Synthesis of 3-Methyl-substituted Pyrazolotriazolopyrimidin-4-one and Pyrazolothiazolopyrimidin-4-one Derivatives

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As a part of a research on anti-inflammatory analgesic compounds 3-methyl substituted pyrazolotriazolopyrimidin-4-one and pyrazolothiazolopyrimidin-4-one derivatives were prepared by previously reported procedures. None of the compounds showed improved activity when compared with the previously reported unsubstituted analogs.

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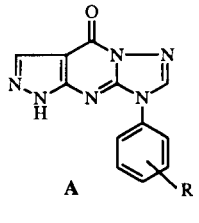
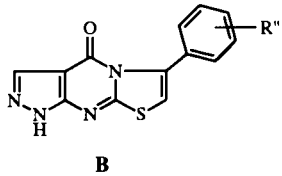
Introduction.

Previous disclosures by our laboratories, part of the work carried out by Russo *et al.*, underlined the potential of functionalized polycondensed heterocycles containing the pyrimidine ring as the biological active agents [1-6]. In this subject pyrazolotriazolopyrimidin-4-ones and pyrazolothiazolopyrimidin-4-ones (General Formulas **A** and **B**) showed interesting properties as *in vivo* anti-inflammatory/analgesic agents, while there was no ulcerogenic activity probably due to a mechanism of action different from the common NSAIDs (nonsteroidal anti-inflammatory drugs) [1-3].

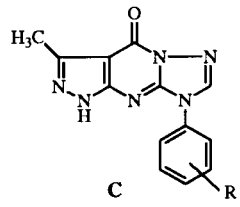


A

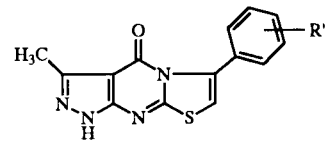


B

Members of the pyrazolothiazolopyrimidin-4-one series **B** are currently being investigated *in vitro* as tools for the characterization of the Neurokinin Receptor System [7]. Because peptides and peptide analogues in general are inefficient drugs, mainly due to their unfavorable bioavailability and stability, nonpeptide compounds are currently being developed in many peptide systems not only as drugs but also as pharmacological and physiological tools. These nonpeptide compounds may become a new class of analgesic and anti-inflammatory drugs, since the above neuropeptides are believed to play an important role in afferent transmission of pain stimuli in the spinal cord and in the neurogenic contribution to the inflammatory process. The rationale design of such compounds represents a challenging problem in molecular recognition for which there is no established rational approach. File chemical approaches [2,3,8] many times represented useful starting points for *ex post facto* rationalizations by which potent and selective NK ligands arose. This subject was recently presented in an exhaustive review by Longmore *et al.* [8]. In order to go deeply into the *in vivo* structure-activity relationships, further evaluation of the effect of the methyl substitution on the pyrazole ring and, as a consequence, the change in the lipophilicity of the molecule, the 3-methyl analogs, Formulas **C** and **D**, of the reported most active forms were prepared following our previously reported procedures [1-3,9]. An additional purpose was the extension of our chemical archives, thus exploring new synthetic methodologies [6,9], taking into account the possible use of the compounds, Formula **D**, as potential Neurokinin Antagonists [1-3,8].



