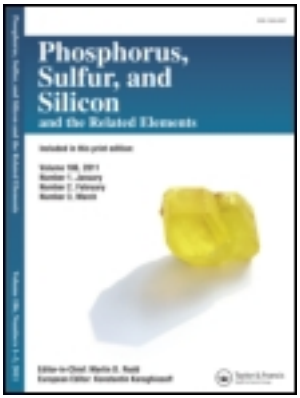

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

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Published online: 20 Feb 2008.

To cite this article: H. H. Sayed & M. A. Ali (2007) Synthesis of 3-[(4-Chloro-phenyl) oxiranyl]thiophen-2-yl-propanone and Their Reactions with Some Nucleophilles for Antiviral Evaluations, Phosphorus, Sulfur, and Silicon and the Related Elements, 183:1, 156-167, DOI: 10.1080/10426500701564225

To link to this article: http://dx.doi.org/10.1080/10426500701564225

Phosphorus, Sulfur, and Silicon, 183:156–167, 2008

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426500701564225

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Synthesis of 3-[(4-Chloro-phenyl) oxiranyl]thiophen-2-yl-propanone and Their Reactions with Some Nucleophilles for Antiviral Evaluations

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Compounds 2, 3, 4, 7, 10, 11, 12 and 13 were formed via the reactions of [3-(4-chlorophenyl)oxiranyl]thiophen-2-yl-propanone with hydrazine derivatives, hydroxyl-amine hydrochloride, thiourea, thiosemicarbazide, carbon disulfide, phenyl isothiocyanate, methyl isothiocyanate and phosphorus pentasulfide, respectively. Pyrimidine derivative 4 was in turn used as precursor for preparation of thiazolopyrimidines 5 and 6. Pyrazolothioamide 7 was treated with D-glucose and arbinose to afford the corresponding hydrazones 8 and 9.

Keywords Dithiole; HSV-1; oxathiolane; oxazine; oxazole; pyrazole; pyrimidine

INTRODUCTION

Pyrazoles, oxazoles, pyrimidines, thiazolopyrimidines, oxazines, oxathioles and dithioles are of current interest by versatile biological activities. Pyrazoles moieties possesses analgesic, antipyretic and hyperglycemic.[1–3] Oxazoles moieties have antidepressant,[4] antibiotic,[5] and antimicrobial properties.[6] Pyrimidines and thiazolopyrimidines possess tyrosine kinas inhibitor,[7,8] analgesic, anticonvulsant, and antiparkinsonian agent properties.[9] On the other hand, oxathiolanes have antitumor,[10] plant growth regulator,[11] herbicides,[12] and ectoparasiticides properties,[13] while oxazines have antitumor[14] and anticonvulsant attributes.[15] This information stimulated us to obtain new compounds to possess notable chemical and biological activities.

RESULTS AND DISCUSSION

[3-(4-Chlorophenyl)oxiranyl]thiophen-2-yl-propanone (1) was prepared according to our previously work[16–18] from arylidenethiophene-2-yl-

