ELSEVIER

www.elsevier.nl/locate/farmac

Il Farmaco 55 (2000) 596–602

IL FARMACO

Studies on aminopyrazoles: antibacterial activity of some novel pyrazolo[1,5-*a*]pyrimidines containing sulfonamido moieties

M.S.A. El-Gaby *, A.A. Atalla, A.M. Gaber, K.A. Abd Al-Wahab

Department of Chemistry, Faculty of Science, Al-Azhar University at Assiut, Assiut 71524, Egypt

Received 9 February 2000; accepted 31 July 2000

Abstract

Hydrazones **2a**–**d** were prepared from diazotiazation of sulfanilamide or its derivatives followed by coupling with ethyl cyanoacetate. 3-Aminopyrazoles **3a**–**d** were obtained by refluxing of **2a**–**d** with hydrazine hydrate in ethanol. [Bis(-methylthio)methylene]malononitrile (**4**) was reacted with aminopyrazoles **3a**–**d** in refluxing DMF containing triethylamine to yield the novel pyrazolo[1,5-*a*]pyrimidines **6a**–**d**. The anilino derivatives **8a**–**h** were obtained by fusion of compounds **6a**–**d** with aromatic amines. When compounds **6a**,**c**,**d** were subjected to the reaction with hydrazine hydrate, the hydrazino derivatives **9a**–**c** were isolated. Also, the aminopyrazoles **3** were reacted with some electrophiles such as arylidenemalononitriles, ethoxymethylene malononitrile and ethyl ethoxymethylene cyanoacetate to yield the novel substituted pyrazolo[1,5-*a*]pyrimidines **13**, **17** and **19**, respectively. Structures of the new compounds were established by their elemental analyses and spectral data. Most of these compounds were also tested in vitro for their antibacterial activity against some Gram positive and Gram negative bacteria.

Keywords: Aminopyrazoles; Pyrazolo[1,5-*a*]pyrimidines; Sulfonamides and antibacterial activity

1. Introduction

Pyrazolo[1,5-*a*]pyrimidines are of considerable chemical and pharmacological importance as purine analogs [1]. On the other hand, sulfonamides have a variety of biological activities such as antibacterial [2], insulin releasing [3], carbonic anhydrase inhibitory [4,5], anti-inflammatory [6] and antitumor [7] activities. These findings encourged us to explore the synthesis of pyrazolo[1,5-*a*]pyrimidines containing sulfonamido moieties in order to examine their antibacterial activity.

2. Chemistry

Diazotiazation of sulfanilamide or its derivatives **1a**–**d** followed by coupling with ethyl cyanoacetate in aqueous ethanol containing sodium acetate at 0–5°C yielded the key intermediate hydrazones **2a**–**d**. The spectral data revealed that these compounds exist in the hydrazone form **2a**–**d**. Refluxing of compounds **2a**–**d** with hydrazine hydrate in ethanol furnished the corresponding 3-aminopyrazoles **3a**–**d** in good yields (Scheme 1). The structures of **3a**–**d** were established on the basis of elemental analyses and spectral data.

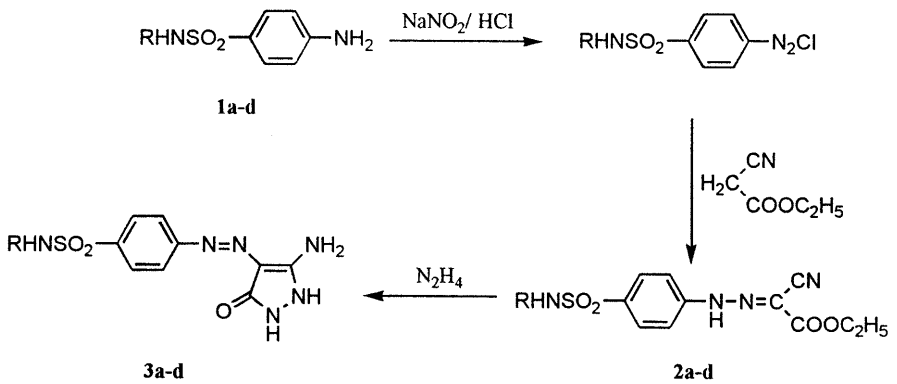
It has been reported that ketene dithioacetals and related compounds are well known as useful starting materials for the synthesis of heterocycles [8]. The behavior of **3a**–**d** towards ketene dithioacetals like compounds **4** and **7** was investigated. Thus, it has been found that [bis(methylthio)methylene]malononitrile (**4**) [9] reacts with aminopyrazoles **3a**–**d** in refluxing DMF containing catalytic amounts of triethylamine to yield the corresponding pyrazolo[1,5-*a*]pyrimidines (**6a**–**d**). The structure of compounds **6a**–**d** were established on the basis of their elemental analysis and spectral data. Thus, the IR spectra of **6a**–**d** revealed characteristic bands for NH_2, NH, C≡N, N=N and S=O functional groups. The ^1H NMR spectrum of compound **6a**

* Corresponding author. Fax: +20-88-325436.
E-mail address: m_elgaby@hotmail.com (M.S.A. El-Gaby).