C

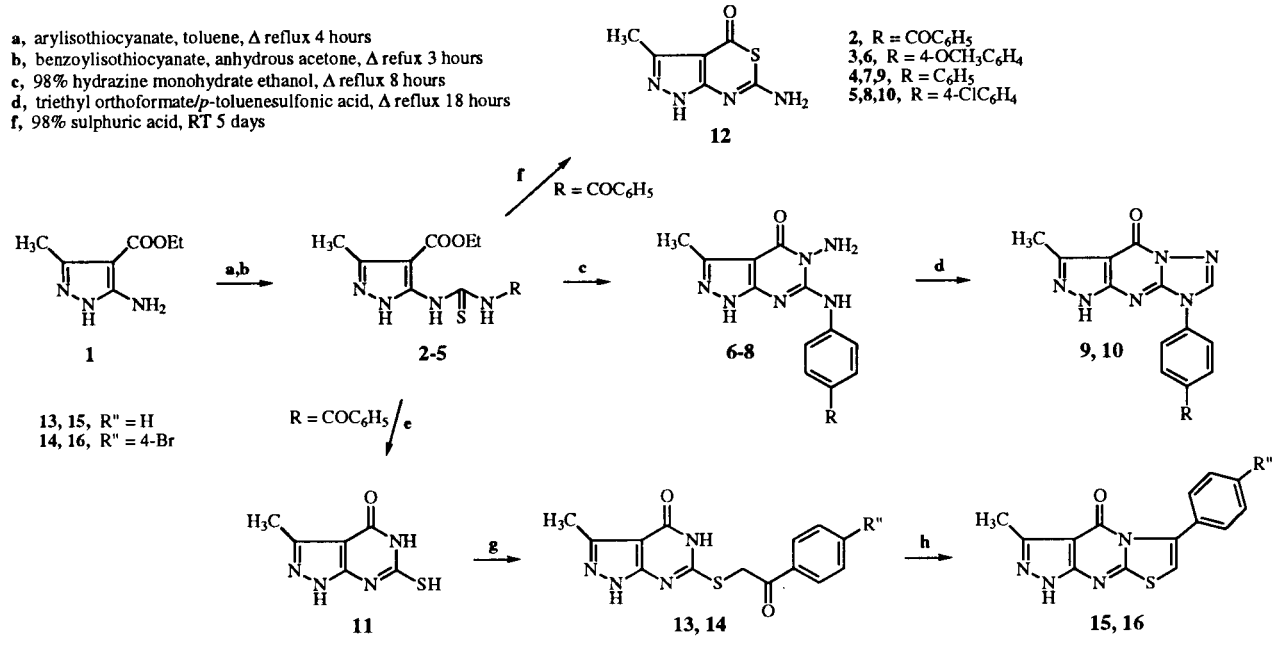


D

Chemistry.

The synthetic pathways (Scheme) we choose to obtain the 3-methyl substituted pyrazolotriazolopyrimidin-4-one derivatives, Formula **C**, and their isosteres containing the thiazole in the place of triazole ring, Formula **D**, were the ones previously applied for the synthesis of the reported 3H analogs [1-3,9]. Therefore, the 3-methyl substituted pyrazolotriazolopyrimidin-4-one derivatives **9, 10**, Formula **C**, were prepared by cyclization of the appropriate 3-methyl-substituted 2-(4-aryl)amino-3-aminopyrazolo[3,4-*d*]pyrimidin-4-one derivatives **7, 8** with triethyl orthoformate, *p*-toluenesulfonic acid (*p*-TsOH) as the catalyst. The 4-methoxyphenyl

Scheme Synthetic Routes to 3-Methyl-substituted Pyrazolotriazolopyrimidines **9, 10** and Pyrazolothiazolopyrimidine **15, 16** Derivatives



e, 1) 2*N* methanolic sodium hydroxide, Δ reflux 6 hours; 2) 10% hydrochloric acid
g, α-aloketone, acetone/sodium carbonate stirring RT 24 hours
h, 98% sulphuric acid, RT 5 days

