Triazolylbenzimidazolthiones and Derivatives of the New 1,2,3-Triazolo[1,5-*a*][1,3,5]benzotriazepine Heterocycle

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Four new triazolylbenzimidazolthione derivatives (2a-d), analogous to triazolylbenzimidazolone derivatives previously tested as activators of the BK_{Ca} potassium channels, were prepared and assayed without success. Some derivatives of a new tricyclic nitrogen heterocycle, 1,2,3-triazolo[1,5-*a*][1,3,5]benzotriazepine, bearing a carboxamido group in the 3 position, other substituents in the 8 position and a carbonyl (5a-d) or thione (6a-c) or methylthio (7a-c) function in the 5 position were synthesised. The nucleophilic displacement of the methylthio substituent with morpholine or cyclopentylamine provided the 5-amino-substituted tricyclic derivatives 8a-d. Starting from the 1-(2-nitrophenyl)-4-cyano-5-amino-1,2,3-triazole (9), the 3-cyano-triazolobenzotriazepin-5-one derivative 12 was also obtained. The majority of the new compounds were tested towards the BK_{Ca} potassium channels, the benzodiazepine and adenosine A_1 and A_{2A} receptors, but no remarkable activity was detected.

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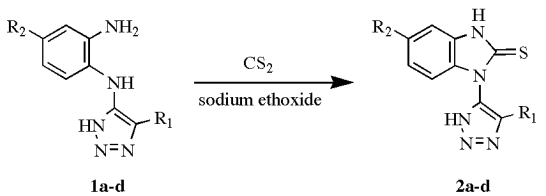
For some time we have been interested in the investigation of compounds with potential activity towards potassium channels [1]. In particular our attention was directed to compounds active towards high conductance calcium activated potassium channels (BK_{Ca}), because of the correlation of their structure with that of the reference benzimidazolone compounds NS 004 and NS 1619 [2-5].

The pharmacological experimentation of several 5-substituted-1-(triazol-5-yl)-benzotriazole and 5-substituted-1-(triazol-5-yl)-benzimidazolone derivatives [3,4] had shown that the benzotriazole compounds possessed an activity higher than that of the benzimidazolone compounds. However we decided on substituting the oxygen atom of the benzimidazolone ring with a sulphur atom, to evaluate the effect afforded to the biological properties. In fact the change of the biological activity related to the structural change induced by the passage from nitrogen (benzotriazole) to oxygen (benzimidazolone) to sulphur (benzimidazolthione) as acceptor sites of a hydrogen bond, could give information about this pharmacophoric parameter.

Thus starting from the suitable 5-(2-aminoanilino)-1,2,3-triazoles **1a-d** (Scheme 1), previously described in the literature [6,2], by reaction with carbon disulphide in ethanolic solution in the presence of sodium ethoxide at 50 °C for several hours, the corresponding benzimidazolthione derivatives **2a-d** were obtained in good yield. In addition, by

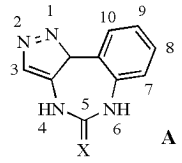
Scheme 1



1a-d **2a-d**

a: $R_1 = CONH_2$, $R_2 =$ H; **b**: $R_1 = CONH_2$, $R_2 = CH_3$; **c**: $R_1 = CONH_2$, $R_2 = Cl$; **d**: $R_1 = R_2 = H$

the correlation with tricyclic structures having *in vivo* biological activity, like dibenzo[1,3]diazepines (excitant, aggressant, motor stimulant and anticonvulsant activity) [7] or 4-aryl-1,3-benzodiazepines (antihypertensive activity) [8], we decided to employ some synthesis intermediates of previous structures for the preparation of the new tricyclic nitrogen heterocycle 1,2,3-triazolo[1,5-*a*][1,3,5]benzotriazepine, corresponding to the general structure A (Figure 1).



