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Double Michael adducts: Source for spiro heterocycles

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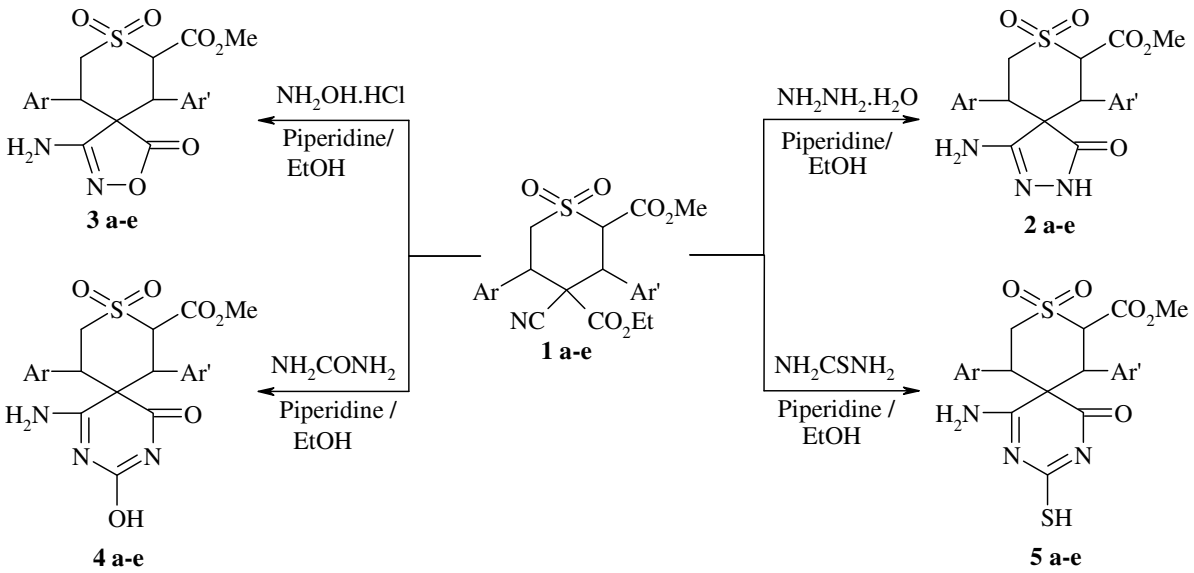
The *gem* cyano ester functionality in double Michael adduct, 4-carboethoxy-2-carbomethoxy-4-cyano-3,5-diaryltetrahydro[2*H*]thiopyran-1,1-dioxide **1** has been exploited to develop three different types of spiro heterocycles *viz.,* spiro pyrimidine, pyrazole and isoxazole derivatives in the presence of appropriate nucleophiles.

Keywords: Spiro-pyrimidines, spiro-pyrazoles, spiro-isoxazoles, cyclocondensation, piperidine.

Over the years pyrazoles, isoxazoles and pyrimidines have emerged as interesting heterocycles with a wide range of applications in pharmaceutical chemistry. Barbituric acid and its derivatives are known as sedatives and hypnotics since a long time. Substituted barbituric and thiobarbituric acids show analgesic, antipyretic and anti-inflammatory activities[1]. Spiro cyclohexano barbituric acid and thiobarbituric acids are also used as hypnotics, convulsants, transquilizers for fish, plant growth regulators, fungicides and sedatives[2,3]. Similarly, pyrazolidine derivatives are effective in the treatment of rheumatoid arthritis and allied conditions[4]. Isoxazoline derivatives possess potent antithrombic effect and improved pharmacokinetic properties[5]. In fact, a variety of pyrazole and isoxazole derivatives exhibit COX-I/COX-II inhibiting activity. It is found that Valdecoxib, a diaryl isoxazole derivative, a sedative COX-II inhibitor has no effect on platelet aggregation and does not reduce increased PG levels in cerebrospinal fluid[6]. Besides, the spiro-isoxazoline motif is present in a number of biologically active natural products *viz.,* 11-deoxyfistularin-3 and 11-oxoaerothionin which exhibit activity against human breast[1] and human colon cancers[7], respectively. Besisdes, spiro heterocyclic compounds exhibit structural rigidity because of conformational restriction. The spirocarbon induces a relatively large steric strain and hence undergoes rearrangement reactions yielding to unexpected heterocycles[8]. Recent experiences from our laboratory have permitted an extension of general methods for the synthesis of some asymmetric spiro heterocycles exploiting the relationship between Michael acceptors and Michael donors[9-12]. In a continuing quest for further ways of utilizing Michael adducts, the present work has been taken up.

