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Original article

Synthesis and biological activity of pyrazolothienotetrahydroisoquinoline and [1,2,4]triazolo[3,4-a]thienotetrahydroisoquinoline derivatives

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ABSTRACT

1-Hydrazino-3-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**3**) was subjected to react with bifunctional compounds namely: acetylacetone, ethyl cyanoacetate, ethyl benzoylactate, diethylmalonate and ethyl acetoacetate to produce pyrazololthienotetrahydroisoquinoline derivatives **6**–**11**. Also, heating of compound (**3**) with formic acid afforded triazolothienotetrahydroisoquinoline compound **5** which reacted with α-halogenated compounds to afford compounds **13a**–**e**. Compound **13c** when heated with triethylorthoformate afforded triazolo derivative **14**. Also, compound **6** was used for synthesizing compounds **18**–**20**. Representative compounds of the synthesized triazolo and pyrazolothienotetrahydroisoquinoline products were tested and evaluated as antimicrobial agents.

1. Introduction

1,2,3,4-Tetrahydroisoquinoline (THIQ) was a common core structure of many alkaloids isolated from natural sources and showed antitumor [1], antimicrobial [2], and other biological activities [3–7]. The recent success in total synthesis of ecteinascidin 743 [8,9] and its human clinical trials [10,11] have shed light on this class of natural products.

In 1990, the isolation of the ecteinascidins, a new family of tetrahydroisoquinoline alkaloids [1] was reported from the marine tunicate Ecteinascidin tubinata [12]. Among these compounds, ecteinascidin 743 (Et-743, Yondelis TM, **I**) is presently in phase II/III clinical trials due to its exceedingly low nanomolar activity against different tumor cell lines (Fig. 1) [13–15]. It has been demonstrated that Et-743 (**I**) binds to guanine in the minor groove of DNA at the reactive C-21 carbinolamine position. The restricted natural availability of Et-743 (**I**) from the tunicate has been overcome through semi-synthesis of multigram quantities from the more readily available metabolite cyanosafracin B (**IIa**). Cyanosafracin B (**IIa**) is available in kilogram quantities through bacterial fermentation. The route, developed by Cuevas and Manzanares at PharmaMar, supports current clinical trials [16,17]. Closely related to the ecteinascidins, safracins **IIa**–**c** were isolated in 1983 from *Pseudomonas fluorescens* and also display potent antimicrobial and antitumor activities [18–20].

Tetrahydroisoquinoline derivatives are a class of selective estrogen receptor modulators (SERMs) have high binding affinity and specificity exhibiting up to 50 folds for ERa over ERb and attractive targets in the treatment of breast cancer and the development of receptor-based breast cancer imaging agents for diagnostic use in biomedical imaging technique positron emission tomography (PET) [21].

Tetrahydroisoquinolines were identified as anti-platelet aggregation agents. The investigations of the anti-platelet aggregation mechanism of tetrahydroisoquinolines indicated that in addition to receptor and β-adrenergic/α2-adrenergic receptor system [22].

2. Results and discussion

2.1. Chemistry

Reaction of 4-cyano-1-morpholin-4-yl-5,6,7,8-tetrahydroisoquinoline-3(2*H*)thione (**1**) with hydrazine hydrate under neat condition followed by addition of ethanol afforded 1-hydrazino-3-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**3**) with loss of morpholine molecule instead of the expected 1-morpholin-4-yl-3-hydrazino-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**2**). The structure of the produced compound **3** was elucidated on the basis of ^{1}H NMR spectra which revealed the appearance of signals characteristic to NH_2, NH group at δ 7.8 and 10.5 ppm respectively with disappearance of signals characteristic to aliphatic protons of morpholine ring. The structure of compound **3** also confirmed by mass spectrum which show molecular ion peak at 220.08 (*m*/*z*).

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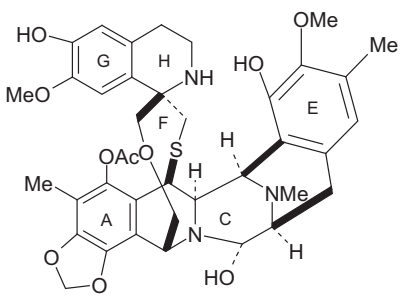
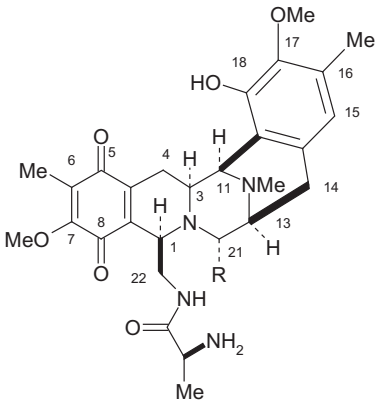
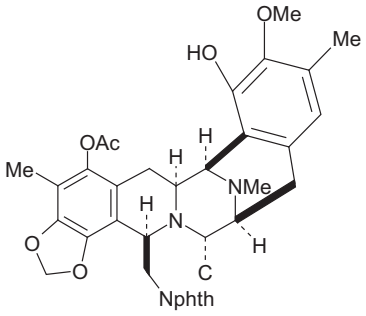


I. Ecteinascidin 743



IIa, Cyanosafarin B; R= CN
IIb, Safracin A; R=H
IIc, Safracin B; R=OH



III. phtalascidin 650

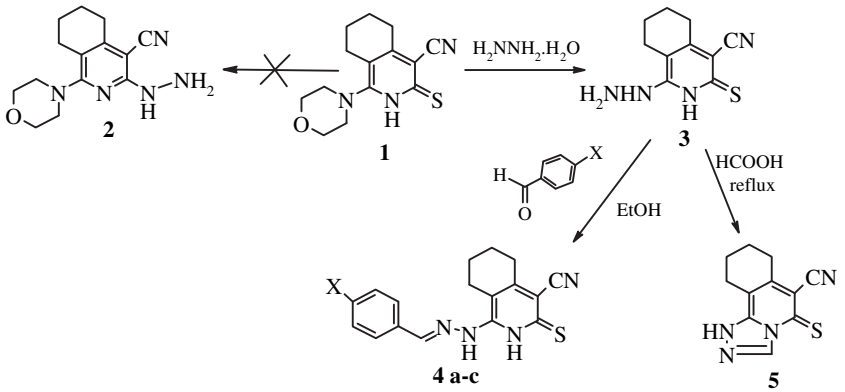
Fig. 1. Ecteinacidin 743, the safracins and phtalasidin 650.

Thus hydrazino compound **3** was used as a key intermediate for synthesis of new fused heterocyclic systems condensed with tetrahydroisoquinoline moiety.

When compound **3** condensed with aromatic aldehydes namely benzaldrhyde, *p*-anisaldehyde and *p*-chlorobenzaldehyde in refluxed ethanol afforded the corresponding hydrazones **4a**–**c**.

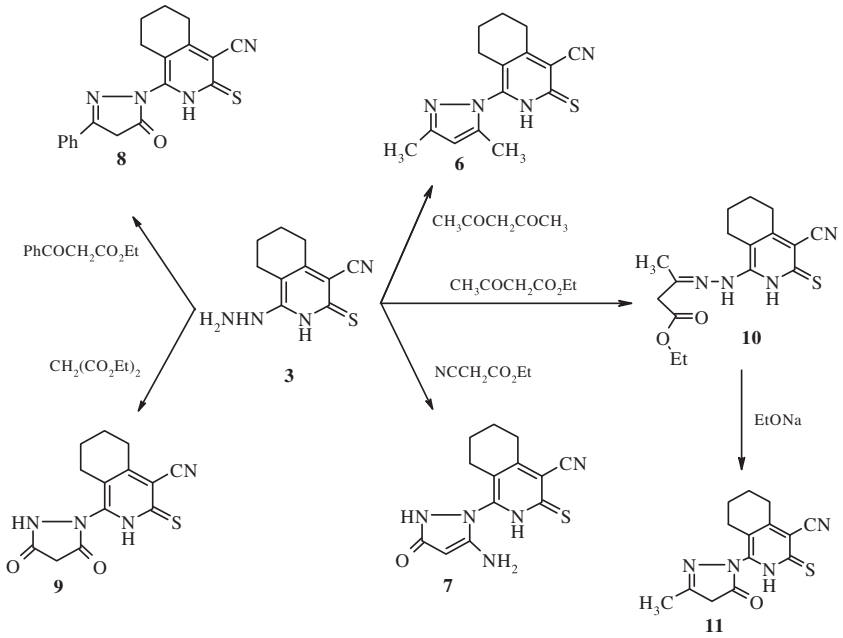
Hydrazino derivative **3** underwent ring closure upon heating with formic acid to give 5-thioxo-7,8,9,10-tetrahydro-1*H*[1,2,4] triazolo[3,4-a]isoquinoline-6-carbonitrile (**5**). The structure of compound **5** was confirmed using spectral analysis. IR spectrum of compound **5** revealed the disappearance of absorption bands at 3280, 3200 cm^{-1} characteristic for NH, NH_2 groups. ^1H NMR spectra of **5** showed the disappearance of signals characteristic for NH, NH_2 groups and appearance of new signals at δ 9.6 ppm corresponding to CH triazole Scheme 1.

Condensation of hydrazino derivative **3** with different bifunctional compounds namely acetylacetone, ethyl cyanoacetate, ethyl benzoylacetate and diethylmalonate yielded the hydrazones as intermediate that can't be separated and underwent ring closure under the same conditions (*in situ*) except in case of reaction with ethyl acetoacetate which hydrazone derivative **10** was separated and underwent ring closure by using ethanolic sodium ethoxide solution to give a variety of pyrazolo derivatives **6**–**11** Scheme 2.



X: a= H, b= OCH_3, c= Cl

Scheme 1. Synthesis of mercaptohydrazinoisoquinoline **3** and its condensation reactions with aromatic aldehydes and formic acid giving mercaptotriazolo, mercapto-*p*-chloro benzylidenehydrazinyl derivatives **4a-c**, **5**.



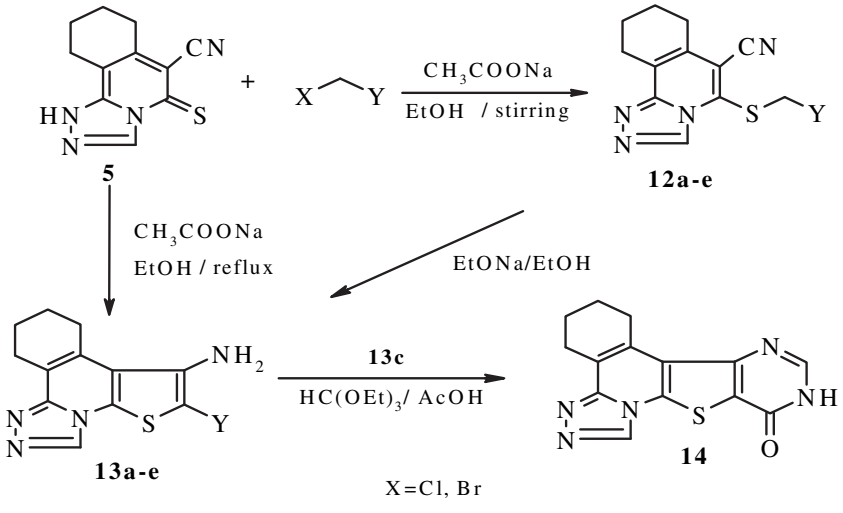
Scheme 2. Synthesis of mercatopyrazolotetrahydroisoquinolines **6-11**.

