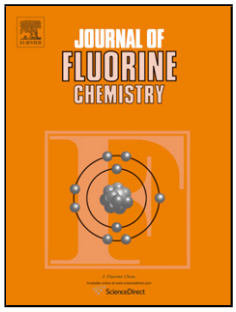


Title: Carbocyclic functionalization of quinoxalines, their chalcogen congeners 2,1,3-benzothia/selenadiazoles, and related 1,2-diaminobenzenes based on nucleophilic substitution of fluorine

Author: Tatiana F. Mikhailovskaya Arkady G. Makarov Natalia Yu. Selikhova Alexander Yu. Makarov Elena A. Pritchina Irina Yu. Bagryanskaya Elena V. Vorontsova Igor D. Ivanov Vera D. Tikhova Nina P. Gritsan Yuri G. Slizhov Andrey V. Zibarev

PII: S0022-1139(16)30009-4
DOI: http://dx.doi.org/doi:10.1016/j.jfluchem.2016.01.009
Reference: FLUOR 8718

To appear in: *FLUOR*

Received date: 23-10-2015
Revised date: 20-1-2016
Accepted date: 20-1-2016

Please cite this article as: Tatiana F.Mikhailovskaya, Arkady G.Makarov, Natalia Yu.Selikhova, Alexander Yu.Makarov, Elena A.Pritchina, Irina Yu.Bagryanskaya, Elena V.Vorontsova, Igor D.Ivanov, Vera D.Tikhova, Nina P.Gritsan, Yuri G.Slizhov, Andrey V.Zibarev, Carbocyclic functionalization of quinoxalines, their chalcogen congeners 2,1,3-benzothia/selenadiazoles, and related 1,2-diaminobenzenes based on nucleophilic substitution of fluorine, Journal of Fluorine Chemistry http://dx.doi.org/10.1016/j.jfluchem.2016.01.009

Carbocyclic functionalization of quinoxalines, their chalcogen congeners 2,1,3-benzothia/selenadiazoles, and related 1,2-diaminobenzenes based on nucleophilic substitution of fluorine†

Tatiana F. Mikhailovskaya[a], Arkady G. Makarov[a,b,c], Natalia Yu. Selikhova[b], Alexander Yu. Makarov[a,b], Elena A. Pritchina[c,d], Irina Yu. Bagryanskaya[a,c], Elena V. Vorontsova[e], Igor D. Ivanov[e], Vera D. Tikhova[a], Nina P. Gritsan[d,f], Yuri G. Slizhov[b,**], Andrey V. Zibarev[a,b,f,*]

[a] *Institute of Organic Chemistry, Russian Academy of Sciences, 630090 Novosibirsk, Russia*

[b] *Department of Chemistry, Tomsk State University, 634050 Tomsk, Russia*

[c] *Department of Natural Sciences, Novosibirsk State University, 630090 Novosibirsk, Russia*

[d] *Institute of Chemical Kinetics and Combustion, Russian Academy of Sciences, 630090 Novosibirsk, Russia*

[e] *Institute of Molecular Biology and Biophysics, Russian Academy of Sciences, 630117 Novosibirsk, Russia*

[f] *Department of Physics, Novosibirsk State University, 630090 Novosibirsk, Russia*

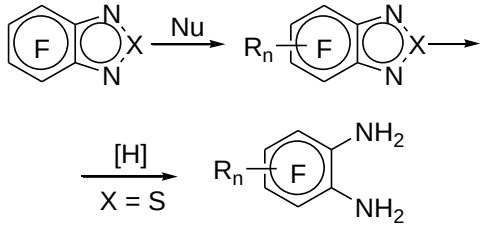
* Corresponding author at: Institute of Organic Chemistry, Russian Academy of Sciences, 630090 Novosibirsk, Russia. Fax: +7 383 330 9752.

** Corresponding author at: Department of Chemistry, Tomsk State University, 634050 Tomsk, Russia. Fax: +7 3822 423 944.

E-mail addresses: zibarev@nioch.nsc.ru (A.V. Zibarev), decan@xf.tsu.ru (Yu.G. Slizhov).

† This work was performed under Agreement no. 79/12 between Institute of Organic Chemistry, Russian Academy of Sciences, Novosibirsk, and Tomsk State University, Tomsk, and within Joint Laboratory of the University and the Academy. The authors declare no competing financial interest.

Graphical abstract



X = CH=CH, S, Se; Nu = MeO^-, Me_2NH; R = MeO, Me_2N; n = 1-4

Highlights

- The title compounds were functionalized by nucleophilic substitution of 1-4 F atoms
- The functions were MeO- or / and Me_2N-
- Regioselectivity of the 1 : 1 substitution was explained with DFT calculations
- Functionalized 2,1,3-benzothiadiazoles were reduced into 1,2-diaminobenzenes

ABSTRACT

Previously unknown mono-, di- and in some cases tri- and tetra- carbocycle-substituted quinoxalines (**2**-**8**), 2,1,3-benzothiadiazoles (**11**, **12**, **14**-**17**) and 2,1,3-benzoselenadiazoles (**20**-**25**) were synthesized by nucleophilic substitution of fluorine in 5,6,7,8-tetrafluoroquinoxaline (**1**) and 4,5,6,7-tetrafluoro-2,1,3-benzothia/selenadiazoles (**10** and **19**, respectively) with methoxide and dimethylamine. In the 1 : 1 reactions, the nucleophiles attacked selectively the position 6 of **1** or the position 5 of **10** and **19**. The regioselective nature of the 1 : 1 reactions was confirmed by the DFT calculations at the M06-2X/6-31+G(d,p) level of theory. Disubstituted quinoxaline (**28**), thia- (**29**) and selena- (**30**) diazoles bearing two different substituents, *i.e.* MeO- and Me_2N-, were synthesized in a similar way. New substituted 1,2-diaminobenzenes (**31**-**33**) were prepared by reduction of corresponding thiadiazoles (**12**, **14**, **15**) and isolated in the form of hydrochlorides. Compound **33** was converted into a new quinoxaline (**34**) by reaction with $(PhCO)_2$. Compounds **5**, **7** and **14** were studied for cytotoxicity towards the human cancer cells and effects on the cytochrome P450 mRNA expression. They did not cause any significant modulations in the expression of several cytochrome P450 genes, and **7** was weakly toxic for the Hep2 (carcinoma) and U937 (leukemia) cells, particularly, apoptosis was observed.

Keywords: 1,2-diaminobenzenes, nucleophilic substitution, organofluorine, quinoxalines, 2,1,3-benzothia/selenadiazoles

1. Introduction

Organic heterocyclic compounds, both natural and synthetic, are of permanent interest to fundamental and applied biomedicine.[1,2] Amongst them, aromatic and heteroaromatic derivatives are especially important. *In silico* examination of virtual library of ~600 000 of mono-, bi- and tri-cyclic heteroaromatic scaffolds based on *current knowledge* revealed that bioactivity is very sparsely distributed and forms only several relatively small, well-defined islands around ~25 common 5- and 6-membered mono-cyclic and 5-6- and 6-6-membered bi-cyclic systems with N and / or O atoms.[2] A continued exploration of novel substituted bicyclic aromatic scaffolds is hence guaranteed to yield new molecules of biological interest.

