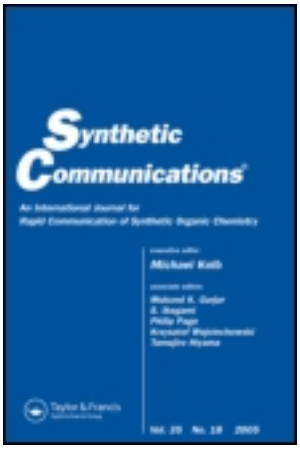


Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

Synthesis and Characterization of a New Series of Hydroxy Pyrazolines

Humaira Parveen [a], Prince Firdoos Iqbal [a] & Amir Azam [a]

[a] Department of Chemistry, Jamia Millia Islamia, Jamia Nagar, New Delhi, India

Version of record first published: 20 Oct 2008

To cite this article: Humaira Parveen, Prince Firdoos Iqbal & Amir Azam (2008): Synthesis and Characterization of a New Series of Hydroxy Pyrazolines, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 38:22, 3973-3983

To link to this article: http://dx.doi.org/10.1080/00397910802241407

Synthetic Communications®, 38: 3973–3983, 2008

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802241407

Taylor & Francis
Taylor & Francis Group

Synthesis and Characterization of a New Series of Hydroxy Pyrazolines

Humaira Parveen, Prince Firdoos Iqbal, and Amir Azam
Department of Chemistry, Jamia Millia Islamia, Jamia Nagar, New Delhi, India

Abstract: 3-Phenyl-1-(thiophen-2-yl)prop-2-en-1-one obtained by Claisen–Schmidt condensation of 2-acetyl thiophene with benzaldehyde was converted into 2,3-dibromo-3-phenyl-1-(thiophen-2-yl)propan-1-one, which on treatment with various thiosemicarbazides in the presence of triethylamine in absolute ethanol, yielded the corresponding hydroxy pyrazolines **3a–h**. All the compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra.

Keywords: Chalcone, chalcone dibromide, hydroxy pyrazoline, pyrazoline

INTRODUCTION

Chalcones constitute an important class of naturally occurring flavonoid compounds that exhibit a wide spectrum of biological activities and are well-known intermediates for synthesizing various heterocycles. Chalcone dibromides are useful synthons in the synthesis of a large number of bioactive molecules such as pyrazolines, hydroxy pyrazolines, and isoxazoles. Pyrazoles and their reduced forms, pyrazolines, are well-known nitrogen-containing heterocyclic compounds, and various procedures have been developed for their syntheses.[1,2] The discovery of this class of compounds provides an outstanding case history of modern drug development and also points out the unpredictability of biological

Received April 1, 2008.
Address correspondence to Amir Azam, Department of Chemistry, Jamia Millia Islamia, Jamia Nagar, New Delhi 110025, India. E-mail: amir_sumbul@yahoo.co.in

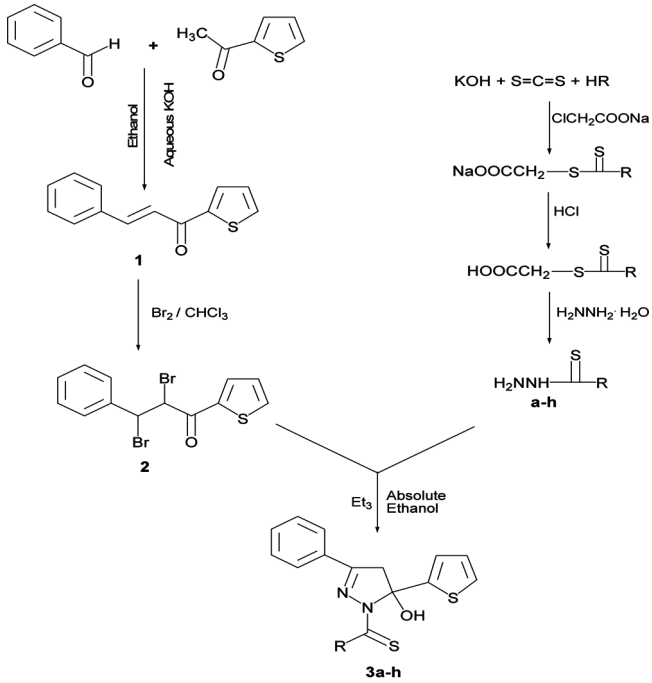
activity from structural modification of a prototype drug molecule. Considerable interest has been focused on the pyrazoline structure, which has been known to possess a broad spectrum of biological activities such as antitumor,[3] immunosuppressive,[4] antibacterial,[5] anti-inflammatory,[6] anticancer,[7] antidiabetic,[8] and antidepressant.[9]

