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Novel synthesis and antifungal activity of pyrrole and pyrrolo[2,3-d]pyrimidine derivatives containing sulfonamido moieties

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Abstract

Several sulfonamides containing pyrroles (**2a**–**c**, **6a**–**d**, **8a**–**d**), pyrrolo[2,3-d] pyrimidines (**3a**–**c**), acetanilides (**11a**–**c**) and tetrahydrobenzothiophenes (**13a**–**c**) were synthesized starting from N^4-chloroacetylsulfanilamides (**1a**–**d**). The structures of synthesized compounds were elucidated by elemental analyses and spectral data. Compounds **2b**, **3b**, **6b**, **8b** and **8d** exhibited a remarkable antifungal activity compared with the standard fungicide mycostatine. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: Pyrrole; Pyrrolo[2,3-d]pyrimidine benzothiophene derivatives; Antifungal activity

1. Introduction

It is observed from the literature that the pyrrole nucleus plays a vital role in many biological activities [1–5]. Also, pyrrolo[2,3-d]pyrimidines [6,7] and sulfonamides have a variety of biological activities such as antibacterial [8], insulin releasing [9], carbonic anhydrase inhibitory [10], antiinflammatory [11] and antitumor activities [12]. In view of these findings and in continuation of our work [13–17] on the synthesis of novel heterocyclic systems exhibiting biological activity, we undertook the synthesis of a new series of compounds incorporating the above mentioned biologically active moieties in one molecule and evaluated their antifungal activity.

2. Chemistry

The starting materials N^4-chloroacetylsulfanilamides (**1a**–**d**) were synthesized from the reaction of sulfanilamide or its derivatives with chloroacetyl chloride at room temperature in acetone containing 10% caustic soda [18]. The reactivity of compound **1** towards active methylene compounds was investigated. First, when compounds **1a**–**d** were refluxed with malononitrile in dioxane in the presence of triethylamine, adopting the reaction conditions [19] reported by Gewald, the pyrrole derivatives **2a**–**c** were produced. The IR spectra of compounds **2a**–**c** were characterized by the presence of NH_2, C≡N, C=O and SO_2 absorption bands. The ^{1}H NMR spectra of compounds **2a**,**c** showed a singlet assigned to the CH_2 group of the pyrrole ring. The formation of **2** from the reaction of **1** and malononitrile is assumed to proceed via alkylation of malononitrile followed by intramolecular cyclization [18] to give the pyrrole derivatives **2a**–**c** (Scheme 1). Refluxing **2a**,**c**,**d** in formamide afforded the pyrrolo[2,3-d]pyrimidine derivatives **3a**–**c**. The formation of pyrrolopyrimidines **3** was proved by the disappearance of the C≡N group absorption band in the IR spectra.

On the other hand, when compounds **1a**–**c** were reacted with ethyl cyanoacetate in refluxing DMF containing anhydrous potassium carbonate, two possible structures **4** and **6** can be formed. Structure **4** was readily excluded on the basis of analytical and spectral data. IR spectra of **6a**–**c** exhibited absorption band for C≡N and the absence of OC_2H_5 fragment in ^{1}H NMR