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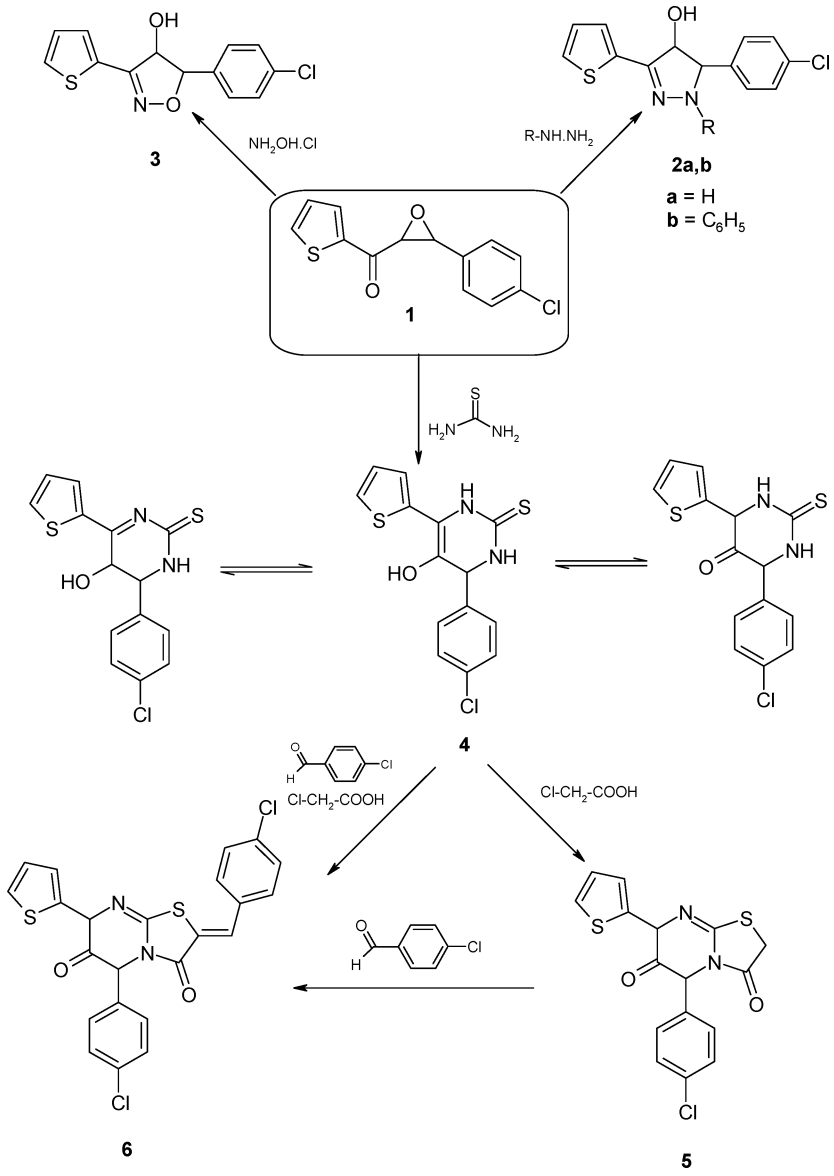
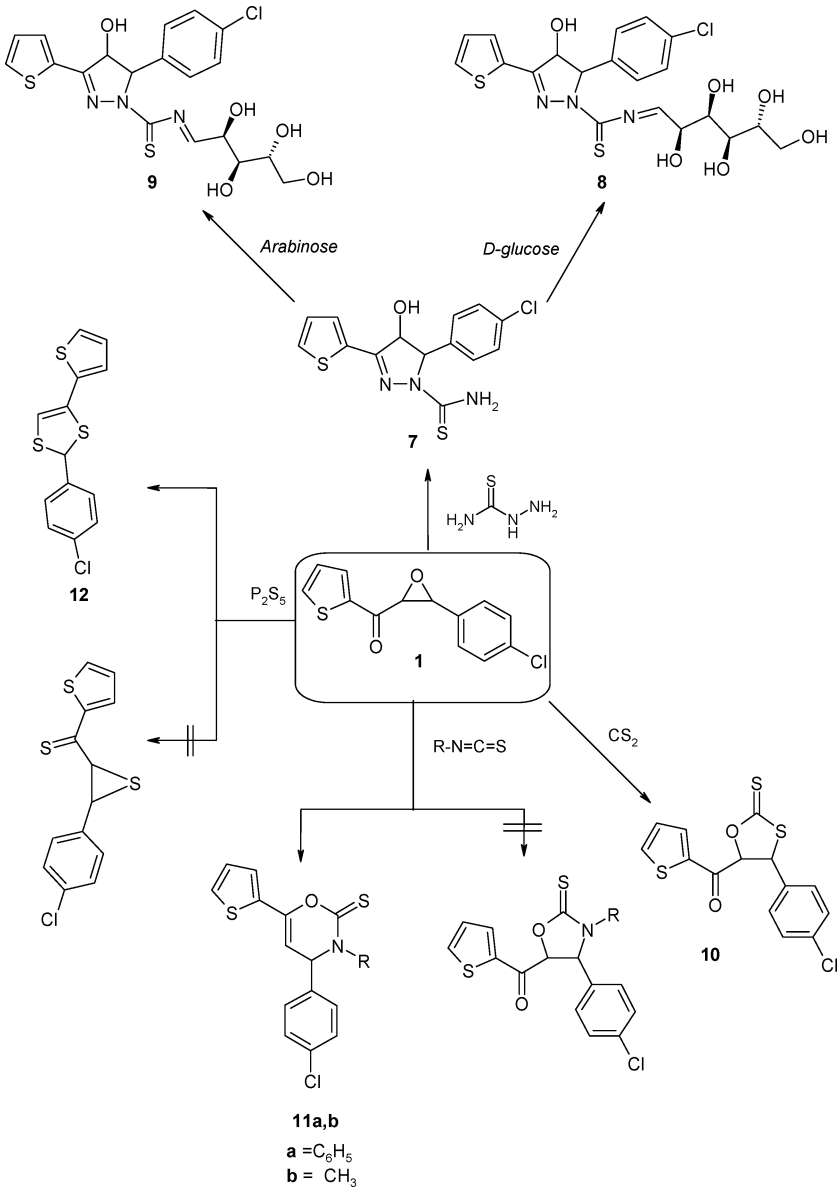
propanone.[19–20] The structure of compound 1 was confirmed with spectral data. The IR spectrum showed a band at (ν, cm^{-1}) 1693 (C=O), and the ^1H NMR showed signals at (δ, ppm) 3.70 (d, 1H, oxiranyl ring proton) and 3.90 (d, 1H, other oxiranyl ring proton). The MS gave a molecular ion peak at m/z 264. Compound 1 reacted with different amines, hydrazine hydrate, phenylhydrazine, hydroxylamine hydrochloride, thiourea, and thiosemicarbazide via Micheal addition to afford 2a,b, 3, 4, and 7, respectively (Schemes 1 and 2). The spectral data of these compounds assigned their structures (cf. Experimental Section). The IR spectrum of 2a, as an example, showed bands at (ν, cm^{-1}) 3100–3125 (NH), 3320–3380 (OH), and the absence of a (C=O) band. Its ^1H NMR spectrum showed signals at (δ, ppm) 3.85 (d, 1H, C^4—H), 4.00 (d, 1H, C^5—H), 9.4 (s, 1H, NH, D_2O exchangeable) and 10.2 (s, 1H, OH, D_2O exchangeable). Its MS spectrum gave the molecular ion peak at m/z 278. The IR spectra of isoxazole 3 showed bands at (ν, cm^{-1}) 3325–3390 (OH) and the absence of a (C=O) band. Its ^1H NMR spectrum showed signals at (δ, ppm): 3.80 (d, 1H, C^4—H), 4.6 (d, 1H, C^5—H) and 10.35 (s, 1H, OH, D_2O exchangeable). Its MS spectrum gave the molecular ion peak at m/z 279. When compound 1 reacted with thiourea in the presence of an alkaline medium it afforded thioxopyrimidinone derivative 4 (Scheme 1). The spectral data of this compound assigned its structures. Its IR spectrum showed bands at (ν, cm^{-1}) 3115–3180 (2NH) and 1700 (C=O) band. Its ^1H NMR spectrum showed signals at (δ, ppm) 5.6 (s, 2H, pyrimidine-H), 9.8 (s, 1H, NH, D_2O exchangeable) and 11.0 (s, 1H, NH, D_2O exchangeable). Its MS spectrum gave the molecular ion peak at m/z 322. It also was proven chemically via reaction with chloroacetic acid to afford the thiazolopyrimidine-3,6-dione derivative 5. Its IR spectrum showed bands at (ν, cm^{-1}) 1698 (C=O) and 1705 (C=O). Its ^1H NMR spectrum showed signals at (δ, ppm): 3.40 (s, 2H, C^2—H) (cf. Experimental). When the latter compound condensed with *p*-chlorobenzaldhyde, it afforded compound 6 which could be prepared directly via a one pot reaction by treating compound 4 with chloroacetic acid and *p*-chlorobenzaldhyde. The spectral data of compounds 5 and 6 assigned their structures (cf. Experimental Section).

