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Synthesis and Biological Activity of Novel 6-Substituted Purine Derivatives

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Abstract. A series of 6-substituted purines were synthesized from commercially available 2-amino-6-chloropurine with appropriate reagents, and nine new compounds **7**, **8**, and **11-17** have been discovered. The compounds synthesized were identified by elemental analysis, ^{1}H NMR, as well as mass spectral data. All the title compounds were screened for their antifungal activities, under the method of the disc diffusion, using three species of fungi — *Bacillus subtillis*, *Aspergillus niger*, and *Candida tropicalis*— and some of the compounds showed promising activities.
Key words: 6-Substituted purines, 2-amino-6-chloropurine, Synthesis, Antifungal Activity.

Resumen. Se preparó una serie de purinas 6-sustituidas a partir de la 2-amino-6-cloropurina, que está disponible comercialmente, y de los reactivos apropiados, de los cuales los derivados **7**, **8** y **11-17** no han sido reportados previamente. Los compuestos sintetizados se caracterizaron por análisis elemental, RMN ^{1}H y espectrometría de masas. Todos los compuestos se evaluaron en su actividad antifúngica, a través del método de difusión de discos, sobre tres especies de hongos — *Bacillus subtillis*, *Aspergillus niger* y *Candida tropicalis*—, mostrando algunos de ellos una actividad promisoria.
Palabras clave: Purinas 6-sustituidas, 2-amino-6-cloropurina, síntesis, actividad antifúngica.

Introduction

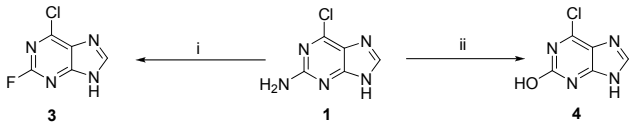
The purine derivatives are of great importance to chemists as well as to biologists as they have been found in a large variety of naturally occurring compounds and also in clinically useful molecules having diverse biological activities [1,2]. Purine bases modified in the 6-position and their derivatives and analogues possess a wide range of biological properties such as antitubercular, fungicidal, antiallergic, antimicrobial, antitumor, antihistamic, myocardium inhibiting agent, etc [3-14].

Encouraged by the above reports and as a part of a research program on the synthesis of some biologically active heterocyclic compounds containing nitrogen, it was planned to synthesize some new 6-substituted purine derivatives carrying 2-amino-6-chloropurine, aiming at an investigation of the new heterocycles of enhanced biological activities. The present study describes the synthesis of a variety of 6-substituted purines including some unreported heterocycles of interest as imaging agent precursors for radiolabeling and unlabeled standard samples and an evaluation of their antifungal activities.

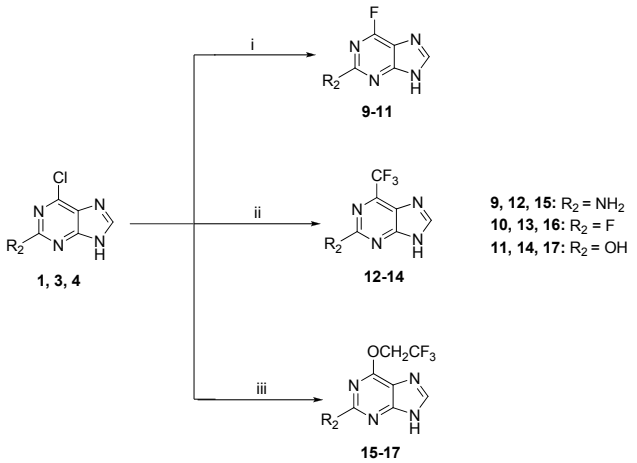
Results and Discussion

The two key intermediates 2-fluoro-6-chloropurine **3** and 2-hydroxyl-6-chloropurine **4** were synthesized by known diazotization methods [15] from commercially available 2-amino-6-chloropurine **1** (Scheme 1). The intermediate 2-amino-6-methylthiopurine **2** was prepared by the known method [16] from **1** and benzyl mercaptan, thus compound **2** reacted with four kinds of amines in the presence of DMF to form N^6-substituted-9H-purine-2,6-diamine (**5**–**8**) according to the well established procedures [17,18]. Among these compounds, **5** and **6** were previously reported [17,18], and two new compounds **7** and **8** were discovered (Scheme 2).

