AN EFFICIENT PROCEDURE FOR THE SYNTHESIS OF PYRAZOLO[3,4-*d*][1,3]THIAZIN-4-ONES

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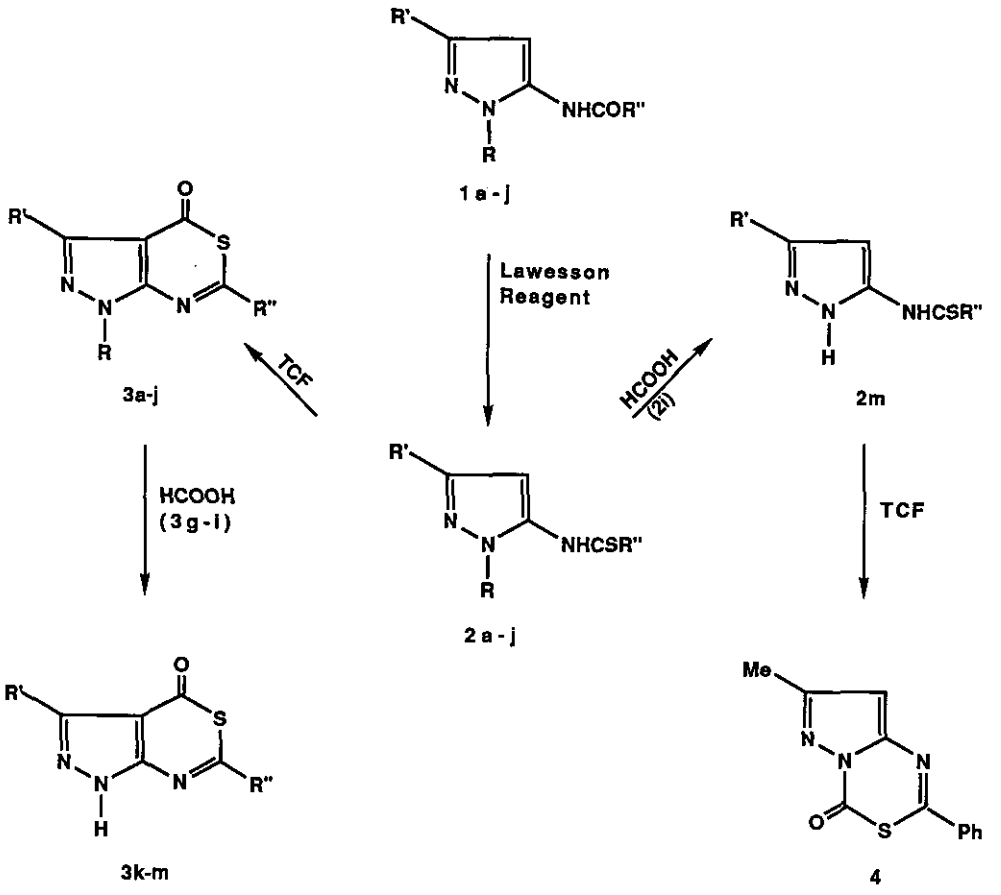
Abstract- Trichloromethyl chloroformate reacts with *N*-(1-alkyl/aryl-5-pyrazolyl) thiocarboxamides (**2a-j**) to give pyrazolo[3,4-*d*][1,3]thiazin-4-ones (**3**) while it reacts with *N*-(3-methyl-5-pyrazolyl)thiobenzamide (**2m**) to give the pyrazolo[1,5-*c*] [1,3,5]thiadiazine-4-one (**4**). Heating under reflux in formic acid of homologues (**3g-i**) bearing a *tert*-butyl group linked to pyrazole N-1 atom afforded the dealkylated derivatives (**3k-m**).

Human leukocyte elastase (HLE) is a serine protease implicated in several human deseases such as emphysema,[1] cystic fibrosis[2] and reumathoid artritis.[3] One of the overcoming approaches to the treatment of these deseases is to supplement the HLE natural inhibitors with synthetic molecules capable of reversible or irreversible binding to the enzyme. Our efforts in this area were directed toward the design of heterocycles reactive toward bionucleophiles such as pyrazolo[4,3-*c*][1,2,5]oxadiazinones[4] and 6-aminopyrazolo[3,4-*d*][1,3]thiazinones,[5] which could behave as acylating agents of the enzyme active site serine. The first results obtained from *in vitro* tests confirmed that both classes of heterocycles are potential HLE inhibitors.[6,7]

Continuing the search for biological activity optimization, we became interested in the synthesis of 6-alkyl/arylpyrazolo[3,4-*d*][1,3]thiazin-4-ones. Beside a minor method based on the use of 4-halo-6-oxo-1,3-thiazines as starting materials,[8] the synthetic entries to these products up to now available in the literature are: a) the reaction of aminopyrazolones with carbon disulfide,[9] b) the reaction of 5-amino-4-cyanopyrazoles with carbon disulfide,[10] c) the condensation of 5-amino-4-arylidenpyrazoles with thiourea,[11] d) the intramolecular cyclization of *N*-alkyl-*N'*-(4-ethoxycarbonyl-5-pyrazolyl)thioureas.[12] All these methods have applications limited to the synthesis of 6-functionalized pyrazolothiazines and were not applicable to prepare the target products. Thus we decided to investigate an alternative procedure, depicted in the Scheme.



