported that some indole derivatives were used as coupling agents in oxidative hair dyes (Junino *et al*., 1990; Gotten, 1992) and other applications (Balon *et al*., 1993; Ghanem *et al*., 1996; Adam and Reinhardt, 1994; Adam *et al*., 1993) (Adam *et al*., 1994; Culton *et al*., 1997; Biswas *et al*., 1991). Based on these findings and in continuation to our work directed towards the synthesis of heterylindoles (Mithani *et al*., 1997; Bhuyan *et al*., 1997) (Elgemeie *et al*., 1997), some selected derivatives have been evaluated for their antibacterial activities (El-Bahnasway, 2002). The chemical structure activity relationship was also discussed (Hiremath *et al*., 1998; Shrimali *et al*., 1989; Von Angeret *et al*., 1985).

3-(2,3-Diphenyl-5-melhoxyindole-6-yl)-1-phenyl-1-propen-3-one(**1**) and l-(2,3-diphenyl-5-methoxyindol-6-yl)-l ,3-butanedione (**10**) (El-Bahnasway, 2002), were selected as reaction intermediates in the synthesis of some new substituted heterylindoles. Thus compound **1** could be reacted with *o*-phenylene-di-amine in ethanol/piperidine or dry HC1 gas/AcOH to produce indolyl ben-zodiazepine derivatives **2** and **3**, respectively. In the same manner compound 1 could be reacted with phenylhydrazine to afford indolyl pyrazole derivatives **5** and **6**, respectively. Compound **1** on reacted with hydroxylamine hydrochloride, cyanoacetyl hydrazine, thiourea and/or 3-amino-4-bromo-5-phenylpyrazole produce indolyl isoxazole derivative (**4**), indolylpyrazole derivative (**7**), indolylpyrimidine derivative (**8**) and/or indolylpyrazolo (l,5-b) pyrimidine derivative (**9**), respectively **(Scheme-l).**

