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Synthesis of some heterocyclic compounds derived from indole as antimicrobial agents

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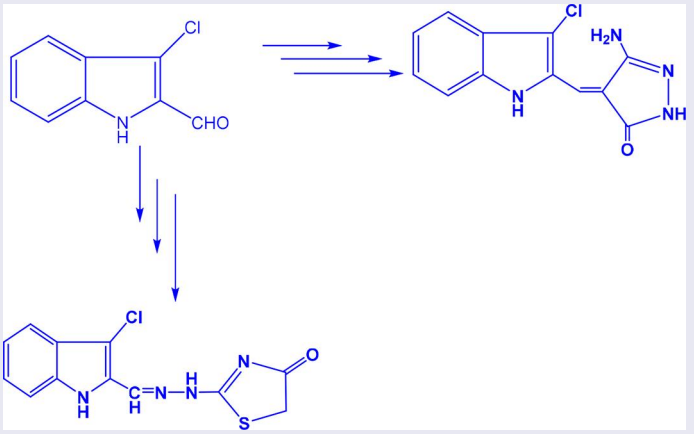
ABSTRACT

Recently, indoles are considered interesting heterocyclic compounds due to their wide range of biological activities such as antimicrobial activity. Herein, some new indole derivatives containing heterocyclic moieties were synthesized using 3-chloro-1*H*-Indole-2-carbaldehyde (**1**) as a starting material, then allowed to react with compounds containing active methylene under Knoevenagel condensation and afforded the corresponding compounds (**2, 3, 9**). Also, the compound (**1**) when allowed to react with hydrazine derivatives gave the corresponding thiosemiccarbazone, semicarbazone, and hydrazone derivatives (**4, 5, 6**). Reaction of thiosemicarbazone derivatives with α-halognated carbonyl compounds gave the thiazolyl indole derivatives (**10, 12a–b**). Cyclic chalcones (**11a–c**) were obtained when compound (**10**) reacted with different aromatic aldehydes. The structures of all new synthesized compounds were confirmed on the basis of spectral analysis, IR, 1H NMR, 13C NMR, and MS spectroscopy. All synthesized compounds were evaluated for their antimicrobial activity. Compounds (**2, 5, 7, 8, 11a, 12a**) showed high antibacterial activity and compounds (**3, 6, 9, 10, 11a, 12a**) showed high antifungal activity.

GRAPHICAL ABSTRACT



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Supplemental data (full experimental detail, ^{1}H and ^{13}C NMR spectra) can be accessed on the publisher's website.