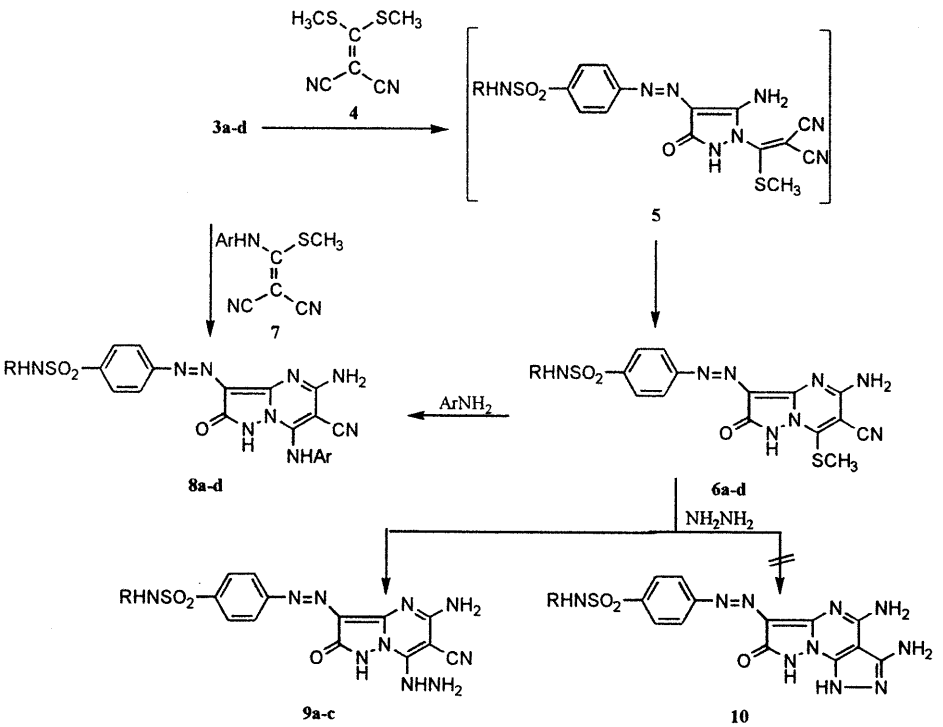
0014-827X/00/$ - see front matter
PII: S0014-827X(00)00079-3

showed a signal $\delta = 2.80$ assignable to the SCH_3 group, a multiplet at $\delta = 7.31–8.00$ assigned to aromatic protons and two broad singlets at $\delta = 4.80$ and 7.10 assignable to two amino groups. The formation of **6** from the reaction of **3** with dithioacetals **4** proceeds via initial alkylation of the ring nitrogen in **3** to give **5** followed by cyclization [10] to yield the final products **6**, (Scheme 2). Fusion of **6a–d** with aromatic amines at 150°C furnished the corresponding anilino derivatives **8a–h**. Compounds **8a–h** were also conveniently synthesized in a one-pot reaction by refluxing the corresponding aminopyrazoles **3a–d** with [(arylamino)(methylthio)methylene]malononitriles (**7a**,**b**) [9] in DMF containing catalytic amounts of triethylamine. When compounds **6a**,**c**,**d** were subjected to the reaction with hydrazine, the hydrazino derivatives **9a–c** were isolated and the dipyrazolo[1,5-*a*:4′.3′-*e*]pyrimidines **10** were eliminated on the basis of spectral data. Thus, the IR spectra of compounds **9a–c** revealed the presence of a C≡N band (Scheme 2).

