

Synthesis and Biological Activity of Novel Thieno [2,3-*d*] [1,2,4] triazolo [4,3-*a*] pyrimidine and Pyrazolo [3,4-*c*] pyrazole Derivatives

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REACTION of hydrazonoyl halides (2a-e) with either 1,2,3,5,6,7-hexahydro-4*H*-cyclopenta[4,5]thieno[2,3-*d*] pyrimidin-2, 4-dithione (1) or 2 (4-Dihydro - 5 - oxo - 3 - methyl - 1*H* - pyrazolo - 1 - yl) -5,6,7,8-tetrahydrothieno[2,3-*d*]pyrimidin-4(3*H*,4*H*) -one (11) in the presence of sodium ethoxide in refluxing ethanol / DMF mixture afforded the cyclopenta [4,5]thieno[2,3-*d*]triazolo [4,3-*a*]pyrimidines-4-thiones (7a-d) and the phenylpyrazolo[3,4-*c*]pyrazolcyclopenta [4,5] thieno [2,3-*d*] pyrimidin-4-ones (14a-e), respectively. The mechanism of the studied reactions has been discussed and the biological activity of the products 7a-d has been evaluated.

Keywords: Hydrazonoyl halides, [1,2,4] Triazolopyrimidine, Rearrangement, Pyrazole and Biological activities.

The biological⁽¹⁻³⁾, bactericidal⁽⁴⁾ and medicinal^(5, 6) activities of theino[2,3-*d*] pyrimidine derivatives have recently attracted considerable attention^(7, 8). In view of the above findings and in continuation to our interest on the use of hydrazonoyl halides for the synthesis of heterocyclic compounds incorporating different functionalities of biological importance^(9,10) we reported here a facile and short synthesis of the title compounds starting from either 2,4-thioxo-1,2,3,4,5,6,7-hexahydro-4*H*-cyclopenta[4,5] thieno[2,3-*d*] pyrimidin-2,4-dithione (1) or 2(4-dihydro-5-oxo-3-methyl-1*H*-pyrazolo-1-yl)-5,6,7,8-tetrahydrothieno [2,3-*d*] pyrimidin- 4 (3*H*,1*H*)-one (11) and hydrazonoyl halides (2).

Results and Discussion

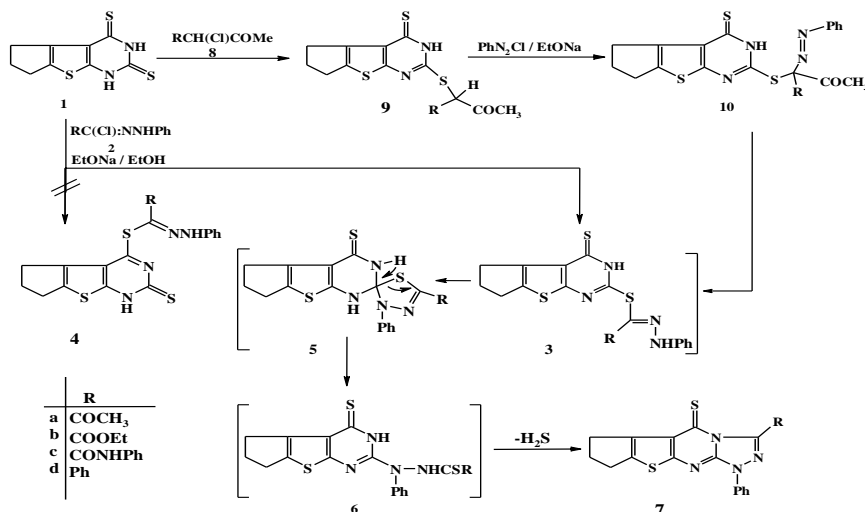
Reaction of 3,5,6,7-hexahydrocyclopenta[4,5]thieno[2,3-*d*] pyrimidin-2,4-dithione (1) which was prepared from 3-(2-amino-thiophene)-carbonitrile derivatives with carbon disulfide in dry pyridine as previously reported⁽¹¹⁾ with hydrazonoyl halides (2a-d)⁽¹²⁻¹⁵⁾ in sodium ethoxide in refluxing ethanol for 7-10 hr afforded a single product as evidenced by TLC. The structures of the isolated products were established by analytical and spectroscopic data (MS, IR and