When compound 1 reacted with thiosemicarbazide, it afforded pyrazole carbothioamide derivative 7 (Scheme 2). The spectral data of this compound assigned its structure (cf. Experimental Section). The ^1H NMR spectrum showed signal at (δ, ppm) 4.00, characteristic for pyrazole ring. Also compound 7 was confirmed chemically via condensation with monosaccharides namely arbinose and *D*-glucose, to give the corresponding hydrazones 8 and 9 (Scheme 2). The IR spectrum of 8 showed bands at (ν, cm^{-1}) 3320–3380 (OH groups) and the absence of NH_2. Its ^1H NMR spectrum showed signals at (δ, ppm) 3.30–3.63 (m, 11H, 6-CH-glucose +5OH, D_2O exchangeable), 3.8 (d, 1H, C^4—H), 4.1 (s, 1H,



SCHEME 1

C^5—H), 7.0–7.3 (m, 7H, A—H), 7.8 (d, 1H, hydrazone), and 10.3 (s, 1H, OH, D_2O exchangeable). On the other hand, compound 1 reacted with CS_2 via a [3+2] cycloaddition to afford the 1,3-oxathiolane derivative 10. The structure of the latter compound was confirmed from the spectral



SCHEME 2

data since the IR spectrum showed a band at (ν, cm^{-1}) 1695 (C=O) and its ^1H NMR spectrum showed signals at (δ, ppm) 4.2 (d, 1H, oxathiolane-H) and 4.8 (d, 1H, oxathiolane-H). Its MS spectrum gave the molecular ion peak at m/z 340. Compound 1 reacted with isothiocyanates via a

