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ORIGINAL ARTICLE

Synthesis, characterization and antimicrobial investigation of new piperidinyl tetrahydrothieno [2,3-*c*]isoquinolines

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Synthesis;
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Abstract Herein, we describe the synthesis of novel piperidinyl thieno tetrahydroisoquinolines attached or fused to other new heterocycles. The diazotization of the previously synthesized pyrrolyl carbohydrazide **1** followed by several reactions with ethanol, aniline and heterocyclization after boiling in dry xylene under *Curtius* rearrangement conditions yielded the corresponding carbamate, phenyl urea and pyrazino derivatives **3**–**5**. Furthermore, the condensation of **1** with various aromatic aldehydes and ethyl acetoacetate afforded the consistent Schiff's bases **6a-c** and **7**. The ring closure of the ethyl butanoate ester **7** furnished pyrazolyl compound **8** after heating in an ethanolic sodium ethoxide solution. Moreover, the nucleophilic addition of the carbohydrazide **1** to carbon disulfide in pyridine produced oxadiazolyl thione **9** which was reacted with ethyl chloroacetate to give ethyl sulfanyl acetate ester **10**. The assignments of the chemical structures of these new heterocycles were confirmed by using elemental and spectral analysis. Alternatively, selected compounds were examined for antibacterial and antifungal screening. The results revealed highly promising influences against the nominated pathogenic strains.

1. Introduction

Tetrahydroisoquinoline moiety is one of the most privileged heterocyclic scaffolds and is abundantly originated in several plants, soils, and marine microorganisms (Bentley, 2005). Molecules containing this skeleton are essential intermediates in medicinal and pharmaceutical chemistry and have received unique attention as a result of their broad spectrum of pharmaceutical features. Many tetrahydroisoquinolines are considered as antibacterial, antifungal (Scott and Williams, 2002),

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antitumor (Castillo et al., 2018; Pingaew et al., 2014), anti-inflammatory (Siegfried et al., 1987), anticonvulsant (Gitto et al., 2010), antileukemic, anti-HIV ((Scott and Williams, 2002; Iwasa et al., 2001), antithrombotic (Ko et al., 2017) and analgesic agents (Fodale and Santamaria, 2002). Further, tetrahydroisoquinolines have cardiovascular efficacy and are beneficial frameworks as antagonists to NMDA, D1 receptors (Gao et al., 2006) and Parkinson's disease (Sano et al., 1997). Furthermore, the isolated alkaloids from natural sources holding a THIQ nucleus are highly abundant in several medications. For instance: noscapine **(1)** is applied as an antitussive, antitumor and anti-ischemic agents (Ko et al., 2006); almorexant, an antagonist of the orexin receptor **(2)**, is used for the insomnia treatment (Perrey et al., 2013), the clinical drug Solifenacin **(3)**; is utilized for the urinary incontinence therapy (Hoffstetter and Leong, 2009); the antimuscarinic agent for the treatment of overactive bladder (Xie et al., 2014), EDL-155 **(4)** showed an anti-glioma profile (Patil et al., 2011); and elacridar **(5)** has been established as a suppressor of tumor resistance to chemotherapy. Nowadays, THIQ's are emphasized as being P-glycoprotein blocker in cell biology investigation (Colabufo et al., 2010). Trabectedin **(6)** is considered to be illustrative of a large group of THIQ anticancer antibiotics (Scott and Williams, 2002), which was recently affirmed as a remedy for delicate tissue sarcomas (D'Incalci and Galmarini, 2010) **(**Fig. 1**)**.

In the light of the above biological significance of tetrahydroisoquinolines and continuing our plan to provide novel heterocycles involving thienotetrahydroisoquinoline moiety (Zaki et al., 2020; Zaki et al., 2017; Kamal et al., 2011; Zaki et al., 2016; Zaki et al., 2011a,b; Kamal El-Dean et al. 2010; Kamal El-Dean et al., 2008), here we have reported on the preparation of pyrrolyl tetrahydrothieno[2,3-*c*]isoquinoline carbohydrazide **1** and its analogues which proved to have promising antimicrobial impact compared to standard drugs.

2. Results and discussion

2.1. Chemistry

Building on the stimulating proficiency of and ongoing efforts to produce new thienotetrahydroisoquinolines based hybrids, here, we described the synthesis of new heterocycles such as: pyrazine, pyrazole and oxadiazole ring systems. Diazotization of the carbohydrazide **1** (Zaki et al., 2020) with sodium nitrite yielded the carbonyl azide **2**. FT-IR revealed the disappearance of those bands distinctive of the hydrazino group and the release of bands at 2143 cm^{-1} that are unique to the azido set. The carboazide **2** was reacted with aniline under *Curtius* rearrangement conditions to produce the phenyl urea **3.** FT-IR of **3** displayed bands at 3361, 3285 cm^{-1} which are distinc-

