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Synthesis and Antimicrobial Activity of New Heterocyclic Compounds Containing Thieno[3,2-*c*]coumarin and Pyrazolo[4,3-*c*]coumarin Frameworks[1]

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Abstract—Reaction of 4-chlorocoumarin-3-carbonitrile with ethyl thioglycolate and ethyl glycinate hydrochloride leads to a series of title products. Hydrazinolysis of amino thienocoumarin carboxylate afforded the hydrazino derivative which underwent various reactions to build new heterocyclic rings containing thienocoumarin moiety. Chloro acetylation of aminoester compound afforded the chloro acetyl amino which underwent nucleophilic substitution reactions with various amines. The following treatment with formaldehyde under Mannich conditions afforded the corresponding imidazo derivatives. Reaction of chloroacetylamino with potassium thiocyanate yielded ethylpyrimidothieno coumarin sulfanylacetate which was used as a versatile precursor for synthesis of other heterocycles. On the other hand, reaction of chloro coumarin carbonitrile with hydrazine gave the aminopyrazolocoumaine which reacted with bifunctionally compounds to give the substituted pyrimido derivatives. Diazotization and coupling of aminopyrazole with ethylcyanoacetate yielded ethylaminotriazinopyrazolocoumarine carboxylate. Several of the compounds obtained demonstrated considerable antifungal and antibacterial activity in the in vitro test systems.

Keywords: thienocoumarine, pyrazolocoumarine, pyrimidothienocoumarine, imidazo thienocoumarine, synthesis, anti-microbial activity

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INTRODUCTION

Coumarins contain the parent nucleus of benzo(-pyrone) and occur in plants of Orchidaceae and Leguminaceae families [1]. Naturally occurring and synthetic coumarins display important pharmacological properties, such as antitumor [2], anticonvulsant [3], anti-inflammatory [4, 10], anti-HIV [5], anticoagulant [6], antibacterial [7] and antioxidant [8, 9] activities. Among the diverse activities of coumarin the effect against breast cancer seems to draw special attention [11–13]. Coumarins are also used to prepare other chemicals, in particular rodent poisons, such as warfarin or insecticides such as hymecromone. Their anti-inflammatory properties are usually associated with the capability of modulating the inflammatory cells [14].

The main representatives of the class are the hydroxyl derivatives, 4- and 7-hydroxy coumarins, also biologically active and very important for the synthesis of other coumarin derivatives. Bearing in mind the above benefits of coumarin derivatives, in this work we aimed to build a heterocyclic ring on coumarin starting from the commercially available 4-hydroxycoumarin and hoping that the new products described below are biologically useful.

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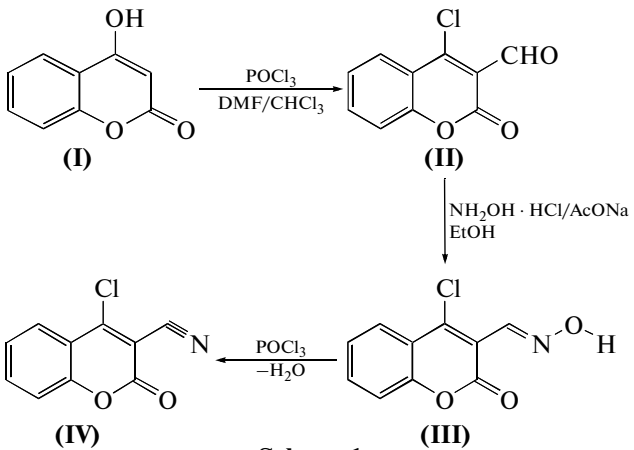
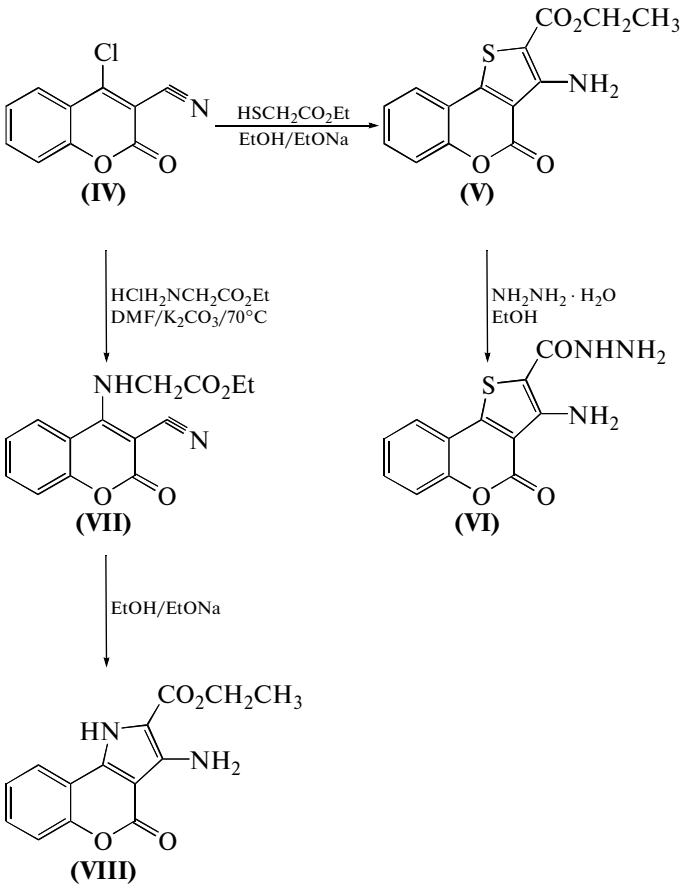
RESULTS AND DISCUSSION

Reaction of 4-hydroxycoumarin (**I**) with $HCONMe_2$: $POCl_3$ mixture in chloroform under Vilsmeier–Haack reaction conditions afforded chlorocoumarin carboxaldehyde (**II**) [15]. Aldehyde (II) was condensed with hydroxyl-amine hydrochloride in refluxing ethanol in the presence of fused sodium acetate to give the corresponding oxime (**III**). The latter compound was dehydrated using $POCl_3$ to afford *4-chloro-2H-coumarin-3-carbonitrile* **(IV)** (Scheme 1).



Scheme 1.

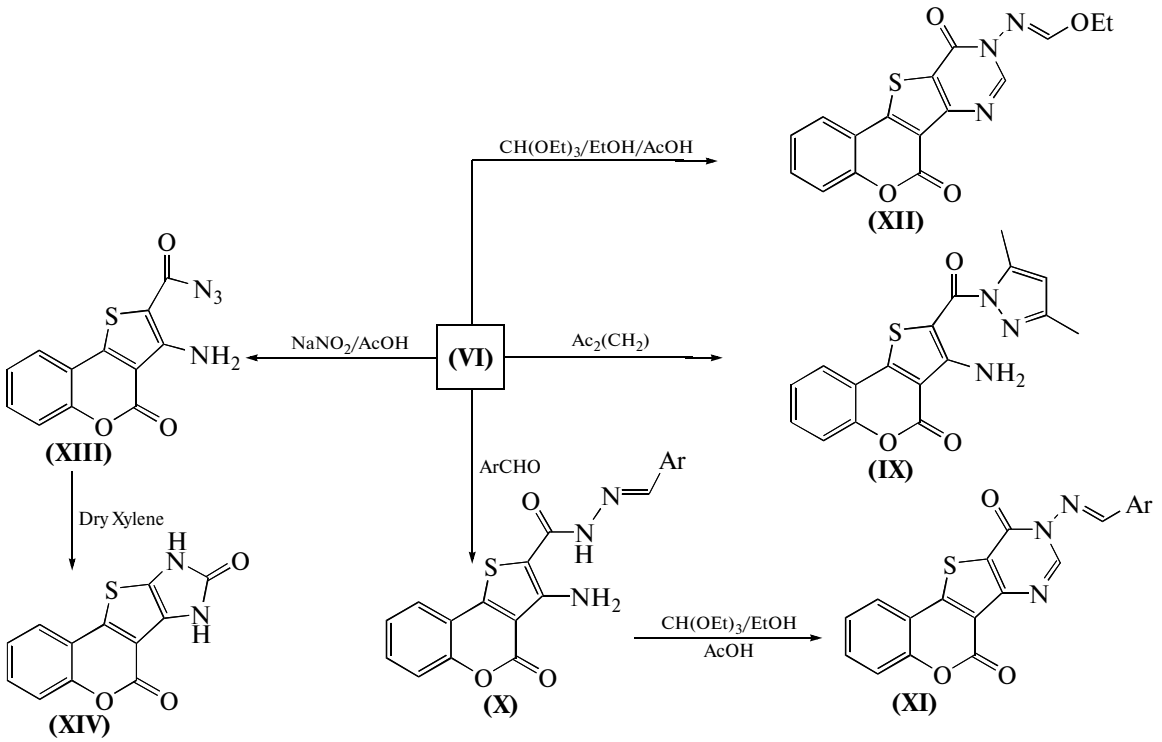
Chlorocarbonitrile (**IV**) was reacted with ethyl thioglycolate in ethanolic sodium ethoxide to afford ethyl aminothienocoumarincarboxylate (**V**). Reaction of amino ester (**V**) with hydrazine under neat conditions afforded the corresponding carbohydrazide (**VI**). On the other hand, chlorocarbonitrile (**V**) was reacted with ethyl glycinate hydrochloride in DMF in the presence of K_2CO_3 to afford glycinate derivative (**VII**), which cyclized in ethanolic sodium ethoxide solution to ethyl 3-amino-4-oxo-1,4-dihydrochromeno[4,3-b]pyrrole-2-carboxylate (**VIII**) (Scheme 2).



