

Synthesis of Novel Disubstituted Pyrazolo[1,5-*a*]pyrimidines, Imidazo[1,2-*a*]pyrimidines, and Pyrimido[1,2-*a*]benzimidazoles Containing Thioether and Aryl Moieties

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A series of novel 6-[(1,3,4-thiadiazol-2-yl)sulfanyl]-7-phenylpyrazolo[1,5-*a*]pyrimidines, 5-phenyl-6-[(1,3,4-thiadiazol-2-yl)sulfanyl]imidazo[1,2-*a*]pyrimidines, and 2-phenyl-3-[(1,3,4-thiadiazol-2-yl)sulfanyl]pyrimido[1,2-*a*]benzimidazoles have been synthesized in four steps starting with 2-hydroxyacetophenone. The intermediate 3-[(1,3,4-thiadiazol-2-yl)sulfanyl]-4*H*-1-benzopyran-4-ones reacted with pyrazol-3-amines, 5-methylpyrazol-3-amine, and 1*H*-imidazol-2-amine, 1*H*-benzimidazol-2-amine *via* a cyclocondensation to give the title compounds in the presence of MeONa as base, respectively. The approach affords the target compounds in acceptable-to-good yields. The new compounds were characterized by their IR, NMR, and HR mass spectra.

Introduction. – Fused heterocyclic compounds commonly exhibit various biological activities, and they mainly include [5,6], [6,6], and [7,6] ring systems [1]. In particular, the fused [5,6] structural scaffold occurs in many pharmaceutical agents with diverse physiological and pharmacological activities. For this reason, organic chemists paid high attention to pyrimidine derivatives due to their chemotherapeutic relevance [2][3]. There are a great number of compounds involving pyrimidines, such as pyrazolo[1,5-*a*]pyrimidines (**a**), imidazo[1,2-*a*]pyrimidines (**b**), and pyrimido[1,2-*a*]benzimidazoles (**c**; Fig.).

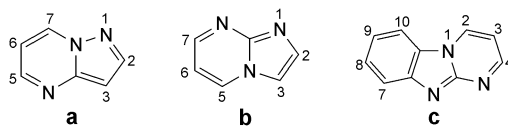


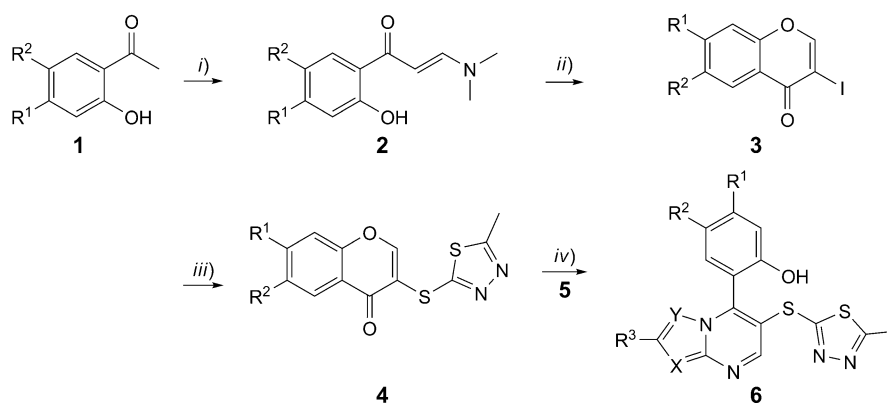
Figure. Structures of pyrazolo[1,5-*a*]pyrimidines, imidazo[1,2-*a*]pyrimidines, and pyrimido[1,2-*a*]benzimidazoles, **a–c**, respectively