[4+2] cycloaddition to afford the 1,3-oxazinethione derivatives 11a,b and not the 1,3 oxazole derivative. The IR spectrum of compound 11a revealed the absence of C=O band and ^{1}H NMR spectrum showed signals at (δ, ppm) 4.6 (d, 1H, oxazine-H), 6.5 (d, 1H, oxazine-H) and 6.7–7.3 (m, 12H, Ar—H). Its MS spectrum gave the molecular ion peak at m/z 383. (cf. Experimental Section) (Scheme 2). Thiation of compound 1 with phosphorus pentasulfide in dry pyridine afforded [1,3]dithiole derivative 12. The structure of compound 12 was confirmed from the spectral data. The IR spectrum showed the absence of a C=O band. The^{1}H NMR spectrum showed signals at (δ, ppm) 4.9 (s, 1H, dithiol-H), 6.4 (s, 1H, dithiol-H) and 7.0–7.3 (m, 7H, Ar=H). Its MS spectrum gave the molecular ion peak at m/z 296.

Antiviral Screening

Preparation of Synthetic/Compounds for Bioassay

Tested compounds were dissolved as 100 mg each in 1 ml of 10% DMSO in water. The final concentration was 100 μg/μl (Stock solution). The dissolved stock solutions were sterilized by addition of 50 μg/ml antibiotic-antimycotic mixture (10,000 U penicillin G sodium, 10,000 μg streptomycin sulfates, and 250 μg amphotericin B, PAA Laboratories GmbH, Austria).

Cell Culture. African green monkey, kidney-derived cells (Vero), and human hepatoma cell line (HepG2) were used. The cells were propagated in Dulbeccos' Minimal essential medium; DMEM supplemented with 10% Foetal bovine serum, and 1% antibiotic-antimycotic mixture. The pH was adjusted at 7.20–7.40 by 7.50% sodium bicarbonate solution. The mixture was sterilized by filtration through 0.2 μm pore size nitrocellulose membrane.

Viruses. Herpes Simplex Virus type-1 and Hepatitis A Virus (MBB strain) were obtained from Environmental Virology Lab., Department of Water Pollution Research, National Research Centre, Cairo, Egypt.

Cytotoxicity Assay. Cytotoxicity was assayed for both dimethyl sulfoxide (DMSO) and the tested compounds. Serial dilutions were prepared and inoculated on Vero cells grown in 96 well tissue culture plates. The maximum tolerated concentration (MTC) for each compound was determined by both cell morphology and cell viability by staining with tryban blue dye.

Plaque Reduction Assay. A 6-well plate was cultivated with cell culture (10^5cell/ml) and incubated for 2 days at 37°C. HAV was diluted to give 10^4PFU/ml final concentrations for each virus and mixed with the

tested compound at the previous concentration and incubated overnight at 4°C. Growth medium was removed from the multiwell plate, and virus-compound mixture was inoculated (100 μl/well). After 1 h contact time, the inoculum was aspirated, and 3 ml of MEM with 1% agarose was overlaid the cell sheets. The plates were left to solidify and incubated at 37°C until the development of virus plaques. Cell sheets were fixed in 10% formalin solution for 2 h and stained with crystal violet stain. Control virus and cells were treated identically without chemical compound. Virus plaques were counted, and the percentage of reduction was calculated.[21]

Plaque infectivity assay was carried out to test compounds 2a,b, 3, 4, 5, 6 7, 8, 9, 10, 11a,b, and 12 for antiviral activity. The test was performed to include the three possibilities for antiviral activity: virucidal effect, virus adsorption, and an effect on virus replication for HSV-1. It was observed that, compounds 2a, 4, 7, 8, and 9 revealed the highest anti-HSV-1 activity in comparison with Acyclovir as a control (Figure 1). In general, compounds 8 and 9 showed the highest effect on HSV-1 than the other tested compounds, where their antiviral activity increased from 60%, 64% at concentration of 20 μg/10^5 cells to 86%, 88% at concentration of 40 μg/10^5 cells, respectively. Compounds 5, 6, 10, 11a,b, and 12 didn't show any activity against HSV-1.