Functional derivatives of quinoxaline and its S and Se congeners, *i.e.* 2,1,3-benzothia/selenadiazoles, are important for fundamental organic chemistry and its applications to biomedicine (and also to materials science; relevant literature is too abundant to be cited completely, for selected works see refs. 3 and 4 and references cited therein). Despite chemistry of these substances is well-studied,[5,6] there is a permanent demand for new methods of their synthesis. In the field, most of recently suggested methods deal with hetero-ring formation[6,7] whereas those based on functionalization of the easily accessible parent compounds are also of interest. One of efficient ways of functionalizing (hetero) arenes is nucleophilic substitution, especially that of fluorine in (poly)fluorinated derivatives including regioselective substitution.[8-11] At the same time smooth nucleophilic substitution of fluorine in some heteroarenes such as the title quinoxalines and 2,1,3-benzothia/selenadiazoles is not *a priori* guaranteed in a general case since nucleophilic addition to the hetero-ring of quinoxalines including that leading to ring-contraction to give benzimidazoles,[12] as well as nucleophilic cleavage of 1,2,5-chalcogenadiazole cycle,[13] are known.

In this paper we report on a functionalization of quinoxalines and 2,1,3-benzothia/selenadiazoles using nucleophilic substitution of fluorine in tetrafluoro derivatives of the archetypal compounds (**1**, **10**, **19**; Chart 1). The approach also covers 1,2-diaminobenzenes since 2,1,3-benzothia/selenadiazoles are their well-known protected forms and can be easily reduced into the diamines.[14] The latter are suitable starting materials for numerous further preparations. Examples given in this paper (compounds **2**-**8**, **11**, **12**, **14**-**17**, **20**-**25**, **28**-**34**, Chart 1) cover substitution with MeO- and Me_2N- functions only but the approach can potentially be expanded onto many other substituents including pharmacophore ones.

It should be emphasized that in many cases hydrogen substitution by fluorine (mostly in aliphatic moieties but also in aromatic ones) produces positive impact on ADME-toxicity of

compounds (in pharmacokinetics, ADME: absorption, distribution, metabolism and excretion), and in some cases on their bioactivity, making low-fluorinated (and normally not high-fluorinated; see, however, ref. 15) pharmaceuticals and agrochemicals to be of keen interest.[16] Nowadays, fluorinated compounds are used increasingly in medicinal chemistry. Suggested approach based on high-fluorinated starting materials allows synthesizing low-fluorinated and variously functionalized final products.

Importantly, current interest to bioactivity of organochalcogen compounds is also growing.[17]

Three of compounds synthesized, one low-fluorinated and two other non-fluorinated, were tested for cytotoxicity and effects on the mRNA expression in a preliminary work before further in-depths investigation.

2. Results and discussion

Earlier, we described synthesis of compounds **1**, **10** and **19** by reactions of corresponding 1,2-diaminobenzene with glyoxal, SF_4 or $(C_6H_5\text{-}SO_2\text{-}N=)_2S$, and $SeCl_4$ or SeO_2, respectively, and that of **10** also by the intramolecular nucleophilic *ortho*-cyclization of $C_6F_5\text{-}N=S=N\text{-}SiMe_3$ under the action of CsF.[4,18] In this work, a new synthetic protocol for **10** was elaborated to be based on interaction of the same 1,2-diamine with $SOCl_2$ proceeding via N,N'-disulfinyl derivative[19] (Scheme 1).

Previously, it was found that attack on 2,3,5,6,7,8-hexafluoroquinoxaline by methoxide occurs readily at the positions 2 and 3 and, under forcing conditions, also at the position 6.[10] Treatment of **1** with NaOMe in MeOH or its mixture with Me_2SO; or with aqueous Me_2NH in dioxane, DMF or N-methyl-2-pyrrolidone, gave previously unknown mono-, di-, tri- and tetra-substituted derivatives of **1** (**2**-**8**, Scheme 2). Attempts to prepare compound **9** were unsuccessful even under rather drastic reaction conditions. A minor amount of **9** was detected by GC-MS in the reaction mixtures in preparation of **8** but was not isolated by silica-column chromatography probably due to decomposition during work-up.

Similar treatment of **10** and **19** afforded earlier undescribed mono-, di-, tri- and tetra-substituted derivatives of **10** (**11**-**17**, Scheme 3) and **19** (**20**-**25**, Scheme 4), respectively. In preparation of **6**-**8**, **17**, **24** and **25**, formation of their minor isomers was observed by ^{1}H and ^{19}F NMR and GC-MS (see below) but they were not isolated. In experiments on preparation of **13** and **22**, co-crystals **12** / **13**, and **22** / **21** and **21** / **23**, respectively, were obtained, in the first case as major product and in the second as minor admixtures. Compound **13** was not isolated from the co-crystal thus being observed in this work only in the form of **12** / **13**. Attempted syntheses of **18**, **26** and **27** were unsuccessful even under relatively drastic reaction conditions.

Overall with NaOMe, for all scaffolds **1**, **10** and **19** tetra-substitution of fluorine was achieved (compounds **5**, **14** and **23**). With Me_2NH, however, tetra-substituted derivatives **9**, **18** and **27** were not obtained in all three cases, as well as tri-substituted derivative **26** in the selenadiazole series. Dimethylamide Me_2N^- is a stronger nucleophile but, as mentioned above, anions Alk_2N^- as some other charged nucleophiles are known to open the 1,2,5-chalcogenadiazole ring[13] and interact with ether solvents at higher temperatures. Attempt to obtain compound **26** from compound **19** and $LiNMe_2$ generated in situ in DME led to a mixture of compounds **20** and **24** in molar ratio 1.5 : 1 (GC-MS, NMR ^{19}F), respectively, together with unreacted **19**.

According to ^{1}H and ^{19}F NMR and GC-MS of the reaction mixtures, in all 1 : 1 reactions both MeO^- and Me_2NH attacked selectively the position 6 of **1** or the position 5 of **10** and **19**. For these reactions, the regioselectivity was higher with MeO^- than with Me_2NH, and with quinoxaline **1** and selenadiazole **19** than with thiadiazole **10**. Thus, in the 1 : 1 reactions between Me_2NH and **1**, **10** and **19** minor (~3 % for **1** and **19**, and ~10 % for **10**) isomers of the major products **6**, **15** and **24** were identified.[20] In the corresponding 2 : 1 reaction total amount of minor isomers of **7** and **25** reached ~10 % but their identification was complicated since, for example, for compound **25** three minor isomers were observed. In the 3 : 1 reaction between Me_2NH and **10**, an isomer[20] of compound **17** was observed in the reaction mixture at practically the same abundance but, however, was isolated only in the form of non-crystallizable contaminated oil contained 80 % of the target derivative (GC-MS, NMR ^{1}H and ^{19}F).