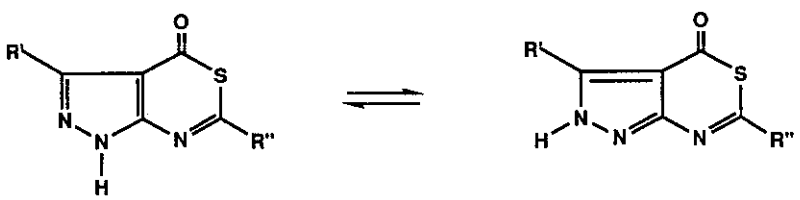
a: R= Me, R'= Me, R"= Me
b: R= Me, R'= Me, R"= CH_2Ph
c: R= Me, R'= Me, R"= Ph
d: R= Ph, R'= Me, R"= Me
e: R= Ph, R'= Me, R"= CH_2Ph
f : R= Ph, R'= Me, R"= Ph
g : R= *t*-Bu, R'= Me, R"= Me
h : R= *t*-Bu, R'= Me, R"= CH_2Ph
l : R= *t*-Bu, R'= Me, R"= Ph
j : R= Me, R'= H, R"= Ph
k : R'= Me, R"= Me
l : R'= Me, R"= CH_2Ph
m: R'= Me, R"= Ph

N-(5-Pyrazolyl)carboxamides (**1a-j**) were obtained by acylation of the corresponding 5-aminopyrazoles. Thiation of **1** with the Lawesson reagent provided the thiocarboxamides (**2a-j**). Heating under reflux of equimolar amounts of **2a-j** and trichloromethyl chloroformate (TCF) in anhydrous toluene gave satisfactory yields of the target 6-alkyl/arylpyrazolothiazinones (**3a-j**). Owing to the likely higher nucleophilicity of the pyrazole N-1 atom in comparison with that of the C-4 atom, the 1-unsubstituted homologues (**3k-m**) were not achievable by direct TCF acylation of the corresponding thiocarboxamides. In order to supply this gap, we thought to use the *tert*-butyl substituent of **3g-i** as a masking group for the pyrazole N-1 atom. As previously found in our laboratories,[13] the *tert*-butyl group is cleavable from pyrazole nitrogen atom by acidic medium; in

the present case, 1-*tert*-butylpyrazolothiazinones (**3g-i**) when heated under reflux in formic acid gave nearly quantitative yields of the dealkylated homologues (**3k-m**).

In an exploratory experiment, the *N*-(1-*tert*-butyl-3-methyl-5-pyrazolyl)thiobenzamide (**2i**) was converted by heating in formic acid into the dealkylated homologue (**2m**). As expected, the reaction of **2m** with TCF proceeded smoothly at room temperature to afford the pyrazolo[1,5-*c*][1,3,5]thiadiazinone (**4**) as the lone reaction product.

All the assigned structures are supported by analytical and spectral data (see Experimental). The nmr spectra of compounds (**3k-m**) in DMSO-d_6 show the presence of two species. The ^{1}H-nmr spectra indicate that the two species are in a molar ratio 3:2. The ^{13}C-nmr spectra show two sets of clearly distinct resonances. One set, corresponding to the major species, shows frequencies close similar to those of compounds (**3a-i**); in particular the methyl group linked to C-3 atom, the C-3 and the C-7a atoms absorb at *ca.* 14, 145 and 154 ppm respectively. The second set of resonances, corresponding to the minor species, shows peaks at *ca.* 11 (methyl group linked to C-3), 139 (C-3) and 159 (C-7a) ppm, values which are significantly different from the previous ones. These data can be explained by admitting a slow equilibrium between the two tautomers (**3k-m**) and (**3'k-m**). Based on the similarity of the ^{13}C resonances of the major tautomers with those of compounds (**3a-i**), the structure (**3**) was attributed to these tautomers.



3k-m **3'k-m**

EXPERIMENTAL

Melting points were determined with a Büchi capillary apparatus and are uncorrected. The ir spectra were recorded from potassium bromide discs on a Perkin-Elmer 299B spectrophotometer. The ^{1}H-nmr and ^{13}C-nmr spectra were recorded on a Bruker AC 200 spectrometer; chemical shifts (δ) are given in parts per million (ppm) relative to tetramethylsilane as internal standard and coupling constans are in Hz.

Compounds (**1a**), (**1c**), (**1d**) and (**1f**) were prepared according to the literature methods.[14]

Procedure for the synthesis of *N*-(5-pyrazolyl)carboxamides (1b), (1j).

A suspension of the appropriate 5-aminopyrazole (40 mmol) and acyl chloride (20 mmol) in anhydrous toluene (120 ml) was heated at 80°C for 1 h. After cooling, the precipitate was separated and the filtrate was evaporated to give a crude solid which was recrystallized from the indicated solvent.