Alkylation of 5-thioxo-7,8,9,10-tetrahydro-1*H*[1,2,4]triazolo[3,4-a]isoquinoline-6-carbonitrile (**5**) with α-halogenated carbonyl compounds in ethanol in the presence of sodium acetate furnished compounds **12a**–**e**. Compounds **12a**–**e** underwent *Thorpe-Ziegler* cyclization upon heating with ethanolic sodium ethoxide solution to give 7-amino-6-substituted-8,9,10,11-tetrahydrothieno[2,3-c][1,2,4]triazolo[3,4-a]isoquino-line (**13a**–**e**). 1,2,3,4-Tetrahydro-10-oxopyrimido[4′,5′:4,5]thieno[2,3-c][1,2,4]triazolo [3,4-a]isoquinoline (**14**) was synthesized via condensation of compound **13c** with triethylorthoformate Scheme 3.

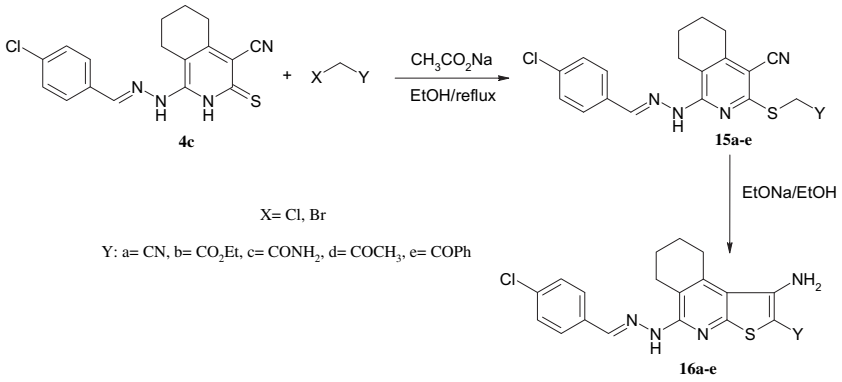
Also compound **4c** reacts with α-halogenated carbonyl compounds in ethanol in the presence of fused sodium acetate to afford compounds **15a**–**e**. Compounds **15a**–**e** underwent *Thorpe–Ziegler* cyclization reaction upon refluxing with ethanolic sodium ethoxide solution to give 1-amino-2-substituted-5-(2-*p*-chlorobenzylidenehydrazinyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (**16a**–**e**) Scheme 4.

Compound **16e** was synthesized by an alternative method through a reaction of 1-hydrazino-3-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**3**) with ethyl chloroacetate and fused sodium acetate in refluxing ethanol to afford ethyl(4-cyano-1-hydrazino-5,6,7,8-tetrahydroisoquinolin-3-ylsulfanyl)acetate (**17**). Condensation of compound **17** with *p*-chlorobenzaldehyde afforded ethyl-1-(2-*p*-chlorobenzylidene hydrazinyl)-4-cyano-5,6,7,8-tetrahydroisoquinoline-3-sulfanyl-acetate (**15b**) which underwent *Thorpe–Ziegler* cyclization to afford ethyl-1-amino-5-(2-*p*-chlorobenzylidenehydrazinyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxy-late (**16b**). Compounds **15b, 16b** prepared by the two methods were identical in all aspects Scheme 5.

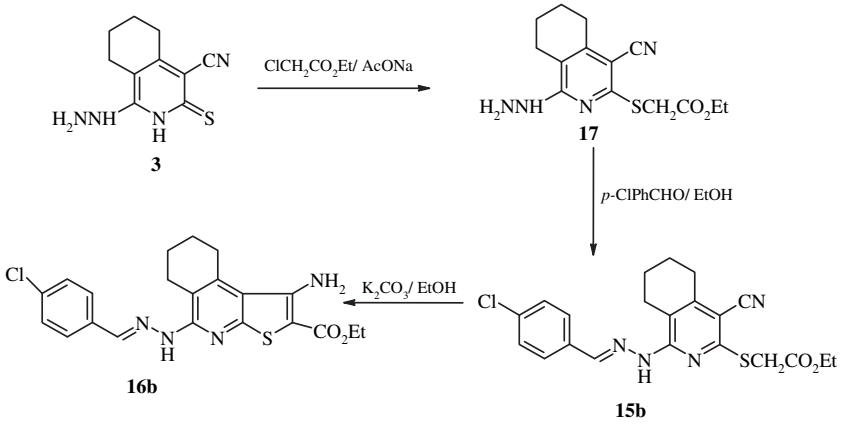
In analogues manner, reaction of compound **6** with α-halogenated carbonyl compounds in ethanol in the presence of sodium acetate gave S-alkylated products **18a**–**e**. Compounds **18a**–**e** underwent *Thorpe–Ziegler* cyclization reaction to give 2-substituted-1-amino-5-



Scheme 3. Synthesis of triazolothienotetrahydroisoquinolines **13a-e**.



Scheme 4. Synthesis of -*p*-chlorobenzylidenehydrazinylthienotetra hydroisoquinolines **16a-e**.



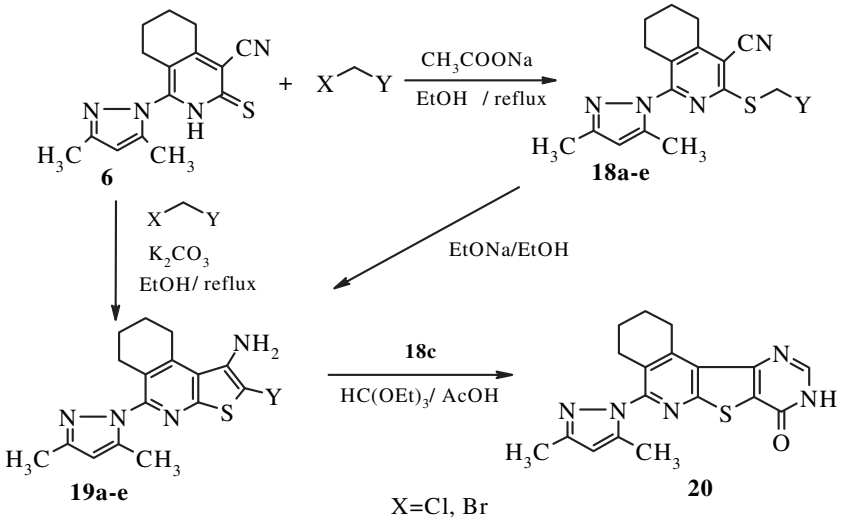
Scheme 5. An alternative method for synthesis of ethyl-amino-*p*-chlorobenzylidenehydrazinyl thienotetrahydroisoquinolinecarboxylate **16b**.

morpholin-4-yl-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (**19a**–**e**). Also compounds **19a**–**e** were obtained directly from pyrazolylthione derivative **6** using α-halogenated compounds in refluxing ethanol in the presence of anhydrous potassium carbonate. Heating compound **19c** with triethylorthoformate yielded 5-(3,5-dimethylpyrazol-1-yl)-1,2,3,4-tetrahydropyrimido[4′,5′:4,5]thieno[2,3-c]isoquinolin-8(9*H*)-one (**20**) Scheme 6.

3. Pharmacology

3.1. Antimicrobial activity

Some of the synthesized compounds in this work were chosen and screened in *vitro* for their antimicrobial activity against some strains of bacteria and fungi Tables 1 and 2, **2**. The antifungal activities



Scheme 6. Synthesis of pyrazolothienotetra hydroisoquinolines **19a-e**.

of tested compounds were evaluated by the reported method [23] using 2% concentration of selected compounds in DMSO as a solvent. The inhibition zone (mm) was compared with clotrimazole as a reference. In the case of antibacterial activities also the concentration of tested compounds was 2% and the inhibition zone in (mm) was compared with chloramphenicol as a reference.

3.2. Conclusion

The tested compounds of novel synthesized triazolo and pyrazolothienotetrahydro isoquinolines showed antibacterial and antifungal activities. For example, compound **3** showed antibacterial against most strains either gram (+ve) bacteria such as *Bacillus cereus*, *Staphylococcus aureus* and *Micrococcus luteus* or gram (−ve) bacteria such as *Escherichia coli*. Also, compound **3** showed antifungal activity against certain fungi like *Candida albicans*, *Trichophyton rubrum*, *Fusarium oxysporum* and *Aspergillus niger*. For triazolo derivatives, It's noticeable that 5-substituted-mercapto-6-cyano-7,8,9,10-tetrahydro [1,2,4]triazolo[3,4-a]isoquinoline compounds **12a**–**e** have antibacterial effect higher than the cyclized 7-amino-6-substituted-8,9,10,11-tetrahydrothieno[2,3-c][1,2,4]triazolo[3,4-a]isoquinoline compounds **13a**–**e** in most cases except for **12a**, **13a** towards *Serratia marcescens* and *E. coli* which the amino derivatives have the higher effect. In case of pyrazolo derivatives different results were observed, the cyclized 1-amino-2-substituted-5-(3,5-dimethylpyrazol-1-yl)-6,7,8,9-tetrahydro thieno[2,3-c]isoquinoline **19a**–**e** showed equal (or higher in some cases) antibacterial activities than 3-substitutedsulfanyl-1-(3,5-dimethylpyrazol-1-yl)-5,6,7,8-tetrahydro isoquinoline-4-carbonitrile **18a**–**e**. It's noticeable that presence of carbonitrile group in triazolo and pyrazolo derivatives **12a**, **13a**, **17a** and **18a** increases their antibacterial activity towards *S. marcescens*. While the triazolo derivatives show higher antibacterial activity towards *B. cereus* and *M. luteus*. The benzoyltriazolo derivatives show the highest antifungal activity than the other tested compounds especially towards *Aspergillus flavus* and *A. niger*.

On the other hand, 1-hydrazino-3-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbo-nitrile (**3**) showed remarkable antifungal activities towards most tested fungi. In triazolo derivatives only 6-cyano-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-a]isoquinoline-5-sulfanylacetophenone (**12e**) and 7-amino-6-benzoyl-8,9,10,11-tetrahydrothieno [2,3-c][1,2,4]triazolo[3,4-a]isoquinoline (**13e**) have significant antifungal activity towards most strains but in case of pyrazolo derivatives **17d**, **18d** showed higher antifungal activities than the other pyrazolo substituents.