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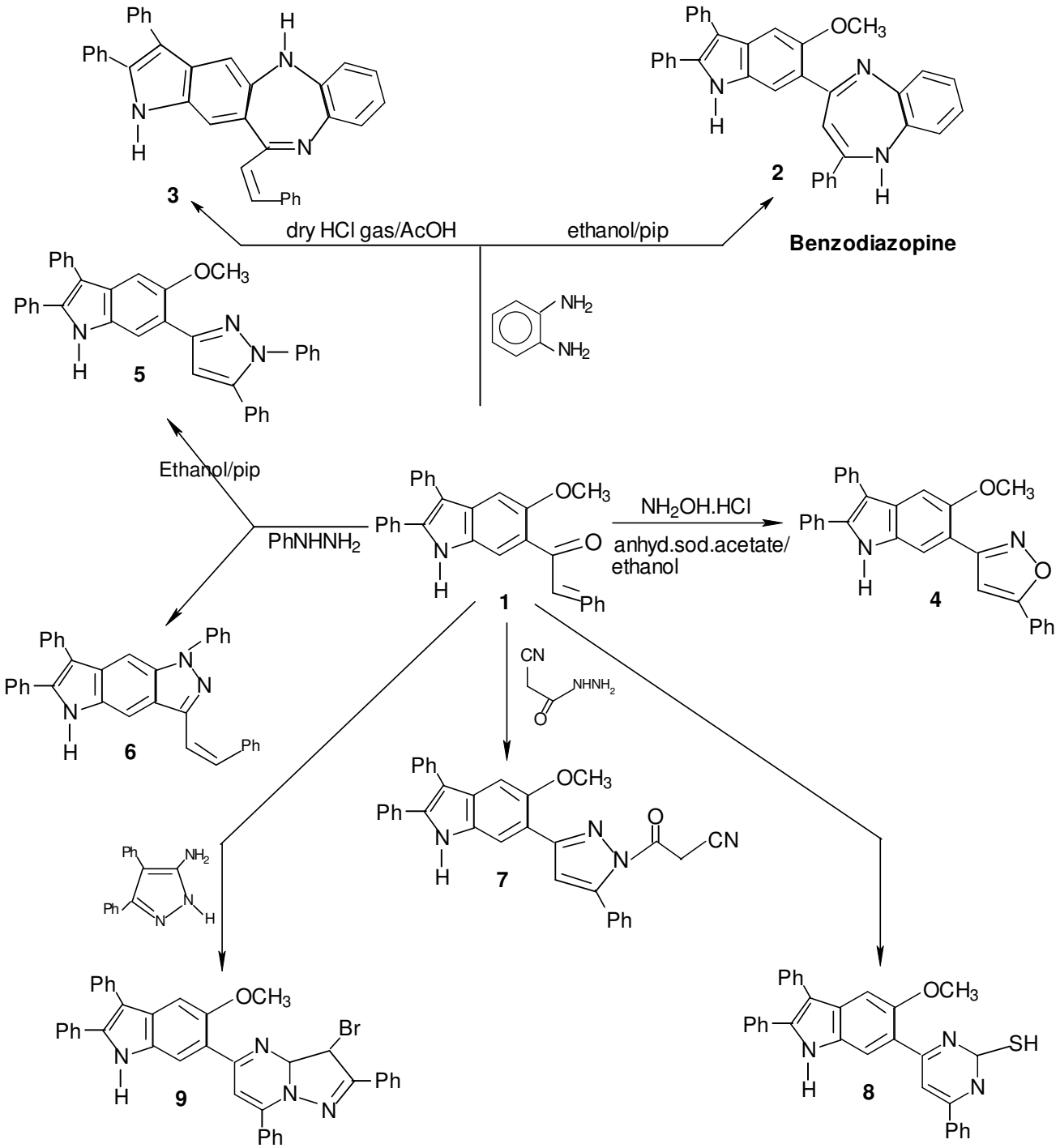
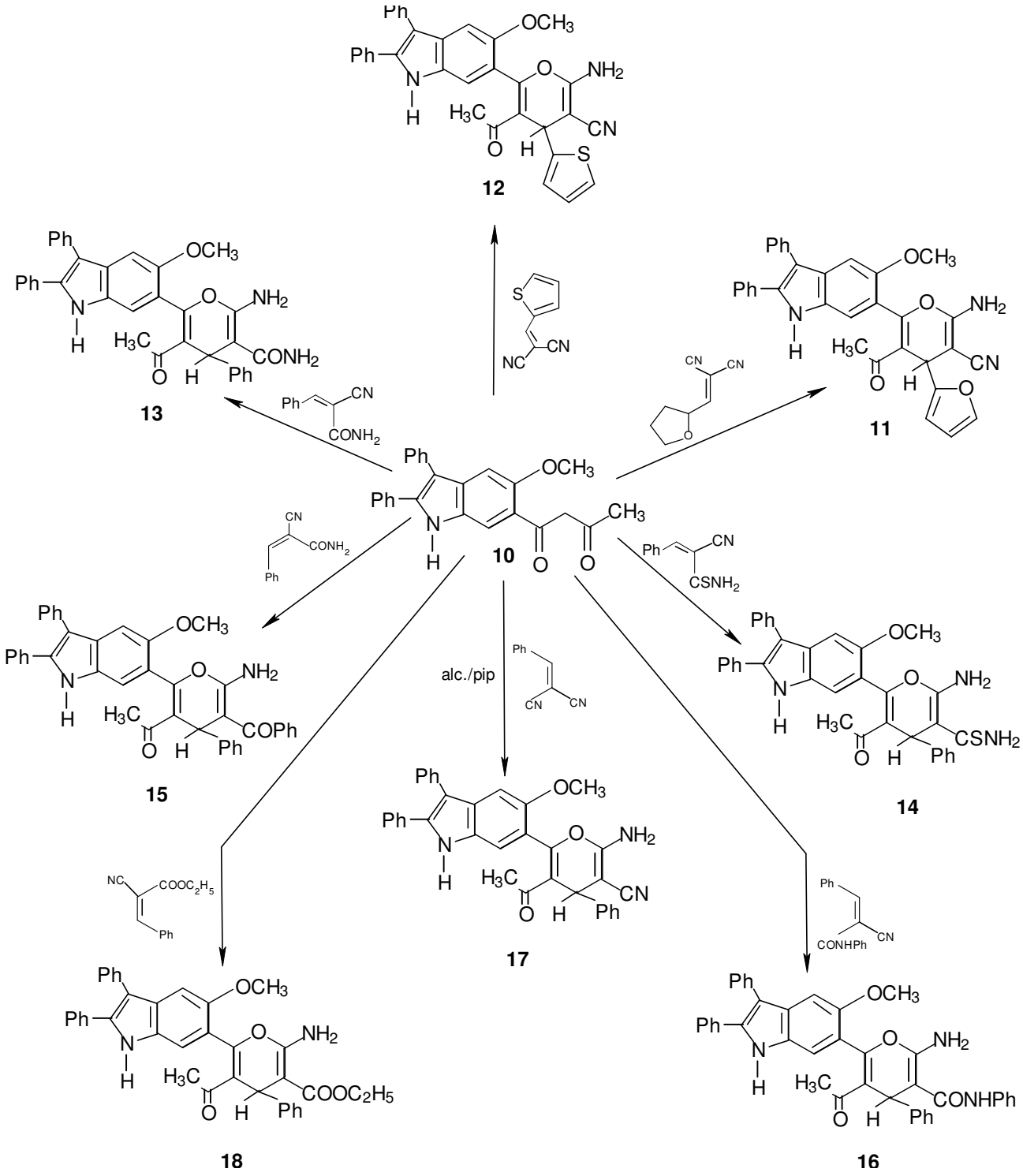