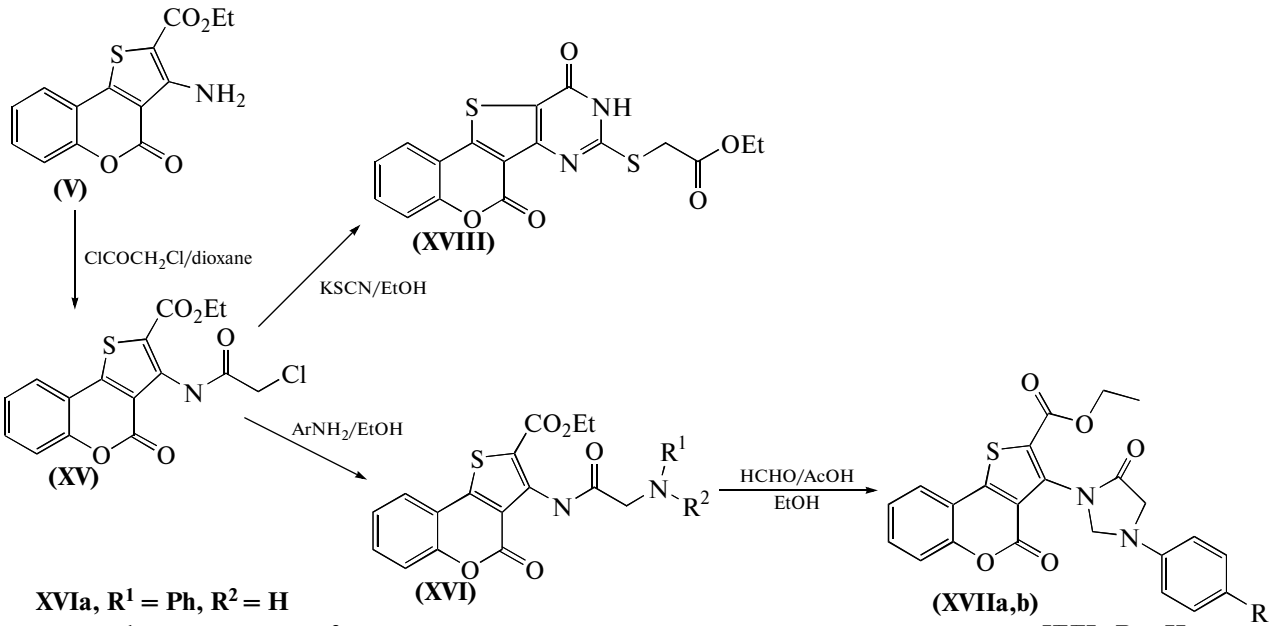
Scheme 2.

Thienochromenecarbohydrazide (**VI**) was considered as precursor of other heterocyclic compounds. Condensation of carbohydrazide (**VI**) with acetyl acetone in ethanol afforded pyrazolyl derivative (**IX**). Condensation of carbohydrazide (**VI**) with aromatic aldehyde to gave the corresponding hydrazone (**X**). Which was cyclized using triethyl orthoformate in ethanol in the presence of catalytic drops of acetic acid to give pyrimidothienochromene (**XI**). Carbohydrazide (**VI**) was also reacted with triethyl orthoformate in ethanol in the presence of catalytic drops of acetic acid to give pyrimidothienocoumarine (**XII**). Also, carbohydrazide (**VI**) was converted to the corresponding carboazide (**XIII**) using sodium nitrite solution in acetic acid. The product underwent Curtius rearrangement upon boiling in an inert solvent (dry xylene) to afford imidazothienocoumarine (**XIV**) (Scheme 3).

Aminothienochromene (**V**) was reacted with chloroacetyl chloride in dioxane at 70°C to afford the corresponding chloroacetyl amino derivative (**XV**). The latter underwent nucleophilic substitution reaction with aromatic amines to give arylaminoacetyl derivatives (**XVIa–f**). Treatment of compounds (**XVIa,b**) with formaldehyde under *Mannich* conditions afforded 1,3–diaminourea compounds (**XVIIa,b**). Reaction of chloroacetyl derivative (**XV**) with potassium thiocyanate in ethanol lead to pyrimidothienolcoumarinysulfanylacetate (**XVIII**) in one step [16] (Scheme 4).

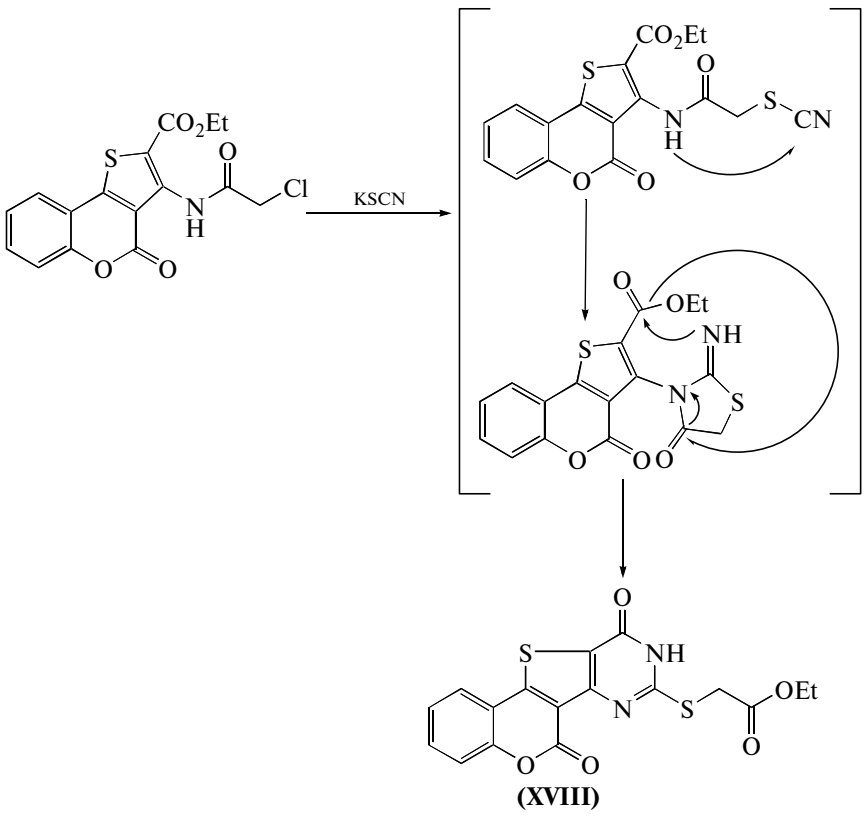


Scheme 3.



XVIa, R^1 = Ph, R^2 = H
XVIb, R^1 = $C_6H_4CH_3$-p, R^2 = H
XVIc, R^1, R^2 = piperidinyl
XVId, R^1, R^2 = morpholinyl
XVIe, R^1, R^2 = piperazinyl
XVIf, R^1 = $C_6H_4SO_2NH_2$-p, R^2 = H
XVIg, R^1 = $C_6H_4SO_2NH$-diazine-p, R^2 = H

Scheme 4.



(XVIII)

Scheme 5.

The putative intermediates on the route to pyrimidothienocoumarin (**XVIII**), are showen in Scheme 5.

The ethyl thioacetate compound ester (**XVIII**) was used as versatile precursor for synthesis of other pyrimidothienocoumarine derivatives (**XIX–XXI**). Hydrazinolysis of ester (**XVIII**) with hydrazine under neat conditions afforded the corresponding carbohydrizde derivative (**XIX**). Reaction of carbohydrazide (**XIX**) with acetyl acetone in ethanol gave the dimethylpyrazolyl derivative (**XX**), while reaction with bezaldehyde in presence of piperidine as a basic catalyst afforded the corresponding Schiff's base (**XXI**) (Scheme 6).

Reaction of chlorocoumarinecarbonitrile (**IV**) with hydrazine in ethanol afforded the aminopyrazolocoumarine (**XXII**) which was used as a starting material for synthesis of other heterocyclic compounds. Thus, condensation of (**XXII**) with bifunctional compounds namely: acetyl acetone, ethyl cyanoacetate, diethyl malonate, ethyl acetoacetate and ethyl benzoylacetate in acetic acid afforded the corresponding pyrimido derivatives (**XXIII)–(XXIV**) (Scheme 7).