***N*-(1,3-Dimethylpyrazol-5-yl)phenylacetamide (1b).**

Colorless crystals, yield 60%, mp 111.5-112.5°C (toluene); ir (KBr) cm^{-1}: 3260 (br), 1670 (br), 1540 (br); ^{1}H-nmr ($CDCl_3$) δ: 2.14 (s, 3H, Me), 3.42 (s, 3H, NMe), 3.67 (s, 2H, CH_2), 5.94 (s, 1H, CH), 7.25-7.36 (m, 5H, Ph), 7.58 (s, 1H, NH). Anal. Calcd for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 67.88; H, 6.70; N, 18.46.

***N*-(1-Methylpyrazol-5-yl)benzamide (1j).**

White crystals, yield 60%, mp 133-134 °C (ethyl acetate); ir (KBr) cm^{-1}: 3240 (br), 1650, 1530; ^{1}H-nmr (DMSO-d_6) δ: 3.68 (s, 3H, Me), 6.22 (d, J=1.7 Hz, 1H, CH), 7.38 (d, J=1.7 Hz, 1H, CH), 7.61-7.52 (m, 3H, Ph), 7.97 (d, J=7.0 Hz, 2H, Ph), 10.31 (s, 1H, NH). Anal. Calcd for $C_{11}H_{11}N_3O$: C, 65.66; H, 5.51; N, 20.88. Found: C, 65.72; H, 5.48; N, 20.86.

Procedure for the synthesis of *N*-(5-pyrazolyl)carboxamides (1e), (1h), (1i).

A solution of the pertinent acyl chloride (20 mmol) in methylene chloride (10 ml) was added dropwise to a mixture of the appropriate 5-aminopyrazole (20 mmol) in methylene chloride (100 ml) and sodium hydrogen carbonate (1.68 g, 20 mmol) in water (50 ml). After 24 h stirring at room temperature, the organic phase was washed with 5% sodium hydrogen carbonate and water and then anhydrified over anhydrous magnesium sulfate. After removal of the solvent, the residue was recrystallized from the indicated solvent to give colorless crystals.

***N*-(3-Methyl-1-phenylpyrazol-5-yl)phenylacetamide (1e).**

Yield 60%, mp 108.5-109.5°C (ethyl acetate/hexane); ir (KBr) cm^{-1}: 3240 (br), 1665, 1540; ^{1}H-nmr (DMSO-d_6) δ: 2.19 (s, 3H, Me), 3.60 (s, 2H, CH_2), 6.23 (s, 1H, CH), 7.21-7.42 (m, 10H, 2Ph), 10.10 (s, 1H, NH). Anal. Calcd for $C_{18}H_{17}N_3O$: C, 74.21; H, 5.88; N, 14.42. Found: C, 74.52; H, 5.80; N, 14.40.

***N*-(1-*tert*-Butyl-3-methylpyrazol-5-yl)phenylacetamide (1h).**

Yield 85%, mp 169.5-170°C (ethanol); ir (KBr) cm^{-1}: 3200 (br), 3000 (br), 1670, 1570; ^{1}H-nmr ($CDCl_3$) δ: 1.29 (s 9H, *t*-Bu), 2.18 (s, 3H, Me), 3.76 (s, 2H, CH_2), 6.21 (s, 1H, CH), 7.05 (br, 1H, NH), 7.31-7.45 (m, 5H, Ph). Anal. Calcd for $C_{16}H_{21}N_3O$: C, 70.82; H, 7.80; N, 15.48. Found: C, 71.02; H, 7.68; N, 15.40.

***N*-(1-*tert*-Butyl-3-methylpyrazol-5-yl)benzamide (1i).**

Yield 69%, mp 221-222 °C (ethanol); ir (KBr) cm^{-1}: 3300 (br), 1665, 1565, 1520; ^{1}H-nmr ($CDCl_3$) δ: 1.65 (s, 9H, *t*-Bu), 2.25 (s, 3H, Me), 6.17 (s, 1H, CH), 7.41-7.59 (m, 3H, Ph), 7.22 (br, 1H, NH), 7.85 (d, J=6.9 Hz, 2H, Ph). Anal. Calcd for $C_{15}H_{19}N_3O$: C, 70.01; H, 7.44; N, 16.33. Found: C, 70.12; H, 7.32; N, 16.42.

***N*-(1-*tert*-Butyl-3-methylpyrazol-5-yl)acetamide (1g).**

A solution of 5-amino-1-*tert*-butyl-3-methylpyrazole (3.06 g, 20 mmol) in acetic anhydride (20 ml) was stirred at room temperature for 1 h. The precipitate was collected, washed with ether and recrystallized from *tert*-butyl methyl ether. White crystals, yield 73%, mp 150.5°C (*tert*-butyl methyl ether); ir (KBr) cm^{-1}: 3180, 1670,

1560; ^{1}H-nmr (DMSO-d_6) δ: 1.48 (s, 9H, *t*-Bu), 1.98 (s, 3H, Me), 2.08 (s, 3H, Me), 5.79 (s, 1H, CH), 9.41 (s, 1H, NH). Anal. Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.78; N, 21.52. Found: C, 61.70; H, 8.70; N, 21.38.

General procedure for the synthesis of *N*-(5-pyrazolyl)thiocarboxamides (2a-j).