M06-2X/6-31+G(d,p) calculations performed with account for solvents confirmed regioselective character of the mono-substitution reactions (Figure 1, Table 1; ESI, Tables S2-S4; for generality, the calculations were also carried out for Me_2N^-). Figure 1 demonstrates that the substitution in the position 6 of **1** (leading to compound **2**) is both kinetically and

thermodynamically more attractive than that in the position 5. Slight thermodynamic destabilization of 5-MeO isomer of **2** may be caused by the in-plane interaction between lone-pair MOs of neighboring atoms O and N. Similar results were obtained for compounds **10** and **19** (Table 1), namely, substitution at position 5 for them is preferable. Overall, the major / minor isomer ratio in the 1 : 1 reaction with MeO^- was predicted to be 99 / 1 in the case of **1**, 82 / 18 in the case of **10**, and 94 / 6 in the case of **19**. For compounds **1**, **10** and **19**, the free energies of activation at the rate determining step of the reaction main route are within 0.7 kcal·mol^{-1}. This is in agreement with comparable yields of products in their mono-substitution reaction with MeONa in MeOH at ambient-temperature revealed by competitive experiment[21] although experimental relative activities **1** > **19** > **10** contradict with theoretical prediction (Table 1). This is quite understandable due to the small energy differences under discussion.

It should be noted that the regioselectivity of the discussed 1 : 1 reactions corresponds to phenomenological rules for orientation of aromatic nucleophilic substitution in polyfluorinated (hetero) arenes formulated by R.D. Chambers e. a. (for review, see ref. 11).

New disubstituted quinoxaline (**28**) and 2,1,3-benzothia/selenadiazoles (**29**, **30**; respectively) bearing two different substituents, *i.e.* MeO- and Me_2N-, were synthesized in a similar way via two-step procedure (Scheme 5). The structure of final products did not depend on the order of substitution.

New substituted 1,2-diaminobenzenes (**31**-**33**, Scheme 6) were synthesized by reduction of corresponding thiadiazoles (**12**, **14**, **15**, Scheme 4). All diamines revealed high activity towards oxidation and were isolated in the form of hydrochlorides. In the case of **33** even the hydrochloride was highly unstable in the air and the compound was converted into derivative **34** (75 %) by reaction with 1,2-diphenylethane-1,2-dione (Scheme 7).

Structures of compounds **4**, **7** (two polymorphs), **8**, **11**, **12**, **14**, **15**, **17**, **19** (racemic twin), **21**, **25**, and co-crystals **12** / **13**, **22** / **21** and **21** / **23** (Figure 2, Table 2; ESI, Figure S1) were characterized by single-crystal XRD (ESI, Table S5). Two polymorphs of compound **6** were identified by powder XRD (ESI, Figure S2).

Overall, substitution in the carbocycles of **1**, **10** and **19** with MeO- and Me_2N-groups does practically not affect geometries of their hetero-rings. At the same time, propensity of Me_2N-substituted quinoxalines **6** and **7** to form polymorphs was observed, as well as that of MeO-substituted thia/selenadiazoles to form co-crystals (S: **12** / **13**; Se: **22** / **21**, **21** / **23**). Together with the aforementioned lack of absolute regioselectivity of substitution (*i.e.* observation of minor isomers in some cases), the propensity to form co-crystals reduces *isolated* yields of the target products.

Compound **5**, **7** and **14** were studied for cytotoxicity towards the human cancer cells HepG2 (hepatocarcinoma), Hep2 (carcinoma) and U937 (leukemia) as well as effects on the mRNA expression. Fluorine-less compounds **5** and **14** did not affect cellular viability whereas fluoro-containing derivative **7** was weakly toxic for both the Hep2 and U937. It was found that **7** inhibits Hep2 and U937 cells at concentration of 125 μM. Therefore, cytotoxicity of **7** towards Hep2 cells was examined through the induction of apoptosis (50%). U937 cells were more sensitive to **7**. With this compound, the growth of treated cells (625 μM) was reduced by 98% compared to untreated cells (Figure 3; ESI, Figures S3-S5 and relevant text). At the same time, compounds **5**, **7** and **14** did not cause any significant modulations in the expression of several cytochrome P450 genes, *i.e.* they are not xenobiotics (ESI, Figures S3-S5 and relevant text). These studies will be continued.

3. Conclusions

This work contributes to attracted much current attention applications of organofluorine chemistry into heterocyclic chemistry.[22] The approach was developed allowing with such reagents as MeO^- and Me_2NH synthesis of new and hardly accessible by other methods mono-, di- and, with some exceptions, tri- and tetra- carbocycle-substituted quinoxalines (**2**-**8**), 2,1,3-benzothiadiazoles (**11**, **12**, **14**-**17**) and 2,1,3-benzoselenadiazoles (**20**-**25**) based on nucleophilic substitution of fluorine in 5,6,7,8-tetrafluoroquinoxaline (**1**) and 4,5,6,7-tetrafluoro-2,1,3-benzothia/selenadiazoles (**10** and **19**, respectively). Previously unknown disubstituted quinoxaline (**28**), thia- (**29**) and selena- (**30**) diazoles bearing two different substituents were synthesized in a similar way. New substituted 1,2-diaminobenzenes (**31**-**33**) were prepared by reduction of corresponding thiadiazoles (**12**, **14**, **15**). These compounds may be used in

numerous further preparations. As an example, diamine **33** was converted into quinoxaline **34** by reaction with 1,2-diphenylethane-1,2-dione.

At the same time, full substitution of fluorine was not achieved in some cases with neutral nucleophile Me_2NH even under rather drastic reaction conditions. One may think that activation of C-F bonds with metal complexes[23] might be useful in this context in the further work.

It should be emphasized that the starting material in the synthesis of initial compounds **1**, **10** and **19** was C_6F_5-NH_2 subsequently functionalized into C_6F_5-N=S=O and C_6F_5-N=S=N-$SiMe_3$.[4,18] The nucleophilic substitution of fluorine in polyfluorinated (hetero) aromatics was then used for CsF-induced cyclization of C_6F_5-N=S=N-$SiMe_3$ into thiadiazole **10** reduced further into corresponding diamine followed by cyclization of the latter into quinoxaline **1** with glyoxal and into selenadiazole **19** with $SeCl_4$ or SeO_2.[4,18] This work reveals that the nucleophilic substitution of fluorine, being the key step in the synthesis of the key compound of the methodology under discussion, *i.e.* **10**, can be exploited further until tetra-substituted, *i.e.* fluorine-less, derivatives **5**, **14**, **23**, and **31** are obtained. Suggested methodology of using C_6F_5-NH_2 as starting material for synthesis of various polyfunctionalized derivatives, including fluorine-less ones, via nucleophilic substitution can potentially be extended onto many other nucleophiles bearing, particularly, pharmacophore groups. This will be direction of our further research in the field.