4. Experimental

All melting points are uncorrected and measured on a Fisher-John apparatus. IR spectra were recorded with a Perkin–Elmer 1430 Spectrophotometer using KBr wafer technique. ^{1}H NMR and ^{13}C NMR spectra were obtained on a Varian EM-390 (90 MHz) and Joel 400 MHz spectrometer in $CDCl_3$, DMSO-d_6 and CF_3CO_2D using Me_4Si as internal standard, and chemical shifts are expressed as ppm. Mass spectra were measured on a Jeol-JMS 600 spectrometer. Analytical data were obtained on Elementar Analysensysteme GmbH-VarioEL V.3 microanalyzer in the central lab of Assiut University. 1-Morpholin-4-yl-3-mercapto-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**1**) was prepared according to reported procedure [24]. Numbering of carbon atoms used in ^{13}C NMR analysis is shown in Fig. 2.

4.1. 1-Hydrazino-3-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (*3*)

Compound **1** (2.75 g, 0.01 mol) and hydrazine hydrate (3 mL, 0.06 mol) was fused for 1 h then ethanol (10 mL) was added and

Table 1
Antibacterial activity of the chemical compounds tested by well diffusion assay (50 μL/well).

Bacterial strains	Sample No. Inhibition zone in mm																								Ref
	3	**5**	**6**	**7**	**8**	**12a**	**13a**	**12b**	**13b**	**12c**	**13c**	**12d**	**13d**	**12e**	**13e**	**17a**	**18a**	**17b**	**18b**	**17c**	**18c**	**17d**	**18d**	**17e**	**18e**	
Serratia marcescens (−ve)	0	10	0	0	0	12	11	0	10	0	0	12	0	0	0	10	10	0	10	8	0	8	8	0	0	40
Pseudomonas aeruginosa (−ve)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	17
Escherichia coli (−ve)	14	10	0	0	13	8	0	0	11	12	0	8	0	10	10	0	0	0	10	11	0	12	13	0	0	34
Bacillus cereus (+ve)	20	15	16	9	0	12	11	11	8	13	10	12	0	14	0	0	8	8	0	0	0	11	0	0	0	30
Staphylococcus aureus (+ve)	11	8	8	0	0	10	9	0	10	8	8	10	0	0	0	8	8	8	7	0	10	0	0	10	10	20
Micrococcus luteus	14	12	0	10	0	11	0	10	0	0	0	12	0	14	11	0	0	0	0	0	0	0	0	0	0	18

Ref = Chloramphenicol as antibacterial standard.

Table 2
Antifungal activity of the chemical compounds tested by well diffusion assay (50 μL/well).

Fungal strains	Sample No. Inhibition zone in mm																								Ref
	3	**5**	**6**	**7**	**8**	**12a**	**13a**	**12b**	**13b**	**12c**	**13c**	**12d**	**13d**	**12e**	**13e**	**17a**	**18a**	**17b**	**18b**	**17c**	**18c**	**17d**	**18d**	**17e**	**18e**	
Candida albicans	12	10	0	0	0	0	0	0	10	0	0	0	0	11	11	10	12	0	0	0	0	11	10	0	0	27
Geotrichum candidum	0	0	0	8	0	0	0	0	0	0	0	0	0	8	8	0	10	0	10	10	0	12	8	12	0	26
Trichophyton rubrum	17	0	0	0	14	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	20	17	12	0	40
Scopulariopsis brevicaulis	0	0	0	0	0	0	0	0	0	0	0	0	0	10	8	0	0	0	0	0	0	0	0	0	0	27
Fusarium oxysporum	13	0	0	0	0	0	0	0	0	0	0	0	0	11	0	0	8	0	0	10	0	0	10	0	0	25
Aspergillus flavus	10	0	0	0	0	0	0	0	8	0	0	0	0	20	15	0	0	0	0	0	0	0	0	0	0	26
Aspergillus niger	12	0	0	0	0	0	0	0	0	0	0	0	0	16	13	0	8	0	0	0	8	0	0	0	0	25

Ref = Clotrimazole as antifungal standard.

reflux continued for additional 1 h. The yellow precipitate, which formed, was filtered off and recrystallized from a mixture of ethanol/dioxane as yellow crystals in 73% yield. M.p.: 298–300 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3450, 3290, 3190 (NH, NH_2), 2200 (CN), 2930 (CH aliphatic), 1640 (C=N), 1250 (C=S). ^{1}H NMR (400 MHz, DMSO-d_6): δ_{ppm} = 1.65–1.70 (m, 2H, CH_2), 2.05–2.15 (m, 4H, $2CH_2$), 2.70–2.75 (m, 2H, CH_2), 7.50–7.80 (s br, 3H, NH + NH_2 disappeared by D_2O), 9.50 (s, 1H, NH disappeared by D_2O). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 170.90 (C=S), 152.40 (C-3), 152.30 (C-9), 115.60 (CN), 105.70 (C-8), 99.00 (C-4), 21.20–40.80 (m, $4CH_2$). MS *m/z* (%): 220.08 (M^+, 100), 217.07 (38.20), 202.05 (44.90), 190.05 (71.40), 170.07 (39.10). 162.03 (21.50), 104.05 (24.60). Anal. Calcd. for: $C_{10}H_{12}N_4S$: C, 54.52; H, 5.49; N, 25.43; S, 14.55%. Found: C, 54.32; H, 5.70; N, 25.25; S, 14.72%.

4.2. 1-(2-Arylidenehydrazinyl)-3-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbo nitrile (**4a–c**)

General procedure: Compound **3** (1 g, 4.5 mmol) was fused with the appropriate aromatic aldehyde (2 mL) for 5 min then ethanol (5 mL) was added and reflux continued for additional 2 h. The solid precipitate, which formed, was filtered off and recrystallized from dioxane.

4.2.1. 1-(2-Benzylidenehydrazinyl)-4-cyano-5,6,7,8-tetrahydroisoquinoline-3(2H)-thione (**4a**)

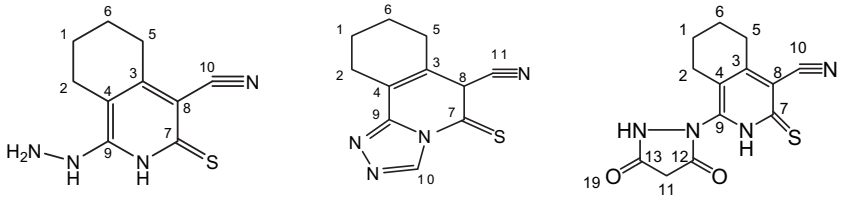
Obtained from compound **3** and benzaldehyde as green crystals in 82% yield. M.p. 310–312 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3450 (NH), 3020 (CH aromatic), 2920, 2850 (CH aliphatic), 2200 (CN), 1610 (C=N), 1255 (C=S). ^{1}H NMR (90 MHz, CF_3CO_2D): δ_{ppm} = 1.90–2.00 (m, 2H, CH_2), 2.60–2.70 (m, 4H, $2CH_2$), 3.00–3.05 (m, 2H, CH_2), 7.60–7.90 (m, 5H, ArH), 8.65 (s, 1H, N=CH). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 173.20 (C=S), 154.57 (C-3), 154.25 (C-9), 145.20 (CH=N), 127.25–134.20 (5C-aromatic), 118.15 (CN), 106.48 (C-8), 20.01–40.54 ($4CH_2$ cyclohexeno). Anal. Calcd. for: $C_{17}H_{16}N_4S$: C, 66.21; H, 5.23; N, 18.17; S, 10.40%. Found: C, 66.00; H, 5.45; N, 18.25; S, 10.30%.

4.2.2. 4-Cyano-1-(2-p-methoxybenzylidenehydrazinyl)-5,6,7,8-tetrahydroiso quinoline-3(2H)-thione (**4b**)

Obtained from compound **3** and *p*-anisaldehyde as yellow crystals in 84% yield. M.p. 316–318 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3400 (NH), 3030 (CH aromatic), 2920 (CH aliphatic), 2200 (CN), 1610 (C=N), 1250 (C=S). ^{1}H NMR (90 MHz, CF_3CO_2D): δ_{ppm} = 2.00–2.10 (m, 2H, CH_2), 2.65–2.70 (m, 4H, $2CH_2$), 3.00–3.05 (m, 2H, CH_2), 4.10 (s, 3H, CH_3) 7.20, 7.80 (2d, *J* = 9.0, 8.4 Hz, 4H, *p*-sub ArH), 8.6 (s, 1H, N=CH). MS *m/z* (%): 338.21 (M^+, 9.3), 204.98 (100), 189.96 (8.70), 150.03 (11.30), 134.03 (26.30), 76.96 (26.80). Anal. Calcd. for: $C_{18}H_{18}N_4OS$: C, 63.88; H, 5.36; N, 16.55; S, 9.47%. Found: C, 64.00; H, 5.25; N, 16.45; S, 9.60%.

4.2.3. 1-(2-p-Chlorobenzylidenehydrazinyl)-3-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**4c**)

Hydrazino compound **3** (1 g, 4.5 mmol) and *p*-chlorobenzaldehyde (0.63 g, 4.5 mmol) was refluxed in ethanol (20 mL) in presence of piperidine for 2 h. The solid precipitate, which formed, was filtered off and recrystallized from dioxane as orange crystals in 82% yield. M.p.: 348–350 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3450 (NH), 3050 (CH aromatic), 2920 (CH aliphatic), 2210 (CN), 1620 (C=N), 1260 (C=S). ^{1}H NMR (90 MHz, CF_3CO_2D): δ_{ppm} = 1.90–1.95 (m, 2H, CH_2), 2.60–2.70 (m, 4H, $2CH_2$), 3.15–3.20 (m, 2H, CH_2), 7.40, (d, *J* = 7.5 Hz, 2H, *p*-sub. ArH), 7.80 (d, *J* = 10.5 Hz, 2H, *p*-sub. ArH), 8.50 (s, 1H, N=CH). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 176.38 (C=S), 157.62 (C-3), 157.00 (C-9), 144.26 (CH=N), 128.55–133.63 (5C-aromatic), 120.25 (CN), 106.34 (C-8), 20.15–40.50 ($4CH_2$ cyclohexeno). Anal.



3 **5** **9**

Fig. 2. Numbering of carbon atoms for compounds **3,5** and **9**.

Calcd. for: $C_{17}H_{15}ClN_4S$: C, 59.56; H, 4.41; Cl, 10.34; N, 16.34; S, 9.35%. Found: C, 59.32; H, 4.60; Cl, 10.50, N, 16.28; S, 9.30%.

4.3. 5-Thioxo-7,8,9,10-tetrahydro-1H[1,2,4]triazolo[3,4-a] isoquinoline-6-carbo nitrile (**5**)

Hydrazino derivative **3** (1 g, 4.5 mmol) and formic acid (10 mL) was refluxed for 1/2 h. The solid product, which formed, was filtered off and recrystallized from ethanol as white crystals in 80% yield. M.p.: >360 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3120 (NH), 2950 (CH aliphatic), 2200 (CN), 1615 (C=N), 1250 (C=S). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.65–1.80 (m, 4H, $2CH_2$), 2.75–2.85 (m, 4H, $2CH_2$), 9.70 (s, 1H, CH triazole), 10.90 (s, 1H, NH pyridine). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 178.43 (C=S), 152.76 (C-3), 149.76 (C-9), 137.38 (C-10), 122.63 (C-11), 105.87 (C-8), 99.96 (C-4), 22.21–42.52 (4CH2 cyclohexeno). MS *m*/*z* (%): 230.09 (M^+, 41.30), 185.08 (34), 183.12 (100), 107.12 (21), 93.12 (42), 83.17 (20), 77.09 (49), 69.10 (29). Anal. Calcd. for: $C_{11}H_{10}N_4S$: C, 57.37; H, 4.38; N, 24.33; S, 13.92%. Found: C; 57.50, H, 4.18; N, 24.55; S, 13.77%.