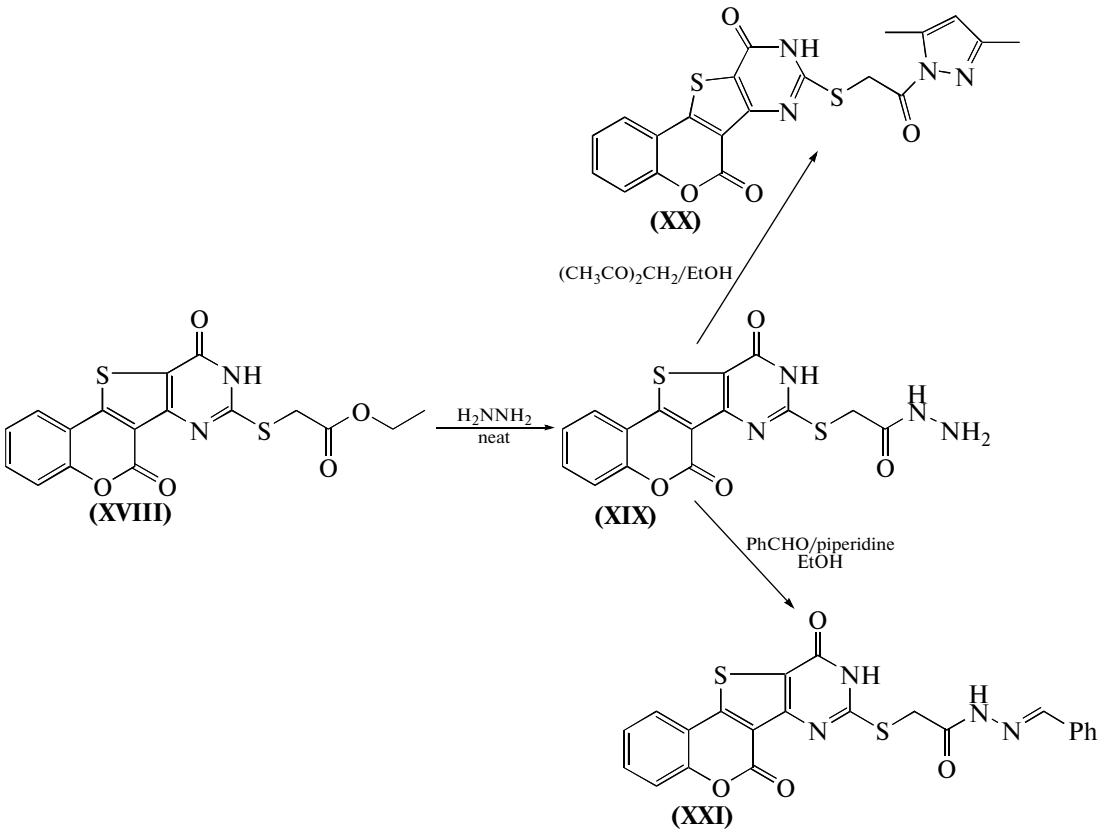
Reaction of aminopyrazolocoumarine (**XXII**) with ethyl-2-cyano-3-ethoxyacrylate afforded ethylcyanodihydropyrazolocoumarinylaminoacrylate (**XXVIII**). Refluxing ethyl acrylate ester with acetic acid yielded ethylaminopyrimidopyrazolocoumarine carboxylate (**XXIX**). In this case the pyrazole NH acted as a nucleophile and attack carbonitrile group.That step was followed by tautomerisation, rather than loss of ethanol molecule which would afford oxopyrimidocoumarine carbonitrile (**XXX**). Diazotization of amino group in compound (**XXII**) with sodium nitrite solution in conc HCl afforded the diazonium salt (**XXXI**) which was coupled (in situ) with ethyl cyanoacetate and ethyl acetoacetate in presence of sodiumacetat giving rise to ethylaminotriazinooyrazolocoumarinecarboxylate (**XXXII**) andethylbutanoate compounds (**XXXIII**) respectively (Scheme 8).

Chemical structure and homogeneity of all products obtained was confirmed by IR and NMR spectroscopy, mass-spectrometry and elemental microanalysis.

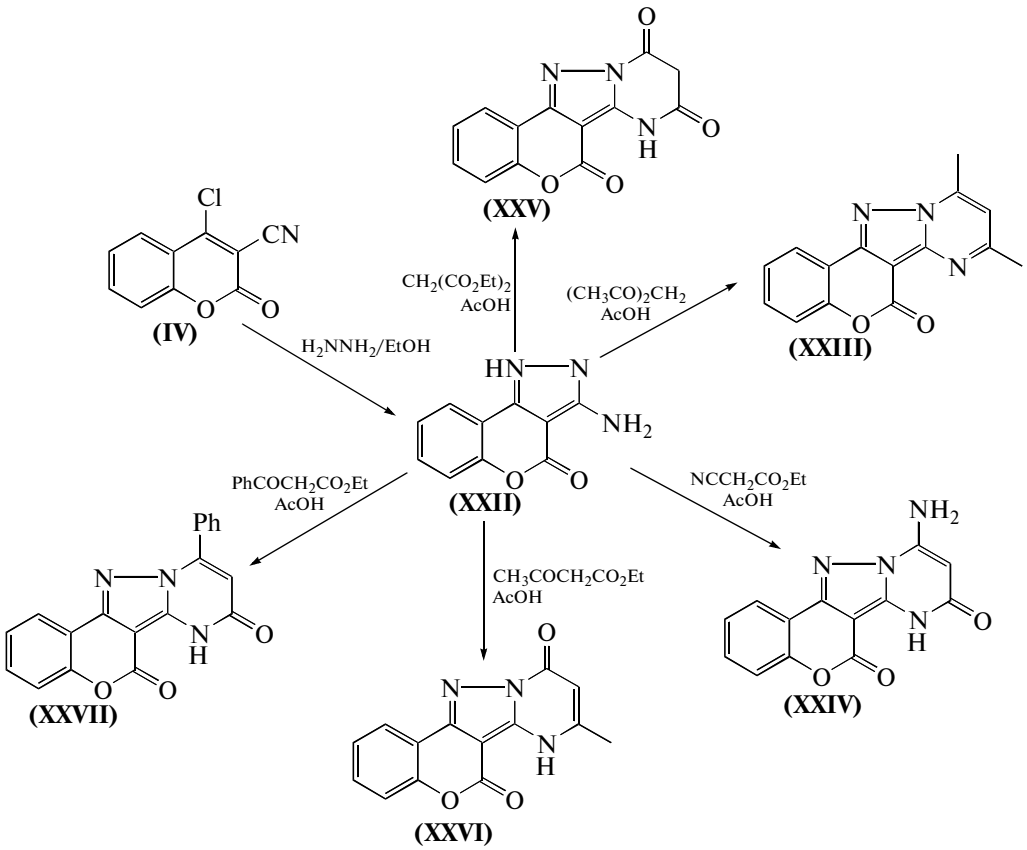
Biological Activities

Some of the synthesized compounds in this work screened in vitro for their antimicrobial activity against some strains of bacteria and fungi by technique described in [17]. 2% concentration of selected compounds in DMSO was used in all cases. The inhibition zone (mm) compared with clortrimazole as a reference.in the case of antifungal tests and with chloramphenicol in case of antibacterial tests.

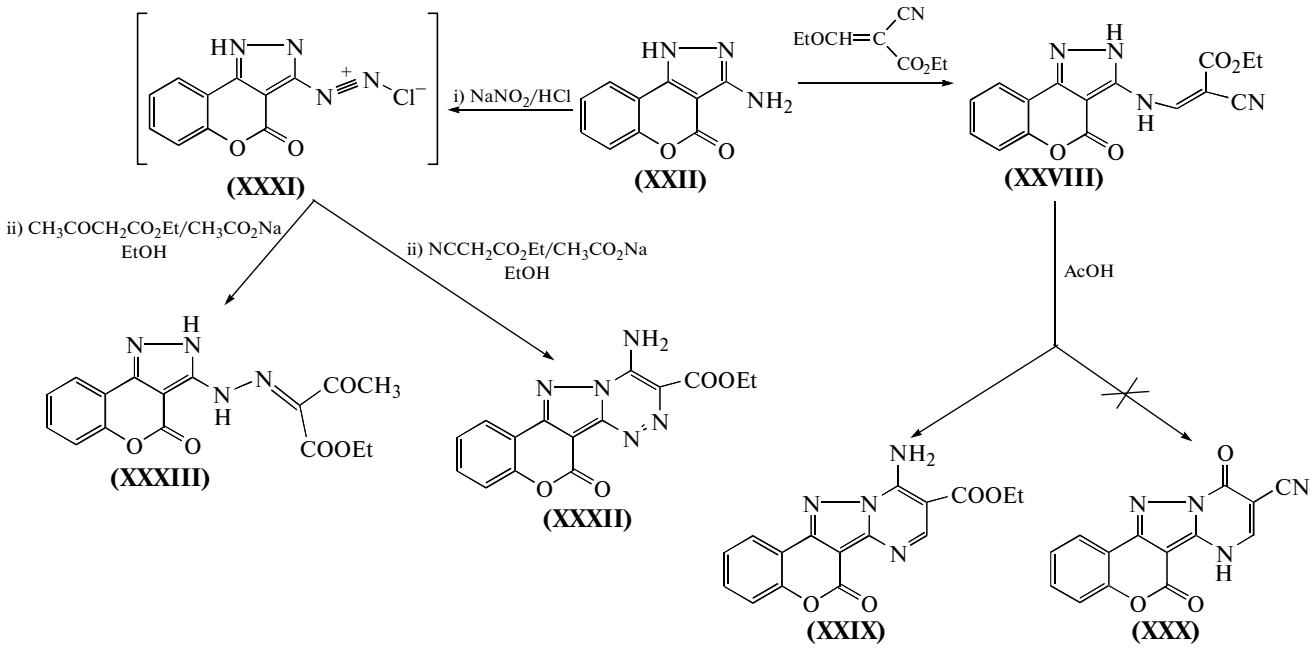
Some tested compounds showed remarkable antibacterial and anti fungal activities. In case of anti-fun-



Scheme 6.