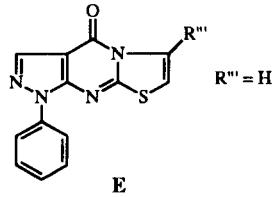
derivative **6** and the starting compounds **7, 8** were in turn prepared by reaction of 98% hydrazine monohydrate with the appropriate 3-methyl-substituted *N*-(4-carboethoxypyrazol-3-yl)-*N'*-arylthioureas **2-5**. The thiourea intermediates **2-5** were obtained by reaction of 3-methyl-4-ethoxycarbonyl-5-aminopyrazolo-**1** [10,11] with the pertinent commercially available (Aldrich) aryl isothiocyanate, in toluene at reflux (Scheme). The 3-methyl-substituted pyrazolothiazolopyrimidin-4-one derivatives **15, 16** were prepared by a simple acid cyclodehydration in 98% sulphuric acid (5 ml) of the 3-methyl-4-hydroxy-6-(phenacylthio)-pyrazolo-[3,4-*d*]pyrimidines **13, 14** at room temperature for 5 days [2,3]. The intermediates **13, 14** were prepared stirring the 3-methyl-4-hydroxy-6-mercaptopyrazolo[3,4-*d*]pyrimidine **11** with the pertinent α-haloketone, commercially available, in anhydrous acetone/sodium carbonate at room temperature for 24 hours. The starting 3-methyl-4-hydroxy-6-mercaptopyrazolo[3,4-*d*]pyrimidine **11** was prepared by alkaline cyclization of 5-methyl-substituted *N*-(4-carboethoxypyrazol-3-yl) *N*-benzoylthiourea **2**, obtained by reaction of 3-amino-4-ethoxycarbonyl-5-methylpyrazolo-**1** [10,11] with an equimolar amount of benzoyl isothiocyanate, either commercially available or *in situ* prepared [12,13], in acetone at reflux for 3 hours. The "by pass" reaction with benzoyl isothiocyanate [12] was necessary because of the lack of reactivity of compound **1** [10,11] with ammonium or potassium thiocyanate. The cyclic amide structure of compound **11** furthermore was defined using as a comparison its cyclic thioester isomer **12** obtained by ring closure in 98% sulphuric acid at room temperature [14,15]. The two isomeric derivatives **11, 12** are well differentiated according to the alkaline solubility and their infrared spectra. Compound **12** shows a different stretching of the carbonyl group as a consequence of the "lactone" structure [14]. The starting compound **1** [10,11] was prepared following the method of Beyer and Wolter [10] or by the Baba *et al.* [11]. The first method employs the thermal decomposition in a 2*N* ethanolic hydrochloric acid solution of the 2-amino-5-carboethoxy-1,3,4-thiadiazine hydrochloride [10]. The more recent method of Baba *et al.* [11], based on the reaction between the α-cyano-β-methoxy-β-methylacrylic ester with hydrazine, is less tedious but it cannot be applied on a large scale in our laboratories because of the diazomethane use. All the spectral data (ir, ^{1}H nmr) are in accordance with the assigned structures [1-3,6-9,14] and are consistent with the literature data for the reported compound **1** [10,11]. They are listed below for some representative examples of the new compounds synthesized.

Conclusion.

Compounds **9, 10, 15, 16,** are not cyclized products of compound **6**. None of the tested new compounds (**6, 9, 10, 15,** and **16** (Scheme), following the pharmacological protocol reported in our previous papers (Carrageenan-induced rat paw oedema at 10-30 mg/kg, p.o. and Phenylquinone writhing test at 10 mg/kg, p.o.) [1-3] showed *in vivo* any improved activity in comparison with the previously reported analogs without the 3-methyl

group [1-3]. In the case of the pyrazolotriazolopyrimidine derivatives **9, 10**, 3-methyl-substitution produced completely inactive compounds.

Therefore the biological evaluation in this protocol will be discontinued. A quite similar *in vivo* biological result came from the pyrazole nitrogen substitution of both pyrazolotriazolopyrimidin-4-one and pyrazolothiazolopyrimidin-4-one derivatives with a methyl group, as previously reported by us [1-3,9], and by the N1-phenyl-substitution in the pyrazolothiazolopyrimidinones (1-phenylpyrazolo[3,4-*d*]thiazolo-[3,2-*a*]pyrimidin-4-one) (Formula **E**) [3,7,15].