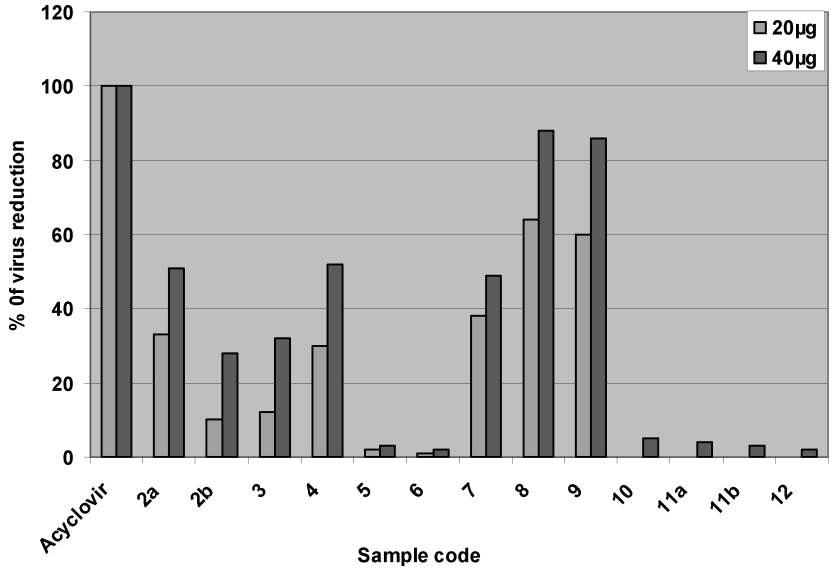


FIGURE 1 Effect of novel derivatives on HSV-1.

EXPERIMENTAL

All melting points were uncorrected and were measured using an Electrothermal IA 9100 apparatus. Analytical data were performed by Vario El Mentar apparatus, organic microanalysis section, National Research Centre, Cairo, Egypt. Their results were found to be in agreement with the calculated values (±0.3). The IR spectra (KBr) were recorded on a Pye Unicam Sp-1000 spectrophotometer. ^{1}H NMR spectra were determined on a Varian ^{1}H-Gemini 200 in DMSO-d_6, and the chemical shifts were expressed in ppm relative to TMS as internal reference. Mass spectra were run at 70 eV on GC MSQR 1000Ex.

[3-(4-Chlorophenyl)oxiranyl]thiophen-yl-propanone (1)

Hydrogen peroxide (9 ml, 36%) was added dropwise to a mixture of 3-(4-chlorophenyl)-1-thiophen-2-ylpropenone (2.48 g, 10 mmol) in acetone (30 ml), and methanol (10 ml) containing NaOH (1 g) at 10–15°C with stirring for 2 h. The solid substance was filtered off, washed with water and crystallized from methanol. White needle crystals were obtained to give compound 1 (80%); m.p. 119–120°C. IR spectrum (KBr, ν, cm^{-1}): 1693 (C=O);^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.70 (d, 1H, oxiranyl ring proton), 3.90 (d, 1H, other oxiranyl rang proton) and 6.90–7.55 (m, 7H, Ar–H); MS, *m/z* (%): 264 (M^+, 70). Analysis for $C_{13}H_9ClO_2S$ (264.73): required C, 58.98; H, 3.43; Cl, 13.39; S, 12.11; found C, 58.90; H, 3.42; Cl, 13.36; S, 12.09.

5-(4-Chlorophenyl)-3-thiophen-2-yl-4,5-dihydro-1*H*-pyrazol-4-ol (2a)

A mixture of compound 1 (1.32 g, 5 mmol) and hydrazine hydrate (0.4 ml, 10 mmol) was refluxed in 25 ml of absolute ethanol for 3 h. The solid substance was filtered off and crystallized from ethanol, to give compound 2a as yellow crystals (70%); m.p. 133–134°C. IR spectrum (KBr, ν, cm^{-1}): 3100–3125 (NH), 3320–3380 (OH);^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.85 (d, 1H, C^4-H), 4.00 (d, 1H, C^5-H) and 7.0–7.35 (m, 7H, Ar-H), 9.4 (s, 1H, NH of pyrazole, D_2O exchangeable), 10.2 (s, 1H, OH, D_2O exchangeable); MS, *m/z* (%): 278 (M^+, 25). Analysis for $C_{13}H_{11}ClN_2OS$ (278.76): required C, 56.01; H, 3.98; Cl, 12.72; N, 10.05; S, 12.11; found C, 56.30; H, 3.96; Cl, 12.52; N, 10.00; S, 12.39.

5-(4-Chlorophenyl)-1-phenyl-3-thiophen-2-yl-4,5-dihydro-1*H*-pyrazol-4-ol (2b)

A mixture of compound 1 (1.32 g, 5 mmol) and phenyl hydrazine (1.06 ml, 10 mmol) was refluxed in 30 ml of absolute ethanol for 2 h. The

reaction mixture was cooled. The solid substance was filtered off and crystallized from dioxane to give compound 2b (85%); m.p. 197–198°C. IR spectrum (KBr, ν, cm^{-1}): 3330–3390 (OH);^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.85 (d, 1H, C^4-H), 4.00 (d, 1H, C^5-H) and 7.1–7.4 (m, 7H, Ar-H), 10.35 (s, 1H, OH, D_2O exchangeable); MS, *m/z* (%): 354 (M^+, 50). Analysis for $C_{19}H_{15}ClN_2OS$ (354.85): required C, 64.31; H, 4.26; Cl, 9.99; N, 7.89; S, 9.04; found C, 64.13; H, 4.22; Cl, 10.12; N, 7.70; S, 9.00.