The Lawesson reagent (1.01 g, 2.5 mmol) was added to a solution of carboxamide (**1**) (5 mmol) in anhydrous toluene (50 ml) at 80°C. The mixture was kept under stirring at 80°C until no more of the starting material could be detected by tlc (5-6 h). The solution was extracted with 1N sodium hydroxide (3 x 50 ml), the aqueous layer was acidified to pH 5 with 10% hydrochloric acid and then extracted with ethyl acetate (3 x 50 ml). After drying over anhydrous magnesium sulfate, the solvent was removed and the solid residue was recrystallized from the indicated solvent to give a pale yellow crystalline product.

***N*-(1,3-Dimethylpyrazol-5-yl)thioacetamide (2a).**

Yield 60%, mp 86-87°C (toluene); ir (KBr) cm^{-1}: 3420 (br), 3200 (br), 2920 (br), 1600, 1360 (br); ^{1}H-nmr (DMSO-d_6) δ: 2.11 (s, 3H, Me), 2.58 (s, 3H, Me), 3.57 (s, 3H, NMe) 6.05 (s, 1H, CH), 11.37 (br, 1H, NH). Anal. Calcd for $C_7H_{11}N_3S$: C, 49.68; H, 6.55; N, 24.83; S, 18.94. Found: C, 49.50; H, 6.54 ; N, 24.98; S, 18.82.

***N*-(1,3-Dimethylpyrazol-5-yl)phenylthioacetamide (2b).**

Yield 83%, mp 134.5-135.5°C (toluene); ir (KBr) cm^{-1}: 3400 (br), 3150 (br), 2850 (br), 1560 (br), 1370; ^{1}H-nmr (DMSO-d_6) δ: 2.11 (s, 3H, Me), 3.45 (s, 3H, NMe), 4.10 (s, 2H, CH_2), 6.01 (s, 1H, CH), 7.30-7.41 (m, 5H, Ph), 11.70 (br, 1H, NH). Anal. Calcd for $C_{13}H_{15}N_3S$: C, 63.64; H, 6.16; N, 17.13; S, 13.07. Found: C, 63.80; H, 6.20; N, 17.27; S, 13.00.

***N*-(1,3-Dimethylpyrazol-5-yl)thiobenzamide (2c).**

Yield 62%, mp 152.5-153.5°C (toluene); ir (KBr) cm^{-1}: 3140 (br), 2920 (br), 1560, 1530, 1340; ^{1}H-nmr (DMSO-d_6) δ: 2.15 (s, 3H, Me), 3.60 (s, 3H, NMe), 6.13 (s, 1H, CH), 7.40-7.60 (m, 3H, Ph), 7.91 (d, J=7.1 Hz, 2H, Ph), 11.60 (s, 1H, NH). Anal. Calcd for $C_{12}H_{13}N_3S$: C, 62.31; H, 5.66; N, 18.17; S, 13.86. Found: C, 62.51; H, 5.78; N, 18.20; S, 13.72.

***N*-(3-Methyl-1-phenylpyrazol-5-yl)thioacetamide (2d).**

Yield 77%, mp 173-175°C (toluene); ir (KBr) cm^{-1}: 3140 (br), 2910 (br), 1670, 1630 (br), 1360; ^{1}H-nmr (DMSO-d_6) δ: 2.24 (s, 3H, Me), 2.50 (s, 3H, Me), 6.27 (s, 1H, CH), 7.30-7.50 (m, 5H, Ph), 11.53 (br, 1H, NH). Anal. Calcd for $C_{12}H_{13}N_3S$: C, 62.31; H, 5.66; N, 18.17; S, 13.86. Found: C, 62.12; H, 5.60; N, 18.30; S, 13.68.

***N*-(3-Methyl-1-phenylpyrazol-5-yl)phenylthioacetamide (2e).**

Yield 91%, mp 147-148°C (methanol); ir (KBr) cm^{-1}: 3140 (br), 2900 (br), 1675, 1605, 1380, 1360; ^{1}H-nmr (DMSO-d_6) δ: 2.23 (s, 3H, Me), 4.01 (s, 2H, CH_2), 6.29 (s, 1H, CH), 7.30 (s, 10H, 2Ph), 11.72 (s, 1H,

NH). Anal. Calcd for $C_{18}H_{17}N_3S$: C, 70.33; H, 5.57; N, 13.67; S, 10.43. Found: C, 70.20; H, 5.62; N, 13.80; S, 10.34.

***N*-(3-Methyl-1-phenylpyrazol-5-yl)thiobenzamide (2f).**
Yield 95%, mp 185-187°C (ethanol); ir (KBr) cm^{-1}: 2900 (br), 1670, 1600 (br), 1350; ^{1}H-nmr (DMSO-d_6) δ: 2.28 (s, 3H, Me), 6.36 (s, 1H, CH), 7.32-7.55 (m, 8H, Ph), 7.78 (d, J=6.8 Hz, 2H, Ph), 11.71 (s, 1H, NH). Anal. Calcd for $C_{17}H_{15}N_3S$: C, 69.60; H, 5.15; N, 14.32; S, 10.93. Found: C, 69.86; H, 5.13; N, 14.44; S, 10.74.