Scheme 7.



Scheme 8.

gal activity (Table 1) aminothienocoumarinecarboxylate (**V**) is effective only *Candida albicans* and *Scopulariopsis*, while replacement of the ester group with carbohydrazide group in compound (**VI**) considerably broadens the spectrum of activity and leads to highly active product. The glycinate derivative (**VII**) is also quite active. The cyclized compound (**VIII**) shows low activity, as well as compounds (**XV**, **XVIb**, **XVId**, **XVIe**, **XVIf**, **XVIg**). Somewhat unexpectedly compound (**XVIa**) shows high activity, comparable to that of (**VI**) and (**VII**). Replacement of the thieno ring in compound (**V**) by pyrazole ring leads to active derivative (**XXXII**); compound (**XXIV**) is active only against *Candida albicans* and *Geotrichum candidum*.

As for the antibacterial activity, compounds (**XVIa**, **XVIb**, **XVIe** and **XXXII**) showed no anti-bacterial activity against all bacterial species (Table 2). Almost all of the remaining samples were active

Table 1. Antifungal activity (inhibtion zone, mm)

Compd.	*Candida albicans*	*Trichphyton rubrum*	*Aspergillus flavus*	*Fusarium oxysporum*	*Scopulariopsis brevicaulis*	*Geotrichum candidum*
(V)	13	0	0	0	8	0
(VI)	14	0	10	16	13	13
(VII)	9	10	0	9	10	0
(VIII)	12	0	0	0	0	12
(XV)	10	0	0	0	0	0
(XVIa)	13	10	12, p.i.	0	10	11
(XVIb)	13	0	0	0	0	8
(XVId)	0	0	0	0	0	0
(XVIe)	0	0	0	0	0	0
(XVIf)	0	0	0	0	0	10
(XVIg)	13	0	0	0	0	0
(XXIV)	10	0	0	0	0	8
(XXXII)	14	12, pi	9	9	10	12
Clotrimazole	20	36	44	28	20	24

p.i., partial inhibition.

Table 2. Antibacterial activity (inhibtion zone, mm)

Compd.	*Staphlococcus aureus* (+ve)	*Bacillus cereus* (+ve)	*Escherichia coli* (−ve)	*Pseudomonas aeruginos* (−ve)	*Serratia marcescens* (−ve)	*Micrococcus luteus* (+ve)
(V)	9	0	0	10	8	8
(VI)	10	0	0	10	11	0
(VII)	8	9	0	8	0	8
(VIII)	10	0	10	0	0	0
(XV)	8	0	0	0	0	0
(XVIa)	0	0	0	0	0	0
(XVIb)	0	0	0	0	0	0
(XVId)	0	0	0	9	0	0
(XVIe)	0	0	0	0	0	0
(XVIf)	9	0	0	11	12	0
(XVIg)	10	0	9	0	0	0
(XXIV)	10	0	9	9	0	0
(XXXII)	0	0	0	0	0	0
Chloramphenicol	18	22	18	18	20	20

against *Staphylococcus aureus*. Other bacterial strains were selectively susseptible to the action of tested derivatives. For example, the aminothieno coumarin-ecarboxylate (**V**) and carbohydrazide (**VI**) exhibited remarkable activity especially against *Pseudomonas aeruginosa*.

EXPERIMENTAL

All melting points are uncorrected and measured on a Fisher–John apparatus. Elemental analyses were determined on an Elementar Analysensystem GmbH VarioEL V.3 microanalyzer 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. NMR spectra were recorded on a varian EM-390 90 MHz and Joel 400 MHz spectrometers in a suitable deutrated solvent using TMS as internal standard (chemical shifts in ppm). MS spectra were recorded on Jeol JMS-600 apparatus. Compounds (**I**) and (**IV**) were prepared according to literature procedure [15] with melting points 120–122°C, 190–192°C, 152–154°C respectively.

Ethyl 3-amino-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (V). A mixture of chloro compound (**IV**) (4.9 g, 0.024 mol) and ethyl thioglycolate (3 mL, 0.025 mol) was stirred in absolute ethanol (20 mL) in presence of sodium ethoxide (1 mL, 0.1 mol) for 1 h. The solid product formed was collected, dried and recrystallized from ethanol as a yellow precipitate in 88% yield, m.p. 208–210°C; IR: 3480, 3350 (NH_2), 3030 (CH aromatic), 2900, 2850 (CH aliphatic), 1725 (C=O *chromene*), 1695 (C=O ester) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.30–1.45 (3H, $J = 7.0$ Hz, t, CH_3), 4.30–4.50 (2H, $J = 6.0$ Hz, q, CH_2), 6.90 (2H, s, NH_2), 7.20–7.80 (4H, m, ArH). Mass: *m/z*: 289.71 [M^+], 288.70 [$M^+ - 1$]. Found: C, 58.23; H, 3.96; N, 4.78; S, 11.15%. Calculated: $C_{14}H_{11}NO_4S$ (289.31): C, 58.12; H, 3.83; N, 4.84; S, 11.08%.

3-Amino-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carbohydrazide (VI). A mixture of amino ester (**V**) (2 g, 7 mmol) and hydrazine 99% (3 mL, 0.06 mol) was fused for 1 h then absolute ethanol (7 mL) was added dropwise. The reaction mixture was refluxed for additional two h. The solid product formed on hot during reflux was recrystallized from ethanol to give pale yellow crystals in 76% yield, m.p. 280–282°C. IR: 3470, 3300, 3180 (NH, NH_2), 3050 (CH aromatic), 2900, 2870 (CH aliphatic), 1725 (C=O *chromene*), 1630 (CONH). ^1H NMR (DMSO-d_6): δ 4.40, 4.70 (4H, 2s, $2NH_2$), 6.90–7.60 (4H, 2s, $2NH_2$), 6.90–7.60 (4H, m, ArH), 7.85 (1H, s, NH). Mass: *m/z* 274.6 [M^+], 243.19 [$M^+ - 31$]. Found: C, 52.30; H, 3.35; N, 15.15; S, 11.75%. Calculated: $C_{12}H_9N_3O_3S$ (275.29): C, 52.36; H, 3.30; N, 15.26; S, 11.65%.

(3-Cyano-2-oxo-2*H*-chromen-4-ylamino)-acetic acid ethyl ester (VII). A mixture of 4-chloro-2-oxo-2*H*-chromene-3-carbonitrile (**IV**) (0.88 g, 4.3 mmol) and ethyl glycinate hydrochloride in DMF (10 mL) was heated on steam bath in presence of anhydrous potassium carbonate (0.5 g, 3.6 mmol) for 4 h to afford a brown precipitate which was recrystallized from ethanol as brown crystals in 50% yield, m.p. 198–200°C. IR: 3300 (NH), 3100 (CH aromatic), 2900, 2850 (CH aliphatic), 2150 (CN), 1720 (C=O *chromene*), 1700 (C=O ester). ^1H NMR (DMSO-d_6): δ 1.20–1.35 (3H, t, CH_3), 3.80 (2H, s, CH_2), 4.15–4.40 (2H, q, CH_2), 7.30–7.80 (4H, m, ArH), 10.30 (1H, s, NH). Found:

C, 61.70; H, 4.60; N, 10.10%. Calculated: $C_{14}H_{12}N_2O_4$ (272.26): C, 61.76; H, 4.44; N, 10.29%.

Ethyl 3-amino-4-oxo-1,4-dihydrochromeno[4,3-*b*]pyrrole-2-carboxylate (VIII). A solution of ethyl amino acetate ester (**VII**) (0.27 g, 1 mmol) in DMF (10 mL) was heated on steam bath in presence of anhydrous potassium carbonate (0.3 g, 2.17 mmol) for 10 h. The solid precipitate which formed on cooling and diluted with water was filtered off, dried and recrystallized from ethanol as pale brown crystals in 53%, m.p.: 260–264°C; IR: 3300, 3250, 3150 (NH + NH_2), 3030 (CH aromatic), 2900, 2850 (CH aliphatic), 1720 (C=O *chromene*), 1690 (C=O unsaturated ester). ^{1}H NMR (DMSO-d_6): δ 1.35–1.50 (3H, J = 9.0 Hz, t, CH_3), 4.20–4.40 (2H, J = 7.5 Hz, q, CH_2), 6.20 (2H, s, NH_2), 7.30–7.80 (4H, m, ArH), 10.10 (1H, s, NH). Mass: m/z 273.15 [M^++ 1], 272.10 [M^+]. Found: C, 61.80; H, 4.52; N, 10.35%. Calculated: $C_{14}H_{12}N_2O_4$ (272.26): C, 61.76; H, 4.44; N, 10.29%.