4.4. Synthesis of pyrazolo compounds (**6**–**11**)

General procedure: A mixture of 1-hydrazino-3-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**3**) (1 g, 4.5 mmol) and active methylene compound (20 mmol) was fused for 1 h then absolute ethanol (20 mL) was added dropwise and reflux continued for additional 2 h. The solid product, which formed, was filtered off and recrystallized from the proper solvent.

4.4.1. 4-Cyano-1-(3,5-dimethylpyrazol-1-yl)-5,6,7,8-tetrahydroisoquinoline-3(2H)-thione (**6**)

Obtained from compound **3** and acetylacetone which was recrystallized from dioxane as brilliant yellow crystals in 86% yield. M.p.: 322–324 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3120 (NH), 2950, 2820 (CH aliphatic), 2210 (CN), 1600 (C=N), 1200 (C=S). ^{1}H NMR (90 MHz, CF_3CO_2D): δ_{ppm} = 1.95–2.05 (m, 4H, $2CH_2$), 2.50, 2.70 (2s sharp, 6H, $2CH_3$ pyrazole), 2.60–2.65 (m, 2H, CH_2), 3.10–3.15 (m, 2H, CH_2), 6.60 (s, 1H, CH pyrazole). Mass spectrum *m*/*z* (%): 284.02 (M^+, 100), 283.03 (33), 251.04 (90), 241.99 (37), 227.99 (12), 210.04 (7), 115.93 (5). Anal. Calcd. for: $C_{15}H_{16}N_4S$: C, 63.35; H, 5.67; N, 19.70; S, 11.27%. Found: C, 63.57; H, 5.73; N, 20.00; S, 1138%.

4.4.2. 1-(5-Amino-3-oxo-2,3-dihydropyrazol-1-yl)-3-thioxo-5,6,7,8-tetrahydroiso quinoline-4-carbonitrile (**7**)

Obtained from compound **3** and ethyl cyanoacetate which was recrystallized from a mixture of ethanol/dioxane as brown crystals in 72% yield. M.p.: 318–320 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3250, 3240, 3120 (NH, NH_2), 2200 (CN), 1700 (C=O), 1600 (C=N), 1200 (C=S). ^{1}H NMR (90 MHz, CF_3CO_2D): δ_{ppm} = 2.10–2.20 (m, 4H, $2CH_2$), 2.85–3.95 (m, 4H, $2CH_2$), 5.15 (s, 1H, CH pyrazole). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 179.88 (C=S), 166.20 (C-3), 162.38 (C-13), 154.54 (C-9), 118.76 (C-10), 110.87 (C-8), 92.24 (C-11), 22.84–41.36 ($4CH_2$ cyclohexeno). Anal. Calcd. for: $C_{13}H_{13}N_5OS$: C, 54.34; H, 4.56; N, 24.37; S, 11.16%. Found: C, 54.15; H, 4.66; N, 24.50; S, 11.25%.

4.4.3. 1-(3-Phenyl-5-oxo-4,5-dihydropyrazol-1-yl)-3-thioxo-5,6,7,8-tetrahydroiso quinoline-4-carbonitrile (**8**)

Obtained from compound **3** and ethyl benzoylacetate which was recrystallized from a mixture of ethanol/dioxane as pale brown crystals in 63% yield. M.p.: 310–312 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3120 (NH), 3050 (CH aromatic), 2920, 2850 (CH aliphatic), 2200 (CN), 1630 (CO), 1600 (C=N), 1250 (C=S). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.80–1.90 (m, 4H, $2CH_2$), 2.45–2.55 (m, 4H, $2CH_2$), 2.70 (s, 2H, CH_2CO), 7.30–7.90 (m, 5H, ArH), 10.50 (s, 1H, NH pyridine). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 178.58 (C=S), 170.37 (C-3), 168.85 (C-12), 159.70 (C-9), 122.78–134.53 (5C-aromatic), 118.00 (CN), 49.85 (CH_2 pyrazole), 22.26–40.58 ($4CH_2$ cyclohexeno). Anal. Calcd. for: $C_{19}H_{16}N_4OS$: C, 65.50; H, 4.63; N, 16.08; S, 9.20%. Found: C, 65.32; H, 4.74; N, 16.24; S, 9.00%.

4.4.4. 4-Cyano-1-(3,5-dioxopyrazol-1-yl)-5,6,7,8-tetrahydroisoquinoline-3(2H)-thione (**9**)

Obtained from compound **3** and diethylmalonate which was recrystallized from dioxane as pale yellow crystals in 88% yield. M.p.: 328–330 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3220, 3120 (2NH), 2920, 2850 (CH aliphatic), 2200 (CN), 1730, 1685 (2CO), 1600 (C=N), 1210 (C=S). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.80–1.90 (m, 4H, $2CH_2$), 2.60–2.65 (m, 2H, CH_2), 2.70–2.80 (m, 2H, CH_2), 4.70 (s, 2H, CH_2 pyrazole), 9.80 (s, 1H, NH pyrazole), 10.30 (s, 1H, NH pyridine). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 180.72 (C=S), 174.15 (C-13), 165.24 (C-13), 158.95 (C-12), 150.54 (C-9), 119.18 (C-10), 110.85 (C-8), 51.80 (C-11), 21.32–38.65 ($4CH_2$ cyclohexeno). Anal. Calcd. for: $C_{13}H_{12}N_4O_2S$: C, 54.15; H, 4.20; N, 19.43; S, 11.12%. Found: C, 54.35; H, 4.00; N, 19.65; S, 11.25%.

4.4.5. Ethyl-3-[(4-cyano-3-thioxo-5,6,7,8-tetrahydroisoquinolin-1-yl)hydrazono] butyrate (**10**)

Obtained from compound **3** and ethyl acetoacetate which was recrystallized from dioxane as orange crystals in 73% yield. M.p.: 208–210 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3350, 3120 (2NH), 2920, 2850 (CH aliphatic), 2200 (CN), 1740 (CO ester), 1600 (C=N), 1220 (C=S). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.30 (t, *J* = 7.5 Hz, 3H, CH_3 ester), 1.70–1.80 (m, 4H, $2CH_2$), 2.30 (s sharp, 3H, CH_3), 2.50–2.60 (m, 2H, CH_2), 3.30–3.40 (m, 2H, CH_2), 3.65 (s, 2H, CH_2CO), 4.10 (q, *J* = 6.0 Hz, 2H, CH_2 ester), 8.10 (s, 1H, NH hydrazone), 10.25 (s, 1H, NH pyridine). Anal. Calcd. for: $C_{16}H_{20}N_4O_2S$: C, 57.81; H, 6.06; N, 16.85; S, 9.65%. Found: C, 58.00; H, 5.93; N, 17.05; S, 9.84%.

4.4.6. 1-(3-Methyl-5-oxo-4,5-dihydropyrazol-1-yl)-3-thioxo-5,6,7,8-tetrahydroiso quinoline-4-carbonitrile (**11**)

A solution of compound **10** (0.33 g, 1 mmol) in absolute ethanol (20 mL) and few drops of sodium ethoxide solution were refluxed for 20 min. The solid precipitate, which formed, was filtered off and recrystallized from ethanol as brown crystals in 53% yield. M.p.: 312–314 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3120 (NH), 2920, 2850 (CH aliphatic), 2210 (CN), 1640 (CO), 1600 (C=N), 1230 (C=S). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.10 (s, 3H, CH_3), 1.60–1.70 (m, 4H, $2CH_2$), 2.20–2.25 (m, 2H, CH_2), 2.75–2.80 (m, 2H, CH_2), 4.00 (s, 2H, CH_2), 11.00 (s, 1H, NH pyridine). ^{13}C NMR (400 MHz, DMSO-d_6):

δ_{ppm} = 177.73 (C=S), 161.23 (C-3), 159.41 (C-9), 156.90 (C-13), 119.12 (C-10), 111.52 (C-8), 50.78 (CH_2 pyrazole), 21.35–43.68 ($4CH_2$ cyclo-hexeno), 15.30 (CH_3 pyrazole). Anal. Calcd. for: $C_{14}H_{14}N_4OS$: C, 58.72; H, 4.93; N, 19.57; S, 11.20%. Found: C, 58.85; H, 5.10; N, 19.70; S, 11.38%.

4.5. Alkylation of 5-thioxo-7,8,9,10-tetrahydro-1H[1,2,4]triazolo [3,4-a]isoquinoline-6-carbonitrile (**12a–e**)

General procedure: A mixture of **5** (1.00 g, 4 mmol) and of alkylating agent (4 mmol) in presence of fused sodium acetate (1.20 g, 1.50 mmol) was stirred in ethanol (30 mL) for 1/4 h. A white precipitate, which formed on cooling and dilution with water, was filtered off and recrystallized from ethanol.

4.5.1. 6-Cyano-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-a] isoquinoline-5-sulfanyl acetonitrile (**12a**)

Obtained from 6-cyano-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-a] isoquinoline (**5**) and chloroacetonitrile which was recrystallized from ethanol as pale yellow crystals in 54% yield. M.p.: 230–232 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 2950, 2850 (CH aliphatic), 2210 (CN), 1610 (C=N). Anal. Calcd. for: $C_{13}H_{11}N_5S$: C, 57.98; H, 4.12; N 26.00; S 11.91%. Found: C, 58.10; H, 4.25; N, 25.82; S, 11.82%.

4.5.2. Ethyl-6-cyano-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-a] isoquinoline-5-sulfanyl acetate (**12b**)

Obtained from compound **5** and ethyl chloroacetate which was recrystallized from ethanol as white crystals in 60% yield. M.p.: 180–182 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 2920, 2850 (CH aliphatic), 2200 (CN), 1660 (CO ester), 1610 (C=N). MS *m/z* (%): 315.97 (M^+, 100), 269.97 (68), 241.05 (22), 215.94 (7), 160.97 (8). Anal. Calcd. for: $C_{15}H_{16}N_4O_2S$: C, 56.95; H, 5.10; N, 17.71; S, 10.13%. Found: C, 57.10; H, 5.25; N, 17.54; S, 10.25%.

4.5.3. 6-Cyano-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-a] isoquinoline-5-sulfanyl acetamide (**12c**)

Obtained from compound **5** and chloroacetamide which was recrystallized from ethanol as pale yellow crystals in 58% yield. M.p.: 218–220 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3400, 3350 (NH_2), 2920 (CH aliphatic), 2210 (CN), 1660 (CO amide), 1610 (C=N). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.65–1.75 (m, 4H, $2CH_2$), 2.80–2.90 (m, 2H, CH_2), 3.30–3.40 (m, 2H, CH_2), 3.90 (s, 2H, CH_2), 7.20 (s, 2H, NH_2), 9.60 (s, 1H, CH triazole). Anal. Calcd. for: $C_{13}H_{13}N_5OS$: C, 54.34; H, 4.56; N, 24.37; S, 11.16%. Found: C, 54.52; H, 4.63; N, 24.50; S, 11.00%.