5-(4-Chlorophenyl)-3-thiophen-2-yl-4,5-dihydroisoxazol-4-ol (3)

A mixture of compound 1 (1.32 g, 5 mmol), hydroxylamine hydrochloride (0.35 g, 5 mmol) was stirred under reflux in ethanolic sodium hydroxide (0.5 g, 30 ml) for 2 h. The reaction mixture was cooled and poured into water (100 ml).The solid substance was filtered off and crystallized from methanol to give compound 3 (60%); m.p. 143–144°C. IR spectrum (KBr, ν, cm^{-1}): 3325–3390 (OH);^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.80 (d, 1H, C^4-H), 4.6 (d, 1H, C^5-H) and 7.10–7.38 (m, 7H, Ar-H), 10.35 (s, 1H, OH, D_2O exchangeable); MS, *m/z* (%): 279 (M^+, 30). Analysis for $C_{13}H_{10}ClNO_2S$ (279.74): required C, 55.82; H, 3.60; Cl, 12.67; N, 5.01; S, 11.46; found C, 55.60; H, 3.55; Cl, 12.45; N, 4.88; S, 11.33.

4-(4-Chlorophenyl)-6-thiophen-2-yl-2-thioxotetrahydropyrimidin-5-one (4)

A mixture of compound 1 (1.32 g, 5 mmol), thiourea (0.76 g, 10 mmol) was refluxed in ethanolic sodium hydroxide (1 g, 30 ml) for 3 h. The reaction mixture was cooled and poured into water (100 ml), extracted with benzene (50 ml), then dried with (anhydrous Na_2SO_4). The inorganic was filtered off, and the mother liquor was concentrated under reduced pressure, and yellowish white crystals were obtained which recrystallized from dioxane to give compound 4 (60%); m.p. 206–207°C. IR spectrum (KBr, ν, cm^{-1}): 3115–3180 (2NH), 1700 (C=O);^{1}H NMR spectrum ($CDCl_3$, δ ppm): 5.6 (s, 2H, pyrimidine-H), 6.6–7.2 (m, 7H, Ar-H), 9.8 (s, 1H, NH, D_2O exchangeable), 11.0 (s, 1H, NH, D_2O exchangeable); MS, *m/z* (%): 322 (M^+, 9). Analysis for $C_{14}H_{11}ClN_2OS_2$ (322.83): required C, 52.09; H, 3.43; Cl, 10.98; N, 8.68; S, 19.87; found C, 51.89; H, 3.44; Cl, 11.12; N, 8.70; S, 20.00.

5-(4-Chlorophenyl)-7-thiophen-2-yl-7*H*-thiazolo[3,2-*a*]pyrimidine-3,6-dione (5)

A mixture of compounds 4 (1.61 g, 5 mmol) with chloroacetic acid (0.96 g, 10 mmol) and anhydrous sodium acetate (3 g) was refluxed in glacial

acetic acid (30 ml)/ acetic anhydride (10 ml) for 3 h. The reaction mixture was cooled and poured gradually with stirring into cold water (100 ml). The formed solid was filtered off and recrystallized from ethanol to give compound 5 (55%); m.p. 167–168°C. IR spectrum (KBr, ν, cm^{-1}): 1696 (C=O), 1705 (C=O);^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.40 (s, 2H, thiazole-H), 5.7 (s, 2H, pyrimidine-H), 7.0–7.4 (m, 7H, Ar-H); MS, *m/z* (%): 362 (M^+, 7.5). Analysis for $C_{16}H_{11}ClN_2O_2S$ (362.86): required C, 52.96; H, 3.06; Cl, 9.77; N, 7.72; S, 17.67; found C, 52.70; H, 3.00; Cl, 9.99; N, 7.92; S, 17.55.