3-Amino-2-[(3,5-dimethyl-1*H*-pyrazol-1-yl)carbonyl]-4*H*-thieno[3,2-*c*]chromen-4-one (IX). A mixture of carbohydrazide (**VI**) (1 g, 3.6 mmol) and acetyl acetone (0.4 mL, 4 mmol) was refluxed in ethanol (10 mL) for 4 h. The yellow precipitate was filtered off and recrystallized from ethanol as yellow crystals in 77% yield, m.p. 216–218°C. IR: 3450, 3350 (NH_2), 3050 (CH aromatic), 2930 (CH aliphatic), 1700 (C=O *chromene*), 1680 (C=O). ^{1}H NMR (CF_3CO_2D): δ 2.40–2.60 (6H, 2s, $2CH_3$), 6.00 (1H, 2s, $2CH_3$), 6.00 (1H, s, CH *pyrazole*), 7.10–7.60 (4H, m, ArH. Mass: m/z 338.89 [M^+]. Found: C, 60.20; H, 3.75; N, 12.45; S, 9.54%. Calculated: $C_{17}H_{13}N_3O_3S$ (339.38): C, 60.17; H, 3.86; N, 12.38; S, 9.45%.

3-Amino-4-oxo-*N*'-[(1*E*)-phenylmethylene]-4*H*-thieno[3,2-*c*]chromene-2-carbo hydrazide (X). A mixture of carbohydrazide (**V**) (0.5 g, 1.82 mmol) and benzaldehyde (1 mL, 10 mmol) in ethanol (10 mL) was refluxed for 3 h. in presence of few drops of piperdiene (0.5 mL) as a catalyst. The solid product formed on hot during reflux was collected and recrystalized from dioxane to give yellow crystals in 60% yield, m.p. 165–167°C; IR: 3580, 4470, 3380 (NH, NH_2), 1670 (C=O amide), 1618 (C=N), 1720 (C=O *chromene*). ^{1}H NMR (CF_3CO_2D): δ 7.70–7.90 (m, ArH). Found: C, 62.73; H, 3.54; N, 11.48; S, 8.65%. Calculated: $C_{19}H_{13}N_3O_3S$ (363.40): C, 62.80; H, 3.61; N, 11.56; S, 8.82%.

9-{[(1*E*)-Phenylmethylene]amino}-6*H*-chromeno-[3',4':4,5]thieno[3,2-*d*]pyrimidine-6,10(9*H*)-dione (XI) Amixture of 3-amino-4-oxo-*N*'-[(1*E*)-phenylmethylene]-4*H*-thieno[3,2-*c*]chromene-2-carbohydrazide (**X**) (0.25 g, 0.60 mmol) and triethyl orthoformate (2 mL, 0.014 mol) was refluxed in ethanol (10 mL) and a few drops of glacial acetic acid (0.3 mL) was added and the mixture refluxed for 3 h. The solid product which formed on hot during reflux filtered off, dried and recrystallized from dioxane as yellow precipitate in 80% yield, m.p. 298–300°C. IR: 3150 (CH aromatic), 2900–2850 (CH aliphatic), 1710 (C=O *chromene*), 1610 (CO). ^{1}H NMR (CF_3CO_2D) δ: 7.50–7.90 (9H, m, ArH), 8.20 (1H, s, CH pyrimidine), 9.80 (1H, s, CH=N). Found: C, 64.25; H, 2.85; N, 11.38; S, 8.46%. Calculated: $C_{20}H_{11}N_3O_3S$ (373.39): C, 64.34; H, 2.97; N, 11.25; S, 8.59%.

Ethyl (6,10-dioxo-6*H*-chromeno[3',4':4,5]thieno[3,2-*d*]pyrimidin-9(10*H*)-yl)imido-formate (XII). A mixture of 3-amino-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carbohydrazide (**VI**) (2 g, 0.01 mol) and triethyl orthoformate (4 mL, 0.027 mol) was refluxed in presence of glacial acetic acid (1 mL) for 1 h. A white precipitate was formed on hot during reflux. The solid product filtered off, dried and recrystallized from ethanol-dioxane mixture as white crystals in 75% yield, m.p. 318–320°C. IR: 3030 (CH aromatic), 2910, 2850 (CH aliphatic), 1740 (C=O *chromene*), 1675 (C=O pyrimidine). ^{1}H NMR (CF_3CO_2D): δ 1.25–1.40 (3H, t, CH_3), 4.35–4.50 (2H, q, CH_2), 7.60–8.30 (4H, m, ArH), 9.80 (1H, s, CH=N), 10.20 (1H, s, CH pyrimidine). Mass: m/z 340.13 [M^+– 1], 338.76 [M^+– 2]. Found: C, 56.42; H, 3.18; N, 12.26; S, 9.43%. Calculated: $C_{16}H_{11}N_3O_4S$ (341.35): C, 56.30; H, 3.25; N, 12.31; S, 9.39%.

3-Amino-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carbonylazide (XIII). To a Stirred a solution of 3-amino-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carbohydrazide (**VI**) (0.5 g, 1.80 mmol) in of glacial acetic acid (15 mL) then adding sodium nitrite solution (0.5 g, 7.25 mmol, 10%) was added drop wise at 0°C for 1/2 h a dark brown precipitate is formed. The product formed filtered off, washed with water, dried and used without recrystallization for the following step, in 47% yield, m.p. 160–162°C. IR: 3450, 3350 (NH_2), 2950, 2850 (CH aliphatic), 2100 (N_3), 1720 (C=O *chromene*), 1665 (C=O azide). ^{1}H NMR (DMSO-d_6): δ 6.55 (2H, s, NH_2), 7.20–7.60 (4H, m, ArH). Found: C, 50.39; H, 2.07; N, 19.52; S, 11.26%. Calculated: $C_{12}H_6N_4O_3S$ (286.27): C, 50.35; H, 2.11; N, 19.57; S, 11.20%.

Rearrangement of 3-amino-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carbonylazide (XIII): Formation of 7,9-dihydro-6*H*,8*H*-chromeno[3',4':4,5]thieno[2,3-*d*]imidazole-6,8-dione (XIV). 3-Amino-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carbonylazide (**XIII**) (1 g, 3.5 mmol) in dry xylene (10 mL) was refluxed for 1½ h. The solid product which formed on hot was filtered off, washed several times with xylene, dried and recrystallized from xylene as dark green crystals in 60% yield, m.p. 345–347°C. IR: 3450, 3250 (2NH), 3050 (CH aliphatic), 2950–2860 (CH aliphatic), 1720 (C=O *chromene*), 1630 (C=O *imidazole*). ^{1}H NMR (CF_3CO_2D): δ 7.20–7.70 (m, ArH). Found: C, 55.88; H, 2.30; N, 10.81; S, 12.50%. Calculated: $C_{12}H_6O_3N_2S$ (258.26): C, 55.81; H, 2.34; N, 10.85; S, 12.42%.

Ethyl 3-[(chloroacetyl)amino]-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (XV) Carbohydrazide (**V**) (4 g, 13.84 mmol) and (4 g, 35.4 mmol) of chloro acetyl choride were heated under neat conditions on water bath at 70°C for 2 h, the mixture then was allowed to cool and poured into cold water (100 mL),

then the mixture was neutralized with sodium carbonate solution (10%) till just alkaline. The solid product was collected and recrystallized from ethanol as white crystals in 77.5% yield, m.p. 155–158°C. IR: 3350 (NH), 3000 (CH aromatic), 2950 (CH aliphatic), 1720 (C=O *chromene*), 1700 (unsat. ester), 1680 (CO amide) cm^{-1}. ^1H NMR (DMSO-d_6): δ 1.35–1.50 (3H, J = 8.5 Hz t, CH_3), 3.50 (2H, s, CH_2), 4.30–4.50 (2H, J = 7.0 Hz, q, CH_2), 7.40–8.30 (4H, m, ArH), 10.40 (1H, s, NH). Found: C, 52.60; H, 3.28; Cl, 9.74; N, 3.78; S, 8.80%. Calculated: $C_{16}H_{12}ClNO_5S$ (365.79) C, 52.54; H, 3.31; Cl, 9.69; N, 3.83; S, 8.77%.

Ethyl 4-oxo-3-[(*N*-alkyl(aryl)glycyl)amino]-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (XVIa–d). General procedure. A mixture of chloro acetamide compound (**XV**) (1 g, 2.74 mmol) and the corresponding primaryor secondary amine (2.74 mmol) was refluxed in ethanol (20 mL) for 2 h. The solid product which formed on cooling filtered off, dried and recrystallized from ethanol.

Ethyl 4-oxo-3-[(*N*-phenylglycyl)amino]-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (XVIa). Obtained as the above procedure by the reaction with aniline as white crystals in 69% yield, m.p.: 234–236°C. IR: 3380, 3250 (2NH), 3050 (CH aromatic), 2950 (CH aliphatic), 1720 (C=O *chromene*), 1695 (CO ester), 1660 (C=O *amide*). ^1H NMR (DMSO-d_6): δ 1.35–1.55 (3H, J = 7.5 Hz, t, CH_3), 4.00 (2H, s, CH_2), 4.30–4.60 (2H, J = 6.5 Hz, q, CH_2), 6.80 (1H, t, NHPh), 7.20–7.80 (9H, m, ArH), 10.30 (1H, s, NHCO). Found: C, 62.49; H, 4.20; N, 6.66; S, 7.67%. Calculated: $C_{22}H_{18}N_2O_5S$ (422.46): C, 62.55; H, 4.29; N, 6.63; S, 7.59%.