Compounds **5**, **7** and **14** were tested for cytotoxicity towards the human cancer cells and effects on the mRNA expression. They were found to be low toxic. In addition **7** was found to promote apoptosis without any significant modulation of cytochrome P450 expression. Further studies of the biological activity of these compounds are under way.

4. Experimental

4.1. General

NMR spectra were measured with Bruker AV-300 (^{1}H, 300 MHz; ^{19}F, 282.4 MHz), Bruker DRX-500 (^{13}C, 125.76 MHz) and Bruker AV-600 (^{1}H, 600.1 MHz; ^{77}Se, 114.5 MHz) spectrometers for solutions in $CDCl_3$ unless otherwise indicated. The standards were TMS (^{1}H, ^{13}C), $CFCl_3$ (^{19}F) and Me_2Se (^{77}Se).

High-resolution mass-spectra (EI, 70 eV) were taken with a Thermo Electron Corporation DFS mass-spectrometer. Gas-chromatography – mass-spectrometry (GC-MS) experiments were performed with Hewlett-Packard G1800A instrument.

UV-Vis and fluorescent (FL) spectra were collected with Varian Cary 5000 and Varian Cary Eclipse spectrophotometers, respectively, for heptane solutions unless otherwise indicated.

Elemental analyses for C, H, N and S were performed with Carlo Erba Model 1106 instrument. Analyses for F were carried out by standard spectrophotometric method with La complex of alizarin complexone, analyses for Se by spectrophotometric method described in ref. 24, and those for O by classical Schutze-Unterzaucher method with Eurovector Model 1028 analyzer.

Starting materials **1**, **10** and **19** were synthesized as described earlier,[4,18] and **10** also by a new approach suggested in this work. In the preparations described below, reaction solutions were stirred, solvents distilled off under reduced pressure and sublimations performed in vacuo.

Tables 3-5 contain physical, analytical and NMR data of the compounds synthesized.

4.2. X-ray diffraction

Single-crystal XRD data (ESI, Table S5) were collected on a Bruker Kappa Apex II CCD diffractometer using φ,ω-scans of narrow (0.5°) frames with Mo Kα (λ = 0.71073 Å) radiation with a graphite monochromator. The structures were solved by direct methods and refined by full-matrix least-squares method against all F^2 in anisotropic approximation using the *SHELX-97* programs set.[25] The H atoms positions were calculated with the riding model. Absorption corrections were applied empirically using the *SADABS* programs.[26] For compound **7** two monoclinic polymorphs were observed, one with four crystallographically independent molecules and another with two. Compound **19** was refined as a 0.52 : 0.48 racemic twin for which C, F and N atoms were refined isotropically. The compounds **12** and **13**, **21** and **22**, and **21** and **23** form the co-crystal with 0.65 : 0.35, 0.25 : 0.75, and 0.77 : 0.23 occupation ratio, respectively. For the co-crystals, atoms C and O of groups OCH_3 were refined isotropically with geometrical restrictions. The crystal structures obtained were analyzed for short contacts between non-bonded atoms with the *PLATON* program.[27]

CCDC 1408516 (**4**), 1408517 and 1408518 (**7**, two polymorphs), 1408519 (**8**), 1408520 (**11**), 1408521 (**12**), 1408522 (**14**), 1408523 (**15**), 1408524 (**17**), 1408525 (**19**), 1408526 (**21**),

1408527 (**22** / **21**), 1408529 (**21** / **23**), and 1408528 (**25**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Powder XRD data (ESI, Figure S2) for two polymorphs of compound **6** were obtained at 200 K with a Bruker Kappa Apex II CCD diffractometer using Mo Kα radiation (λ = 0.71073 Å) and a graphite monochromator, over the 2θ range 3-20º (*R* = 110 mm, cycle per φ with 300 s on the cycle, χ = –30° and 30°). The polycrystalline samples were ground with silicone grease prior to measurement.

4.3. Quantum chemical calculations

The geometries and harmonic vibrational frequencies of **1**, **10** and **19** and species involved in their reactions with MeO^- in MeOH and Me_2NH or Me_2N^- in DMF were calculated at the M06-2X/6-31+G(d,p) level of theory[28] with the *Gaussian 09* suite of programs.[29] All stationary points on the potential energy surfaces were ascertained to be the minima or transition states and the stability of the SCF solutions was tested. Calculations for MeOH and DMF solutions were carried out using the polarizable continuum model (IEFPCM)[30] with radii and non-electrostatic terms of the SMD solvation model[31] as implemented in the *Gaussian 09*.

4.4. Preparations

Where needed, one-day experiments were performed with $CaCl_2$ protection from atmospheric moisture whereas longer ones in an argon atmosphere. The diamines **31-33** were synthesized and kept under argon until their conversion into hydrochlorides.

4.4.1. Quinoxalines **2-8**, **28**

(a) At ambient temperature, a solution of 0.202 g (1 mmol) of **1** and (a) 0.054 g (1 mmol), or (b) 0.108 (2 mmol), of NaOMe in 6 ml of MeOH was (a) stirred for 24 h or (b) stirred for 24 h and then refluxed for 8 h. The solvent was distilled off and the residue was (a) chromatographed on silica column with ethyl acetate / CH_2Cl_2 1 : 3 and recrystallized from hexane, or (b) sublimed and recrystallized from hexane. Compound **2** (a) or **3** (b) was obtained in the form of colorless crystals.

(b) A solution of 0.202 g (1 mmol) of **1** and 0.162 g (3 mmol) of NaOMe in 2 ml of MeOH and 5 ml of Me_2SO was refluxed for 1 h, cooled to room temperature, diluted with 50 ml

of H_2O and extracted with 3 × 20 ml of Et_2O. The extract was dried with $MgSO_4$, evaporated and the residue chromatographed on silica column with hexane / ethyl acetate / CH_2Cl_2 1 : 1 : 1. The first colorless zone contained compound **3**, the second and third pale-yellow zones contained compounds **4** and **5** respectively. Evaporation of the eluate and recrystallization of the residue from hexane gave compound **4** in the form of colorless crystals.

(c) A solution of 0.202 g (1 mmol) of **1** and 0.270 g (5 mmol) of NaOMe in 3 ml of MeOH and 5 ml of Me_2SO was kept at 100 °C for 3 h, cooled to room temperature, diluted with 5 ml of H_2O and extracted with 4 × 10 ml of Et_2O. The extract was dried with $MgSO_4$, evaporated and the residue sublimed and recrystallized from hexane. Compound **5** was obtained in the form of yellow crystals.

(d) A solution of 0.202 g (1 mmol) of **1** and 0.450 g (4 mmol) of 40% aqueous Me_2NH in 9 ml of dioxane was kept at 60°C for 7 h, cooled to room temperature, diluted with equal volume of H_2O and extracted with 4 × 10 ml of $CHCl_3$. The extract was dried with $MgSO_4$, evaporated and the residue sublimed and recrystallized from hexane. Crystallization at ambient temperature (1 h) and at 7 °C (16 h) gave different polymorphs of compound **6** with melting points 78-79 and 86-87 °C, respectively, in both cases in the form of bright yellow crystals.