Pyrazolo[1,5-*a*]pyrimidines have shown biological activities, *e.g.*, as inhibitors of protein kinases [4] and in the treatment of *Alzheimer's* disease [5]. Meanwhile, the importance of the imidazo[1,2-*a*]pyrimidines has been well established in pharmaceutical chemistry due to their activities as HIV inhibitors [6]. Similarly, some pyrimido[1,2-*a*]benzimidazoles are known as compounds with antiparasitic [7] and substance P receptor-binding activity [8], as antibacterial drugs [9], anti-arrhythmics [10], and central nervous system-depressing agents [11], as well as substances with marked

herbicidal activity [12]. The synthesis of pyrazolo[1,5-*a*]pyrimidines involved the reaction between aminopyrazoles and 1,3-biselectrophilic compounds [13][14]. The formation of imidazo[1,2-*a*]pyrimidines relied on the condensation of substituted pyridin-2-amine or pyrimidin-2-amine with the appropriate α -halogenocarbonyl compounds [15]. Construction of the pyrimido[1,2-*a*]benzimidazole scaffold involved the condensation of 1*H*-benzimidazol-2-amine with acetylene esters [16], enamino ester [17], 1,3-diketone [10], and α,β -unsaturated ketones [18], respectively.

Recently, we reported the synthesis of new 6,7-diarylpyrazolo[1,5-*a*]pyrimidines, 2,3-diarylpyrimido[1,2-*a*]benzimidazoles, and 1,2,4-triazole[4,3-*a*]pyrimidines based on reactions with isoflavones [19]. Continuing our studies on the intriguing fused [5,6] ring system, here, we describe a simple and concise method to synthesize a range of 6,7-disubstituted pyrazolo[1,5-*a*]pyrimidines, 5,6-disubstituted imidazo[1,2-*a*]pyrimidines, and 2,3-disubstituted pyrimido[1,2-*a*]benzimidazole derivatives, which contain thioether and aryl moieties *via* the intermediate 3-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-4*H*-1-benzopyran-4-ones **4** and its reaction with azol-amines **5** (*Scheme 1*).

Scheme 1. Synthesis of Pyrimidine Derivatives



i) *N,N*-Dimethylformamide dimethyl acetal, oil bath, 70–75°, 30 min. ii) I₂ in CHCl₃, room temperature, 30 min. iii) 5-Methyl-1,3,4-thiadiazole-2-thiol, *t*BuOK, DMF, 85°, MW 240 W. iv) Azol-amines, MeONa, MeOH, 20–30 min.

Results and Discussion. – To the best of our knowledge, the first synthetic route of 3-iodochromones **3** was reported by *Gammill* [20a], and substituted compounds **3** were also synthesized [20b][20c]. The condensation of 2-hydroxyacetophenones **1** with *N,N*-dimethylformamide dimethyl acetal (3.5 equiv.) gave enamines **2** in desired yield. Cyclization of **2** without further purification using I₂ (3 equiv.) in CHCl₃ afforded 3-iodochromones in good yield (*Scheme 1*). The reaction of **3** with 5-methyl-1,3,4-thiadiazole-2-thiol in the presence of *t*BuOK (1.1 equiv.) at 85° afforded compounds **4** in moderate-to-good yields [21]. A plausible mechanism for the reaction of **3** with azolethiols was proposed by *Sugita et al.* [22]. Under basic reaction conditions (3 equiv. MeONa, MeOH, reflux, 30 min), **4** reacted with **5** (1*H*-pyrazol-3-amine (**5a**), 5-methyl-

1*H*-pyrazol-3-amine (**5b**), 1*H*-imidazol-2-amine (**5c**)) to give cyclocondensation products **6** in fair yields.

The synthesis of compound **6a** was chosen as model to optimize the reaction (Table 1). A mixture of **4a** (1 mmol) and **5a** (3 mmol) was heated to reflux in MeOH. In the course of optimizing the reaction, it was noted that 3 equiv. of MeONa gave **6a** in the highest yield (Table 1, Entry 3; 75%). NaOH, K₂CO₃, and Et₃N were also investigated, and their yields were inferior to those with MeONa as base (Table 1, Entries 6–8).

Table 1. Base Effects on the Cyclocondensations of **4a** and **5a**^{a)}

Entry	Base	Molar ratios (4a / 5a /base)	Yield ^{b)} [%]
1	MeONa	1 : 3 : 1	46
2	MeONa	1 : 3 : 2	52
3	MeONa	1 : 3 : 3	75
4	MeONa	1 : 3 : 4	60
5	MeONa	1 : 3 : 5	51
6	NaOH	1 : 3 : 3	28
7	K ₂ CO ₃	1 : 3 : 3	19
8	Et ₃ N	1 : 3 : 3	13

^{a)} All reactions were carried out in boiling MeOH (8 ml) for 20–30 min. ^{b)} Yields of isolated products after chromatography.