Ethyl-3-[*N*-(4-methylphenyl)glycyl]amino}-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (XVIb). Obtained as the above procedure by the reaction of (**XV**) with *p*-toluidine as white needles in 81.50% yield, m.p. 240–242°C. IR: 3460, 3350 (2NH), 1725 (C=O *chromene*), 1665 (CO *amide*). ^1H NMR (DMSO-d_6): δ 1.25–1.40 (3H, J = 8.0 Hz, t, CH_3), 2.20 (3H, s, CH_3 *o*-toluidine), 3.90 (2H, s, CH_2CO), 4.10–4.25 (2H, q, J = 6.5 Hz, CH_2), 6.60 (1H, s, NH-Ph), 7.20–7.80 (8H, m, ArH), 10.30 (1H, s, CONH). Found: C, 63.36; H, 4.66; N, 6.38; S, 7.42%. Calculated: $C_{23}H_{20}N_2O_5S$ (436.49): C, 63.29; H, 4.62; N, 6.42; S, 7.35%.

Ethyl 4-oxo-3-[(piperidin-1-ylacetyl)amino]-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (XVIc). Obtained as the above procedure by the reaction with piperidine as greenish yellow crystals in 62% yield, m.p. 283–285°C. IR: 3350 (NH), 3040 (CH aromatic), 2920, 2850 (CH aliphatic), 1715 (C=O *chromene*), 1690 (C=O unsaturated ester), 1630 (CO amide). ^1H NMR ($CDCl_3$): δ 1.35–1.50 (3H, J = 7.5 Hz, t, CH_3), 1.60 (6H, s, $3CH_2$), 2.30–2.40 (4H, m, $2CH_2$), 3.30 (2H, s, CH_2), 4.20 (2H, J = 6.0 Hz, q, CH_2), 7.20–7.80 (4H, m, ArH), 8.00 (1H, s, NH). Found: C, 60.91; H, 5.28; N, 6.68; S, 7.80%. Calculated: $C_{21}H_{22}N_2O_5S$ (414.48): C, 60.85; H, 5.35; N, 6.76; S, 7.74%.

Ethyl 3-[(morpholin-4-ylacetyl)amino]-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (XVId). Obtained as the above procedure by the reaction with morpholine for 5 min. as pale yellow needles in 80% yield, m.p. 265–266°C. IR: 3300 (NH), 2990 (CH aromatic), 2850 (CH aliphatic), 1610 (CO amide), 1690 (C=O unsat ester). ^1H NMR (DMSO-d_6): δ 1.10–1.50 (3H, J = 7.5 Hz t, CH_3), 4.20–4.35 (2H, J = 6.0 Hz, q, CH_2), 3.80 (2H, s, CH_2), 3.25 (4H, s, CH_2–O), 2.80 (4H, s, $2CH_2$–N), 7.20–7.80 (4H, m, ArH), 10.70 (1H, s, NH). Found: C, 57.73; H, 4.82; N, 6.75; S, 7.77%. Calculated: $C_{20}H_{20}N_2O_6S$ (416.46): C, 57.68; H, 4.84; N, 6.73; S, 7.70%.

Ethyl 4-oxo-3-[(piperazin-1-ylacetyl)amino]-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (XVIe). A mixture of chloro acetamide derivative (**XV**) (0.5 g, 1.37 mmol) and piperazine (0.15 g,1.74 mmol) was refluxed in ethanol (10 mL) in presence triethylamine (0.5 mL) for 4 h. The solid product was collected, recrystallized from ethanol as yellow crystals in 80% yield, m.p.: 268–270°C. IR: 3250 (NH), 3050 (CH aromatic), 2900–2850 (CH aliphatic), 1680 (CO amide). ^1H NMR (DMSO-d_6) δ: 1.00–1.25 (3H, J = 9.5 Hz, t, CH_3), 2.50 (4H, m, $2CH_2$), 2.70 (4H, m, $2CH_2$), 3.20 (2H, s, CH_2CO), 4.35–4.50 (2H, J = 7.5 Hz, q, CH_2), 6.80 (1H, s, NH piperazine), 7.20–7.70 (4H, m, ArH), 10.10 (1H, s, NHCO). Found: C, 57.79; H, 5.13; N, 10.07; S, 7.80%. Calculated: $C_{20}H_{21}N_3O_5S$ (415.47): C, 57.82; H, 5.09; N, 10.11, S, 7.72%.

Ethyl-3-(2-(4-sulfamoylphenylamino)acetamido)-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (XVIf). A mixture of ethyl 3-[(chloroacetyl)amino]-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (**XV**) (0.5 g, 1.37 mmol) and sulfanilamide (0.34 g, 2 mmol) in presence of fused sodium acetate (0.3 g, 3.4 mmol) was refluxed in ethanol (10 mL) for 4 h. The solid product was collected, recrystallized from ethanol as white crystals in 72% yield, m.p. 205–207°C. IR: 3480, 3400, 3380 (NH, NH_2), 3030 (CH aromatic), 2900 (CH aliphatic), 1740 (C=O *chromene*), 1700 (C=O unsaturated ester), 1680 (CONH). ^1H NMR (DMSO-d_6): δ 1.25–1.40 (3H, J = 7.5 Hz, t, CH_3), 3.80 (2H, s, CH_2), 4.00–4.20 (2H, J = 6.0 Hz, q, CH_2), 6.20 (1H, s, NHph), 7.50 (2H, s, NH_2), 6.70–7.70 (8H,m, ArH), 10.10 (1H, s, NHCO). Mass; m/z 499.92 [M^+– 1]. Found: C, 52.75; H, 3.77; N, 8.42; S, 12.70%. Calculated: $C_{22}H_{19}N_3O_7S_2$ (501.54): C, 52.69; H, 3.82; N, 8.38; S, 12.79%.

Ethyl 4-oxo-3-[(*N*-{4-[(pyrimidin-2-ylamino)sulfonyl]phenyl}glycyl)amino]-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (XVIg). A mixture of ethyl 3-[(chloroacetyl)amino]-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (**XV**) (0.5 g, 1.37 mmol) and sulfadiazine (0.4 g, 1.6 mmol) in presence of triethyl amine (0.3 mL) was refluxed in ethanol (10 mL) for 4 h. The product solid was collected, recrystallized from ethanol as white crystals in 80% yield, m.p. 222–224°C. IR: 3400, 3380, 3290 (3NH), 3030 (CH aromatic),

2900, 2850 (CH aliphatic), 1735 (C=O *chromene*), 1700 (C=O unsaturated ester), 1690 (CONH). ^{1}H NMR (DMSO-d_6): δ 1.20–1.35 (3H, J = 7.5 Hz, t, CH_3), 4.20–4.45 (2H, J = 6.5 Hz, q, CH_2), 3.40 (2H, s, CH_2), 6.00 (1H, s, NHph), 7.20–7.60 (9H, m, ArH + CH *diazine*), 8.50 (2H, d, 2CH *diazine*), 10.50, 11.20 (2H, 2s, NHCO + $NHSO_2$). Mass: m/z 579.00 [M^+], 577.1 [$M^+ - 2$]. Found: C, 53.91; H, 3.62; N, 12.12; S, 11.00%. Calculated: $C_{26}H_{21}N_5O_7S_2$ (579.61): C, 53.88; H, 3.65; N, 12.08; S, 11.06%.

Ethyl 4-oxo-3-(5-oxo-3-arylimidazolidin-1-yl)-4*H*-thieno[3,2-*c*]chromene-2-carboxylates. General procedure (XVIIa, b). To a solution of compounds (**XVIa, b**) (0.5 g, 1.2 mmol) in ethanol (20 mL) and formaldehyde (2 mL) was refluxed for 4 h. The solid obtained on hot, filtered off, dried and recrystallized from ethanol.

Ethyl 4-oxo-3-(5-oxo-3-phenylimidazolidin-1-yl)-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (XVIIa). Obtained by the above procedure from compound (**XVIa**) as white crystals in 50% yield, m.p. 236–238°C. IR: 3050 (CH aromatic), 2950 (CH aliphatic), 1720 (C=O *chromene*), 1690 (C=O unsaturated ester), 1660 (CO imidazole). Found: C, 63.47; H, 4.25; N, 6.48; S, 7.37%. Calculated: $C_{23}H_{18}N_2O_5S$ (434.37): C, 63.58; H, 4.18; N, 6.45; S, 7.38%.

Ethyl 3-[3-(4-methylphenyl)-5-oxoimidazolidin-1-yl]-4-oxo-4*H*-thieno[3,2-*c*]chromene-2-carboxylate (XVIIb). Obtained by the above procedure from compound (**XVIb**) as greenish white crystals in 75%, m.p. 200–202°C. IR: 2900–2850 (CH aliphatic), 1725 (C=O *chromene*), 1700 (C=O unsaturated ester), 1680 (CO imidazole). ^{1}H NMR (CF_3CO_2D): δ 1.20–1.35 (3H, J = 9.0 Hz, t, CH_3 ester), 2.70 (3H, s, CH_3 *o-tolyl*), 4.10 (2H, s, CH_2CO imidazole), 4.30–4.50 (2H, J = 8.0 Hz, q, CH_2), 5.1 (2H, s, CH_2N *imidazole*), 7.20–8.00 (8H, m, ArH). Found: C, 64.32; H, 4.52; N, 6.18; S, 7.27%. Calculated: $C_{24}H_{20}N_2O_5S$ (448.50): C, 64.27; H, 4.49; N, 6.25; S, 7.15%.

