Cycloaddition of 4-Acyl-1H-pyrrole-2,3-diones Fused at [e]-Side and Cyanamides: Divergent Approach to 4H-1,3-Oxazines

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Abstract: 4-Acyl-1H-pyrrole-2,3-diones fused at [e]-side with a heterocyclic moiety are suitable platforms for the development of a hetero-Diels–Alder-reaction-based, diversity-oriented approaches to series of skeletally diverse heterocycles. These platforms are known to react as oxa-dienes with dienophiles to form angular 6/6/5/6-tetracyclic alkaloid-like heterocycles and are also prone to decarbonylation at high temperatures resulting in generation of acyl(imidoyl)ketenes, bidentate aza- and oxa-dienes, which can react with dienophiles to form skeletally diverse products (angular tricyclic products or heterocyclic ensembles). Based on these features, we have developed an approach to two series of skeletally diverse 4H-1,3-oxazines (tetracyclic alkaloid-like 4H-1,3-oxazines and 5-heteryl-4H-1,3-oxazines) via a hetero-Diels–Alder reaction of 4-acyl-1H-pyrrole-2,3-diones fused at [e]-side with cyanamides. The products of these transformations are of interest for drug discovery, since compounds bearing 4H-1,3-oxazine moiety are extensively studied for inhibitory activities against anticancer targets.

Keywords: acyl(quinoxalin-2-yl)ketene; cycloaddition; cyanamide; heterocumulene; hetero-Diels–Alder reaction; 4H-1,3-oxazine; thermolysis

1. Introduction

Diversity-oriented synthesis (DOS) is a strategy to access structurally diverse libraries of small molecules from a single set of reagents [1,2]. This approach allows efficient exploration of the chemical space for the development of new drugs [3,4].

4H-1,3-Oxazine moiety is a valuable pharmacophore. Compounds bearing this moiety were extensively studied for inhibitory activities against various targets important for the anticancer therapy (Figure 1) [5–10]. By varying the substituents around the 4H-1,3-oxazine core, it was possible to tune the selectivity of inhibition (Figure 1) [5–8]. It should be mentioned that 4H-1,3-oxazine based inhibitors (LTURM34, LTUR6) were found to be more selective than their 4H-pyran analogs (NU7441, LY294002) (Figure 1) [6,9,11,12], which is preferable for the development of new drugs and inhibitors for biological assays.

The hetero-Diels–Alder reaction (HDA) is an atom and step economic synthetic strategy for assembling six-membered heterocycles [13]. HDA of oxa-dienes and nitriles affords 4H-1,3-oxazines [14–19].

4-Acyl-1H-pyrrole-2,3-diones fused at [e]-side with a heterocyclic moiety (FPDs) 1 are well known to react as oxa-dienes with various electron-rich C=C dienophiles A to form angular 6/6/5/6-tetracyclic alkaloid-like pyrano[4,3-b]pyrroles B (Scheme 1, path a) [20–23]. At the same time, FPDs 1 are also known to readily undergo decarbonylation at temperatures above ~140 °C resulting in generation of highly reactive acyl(imidoyl)ketenes C (Scheme 1, path b) [24]. In turn, acyl(imidoyl)ketenes C are bidentate heterodienes prone to participate in HDA with heterodienophiles D (aldehydes, ketones, Schiff bases, carbodiimides, and etc.) both as aza- and oxa-dienes with the formation of corresponding angular heterocycles E or heterocyclic ensembles F [24,25]. Thus, FPDs 1 are suitable
platforms for the development of an HDA-based DOS approaches to series of skeletally diverse heterocycles.

Figure 1. 4H-1,3-Oxazine based inhibitors and their 4H-pyran analogs.

Scheme 1. Modes of participation of FPDs 1 as heterodienes in HDA.
To the best of our knowledge, for today, there are no reported examples of a DOS, in which FPDs 1 react with a single dienophile (Scheme 1, A = D) both as oxa-dienes 1 (Scheme 1, path a) and heterodiens 1 (Scheme 1, path b). Herein, we present such an approach to two series of skeletally diverse 4H-1,3-oxazines via an HDA of FPDs 1 with cyanamides 2.

2. Results and Discussion

Since acyl(Imidoyl)ketenes C were reported not to react with common nitriles (benzonitrile, acetonitrile) [19,24,25], we decided to develop our DOS approach to 4H-1,3-oxazines utilizing so-called push–pull nitrile system, viz. cyanamides (aminonitriles) 2, which are known to have higher reactivity in [4 + 2] cycloaddition reactions [26–31].

Initially, we tested the reaction of FPD 1a with cyanamide 2a in acetonitrile at room temperature (Table 1). According to UPLC-UV-MS data of the reaction mixture, the reaction proceeded very slowly. In a week, several unidentified side products were observed along with unreacted starting materials (conversion degree of FPD 1a of ~20%). The UPLC-UV-MS yield of the desired product 3a was ~10%. However, at elevating the reaction temperature up to 95 °C, the test reaction of FPD 1a with cyanamide 2a in acetonitrile proceeded smoothly and afforded the desired tetracyclic alkaloid-like 4H-1,3-oxazine 3a in an isolated yield of 85% (Table 1, Entry 3a). The reaction progress was monitored visually by the change of colour of the reaction mixture (FPD 1a has a deep violet colour, and product 3a is yellow). According to UPLC-UV-MS data of the reaction mixture, compound 3a was formed as a single product, and no side products were observed. Product 3a was isolated by a simple filtration directly from the reaction mixture. Since test results were satisfactory, we examined the substrate scope of this reaction by involving FPDs 1a–i, bearing various acyl substituents R¹ and heteroatoms X and cyanamides 2a–f, bearing various substituents at amino nitrogen atom (Table 1).

| Entry | FPD 1 | Cyanamide 2 | X            | R¹         | Yield 1 of 3, % |
|-------|-------|-------------|--------------|------------|----------------|
| 3a    | 1a    | 2a          | NPh          | Ph         | 85             |
| 3b    | 1a    | 2b          | NPh          | Ph         | 89             |
| 3c    | 1a    | 2c          | NPh          | Ph         | 78             |
| 3d    | 1a    | 2d          | NPh          | Ph         | 83             |
| 3e    | 1b    | 2b          | NPh          | 4-ClC₆H₄  | 88             |
| 3f    | 1c    | 2b          | NPh          | 4-MeOC₆H₄ | 91             |
| 3g    | 1d    | 2c          | NPh          | 4-NO₂C₆H₄ | 81             |
| 3h    | 1e    | 2b          | NMe          | 4-MeC₆H₄ | 86             |
Table 1. Cont.

| Entry | FPD 1 | Cyanamide 2 | X     | R¹   | R²     | Yield ¹ of 3, % |
|-------|-------|-------------|-------|------|--------|----------------|
| 3i    | 1f    | 2b          | NPh   | t-Bu | O      | 79             |
| 3j    | 1g    | 2b          | NH    | Ph   | N      | 92             |
| 3k    | 1h    | 2b          | NPh   | MeO  | O      | 0²             |
| 3l    | 1i    | 2b          | O     | Ph   | O      | 81             |
| 3m    | 1i    | 2c          | O     | Ph   | NMe₂  | 74             |
| 3n    | 1d    | 2b          | NPh   | 4-NO₂C₆H₄ | O | Traces ² |
| 3o    | 1a    | 2e          | NPh   | Ph   | OHC₆H₂Cl-4 | Traces ² |
| 3p    | 1a    | 2f          | NPh   | Ph   | OHC₆H₂OMe-4 | Traces ² |
| 3q    | 1l    | 2e          | O     | Ph   | OHC₆H₂Cl-4 | Traces ² |

¹ Isolated yields (reaction scale of 0.76 mmol). ² According to UPLC-UV-MS.