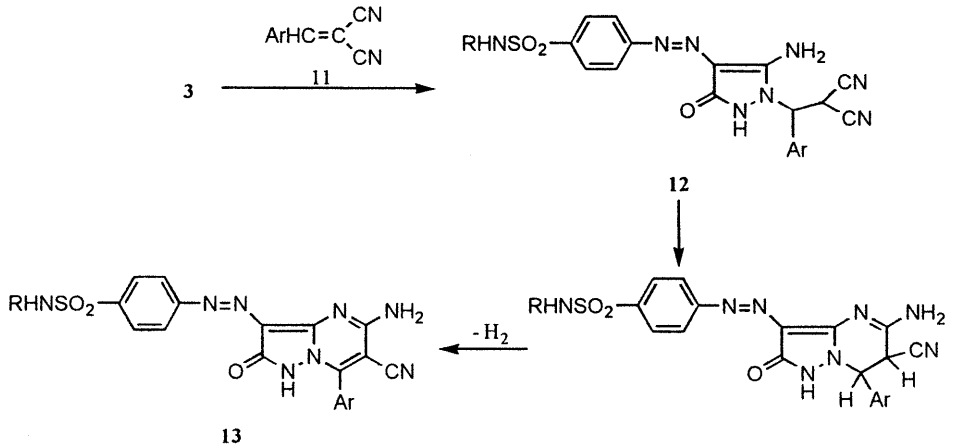
Compounds **3a–c** react with arylidenemalononitriles **11** in refluxing DMF catalyzed by pyridine to yield pyrazolo[1,5-*a*]pyrimidines **13**. The structure of compounds **13** was established on the basis of elemental analysis and spectral data. The formation of **13** from the reaction of **3** with **11** is assumed to proceed via initial Michael addition [11] of the ring nitrogen atom in **3** to the activated double bond in **11** to yield Michael adduct **12** which then cyclizes and loses H_2 to give **13** (Scheme 3).



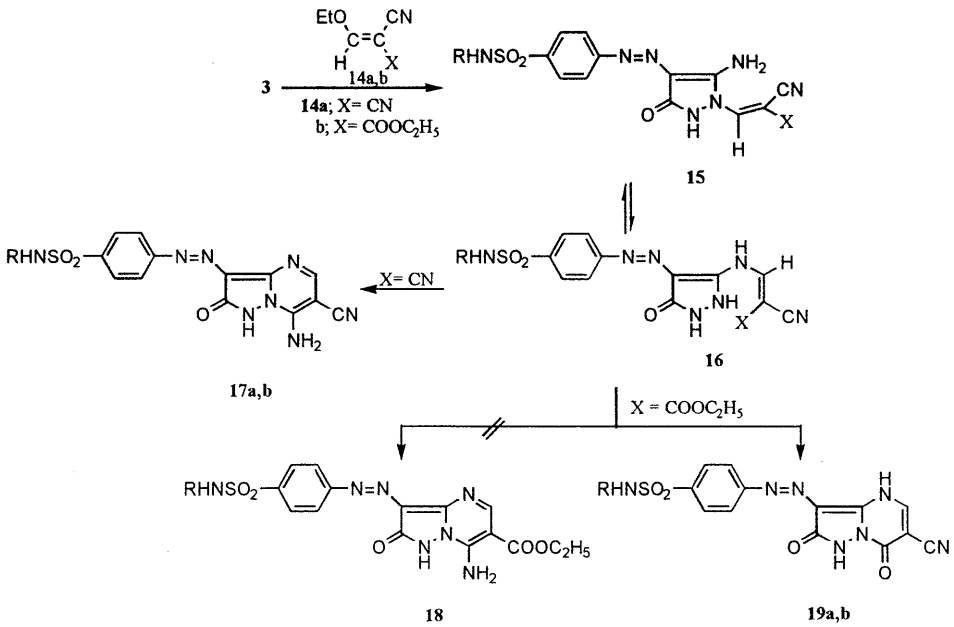
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

The study was extended to investigate the behavior of **3** with ethoxymethylenemalononitrile and ethyl ethoxymethylene cyanoacetate. Thus, when ethoxymethylene malononitrile **14a** was reacted with compounds **3a**,**d** in refluxing DMF–pyridine furnished the corresponding pyrazolopyrimidines **17a**,**b**. The formation of **17** proceeds via intermediate formation **15**, which rearranges to **16** [12] before cyclization into **17** (Scheme 4). On the other hand, when compounds **3a**,**d** were treated with ethyl ethoxymethylene cyanoacetate **14** in refluxing pyridine for which two products **18** and **19a**,**b** seemed possible. Structure **18** was readily ruled out on the basis of analytical and spectral data. Thus, the IR spectra of **19a**,**b** exhibited absorption bands for C≡N.