***N*-(1-*tert*-Butyl-3-methylpyrazol-5-yl)thioacetamide (2g).**
Yield 71%, mp 114-115°C (hexane); ir (KBr) cm^{-1}: 3200, 1560, 1520, 1360 (br); ^{1}H-nmr (DMSO-d_6) δ: 1.48 (s, 9H, *t*-Bu), 2.11 (s, 3H, Me), 2.54 (s, 3H, Me), 5.83 (s, 1H, CH), 11.18 (s, 1H, NH). Anal. Calcd for $C_{10}H_{17}N_3S$: C, 56.84; H, 8.11; N, 19.88; S, 15.17. Found: C, 56.54; H, 8.02; N, 19.98; S, 15.20.

***N*-(1-*tert*-Butyl-3-methylpyrazol-5-yl)phenylthioacetamide (2h).**
Yield 82%, mp 103.5-104°C (hexane); ir (KBr) cm^{-1}: 3220, 1560, 1520, 1380; ^{1}H-nmr (DMSO-d_6) δ: 1.35 (s, 9H, *t*-Bu), 2.10 (s, 3H, Me), 4.06 (s, 2H, CH_2), 5.86 (s, 1H, CH), 7.28-7.42 (m, 5H, Ph), 11.35 (s, 1H, NH). Anal. Calcd for $C_{16}H_{21}N_3S$: C, 66.86; H, 7.36; N, 14.62; S, 11.15. Found: C, 67.00; H, 7.32; N, 14.50; S, 11.00.

***N*-(1-*tert*-Butyl-3-methylpyrazol-5-yl)thiobenzamide (2i).**
Yield 88%, mp 154.5-155.5°C (ethanol); ir (KBr) cm^{-1}: 3220, 1610, 1550, 1520, 1330; ^{1}H-nmr (DMSO-d_6) δ: 1.54 (s, 9H, *t*-Bu), 2.15 (s, 3H, Me), 5.95 (s, 1H, CH), 7.40-7.60 (m, 3H, Ph), 7.86 (d, J=8.3 Hz, 2H, Ph), 11.42 (s, 1H, NH). Anal. Calcd for $C_{15}H_{19}N_3S$: C, 65.90; H, 7.00; N, 15.37; S, 11.73. Found: C, 65.80; H, 7.12; N, 15.52; S, 11.60.

***N*-(1-Methylpyrazol-5-yl)thiobenzamide (2j).**
Yield 62%, mp 111-111.5°C (toluene); ir (KBr) cm^{-1}: 3200-2700, 1550 (br), 1340 (br); ^{1}H-nmr (DMSO-d_6) δ: 3.69 (s, 3H, Me), 6.34 (d, J=1.9 Hz, 1H, CH), 7.45 (d, J=1.9 Hz, 1H, CH), 7.57-7.47 (m, 3H, Ph), 7.93-7.89 (m, 2H, Ph), 11.62 (s, 1H, NH). Anal. Calcd for $C_{11}H_{11}N_3S$: C, 60.80; H,5.10; N, 19.34; S, 14.75. Found: C, 60.75; H, 5.14 ; N, 19.38; S, 14.82.

General procedure for the synthesis of 1,6-alkyl/arylpyrazolo[3,4-*d*][1,3]thiazin-4-ones (3a-j).
Trichloromethyl chloroformate (1.20 ml, 10 mmol) was added to a suspension of thiocarboxamide (2) (10 mmol) in anhydrous toluene (160 ml), placed in a round-bottomed flask equipped with a Vigreaux reflux condenser. The mixture was stirred at room temperature for 30 min and then heated under reflux until hydrogen chloride evolution ceased (*ca.* 1.5 h). After removal of the solvent, the solid residue was recrystallized from the indicated solvent to give a white crystalline product.

1,3,6-Trimethylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3a).
Yield 79%, mp 153.5-154.5°C (methanol); ir (KBr) cm^{-1}: 1680, 1570, 1520; ^{1}H-nmr ($CDCl_3$) δ: 2.54 (s, 3H, Me), 2.64 (s, 3H, Me), 3.95 (s, 3H, NMe); ^{13}C-nmr ($CDCl_3$) δ: 14.09 (q, J=128.3 Hz, Me), 27.47 (q, J=129.9 Hz, Me), 34.45 (q, J=140.3 Hz, Me), 102.79 (s, C-3a), 145.57 (s, C-3), 153.18 (s, C-7a), 173.01 (s, C-6), 176.83 (s, C=O). Anal. Calcd for $C_8H_9N_3OS$: C, 49.22; H, 4.65; N, 21.52; S, 16.42. Found: C, 49.02; H, 4.60; N, 21.61; S, 16.44.

6-Benzyl-1,3-dimethylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3b).
Yield 84%, mp 85.5-87.5°C (methanol); ir (KBr) cm^{-1}: 1675, 1555, 1510; ^{1}H-nmr ($CDCl_3$) δ: 2.53 (s, 3H, Me), 3.96 (s, 3H, NMe), 4.14 (s, 2H, CH_2), 7.31-7.34 (m, 5H, Ph); ^{13}C-nmr ($CDCl_3$) δ: 14.12 (q, J=128.3 Hz, Me), 34.55 (q, J=140.3, Me), 47.40 (t, J=130.5 Hz, CH_2), 103.61 (s, C-3a), 127.65 (d, J=159.3 Hz, Ph), 128.88 (d, J=159.7 Hz, Ph), 129.29 (d, J=157.5 Hz, Ph), 135.17 (s, Ph), 145.72 (s, C-3), 153.17 (s, C-7a), 176.71 (s, C-6), 176.78 (s, C=O). Anal. Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49; S, 11.82. Found: C, 61.80; H, 4.72; N, 15.60; S, 11.70.