A

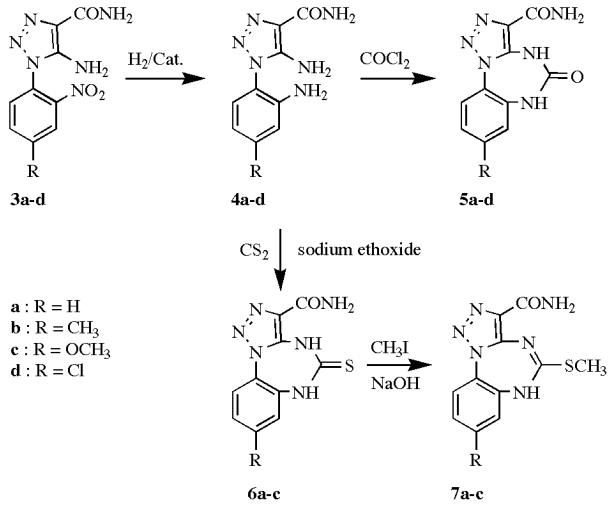
Figure 1. 1,2,3-Triazolo[1,5-*a*][1,3,5]benzotriazepine.

In this case introduction of a sulphur atom in the 5 position in the place of the oxygen, could also allow the preparation of further new derivatives, by the conversion to a methylthio group, well available towards the nucleophilic substitution. The synthesis of this new heterocycle (Scheme 2), required the preparation of the 1-(2-nitrophenyl)-4-carboxamido-5-amino-1,2,3-triazoles **3a-d**, by ionic 1,3-dipolar cycloaddition reaction of the suitable 2-nitrophenylazide to cyanacetamide. This reaction had to be carried out under mild conditions (low temperature) to decrease the formation of the corresponding 4-carboxamido-5-(2-nitroanilino)-1,2,3-triazoles. These compounds were really the main reaction products and came from the Dimroth isomerization of **3**, isomerization which was aided by the alkaline medium and by the presence of a nitro substituent [9]. Compounds **3a** and **3b** have previously been described in the literature [6] while **3c** and **3d** were isolated in 30% and 11% yield respectively.

Reduction of the nitro to amino group by catalytic hydrogenation on Pd/C or Ni-Raney (for the chloroderiva-

tive **3d**), working at a temperature < 30 °C for the isolation of compounds, provided the corresponding derivatives **4a-d** in high yield. In this case also, compounds **4a** and **4b** have previously been described in the literature [6]. The amino derivatives **4a-d** in pyridine solution reacted with phosgene in toluene solution at room temperature overnight, to give the expected tricyclic triazolobenzotriazepine compounds **5a-d**. Compound **5a** was isolated in 62.5% yield, probably due to the greater solubility of **4a** in pyridine, but compounds **5b**, **5c** and **5d** were obtained in 45%, 48% and 32% yield respectively.

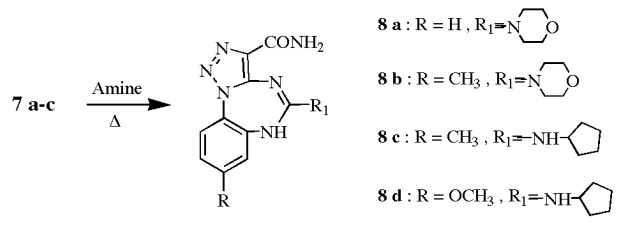
Scheme 2



Similarly, the same diamino derivatives **4a-c** in ethanolic solution in the presence of sodium ethoxide, reacted with excess carbon disulphide at 50 °C for 20-30 hours to give the corresponding tricyclic compounds **6a-c**, bearing a sulphur atom in the 5 position, in 72%, 38% and 53% yield respectively. The 5-methylthio derivatives **7a-c**, useful synthetic intermediates, were obtained in high yield treating the corresponding thione/thiole derivatives **6a-c** in 2.5% sodium hydroxide solution with methyl iodide at room temperature.

The preparation of the derivatives **8a-d** with aliphatic amines is shown in Scheme 3.

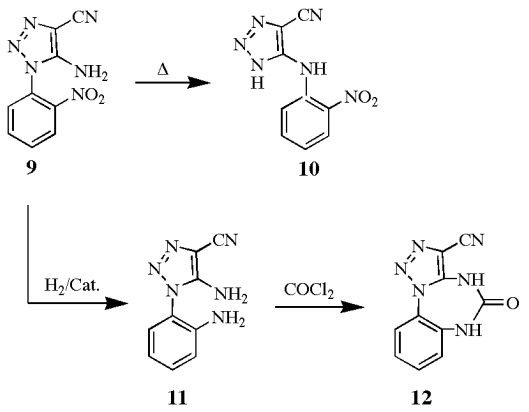
Scheme 3



Thus on heating **7a** and **7b** in excess morpholine at the refluxing temperature for 3 hours, the 5-morpholino derivatives **8a** and **8b** were obtained in high yield; similarly on heating **7b** and **7c** with cyclopentylamine, the derivatives **8c** and **8d** were isolated.

