Carbodiimide mediated synthesis of new thiazolidin-4-ones and thiazinan-4-ones from thiosemicarbazone derivatives of 6,7-dihydro-1*H*-indazole-4(5*H*)-ones

Poonam Gautam and Ram P. Chaudhary*

Department of Chemistry, Sant Longowal Institute of Engineering & Technology, Longowal (Sangrur) Punjab-148106, India

5,5-Dimethyl-2-[(2-substitutedphenylhydrazinyl)methylene]cyclohexane-1,3-dione, obtained from heating dimedone with *N,N′*-dimethylformamide dimethyl acetal (DMF–DMA) and phenyl hydrazines, on cyclisation in ethanol gave 6,7-dihydro-1*H*-indazol-4(5*H*)-ones. The thiosemicarbazone derivative of 6,7-dihydro-1*H*-indazole-4(5*H*)-ones, on cyclocondensation with α and β-haloacids in the presence of *N,N′*-dicyclohexylcarbodiimide afforded new thiazolidin-4-ones and 1,3-thiazinan-4-ones respectively. Thiosemicarbazone of 6,7-dihydro-1*H*-indazol-4(5*H*)-ones on stirring with phenacyl bromides yields 2,4-disubstituted thiazoles. X-ray structure of the intermediate compound 5-dimethyl-2-[(2-phenylhydrazinyl)methylene] cyclohexane-1,3-dione was determined.

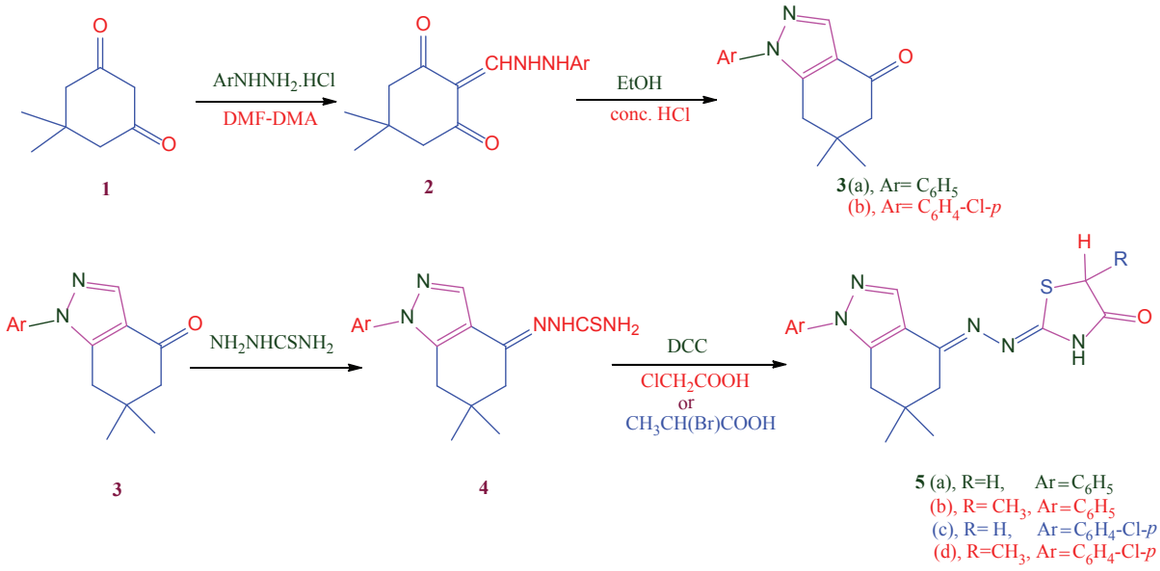
Keywords: cyclocondensation, thiazolidin-4-ones, thiazinan-4-ones, thiazoles, indazole, *N,N′*-dicyclohexylcarbodiimide

The pyrazole scaffold, in general, has drawn a good deal of attention due to its biological and pharmaceutical activities.[1,2] Indazoles, in particular, have been reported to possess antineoplastic activity. As examples, N^2-(substituted benzyl)-3-(4-methylphenyl)-2*H*-indazoles exhibit antiangiogenic activity,[3] pyrimidol[1,2-b]indazoles are potential anticancer agents and lonidamine, 1-(2,4-dichlorobenzyl)-1*H*-indazole-3-carboxylic acid is a new anticancer drug that selectively inhibits the metabolism of neoplastic cells. Thiazoles, 1,3-thiazinan-4-ones and thiazolidin-4-ones are the heterocyclic compounds with multiple applications and have long been known to be biologically active.[4,5] Thiazoles show very intensive antitumour activity especially the phenyl substituted benzothiazoles,[6] while 4-thiazolidinones and their derivatives exert antiviral activity.[7] These heterocycles have been reported to show a broad spectrum of biological activities,[8,9] and a wide range of pharmacological activities such as analgesic,[10] anticonvulsant,[11] and antitubercular[12] activities. Since the combination of pharmacophores on the same scaffold is a well-established approach to the synthesis of biologically more potent compounds, we decided to incorporate thiazole, thiazolodin-4-one and 1,3-thiazinan-4-one rings in the indazole moiety in an effort to synthesise new derivatives of indazoles. Various approaches for the synthesis of thiazolidin-4-ones and 1,3-thiazinan-4-ones are have been reported.[13] Nevertheless, a common synthetic strategy to construct thiazolidin-4-one and 1,3-thiazinan-4-one ring is the cyclisation of thiosemicarbazide derivatives with α-halo esters or acids and β-haloacids in presence of inorganic base (*i.e.* NaOAc) in polar solvents using either a conventional or microwave irradiation methods.[14,15] However, most of the reported procedures suffer from drawbacks of longer reaction times, use of hazardous solvents and moderate yields. In continuation of our research programme on synthesis of thiazolidin-4-ones[16,17] and 1,3-thiazinan-4-ones,[18] we now report the synthesis of new indazole derivatives containing bioactive moieties, thiazoles, thiazolidin-4-ones and thiazinan-4-ones, by using *N,N′*-dicyclohexylcarbodiimide (DCC) as the coupling agent in 50 min at 0 °C with excellent yields.