Scheme-I

On the other hand compound **10** could be reacted with α,β-unsaturated nitriles such as furfurylidene malononitrile, thiophenylidene malononitrile, α-amidocinnamonitrile, α-thioamidocinnamonitrile, α-benzoylcinn-amonitrile, α-benzamidocinnamonitrile, α-cyanocinnamonitrile and/or ethyl α-cyanocinnamate to afford indolylpyrane derivatives **11-18,** respectively **(Scheme-II).**



Scheme-II

EXPERIMENTAL

Melting points unconnected were determined on a Gallen Kampo melting point apparatus, IR spectra were recorded in KBr using a Shimadzu spectra 200-9156 spectrophotometer, ^{1}H NMR in DMDO as a solvent on Varian 90 MHz using TMS as the internal reference. Elemental analyses were carried out in the Micro analysis unit, Cairo University, Giza, Egypt.

Synthesis of 3-(2,3-diphenyl-5-methoxyindol-6-yl)-l-phenyl-l-propen-3-one (1): To a solution of 6-acetyl-2,3-diphenyl-5-methoxyindole (0.01 mol) in ethylene glycol (2 mL) was added benzaldehyde (0.01 mol), then KOH 40% (0.1 mL) and the reaction mixture was heated in an oil bath (120-135°C) for 0.5h. The reaction mixture was left to cool and neutralized by acetic acid. The solid that separated was filtered off and recrystallized from the appropriate solvent.

Preparation of 2,3-diphenyl-5-methoxy-6-(lH-2-phenylbenzo-diazopin -4-yl)indol (2): A mixture of compound 1 (0.01 mol) and *o*-phenylenediamine (0.01 mol) in ethanol (25mL) containing piperidine (0.5 mL) was refluxed for 3h. The reaction mixture was then cooled and poured into ice-HCl mixture. The solid formed was collected by filtration and recrystallized from the proper solvent.

Preparation of indolo (5,6-b) benzodiazepine derivative (3): To a suspension of compound 1 (0.01 mol) with acetic acid (10 mL), an equivalent amount of HC1 gas was passed with stirring over 1 h. The reaction mixture was then poured into an petroleum ether 60:80 and the solid formed was collected by filtration and washed with sodium bicarbonate solution and recrystallized from the proper solvent.

Reaction of compound 1 with hydroxylamine hydrochloride (4): A mixture of compound 1 (0.01 mol) and hydroxylamine HC1 (0.01 mol) in absolute ethanol (25 mL) containing anhydrous sodium acetate (0.5 g) was refluxed 4 h. The reaction mixture was then cooled and poured into ice/HCl mixture. The solid formed was collected by filtration and recrystallized from the appropriate solvent to afford 2,3-diphenyl-5-methoxy-6-(4H-5-phenyl-isoxazol-3-yl)indole**(4).**

Preparation of 2,3-diphenyl-5-methoxy-6-(l,5-diphenylpyrazol-3-yl)-indole (5): A mixture of compound 1 (0.01 mol) and phenylhydrazine (0.01 mol) in ethanol (25 mL) containing piperidine (0.5 mL) was refluxed for 3 h. The reaction mixture was then cooled and poured into ice-HCl mixture. The solid formed was collected by filtration and recrystallized from the appropriate solvent.

Preparation of indolo(3,4-b)pyrazole deriva (6): To a solution of compound 1 (0.01 mol) with acetic acid (10 mL), an equivalent amount of HC1 gas was passed with stirring for 1 h. The reaction mixture was then poured into an petroleum ether 60:80 and the solid formed was collected by filtration and washed with sodium bicarbonate solution and recrystallized from the appropriate solvent.