1,3-Dimethyl-6-phenylpyrazolo[3,4-*d*][1,3]thiazin-4-ones (3c).
Yield 96%, mp 170-171°C (methanol); ir (KBr) cm^{-1}: 1700, 1540; ^{1}H-nmr ($CDCl_3$) δ: 2.56 (s, 3H, Me), 4.02 (s, 3H, NMe), 7.40-7.55 (m, 3H, Ph), 8.02 (d, J=7.9 Hz, 2H, Ph); ^{13}C-nmr ($CDCl_3$) δ: 14.13 (q, J=128.2 Hz, Me), 34.53 (q, J=140.3 Hz, Me), 103.06 (s, C-3a), 127.32 (d, J=159.1 Hz, Ph), 128.95 (d, J=160.6 Hz, Ph), 132.59 (d, J=160.7 Hz, Ph), 136.25 (s, Ph), 145.75 (s, C-3), 153.49 (s, C-7a), 170.82 (s, C-6), 176.34 (s, C=O). Anal. Calcd for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.92; H, 4.30; N, 16.48; S, 12.31.

3,6-Dimethyl-1-phenylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3d).
Yield 72%, mp 123-124.5°C (methanol); ir (KBr) cm^{-1}: 1675, 1570, 1530; ^{1}H-nmr ($CDCl_3$) δ: 2.64 (s, 3H, Me), 2.65 (s, 3H, Me), 7.30-7.55 (m, 3H, Ph), 7.87 (d, J=7.7 Hz, 2H, Ph); ^{13}C-nmr ($CDCl_3$) δ: 14.30 (q, J=128.5 Hz, Me), 27.81 (q, J=129.8 Hz, Me), 103.97 (s, C-3a), 123.78 (d, J=164.4 Hz, Ph), 127.55 (d, J=160.8 Hz, Ph), 128.95 (d, J=161.1 Hz, Ph), 138.00 (s, Ph), 146.84 (s, C-3), 152.65 (s, C-7a), 173.78 (s, C-6), 177.15 (s, C-4). Anal. Calcd for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.90; H, 4.30; N, 16.52; S, 12.30.

6-Benzyl-3-methyl-1-phenylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3e).
Yield 67%, mp 101-101.5°C (methanol); ir (KBr) cm^{-1}: 1675, 1570, 1540; ^{1}H-nmr ($CDCl_3$) δ: 2.63 (s, 3H, Me), 4.16 (s, 2H, CH_2), 7.25-7.50 (m, 8H, Ph), 7.85 (d, J=7.5 Hz, 2H, Ph). Anal. Calcd for $C_{19}H_{15}N_3OS$: C, 68.45; H, 4.53; N, 12.60; S, 9.62. Found: C, 68.72; H, 4.60; N, 12.48; S, 9.60.

3-Methyl-1,6-diphenylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3f).
Yield 90%, mp 167-168°C (methanol); ir (KBr) cm^{-1}: 1685, 1520; ^{1}H-nmr ($CDCl_3$) δ: 2.68 (s, 3H, Me), 7.41-7.58 (m, 6H, Ph), 7.93-8.04 (m, 4H, Ph). Anal. Calcd for $C_{18}H_{13}N_3OS$: C, 67.69; H, 4.10; N, 13.16; S, 10.04. Found: C, 67.79; H, 4.15; N, 13.18; S, 9.94.

1-*tert*-Butyl-3,6-dimethylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3g).
Yield 88%, mp 166-167°C (methanol); ir (KBr) cm^{-1}: 1680, 1575, 1470; ^{1}H-nmr ($CDCl_3$) δ: 1.75 (s, 9H, *t*-Bu), 2.54 (s, 3H, Me), 2.64 (s, 3H, Me); ^{13}C-nmr ($CDCl_3$) δ: 14.23 (q, J=128.0 Hz, Me), 27.69 (q, J=129.6 Hz, Me), 29.56 (q, J=122.8 Hz, *t*-Bu), 61.28 (s, *t*-Bu), 103.80 (s, C-3a), 143.38 (s, C-3), 152.51 (s, C-7a), 169.67 (s, C-6), 177.38 (s, C-4). Anal. Calcd for $C_{11}H_{15}N_3OS$: C, 55.67; H, 6.37; N, 17.71; S, 13.51. Found: C, 55.84; H, 6.44; N, 17.88; S, 13.44.