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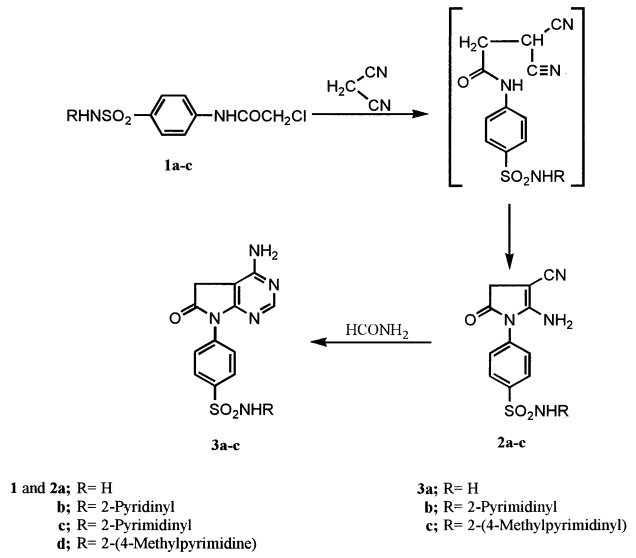
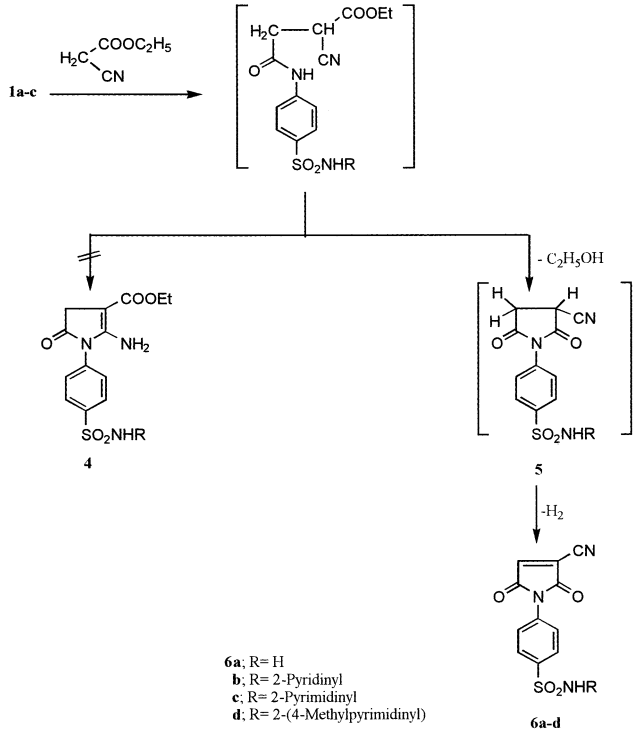


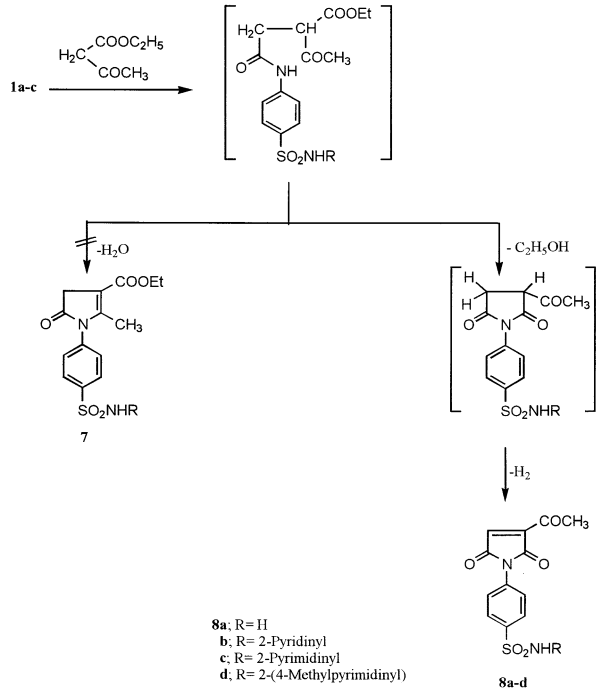
Scheme 1.

spectra. The formation of compound **6** can be explained on the basis of initial alkylation of ethyl cyanoacetate followed by intramolecular cyclization to give the intermediate dihydropyrroles **5**, which are oxidized [20] under the reaction conditions to yield the novel pyrrole derivatives **6** (Scheme 2).

In a similar manner, ethyl acetoacetate was reacted with compounds **1a**–**d** to yield the pyrrole derivatives **8a**–**d** and the other possible structures **7** were discarded on the basis of analytical and spectral data (Scheme 3).



Scheme 2.