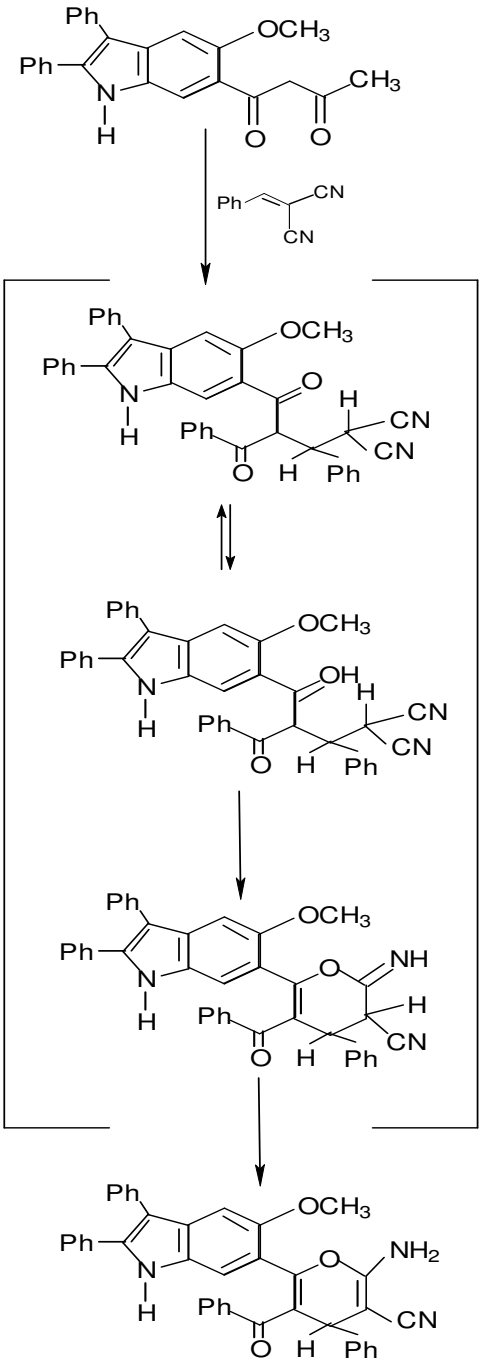
Preparation of 2,3-diphenyl-5-methoxy-6-(l-cyanoacetyl-4H-5-phenyl-pyrazol-3-yl) indole (7): A mixture of compound 1 (0.01 mol) and cyanoacetyl hydrazide (0.01 mol) and ethanol (25 mL) containing piperidne (0.5 mL) was refluxed for 3 h. The reaction mixture was then cooled and poured into ice-HCl mixture. The solid formed was collected by filtration and recrystallized from the appropriate solvent.

Preparation of 2,3-diphenyl-5-methoxy-6-(2-mercapto-4-phenyl-5H-pyrimidin-6-yl) indole (8): To a solution of compound 1 (0.01 mol) and thiourea (0.01 mol) in ethanol (25 mL) containing piperidine (0.5 mL) was refluxed for 3 h. The reaction mixture was then cooled and poured into ice-HCl mixture. The sodium formed was collected by filtration and recrystallized from the appropriate solvent.

Preparation of 2,3-diphenyl-5-methoxy-6(3,8-diphenyl-4-bromo-7H-pyrazolo(l,5-b)pyrimidin-6-yl) indole (9): A solution of compound 1 (0.01 rnol) and aminopyrazole derivative (0.01 mol) in ethanol (25 mL) containing piperidine (0.5 mL) was refluxed for 3 h. The reaction mixture was then cooled and poured into ice-HCl mixture. The solid formed was collected by filtration and recrystallized from the appropriate solvent.

Preparation of l-(2,3-diphenyl-5-methoxyindol-6-yl)-l,3-butanedione (10): A solution of 6-acetyl-2,3-diphenyl-5-methoxyindole (0.01 mol) in ethyl acetate (50 mL) was added slowly to powdered sodium metal (4 g), when the initial vigorous reaction subsided the reaction mixture was refluxed for 5 h and then left to cool. Menthol (5 mL) was added to destroy any excess of sodium metal. The reaction mixture was diluted with water, then acidified with acetic acid and the solid separated was filtered off, recrystallized from ethanol.