6-Benzyl-1-*tert*-butyl-3-methylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3h).
Yield 86%, mp 94-94.5°C (methanol); ir (KBr) cm^{-1}: 1680, 1560, 1430; ^{1}H-nmr ($CDCl_3$) δ: 1.69 (s, 9H, *t*-Bu), 2.51 (s, 3H, Me), 4.12 (s, 2H, CH_2), 7.30-7.40 (m, 5H, Ph); ^{13}C-nmr ($CDCl_3$) δ: 14.25 (q, J=128.1 Hz, Me), 29.55 (q, J=126.9 Hz, *t*-Bu), 47.42 (t, J=130.2 Hz, CH_2), 61.29 (s, *t*-Bu), 103.94 (s, C-3a), 127.51 (d, J=159.9 Hz, Ph), 128.81 (d, J=159.3 Hz, Ph), 129.39 (d, J=157.1 Hz, Ph), 135.42 (s, Ph), 143.50 (s, C-3), 152.34 (s, C-7a), 172.53 (s, C-6), 177.19 (s, C-4). Anal. Calcd for $C_{17}H_{19}N_3OS$: C, 65.15; H, 6.11; N, 13.41; S, 10.23. Found: C, 65.22; H, 6.08; N, 13.40; S, 10.08.

1-*tert*-Butyl-3-methyl-6-phenylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3i).
Yield 97%, mp 135.5-136.5°C (methanol); ir (KBr) cm^{-1}: 1680, 1540; ^{1}H-nmr ($CDCl_3$) δ: 1.84 (s, 9H, *t*-Bu), 2.58 (s, 3H, Me), 7.45-7.55 (m, 3H, Ph), 8.03 (m, 2H, Ph); ^{13}C-nmr ($CDCl_3$) δ: 14.28 (q, J=128.1 Hz, Me), 29.81 (q, J=126.8 Hz, *t*-Bu), 61.36 (s, *t*-Bu), 104.11 (s, C-3a), 127.26 (d, J=159.0 Hz, Ph), 129.04 (d, J=160.9 Hz, Ph), 132.34 (d, J=161.4 Hz, Ph), 136.78 (s, Ph), 143.63 (s, C-3), 152.79 (s, C-7a), 168.06 (s, C-6), 176.81 (s, C=O). Anal. Calcd for $C_{16}H_{17}N_3OS$: C, 64.19; H, 5.72; N, 14.04; S, 10.71. Found: C, 64.34; H, 5.80; N, 14.14; S, 10.64.

1-Methyl-6-phenylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3j).
Yield 97%, mp 165-167°C (methanol); ir (KBr) cm^{-1}: 1670, 1520; ^{1}H-nmr ($CDCl_3$) δ: 4.14 (s, 3H, Me), 7.40-7.60 (m, 3H, Ph), 8.06-8.10 (m, 2H, Ph) 8.11 (s, 1H, CH); ^{13}C-nmr ($CDCl_3$) δ: 35.04 (q, J=140.5 Hz, Me), 104.99 (s, C-3a), 127.43 (d, J=159.1 Hz, Ph), 129.05 (d, J=160.8 Hz, Ph), 134.19 (d, J=160.7 Hz, Ph), 136.18 (d, J=193.6 Hz, C-3), 153.11 (s, C-7a), 170.95 (s, C-6), 175.95 (s, C=O). Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.18. Found: C, 59.30; H, 3.70; N, 17.28; S, 13.21.

Cleavage of *tert*-butyl group from 3g-i:
6-Alkyl/aryl-3-methylpyrazolo[3,4-*d*][1,3]thiazin-4-ones (3k-m).
A suspension of each **3g-i** (5 mmol) in formic acid (25 ml) was heated under reflux for 2 h. The solution was evaporated to give a solid which was taken up with water (50 ml) and extracted with ethyl acetate (3 x 30 ml).

After drying over anhydrous magnesium sulfate, the solvent was removed and the residue was recrystallized from the indicated solvent to give a white crystalline product.

3,6-Dimethylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3k).

Yield 92%, mp 260.5-261.5°C (toluene); ir (KBr) cm^{-1}: 3200-2500 (br), 1670, 1600, 1500, 1430; nmr: two tautomers in a 3:2 ratio; when two resonances are reported, the first value is attributed to the major tautomer. ^{1}H-nmr (DMSO-d_6) δ: 2.42 and 2.49 (s, 3H, Me), 2.55 and 2.61 (s, 3H, Me), 13.95 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ: 13.89 (q, J=127.2 Hz) and 11.35 (q, J=128.2 Hz, Me), 26.92 (q, J=129.7 Hz, Me), 101.55 and 102.50 (s, C-3a), 144.83 and 139.67 (s, C-3), 154.48 and 159.58 (s, C-7a), 172.71 and 166.05 (s, C-6), 175.50 and 178.10 (s, C-4). Anal. Calcd for $C_7H_7N_3OS$: C, 46.40; H, 3.89; N, 23.19; S, 17.69. Found: C, 46.30; H, 3.86; N, 23.30; S, 17.54.

6-Benzyl-3-methylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3l).