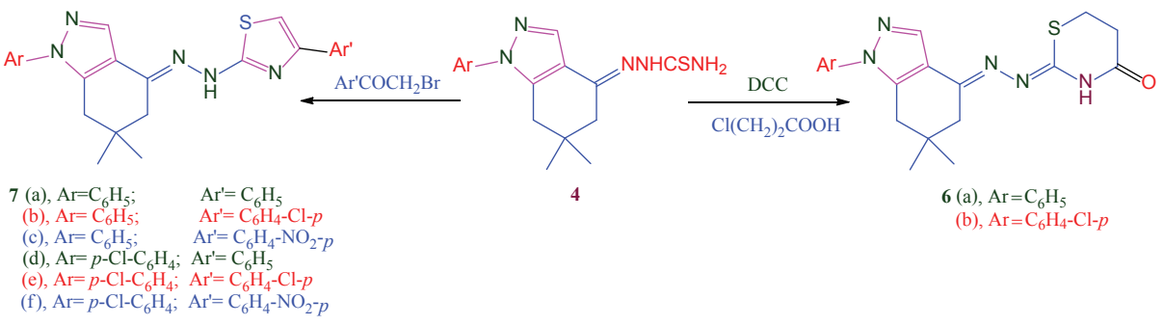
Results and discussion

Enaminoketones, obtained by the reaction of active methylene ketones with dimethylformamide dimethylacetal (DMF–DMA), gave a vast array of heterocyclic compounds with appropriate bidentate nucleophiles. Pyrazoles are generally prepared by reaction of enaminoketones with substituted hydrazines. The reaction is tandem addition–elimination/cyclodehydration, which takes place by a Michael addition of the terminal amino group of hydrazines to form acyclic intermediate **2** followed by intramolecular cyclodehydration to pyrazole derivative **3**. The synthesis of pyrazole **3a** has been reported by refluxing of enaminoketones in butanol or acetic acid[19] or through microwave irradiations[20] without isolation of the acyclic intermediate **2**. In the present investigations, it was found that heating of dimedone with DMF–DMA and phenyl hydrazine at 70 °C just for 5 min without any solvent yielded intermediate **2**, which on refluxing in ethanol for 2 h furnish pyrazoles **3**. The cyclodehydration of compound **2** to yield **3** also occurs during the synthesis of thiosemicarbazone derivative of **2**. The structure of **2a** and **2b** was established by spectral data. The crystal structure of **2a** (Ar=C_6H_5) is reported in the crystallography section of this paper. Pyrazoles **3a** and **3b** have been characterised by display of characteristic CH peak of pyrazole ring in ^{1}H NMR spectrum. Thiosemicarbazone derivative of pyrazole **3**, on condensation with α-or β-halo acids in presence of DCC and tetrahydrofuran (THF) furnished thiazolidin-4-ones **5** and thiazinan-4-ones **6** respectively (Schemes 1 and 2). Compounds **5** and **6** could also be obtained by conventional refluxing of thiosemicarbazones and haloacids in presence of sodium acetate and acetic acid for 6–12 h. In the present investigation, compounds **5** and **6** were assembled from reactants by DCC, as coupling agent, at 0 °C in just 50 min. The reaction was also carried out at room temperature in THF but the yield of products was less than at 0 °C. The ^{1}H NMR spectra of **5a** and **5c** display singlet of two protons each at δ 3.77 and δ 3.79, which is assigned to SCH_2 group of thiazolidin-4-one ring. The IR spectrum of **5a** and **5c** showed peaks at 1710 and 1715 cm^{-1} confirming the formation of thiazolidin-4-one ring. ^{1}H NMR spectrum of **5b** and **5d** display quartet of one proton at δ 4.03 and 4.04 and doublet of methyl group at δ 1.51 and δ 1.56 corroborated by their structures. IR, ^{13}C NMR and mass spectra of these compounds also supported the assigned structure. IR spectra of **6a** and **6b** display peaks at 1690 cm^{-1} and 1685 cm^{-1} which are assigned to carbonyl group of a six membered ring. ^{13}C NMR spectrum and mass support structure of **6a.** Similarly the structure of **6b** has been established by spectral and mass data. Thiosemicarbazone derivatives **4**, on condensation with phenacyl bromides yielded thiazoles **7** (Scheme 2). In compound **7a**, the appearance of a characteristic peak in ^{1}H NMR spectrum at δ 7.22 showed

* Correspondent. E-mail: rpchaudhary65@gmail.com



Scheme 1 Synthesis of 6,7-dihydro-1*H*-indazole-4(5*H*)-ones **3** and thiazolidin-4-ones **5** containing indazole moiety.