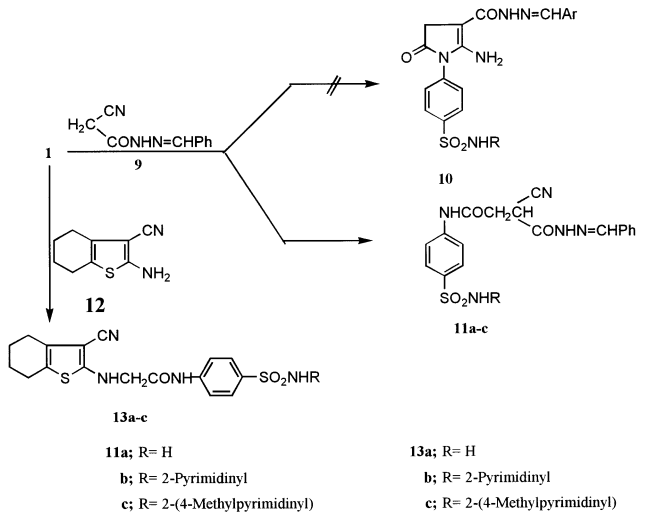


Scheme 3.

This investigation was extended to include the reactivity of compounds **1** towards nitrile **9** as another active methylene. Thus, the novel acetanilides **11a**–**c** were obtained when compounds **1a**,**c**,**d** were refluxed with nitrile **9** in DMF containing anhydrous potassium carbonate. IR spectra revealed the presence of absorption band corresponding to a nitrile function. Thus, the other possible structure **10** was easily excluded on the basis of spectral data. Many compounds containing the benzo[b]-thiophene derivatives have been shown to possess antifungal activity [21]. Thus when aminothiophene **12** was reacted with compounds **1a**,**c**,**d** in the presence of EtOH–K_2CO_3, the novel benzo thiophene derivatives **13** were obtained (Scheme 4).

3. Antifungal activity

The obtained new compounds were screened in vitro for their antifungal activity against four species of fungi *Aspergillus ochraceus* Wilhelm, *Penicillium chrysogenum* Thom, *Aspergillus fleavus* Link and *Candida albicans* (Robin) Berkho using the disc diffusion method [22]. The agar media were inoculated with test organisms and a solution of the test compound in DMSO (1 mg ml^{-1}) was placed separately in cups (8-mm diameter) in the agar medium. A 0.1% solution of mycostatine was used as a reference. The inhibition zones were measured after 24 h. The results of the antifungal activity tests are summarized in Table 1. Most of the synthesized compounds were found to possess antifungal activity



Scheme 4.

towards all the microorganisms used. The introduction of a heterocyclic sulfonamide in the pyrrole ring increased antifungal activity. On the other hand, the lack of any substitutent of sulfonamide caused partial or complete reduction in antifungal activity. Compounds **2b**, **3b**, **6b**, **8b** and **8d** are nearly active as fungicide mycostatine with potency about 84.2–89.5%. However, none of the tested compounds showed superior activity than the reference mycostatine.

4. Experimental

All m.p.s are uncorrected. IR spectra were measured as KBr pellets on a Shimadzu IR 200 spectrophotometer. ^{1}H NMR spectra were recorded in $CDCl_3$ at 200 MHz on a Varian Gemini ^{1}H NMR spectrometer using tetramethylsilane as an internal reference. Elemental analyses were carried out at the Microanalytical Center of Cairo University. Found: C, H, N for all compounds were within $\pm$ 0.4% from the theoretical value. The characteristic data for prepared compounds are given in Table 2. The spectral data are collected in Table 3.

*4.1. Amino-4,5-dihydro-5-oxo-1-[4-(N-substituted sulfamoyl)phenyl]pyrrol-3-carbo-nitriles (**2a**–**d**)*

A mixture of the malononitrile (0.01 mol) and the appropriate N^4-chloro-acetylsulfanilamides (**1a**–**d**) (0.01 mol) in dioxane (30 ml) in the presence of triethylamine was refluxed for 24 h, then left to cool to room temperature (r.t.). The precipitated product was filtered off, wash with ethanol and dried to give **2a**–**d** (Table 2).

*4.2. Amino-5,6-dihydro-6-oxo-7-[4-(N-substituted sulfamoyl)phenyl]pyrrolo[2,3-d]-pyrimidines (**3a**–**c**)*

A solution of **2a**,**c**,**d** (0.01 mol) in formamide (5 ml) was refluxed for 4 h. The solid obtained was recrystallized from proper solvent to give **3a**–**c** (Table 2).