E

These data suggest that the enhanced hydrophobic character as a consequence of the aliphatic or aromatic substitution on the pyrazole ring [1-3,9] is a negative factor in the modulation of the anti-inflammatory/analgesic properties of these molecules. Nevertheless pharmacokinetic and pharmacodynamic parameters might play a role [17]. In consideration of the acidic character of the protons in positions 1-3 of the pyrazole ring, additional non-covalent interactions by hydrogen bond formations may play a role as an important factor in the biological action of these molecules [17,18]. Another explanation may be an unfavourable steric hindrance as a consequence of the methyl or aromatic group at the N1, N2 or 3C positions [2,3,9,16] in the binding interaction of these derivatives with some effector of the inflammatory process [17,19,20].

The nitrogen alkylating effect of the triethyl orthoformate was recently reported by us [6,9]. Moreover, the methyl-substitution does prevent position 3 from being competitive representing another attack point for the triethyl orthoformate action [18]. Thus, the ethyl-donor effect at the pyrazole nitrogen should be more remarkable. Additional studies are currently being carried out about the possible use of alkyl orthoformates as alkylating agents of nitrogen heterocyles [6,9]. We will be very grateful to other authors if they will provide information about further developments of the method together with valuable statistical and technical support coming from their results.

EXPERIMENTAL

Melting points were determined on a Büchi capillary apparatus and are uncorrected. The ir spectra were obtained with potassium bromide discs on a Perkin-Elmer 1600 FT-IR series spectrophotometer. Elemental combustion analyses were performed on a Carlo Erba Model EA 1108 Analyzer instrument by Dr. S. Di Marco of the Microanalysis Laboratory of Dipartimento di Scienze Farmaceutiche Tossicologica, Università di Catania. When analyses are indicated by the elements' symbols or functions, the analytical results were within ±0.40% of the theoretical values. The mp and the elemental analyses of the crude tricyclic compounds and their synthetic intermediates in both the subject series, Formulas **C** and **D**, were within ±0.2 and ±3 respectively, if compared with the pure product. The synthetic intermediates might be used without further purification. The ^{1}H nmr spectra were recorded at 300.13 MHz on a Bruker AMX-R 300 spectrometer in DMSO-d_6 as a solvent at 298 K. All ^{1}H chemical shifts are given as δ values in parts per million (ppm) downfield from tetramethylsilane (TMS, 0.00 ppm) using the residual solvent peak as internal reference and coupling constants in Hz. According to our previous papers [2,3,16] we assumed a linear geometry for the tricyclic derivatives **15, 16** (Scheme). In some spectra the resonance relative to the pyrazole NH is not easily detectable due to the coupling with a quadrupolar ^{14}N nucleus and rapid exchange with the small amount of water present in the solvent [2,3,18]. The tlc was performed on plates RP 18 $F_{254}S$ Merck precoated 5-10 cm, layer thickness 0.25 mm. Reactions were routinely followed by thin layer chromatography (tlc) on silica gel 60 F_{254} aluminum sheets (Merck); system, ethyl acetate-cyclohexane (ϕ = 20%) **1-5**; ethyl acetate-cyclohexane (ϕ = 30%) **1-5**; ethyl acetate **1-16**; ethyl acetate-methanol (ϕ = 10%) **6-16** as an eluent and similarly the purity of each compound was checked. The spots were detected by uv irradiation at 254-365 nm. All chemicals were purchased from Aldrich, Fluka, Merck and Carlo Erba Chemical Co and were used without further purification. Chromatographic eluents were of analytical grade or purified following the usual method.

5-methyl-substituted *N*-(4-carboethoxypyrazol-3-yl) *N'*-(benzoyl) thiourea (**2**).