In order to change the carboxamido substituent on the 1,2,3-triazole ring for a nitrile group (Scheme 4), reaction of 2-nitrophenylazide [10] to malononitrile, carried out at temperature < -5 °C, gave the 1-(2-nitrophenyl)-4-cyano-5-amino-1*H*-1,2,3-triazole (**9**) in 86% yield. On heating **9** under reflux in toluene solution for 2 hours, Dimroth isomerization [9] was induced and the 4-cyano-5-(2-nitroanilino)-1,2,3-triazole (**10**) was characterized for comparison purposes. The nitro derivative **9** underwent a catalytic hydrogenation to give the corresponding aminotriazole **11** which was isolated in 40% yield after chromatography working at a temperature < 30 °C. Finally, the diamino derivative **11** in pyridine solution reacted with excess phosgene (added as triphosgene in toluene solution) at room temperature overnight to give the expected triazolobenzotriazepine derivative **12**, isolated by silica gel column chromatography, in 79% yield.

Scheme 4



The structures of all the new prepared compounds were assigned upon the basis of known reaction mechanisms and our previous evidence concerning triazolylbenzotriazole [6] and triazolylbenzimidazolone [11] derivatives and were confirmed by analytical and spectroscopic methods (mass spectra in Table 1 and ^{1}H-nmr spectra in Table 2).

In addition, as a further structure confirmation and a better characterization, the ^{13}C-nmr spectra in DMSO-d_6 of compounds **2c**, **5a** and **6b** are reported: **2c**: δ 171.0 (CS), 160.0 ($CONH_2$), 138.5(C4'), 136.5 (C5'), 132.9 (C7a), 132.1 (C3a), 127.8 (C5), 122.6 (C6), 110.9 (C4), 109.6 (C7); **5a**: δ 162.8 ($CONH_2$), 155.9 (CO), 137.6 (C3), 130.1 (C8), 129.6 (C3a), 125.8 (C6a), 125.8 (C10a), 124.9 (C9), 121.9 (C7), 121.7 (C10); **6b**: δ 182.4 (CS), 162.3 ($CONH_2$), 139.4 (C8), 136.2 (C3), 127.8 (C3a), 126.0 (C9), 125.0 (C10a), 123.5 (C6a), 122.0 (C7), 120.6 (C10), 20.1 (CH_3).