Yield 93%, mp 185-186°C (toluene); ir (KBr) cm^{-1}: 3200-2700 (br), 1670, 1600, 1495, 1430; nmr: two tautomers in a 3:2 ratio; when two resonances are reported, the first value is attributed to the major tautomer. ^{1}H-nmr (DMSO-d_6) δ: 2.40 and 2.52 (s, 3H, Me), 4.21 and 4.14 (s, 2H, CH_2), 7.23-7.34 (m, 5H, Ph), 14.05 and 13.98 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ: 13.87 (q, J=127.4 Hz) and 11.32 (q, J=128.6 Hz, Me), 45.94 (t, J=130.8 Hz) and 46.14 (t, J=130.8 Hz, CH_2), 101.76 and 102.71 (s, C-3a), 127.19 (d, J=160.0 Hz, Ph), 128.61 (d, J=158.9 Hz, Ph), 129.27 (d, J=157.2 Hz, Ph), 135.48 and 135.71 (s, Ph), 144.91 and 139.80 (s, C-3), 154.36 and 159.49 (s, C-7a), 175.34 and 168.86 (s, C-6), 176.11 and 177.50 (s, C-4). Anal. Calcd for $C_{13}H_{11}N_3OS$: C, 60.68; H, 4.31; N, 16.33; S, 12.46. Found: C, 60.82; H, 4.40; N, 16.28; S, 12.32.

3-Methyl-6-phenylpyrazolo[3,4-*d*][1,3]thiazin-4-one (3m).

Yield 96%, mp 253-254°C (ethyl acetate); ir (KBr) cm^{-1}: 3200-2700, 1690, 1530, 1450; nmr: two tautomers in a 3:2 ratio; when two resonances are reported, the first value is attributed to the major tautomer. ^{1}H-nmr (DMSO-d_6) δ: 2.40 and 2.49 (s, 3H, Me), 7.50-7.55 (m, 3H, Ph), 7.90-7.95 (m, 2H, Ph), 13.95 and 14.09 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ: 13.88 (q, J=128.2 Hz) and 11.36 (q, J=128.6 Hz, Me), 101.82 and 102.90 (s, C-3a), 126.89 (d, J=160.1 Hz, Ph), 129.08 (d, J=164.2 Hz, Ph), 132.61 (d, J=160 Hz) and 132.07 (d, J=160 Hz, Ph), 135.64 and 136.21 (s, Ph), 145.05 and 139.89 (s, C-3), 154.66 and 159.82 (s, C-7a), 169.65 and 164.27 (s, C-6), 175.46 and 177.80 (s, C-4). Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.18. Found: C, 59.40; H, 3.78; N, 17.20; S, 13.14.

Cleavage of *tert*-butyl group from 2i:

***N*-(3-Methylpyrazol-5-yl)thiobenzamide (2m).**

A suspension of **2i** (1.64 g, 6 mmol) in formic acid (30 ml) was heated under reflux for 1 h. The solution was evaporated to give a solid which was suspended in water (100 ml) and extracted with ethyl acetate (3 x 50 ml). After drying over anhydrous magnesium sulfate, the solvent was removed and the residue was recrystallized from toluene. Pale yellow crystals, yield 1.08 g, 93%, mp 187.5-188.5°C; ir (KBr) cm^{-1}: 3200 (br), 1590 (br)

1550, 1370 (br); ^{1}H-nmr (DMSO-d_6) δ: 2.28 (s, 3H, Me), 6.94 (s, 1H, CH), 7.40-7.50 (m, 3H, Ph), 7.81 (d, J=6.9 Hz, 2H, Ph), 12.08 (s, 1H, NH), 12.49 (s, 1H, NH); ^{13}C-nmr (DMSO-d_6) δ: 10.79 (q, J=127.5 Hz, Me), 98.28 (d, J=179.3 Hz, C-4), 127.47 (d, J=162.5 Hz, Ph), 127.75 (d, J=162.5 Hz, Ph), 130.00 (d, J=160.1 Hz, Ph) 138.02 (s, C-5), 142.10 (s, Ph), 148.76 (s, C-3), 195.73 (s, C=S). Anal. Calcd for $C_{11}H_{11}N_3S$: C, 60.80; H, 5.10; N, 19.34; S, 14.75. Found: C, 60.58 ; H, 4.98; N, 19.41; S, 14.58.

7-Methyl-2-phenyl-4*H*-pyrazolo[1,5-*c*][1,3,5]thiadiazine-4-one (4).

Trichloromethyl chloroformate (0.6 ml, 5 mmol) was added to a solution of **2m** (1.08 g, 5 mmol) in anhydrous tetrahydrofuran (50 ml). After 10 h stirring at room temperature, the solvent was removed and the solid residue was purified by column chromatography (eluent: petroleum ether/ethyl acetate 7:3 v/v). White crystals, yield 1.12 g (92%), mp 150-151°C (methanol); ir (KBr) cm^{-1}: 1800, 1720, 1580; ^{1}H-nmr ($CDCl_3$) δ: 2.46 (s, 3H, Me), 6.58 (s, 1H, CH), 7.40-7.55 (m, 3H, Ph); 7.96 (d, J=7.9 Hz, Ph); ^{13}C-nmr ($CDCl_3$) δ: 14.43 (q, J=127.8 Hz, Me), 107.33 (d, J=179.4 Hz, C-8), 126.96 (d, J=160.2 Hz, Ph), 129.12 (d, J=160.6 Hz, Ph), 132.92 (d, J=161.2 Hz, Ph), 134.78 (s, Ph), 149.16 (s, C-8a), 155.62 (s, C-4), 156.37 (s, C-7), 159.92 (s, C-2). Anal. Calcd for $C_{12}H_9N_3OS$: C, 59.24; H, 3.73; N, 17.27; S, 13.18. Found: C, 59.38; H, 3.68; N, 17.18; S, 13.08.

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