Scheme 2 Synthesis of 1,3-thiazinan-4-ones **6** and 2,4-disubstituted thiazoles **7** bearing 6,7-dihydro-1*H*-indazole moiety.

that thiazole ring has been formed. The structures of other thiazole derivatives (**7b–f**) have been established in similar fashion by analytical and spectral data.

Crystallography

X-ray diffraction measurements were performed on X Calibur EOS Oxford Diffractometer at 293 (2) K. The intensity data were collected using graphite monochromated Mo-Kα radiation (λ = 0.71073 Å). The structure was solved by direct method using the SHELX-97 software package[21] and refined by full-matrix least-squares procedures on F^2. All non-hydrogen atoms were refined with anisotropic thermal parameters.

The compound **2a** crystallises in the monoclinic space group C2/c, with Z = 8 and cell parameters a = 26.986(10) Å, b = 9.271(4) Å, c = 12.691(5) Å, α = 90.00°, β = 116.66(5)°, γ = 90.00°. In the compound, O(1)–C(12) and C–C(7) bond distances of 1.242(3) and 1.379(3) Å, respectively, indicate the double character of these bonds. The bond angles N2CC7 and O1C12C7 are 126.4° (2) and 122.1° (2) respectively, which is consistent with the sp^2 hybrid character of C and C12 atoms. The crystallographic data and refinement parameters of **2a** are shown in Fig. 1, and Tables 1 and 2.

Crystallographic data for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre and its CCDC No is 945437.

Table 1 Crystal data and the structure refinement of 5,5-dimethyl-2-[(2-phenylhydrazinyl)methylene]cyclohexane-1,3-dione (**2a**)

CCDC no.	945437
Empirical formula	$C_{15}H_{18}N_2O_2$
Formula weight	258.31
Temperature/K	293 (2)
Wavelength/Å	0.71073
Crystal system	Monoclinic
Space group	C2/c
Unit cell dimensions	
a/Å	26.986(10)
b/Å	9.271(4)
c/Å	12.691(5)
α/°	90.00
β/°	116.66(5)
γ/°	90.00
Volume/Å^3	2837.5(19)
Z	8
Density (calculated)/Mg m^{-3}	1.209
Absorption coefficient/mm^{-1}	0.081
Crystal size/mm^3	0.28×0.24×0.16
Theta range for data collection	3.1818 to 28.8377
Reflections collected	5,136
Independent reflections	1,378
Data/restraints/parameters	2868/0/173
Goodness-of-fit on F^2	1.011
Final R indices [I > 2σ(I) = 2591 data]	R^1 = 0.0579, wR^2 = 0.1475
R indices (all data)	R^1 = 0.1286, wR^2 = 0.1976
Largest diff. peak and hole/eÅ^{-3}	−0.326, 0.342

Table 2 Selected bond parameters of 5,5-dimethyl-2-[(2-phenylhydrazinyl)methylene]cyclohexane-1,3-dione (**2a**)

Bond	Length/Å	Bond	Angle/°
O(1)–C(12)	1.242(3)	C–N(2)–H(2)	119.5
N(2)–C	1.311(3)	N–N(2)–H(2)	119.5
N(2)–N	1.396(3)	N(2)–N–C(5)	116.4(2)
O–C(8)	1.239(3)	C(5)–N–H(0)	121.8
N–C(5)	1.414(3)	C(9)–C(5)–N	123.0(2)
C(5)–C(9)	1.373(4)	N(2)–C–C(7)	126.4(2)
C(5)–C(11)	1.394(3)	N(2)–C–H0(A)	116.8
C(7)–C(12)	1.449(3)	C(7)–C(8)–C(15)	118.9(2)
C(7)–C(8)	1.461(3)	C(5)–C(9)–C(13)	119.9(3)
C–C(7)	1.379(3)	C(7)–C–H0(A)	116.8
		O(1)–C(12)–C(7)	122.1(2)

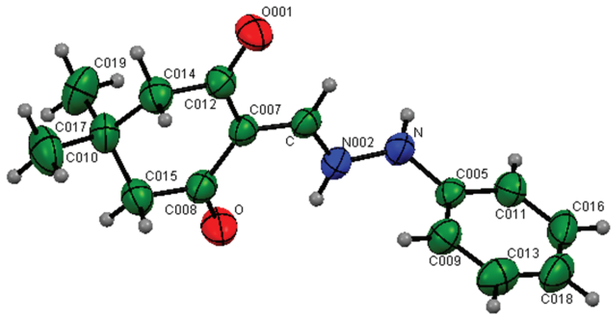


Fig. 1 ORTEP drawing and atomic labelling of 5,5-dimethyl-2-[(2-phenylhydrazinyl)methylene]cyclohexane-1,3-dione (**2a**) with displacement ellipsoids plotted at 50% probability level.