Results and Discussion

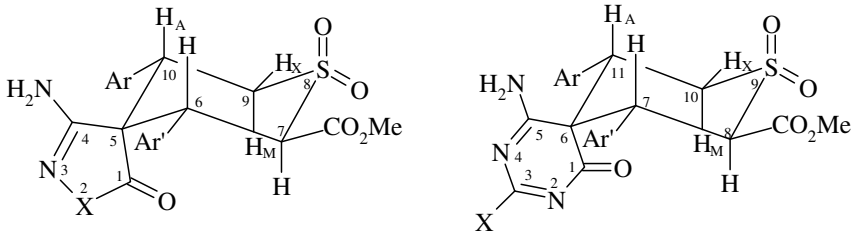
The synthetic intermediate 4-carboethoxy-2-carbomethoxy-4-cyano-3,5-diaryltetrahydro[2*H*]thiopyran-1,1-dioxide **1** was prepared by the double Michael addition of ethyl cyanoacetate to methyl 3-aryl-2-[(*Z*-aryl)ethene-sulfonyl]acrylate in the presence of Triton-B, in toluene[13]. The *gem* cyano ester functionality in **1** was utilized to develop spiro heterocycles. Cyclo-condensation of **1** with hydrazine hydrate and hydroxylamine hydrochloride in the presence of piperidine in ethanol led to the formation of spiro heterocyclic compounds, 4-amino-6,10-diaryl-7-carbomethoxy-8-thia-2,3-diazaspiro-[4.5]decan-3-en-1-one-8,8-dioxide **2** and 4-amino-6,10-diaryl-7-carbomethoxy-8-thia-2-oxa-3-azaspiro [4.5]decan-3-en-1-one-8,8-dioxide **3**. Similar cyclo-condensations of **1** with urea and thiourea produced 5-amino-7,11-diaryl-8-carbomethoxy-3-hydroxy-9-thia-2, 4-diazaspiro[5.5]-undecane-2,4-dien-1-one-9,9-dioxide **4** and 5-amino-7,11-diaryl-8-carbomethoxy-3-mercapto- 9-thia-2,4-diazaspiro[5.5]-undecane-2, 4-dien-1-one-9, 9-dioxide **5**, respectively (**Scheme I**). The IR spectra of **2**-**5** displayed absorption bands at 1132-1145 and 1322-1342 (SO_2), 1602-1615 (C=N), 1654-1712 (CO of heterocyclic ring), 1733-1745 (CO_2Me), 3349-3365 and 3450-3478 cm^{-1} (NH_2). In addition to these, compound **2** exhibited an absorption band at 3324-3335 (NH), compound **4** at 3308-3318 (OH) and compound **5** at 2556-2566 cm^{-1} (SH). The ^1H NMR spectra of **2**-**5** can be rationalized by presuming that the two aryl groups at C-6 and C-10 in **2** and **3** and at



Ar
(a) Ph
(b) 4-Me.Ph
(c) 4-Cl.Ph
(d) Ph
(e) 4-Me.Ph

Ar'
(a) Ph
(b) 4-Me.Ph
(c) 4-Cl.Ph
(d) 4-Me.Ph
(e) 4-Cl.Ph

Scheme I



X = NH / O **X = OH / SH**

Figure 1

C-7 and C-11 in **4** and **5** are in *cis* 1,3-diequatorial arrangement in the preferred rigid chair conformation of thiandioxide moiety. Whereas pyrazole, isoxazole and pyrimidine rings which are nearly planar would be perpendicular to the average plane of thiandioxide ring (**Figure 1**) (Ref 14). The ^{1}H NMR spectra of **2a** and **3a** showed three double doublets at δ 4.18, 4.22 (H_A), 3.69, 3.64 (H_M) and 3.21, 3.25 (H_X). Their coupling constant values were found to be J_{AM} = 10.2, 10.5; J_{AX} = 5.3, 5.5 and J_{MX} = 15.2, 15.6 Hz. Additionally, two doublets were also observed at δ 4.60, 4.54 (C_6-H), 4.07, 4.14 (C_7-H) in **2a** and **3a**, respectively. The coupling constant values J = 14.2, 14.5 Hz indicated that they are in *trans* geometry. In addition, a singlet was observed at δ 3.56 in **2a** and at δ 3.55 in **3a** due to methoxy protons and another broad singlet at δ 5.72 in **2a** and at δ 5.81 in **3a** due to NH_2. Apart from these, a broad singlet was observed at δ 10.51 in **2a** for NH. The ^{1}H NMR spectra of **4a** and **5a** exhibited three double doublets at δ 4.35, 4.45 (H_A), 3.61, 3.72 (H_M) and 3.18, 3.21 (H_X) (J_{AM} = 10.4, 10.3; J_{AX} = 5.0, 5.3 and J_{MX} = 15.7, 15.6 Hz), two doublets at δ 4.61, 4.69 (C_7-H), 4.14, 4.12 (C_8-H) (J = 13.5, 14.1 Hz) and a singlet at δ 3.53, 3.59 (CO_2Me) respectively. Two broad singlets were observed at δ 5.87 and 6.90 due to NH_2 and OH in **4a** and at δ 5.78 and 1.38 due to NH_2 and SH in **5a**. The signals due to OH, NH and NH_2 disappeared on deuteration.

Similarly, structures of all the new compounds **2**-**5** were also ascertained by ^{13}C NMR spectra.

Experimental Section

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The homogeneity of the compounds was checked by TLC (silica gel H, BDH, hexane/ethyl acetate, 3:1). The IR spectra were run on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wave numbers were given in cm^{-1}. The ^1H NMR spectra were recorded in DMSO-d_6, on a Jeol JNM λ-400 MHz spectrometer. The ^{13}C NMR spectra were recorded in DMSO-d_6, on a Jeol JNM spectrometer at 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. The starting compound 2-carbomethoxy-4-cyano-4- carboethoxy-3,5-diaryltetrahydrothiopyran-1,1-dioxide **1** was prepared by the literature procedure[15].

General procedure for the synthesis of compound 2

To a solution of compound **1** (1 mmol) in ethanol (20 mL), hydrazine hydrate (1.5 mmol) and piperidine (3 mL) were added and refluxed for 5-7 hr. On completion of the reaction (TLC), the reaction mixture was extracted with ethyl acetate (20 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The resultant solid was purified by recrystallization from ethanol.