To evaluate the scope of the cyclocondensation, F-, Br-, and MeO-substituted **4** were examined, and the expected compounds **6a–6i** were obtained (Table 2). Whereas the yields of **6c–6g** were *ca.* 80%, the results of the cyclocondensation to give imidazo[1,2-*a*]pyrimidines **6h** and **6i** under the optimized conditions were unsatisfactory (Table 2, Entries 8 and 9), but in DMSO as solvent, **6h** and **6i** were formed in good yields (Table 2, Entries 8 and 9).

Focusing on the synthesis of disubstituted pyrimido[1,2-*a*]benzimidazole **6j–6l**, we reacted 3-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-4*H*-1-benzopyran-4-ones **4** with 1*H*-benzimidazol-2-amine (**5d**) in boiling MeOH. The products were obtained in good yields (Table 3).

A proposed mechanism for the formation of compounds **6** by cyclocondensation of **4a** with azol-amines **5a–5d** in the presence of MeONa is depicted in Scheme 2 in analogy to reactions with isoflavone [19b] [23]. Compounds **4** undergo ring opening in the presence of a base to form α,β -unsaturated ketone intermediates **7**, followed by the attack of the NH₂ group of **5a** on the β -C-atom of **7**. Subsequently, a condensation between the ring N-atom and the C=O group affords the target compounds **6**. Additionally, the concentration of base is very important for the cyclocondensations.

Table 2. *Synthesis of Pyrazolo[1,5-a]pyrimidines and Imidazo[1,2-a]pyrimidines*

$\text{4} + \begin{matrix} \text{5a } X = \text{CH}, Y = \text{N}, R^3 = \text{H} \\ \text{5b } X = \text{CH}, Y = \text{N}, R^3 = \text{Me} \end{matrix} \xrightarrow[\Delta]{\text{MeONa}} \text{6}$

$\text{5c } X = \text{N}, Y = \text{CH}, R^3 = \text{H}$

Entry	R ¹	R ²	R ³	X	Y	Substrate 5	Product	Yield ^{a)} [%]
1	H	H	H	CH	N	5a	6a	75 ^{b)}
2	H	F	H	CH	N	5a	6b	79 ^{b)}
3	MeO	H	H	CH	N	5a	6c	83 ^{b)}
4	H	H	Me	CH	N	5b	6d	85 ^{b)}
5	H	F	Me	CH	N	5b	6e	80 ^{b)}
6	H	Br	Me	CH	N	5b	6f	82 ^{b)}
7	MeO	H	Me	CH	N	5b	6g	88 ^{b)}
8	H	H	H	N	CH	5c	6h	36 ^{b)} , 78 ^{c)}
9	H	F	H	N	CH	5c	6i	47 ^{b)} , 84 ^{c)}

^{a)} Yields of isolated products after chromatography. ^{b)} Reaction in boiling MeOH as solvent. ^{c)} Reaction in DMSO as solvent at 100°.