Preparation of indolylpyranes derivatives (11-18): A mixture of compound 10 (0.01 mol) and $\alpha.\beta$-unsaturated nitriles such as furfurylidene malononitrile, thiophenylidenemalonontrile, α-amido-cinnamonitrile. α-thioamido cinnamonitrile, α-benzoylcinnamonitrile, α-benzamido cinnamonitrile, α-cyanocinnamonitrile, and/or ethyl α-cyanocinnamate (0.01 mol) in ethanol (25 mL) containing piperidine (0.5 mL) was refluxed for 3 h. The reaction mixture was then cooled and poured into ice/HCl mixture. The solid formed was collected by filtration and crystallized from the proper solvent afforded indolylpyranes derivatives **11-18,** respectively **(Scheme-III).**



Scheme-III

RESULTS AND DISCUSSION

The physical and spectral data of the synthesized compounds have been tabulated in Tables 1 and 2. 6-Acetyl-2,3-diphenyl-5-methoxyindole was prepared[16]. **It** has been found that compound **1** could be reacted with *o*-phenylenediamine and/or phenylhydrazine in ethanol/piperidine and/or dry HC1 gas/AcOH to produce indolyl benzodiazopine derivatives **2,3** and indolylpyrazole derivatives **5,6,** respectively. On the other hand compound **1** could be reacted with hydroxylamine. Hydrochloride in absolute ethanol and in the presence of anhydrous sodium acetate to afford indoly) isoxazole derivative **4**. Also compound **1** could be reacted with cyanoacetylhydrazine, thiourea and/or aminopyrazole derivative in ethanol/piperidine, afforded indolyl pyrazole derivatives **7**, indolyl pyrimidine derivative **8** and/or indolyl pyrazolo(l,5-b)pyrimidine derivative **9**, respectively.

Table 1. Physical data of the newly synthesized compounds

Comp No.	m.f. (m.w.)	Cryst. solvent	m.p. (°C)	Yield (%)	%Analysis Calcd. (Found)				
					C	H	N	S	Br
1	$C_{40}H_{23}NO_2$ (549.59)	Ethanol	>300	74	87.41 (87.24)	4.22 (4.37)	2.55 (2.62)	- -	- -
2	$C_{36}H_{27}N_3O$ (518.51)	Methanol/ Acetone	263	68	83.39 (83.61)	5.25 (5.28)	9.11 (7.95)	- -	- -
3	$C_{35}H_{25}N_3$ (487.38)	Methanol/ Acetone	263	68	86.25 (86.41)	5.13 (5.28)	8.62 (8.53)	- -	- -
4	$C_{30}H_{22}N_2O_2$ (442.50)	Ethanol	248	71	81.42 (81.61)	5.01 (5.12)	6.33 (6.24)	- -	- -
5	$C_{36}H_{27}N_30$ (517.61)	Ethanol	274	69	83.53 (83.41)	5.26 (5.32)	8.12 (8.23)	- -	- -
6	$C_{35}H_{25}N_3$ (487.38)	Methanol/ Acetone	263	68	86.25 (86.41)	5.13 (5.28)	8.62 (8.53)	- -	- -
7	$C_{13}H_{24}N_40_2$ (508.56)	Ethanol	256	76	77.93 (77.81)	4.76 (4.82)	11.11 (10.98)	- -	- -
8	$C_{30}H_{23}N_3OS$ (485.58)	Ethanol/ Acetone	209	65	76.67 (76.84)	4.77 (4.63)	8.65 (8.72)	6.60 (6.68)	- -
9	$C_{39}H_{27}N_4OBr$ (627.55)	Ethanol	>300	63	72.33 (73.14)	4.20 (4.17)	8.65 (8.57)	- -	12.34 (12.46)
10	$C_{25}H_{2I}NO_3$ (383.43)	Ethanol	215	70	78.31 (78.18)	5.52 (5.63)	3.65 (3.71)	- -	- -
11	$C_{33}H_{25}N_3O_4$ (527.56)	Ethanol	237	81	75.13 (76.24)	4.78 (4.71)	7.97 (7.90)	- -	- -
12	$C_{33}H_{25}N_3O_3S$ (543.62)	Ethanol	242	74	72.91 (74.21)	4.64 (4.57)	7.73 (7.81)	5.90 (5.84)	- -
13	$C_{35}H_{29}N_3O_4$ (555.61)	Methanol/ Acetone	256	63	75.66 (74.21)	5.26 (5.33)	7.56 (7.62)	- -	- -
14	$C_{35}H_{29}N_3O_3S$ (571.67)	Ethanol	263	68	73.53 (74.62)	5.11 (5.22)	7.35 (7.31)	5.61 (5.70)	- -
15	$C_{4I}H_{32}N_2O_4$ (616.75)	Ethanol	>300	81	79.85 (80.12)	5.23 (5.18)	4.54 (4.60)	- -	- -
16	$C_{4I}H_{33}N_3O_4$ (629.77)	Ethanol/ Acetone	>300	68	78.19 (78.32)	5.28 (5.21)	6.67 (6.71)	- -	- -
17	$C_{35,}H_{27}N_{33}$ (537.60)	Ethanol	271	72	78.20 (79.14)	5.10 (5.18)	7.82 (7.76)	- -	- -
18	$C_{37}H_{32}N_20$, (584.65)	Ethanol	291	74	76.01 (77.23)	5.52 (5.43)	4.80 (4.93)	- -	- -