3. Experimental

All m.p. values are uncorrected. IR spectra were measured as KBr pellets on a Shimadzu IR 200 spectrophotometer. ^{1}H NMR spectra were recorded in deuterated chloroform at 200 MHz on a Varian Gemini NMR spectrometer using tetramethyl-silane as an internal reference. Elemental analyses were carried out at the Microanalytical Center of Cairo University. The characteristics data for prepared compounds are given in Table 1, analytical results for C, H, N, were within $0.0 \pm 0.1\%$ of the calculated values. The spectral data are collected in Tables 2 and 3.

[Bis(methylthio)methylene]malononitrile (**4**) and [(arylamino)(methylthio)methylene]malononitriles (**7a**,**b**) were obtained according to a reported method [9].

3.1. Ethyl{[4-(N-substituted)sulfamoyl]phenylazo}-cyanoacetate (2a–d)

Sulfonamide derivatives (0.01 mol) were dissolved in a mixture of concentrated HCl (4 ml) and water (5 ml) and cooled to 0°C in an ice bath. A cold aqueous solution of sodium nitrite (0.01 mol) was then added. The diazonium salt so obtained was filtered into a cooled mixture of sodium acetate (5 g) and ethyl cyanoacetate (0.01 mol) in ethanol. The resulting solid was washed with water and recrystallized from proper solvent to give **2a**–**d**.

3.2. 4-[4-(N-substituted)sulfamoyl]-phenylazo-3-aminopyrazol-5-ones (3a–d)

A solution of **2** (0.01 mol) and hydrazine hydrate (0.02 mol) in ethanol (30 ml) was refuxed for 1–2 h. The solid product, so formed was collected by filtration and recrystallized from proper solvent to give **3a**–**d**.

3.3. 5-Amino-7-methylthio-1,2-dihydro-3-[4-(N-substituted)sulfamoyl]phenylazo-2-oxo pyrazolo[1,5-a]pyrimidin-6-carbonitriles (6a–d)

To a suspension of compounds **3** (0.01 mol) and [bis-(methylsulfanyl)methylidene]malononitrile **4** [9] (0.01 mol) in dimethylformamide (20 ml), three drops of triethylamine were added. The mixture was refluxed

