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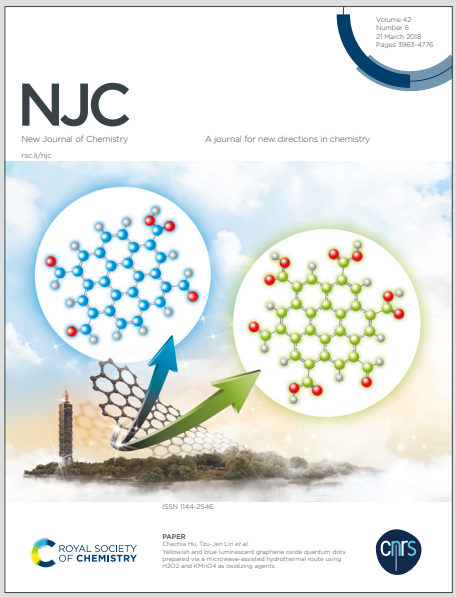

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Synthesis and Characterization of new Heterocycles related to Aryl[*e*][1,3]diazepinediones. Rearrangement to 2,4-Diamino-1,3,5-triazine Derivatives.

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ABSTRACT: Novel non-planar heterocycles make a great contribution to drug design and medicinal chemistry. Fused aryl[*e*][1,3]diazepinediones are a less investigated and appealing class of compounds. Herein, we designed 5 types of polynitrogen containing compounds based on 3-aminobenzo[*e*][1,3]diazepine-1,5-dione and undescribed 3-aminopyrido[3,4-*e*][1,3]diazepine-1,5-dione, 7-aminopyrido[2,3-*e*][1,3]diazepine-5,9-dione and 7-aminopyrazino[2,3-*e*][1,3]diazepine-5,9-dione. The synthesis, characterization, chemical properties, and X-ray structures are presented. Stability studies led to the identification of a novel rearrangement of 2-guanidino-benzo[*e*][1,3]diazepine-4,7-dione to 2,4-diamino-6-phenyl-1,3,5-triazines by hydrolytic ring-opening followed by cyclocondensation. This reactivity has been used to efficiently access, after optimization, an "activated" 2,2,2-trifluoroester, which was successively transformed into variously functionalized derivatives by hydrolysis, transesterification or amide formation. These latter structures present high potential as precursors of drug-like molecules.

Introduction

The fused aryl[*e*][1,3]diazepinediones are an original heterocyclic scaffold. It shows attractivestructural features with a favorable balance between size, rigidity, and number of potential H-bonding sites. Moreover, related fused aryldiazepine derivatives are present in well-known drugs, as demonstrated by the successful family of benzo[1,4] diazepin(on)es that efficiently inhibit GABA receptors in the central nervous system,[1] and were proposed recently for other biomedical applications.[2] 5-Member-ring fused diazepinediones are mainly represented by imidazole-fused or 1,2,3-triazole-fused structures used as purine extended analogs. Among these compounds, some molecules show interesting inhibition of several viruses by targeting NTPase and helicase enzymes, while other derivatives exert modest cytotoxic effects against certain cancer cell lines.[3–7] On the other hand, to the best of our knowledge, there are almost no reports of 6-member-ring fused diazepinediones, which are basically restricted to only two examples.[8,9] Furthermore, the pyridine- and pyrazine-fused 1,3-diazepinedione scaffolds are unknown from the literature yet (**Figure 1**).

Recently, biguanide derivatives have received increasing attention because of their potent pharmacological properties in line with metformin and its analogs, which have many clinical applications in metabolic and cancer diseases.[10] Therefore, combining both features, biguanide and benzodiazepinedione cores (molecules of type C, **Figure 2**), is highly appealing to consider hybrid/dual molecules.