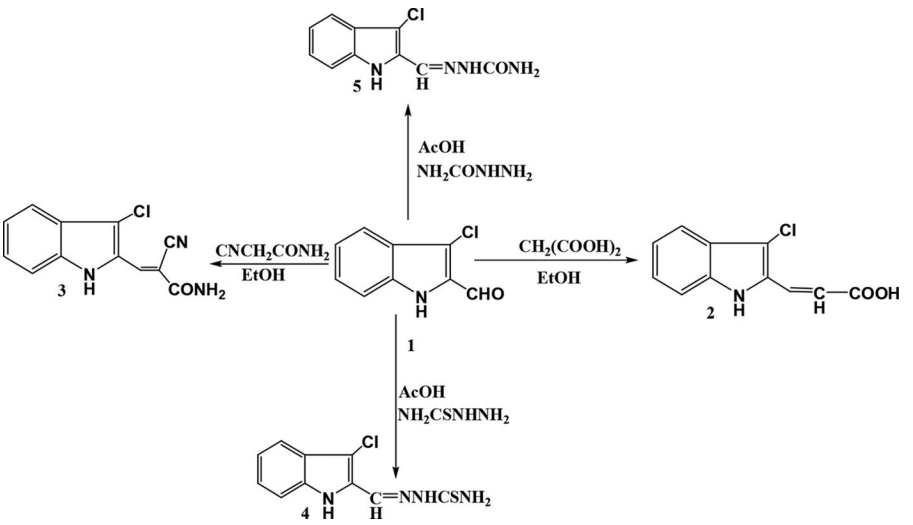
Introduction

In recent years, indole and other heterocyclic compounds containing indole derivatives have attracted great important due to their wide use as alkaloids.[1] Among the myriad of biologically active heterocycles, nitrogen-containing heterocycles[2] play a key role. In fact, recent surveys have reported that a large number of molecules currently under investigation by researchers contain nitrogen heterocycles, and of these, indoles, pyrimidyl, pyrazolyl, thiazolyl, and pyridyl indoles constitute the most important family of compounds. These heterocycles have the common indole framework which is commonly found in pharmaceutical drugs and natural products.[3–7] Indoles are interesting heterocyclic compounds and a lot of derivatives of these compounds are considered compounds of great interest for their wide range of biological activities, such as antitumor,[8,9] antiviral,[10] anti-inflammatory,[11] and anxiolytic[12,13] and are also useful for the treatment of cancer and immune-related diseases.[14] These novel biological activities are due to their ability to interact with DNA. Indole is first prepared by Fischer who proposed that aromatic heterocycle indole derivatives could be obtained by the reaction of a substituted phenylhydrazine and an aldehyde or ketone under acidic conditions.[15] The reaction was discovered in 1883 by Hermann Emil Fischer. Today antimigraine drugs of the triptan class are often synthesized by this method.[16] Also, heterocyclic compounds containing indole have long been the subject of chemical and biological research where some pyrazolo, pyrimidyl indoles used as analgesic.[17–22] The antibacterial activity of this class of compounds has been underexplored. Moreover, indole derivatives have fascinated importance in medicinal chemistry, exhibiting pharmacological and therapeutic properties such as antidepressant,[23–25] antiplatelet,[26–29] antihypertensive,[30] herbicidal,[31] and plant growth regulatory properties.[32,33] Indoles containing other heterocyclic moieties specially pyrazole and thiazole moieties have great importance as antioxidant,[34,35] antiproliferative,[36,37] and anticancer agents[38] in the present work, we report on the efficient synthesis of indole derivatives containing heterocyclic moieties such as pyrazole, thiazole, and thiophen. This study focused on the synthesis and biochemical evaluation of the newly synthesized heterocyclic compounds which was then subjected through antimicrobial evaluations.

Results and discussion

Chemistry

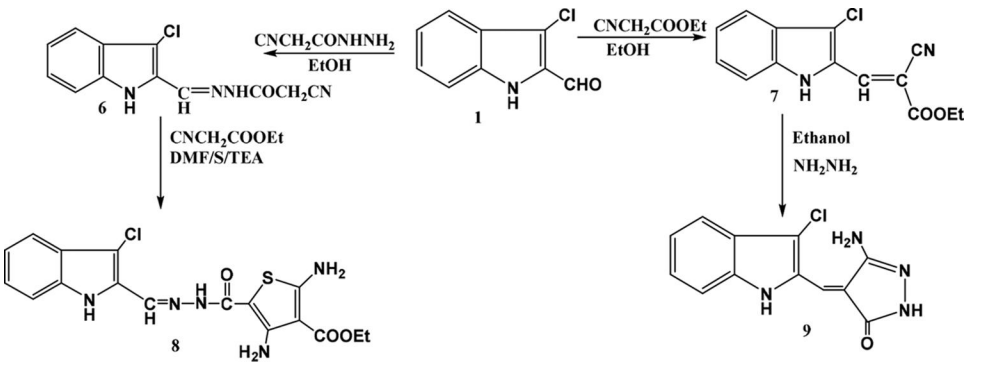
As shown in Scheme 1 when 3-chloro-1*H*-Indole-2-carbaldehyde **(1)**, which synthesized according to the reported procedures by Vilsimeier Haack reaction, when allowed to react with malonic acid in ethanol and piperidine as catalyst, decarboxylation was occurred and gave compound **2**. Also, when compound **1** subjected to react with cyanoacetamide in ethanol in the presence of catalytic amount of piperidine afforded the corresponding compound **2**. The structures of the previous obtained compounds were elucidated by elemental and spectral analyses where IR spectrum of compound **2** showed appearance of new band at 1661 cm^{-1} characteristic of C=O and its ^{1}H NMR spectrum showed appearance of singlet signal at $\delta = 11.5$ ppm characteristic of OH, also IR spectrum of compound **3** showed appearance of new bands at 2211, 3197, 3419, and 3519 cm^{-1} characteristic of CN and NH, NH_2 groups and its ^{1}H NMR spectrum showed appearance