Table 1
Characteristics of the synthesized compounds

Comp. no.	R	Ar	M.p. (°C)	Yield (%)	Molecular formula (molecular wt.)
2a	H		205 [a]	96	$C_{11}H_{12}N_4O_4S$ (296)
2b	2-Pyridinyl		272 [a]	80	$C_{16}H_{15}N_5O_4S$ (373)
2c	2-Pyrimidinyl		223 [a]	85	$C_{15}H_{14}N_6O_4S$ (374)
2d	2-(4-Methyl pyrimidinyl)		218 [a]	87	$C_{16}H_{16}N_4O_4S$ (388)
3a	H		290 [b]	82	$C_9H_{10}N_6O_3S$ (282)
3b	2-Pyridinyl		285 [c]	86	$C_{14}H_{13}N_7O_3S$ (359)
3c	2-Pyrimidinyl		265 [b]	76	$C_{13}H_{12}N_8O_3S$ (360)
3d	2-(4-Methyl pyrimidinyl)		260 [b]	75	$C_{14}H_{14}N_8O_3S$ (374)
6a	H		240 [c]	64	$C_{14}H_{12}N_8O_3S_2$ (404)
6b	2-Pyridinyl		90 [a]	62	$C_{19}H_{15}N_9O_3S_2$ (481)
6c	2-Pyrimidinyl		170 [a]	67	$C_{18}H_{14}N_{10}O_3S_2$ (482)
6d	2-(4-Methyl pyrimidinyl)		108 [a]	65	$C_{19}H_{16}N_{10}O_3S_2$ (496)
8a	H	$C_6H_4CH_3$-*p*	150 [a]	72	$C_{20}H_{17}N_9O_3S$ (463)
8b	H	$C_6H_4OCH_3$-*p*	140 [a]	76	$C_{20}H_{17}N_9O_4S$ (479)
8c	2-Pyrimidinyl	$C_6H_4CH_3$-*p*	145 [a]	74	$C_{25}H_{19}N_{10}O_3S$ (540)
8d	2-Pyrimidinyl	$C_6H_4OCH_3$-*p*	142 [a]	71	$C_{25}H_{20}N_{10}O_4S$ (556)
8e	2-Pyrimidinyl	$C_6H_4CH_3$-*p*	160 [a]	67	$C_{24}H_{19}N_{11}O_3S$ (541)
8f	2-Pyrimidinyl	$C_6H_4OCH_3$-*p*	135 [a]	60	$C_{24}H_{19}N_{11}O_4S$ (557)
8g	2-(4-Methyl pyrimidinyl)	$C_6H_4CH_3$-*p*	140 [a]	72	$C_{25}H_{21}N_{11}O_3S$ (555)
8h	2-(4-Methyl pyrimidinyl)	$C_6H_4OCH_3$-*p*	210 [a]	75	$C_{25}H_{21}N_{11}O_4S$ (571)
9a	H		>300	57	$C_{13}H_{12}N_{10}O_3S$ (388)
9b	2-Pyrimidinyl		>300	60	$C_{17}H_{14}N_{12}O_3S$ (466)
9c	2-(4-Methyl pyrimidinyl)		>300	82	$C_{18}H_{16}N_{12}O_3S$ (480)
13a	H	C_6H_4F-*p*	220 [a]	74	$C_{19}H_{13}FN_8O_3S$ (452)
13b	H	$C_6H_4CH_3$-*p*	265 [a]	72	$C_{20}H_{16}N_8O_3S$ (448)
13c	H	$C_6H_4OCH_3$-*o*	190 [a]	71	$C_{20}H_{16}N_8O_4S$ (464)
13d	2-Pyridinyl	C_6H_4F-*p*	226 [a]	67	$C_{24}H_{16}FN_9O_3S$ (529)
13e	2-Pyridinyl	$C_6H_4CH_3$-*p*	242 [a]	64	$C_{25}H_{19}N_9O_3S$ (525)
13f	2-Pyridinyl	$C_6H_4OCH_3$-*o*	236 [a]	60	$C_{25}H_{19}N_9O_4S$ (541)
13g	2-Pyrimidinyl	C_6H_4F-*p*	223 [a]	74	$C_{23}H_{15}FN_{10}O_3S$ (530)
13h	2-Pyrimidinyl	$C_6H_4CH_3$-*p*	198 [a]	76	$C_{24}H_{18}N_{10}O_3S$ (526)
13i	2-Pyrimidinyl	$C_6H_4OCH_3$-*o*	130 [a]	76	$C_{24}H_{18}N_{10}O_4S$ (542)
17a	H		168 [a]	68	$C_{13}H_{10}N_8O_3S$ (358)
17b	2-(4-Methyl pyrimidinyl)		190 [a]	67	$C_{18}H_{14}N_{10}O_3S$ (450)
19a	H		174 [a]	72	$C_{13}H_9N_7O_4S$ (359)
19b	2-(4-Methyl pyrimidinyl)		178 [a]	75	$C_{18}H_{13}N_9O_4S$ (451)

[a] From ethanol.
[b] From DMF.
[c] From dioxane.

Table 2
IR spectra of the synthesized compounds

Comp. no.	ν_{NH} (NH_2)	$\nu_{C\equiv N}$	$\nu_{C=O}$	$\nu_{N=N}$	ν_{SO_2} asy.	ν_{SO_2} sy.
2a	3450, 3350, 3240	2200	1720		1330	1116
2b	3450, 3250	2205	1710		1370	1140
2c	3480, 3200	2200	1715		1340	1160
2d	3460, 3260	2205	1710		1340	1170
3a	3400, 3300, 3200		1720	1580	1320	1140
3b	3410, 3300, 3200		1685	1590	1350	1130
3c	3450, 3340, 3200		1660	1580	1340	1110
3d	3400, 3320, 3150		1680	1580	1340	1150
6a	3450, 3400, 3250	2200	1670	1600	1340	1160
6b	3460, 3400, 3200	2200	1660	1580	1360	1140
6c	3450, 3400, 3210	2205	1670	1582	1345	1150
6d	3400, 3350, 3100	2200	1660	1580	1340	1152
8a	3450, 3400, 3230	2200	1665	1600	1360	1150
8b	3450, 3400, 3240	2200	1680	1600	1340	1170
8c	3480, 3420, 3250	2200	1660	1600	1360	1150
8d	3460, 3350, 3100	2200	1650	1590	1355	1130
8e	3450, 3400, 3360	2200	1650	1590	1350	1130
8f	3450, 3400, 3230	2200	1650	1600	1330	1140
8g	3400, 3350, 3200	2200	1650	1606	1360	1140
8h	3450, 3410, 3240	2200	1660	1601	1340	1125
9a	3450, 3320	2200	1665	1580	1352	1123
9b	3430, 3350, 3200	2200	1662	1582	1340	1120
9c	3400, 3350, 3200	2200	1667	1585	1332	1122
13a	3460, 3380, 3200	2200	1660	1580	1334	1145
13b	3450, 3400, 3200	2200	1665	1560	1325	1132
13c	3450, 3380, 3230	2200	1650	1567	1325	1142
13d	3430, 3300	2200	1650	1600	1356	1127
13e	3480, 3400, 3220	2200	1645	1595	1365	1130
13f	3400, 3350, 3200	2200	1650	1580	1358	1125
13g	3460, 3400, 3200	2200	1667	1592	1330	1145
13h	3480, 3400	2200	1650	1590	1340	1130
13I	3460, 3400, 3200	2200	1650	1580	1340	1135
17a	3350, 3300	2200	1650	1580	1325	1140
17b	3350, 3200, 3100	2200	1680	1590	1335	1130
19a	3330, 3300, 3100	2200	1690	1582	1340	1154
19b	3350, 3210	2200	1685	1590	1330	1162