On the other hand, it has been reported that α,β-unsaturated nitriles were used as a key intermediate for the synthesis of different heterocyclic compounds; therefore 1-(2,3-diphenyl-5-methoxyindol-6-yl)-1,3-butanedione **(10),** could be reacted with different types of α,β-unsaturated nitriles such as furfurylidene malononitrile, thiophenylidene malononitrile, α-amidocinnamonitrile, α-thioamidocinnamonitrile, α-benzoyl cinnamo-ntrile, α-benzoamido cinnamonitrile, α-cyanocinnamonitrile and/or ethyl α-cyanocnnamate in ethanol/piperidine through reactions such as Michael type addition reaction afforded indolyl pyran derivatives **11-18**, respectively.

Table 2. Spectral data of the newly synthesized compounds

Compd. No	IR (V_{max} Cm^{-1})	^1H NMR (δ ppm)
1	1158, 1191(C-O-C), 1705-1657 (conj. C=O), 3450 (NH), 697 (Ph-mono subst.)	3.5 (s, 3H, OCH_3), 6.5 (d, 2H, CH=CH), 8.7 (m, 2H, aromatic) and 7.2-8.5 (m, 16H, 3Ph, NH)
3	1158, 1191(C-O-C), 750-700 (Ar-mono), 3229 (NH indolyl), 3420 (NH diazopinyl)	6.5 (d, 2H, CH=CH), 7.2-8.4 (m, 16H, 3Ph, NH), 8.8 (m, 6H, aromatic) and 9.2 [br.(s), 1H, NH]
6	750-700 (Ar-mono), 1350 (C=N), 1610-1580 (C=C Conj.), 3230 (NH indolyl)	6.6 (d, 2H, CH=CH), 7.2-8.3 (m, 21H, 4Ph, NH) and 8.7 (m, 2H, aromatic)
7	1360(C=N), 1680(C=O), 2220 (C≡N) and 3235 (NH indolyl)	3.98 (s, 3H, OCH_3), 4.3 (s, 2H, CH_2), 7.2-8.3 (m, 16H, 3Ph, 1NH), 8.8 (m, 2H, aromatic) and 9.1 (s, 1H, pyrazolyl)
10	1158, 1190(C-O-C), 1720 (C=O), 3270 (NH indolyl)	2.6 (s, 3H, CH_3), 2.8 (s, 2H, CH_2), 3.6 (s, 3H, OCH_3), 7.4-8.1 (m, 11H, 2Ph, 1NH) and 8.5 (m, 2H, aromatic)
16	1158, 1190(C-O-C), 1690 (CONH), 3200-3000 (NH_2)	-
18	1158, 1190 (C-O-C), 1670 (C=O), 1730 (ester group) and 3260 (NH indolyl)	1.27 (t, 3H, CH_2CH_3), 2.9 (s, 3H, $COCH_3$), 3.95 (s, 3H, OCH_3), 4.3 (q, 2H, CH_2CH_3), 4.9 (broad, 2H, NH_2), 6.9 (s, 1H, pyran proton), 7.2-8.4 (m, 16H, 3Ph, 1NH) and 8.7 (m, 2H, aromatic)

Heterylindole structure-biological activity relationship

The biological activity obtained of some selected synthesized 6-ibstituted (heteryl)indoles (**1, 2, 4, 5, 6, 7, 9, 10** and **18**) especially against bacterial strains *(Staph, Bacciluus subt., E. coli, Pseudomnous, Salmonella* and *Erowenia)* (Table-3).

Biological activity depends mainly upon both type of substituting group in position 6 of 2,3-diphenyl-5-methoxyindole and the type of bacterial strain used. The bacterial strains used exhibited biological activity range (1.080-1.404 dm^3). Inserting an acetyl group causes an increase in the antibacterial (inhibition) range as well as acetoacetyl group at 6-position. It was obvious that the antibacterial (inhibition) range is largely affected by the changing of 6-heteryl moieties.

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