Experimental

All the chemicals used were obtained from Sigma and used without further purification. Melting points were determined in open capillaries and are reported uncorrected. Elemental analysis was done on a Euro EA 3000 elemental analyser. Mass spectra were recorded on Waters, Q-TOF Micromass (LC-MS) instrument. ^{1}H NMR and ^{13}C NMR were recorded in $CDCl_3$ and DMSO-d_6 on a Bruker Avance II 400 NMR spectrometer using tetramethylsilane (TMS) as an internal standard. The chemical shifts are reported in ppm. IR spectra were recorded on ABB FTIR spectrometer and the results are reported in cm^{-1}. TLC was performed on silica gel G coated plates and using iodine vapour as visualising agent. X-ray diffraction was performed on X Calibur EOS Oxford diffractometer.

Synthesis of **2***; general procedure*

A mixture of dimedone (0.7 g, 5 mmol) and DMF–DMA (1.19 mL, 10 mmol) was stirred at 70 °C for 2 min. Substituted hydrazine (4 mmol)) was then added to the reaction mixture and stirring continued for 5 min. The solid obtained was filtered, washed with benzene and recrystallised from ethanol.

5,5-Dimethyl-2-[(2-phenylhydrazinyl)methylene]cyclohexane-1,3-dione (**2a**): White crystalline solid, yield 81%, m.p. 168–169 °C; IR (cm^{-1}): 1690 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.00 (s, 6H, $2CH_3$), 2.28 (s, 2H, CH_2), 2.38 (s, 2H, CH_2), 6.72–6.74 (d, 2H, C_6H_5, J = 8.0 Hz), 6.85–6.88 (t, 1H, C_6H_5, J = 7.2 Hz), 7.24 (m, 2H, C_6H_5), 8.0 (s, 1H, CH), 9.0 (s, 1H, NH), 12.01 (s, 1H, NH); mass *m/z* 259.1($M+H^+$, 100%). Anal. calcd for $C_{15}H_{18}N_2O_2$: C, 69.74; H, 7.02; N, 10.84; found: C, 69.44; H, 6.65; N, 10.51%.

2-[{2-(4-Chlorophenyl)hydraziny}methylene]-5,5-dimethyl-cyclohexane-1,3-dione (**2b**): Yellow crystalline solid, yield 71%, m.p. 162–164 °C. IR (cm^{-1}): 1690 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.03 (s, 6H, $2CH_3$), 2.28 (s, 2H, CH_2), 2.39 (s, 2H, CH_2), 6.73–6.77 (m, 2H, C_6H_5), 7.20–7.24 (m, 2H, C_6H_5), 8.03–8.05 (d, 1H, CH, J = 8.0 Hz), 9.13 (s, 1H, NH), 12.08 (s, 1H, NH). Anal. calcd for $C_{15}H_{17}ClN_2O_2$: C, 61.54; H, 5.85; N, 9.57; found: C, 61.56; H, 5.78; N, 9.52%.

Synthesis of **3***; general procedure*

A mixture of **2** (0.625 mmol) in ethanol (5.0 mL) and 0.5 mL conc. HCl was refluxed for 3 h. The reaction mixture was then cooled to room temperature and poured in to ice cold water. The solid, obtained was filtered, dried and recrystallised from ethanol.

6,6-Dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-one (**3a**): White crystalline solid, yield 65%, m.p. 116–118 °C. IR (cm^{-1}): 1690 (C=O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (s, 6H, $2CH_3$), 2.43 (s, 2H, CH_2), 2.83 (s, 2H, CH_2), 7.42–7.46 (m, 1H, C_6H_5), 7.49–7.55 (m, 4H, C_6H_5), 8.08 (s, 1H, CH of pyrazole ring). Anal. calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66; found: C, 75.21; H, 6.82; N, 11.38%.

1-(4-Chlorophenyl)-6,6-dimethyl-6,7-dihydro-1H-indazol-4(5H)-one (**3b**): White crystalline solid, yield 81%, m.p. 126–128 °C. IR (cm^{-1}): 1690 (C=O); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.07 (s, 6H, $2CH_3$), 2.37 (s, 2H, CH_2), 2.91 (s, 2H, CH_2), 7.55–7.62 (m, 4H, C_6H_5), 8.16 (s, 1H, CH of pyrazole ring). Anal. calcd for $C_{15}H_{15}ClN_2O$: C, 65.57; H, 5.50; N, 10.20; found: C, 65.78; H, 5.12; N, 9.99%.

Synthesis of **4***; general procedure*

A mixture of **3** (1.0 mmol), thiosemicarbazide (0.09 g, 1.0 mmol) and 0.4 mL conc. HCl in absolute ethanol (10 mL) was stirred at room temperature for 3 h. The reaction mixture was poured into ice-cold water. The solid thus obtained was filtered, dried and recrystallised from ethanol.