for 3 h and then allowed to cool. The solid precipitate was isolated by suction and recrystallized from the appropriate solvent to give **6a**–**d**.

*3.4. 5-Amino-7-arylamino-1,2-dihydro-3-[4-(N-substituted)sulfamoyl]phenylazo-2-oxopyrazolo[1,5-a]pyrimidin-6-carbonitriles (**8a**–**h**)*

Method A: a mixture of **6** (0.01 mol) and the required aromatic amine (0.01 mol) was fused at 150°C for 0.5 h, then triturated with ethanol, poured into water and then acidified with hydrochloric acid. The solid product, formed was collected by filtration and recrystallized from the appropriate solvent to give **8a**–**h**.

Method B: The experimental procedure used for the synthesis of **6** was carried out except for the use of [(arylamino)(methylthio)methylene]malononitrile instead of [bis(methylthio)methylene]malononitrile.

*3.5. 5-Amino-7-hydrazino-1,2-dihydro-3-[4-(N-substituted)sulfamoyl]phenylazo-2-oxopyrazolo[1,5-a]pyrimidin-6-carbonitriles (**9a**–**c**)*

Hydrazine hydrate (0.02 mol) was added to a solution of **6** (0.01 mol) in ethanol (30 ml) and the reaction mixture was heated under reflux for 3 h. The reaction mixture was cooled and poured on crushed ice–HCl. The product was filtered, washed with water and recrystallized from proper solvent to give **9a**–**c**.

3.6. 5-Amino-7-aryl-1,2-dihydro-3-[4-(N-substituted)-sulfamoyl]phenylazo-2-oxo-pyrazolo[1,5-a]pyrimidin-6-carbonitriles (**13a–i**)

Equimolar amounts of **3** (0.01 mol) and **11** (0.01 mol) in DMF (20 ml) containing a catalytic amount of pyridine were heated under reflux for 1 h. The solid product so obtained was collected by filtration and recrystallized from proper solvent to give **13a–i**.

Table 3
^{1}H NMR spectra of some synthesized compounds

Comp. no.	δ (ppm)
2a	1.23 (t, 3H, CH_3), 4.00 (q, 2H, OCH_2), 7.00 (s, 2H, SO_2NH_2; exchangeable), 7.20–7.70 (m, 4H, Ar–H), 12.50 (s, br, 1H, NH; exchangeable).
2b	1.20 (t, 3H, CH_3), 4.10 (q, 2H, OCH_2), 6.80 (s, 1H, SO_2NH; exchangeable), 6.92–7.80 (m, 8H, Ar–H), 12.20 (s, br, 1H, NH; exchangeable).
3a	5.90 (s, br, 2H, NH_2; exchangeable), 7.10 (s, br, 2H, SO_2NH_2; exchangeable), 7.30–7.70 (m, 5H, Ar–H+NH), 10.20 (s, br, NH; exchangeable).
6a	2.80 (s, 3H, SCH_3), 4.80 (s, br, 2H, NH_2; exchangeable), 7.10 (s, br, 2H, SO_2NH_2; exchangeable), 7.31–8.00 (m, 4H, Ar–H), 8.91 (s, br, 1H, NH; exchangeable).
6b	2.81 (s, 3H, SCH_3), 6.76 (s, br, 2H, NH_2; exchangeable), 7.20 (s, br, 1H, SO_2NH; exchangeable), 7.30–8.01(m, 8H, Ar–H), 8.61 (s, br, 1H, NH; exchangeable).
8b	3.70 (s, 3H, OCH_3), 5.60 (s, br, 2H, NH_2; exchangeable), 6.70 (s, 2H, SO_2NH_2; exchangeable), 6.80–7.60 (m, 8H, Ar–H), 7.80 (s, 1H, NH; exchangeable), 10.10 (s, 1H, NH; exchangeable).
8h	2.30 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.60 (s, br, 2H, NH_2; exchangeable), 6.70–7.20 (m, 10H, Ar–H), 7.50 (s, br, 1H, SO_2NH; exchangeable), 8.00 (s, br, NH, exchangeable), 10.10 (s, 1H, NH; exchangeable).
13c	3.90 (s, 3H, OCH_3), 8.7 (s, br, 2H, NH_2; exchangeable), 6.90 (s, br, 2H, SO_2NH_2, exchangeable), 7.00–7.91 (m, 8H, Ar–H), 8.01 (s, 1H, NH; exchangeable).
13h	2.10 (s, 3H, CH_3), 6.50 (s, br, 2H, NH_2; exchangeable), 6.90–7.81(m, 1H, Ar–H), 8.02 (s, 1H, SO_2NH; exchangeable), 8.30 (s, 1H, NH; exchangeable).
17b	2.30 (s, 3H, CH_3), 6.50 (s, br, NH_2; exchangeable), 7.00 (s, br, SO_2NH; exchangeable), 7.10–7.90 (m, 7H, Ar–H), 8.00 (s, 1H, N H; exchangeable).