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¹H NMR) and identified as cyclopenta[4,5]thieno[2,3-*d*]triazolo[4,3-*a*]pyrimidin-5-thiones (7a-d). Their mass spectra revealed in each case the respective molecular ion peak and the (M⁺+1) peak for example 7a gave molecular ion peak at m/z 366 corresponding to C₁₈H₁₄N₄OS₂. The IR spectra of each of the studied compounds 7a-d revealed the absence of the NH absorption band around 3422 cm⁻¹. The IR spectrum of 7a showed three absorption bands at 1652 (C=O), 1245 (C=S) and 3170 (CH-Ar) cm⁻¹. Furthermore the ¹H NMR spectra of 7a-d are characterized by the absence of signal near δ: 10.8-12.00 ppm characteristic of NH and the appearance of signal near 7.00-8.00 ppm (Ar-H) (see Experimental).

To account for the direct formation of the latter products 7a-d, the mechanism outlined in Scheme 1 is proposed. It suggested that the studied reactions involved an initial formation of thiohydrazone esters (3), which undergo S to N migration to give the thiohydrazides (6) via the Spiro-adduct (5) ⁽¹⁶⁾. In all cases examined attempts to isolate the intermediate 3-6 failed however, this finding indicates that such intermediates are consumed as soon as they are formed under the reaction conditions employed as they readily undergo in situ cyclization followed by elimination of hydrogen sulfide to give final products (7a-d).

The assignment of the structure 7 were further substantiated by an alternate synthesis of 7 based on synthesis of the thiohydrazone ester (3) via application of Japp-Klingemann reaction ^(16,17) to the active methine compounds of type 9. The latter compound is prepared in this work by reaction of 1,2,3,5,6,7-hexahydrocyclopenta [4,5] thieno [2,3-*d*] pyrimidin-2,4-dithione (1) with α-chloroacetoacetanilide (compound 8) in ethanol / DMF in the presence of triethylamine. The structure of 9c is evidenced by its microanalyses and spectra (MS, IR and ¹H NMR) (see Experimental). For example, its ¹H NMR spectra showed signal for the methine hydrogen at 5.10 ppm assignable to -SCH- proton which is lost on shaking the solution with deuterium oxide showing its ready exchangeability through enolization, also, a signal at 2.37 ppm assignable to COCH₃. Next, coupling of 9c with diazotized aniline was investigated in ethanol in the presence of sodium acetate at low temperature (0-5C°). On the basis of previous literature on coupling of active chloromethylene compounds with diazonium salts ⁽¹⁷⁾, we anticipated that reactions of 9c with diazotized aniline would give the thiohydrazone ester (3c) directly *via* cleavage of the acetyl group from 10c (Scheme 1). However, in our hands such reactions yielded product proved to be identical in all respects (m.p., mixed m.p. and IR spectra) with 7c obtained above.