Table 1
Antifungal activity of some newly synthesized compounds (inhibition zones, mm) (relative inhibition)

Comp. no.	*A. ochraceus* Wilhelm (AUCC-230)	*P. chrysogenum* Thom (AUCC-530)	*A. fleavus* Link (AUCC-164)	*C. albicans* (Robin) Berkho (AUCC-1720)
2a	12 (30%)	10 (26%)	14 (36%)	16 (40%)
2b	16 (40%)	14 (37%)	32 (84%)	20 (50%)
2c	20 (50%)	16 (42%)	14 (37%)	20 (50%)
2d	15 (37.5%)	12 (31.6%)	12 (36.6%)	18 (45%)
3a	10 (25%)	10 (26%)	10 (26%)	10 (25%)
3b	18 (45%)	14 (37%)	16 (42%)	34 (85%)
3c	19 (47.5%)	11(29%)	10 (26%)	14 (35%)
6a	10 (25%)	14 (37%)	18 (47%)	10 (25%)
6b	20 (50%)	14 (37%)	18 (47%)	34 (85%)
6c	25 (62.5%)	14 (36.8%)	15 (39.5%)	10 (25%)
6d	19 (47.5%)	15 (39.5%)	13 (34.2%)	20 (50%)
8a	18 (45%)	13 (34.2%)	20 (52.6%)	22 (55%)
8b	24 (60%)	34 (89%)	22 (58%)	16 (40%)
8c	16 (40%)	11 (29%)	22 (57.9%)	22 (62.5%)
8d	34 (86%)	16 (42%)	32 (84%)	14 (35%)
11a	27 (67.5%)	14 (36.8%)	14 (36.8%)	18 (45%)
11b	23 (57.5%)	18 (47.4%)	13 (34.2%)	20 (50%)
11c	25 (62.5%)	22 (57.9%)	10 (26%)	17 (42.5%)
13a	20 (50%)	18 (47%)	24 (63%)	20 (50%)
13b	24 (60%)	20 (53%)	20 (53%)	18 (45%)
13c	22 (55%)	20 (53%)	18 (47%)	24 (60%)
Mycostatine	40 (100)	38 (100%)	38 (100%)	40 (100%)

Table 2
Characterization data for newly synthesized compounds

Comp. no.	M.p. (°C)	Yield (%)	Comp. no.	M.p. (°C)	Yield (%)
2a	>300	76	**8a**	110	77
2b	140	75	**8b**	>300	80
2c	170	70	**8c**	>300	81
2d	130	68	**8d**	226	79
3a	220	57	**11a**	295	75
3b	>300	55	**11b**	107	72
3c	>300	60	**11c**	262	76
6a	>300	76	**13a**	250	68
6b	90	74	**13b**	270	65
6c	80	69	**13c**	294	67
6d	98	68			