Quinoxaline derivatives 3a–k were prepared using acetonitrile as the reaction solvent and isolated by a simple filtration directly from the reaction mixture. For the synthesis of 1,4-benzoxazine derivatives (X = O), toluene was used as a reaction solvent since compounds 3l,m were readily soluble in acetonitrile, and no precipitate was formed. In toluene compounds 3l,m formed precipitates after cooling of the reaction mixtures to room temperature, which eased their isolation.

It was found that the studied reaction proceeded well both with 5-oxa (X = O) and 5-aza (X = NH, NPh, NMe) FPDs 1. The reaction also worked well with various aryls and tert-butyl at acyl substituent R¹ of FPDs 1. Expectedly, the reaction of methoxy bearing FPD 1h did not result in cycloadduct 3k, since the methoxycarbonyl group COOMe is not electrophilic enough to participate in cycloaddition as a C=O part of the heterodiene system. The examined substituents in N,N-dialkylcyanamides 2a–d did not affect the reaction noticeably. However, our attempts to involve N-arylcyanamides 2e,f in HDA with FPDs 1a,l were not successful. In this case, the reaction proceeded with formation of insoluble hard-to-purify compounds, whose structure we did not succeed to identify. We assume that in this case other reaction course could occur instead of the formation of the desired compounds 3o–q, since N-arylcyanamides 2e,f has lower nucleophilicity at C≡N nitrogen than N,N-dialkylcyanamides 2a–d.

It is worthy of note that some of products 3 had a very low solubility in organic solvents all available to us. There were problems with acquisition on NMR spectra of such products, that’s why in some cases, we had to record solid-state NMR (ssNMR) spectra. It should be mentioned that in case of the reaction of 4-nitrophenyl substituted FPD 1d with 4-morpholinecarbonitrile 2b, the desired product 3n was observed only in trace amounts by UPLC-UV-MS of the reaction mixture. Prolongation of the reaction time (up to 14 days) and increasing the temperature (up to 120 °C) did not yield any positive results. We suppose that this phenomenon was caused by very low solubility of product 3n, which, possibly, under the examined conditions (FPDs 1 were used as suspensions in acetonitrile), formed a protective insoluble layer on the surfaces of solid particles of FPD 1d and, thus, prevented the reaction. It also should be mentioned that our attempts to perform the reaction of 4-nitrophenyl substituted FPD 1d with carbonitrile 2b in DMSO were also unsuccessful. This experiment was complicated by the fact that DMSO is a highly hygroscopic solvent and facilitated the hydrolysis reactions of the starting FPDs 1 and
the products 3 (for hydrolysis studies of analogs of products 3, see [22]). In the case of compound 1d, NO₂ substituent makes FPD 1d very electrophilic and very reactive towards water.

Moreover, in the case of 1,4-benzoxazine products 3l,m (X = O), there were problems with monitoring them with UPLC-UV-MS and HPLC-UV (acetonitrile–water as eluents). Chromatograms of the reaction mixtures and individual compounds 3l,m (pure according to the NMR spectra) contained a lot of overlapped broad peaks, and the mass detector data showed signals of the desired products 3l,m only in trace amounts. Furthermore, such problems were never observed with quinoxaline products 3a–j (X = NH, NMe, NPh). We think that these could be explained by the occurrence of hydrolysis of compounds 3l,m on the LC column due to the presence of an ester moiety in their structures, which is a common feature of such compounds [22].

The study of melting in a capillary of compounds 3a–i,l,m revealed that under such conditions 5-heteryl-4H-1,3-oxazines 4a–i,l,m (Table 2) were formed as sole products, and no regioisomeric pyrimidines G (Scheme 2) were observed (monitoring by UPLC-UV-MS). This transformation was then easily scaled up to 0.4 mmol (~200 mg) under solvent-free conditions. When scaling up, we found that an addition of small amounts (of about 0.1 equiv.) of the corresponding cyanamides 2a–d was required to increase the isolated yields of compounds 4a–i,l,m by reducing the side reactions leading to compounds H (monitoring by UPLC-UV-MS) (Scheme 2) characteristic of transformations involving in situ generation of acyl(imidoyl)ketenes C [24,32]. Compounds 4a–i,l,m were readily isolated by simple recrystallization of the crude reaction mixtures. No effect of the examined substituents on the formation of compounds 4a–i,l,m was observed. In the case of compound 3j (X = NH), no compound 4j was formed—instead of this compound, furoqinoxaline I was detected (monitoring by UPLC-UV-MS) (Scheme 2) [24,33].

**Table 2.** Thermal decomposition of compounds 3a–j,l,m.

| Entry | Precursor 3 | Cyanamide 2 | X   | R¹  | R²    | Temperature °C | Yield ² of 4, % |
|-------|-------------|-------------|-----|-----|-------|----------------|----------------|
| 4a    | 3a          | 2a          | NPh | Ph  | NEt₂  | 215–220        | 71             |
| 4b    | 3b          | 2b          | NPh | Ph  |       | 235–240        | 85             |
| 4c    | 3c          | 2c          | NPh | Ph  | NMe₂  | 230–235        | 78             |
| 4d    | 3d          | 2d          | NPh | Ph  |       | 230–235        | 77             |
| 4e    | 3e          | 2b          | NPh | CN₆H₄Cl-4 |       | 240–245        | 86             |
| 4f    | 3f          | 2b          | NPh | CN₆H₄OMe-4 |       | 250–255        | 91             |
| 4g    | 3g          | 2c          | NPh | CN₆H₄NO₂-4 | NMe₂  | 220–225        | 79             |
| 4h    | 3h          | 2b          | NMe | CN₆H₄Me-4 |       | 220–225        | 82             |
We assume that the formation of compounds 4a-i,l,m proceeded through three stages (Scheme 2). First, compounds 3a-i,l,m underwent thermally initiated retro-HDA that afforded FPDs 1a-i and cyanamides 2a-d. Second, formed FPDs 1a-i decarbonylated (the evolution of carbon monoxide was indicated by a gas detector tube) to generate acyl(imidoyl)ketenes C. And finally, acyl(imidoyl)ketenes C reacted as oxa-dienes with cyanamides 2a-d to produce the desired 4H-1,3-oxazines 4a-i,l,m. We suppose that ketenes C reacted with cyanamides 2a-d exclusively as oxa-dienes, since this cycloaddition reaction proceeded via a charge-controlled polar transition state, as it was observed earlier in the reaction of ketenes C with carbodiimides [25].