(e) In sealed glass tube placed in steel cylinder, a solution of 0.202 g (1 mmol) of **1** and 0.900 g (8 mmol) of 40% aqueous Me_2NH in 3 ml of DMF was kept at 150 °C for 6 h. The reaction mixture was cooled to room temperature, solvents were distilled off and the residue was sublimed and recrystallized from hexane. Compound **7** was obtained in the form of yellow needles of polymorph with m. p. 113-114 °C; for the second polymorph of **7**, see entry (f).

(f) In sealed glass tube placed into steel cylinder, a solution of 0.202 g (1 mmol) of **1** and 1.35 g (12 mmol) of 40% aqueous Me_2NH in 3 ml of N-methyl-2-pyrrolidone was kept at 230 °C for 22 h. The reaction mixture was cooled to room temperature, diluted with 40 ml of H_2O and extracted with 7 × 40 ml of hexane. The extract was dried with $CaCl_2$ and evaporated to dryness. The residue contained compounds **7**, **8** and **9** in ratio 3 : 8 : 2 (^1H and ^{19}F NMR, GC-MS) together with non-identified minor admixtures. This product was chromatographed on a silica column with 10 : 1 chloroform / ethyl acetate. The first yellow zone contained mixture of unidentified compounds and the second yellow-orange zone compound **7** and **8**. Compound **9** was not isolated from the column on further elution with ethyl acetate and then MeCN. Compounds **7** and **8** were separated by repeated chromatography on a silica column with hexane / ethyl acetate 5 : 1. The first orange zone corresponded to compound **8** and the second yellow one to compound **7**. Eluates were evaporated and residues were recrystallized from hexane.

Compound **8** was obtained in the form of orange crystals and compound **7** in that of greenish-yellow crystals of a polymorph with m. p. 115-116 °C.

(g) A solution of 0.114 g (0.5 mmol) of **6** and 0.054 g (1 mmol) of NaOMe in 6 ml of MeOH was kept at 65 °C for 8 h. The reaction mixture was cooled to room temperature, poured in water, acidified with HCl to pH ~6-7 and extracted with 6 × 10 ml of Et_2O. The Et_2O solution was dried with $MgSO_4$ and evaporated. The residue was sublimed and recrystallized from hexane. Compound **28** was obtained in the form of yellow crystals.

4.4.2. Thiadiazoles **10**-**17**, **29**

(a) Under argon, a mixture of 0.458 g (2.5 mmol) of 3,4,5,6-tetrafluoro-1,2-diaminobenzene[18] and 1 ml of $SOCl_2$ was refluxed for 1 h, the excess of $SOCl_2$ was distilled off and extremely moisture sensitive N,N'-disulfinyl-3,4,5,6-tetrafluoro-1,2-diaminobenzene[19] was obtained. This product was (a) dissolved in 2 ml of absolute pyridine and the solution was heated at 100 °C for 4 h; or (b) dissolved in 5 ml of toluene, 0.333 g (2.5 mmol) of freshly sublimed $AlCl_3$ was added, and the mixture refluxed for 6 h. The solvents were distilled off and the residue sublimed. Compound **10**[18] was obtained in the form of white needles.

(b) A solution of 0.208 g (1 mmol) of **10** and 0.059 g (1.1 mmol) of NaOMe in 10 ml of MeOH was kept at ambient temperature for 4 h. Then aqueous HCl was added to pH ~3, solvent was distilled off and the residue recrystallized from hexane. Compound **11** was obtained in the form of yellowish needles.

(c) A solution of 0.208 g (1 mmol) of **10** and 0.113 g (2.1 mmol) of NaOMe in 1 ml of MeOH and 9 ml of THF was kept at ambient temperature for 60 h, solvents were distilled off and the residue sublimed in vacuo and recrystallized from hexane. Compound **12** was obtained in the form of yellow needles.

(d) A solution of 0.208 g (1 mmol) of **10** and 0.207 g (3.7 mmol) of NaOMe in 6 ml of MeOH and 10 ml of dioxane was kept at 95 °C for 90 h, solvents were distilled off and the residue sublimed and recrystallized from pentane. Yellow co-crystals of compounds **12** and **13**, 0.65 : 0.35 (GC-MS and XRD), were obtained in the yield of 0.022 g (10 %). They were not separated into individual **12** and **13**.

(e) A solution of 0.208 g (1 mmol) of **10** and 0.259 g (4.8 mmol) of NaOMe in 2 ml of MeOH and 10 ml of dioxane was refluxed for 9 h, cooled to room temperature, solvents were

distilled off and the residue sublimed and recrystallized from hexane. Compound **14** was obtained in the form of yellow needles.

(f) A solution of 0.208 g (1 mmol) of **10** and 0.450 g (4 mmol) of 40% aqueous Me_2NH in 5 ml of THF was kept at ambient temperature for 3 h, solvents were distilled off and the residue sublimed and recrystallized from hexane. Compound **15** was obtained in the form of red crystals.

(g) In sealed glass tube placed into steel cylinder, a solution of 0.072 g (0.35 mmol) of **10** and 0.175 g (1.56 mmol) of 40% aqueous Me_2NH in 0.5 ml of DMF was kept at 150 ºC for 7 h. Upon cooling to room temperature, the reaction mixture was diluted with 10 ml of H_2O and extracted with 5 × 10 ml of hexane. Solvent was distilled off and the residue was chromatographed on silica column. Elution with CH_2Cl_2 gave yellow zone of compound **16**. Further elution with CH_2Cl_2 / ethyl acetate 10 : 1 gave orange zones containing compound **17**, its isomer and an isomer of compound **16** along with unidentified compounds (^1H and ^{19}F NMR and GC-MS). The yellow zone was evaporated and the residue recrystallized from hexane. Compound **16** was obtained in the form of orange crystals.

(h) In sealed glass tube placed into steel cylinder, a solution of 0.390 g (1.9 mmol) of **10** and 2.270 g (16 mmol) of 40% aqueous Me_2NH in 3 ml of Me_2SO was kept at 170 ºC for 35 h. Upon cooling to room temperature, the reaction mixture was diluted with 20 ml of H_2O and extracted with 5 × 20 ml of chloroform. Solvents were distilled off and the residue was sublimed and chromatographed on silica plates (200 × 200 × 1 mm) with hexane / ethyl acetate 10 : 1. The bright-yellow zone was extracted with MeCN, solvent distilled off and the residue recrystallized from MeOH. Compound **17** was obtained in the form of yellow crystals. The orange zone was worked-up in the same way, the residue was dark-red oil contained 80 % (GC-MS) of 6-F isomer of **17**.[20]

(i) A solution of 0.105 g (0.45 mmol) of **15** and 0.024 g (0.45 mmol) of NaOMe in 1 ml of MeOH and 5 ml of dioxane was kept at 70ºC for 24 h, cooled to room temperature and the solvents were distilled off. The residue was recrystallized from hexane and sublimed. Compound **29** was obtained in the form of yellow crystals.