Scheme 1

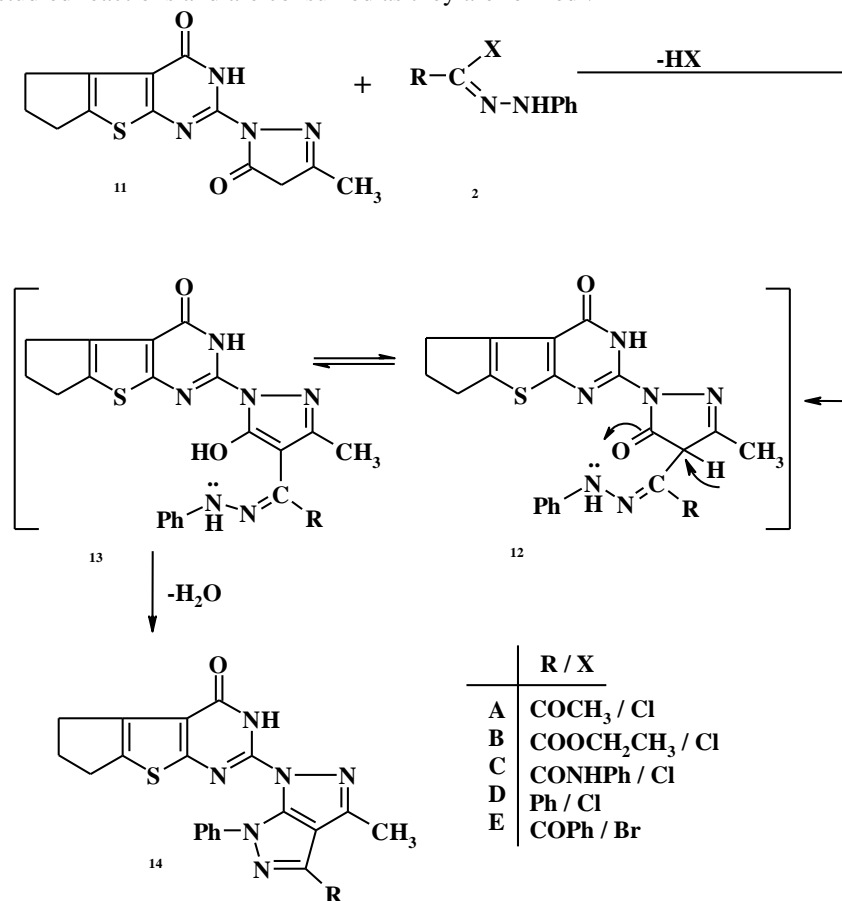
Also, hydrazonoyl halides (2a-e) reacted with 2(4-Dihydro-5-oxo-3-methyl-1*H*-pyrazolo-1-yl)-5,6,7,8-tetrahydrothieno[2,3-*d*]pyrimidin-4(3*H*,1*H*)-one (11)⁽¹⁸⁾ in sodium ethoxide in refluxing ethanol/DMF mixture, after work up of the reaction mixtures only a single product was isolated in each case 14.

The structure of 14 was assigned to the reaction product based on spectral and elemental analysis. For example the IR spectra of 14a displayed absorption bands at 1700, 1670 (2 CO) and 3422 cm⁻¹ (NH) (see Experimental) which provided no additional evidence for cyclic products at NH group. Also, its ¹H NMR spectra showed disappearance of signals at 3.27 ppm assignable to (CH₂) group and showed a signal at 2.25 ppm (COCH₃) and 7.28-8.14 ppm for aromatic protons. Moreover, its mass spectrum gave *m/z* = 430 corresponding to the molecular weight of molecular formula C₂₂H₁₈N₆O₂S of the assigned structure.

To account for the formation of 14 from 11 with 2, the two step reaction sequence outlined in Scheme 2 is suggested. The first step involves nucleophilic attack of 2 on the active methylene of 11 to give the substitution products 12a-d or 13a-d, respectively. The second step in the suggested mechanism (Scheme 2) involves cyclization of the latter intermediates through dehydration of 13a-e to give 14a-e as end product (Scheme 2).

Attempts to isolate one of each of the open chain intermediate 12 or 13 under mild conditions were successful. For example we succeeded in isolating one of such intermediate. Reaction of 11 with 2a in ethanol in the presence of triethylamine at room temperature afforded 12a. The structure of the latter was established on the basis of microanalyses and spectral data (IR, MS and

^1H NMR). When the latter was refluxed in ethanolic sodium ethoxide solution, it yielded 14; this finding indicates that 12a-d and 13a-d are intermediates in the studied reactions and are consumed as they are formed.



Scheme 2

Biological activity

Antimicrobial activities of the tested compounds 7a-d were determined using a modified Kirby-Bauer disk diffusion method⁽¹⁹⁾. Plates inoculated with filamentous fungi as *Aspergillus flavus* at 25 °C for 48 hr; Gram (+) bacteria as *Staphylococcus aureus* and *Bacillus subtilis*; Gram (-) bacteria as *Escherichia coli* and *Pseudomonas aeruginosa* were incubated at 35-37 ° C four 24-48 hr and yeast as *Candida albicans* incubated at 30°C for 24-48 hr and then the diameters of the inhibition zones were measured in millimeters⁽¹⁹⁾. Standard discs of Tetracycline (antibacterial agent), Amphotericin B (antifungal agent) served as positive controls for antimicrobial activity. But filter discs impregnated with 10μl of solvent (distilled water, chloroform DMSO) were used as negative

control. The results showed that all the tested compounds are highly active as antifungal agents compared to the reference (Amphotericin B) to the Gram (+) bacteria (*Staphylococcus aureus*)⁽²⁰⁾. They have antibacterial activity less than tetracycline. The results are summarized in Table 1.