2-[6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-yliden] hydrazinecarbothioamide (**4a**): White crystals, yield 90%, m.p. 180–182 °C. IR (cm^{-1}): 3433, 3256 (NH), 1582 (C=N), 1497 (C=C), 1288 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.05 (s, 6H, $2CH_3$), 2.56 (s, 2H, CH_2), 2.74 (s, 2H, CH_2), 7.38–7.39 (m, 1H, C_6H_5), 7.50–7.53 (m, 4H, C_6H_5), 7.69 (br, 1H, NH), 7.95 (br, 1H, NH), 8.09 (s, 1H, CH), 10.10 (br, 1H, NH). Anal. calcd for $C_{16}H_{19}N_5S$: C, 61.31; H, 6.11; N, 22.34; S, 10.23; found: C, 61.17; H, 5.96; N, 21.95; S, 10.31%.

2-[1-(4-chlorophenyl)-6,6-dimethyl-6,7-dihydro-1H-indazol-4(5H)-ylidene]hydrazinecarbothioamide (**4b**): White crystals yield 90%, m.p. 214–216 °C. IR (cm^{-1}): 3433, 3256 (NH), 1582 (C=N), 1497 (C=C), 1288 (C=S); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.03 (s, 6H, $2CH_3$), 2.75 (s, 2H, CH_2), 2.93 (s, 2H, CH_2), 7.50–7.56 (m, 4H, C_6H_5), 7.79 (br, 1H, NH), 8.12 (br, 1H, NH), 8.17 (s, 1H, CH), 10.20 (br, 1H, NH). Anal. calcd for $C_{16}H_{18}ClN_5S$: C, 55.24; H, 5.22; N, 20.13; S, 9.22; found: C, 55.46; H, 5.27; N, 20.36; S, 9.43%.

Syntheses of **5** *and* **6***; general procedure*

A mixture of thiosemicarbazone **4** (1.0 mmol), chloroacetic acid/2-bromopropionic acid or 3-chloropropionic acid (2.5 mmol) in THF (15 mL) was stirred at 0 °C for 5 min and then DCC (1.2 mmol) was added to the reaction mixture at 0 °C and reaction mixture was stirred for additional 50 min at room temp. The progress of the reaction was monitored by TLC. DCU was removed by filtration and the filtrate was concentrated to dryness under reduced pressure and the residue was taken up in ethyl acetate. The organic layer was successively washed with 10% aq. citric acid, water, 10% aq. sodium hydrogen carbonate and then finally with brine. The organic layer was dried over sodium sulphate and solvent was removed under reduced pressure to get a crude product, which was recrystallised from ethanol.

(E)-2-[(E)-{6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-ylidene}hydrazono]thiazolidin-4-one (**5a**): Yellow crystals, yield 72%, m.p. 190–192 °C. IR (cm^{-1}): 3742 (NH), 1710 (N–C=O), 1620 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.05 (s, 6H, $2CH_3$), 2.14 (s, 2H, CH_2), 2.47 (s, 2H, CH_2), 3.77 (s, 2H, SCH_2), 7.38–7.52 (m, 5H, C_6H_5), 8.57 (s, 1H, CH), 11.70 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 173.0 (C=O), 159.4 (C=N), 159.4 (C=N), 142.8, 142.4, 138.5, 128.8, 127.2, 123.2, 113.6 (C_6H_5), 44.8, 36.9, 33.4, 32.8, 27.4; mass *m/z* 354.1 ($M+H^+$, 100%). Anal. calcd for $C_{18}H_{19}N_5OS$: C, 61.17; H, 5.42; N, 19.81; S, 9.07; found: C, 61.49; H, 5.29; N, 19.61; S, 9.31%.

(E)-2-[(E)-{6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-ylidene}hydrazono]-5-methylthiazolidin-4-one (**5b**): White crystals, yield 75%, m.p. 208–210 °C. IR (cm^{-1}): 3342 (NH), 1705 (N–C=O), 1610 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.99 (s, 6H, $2CH_3$), 1.51–1.53 (d, 3H, CH_3, J = 7.2 Hz), 2.41 (s, 2H, CH_2), 2.73 (s, 2H, CH_2), 4.04–4.09 (q, 1H, H_A, J = 7.0 Hz, 7.2 Hz), 7.47–7.51 (m, 4H, C_6H_5), 8.52 (s, 1H, CH), 11.69 (br, 1H, NH); ^{13}C NMR(100 MHz, DMSO-d_6): δ 176.0 (C=O), 158.1 (C=N), 154.2 (C=N), 143.8, 142.4, 138.6, 129.8, 127.3, 123.3, 113.6 (C_6H_5), 44.8, 41.9, 36.8, 33.5, 27.4, 18.9; mass *m/z* 368.1 (M+H$^+$, 100%). Anal. calcd for $C_{19}H_{21}N_5OS$: C, 62.10; H, 5.76; N, 19.06; S, 8.73; found: C, 62.23; H, 5.81; N, 18.96; S, 8.83%.