Table 1

Chemical and Physical Properties of the Prepared Compounds

Comp. Solvent	Yield %	Crystall.	M.p. (°C)	Formula	Analyses C, H, N Calcd./ Found %	Mass *m/z* M^+ (%)	Base
2a	62	H_2O	270-272 dec.	$C_{10}H_8N_6OS$	46.15, 3.10, 32.29 46.48, 3.05, 32.46	260 (41.82)	44
2b	76	H_2O	273-274 dec.	$C_{11}H_{10}N_6OS$	48.17, 3.67, 30.64 48.50, 3.70, 30.95	274 (9.47)	44
2c	60	H_2O	268-271	$C_{10}H_7N_6OSCl$	40.75, 2.39, 28.52 41.05, 2.50, 28.89	294 (7.21)	44
2d	69	H_2O	282-284 dec.	$C_9H_7N_5S$	49.76, 3.25, 32.24 49.77, 3.23, 32.25	217 (93.70)	39
3c	30	EtOAc/Petr.Eth. [a]	271-273	$C_{10}H_{10}N_6O_4$	43.17, 3.62, 30.21 43.51, 3.73, 30.53	278 (7.98)	44
3d	11	EtOAc/Petr.Eth. [a]	305-308	$C_9H_7N_6O_3Cl$	38.25, 2.50, 29.73 38.43, 2.46, 29.78	282 (5.40)	140
4c	94	Acetone/Petr.Eth.	196-198	$C_{10}H_{12}N_6O_2$	48.38, 4.87, 33.85 48.70, 4.94, 34.17	248 (2.44)	44
4d	96	EtOAc/Petr.Eth.	185-187	$C_9H_9N_6OCl$	42.78, 3.59, 33.26 43.08, 3.48, 33.59	252 (4.28)	44
5a	62	DMF/H_2O	229-231	$C_{10}H_8N_6O_2$	49.18, 3.30, 34.41 48.82, 3.13, 34.39	244 (47.30)	118
5b	45	DMF/H_2O	258-261	$C_{11}H_{10}N_6O_2$	51.16, 3.90, 32.54 51.49, 3.97, 33.34	258 (17.78)	44
5c	48	DMF/H_2O	270-272	$C_{11}H_{10}N_6O_3$	48.18, 3.68, 30.64 48.30, 3.70, 31.00	274 (72.19)	174
5d	32	DMF	279-281	$C_{10}H_7N_6O_2Cl$	43.10, 2.53, 30.16 42.79, 2.74, 30.52	278 (15.63)	44
6a	72	DMF/H_2O	259-261	$C_{10}H_8N_6OS$	46.15, 3.10, 32.29 46.07, 3.12, 32.62	260 (1.62)	44
6b	38	DMF	261-263	$C_{11}H_{10}N_6OS$	48.17, 3.67, 30.64 48.28, 3.70, 30.60	274 (7.26)	44
6c	53	DMF/H_2O	258-260	$C_{11}H_{10}N_6O_2S$	45.51, 3.47, 28.95 45.19, 3.65, 28.61	290 (3.53)	44
7a	85	H_2O	285-287	$C_{11}H_{10}N_6OS$	48.17, 3.67, 30.64 48.51, 3.58, 30.87	274 (3.42)	150
7b	89	H_2O	286-288	$C_{12}H_{12}N_6OS$	49.99, 4.19, 29.15 49.88, 3.99, 29.22	288 (15.11)	44
7c	89	H_2O	280 dec.	$C_{12}H_{12}N_6O_2S$	47.36, 3.97, 27.62 47.05, 3.91, 27.63	304 (25.27)	44
8a	91	EtOH/H_2O	285-287	$C_{14}H_{15}N_7O_2$	53.67, 4.83, 31.29 53.93, 4.93, 30.96	313 (51.63)	44
8b	79	EtOH/H_2O	326-328	$C_{15}H_{17}N_7O_2$	55.04, 5.23, 29.95 54.79, 5.05, 29.65	327 (44.01)	255
8c	92	EtOH	308-310	$C_{16}H_{19}N_7O$	59.06, 5.89, 30.16 59.13, 6.12, 29.88	325 (74:57)	158
8d	90	EtOH	313-315	$C_{16}H_{19}N_7O_2$	56.30, 5.61, 28.72 56.30, 5.68, 29.05	341 (18.51)	41
9	86	Acetone/Petr.Eth. [a]	132-134	$C_9H_6N_6O_2$	46.96, 2.63, 36.51 47.08, 2.81, 36.85	230 (100)	230
10	94	EtOAc/Hexane	186-188	$C_9H_6N_6O_2$	46.96, 2.63, 36.51 47.25, 2.70, 36.83	230 (1.54)	53
11	40	EtOAc/Petr.Eth. [a]	133-135	$C_9H_8N_6$	53.99, 4.03, 41.98 54.23, 4.22, 42.29	200 (8.22)	53
12	79	DMF/H_2O	295-298 [b]	$C_{10}H_6N_6O$	53.10, 2.67, 37.15 53.41, 2.85, 36.88	226 (29.89)	118

[a] crystallized by solution at room temperature, beginning precipitation with petroleum ether and cooling at –20 °C; [b] at 240-245 °C the amorphous solid changed to white needles.

The uv data of the tricyclic derivative **12** are also reported as an example of absorbance of these structures: λ_{max} = 221nm, log ε = 4.520 (c 2.78 10^{-5} *M*, isopropanol).

