Pyrrolo[2,1-*d*][1,2,3,5]tetrazines, a New Class of Azolotetrazines Related to the Antitumor Drug Temozolomide

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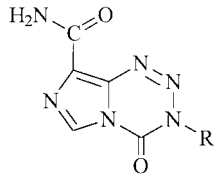
Abstract: A series of derivatives of the new ring system pyrrolo[2,1-*d*][1,2,3,5]tetrazine, potential antineoplastic agents, were obtained in good yield from the reaction of 2-diazopyrroles with isocyanates at room temperature and in the dark. Atomic charges at C-4, a good parameter to predict the antineoplastic activity for this type of compounds, were found to be very close to that of temozolomide (**2**), the antitumor drug currently used in therapy.

Key words: pyrrolotetrazines, azolotetrazines, 2-diazopyrroles, temozolomide, antineoplastic agents

Since the early 1980s azolotetrazine systems have received remarkable attention because of the outstanding antineoplastic activity, exhibited by the two imidazo-tetrazinone derivatives: mitozolomide **1** and temozolomide **2**.[1-3]



1 R=CH_2CH_2Cl (Mitozolomide)
2 R=CH_3 (Temozolomide)

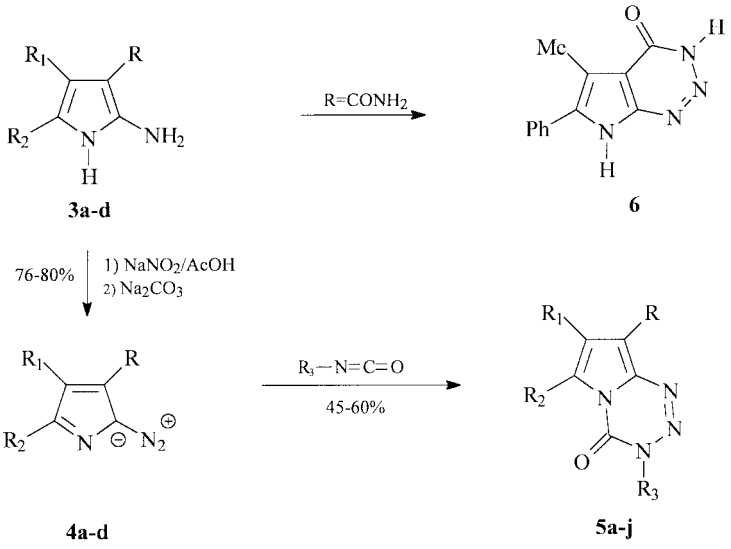
Most syntheses of azolotetrazinones have involved a slow reaction of the corresponding diazoazoles with alkyl or aryl isocyanates at room temperature, in the dark, in an inert organic solvent.[4] The mechanism of this type of reaction is not completely clarified. A concerted mechanism[4a] formerly proposed seems unlikely since concerted mechanisms where heterocumulenes act as dipolarophiles have generally been discounted.[5] A stepwise ionic pathway might involve either an initial nucleophilic attack at the isocyanate carbon, to give a dipolar intermediate which undergoes ring closure or a [3+2] cycloaddition leading to a spiro compound which by a [1,5] sigmatropic rearrangement affords the bicyclic system.[6]

Pyrrolotetrazines, compounds that hold the deaza skeleton of temozolomide, are unknown, probably because of the unavailability of 2-diazopyrroles. In fact, until recently it was believed that 2-aminopyrroles would not behave as aromatic amines, and that their diazotization and subsequent neutralization would not lead to the diazo species. The very few 2-diazopyrroles that are known were prepared by direct introduction of the diazo group into the pyrrole ring and were obtained in very low yields (2-6%).[7]