To validate the proposed pathway of formation of compounds 4 (Scheme 2), we tested the one-pot solvent-free reaction of FPD 1a with cyanamide 2b. At heating of compound 1a with cyanamide 2b (reaction scale of 0.4 mmol, 1a:2b reagents ratio of 1:1.1) at 235–240 °C, we found that compound 4b was formed only in a yield of ~45% (monitoring by UPLC-UV-MS), which was much lower than in the case of decomposition of compound 3b. We think

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### Table 2. Cont.

| Entry | Precursor 3 | Cyanamide 2 | X | R<sup>1</sup> | R<sup>2</sup> | Temperature<sup>1</sup>, °C | Yield<sup>2</sup> of 4, % |
|-------|-------------|-------------|---|------------|------------|------------------------|------------------------|
| 4i    | 3i          | 2b          | NPh | Bt-t       |            | 190–195                | 84                     |
| 4j    | 3j          | 2b          | NH  | Ph         |            | 210–215                | 0<sup>3</sup>           |
| 4l    | 3l          | 2b          | O   | Ph         |            | 230–235                | 65                     |
| 4m    | 3m          | 2c          | O   | Ph         | NMe<sub>2</sub> | 240–245                | 68                     |

<sup>1</sup> Bath temperature. <sup>2</sup> Isolated yields (reaction scale of 0.4 mmol). <sup>3</sup> According to UPLC-UV-MS.
that it was because of violation of heat and mass transfer processes during the solvent-free reaction of compounds 1a and 2b. These violations promoted the thermolytical side reactions leading to compounds H [24,32] (monitored by UPLC-UV-MS) and decreased the yield of compound 4b. Thus, the development of a procedure to compounds 4 from the direct reaction of compounds 1 and 2 without isolation of compounds 3 is rather possible, but it requires additional optimization.

Then, to further validate the proposed pathway of formation of compounds 4 (Scheme 2), we performed the decomposition of compound 3b in the presence of FPD 1b at 240 °C and decomposition of compound 3a in the presence of cyanamide 2b at 240 °C and studied the obtained reaction mixtures by HPLC-UV. As a result, the decomposition of compound 3b (R1 = Ph, R2 = morpholino) in the presence of FPD 1b (R1 = 4-ClC6H4) at 240 °C afforded a mixture of compounds 4b (R1 = Ph, R2 = morpholino) and 4e (R1 = 4-ClC6H4, R2 = morpholino) along with a mixture of corresponding side products H. The decomposition of compound 3a (R1 = Ph, R2 = NEt2) in the presence of cyanamide 2b (R2 = morpholino) at 240 °C afforded a mixture of compounds 4a (R1 = Ph, R2 = NEt2) and 4b (R1 = Ph, R2 = morpholino) along with the corresponding side product H. These crossover experiments indirectly confirm that the proposed pathway of formation of compounds 4 (Scheme 2) includes retro-HDA stage and formation of acyl(imidoyl)ketenes C.

The structures of compounds 3a, 3i, 4b, 4f, and 4i were proved by single crystal X-ray analyses (CCDC 2192396 (3a), 2192397 (3i), 2192400 (4b), 2192399 (4f), 2192398 (4g), and 2196232 (4i)).

3. Materials and Methods
3.1. General Information

1H and 13C NMR spectra (Supplementary Materials) were acquired on a Bruker Avance III 400 HD spectrometer (Switzerland) (at 400 and 100 MHz, respectively) at 313 K in CDCl3 (stab. with Ag) or DMSO-d6 using the TMS or HMDS signal (in 1H NMR) or solvent residual signals (in 13C NMR, 77.00 for CDCl3, 39.51 for DMSO-d6) in 1H NMR, 7.26 for CDCl3, 2.50 for DMSO-d6) as internal standards. 13C ssNMR spectra were acquired on a Bruker Avance III 400 WB NMR spectrometer (Switzerland) (at 100 MHz). Melting points were measured on a Mettler Toledo MP70 apparatus (Switzerland). Elemental analyses were carried out on a Vario MICRO Cube analyzer (Germany). The reaction conditions were optimized using UPLC-UV-MS (Waters ACQUITY UPLC I-Class system (USA)); Acquity UPLC BEH C18 column, grain size of 1.7 µm; acetonitrile–water (water containing 0.1% formic acid) as eluents; flow rate of 0.6 mL/min; ACQUITY UPLC PDA e Detector (wavelength range of 230–780 nm); Xevo TQD mass detector; electrospray ionization (ESI); positive and negative ion detection; ion source temperature of 150 °C; capillary voltage of 3500–4000 V; cone voltage of 20–70 V; vaporizer temperature of 200 °C) and HPLC-UV (Hitachi Chromaster Japan); NUCLEODUR C18 Gravity column (particle size 3 µm; eluent acetonitrile–water, flow rate 1.5 mL/min); Hitachi Chromaster 5430 diode array detector (λ 210–750 nm)). CO was indicated by gas detector tubes Gazopredelitel GH-4 (USSR) (specifications 12.43.20-76). The single crystal X-ray analyses of compounds 3a, 3i, 4b, 4f, 4g, and 4i were performed on an Xcalibur Ruby diffractometer (Agilent Technologies, UK). The empirical absorption correction was introduced by multi-scan method using SCALE3 AB-SPACK algorithm [34]. Using OLEX2 [35], the structures were solved with the SHELXS [36] program and refined by the full-matrix least-squares minimization in the anisotropic approximation for all non-hydrogen atoms with the SHELXL [37] program. Hydrogen atoms were positioned geometrically and refined using a riding model. Thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 plates using EtOAc/toluene, 1:5 v/v, toluene, EtOAc as eluents. Starting compounds 1a–j were obtained according to reported procedures [25,33,38,39]. Toluene for procedures involving compounds 1 was dried over Na before the use. Acetonitrile for procedures involving compounds 1 was dried over molecular sieves 4Å before the use. All other solvents and reagents were purchased from
commercial vendors and used as received. Procedures involving compounds 1, 3 were carried out in oven-dried glassware.

3.2. Synthetic Methods and Analytic Data of Compounds
3.2.1. General Procedure to Compounds 3a–j,l,m
A suspension of the corresponding FPD 1 (0.76 mmol) [25,33,38,39] and the corresponding cyanamide 2 (0.84 mmol) in 4 mL of a solvent (anhydrous acetonitrile (for 1a–h) or anhydrous toluene (for 1i)) was stirred and heated at 95 °C for 16 h (until the disappearance of the dark violet color of the compound 1) in an oven-dried capped vial. Then the reaction mixture was cooled to room temperature, and the resulting precipitate was filtered off to afford the desired compound 3. Compound 3 was pure enough and was used further without additional purification.