To a stirred solution of commercially available or *in situ* prepared benzoyl isothiocyanate (6.00 g, 35.46 mmoles) in anhydrous acetone (10 ml when commercially available benzoyl isothiocyanate was used), a saturated 3-amino-4-carboethoxy-5-methylpyrazolo-**1** solution (6.2 g, 36.64 mmoles) [10,11] in anhydrous acetone (60-65 ml), was slowly added dropwise and the mixture was gently refluxed for 3 hours [15]. The precipitate was collected by filtration, repeatedly washed with cold water and dried. Compound **2** can be processed without recrystallization. An analytically pure sample can be obtained by recrystallization from ethanol.

The yield of **2** was 50%, mp 210-211°; ir (potassium bromide): (neat) ν 3161 (NH), 1694 (C=O) cm^{-1}; ^{1}H nmr (DMSO-d_6): 13.06 (br s, 1H, NH), 12.51 (br s, 1H, NH), 11.61 (br s, 1H, NH), 7.98 (m, 2H, *ortho*-phenyl ring), 7.67 (m, 1H, *para*-phenyl ring), 7.54 (m, 2H, *meta*-phenyl ring), 4.17 (q, ^{3}JHH = 7.7 Hz, 2H, methylene), 2.44 (s, 3H, methyl), 1.22 (t, ^{3}JHH = 7.7 Hz, 3H, methyl); tlc system, ethyl acetate as an eluent.

Anal. Calcd. for $C_{15}H_{16}N_4O_3S$: C, 54.20; H, 4.85; N, 16.85; S, 9.64. Found: C, 54.22; H, 4.82; N, 16.66; S, 9.49.

General Procedure for the Synthesis of 5-Methyl-substituted *N*-(4-Carboethoxypyrazol-3-yl) *N'* -(Aryl)thioureas **3-5**.

A solution of aminoester **1** [10,11] (1 g, 5.91 mmoles) and an equimolar amount of (4-methoxyphenyl) isothiocyanate (0.97 g, 5.91 mmoles) dissolved in toluene (5 ml) was heated at reflux. After 4 hours the mixture was cooled and the solid was collected and dried. A further amount of the compound can be obtained by rotary evaporation of the solution reaction [1,2]. Compounds

3-5 can be processed without recrystallization. An analytically pure sample can be obtained by recrystallization from toluene-ethanol (ϕ = 30%).

The yield of **3** was 60%, mp 199-200°; ir (potassium bromide): (neat) ν 3344-3266 (NH), 1677 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 13.17 (br s, 1H, NH), 11.35 (br s, 1H, NH), 9.50 (br s, 1H, NH), 7.47 (m, 2H, aryl), 6.95 (m, 2H, aryl), 4.29 (q, ^3JHH = 7.1 Hz, 2H, methylene), 3.76 (s, 3H, methoxy), 2.44 (s, 3H, methyl), 1.31 (t, ^3JHH = 7.1 Hz, 3H, methyl); tlc system, ethyl acetate-cyclohexane (ϕ = 20%); ethyl acetate-cyclohexane (ϕ = 30%); ethyl acetate as an eluent.

Anal. Calcd. for $C_{15}H_{18}N_4O_3S$: C, 53.89; H, 5.38; N, 16.76; S, 9.58. Found: C, 53.63; H, 5.48; N, 16.74; S, 9.58.

The yield of **4** was 40%, mp 180-181°; ir (potassium bromide): ν (neat) 3380-3240 (NH), 1665 (C=O) cm^{-1}; tlc system, ethyl acetate-cyclohexane (ϕ = 20%); ethyl acetate-cyclohexane (ϕ30%); ethyl acetate as an eluent.

Anal. Calcd. for $C_{14}H_{16}N_4O_2S$: C, 55.26; H, 5.26; N, 18.42; S, 10.52. Found: C, 55.01; H, 5.30; N, 18.52; S, 10.59.