The ir spectra of the benzimidazolthiones **2a-d** and of the tricyclic compounds **5a-d** and **6a-c** show the expected bands corresponding to NH and CO groups: Compounds

Table 2

^{1}H-NMR Spectra in DMSO-d_6 (δ)

2a	13.10 (s, 1H, NH); 7.89 and 7.53 (2s, 2H, NH_2); 7.25-6.80 (m, 4H, Ar)
2b	7.86 and 7.54 (2s, 2H, NH_2); 7.05-6.68 (m, 3H, Ar); 2.36 (s, 3H, Me)
2c	13.17 (brs, 1H, NH); 12.41 (brs, 1H, NH); 7.89 and 7.53 (2s, 2H, NH_2); 7.27-6.81 (m, 3H, Ar)
2d	8.52 (s, 1H, NH); 7.38-7.10 (m, 5H, Ar and Triaz.)
3c	7.81-7.46(m, 3H, Ar); 7.58 and 7.20 (2s, 2H, NH_2); 6.48 (s, 2H, NH_2); 3.94 (s, 3H, Me)
3d	8.43 (d, 1H, Ar); 8.06 (dd, 1H, Ar); 7.84 (d, 1H, Ar); 7.62 and 7.23 (2 brs, 2H, NH_2); 6.62 (s, 2H, NH_2)
4c	7.52 and 7.13 (2s, 2H, NH_2); 6.98-6.22 (m, 3H, Ar); 5.95 (s, 2H, NH_2); 5.13 (s, 2H, NH_2); 3.72 (s, 3H, Me)
4d	7.54 and 7.14 (2 brs, 2H, NH_2); 7.09-6.63 (m, 3H, Ar); 6.13 (s, 2H, NH_2); 5.48 (s, 2H, NH_2)
5a	9.84 (s, 1H, NH); 8.93 (s, 1H, NH); 8.17 and 7.77 (2s, 2H, NH_2); 7.92-7.22 (m, 3H, Ar)
5b	11.00 (s, 1H, NH); 9.76 (s, 1H, NH); 8.87 and 8.15 (2s, 2H, NH_2); 7.78-7.03 (m, 3H, Ar); 2.31 (s, 3H, Me)
5c	9.74 (s, 1H, NH); 8.90 (s, 1H, NH); 8.13 (s, 1H, NH_2); 7.84-6.80 (m, 4H, Ar and NH_2); 3.78 (s, 3H, Me)
5d	9.92 (s, 1H, NH); 9.04 (s, 1H, NH); 8.17 and 7.76 (2s, 2H, NH_2); 7.94-7.29 (m, 4H, Ar)
6a	11.20 (s, 1H, NH); 10.06 (s, 1H, NH); 8.27 and 7.94 (2s, 2H, NH_2); 7.89-7.28 (m, 4H, Ar)
6b	11.11 (s, 1H, NH); 10.01 (s, 1H, NH); 8.24 and 7.85 (2s, 2H, NH_2); 7.81-7.08 (m, 3H, Ar); 2.29 (s, 3H, Me)
6c	11.07 (s, 1H, NH); 10.03 (s, 1H, NH); 8.21 (s, 1H, NH_2); 7.85-6.80 (m, 4H, Ar and NH_2); 3.77 (s, 3H, Me)
7a	11.19 and 10.05 (2s, 1H, NH); 8.26 (s, 1H, NH_2); 7.93-7.25 (m, 5H, Ar and NH_2); 2.50 (s, 3H, Me)
7b	9.70 (s, 1H, NH); 7.66-6.78 (m, 5H, Ar and NH_2); 2.50 (s, 3H, Me); 2.23 (s, 3H, Me)
7c	9.76 (brs, 1H, NH); 7.70-6.59 (m, 5H, Ar and NH_2); 3.74 (s, 3H, Me); 2.51 (s, 3H, Me)
8a	8.70 (brs, 1H, NH); 7.76 (d, 1H, Ar); 7.43-7.10 (m, 5H, Ar and NH_2); 3.67-3.52 (m, 8H, Morph)
8b	8.68 (brs, 1H, NH); 7.76-6.95 (m, 5H, Ar and NH_2); 3.68-3.50 (m, 8H, Morph); 2.30 (s, 3H, Me)
8c	7.72 and 7.33 (2s, 2H, NH_2); 7.66-6.70 (m, 3H, Ar); 7.29 (brs, 1H, NH); 4.02 (brs, 1H, NH); 2.27 (s, 3H, Me); 1.93-1.47 (m, 9H, Cyclop)
8d	7.72 and 7.34 (2s, 2H, NH_2); 7.70-6.45 (m, 3H, Ar); 7.24 (brs, 1H, NH); 4.00 (brs, 1H, NH); 3.77 (s, 3H, Me); 1.94-1.44 (m, 9H, Cyclop)
9	8.32-7.78 (m, 4H, Ar); 7.35 (s, 2H, NH_2)
10	9.86 (s, 1H, NH); 8.17-7.07 (m, 5H, Ar and NH)
11	7.28-6.61 (m, 4H, Ar); 6.85 (s, 2H, NH_2); 5.26 (s, 2H, NH_2)
12	11.06 (s, 1H, NH); 9.73 (s, 1H, NH); 7.87-7.23 (m, 4H, Ar)