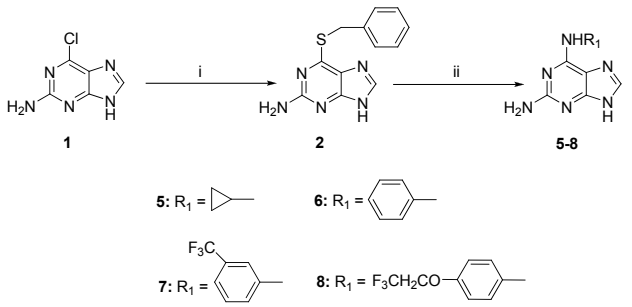
Our target compounds 2-amino-6-fluoropurine **9**, 2-fluoro-6-fluoropurine **10** and 2-hydroxyl-6-fluoropurine **11** were prepared through chlorine-exchange fluorinations between **1** or **3** or **4** and KF by TPPB phase transfer catalysis [19], a new com-



Scheme 1. Reagents: (i) 40%HBF_4, sodium nitrite, -10 °C, 7 h. (ii) 50% H_2SO_4, sodium nitrite, -10 °C, 2 h, then 50 °, 1 h.



Scheme 2. Reagents: (i) KF, TPPB, sulfolane, 60 °C, 4 h. (ii) CF_3COONa, CuI, 160 °C, 20 h, (iii) CF_3CH_2ONa, CuI, DMSO, 160 °C, 10 h.



Scheme 3. Reagents: (i) benzyl mercaptan, DMF, 80 °C, 2 h. (ii) amine, DMF, 80 °C, 18 h.

pound **11** was discovered besides the two known compounds [19] **9** and **10** (Scheme 3). The three target new compounds 2-amino-6-trifluoromethylpurine **12**, 2-fluoro-6-trifluoromethylpurine **13** and 2-hydroxyl-6-trifluoromethylpurine **14** were prepared by treating **1** or **3** or **4** [20], with sodium trifluoroacetate in DMF catalyzed by cuprous iodide at 160°C for 20 h (Scheme 3). Trifluoroethoxylation reactions of **1** or **3** or **4** to synthesize the other three new target compounds 2-amino-6-trifluoroethylpurine **15**, 2-fluoro-6-trifluoroethylpurine **16** and 2-hydroxyl-6-trifluoroethylpurine **17** were carried out with sodium trifluoroethylate in DMSO under the cuprous iodide catalysis (Scheme 3) according to the well established procedures described in previous literatures [21,22]. All the structures of the target compounds were established on the basis of spectral data and elemental analysis (see Experimental).

Antifungal activity.

6-substituted purines synthesized were screened for their antifungal activities against three species of fungi, namely *Bacillus subtillis, Aspergillus niger*, *and Candida tropicalis* using the disc diffusion method [23,24]. The three species of fungi were grown in YGB culture media over a 14-day incubation. The tested compounds were dissolved in 1% NaOH solution (which has no inhibitory activity) to get concentrations of 1 mg/mL solution. The fluconazole was used as standard antifungal reference. The inhibition zones of microbial growth surrounding the filter paper disc (2.5 mm) were measured in millimeters at the end of an incubation period at 30°C for 3 days. Inhibition of the organisms was evidenced by a clear zone surrounding each disk (Table 1).

All the tested compounds showed variable activities toward the three species of fungi, some of them comparable to standard fluconazole. The results of the antifungal screening showed that compounds **5-11** and **13-17** displayed good activity against *Bacillus subtillis*, the compounds **6-8**, **11-13** and **15-16** displayed good activity against *Aspergillus niger*, and compounds **7**, **8**, **10**, **11**, **13** and **6-8**, **11-13** and **15-17** showed good activity against *Candida tropicalis*, and the compounds **7**, **8**, **11**, **13**, **15** and **16** showed fairly good activity against the three fungal strains, while the remaining compounds exhibited moderate activity when compared to fluconazole (Table 1).