4.5.4. 6-Cyano-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-a] isoquinoline-5-sulfanyl acetone (**12d**)

Obtained from compound **5** and chloroacetone which was recrystallized from ethanol as pale yellow crystals in 62% yield. M.p.: 268–270 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 2920, 2850 (CH aliphatic), 2210 (CN), 1710 (C=O), 1600 (C=N). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.70–1.90 (m, 4H, $2CH_2$), 2.30 (s sharp, 3H, CH_3), 2.70–2.80 (m, 2H, CH_2), 2.90–3.05 (m, 2H, CH_2), 4.00 (s, 2H, CH_2), 9.20 (s, 1H, CH triazole). MS *m/z* (%): 285.85 (100), 283.87 (36.50), 269.89 (15), 250.87 (30), 242.9 (39), 115.88 (10), 76.96 (13). Anal. Calcd. for: $C_{14}H_{14}N_4OS$: C, 58.72; H, 4.93; N, 19.57; S, 11.20%. Found: C, 58.55; H, 5.05; N, 19.70; S, 11.00%.

4.5.5. 6-Cyano-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-a] isoquinoline-5-sulfanyl acetophenone (**12e**)

Obtained from compound **5** and phenacyl bromide which was recrystallized from ethanol as pale yellow crystals in 85% yield. M.p.: 176–178 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3050 (CH aromatic), 2920, 2850 (CH aliphatic), 2210 (CN), 1675 (unsaturated CO), 1600 (C=N), ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.80–1.90 (m, 4H, $2CH_2$), 2.75–2.80 (m, 2H, CH_2), 3.05–3.10 (m, 2H, CH_2), 4.70 (s, 2H, CH_2), 7.30–7.90 (m, 5H, ArH), 9.20 (s, 1H, CH triazole). MS *m/z* (%): 347.43 (M^+ – 1, 30.70), 99.26 (100), 83.89 (8.60), 73.37 (34.80). Anal. Calcd. for: $C_{19}H_{16}N_4OS$: C, 65.50; H, 4.63; N, 16.08; S, 9.20%. Found: C, 65.34; H, 4.75; N, 15.96; S, 9.38%.

4.6. Cyclization of 5-substitutedmercapto-6-cyano-7,8,9,10-tetrahydro[1,2,4] triazolo[3,4-a]isoquinoline (**13a–e**)

4.6.1. Method A

General procedure: A solution of the alkylated compound **12a–e**, (1 mmol) in absolute ethanol (20 mL) and few drops of sodium ethoxide solution (prepared from 0.5 g of clean sodium on 20 mL absolute ethanol) were refluxed for 10 min. The solid precipitate which formed on cold or dilution with water was filtered off and recrystallized from the proper solvent.

*4.6.1.1. 7-Amino-8,9,10,11–tetrahydrothieno[2,3-c][1,2,4]triazolo[3,4-a]isoquino-line-6-carbonitrile (**13a**).* Obtained from compound **12a** which was recrystallized from DMSO as white needles in 84% yield. M.p.: 320–322 °C.

*4.6.1.2. Ethyl-7-amino-8,9,10,11-tetrahydrothieno[2,3-c][1,2,4]triazolo[3,4-a] isoquinolin-6-acetate (**13b**).* Obtained from compound **12b** which was recrystallized from dioxane as white needles in 75% yield. M.p.: 248–250 °C.

*4.6.1.3. 7-Amino-8,9,10,11-tetrahydrothieno[2,3-c][1,2,4]triazolo[3,4-a]isoquinoline-6-carboxamide (**13c**).* Obtained from compound **12c** which was recrystallized from ethanol as white needles in 81% yield. M.p.: 272–274 °C.

*4.6.1.4. 6-Acetyl-7-amino-8,9,10,11-tetrahydrothieno[2,3-c][1,2,4]triazolo[3,4-a]iso quinoline (**13d**).* Obtained from compound **12d** which was recrystallized from DMSO as white needles in 87% yield. M.p.: 268–270 °C.

*4.6.1.5. 7-Amino-6-benzoyl-8,9,10,11-tetrahydrothieno[2,3-c][1,2,4] triazolo[3,4-a]isoquinoline (**13e**).* Obtained from compound **12e** which was recrystallized from ethanol as yellow needles in 91% yield. M.p.: 292–294 °C.

4.6.2. Method B

A mixture of 5-thioxo-7,8,9,10-tetrahydro[1,2,4]triazolo[3,4-a] isoquinoline-6-carbo-nitrile (**5**) (1 g, 4 mmol) and alkylating agent (4 mmol) in presence of fused sodium acetate (1.2 g, 1.5 mmol) was refluxed in ethanol (30 mL) for 2 h. A white precipitate is formed on hot filtered off, dried and recrystallized from the proper solvent.

*4.6.2.1. 7-Amino-8,9,10,11-tetrahydrothieno[2,3-c][1,2,4]triazolo[3,4-a]isoquinoline-6-carbonitrile (**13a**).* Obtained from triazolo compound **5** and chloroacetonitrile which was recrystallized from DMSO as white needles in 76% yield. M.p.: 320–322 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3350, 3250, 3100 (NH_2), 2920, 2850 (CH aliphatic), 2200 (CN), 1645 (C=N). ^{1}H NMR (CF_3CO_2D): δ_{ppm} = 2.10–2.15 (m, 2H, CH_2), 3.10–3.20 (m, 4H, $2CH_2$), 3.55–3.60 (m, 2H, CH_2), 9.60 (s, 1H, CH triazole). Anal. Calcd. for: $C_{13}H_{11}N_5S$: C 57.98; H 4.12; N 26.00; S 11.91%. Found: C, 57.75; H, 4.25; N; 26.16; S, 11.84%.

*4.6.2.2. Ethyl-7-amino-8,9,10,11-tetrahydrothieno[2,3-c][1,2,4]triazolo[3,4-a] isoquinoline-6-acetate (**13b**).* Obtained from compound **5** and ethyl chloroacetate which was recrystallized from dioxane as white needles in 69% yield. M.p.: 248–250 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3450, 3320 (NH_2), 2920 (CH aliphatic); 1660 (CO ester), 1610

(C=N). ^{1}H NMR (CF_3CO_2D): δ_{ppm} = 1.40 (t, J = 9.0 Hz, 3H, CH_3), 2.10–2.20 (m, 2H, CH_2), 3.15–3.30 (m, 4H, $2CH_2$), 3.60–3.70 (m, 2H, CH_2), 4.40 (q, J = 7.5 Hz, 2H, CH_2), 9.60 (s, 1H, CH triazole). Mass spectrum m/z (%): 315.87 (M^+, 58), 298.13 (42), 269.84 (100), 243.88 (56), 241.01 (64), 214.95 (94), 199.88 (36), 181.01 (56), 134.86 (25), 116.93 (58). Anal. Calcd. for: $C_{15}H_{16}N_4O_2S$: C 56.95; H 5.10; N 17.71; S 10.13%. Found: C, 57.10; H, 4.98; N, 17.85; S, 10.00%.

*4.6.2.3. 7-Amino-8,9,10,11-tetrahydrothieno[2,3-c][1,2,4]triazolo[3,4-a]isoquinoline-6-carboxamide (**13c**).* Obtained from compound **5** and chloroacetamide which was recrystallized from ethanol as white needles in 75% yield. M.p.: 272–274 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3350, 3300, 3250 ($2NH_2$), 2950 (CH aliphatic), 1665 (C=O). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.70–1.75 (m, 2H, CH_2), 2.80–2.90 (m, 4H, $2CH_2$), 3.10–3.20 (m, 2H, CH_2), 6.90 (s, 2H, $CONH_2$), 7.30 (s, 2H, NH_2), 9.50 (s, 1H, CH triazole). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 169.56 (C=O amide), 155.36 (C-3), 154.83 (C-7), 150.26 (C-9), 144.00 (C-10), 133.05 (C-12), 122.35 (C-11), 93.65 (C-8), 19.85–45.30 ($4CH_2$ cyclohexeno). MS m/z (%): 287.05 (M^+, 16.60), 286.40 ($M^+ - 1$, 28.10), 269.65 (48.20), 248.85 (27.20), 240.71 (29.30), 213.58 (15.70), 190.81 (16.30), 149.84 (100), 104.29 (27.80), 90.89 (34.60). Anal. Calcd. for: $C_{13}H_{13}N_5OS$: C, 54.34; H, 4.56; N, 24.37; S, 11.16%. Found: C, 54.50; H, 4.68; N, 24.46; S, 11.00%.

*4.6.2.4. 6-Acetyl-7-amino-8,9,10,11-tetrahydrothieno[2,3-c][1,2,4]triazolo[3,4-a]iso quinoline (**13d**).* Obtained from compound **5** which was recrystallized from DMSO as white needles in 74% yield. M.p. 268–270 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3420, 3300, 3100 (NH_2), 2950 (CH aliphatic), 1680 (CO), 1610 (C=N). Anal. Calcd. for: $C_{14}H_{14}N_4OS$: C, 58.72; H, 4.93; N, 19.57; S, 11.20%. Found: C, 58.84; H, 4.86; N, 19.42; S, 11.36%.

*4.6.2.5. 7-Amino-6-benzoyl-8,9,10,11-tetrahydrothieno[2,3-c][1,2,4]triazolo[3,4-a]isoquinoline (**13e**).* Obtained from compound **5** and phenacyl bromide which was recrystallized from ethanol as yellow needles in 86% yield. M.p.: 292–294 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3450, 3350 (NH_2), 2950 (CH aliphatic); 1640 (CO). ^{1}H NMR (90 MHz, CF_3CO_2D): δ_{ppm} = 2.00–2.10 (m, 2H, CH_2), 3.10–3.15 (m, 4H, $2CH_2$), 3.50–3.55 (m, 2H, CH_2), 7.80–8.10 (m, 5H, ArH), 9.50 (s, 1H, CH triazole). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 185.50 (C=O), 171.85 (C-3), 156.25 (C-7), 154.00 (C-9), 145.25 (CH triazole), 127.75–135.14 (5C-aromatic), 123.75 (C-11), 92.69 (C-8), 99.80 (C-4), 21.94–42.35 ($4CH_2$ cyclohexeno). Anal. Calcd. for: $C_{19}H_{16}N_4OS$: C, 65.50; H, 4.63; N, 16.08; S, 9.20%. Found: C, 65.65; H, 4.52; N, 15.95; S, 9.34%.