Stable and isolable representatives of 5-hydroxy-2-pyrazolines have been described in the literature.[10] They were mostly obtained by the reaction of 1,3-diketones with derivatives of hydrazine in which there is a strong electron-withdrawing group (aryl, thioacyl, carbamoyl, thiocarbamoyl, etc.). 5-Hydroxy-2-pyrazolineses are of interest as polydendate ligands; their copper and nickel chelates exhibit enhanced antimicrobial activity.[10] In view of the versatile applications of chalcones, pyrazolines, and hydroxy pyrazolines, we herein report the synthesis of a new series of hydroxy pyrazolines.

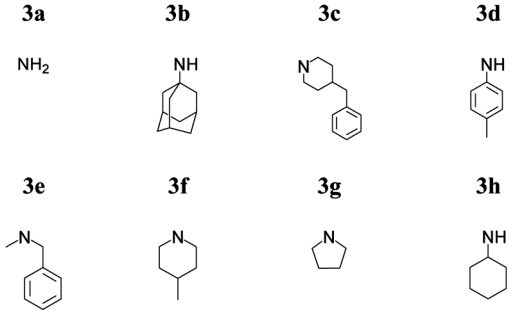
RESULTS AND DISCUSSION

3-Phenyl-1-(thiophen-2-yl)prop-2-en-1-one (chalcone **1**) was obtained by Claisen–Schmidt condensation of 2-acetyl thiophene with benzaldehyde. The chalcone **1** was converted into 2,3-dibromo-3-phenyl-1-(thiophen-2-yl)propan-1-one (chalcone dibromide **2**), which, on treatment with different thiosemicarbazides in the presence of triethylamine in absolute ethanol, yielded corresponding hydroxy pyrazolines **3a–h** (Scheme 1). All the compounds were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectra. The purity of the compounds was confirmed by elemental analysis, $\pm 0.3\%$.

The formation of chalcone **1** and chalcone dibromide **2** was confirmed by IR spectra. The absence of a band at or around 2660 cm^{-1} due to the aldehydic proton and the appearance of characteristic bands at 1620–1650 cm^{-1} and 1415–1450 cm^{-1} due to α,β-unsaturated carbonyl group and ν(C=C), respectively, suggested the condensation of 2-acetyl thiophene and benzaldehyde. In the ^{1}H NMR spectrum of chalcone **1**, two doublets at 7.47 (H-α, $J = 15.2$ Hz) and 7.89 (H-β, $J = 15.2$ Hz) suggested the presence of olefinic protons at the α,β-position to the carbonyl group, whereas two doublets at 6.38 (H-α, $J = 10.5$ Hz) and 5.59 (H-β, $J = 10.5$ Hz) suggested the formation of chalcone dibromide **2**. The structure of these compounds was further confirmed by ^{13}C NMR spectra. A characteristic signal for the chalcone (C=O) appeared in the range of 180–182 ppm, and signals at 121.89 ppm and 143.20 ppm revealed the presence of α,β-unsaturated keto function in chalcone **1**. In the chalcone dibromide **2**, a signal at 185.27 due to (C=O) and two signals at 47.55



Where **R** =



Scheme 1. Synthesis of hydroxy pyrazolines.

(C-α) and 50.91 (C-β) suggested the conversion of chalcone **1** to chalcone bromide **2**.