Scheme 1. Reaction of starting material with malonic acid and semicarbazide derivatives.

of signal at $\delta = 5.91$ ppm characteristic of NH_2 group. Compound **1** was reacted with thiosemicarbazide and semicarbazide in acetic acid affording thiosemicarbazone and semicarbazone derivatives **4, 5.** The structures of thiosemicarbazone and semicarbazone derivatives were confirmed on the basis of spectral data where IR spectrum of compound **5** showed appearance of bands at 1724, 3164, 3425, and 3456 cm^{-1} characteristic of C=O, NH, and NH_2 groups, also IR spectrum of compound **4** showed appearance of bands at 1232, 3297, and 3469 cm^{-1} characteristic of C=S and NH_2 groups, while ^1H NMR spectrum showed appearance of singlet signal at $\delta = 11.68$ ppm characteristic of NH_2 group.

The condensation of 3-chloro-1*H*-indole-2-carbaldehyde with ethyl cyanoacetate in ethanol give compound **7** which allowed to react with hydrazine hydrate to give compound **9.** The IR spectrum of compound **9** showed appearance of new bands at 3245, 3314, and 3350 cm^{-1} characteristics of NH, NH_2, band at 1685 cm^{-1} characteristic of C=O and disappearance of band characteristic of CN group in the starting compound **7**, also ^1H NMR spectrum of compound **9** showed disappearance of signal characteristic of ester group and appearance of new singlet signals for NH, NH_2 at $\delta = 5.58$ and 10.53 ppm, respectively. On the other hand, when compound **1** allowed to react with cyanoacetohydrazide in ethanol in the presence of piperidine as a basic catalyst gave the corresponding *N*′-((3-chloro-1*H*-indol-2-yl) methylene)-2-cyanoacetohydrazide **6**, the latter compound was reacted with ethyl cyanoacetate and elemental sulfur in triethylamine to give compound **8.** The structures of the new compounds were proved by spectral analysis, where IR spectrum of compound **6** showed appearance of new absorption bands at 1693, 2278 cm^{-1} characteristic of C=O and CN groups, also its 1H NMR spectrum showed appearance of new singlet signal at $\delta = 3.94$ ppm characteristic of methylene group. The IR spectrum of compound **8** showed appearance of new absorption bands at 1724, 3378, and 3425 cm^{-1} characteristics of C=O ester and NH_2 group, also its 1H NMR spectrum showed appearance of new triplet signal at $\delta = 1.39$ ppm characteristic



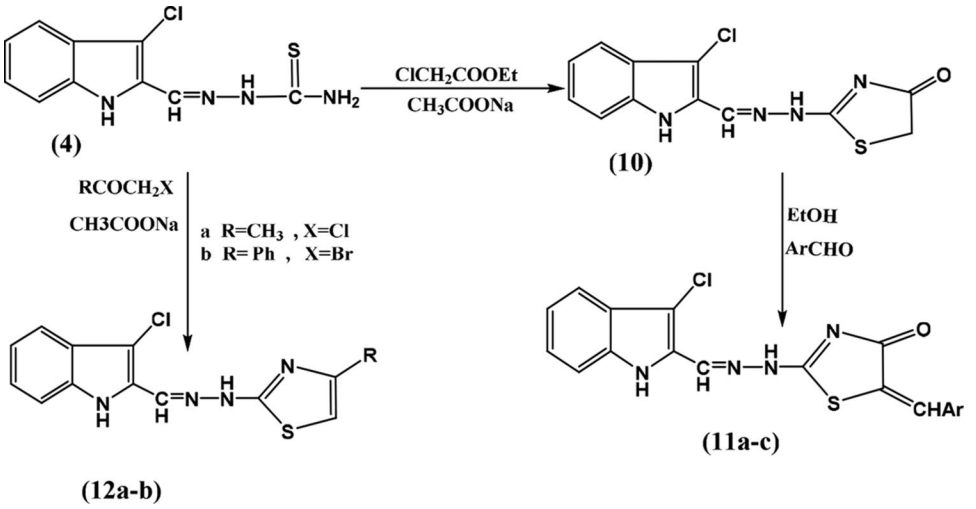
Scheme 2. Synthesis of thienyl and pyrazolylindole derivatives. *Note*: DMF, dimethylformamide; TEA, triethylamine.

of CH_3 and quartet signal at $\delta = 4.43$ ppm characteristic of CH_2 group, as shown in Scheme 2.