Table 1. Fungicidal activity of the title compounds

Compound	Diameter of inhibition zone		
	Bacillus subtillis	*Aspergillus niger*	*Candida tropicalis*
fluconazole	+++	+++	+++
2	+	+	+
5	+++	++	++
6	+++	+++	++
7	+++	+++	+++
8	+++	+++	+++
1	+	+	++
3	++	+	+
4	+	+	+
9	+++	+	++
10	+++	++	+++
11	+++	+++	+++
12	++	+++	++
13	+++	+++	+++
14	+++	++	++
15	+++	+++	+++
16	+++	+++	+++
17	+++	++	+++

Lower active = + (inhibition zone 1-15 mm), moderately active = ++ (inhibition zone 16-30 mm) and highly active = +++ (inhibition zone > 30 mm).

Conclusions

The successful synthesis of a series of biologically active 6-substituted purines from commercially available 2-amino-6-chloropurine and evaluation of the antifungal activities of the title compounds were reported. Thirteen derivatives were prepared and nine new ones were discovered. From the results of the antifungal screening, it can be concluded that the six new derivatives **7**, **8**, **11**, **13**, **15** and **16** were found to be active against the three fungal strains. Therefore they may be used as lead compounds for further development.

Experimental Section

All the chemicals and reagents were of analytical grade and used as obtained. ^{1}H NMR spectra were recorded on a Bruker 400-MHz spectrometer using DMSO-d_6 as the solvent with tetramethylsilane (TMS) as an internal standard. Melting points were recorded on Digital Melting Point Apparatus WRS-1B and are uncorrected. Mass spectra were measured on an HP1100LC (Agilent Technologies, USA). Elemental

analysis was performed on a Vario EL III instrument (GmbH, Germany).

2-Amino-6-methylthiopurine 2. A mixture of compound **1** (1.7 g, 10 mmol), benzyl mercaptan (6.2 g, 50 mol) and DMF (15 mL) was stirred in 50 mL round flask at 80°C for 2 h, after cooling the reaction mixture was filtered, and the residue was dissolved in 30%NaOH (30 mL) and then was neutralized with conc. HCl. The solid obtained was filtered to give a white solid (**2**, 2.2 g, yield 86%). ^{1}H NMR (DMSO-d_6) δ: 3.76 (s, 2H, CH_2), 7.38-7.59 (m, 5H, Ar-H), 7.62 (s, 3H, NH_2 and NH), 8.22 (s, 1H, =CH-N). MS (70 eV) *m/z* 258.21 (M^+); EI-MS *m/z* (rel. int.) 258.21 [M^+] (23), 167.19 (100), 136.18 (80), 121.24 (48). *Anal.* C 55.98%, H 4.29%, N 27.23%, S 12.47%, calcd for $C_{12}H_{11}N_5S$, C 56.01%, H 4.31%, N 27.22%, S 12.46%.

2-Fluoro-6-chloropurine 3 and 2-hydroxyl-6-chloropurine 4. A three-necked flask was loaded with compound **1** (1.7 g, 10 mmol) and 40%HBF_4 or 50%H_2SO_4 (40 mL). The mixture was stirred at room temperature for 30 min. After cooling down to -5°C, the solution of sodium nitrite (0.76 g, 11 mmol) in H_2O (2 mL) was added dropwise slowly, and an evolution of nitrogen gas was observed immediately, then the reaction mixture was stirred at -10°C for 2 h, urea (0.3 g, 5 mmol) was then added to decompose the excess sodium nitrite. After which, the reaction mixture was stirred at -10 or 50°C for another 5 or 1 h. Then 50%NaOH solution was added to regulate pH value of 3~4, the solid so formed was filtered, and then was dissolved completely with NaOH solution (15%, 20 mL) and separated by silica-gel column chromatography using dichloromethane-methanol (9/1) as eluent. The solution obtained was neutralized with conc. HCl. The solid was separated out and filtered to give the corresponding product **3** or **4**.