4.4.3. Selenadiazoles **20**-**25**, **30**

(a) A solution of 0.250 g (1 mmol) of **19** and 0.054 g (1 mmol) of NaOMe in 2 ml of MeOH and 5 ml of THF was kept at 50 ºC for 5 h and cooled to room temperature. The

precipitate was filtered off, sublimed and recrystallized from EtOH. Compound **20** was obtained in the form of crystalline yellow solid.

(b) A solution of 0.250 g (1 mmol) of **19** and 0.108 g (2 mmol) of NaOMe in 2 ml of MeOH and 5 ml of dioxane was kept at 85 ºC for 8 h, cooled to room temperature and solvents were distilled off. The residue was recrystallized from toluene / hexane 1 : 1 and sublimed. Compound **21** was obtained in the form of yellow crystals.

(c) A solution of 0.250 g (1 mmol) of **19** and 0.162 g (3 mmol) of NaOMe in 2 ml of MeOH and 5 ml of dioxane was kept at 85 ºC for 16 h, cooled to room temperature and passed though alumina column (d = 25, h = 50 mm) which was additionally washed with 150 ml of CH_2Cl_2. The combined solution was evaporated and the residue (0.174 g) was sublimed to give 1 : 5 : 1 (^{1}H and ^{19}F NMR, GC-MS) mixture of compounds **21**, **22** and **23**. The mixture was separated by fractional sublimation controlled by GC-MS. The fraction contained 74% of **22** was chromatographed on alumina column with hexane followed by hexane / ethyl acetat 3 : 1. Compound **22** was obtained in the form of yellow crystals. Additionally, two minor fractions were isolated from the column to be co-crystals **22** / **21** and **21** / **23** (XRD).

(d) A solution of 0.250 g (1 mmol) of **19** and 0.216 g (4 mmol) of NaOMe in 2 ml of MeOH and 5 ml of Me_2SO was refluxed for 8 h, cooled to room temperature and passed though alumina column (d = 35, h = 25 mm) which was additionally washed with 150 ml of CH_2Cl_2. Combined solution was evaporated under reduced pressure and the residue recrystallized from EtOH. Compound **23** was obtained in the form of yellow crystals.

(e) A solution of 0.160 g (0.63 mmol) of **19** and 0.215 g (4.7 mmol) of 40% aqueous Me_2NH in 5 ml of dioxane was kept at ambient temperature for 5 h, solvents were distilled off and the residue was sublimed and recrystallized from EtOH. Compound **24** was obtained in the form of yellow crystals.

(f) In sealed glass tube placed in steel cylinder, a mixture of 0.255 g (1 mmol) of **19** and 0.900 g (8 mmol) of 40% aqueous Me_2NH in 7 ml of Me_2SO was kept at 175 ºC for 12 h and cooled to room temperature. The reaction mixture was passed through alumina column (d = 25, h = 45 mm) which was additionally washed with 200 ml of CH_2Cl_2. Combined solution was evaporated and the residue recrystallized from toluene / hexane 2 : 1. Compound **25** was obtained in the form of yellow crystals.

(g) A solution of 0.100 g (0.36 mmol) of **24** and 0.019 g (0.36 mmol) of NaOMe in 1 ml of MeOH and 5 ml of dioxane was kept at 65 ^{o}C for 7 h, cooled to room temperature and solvents were distilled off. The residue was recrystallized from toluene / hexane 1 : 1 and sublimed. Compound **30** was obtained in the form of brick-red crystals.

4.4.4. Diamines **31**-**33** *and quinoxaline* **34**

(a) At 0^{o}C, a solution of 0.100 g (0.4 mmol) of compound **14** in 5 ml of THF was added to suspension of 0.204 g (5.3 mmol) of $LiAlH_4$ in 10 ml of THF. The reaction mixture was kept at 0 ^{o}C for 1 h and 5 ml of saturated water solution of NH_4Cl was carefully added. The reaction mixture was filtered under argon and the filter washed with 2 × 10 ml of Et_2O. The filtrate was added to solution of NaOH in methanol (pH ~11), the solvents were distilled off and the residue was sublimed. Sublimed product was dissolved in a mixture of 3 ml of Et_2O and 1 ml of MeOH and 2 ml of Me_3SiCl was added. The resulting white precipitate was filtered off and washed twice with Et_2O. Compound **31**·2HCl was obtained in the form of colorless crystals.

(b) At 0 ^{o}C, 0.177 g (4.7 mmol) of $LiAlH_4$ was added to a solution of 0.153 g (6.6 mmol) of compound **12** in 15 ml of THF. The reaction mixture was kept at 0 ^{o}C for 1 h and 1 ml of methanol was carefully added. The solvents were distilled off and the residue was extracted with 3 × 5 ml of benzene. The extract was evaporated to dryness, the residue sublimed and the sublimate dissolved in mixture of 5 ml of Et_2O with 1 ml MeOH. Then 2 ml of Me_3SiCl was added to the solution, the precipitate was filtered off and washed twice with Et_2O. Compound **32**·2HCl was obtained in form of white powder.

(c) A mixture of 0.146 g (0.6 mmol) of compound **15**, 0.780 g (3.5 mmol) of $SnCl_2·2H_2O$ and 6 ml of conc. HCl was refluxed for 1 h, cooled to room temperature, neutralizated with aqueous NaOH to pH ~8, and extracted with 6×20 ml of Et_2O. The extract was dried with $MgSO_4$, filtered, concentrated to a volume of ~2 ml. and treated by solution of 0.1 ml of MeOH and 0.3 ml of Me_3SiCl in 2 ml of Et_2O. Compound **33**·2HCl was obtained in the form of white powder.

In all cases, free bases for spectral measurements were recovered by the action of Et_3N in suitable solvent.

(d) A mixture of 0.457 g (0.16 mmol) of **33**·2HCl and 0.336 g (0.16 mmol) of PhCOCOPh in 6 ml of MeOH was refluxed for 4.5 h, cooled to room temperature and the

solvent was distilled off. The residue was chromatographed on silica column with toluene, bright yellow fraction was evaporated to dryness and the residue recrystallized from pentane. Compound **34** was obtained in the form of bright yellow powder.

4.4.5. Competitive interaction of compounds **1**, **10** *and* **19** *with methoxide*

At ambient temperature, a solution of 0.05 mmol of NaOMe in 1 ml of MeOH was slowly added with syringe to a solution of equimolar (0.05 mmol) mixture of **1**, **10** and **19** in 15 ml of MeOH. After 48 h the reaction mixture was studied by ^{19}F NMR and GC-MS.[21]

4.4.6. Reaction of compound **19** *with* $LiNMe_2$

At –30 °C and under argon, 1.8 ml of 1.7 M hexane solution of BuLi (3.0 mmol) were added to a suspension of 0.123 g (1.5 mmol) of $Me_2NH{\cdot}HCl$ in 10 ml of DME. After 30 min, a solution of 0.127 g (0.5 mmol) of compound **19** in 5 ml of DME was added during 15 min. Reaction mixture was slowly (~3 h) warmed to ambient temperature. According to NMR ^{19}F and GC-MS data, the reaction mixture contained compounds **19**, **20** and **24** in molar ratio 1 : 1.5 : 1, respectively.