*4.7. 1,2,3,4-Tetrahydropyrimido[4′,5′:4,5]thieno[2,3-c][1,2,4]triazolo[3,4-a]isoquinolin-10(11H)-one (**14**)*

Compound **13c** (0.6 g, 2 mmol) and trietyl orthoformate (2 mL) and few drops of glacial acetic acid were refluxed for 1/2 h. The precipitated solid, which formed, was filtered off and recrystallized from dioxane as white crystals in 68% yield. M.p.: >360 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3100 (NH), 2920, 2850 (CH aliphatic), 1660 (CO imide), 1575 (C=N). ^{1}H NMR (90 MHz, CF_3CO_2D): δ_{ppm} = 2.10–2.30 (m, 4H, $2CH_2$), 3.10–3.20 (m, 2H, CH_2), 3.80–3.90 (m, 2H, CH_2), 8.90 (s, 1H, CH pyrimidine), 9.70 (s, 1H, CH triazole). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 172.71 (C-3), 166.05 (CONH), 163.80 (C-7), 152.98 (C-9), 149.13 (CH=N pyrimidine), 145.25 (C-10), 126.86 (C-12), 124.35 (C-11), 92.86 (C-8), 99.70 (C-4), 22.25–43.85 ($4CH_2$ cyclohexeno). MS m/z (%): 297.93 (M^+, 85), 284.05 (81.50), 251.09 (63), 108.65 (28), 89.87 (52), 79.06 (51), 70.04 (72), 59.86 (72), 56.87 (100). Anal. Calcd. for: $C_{14}H_{11}N_5OS$: C, 56.55; H, 3.73; N, 23.55; S, 10.78%. Found: C, 56.34; H, 3.85; N, 23.32; S, 10.86%.

*4.8. Alkylation of 1-(2-p-Chlorobenzylidenehydrazinyl)-3-thioxo-5,6,7,8-tetra hydroisoquinoline-4-carbonitrile (**15a–e**)*

General procedure: A mixture of *p*-chlorobenzylidene derivative **4c** (0.5 g, 1.5 mmol) and alkylating agent (1.5 mmol) in presence of fused sodium acetate (0.6 g, 6.8 mmol) in ethanol (20 mL) was refluxed for 2 h. The solid product, which formed, was filtered off and recrystallized from ethanol.

*4.8.1. 1-(2-p-Chlorobenzylidenehydrazinyl)-4-cyano-5,6,7,8-tetrahydroiso quinoline-3-thiomethylcyanide (**15a**)*

Obtained from compound **4c** and chloroacetonitrile as white crystals in 81% yield. M.p. 188–190 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3300 (NH), 3050 (CH aromatic), 2950, 2850 (CH aliphatic), 2190 (CN), 1630 (C=N). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.70–1.75 (m, 4H, $2CH_2$), 2.50–2.55 (m, 2H, CH_2), 3.25–3.30 (m, 2H, CH_2), 4.40 (s, 2H, CH_2CN), 7.40 (d, J = 10.5 Hz, 2H, *p*-sub ArH), 7.65 (d, J = 7.5 Hz, 2H, *p*-sub ArH), 8.40 (s, 1H, CH=N), 10.70 (s, 1H, NH). Anal. Calcd. for: $C_{19}H_{16}ClN_5S$: C, 59.76; H, 4.22; Cl, 9.28; N, 18.34; S, 8.40%. Found: C, 59.65; H, 4.45; Cl, 9.50; N, 18.18; S, 8.22%.

*4.8.2. Ethyl-1-(2-p-chlorobenzylidenehydrazinyl)-4-cyano-5,6,7,8-tetrahydroiso quinoline-3-sulfanylacetate (**15b**)*

Method A: Obtained from compound **4c** and ethyl chloroacetate as white crystals in 78% yield. M.p.: 186–188 °C.

Method B: A mixture of compound **17** (0.61 g, 2 mmol) and *p*-chlorobenzaldehyde (0.28 g, 2 mmol) was refluxed in ethanol (20 mL) for 2 h. The solid product, which formed, was filtered off and recrystallized from ethanol as white crystals in 80% yield. M.p.: 186–188 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3320 (NH), 3030 (CH aromatic), 2920 (CH aliphatic), 2200 (CN), 1720 (CO ester), 1640 (C=N). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.30 (t, J = 9.0 Hz, 3H, CH_3 ester), 1.70–1.80 (m, 4H, $2CH_2$), 2.60–2.65 (m, 2H, CH_2), 3.75–3.80 (m, 2H, CH_2), 4.00 (s, 2H, CH_2CO), 4.40 (q, J = 6.0 Hz, 2H, CH_2 ester), 7.30 (d, J = 9.0 Hz, 2H, *p*-sub ArH), 7.70 (d, J = 9.0 Hz, 2H, *p*-sub ArH), 8.70 (s, 1H, CH=N), 11.20 (s, 1H, NH). Anal. Calcd. for: $C_{21}H_{21}ClN_4O_2S$: C, 58.80; H, 4.93; Cl, 8.27; N, 13.06; S, 7.48%. Found: C; 59.00; H, 4.85; N, 12.95; S, 7.63%.

*4.8.3. 1-(2-p-Chlorobenzylidinehydrazinyl)-4-cyano-5,6,7,8-tetrahydroiso quinoline-3-sulfanylacetamide (**15c**)*

Obtained from compound **4c** and chloroacetamide as white crystals in 75% yield. M.p.: 264–266 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3420, 3320, 3120 (NH, NH_2), 3050 (CH aromatic), 2920 (CH aliphatic), 2210 (CN), 1670 (CO amide), 1600 (C=N). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.80–1.90 (m, 4H, $2CH_2$), 2.75–2.80 (m, 2H, CH_2), 3.30–3.40 (m, 2H, CH_2), 3.90 (s, 2H, CH_2), 6.8 (s, 2H, NH_2), 7.50 (d, J = 10.5 Hz, 2H, *p*-sub ArH), 7.80 (d, J = 7.5 Hz, 2H, *p*-sub ArH), 8.40 (s, 1H, CH), 11.00 (s, 1H, NH). Anal. Calcd. for: $C_{19}H_{18}ClN_5OS$: C, 57.07; H, 4.54; Cl, 8.87; N, 17.51; S, 8.02%. Found: C, 56.95; H, 4.66; Cl, 9.00; N, 17.61; S, 7.85%.

*4.8.4. 1-(2-p-Chlorobenzylidine)hydrazinyl-4-cyano-5,6,7,8-tetrahydroiso quinoline-3-sulfanylacetone (**15d**)*

Obtained from compound **4c** and chloroacetone as white crystals in 83% yield. M.p.: 256–258 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3300 (NH), 3030 (CH aromatic), 2930 (CH aliphatic), 2210 (CN), 1720 (CO ester), 1640 (C=N). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.90–2.00 (m, 4H, $2CH_2$), 2.40–2.45 (m, 3H, CH_3), 2.60–2.65 (m, 2H, CH_2), 3.35–3.40 (m, 2H, CH_2), 4.40 (s, 2H, CH_2), 7.50 (m, J = 9.0 Hz, 2H, *p*-sub ArH), 7.80, (m, J = 7.5 Hz, 2H, *p*-sub ArH), 8.3 (s, 1H, CH=N), 10.80 (s, 1H, NH). MS m/z (%): 400.33 ($M^+ + 2$, 38.9), 398.33 (M^+, 100), 355.24 (35), 343.24 (15), 341.24 (47), 261.21 (34.50), 260.22 (24), 218.22 (66), 216.21 (23). Anal. Calcd. for: $C_{20}H_{19}ClN_4OS$: C, 60.22; H, 4.80; Cl, 8.89; N, 14.04; S, 8.04%. Found: C, 60.00; H, 4.92; Cl, 9.03; N, 13.88; S, 8.20%.

*4.8.5. 1-(2-p-Chlorobenzylidenehydrazinyl)-4-cyano-5,6,7,8-tetrahydroiso quinoline-3-sulfanylacetophenone (**15e**)*

Obtained from compound **4c** and phenacyl bromide as orange crystals in 85% yield. M.p.: 248–250 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3350 (NH), 3050 (CH aromatic), 2920, 2850 (CH aliphatic), 2200 (CN), 1670 (unsaturated CO), 1560 (C=N). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.70–1.80 (m, 4H, $2CH_2$), 2.50–2.55 (m, 2H, CH_2), 3.25–3.30 (m, 2H, CH_2), 5.00 (s, 2H, CH_2 doesn't disappear by D_2O), 7.20–8.10 (m, 9H, ArH), 8.30 (s, 1H, CH), 11.00 (s, 1H, NH disappears by D_2O). Anal. Calcd. for: $C_{25}H_{21}ClN_4OS$: C, 65.14; H, 4.59; Cl, 7.69; N, 12.15; S, 6.96%. Found: C, 65.28; H, 4.63; Cl, 7.82; N, 12.25; S, 7.10%.

*4.9. Cyclization of 3-substitutedmercapto-1-(2-p-chlorobenzylidinehydrazinyl)-4-cyano-5,6,7,8-tetrahydroisoquinoline (**16a**–**e**)*

General procedure: A solution of (1 mmol) of alkylated compound **15a**–**e** in absolute ethanol (20 mL) and few drops of sodium ethoxide solution (prepared from 0.5 g of clean sodium on 20 mL absolute ethanol) were refluxed for 20 min. The solid precipitate which was formed on cold or dilution with water filtered off, dried and recrystallized from the proper solvent.

*4.9.1. 1-Amino-5-(2-p-chlorobenzylidenehydrazinyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carbonitrile (**16a**)*

Obtained as pale yellow crystals when the solid precipitate was recrystallized from ethanol-dioxane mixture as in 80% yield. M.p.: 232–234 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3400, 3350, 3150 (NH_2), 2920, 2850 (CH aliphatic), 2210 (CN), 1620 (C=N). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.70–1.80 (m, 4H, $2CH_2$), 2.50–2.55 (m, 2H, CH_2), 3.25–3.30 (m, 2H, CH_2), 6.10 (s, 2H, NH_2), 7.50 (d, J = 9.6 Hz, 2H, *p*-substituted ArH), 7.80 (d, J = 6.6 Hz, 2H, *p*-substituted ArH), 8.30 (s, 1H, CH=N), 10.50 (s, 1H, NH). Anal. Calcd. for: $C_{19}H_{16}ClN_5S$: C, 59.76; H, 4.22; Cl, 9.28; N, 18.34; S, 8.40%. Found: C, 59.68; H, 4.43; Cl, 9.50; N, 18.17; S, 8.20%.