(E)-2-[(E)-{1-(4-chlorophenyl)-6,6-dimethyl-6,7-dihydro-1H-indazol-4(5H)-ylidene}hydrazono]thiazolidin-4-one (**5c**): Yellow crystalline compound, yield 72%, m.p. 198–200 °C. IR (cm^{-1}): 3742 (NH), 1715 (N–C=O), 1620 (C=N) ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (s, 6H, $2CH_3$), 2.68 (s, 2H, CH_2), 2.70 (s, 2H, CH_2), 3.79 (s, 2H, SCH_2), 7.43–7.45 (m, 4H, C_6H_5), 8.03 (br, 1H, NH), 8.10 (s, 1H, NH); ^{13}C NMR(100 MHz, $CDCl_3$): δ 173.4 (C=O), 162.6, 160.8, 157.3 (C=N), 143.5, 142.7, 137.6, 137.3, 133.17, 129.4, 124.9, 117.6 (C_6H_5), 45.4, 39.4, 39.2, 37.6, 36.5, 34.0, 33.9, 31.4, 28.4, 27.9; mass *m/z* 388.1 (M+H$^+$, 100%). Anal. calcd for $C_{18}H_{18}ClN_5OS$: C, 55.74; H, 4.68; N, 18.06; S, 8.27; found: C, 55.61; H, 4.78; N, 18.21; S, 8.34%.

(E)-2-[(E)-{1-(4-chlorophenyl)-6,6-dimethyl-6,7-dihydro-1H-indazol-4(5H)-ylidene}hydrazon]-5-methylthiazolidin-4-one (**5d**): White crystals, yield 75%, m.p. 194–196 °C. IR (cm^{-1}): 3342 (NH), 1705 (N–C=O), 1610 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.04 (s, 6H, $2CH_3$), 1.56–1.58 (d, 3H, CH_3, J = 6.9 Hz), 2.45 (s, 2H, CH_2), 2.75 (s, 2H, CH_2), 4.03–4.08 (q, 1H, H_A, J = 7.1 Hz, 6.9 Hz), 7.52–7.53 (d, 4H, C_6H_5, J = 5.0 Hz), 8.57 (s, 1H, CH), 11.68 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 176.0 (C=O), 158.1 (C=N), 154.2 (C=N), 143.8, 142.4, 138.6, 129.8, 127.3, 123.3, 113.6 (C_6H_5), 44.8, 41.9, 36.8, 33.5, 27.4, 18.9; mass *m/z* 402.1 (M+H$^+$, 100%). Anal. calcd for $C_{19}H_{20}ClN_5OS$: C, 56.78; H, 5.02; N, 17.43; S, 7.98; found: C, 56.78; H, 4.88; N, 17.39; S, 7.92%.

(E)-2-[(E)-{6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-ylidene}hydrazono]-1,3-thiazinan-4-one (**6a**): Light yellow crystals, yield 55%, m.p. 218–220 °C. IR (cm^{-1}): 3241 (NH), 1690 (N–C=O), 1595 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (s, 6H, $2CH_3$), 2.53 (m, 2H, CH_2), 2.77 (m, 4H, CH_2), 3.07 (s, 2H, CH_2), 7.50 (s, 1H, C_6H_5), 7.52–7.57 (m, 4H, C_6H_5), 8.74 (s, 1H, CH), 11.13 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.9 (C=O), 154.9 (C=N), 154.2 (C=N), 142.9, 142.9, 138.7, 129.0, 129.0, 127.3, 123.3, 122.7, 113.54 (C_6H_5), 44.9, 36.9, 33.9, 33.4, 28.0, 27.4, 21.9; mass *m/z* 368.1 (M+H$^+$, 100%). Anal. calcd for $C_{19}H_{21}N_5OS$: C, 62.10; H, 5.76; N, 19.06; S, 8.73; found: C, 61.47; H, 5.41; N, 18.91; S, 8.43%.

(E)-2-[(E)-{1-(4-chlorophenyl)-6,6-dimethyl-6,7-dihydro-1H-indazol-4(5H)-ylidene}hydrazono]-1,3-thiazinan-4-one (**6b**): Light yellow crystals, yield 55%, m.p. 210–212 °C. IR (cm^{-1}): 3265 (NH), 1685 (N–C=O), 1605 (C=N); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.04 (s, 6H, $2CH_3$), 2.41 (m, 2H, CH_2), 2.75–2.78 (m, 4H, CH_2), 3.06 (s, 2H, CH_2), 7.51–7.58 (m, 4H, C_6H_5), 8.74 (s, 1H, CH), 11.11 (br, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 169.9 (C=O), 155.2 (C=N), 154.0 (C=N), 143.1, 143.1, 137.5, 132.0, 129.2, 129.1, 124.8, 113.8, (C_6H_5), 44.9, 36.8, 33.9, 33.4, 27.4, 21.9; mass *m/z* 402.1 (M+H$^+$, 100%). Anal. calcd for $C_{19}H_{20}ClN_5OS$: C, 56.78; H, 5.02; N, 17.43; S, 7.98; found: C, 56.96; H, 5.12; N, 17.56; S, 8.26%.

Synthesis of **7***; general procedure*

A mixture of **4** (0.5 mmol) and phenacyl bromides (0.5 mmol) in 5.0 mL ethanol was stirred at room temperature for 15 minutes. The separated solid was filtered, dried and recrystallised from ethanol.