4-Amino-6,10-diaryl-7-carbomethoxy-8-thia-2,3-diazaspiro[4.5]decan-3-en-1-one-8,8-dioxide, 2a: White solid, yield 67%, m.p. 147-49°C. IR (KBr): 1144, 1339 (SO_2), 1608 (C=N), 1659 (*CO*-NH), 1740 (CO_2Me), 3324 (NH), 3362, 3474 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.21 (dd, 1H, H_X, J_{AX} = 5.3 Hz, J_{MX} = 15.2 Hz), 3.56 (s, 3H, OCH_3), 3.69 (dd, 1H, H_M), 4.07 (d, 1H, C_7-H), 4.18 (dd, 1H, H_A, J_{AM} = 10.2 Hz), 4.60 (d, 1H, C_6-H, *J*=14.2 Hz), 5.72 (bs, 2H, NH_2), 7.05- 7.60 (m, 10H, Ar-H), 10.51 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.6 (C-6), 26.5 (C-10), 51.0 (CO_2CH_3), 55.7 (C-9), 58.6 (C-7), 66.7 (C-5), 165.1 (C-4), 173.8 (C=O), 191.3 (C-1), 126.1, 127.4, 128.5, 129.1, 129.8, 131.0, 132.4, 133.6 (aromatic carbons). Anal. Calcd for $C_{21}H_{21}N_3O_5S$: C, 59.00; H, 4.95; N, 9.83. Found: C, 59.05; H, 4.97; N, 9.90%.

4-Amino-6,10-di(*p*-methylphenyl)-7-carbomethoxy-8-thia-2, 3-diazaspiro-[4.5]decan-3-en-1-one-8,8-dioxide, 2b: White solid, yield 71%, m.p. 170-72°C. IR (KBr): 1138, 1340 (SO_2), 1613 (C=N), 1662 (*CO*-NH), 1745 (CO_2Me), 3329 (NH), 3355, 3478 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.21, 2.29 (s, 6H, Ar-CH_3 and Ar′-CH_3), 3.16 (dd, 1H, H_X, J_{AX} = 5.1 Hz, J_{MX} = 15.1 Hz), 3.49 (s, 3H, OCH_3), 3.56 (dd, 1H, H_M), 4.10 (d, 1H, C_7-H), 4.20 (dd, 1H, H_A, J_{AM} = 10.1 Hz), 4.54 (d, 1H, C_6-H, *J*=14.0 Hz), 5.64 (bs, 2H, NH_2), 7.09- 7.54 (m, 8H, Ar-H), 10.56 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 19.7 (Ar-CH_3 and Ar′CH_3), 24.1 (C-6), 26.9 (C-10), 50.8 (CO_2CH_3), 56.3 (C-9), 59.4 (C-7), 66.9 (C-5), 166.3 (C-4), 174.2 (C=O), 190.5 (C-1), 126.4, 127.2, 128.1, 128.6, 129.2, 130.0, 133.1, 131.4 (aromatic carbons). Anal. Calcd for $C_{23}H_{25}N_3O_5S$: C, 60.64; H, 5.53; N, 9.22. Found: C, 60.71; H, 5.52; N, 9.31%.

4-Amino-6, 10-di(*p*-chlorophenyl)-7-carbomethoxy-8-thia-2, 3-diazaspiro-[4.5]decan-3-en-1-one-8,8-dioxide, 2c: White solid, yield 74%, m.p. 176-78°C. IR (KBr): 1139, 1328 (SO_2), 1610 (C=N), 1657 (*CO*-NH), 1742 (CO_2Me), 3330 (NH), 3361, 3476 (NH_2); cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.22 (dd, 1H, H_X, J_{AX} = 5.5 Hz, J_{MX} = 15.4 Hz), 3.52 (s, 3H, OCH_3), 3.62 (dd, 1H, H_M), 4.15 (d, 1H, C_7-H), 4.21 (dd, 1H, H_A, J_{AM} = 10.4 Hz), 4.53 (d, 1H, C_6-H, *J*=14.5 Hz), 5.76 (bs, 2H, NH_2), 7.11- 7.75 (m, 8H, Ar-H), 10.62 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.3 (C-6), 27.6 (C-10), 51.5 (CO_2CH_3), 56.5 (C-9), 59.3 (C-7), 67.4 (C-5), 166.9 (C-4), 174.4 (C=O), 190.9 (C-1), 127.0, 127.8, 128.4, 129.3, 130.9, 132.3, 133.2, 135.1 (aromatic carbons). Anal. Calcd for $C_{21}H_{19}Cl_2N_3O_5S$: C, 50.81; H, 3.86; N, 8.47. Found: C, 50.77; H, 3.89; N, 8.53%

4-Amino-6-(*p*-methylphenyl)-10-phenyl-7-carbomethoxy-8-thia-2,3-diazaspiro[4.5]decan-3-en-1-one-8,8-dioxide, 2d: White solid, yield 65%, m.p. 169-71°C. IR (KBr): 1145, 1336 (SO_2), 1604 (C=N), 1654 (*CO*-NH), 1741 (CO_2Me), 3335 (NH), 3364, 3478 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.32 (s, 3H, Ar′-CH_3), 3.20 (dd, 1H, H_X, J_{AX} = 5.2 Hz, J_{MX} = 15.5 Hz), 3.50 (s, 3H, OCH_3), 3.60 (dd, 1H, H_M), 4.12 (d, 1H, C_7-H), 4.18 (dd, 1H, H_A, J_{AM} = 10.3 Hz), 4.48 (d, 1H, C_6-H, *J* = 14.3 Hz), 5.80 (bs, 2H, NH_2), 7.06-7.59 (m, 9H, Ar-H), 10.58 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.6 (Ar′-CH_3), 23.8 (C-6), 28.4 (C-10), 52.2 (CO_2CH_3), 56.9 (C-9), 59.7 (C-7), 66.8 (C-5), 166.6 (C-4), 174.7 (C=O), 191.4 (C-1), 126.9, 127.6, 128.3, 129.6, 130.4, 131.7, 133.2, 135.8 (aromatic carbons). Anal. Calcd for $C_{22}H_{23}N_3O_5S$: C, 59.85; H, 5.25; N, 9.52. Found: C, 59.89; H, 5.29; N, 9.57%.