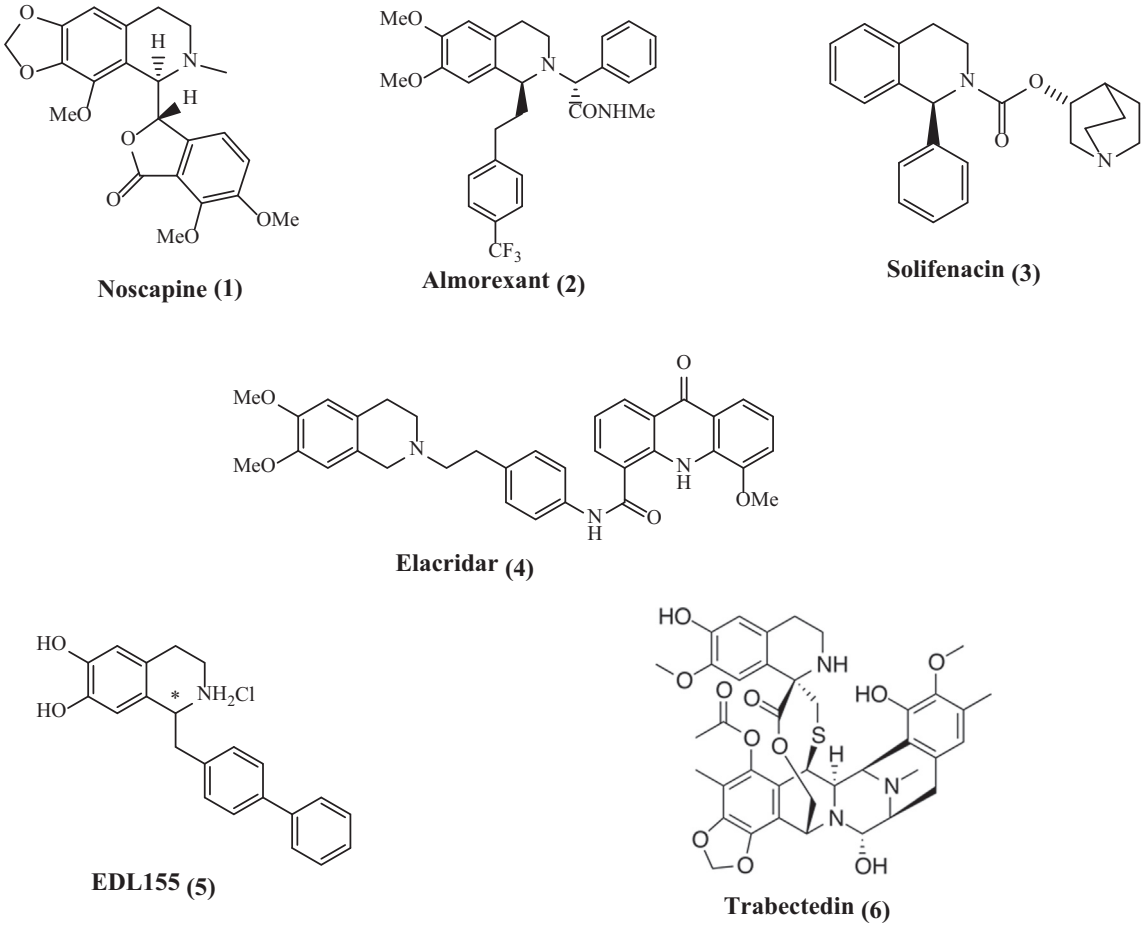


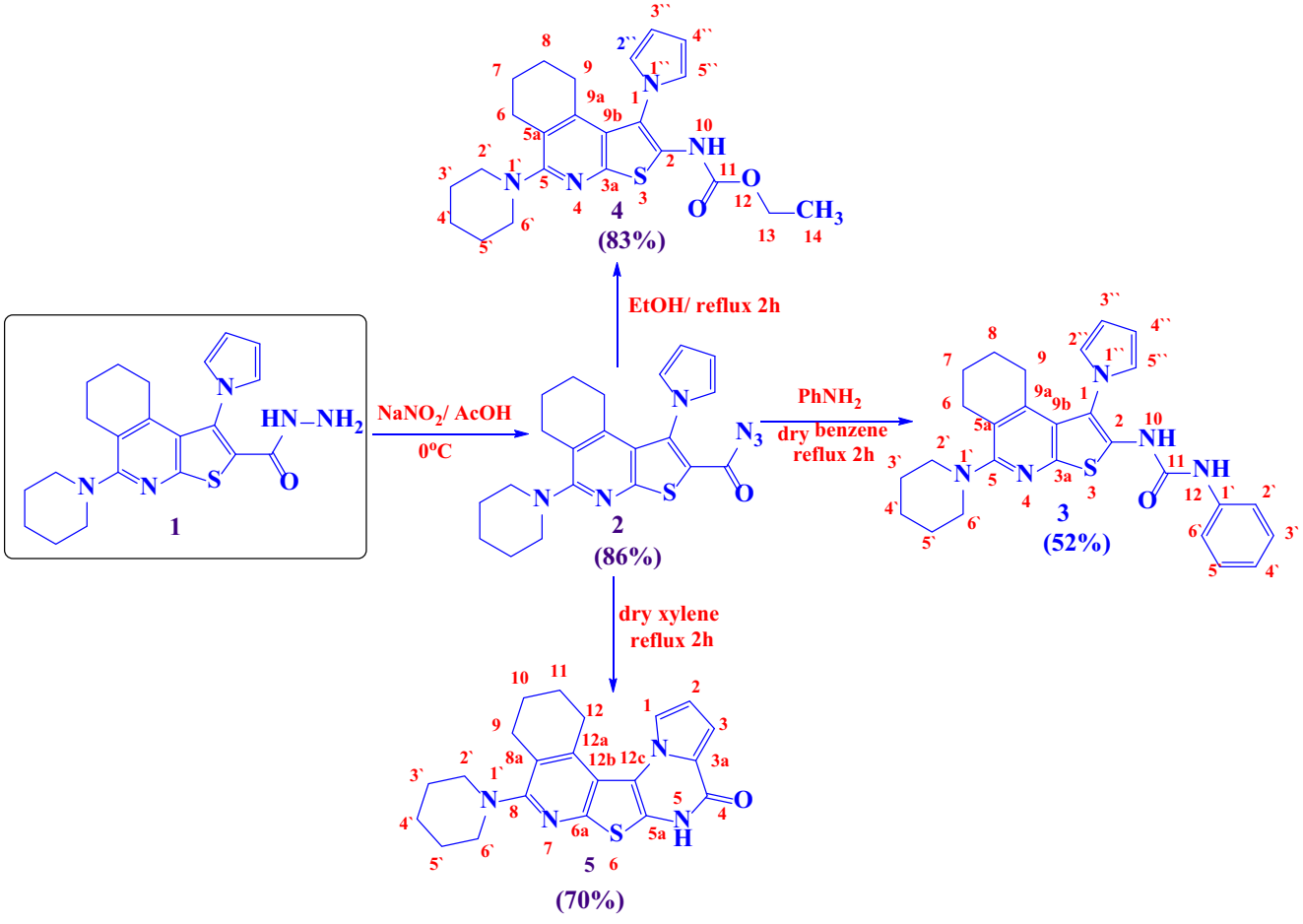
Fig. 1 Some Naturally Occurring Medicines holding a THIQ moiety.

tive of the 2NH groups as well as a band at 1691 cm^{-1} characteristic of amidic CO. ^1H NMR of **3** in TFA exhibited multiplet signals at 7.01–7.46 ppm specific to NHCO and aromatic protons as well as a singlet signal at 9.59 ppm that refers to NHPh. ^{13}C NMR spectrum exhibited a signal at 156.03 ppm that is characteristic of amidic CO group.

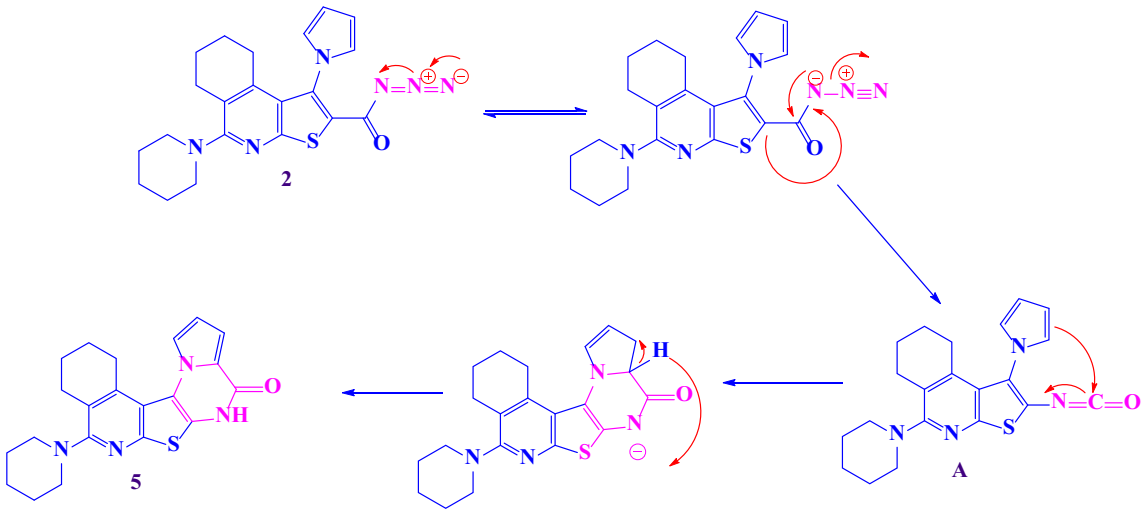
Moreover, the carboazide **2** was refluxed in absolute ethanol to provide the ethyl carbamate **4**. This compound was elucidated by IR, ^1H and ^{13}C NMR analyses. FT-IR represented absorption bands at 3306 and 1660 cm^{-1} for NH and CO ester groups. ^1H NMR of **4** emerged triplet and quartet signals at 1.24–1.29 ppm and at 4.21–4.27 ppm that are attributed to the ethoxyl protons, as well as singlet signal at 6.82 ppm unique for NH. ^{13}C NMR exhibited signals at 14.42 and 62.44 ppm typical of the ethyl group and a signal at 160.31 ppm attributed to the CO ester. In an analogues manner, the carboazide **2** underwent *Curtius* reaction accompanied by heterocyclization after heating in an inert solvent to yield a newly fused pentacyclic system namely: pyrrolopyrazinothienotetrahydroisoquinoline compound **5**. FT-IR analysis of **5** showed absence of the band specific to the azido group and attendance of bands at 3286 and 1643 cm^{-1} special for NH and CO of pyrazine. ^1H NMR in $CDCl_3$ displayed triplet and 2 doublet signals at 6.66 and 7.28–7.82 ppm assigned to the pyrrole protons as well as singlet signal at 11.13 ppm for NH. ^{13}C NMR of **5** revealed a signal at 156.47 ppm attributed to CO pyrazinone (Scheme 1).