(E)-2-[2-{6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-yliden}hydrazinyl]-4-phenylthiazole (**7a**): Orange crystals, yield 80%, m.p. 208–210 °C. IR (cm^{-1}): 3112 (NH), 1601 (C=N), 1494 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (s, 6H, $2CH_3$), 2.63 (s, 2H, CH_2), 2.77 (s, 2H, CH_2), 7.22 (s, 1H, CH of thiazole ring), 7.35–7.46 (m, 4H, C_6H_5), 7.51–7.59 (m, 4H, C_6H_5), 7.79–7.81 (m, 2H, C_6H_5), 8.01 (s, 1H, CH), 8.24–8.26 (d, 2H, C_6H_4, J = 8.9 Hz); mass *m/z* 414.2 (M+H$^+$, 100%). Anal. calcd for $C_{24}H_{23}N_5S$: C, 69.71; H, 5.61; N, 16.94; S, 7.75; found: C, 69.88; H, 5.78; N, 17.12; S, 7.92%.

(E)-4-(4-chlorophenyl)-2-[2-{6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-ylidene}hydrazinyl]thiazole (**7b**): Yellow solid, yield 78%, m.p. 212–215 °C. IR (cm^{-1}): 3112 (NH), 1601 (C=N), 1494 (C=C), 728 (C–Cl); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (s, 6H, $2CH_3$), 2.60 (s, 2H, CH_2), 2.77 (s, 2H, CH_2), 7.13 (s, 1H, CH of thiazole ring), 7.38–7.40 (m, 3H, C_6H_5), 7.52–7.53 (m, 4H, C_6H_5), 7.80–7.82 (m, 2H, C_6H_5), 7.94 (s, 1H, CH), 8.00 (br, 1H, NH). Anal. calcd for $C_{24}H_{22}ClN_5S$: C, 64.35; H, 4.95; N, 15.63; S, 7.16; found: C, 64.48; H, 5.19; N, 15.88; S, 7.02%.

(E)-2-[2-{6,6-dimethyl-1-phenyl-6,7-dihydro-1H-indazol-4(5H)-ylidene}hydrazinyl]-4-(4-nitrophenyl)thiazole (**7c**): Orange solid, yield 72%, m.p. 210–212 °C. IR (cm^{-1}): 3342 (NH), 1641 (C=N), 1494 (C=C), 1558, 1328 (NO_2), 1509 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.09 (s, 6H, $2CH_3$), 2.57 (s, 2H, CH_2), 2.77 (s, 2H, CH_2), 7.43 (s, 1H, C_6H_5), 7.52 (s, 1H, CH of thiazole ring), 7.53 (m, 4H, C_6H_5), 8.01 (s, 1H, CH), 8.08–8.09 (d, 2H, C_6H_4, J = 6.9 Hz), 8.24–8.26 (d, 2H, C_6H_4, J = 8.9 Hz). Anal. calcd for $C_{24}H_{22}N_6O_2S$: C, 62.86; H, 4.84; N, 18.33; S, 6.99; found: C, 62.57; H, 4.88; N, 18.42; S, 6.88%.

(E)-2-[2-{1-(4-chlorophenyl)-6,6-dimethyl-6,7-dihydro-1H-indazol-4(5H)-ylidene}hydrazinyl]-4-phenylthiazole (**7d**): Black compound, yield 80%, m.p. 190–192 °C. IR (cm^{-1}): 3115 (NH), 1610 (C=N), 1501 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.90 (s, 6H, $2CH_3$), 2.63 (s, 2H, CH_2), 2.79 (s, 2H, CH_2), 7.14 (s, 1H, CH of thiazole ring), 7.38–7.49 (m, 4H, C_6H_5), 7.50–7.54 (m, 4H, C_6H_5), 7.70–7.71 (m, 1H, C_6H_5), 8.02 (s, 1H, CH). Anal. calcd for $C_{24}H_{22}ClN_5S$: C, 64.35; H, 4.95; N, 15.63; S, 7.16; found: C, 64.55; H, 5.13; N, 15.78; S, 7.32%.

(E)-4-(4-chlorophenyl)-2-[2-{1-(4-chlorophenyl)-6,6-dimethyl-6,7-dihydro-1H-indazol-4(5H)-ylidene}hydrazinyl]thiazole (**7e**): Yellow compound, yield 80%, m.p. 202–204 °C. IR (cm^{-1}): 3118 (NH), 1615 (C=N), 1510 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.03 (s, 6H, $2CH_3$), 2.49 (s, 2H, CH_2), 2.69 (s, 2H, CH_2), 7.20 (s, 1H, CH of thiazole ring), 7.37–7.58 (m, 4H, C_6H_5), 7.83–7.90 (m, 4H, C_6H_5), 7.93 (s, 1H, CH). Anal. calcd for $C_{24}H_{21}Cl_2N_5S$: C, 59.75; H, 4.39; N, 14.52; S, 6.65; found: C, 59.71; H, 4.63; N, 14.69; S, 6.59%.