3.7. 7-Amino-3-[4-(N-substituted)sulfamoyl]phenylazo-1,2-dihydro-2-oxopyrazolo-[1,5-a]pyrimidin-6-carbonitriles (**17a,b**)

A suspension of **3** (0.01 mol) in DMF (20 ml) was treated with **14a** (0.01 mol) and two drops of piperidine. The mixture was heated for 3 h and then left to cool at room temperature. The solid product obtained was collected by filtration and recrystallized from proper solvent to give **17a**,**b**.

3.8. 3-[4-(N-substituted)sulfamoyl]phenylazo-2,7-dioxo-1,2,4,7-tetrahydropyrazolo-[1,5-a]pyrimidin-6-carbonitriles (**19a,b**)

Prepared by the same procedure as **17** using **14b** instead of **14a**. The solid obtained recrystallized from proper solvent to give **19a**,**b**.

4. Preliminary antibacterial screening

The antibacterial activity of the compounds **3c**, **6c**,**d**, **8b**,**f**,**h**, **9c**, **13c**,**f** and **19a**,**b** was determined by the agar diffusion technique [13,14]. The test organisms were *Staphylococcus aureus* (NCTC 7447), *Bacillus subtilis* (NCTC 10400), *Sarcina sp*. (NCTC 1117), *Escherichia coli* (NCTC 10416) and *Serratia marcescens* (IMRU 70). The agar media were inoculated with test organisms and a solution of the tested compound in DMSO (1 mg/ml) was placed separately in cups (8 mm diameter) in the agar medium. A 0.1% solution of streptomycin was used as a reference. The inhibition zones were measured after 24 h incubation. The results of the antibacterial activity tests are summarized in (Table 4).

Most of the synthesized compounds were found to possess various antibacterial activity towards all the microorganisms used. Compounds **3c**, **6c**, **6d**, **8f** and **8h**, which all contain a pyrimidine moiety, possess high antibacterial activities towards *S. marcescens* (IMRU-70). Compounds **8f**, **8h** and **9c**, which also contain a pyrimidine moiety possess the highest antibacterial activities towards *Sarcina sp*. (NCTC-1117). On the other hand, compound **13f** which contains a pyridine moiety was found to possess the highest antibacterial activity towards *S. aureus* (NCTC 7447) as compared to the remaining compounds. Compounds **8b**, **13c**, **19a** and **19b** which contain a SO_2NH_2 group were weakly active against *S. aureus* (NCTC 7447). However, none of the tested compounds showed superior activity than the reference streptomycin.

Table 4
Antibacterial activity of some synthesized compounds [a]

Comp. no.	Gram positive		Gram negative		
	Staphylococcus aureus (NCTC 7447)	*Bacillus subtilis* (NCTC 10400)	*Sarcina sp.* (NCTC 1117)	*Escherichia coli* (NCTC 10416)	*Serratia marcescens* (IMRU 70)
3c	+	++	++	+++	+++
6c	+	+	++	+++	+++
6d	+	+	++	++	+++
8b	+	+	++	+	++
8f	++	+	+++	+++	+++
8h	++	+	+++	++	+++
9c	+	+	++	++	+++
13c	+	+++	++	++	++
13f	+++	+++	++	++	++
19a	+	++	+	+	+
19b	+	+++	+++	++	+
Streptomycin	++++	++++	++++	++++	++++

[a] +, moderately sensitive giving a zone of inhibition 9–11 mm; ++, sensitive giving a zone of inhibition 12–14 mm; +++, very sensitive giving a zone of inhibition 15–18 mm; ++++, very highly sensitive giving a zone of inhibition over 18 mm.

