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Abstract: The reaction of [2-(chloromethyl)-4-oxo-3,4-dihydroquinazolin-3-yl]acetonitrile and 2-(chloromethyl)-3-(2-oxopropyl)quinazolin-4(3H)-one with aliphatic primary amines was shown to yield 2-alkyl-3-(alkylimino)-1,2,3,4-tetrahydro-6H-quinazino[2,1-b]quinazolin-6-ones and 2-alkyl-3-methyl-1,2-dihydro-6H-pyrazino[2,1-b]quinazolin-6-ones, respectively. The starting materials were prepared by alkylation of 2-(chloromethyl)quinazolin-4(3H)-one with chloroacetamide or chloroacetone. Furthermore, 2-alkyl-3-(alkylimino)-1,2,3,4,7,8,9,10-octahydro-6H-pyrazino[2,1-b]quinazolin-6-ones were prepared by alkylation of 2-(chloromethyl)quinazolin-4(3H)-one with 2-azidobenzoyl chloride and further Staudinger amination of the initial adducts, e.g.

Key words: alkylations, heterocycles, nitriles, pyrazines, ring closure

The pyrazino[2,1-b]quinazoline system has been shown to be the core of a number of fungal metabolites such as glyantin, fumiquinazolines, fiscalines, alantarpyrimine, and spiroquinazoline. These natural compounds are useful in cancer chemotherapy and their biological properties have been assigned to the pyrazinoquinazoline pharmacophore. Thus, several synthetic pyrazino[2,1-b]quinazoline derivatives have exhibited a comparable level of activity. Furthermore, certain pyrazinoquinazolines have been claimed to be sedatives. To date three general approaches to this system have been developed: (1) double cyclization of tripeptide analogues containing the anthranilic acid moiety as the central amino acid residue; (2) N-acylation of piperazin-2-one derivatives with 2-azidobenzoyl chloride and further Staudinger aza-Wittig reaction sequence; and (3) the reaction of piperazine-derived imino esters with anthranilic acid or its derivatives. Additionally, a few less common approaches have been reported. However, in most of these methods readily available amino acids are used as building blocks for the preparation of the key precursors. Therefore the substitution pattern at the C3–C4–N5 moiety of pyrazinoquinazoline is derived from the appropriate amino acid (Figure 1). Hence, except for a few instances, the majority of the pyrazinoquinazolines described are the 3-oxo derivatives of type 1. Moreover the known methods are inapplicable for the preparation of hetero analogues of 1, for example the thieno-annulated bioisosteres 2. To the best of our knowledge only three derivatives of the pyrazino[1,2-a]thieno[2,3-d]pyrimidine framework 2 have been reported to date. Hence it would be relevant to elaborate an alternative approach to the pyrazino[2,1-b]quinazoline system providing substituent diversity at position 3 and, simultaneously, being suitable for the preparation of thieno analogues. Our recent results in the field are reported herein.

The readily available 2-(chloromethyl)quinazolin-4(3H)-one 3 and related thienopyrimidine 7 were chosen as the starting materials. Their alkylation with chloroacetamide afforded compounds 4 and 8 in good yields (Scheme 1). Although quinazolin-4(3H)-ones are known to undergo alkylation predominantly at N3, a few instances of N1- and O-alkylation have been reported. Therefore, to confirm without doubt the position of the cyanoethyl group in compounds 4 and 8 an X-ray crystallographic study was carried out for derivative 8 (Figure 2). It indicated clearly that alkylation had proceeded at N3.

Treatment of the chloronitriles 4 and 8 with excess ammonia or primary amines was found to give the target pyrazinoquinazolines 6a–d and their thieno analogues 9a–d. Apparently the products 6 and 9 are formed through reamination of the initial adducts, e.g. 5. The structure of the amidinium salts 6 and 9 was confirmed by 1H- and 13C NMR data. First of all the absence of nitrile absorption both in IR and 13C NMR (δ = 115.8 for the starting materials 4 and 8) spectra of compounds 6 and 9 indicated clearly that ring closure had taken place with its participa-
The characteristic amidinium carbon (C3) signal appeared in the 13C NMR spectra of derivatives 6 and 9 at δ = 153–158. The signals from the remaining hydrogen and carbon atoms were observed at the usual values and were in good agreement with the structures of 6 and 9.