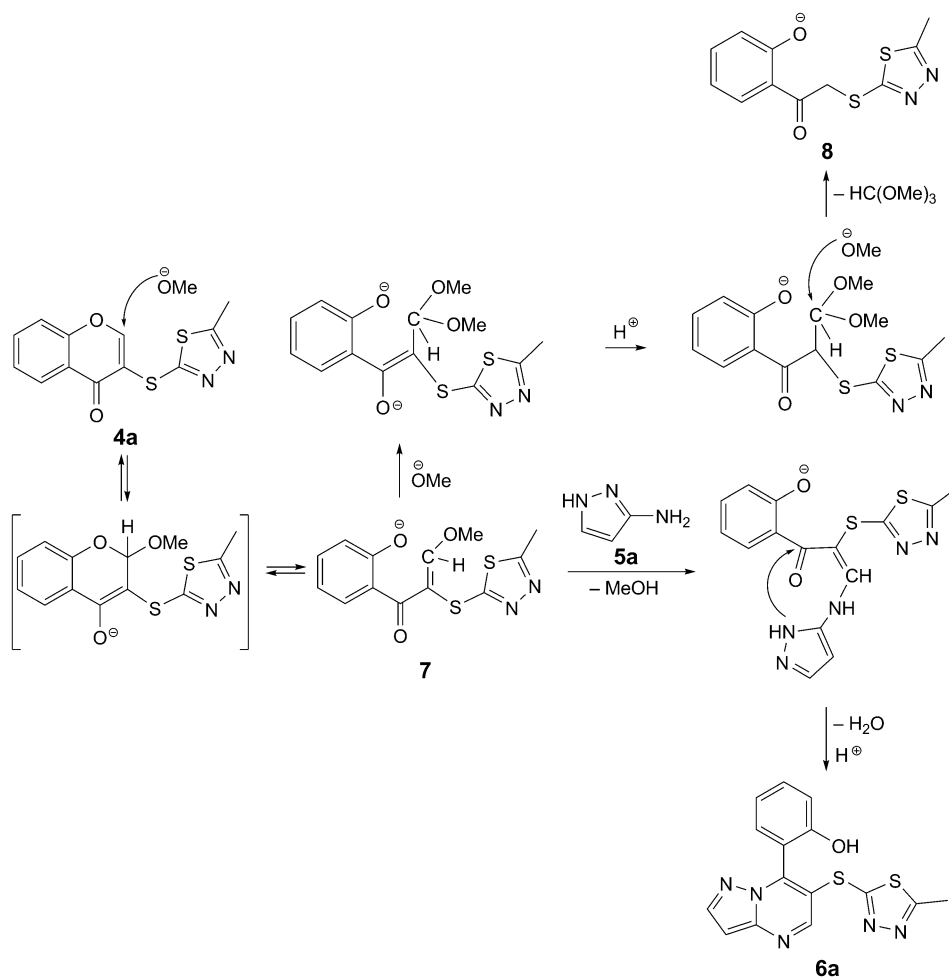
Table 3. *Synthesis of Pyrimido[1,2-a]benzimidazoles from 4 and 1H-Benzimidazol-2-amine (5d)*

$\text{4} + \text{5d} \xrightarrow[\text{reflux}]{\text{MeONa, MeOH}} \text{6j - 6l}$

Entry	R ¹	R ²	Product	Yield ^{a)} [%]
1	H	H	6j	83
2	H	F	6k	75
3	MeO	H	6l	82

^{a)} Yields of isolated products after chromatography.

Intermediate **7** would be converted to the ketone **8** at high concentration of base by elimination of HC(OMe)_3 . However, it would be too difficult for **4** to produce the intermediate **7** in low base concentration.

Scheme 2. Proposed Mechanism of Cyclocondensation **4a** with **5a**


Conclusions. – In summary, we have developed a simple and efficient method for the synthesis of 6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-7-phenylpyrazolo[1,5-*a*]pyrimidines, 5-phenyl-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]imidazol[1,2-*a*]pyrimidines, and 2-phenyl-3-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrimido[1,2-*a*]benzimidazoles in the presence of base by reaction of 3-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-4*H*-1-benzopyran-4-ones **4** with azol-amines **5**. The target compounds present an imported core with respect to biological activity. In further studies, we will investigate the biological activities.

Experimental Part

General. TLC: silica gel 60 GF_{254} plates (SiO_2); visualization under UV light (254 nm). M.p.: *X*-5 Macro melting-point instrument; uncorrected. IR Spectra: Nicolet 170SX FT-IR spectrophotometer; in

KBr pellets; $\tilde{\nu}$ in cm^{-1} . ^1H - and ^{13}C -NMR spectra: Bruker Avance 300 at 300 and 75 MHz, resp.; in (D_6)DMSO, unless otherwise indicated; δ in ppm rel. to Me_4Si as internal standard, J in Hz. LC/MS: Mson Brukermicro TOF-Q II ESI-Q-ToF; in m/z . Elemental Analyses: elementar Analysensysteme GmbH Vario EL III.