References

[1] M.H. Elnagdi, M.R.H. Elmoghayar, G.H. Elgemeie, Chemistry of pyrazolopyrimidines, Adv. Heterocyclic Chem. 41 (1987) 320–367.

[2] F. Zoni, P. Vicini, Antimicrobial activity of some 1,2-benzisothiazoles have a benzenesulfonamides moiety, Arch. Pharm. 331 (1998) 219–223.

[3] T.H. Maren, Reactions between structure and biological activity of sulfonamides, Ann. Rev. Pharmacol. Toxicol. 16 (1976) 309–327.

[4] C.T. Supuran, A. Scozzafava, B.C. Jurca, M.A. Iiies, Carbonic anhydrase inhibitors. Part 49: Synthesis of substituted ureido and thioureido derivatives of aromatic/heterocyclic sulfonamides with increased affinities of isozyme I, Eur. J. Med. Chem. 33 (1998) 83–93.

[5] C.T. Supuran, A. Scozofava, A. Popescu, R.B. Tureac, A. Banciu, A. Creanga, G.B. Tureac, M.D. Banciu, Carbonic anhydrase inhibitors. Part 43: Schiff bases derived from aromatic sulfonamides: towards more specific inhibitors for membrane-bound versus cytosolic isozymes, Eur. J. Med. Chem. 32 (1997) 445–452.

[6] J.J. Li, D. Anderson, E.G. Burton, J.N. Cogburn, J.T. Collins, D.J. Garland, S.A. Gregory, H.C. Huang, P.C. Isakson, C.M. Koboldt, E.W. Logusch, M.B. Norton, W.E. Perkins, E.J. Reinhard, K. Seibert, A.W. Veenhuizem, Y. Zang, D.B. Reitz, 1,2-Diarylcyclopentens as selective cyclooxygenase-2 inhibitors and orally active anti-inflammatory agents, J. Med. Chem. 38 (1995) 4570–4578.

[7] H. Yoshino, N. Ueda, J. Niijima, H. Sugumi, Y. Kotake, N. Koyanagi, K. Yoshimatsu, M. Asada, T. Watanabe, T. Nagasu, K. Tsukahara, A. Lijima, K. Kitoh, Novel sulfonamides as potential systemically active antitumor agents, J. Med. Chem. 35 (1992) 2496–2497.

[8] M. Yokoyama, H. Togo, S. Kondo, Synthesis of heterocycles from ketene dithioacetals, Sulf. Rep. 10 (1990) 23–47.

[9] Y.A. Ammar, A.M. Sh. El-Sharief, M.H. Zahran, M.Z. El-Said, U.H. El-Said, Studies on activated nitriles: synthesis of new 3-cyano-2-(3-tolyl-amino)pyrazolo[1,5-*a*]pyrimidines, J. Chem. Res. (S) (1995) 324–325.

[10] G.H. Elgemeie, S.E. Elezbay, H.A. Ali, A. Mansour, Novel synthesis of mercapto purine and pentaaza-as-indacene analogues: Reaction of [bis(methylthio)methylene]malononitrile and ethyl 2-cyano-3,3-bis(methylthio)acrylate with 5-aminopyrazoles, Bull. Chem. Soc. Jpn. 67 (1994) 738–741.

[11] N.S. Ibrahim, Reaction of isothiocyanates with active methylene: A new approach for the synthesis of pyrazole, pyrimidine and pyrazolo[1,5-*a*]-pyrimidine derivatives, Chem. Ind. (1989) 654–655.

[12] G.H. Elgemeie, A.H. Elghandour, H.M. Elshimy, Studies on aminopyrazoles: synthesis of pyrazolo[1,5-*a*]pyrimidines and their aza derivatives, J. Prakt. Chem. 331 (1989) 466–474.

[13] L.P. Carrod, F.D. Grady, Antibiotic and Chemotherapy, third ed., Churchill Livingstone, Edinburgh, UK, 1972, p. 477.

[14] O. Söhnel, P. Novotný, Densities of Aqueous Solutions of Inorganic Substances, Elsevier, Amsterdam, 1985.