4-Amino-6-(*p*-chlorophenyl)-10-(*p*-methylphenyl)-7-carbomethoxy-8-thia-2,3-diazaspiro[4.5]decan-3-en-1-one-8,8-dioxide, 2e: White solid, yield 72%. m.p. 165-67°C. IR (KBr): 1140, 1342 (SO_2), 1615 (C=N), 1661 (*CO*-NH), 1739 (CO_2Me), 3331 (NH), 3358, 3472 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.24 (s, 3H, Ar-CH_3), 3.18 (dd, 1H, H_X, J_{AX} = 5.8 Hz, J_{MX} = 15.4 Hz), 3.53 (s, 3H, OCH_3), 3.58 (dd, 1H, H_M), 4.09 (d, 1H, C_7-H), 4.20 (dd, 1H, H_A, J_{AM} = 10.1 Hz), 4.51 (d, 1H, C_6-H, J = 14.1 Hz), 5.74 (bs, 2H, NH_2), 7.10-7.77 (m, 8H, Ar-H), 10.60 (bs, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.3 (Ar-CH_3), 24.6 (C-6), 28.0 (C-10), 52.6 (CO_2CH_3), 57.4 (C-9), 59.0 (C-7), 67.3 (C-5), 167.1 (C-4), 173.6 (C=O), 191.8 (C-1), 127.3, 128.6, 129.1, 129.9, 131.3, 132.8, 133.5, 136.5 (aromatic carbons). Anal. Calcd for $C_{22}H_{22}ClN_3O_5S$: C, 55.52; H, 4.66; N, 8.83. Found: C, 55.50; H, 4.68; N, 8.80%.

General procedure for the synthesis of compound 3

A mixture of compound **1** (1 mmol), hydroxylamine hydrochloride (1.0 mmol), ethanol (20 mL) and piperidine (3 mL) was refluxed for 7-9 hr. On completion of the reaction (TLC), the reaction mixture was extracted with ethyl acetate (20 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and the solvent was removed under *vacuum*. The resultant solid was purified by recrystallization from ethanol.

4-Amino-6,10-diaryl-7-carbomethoxy-8-thia-2-oxa-3-azaspiro[4.5]decan-3-en-1-one-8,8-dioxide, 3a: White solid, yield 66%, m.p. 171-73°C. IR (KBr): 1141, 1326 (SO_2), 1610 (C=N), 1708 (*CO*-O), 1736 (CO_2Me), 3363, 3475 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.25 (dd, 1H, H_X, J_{AX} = 5.5 Hz, J_{MX} = 15.6 Hz), 3.55 (s, 3H, OCH_3), 3.64 (dd, 1H, H_M), 4.14 (d, 1H, C_7-H), 4.22 (dd, 1H, H_A, J_{AM} = 10.5 Hz), 4.54 (d, 1H, C_6-H, J = 14.5 Hz), 5.81 (bs, 2H, NH_2), 7.13-7.73 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.2 (C-6), 27.4 (C-10), 51.4 (CO_2CH_3), 56.5 (C-9), 59.3 (C-7), 66.9 (C-5), 164.5 (C-4), 173.9 (C=O), 192.4 (C-1), 126.4, 127.5, 128.2, 129.4, 130.0, 130.8, 132.5, 134.4 (aromatic carbons). Anal. Calcd for $C_{21}H_{20}N_2O_6S$: C, 58.87; H, 4.70; N, 6.54. Found: C, 58.90; H, 4.71; N, 6.60%.

4-Amino-6,10-di(*p*-methylphenyl)-7-carbomethoxy-8-thia-2-oxa-3-azaspiro-[4.5]decan-3-en-1-one-8, 8-dioxide, 3b: White solid, yield 70%. m.p. 190-92°C. IR (KBr): 1135, 1333 (SO_2), 1602 (C=N), 1710 (*CO*-O), 1738 (CO_2Me), 3357, 3472 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.20, 2.27 (s, 6H, Ar-CH_3 and Ar′-CH_3), 3.20 (dd, 1H, H_X, J_{AX} = 5.2 Hz, J_{MX} = 15.6 Hz), 3.51 (s, 3H, OCH_3), 3.60 (dd, 1H, H_M), 4.10 (d, 1H, C_7-H), 4.21 (dd, 1H, H_A, J_{AM} = 10.3 Hz), 4.51 (d, 1H, C_6-H, J = 14.2 Hz), 5.75 (bs, 2H, NH_2), 7.11-7.68 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.6 (Ar-CH_3 and Ar′CH_3), 23.9 (C-6), 26.9 (C-10), 51.0 (CO_2CH_3), 56.1 (C-9), 59.0 (C-7), 67.4 (C-5), 164.0 (C-4), 174.1 (C=O), 191.2 (C-1), 127.2, 128.6, 129.4, 130.3, 131.3, 132.7, 134.1 (aromatic carbons). Anal. Calcd for $C_{23}H_{24}N_2O_6S$: C, 60.51; H, 5.30; N, 6.14. Found: C, 60.57; H, 5.27; N, 6.22%.