The mechanism used to form compound **5** was proposed to occur through the *Curtius* reaction of carboazido **2** to produce the non-isolable intermediate (**a**). After that, cyclization occurred through the nucleophilic addition of the C2-C3 π bond of the pyrrolyl ring to the carbon of isocyanate group. These rearrangements led to the formation of the target pyrrolopyrazinothienotetrahydroisoquinoline **5** (Scheme 2).

The carbohydrazide **1** was considered as an adaptable precursor for synthesis of new heterocyclic systems. Consequently, condensation with various aromatic aldehydes such as benzaldehyde, *p*-nitrobenzaldehyde and *p*-anisaldehyde in refluxing ethanol provided the Schiffs bases analogous **6a-c**. Elemental and spectral analyses of the latter compounds were in consistent with the postulated structures. FT-IR of **6a** revealed the appearance of a sharp absorption band at 3295 cm^{-1} typical of NH. ^1H NMR exhibited the absence of a signal unique for NH_2 in **1** and the presence of multiplet signals at δ 7.25–7.39 ppm and 7.80–7.81 ppm distinctive of the protons of the phenyl ring and a singlet at 11.66 ppm attributed to NH. ^{13}C NMR analysis of **6a** exhibited signals at δ 113.80, 117.61, 118.27 ppm characteristic to aromatic protons and at 155.37 ppm for CO. Moreover, condensation of the carbohydrazide **1** with a 1,3–dicarbonyl compound such as ethyl acetoacetate in refluxing ethanol afforded the ethyl butanoate



Scheme 1 Synthesis and reactions of the pyrrolyl carboazide **2** with aniline, ethanol and boiling xylene under *Curtius* rearrangement producing compounds **3**–**5**.



Scheme 2 The proposed mechanism of *Curtius* rearrangement for the formation of the newly pentacyclic pyrrolopyrazinothienotetrahydroisoquinoline ring system **5.**

compound **7**. Cyclization of **7** was successfully carried out after heating in ethanolic solution of sodium ethoxide to produce the methyl pyrazolone **8** in a quantitative yield. FT-IR of **8** exhibited disappearance of bands at 3330, 1734 and 1662 cm^{-1} attributed to NH and 2CO for the ester and amide groups, respectively. ^1H NMR in $CDCl_3$ represented two singlets at 1.19, 4.19 ppm ascribed to CH_3 and CH_2 of the pyrazolyl ring. ^{13}C NMR displayed signals at 13.95 and 51.00 ppm are attributed to the CH_3 and CH_2 pyrazolyl groups as well as signals at 161.36 and 163.13 ppm typical for 2 CO groups (Scheme 3**).**

In addition, the nucleophilic addition of the carbohydrazide **1** to carbon disulfide followed by elimination of H_2S in pyridine upon heating in a steam bath afforded the oxadiazolyl thione **9**. The thione group in compound **9** was S-alkylated through the reaction with ethyl chloroacetate to yield the ethyl oxadiazolyl sulfanyl acetate **10**. FT-IR spectrum of **10** exhibited a band at 1721 cm^{-1} that is distinctive for CO ester. Also, ^1H nuclear magnetic resonance revealed triplet and quartet signals at 1.25–1.30 ppm and 4.19–4.24 ppm characteristic to the ethyl ester and singlet signal at 3.82 ppm representative for SCH_2. ^{13}C NMR spectrum emerged signals at 14.08 and 62.28 ppm unique to the ethoxyl group as well as signals at 33.74 and 167.34 ppm specific to the SCH_2 and CO ester groups, respectively (Scheme 4**)**.

2.2. Biological screening

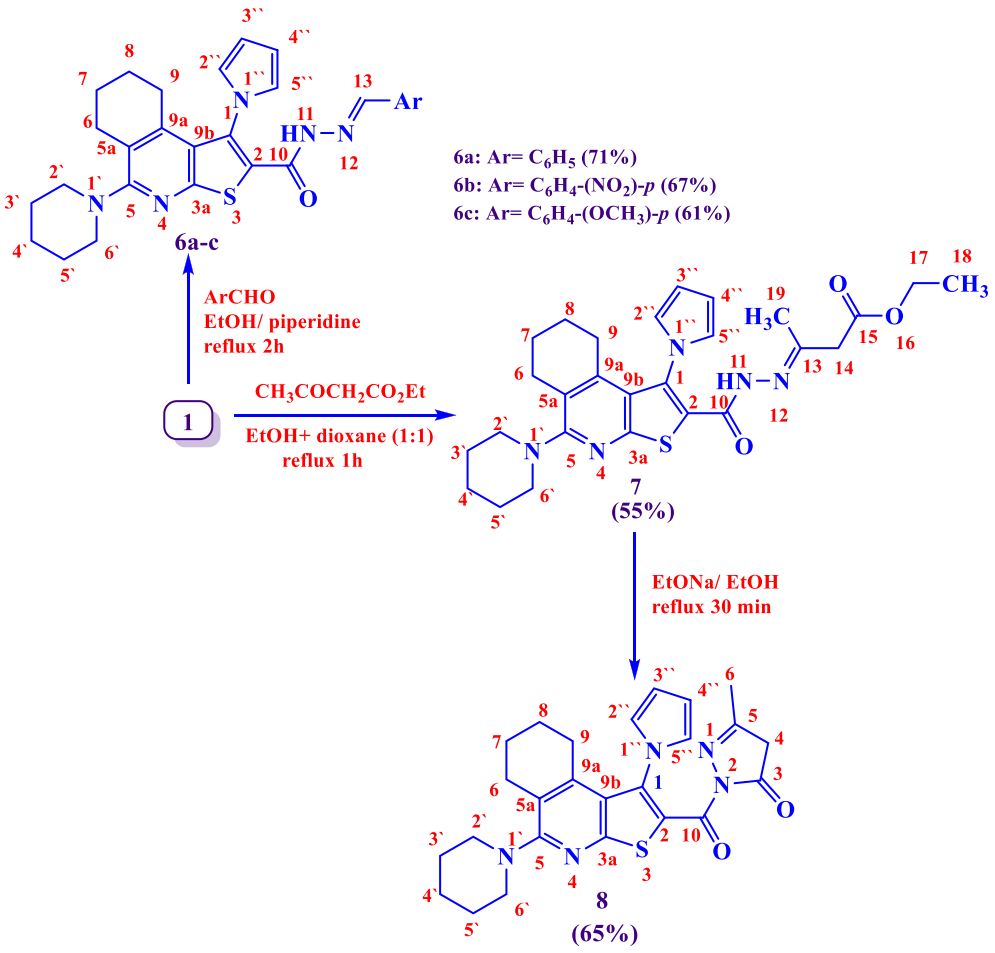
Currently, one of the prominent problems for people's health is the resistance to the current antimicrobial medications. So, the main target of our work is the development of new and more efficient antimicrobial therapies through the synthesis of novel heterocyclic compounds. In our study, we focused on comparing the antimicrobial impacts between the cabohydrazide **1**, phenyl urea **3**, carbamate derivatives **4**, pyrazinone **5** and some Schiff's bases **6a-c** which have similar functional groups to each other. Thus, we have chosen compounds **1**, **3**, **4**, **5** and **6a-c** in order to screen their *in vitro* antimicrobial inhibitory activity against a set of Gram positive and Gram negative strains (*Staphylococcus aureus*, *Bacillus cereus*, *Pseudomonas aeruginosa* and *Escherichia coli*) as well as four strains of pathogenic fungi (*Candida albicans*, *Aspergillus flavus*, *Geotrichum candidium* and *Trihophyton rubrum*). The inhibition zones and MIC of the screened derivatives were compared with Amoxicillin and Clotrimazole as references medicines.