The treatment of 2-((3-chloro-1*H*-indol-yl)methylene)hydrazinethiocarboxamide **4** with ethyl chloroacetate in the presence of fused sodium acetate and pyridine afforded compound **10**, when the latter compound allowed to react with aromatic aldehydes afforded corresponding cyclic chalcones **11a–c**. Also, when compound **4** reacted with phenacyl bromide or chloroacetone gave thiazolidine derivatives **12a, b**. The structures of the obtained compounds were elucidated by elemental and spectral analyses, where IR spectrum of compound **10** showed appearance of new band at 1722 cm^{-1} characteristic of C=O group and showed also disappearance of band characteristic of NH_2 group in the starting material **4**, while ^{1}H NMR spectrum showed appearance of singlet signal at $\delta = 3.90$ ppm characteristic of CH_2. Also, IR spectrum of compound **11b** showed appearance of bands at 1716, 3435 cm^{-1} characteristics of C=O and NH groups, while ^{1}H NMR spectrum of the same compound showed appearance of singlet signal at $\delta = 9.46$ ppm characteristic of CH and showed also disappearance of signal characteristic of CH_2 group which existed in the starting material. The structure of compound **12a** was elucidated by spectral analyses, where IR spectrum showed appearance of new band at 3460 cm^{-1} characteristics of NH group and disappearance of band characteristic of amino group in the starting material **4**, ^{1}H NMR spectrum showed appearance of two singlet signals at $\delta = 9.52$ and 2.44 ppm characteristic of CH=N and CH_3 groups as shown in Scheme 3.

Antimicrobial activity

All the new synthesized compounds listed in Table 1 were screened for their *in vitro* antimicrobial activity against model Gram-positive (*Staphylococcus aureus, Streptococcus pneumonia,* and *Bacillus subtilis*) and Gram-negative bacteria (*Pseudomonas sp, Haemophilus influenza,* and *Pseudomonas aeruginosa*), including multidrug-resistant species, yeasts, and mold. The MICs are compared with the results obtained for standard antibacterial ciprofloxacin and streptomycin, and their antifungal activity against five fungal strains (*Candida albicans, Aspergillus fumigatus, Penicillium sp, Geotrichum candidum,* and *Syncephalastrum racemosum*). The antimicrobial activities of the tested compounds were evaluated by the reported method[13] using 0.005% (50 μg mL^{-1}) concentration of selected compounds in dimethyl sulfoxide (DMSO) as a solvent. The inhibition zone



Scheme 3. Reaction of thiosemicarbazone derivatives with α-halocarbonyl compounds.

(mm) was compared with clotrimazole as a standard for antifungal activity. In the case of antibacterial activity, the inhibition zone (mm) was compared with a series of antibiotics according to the sensitivity of each type of bacteria to the most effective antibiotic for it as a standard. The biological activity as expressed by the growth inhibition zone of the tested microorganism is listed in Tables 1 and 2.

From the data in Table 1, it could be stated that all the investigated compounds presented remarkable antibacterial properties against Gram-positive bacteria and compounds (**2, 12a**) have the highest antibacterial activity against all strains of bacteria, with values close to those of the corresponding reference antibiotics (*ciprofloxacin* and *streptomycin,* respectively), while compound **(1)** showed low antibacterial activity among all the tested compounds. Furthermore, compounds **(5, 8, 11a)** displayed also excellent

Table 1. Antibacterial activity, (inhibition zone, mm) and MIC (μg mL^{-1}) of the synthesized compounds.