4.5. Determination of cytotoxicity and effects on the mRNA expression

For compounds **5**, **7** and **14**, cytotoxicity and effects on the mRNA expression were investigated. The studied cell lines included HepG2, Hep2 (human carcinoma) and U937 (human leukemia). All reagents for cell cultures were purchased from Thermo Scientific. The HepG2 and Hep2 cell lines were cultured in Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% (v/v) fetal bovine serum (FBS). The U937cell lines were cultured in RPMI supplemented with 10% (v/v) FBS. All cell lines were cultured at 37 °C in a 5% CO_2 humidified incubator. For the full data obtained and their discussion, see ESI (section Bioactivity studies, Figure S3).

To determine the effects of compounds **5**, **7** and **14** on the mRNA expression CYP1a1, CYP1A2, CYP4a11, CYP3A4 and TNF-alfa, HepG2 and U937 cells were treated with low toxicity concentration of the compounds (25 μM) for 16 h. The compounds were dissolved in Me_2SO, the concentration of Me_2SO in treated cells did not exceed 0.1% (v/v). Control cells were treated with Me_2SO (50% v/v) to yield a final concentration of 0.1% (v/v). After 16 h of treatment, either the total RNA was isolated using *Tri Reagent* according to the standard protocol. The purity of each RNA preparation was evaluated by the ratio of the absorbance at

260 nm to that at 280 nm. RNA was transcribed using *High Capacity cDNA Reverse Transcription Kit* (Applied Biosystems). Reaction was stopped by heating the mixture at 85 °C for 5 min and storing at −20 °C until subsequent analysis. The primer sets was designed using *GenBank* database: GAPDH, CYP1a, CYP1a2, CYP2a1, CYP3a4 and TNF-alfa (for details, see ESI: Section Bioactivity studies). The quantitative real-time reverse-transcription polymerase chain reactions (RT-PCRs) were performed using *qPCRmix-HS SYBR* (Eurogen) and a LightCycler instrument (Roche Diagnostics). Reactions conditions were: preheating at 95 ^{o}C, 300 s; amplification, 45 cycles; 95 ^{o}C, 12 s; 58 ^{o}C, 15 s; 72 ^{o}C, 20 s; detection, respectively. Melting point analysis was carried out by heating the DNA synthesis product from 65 °C to 95 °C and a characteristic melting point curve was obtained. All PCR reactions were performed in triplicates. Calibration curve was constructed by plotting the cross point (Ct) against a serial dilution with cDNA produced from heart total RNA extracts using 1 : 4 dilution steps The Ct is the cycle number at which the fluorescence signal is greater than a defined threshold, one in which all the reactions are in the logarithmic phase of amplification. Negative control samples contained water instead of cDNA; occasionally dimer production was seen being easily distinguished by melting point analysis. The effect of compounds **5**, **7** and **14** on the Cytochrome P450 (CYP) induction of HepG2 and U937 cells was determined. The non-toxic concentrations of **5**, **7** and **14** (more than 90% viability) used for mRNA expression study of HepG2 and U937 cells were 25 μM. The change in expression of CYP mRNA by **5**, **7** and **14** was interpreted in fold induction pattern. The inducing effect of **5**, **7** and **14** for CYPs 1A1, 1A2, 3A4 and 4A11 mRNA was fairly low in that almost all of the fold induction was in the range of only 1- to 2-fold. Therefore, the compounds were unlikely to potentiate the CYP induction of the inducers. For CYP1A1, it was the only gene that could be greater induced in HepG2 cells by compound **5** to about 4-fold, but not remarkable as compared with such classic inductor as benzopiren. According to the result, more obvious change in the U937 cells was seen in CYP1A1 mRNA expression for compound **14**. It should be noted that TNF-alfa (a major marker of inflammation) was *slightly* elevated in U937 cells treated with **14** than in control cells. For the full data obtained and their discussion, see ESI (section Bioactivity studies, Figures S4 and S5).

Acknowledgments

The authors thank the Collective Service Center of Siberian Branch of the Russian Academy of Sciences for spectral and analytical measurements, and the Siberian Supercomputer Center for computational facilities. Financial support from the Ministry of Education and Science of the Russian Federation (project of Joint Laboratories of Siberian Branch of the Russian Academy of

Sciences and National Research Universities) is gratefully acknowledged. The authors affiliated with Tomsk State University are grateful to the Foundation named after D.I. Mendeleev for support of their work.

Appendix A. Electronic supplementary information

Electronic supplementary information (ESI) associated with this article and containing XRD and DFT data, chemical names of compounds, and details of the cytotoxicity and effects on the mRNA expression studies can be found, in the online version, at http://

References and notes

[1] R. Dua, S. Shrivastava, S.K. Sonwane, S.K. Srivastava, Adv. Biological Res. 5 (2011) 120–144.

[2] P. Ertl, S. Jelfs, J. Mühlbacher, A. Schuffenhauer, P. Selzer, J. Med. Chem. 49 (2006) 4568–4573. According to this work, ~95 % of known bioactive compounds contain rings 75 % of which are (hetero) aromatic. At the same time, most of ring systems observed for natural products are aliphatic and only ~38 % aromatic.

[3] B.A.D. Neto, P.H.P.R. Carvalho, J.R. Correa, Acc. Chem. Res. 48 (2015) 1560–1569.

[4] A.G. Makarov, N.Yu. Selikhova, A.Yu. Makarov, V.S. Malkov, I.Yu. Bagryanskaya, Yu.V. Gatilov, A.S. Knyazev, Yu.G. Slizhov, A.V. Zibarev, J. Fluorine Chem. 165 (2014) 123–131.

[5] (a) Y. Chen, K. Li, M. Zhao, Y. Li, B. Chen, Tetrahedron Lett. 54 (2013) 1627–1630;

(b) M.P. Cabal, Modern Heterocyclic Chemistry, J. Alvarez-Builla, J.J. Vaquero, J. Barluengo (Eds.), Wiley-VCH, Vol. 3 (2011) 1683–1776;

(c) N. Sato, Comprehensive Heterocyclic Chemistry II, A.R. Katritzky, C.W. Rees, E.F.V. Scriven (Eds.), Pergamon Press, Vol. 6 (1996) 233–278;

(d) A.E.A. Porter, Comprehensive Heterocyclic Chemistry, A.R. Katritzky, C.W. Rees (Eds.), Pergamon Press, Vol. 3 (1984) 157–198;

(e) H. Schutz, Benzodiazepines, Springer (1982).