General Procedure for the Preparation of 3-Iodochromone (3) [20c]. A mixture of a substituted 2-hydroxyacetophenone **1** (5 mmol) and N,N -dimethylformamide dimethyl acetal (17.5 mmol, 3.5 equiv.) was heated to 70–75° in DMF (25 ml) for 30 min in an oil bath. The mixture was washed with sat. aq. NaCl (100 ml), a yellow precipitation of 3-(dimethylamino)-1-(2-hydroxyphenyl)prop-2-enone (**2**; 99%) was obtained. Then, to a soln. of **2** (10 mmol) in CHCl_3 (15 ml) was added I_2 (30 mmol, 3 equiv.), and the mixture was stirred at r.t. for 30 min. The reaction was quenched with 5% aq. NaHSO_3 (30 ml), and the aq. layer was extracted with CHCl_3 (3×10 ml). The org. phase was washed neutrally with 5% aq. NaHCO_3 , dried (Na_2SO_4), and concentrated *in vacuo*, and recrystallized from abs. EtOH to give **3** as colorless crystals.

General Procedure for the Preparation of Substituted 3-[(5-Methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-4H-1-benzopyran-4-ones 4 [21]. Compound **3** (1 mmol) was added to a soln. of 5-methyl-1,3,4-thiadiazole-2-thiol (132 mg, 1 mmol) and tBuOK (134 mg, 1.2 mmol) in 8 ml of DMF. The mixture was irradiated by 240 W microwave (MW) at 85° for 20–30 min. The reaction was monitored by TLC. The resulting mixture was cooled and diluted with 40 ml of ice H_2O . The obtained solid product was filtered and purified by CC (SiO_2 ; petroleum ether/AcOEt 5: 1) to afford the product **4**.

3-[(5-Methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-4H-1-benzopyran-4-one (4a) [21]. Yield: 215.5 mg (78%). Yellow powder. M.p. 75–76°. ^1H -NMR (300 MHz, (D_6)DMSO): 9.10 (s, 1 H); 8.11 (d, $J = 7.5$, 1 H); 7.90 (d, $J = 7.5$, 1 H); 7.77 (d, 1 H); 7.61 (m, 1 H); 2.63 (s, 3 H). Anal. calc. for $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_2\text{S}_2$ (276.33): C 52.16, H 2.92, N 10.14; found: C 52.00, H 2.99, N 10.06.

6-Fluoro-3-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-4H-1-benzopyran-4-one (4b). Yield: 247.3 mg (84%). Yellow powder. M.p. 179–180°. ^1H -NMR (300 MHz, CDCl_3): 8.51 (s, 1 H); 7.80 (d, $J = 7.5$, 1 H); 7.42 (m, 2 H); 2.63 (s, 3 H). Anal. calc. for $\text{C}_{12}\text{H}_7\text{FN}_2\text{O}_2\text{S}_2$ (294.32): C 48.97, H 2.40, N 9.52; found: C 48.99, H 2.38, N 9.51.

6-Bromo-3-[(5-Methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-4H-1-benzopyran-4-one (4c). Yield: 284.2 mg (80%). Yellow powder. M.p. 145–146°. ^1H -NMR (300 MHz, CDCl_3): 8.44 (s, 1 H); 8.29 (s, 17.75 (d, $J = 7.4$, 17.3 (d, $J = 8.9$, 12.68 (s, 3 H). Anal. calc. for $\text{C}_{12}\text{H}_7\text{BrN}_2\text{O}_2\text{S}_2$ (355.23): C 40.57, H 1.99, N 7.89; found: C 40.60, H 1.98, N 7.88.

7-Methoxy-3-[(5-Methyl-1,3,4-thiadiazol-2-yl)sulfanyl]-4H-1-benzopyran-4-one (4d). Yield: 229.8 mg (75%). Yellow powder. M.p. 190–191°. ^1H -NMR (300 MHz, CDCl_3): 8.44 (s, 1 H); 8.15 (d, $J = 8.9$, 1 H); 7.03 (d, $J = 8.8$, 1 H); 6.88 (s, 1 H); 3.92 (s, 3 H); 2.69 (s, 3 H). Anal. calc. for $\text{C}_{13}\text{H}_{10}\text{N}_2\text{O}_3\text{S}_2$ (306.36): C 50.97, H 3.29, N 9.14; found: C 50.94, H 3.30, N 9.16.