5-(Diethylamino)-3,8-diphenyl-1,3]oxazino[4',5',2,3]pyrrolo[1,2-alquinoxaline-1,2,7(8H)-trione (3a). Yield: 318 mg (85%); yellow solid; mp 200–204 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ = 8.07 (m, 2 H), 7.82 (m, 1 H), 7.74 (m, 1 H), 7.66 (m, 2 H), 7.59 (m, 2 H), 7.51 (m, 1 H), 7.27–7.18 (m, 4 H), 6.43 (m, 1 H), 3.56–3.47 (m, 2 H), 3.36–3.26 (m, 2 H), 1.15 (t, J = 7.1 Hz, 6 H) ppm. 13C NMR (100 MHz, DMSO-d6): δ = 177.0, 163.2, 159.4, 159.0, 150.5, 136.9, 133.7, 132.9, 129.9 (2C), 129.8 (2C), 128.8 (2C), 128.5 (2C), 126.5 (2C), 123.0, 122.7, 116.0, 104.1, 71.6, 42.4 (2C), 13.3 (2C) ppm. Anal. Calcd (%) for C39H28N2O4: C 78.52; H 4.23; N 11.08. Found: C 78.39; H 4.11; N 11.18. Crystal structure of compound 3a was deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 192396. Crystal Data of 3a: Cu2H2NiO4, M = 492.52, triclinic, a = 9.507(2) Å, b = 10.481(2) Å, c = 13.277(4) Å, α = 74.93(2)°, β = 79.69(2)°, γ = 79.352(19)°, V = 1243.46 Å3, T = 295(2), space group P–1, Z = 2, μ(MoKα) = 0.090 mm–1. The final refinement parameters: R1 = 0.0697 [for observed 2640 reflections with I > 2σ(I)], wR2 = 0.1951 (for all independent 5764 reflections, Rint = 0.0711), S = 1.023. Largest diff. peak and hole 0.223 and –0.217 eÅ–3.

5-Morpholino-3,8-diphenyl-1,3]oxazino[4',5',2,3]pyrrolo[1,2-alquinoxaline-1,2,7(8H)-trione (3b). Yield: 343 mg (89%); yellow solid; mp 223–224 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ = 8.05 (m, 2 H), 7.81 (m, 1 H), 7.74 (m, 1 H), 7.67–7.57 (m, 4 H), 7.51 (m, 1 H), 7.27 (m, 2 H), 7.21 (m, 2 H), 6.41 (m, 1 H), 3.65 (m, 4 H), 3.47 (m, 4 H) ppm. 13C ssNMR (100 MHz): δ = 177.0, 163.8, 160.5, 151.3, 137.3, 134.1, 129.8, 127.7, 126.2, 122.4, 115.2, 104.4, 72.3, 66.7, 44.9 ppm. Anal. Calcd (%) for C29H22N4O4: C 68.77; H 4.38; N 11.06. Found: C 68.59; H 4.23; N 11.08.

5-(Diethylamino)-3,8-diphenyl-1,3]oxazino[4',5',2,3]pyrrolo[1,2-alquinoxaline-1,2,7(8H)-trione (3c). Yield: 275 mg (78%); yellow solid; mp 220–221 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ = 8.08 (m, 2 H), 7.81 (m, 1 H), 7.74 (m, 1 H), 7.65 (m, 2 H), 7.59 (m, 2 H), 7.51 (m, 1 H), 7.27 (m, 2 H), 7.20 (m, 2 H), 6.41 (m, 1 H), 3.01 (s, 6 H) ppm. 13C ssNMR (100 MHz): δ = 176.8, 162.2, 151.5, 139.4, 136.3, 131.3, 129.9, 126.9, 124.0, 116.7, 104.2, 74.0, 36.8 ppm. Anal. Calcd (%) for C27H20N4O4: C 69.82; H 4.34; N 12.06. Found: C 70.03; H 4.35; N 12.42.

3,8-Diphenyl-5-(piperidin-1-yl)-1,3]oxazino[4',5',2,3]pyrrolo[1,2-alquinoxaline-1,2,7(8H)-trione (3d). Yield: 318 mg (83%); yellow solid; mp 221–224 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ = 8.04 (m, 2 H), 7.82 (m, 1 H), 7.74 (m, 1 H), 7.65 (m, 2 H), 7.59 (m, 2 H), 7.51 (m, 1 H), 7.26–7.17 (m, 4 H), 6.41 (m, 1 H), 3.49 (m, 4 H), 1.57 (m, 6 H) ppm. 13C ssNMR (100 MHz): δ = 165.1, 160.9, 151.4, 135.8, 131.0, 128.7, 126.4, 123.1, 117.9, 104.2, 87.1, 48.2, 25.3, 21.9 ppm. Anal. Calcd (%) for C30H24N4O4: C 71.42; H 4.79; N 11.10. Found: C 71.21; H 4.82; N 11.10.

3-(4-Chlorophenyl)-5-morpholino-8-phenyl-1,3]oxazino[4',5',2,3]pyrrolo[1,2-alquinoxaline-1,2,7(8H)-trione (3e). Yield: 362 mg (88%); yellow solid; mp 230–235 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ = 8.05 (m, 2 H), 7.81 (m, 1 H), 7.72 (m, 2 H), 7.59 (m, 2 H), 7.51 (m, 1 H), 7.27–7.16 (m, 4 H), 6.41 (m, 1 H), 3.65 (m, 4 H), 3.46 (m, 4 H) ppm. 13C ssNMR (100 MHz): δ = 178.3, 161.0, 159.1, 150.4, 141.3, 136.1, 132.7, 129.8, 127.9, 124.1, 115.0, 103.8, 66.3, 45.1 ppm. Anal. Calcd (%) for C29H21ClN4O4: C 64.39; H 3.91; N 10.36. Found: C 64.02; H 3.85; N 10.11.
3-(4-Methoxyphenyl)-5-morpholino-8-phenyl-[1,3]oxazino[4',5':2,3]pyrrolo[1,2-a]quinazoline-1,2,7(8H)-trione (3f). Yield: 371 mg (91%); yellow solid; mp 242–244 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ = 8.08 (m, 2 H), 7.81 (m, 1 H), 7.59 (m, 2 H), 7.50 (m, 1 H), 7.28–7.16 (m, 5 H), 6.40 (m, 1 H), 3.92 (s, 3 H), 3.65 (m, 4 H), 3.46 (m, 4 H) ppm. 13C ssNMR (100 MHz): δ = 178.7, 165.5, 160.2, 152.2, 134.0, 128.8, 125.9, 120.8, 114.9, 99.4, 72.7, 65.7, 56.6, 43.6 ppm. Anal. Calcd (%) for C30H25N4O6: C 67.16; H 6.41; N 10.44. Found: C 67.40; H 4.66; N 10.38.

5-(Dimethylamino)-3-(4-nitrophenyl)-8-phenyl-[1,3]oxazino[4',5':2,3]pyrrolo[1,2-a]quinazoline-1,2,7(8H)-trione (3g). Yield: 301 mg (92%); yellow solid; mp 201–203 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ = 8.46 (m, 1 H), 8.29 (m, 2 H), 7.81 (m, 1 H), 7.60 (m, 2 H), 7.51 (m, 1 H), 7.27 (m, 2 H), 7.22 (m, 2 H), 6.43 (m, 1 H), 3.02 (s, 6 H) ppm. 13C NMR (100 MHz, DMSO-d6): δ = 177.3, 163.2, 158.6, 156.6, 151.6, 149.9, 136.8, 134.0, 132.9, 131.4 (2C), 129.9 (2C), 128.9 (2C), 128.7, 126.6, 123.4, 123.1 (2C), 122.8, 122.1, 116.0, 106.1, 71.7, 37.2 (2C) ppm. Anal. Calcd (%) for C27H19N4O6: C 65.69; H 3.76; N 13.75. Found: C 65.87; H 4.06; N 13.91.