*4.9.2. Ethyl-1-amino-5-(2-p-chlorobenzylidenehydrazinyl)-6,7,8,9-tetrahydro thieno[2,3-c]isoquinoline-2-carboxylate (**16b**)*

Obtained as white crystals when the solid precipitate was recrystallized from ethanol in 73% yield. M.p.: 228–230 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3500, 3350, 3250 (NH, NH_2), 3070 (CH aromatic), 2920, 2830 (CH aliphatic), 2200 (CN), 1645 (CO unsaturated ester), 1590 (C=N). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.10 (t, J = 9.0 Hz, 3H, CH_3 ester), 1.70–1.80 (m, 4H, $2CH_2$), 2.50–2.55 (m, 2H, CH_2), 3.2–3.25 (m, 2H, CH_2), 4.20 (q, J = 4.5 Hz, 2H, CH_2), 5.90 (s, 2H, NH_2 disappears by D_2O), 7.40 (d, J = 6.0 Hz, 2H, *p*-substituted ArH), 7.8 (d, J = 9.0 Hz, 2H, *p*-substituted ArH), 8.20 (s, 1H, CH=N), 10.10 (s, 1H, NH disappeared by D_2O). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 166.30 (C=O ester), 156.22 (C-7), 153.34 (C-9), 136.86 (CH=N), 126.16–134.02 (5C-aromatic), 115.28 (C-8), 111.15 (C-4), 95.32 (C-11), 59.95 (CH_2 ester), 23.52–39.34 ($4CH_2$ cyclohexeno), 15.10 (CH_3 ester). Anal. Calcd. for: $C_{21}H_{21}ClN_4O_2S$: C, 58.80; H, 4.93; Cl, 8.27; N, 13.06; S, 7.48%. Found: C, 58.68; H, 5.04; Cl, 8.42; N, 13.25; S, 7.70%.

*4.9.3. 1-Amino-5-(2-p-chlorobenzylidenehydrazinyl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline-2-carboxamide (**16c**)*

Obtained as orange crystals when the solid precipitate was recrystallized from ethanol/dioxane mixture in 76% yield. M.p.: 280–282 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3450, 3300, 3200 (NH, NH_2), 3050 (CH aromatic), 2920, 2850 (CH aliphatic), 1640 (CO amide), 1570 (C=N). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.80–1.90 (m, 4H, $2CH_2$), 2.60–2.70 (m, 2H, CH_2), 3.15–3.20 (m, 2H, CH_2), 6.70 (s, 4H, $2NH_2$ disappeared by D_2O), 7.30 (d, J = 7.5 Hz, 2H, *p*-substituted ArH), 7.70 (d, J = 6.6 Hz, 2H, *p*-substituted ArH), 8.20 (s, 1H, CH=N), 11.00 (s, 1H, NH disappeared by D_2O). Anal. Calcd. for: $C_{19}H_{18}ClN_5OS$: C, 57.07; H, 4.54; Cl, 8.87; N, 17.51; S, 8.02%. Found: C, 56.95; H, 4.66; Cl, 9.00; N, 17.23; S, 7.85%.

*4.9.4. 2-Acetyl-1-amino-5-(2-p-chlorobenzylidinehydrazinyl)-6,7,8,9-tetrahydro thieno[2,3-c]isoquinoline (**16d**)*

Obtained as orange crystals when the solid precipitate was recrystallized from dioxane in 85% yield. M.p.: 294–296 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3500, 3400, 3280 (NH, NH_2), 3050 (CH aromatic), 2920, 2850 (CH aliphatic), 1670 (CO), 1610 (C=N). ^{1}H NMR (90 MHz, CF_3CO_2D): δ_{ppm} = 1.85–1.95 (m, 4H, $2CH_2$), 2.50–2.55 (m, 2H, CH_2), 2.60 (s sharp, 3H, CH_3), 3.20–3.30 (m, 2H, CH_2), 7.30 (d, J = 9.0 Hz, 2H, *p*-substituted ArH), 7.80 (d, J = 7.5 Hz, 2H, *p*-substituted ArH), 8.50 (s, 1H, CH=N). Anal. Calcd. for: $C_{20}H_{19}ClN_4OS$: C, 60.22; H, 4.80; Cl, 8.89; N, 14.04; S, 8.04%. Found: C, 60.37; H, 4.67; Cl, 9.04; N, 14.24; S, 7.90%.

*4.9.5. 1-Amino-2-benzoyl-5-(2-p-chlorobenzylidenehydrazinyl)-6,7,8,9-tetrahydro thieno[2,3-c]isoquinoline (**16e**)*

Obtained as red crystals when the solid precipitate was recrystallized from dioxane in 81% yield. M.p.: 284–286 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3500, 3300, 3250 (NH, NH_2), 3050 (CH aromatic), 2920, 2850 (CH aliphatic), 1650 (CO), 1600 (C=N). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.70–1.80 (m, 4H, $2CH_2$), 2.35–2.40 (m, 2H, CH_2), 3.20–3.25 (m, 2H, CH_2), 7.30–7.80 (m, 9H, ArH), 8.00 (s, 2H, NH_2), 8.20 (s, 1H, CH=N), 10.80 (s, 1H, NH). MS *m/z* (%): 462.13 (27), 460.30 (M^+, 18), 391.16 (45), 390.05 (42.50), 386.18 (100), 389.3 (25), 388.35 (56), 386.18 (100), 372.28 (23), 357.13 (26), 325.25 (26), 323.34 (49), 322.35 (61), 286.92 (34), 259.24 (21), 201.05 (22), 163.10 (20), 149.04 (61), 143.03 (28), 119.12 (26), 118.05 (22), 104.99 (32), 101.05 (24), 97.12 (37). Anal. Calcd. for: $C_{25}H_{21}ClN_4OS$: C, 65.14; H, 4.59; Cl, 7.69; N, 12.15; S, 6.96%. Found: C, 65.34; H, 4.76; Cl, 7.54; N, 12.03; S, 7.14%.

*4.10. Ethyl(4-cyano-1-hydrazino-5,6,7,8-tetrahydroisoquinolin-3-ylsulfanyl)acetate (**17**)*

A mixture of 1-hydrazino-3-thioxo-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**3**) (1 g, 4.50 mmol), ethyl chloroacetate (0.55 mL, 4.50 mmol) and fused sodium acetate (0.6 g, 6.80 mmol) in ethanol (20 mL) was refluxed for 2 h. The solid precipitate, which formed on cold, was filtered off and recrystallized from ethanol as white needles in 84% yield. M.p.: 120–122 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3450, 3380, 3320 (NH_2, NH), 2190 (CN), 1740 (CO ester). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.20 (t, J = 7.5 Hz, 3H, CH_3), 1.75–1.85 (m, 4H, $2CH_2$), 2.40–2.45 (m, 4H, $2CH_2$), 3.40 (s, 2H, SCH_2), 4.15 (q, J = 4.5 Hz, 2H, CH_2), 6.60 (s, 2H, NH_2), 8.10 (s, 1H, NH). Anal. Calcd. for: $C_{14}H_{18}N_4O_2S$: C, 54.88; H, 5.92; N, 18.29; S, 10.47%. Found: C, 54.68; H, 6.00; N, 18.40; S, 10.54%.

*4.11. Alkylation of 1-(3,5-dimethylpyrazol-1-yl)-4-cyano-5,6,7,8-tetrahydroiso quinoline-3(2H)-thione (**6**): formation of (**18a**–**e**)*

General procedure: A mixture of pyrazolo derivative **6** (0.58 g, 2 mmol) and alkylating agent (2 mmol) in presence of fused sodium acetate (0.75 g, 8.50 mmol) in ethanol (20 mL) was refluxed for 2 h. The solid product, which formed on cooling, was filtered off and recrystallized from ethanol.

*4.11.1. 3-Cyanomethylsulfanyl-1-(3,5-dimethylpyrazol-1-yl)-5,6,7,8-tetrahydro isoquinoline-4-carbonitrile (**18a**)*

Obtained from compound **6** and chloroacetonitrile as white crystals in 89% yield. M.p.: 142–144 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 2950, 2850 (CH aliphatic), 2200 (CN), 1630 (C=N). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.80–1.95 (m, 4H, $2CH_2$), 2.35, 2.40 (2s sharp, 6H, $2CH_3$), 2.70–2.75 (m, 2H, CH_2), 3.00–3.10 (m, 2H, CH_2), 4.00 (s, 2H,

CH_2CN), 6.00 (s, 1H, CH pyrazole). MS *m/z* (%): 323.97 (M^+, 23.8), 322.95 ($M^+ - 1$, 100), 284.02 (32.3), 282.98 (27.9), 280.98 (19.1), 251.01 (19.5). Anal. Calcd. for: $C_{17}H_{17}N_5S$: C, 63.13; H, 5.30; N, 21.65; S, 9.91%. Found: C, 63.35; H, 5.18; N, 21.76; S, 9.71%.

*4.11.2. Ethyl[4-cyano-1-(3,5-dimethylpyrazol-1-yl)-5,6,7,8-tetrahydroisoquinolin-3-ylsulfanyl]acetate (**18b**)*

Obtained from compound **6** and ethyl chloroacetate as white needles in 85% yield. M.p.: 140–142 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 2950 (CH aliphatic), 2210 (CN), 1745 (CO ester), 1620 (C=N). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.15 (t, *J* = 9.0 Hz, 3H, CH_3 ester), 1.80–1.90 (m, 4H, $2CH_2$), 2.20, 2.25 (2s sharp, 6H, $2CH_3$), 2.65–2.70 (m, 2H, CH_2), 2.90–2.95 (m, 2H, CH_2), 3.95 (s, 2H, CH_2CO), 4.10 (q, *J* = 7.5 Hz, 2H, CH_2 ester), 5.90 (s, 1H, CH triazole). Anal. Calcd. for: $C_{19}H_{22}N_4O_2S$: C, 61.60; H, 5.99; N, 15.12; S, 8.65%. Found: C, 61.45; H, 6.14; N, 15.27; S, 8.78%.

*4.11.3. 2-[4-Cyano-1-(3,5-dimethylpyrazol-1-yl)-5,6,7,8-tetrahydroisoquinoline-3-ylsulfanyl]acetamide (**18c**)*

Obtained from compound **6** and chloroacetamide as white crystals in 79% yield. M.p.: 200–202 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3450, 3350, 3200 (NH_2), 2920, 2850 (CH aliphatic), 2210 (CN), 1670 (CO amide), 1620 (C=N). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.75 (m, 4H, $2CH_2$), 2.20, 2.25 (2s sharp, 6H, $2CH_3$), 2.65 (m, 2H, CH_2), 2.95 (m, 2H, CH_2), 3.80 (s, 2H, CH_2CO), 5.90 (s, 1H, CH pyrazole), 6.40 (s, 2H, NH_2). Anal. Calcd. for: $C_{17}H_{19}N_5OS$: C, 59.80; H, 5.61; N, 20.51; S, 9.39%. Found: C, 59.95; H, 5.74; N, 20.27; S, 9.56%.

*4.11.4. 1-(3,5-Dimethylpyrazol-1-yl)-3-(2-oxopropylsulfanyl)-5,6,7,8-tetrahydro isoquinoline-4-carbonitrile (**18d**)*

Obtained from compound **6** and chloroacetone as pale yellow crystals in 92% yield. M.p.: 128–130 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 2920, 2850 (CH aliphatic), 2210 (CN), 1715 (CO), 1620 (C=N). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.85–1.95 (m, 4H, $2CH_2$), 2.25, 2.30, 2.35 (3s sharp, 9H, $3CH_3$), 2.65–2.70 (m, 2H, CH_2), 2.95–3.00 (m, 2H, CH_2), 4.00 (s, 2H, CH_2), 5.90 (s, 1H, CH pyrazole). Anal. Calcd. for: $C_{18}H_{20}N_4OS$: C, 63.50; H, 5.92; N, 16.46; S, 9.42%. Found: C, 63.36; H, 6.12; N, 16.28; S, 9.60%.