2-(4-Chlorobenzylidene)-5-(4-chloro-phenyl)-7-thiophen-2-yl-7*H*-thiazolo[3,2-*a*]pyrimidine-3,6-dione (6)

Method A

A mixture of compounds 5 (1.81 g, 5 mmol), 4-chlorobenzaldehyde (0.7 g, 5 mmol) and anhydrous sodium acetate (3 g) was refluxed in glacial acetic acid (30 ml) / acetic anhydride (10 ml) mixture for 3 h. The reaction mixture was cooled and poured gradually with stirring into cold water (100 ml). The formed solid was filtered off and recrystallized from acetic acid to give compound 6 (65%); m.p. 227–228°C. IR spectrum (KBr, ν, cm^{-1}): 1692 (C=O), 1710 (C=O); ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 5.8 (s, 2H, pyrimidine-H), 7.0–7.3 (m, 11H, Ar-H), 7.8 (s, 1H, benzylic-H).

Method B

A mixture of compounds 4 (1.61 g, 5 mmol), chloroacetic acid (0.96 g, 10 mole), 4-chloro benzaldehyde (0.7 g, 5 mmol) and anhydrous sodium acetate (3 g) was refluxed in glacial acetic acid (30 ml)/acetic anhydride (10 ml) mixture for 3 h. The reaction mixture was cooled and poured gradually with stirring into cold water (100 ml). The formed solid was filtered off and recrystallized from acetic acid to give compound identical in all aspects with an authentic sample (m.p., mixed m.p., and *tlc*).

5-(4-Chlorophenyl)-4-hydroxy-3-thiophen-2-yl-4,5-dihydropyrazol-1-Thiocarboxilic Acid Amide (7)

A mixture of compound 1 (1.32 g, 5 mmol) and thiosemicarbazide (0.46 ml, 5 mmol) was refluxed in 25 ml of absolute ethanol for 2 h. The solid substance was filtered off and crystallized from ethanol to give compound 7 as orange crystals (80%); m.p. 194–195°C. IR spectrum (KBr, ν, cm^{-1}): 3110–3190 (NH_2), 3340–3395 (OH);^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.77 (d, 1H, C^4-H), 4.15 (d, 1H, C^5-H), 4.8 (br, 2H, NH_2, D_2O exchangeable), 7.0–7.65 (m, 7H, Ar-H), 10.0 (s, 1H, OH, D_2O

exchangeable); MS, *m/z* (%): 237 (M^+, 12). Analysis for $C_{14}H_{12}ClN_3OS_2$ (337.85): required C, 49.77; H, 3.58; Cl, 10.49; N, 12.44; S, 18.98; found C, 49.47; H, 3.55; Cl, 10.52; N, 12.50; S, 19.20.

5-(4-Chlorophenyl)-4-hydroxy-3-thiophen-2-yl-4,5-dihydropyrazol-1-thiocarboxilic Acid (2,3,4,5,6-Pentahydroxyhexylidene)amide (8)

To a solution of D-glucose (0.83 g, 5 mmol) in water (0.5 ml), compound 7 (1.63 g, 5 mmol) in absolute ethanol (30 ml) and few drops of acetic acid was added. The mixture was stirred at 50°C for 4 h. The product that separated out on cooling was filtered off and washed with water, followed by ethanol and dried to give compound 8 (40%); m.p. 163–164°C. IR spectrum (KBr, ν, cm^{-1}): 3320–3380 (OH groups);^{1}H NMR spectrum ($CDCl_3$, δ ppm): 3.30–3.63 (m, 11H, 6-CH-glucose +5OH, D_2O exchangeable), 3.8 (d, 1H, C^4-H), 4.1 (s, 1H, C^5-H), 7.0–7.3 (m, 7H, Ar-H), 7.8 (d, 1H, hydrazone), 10.3 (s, 1H, OH, D_2O exchangeable). Analysis for $C_{20}H_{22}ClN_3O_6S_2$ (499.06): required C, 48.04; H, 4.44; Cl, 7.09; N, 8.40; S, 12.83; found C, 48.34; H, 4.50; Cl, 7.00; N, 8.10; S, 12.53.

5-(4-Chlorophenyl)-4-hydroxy-3-thiophen-2-yl-4,5-dihydropyrazol-1-thiocarboxilic Acid (2,3,4,5-Tetrahydroxypentylidene)amide (9)

To a solution of arabinose (0.74 g, 5 mmol) in water (0.5 ml), compound 8 (1.63 g, 5 mmol) in absolute ethanol (30 ml) and few drops of acetic acid was added. The mixture was stirred at 50°C for 5 h. The product that separated out on cooling was filtered off and washed with water, followed by ethanol and dried to give compound 9 (45%); m.p. 163–164°C. IR spectrum (KBr, ν, cm^{-1}): 3280–3350 (OH groups);^{1}H NMR spectrum (DMSO-d_6, δ ppm): 3.35–3.68 (m, 9H, 5-CH-arabinose+4OH, D_2O exchangeable), 3.8 (d, 1H, C^4-H), 4.0 (d, 1H, C^5-H) and 7.1–7.4 (m, 7H, Ar-H), 7.9 (s, 1H, hydrazone), 10.4 (s, 1H, OH, D_2O exchangeable). Analysis for $C_{19}H_{20}ClN_3O_5S_2$ (469.96): required C, 48.56; H, 4.29; Cl, 7.54; N, 8.94; S, 13.65; found C, 48.30; H, 4.32; Cl, 7.60; N, 9.00; S, 13.35.