In the IR spectra of hydroxy pyrazolines **3a–h**, a characteristic broad band appeared at 3360–3390 cm^{-1}, indicating the presence of a hydrogen-bonded hydroxyl group. The thionyl ν(C=S) stretching frequency was observed at 1121–1190 cm^{-1}. The other prominent absorption bands

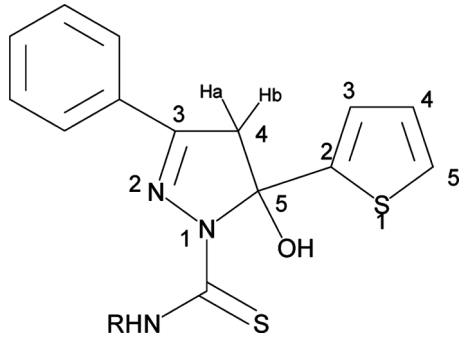


Figure 1. Methylene protons of pyrazoline ring.

observed in the IR spectrum of compound **3a** are 3280 (N–H), 3075 (Ar–H), 2921 (C–H), 1532 (C=N), and 1447 (C=C). The ^{1}H NMR spectra showed that the proton of the hydroxyl group resonated as a singlet at 4.61–4.91 ppm. The methylene protons of hydroxy pyrazoline ring (Fig. 1) appeared as two doublets, one at 5.03–5.17 ppm (H4a, $J = 16.6$–17.4 Hz) and the other at 5.17–5.42 (H4b, $J = 16.2$–17.4 Hz). The appearance of these two doublets clearly revealed the magnetic non-equivalence of the two protons of the CH_2 group adjacent to a chiral center. The protons of the phenyl ring resonated as a multiplet at 7.01–7.65 ppm. A double doublet at 7.34–7.65 ppm ($J = 2.1$–3.4, 1.0–2.0 Hz) integrating for one proton was attributed to the C_3 proton of thiophenyl moiety, and a double doublet at 7.72–7.81 ppm ($J = 4.3$–5.5, 1.0–1.8 Hz) was due to the C_5 proton of the thiophenyl moiety. The C_4 proton of the thiophenyl moiety resonated as a multiplet at 7.01–7.35 ppm.

Further evidence for the formation of hydroxy pyrazolines **3a–h** was obtained from ^{13}C NMR spectra. A signal at 179.2–184.8 ppm and 153.4–159.8 ppm was attributed to (C=S) and (C=N) respectively in all the compounds. The (C–OH) signal due to C_5 of pyrazoline ring in the range of 87.4–91.5 ppm and a characteristic signal for C_4 of pyrazoline ring found in the range of 49.1–54.5 ppm clearly favored the formation of hydroxy pyrazolines. The signals due to the phenyl ring and thiophenyl ring resonate at their usual positions, and the values are given in the Experimental section.

EXPERIMENTAL

Precoated aluminium sheets (Merck silica gel 60 F_{254}) were used for thin-layer chromatography (TLC). Column chromatography was

accomplished using silica gel, 60 Å (200–400 mesh). Elemental analyses were performed at Central Drug Research Institute, Lucknow, India, using an Elementar Vario EL III analyzer, and the results were within ±0.3% of the theoretical values. IR spectra were taken as KBr pellets on a Perkin-Elmer model 1600 Fourier transform infrared (FT-IR) spectrum RX1 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer using dimethyl sulfoxide (DMSO)-d_6 as solvent with TMS as internal standard. Splitting patterns are designated as follows: s, singlet; d, doublet; dd, double doublet; t, triplet; m, multiplet. Chemical shift (δ) values are given in parts per million (ppm) and coupling constant (J) in hertz (Hz).

Procedure for the Preparation of 3-Phenyl-1-(thiophen-2-yl)prop-2-en-1-one: Chalcone 1

To a mixture of 2-acetyl thiophene (0.01 mol) and benzaldehyde (0.01 mol) in ethanol (50 ml), a solution of potassium hydroxide (5%, 25 ml) was added slowly. The mixture was stirred for 24 h. The precipitated solid was filtered, washed with water, dried, and recrystallized from ethanol.

Yield: 98%; mp: 55 °C; cream-colored crystals. Anal. calc. for $C_{13}H_{10}OS$: C, 72.89; H, 4.67; O, 7.47%. Found: C, 72.62; H, 4.51; O, 7.71%. IR ν_{max} cm^{-1}: 3090 (Ar–H), 2921 (C–H), 1640 (C=O), 1447 (C=C); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.37–8.02 (m, 5H, phenyl), 7.94 (dd, 1H, H5, $J = 3.7$, 1.5 Hz, thiophene), 7.89 (d, 1H, H-β, $J = 15.2$ Hz), 7.73 (dd, 1H, H3, $J = 2.3$, 1.3 Hz, thiophene), 7.47 (d, 1H, H-α, $J = 15.2$ Hz), 7.33 (m, 1H, H4, thiophene); ^{13}C NMR (DMSO-d_6) δ (ppm): 181.65 (C=O), 143.20 (C-β), (145.50, 135.65, 133.77, 130.71, thiophene), (134.51, 128.95, 128.22, 127.63, phenyl), 121.89 (C-α).