TABLE 1

Sample		Inhibition zone diameter (mm / mg sample)			
		<i>Escherichia coli</i> (G ⁻)	<i>Staphylococcus aureus</i> (G ⁺)	<i>Aspergillus flavus</i> (Fungus)	<i>Candida albicans</i> (Fungus)
Control: DMSO		0.0	0.0	0.0	0.0
Standard	Tetracycline Antibacterial agent	30	29	--	--
	Amphotericin B Antifungal agent	--	--	19	21
7a		0.0	14	0.0	0.0
7b		12	13	0.0	0.0
7c		13	14	0.0	0.0
7d		0.0	12	0.0	0.0

G: Gram reaction.

The samples have antibacterial activity but don't have any antifungal activity on tested microorganisms.

Experimental

Melting points were determined on a Gallenkamp apparatus and are uncorrected, IR spectra were recorded in potassium bromide using PU 9712 spectrophotometer, ¹H NMR spectra were recorded in deuterated chloroform using a Varian Gemini 300 NMR spectrometer. Mass spectra were recorded on a 75 Kratos spectrometer. Elemental analyses were carried out at the Micro Analytical Laboratory of National Research Center, Giza, Egypt. Biological activity was carried out at the Microbiology Laboratory of Faculty of Science-Cairo University.

Synthesis of 7a-d and 14a-e

General procedure

To a stirred solution of each of 1 or 11 (10 mmoles) in ethanol sodium ethoxide solution, prepared by dissolving sodium metal (0.23g, 10 mmoles) in absolute ethanol (50ml) and few drops of DMF, was added the appropriate hydrazonoyl halides 2A-E (1mmoles). The reaction mixture was heated under reflux for 6-8 hr (monitored with TLC). The reaction mixture was then cooled

and the solid that precipitated was filtered off and crystallized from the proper solvent to give 7a-d & 14a-e, respectively. The physical constants of the compounds prepared are given below.

3-Acetyl-1-phenyl-cyclopenta [4,5] thieno [2,3-d] triazolo [4,3-a] pyrimidin-5(1H,5H)-5-thione (7a): white crystals, Yield (2.56 g, 70%), m.p.162-164°C (EtOH); IR (KBr) ν cm^{-1} : (3170,CH-Ar), 1652(CO),1245(C=S). MS m/z (%): 366(M^+ , 91), 367(M^+ +1). ^1H NMR (DMSO- d_6) δ ppm: 2.12(t, 2H, CH_2), 2.28(s, 3H, CH_3), 2.50(m, 4H, 2 CH_2), 2.72(t, 2H, CH_2), 7.23-7.95(m, 5H, Ar-H); Anal. Calcd. For $\text{C}_{18}\text{H}_{14}\text{N}_4\text{OS}_2$ (366.47): C, 59.00; H, 3.85; N, 15.29, 9.13; S, 17.50 %. Found: C, 59.00; H, 3.90; N, 15.13; S, 17.47%.

3-Ethoxycarbonyl-1-phenyl-cyclopenta[4,5]thieno[2,3-d]triazolo[4,3-a] pyrimidin-5(1H,5H)-5-thione (7b): Pale brown crystals, Yield (2.65g, 72%) m.p. (169°-170)°C (EtOH). IR (KBr) ν cm^{-1} : 3170(CH-Ar), 1735(CO), 1245(C=S). MS m/z (%):396(M^+ , 73), 397(M^+ +1). ^1H NMR (CDCl_3) δ ppm: 1.23- 1.28(t, 3H, CH_3), 2.20(t, 3H, CH_2), 2.51(m, 4H, 2 CH_2),4.11-4.30(q, 2H, CH_2CH_3), 7.12-7.49(m, 5H, Ar-H). Anal. Calcd. For $\text{C}_{19}\text{H}_{16}\text{N}_4\text{O}_2\text{S}_2$ (396.49): C, 57.56; H, 4.07; N, 14.13; S, 16.17%. Found: C, 58.09; H, 4.02; N, 14.11; S, 16.09%.