2.2.1. Antibacterial activity

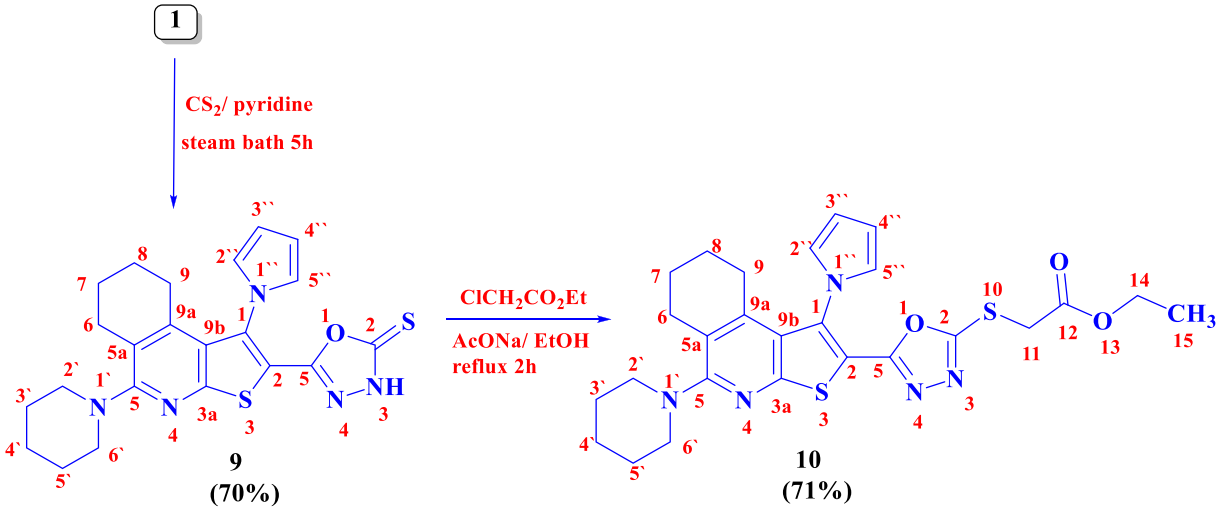
The results of the screened heterocycles displayed significant activities and were listed in Table 1. It was found that compounds **1** and **3** revealed the highest effect against all strains of bacteria (MIC 7–11 μg/ml). Furthermore, compound **6a** exposed the least activity comparable to Amoxicillin (MIC 3.0 μg/ml). Compounds **1, 3, 4, 6b** and **6c** revealed the best efficacy against *B. cereus* with (MIC 8.0–11.0 μg/ml), while compounds **4**, **6a** and **6b** showed inferior effect. With regard to *S. aureus*, compounds **1**, **3**, **5** and **6b** displayed excellent effect against every strains of the pathogenic bacteria (MIC 8.0–9.0 μg/ml) in comparison to Amoxicillin (MIC 3.0 μg/ml). Consequently, compounds **5**, **6b** and **6c** were detected to be the most active derivatives versus *P. aeruginosa* (MIC 8.0 and 9.0 μg/ml) compared to Amoxicillin (3.0 μg/ml), while compounds **1** and **3** showed good to moderate activities. Conversely, *P. aeruginosa* was resistant to **4** and **6a**. Furthermore, compounds **1** and **6b** represented the best influence against *E. coli* (MIC 7.0 μg/ml), whereas compounds **3**, **5** and **6a** exhibited moderate activity compared to the authentic drug (MIC 3.0 μg/ml). Otherwise, *E. coli* was resistant to compounds **4** and **6c**.

2.2.2. Antifungal Activity

It is fascinating to assume that all the screened derivatives displayed distinctive influence against most species of fungi, as present in Table 2. Based on the results, we found that compounds **4**, **6b** and **6c** exhibited the highest activity against *G. candidium* (MIC 8.0–9.0 μg/ml), while compound **1** represented the best inhibition zone (19 mm) which is very close to that of Clotrimazole (22 mm). Otherwise, compounds **5** and **6a** displayed good to moderate effects. Whereas *C. albicans* and *G.*



Scheme 3 Condensation and cyclization of the carbohydrazide **1** with aromatic aldehydes and 1,3-dicarbonyl compounds producing Schiff's bases **6a-c**, **7** and **8.**



Scheme 4 Condensation and cyclocondensation reactions of the carbohydrazide **1** with carbon disulfide affording compounds **9**–**10**.

candidium were resistant to compound **3**. Subsequently, compound **6c** represented the best activity against *C. albicans* (MIC 6.0 µg/ml) compared to the reference drug (3.0 µg/ml), whereas, compounds **6a** and **6b** revealed excellent efficacy (MIC 7.0–8.0 µg/ml) in comparison to Clotrimazole (MIC 3.0 µg/ml). In case of *T. rubrum*, compounds **1**, **4** and **6b** exhib-

Table 1 Antibacterial activities of compounds **1**, **3**–**5** and **6a-c**.

	Strains of Bacteria (inhibition zone, mm) and (MIC, μg/ml)			
	Gram-(+ve) bacteria		Gram-(−ve) bacteria	
Compound.	*B. cereus*	*S. aureus*	*P. aeruginosa*	*E. coli*
1	13 (11)	18 (9.0)	10 (11)	12 (7.0)
3	13 (8.0)	17 (9.0)	14 (10)	15 (10)
4	–	18 (9.0)	–	–
5	12 (10)	11 (11)	10 (9.0)	9 (13)
6a	–	–	–	8 (13)
6b	–	18 (9.0)	17 (8.0)	15 (7.0)
6c	13 (10)	13 (8.0)	18 (9.0)	–
Amoxicillin	26 (3.0)	28 (3.0)	22 (3.0)	29 (3.0)

Table 2 Antifungal activities of compounds **1**, **3**–**5** and **6a-c**.

	Fungal strains (inhibition zone, mm) and (MIC, μg/ml)			
Compd.	*G. candidium*	*C. albicans*	*T. rubrum*	*A. flavus*
1	19 (10)	13 (13)	18 (9.0)	19 (9.0)
3	–	–	15 (12)	15 (9.0)
4	13 (9.0)	18 (10)	19 (9.0)	14 (8.0)
5	10 (10)	12 (11)	12 (11)	11 (9.0)
6a	10 (10)	19 (8.0)	14 (11)	11 (10)
6b	15 (9.0)	18 (7.0)	16 (9.0)	14 (9.0)
6c	14 (8.0)	20 (6.0)	–	15 (9.0)
Clotrimazole	22 (5.0)	26 (3.0)	25 (6.0)	21 (4.0)

ited excellent activity (MIC 9.0 μg/ml) compared to Clotrimazole (MIC 6.0 μg/ml), while compounds **3**, **5** and **6a** showed moderate impact. However, *T. rubrum* was resistant to compound **6c**. Additionally, compounds **1**, **3**, **4**, **5**, **6b** and **6c** represented strong activity against *A. flavus* (MIC 8.0–9.0 μg/ml), while **6a** displayed medium efficacy (MIC 10.0 μg/ml), in comparison to the authentic antifungal agent (MIC 4.0 μg/ml) (Table 2).

2.2.3. Structure activity relationship (SAR) study

Tetrahydroisoquinoline is an important scaffold in organic and medicinal chemistry. Therefore, we attempted to study the effect of several carboxamides and carbohydrazone derivatives including the piperidinyl thienotetrahydroisoquinoiline nucleus on the bacterial inhibitory action. The information that was recorded in Table 1 illustrated that the pyrrolyl carbohydrazide **1** exhibited promising antibacterial activity against most of the pathogenic bacterial strains. Conversion to the phenyl urea **3** greatly enhanced the activity against *B. cereus* and *P. aeruginosa* and significantly reduced the activity towards *E. coli*, while the effect against *S. aureus* remained unchanged. Alternatively, the formation of carbamate ester **4** highly suppressed the activity against *B. cereus*, *P. aeruginosa* and *E. coli*, revealing a similar effect to that of the carbohydrazide **1** versus *S. aureus*. In addition, the pyrazinone **5** showed higher activity against *B. cereus* and *P. aeruginosa* than the pyrrolyl carbohydrazide starting compound **1** and was slightly less efficacious against the other strains. Moreover, condensation of the carbohydrazide **1** with various aldehydes to form the identical Schiff's bases **6a-c** strongly affected on the antibacterial impact. Therefore, condensation with benzaldehyde to from **6a** greatly diminished the activity against *B. cereus*, *S. aureus* and *P. aeruginosa*, while displaying moderate activity versus *E. coli*. It is fascinating to observe that replacing the hydrogen in the para position of the phenyl ring with the electron withdrawing group (NO_2) in **6b** highly enhanced the activity against *P. aeruginosa*, *S. aureus* and *E. coli*, while revealing inferior activity against *B. cereus*. Contrarily, replacing the nitro with the methoxy group (electron donating group) in **6c** greatly enhanced the activity against *B. cereus*, while displaying the same excellent activity versus *P. aeruginosa* and *S. aureus*, whereas *E. coli* was resistant to compound **6c**. Compound **4** revealed inferior activity against every tested strain of bacteria except *S. aureus*.