2-Fluoro-6-chloropurine 3. Yield 91%, m.p. 162-163°C. ^{1}H NMR (DMSO-d_6) δ: 8.65 (s, 1H, =CH-N), 11.97 (s, 1H, NH). EI-MS *m/z* (rel. int.) 171.03 [M^+] (88), 134.95 (100), 90.08 (80). *Anal.* C 34.76%, H 1.17%, Cl 20.53%, F 11.02%, N 32.48%, calcd. for $C_5H_2ClFN_4$, C 34.80%, H 1.17%, Cl 20.55%, F 11.01%, N 32.47%.

2-Hydroxyl-6-chloropurine 4. Yield 88%, m.p. >250°C. ^{1}H NMR (DMSO-d_6) δ: 8.01 (s, 1H, =CH-N), 13.30 (s, 2H, OH and NH). EI-MS *m/z* (rel. int.) 170.97 [M^+] (86), 145.90 (66), 138.87 (68), 127.88 (100), 99.92 (68). *Anal.* C 35.22%, H 1.78%, Cl 20.77%, N 32.82%, O 9.39%, calcd. for $C_5H_3ClN_4O$, C 35.21%, H 1.77%, Cl 20.79%, N 32.85%, O 9.38%.

General procedure for compounds 5-8. A mixture of compound **2** (2.57 g, 10 mmol), amine (30 mmol) and DMF (30 mL) were stirred at 80°C for about 18 h. After cooling the mixture was filtered, and the residue was washed several times with water and crystallized to give **5-8.**

N^6-cyclopropyl-9H-purine-2,6-diamine 5. Yield 87%, m.p. 189-192°C. ^{1}H NMR (DMSO-d_6) δ: 0.30-0.51 (m, 4H, CH_2CH_2), 2.53 (m, 1H, N-CH), 7.57 (s, 4H, NH_2, N^{8}H and N^{2}H), 8.18 (s, 1H, =CH-N). EI-MS *m/z* (rel. int.) 190.98 [M^+] (48), 175.01 (100), 136.00 (76). *Anal.* C 50.49%, H 5.31%, N 44.17%, calcd. for $C_8H_{10}N_6$, C 50.52%, H 5.30%, N 44.18%.

N^6-phenyl-9H-purine-2,6-diamine 6. Yield 90%, m.p. 177-179°C. ^{1}H NMR (DMSO-d_6) δ: 6.67-7.49 (m, 5H, Ar-H), 8.06 (s, 1H, =CH-N), 8.43 (s, 4H, NH_2, N^{8}H and N^{2}H). EI-MS *m/z* (rel. int.) 227.13 [M^+] (28), 211.12 (100), 136.12 (83). *Anal.* C 58.37%, H 4.46%, N 37.14%, calcd. for $C_{11}H_{10}N_6$, C 58.40%, H 4.46%, N 37.15%.

N^6-[3-(trifluoromethyl)phenyl]-9H-purine-2,6-diamine 7. Yield 78%, m.p. 210-213°C. ^{1}H NMR (DMSO-d_6) δ: 7.00-7.57 (m, 4H, Ar-H), 8.07 (s, 1H, =CH-N), 8.45 (s, 4H, NH_2, N^{8}H and N^{2}H). ^{13}C NMR (DMSO-d_6) δ: 113.7, 115.4, 121.2, 122.6, 124.9, 130.1, 132.3, 135.9, 140.7, 143.2, 150.6, 157.5. EI-MS *m/z* (rel. int.) 295.06 [M^+] (22), 279.05 (100), 226.06 (46), 136.10 (92). *Anal.* C 48.96%, H 3.07%, F 19.38%, N 28.54%, calcd. for $C_{12}H_9F_3N_6$, C 48.98%, H 3.08%, F 19.37%, N 28.56%.