Continuing our research, we attempted to extend the scope of the method by changing the nature of electrophilic group attached to N3 of compounds 4 and 8. For this purpose the quinazoline 3 and thienopyrimidine 13 were alkylated with chloroacetone to give derivatives 10 and 14 in 50–70% yields (Scheme 2). Similarly to the previous case, the alkylation occurred smoothly and selectively at N3. Furthermore, the reaction of the chloro ketones 10 and 14 with primary amines was examined. It was found to give the pyrazinoquinazolines 12a–d and their thieno analogues 15a–d. It should be emphasized that elimination of water from the intermediates 11 proceeded exclusively with formation of the endocyclic double bond. By contrast, the closely related adducts that arise after addition of organometallics to the 3-CO of derivatives 1 (Figure 1) prefer exocyclic dehydration.12b

Figure 2 X-ray molecular structure of compound 8 with the atom numbering used in the crystallographic analysis

Scheme 2 a R = Et; b R = Pr; c R = cyclopropyl; d R = Bn

different behavior can be, most probably, explained by the influence of the substituent at position 4.

The structure of compounds 12 and 15 was initially deduced from 1H and 13C NMR spectra and then confirmed unambiguously by an X-ray crystallographic study carried out for derivative 15a (Figure 3). As regards the spectral data the especially noticeable signals of the enamine moiety, namely the H4 at δ = 6.5–6.7 ppm and C4 at δ = 95–97 ppm deserve to be mentioned. Moreover, the method allows pyrazino[2,1-d]pyrimidine derivatives 9 and 15, the bioisosteres of pyrazinoquinazolines 6 and 12, to be obtained. Contrary to known procedures, no air- or moisture-sensitive substances were used in the present synthesis thus making it more convenient. The starting materials and reagents are readily available. Finally, the present approach provides substitution diversity at positions 2 and 3. Hence this method appears to be a good addition to the known set of synthetic tools in the field.

To summarize, the present investigation has resulted in a new approach to pyrazino[2,1-b]quinazolines. The key step is the amination of 2-(chloromethyl)quinazolin-4(3H)-one derivatives 4 and 10 bearing an electrophilic functionality tethered to N3. Moreover, the method allows pyrazino[1,2-a]thieno[2,3-d]pyrimidines 9 and 15, the bioisosteres of pyrazinoquinazolines 6 and 12, to be obtained.

Figure 3 X-ray molecular structure of compound 15a with the atom numbering used in the crystallographic analysis

Compounds 31H and 71H were prepared as reported. Other materials and reagents were commercially available. All melting points were determined in open capillary tubes in a Thiele apparatus and are uncorrected. 1H and 13C NMR spectra were recorded on a Varian UNITYplus 400 spectrometer (400 MHz for 1H and 100 MHz for 13C) in DMSO-d6 solns unless otherwise stated and with TMS as internal standard. The purity of all compounds obtained was checked by 1H NMR and LC/MS on an Agilent 1100 instrument.

Chloronitriles 4 and 8; General Procedure
Chloroacetoniitrile (2.27 g, 0.03 mol) was added to a suspension of 3 or 7 (0.01 mol) and i-Pr2NEt (3.23 g, 0.025 mol) in DMF (10 mL) and resulting mixture was stirred at 60–70 °C for 5–6 h. After cooling, a small amount of insoluble material was removed by filtration and the solvent was evaporated to dryness in vacuo. The residue was triturated with H2O, filtered, and recrystallized (i-PrOH) to yield derivatives 4 or 8.

[2-(Chloromethyl)-4-oxo-3,4-dihydroquinazolin-3-yl]acetonitrile (4)
Yield: 4.20 g (60%); mp 154 °C (i-PrOH).

[2-(Chloromethyl)-4-oxo-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-d]pyrimidin-3-yl]acetonitrile (8)
Yield: 6.26 g (71%); mp 194 °C (i-PrOH).