The yield of **5** was 50%, mp 210-211°; ir (potassium bromide): ν (neat) 3350-3300 (NH), 1650(C=O) cm^{-1}; tlc system, ethyl acetate-cyclohexane (ϕ = 20%); ethyl acetate-cyclohexane (ϕ = 30%); ethyl acetate as an eluent.

Anal. Calcd. for $C_{14}H_{15}ClN_4O_2S$: C, 49.70; H, 4.43; N, 16.56; S, 9.46. Found: C, 49.40; H, 4.33; N, 16.51; S, 9.47.

General Procedure for the Synthesis of 3-Methyl-substituted 2-(4-Aryl)amino-3-aminopyrazolo[3,4-*d*]pyrimidin-4-ones **6-8**.

To a stirred solution of the 3-methyl *N*-(4-carboethoxy-pyrazol-3-yl) *N'*-(phenyl)thiourea **4** (2.5 g, 8.21 mmoles) dissolved in 15 ml of ethanol, 98% hydrazine monohydrate (3 ml) was slowly added. The mixture was refluxed for 8 hours and the solid crystallized on cooling was collected, repeatedly washed with water and dried [1,2,6,9]. Compounds **6-8** can be processed without recrystallization. An analytical pure sample can be obtained by recrystallization from ethanol.

The yield of **6** was 70%, mp 263-264°; ir (potassium bromide): (neat) ν 3336-3216 (NH), 1656 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 12.52 (br s, 1H, NH), 9.23 (br s, 1H, NH), 7.56 (m, 2H, aryl), 6.91 (m, 2H, aryl), 5.42 (s, 2H, NH_2), 3.74 (s, 3H, methoxy), 2.34 (s, 3H, methyl); tlc system, ethyl acetate; ethyl acetate-methanol (ϕ = 10%) as an eluent.

Anal. Calcd. for $C_{13}H_{14}N_6O_2$: C, 54.54; H, 4.89; N, 29.37. Found: C, 54.63; H, 4.82; N, 29.28.

The yield of **7** was 80%, mp 269-270°; ir (potassium bromide): (neat) ν 3339-3101 (NH), 1699 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 12.61 (br s, 1H, NH), 9.39 (br s, 1H, NH), 7.75 (m, 2H, *ortho*-phenyl ring), 7.34 (m, 2H, *meta*-phenyl ring), 7.08 (m, 1H, *para*-phenyl ring), 5.47 (s, 2H, NH_2), 2.37 (s, 3H, methyl); tlc system, ethyl acetate; ethyl acetate-methanol (ϕ = 10%) as an eluent.

Anal. Calcd. for $C_{12}H_{12}N_6O$: C, 56.25; H, 4.68; H, 32.81. Found. C, 56.29; H, 4.44; N, 32.69.

The yield of **8** was 80%, mp 288-290°; ir (potassium bromide): (neat) ν 3324-3203-3140 (NH), 1659 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 12.66 (br s, 1H, NH), 9.54 (br s, 1H, NH), 7.81 (m, 2H, aryl), 7.38 (m, 2H, aryl), 5.47 (s, 2H, NH_2), 2.36 (s, 3H, methyl); tlc system, ethyl acetate; ethyl acetate-methanol (ϕ = 10%) as an eluent.

Anal. Calcd. for $C_{12}H_{11}ClN_6O$: C, 49.65; H, 3.79; N, 28.96. Found: H, 49.63; H, 3.82; N, 28.73.

General Procedure for the Synthesis of 3-Methyl-substituted 8-(Aryl)-1*H*, (2*H*),4*H*,8*H*-pyrazolo[3,4-*d*][1,2,4]triazolo[1,5-*a*]-pyrimidin-4-ones **9, 10**.

A suspension of 3-methyl-substituted 2-(phenyl)amino-3-aminopyrazolo[3,4-*d*]pyrimidin-4-one **7** (1.5 g, 5.85 mmoles) end *p*-toluenesulfonic acid (*p*-TsOH) (1.5 g, 8.72 mmoles) in triethyl orthoformate (45 ml) was refluxed under stirring for 18 hours. The solid material was collected by filtration, washed with water, dried and recrystallized from dimethylformamide.