Procedure for the Preparation of 2,3-Dibromo-3-phenyl-1-(thiophen-2-yl)propan-1-one: Chalcone Dibromide 2

Bromine (0.01 mol) in chloroform (25 ml) was added slowly to a solution of 3-phenyl-1-(thiophen-2-yl)prop-2-en-1-one **1** (0.01 mol) in chloroform (50 ml) with stirring. After the addition of the bromine solution, the reaction mixture was stirred for 24 h. Excess chloroform was distilled off under reduced pressure. The precipitated solid was filtered, dried, and recrystallized from chloroform.

Yield: 96%; mp: 135 °C; white crystals. Anal. calc. for $C_{13}H_{10}OSBr_2$: C, 41.73; H, 2.67; O, 4.28%. Found: C, 41.61; H, 2.64; O, 4.33%. IR ν_{max} cm^{-1}: 3090 (Ar–H), 2930 (C–H), 1665 (C=O), 1415 (C=C); ^{1}H NMR

(DMSO-d_6) δ (ppm): 8.0–8.09 (m, 5H, phenyl), 7.68 (dd, 1H, H5, $J = 3.6$, 1.2 Hz, thiophene), 7.39 (dd, 1H, H3, $J = 2.2$, 1.4 Hz, thiophene), 7.24 (m, 1H, H4, thiophene), 6.38 (d, 1H, H-α, $J = 10.5$ Hz), 5.59 (d, H-β, $J = 10.5$ Hz); ^{13}C NMR (DMSO-d_6) δ (ppm): 185.27 (C=O), 47.55 (C-α), (141.10, 138.54, 138.18, 129.60, thiophene), (135.99, 129.52, 129.03, 128.9, phenyl), 50.91 (C-β).

General Procedure for the Synthesis of Substituted Thiosemicarbazides (a–h)

Substituted thiosemicarbazides **a–h** were prepared by a reported method.[11]

Preparation of Substituted Thioglycolic Acid

Carbon disulphide (1 equiv.) was added dropwise to a solution of primary or secondary amines (1 equiv.) containing potassium hydroxide (1 equiv.) in a water–ethanol (1:3) mixture. The temperature of the reaction was maintained at less than 10 °C. Sodium chloroacetate (1 equiv.) was added, and the reaction mixture was left overnight at room temperature. Addition of conc. hydrochloric acid (pH ~ 1) precipitated substituted thioglycolic acid, which was crystallized by the appropriate solvent.

Conversion of Thioglycolic Acid into Thiosemicarbazides (a–h)

A solution of thioglycolic acid (1 equiv.) in water (15 ml) containing sodium hydroxide (1 equiv.) and hydrazine hydrate (1 equiv.) was refluxed for 2 h with continuous stirring. The compound separated out during the reaction or on cooling at 0 °C for 12 h. The product was filtered and crystallized from a suitable solvent.

Procedure for the Synthesis of Hydroxy Pyrazolines (3a–h)

Thiosemicarbazides **a–h** (0.01 mol) and triethylamine (10 ml) were added to a mixture of chalcone dibromide **2** (0.01 mol) in absolute ethanol (75 ml). The reaction mixture was refluxed for 24 h. The contents were reduced, cooled, and poured onto crushed ice and kept overnight. The resulting hydroxy pyrazolines **3a–h** were collected by filtration and purified by column chromatography using hexane–dichloromethane (80:20, v/v) as eluent.