Our recent studies demonstrated that 2- and 3-aminopyrroles behave similarly towards protonation.[8] These results allowed us to believe that the failure in the diazotization of 2-aminopyrroles might be ascribed to the instability of the reaction products rather than to a lack of reactivity of the reagents. Under suitable reaction conditions, however, it was possible to diazotize 2-aminopyrroles **3a-d**, which led to the isolation of the corresponding 2-diazopyrroles **4a-d** in preparative yields.[9] Compounds **3c** and **3d** were synthesized from 2-acetamido-3-cyano-4-methyl-5-phenylpyrrole (**7**) which was derived from **3a**. The diazotization of **3d** to **4d** also led to a small quantity of 5-methyl-6-phenylpyrrolo[2,3-*d*][1,2,3]triazine-4-one (**6**) due to an intramolecular coupling reaction of the diazo group with the carboxamide moiety. It was impossible to obtain pure **4d** even after flash chromatography since it slowly but continuously transformed into the pyrrolotriazine compound **6**. Thus **4d** was used as crude product obtained from the diazotization. The pyrrolotriazine derivative **6**, instead, was obtained as pure compound (Table).

The preparation of these useful synthons constituted the synthetic entry to the pyrrolo[2,1-*d*][1,2,3,5]tetrazine ring system **5**. However, when the 2-diazopyrroles **4a-d** obtained from the corresponding 2-aminopyrroles **3a-d** were reacted under the same reaction conditions employed for the synthesis of the azolotetrazine (equimolecular amounts of isocyanates in dichloromethane or ethyl acetate at room temperature, in the dark), there was no reaction at all, even after one month. The title compounds were instead obtained in 45-60% yields using a ten-fold excess of isocyanate and dimethylformamide as a solvent. Considering that the negative charge of the 2-diazopyrroles is mainly located on the ipso carbon,[9] the mechanism leading to the pyrrolotetrazinones, involving the formation of a spiro compound, seems likely. Also, more severe reaction conditions, necessary for the cycloaddition of the isocyanates to the 2-diazopyrroles are due to the reduced electrophilicity of the diazo group bounded to the pyrrole nucleus, the more electron rich azole ring.

The structures of the pyrrolotetrazinones were confirmed by spectroscopic data, in particular, the ^{13}C NMR spectra showed a pattern of the pyrrole carbons compatible with a 1H-pyrrole structure and completely different from that of the starting 2-diazopyrroles which have a 2H-pyrrole



3a-d **6** **4a-d** **5a-j**

3-5	a	b	c	d	e	f	g	h	i	j
R	CN	CN	CO_2Et	$CONH_2$	CN	CN	CN	CN	CN	CN
R_1	Me	Ph	Me	Me	Me	Me	Me	Me	Ph	Ph
R_2	Ph	Me	Ph	Ph	Ph	Ph	Ph	Ph	Me	Me
R_3	Me	Ph	Ph	Ph	Ph	4-OMe-Ph	4-Cl-Ph	3-Cl-Ph	4-Cl-Ph	3-Cl-Ph

Scheme

structure.[9] The signals of carbonyl carbon of the tetrazine moiety were found in the range 137-141 ppm, in agreement with the values observed for azolotetrazinones.[10] In the ^1H NMR spectrum of the carboxamido derivative **5d**, the amide protons appeared as two distinct signals, δ 5.81, 1H and 8.01, 1H, due to a hydrogen bond with N-1 of the tetrazine moiety.

Since the key step of the proposed mode of action of temozolomide is the nucleophilic attack at the electron-deficient C-4 position, calculation of atomic charges at this site of pyrrolotetrazinones and comparison with that of temozolomide can be a good parameter to predict the electrophilic and antineoplastic activity. Thus we calculated the atomic charge at C-4 for all the pyrrolotetrazinone derivatives and for temozolomide.[11] The values were found in the range 0.438-0.442, very close to that of temozolomide (0.444), and point to the potential biological activity of this new class of azolotetrazinones.

All mps points were taken on a Buchi-Tottoli capillary apparatus and are uncorrected. IR spectra were determined with a Jasco FT/IR 5300 spectrophotometer in $CHBr_3$. ^1H (200 MHz) and ^{13}C (50.3 MHz) NMR spectra were measured in DMSO-d_6 solution (TMS as internal reference) using a Bruker AC series 200 MHz spectrometer. Column chromatography was performed with Merck silica gel (230-400 mesh) ASTM. Satisfactory microanalyses were obtained for all new compounds: C ± 0.2, H, ± 0.1, N, ± 0.1.