The yield of **9** was 50%, mp >300°; ir (potassium bromide): (neat) ν 3076 (NH), 1709 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 12.97 (br s, 1H, NH), 9.18 (s, 1H, triazole), 7.86 (m, 2H, *ortho*-phenyl ring), 7.62 (m, 2H, *meta*-phenyl ring), 7.51 (m, 1H, *para*-phenyl ring), 2.47 (s, 3H, methyl); tlc system, ethyl acetate; ethyl acetate-methanol (ϕ = 10%) as an eluent.

Anal. Calcd. for $C_{13}H_{10}N_6O$: C, 58.64; H, 3.75; N, 31.57. Found: C, 58.42; H, 3.83; N, 31.20.

The yield of **10** was 65%, mp >300°, ir (potassium bromide): (neat) ν 3084 (NH), 1716 (C=O) cm^{-1}; tlc system, ethyl acetate; ethyl acetate-methanol (ϕ = 10%) as an eluent.

Anal. Calcd. for $C_{13}H_{10}ClN_6O$•0.5DMF: C, 51.70; H, 3.71; N, 27.04. Found: C, 51.63; H, 3.40; N, 26.78.

3-Methyl-4-hydroxy-6-mercaptopyrazolo[3,4-*d*]pyrimidine (**11**).

A solution of 5-methyl substituted *N*-(4-carboethoxy-pyrazol-3-yl) *N'*-(benzoyl)thiourea **2** (10 g, 30.08 mmoles) dissolved in 2*N* methanolic sodium hydroxide (300 ml) was refluxed for 6 hours then filtered. The clear solution acidified (*p*H = 5,6) with 10% hydrochloric acid gave the compound **11** as a white solid. The compound can be processed without recrystallization. An analytically pure sample can be obtained by recrystallization from dimethylformamide-water.

The yield of **11** was 90%, mp >300°; ir (potassium bromide): (neat) ν 3142 (NH), 1685 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 13.25 (br s, 1H, NH), 12.82 (br s, 1H, NH), 11.67 (br s, 1H, SH), 2.44 (s, 3H, methyl); tlc, ethyl acetate, ethyl acetate methanol (ϕ = 10%) as an eluent.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.56; H, 3.29; N, 30.76; S, 17.58. Found: C, 39.28; H, 3.44; N, 30.48; S, 17.68.

3-Methyl-substituted 6-Aminopyrazolo[3,4-*d*][1,3]thiazin-4(1*H*)-one (**12**).

A suspension of 5-methyl-substituted *N*-(4-carboethoxypyrazol-3-yl) *N'*-(benzoyl)thiourea **2** (0.6 g, 1.80 mmoles) in 98% sulphuric acid (4 ml) was left at room temperature for 4 days. The resultant clear solution was slowly added to ice water (30 ml) and the solid residue was collected, washed with sodium bicarbonate solution (ω = 5%) and cold water, dried and recrystallized from ethanol. An analytically pure sample can be also obtained by preparative tlc (plc), ethyl acetate as an eluent.

The yield of **12** was 40%, mp >300°; ir (potassium bromide): (neat) ν 3244-3086 (NH), 1661 (C=O) cm^{-1}; tlc system, ethyl acetate as an eluent.

Anal. Calcd. for $C_6H_6N_4OS$: C, 39.56; H, 3.29; N, 30.76; S, 17.58. Found: C, 39.63; H, 3.38; N, 30.38; S, 17.42.

General Procedure for the Synthesis of 3-Methyl-substituted 4-Hydroxy-6-(thioketomethylene)-pyrazolo[3,4-*d*]pyrimidines **13, 14**.