Synthesis of 7c

To a solution of 9 (10 m mole) in ethanol/DMF was added sodium acetate trihydrate (3g) and the mixture was cooled in an ice bath to 0-5°C while being stirred. To the resulting cold solution was added portionwise a cold solution of benzenediazonium chloride, prepared as usual by diazotizing aniline (10mmole) in hydrochloric acid (6 ml, 6 moles) with sodium nitrite (0.7g, 10 m mole) in water (10 ml). After all diazonium salt added, the reaction mixture was stirred for 1 hr while cooling in ice bath and left overnight in a refrigerator. The solid that precipitated was filter washed with water, air dried and finally crystallized by ethanol.

N-Phenyl-1-phenyl-cyclopenta [4,5] thieno [2,3-d]triazolo[4,3-a]pyrimidin-5(1H,5H)-5-thione -3-carboxamide (7c): Pale brown, Yield (2.96g,67%), m.p.136-138°C (EtOH). IR (KBr) ν cm^{-1} : 3130 (CH-phenyl), 3222 (NH), 1610(CO),1360(C=S). MS m/z (%): 443(M^+ +61) 444(M^+ +1). ^1H NMR (CDCl_3) δ ppm: 1.72(m, 4H, 2 CH_2), 2.82(t, 2H, CH_2), 3.01(t, 2H, CH_2), 7.12-8.10(m, 10H, 2Ar-H), 8.64(s, 1H, NH). ^{13}C NMR (CDCl_3) δ ppm: 28.2, 29.9, 32.3, 115.1, 120.7, 121.3, 125.2, 127.8, 129.1, 129.3, 135.2, 136.1, 136.6, 137.8, 139.6, 145.3, 151.6, 154.8, 177.8. Anal. Calcd. For $\text{C}_{23}\text{H}_{17}\text{N}_5\text{OS}_2$ (443.55): C, 62.28; H, 3.86; N, 15.79; S, 14.46 %. Found: C, 61.97; H, 3.77; N, 15.69; S, 14.41%.

1,3-Diphenyl-cyclopenta[4,5]thieno[2,3-d]triazolo[4,3-a]pyrimidin -5(1H,5H)-5-thione (7d): balk crystals, Yield (2.80 g,72%) m.p. 261°C (EtOH/ Dioxane). IR (KBr) ν cm^{-1} : 3012 (CH-Ar),1245(C=S), . MS m/z (%): 400(M^+ , 100). ^1H NMR (DMSO- d_6) δ ppm: 1.51(m, 4H, 2 CH_2), 2.1(t, 2H, CH_2), 2.62(t, 2H, CH_2), 7.10-

7.39 (m, 10H, Ar-H). Anal. Calcd. For $C_{22}H_{16}N_4S_2$ (400.53): C, 65.97; H, 4.03; N, 13.99; S, 16.01%. Found: C, 65.88; H, 4.00; N, 13.79; S, 16.00%.

Synthesis of 9

To a mixture of equimolar quantities of α -chloroacetoacetanilide (8) and 3,5,6,7-hexahydrocyclopenta [4,5] thieno [2,3-d] pyrimidin - 2,4 - dithione 1 (10 mmoles) in absolute ethanol/DMF mixture (40ml) was added triethylamine (1.4 ml, 10 mmoles). The mixture was stirred for two days at room temperature. During this period the reactants dissolved. The solvent was evaporated under reduced pressure. The oily residue left was triturated with methanol and left in a refrigerator overnight. The solid that was produced was collected by filtration and crystallized to give 9 in good yield.

N-Phenyl-3-thio-2-[1,2,3,5,6,7-hexahydrocyclopenta[4,5]thieno [2,3-d] pyrimidin-4-thione] Butanamide (9)

Pale black, Yield (2.82 g, 68%), m.p.180-182 °C (EtOH/Dioxane). IR (KBr) ν cm^{-1} : 3422(NH), 3129(CH-Ar), 2920(CH), 1627, 1650, 1243(C=S). MS m/z (%): 415(M^+ , 70). 1H NMR (DMSO- d_6) δ ppm: 1.35(m, 4H, 2CH₂), 1.84(s, 3H, CH₃), 2.80(t, 2H, CH₂), 3.25(t, 2H, CH₂), 5.01(s, 1H, CH), 7.01-7.81(m, 5H, Ar-H). Anal. Calcd. For $C_{19}H_{17}N_3O_2S_3$ (415.56): C, 54.92; H, 4.12; N, 10.11; S, 23.15%. Found: C, 54.89; H, 4.08; N, 10.04; S, 23.04%.