Herein, we present several original classes of molecules based on 3-amino-benzo[*e*][1,3]diazepine-1,5-dione**1**, and we report the syntheses of three new heterocycles, namely 7-amino-pyrido[2,3-*e*][1,3]diazepine-5,9-dione **2**, 3-amino-pyrido[3,4-*e*][1,3]diazepine-1,5-dione **3**, 2-amino-pyrido[3,4-e][1,3]diazepine-4,7-dione and 7-amino-pyrazino[2,3-*e*][1,3]diazepine-5,9-dione **4**, as well as analogs thereof. In total, 28 new derivatives have been prepared and fully characterized (**Figure 2**). The structural properties, solubility and stability profiles and X-ray crystal structures of representative compounds were studied. In addition, a rearrangement by cyclocondensation of bisamidine derivatives toward phenyltriazines was remarkably observed, which was then extended through several representative examples.

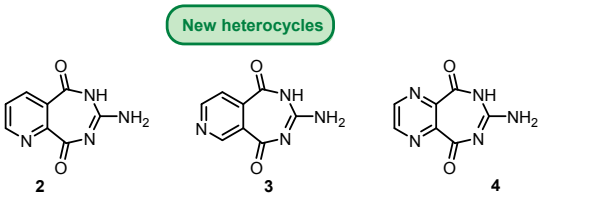

Figure 1. New heterocycles based on fused aryl[*e*][1,3]diazepinediones.

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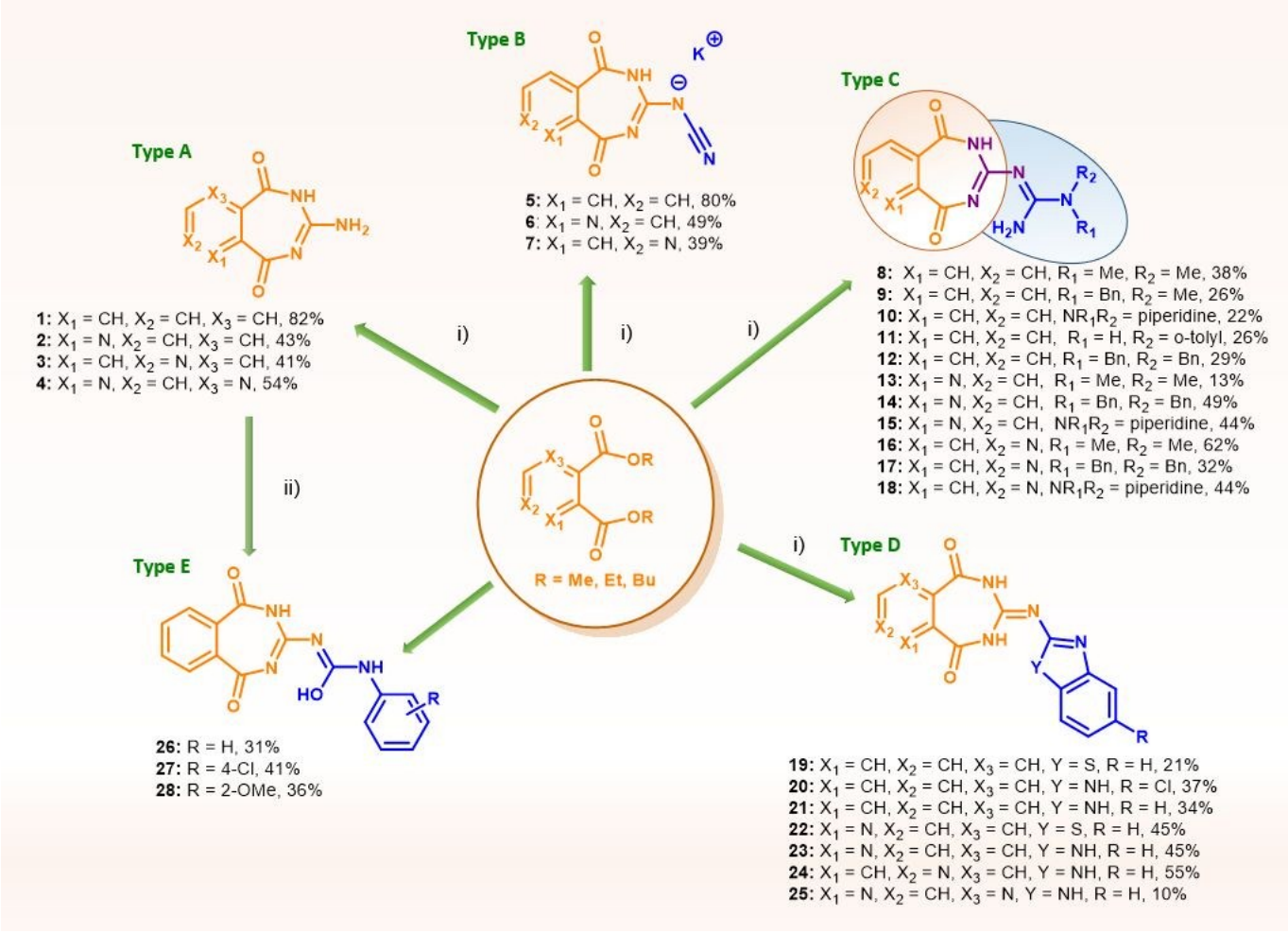