4,5-Dihydro-5-hydroxy-3-phenyl-5-(thiophen-2-yl)pyrazole-1-carbothioamide (3a)

Yield: 35%; oil. Anal. calc. for $C_{14}H_{13}OS_2N_3$: C, 55.44; H, 4.29; O, 13.86%. Found: C, 55.49; H, 4.36; O, 13.66%. IR ν_{max} cm^{-1}: 3377 (O–H), 3075 (Ar–H), 2921 (C–H), 3280 (N–H), 1532 (C=N), 1447 (C=C), 1121 (C=S); ^{1}H NMR (DMSO-d_6) δ (ppm): 9.12 (s, 2H, NH), 7.81, (dd, 1H, H5, $J = 4.3$, 1.1 Hz, thiophene), 7.65 (dd, 1H, H3, $J = 2.6$, 1.4 Hz, thiophene), 7.45–7.02 (m, 5H, phenyl), 7.35 (m, 1H, H4, thiophene), 5.31 (d, 1H, H4b, $J = 17.2$ Hz, pyrazoline ring), 5.09 (d, 1H, H4a, $J = 17.2$ Hz, pyrazoline ring), 4.70 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ (ppm): 181.5 (C=S), 153.4 (C=N), (144.6, 141.9, 134.5, 126.3, thiophene), (135.2, 132.4, 128.3, 127.6, phenyl), 88.7 (C5, pyrazoline ring), 53.5 (C4, pyrazoline ring).

N-Adamantyl-4,5-dihydro-5-hydroxy-3-phenyl-5-(thiophen-2-yl) pyrazole-1-carbothioamide (3b)

Yield: 25%; oil. Anal. calc. for $C_{24}H_{27}OS_2N_3$: C, 65.90; H, 6.17; O, 9.61%. Found: C, 65.83; H, 6.27; O, 9.58%. IR ν_{max} cm^{-1}: 3380 (O–H), 3225 (N–H), 3031 (Ar–H), 2920 (C–H), 1616 (C=N), 1434 (C=C), 1185 (C=S); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.60 (s, 1H, NH), 7.84 (dd, 1H, H5, $J = 4.5$, 0.9 Hz, thiophene), 7.52 (dd, 1H, H3, $J = 3.4$, 1.9 Hz, thiophene), 7.34–7.11 (m, 5H, phenyl), 7.16 (m, 1H, H4, thiophene), 5.29 (d, 1H, H4b, $J = 16.2$ Hz, pyrazoline ring), 5.17 (d, 1H, H4a, $J = 16.2$ Hz, pyrazoline ring), 4.62 (s, 1H, OH), 2.33–1.12 (m, 15H, adamantyl ring); ^{13}C NMR (DMSO-d_6) δ (ppm): 182.8 (C=S), 154.1 (C=N), (146.2, 141.2, 133.5, 126.2, thiophene), (134.4, 131.2, 128.4, 127.9, phenyl), 84.7 (C5, pyrazoline ring), 52.4 (C4, pyrazoline ring), 49–23 (adamantyl ring).

(4-Benzylpiperidin-1-yl)(4,5-dihydro-5-hydroxy-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)methanethione (3c)

Yield: 18%; oil. Anal. calc. for $C_{26}H_{27}OS_2N_3$: C, 67.67; H, 5.85; O, 9.11%. Found: C, 67.52; H, 5.75; O, 9.27%. IR ν_{max} cm^{-1}: 3385 (O–H), 3080 (Ar–H), 2915 (C–H), 1630 (C=N), 1444 (C=C), 1124 (C=S); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.79 (dd, 1H, H5, $J = 5.25$, 1.3 Hz, thiophene), 7.63–7.02 (m, 10H, phenyl), 7.43 (dd, 1H, H3, $J = 2.7$, 1.13 Hz, thiophene), 7.13 (m, 1H, H4, thiophene), 5.17 (d, 1H, H4b, $J = 16.6$ Hz, pyrazoline ring), 5.04 (d, 1H, H4a, $J = 16.6$ Hz, pyrazoline ring), 4.88

(s, 1H, OH), 3.13–2.51 (m, 4H, CH_2, piperidine), 2.54 (d, 2H, CH_2, $J = 6.7$ Hz), 1.69–1.33 (m, 4H, CH_2, piperidine), 1.83–1.60 (m, 1H, CH, piperidine); ^{13}C NMR (DMSO-d_6) δ (ppm): 179.2 (C=S), 159.8 (C=N), (146.5, 138.2, 132.5, 125.5, thiophene), (138.4, 134.6, 131.3, 129.4, 129.9, 128.6, 128.2, 124.0, phenyl), 84.3 (C5, pyrazoline ring), 50.8 (C4, pyrazoline ring), 50.2 ($2 \times CH_2$, piperidine), 42.7 (CH_2), 31.9 (CH, piperidine), 29.7 ($2 \times CH_2$, piperidine).