8-Methyl-3-(4-methylphenyl)-5-morpholino-8-phenyl-[1,3]oxazino[4',5':2,3]pyrrolo[1,2-a]quinazoline-1,2,7(8H)-trione (3h). Yield: 310 mg (79%, solvate with toluene); yellow solid; mp 176–179 °C. 1H NMR (400 MHz, DMSO-d6): δ = 7.96 (m, 2 H), 7.74 (m, 1 H), 7.46 (m, 2 H), 7.42–7.35 (m, 2 H), 7.25 (m, 1 H), 3.60 (m, 4 H), 3.42–3.32 (m, 7 H), 2.47 (s, 3 H) ppm. 13C NMR (100 MHz, DMSO-d6): δ = 176.5, 163.6, 159.9, 159.0, 151.2, 144.7, 132.0, 130.2 (2C), 129.0 (2C), 126.9, 125.7, 122.9, 122.7, 122.1, 115.5, 103.5, 71.3, 65.2 (2C), 44.7 (2C), 29.5, 21.3 ppm. Anal. Calcd (%) for C25H22N4O6: C 64.32; H 4.04; N 9.50. Found: C 64.01; H 4.25; N 9.74.

3-(tert-Butyl)-5-morpholino-8-phenyl-[1,3]oxazino[4',5':2,3]pyrrolo[1,2-a]quinazoline-1,2,7(8H)-trione (3i). After cooling the reaction mixture, no precipitate was formed. As such, the reaction solvent (acetonitrile) was removed on a rotary evaporator. The resulting solid was dissolved in toluene (2 mL). Then, petroleum ether (bp 70–100 °C) (6 mL) was added to the toluene solution, and the resulting precipitate was filtered off to afford compound (3i). Yield: 266 mg (81%); yellow solid; mp 214–219 °C (decomp.). 1H NMR (400 MHz, DMSO-d6): δ = 8.06 (m, 2 H), 7.82–7.73 (m, 2 H), 7.66 (m, 2 H), 7.43–7.31 (m, 3 H), 3.62 (m, 4 H), 3.43 (m, 4 H) ppm. 13C NMR (100 MHz, DMSO-d6): δ = 164.8, 160.9, 158.3, 149.5, 144.6, 139.4, 133.0, 128.4, 121.6, 117.9, 105.6, 89.4, 67.6, 45.6 ppm. Anal. Calcd (%) for C23H19N4O6: C 64.18; H 5.59; N 10.83. Found: C 64.01; H 4.25; N 9.74.
A mixture of the corresponding compound 3 (0.4 mmol) and the corresponding cyanamide (0.04 mmol) was put into an oven-dried tube, pressed slightly, and then heated in a metal bath at 190–245 °C (the temperature for each compound is given in Table 2; caution: CO evolves during the reaction) for 5 min. The reaction mixture was cooled to room temperature and recrystallized from about 3 mL of a solvent (acetonitrile for 3a–h) or toluene (for 3l–m) to give the appropriate compound 4. In the case of compound 3l, the reaction mixture was cooled to room temperature, dissolved in 1 mL of ethyl acetate. Then, 5 mL of n-hexane were added to it, and the resulting precipitate was filtered off to afford compound 4i.

2-(Diethylamino)-5-(3-oxo-4-phenyl-3,4-dihydroquinoxalin-2-yl)-6-phenyl-4H-1,3-oxazin-4-one (4a). Yield: 132 mg (71%); yellow solid; mp 271–273 °C. 1H NMR (400 MHz, DMSO-d6): δ = 7.80 (m, 1 H), 7.70–7.32 (m, 12 H), 3.58 (m, 4 H), 1.25 (m, 6 H) ppm. 13C NMR (100 MHz, DMSO-d6): δ = 166.1, 158.0, 156.9, 154.1, 153.2, 133.9, 131.9, 131.1, 130.9, 130.2, 129.4, 129.3, 128.9 (2 C), 128.3, 128.2, 127.5 (2 C), 123.8, 115.2, 114.0, 41.7 (2 C), 12.3 (2 C) ppm. Anal. Calcd (%) for C28H23N3O3: C 74.12; H 4.56; N 10.53. Found: C 74.20; H 4.58; N 10.63.

Crystal structure of compound 4b was deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 2192400. 

Crystal Data of 4b: C28H22N4O4, M = 478.49, monoclinic, a = 12.995(5) Å, b = 9.3586(15) Å, c = 19.719(6) Å, β = 105.98(3) °, V = 2305.5(10) Å3, T = 295(2), space group P21/c. µ(Mo Kα) = 0.094 mm−1. The final refinement parameters: R1 = 0.0498 [for observed 5363 reflections with I > 2σ(I)], wR2 = 0.1360 (for all independent 5442 reflections, Rint = 0.0265), S = 1.043. Largest diff. peak and hole 0.191 and −0.230 e Å−3.

2-Morpholino-5-(3-oxo-4-phenyl-3,4-dihydroquinoxalin-2-yl)-6-phenyl-4H-1,3-oxazin-4-one (4c). Yield: 163 mg (85%); yellow solid; mp 285–287 °C. 1H NMR (400 MHz, DMSO-d6): δ = 7.87 (m, 1 H), 7.58–7.26 (m, 11 H), 7.06 (brs, 1 H), 6.67 (m, 1 H), 3.78 (m, 8 H) ppm. 13C NMR (100 MHz, CDCl3): δ = 167.2, 159.6, 157.1, 153.6, 153.5, 136.4, 132.8, 131.1, 130.9, 130.6, 130.2 (2 C), 130.0, 129.3, 128.7 (2 C), 128.6, 128.2, 128.1 (2 C), 123.7, 115.4, 114.8, 66.3 (2 C), 44.5 (2 C) ppm. Anal. Calcd (%) for C28H22N4O4: C 72.80; H 4.63; N 11.71. Found: C 70.38; H 4.41; N 11.53. 