Figure 2. Synthesis of the aryl[*e*][1,3]diazepinedione analogs. Conditions: i) guanidine derivative (1 eq.), *tert*-BuOK (3eq.), DMF, 0°C to r.t., 2h-24h; ii) Arylisocyanate (1eq.), DMF, 0°C to r.t., 24-48h.

As shown in **Figure 2**, five types of structures based on the four different heterocycles were prepared. They encompass an amino group in position 3 (Type A), a cyanamide (Type B), a guanidine (Type C), an aminobenzazole moiety (Type D) or an arylurea (Type E). All compounds were synthesized from the reaction between phthalic diesters (or their pyrido-/pyrazo-analogs) and guanidine derivatives (guanidine, cyanoguanidine, biguanides, heteroarylguanidines).

Results and discussion

A survey of the reaction conditions proved that the optimal method to produce heterocycles **1-4** is a double ester condensation in the presence of the guanidine derivative, deprotonated beforehand by a strong base (*t*-BuOK, DMF, r.t.). Neither Brønsted acid activation (AcOH, H_2SO_4), nor non-deprotonative basic conditions (DBU) or higher temperatures could afford satisfactory conversion. The counter cation was also found to have a significant effect since the guanidine sodium salt gave a lower yield than the potassium salt under the same reaction conditions (60% *vs.* 82% for compound **1**). Compounds from Type A-B-C-D were obtained after careful neutralization and recrystallization in good yields (see general procedures). Type E derivatives were prepared from the already formed heterocycle **1**, by reaction with arylisocyanates.

The heterocycles **1**-**4** (Type A) were isolated as crystalline powders, poorly soluble in water with slow decomposition, but

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easily dissolved in 1 M aqueous NaOH, which might indicate a pKa < 14.

The cyanamide derivatives **5**-**7** (Type B) were synthesized in a similar way from cyanoguanidine in moderate to good yields. Surprisingly, the neutralization of the reaction media at pH 5 resulted only in isolation products in the form of potassium salt. This suggests a high acidity of the proton on the conjugated cyanoamine group. The presence of the cyanoamine group was attested by a typical strong band at 2180 cm^{-1} by IR analysis and the potassium was dosed by atomic absorption spectrometry. Consequently, these compounds evince high solubility in water (~1 g/L), but are easily decomposed in 1 M aqueous NaOH, diluted aqueous NH_3 or 1 M aqueous HCl solutions.

Table 1. Aqueous solubility and solubility in DMF of synthesized aryl[*e*][1,3]diazepinedione analogs of Type A-B-C-D-E

Compound	Aqueous solubility	Solubility in DMF
Type A	-	+
Type B	+	++
Type C	+[a]	++
Type D	-	+
Type E	-	++

[a] except for compounds **9**, **12**, **14** and **17**: solubility: **+/-**.