4,5-Dihydro-5-hydroxy-3-phenyl-5-(thiophen-2-yl)-N-p-tolylpyrazole-1-carbothioamide (3d)

Yield: 31%; oil. Anal. calc. for $C_{21}H_{19}OS_2N_3$: C, 64.12; H, 4.83; O, 10.68%. Found: C, 64.16, H, 4.66; O, 10.73%. IR ν_{max} cm^{-1}: 3390 (O–H), 3254 (N–H), 3066 (Ar–H), 2890 (C–H), 1660 (C=N), 1450 (C=C), 1123 (C=S); ^{1}H NMR (DMSO-d_6) δ (ppm): 8.62 (s, 1H, NH), 7.77 (dd, 1H, H5, $J = 4.1$, 1.3 Hz, thiophene), 7.43 (dd, 1H, H3, $J = 3.12$, 1.6 Hz, thiophene), 7.20 (m, 1H, H4, thiophene), 7.22–7.01 (m, 5H, phenyl), 6.97 (d, 2H, $J = 7.6$ Hz, phenyl), 6.53 (d, 2H, $J = 7.6$ Hz, phenyl), 5.33 (d, 1H, H4b, $J = 16.4$ Hz, pyrazoline ring), 5.13 (d, 1H, H4a, $J = 16.4$ Hz, pyrazoline ring), 4.82 (s, 1H, OH), 2.32 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ (ppm): 184.4 (C=S), 153.9 (C=N), (145.4, 138.6, 131.4, 126.5, thiophene), (134.8, 134.0, 134.4, 131.3, 129.5, 129.2, 128.9, 126.2, phenyl), 87.4 (C5, pyrazoline ring), 52.6 (C4, pyrazoline ring), 25.3 (CH_3).

N-Benzyl-4,5-dihydro-5-hydroxy-N-methyl-3-phenyl-5-(thiophen-2-yl)pyrazole-1-carbothioamide (3e)

Yield: 23%; oil. Anal. calc. for $C_{22}H_{21}OS_2N_3$: C, 62.41; H, 4.96; O, 9.92%. Found: C, 62.24; H, 4.72; O, 9.73%. IR ν_{max} cm^{-1}: 3380 (O–H), 3070 (Ar–H), 2885 (C–H), 1613 (C=N), 1436 (C=C), 1124 (C=S); ^{1}H NMR (DMSO-d_6) δ (ppm): 7.79 (dd, 1H, H5, $J = 5.3$, 1.22, thiophene), 7.63 (m, 10H, phenyl), 7.34 (dd, 1H, H3, $J = 2.3$, 1.6, thiophene), 7.01 (m, 1H, H4, thiophene), 5.31 (d, 1H, H4b, $J = 17.2$ Hz, pyrazoline ring), 5.09 (d, 1H, H4a, $J = 17.2$ Hz, pyrazoline ring), 4.86 (s, 1H, OH), 4.67 (s, 2H, CH_2), 2.53–2.02 (s, 3H, CH_3); ^{13}C NMR (DMSO-d_6) δ (ppm): 182.2 (C=S), 159.3 (C=N), (143.5, 138.7, 128.4, 126.6, thiophene), (136.5, 134.4, 132.6, 129.2, 128.7, 128.4, 128.2, 127.1, phenyl), 88.3 (C5, pyrazoline ring), 60.1 (CH_2), 51.6 (C4, pyrazoline ring), 42.8 (CH_3).