N^6-[4-(2,2,2-trifluoroethoxy)phenyl]-9H-purine-2,6-diamine 8. Yield 80%, m.p. 234-238°C. ^{1}H NMR (DMSO-d_6) δ: 3.79-3.96 (m, 2H, CH_2), 6.56-6.71 (m, 4H, Ar-H), 8.05 (s, 1H, =CH-N), 8.42 (s, 4H, NH_2, N^{8}H and N^{2}H). ^{13}C NMR (DMSO-d_6) δ: 83.2, 114.8, 120.5, 121.6, 123.2, 133.9, 137.3, 145.1, 149.2, 151.2, 156.7. EI-MS *m/z* (rel. int.) 325.16 [M^+] (34), 309.15 (100), 305.17 (97), 285.17 (76), 265.16 (42), 136.12 (80). *Anal.* C 48.13%, H 3.42%, F 17.57%, N 25.93%, O 4.91%, calcd. for $C_{13}H_{11}F_3N_6O$, C 48.15%, H 3.42%, F 17.58%, N 25.92%, O 4.93%.

General procedure for compounds 9-11. A mixture of compound **1** or **3** or **4** (10 mmol), KF (50 mmol), TPPB (0.21 g, 0.5 mmol), and sulfolane (30 mL) were stirred at 60°C for about 4 h. The mixture was filtered immediately, then the solvent was removed and the residue was washed several times with water to give **9** or **10** or **11** as yellow crystals.

2-Amino-6-fluoropurine 9. Yield 69%, m.p. 206-208°C. ^{1}H NMR (DMSO-d_6) δ: 7.76 (s, 3H, NH_2 and NH), 8.15 (s, 1H, =CH-N). EI-MS *m/z* (rel. int.) 153.06 [M^+] (34), 137.07 (100), 133.12 (58). *Anal.* C 39.19%, H 2.62%, F 12.43%, N 45.76%, calcd. for $C_5H_4FN_5$, C 39.22%, H 2.63%, F 12.41%, N 45.74%.

2-Fluoro-6-fluoropurine 10. Yield 64%, m.p. 179-182°C. ^{1}H NMR (DMSO-d_6) δ: 8.23 (s, 1H, =CH-N), 12.09 (s, 1H, NH). EI-MS *m/z* (rel. int.) 157.10 [M^+] (32), 137.09 (100), 118.12 (67). *Anal.* C 38.44%, H 1.30%, F 24.35%, N 35.88%, calcd. for $C_5H_2F_2N_4$, C 38.47%, H 1.29%, F 24.34% N 35.89%.

2-Hydroxyl-6-fluoropurine 11. Yield 56%, m.p. 223-225°C. ^{1}H NMR (DMSO-d_6) δ: 8.32 (s, 1H, =CH-N), 12.53 (s, 2H, NH and OH). ^{13}C NMR (DMSO-d_6) δ: 126.5, 142.2, 143.7,

150.6, 154.3. EI-MS *m/z* (rel. int.) 155.08 [M^+] (35), 138.06 (100), 136.22 (27). *Anal.* C 38.95%, H 1.96%, F 12.34%, N 36.33%, O 10.39%, calcd. for $C_5H_3FN_4O$, C 38.97%, H 1.96%, F 12.33%, N 36.36%, O 10.38%.

General procedure for compounds 12-14. A mixture of compound **1** or **3** or **4** (10 mmol), CF_3COONa (6.8 g, 50 mmol), CuI (3.84 g, 20 mmol), and DMF (20 mL) were stirred at 160°C for about 20 h. The mixture was filtered immediately, then the solvent was removed and the residue was dissolved completely with 20%NaOH solution (20 mL) and separated by silica-gel column chromatography using dichloromethane-methanol (9/1) as eluent. The solution obtained was neutralized with conc. HCl. The solid was separated out and filtered to give **12** or **13** or **14** as yellow crystals.

2-Amino-6-trifluoromethylpurine 12. Yield 53%, m.p. 216-218°C. ^{1}H NMR (DMSO-d_6) δ: 6.15 (s, 1H, =CH-N), 7.87 (s, 3H, NH_2 and NH). EI-MS *m/z* (rel. int.) 204.05 [M^+] (100), 202.80 (60), 128.01 (77). *Anal.* C 35.44%, H 1.98%, F 28.07%, N 34.46%, calcd. for $C_6H_4F_3N_5$, C 35.48%, H 1.98%, F 28.06%, N 34.48%.