Ethyl[(6,10-dioxo-9,10-dihydro-6*H*-chromeno[3',4':4,5]thieno[3,2-*d*]pyrimidin-8-yl) thio] acetate (XVIII). A mixture of chloro acetamide derivative (**XV**) (0.5 g, 1.37 mmol) and slightly excess of potassium thiocynate (0.15 g, 1.55 mmol) in ethanol (5 mL) was refluxed for 2 h. The solid product was collected and recrystallized from ethanol-dioxane mixture (3 : 1) as white crystals in 66% yield, m.p. 238–240°C. IR: 3300 (NH), 3030 (CH aromatic), 2980–2850 (CH aliphatic), 1720 (C=O *chromene*), 1700 (unsaturated ester), 1645 (CONH) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ 1.10–1.30 (3H, J = 7.5 Hz, t, CH_3), 4.10–4.40 (2H, J = 6.25 Hz, q, CH_2), 3.50 (2H, s, CH_2), 7.30–8.00 (4H, m, ArH), 10.20 (1H, s, NH). Mass: m/z 389.5 [M^+ + 1], 388.62 [M^+], 387.62 [M^+ – 1]. Found: C, 52.61; H, 3.18; N, 7.32; S, 16.48%. Calculated: $C_{17}H_{12}N_2O_5S_2$ (388.42) C, 52.57; H, 3.11; N, 7.21; S, 16.51%.

2-[(6,10-Dioxo-9,10-dihydro-6*H*-chromeno[3',4':4,5]thieno[3,2-*d*]pyrimidin-8-yl)thio] acetohydrazide (XIX). A mixture of ester (**XVIII**) (0.45 g, 1.16 mmol) and hydrazine hydrate (0.6 mL, 0.012 mol) was fused for 5 min and absolute ethanol (5 mL) was added. The reaction mixture was refluxed for 2 h. The precipitated solid which formed on hot during reflux was filtered off, dried and recrystallized from ethanol as white precipitate in 71% yield, m.p. >360°C. IR: 3480, 3350, 3200 (NH, NH_2), 1710 (C=O *chromene*), 1675 (C=O carbohydrazide) 1630 (CO pyrimidine). ^{1}H NMR (DMSO-d_6): δ 3.90 (2H, s, CH_2), 7.00 (2H, s, NH_2), 7.30–7.70 (4H, m, ArH), 8.60 (1H, s, CONH), 11.20 (1H, s, NH pyrimidine). Found: C, 48.26; H, 2.73; N, 15.00; S, 17.20%. Calculated: $C_{15}H_{10}N_4O_4S_2$ (374.40): C, 48.12; H, 2.69; N, 14.96; S, 17.13%.

8-{[2-(3,5-Dimethyl-1*H*-pyrazol-1-yl)-2-oxoethyl]thio}-6*H*-chromeno[3',4':4,5]thieno[3,2-*d*]pyrimidine-6,10(9*H*)-dione (XX). A mixture of hydrazide (**XIX**) (0.5 g, 1.34 mmol) and acetyl acetone (0.2 mL, 2 mmol) was refluxed in ethanol for 2 h. The solid product which formed on hot, collected and recrystallized from ethanol as orange crystals in 55% yield, m.p. 340–342°C. IR: 3250 (NH pyrimidine), 3080 (CH aromatic), 2980 (CH aliphatic), 1720 (CO *chromene*), 1690 ($CH_2C{=}O$). ^{1}H NMR (CF_3CO_2D): δ 2.70–2.90 (6H, 2s, $2CH_3$ *pyrazole*), 4.20 (2H, s, CH_2), 7.50–8.20 (4H, m, ArH). Found: C, 54.79; H, 3.21; N, 12.77; S, 14.63%. Calculated: $C_{20}H_{14}N_4O_4S_2$ (438.49): C, 54.78; H, 3.22; N, 12.78; S, 14.62%.

2-[(6,10-Dioxo-9,10-dihydro-6*H*-chromeno[3',4':4,5]thieno[3,2-*d*]pyrimidin-8-yl)thio]-*N*'-[(1*E*)-phenylmethylene]acetohydrazide (XXI). A mixture of hydrazide (**XIX**) (0.5 g, 1.34 mmol), benzaldehyde (1 mL, 9.4 mmol) and piperidine (0.5 mL) was heated under neat conditions for 5 min then the mixture was refluxed in ethanol (15 mL) for additional 3 h. A pale yellow precipitate which obtained upon cooling was recrystallized from ethanol in 70% yield, m.p. >340°C. IR: 3380, 3100 (2NH), 3050 (CH aromatic), 1725 (C=O *chromene*), 1650, 1630 (2CONH), 1600 (C=N). ^{1}H NMR (CF_3CO_2D): δ 4.10 (2H, s, CH_2), 7.40–7.90 (9H, m, ArH), 8.20 (1H, s, CHph). Found: C, 57.20; H, 3.10; N, 12.00; S, 13.95%. Calculated: $C_{22}H_{14}N_4O_4S_2$ (462.51): C, 57.13; H, 3.05; N, 12.11; S, 13.87%.

3-Aminochromeno[4,3-*c*]pyrazol-4(1*H*)-one (XXII). ***Method A.*** A mixture of 4-chlorocoumarin-3-carbonitrile (**IV**) (1.5 g, 7.4 mmol) and hydrazine 99% (0.71 mL) was refluxed in ethanol (20 mL) for 3 h. The solid precipitate which obtained after cooling filtered off, dried and recystallized from ethanol as brown crystals in 80% yield, m.p. >300°C.

Method B. 4-Chlorocoumarin-3-carbonitrile (**IV**) (1.5 g, 7.4 mmol) and hydrazine hydrate (0.71 mL) were heated under neat conditions for 1 h. then a few amount of ethanol was added and reflux was continued for 3 h. The solid precipitate which formed on hot during reflux was collected and recystallized from ethanol in 52% yield, m.p. >300°C. IR: 3400, 3300, 3200 (NH, NH_2), 3050 (CH aromatic) 2900, 2850 (CH aliphatic) 17250 (C=O *chromene*). ^{1}H NMR (DMSO-d_6): δ 6.40 (s, 2H, NH_2), 7.20–7.80 (m, 4H, ArH), 8.00

(d, 1H, NH). Found: C, 59.64; H, 3.56; N, 20.93%. Calculated: $C_{10}H_7N_3O_2$ (201.19): C, 59.70; H, 3.51; N, 20.89%.

8,10-Dimethyl-6*H*-chromeno[4',3':3,4]pyrazolo[1,5-*a*]pyrimidin-6-one (XXIII). A mixture of 3-aminochromeno[4,3-*c*]pyrazol-4(1*H*)-one (**XXII**) (0.25 g, 1.25 mmol)and acetyl acetone (0.20 mL, 2 mmol) was refluxed in glacial acetic acid (5 mL) for 1.5 h. An orange crystal was obtained on hot during reflux. The solid product which formed during reflux was left to cool then filtered off, dried and recystallized from ethanol as browen solid in 92% yield, m.p. 293–295°C. IR: 3050 (CH aromatic), 2900, 2850 (CH aliphatic), 1725 (C=O). ^{1}H NMR (CF_3CO_2D): δ 3.20–3.50 (6H, 2s, $2CH_3$), 7.40–7.90 (4H, m, ArH), 8.50 (1H, d, CH pyrimdine). Mass: *m*/*z* 267.05 [M^+ + 2], 265 [M^+]. Found: C, 67.87, H, 4.25; N, 15.88%. Calculated: $C_{15}H_{11}N_3O_2$ (265.27): C, 67.92; H, 4.18; N, 15.84%.

10-Amino-6*H*-chromeno[4',3':3,4]pyrazolo[1,5-*a*]pyrimidine-6,8(7*H*)-dione (XXIV). 3-Aminochromeno[4,3-*c*]pyrazol-4(1*H*)-one (**XXII**) (0.5 g, 2.48 mmol) and ethyl cyanoacetate (0.7 mL) were refluxed in glacial acetic acid (10 mL) for 3 h. The yellow crystal was formed on hot recrystallized from dioxane in 78% yield, m.p. 180°C. IR: 3450, 3300, 3200 (NH + NH_2), 2930 (CH aliphatic), 1720 (C=O *chromene*), 1650 (CONH). ^{1}H NMR (DMSO-d_6): δ 6.30 (2H, s, NH_2), 6.90 (1H, s, NH), 7.50–8.10 (4H, m, ArH), 8.40 (1H, s, CH pyrimidine). Mass: *m*/*z* 269 [M^+ + 1], 268.12 [M^+]. Found: C, 58.19; H, 3.00; N, 20.85%. Calculated: $C_{13}H_8N_4O_3$ (268.23): C, 58.21; H, 3.01; N, 20.89%.

6*H*-Chromeno[4',3':3,4]pyrazolo[1,5-*a*]pyrimidine-6,8,10(7*H*,9*H*)-trione (XXV). The mixture of 3–aminochromeno[4,3-*c*]pyrazol-4(1*H*)-one (**XXII**) (0.50 g, 2.5 mmol) and diethyl malonate (0.40 mL, 2.5 mmol) was refluxed in glacial acetic acid (10 mL) for 3 h. The solid product which obtained after cooling was filtered off, dried and recrystallized from dioxane as yellow crystals in 70% yield, m.p. 315–317°C. IR: 3200 (NH), 3030 (CH aromatic), 2900, 2850 (CH aliphatic), 1720 (C=O *chromene*), 1700, 1660 (2C=O). ^{1}H NMR (DMSO-d_6): δ 3.10 (2H, s, CH_2), 6.80 (1H, s, NH), 7.10–8.30 (4H, m, ArH). Found: C, 58.12; H, 2.57; N, 15.67%. Calculated: $C_{13}H_7N_3O_4$ (269.22) C, 58.00; H, 2.62; N, 15.61%.