2-Aminopyrroles 3a,d

Derivatives **3a,b** were prepared from 1-acetamido-1-phenylpropan-2-one[12] or 2-acetamido-1-phenylpropan-1-one[13] and malononitrile according to the procedure described in the literature.[14]

2-Acetamido-3-cyano-4-methyl-5-phenylpyrrole (7)

Compound **3a** (3.94 g, 20 mmol) dissolved in Ac_2O (30 mL) was heated for 10 min on a steam bath. The precipitate formed was filtered and dried under vacuum to give **7** (4.78 g, 100%).

2-Aminopyrroles 3c,d

To a solution of the acetylamino derivative **7** (10.0 g, 41.8 mmol) in anhyd EtOH (100 mL), dry HCl was bubbled for 10 h at 0°C to obtain **3d** or at 60°C to obtain **3c**. The mixture was then refluxed for 10 min. After cooling, the solvent was evaporated under reduced pressure and the solid residue was taken up with H_2O (100 mL) and neutralized with aq NH_3 (14%). The precipitate obtained was filtered off, air-dried and recrystallized from EtOH to give **3c,d** (Table).

2-Diazopyrroles 4a-d; General Procedure

$NaNO_2$ (207 mg, 3 mmol) dissolved in the minimum volume of H_2O was added dropwise to a solution of the aminopyrroles **3a-d** (3 mmol) in HOAc (80%, 6 mL), at 0°C with stirring and under a N_2 atm. The mixture was kept at 0°C for 30 min and aq Na_2CO_3 solution (20%, 25 mL) was added. A gummy residue that soon solidified was formed. Purification by flash chromatography, eluting with CH_2Cl_2 gave **4a-d** (Table).

Compound **4a**

Yield = 76%

Mp: 72-73°C (EtOH). [Lit:[9] 72-73°C]