(4,5-Dihydro-5-hydroxy-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)(4-methylpiperidin-1-yl)methanethione (3f)

Yield: 39%; oil. Anal. calc. for $C_{20}H_{23}OS_2N_3$: C, 62.33; H, 5.97; O, 10.90%. Found: C, 62.12, H, 5.92; O, 10.77%. IR ν_{max} cm^{-1}: 3372 (O–H), 3095 (Ar–H), 2870 (C–H), 1620 (C=N), 1460 (C=C), 1143 (C=S); ^1H NMR (DMSO-d_6) δ (ppm): 7.72 (dd, 1H, H5, $J = 5.4$, 1.7 Hz, thiophene), 7.43–7.02 (m, 5H, phenyl), 7.40 (dd, 1H, H3, $J = 3.1$, 2.0 Hz, thiophene), 7.12 (m, 1H, H4, thiophene), 5.42 (d, 1H, H4b, $J = 16.6$ Hz, pyrazoline ring), 5.13 (d, 1H, H4a, $J = 16.6$ Hz, pyrazoline ring), 4.90 (s, 1H, OH), 3.47 (m, 4H, CH_2, piperidine), 1.68 (m, 4H, CH_2, piperidine), 1.49 (m, 1H, CH, piperidine), 1.02 (d, 3H, CH_3, $J = 5.4$ Hz); ^{13}C NMR (DMSO-d_6) δ (ppm): 181.2 (C=S), 157.3 (C=N), (144.4, 138.2, 133.5, 126.2, thiophene), (134.4, 131.6, 129.2, 128.6, phenyl), 84.3 (C5, pyrazoline ring), 53.7 (C4, pyrazoline ring), 46.7 ($2 \times CH_2$, piperidine), 32.8 ($2 \times CH_2$, piperidine), 35.3 (CH, piperidine), 14.4 (CH_3).

(4,5-Dihydro-5-hydroxy-3-phenyl-5-(thiophen-2-yl)pyrazol-1-yl)(pyrrolidin-1-yl)methanethione (3g)

Yield: 21%; oil. Anal. calc. for $C_{18}H_{19}OS_2N_3$: C, 60.50; H, 5.32; O, 11.76%. Found: C, 60.32; H, 5.46; O, 11.73%. IR ν_{max} cm^{-1}: 3376 (O–H), 3033 (Ar–H), 2920 C–H), 1595 (C=N), 1437 (C=C), 1145 (C=S); ^1H NMR (DMSO-d_6) δ (ppm): 7.66 (dd, 1H, H5, $J = 4.3$, 1.3 Hz, thiophene), 7.39 (dd, 1H, H3, $J = 3.4$, 2.2 Hz, thiophene), 7.23–7.01 (m, 5H, phenyl), 7.13 (m, 1H, H4, thiophene), 5.25 (d, 1H, H4b, $J = 16.4$ Hz, pyrazoline ring), 5.08 (d, 1H, H4a, $J = 16.4$ Hz, pyrazoline ring), 4.91 (s, 1H, OH), 2.15–3.23 (m, 4H, CH_2, pyrolidine), 1.23–2.02 (m, 4H, CH_2, pyrolidine); ^{13}C NMR (DMSO-d_6) δ (ppm): 179.5 (C=S), 157.6 (C=N), (144.4, 138.6, 132.8, 126.3, thiophene), (134.7, 130.2, 129.6, 128.9, phenyl), 89.6 (C5, pyrazoline ring), 53.2 (C4, pyrazoline ring), 45.2 ($2 \times CH_2$), 31.6 ($2 \times CH_2$).

N-Cyclohexyl-4,5-dihydro-5-hydroxy-3-phenyl-5-(thiophen-2-yl)pyrazole-1-carbothioamide (3h)

Yield: 27%; oil. Anal. calc. for $C_{20}H_{23}OS_2N_3$: C, 62.33; H, 5.97; O, 10.90%. Found: C, 62.24; H, 5.93; O, 10.81%. IR ν_{max} cm^{-1}: 3375 (O–H), 3085 (Ar–H), 2915 (C–H), 1559 (C=N), 1453 (C=C), 1166 (C=S); ^1H NMR (DMSO-d_6) δ (ppm): 8.57 (d, 1H, NH, $J = 6.8$ Hz),