Synthesis of the intermediate 12a

To a mixture of 11 and 2a (0.01 mol each) in ethanol (50 ml) and few drops from DMF, was added triethylamine (1.4 ml, 0.01mol) and the reaction mixture was stirred for 3hr at room temperature. The solid that precipitated was filtered off and crystallized from (EtOH) to give 12a; 1HNMR ($CDCl_3$) δ ppm: pale brown, (2.69g, 60%), m.p. 148 °C. IR (KBr) ν cm^{-1} : 3432, 3385, 1668. MS m/z (%): 448(M^+ , 22). 1HNMR ($CDCl_3$) δ ppm: 2.11(s, 3H, CH₃), 2.28(s, 3H, CH₃), 2.40-3.56(m, 6H, 3CH₂), 7.20-8.10(m, 5H, Ar-H), 10.95(s, 1H, NH), 11.20(s, 1H, OH). Anal. Cald. for $C_{22}H_{20}N_6O_3S$ (448.42): C, 58.92 ;H ,4.95 ;N, 18.73; S, 7.13%. Found: C, 58.89; H, 4.90; N, 18.70; S, 7.12.

Cyclization of 12a to give 14a

To a stirred sodium ethoxide solution, prepared from sodium metal (0.046 g, 0.002 mol) and absolute ethanol (40 ml), compound 12a (0.85 g, 0.002 mol) in ethanol/DMF was added. The mixture was refluxed while being stirred for 5 hr and left to cool. The solid that precipitated was filtered off, washed with water, air dried and finally crystallized from (EtOH) to give brown powder product that proved identical in all respects to 14a (m.p.IR, yield 65%) obtained above from 11 and 2a.

2-(4-Acetyl-3-methyl-6-phenylpyrazolo[3,4-c]pyrazol-1(6H)-yl)-3,5,6,7-tetrahydro-4H - cyclopenta [4,5] thieno [2,3-d] pyrimidin - 4 - one (14a)

Brown crystals, Yield (2.66g, 62%), 201°C (EtOH). IR (KBr) ν cm^{-1} : 3432, 1677, 1620. MS m/z (%): 430(M^+ , 65). 1HNMR (DMSO- d_6) δ ppm: 2.24(s, 3H,

CH₃), 2.32(s, 3H, CH₃), 2.4-3.4(m, 6H, 3CH₂), 7.26-8.14(m, 5H, Ar-H), 10.88 (s, 1H, NH). Anal. Calcd. For C₂₂H₁₈N₆O₂S (430.49): C, 61.38; H, 4.21; N, 19.52; S, 7.45 %. Found: C, 61.22; H, 4.19; N, 19.52; S, 7.46 %.

2-(4-Ethyl-3-methyl-6-phenylpyrazolo[3,4-c]pyrazol-1(6H)-yl)-3,5,6,7-tetrahydro-4H-cyclopenta[4,5]thieno[2,3-d]pyrimidin-4-one-4-Carboxylate (14b)

Yellow crystals, Yield (2.75g, 60%), m.p 256 °C (EtOH). IR (KBr) ν cm⁻¹: 310, 1738, 1665. MS m/z (%): 460(M⁺, 52). ¹HNMR (DMSO-d₆) δ ppm: 1.45(t, 3H, CH₃), 2.25(s, 3H, CH₃), 2.40-3.41(m, 6H, 3CH₂), 4.29(q, 2H, CH₂), 7.25-8.11(m, 5H, Ar-H), 10.96(s, 1H, NH). Anal. Calcd. for C₂₃H₂₀N₆O₃S (460.43): C, 59.48; H, 4.35; N, 18.10; S, 6.89%. Found: C, 59.44; H, 4.38; N, 18.21; S, 6.91 %.