4-Amino-6, 10-di(*p*-chlorophenyl)-7-carbomethoxy-8-thia-2-oxa-3-azaspiro-[4.5]decan-3-en-1-one-8,8-dioxide, 3c: White solid, yield 73%. m.p. 197-99°C. IR (KBr): 1136, 1328 (SO_2), 1602 (C=N), 1706 (*CO*-O), 1735 (CO_2Me), 3360, 3472 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.17 (dd, 1H, H_X, J_{AX} = 5.6 Hz, J_{MX} = 15.5 Hz), 3.50 (s, 3H, OCH_3), 3.57 (dd, 1H, H_M), 4.11 (d, 1H, C_7-H), 4.19 (dd, 1H, H_A, J_{AM} = 10.3Hz), 4.48 (d, 1H, C_6-H, J = 14.7 Hz), 5.84 (bs, 2H, NH_2), 7.08-7.69 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.3 (C-6), 27.7 (C-10), 51.7 (CO_2CH_3), 56.3 (C-9), 59.6 (C-7), 67.6 (C-5), 164.9 (C-4), 174.5 (C=O), 190.9 (C-1), 126.9, 127.5, 128.3, 129.8, 130.5, 131.6, 132.7, 135.9 (aromatic carbons). Anal. Calcd for $C_{21}H_{18}Cl_2N_2O_6S$: C, 50.71; H, 3.65; N, 5.63. Found: C, 50.75; H, 3.64; N, 5.67%.

4-Amino-6-(*p*-methylphenyl)-10-phenyl-7-carbomethoxy-8-thia-2-oxa-3-azaspiro[4.5]decan-3-en-1-one-8,8-dioxide, 3d: White solid, yield 68% m.p. 191-93°C. IR (KBr): 1137, 1337 (SO_2), 1611 (C=N), 1712 (*CO*-O), 1739 (CO_2Me), 3359, 3470 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H, Ar′-CH_3), 3.23 (dd, 1H, H_X, J_{AX}=5.5 Hz, J_{MX}=15.8 Hz), 3.54 (s, 3H, OCH_3), 3.65 (dd, 1H, H_M), 4.12 (d, 1H, C_7-H), 4.22 (dd, 1H, H_A, J_{AM} = 10.1 Hz), 4.51 (d, 1H, C_6-H, J = 14.8 Hz), 5.79 (bs, 2H, NH_2), 7.11-7.75 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.8 (Ar′-CH_3), 24.3 (C-6), 27.4 (C-10), 51.2 (CO_2CH_3), 56.7 (C-9), 59.5 (C-7), 67.0 (C-5), 165.1 (C-4), 173.8 (C=O), 191.0 (C-1), 127.3, 128.5, 129.6, 130.8, 132.5, 133.0, 134.2, 135.1 (aromatic carbons). Anal. Calcd for $C_{22}H_{22}N_2O_6S$: C, 59.72; H, 5.01; N, 6.33. Found: C, 59.69; H, 5.05; N, 6.39%.

4-Amino-6-(*p*-chlorophenyl)-10-(*p*-methylphenyl)-7-carbomethoxy-8-thia-2-oxa-3-azaspiro[4.5]decan-3-en-1-one-8,8-dioxide, 3e: White solid, yield 75% m.p. 186-88°C. IR (KBr): 1140, 1339 (SO_2), 1615 (C=N), 1711 (*CO*-O), 1740 (CO_2Me), 3354, 3461 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.23

(s, 3H, Ar-CH_3), 3.22 (dd, 1H, H_X, J_{AX} = 5.3 Hz, J_{MX} = 15.5 Hz), 3.53 (s, 3H, OCH_3), 3.63 (dd, 1H, H_M), 4.11 (d, 1H, C_7-H), 4.20 (dd, 1H, H_A, J_{AM} = 10.2 Hz), 4.56 (d, 1H, C_6-H, J = 14.6 Hz), 5.83 (bs, 2H, NH_2), 7.10-7.67 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1 (Ar-CH_3), 24.6 (C-6), 27.3 (C-10), 51.5 (CO_2CH_3), 56.6 (C-9), 59.3 (C-7), 67.3 (C-5), 165.4 (C-4), 174.1 (C=O), 191.5 (C-1), 126.7, 127.5, 128.5, 129.2, 130.6, 131.0, 133.4, 134.7 (aromatic carbons). Anal. Calcd for $C_{22}H_{21}ClN_2O_6S$: C, 55.40; H, 4.44; N, 5.87. Found: C, 55.46; H, 4.47; N, 5.84%.

General procedure for the synthesis of compound 4

To a solution of the compound **1** (1 mmol) in ethanol (10 mL), a solution of urea (1.5 mmol) in ethanol (10 mL) and piperidine (3 mL) were added and heated under reflux for 12-15 hr. Once the reaction completed (TLC), the reaction mixture was cooled, poured with stirring into ice-cold water (40 mL) containing conc. HCl (5 mL) and then extracted with ethyl acetate. The organic layer was washed with brine and dried over anhyd. Na_2SO_4. Evaporation of the solvent *in vacuo* resulted in a crude product which was purified by recrystallization from ethanol.