*4.11.5. 1-(3,5-Dimethylpyrazol-1-yl)-3-(phenyl-2-oxoethylsulfanyl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**18e**)*

Obtained from compound **6** and phenacyl bromide as white crystals in 75% yield. M.p.: 180–182 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 2950 (CH aliphatic), 2210 (CN), 1690 (unsaturated CO), 1600 (C=N). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.70–1.80 (m, 4H, $2CH_2$), 2.00, 2.20 (2s sharp, 6H, $2CH_3$), 2.55 (m, 2H, CH_2), 2.95 (m, 2H, CH_2), 4.65 (s, 2H, CH_2CO), 5.80 (s, 1H, CH pyrazole), 7.30–8.00 (m, 5H, ArH). Anal. Calcd. for: $C_{23}H_{22}N_4OS$: C, 68.63; H, 5.51; N, 13.92; S, 7.97%. Found: C, 68.75; H, 5.27; N, 14.14; S, 8.16%.

*4.12. Cyclization of 3-substitutedsulfanyl-1-(3,5-dimethylpyrazol-1-yl)-5,6,7,8-tetrahydroisoquinoline-4-carbonitrile (**19a**–**e**)*

4.12.1. Method A

General procedure: A solution of compound **18a**–**e** (1 mmol) in absolute ethanol (20 mL) and few drops of sodium ethoxide solution were refluxed for 20 min. The solid precipitate which was formed on cold or dilution with water filtered off, dried and recrystallized from ethanol.

*4.12.1.1. 1-Amino-5-(3,5-dimethylpyrazol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]iso-quinolin-2-carbonitrile (**19a**).* Obtained as the above procedure to afford greenish yellow needles in 84% yield. M.p.: 194–196 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3300, 3220 (NH_2), 2920, 2850 (CH aliphatic), 2200 (CN), 1640 (C=N). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.70–1.80 (m, 4H, $2CH_2$), 2.15, 2.25 (2s sharp, 6H, $2CH_3$), 2.55–2.30 (m, 2H, CH_2), 3.10–3.2 (m, 2H, CH_2), 5.00 (s, 2H, NH_2), 5.90 (s, 1H, CH pyrazole). Anal. Calcd. for: $C_{17}H_{17}N_5S$: C, 63.13; H, 5.30; N, 21.65; S, 9.91%. Found: C, 63.25; H, 5.12; N, 21.48; S, 10.15%.

*4.12.1.2. Ethyl-1-amino-5-(3,5-dimethylpyrazol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c] isoquinolin-2-carboxylate (**19b**).* Obtained as pale yellow crystals in 80% yield. M.p.: 168–170 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3400, 3320 (NH_2), 2920, 2850 (CH aliphatic), 1670 (CO ester), 1610 (C=N). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.45 (t, *J* = 7.5 Hz, 3H, CH_3 ester), 1.85–1.95 (m, 4H, $2CH_2$), 2.35, 2.40 (2s sharp, 6H, $2CH_3$), 2.70–2.75 (m, 2H, CH_2), 3.35–3.40 (m, 2H, CH_2), 4.40 (q, *J* = 6.0 Hz, 2H, CH_2 ester), 6.05 (s, 1H, CH triazole), 6.40 (s, 2H, NH_2). MS *m/z* (%) 370.31 (M^+, 79), 344.41 (21), 343.04 (100), 342.11 (24), 330.59 (29), 329.11 (70), 327.87 (36), 315.04 (35), 300.72 (21), 295.13 (24), 282.88 (46.50), 281.79 (35), 268.63 (45), 255.77 (60.50). Anal. Calcd. for: $C_{19}H_{22}N_4O_2S$: C, 61.60; H, 5.99; N, 15.12; S, 8.65%. Found: C, 61.76; H, 6.14; N, 14.95; S, 8.50%.

*4.12.1.3. 1-Amino-5-(3,5-dimethylpyrazol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]iso-quinolin-2-carboxamide (**19c**).* Obtained as yellow needles in 89% yield. M.p.: 258–260 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3450, 3400, 3300, 3120 ($2NH_2$), 2920, 2850 (CH aliphatic), 1650 (CO amide), 1600 (C=N). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.75–1.80 (m, 4H, $2CH_2$), 2.25, 2.30 (2s sharp, 6H, $2CH_3$), 2.60–2.65 (m, 2H, CH_2), 3.45–3.50 (m, 2H, CH_2), 6.10 (s, 1H, CH pyrazole), 7.00 (s, 2H, NH_2), 7.30 (s, 2H, NH_2 amide). Anal. Calcd. for: $C_{17}H_{19}N_5OS$: C, 59.80; H, 5.61; N, 20.51; S, 9.39%. Found: C, 60.02; H, 5.43; N, 20.36; S, 9.46%.

*4.12.1.4. 2-Acetyl-1-amino-5-(3,5-dimethylpyrazol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (**19d**).* Obtained as yellow crystals in 93% yield. M.p.: 178–180 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3400, 3280 (NH_2), 2920, 2850 (CH aliphatic), 1660 (CO), 1600 (C=N). ^{1}H NMR (90 MHz, $CDCl_3$): δ_{ppm} = 1.80–1.90 (m, 4H, $2CH_2$), 2.15, 2.20, 2.40 (3s sharp, 9H, $3CH_3$), 2.55–2.60 (m, 2H, CH_2), 3.25 (m, 2H, CH_2), 5.90 (s, 1H, CH pyrazole), 7.10 (s, 2H, NH_2). MS *m/z* (%): 340.81 (M^+, 25), 339.81 ($M^+ - 1$, 100), 324.81 (25), 297.93 (38), 283.91 (14), 253.97 (10). Anal. Calcd. for: $C_{18}H_{20}N_4OS$: C, 63.50; H, 5.92; N, 16.46; S, 9.42%. Found: C, 63.40; H, 6.05; N, 16.58; S, 9.24%.

*4.12.1.5. 1-Amino-2-benzoyl-5-(3,5-dimethylpyrazol-1-yl)-6,7,8,9-tetrahydrothieno [2,3-c]isoquinoline (**19e**).* Obtained as brilliant yellow needles in 85% yield. M.p.: 218–220 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3450, 3300 (NH_2), 3030 (CH aromatic), 2920, 2850 (CH aliphatic), 1645 (unsaturated CO), 1600 (C=N). ^{1}H NMR (90 MHz, CF_3CO_2D): δ_{ppm} = 1.95–2.05 (m, 4H, $2CH_2$), 2.40, 2.60 (2s sharp, 6H, $2CH_3$), 2.45–2.50 (m, 4H, $2CH_2$), 6.80 (s, 1H, CH pyrazole), 7.70–7.90 (m, 5H, ArH). Mass spectrum *m/z* (%): 401.38 (M^+, 25), 322.09 (27), 261.27 (26), 184.3 (20.50), 167.22 (21), 149.1 (27), 109.24 (22), 82.15 (38), 71.09 (100). Anal. Calcd. for: $C_{23}H_{22}N_4OS$: C, 68.63; H, 5.51; N, 13.92; S, 7.97%. Found: C, 68.75; H, 5.37; N, 14.10; S, 8.12%.

4.12.2. Method B

General procedure: A mixture of pyrazolo derivative **6** (0.58 g, 2 mmol) and alkylating agent (2 mmol) in presence of anhydrous potassium carbonate (0.70 g, 5 mmol) in ethanol (20 mL) was refluxed for 3 h. The solid product, which formed on cooling, was filtered off and recrystallized from ethanol.

*4.12.2.1. 1-Amino-5-(3,5-dimethylpyrazol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]iso-quinoline-2-carbonitrile (**19a**).* Obtained from compound **6** and chloroacetonitrile as greenish yellow crystals in 77% yield. M.p.: 194–196 °C.

*4.12.2.2. Ethyl-1-amino-5-(3,5-dimethylpyrazol-1-yl)-6,7,8,9-tetrahydrohieno[2,3-c]isoquinoline-2-carboxylate (**19b**).* Obtained from compound **6** and ethyl chloroacetate as pale yellow crystals in 72% yield. M.p.: 168–170 °C.

*4.12.2.3. 1-Amino-5-(3,5-dimethylpyrazol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]iso-quinoline-2-carboxamide (**19c**).* Obtained from compound **6** and chloroacetamide as pale yellow crystals in 76% yield. M.p.: 258–260 °C.

*4.12.2.4. 2-Acetyl-1-amino-5-(3,5-dimethylpyrazol-1-yl)-6,7,8,9-tetrahydrothieno[2,3-c]isoquinoline (**19d**).* Obtained from compound **6** and chloroacetone as yellow crystals in 87% yield. M.p.: 178–180 °C.

*4.12.2.4. 1-Amino-2-benzoyl-5-(3,5-dimethylpyrazol-1-yl)-6,7,8,9-tetrahydrothieno [2,3-c]isoquinoline (**19e**).* Obtained from compound **6** and phenacyl bromide as yellow crystals in 78% yield. M.p.: 218–220 °C.

*4.13. 5-(3,5-Dimethylpyrazol-1-yl)-1,2,3,4-tetrahydropyrimido [4′,5′:4,5]thieno[2,3-c]isoquinolin-8(9H)-one (**20**)*

Compound **19c** (0.68 g, 2 mmol) and triethylorthoformate (2 mL) were refluxed for 1/2 h in presence of catalytic drops of glacial acetic acid. The precipitated solid, which formed on hot, was filtered off and recrystallized from dioxane as pale yellow crystals in 72% yield. M.p.: >360 °C. IR (cm^{-1} KBr) $\bar{\nu}$ = 3200 (NH), 2920, 2850 (CH aliphatic), 1670 (CO imide), 1600 (C=N). ^{1}H NMR (90 MHz, DMSO-d_6): δ_{ppm} = 1.75–1.85 (m, 4H, $2CH_2$), 2.15, 2.20 (2s sharp, 6H, $2CH_3$), 2.50–2.55 (m, 4H, $2CH_2$), 3.50–3.60 (m, 2H, CH_2), 6.10 (s, 1H, CH triazole), 8.40 (s, 1H, CH pyrimidine), 10.40 (s, 1H, NH). ^{13}C NMR (400 MHz, DMSO-d_6): δ_{ppm} = 162.89 (CONH), 156.02 (C-12), 155.54 (C-7), 143.27 (C-16), 139.88 (C-3), 135.64 (C-11), 117.26 (C-8), 108.00 (C-15), 21.42–40.35 ($4CH_2$ cyclohexeno), 12.78, 13.52 (2 CH_3 pyrazole). Anal. Calcd. for: $C_{18}H_{19}N_5OS$: C, 61.17; H, 5.42; N, 19.81; S, 9.07%. Found: C, 60.94; H, 5.26; N, 20.00; S, 9.20%.

5. Procedure of antimicrobial activity

The fungal species were previously isolated from cases of human dermatophytosis (Moubasher et al., 1993) [25]. 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) [26]. 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 left to 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) [27] using 3-mm diameter filter paper discs (Watmann 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 previous method was used for determining antibacterial activity too.

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