Pyrazino[2,1-b]quinazolines 6a–d and Pyrazino[1,2-a]thieno[2,3-d]pyrimidines 9a–d; General Procedure
An appropriate amine (12 mmol) was added to a soln of 4 or 8 (3 mmol) in EtOH (10 mL) and resulting mixture was kept at 30–40 °C for 2 h. The solvent was removed in vacuo and the residue was recrystallized (MeOH or i-PrOH) to give derivatives 6a–d or 9a–d.

3-Imino-1,2,3,4-tetrahydro-6H-pyrazino[2,1-b]quinazolins-6-one Hydrochloride (6a)
Yield: 0.57 g (76%); mp >300 °C (MeOH).

2-Methyl-3-(methylimino)-1,2,3,4-tetrahydro-6H-pyrazino[2,1-b]quinazolin-6-one Hydrochloride (6b)
Yield: 0.69 g (83%); mp 152 °C (MeOH).

2-Ethyl-3-(ethylimino)-1,2,3,4-tetrahydro-6H-pyrazino[2,1-b]quinazolin-6-one Hydrochloride (6c)
Yield: 6.26 g (71%); mp 194 °C (i-PrOH).

Pyrazino[2,1-b]quinazolines 6a–d and Pyrazino[1,2-a]thieno[2,3-d]pyrimidines 9a–d; General Procedure
An appropriate amine (12 mmol) was added to a soln of 4 or 8 (3 mmol) in EtOH (10 mL) and resulting mixture was kept at 30–40 °C for 2 h. The solvent was removed in vacuo and the residue was recrystallized (MeOH or i-PrOH) to give derivatives 6a–d or 9a–d.

3-Imino-1,2,3,4-tetrahydro-6H-pyrazino[2,1-b]quinazolins-6-one Hydrochloride (6a)
Yield: 0.57 g (76%); mp >300 °C (MeOH).

[2-(Chloromethyl)-4-oxo-3,4-dihydroquinazolin-3-yl]acetonitrile (4)
Yield: 4.20 g (60%); mp 154 °C (i-PrOH).

[2-(Chloromethyl)-4-oxo-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-d]pyrimidin-3-yl]acetonitrile (8)
Yield: 6.26 g (71%); mp 194 °C (i-PrOH).

Pyrazino[2,1-b]quinazolines 6a–d and Pyrazino[1,2-a]thieno[2,3-d]pyrimidines 9a–d; General Procedure
An appropriate amine (12 mmol) was added to a soln of 4 or 8 (3 mmol) in EtOH (10 mL) and resulting mixture was kept at 30–40 °C for 2 h. The solvent was removed in vacuo and the residue was recrystallized (MeOH or i-PrOH) to give derivatives 6a–d or 9a–d.

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Yield: 4.20 g (60%); mp 154 °C (i-PrOH).

[2-(Chloromethyl)-4-oxo-3,4,5,6,7,8-hexahydro[1]benzothieno[2,3-d]pyrimidin-3-yl]acetonitrile (8)
Yield: 6.26 g (71%); mp 194 °C (i-PrOH).

Pyrazino[2,1-b]quinazolines 6a–d and Pyrazino[1,2-a]thieno[2,3-d]pyrimidines 9a–d; General Procedure
An appropriate amine (12 mmol) was added to a soln of 4 or 8 (3 mmol) in EtOH (10 mL) and resulting mixture was kept at 30–40 °C for 2 h. The solvent was removed in vacuo and the residue was recrystallized (MeOH or i-PrOH) to give derivatives 6a–d or 9a–d.

3-Imino-1,2,3,4-tetrahydro-6H-pyrazino[2,1-b]quinazolins-6-one Hydrochloride (6a)
Yield: 0.57 g (76%); mp >300 °C (MeOH).

2-Methyl-3-(methylimino)-1,2,3,4-tetrahydro-6H-pyrazino[2,1-b]quinazolin-6-one Hydrochloride (6b)
Yield: 0.69 g (83%); mp 152 °C (MeOH).