5-Amino-7, 11-diaryl-8-carbomethoxy-3-hydroxy-9-thia-2, 4-diazaspiro[5.5]undecane-2,4-dien-1-one-9,9-dioxide, 4a: White solid, yield 69%, m.p.177-79°C. IR (KBr): 1134, 1340 (SO_2), 1613 (C=N), 1661 (*CO*-N=), 1733 (CO_2Me), 3315 (OH), 3349, 3450 (NH_2) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.18 (dd, 1H, H_X, J_{AX} = 5.0 Hz, J_{MX} = 15.7 Hz), 3.53 (s, 3H, OCH_3), 3.61 (dd, 1H, H_M), 4.14 (d, 1H, C_8-H), 4.35 (dd, 1H, H_A, J_{AM} = 10.4 Hz), 4.61 (d, 1H, C_7-H, J = 13.5 Hz), 5.87 (bs, 2H, NH_2), 6.90 (bs, 1H, OH), 7.09-7.72 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.0 (C-7), 26.8 (C-11), 50.8 (CO_2CH_3), 56.1 (C-10), 59.3 (C-8), 66.8 (C-6), 157.3 (C-3), 165.1 (C-5), 174.9 (C=O), 190.4 (C-1), 126.3, 127.1, 127.8, 128.4, 129.5, 130.8, 132.2, 134.5 (aromatic carbons). Anal. Calcd for $C_{22}H_{21}N_3O_6S$: C, 58.01; H, 4.65; N, 9.23. Found: C, 58.05; H, 4.62; N, 9.31%.

5-Amino-7,11-di(*p*-methylphenyl)-8-carbomethoxy-3-hydroxy-9-thia-2, 4-diazaspiro[5.5]undecane-2,4-dien-1-one-9,9-dioxide, 4b: White solid, yield 64%, m.p. 195-97°C. IR (KBr): 1139, 1327 (SO_2), 1608 (C=N), 1659 (*CO*-N=), 1738 (CO_2Me), 3318 (OH), 3352, 3457 (NH_2) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30, 2.18 (s, 6H, Ar-CH_3 and Ar′-CH_3), 3.16 (dd, 1H, H_X, J_{AX} = 5.4 Hz, J_{MX} = 15.5 Hz), 3.50 (s, 3H, OCH_3), 3.58 (dd, 1H, H_M), 4.13 (d, 1H, C_8-H), 4.17 (dd, 1H, H_A, J_{AM} = 10.2 Hz), 4.49 (d, 1H, C_7-H, J = 13.7 Hz), 5.81 (bs, 2H, NH_2), 6.86 (bs, 1H, OH), 7.12-7.78 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.6 (Ar-CH_3 and Ar′CH_3), 24.5 (C-7), 27.5 (C-11), 51.6 (CO_2CH_3), 55.9 (C-10), 59.8 (C-8), 67.6 (C-6), 157.6 (C-3), 165.6 (C-5), 174.6 (C=O), 191.9 (C-1), 126.6, 127.3, 128.4, 129.5, 131.3, 132.6, 133.1, 134.9 (aromatic carbons). Anal. Calcd for $C_{24}H_{25}N_3O_6S$: C, 59.61; H, 5.21; N, 8.69. Found: C, 59.68; H, 5.34; N, 8.75%.

5-Amino-7, 11-di(*p*-chlorophenyl)-8-carbomethoxy-3-hydroxy-9-thia-2, 4-diazaspiro[5.5]undecane-2,4-dien-1-one-9,9-dioxide, 4c: White solid, yield 67%, m.p. 203-205°C. IR (KBr): 1132, 1336 (SO_2), 1612 (C=N), 1667 (*CO*-N=), 1736 (CO_2Me), 3310 (OH), 3358, 3461 (NH_2) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.18 (dd, 1H, H_X, J_{AX} = 5.6 Hz, J_{MX} = 15.4 Hz), 3.51 (s, 3H, OCH_3), 3.60 (dd, 1H, H_M), 4.12 (d, 1H, C_8-H), 4.21 (dd, 1H, H_A, J_{AM} = 10.4 Hz), 4.52 (d, 1H, C_7-H J = 14.0 Hz), 5.90 (bs, 2H, NH_2), 6.92 (bs, 1H, OH), 7.10-7.79 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.4 (C-7), 27.1 (C-11), 51.0 (CO_2CH_3), 56.1 (C-10), 59.5 (C-8), 67.1 (C-6), 157.8 (C-3), 166.1 (C-5), 174.5 (C=O), 190.2 (C-1), 127.5, 128.1, 128.8, 130.2, 131.6, 132.8, 133.2, 134.4 (aromatic carbons). Anal. Calcd for $C_{22}H_{19}Cl_2N_3O_6S$: C, 50.39; H, 3.65; N, 8.01. Found: C, 50.37; H, 3.66; N, 8.05%.

5-Amino-7-(*p*-methylphenyl)-11-(phenyl)-8-carbomethoxy-3-hydroxy-9-thia-2, 4-diazaspiro[5.5]undecane-2,4-dien-1-one-9,9-dioxide, 4d: White solid, yield 63%, m.p. 198-200°C. IR (KBr): 1136, 1334 (SO_2), 1607 (C=N), 1662 (*CO*-N=), 1740 (CO_2Me), 3314 (OH), 3351, 3462 (NH_2) cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.30 (s, 3H, Ar′-CH_3), 3.24 (dd, 1H, H_X, J_{AX} = 5.4 Hz, J_{MX} = 15.5 Hz), 3.53 (s, 3H, OCH_3), 3.57 (dd, 1H, H_M), 4.15 (d, 1H, C_8-H), 4.22 (dd, 1H, H_A, J_{AM} = 10.3 Hz), 4.50 (d, 1H, C_7-H, J=13.9 Hz), 5.85 (bs, 2H, NH_2), 6.93 (bs, 1H, OH), 7.13-7.73 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.5 (Ar′-CH_3), 24.0 (C-7), 27.0 (C-11), 50.6 (CO_2CH_3), 56.2 (C-10), 59.3 (C-8), 67.5 (C-6), 158.0 (C-3), 166.4 (C-5), 174.1 (C=O), 190.9 (C-1), 127.1, 127.9, 129.3, 130.2, 131.3, 132.6, 133.4, 135.1 (aromatic carbons). Anal. Calcd for $C_{23}H_{23}N_3O_6S$: C, 58.84; H, 4.94; N, 8.95. Found: C, 58.90; H, 4.98; N, 8.90%.