Further, the newly synthesized compounds represented excellent activity against all strains of fungi. It is worth mentioning that compound **6b** exhibited the best effect versus all the fungal strains. The pyrrolyl carbohydrazide **1** revealed promising activity against *G. candidium*, *T. rubrum* and *A. fla-*

Table 3 Physical constants for the synthesized compounds **2**–**10**.

Compound	Empirical Formula (M. Wt)	Found/Calculated (%)				M.P. °C	Yield
		C	H	N	S		
2	$C_{21}H_{22}N_6OS$	61.93	5.34	20.52	8.00	138–140	86 %
	406.51	62.05	5.46	20.67	7.89		(0.26 g)
3	$C_{27}H_{29}N_5OS$	68.64	6.32	14.73	6.94	248–250	52 %
	471.62	68.76	6.20	14.85	6.80		(0.30 g)
4	$C_{23}H_{28}N_4O_2S$ (424.56)	64.94	6.80	13.35	7.70	298–300	83 %
		65.07	6.65	13.20	7.55		(0.83 g)
5	$C_{21}H_{22}N_4OS$	66.52	5.74	14.68	8.35	270–272	70 %
	(378.49)	66.64	5.86	14.80	8.47		(0.65 g)
6a	$C_{28}H_{29}N_5OS$	69.40	6.20	14.36	6.50	238–240	71 %
	(483.63)	69.54	6.04	14.48	6.63		(0.85 g)
6b	$C_{28}H_{28}N_6O_3S$ (528.63)	63.50	5.48	15.78	6.20	230–232	67 %
		63.62	5.34	15.90	6.06		(0.90 g)
6c	$C_{29}H_{31}N_5O_2S$ (513.66)	67.94	6.22	13.50	6.36	254–256	61 %
		67.81	6.08	13.63	6.24		(0.80 g)
7	$C_{27}H_{33}N_5O_3S$ (507.65)	63.76	6.43	13.70	6.18	238–240	55 %
		63.88	6.55	13.80	6.32		(0.35 g)
8	$C_{25}H_{27}N_5O_2S$ (461.58)	64.93	5.78	15.00	7.10	138–140	65 %
		65.05	5.90	15.17	6.95		(0.09 g)
9	$C_{22}H_{23}N_5OS_2$ (437.58)	60.50	5.42	15.90	14.77	228–230	70 %
		60.39	5.30	16.01	14.65		(0.84 g)
10	$C_{26}H_{29}N_5O_3S_2$ (523.67)	59.51	5.46	13.25	12.12	148–150	71 %
		59.63	5.58	13.37	12.24		(0.40 g)

vus with moderate effect versus *C. albicans*. The antifungal activity of the carbamate **4** was very close to that of compound **1** versus all of the tested genera of fungi, while the formation of phenyl urea derivative **3** inhibited the activity against *G. candidium* and *C. albicans*. Contrary to the antibacterial activity, the carbamate ester **4** was more efficacious versus all of the genera of fungi except the carbohydrazide **1** and phenyl urea **3**. Moreover, condensation of the carbohydrazide **1** with benzaldehyde to afford the benzylidene Schiff's base **6a** significantly increased the activity against *C. albicans* and slightly decreased the activity against *T. rubrum* and *A. flavus*. Replacing the proton in the para position of phenyl ring with the nitro group (EWG) is compound **6b** improved the efficiency against all genera of fungi, while replacement with the methoxyl group (EDG) in **6c** greatly improved the influence against *G. candidium*, *C. albicans* and *A. flavus* which was very close to the effect of the nitro group in **6b**. In contrast, *T. rubrum* was resistant to compound **6c**. In conclusion, we can deduce that the phenyl urea **3** revealed higher antibacterial and lower antifungal activities than the carbamate **4**. Also, replacing the protons of the phenyl ring in the Schiff's bases **6a-c** by either electron donating and electron withdrawing groups highly improved the antimicrobial activity.

3. Experimental

3.1. Chemistry

The chemicals utilized in this research were purchased from the Loba and Merck Sigma-Aldrich companies. Melting points were estimated using a Fisher-John apparatus. Elemental analyses was measured at the Micro Analytical Center at Chemistry Department at Assiut University. The Fourier transform infrared (FT-IR, ν (cm^{-1})) spectra were recorded on a FT-IR 8201PC Shimadzu using potassium bromide disks. ^1H and ^{13}C NMR spectra (δ, ppm) for all of the above mentioned heterocycles were evaluated in $CDCl_3$ except compound **3**, which was determined in CF_3CO_2D using tetramethyl silane (Me_4Si) as the internal standard on Bruker BioSpinGmbH spectrometers and Varian Mercury VX-300NMR (^1H NMR 400 MHz, ^{13}C NMR 100 MHz). All reactions were monitored using the TLC technique on silica gel covered with aluminum sheets (Silica gel60 F_{254}, Merck). The pyrrolyl carbohydrazide **1** was synthesized according to literature procedure (Zaki et al., 2020). Physical constants of the synthesized compounds **2-10** were listed in (Table 3).

3.1.1. 5-(Piperidino)-1-(1H-pyrrolyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carbonyl azide (**2**)

A solution of sodium nitrite (0.30 g, 0.05 mmol, 10 %) was added dropwise with stirring to the carbohydrazide solution **1** (0.30 g, 0.75 mmol) in glacial acetic acid (20 ml) in an ice bath at 0 °C for 5 min. The solid precipitate that was produced on cooling was filtered off, dried and used without any additional purification for the next reactions. IR: 3107 (CH - py), 2934, 2848 (CH- aliph), 2143 (N_3), 1707 (CO azide), 1650 (C═N). ^1H NMR: 1.60–1.62 (6H, m, $3CH_2$: C_3 - C_5 piperidine), 1.72–1.75 (4H, m, $2CH_2$: C_7, C_8 cyclohexene), 2.33–2.37 (2H, m, CH_2: C_6 cyclohexene), 2.65–2.67 (2H, m, CH_2: C_9 cyclohexene), 3.18–3.20 (4H, m, $2CH_2$: C_2', C_6' piperidine), 6.42–6.44 (2H, m, C_3'', C_4'' pyrrole), 6.75–6.78 (2H, m, C_2'', C_5'' pyrrole). ^{13}C NMR: 22.13 (C_7 cyclohexene), 22.43 (C_8 cyclohexene), 22.48 (C_4' piperidine), 24.58 (C_3', C_5' piperidine), 26.66 (C_6 cyclohexene), 29.70 (C_9 cyclohexene), 51.03 (C_2', C_6'

piperidine), 111.47 (C_3'', C_4'' pyrrole), 122.47 (C_{5a}), 122.85 (C_2'', C_5'' pyrrole), 123.41 (C_{9b}), 123.85 (C_{9a}), 129.43 (C_2), 131.03 (C_1), 143.66 (C_{3a}), 156.12 (C_5), 162.70 (C_{10}, C═O).