Table Spectroscopic Data for Compounds **3-7**

Product	Yield %	Mp °C[a]	IR ($CHBr_3$) ν (cm^{-1})	^{1}H NMR (DMSO/TMS) ppm, *J* (Hz)	^{13}C NMR (DMSO/TMS) ppm
3c	80	118-119[b]	3474 and 3397 (NH_2), 3326 (NH), 1647 (CO)	1.26 (t, 3H, *J* = 6.9 , CH_3), 2.27 (s, 3H, CH_3), 4.16 (q, 2H, *J* = 6.9 , CH_2), 5.68 (s, 2H, NH_2) 7.16 (t, 1H, *J* = 7.9 , C_6H_5), 7.25-7.35 (m, 4H, C_6H_5), 10.35 (br s, 1H, NH)	12.2 (q, CH_3), 14.6 (q, CH_3), 57.9 (t, CH_2), 93.4 (s, C-3), 113.4 (s, C-4), 120.2 (s, C-5), 125.0 (d, C_6H_5), 126.0 (d, C_6H_5), 128.4 (d, C_6H_5), 133.1 (s, C_6H_5), 148.0 (s, C-2), 165.8 (s, CO)
3d	90	173-175	3391 and 3304 (NH_2), 3153 (NH), 1659 (CO)	2.54 (s, 3H, CH_3), 5.66 (br s, 2H, NH_2), 6.30 (br s, 2H, NH_2) 7.15 (t, 1H, *J* = 8.1 , C_6H_5), 7.30 (d, 2H, *J* = 8.1 , C_6H_5), 7.36 (t, 2H, *J* = 8.1 , C_6H_5), 10.35 (s, 1H, NH)	12.4 (q, CH_3), 97.3 (s, C-3), 111.4 (s, C-4), 119.8 (s, C-5), 124.9 (d, C_6H_5) 126.3 (d, C_6H_5), 128.5 (d, C_6H_5), 133.30 (s, C_6H_5), 146.4 (s, C-2), 168.9 (s, CO)
4b	80	80-82	2218 (CN), 2096 (N_2)	2.35 (s, 3H, CH_3), 7.43-7.49 (m, 2H, C_6H_5), 7.51-7.55 (m, 3H, C_6H_5)	16.7 (q, CH_3), 85.3 (s, C-2), 104.1 (s, C-3), 112.8 (s, CN), 128.4 (d, C_6H_5), 128.6 (d, C_6H_5), 128.9 (d, C_6H_5), 131.3 (s, C_6H_5), 132.0 (s, C-3), 136.4 (s, C-4), 151.7 (s, C-5)
4c	77	77-80	2112 (N_2), 1713 (CO)	1.34 (t, 3H, *J* = 7.4 , CH_3), 2.55 (s, 3H, CH_3), 4.34 (q, 2H, *J* = 7.4 , CH_2), 7.27-7.47 (m, 4H, C_6H_5), 7.70-7.74 (m, 1H, C_6H_5)	12.9 (q, CH_3), 13. 9 (q, CH_3), 60.6 (t, CH_2), 89.0 (s, C-2), 127.9 (d, C-2' and C-6'), 128.3 (d, C-4'), 128.5 (d, C-3' and C-5'), 130.5 (s, C-1'), 135.9 (s, C-4), 153.9 (s, C-3), 155.3 (s, C-5), 172.0 (s, CO)
5a	45	113-115	2234 (CN), 1736 (CO)	2.30 (s, 3H, CH_3), 3.92 (s, 3H, CH_3), 7.32-7.39 (m, 2H, C_6H_5), 7.44-7.51 (m, 3H, C_6H_5)	10.7 (q, CH_3), 37.0 (q, CH_3), 94.8 (s, C-8), 112.1 (s, CN), 127.8 (d, C_6H_5), 128.1 (s, C-7), 128.4 (s, C-6), 129.1 (s, C_6H_5), 129.4 (d, C_6H_5), 130.8 (d, C_6H_5), 138.9 (s, C-8a), 140.2 (s, C-4)