5-Amino-7-(*p*-chlorophenyl)-11-(*p*-methylphenyl)-8-carbomethoxy-3-hydroxy-9-thia-2,4-diazaspiro[5.5]-undecane-2,4-dien-1-one-9,9-dioxide, 4e: White

solid, yield 62%, m.p. 192-94°C. IR (KBr): 1134, 1324 (SO_2), 1606 (C=N), 1665 (*CO*-N=), 1738 (CO_2Me), 3308 (OH), 3360, 3468 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.31 (s, 3H, Ar-CH_3), 3.22 (dd, 1H, H_X, J_{AX} = 5.3 Hz, J_{MX} = 15.6 Hz), 3.54 (s, 3H, OCH_3), 3.62 (dd, 1H, H_M), 4.10 (d, 1H, C_8-H), 4.20 (dd, 1H, H_A, J_{AM} = 10.1 Hz), 4.54 (d, 1H, C_7-H, J = 14.2 Hz), 5.91 (bs, 2H, NH_2), 6.89 (bs, 1H, OH), 7.08-7.69 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1 (Ar-CH_3), 24.8 (C-7), 27.5 (C-11), 51.7 (CO_2CH_3), 56.7 (C-10), 59.8 (C-8), 67.5 (C-6), 158.5 (C-3), 166.5 (C-5), 173.8 (C=O), 192.5 (C-1), 126.8, 127.5, 128.4, 129.5, 130.6, 131.5, 132.8, 134.5 (aromatic carbons). Anal. Calcd for $C_{23}H_{22}ClN_3O_6S$: C, 54.82; H, 4.40; N, 8.34. Found: C, 54.85; H, 4.39; N, 8.30%.

General procedure for the synthesis of compound 5

To an equimolar mixture (1.0 mmol) of compound **1** and thiourea in ethanol (20 mL), piperidine (3 mL) was added and refluxed for 14-18 hr. On completion of the reaction (TLC), the contents were cooled, poured into ice-cold water (40 mL) containing conc. HCl (5 mL) and extracted with ethyl acetate. The organic layer was washed with brine and dried over anhyd. Na_2SO_4. Evaporation of the solvent under reduced pressure afforded crude product which was purified by recrystallization from ethanol.

5-Amino-7,11-diaryl-8-carbomethoxy-3-mercapto-9-thia-2,4-diazaspiro[5.5]undecane-2,4-dien-1-one-9,9-dioxide, 5a: White solid, yield 70%, m.p.: 185-87°C. IR (KBr): 1138, 1330 (SO_2), 1615 (C=N), 1668 (*CO*-N=), 1736 (CO_2Me), 2564 (SH), 3362, 3471 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.38 (bs, 1H, SH), 3.21 (dd, 1H, H_X, J_{AX} = 5.3 Hz, J_{MX} = 15.6 Hz), 3.59 (s, 3H, OCH_3), 3.72 (dd, 1H, H_M), 4.12 (d, 1H, C_8-H), 4.45 (dd, 1H, H_A, J_{AM} = 10.3 Hz), 4.69 (d, 1H, C_7-H, J = 14.1 Hz), 5.78 (bs, 2H, NH_2), 7.09-7.56 (m, 10H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.9 (C-7), 25.6 (C-11), 51.9 (CO_2CH_3), 57.3 (C-10), 59.4 (C-8), 66.2 (C-6), 164.5 (C-3), 165.8 (C-5), 175.1 (C=O), 191.0 (C-1), 127.2, 128.3, 129.4, 130.1, 130.9, 131.7, 132.3, 135.4 (aromatic carbons). Anal. Calcd for $C_{22}H_{21}N_3O_5S_2$: C, 56.04; H, 4.49; N, 8.91. Found: C, 56.02; H, 4.50; N, 8.95%.

5-Amino-7,11-di(*p*-methylphenyl)-8-carbomethoxy-3-mercapto-9-thia-2, 4-diazaspiro[5.5]undecane-2,4-dien-1-one-9,9-dioxide, 5b: White solid, yield 72%, m.p. 208-10°C. IR (KBr): 1132, 1335 (SO_2), 1609 (C=N), 1661 (*CO*-N=), 1742 (CO_2Me), 2556 (SH), 3361, 3469 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.34 (bs, 1H, SH), 2.22, 2.31 (s, 6H, Ar-CH_3 and Ar′-CH_3), 3.20 (dd, 1H, H_X, J_{AX} = 5.4 Hz, J_{MX} = 15.3 Hz), 3.51 (s, 3H, OCH_3), 3.63 (dd, 1H, H_M), 4.15 (d, 1H, C_8-H), 4.40 (dd, 1H, H_A, J_{AM} = 10.2 Hz), 4.63 (d, 1H, C_7-H, J = 14.0 Hz), 5.88 (bs, 2H, NH_2), 7.14-7.72 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 20.8 (Ar-CH_3 and Ar′-CH_3), 24.3 (C-7), 26.4 (C-11), 51.7 (CO_2CH_3), 58.2 (C-10), 59.7 (C-8), 67.6 (C-6), 165.6 (C-3), 166.2 (C-5), 174.6 (C=O), 190.5 (C-1), 127.7, 128.5, 129.7, 130.6, 132.0, 133.1, 134.9 (aromatic carbons). Anal. Calcd for $C_{24}H_{25}N_3O_5S_2$: C, 57.70; H, 5.04; N, 8.41. Found: C, 57.76; H, 5.07; N, 8.47%.