The guanidine derivatives **8**-**18** (Type C) were synthesized following the same protocol (*t*-BuOK/DMF) from biguanide reagents. These biguanide intermediates were prepared by reaction of amines with cyanoguanidine under TMSCl/THF conditions adapted from the literature,[11] except for *N,N*-dimethylbiguanide hydrochloride and *o*-tolylbiguanide that were commercially available. In all cases, the addition proved selective to the nitrogen atom in δ position of the substituted nitrogen, leading to the compounds displayed in **Figure 2** with substitutions in terminal position of the guanidine.

Then, we tested the addition of substituted guanidines to produce *N*-benzazoyl derivatives **19**-**25** (Type D). The guanidinobenzazole intermediates were prepared according to adapted described procedures.[12,13] Attempts to produce the benzoxazole derivatives failed because of hydrolytic ring-opening upon work-up.

Derivatives from Type E were synthesized by substitution of the already formed aryl[*e*][1,3]diazepinedione compound **1** with phenylisocyanates at room temperature in DMF. The selective addition of the isocyanates to the exocyclic nitrogen of **1**, followed by prototropy, delivered urea compounds **26**-**28** in moderate yields, after extended reaction time (24-48 h).

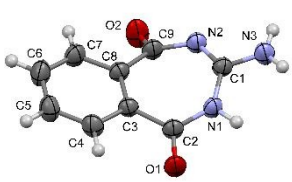
The moderate yields obtained with some compounds are mainly due to the isolation and purification protocols by recrystallization, which could be optimized for each compound. The polarity of the synthesized compounds (as spotted by the retention times of the monoprotonated forms in HPLC) proved as follows: A ≈ B > C > D > E and the solubility properties of these compounds are summarized in **Table 1**.

Concerning the stability of this core, these aryl[*e*][1,3]aryldiazepinediones proved to be generally highly stable in aprotic solvents. However, in acidic water (pH = 1) or alcohols, a slow ring-opening occurred, leading to the corresponding guanidine-ester or guanidine-acid derivatives. Under these conditions, the relative stability was as follows: Type B > C > D ≈ A. For a defined Type, the aryl[*e*][1,3]benzodiazepinediones also proved somewhat more stable than the corresponding pyridine or pyrazine derivatives. The thermal stability also proved to be high, so that some compounds could be obtained after recrystallization in hot DMF (100°C), and all of them present high melting points above 180°C.

To further investigate the properties of these heterocycles, the crystal structures of compounds **1**, **8**, **10** and **14** were resolved. The position of all hydrogen atoms was determined following the interatomic distances corresponding to the atoms hybridization. The X-ray molecular structures, depicted in **Figure 3**, revealed first the non-planarity of the diazepinedione core. The dihedral angle between the aryl ring of aryl[*e*][1,3]diazepinedione and the guanidine fragment including atoms N(1), N(2), N(3) and C(1) was determined to be 34.8°-38.9° (**Figure 3b**).

In addition, an intramolecular hydrogen bond

a



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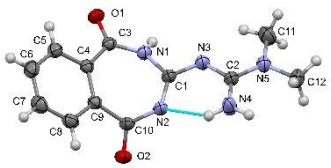

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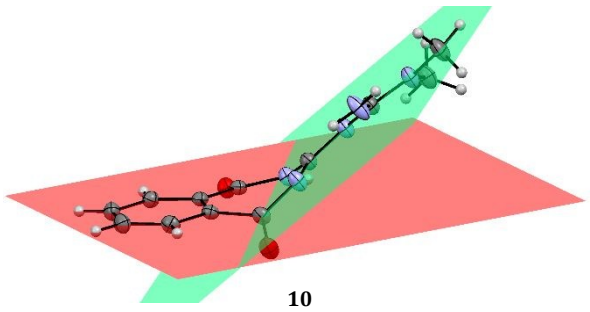
b



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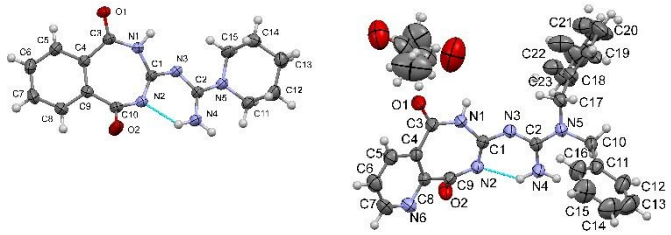