5b	60	152-154	2230 (CN), 1736 (CO)	2.85 (s, 3H, CH_3), 7.45-7.61 (m, 10H, 2 x C_6H_5)	13.2 (q, CH_3), 93.9 (s, C-8), 112.2 (s, CN), 126.1 (d, C_6H_5), 127.3 (s, C-6), 129.0 (d, C_6H_5), 129.1 (d, C_6H_5), 129.3 (d, C_6H_5), 129.4 (d, C_6H_5), 129.5 (d, C_6H_5), 129.7 (s, C-7), 131.9 (s, C_6H_5), 137.0 (s, C_6H_5), 138.5 (s, C-8a), 141.2 (s, C-4)
5c	49	123-125	1732 (CO), 1708 (CO)	1.43 (t, 3H, *J* = 7.1 , CH_3) 2.34 (s, 3H, CH_3), 4.47 (q, 2H, *J* = 7.1 , CH_2) 7.47-7.69 (m, 10H, 2 x C_6H_5)	11.3 (q, CH_3), 14.5 (q, CH_3), 60.7 (t, CH_2),112.0 (s, C-8), 122.0 (s, C-7), 127.0 (d, C_6H_5), 127.1 (s, C-6), 127.4 (d, C_6H_5), 128.5 (d, C_6H_5), 129.1 (d, C_6H_5), 129.2 (d, C_6H_5), 129.8 (s, C_6H_5), 131.3 (d, C_6H_5), 136.1 (s, C_6H_5), 138.0 (s, C-8a), 140.5 (s, C-4), 162.7 (s, *CO*OEt)
5d	51	152-154	3490 and 3411 (NH_2), 1757 (CO), 1735 (CO)	2.47 (s, 3H, CH_3), 5.81 (br s, 1H, NH), 7.42-7.54 (m, 10H, 2 x C_6H_5), 8.01 (br s, 1H, NH)	11.5 (q, CH_3), 114.5 (s, C-8), 126.3 (d, C_6H_5), 127.6 (d, C_6H_5), 129.0 (d, C_6H_5), 129.1 (d, C_6H_5), 129.2 (s, C-7), 129.3 (d, C_6H_5), 129.7 (s, C-6), 130.6 (s, C_6H_5), 131.1 (d, C_6H_5), 134.5 (s, C-8a), 137.3 (s, C_6H_5), 140.4 (s, C-4), 164.0 (s, $CONH_2$)
5e	55	148-149	2233 (CN), 1753 (CO)	2.33 (s, 3H, CH_3), 7.37-7.55 (m, 10H, 2 x C_6H_5)	10.8 (q, CH_3), 95.7 (s, C-8), 112.1 (s, CN), 126.2 (d, C_6H_5), 127.9 (d, C_6H_5), 128.4 (s, C-7), 129.1 (d, C_6H_5), 129.2 (s, C_6H_5), 129.3 (d, C_6H_5),129.4 (d, C_6H_5), 129.5 (s, C-6), 130.8 (d, C_6H_5), 137.0 (s, C_6H_5), 138.1 (s, C-8a), 139.9 (s, C-4)
5f	53	158	2236 (CN), 1746 (CO)	2.27 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 7.09 (d, 2H, *J* = 8.8, C-3' and C-5'), 7.30-7.45 (m, 5H, C_6H_5), 7.50 (d, 2H, *J* = 8.8 , C-2' and C-6'	10.4 (q, CH_3), 55.4.(q, OCH_3), 92.2 (s, C-8), 112.8 (s, CN), 114.0 (d, C_6H_4), 127.3 (d, C_6H_5), 127.5 (s, C_6H_4), 127.7 (s, C-7), 128.1 (d, C_6H_5), 128.5 (s, C-6), 128.6 (d, C_6H_5), 130.3 (s, C_6H_5), 130.9 (d, C_6H_4), 139.2 (s, C-8a), 139.9 (s, C-4), 159.6 (s, C_6H_4)