2-Ethyl-3-(ethylimino)-1,2,3,4-tetrahydro-6H-pyrazino[2,1-b]quinazolin-6-one Hydrochloride (6c)
Yield: 6.26 g (71%); mp 298 °C (i-PrOH).
2-Benzyl-3-(benzylimino)-1,2,3,4-tetrahydro-6H-pyrazino[2,1-b]quinoxalin-6-one Hydrochloride (6d)

Yield: 1.02 g (79%); mp >300 °C (i-PrOH).

2-Methyl-3-((methylimino)-1,2,3,4-tetrahydro-6H-pyrazino[2,1-b]quinoxalin-6-one Hydrochloride (9a)

Yield: 1.09 g (74%); mp >300 °C (MeOH).

2-Methyl-3-((methylimino)-1,2,3,4,7,8,9,10-octahydro-6H-[1]benzo[b]thieno[2,3-d]pyrazino[1,2-a]pyrimidin-6-one Hydrochloride (9c)

Yield: 0.85 g (84%); mp 223 °C (MeOH).

2-Ethyl-3-(ethylimino)-1,2,3,4,7,8,9,10-octahydro-6H-[1]benzo[b]thieno[2,3-d]pyrazino[1,2-a]pyrimidin-6-one Hydrochloride (9e)

Yield: 0.92 g (84%); mp 176 °C (i-PrOH).

2-Benzyl-3-((benzylimino)-1,2,3,4-tetrahydro-6H-pyrazino[2,1-b]quinoxalin-6-one Hydrochloride (9d)

Yield: 1.01 g (69%); mp 121 °C (i-PrOH).

Chloroacetone (2.78 g, 0.03 mol) was added to a suspension of 3 or 13 (0.01 mol) and i-Pr2NEt (3.23 g, 0.025 mol) in DMF (10 mL) and resulting mixture was stirred at 60–70 °C for 7–8 h. After cooling, a small amount of insoluble material was removed by filtration and the solvent was evaporated to dryness in vacuo. The residue was triturated with H2O, filtered, and recrystallized (i-PrOH) affording derivatives 10 or 14.

2-(Chloromethyl)-3-(2-oxopropyl)quinoxalin-4(3H)-one (10)

Yield: 1.70 g (68%); mp 171 °C (i-PrOH).

2-Chloroethanol (2.78 g, 0.03 mol) was added to a suspension of 3 or 13 (0.01 mol) and i-Pr2NEt (3.23 g, 0.025 mol) in DMF (10 mL) and resulting mixture was stirred at 60–70 °C for 7–8 h. After cooling, a small amount of insoluble material was removed by filtration and the solvent was evaporated to dryness in vacuo. The residue was triturated with H2O, filtered, and recrystallized (i-PrOH) affording derivatives 10 or 14.

2-(Chloromethyl)-5,6-dimethyl-3-(2-oxopropyl)thieno[2,3-d]pyrimidin-4(3H)-one (14)

Yield: 1.40 g (49%); mp 177 °C (i-PrOH).

2-Chloroethanol (2.78 g, 0.03 mol) was added to a suspension of 3 or 13 (0.01 mol) and i-Pr2NEt (3.23 g, 0.025 mol) in DMF (10 mL) and resulting mixture was stirred at 60–70 °C for 7–8 h. After cooling, a small amount of insoluble material was removed by filtration and the solvent was evaporated to dryness in vacuo. The residue was triturated with H2O, filtered, and recrystallized (i-PrOH) affording derivatives 10 or 14.

2-Ethyl-3-methyl-1,2-dihydrosulfur-6H-pyrazino[2,1-b]quinazolin-6-one (12a)

Yield: 0.56 g (77%); mp 116 °C (MeOH).

Pyrazino[2,1-b][quinazolines 12a-d and Pyrazino[1,2-a]thieno[2,3-d]pyrimidines 15a-d; General Procedure

An appropriate amine (9 mmol) was added to a soln of 10 or 14 (3 mmol) in EtOH (10 mL) and resulting mixture was kept at 30–40 °C for 2 h. The solvent was removed in vacuo and the residue was recrystallized (MeOH or i-PrOH) to give derivatives 12a-d or 15a-d.