2-Fluoro-6-trifluoromethylpurine 13. Yield 84%, m.p. 184-186°C. ^{1}H NMR (DMSO-d_6) δ: 6.21 (s, 1H, =CH-N), 12.11 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 119.4, 128.7, 142.6, 143.5, 151.9, 156.2. EI-MS *m/z* (rel. int.) 207.15 [M^+] (78), 187.24 (100), 149.10 (46). *Anal.* C 34.94%, H 0.99%, F 36.89%, N 27.17%, calcd. for $C_6H_2F_4N_4$, C 34.97%, H 0.98%, F 36.87%, N 27.18%.

2-Hydroxyl-6-trifluoromethylpurine 14. Yield 62%, m.p. 173-175°C. ^{1}H NMR (DMSO-d_6) δ: 6.39 (s, 1H, =CH-N), 14.43 (s, 2H, NH and OH). EI-MS *m/z* (rel. int.) 204.92 [M^+] (46), 173.02 (100), 129.93 (42). *Anal.* C 35.27%, H 1.49%, F 27.94%, N 27.44%, O 7.83%, calcd. for $C_6H_3F_3N_4O$, C 35.31%, H 1.48%, F 27.92%, N 27.45%, O 7.84%.

General procedure for compounds 15-17. A mixture of compound **1** or **3** or **4** (10 mmol), CF_3CH_2ONa (6.1 g, 50 mmol), CuI (3.84 g, 20 mmol), and DMSO (20 mL) were stirred at 160°C for about 10 h. After the reaction, the solvent was removed under vacuum, the residue was dissolved in water (30 mL), and then toluene (20 mL) was added to the mixture and stirred for 20 min, the water layer was separated and neutralized with conc. HCl. The solid obtained was filtered, washed several times with water to give **15** or **16** or **17** as yellow crystals.

2-Amino-6-trifluoroethylpurine 15. Yield 89%, m.p. 236-239°C. ^{1}H NMR (DMSO-d_6): 3.91-3.96 (m, 2H, CH_2), 7.99 (s, 1H, =CH-N), 8.15 (s, 3H, NH_2 and NH). ^{13}C NMR (DMSO-d_6) δ: 83.6, 120.3, 121.5, 142.7, 151.1, 157.4, 159.5. EI-MS *m/z* (rel. int.) 234 [M^+] (100), 217 (43). *Anal.* C 36.07%, H 2.61%, F 24.44%, N 30.03%, O 6.81%, calcd. for $C_7H_6F_3N_5O$, C 36.06%, H 2.59%, F 24.45%, N 30.04%, O 6.86%.

2-Fluoro-6-trifluoroethylpurine 16. Yield 90%, m.p. 166-168°C. ^{1}H NMR (DMSO-d_6) δ: 3.93-3.97 (m, 2H, CH_2), 7.92 (s, 1H, =CH-N), 12.13 (s, 1H, NH). ^{13}C NMR (DMSO-d_6) δ: 83.4, 119.7, 121.8, 143.3, 152.4, 157.1, 160.1. EI-MS *m/z* (rel. int.) 237.21 [M^+] (67), 217.20 (100). *Anal.* C 35.58%, H 1.72%, F 32.19%, N 23.71%, O 6.76%, calcd. for $C_7H_4F_4N_4O$, C 35.61%, H 1.71%, F 32.18%, N 23.73%, O 6.78%.

2-Hydroxyl-6-trifluoroethylpurine 17. Yield 72%, m.p. 186-189°C. ^{1}H NMR (DMSO-d_6) δ: 3.92-3.94 (m, 2H, CH_2), 8.16 (s, 1H, =CH-N), 13.37 (s, 2H, NH and OH). EI-MS *m/z* (rel. int.) 235.08 [M^+] (100), 219.14 (79). *Anal.* C 35.89%, H 2.17%, F 24.36%, N 23.91%, O 13.66%, calcd. for $C_7H_5F_3N_4O_2$, C 35.91%, H 2.15%, F 24.34%, N 23.93%, O 13.67%.

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