5-Amino-7, 11-di(*p*-chlorophenyl)-8-carbomethoxy-3-mercapto-9-thia-2, 4-diazaspiro[5.5]undecane-2,4-dien-1-one-9,9-dioxide, 5c: White solid, yield 75%. m.p. 213-15°C. IR (KBr): 1135, 1325 (SO_2), 1613 (C=N), 1665 (*CO*-N=), 1739 (CO_2Me), 2561 (SH), 3365, 3470 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.39 (bs, 1H, SH), 3.25 (dd, 1H, H_X, J_{AX} = 5.5 Hz, J_{MX} = 15.6 Hz), 3.53 (s, 3H, OCH_3), 3.67 (dd, 1H, H_M), 4.14 (d, 1H, C_8-H), 4.47 (dd, 1H, H_A, J_{AM} = 10.4 Hz), 4.71 (d, 1H, C_7-H, J = 14.3 Hz), 5.91 (bs, 2H, NH_2), 7.10-7.74 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.6 (C-7), 25.9 (C-11), 51.4 (CO_2CH_3), 57.9 (C-10), 60.2 (C-8), 67.1 (C-6), 166.1 (C-3), 166.7 (C-5), 174.0 (C=O), 190.2 (C-1), 126.9, 127.8, 129.3, 130.4, 131.0, 131.8, 133.4, 135.7 (aromatic carbons). Anal. Calcd for $C_{22}H_{19}Cl_2N_3O_5S_2$: C, 48.89; H, 3.54; N, 7.78. Found: C, 48.93; H, 3.53; N, 7.80%.

5-Amino-7-(*p*-methylphenyl)-11-phenyl-8-carbomethoxy-3-mercapto-9-thia-2, 4-diazaspiro[5.5]undecane-2,4-dien-1-one-9,9-dioxide, 5d: White solid, yield 68%, m.p. 204-206°C. IR (KBr): 1134, 1341 (SO_2), 1610 (C=N), 1660 (*CO*-N=), 1743 (CO_2Me), 2557 (SH), 3363, 3474 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.42 (bs, 1H, SH), 2.30 (s, 3H, Ar′-CH_3), 3.23 (dd, 1H, H_X, J_{AX} = 5.3 Hz, J_{MX} = 15.4 Hz), 3.55 (s, 3H, OCH_3), 3.64 (dd, 1H, H_M), 4.15 (d, 1H, C_8-H), 4.42 (dd, 1H, H_A, J_{AM} = 10.4 Hz), 4.73 (d, 1H, C_7-H, J = 14.2 Hz), 5.96 (bs, 2H, NH_2), 7.14-7.71 (m, 9H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.9 (Ar′-CH_3), 24.1 (C-7), 25.4 (C-11), 51.5 (CO_2CH_3), 58.3 (C-10), 60.5 (C-8), 68.5 (C-6), 164.9 (C-3), 165.8 (C-5), 173.7 (C=O), 189.4 (C-1), 127.1, 128.3, 129.0, 130.2, 131.3, 132.5, 133.7, 135.9 (aromatic carbons). Anal. Calcd for $C_{23}H_{23}N_3O_5S_2$: C, 56.89; H, 4.77; N, 8.65. Found: C, 56.84; H, 4.80; N, 8.72%.

5-Amino-7-(*p*-chlorophenyl)-11-(*p*-methylphenyl)-8-carbomethoxy-3-mercapto-9-thia-2,4-diazaspiro-[5.5]undecane-2,4-dien-1-one-9,9-dioxide, 5e: White solid, yield 71%, m.p. 199-201°C. IR (KBr): 1140, 1322 (SO_2), 1604 (C=N), 1663 (*CO*-N=), 1741 (CO_2Me), 2566 (SH), 3471, 3359 (NH_2) cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.37 (bs, 1H, SH), 2.24 (s, 3H, Ar-CH_3), 3.21 (dd, 1H, H_X, J_{AX} = 5.5 Hz, J_{MX} = 15.6 Hz), 3.57 (s, 3H, OCH_3), 3.67 (dd, 1H, H_M), 4.18 (d, 1H, C_8-H), 4.41 (dd, 1H, H_A, J_{AM} = 10.6 Hz), 4.75 (d, 1H, C_7-H, J = 14.3 Hz), 5.87 (bs, 2H, NH_2), 7.09-7.80 (m, 8H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.3 (Ar-CH_3), 24.3 (C-7), 26.2 (C-11), 51.8 (CO_2CH_3), 58.0 (C-10), 59.6 (C-8), 67.9 (C-6), 166.1 (C-3), 166.8 (C-5), 174.1 (C=O), 190.6 (C-1), 126.8, 127.1, 128.4, 129.5, 130.7, 132.1, 133.3, 135.4 (aromatic carbons). Anal. Calcd for $C_{23}H_{22}ClN_3O_5S_2$: C, 53.12; H, 4.26; N, 8.08. Found: C, 53.15; H, 4.28; N, 8.13%.

Conclusion

The *gem* cyano ester functionality in double Michael adduct, 4-carboethoxy-2-carbomethoxy-4-cyano-3,5-diaryltetrahydro[2*H*]thiopyran-1,1-dioxide **1** was utilized to get a new class of spiro-pyrimidine, pyrazole and isoxazole derivatives on cyclo-condensation reaction with appropriate nucleophiles.

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