General Procedure for the Preparation of the Compounds 6a–6l (Table 2, Entry 1–9; and Table 3, Entry 1–3). A mixture of **4** (1 mmol), **5** (3.0 mmol), and MeONa (3 mmol) in boiling MeOH (DMSO, at 100°, **5c**) was heated for 20–30 min. The reaction was monitored by TLC, until the disappearances of the starting materials. After addition of H_2O (25 ml), the soln. was washed neutrally with aq. 5% HCl. A yellow precipitate was formed and filtered. The crude product was obtained and purified by CC (SiO_2 ; $\text{CHCl}_3/\text{MeOH}$ 30:1) to give the corresponding pure product **6**.

2-[6-[(5-Methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrazolo[1,5-a]pyrimidin-7-yl]phenol (6a). Yield: 256.1 mg (75%). Yellow solid. M.p. 207–208°. IR (KBr): 3289, 3186, 3131, 1585, 1517, 1448, 1371, 755. ^1H -NMR (300 MHz, (D_6)DMSO): 10.08 (s, 1 H); 8.78 (s, 1 H); 8.26 (s, 1 H); 7.34 (m, 2 H); 7.04 (m, 2 H); 6.91 (s, 1 H); 2.62 (s, 3 H). ^{13}C -NMR (75 MHz, (D_6)DMSO): 15.7; 98.2; 112.1; 116.4; 117.1; 119.2; 130.7; 132.5; 146.7; 148.6; 149.5; 153.9; 155.6; 166.6; 166.9. ESI-HR-MS: 364.0304 ($[M + K]^+$, $\text{C}_{15}\text{H}_{11}\text{KN}_5\text{S}_2^+$; calc. 364.0303).

4-Fluoro-2-[6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrazolo[1,5-a]pyrimidin-7-yl]phenol (6b). Yield: 283.9 mg (79%). Yellow solid. M.p. 219–220°. IR (KBr): 3243, 3186, 3068, 1588, 1427, 1380, 1182, 819, 780. ^1H -NMR (300 MHz, (D_6)DMSO): 10.16 (s, 1 H); 8.80 (s, 1 H); 8.29 (s, 1 H); 7.28 (d, $J = 8.1$, 2 H); 7.01 (s, 1 H); 6.94 (s, 1 H); 2.62 (s, 3 H). ^{13}C -NMR (75 MHz, (D_6)DMSO): 15.2; 97.8; 111.8; 116.3; 116.7; 117.0; 117.1; 118.8; 146.3; 148.1; 151.6; 153.3; 156.2; 165.5; 166.7. ESI-HR-MS: 382.0200 ($[M + \text{Na}]^+$, $\text{C}_{15}\text{H}_{10}\text{FN}_5\text{NaOS}_2^+$; calc. 382.0208).

5-Methoxy-2-[6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrazolo[1,5-a]pyrimidin-7-yl]phenol (6c). Yield: 308.3 mg (83%). Yellow solid. M.p. 119–120°. IR (KBr): 3378, 3079, 1615, 1589, 1494, 1197, 839, 781. ¹H-NMR (300 MHz, (D₆)DMSO): 10.24 (s, 1 H); 8.75 (s, 1 H); 8.26 (s, 1 H); 7.30 (d, *J* = 8.8, 2 H); 6.90 (s, 1 H); 6.56 (s, 1 H); 3.79 (s, 3 H); 2.50 (s, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 15.7; 55.7; 98.1; 101.6; 105.6; 109.7; 112.3; 131.8; 146.5; 148.7; 149.4; 153.8; 156.9; 157.2; 162.8; 166.8. ESI-HR-MS: 394.0411 ([*M* + Na]⁺, C₁₆H₁₃N₅NaO₂S₂⁺; calc. 394.0408).

2-[2-Methyl-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrazolo[1,5-a]pyrimidin-7-yl]phenol (6d). Yield: 302.1 mg (85%). Yellow solid. M.p. 232–233°. IR (KBr): 3400, 3033, 1594, 1492, 1380, 1148, 760. ¹H-NMR (300 MHz, (D₆)DMSO): 10.10 (s, 1 H); 8.71 (s, 1 H); 7.36 (m, 2 H); 7.00 (m, 2 H); 6.72 (s, 1 H); 2.62 (s, 3 H); 2.38 (s, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 14.9; 15.7; 97.6; 111.1; 116.5; 117.4; 119.3; 130.5; 132.4; 149.1; 149.3; 153.7; 155.5; 156.5; 166.8; 170.0. ESI-HR-MS: 378.0460 ([*M* + Na]⁺, C₁₆H₁₃N₅NaOS₂⁺; calc. 378.0459).