6-(4-Chlorophenyl)-2-morpholino-5-(3-oxo-4-phenyl-3,4-dihydroquinoxalin-2-yl)-4H-1,3-oxazin-4-one (4e). Yield: 176 mg (86%); yellow solid; mp 311–315 °C. 1H NMR (400 MHz, DMSO-d6): δ = 7.81 (m, 1 H), 7.70–7.48 (m, 8 H), 7.38 (m, 3 H), 6.64 (m, 1 H), 3.71 (m, 8 H) ppm. 13C ssNMR (100 MHz): δ = 167.0, 157.3, 155.3, 152.6, 138.7, 134.2, 131.4, 129.5, 127.6,
105 mg (65%); yellow solid; mp 208–211 °C. 1H NMR (400 MHz, DMSO-d6): δ = 7.82 (m, 1 H), 7.71–7.48 (m, 6 H), 7.42–7.35 (m, 3 H), 7.01 (m, 2 H), 6.64 (m, 1 H), 3.77 (s, 3 H), 3.72 (m, 8 H) ppm. 13C NMR (100 MHz, DMSO-d6): δ = 166.4, 161.4, 157.8, 156.9, 154.2, 153.1, 135.3, 134.0, 131.9, 130.9, 130.1 (2 C), 129.4 (4 C), 129.3, 128.2, 123.8, 122.1, 115.2, 114.4 (2 C), 112.7, 65.3 (2 C), 55.3, 43.9 (2 C) ppm. Anal. Calcd (%) for C29H24N6O5: C 68.49; H 4.76; N 11.02. Found: C 68.78; H 4.71; N 11.08. Crystal structure of compound 4f was deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 2192399. Crystal Data of 4f: C29H24N6O5, M = 508.52, monoclinic, a = 13.137(2) Å, b = 10.009(3) Å, c = 19.142(4) Å, β = 101.80(2) °, V = 2463.8(10) Å³, T = 295(2), space group P21/c, Z = 4, μ(Mo Kα) = 0.096 mm⁻¹. The final refinement parameters: R₁ = 0.0651 [for observed 3086 reflections with I > 2σ(I)], wR₂ = 0.2110 (for all independent 5836 reflections, Rint = 0.0479), S = 1.036. Largest diff. peak and hole 0.324 and −0.238 eÅ⁻³.

2-(Dimethylamino)-6-(4-nitrophenyl)-5-(3-oxo-3,4-dihydroquinazolin-2-yl)-4H-1,3-oxazin-4-one (4g). Yield: 152 mg (79%); pale yellow solid; mp 298–300 °C. 1H NMR (400 MHz, DMSO-d6): δ = 8.30 (m, 2 H), 7.87 (m, 2 H), 7.80 (m, 1 H), 7.70–7.34 (m, 7 H), 6.65 (m, 1 H), 3.17 (m, 6 H) ppm. 13C NMR (100 MHz, DMSO-d6): δ = 170.1, 165.6, 157.6, 155.9, 153.3, 153.1, 148.5, 136.0, 135.2, 134.1, 131.9, 131.1, 130.1 (2 C), 129.5, 129.4, 129.2 (2 C), 128.1, 124.0 (2 C), 123.8, 115.5, 115.3, 37.1, 36.0 ppm. Anal. Calcd (%) for C39H28N6O5: C 64.86; H 3.98; N 14.55. Found: C 64.89; H 4.01; N 14.19. Crystal structure of compound 4g was deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 2192398. Crystal Data of 4g: C39H28N6O5, M = 481.46, triclinic, a = 9.8633(13) Å, b = 10.7810(14) Å, c = 11.3896(14) Å, α = 74.960(11) °, β = 86.914(10) °, γ = 75.706(11) °, V = 1132.8(3) Å³, T = 295(2), space group P1, Z = 2, μ(Mo Kα) = 0.101 mm⁻¹. The final refinement parameters: R₁ = 0.0530 [for observed 3900 reflections with I > 2σ(I)], wR₂ = 0.1505 (for all independent 5227 reflections, Rint = 0.0300), S = 1.043. Largest diff. peak and hole 0.310 and −0.309 eÅ⁻³.

5-(4-Methyl-3-oxo-3,4-dihydroquinazolin-2-yl)-6-(4-methylphenyl)-2-morpholino-4H-1,3-oxazin-4-one (4h). Yield: 141 mg (82%); yellow solid; mp 271–273 °C. 1H NMR (400 MHz, DMSO-d6): δ = 7.75 (m, 1 H), 7.69 (m, 1 H), 7.61 (m, 1 H), 7.43–7.36 (m, 3 H), 7.20 (m, 2 H), 3.72 (m, 8 H), 3.66 (s, 3 H), 2.26 (s, 3 H) ppm. 13C ssNMR (100 MHz): δ = 167.4, 165.9, 162.6, 161.3, 156.4, 152.6, 150.6, 143.5, 142.4, 131.6, 130.1, 127.6, 122.8, 115.0, 113.6, 110.6, 66.8, 44.5, 28.4, 22.7, 20.6 ppm. Anal. Calcd (%) for C31H26N6O4: C 66.97; H 5.15; N 13.02. Found: C 66.81; H 4.99; N 13.19.

6-(tert-Butyl)-2-morpholino-5-(3-oxo-4-phenyl-3,4-dihydroquinazolin-2-yl)-4H-1,3-oxazin-4-one (4i). Yield: 154 mg (84%); pale yellow solid; mp 160–162 °C. 1H NMR (400 MHz, DMSO-d6): δ = 7.88 (m, 1 H), 7.69–7.58 (m, 4 H), 7.52 (m, 1 H), 7.43–7.32 (m, 3 H), 6.65 (m, 1 H), 3.71 (m, 4 H), 3.65 (m, 4 H), 1.19 (s, 9 H) ppm. 13C NMR (100 MHz, DMSO-d6): δ = 167.1 (2 C), 157.2, 155.2, 153.3, 135.3, 133.9, 131.5, 130.8, 130.2 (2 C), 129.4 (2 C), 129.3, 128.2, 123.8, 115.2, 112.9, 65.2 (2 C), 43.8 (2 C), 37.1, 28.0 (3 C) ppm. Anal. Calcd (%) for C39H30N6O4: C 68.11; H 5.72; N 12.22. Found: C 68.27; H 5.59; N 12.30. Crystal structure of compound 4i was deposited at the Cambridge Crystallographic Data Centre with the deposition number CCDC 2196232. Crystal Data of 4i: C39H30N6O4, M = 548.51, orthorhombic, a = 17.435(7) Å, b = 15.185(4) Å, c = 17.942(4) Å, V = 4750.3(3) Å³, T = 295(2), space group Pbca, Z = 8, μ(Mo Kα) = 0.088 mm⁻¹. The final refinement parameters: R₁ = 0.0984 [for observed 1995 reflections with I > 2σ(I)], wR₂ = 0.2775 (for all independent 5956 reflections, Rint = 0.1670), S = 1.025. Largest diff. peak and hole 0.255 and −0.215 eÅ⁻³.

3-(2-Morpholino-4-oxo-6-phenyl-4H-1,3-oxazin-5-yl)-2H-benzo[b][1,4]oxazine-2-one (4j). Yield: 105 mg (65%); yellow solid; mp 208–211 °C. 1H NMR (400 MHz, DMSO-d6): δ = 7.73 (m, 1 H), 7.65 (m, 3 H), 7.54–7.42 (m, 5 H), 3.72 (m, 8 H) ppm. 13C NMR (100 MHz, DMSO-d6): δ = 166.0, 159.1, 156.9, 151.4, 150.4, 146.1, 132.2, 131.5, 130.5, 129.4, 129.0, 128.9 (2 C), 128.1
(2 C), 125.8, 116.5, 112.5, 65.2 (2 C), 44.0 (2 C) ppm. Anal. Calcd (%) for C_{22}H_{17}N_{3}O_{5}: C 65.50; H 4.25; N 10.42. Found: C 65.67; H 4.12; N 10.32.