2-Ethyl-3-methyl-1,2-dihydrosulfur-6H-pyrazino[2,1-b]quinazolin-6-one (12a)

Yield: 0.56 g (77%); mp 116 °C (MeOH).
1H NMR: δ = 1.09 (t, J = 11.6 Hz, 3 H, CH3), 1.96 (s, 3 H, CH3), 3.20 (q, J = 11.6 Hz, 2 H, NCH2), 4.20 (s, 2 H, 1-CH2), 6.52 (s, 1 H, H4), 7.47 (t, J = 7.8 Hz, 1 H, H8), 7.59 (d, J = 7.8 Hz, 1 H, H10), 7.75 (t, J = 7.8 Hz, 1 H, H7), 8.12 (d, J = 7.8 Hz, 1 H, H7).

13C NMR: δ = 13.0 (CH3), 16.2 (CH2), 43.7 (NCH2), 51.0 (C1), 95.6 (C4), 120.5 (C6a), 126.8 (C8), 127.0 (C10), 127.4 (C7), 134.2 (C9), 136.1 (C3), 146.9 (C10a), 151.6 (C11a), 156.1 (6-CO).


8-Ethyl-2,3,7-trimethyl-8,9-dihydro-4H-pyrazino[1,2-a]thieno[2,3-d]pyrimidin-4-one (15a)

Yield: 0.65% (79%); mp 137 °C (MeOH).

1H NMR: δ = 1.15 (t, J = 8.4 Hz, 3 H, CH3), 1.97 (s, 3 H, CH3), 2.37 (s, 3 H, 3-CH3), 2.49 (s, 3 H, 3-CH3), 3.17 (q, J = 8.4 Hz, 2 H, NCH2), 4.16 (s, 2 H, 9-CH3), 6.67 (s, 1 H, H6).

13C NMR: δ = 12.9 (CH3), 13.0 (2-CH2), 13.3 (3-CH3), 16.2 (7-CH3), 43.6 (NCH2), 50.9 (C9), 95.5 (C6), 120.9 (C3a), 129.2 (C3), 129.3 (C2), 136.1 (C7), 145.1 (C10a), 153.5 (C9a), 160.1 (4-CO).

Anal. Calcd for C15H13N3OS: C, 61.06; H, 6.22; N, 15.26; S, 11.64. Found: C, 61.28; H, 6.28; N, 15.34; S, 11.82.

2,3,7-Trimethyl-8-propyl-9,9-dihydro-4H-pyrazino[1,2-a]thieno[2,3-d]pyrimidin-4-one (15b)

Yield: 0.76% (87%); mp 115 °C (i-PrOH).

1H NMR: δ = 0.93 (t, J = 6.9 Hz, 3 H, CH3), 1.57 (m, 2 H, CH2), 1.97 (s, 3 H, 7-CH3), 2.36 (s, 3 H, 2-CH3), 2.41 (s, 3 H, 3-CH3), 3.10 (t, J = 7.4 Hz, 2 H, NCH2), 4.10 (s, 2 H, 9-CH3), 6.51 (s, 1 H, H6).

13C NMR: δ = 11.4 (CH3), 13.1 (2-CH2), 13.3 (3-CH3), 16.4 (7-CH2), 21.2 (CH2), 50.8 (NCH2), 51.4 (C9), 95.2 (C6), 120.9 (C3a), 129.2 (C3), 136.4 (C7), 144.9 (C10a), 153.6 (C9a), 160.2 (4-CO).


8-Isopropyl-2,3,7-trimethyl-8,9-dihydro-4H-pyrazino[1,2-a]thieno[2,3-d]pyrimidin-4-one (15c)

Yield: 0.78% (90%); mp 133 °C (i-PrOH).

1H NMR: δ = 1.10 (d, J = 7.8 Hz, 6 H, 2 CH3), 1.95 (s, 3 H, 7-CH3), 2.31 (s, 3 H, 2-CH3), 2.36 (s, 3 H, 3-CH3), 3.84 (m, 1 H, NCH2), 4.07 (s, 2 H, 9-CH3), 6.53 (s, 1 H, H6).