*3.1.2. N-Phenyl-N′-(5-(piperidino)-1-pyrrolyl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-2-yl) urea (**3**)*

The carbonyl azide **2** (0.50 g, 1.20 mmol) and aniline (0.50 ml, 5.40 mmol) in dry benzene (5 ml) were refluxed for 2 h. The produced solid that was separated out on cooling was collected and recrystallized from dioxane as light brown crystals. IR: 3361, 3285 (2NH), 3104 (CH– py), 2932, 2853, 2818 (CH - aliph), 1691 (CO amide). ^{1}H NMR: 1.49–1.61 (6H, m, $3CH_2$: C_3' - C_5' piperidine) , 1.62–1.69 (4H, m, $2CH_2$: C_7, C_8 cyclohexene), 2.11– 2.15 (2H, m, CH_2 : C_6 cyclohexene), 2.61–2.65 (2H, m, CH_2: C_9 cyclohexene), 3.13–3.20 (4H, m, $2CH_2$: C_2', C_6' piperidine), 6.33–6.55 (2H, m, C_3'', C_4'' pyrrole), 6.87–6.99 (2H, m, C_2'', C_5'' pyrrole), 7.01–7.46 (6H, m, ArH + NHCO), 9.59 (1H, s, NHPh). ^{13}C NMR: 22.50 (C_7 cyclohexene), 23.45 (C_8 cyclohexene), 24.44 (C_3' - C_5' piperidine), 24.69 (C_6 cyclohexene), 26.31 (C_9 cyclohexene), 51.65 (C_2', C_6' piperidine), 110.05 (C_3'', C_4'' pyrrole, C_{5a}), 111.48 (C_2'', C_5'': pyrrole), 114.30 (C_2', C_6': Ph), 115.95 (C_{9b}), 118.65 (C_3'.C_5': Ph), 123.63 (C_{9a}), 125.28 (C_1': Ph), 129.14 (C_2), 129.24 (C_1 + C_{3a}), 129.39 (C_5), 156.03 (C11: CONH).

*3.1.3. Ethyl (5-(piperidino)-1-pyrrolyl-6,7,8,9-tetrahydrothieno[2,3-c] isoquinolin-2-yl) carbamate (**4**)*

The carboazide **2** (1.00 g, 2.50 mmol) in absolute ethanol (20 ml) were heated under reflux for 2 h. The solid precipitate that was separated out on reflux was collected and recrystallized from a mixture of ethanol/ dioxane (1:1) as white crystals. IR: 3306 (NH), 3122, 3105 (CH - py), 2925, 2850 (CH - aliph), 1660 (CO carbamate), 1635 (C═N). ^{1}H NMR: 1.24–1.29 (3H, t, J = 7.0 Hz, CH_3 ester), 1.47–1.64 (6H, m, $3CH_2$-N: C_3- C_5), 1.69–1.70 (4H, m, $2CH_2$: C_7, C_8), 2.41–2.11 (2H, m, CH_2: C_6), 2.73–2.57 (2H, m, CH_2: C_9), 3.06–3.09 (4H, m, $2CH_2$-N: C_2, C_6), 4.21–4.27 (2H, q, J = 7.0 Hz, CH_2: ethyl ester), 6.37–6.38 (2H, m, C_3, C_4), 6.70–6.82 (2H, m, C_2, C_5), 7.26 (1H, s, NH). ^{13}C NMR: 14.42 (C_{14}, CH_3 : ethyl ester), 22.32 (C_7), 22.56 (C_8), 22.81 (C_4), 24.62 (C_3, C_5), 26.03 (C_6), 26.31 (C_9), 51.43 (C_2, C_6'), 62.44 (C_{13}, CH_2 ester), 109.13 (C_3, C_4), 110.17 (C_{5a}), 122.24, 122.69 (C_2, C_5), 123.45 (C_{9b}), 123.61 (C_{9a}), 133.99 (C_2), 140.47 (C_1), 149.93 (C_{3a}), 152.75 (C_5), 160.31 (C_{11}, CO ester).

*3.1.4. 8-(Piperidino)-9,10,11,12-tetrahydropyrrolo[1′′,2′′:1′,6′]pyrazino[2′,3′:4,5]thieno[2,3-c]isoquinolin-4(5H)-one (**5**)*

A suspension of the carboazide **2** (1.00 g, 25.00 mmol) in dry xylene (6 ml) was heated under reflux for 2 h. The precipitated solid that was produced during reflux was collected and recrystallized from dioxane into pale brown crystals. IR: 3286 (NH), 2930, 2853 (CH - aliph), 1643 (CO, pyrazino). ^{1}H NMR: 1.67–1.74 (6H, m, $3CH_2$-N: C_3' - C_5), 1.76–1.79 (4H, m, $2CH_2$: C_7, C_8), 1.91 (2H, m, CH_2: C_6), 2.87 (2H, m, CH_2: C_9), 3.19 (4H, m, $2CH_2$-N: C_2, C_6), 6.66 (1H, t, J = 3.10 Hz, C_3), 7.28, 7.40 (1H, d, J = 2.70 Hz, C_4), 7.81, 7.82 (1H, d, J = 4.00 Hz, C_2), 11.13 (1H, s, NH). ^{13}C NMR: 22.15 (C10 cyclohexene), 22.95 (C11 cyclohexene), 2312 (C4 piperidine), 24.16 (C_3, C_5' piperidine), 26.24 (C_9 cyclohexene), 26.87 (C_{12} cyclohexene), 51.04 (C_2, C_6' piperidine), 109.60 (C_2 pyrrole), 110.83 (C_3 pyrrole), 120.44 (C_{8a}), 122.15 (C_{12b}), 124.10 (C_{3a}), 128.65 (C_{12c}), 129.52 (C_{12a}), 131.18 (C_1 pyrrole), 132.05 (C_{6a}), 151.90 (C_{5a}), 152.30 (C_8), 158.47 (C_4: CO).

*3.1.5. N′-Arylidene-5-(piperidino)-1-pyrrolyl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carbohydrazide (**6a-c**)*

General procedure

The compound **1** (1.00 g, 2.00 mmol) and the corresponding aldehyde (2.50 mmol) in ethanol (20 ml) with catalytic drops of acetic acid (0.50 ml) were refluxed for 2 h. The precipitated solid which was obtained during reflux was collected and recrystallized from an appropriate solvent.

*3.1.5.1. N′-Benzylidene-5-(piperidino)-1-pyrrolyl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carbohydrazide (**6a**).*

Benzaldehyde, white crystals (EtOH). IR: 3295 (NH), 3117, 3102 (CH - py), 3027 (CH - aromatic), 2954, 2925, 2850 (CH - aliph), 1657 (CONH), 1610 (C═N). ^{1}H NMR: 1.62–1.71 (6H, m, $3CH_2$-N : C_3' - C_5), 1.72–1.89 (4H, m, $2CH_2$: C_7, C_8), 2.78–2.82 (2H, m, CH_2 : C_6), 3.05–3.11 (2H, m, CH_2 : C_9), 3.12–3.17 (4H, m, $2CH_2$-N : C_2, C_6), 6.64–6.65 (2H, m, C_3, C_4), 7.26–7.39 (6H, m, ArH + N═CH benzylidene), 7.80–7.81 (2H, m, C_2, C_5), 11.66 (1H, s, NH). ^{13}C NMR: 16.92 (C_7), 17.01 (C_8), 19.50 (C_3- C_5), 21.45 (C_6), 27.02 (C_9), 46.81 (C_2, C_6), 104.47 (C_3, C_4), 106.73 (C_{5a}), 107.72 (C_2, C_5), 108.86 (C_{9b}), 113.80 (C_3, C_5': Ph), 117.61 (C_2, C_4', C_6': Ph), 118.27 (C_{9a}, C_1: Ph), 119.93 (C_2), 120.63 (C_{13}, N═CH), 137.15 (C_1), 145.09 (C_{3a}), 152.49 (C_5), 155.37 (C_{10} : CO).