Table 3
IR and ^{1}H NMR spectra of the synthesized compounds

Comp.	IR (KBr) (cm^{-1})	^{1}H NMR (DMSO-d_6), δ (ppm)
2a	3450, 3350, 3200 (NH_2), 2200 (C≡N), 1680 (C=O), 1325, 1150 (SO_2)	3.46 (s, 2H, CH_2); 6.67 (s, 2H, NH_2); 7.31 (s, 2H, SO_2NH_2); 7.52–7.94 (m, 4H, Ar–H)
2b	3400, 3300 (NH, NH_2), 2200 (C≡N), 1690 (C=O), 1340, 1135 (SO_2)	
2c	3420, 3300, 3190 (NH, NH_2), 2200 (C≡N), 1685 (C=O), 1315, 1125 (SO_2)	3.51 (s, 2H, CH_2); 6.69 (s, 2H, NH_2); 7.20 (s, 2H, SO_2NH_2); 7.08–8.20 (m, 7H, Ar–H)
2d	3480, 3320 (NH, NH_2), 2200 (C≡N), 1665 (C=O), 1310, 1150 (SO_2)	
3a	3320, 3200 (NH_2), 1680 (C=O), 1320, 1140 (SO_2)	3.47 (s, 3H, CH_2), 4.92 (s, 2H, NH_2), 6.94 (s, 2H, SO_2NH_2), 7.10–7.56 (m, 4H, Ar–H), 8.51 (s, 1H, pyrimidine-H)
3b	3325, 3200 (NH_2), 1690 (C=O), 1320, 1145 (SO_2)	
3c	3350, 3200 (NH_2), 1680 (C=O), 1310, 1135 (SO_2)	
6a	3450, 3300 (NH_2), 2200 (C≡N), 1710 (C=O), 1327, 1150 (SO_2)	
6b	3400 (NH), 2200 (C≡N), 1700 (C=O), 1310, 1125 (SO_2)	
6c	3450 (NH), 2200 (C≡N), 1710 (C=O), 1320, 1123 (SO_2)	6.51 (s, 1H, CH), 7.0–7.83 (m, 7H, Ar–H), 8.43 (s, 1H, SO_2NH).
6d	3410 (NH), 2200 (C≡N), 1710 (C=O), 1310, 1140 (SO_2)	2.51 (s, 3H, CH_3), 6.57 (s, 1H, CH), 7.15–7.94 (m, 6H, Ar–H), 8.39 (s, 1H, SO_2NH)
8a	3400, 3300 (NH_2), 1720 (C=O), 1320, 1146 (SO_2)	
8b	3400 (NH), 1710 (C=O), 1310, 1125 (SO_2)	2.53 (s, 3H, $COCH_3$), 4.79 (s, 1H, CH), 6.73–8.01 (m, 8H, Ar–H), 10.29 (s, 1H, NH)
8c	3350 (NH), 1700 (C=O), 1310, 1130 (SO_2)	
8d	3400 (NH), 1700 (C=O), 1305, 1150 (SO_2)	
11a	3450, 3300 (NH); 2200 (C≡N), 1665 (C=O), 1310, 1125 (SO_2)	
11b	3380, 3200 (NH), 2200 (C≡N), 1660 (C=O), 1320, 1140 (SO_2)	
11c	3360, 3200 (NH), 2200 (C≡N), 1680 (C=O), 1305, 1140 (SO_2)	
13a	3450, 3360, 3200 (NH, NH_2), 2950 (CH-aliphatic), 2200 (C≡N), 1660 (C=O), 1325, 1150 (SO_2)	
13b	3450, 3300 (NH), 2960 (CH-aliphatic), 2200 (C≡N), 1650 (C=O), 1310, 1130 (SO_2)	2.50 (s, 8H, $4CH_2$), 3.81 (s, 2H, NCH_2), 6.82–7.42 (m, 7H, Ar–H), 7.92, 8.46, 9.56 (3s, 3H, 3NH)
13c	3480, 3350 (NH), 2950 (CH-aliphatic), 2200 (C≡N), 1650 (C=O), 1305, 1120 (SO_2)	2.31 (s, 3H, CH_3), 2.49 (m, 8H, $4CH_2$), 3.91 (s, 2H, CH_2), 4.92 (s, 1H, NH), 6.74–7.93 (m, 6H, Ar–H), 8.28 and 10.8 ppm (2s, 2H, 2NH)

*4.3. 2,5-Dihydro-2,5-dioxo-1-[4-(N-substituted sulfamoyl)phenyl]pyrrol-3-carbonitriles (**6a–d**) and 3-acetyl-2,5-dihydro-2,5-dioxo-1-[4-(N-substituted sulfamoyl)phenyl]-pyrroles (**8a–d**)*

A mixture of compounds **1a**,**c**,**d** (0.01 mol) and ethyl cyanoacetate or ethyl acetoacetate (0.01 mol) in dimethylformamide (20 ml) containing anhydrous potassium carbonate (0.5 g) was heated under reflux for 2 h, then left to cool to r.t. The precipitated product was filtered off and recrystallized from the appropriate solvent (Table 2).

4.4. Derivatives of acetamide (**11a–c**) and aminothiophene (**13a–c**)

A mixture of compounds **1a**,**c**,**d** (0.01 mol) and nitrile ?compound **9** (0.01 mol) or aminothiophene **13** (0.01 mol) in ethanol containing anhydrous potassium carbonate (0.5 g) was heated under reflux for 2 h, then left to cool to r.t. The precipitated product was filtered off and recrystallized from proper solvent to give **11a–c** and aminothiophene **13a–c**, respectively (Table 2).

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