4-(4-Chlorophenyl)-2-thioxo[1,3]oxathiolane-5-yl]thiophen-2-yl methanone (10)

A mixture of compound 1 (1.32 g, 5 mmol) and CS_2 (5 ml) was stirred in absolute ethanol containing H_2O_2 (36%) as a catalyst (1 ml), and then refluxed for 2 h. After cooling the product was filtered off and crystallized from ethanol to give compound 10 (70%); m.p. 183–184°C.

IR spectrum (KBr, ν, cm^{-1}): 1695 (C=O);^{1}H NMR spectrum (DMSO-d_6, δ ppm): 4.2 (d, 1H, oxathiolane-H), 4.8 (d, 1H, oxathiolane-H) and 6.9–7.4 (m, 7H, Ar-H); MS, *m/z* (%): 340 (M^+, 10). Analysis for $C_{14}H_9ClO_2S_3$ (340.87): required C, 49.33; H, 2.66; Cl, 10.40; S, 28.22; found C, 49.60; H, 2.60; Cl, 10.60; S, 28.50.

4-(4-Chlorophenyl)-3-phenyl-6-thiophen-2-yl-3,4-dihydro [1,3]oxazine-2-thione (11a)

A mixture of compound 1 (1.32 g, 5 mmol) and phenyl isothiocyanate (0.67 ml, 5 mmol) was refluxed in dry pyridine for 6 h. After cooling the reaction mixture was poured gradually with stirring into cold water (100 ml). The solid substance was filtered off and recrystallized from benzene to give compound 11a (50%); m.p. 204–205°C. ^{1}H NMR spectrum (DMSO-d_6, δ ppm): 4.6 (d, 1H, oxazine-H), 6.5 (d, 1H, oxazine-H) and 6.7–7.3 (m, 12H, Ar-H); MS, *m/z* (%): 383 (M^+, 8). Analysis for $C_{20}H_{14}ClNOS_2$ (383.92): required C, 62.57; H, 3.68; Cl, 9.23; N, 3.65; S, 16.70; found C, 62.72; H, 3.80; Cl, 9.00; N, 3.80; S, 17.00.

4-(4-Chlorophenyl)-3-phenyl-6-thiophen-2-yl-3,4-dihydro [1,3]oxazine-2-thione (11b)

A mixture of compound 1 (1.32 g, 5 mmol) and methyl isothiocyanate (0.37 ml, 5 mmol) was refluxed in dry pyridine for 6 h. After cooling the reaction mixture was poured gradually with stirring into cold water (100 ml). The solid substance was filtered off and recrystallized from benzene to give compound 11a (55%); m.p. 188–189°C. ^{1}H NMR spectrum ($CDCl_3$, δ ppm): 2.5 (s, 3H, CH_3), 4.7 (d 1H, CH-Ar), 6.8 (d, 1H, C=CH) and 7.0–7.25 (m, 7H, Ar-H). MS, *m/z* (%): 321 (M^+, 7.8). Analysis for $C_{15}H_{12}ClNOS_2$ (321.85): required C, 55.98; H, 3.76; Cl, 11.02; N, 4.35; S, 19.93; found C, 56.20; H, 3.80; Cl, 11.00; N, 4.50; S, 20.00.

2-(4-Chlorophenyl)-4-thiophen-2-yl[1,3]dithiol (12)

A mixture of compound 1 (1.32 g, 5 mmol) and P_2S_5(1.11 g, 5 mmol) was refluxed in dry benzene for 3 h. The reaction mixture was filtered off and the filtrate was concentrated under reduced pressure. The solid substance was recrystallized from methanol to give compound 12 (50%); m.p 143–144°C. ^{1}H NMR spectrum ($CDCl_3$, δ ppm): 4.9 (s, 1H, dithiol-H), 6.4 (s, 1H, dithiol-H) and 7.0–7.3 (m, 7H, Ar-H); MS, *m/z* (%): 296 (M^+, 8). Analysis for $C_{13}H_9ClS_3$ (295.89): required C, 52.60; H, 3.06; Cl, 11.94; S, 32.41; found C, 52.30; H, 3.00; Cl, 12.20; S, 32.63.

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