To a stirred (45 minutes) suspension of 3-methyl-4-hydroxy-6-mercaptopyrazolo[3,4-*d*]pyrimidine **11** (4 g, 21.95 mmoles) and

sodium carbonate in anhydrous acetone (180 ml) a saturated 4'-bromophenacylbromide solution (4 g, 20.08 mmoles) was slowly added for 2 hours. The mixture was then stirred for an additional 24 hours and the solid was collected by filtration under reduced pressure, repeatedly washed with water and dried. The compounds can be processed without recrystallization. An analytically pure sample can be obtained by recrystallization from acetic acid

The yield of **13** was 70%, mp 231-233°; ir (potassium bromide): ν (neat) 3105 (NH), 1681 (C=O) cm^{-1}; tlc system, ethyl acetate; ethyl acetate-methanol (ϕ = 10%) as an eluent.

Anal. Calcd. for $C_{14}H_{12}N_4O_2S$: C, 56.00; H, 4.00; N, 18.66; S, 10.66. Found: C, 55.80; H, 4.11; N, 18.48; S, 10.56.

The yield of **14** was 50%, mp >300° (undergoes transformation during the heating progression); ir (potassium bromide): (neat) ν 3055 (NH), 1667 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 12.21 (v br s, 1H, NH), 7.98 (m, 2H, aryl), 7.78 (m, 2H, aryl), 4.84 (s, 2H, methylene), 2.39 (s, 3H, methyl); tlc system, ethyl acetate; ethyl acetate-methanol (ϕ = 10%) as an eluent.

Anal. Calcd. for $C_{14}H_{11}BrN_4O_2S$: C, 44.32; H, 2.90; N, 14.77; S, 8.44. Found: C, 44.27; H, 3.03; N, 14.44; S, 8.31.

General Procedure for the Synthesis of 3-Methyl substituted 6-aryl-1*H*-pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidin-4-ones **15, 16**.

A suspension of 3-methyl substituted 4-hydroxy-6-(phenacylthio)pyrazolo[3,4-*d*]pyrimidine **14** (1 g, 3.33 mmoles) in 98% sulphuric acid (5 ml) was stirred for 1 hour, then left at room temperature for 1 week. The solid formed pouring the clear solution in ice-water (100 ml) under stirring was collected, washed with water, dried and recrystallized from dimethylformamide-water.

The yield of **15** was 50%, mp 254-256°; ir (potassium bromide): (neat) ν 3191-3126 (NH), 1713 (C=O) cm^{-1}; tlc system, ethyl acetate; ethyl acetate-methanol (ϕ = 10%) as an eluent.

Anal. Calcd. for $C_{14}H_{10}N_4OS$: C, 59.57; H, 3.54; N, 19.85; S, 11.34. Found: C, 59.35; H, 3.63; N, 19.50; S, 11.51.

The yield of **16** was 70%, mp 249-252° (241° undergoes transformation); ir (potassium bromide): (neat) ν 3197 (NH), 1712 (C=O) cm^{-1}; ^1H nmr (DMSO-d_6): 13.16 (v br s, 1H, NH), 7.58 (m, 2H, aryl), 7.38 (m, 2H, aryl), 7.10 (br s, 1H, thiazole), 2.38 (s, 3H, methyl); tlc system: ethyl acetate, ethyl acetate-methanol (ϕ = 10%) as an eluent.

Anal. Calcd. for $C_{14}H_9BrN_4OS$: C, 46.54; H, 2.51; N, 15.50; S, 8.87. Found: C, 46.52; H, 2.23; N, 15.25; S, 8.90.

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[16] R"' = H: ^1H nmr (DMSO-d_6): 8.45 (s, 1H, pyrazole), 8.07 (d, ^3JHH = 5 Hz, 1H arom), 8.06 (m, 2H, *ortho* phenyl), 7.57 (m, 2H, *meta* phenyl), 7.42 (d, ^3JHH= 5 Hz, 1H, arom), 7.39 (m, 1H, *para* phenyl).

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