13C NMR: δ = 13.1 (2-CH2), 13.4 (3-CH3), 16.5 (7-CH2), 20.0 (2 CH2), 45.1 (NCH2), 47.5 (C9), 96.1 (C6), 120.8 (C3a), 129.2 (C3), 129.3 (C2), 136.5 (C7), 145.2 (C10a), 153.5 (C9a), 160.2 (4-CO).


8-Benzyl-2,3,7-trimethyl-8,9-dihydro-4H-pyrazino[1,2-a]thieno[2,3-d]pyrimidin-4-one (15d)

Yield: 0.71% (70%); mp 164 °C (i-PrOH).

1H NMR: δ = 2.03 (s, 3 H, 7-CH3), 2.31 (s, 3 H, 2-CH3), 2.39 (s, 3 H, 3-CH3), 4.13 (s, 2 H, 9-CH3), 4.37 (s, 2 H, NCH2), 6.58 (s, 1 H, H6), 7.26–7.35 (m, 5 H, C6H5).

13C NMR: δ = 13.1 (2-CH2), 13.3 (3-CH3), 16.7 (7-CH3), 51.7 (C9), 52.8 (NCH2), 95.9 (C6), 121.0 (C3a), 127.8 (C4), 128.0 (C3), 129.1 (C2), 129.3 (C3), 129.5 (C2), 136.1 (C7), 138.1 (C1a), 145.0 (C10a), 153.6 (C9a), 160.1 (4-CO).


X-ray Crystal Structure Determination

Compound 8: Intensities of 2512 reflections (2355 independent, Rint = 0.079) were measured on an automatic four circles Siemens P3/PC diffractometer (graphite monochromated Mo Kα radiation, 0/20 scanning, 2Θmax = 50°). Crystal data: C15H13N3OS, M = 293.77, monoclinic, a = 12.106(2), b = 16.620(3), c = 9.456(2) Å, β = 110.64(3)°, V = 1349.8(5) Å3, T = 293 K, space group P21/c, Z = 4, μ(Mo Kα) = 0.432 mm−1. The structure was solved by direct method with the SHELXTL program package.16 Positions of hydrogen atoms were located from electron density difference maps and refined isotropically. Full-matrix least-squares refinement against F2 in anisotropic approximation using 2349 reflections was converged to R1 = 0.044 [for 1810 reflections with F > 4σ(F)], wR2 = 0.112, S = 1.041. Full crystallographic parameters have been deposited at Cambridge Crystallographic Data Centre (CCDC); reference number CCDC 616747.

Compound 15a: Crystallographic measurements were performed at 120 K on a Bruker Smart 6 CCD diffractometer. The intensities of 10735 reflections (2178 unique, Rint = 0.063) were collected within the range 1.2 < θ < 30.3° (–6 < h < 6, –11 < k < 10, –47 < l < 44) using graphite monochromated Mo Kα radiation (λ = 0.7073 Å). The data were corrected for Lorentz and polarization effects and absorption correction using the SADABS17 procedure was applied.
Crystal data: C$_3$H$_7$N$_2$OS, $M_r$ = 275.38, orthorhombic, $a = 5.0003(3)$, $b = 7.8752(4)$, $c = 33.681(2)$ Å, $V = 1326.3(1)$ Å$^3$, $Z = 4$, $T = 120$ K, space group $P2_12_12$, $\mu$(Mo K$\alpha$) = 0.240 mm$^{-1}$. The structure was solved by direct methods and refined by full-matrix least-squares technique in the anisotropic approximation using the CRYSALS program package. In the refinement 883 reflections with $I > 3\sigma(I)$ were used. All hydrogen atoms were located in the difference Fourier maps and included in the refinement with the fixed positional and thermal parameters. Convergence was obtained at $R_I = 0.047$ and $wR_2 = 0.048$, GOF = 1.181. Chebushiev weighting scheme$^{18}$ with parameters 2.63, –2.90, 2.11, and –0.76 was applied. Full crystallographic parameters have been deposited at Cambridge Crystallographic Data Centre (CCDC); reference number CCDC 614542.

References


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