3-(2-(Dimethylamino)-4-oxo-6-phenyl-4H-1,3-oxazin-5-yl)-2H-benzo[b][1,4]oxazin-2-one (4m). Yield: 98 mg (68%); yellow solid; mp 159–163 °C. 1H NMR (400 MHz, DMSO-d_{6}): δ = 7.73 (m, 1 H), 7.64 (m, 3 H), 7.54–7.42 (m, 5 H), 3.17 (m, 6 H) ppm. 13C NMR (100 MHz, DMSO-d_{6}): δ = 166.0, 158.9, 157.8, 151.4, 150.6, 146.0, 132.2, 131.4, 130.5, 129.5, 129.0, 128.9 (2 C), 128.0 (2 C), 125.8, 116.5, 112.2, 37.1, 36.0 ppm. Anal. Calcd (%) for C_{20}H_{15}N_{3}O_{4}: C 66.48; H 4.18; N 11.63. Found: C 66.09; H 4.00; N 11.71.

3.2.3. Procedure to Compound I

Compound 3j (22 mg, 0.05 mmol) was put into an oven-dried tube, pressed slightly, and heated in a metal bath at 210–215 °C (caution: CO evolves during the reaction) for 3 min. The reaction mixture was cooled to room temperature and recrystallized from about 5 mL of 1,4-dioxane to give compound I.

3-Benzoylfuro[2,3-b]quinoxalin-2(4H)-one (I) [33]. Yield: 9.9 mg (68%); yellow solid; mp 273–274 °C (reported mp 274–275 °C [33]). 1H NMR (400 MHz, DMSO-d_{6}): δ = 13.98 (br.s, 1 H), 8.20 (m, 1 H), 7.84 (m, 3 H), 7.66–7.48 (m, 5 H) ppm. 13C NMR (100 MHz, DMSO-d_{6}): δ = 188.4, 163.9, 154.6, 141.9, 137.8, 134.6, 131.8, 128.6, 128.4 (2 C), 128.3, 127.9, 127.7 (2 C), 126.4, 118.6, 91.6 ppm. Anal. Calcd (%) for C_{17}H_{10}N_{2}O_{3}: C 70.34; H 3.47; N 9.65. Found: C 70.53; H 3.37; N 9.71.

4. Conclusions

In conclusion, we have developed a novel diversity-oriented approach to two series of skeletally diverse 4H-1,3-oxazines (tetracyclic alkaloid-like 4H-1,3-oxazines 3 and 5-heteryl-4H-1,3-oxazines 4) via a hetero-Diels–Alder reaction of 4-acyl-1H-pyrrole-2,3-diones fused at [e]-side 1 with cyanamides 2. Tetracyclic alkaloid-like 4H-1,3-oxazines 3 were achieved through [4 + 2] cycloaddition of cyanamides 2 to oxa-diene system of 4-acyl-1H-pyrrole-2,3-diones fused at [e]-side 1. 5-Heteryl-4H-1,3-oxazines 4 were formed as the result of thermal decomposition of tetracyclic alkaloid-like 4H-1,3-oxazines 3, which proceeded via three steps (retro-Diels–Alder reaction that afforded 4-acyl-1H-pyrrole-2,3-diones fused at [e]-side 1 and cyanamides 2; thermolytical decarbonylation of 4-acyl-1H-pyrrole-2,3-diones fused at [e]-side 1 that resulted in formation of highly reactive acyl(imidoyl)ketenes C; [4 + 2] cycloaddition of acyl(imidoyl)ketenes C as oxa-diens with cyanamides 2 that produced 5-heteryl-4H-1,3-oxazines 4).

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/molecules27165257/s1, Copies of NMR spectra for all new compounds, ORTEP images of X-ray crystal structures.

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References

1. Burke, M.D.; Schreiber, S.L. A Planning Strategy for Diversity-Oriented Synthesis. Angew. Chem. Int. Ed. 2004, 43, 46–58. [CrossRef] [PubMed]

2. Gerry, C.J.; Schreiber, S.L. Recent achievements and current trajectories of diversity-oriented synthesis. Curr. Opin. Chem. Biol. 2020, 56, 1–9. [CrossRef] [PubMed]

3. Schreiber, S.L. Target-Oriented and Diversity-Oriented Organic Synthesis in Drug Discovery. Science 2000, 287, 1964–1969. [CrossRef]

4. Galloway, W.R.; Isidro-Llobet, A.; Spring, D. Diversity-oriented synthesis as a tool for the discovery of novel biologically active small molecules. Nat. Commun. 2010, 1, 80. [CrossRef] [PubMed]

5. Morrison, R.; Al-Rawi, J.M.A. Synthesis, structure elucidation, DNA-PK, PI3K, anti-platelet and anti-bacteria activity of linear 5, 6 and 10-substituted-2-morpholino-chromen-oxazine-dione and angular 3, 4, 6-substituted-8-morpholino-chromen-oxazine-2,10-dione. J. Enzym. Inhib. Med. Chem. 2016, 31, 86–95. [CrossRef]

6. Morrison, R.; Al-Rawi, J.M.A.; Jennings, I.G.; Thompson, P.E.; Angove, M.J. Synthesis, structure elucidation, DNA-PK and PI3K and anti-cancer activity of 8- and 6-arlylidene-1,3-benzoxazines. Eur. J. Med. Chem. 2016, 110, 326–339. [CrossRef]

7. Morrison, R.; Zheng, Z.; Jennings, I.G.; Thompson, P.E.; Al-Rawi, J.M.A. Synthesis of linear and angular aryldihydropyridinone, their DNA-PK, PI3K, PDE3A and antiplatelet activity. Bioorg. Med. Chem. Lett. 2016, 26, 5534–5538. [CrossRef]

8. Saifuzzaman, M.; Morrison, R.; Zheng, Z.; Orive, S.; Hamilton, J.; Thompson, P.E.; Al-Rawi, J.M.A. Synthesis and biological evaluation of 8-aryl-2-morpholino-7-O-substituted benzo[e][1,3]oxazin-4-ones against DNA-PK, PI3K, PDE3A enzymes and platelet aggregation. Bioorg. Med. Chem. 2017, 25, 5531–5536. [CrossRef]

9. Suraj, R.; Radhamani, S.; Meehan-Andrews, T.; Bradley, C. Role of a novel benzoxazine derivative in the chemosensitization of colon cancer. Apoptosis 2017, 22, 988–1000. [CrossRef]

10. Suraj, R.; Al-Rawi, J.J.; Bradley, C. Inhibition of Akt signalling by benzoxazine derivative LTUR6 through the modulation of downstream kinases. Investig. New Drugs 2019, 37, 779–783. [CrossRef]

11. Arrowsmith, C.H.; Audia, J.E.; Austin, C.; Baell, J.; Bennett, J.; Blagg, J.; Bountra, C.; Brennan, P.J.; Brown, P.J.; Bunnage, M.E.; et al. The promise and peril of chemical probes. Nat. Chem. Biol. 2015, 11, 536–541. [CrossRef] [PubMed]