8-Methyl-6*H*-chromeno[4',3':3,4]pyrazolo[1,5-*a*]pyrimidine-6,10(7*H*)-dione (XXVI). 3-Aminochromeno[4,3-*c*]pyrazol-4(1*H*)-one (**XXII**) (0.5 g, 2.50 mmol) and ethyl acetoacetate (0.30 mL, 2.5 mmol) was refluxed in glacial acetic acid for 3 h. The white crystals which was recrystallized from ethanol into 80% yield, m.p. 326–328°C. IR: 3050 (CH aromatic), 2980 (CH aliphatic), 1725 (C=O *chromene*), 1720, 1680 (2C=O). ^{1}H NMR (CF_3CO_2D): δ 2.80 (3H, s, CH_3), 6.60 (1H, s, NH pyrimidine), 7.40–8.10 (4H, m, ArH), 8.30 (1H, s, CH *pyrimidine*). Mass: *m*/*z* = 267 [M^+]. Found: C, 62.90; H, 3.36; N, 15.65%. Calculated: $C_{14}H_9N_3O_3$ (267.25): C, 62.92; H, 3.39; N, 15.72%.

10-Phenyl-6*H*-chromeno[4',3':3,4]pyrazolo[1,5-*a*]pyrimidine-6,8(7*H*)-dione (XXVII). To a solution of 3-aminochromeno[4,3-*c*]pyrazol-4(1*H*)-one (**XXII**) (0.25 g, 1.25 mmol) in ethanol (5 mL), ethyl benzoylacetate (0.25 mL, 1.25 mmol) was added drop wise then the mixture was refluxed for 2 h. The solid product which was obtained on hot during reflux was filtered off, dried and recystallized from ethanol into yellow crystals in 84% yield, m.p. 325–327°C. IR: 3430 (NH), 3050 (CH aromatic), 2900, 2850 (CH aliphatic), 1720 (C=O coumarin), 1640 (CONH). ^{1}H NMR (DMSO-d_6): δ 6.70 (1H, s, NH), 7.20–7.80 (9H, m, ArH), 8.20 (1H, s, CH pyrimidine). Found: C, 69.38; H, 3.30; N, 12.84%. Calculated: $C_{19}H_{11}N_3O_3$ (329.32): C, 69.30; H, 3.37; N, 12.76%.

Ethyl (2*Z*)-2-cyano-3-[(4-oxo-2,4-dihydrochromeno[4,3-*c*]pyrazol-3-yl)amino]acrylate (XXVIII). A solution of 3-aminochromeno[4,3-*c*]pyrazol-4(1*H*)-one (**XXII**) (0.5 g, 2.5 mmol) in ethanol (10 mL) and ethyl 2-cyano-3-ethoxyacrylate (0.5 g, 3.0 mmol) was refluxed for 3 h. The solid product which formed on hot during reflux, filtered off, dried and recrystallized from ethanol into pale buff crystals in 70% yield, m.p. 280–282°C. IR: 3350, 3290 (2NH), 3050 (CH aromatic), 2900, 2850 (CH aliphatic), 2100 (CN), 1720 (C=O *chromene*), 1690 (C=O unsaturated ester). ^{1}H NMR (DMSO-d_6): δ 1.30–1.55 (3H, *J* = 9.0 Hz, t, CH_3), 4.30–4.60 (2H, *J* = 7.5 Hz, q, CH_2), 7.30–8.20 (5H, m, ArH + CH=C), 10.70 (1H, s, 1NH pyrazole), 11.20 (1H, s, NHCH). Found: C, 59.32; H, 3.77; N, 17.34%. Calculated: $C_{16}H_{12}N_4O_4$ (324.30): C, 59.26; H, 3.73; N, 17.28%.

Ethyl-10-amino-6-oxo-6*H*-chromeno[4',3':3,4]pyrazolo[1,5-*a*]pyrimidine-9-carboxylate (XXIX) Ethyl ester (**XXVIII**) (0.25 g, 0.77 mmol) was refluxed in acetic acid (10 mL) for 4 h. The solid precipitate which formed on hot during reflux was collected, dried and recrystallized form ethanol as white crystals in 80% yield, m.p. 320–322°C. IR: 3400, 3300 (NH_2), 3050 (CH aromatic), 2920, 2850 (CH aliphatic), 1720 (C=O *chromene*), 1680 (C=O unsaturated ester). ^{1}H NMR (CF_3CO_2D): δ 1.35–1.50 (3H, *J* = 7.0 Hz, t, CH_3), 4.30–4.55 (2H, *J* =6.0 Hz, q, CH_2), 7.40–8.40 (4H, m, ArH), 8.60 (CH pyrimidine). Found: C, 59.28; H, 3.78; N, 17.34%. Calculated: $C_{16}H_{12}N_4O_4$ (324.30): C, 59.26; H, 3.73; N, 17.28%.

Ethyl-10-amino-6-oxo-6*H*-chromeno[4',3':3,4]pyrazolo[5,1-*c*][1,2,4]triazine-9-carboxylate (XXXII). A solution of sodium nitrite (0.5 g in 5 mL) was added to asolution of 3-aminochromeno[4,3-*c*]pyrazol-4(1*H*)-one (**XXII**) (0.5 g, 2.50 mmol) in concentrated HCl (5 mL) with stirring at 0°C then ethanolic solution of ethyl cyanoacetate (1 mL, 8.85 mmol) in presence of sodium acetate (3 g, 0.034 mmol) was added dropwise to the reaction mixture to afford a solid precipitate which was recrystallized from ethanol as reddish brown crystals in 60% yield, m.p. 260°C. IR: 3390, 3230 (NH_2), 2950 (CH aromatic), 2900, 2850 (CH aliphatic), 1720 (C=O *chromene*), 1680 (C = O

unsaturated ester). ^{1}H NMR CF_3CO_2D): δ 1.50–1.75 (3H, J = 9.0 Hz, t, CH_3), 4.70–4.90 (2H, J = 7.5 Hz, q, CH_2), 7.50–8.00 (4H, m, ArH). Mass: m/z 325.38 [M^+], 324.5 [M^+ – 1]. Found: C, 55.42; H, 3.37; N, 21.63%. Calculated: $C_{15}H_{11}N_5O_4$ (325.29): C, 55.39; H, 3.41; N, 21.53%.

Ethyl(2*Z*)-3-oxo-2-[(4-oxo-2,4-dihydrochromeno[4,3-*c*]pyrazol-3-yl)hydrazono] butanoate (XXXIII). A solution of sodium nitrite (0.5 g, in 5 mL, 7.25 mmol) was added to a solution 3-aminochromeno [4,3-*c*]pyrazol-4(1*H*)-one (**XXII**) (0.5 g, 2.5 mmol) in concentrated HCl (5 mL) with stirring at 0°C then ethanolic solution of ethyl acetoacetate (1 mL, 8.0 mmol) in presence of sodium acetate (3 g, 0.034 mmol) was added dropwise to the reaction mixture to afford a solid precipitate which was recrystallized from ethanol as brown crystals in 50% yield, m.p. 270–272°C. IR: 3300, 3200 (2NH), 3030 (CH aromatic), 2900, 2850 (CH aliphatic), 1720 (C=O coumarin), 1690 (C=O unsaturated ester), 1680 ($COCH_3$), 1610 (C=N). ^{1}H NMR (DMSO-d_6): δ 1.10–1.30 (3H, J = 7.5 Hz, t, CH_3), 3.80 (3H, s, $COCH_3$), 4.20–4.50 (2H, J = 6.0 Hz, q, CH_2), 6.7 (1H, s, NH), 7.20–7.80 (4H, s, ArH), 11.20 (1H, s, NH). Found: C, 56.18; H, 4.20; N, 16.45%. Calculated $C_{16}H_{14}N_4O_5$ (342.31): C, 56.14; H, 4.12; N, 16.37%.

Testing of Biological Activity

The fungal species were previously isolated from cases of human dermatophytosis (Moubasher et al., 1993) [18]. The fungi were grown in sterilized 9-cm Perti dishes containing sabouraud's Dextrose agar (SDA) supplemented with 0.05% chloramphenicol to suppress bacterial contamination (Al-Doory, 1980) [19] from these cultures, agar discs (10 mm diam.) containing spores and hyphae were transferred aseptically to screw-topped vials containing 20 mL sterile distilled water. After thorough shaking, 1-mL samples of the spore suspension were pipetted into sterile perti dishes, followed by the addition of 15 mL liquefied SDA medium which was then leftto solidify.

The tested compounds and tolnaftate were dissolved in DMSO to give 2.0% concentration. Antifungal and antibacterial activities were determined according to the method reported by Bauer et al. (1966) [20] using 3-mm diameter filter paper discs (Whatmann No. 3) loaded with 10 μL of the solution under investigation(200 μL/disc, 2.0%). The discs were placed on the surface of the fungal cultures which were incubated at 30°C. The diameter of the inhibition zone around each disc was measured. The same method was used for determining antibacterial activity.

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