*3.1.5.2. N′-(4-Nitrobenzylidene)-5-(piperidino)-1-pyrrolyl-6,7,8,9-tetrahydrothieno[2,3-c] isoquinoline −2-carbohydrazide (**6b**).*

p-Nitrobenzaldehyde, pale-yellow crystals (ethanol-dioxane mixture (1:1)). IR: 3294 (NH), 3101 (CH - py), 3050 (CH aromatic), 2937, 2856 (CH - aliphatic), 1663 (C═O), 1561 (C═N). ^{1}H NMR: 1.70–1.80 (6H, m, $3CH_2$-N: C_3' - C_5), 2.44–2.45 (4H, m, $2CH_2$: C_7, C_8), 2.75 (2H, m, CH_2: C_6), 3.29 (2H, m, CH_2: C_9), 3.72 (4H, m, $2CH_2$-N: C_2, C_6), 6.63 (2H, m, C_3, C_4), 6.96 (2H, m, C_2, C_5), 7.28 (1H, s, N═CH benzylidene), 7.43–7.85 (4H, 2d, ArH *p*-sub), 8.21–8.23 (1H, s, NH) ppm. ^{13}C NMR: 15.80 (C_7), 18.92 (C_8), 21.64 (C_3- C_5), 24.53 (C_6), 36.20 (C_9), 52.75 (C_2, C_6'), 112.36 (C_3, C_4), 113.45 (C_{5a}), 114.60 (C_2, C_5), 122.84 (C_{9b}), 126.46 (C_3, C_5': Ph), 128.78 (C_2, C_4', C_6': Ph), 134.68 (C_{9a}, C_1: Ph), 134.85 (C_2), 152.25 (C_{13}: N═CH), 156.74 (C_1), 158.88 (C_{3a}), 164.54 (C_5), 170.75 (C_{10} : CO).

*3.1.5.3. N′-(4-Methoxybenzylidene)-5-(piperidino)-1-pyrrolyl-6,7,8,9-tetrahydrothieno[2,3-c] isoquinoline −2-carbohydrazide (**6c**).*

p-Anisaldehyde, yellow crystals (dioxane). IR: 3309 (NH amide), 3109 (CH - py), 3090 (CH - aromatic), 2928, 2842 (CH - aliphatic), 1659 (C═O), 1564 (C═N). ^{1}H NMR: 1.61–1.67 (6H, m, $3CH_2$-N: C_3' - C_5'), 1.71–1.90 (4H, m, $2CH_2$: C_7, C_8), 2.24–2.40 (2H, m, CH_2: C_6), 2.51–2.65 (2H, m, CH_2: C_9), 3.18–3.20 (4H, m, $2CH_2$-N: C_2', C_6'), 3.71 (3H, s, OCH_3), 6.60–6.61 (2H, m, C_3'', C_4''), 6.93–6.94 (2H, m, C_2'', C_5''), 7.26 (1H, s, N═CH), 7.34 (1H, s, NH), 7.81–8.21 (4H, 2d, ArH *p*-sub) ppm. ^{13}C NMR: 14.14 (C_7), 15.41 (C_8), 21.84, 22.40 (C_3', C_5'), 24.58 (C_4') 26.70 (C_6), 44.46 (C_9), 50.99 (C_2', C_6'), 61.05 (C_{15}, OCH_3), 111.39 (C_3'', C_4''), 111.94 (C_{5a}), 122.84 (C_2'', C_5''), 123.23 (C_{9b}), 123.63 (C_3', C_5': Ph), 123.75 (C_2', C_4', C_6': Ph), 130.13 (C_{9a}, C_1' Ph), 130.67 (C_2),

150.73 (C_{13} N═CH), 156.51 (C_1), 157.66 (C_{3a}), 162.71 (C_5), 169.64 (C_{10}: CO).

3.1.6. Ethyl-3-(2-(5-(piperidino)-1-pyrrolyl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carbonyl) hydrazono) butanoate (7)

A mixture of the carbohydrazide **1** (0.50 g, 1.20 mmol) and ethyl acetoacetate (0.15 ml, 1.20 mmol) in an ethanol/dioxane mixture (1:1) was heated under reflux for 1 h. The produced solid which was formed on heating was collected and recrystallized from ethanol as white crystals. IR: 3330 (NH), 3107 (CH - pyrrole), 2956, 2925, 2851 (CH - aliph), 1734 (C═O ester), 1662 (CONH), 1560 (C═N). ^{1}H NMR: 1.23–1.26 (3H, t, J = 7.20 Hz, CH_3 ester), 1.61–1.63 (6H, m, $3CH_2$-N: C_3' - C_5), 1.70 –1.75 (4H, m, $2CH_2$: C_7, C_8), 1.97 (3H, s, N═CCH_3), 2.65–2.73 (2H, m, CH_2: C_6), 2.93–2.98 (2H, m, CH_2: C_9), 3.14–3.17 (4H, m, $2CH_2$: C_2, C_6), 3.70 –3.75 (2H, q, J = 7.20 Hz, CH_2 ester), 4.56 (2H, s, $COCH_2$), 6.24–6.25 (2H, m, C_3, C_4), 6.71–6.79 (2H, m, C_2, C_5), 7.26 (1H, s, NH). ^{13}C NMR: 16.02 (C_{19}, N═C-CH_3), 22.22 (C_{18}, CH_3 ester), 22.47 (C_7), 22.84 (C_8), 24.62 (C_4), 26.16 (C_3, C_5), 26.42 (C_6), 26.50 (C_9), 29.70 (C_{14}:CH_2-C═O), 51.17 (C_2, C_6), 62.33 (C_{17}, CH_2 ester), 108.71 (C_3, C_4), 122.50 (C_{5a}), 123.37 (C_2, C_5), 123.51 (C_{9b}), 123.71 (C_{9a}), 125.96 (C_2), 134.29 (C_{13}), 143.81 (C_1), 154.98 (C_{3a}), 156.49 (C_5), 161.02 (C═O, C_{15} ester), 162.55 (C═O, C_{10}).

3.1.7. 5-Methyl-2-(5-(piperidino)-1-pyrrolyl-1–6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carbonyl)-2,4-dihydro-3H-pyrazol-3-one (8)

The butanoate derivative **7** (0.15 g, 2.00 mmol) in an ethanolic sodium ethoxide solution (0.1 g Na in 5 ml EtOH) was refluxed for 30 min. The produced solid that was separated out during reflux was filtered off, dried and recrystallized from ethanol as white crystals. IR: 3127 (CH - pyrrole), 2989–2824 (CH - aliph), 1629 (2C═O). ^{1}H NMR: 1.19 (3H, s, CH_3 pyrazolone), 1.59–1.65 (6H, m, $3CH_2$: C_3' - C_5'), 1.71–1.72 (4H, m, $2CH_2$: C_7, C_8), 2.28–2.38 (2H, m, CH_2: C_6), 2.57–2.65 (2H, m, CH_2: C_9), 3.18–3.20 (4H, m, $2CH_2$-N: C_2', C_6'), 4.19 (2H, s, CH_2 pyrazolone), 6.32–6.33 (2H, m, C_3'', C_4''), 6.69–6.70 (2H, m, C_2'', C_5''). ^{13}C NMR: 13.95 (C_6, CH_3 pyrazolyl), 22.17 (C_7), 22.40 (C_8), 22.42 (C_4'), 24.60 (C_3', C_5'), 26.12 (C_6), 26.74 (C_9), 51.00 (C_4, CH_2 pyrazolyl), 61.20 (C_2', C_6'), 109.06 (C_3'', C_4''), 122.84 (C_{5a}), 123.58 (C_2'', C_5'', C_{9b}), 123.77 (C_{9a}), 124.09 (C_2), 136.96 (C_1, C_{3a}), 144.43 (C_5 pyrazolyl), 156.37 (C_5), 161.36 (C_3, CO pyrazolyl), 163.13 (C_{10}: C═O).