No.	*Staphylococcus aureus* (Gram+)	*Streptococcus pneumoniae* (Gram+)	*Bacillus subtilis* (Gram+)	*Pseudomonas aeruginosa* (Gram−)	*Pseudomonas sp* (Gram−)	*Haemophilus influenza* (Gram−)
1	5 (6.0)	8 (7.0)	7 (8.0)	8 (9.0)	9 (5.0)	11 (8.0)
2	18 (5.0)	19 (5.0)	17 (5.0)	22 (5.0)	21 (6.0)	17 (6.0)
3	15 (5.0)	16 (4.0)	11 (0.7)	20 (5.0)	20 (5.0)	18 (5.0)
4	14 (0.7)	14 (6.0)	18 (6.0)	16 (5.0)	19 (6.0)	17 (0.8)
5	17 (6.0)	14 (4.0)	19 (4.0)	16 (5.0)	19 (5.0)	19 (4.0)
6	12 (7.0)	15 (8.0)	17 (5.0)	17 (6.0)	18 (8.0)	22 (4.0)
7	11 (4.0)	17 (4.0)	20 (7.0)	14 (5.0)	15 (4.0)	19 (5.0)
8	9 (5.0)	18 (6.0)	19 (6.0)	16 (5.0)	18 (0.5)	13 (8.0)
9	10 (5.0)	20 (4.0)	18 (4.0)	20 (3.0)	16 (6.0)	19 (6.0)
10	19 (4.0)	16 (6.0)	17 (7.0)	19 (4.0)	19 (4.0)	20 (5.0)
11a	17 (6.0)	19 (4.0)	16 (6.0)	13 (4.0)	15 (5.0)	19 (5.0)
12a	21 (7.0)	17 (6.0)	20 (4.0)	12 (5.0)	12 (8.0)	18 (4.0)
	25 (5.0)	22 (5.0)	21 (4.0)	25 (4.0)	22 (5.0)	21 (4.0)
Ref.	*Ciprofloxecin*			*Strptomycin*		

Note: Numbers out parentheses represent the diameter of inhibition zone in (mm) of compounds 1-12; Numbers in parentheses represent the MIC (minimum inhibition concentration) in (mg mL^{-1}) of compounds 1-12.

Table 2. Antifungal activity, (inhibition zone, mm) and MIC (μg mL^{-1}) of the synthesized compounds.

No.	*Penicillium sp*	*Candida albicans*	*Geotrichum candidum*	*Aspergillus fumigatus*	*Syncephalastrum racemosum*
1	10 (4.0)	11 (5.0)	13 (4.0)	11 (5.0)	9 (5.0)
2	15 (5.0)	15 (5.0)	14 (4.0)	18 (7.0)	18 (4.0)
3	17 (6.0)	14 (7.0)	20 (5.0)	14 (6.0)	17 (5.0)
4	15 (4.0)	19 (5.0)	17 (5.0)	17 (5.0)	14 (6.0)
5	19 (5.0)	14 (5.0)	16 (5.0)	15 (4.0)	17 (4.0)
6	11 (6.0)	19 (6.0)	18 (5.0)	16 (6.0)	19 (10)
7	14 (4.0)	17 (5.0)	17 (4.0)	15 (6.0)	18 (4.0)
8	15 (5.0)	16 (6.0)	18 (4.0)	17 (6.0)	21 (4.0)
9	17 (5.0)	17 (6.0)	21 (5.0)	14 (5.0)	20 (5.0)
10	16 (4.0)	19 (7.0)	17 (5.0)	18 (9.0)	17 (3.0)
11a	14 (6.0)	15 (5.0)	18 (5.0)	17 (4.0)	15 (5.0)
12a	19 (5.0)	20 (5.0)	22 (4.0)	20 (9.0)	20 (8.0)
Ref. Ketocanazole	20 (4.0)	22 (5.0)	26 (5.0)	21 (4.0)	22 (7.0)