10 **14**

c

#	Contact D–H···A	Distances, Å			Angle D–H···A, deg
		D–H	H···A	D···A	
8	N(4)–H4B···N(2)	0.860	2.075	2.676(2)	126.4
10	N(4)–H4A···N(2)	0.914	1.962	2.682(2)	134.3
14	N(4)–H4B···N(2)	0.952	1.994	2.704(3)	129.8

Figure 3. a) X-ray structures of compounds **1**, **8**, **10** and **14**. The crystals of compound **12** display organic solvent molecules (CH_3COCH_3) in the unit cell. Compounds **8**, **10** and **12**, are connected by intermolecular bonding between O(1)···H–N(1)–H···O(1) and O(2)···H–N(4) – H···O(2).. Compound **1** presents O(1)···H–N(3)–H··· O(1) and O(2)···H–N(3)–H···O(2) bonds. b) Bis-planar organization of the structure with representative compound **8**. c) Geometric characteristics of intramolecular hydrogen bonds.

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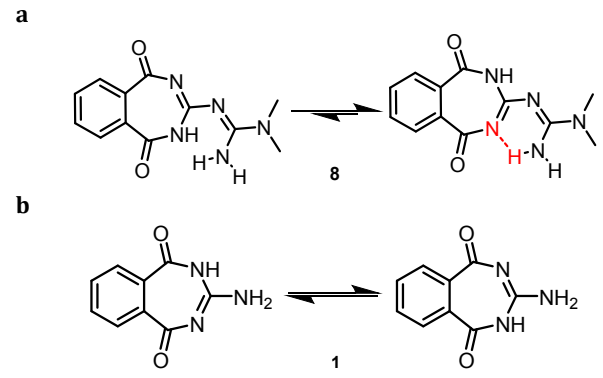

c

Compound	d(N(1)-C(1)), Å	d(N(2)-C(1), Å	d(N(3)-C(1), Å
1	1.387(2)	1.313(2)	1.320(2)
8	1.400(2)	1.314(2)	1.334(2)
10	1.406(2)	1.311(2)	1.330(2)
14	1.399(3)	1.311(2)	1.333(3)

Figure 4. Structure and tautomers in solution: a). Compound **8** offers an intramolecular H-bonding possibility that congeals the equilibrium toward one tautomer and breaks the symmetry of the molecule b). Compound **1** is in permanent equilibrium between two tautomers and displays symmetric signals in ^{1}H NMR. c). C-N bond lengths of the guanidine within compounds **1**, **8**, **10** and **14** in crystal solid state.

N(4) –H···N(2) is observed for **8**, **10** and **14 (Figure 3c)**. This interaction, stabilizing one tautomer form, could explain the asymmetric shifts observed in the ^{1}H NMR spectra for the benzene ring: 8.03 – 7.87 (m, 1H) and 7.81 – 7.57 (m, 3H) **(Figure 4a)**. On the contrary, compound **1**, devoid of intramolecular bond possibility, presents in solution an equilibrium between two tautomer forms and shows symmetric signals for the benzene ring: 7.85 (br s, 2H) and 7.70 (dd, *J* = 5.6, 3.4 Hz, 2H) **(Figure 4b)**. The respective C-N bond lengths of the guanidine group display smaller relative difference for compound **1**, than for **8**, **10** and **14 (Figure 4c)**. This supports a higher delocalization within the guanidine for compound **1**, despite undeniable different behaviors between crystal solid state and solution. The diazepinedione moiety always presented two C=O bonds, correlating with ^{13}C NMR shifts for all compounds in the range of 175-165 ppm (to be compared to the shifts for the N=C–OH tautomer described around 158 ppm in the literature). [14]

Investigating the chemical stability of the guanidine derivatives of Type C, we identified surprising side-products. First, we demonstrated that compound **8** degrades in acidic water at pH = 1 by hydrolysis, with ring-opening of the diazepinedione to the corresponding carboxylic acid **29** (**Figure 5**). Then, after leaving this hydrolyzed product for several days, we progressively observed the formation of the 1,3,5-triazine **30**. This compound could originate from a cyclocondensation of the biguanide onto the carbonyl.