4-Fluoro-2-[2-methyl-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrazolo[1,5-a]pyrimidin-7-yl]phenol (6e). Yield: 298.7 mg (80%). Yellow solid. M.p. 107–108°. IR (KBr): 3371, 3066, 1592, 1500, 1268, 1183, 819, 784. ¹H-NMR (300 MHz, (D₆)DMSO): 10.13 (s, 1 H); 8.73 (s, 1 H); 7.25 (d, *J* = 8.2, 2 H); 7.00 (s, 1 H); 6.74 (s, 1 H); 2.62 (s, 3 H); 2.35 (s, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 14.4; 15.2; 97.2; 110.7; 115.8; 116.4; 117.3; 118.3; 118.7; 147.0; 148.8; 151.5; 153.1; 155.5; 166.0; 166.5. ESI-HR-MS: 396.0369 ([*M* + Na]⁺, C₁₆H₁₂FN₅NaOS₂⁺; calc. 396.0365).

4-Bromo-2-[2-methyl-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrazolo[1,5-a]pyrimidin-7-yl]phenol (6f). Yield: 356.2 mg (82%). Yellow solid. M.p. 219–220°. IR (KBr): 3404, 3125, 1591, 1485, 1285, 813, 784. ¹H-NMR (300 MHz, (D₆)DMSO): 10.43 (s, 1 H); 8.72 (s, 1 H); 7.53 (t, 2 H); 6.98 (d, *J* = 8.6, 1 H); 6.73 (s, 1 H); 2.62 (s, 3 H); 2.39 (s, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 14.9; 15.7; 97.7; 110.0; 111.3; 118.7; 119.5; 132.7; 134.9; 147.3; 149.2; 153.5; 155.0; 156.7; 166.3; 167.0. ESI-HR-MS: 455.9574 ([*M* + Na]⁺, C₁₆H₁₂BrN₅NaOS₂⁺; calc. 455.9564).

5-Methoxy-2-[2-methyl-6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrazolo[1,5-a]pyrimidin-7-yl]phenol (6g). Yield: 339.2 mg (88%). Yellow solid. M.p. 135–136°. IR (KBr): 3401, 1615, 1591, 1494, 1204, 1033, 837, 788. ¹H-NMR (300 MHz, (D₆)DMSO): 10.19 (s, 1 H); 8.68 (s, 1 H); 7.25 (d, *J* = 8.9, 2 H); 6.70 (s, 1 H); 6.62 (s, 1 H); 3.76 (s, 3 H); 2.60 (s, 3 H); 2.38 (s, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 14.9; 15.7; 55.5; 97.3; 101.7; 105.0; 109.9; 111.4; 131.5; 148.9; 149.4; 153.4; 156.8; 157.0; 162.5; 166.7; 167.4. ESI-HR-MS: 408.0568 ([*M* + Na]⁺, C₁₇H₁₅N₅NaO₂S₂⁺; calc. 408.0565).

2-[6-[(5-Methyl-1,3,4-thiadiazol-2-yl)sulfanyl]imidazo[1,2-a]pyrimidin-5-yl]phenol (6h). Yield: 266.3 mg (78%). Yellow solid. M.p. 194–195°. IR (KBr): 3440, 1576, 1488, 1296, 1142, 1053, 755. ¹H-NMR (300 MHz, (D₆)DMSO): 10.41 (s, 1 H); 8.82 (s, 1 H); 7.81 (s, 1 H); 7.50–7.37 (m, 3 H); 7.10–6.98 (m, 3 H); 2.61 (s, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 15.7; 112.4; 112.6; 116.9; 117.2; 119.9; 130.4; 133.3; 136.2; 147.9; 148.7; 154.4; 155.5; 166.5; 167.0. ESI-HR-MS: 364.0304 ([*M* + Na]⁺, C₁₅H₁₁N₅NaOS₂⁺; calc. 364.0303).