activity against other bacterial strains *S. aureus, S. pneumonia,* and *H. influenza,* the inhibition of *B. subtilis* and *P. aeruginosa* was achieved by compounds **(7)** and **(2).** In conclusion, the data in Table 1 showed that compounds **2,3** which have the acrylic acid and cyan acrylamide moieties in position 2 in indole system has the highest antibacterial activity, while the starting previously reported compound **(1)** which has only indole moiety has low activity against Gram-positive and Gram-negative bacteria also, we could see that all new synthesized compounds have antibacterial activity against all the strains of bacteria higher than that of the starting compound **(1)** making our work is useful for improving the antibacterial activity. The antifungal results for tested compounds against five fungal species are summarized in Table 2. From Table 2, it could be stated that all the investigated compounds presented remarkable antifungal activities against five types of fungi *C. albicans, A. fumigatus, Penicillium sp, G. candidum,* and *S. racemosum,* where the data showed that the compound **(12a)** which has the indole nucleus with 2-methylthiazolyl substituent has the highest antifungal activity against all the strains of fungi, from Tables 1 and 2, it could be stated that compound **(12a)** has an antibacterial activity against all the strains of Gram-positive and Gram-negative bacteria, with values close to those of the corresponding standers and has high antifungal activity against different types of fungal species. On the other hand, compounds **(9)** and **(10)** have antifungal activity close to stander *ketoconazole* against fungal *species,* whereas the starting compound **(1)** has the lowest antifungal activity against the same fungal strains which states that the new synthesized compounds improved the activity. On the other hand, compounds **(3), (6)**, and **(9)** showed high antifungal activity against *G. candidum* and *S. racemosum,* while compound **(11a)** showed the highest antifungal activity against *C. albicans*. However, compounds **(2), (5)**, and **(7)** showed moderate activity.

Conclusion

In this study, some new indole derivatives containing heterocyclic moieties were synthesized using 3-chloro-1*H*-Indole-2-carbaldehyde (1) as a starting material. All new synthesized compounds were screened against their *in vitro* antimicrobial activity, compound **(12a)** which has the indole nucleus with 2-methylthiazolyl substituent has the highest antibacterial and antifungal activities.

Experimental

All melting points are uncorrected and measured on a Fischer-Johns apparatus. Elemental analyses were determined on an Elementar Analysen system GmbH-VarioEL V.3 micro-analyzer in the central lab of Assiut University. Their results were found to be in good agreement (±0.2%) with the calculated values. IR spectra were recorded on a Pye-Unicam Sp-100 spectrophotometer using KBr wafer technique. ^{1}H NMR experiments were run at 300 MHz on a Varian Mercury VX-300 NMR and Bruker (400 MHz) spectrometer using tetramethylsilane (TMS) as an internal standard in deuterated dimethyl sulfoxide (d_6). Mass spectra were obtained on JEOL JMS-600 apparatus. Preparative and analytical TLC were performed on silica gel plates (Fluka 70643-50EA. Sigma-Aldrich, Germany) using UV light. All reactions were performed under air atmosphere. Compound **(1)** was prepared according to the literature procedure.[39]

General procedure for the synthesis of compound (11a–c)

A mixture of compound **(10)** (0.5 g, 1.7 mmol), aromatic aldehyde (1.7 mmol), and catalytic amount of piperidine was added to ethanol, the resultant mixture was heated at reflux for 4 h, the reaction mixture was allowed to cool, the precipitate obtained was collected, dried, and recrystallized from the appropriate solvent.

5-Benzylidene-2-(2-((3-chloro-1H-indol-2-yl) methylene)hydrazinyl)thiazol-4(5H)-one(11a)

The compound obtained recrystallized from ethanol/dioxane as a yellow crystal in 83.3% yield, mp >300 °C IR: υ (cm^{-1}): 3051 (CH aromatic), 2923(CH aliphatic), 1702 (C=O), 3435 (NH), ^{1}H NMR (DMSO-d_6) δ (ppm) 7.02–7.77 (m, 9H, Ar–H), 7.77 (s, 1H, CH), 9.66 (s, 1H, CH), 11.85 (s, 1H, NH), 13.5 (s, 1H, NH), ^{13}C NMR (DMSO-d_6) δ (ppm) 112.44, 112.88, 119.52, 121.30, 124.46, 124.60, 127.64, 128.84, 128.84, 129.38, 129.38, 130.07, 132.83, 132.97, 134.39, 136.43, 176.95, 181.53, Anal. Calcd. for $C_{19}H_{13}ClN_4OS$ (380.05) C, 59.92; H, 3.44; Cl, 9.31; N, 14.71; S, 8.42%. Found: C, 59.85; H, 3.49; Cl, 9.40; N, 14.65; S, 8.0%.

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