12. Cano, C.; Saravanan, K.; Bailey, C.; Bardos, J.; Curtin, N.J.; Frigerio, M.; Golding, B.T.; Hardcastle, I.R.; Hummersone, M.G.; Meneer, K.A.; et al. 1-Substituted (Dibenzo[2,1,4]oxazine-3,4,6-trifluoropropionate. Russ. J. Gen. Chem. 2012, 82, 1728–1730. [CrossRef]

13. Bhuyan, D.; Sarma, R.; Dommaraju, Y.; Prajapati, D. Catalyst- and solvent-free, pot, atom and step economic synthesis of angularly fused pyrano[4,3-b]thiophen-4-yl)-2-morpholino-4H-chromen-4-ones Endowed with Dual DNA-PK/PI3-K Inhibitory Activity. J. Med. Chem. 2013, 56, 6386–6401. [CrossRef] [PubMed]

14. England, D.C. Fluoroketenes. 11. Synthesis and chemistry of a perfluoroacylketene and related compounds containing a perfluoroisopropyl sulfide group. Russ. J. Gen. Chem. 2014, 84, 153–157. [CrossRef]

15. Ried, W.; Nenninger, H. Synthese neuer 1,3-Oxazinone aus Cyanamiden und Chlorocarbonylketen. Synthesis 1990, 02, 167–170. [CrossRef]

16. Kappe, C.O.; Wentrup, C.; Kollenz, G. 2[4+4] Cycloaddition reactions of neat dipivaloylketene. Monatsh. Chem. 1993, 124, 1133–1141. [CrossRef]

17. Sokolov, V.B.; Aksinenko, A.Y.; Epishina, T.A.; Goreva, T.V. Fluoro-containing 4-ethylidenede-2,4-dihydropriazol-3-ones in the Diels-Alder reaction with cyclopentadiene and cyanamines. Russ. J. Gen. Chem. 2012, 82, 1728–1730. [CrossRef]

18. Sokolov, V.B.; Aksinenko, A.Y. Cycloaddition and cyclocondensation of methyl 2-(4,4-Dimethyl-2,6-dioxocyclohexyldiene)-3,3,3-trifluoropropionate. Russ. J. Gen. Chem. 2014, 84, 1243–1245. [CrossRef]

19. Lisovenko, N.Y.; Nekrasov, D.D.; Karmanov, V.I. Thermolytic transformations of 5-aryl-4-quinoxalin-2-ylfurcan-2,3-diones in the presence of N-cyano compounds. Chem. Heterocycl. Compd. 2012, 48, 1357–1360. [CrossRef]

20. Stepanova, E.E.; Masliyets, A.N. [4 + 2]-Cycloaddition of vinyl acetate to pyrrolbenzoxazinetriones. Diastereoselective synthesis of angularly fused pyrano[4,3-b]pyrroles. Russ. J. Org. Chem. 2016, 52, 879–882. [CrossRef]

21. Stepanova, E.E.; Dmitriev, M.V.; Masliyets, A.N. Hetero-Diels–Alder reaction of 3-arylp pryrollo[2,1-c][1,4]benzoxazines with styrene. Synthesis of pyrano[4′,3′,2′,3]pyrrollo[2,1-c][1,4]benzoxazines. Russ. J. Org. Chem. 2017, 53, 1851–1856. [CrossRef]

22. Khramtsova, E.E.; Dmitriev, M.V.; Bormotov, N.I.; Serova, O.A.; Shishkina, L.N.; Masliyets, A.N. Alkaloid-like annulated pyrano[4,3-d]pyrroles: Antiviral activity and hydrolysis. Chem. Heterocycl. Compd. 2021, 57, 483–489. [CrossRef]

23. Khramtsova, E.E.; Lystsova, E.A.; Dmitriev, M.V.; Masliyets, A.N.; Jasiski, R. Reaction of Aroylpyrrolbenzothiazinetriones with Electron-Rich Dienophiles. ChemistrySelect 2021, 6, 6295–6301. [CrossRef]

24. Lystsova, E.A.; Khramtsova, E.E.; Masliyets, A.N. Acyl[imidoyl]ketenes: Reactive Bidentate Oxa/Aza-Dienes for Organic Synthesis. Symmetry 2021, 13, 1509. [CrossRef]

25. Kasatkina, S.; Stepanova, E.; Dmitriev, M.; Mokrushin, I.; Masliyets, A. Divergent synthesis of (quinoxalin-2-yl)-1,3-oxazines and pyrimido[1,6-a]quinoxalines via the cycloaddition reaction of acyl(quinoxaliny1)ketenes. Tetrahedron Lett. 2019, 60, 151088. [CrossRef]
26. Lane, T.K.; Nguyen, M.H.; D'Souza, B.R.; Spahn, N.A.; Louie, J. The Iron-Catalyzed Construction of 2-Aminopyrimidines from Alkynenitriles and Cyanamides. *Chem. Commun.* **2013**, *49*, 7735–7737. [CrossRef]

27. Spahn, N.A.; Nguyen, M.H.; Renner, J.; Lane, T.K.; Louie, J. Regioselective Iron-Catalyzed [2 + 2 + 2] Cycloaddition Reaction Forming 4,6-Disubstituted 2-Aminopyrimidines from Terminal Alkynes and Cyanamides. *J. Org. Chem.* **2017**, *82*, 234–242. [CrossRef]

28. Dubovtsev, A.Y.; Dar’in, D.V.; Kukushkin, V.Y. Three-Component [2 + 2 + 1] Gold(I)-Catalyzed Oxidative Generation of Fully Substituted 1,3-Oxazoles Involving Internal Alkynes. *Adv. Synth. Catal.* **2019**, *361*, 2926–2935. [CrossRef]

29. Dubovtsev, A.Y.; Shcherbakov, N.V.; Dar’in, D.V.; Kukushkin, V.Y. The Dichotomy of Gold-Catalyzed Interplay between Cyanamides and Ynamides: Controllable Switch from [2 + 2 + 2] to [4 + 2] Cycloaddition. *Adv. Synth. Catal.* **2020**, *362*, 2672–2682. [CrossRef]

30. Mashevskaya, I.V.; Mokrushin, I.G.; Maslivets, A.N. Five-Membered 2,3-Dioxoheterocycles: LXXIII. Synthesis and Thermolysis of 3-Aroyl- and 3-Heteroyl-5-phenyl-1,2,4,5-tetrahydropyrrolo[1,2-a]quinoxalin-1,2,4-triones. *Russ. J. Org. Chem.* **2005**, *41*, 1081–1088. [CrossRef]

31. Maslivets, A.N.; Mashevskaya, I.V.; Krasnykh, O.P.; Shurov, S.N.; Andreichikov, Y.S. Five-membered 2,3-dioxoheterocycles. XXXIII. Synthesis of 3-aroyl-1,2-dihydro-4H-pyrrolo[5,1-c][1,4]benzoazaine-1,2,4-triones and their reaction with water and alcohols. *Zhurn. Org. Khim.* **1992**, *28*, 2545–2553.