3.1.8. 5-(5-(Piperidino)-1-(1H-pyrrolyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinolin-2-yl)-1,3,4-oxadiazole-2 (3H)-thione (9)

A sample of the carbohydrazide **1** (1.00 g, 3.00 mmol) and carbon disulfide (2.00 ml, 0.03 mol) in dry pyridine (4 ml) was heated at 100 °C in a steam bath for 5 h. The precipitated solid which was separated out during reflux was triturated with ethanol, filtered, dried and recrystallized from a mixture of ethanol / dioxane (1:1) into yellow crystals. IR: 3119 (NH), 3106 (CH - pyrrole), 2927, 2849 (CH - aliph), 1251 (C═S). ^{1}H NMR: 1.45–1.64 (6H, m, $3CH_2$-N: C_3' - C_5), 1.66–1.72 (4H, m, $2CH_2$: C_7, C_8), 2.16–2.37 (2H, m, CH_2: C_6), 2.54–2.66 (2H, m, CH_2: C_9), 3.19–3.22 (4H, m, $2CH_2$-N, C_2, C_6), 6.39–6.40 (2H, m, C_3, C_4), 6.72–6.74 (2H, m, C_2, C_5), 7.26 (1H, s, NH). ^{13}C NMR: 22.06 (C_7), 22.37 (C_8), 22.39 (C_4), 24.56 (C_3, C_5), 26.79 (C_6), 29.70 (C_9), 50.99 (C_2, C_6'), 110.03 (C_3, C_4), 115.10 (C_{5a}), 122.70 (C_2, C_5), 124.09 (C_{9b}), 134.76 (C_2), 136.86 (C_{9a}), 144.12 (C_1), 149.06 (C_{3a}), 156.36 (C_5: oxadiazole), 162.96 (C_5), 177.70 (C═S, C_2 oxadiazole).

3.1.9. Ethyl 2-((5-(5-(piperidino)-1-(1H-pyrrolyl)-6,7,8,9-tetrahydrothieno[2,3-c] isoquinolin-2-yl)-1,3,4-oxadiazol-2-yl) thio) acetate (10)

The oxadiazolyl thione **9** (0.50 g, 1.00 mmol) and ethyl chloroacetate (0.20 ml, 1.30 mmol) in ethanol (20 ml) and fused sodium acetate (0.90 g, 0.01 mol) were refluxed for 2 h. The precipitate that was separated out during reflux was collected and recrystallized from ethanol as green crystals. IR: 3125, 3106 (CH - pyrrolyl), 2955–2831 (CH - aliphatic), 1721 (C═O ester). ^{1}H NMR: 1.25–1.30 (3H, t, J = 7.10 Hz, CH_3 ester), 1.37–1.65 (6H, m, $3CH_2$: C_3' - C_5'), 1.71–1.97 (4H, m, $2CH_2$: C_7, C_8), 2.36–2.39 (2H, m, CH_2: C_6), 2.66–2.78 (2H, m, CH_2: C_9), 3.18–3.19 (4H, m, $2CH_2$: C_2', C_6'), 3.82 (2H, s, SCH_2), 4.19–4.24 (2H, q, J = 7.10 Hz, CH_2 ester), 6.34–6.35 (2H, m, C_3'', C_4''), 6.71–6.72 (2H, m, C_2'', C_5''). ^{13}C NMR: 14.08 (C_{15}, CH_3 ethyl ester), 22.11 (C_7), 22.42 (C_8), 24.57 (C_4'), 26.11 (C_3', C_5'), 26.72 (C_6), 29.70 (C_9), 33.74 (C_{11}, SCH_2), 51.01 (C_2', C_6'), 62.28 (C_{14}, CH_2 ethyl ester), 109.79 (C_3'', C_4''), 116.39 (C_{5a}), 122.98 (C_2'', C_5''), 123.06 (C_{9b}), 123.98 (C_{9a}), 133.76 (C_2), 143.81 (C_1), 156.23 (C_{3a}), 160.94 (C_5, oxadiazolyl), 162.75 (C_2, oxadiazolyl) 162.86 (C_5), 167.34 (C_{10} : CO ester).

3.2. The in-vitro antibacterial assessment procedure

All of the used microorganisms were attained from the culture collection of the Microbiology Department at the Faculty of Medicine at Assiut University. The activities of several compounds were determined in comparison to bacterial strains using a 5 ml concentration of the verified compounds in DMSO as a solvent. The synthesized compounds were first screened in DMSO at a maximum concentration of 100 g/mL with Amoxicillin as a control. Each Petri dish's sterile medium (Nutrient Agar Medium, 15 ml) was uniformly smeared with Gram (+ve) and Gram (-ve) bacteria cultures.

3.3. The in-vitro antifungal assessment procedure

The strains of fungi (*Candida albicans*, *Aspergillus flavus*, *Geotrichum candidium* and *Trichophyton rubrum*) were obtained from human dermatophytosis at the Mycological Center at Assiut University (AUMC). To prevent bacterial contamination, the strains were grown in 9-cm sterilized Petri dishes with Sabouraud's dextrose agar (SDA) supplemented with 0.05 percent chloramphenicol (Al-Doory, 1980). The spore-containing agar discs from these cultures (10 mm diameter) were aseptically transferred to screw-top vials containing 20 ml sterile distilled water.

After shaking, the spore suspension samples (1 ml) were pipetted into sterile Petri dishes, and a liquefied SDA medium was added (15 ml). The samples were then allowed to solidify. To achieve a 2.0 percent concentration, the studied compounds **1**, **3**–**5**, and **6a-c**, as well as Clotrimazole, were dissolved in DMSO.

Antibacterial and antifungal activities were measured using 5-mm-diameter filter wells loaded with 50 μL of the solution under study (2.0 %) according to Kwon-Chung and Bennett's methodology (Kwon-Chung and Bennett, 1992). The inhibition zones were measured in mm (Tables 1 and 2) after 24 h of incubation 37 ± 2 °C.

3.4. The minimum inhibitory concentration (MIC) technique

The synthesized compounds **1**, **3**, **4**, **5**, and **6a-c** were dissolved in DMSO to make a solution of 2 % concentration. Filter paper discs (Whatman No. 3) approximately 5 mm in diameter were soaked in 15 ml of the tested compound solutions before being put onto a surface of the previously prepared agar plates seeded by the tested bacteria. To ensure full contact with the agar surface, each disc was immersed. The agar plates were then incubated for bacteria at 37 °C for 16–18 h, and at room temperature for the rest of time. The diameters of the compound inhibition zones were calculated and described in the table above. The commercial antibiotic Amoxicillin, which was used as a positive control for bacteria, underwent a similar procedure (Kwon-Chung and Bennett, 1992; Al-Doory, 1980). The micro dilution technique was used to measure each compound's minimum inhibitory concentration (MIC). The biologically active compounds were serially diluted in DMSO and inoculated with the test culture in 10 ml broth tubes for 24 h. The MIC of each compound was described as the lowest concentration (μg mL^{-1}) at which no detectable bacteria were present.

4. Conclusion

In the current study, we have provided an easy and simple way to synthesize new piperidinyl thienotetrahydroisoquinoline heterocycles. The pyrrolyl carbohydrazide **1** was used as an adaptable precursor for synthesizing novel heterocycles attached or fused to the thieno tetrahydroisoquinoline moiety. The reactions based on diazotization of **1** followed by reactions with ethanol and aniline and boiling in dry xylene under *Curtius* reaction conditions producing compounds **3**–**5**. Moreover, condensation of **1** with various aromatic aldehydes and 1,3-dicarbonyl compounds furnished the corresponding Schiff's bases in addition to the pyrazolone derivative **8**. The new oxadiazolyl thione **9** was produced by nucleophilic addition to carbon disulfide, which was S-alkylated to compound **10** through the reaction with ethyl chloroacetate. The reaction products were isolated simply and cleaned by recrystallization. Selected compounds were chosen for screening the antibacterial and antifungal evaluation. The results confirmed that compounds **1** and **3** revealed the best antibacterial activity, while compounds **4**, **6b** and **6c** displayed the highest antifungal effects. Therefore, this sophisticated approach could be applied for synthesizing medicinally and pharmaceutically important compounds.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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