2a-d: NH signals at 3450-3170 cm^{-1} and $CONH_2$ signal at 1676-1650 cm^{-1}; Compounds **5a-d**: NH signals at 3360-3250 cm^{-1} and clear carbonyl signals for NHCONH at 1747-1733 cm^{-1} and for $CONH_2$ at 1680-1668 cm^{-1}; Compounds **6a-c** : NH signals at 3390-3170 cm^{-1} and $CONH_2$ signal at 1666-1661 cm^{-1}.

Finally, a chemical confirmation of the new 1,2,3-triazolo[1,5-*a*][1,3,5]benzotriazepine structure was achieved by the following reactions. The 1-benzyl-4-carboxamido-5-amino-1*H*-1,2,3-triazole [12] was reacted either with phosgene or thiophosgene under the previously employed reaction conditions, which did not induce Dimroth isomerization, but no azapurine derivative was isolated. Thus the involvement of the carboxamido group in the cyclization could be excluded; the only effect of the reagent was the partial dehydration of the carboxamido to cyano group.

The reaction of 1-(2-aminophenyl)-4-carboxamido-5-amino-1*H*-1,2,3-triazole (**4a**) with excess phosgene under prolonged reaction times did not provide the tricyclic derivative **5a**, but the tricyclic cyanoderivative **12**, involving the cyclization between the two amino groups and the dehydration of the carboxamido group.

Several compounds were tested to evaluate their activity towards potassium channels (**2a**,**b**,**c**, **d**; **5a**,**c**; **6a**,**c**; **12**), A_1 and A_{2A} adenosine receptors (**2b**,**d**; **5b**,**d**; **6a**,**b**,**d**; **12**; **7b**,**c**; **8a**,**b**) and benzodiazepine receptors (**2b**,**d**; **5b**,**d**; **6a**,**b**,**d**; **12**), but no remarkable activity was detected.

The experimental procedures are reported in our previous papers : [5], [13] and [13] respectively.

EXPERIMENTAL

Melting points were determined on a Kofler hot-stage and are uncorrected. IR spectra in nujol mulls were recorded on a Mattson Genesis series FTIR spectrometer. UV spectrum was obtained on a Perkin-Elmer Lambda 15 UV/VIS spectrophotometer in isopropanol. ^{1}H-NMR and ^{13}C-NMR spectra were recorded with a Varian Gemini 200 spectrometer in δ units, using TMS as internal standard. Mass spectra were performed with a Hewlett Packard MS/System 5988 A. Elemental analyses (C,H,N) were within ± 0.4% of theoretical values and were performed on a Carlo Erba Elemental Analyzer Mod. 1106 apparatus. TLC data were obtained with Merck silica gel 60 F_{254} aluminum sheets. Petroleum ether corresponds to fraction boiling at 40-60 °C. Phosgene, azides and carbon disulphide are very toxic and dangerous reagents which requires an appropriate personal protection.

1-(1,2,3-Triazol-5-yl)-benzimidazolthiones (**2a-d**).

To a stirred solution of sodium ethoxide, prepared from sodium (0.043 g, 1.87 mmol) in 16 mL of absolute ethanol, 1.70 mmoles of the appropriate 5-(2-aminoanilino)-1,2,3-triazoles (**1a**, **1b, 1c** or **1d**) [6,2] and 10 mL of carbon disulphide were added and the mixture was heated at 50 °C for 18 hours under stirring. After 1 hour the solution colour changed from brown to yellow. The solvent was evaporated *in vacuo*, the residue was treated with water and the resulting solution was acidified with 10% hydrochloric acid to precipitate the title compounds which were collected by filtration and washed with water (Table 1).