4-Fluoro-2-[6-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]imidazo[1,2-a]pyrimidin-5-yl]phenol (6i). Yield: 301.9 mg (84%). Yellow solid. M.p. 149–150°. IR (KBr): 3430, 1582, 1496, 1426, 1250, 1194, 817, 733. ¹H-NMR (300 MHz, (D₆)DMSO): 10.33 (s, 1 H); 8.81 (s, 1 H); 7.81 (s, 1 H); 7.44 (s, 1 H); 7.36 (m, 2 H); 7.06 (m, 1 H); 2.50 (s, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 15.2; 112.1; 116.1; 116.5; 117.7; 119.3; 119.6; 135.8; 146.6; 147.4; 151.4; 153.5; 156.5; 165.4; 166.7. ESI-HR-MS: 382.0218 ([*M* + Na]⁺, C₁₅H₁₀FN₅NaOS₂⁺; calc. 382.0208).

2-[3-[(5-Methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrimido[1,2-a]benzimidazol-4-yl]phenol (6j). Yield: 324.9 mg (83%). Yellow solid. M.p. 263–264°. IR (KBr): 3408, 1604, 1572, 1481, 1447, 1368, 1196, 756. ¹H-NMR (300 MHz, (D₆)DMSO): 10.48 (s, 1 H); 9.30 (s, 1 H); 8.12 (d, *J* = 6.8, 1 H); 7.76 (t, 2 H); 7.62 (d, *J* = 6.6, 1 H); 7.34 (t, 3 H); 6.65 (d, *J* = 8.0, 1 H); 2.83 (s, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 15.7; 110.8; 114.7; 116.9; 117.7; 120.3; 120.4; 122.9; 127.0; 128.1; 129.9; 133.6; 144.9; 150.5; 152.4; 155.4; 160.3; 166.5; 167.0. ESI-HR-MS: 414.0474 ([*M* + Na]⁺, C₁₉H₁₃N₅NaOS₂⁺; calc. 414.0459).

4-Fluoro-2-[3-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrimido[1,2-a]benzimidazol-4-yl]phenol (6k). Yield: 307.1 mg (75%). Yellow solid. M.p. 278–279°. IR (KBr): 3425, 1574, 1486, 1443, 1269, 1199, 767. ¹H-NMR (300 MHz, (D₆)DMSO): 10.28 (s, 1 H); 9.11 (s, 1 H); 7.94 (d, *J* = 8.2, 1 H); 7.55 (m, 3 H); 7.43 (m, 2 H); 6.54 (d, *J* = 8.5, 1 H); 2.50 (s, 3 H). ¹³C-NMR (75 MHz, (D₆)DMSO): 15.3; 110.5; 114.0;

115.9; 116.2; 117.7; 119.6; 119.9; 122.6; 126.5; 127.5; 144.4; 150.5; 151.4; 153.7; 156.8; 159.6; 165.4; 166.8. ESI-HR-MS: 432.0377 ($[M + Na]^+$, $C_{19}H_{12}FN_5NaOS_2^+$; calc. 432.0365).

5-Methoxy-2-[3-[(5-methyl-1,3,4-thiadiazol-2-yl)sulfanyl]pyrimido[1,2-a]benzimidazol-4-yl]phenol (**6l**). Yield: 345.6 mg (82%). Yellow solid. M.p. 278–279°. IR (KBr): 3438, 2359, 1613, 1485, 1442, 1296, 1200, 742. 1H -NMR (300 MHz, (D_6) DMSO): 10.31 (s, 1 H); 9.05 (s, 1 H); 7.90 (s, 1 H); 7.51 (d, $J = 6.4$, 1 H); 7.34 (d, $J = 7.34$, 1 H); 7.20 (d, $J = 6.2$, 1 H); 6.66 (s, 3 H); 3.84 (s, 3 H); 2.50 (s, 3 H). ^{13}C -NMR (75 MHz, (D_6) DMSO): 15.7; 55.8; 102.2; 106.5; 110.4; 111.4; 120.2; 122.8; 126.9; 128.3; 130.9; 144.9; 150.6; 152.4; 156.9; 160.1; 163.4; 166.7; 166.8; 166.9. ESI-HR-MS: 444.0576 ($[M + Na]^+$, $C_{20}H_{15}N_5NaO_2S_2^+$, calc. 444.0565).

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