2-(N-Phenyl-3-methyl-6-phenylpyrazolo[3,4-c]pyrazol-(6H)-yl)-3,5,6,7-tetrahydro-4H-cyclopenta[4,5]thieno[2,3-d]pyrimidin-4-one-4-carboxamide (14c)

Brown crystals, Yield (3.45g, 62%), m.p.186 °C (MeOH) IR (KBr) ν cm⁻¹: 3396-3128, 1695, 1625. MS m/z (%): 507(M⁺, 46). ¹HNMR (CDCl₃) δ ppm : 2.29(s, 3H, CH₃), 2.31-3.00(m, 6H, 3CH₂), 7.10-8.12(m, 10H, Ar-H), 8.53(s, 1H, NH), 10.96(s, 1H, NH). Anal. Calcd. for C₂₇H₂₁N₇O₂S (507.58): C, 63.89; H, 4.17; N, 19.32; S, 6.32%. Found: C, 63.88; H, 4.20; N, 19.23; S, 6.31%.

2-(3-Methyl-4-phenyl-6-phenylpyrazolo[3,4-c]pyrazol-1(6H)-yl)-3,5,6,7-tetrahydro-4H-cyclopenta[4,5]thieno[2,3-d]pyrimidin-4-one (14d)

Yellow crystals, Yield (2.92g, 63%), m.p. 162 °C (EtOH) . IR (KBr) ν cm⁻¹: 3420, 1695. MS m/z (%): 464(M⁺, 71). ¹HNMR (CDCl₃) δ ppm: 2.23(s, 3H, CH₃), 2.41-3.50(m, 6H, 3CH₂), 7.11-8.00(m, 10H, Ar-H), 10.98(s, 1H, NH). Anal. Calcd. for C₂₆H₂₀N₆OS (464.26): C, 67.22; H, 4.34; N, 18.9; S, 6.90%. Found: C, 67.23; H, 4.35; N, 18.9; S, 6.92%.

2-(4-Benzoyl-3-methyl-6-phenyl pyrazolo[3,4-c]pyrazol-1(6H)-yl)-3,5,6,7,4H-cyclopenta[4,5]thieno[2,3-d]Pyrimidin-4-one (14e)

Brown crystal, Yield (2.85g, 58%), m.p. 186°C MeOH). IR (KBr) ν cm⁻¹: 3400, 1688, 1650. MS m/z (%) 492(M⁺, 64). ¹HNMR (CDCl₃) δ ppm: 2.22(s, 3H, CH₃), 2.42-3.53 (m, 6H, 3CH₂), 7.00-8.12(m, 10H, Ar-H), 10.98(s, 1H, NH). Anal. Calcd. for C₂₇H₂₀N₆O₂S (492.56): C, 65.84; H, 4.09; N, 17.06; S, 6.51%. Found: C, 65.81; H, 4.12; N, 17.11; S, 6.53%.

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تشبيد وعمل النشاط البيولوجي لمركبات جديدة من الثينيو[2,3-d][1,2,4] ترايزولو[4,3-a] بيريميدين و بيرازولو- [3,4-c] بيرازول

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تم في هذا البحث تشبيد مركبات جديدة من مشتقات سيكلوبنتا [5و4] ثينيو [1,2,4][2,3-d] ترايزولو [4,3-a] بيريميدين-5-تايون-7a-d عن طريق إضافة الهيدرازونويل هاليد a-d 2 الي 1 و2 و3 و5 و6 و7 هكساهديرو-4H سيكلوبنتا [5و4] ثينيو [2,3-d] بيريميدين-2,4 - داي تايون 1

كما تم تشبيد مشتقات جديدة من فينيلبيرازولو [3,4-c] بيرازول- سيكلوبنتا [5و4] ثينيو [2,3-d] بيريميدين 4(3H,4H) -اون 14a-e

وتم التحقق من التركيب الكيميائي للمركبات المحضرة عن طريق إجراء التحليل الدقيقة للعناصر وأطياف الأشعة تحت الحمراء والرنين المغناطيسي

وكذلك تم دراسة النشاط البيولوجي لبعض المركبات 7a-d ووجد أن لها درجة تثبيط لنشاط الجرام (+) بكتيريا مقارنة بالنتراسيكلين كما انه ليس لها نشاط ضد فطر اسبرجلسفلافيس أو كناد يدا البيكانس.