1-(2-Nitro-4-substituted-phenyl)-4-carboxamido-5-amino-1*H*-1,2,3-triazoles (**3c** and **3d**).

To a stirred solution of sodium ethoxide, prepared from sodium (1.20 g, 52 mmol) in 80 mL of absolute ethanol, cyanacetamide (

4.37 g, 52 mmol) was added. After 15 minutes the suspension was cooled into an ice-salt bath at -10 °C and a solution of 43.8 mmoles of the appropriate azide (2-nitro-4-methoxy-phenylazide [14] or 2-nitro-4-chloro-phenylazide [15]) in 120 mL of absolute ethanol was added drop by drop, keeping the temperature < -5 °C. The reaction mixture was stirred for 1 hour into the ice-bath, then overnight at room temperature. Water was added to precipitate the title compounds which were collected by filtration and washed with water (Table 1). The ethanolic-aqueous filtrate was concentrated *in vacuo*, treated with 10% sodium hydroxide and heated to boiling for 10 minutes. By cooling 15-30 % of the 2-nitro-4-substituted-phenyl derivative precipitated and was filtered off. From the filtrate, by acidification to pH 2 with 36% hydrochloric acid, the corresponding Dimroth isomer precipitated: 4-carboxamido-5-(2-nitro-4-methoxy-anilino)-1,2,3-triazole [2] in 23% yield or 4-carboxamido-5-(2-nitro-4-chloro-anilino)-1,2,3-triazole [2] in 53% yield.

1-(2-Amino-4-methoxyphenyl)-4-carboxamido-5-amino-1*H*-1,2,3-triazole (**4c**).

To a suspension of **3c** (1.00 g, 3.57 mmol) in 200 mL of acetic acid, 0.100 g of 10% Pd/C were added and the mixture was hydrogenated at room temperature and pressure. The catalyst was filtered off, washed with acetic acid and the combined filtrates were evaporated *in vacuo* keeping the temperature < 30 °C. The solid residue was treated with 5% sodium hydrogen carbonate and the insoluble material, consisting of **4c**, was collected by filtration and washed with water (Table 1).

1-(2-Amino-4-chlorophenyl)-4-carboxamido-5-amino-1*H*-1,2,3-triazole (**4d**).

To a solution of **3d** (1.25 g, 4.40 mmol) in 160 mL of methanol, 3 g of Ni-Raney as suspension in water were added and the mixture was hydrogenated at room temperature and pressure. The catalyst was filtered off, washed with methanol and the combined filtrates were evaporated *in vacuo* keeping the temperature < 30 °C. The solid residue consisted of **4d** (Table 1).

3-Carboxamido-1,2,3-triazolo[1,5-*a*][1,3,5]benzotriazepin-5-one (**5a**).

To a solution of **4a** (0.590 g, 2.70 mmol) in 8 mL of anhydrous pyridine, 2.15 mL (4.0 mmol) of 20% phosgene in toluene solution were added and the mixture was stirred at room temperature for 20 hours. Water was added and stirring continued for 2-3 hours, then the solution was acidified with 10% hydrochloric acid (pH 3) to precipitate the crude title compound which was collected by filtration, washed and dried. The solid could be purified by extraction with boiling toluene then recrystallized (Table 1).

8-Substituted-3-carboxamido-1,2,3-triazolo[1,5-*a*][1,3,5]benzotriazepin-5-ones (**5b** and **5c**).

To a solution of 5.0 mmoles of the suitable diamino derivative (**4b** or **4c**) in 38 mL of anhydrous pyridine, a solution of 0.600 g (6.0 mmol) of triphosgene in 10 mL of toluene was added and the mixture was stirred at room temperature for a night. Water was added to precipitate the title compounds and stirring was continued for 2-3 hours, then the solid was collected by filtration, washed and dried (Table 1).

8-Chloro-3-carboxamido-1,2,3-triazolo[1,5-*a*][1,3,5]benzotriazepin-5-one (**5d**).

To a solution of **4d** (1.00 g, 3.96 mmol) in 20 mL of anhydrous pyridine, 3.2 mL (6.0 mmol) of 20% phosgene in toluene solution were added and the mixture was stirred at room temperature for a night. Water was added and stirring continued for 2 hours, the precipitate was collected by filtration, washed and purified by extraction with a little methanol then recrystallized (Table 1).