7.67 (dd, 1H, H5, $J = 4.5$, 0.9 Hz, thiophene), 7.36–7.01 (m, 5H, phenyl), 7.35 (dd, 1H, H3, $J = 2.8$, 1.2 Hz, thiophene), 7.11 (m, 1H, H4, thiophene), 5.23 (d, 1H, H4b, $J = 16.2$ Hz, pyrazoline ring), 5.03 (d, 1H, H4a, $J = 16.2$ Hz, pyrazoline ring), 4.67 (s, 1H, OH), 3.72 (m, 1H, CH, cyclohexyl ring), 2.37–1.15 (m, 10H, CH_2, cyclohexyl ring); ^{13}C NMR (DMSO-d_6) δ (ppm): 184.8 (C=S), 156.8 (C=N), (142.1, 138.5, 132.8, 126.2, thiophene), (134.4, 131.2, 129.5, 128.6, phenyl), 91.5 (C5, pyrazoline ring), (53.2, 31.5, 26.5, 22.5, cyclohexyl ring), 49.5 (C4, pyrazoline ring).

ACKNOWLEDGMENTS

This work was supported by the Department of Science and Technology (Grant No. Vll-PRDSF/44/2004-05/TT), New Delhi, India.

REFERENCES

1. Elguero, J. In *Comprehensive Heterocyclic Chemistry*; A. R. Katritzky, C. W. Rees (Eds.); Pergamon: Oxford, 1984; vol. 5, pp. 167–302.
2. Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; A. R. Katritzky, C. W. Rees, E. F. Scriven (Eds.); Pergamon: Oxford, 1996; vol. 3, pp. 1–75.
3. Taylor, E. C.; Patel, H.; Kumar, H. Synthesis of pyrazolo 3,4-*d*pyrimidine analogues of the potent agent N-4-2-2-amino-4 3*H*-oxo-7*H*-pyrrolo 2,3-*d* pyrimidin-5-yl ethylbenzoyl-L-glutamic acid (LY231514). *Tetrahedron.* **1992**, *48*, 8089–8100.
4. Karthikeyan, M. S.; Holla, B. S.; Kumari, N. S. Synthesis and antimicrobial studies on novel chloro-fluorine containing hydroxy pyrazolines. *Eur. J. Med. Chem.* **2007**, *42*, 30–36.
5. Holla, B. S.; Akberali, P. M.; Shivananda, M. K. Studies on arylfuran derivatives, Part X: Synthesis and antibacterial properties of arylfuryl-Δ^2-pyrazolines. *Farmaco* **2000**, *55*, 256–263.
6. Bansal, E.; Srivatsava, V. K.; Kumar, A. Synthesis and anti-inflammatory activity of 1-acetyl-5-substitute daryl-3-(β-aminonaphthyl)-2-pyrazolines and β-(substitute daminoethyl) amidonaphthalenes. *Eur. J. Med. Chem.* **2001**, *36*, 81–92.
7. Manna, F.; Chimenti, F.; Fioravanti, R.; Bolasco, A.; Seecci, D.; Chimenti, P.; Ferlini, C.; Scambia, G. Synthesis of some pyrazole derivatives and preliminary investigation of their affinity binding to P-glycoprotein. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4632–4635.
8. Ahn, J. H.; Kim, H. M.; Jung, S. H.; Kang, S. K.; Kim, K. R.; Rhee, S. D.; Yang, S. D.; Cheon, H. G.; Kim, S. S. Synthesis and DP-IV inhibition of cyano-pyrazoline derivatives as potent anti-diabetic agents. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4461–4465.

9. Rajendera Prasad, Y.; Lakshmana Rao, A.; Prasoona, L.; Murali, K.; Ravi Kumar, P. Synthesis and antidepressant activity of some 1,3,5-triphenyl-2-pyrazolines and 3-(2″-hydroxy naphthalen-1″-yl)-1,5-diphenyl-2-pyrazolines. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5030–5034.
10. Zelenin, K. N.; Tugusheva, A. R.; Yakimovich, S. I.; Alekseev, V. V.; Zerova, E. V. 5-Hydroxy-2-pyrazolines and their 1-substituted analogs. *Chem. Heterocyc. Comp.* **2002**, *38*, 668–676.
11. Budakoti, A.; Abid, M.; Azam, A. Synthesis and antiamoebic activity of new 1-N-substituted thiocarbamoyl-3,5-diphenyl-2-pyrazoline derivatives and their Pd(II) complexes. *Eur. J. Med. Chem.* **2006**, *41*, 63–70.