(E)-2-[2-{1-(4-chlorophenyl)-6,6-dimethyl-6,7-dihydro-1H-indazol-4(5H)-ylidene}hydrazinyl]-4-(4-nitrophenyl)thiazole (**7f**): Yellow compound, yield 80%, m.p. > 240 °C. IR (cm^{-1}): 3120 (NH), 1618 (C=N), 1512 (C=C); ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.04 (s, 6H, $2CH_3$), 2.49 (s, 2H, CH_2), 2.71 (s, 2H, CH_2), 7.25 (s, 1H, CH of thiazole ring), 7.39–7.59 (m, 4H, C_6H_5), 7.84–7.91 (m, 4H, C_6H_5), 7.98 (s, 1H, CH). Anal. calcd for $C_{24}H_{21}ClN_6O_2S$: C, 58.47; H, 4.29; N, 17.05; S, 6.50; found: C, 58.63; H, 4.41; N, 16.89; S, 6.38%.

Electronic supplementary information

NMR and mass spectra of the new compounds are available through:
stl.publisher.ingentaconnect.com/content/stl/jcr/supp-data.

The facilities provided by authorities of Sant Longowal Institute of Engineering and Technology, Longowal are gratefully acknowledged. We are thankful to Prof. S. Bhattacharya, BHU, Varanasi for crystallographic studies.

Received 18 December 2013; accepted 12 February 2014
Paper 1302355 doi: 10.3184/174751914X13940194215183
Published online: 2 April 2014

References

1 L.C. Behr, R. Fusco and C.H. Jarboe, *Pyrazoles, pyrazolines, pyrazolidines, indazoles and condensed rings.* Wiley-Interscience Publishers, New York, 1967.

2 J. Elguero, A.R. Katritzky and C.W. Rees, eds, *Comprehensive heterocyclic chemistry.* Pergamon, Oxford, 1984, Vol. 5, 167.

3 H.L. Jiau, S.M. Ling, C.H. Sin, P.S. Lin, T.C. Ming, L.F. Yu and L.S. Chu, *Bioorg. Med. Chem.,* 2006, **14**, 528.

4 K. Tsuji and H. Ishikawa, *Bioorg. Med. Chem. Lett.,* 1994, **4**, 1601.

5 G. Capan, N. Ulusoy, N. Ergenc and M. Kiraz, *Monatsh Chem.,* 1999, **130**, 1399.

6 A. Furlan, F. Colombo, A. Kover, N. Issaly, C. Tintori, L. Angeli, V. Leroux, S. Letard, M. Amat, Y. Asses, B. Maigret, P. Dubreuil, M. Botta, R. Dono, J. Bosch, O. Piccolo, D. Passarella and F. Maina, *Eur. J. Med. Chem.,* 2012, **47**, 239.

7 G. Stamatiou, A. Kolokouris, N. Kolocouris, G. Fytas, G.B. Foscolos, J. Neyts and E.D. Clercq, *Bioorg. Med. Chem. Lett.,* 2001, **11**, 2137.

8 K. Liu, W. Rao, H. Parikh, Q. Li, L.G. Tai, S. Grant, G.E. Kellogg and S. Zhang, *Eur. J. Med. Chem.,* 2012, **47**, 125.

9 D. Havrylyuk, L. Mosula, B. Zimenkovsky, O. Vasylenko, A. Gzella and R. Lesyk, *Eur. J. Med. Chem.,* 2010, **45**, 5012.

10 R.P. Tenorio, C.S. Carvalho, C.S. Pessanha, J.G. Lima de, A.R. Faria de, A.J. Alves, E.J.T. Melo-de and A.J.S. Góe, *Bioorg. Med. Chem. Lett.,* 2005, **15**, 2575.

11 K. Omar, A. Geronikaki, P. Zoumpoulakis, C. Camoutsis, M. Sokovic, A. Ciric and J. Glamoclija, *Bioorg. Med. Chem.,* 2010, **18**, 426.

12 V.V. Kachhadia, M.R. Patel and H.S. Joshi, *J. Serb. Chem. Soc.,* 2005, **70**, 153.

13 D.P. Gouvea, V.D.O. Bareno and J. Bosenbecker, *Ultrason. Sonochem.,* 2012, **19**, 1127.

14 X. Li, T. Qin and T. Yang, *Bioorg. Med. Chem. Lett.,* 2012, **22**, 2712.

15 K.M. Souad, D. Ayada, P. Ludovic, H. Jack and R. Mustapha, *Molecules,* 2006, **11**, 597.

16 R. Gupta and R.P. Chaudhary, *J. Chem. Res.,* 2012, **36**, 718.

17 R. Gupta and R.P. Chaudhary, *Phosphorus Sulfur Silicon Relat. Elem*., 2012, **187**, 735.

18 D. Gautam, P. Gautam and R.P. Chaudhary, *Heterocycl. Commun.,* 2013, **19**, 43.

19 P. Schenone, L. Mosti and G. Menozzi, *J. Heterocycl. Chem.,*1982, **19**, 1355.

20 V. Molteni, M.M. Hamilton, L. Mao, M.C. Crane, P.A. Termin and M.D. Wilson, *Synthesis*, 2002, **12**, 1669.

21 G.M. Sheldrick, SHELXTL-97, *Program for Refinement of Crystal Structure*, 1997, University of Gottingen, Gottingen, Germany.