We deduced from this observation that the addition of alcohol nucleophiles could result in the formation of the related triazine-esters. A screening of conditions identified 2,2,2-trifluoroethanol (TFE) as a good reactant to proceed to this

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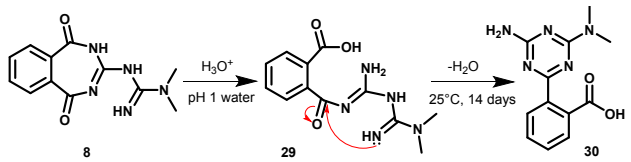

Figure 5. Degradation pathway of compound **8** in acidic water. After 1 day, almost full hydrolysis to acid **29** is observed. Then slow cyclocondensation to triazine **30** occurred (25% conversion after 14 days

rearrangement, and optimized conditions delivered the desired triazine-trifluoroester **31** under mild conditions (25°C, 24h) with excellent 97% yield. Then, we took advantage of the lability of 2,2,2-trifluoroesters to use this molecule as a versatile precursor to produce analogs: the corresponding acid **30** by hydrolysis, the esters **32** and **33** by transesterification, or the amides **34-37** by amide condensation (**Figure 6**). These reactions proceeded cleanly with a full conversion. From those compounds, only the acid **30** was known, prepared conventionally(condensation of biguanide and *ortho*-ester).[15]

Therefore, this sequence opens access to a variety of original "drug-like" compounds with two derivatization sites, by modulating of the biguanide substitution pattern and by substitution of the trifluoroester with different nucleophiles. Here, we provide an exemplification with alcohols; and primary or secondary, aromatic or aliphatic amines, eventually bearing additional functionalization like **35**.

Conclusions

In conclusion, we described the synthesis and characterization of 5 types of original polynitrogen-containing compounds, based on 4 different aryl[*e*][1,3]diazepinedione cores. Three of them, the pyrido- and pyrazino- derivatives constitute unprecedented heterocycles. The chemical properties, X-ray structures of 4 derivatives were studied, and the investigation of their stability led to the of an original rearrangement to 1,3,5-triazine compounds. The

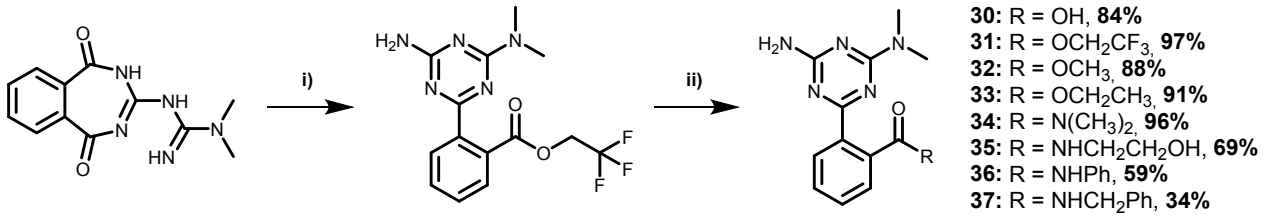

Figure 6. Synthesis of 2,2,2-trifluoroester rearranged product 31 and derivatization to analogs 30 and 32-37 by the introduction of various nucleophiles. Conditions: i) 2,2,2-trifluoroethanol, 25°C, 24h. ii) alcohol or water, reflux, 15h; or amine (3 eq), dioxane, reflux, 15h.

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optimization of this last transformation has been used to create a versatile "activated" 2,2,2-trifluoroester which can be derivatized into various functionalized 1,3,5-triazine-based bis-aryl products. In total, 36 new drug-like heterocyclic structures have been prepared, useful as derivatization platforms towards biologically active molecules, *e.g.* antimetabolic or anticancer drugs.

Acknowledgments

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Divergence-oriented synthesis of new heterocycles relevant for medicinal chemistry