8-Substituted-3-carboxamido-1,2,3-triazolo[1,5-*a*][1,3,5]benzotriazepin-5-thiones (**6a-c**).

To a stirred solution of sodium ethoxide, prepared from sodium (0.046 g, 2.00 mmol) in 20 mL of absolute ethanol, 2.00 mmoles of the suitable diamino derivative (**4a**, **4b** or **4c**) and 20 mL of carbon disulphide were added and the mixture was heated at 50 °C under stirring for 30 hours. The reaction mixture was evaporated *in vacuo*, the residue was treated with water and the resulting solution was acidified with 10% hydrochloric acid to precipitate the title compounds which were collected by filtration and washed with water then recrystallized (Table 1).

8-Substituted-3-carboxamido-5-methylthio-1,2,3-triazolo[1,5-*a*]-[1,3,5] benzotriazepines (**7a-c**).

A suspension of 0.600 mmoles of the suitable triazolo-benzotriazepin-thione (**6a**, **6b** or **6c**) in 15 mL of 2.5% sodium hydroxide was stirred for 10-15 minutes, 0.045 mL (0.720 mmol) of iodomethane were added and stirring was continued at room temperature for 30 minutes. The title compounds precipitated and were collected by filtration then recrystallized (Table 1).

8-Substituted-3-carboxamido-1,2,3-triazolo[1,5-*a*][1,3,5]benzotriazepine-5-morpholino or Cyclopentylamino Derivatives (**8a-d**).

A solution of 0.50 mmoles of the suitable methylthio derivative (**7a**,**7b** or **7c**) in 6 mL of the appropriate amine (morpholine or cyclopentylamine) was heated under reflux for 3 hours. The title compounds precipitated by cooling. However the reaction mixture was evaporated *in vacuo* and the residue was treated with water and collected by filtration then recrystallized (Table 1).

1-(2-Nitrophenyl)-4-cyano-5-amino-1*H*-1,2,3-triazole (**9**).

A stirred solution of sodium ethoxide, prepared from sodium (0.340 g, 0.015 mmol) in 30 mL of absolute ethanol, was cooled at -10 °C into an ice-salt bath. Under stirring a solution of 2-nitrophenylazide (2.00 g , 12.19 mmol) and malononitrile (0.805 g, 12.19 mmol) in 50 mL of absolute ethanol was dropped very slowly, keeping the temperature < -5 °C. After 1 hour the ice bath was removed and stirring was continued for 1 hour. Water was added until the triazole **9** precipitated as a solid which was collected by filtration and washed with water then recrystallized (Table 1).

4-Cyano-5-(2-nitroanilino)-1,2,3-triazole (**10**).

A solution of 0.100 g (0.43 mmol) of **9** in 10 mL of toluene was heated under reflux for 2 hours. The white colour changed to yellow. By cooling, the title compound precipitated; it was recovered by filtration and recrystallized (Table 1).

1-(2-Aminophenyl)-4-cyano-5-amino-1*H*-1,2,3-triazole (**11**).

To a solution of the nitrophenyltriazole **9** (0.375 g, 1.30 mmol) in 10 mL of methanol, 10% Pd/C (0.030 g) was added and the mixture was hydrogenated at room temperature and pressure. The catalyst was filtered off, repeatedly washed with methanol and the combined filtrates were evaporated *in vacuo* keeping the temperature < 30 °C. The crude residue (0.260 g) was purified by absorption on silica gel and flash-chromatography through a

silica gel column, eluting with ethyl acetate/petroleum ether 2:1.(Table 1).

3 Cyano-1,2,3-triazolo[1,5-*a*][1,3,5]benzotriazepin-5-one (**12**).

To a solution of **11** (0.200 g, 1.00 mmol) in 5 mL of anhydrous pyridine, a solution of triphosgene (0.100 g, 1.0 mmol) in 5 mL of toluene was added and the mixture was stirred at room temperature for a night. Water was added to precipitate the title compound and stirring was continued for 3 hours, then the solid was collected by filtration and washed with water. The crude residue (0.220 g) was purified by absorption on silica gel and flash-chromatography through a silica gel column, eluting with ethyl acetate/petroleum ether 4:5 (Table 1).

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