Table Continued

Product	Yield %	Mp °C[a]	IR ($CHBr_3$) ν (cm^{-1})	^{1}H NMR (DMSO/TMS) ppm, *J* (Hz)	^{13}C NMR (DMSO/TMS) ppm
5g	60	109-110	2240 (CN), 1741 (CO)	2.25 (s, 3H, CH_3), 7.43-7.50 (m, 5H, C_6H_5), 7.64 (s, 4H, C_6H_4)	10.4 (q, CH_3), 92.8 (s, C-8), 112.7 (s, CN), 127.4 (d, C_6H_4), 127.6 (s, C_6H_4), 128.1 (s, C-7), 128.4 (s, C_6H_5), 128.5 (d, C_6H_5), 128.6 (s, C-6), 128.7 (d, C_6H_5), 129.0 (d, C_6H_5), 130.9 (d, C_6H_4), 133.7 (s, C_6H_4), 136.4 (s, C-8a), 139.7 (s, C-4)
5h	50	137	2237 (CN), 1738 (CO)	2.28 (s, 3H, CH_3), 7.38-7.43 (m, 5H, C_6H_5), 7.54-7.57 (m, 3H, C_6H_4), 7.66 (br s, 1H, C_6H_4)	10.5 (q, CH_3), 93.0 (s, C-8), 112.7 (s, CN), 125.6 (d, C_6H_4), 126.7 (d, C_6H_4), 127.4 (d, C_6H_5), 127.7 (s, C_6H_5), 128.2 (s, C-7), 128.4 (s, C-6), 128.8 (d, C_6H_5), 129.3 (d, C_6H_4), 130.7 (d, C_6H_4), 130.9 (d, C_6H_5), 132.9 (s, C_6H_4), 138.7 (s, C_6H_4), 139.0 (s, C-8a), 139.7 (s, C-4)
5i	55	163	2230 (CN), 1743 (CO)	2.75 (s, 3H, CH_3), 7.53-7.61 (m, 5H, C_6H_5), 7.68 (br s, 4H, C_6H_4)	12.8 (q, CH_3), 90.8 (s, C-8), 112.9 (s, CN), 126.5 (s, C-6), 128.6 (d, C_6H_4), 128.9 (d, C_6H_5), 129.1 (d, C_6H_5), 129.2 (d, C_6H_5), 129.3 (d, C_6H_4), 129.7 (s, C-7), 129.8 (s, C_6H_5), 133.9 (s, C_6H_4), 136.3 (s, C_6H_4), 139.4 (s, C-8a), 141.1 (s, C-4)
5j	50	160	2232 (CN), 1740 (CO)	2.75 (s, 3H, CH_3), 7.53-7.61 (m, 5H, C_6H_5), 7.65 (br s, 3H, C_6H_4), 7.76 (br s, 1H, C_6H_4)	12.8 (q, CH_3), 91.4 (s, C-8), 112.8 (s, CN), 125.7 (d, C_6H_4), 126.6 (s, C-6), 126.8 (d, C_6H_4), 128.9 (d, C_6H_4), 129.1 (d, C_6H_5), 129.2 (d, C_6H_5), 129.4 (d, C_6H_4), 129.7 (s, C-7), 129.8 (s, C_6H_5), 130.8 (d, C_6H_5), 133.0 (s, C_6H_4), 138.5 (s, C_6H_4), 139.2 (s, C-8a), 141.0 (s, C-4)
6	5	235 (dec)	3169-2856 (br, NH), 1666 (CO)	2.51 (s, 3H, CH_3), 7.43 (dt, 1H, *J* = 7.9, 1.2 , H-4'), 7.54 (dt, 2H, *J* = 7.9, 1.2 , H-3' and H-5'), 7.69 (dd, 2H, *J* = 7.9, 1.2 , H-2' and H-6'), 13.03 (br s, 1H, NH), 14.41 (br s, 1H, NH)	10.8 (q, CH_3), 109.6 (s, C-4a), 110.9 (s, C-5), 127.9 (d, C_6H_5), 128.1 (d, C_6H_5), 128.7 (d, C_6H_5), 130.6 (s, C-6), 134.4 (s, C_6H_5), 144.2 (s, C-7a), 156.2 (s, C-4)
7		219 (EtOH)	3358 (NH), 3212 (NH), 2214 (CN), 1682 (CO) cm^{-1}.	δ = 2.09 (s, 3H, CH_3), 2.22 (s, 3H, CH_3), 7.28 (dt, ,1H, *J* = 7.5, 1.0 Hz, H-4'), 7.42 (dt, 2H, *J* = 7.5, 1.0 Hz,, H-3' and H-5'), 7.46 (dd, 2H *J* = 7.5, 1.0 Hz, H-2' and H-6'), 10.58 (br s, 1H, NH), 11.70 (br s, 1H, NH).	δ = 11.0 (q, CH_3), 22.8 (q, CH_3), 86.1 (s, C-3), 115.8 (s, CN), 115.9 (s, C-4), 124.5 (s, C-5), 126.6 (d, C_6H_5), 128.7 (d, C_6H_5), 128.8 (d, C_6H_5),131.5 (s, C_6H_5), 133.7 (s, C-2), 169.3 (s, CO).

[a]Recrystallization solvent: EtOH.
[b]Lit.[15] 135-136°C

Pyrrolo[2,1-*d*][1,2,3,5]tetrazines 5a-j; General Procedure
To a solution of **4a-d** (2 mmol) in anhyd DMF (10 mL), the suitable isocyanate (20 mmol) in anhyd DMF (10 mL) was added dropwise at r.t., in the dark. The mixture was stirred until the diazo band at ~ 2110 cm^{-1} disappeared (24-48 h), then poured onto crushed ice (100 g). The precipitate was filtered off, air-dried and purified by flash chromatography with CH_2Cl_2 as eluant to give **5a-j** (Table).

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