[6] (a) B.A.D. Neto, A.A.M. Lapis, E.N. da Silva Junior, J. Dupont, Eur. J. Org. Chem. 2013 (2013) 228–255;

(b) S. Yamazaki, Comprehensive Heterocyclic Chemistry III, A.R. Katritzky, C.W. Rees, E.F.V. Scriven, R.J.H. Taylor (Eds.), Wiley, Vol. 6 (2008) 518–581;

(c) P.A. Koutentis, Sci. Synth. 13 (2004) 297–348;

(d) R.A. Aitken, Sci. Synth. 13 (2004) 777–822;

(e) S. Grivas, Cur. Org. Chem. 4 (2000) 707–726;

(f) I. Shinkai, P. Reider, Comprehensive Heterocyclic Chemistry II, A.R. Katritzky, C.W. Rees, E.F.V. Scriven (Eds.), Pergamon Press, Vol. 4 (1996) 355–377.

[7] (a) L.S. Konstantinova, E.A. Knyazeva, O.A. Rakitin, Molecules 20 (2015) 14522–14532;

(b) L.S. Konstantinova, I.E. Bobkova, Yu.V. Nelyubina, E.A. Chulanova, I.G. Irtegova, N.V. Vasilieva, P.S. Camacho, S.E. Ashbrook, G. Hua, A.M.Z. Slawin, J.D. Woollins, A.V. Zibarev, O.A. Rakitin, Eur. J. Org. Chem. 2015 (2015) 5585–5593;

(c) L.S. Konstantinova, E.A. Knyazeva, A.A. Nefyodov, P.S. Camacho, S.E. Ashbrook, J.D. Woollins, A.V. Zibarev, O.A. Rakitin, Tetrahedron Lett. 56 (2015) 1107–1110;

(d) L.S. Konstantinova, E.A. Knyazeva, O.A. Rakitin, Org. Prep. Proc. Int. 46 (2014) 475–544;

(e) A.V. Lonchakov, O.A. Rakitin, N.P. Gritsan, A.V. Zibarev, Molecules 18 (2013) 9850–9900.

[8] (a) P. Kirsch, Modern Organofluorine Chemistry: Synthesis, Reactivity, Applications, Wiley (2013);

(b) R.D. Chambers, Polyfluoroaromatic Compounds, in Fluorine in Organic Chemistry, Blackwell: Oxford (2004);

(c) G.G. Yakobson, T.D. Petrova, L.S. Kobrina, Fluor. Chem. Rev. 7 (1974) 115–223.

[9] S. Van Brandt, F.J.R. Rombouts, C. Martinez-Lamenca, J. Leenaerts, T.R.M. Rauws, A.A. Trabanco, Eur. J. Org. Chem. 2012 (2012) 7048–7052.

[10] C.G. Allison, R.D. Chambers, J.A.H. MacBride, W.K.R. Musgrave, J. Fluorine Chem. 1 (1971) 59–67.

[11] G.M. Brooke, J. Fluorine Chem. 86 (1997) 1–76.

[12] (a) The Chemistry of Heterocyclic Compounds: Condensed Pyrazines, G.W.H. Cheeseman, R.F. Cookson (Eds.), Wiley (2009);

(b) U. Urleb, Houben-Weyl Methods of Organic Chemistry, Thieme, Vol. E9/b (1997) 193–255.

[13] (a) A.I. Rosenbaum, C.C. Cosner, C.J. Mariani, F.R. Maxfield, O. Wiest, P. Helquist, J. Med. Chem. 53 (2010) 5281–5289;

(b) A. Merschaert, P. Boquel, H. Gorissen, J.-P. Van Hoeck, A. Borghese, L. Antoine, V. Mancuso, A. Mockel, M. Vanmarsenille, Tetrahedron Lett. 47 (2006) 8285–8288;

(c) Z. Rykowski, E. Sczesna, Polish J. Chem. 63 (1989) 307–309;

(d) L.M. Weinstock, I. Shinkai, Comprehensive Heterocyclic Chemistry, A.R. Katritzky, C.W. Rees (Eds.), Pergamon Press, Vol. 6 (1984) 515–543;

(e) V. Bertini, F. Lucchesini, A. De Munno, Synthesis 8 (1982) 681–683.

[14] (a) P.J. Kocienski, Protecting Groups, Thieme: New York (2005);

(b) T.W Greene, P.G.M. Wuts, Protective Groups in Organic Synthesis, Wiley: New York (1991).

[15] (a) L.V. Politanskaya, I.P. Chuikov, E.V. Tretyakov, V.D. Shteingarts, L.P. Ovchinnikova, O.D. Zakharova, G.A. Nevinsky, J. Fluorine Chem. 178 (2015) 142–153;

(b) O.D. Zakharova, L.P. Ovchinnikova, L.I. Goryunov, N.M. Troshkova, V.D. Shteingarts, G.A. Nevinsky, Bioorg. Med. Chem. 19 (2011) 256–260;

(c) O.D. Zakharova, L.P. Ovchinnikova, L.I. Goryunov, N.M. Troshkova, V.D. Shteingarts, G.A. Nevinsky, Eur. J. Med. Chem. 45 (2010) 2321–2326;

(d) O.D. Zakharova, L.I. Goryunov, N.M. Troshkova, L.P. Ovchinnikova, V.D. Shteingarts, G.A. Nevinsky, Eur. J. Med. Chem. 45 (2010) 270–274;

(e) H. Park, B.I. Carr, M. Li, S.W. Ham, Bioorg. Med. Chem. Lett. 17 (2007) 2351–2354;

(f) S.W. Ham, L.I. Choe, M.F. Wang, V. Peyregne, B.I. Carr, Bioorg. Med. Chem. Lett. 14 (2004) 4103–4105.

[16] (a) M. Bassetto, S. Feria, F. Pertusati, Future Med. Chem. 7 (2015) 527–546;

(b) J. Wang, M. Sanchez-Rosello, J.L. Acena, C. Del Pozo, A.E. Sorochinsky, S. Fustero, V.A. Soloshonok, H. Liu, Chem. Rev. 114 (2014) 2432–2500;

(c) T. Fujiwara, D. O'Hagan, J. Fluorine Chem. 167 (2014) 16–29;

(d) Molecular Medicine and Medicinal Chemistry. Vol. 6: Fluorine in Pharmaceuticals and Medicinal Chemistry: From Biophysical Aspects to Clinical Applications, V. Gouverneur, K. Mueller (Eds.), World Scientific (2012);

(e) D. O'Hagan, J. Fluorine Chem. 131 (2010) 1071–1081;

(f) I. Ojima, Fluorine in Medicinal Chemistry and Chemical Biology, Wiley (2009);

(g) J.P. Begue, D. Bonnet-Delpon, Bioorganic and Medicinal Chemistry of Fluorine, Wiley (2008);

(h) Fluorine and Health. Molecular Imaging, Biomedical Materials and Pharmaceuticals, A. Tressaud, G. Haufe (Eds.), Elsevier: Amsterdam (2008);

(i) S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320–330;

(j) K.L. Kirk, J. Fluorine Chem. 127 (2006) 1013–1029;

(k) J.P. Begue, D. Bonnet-Delpon, J. Fluorine Chem. 127 (2006) 992–1012;

(l) C. Isanbor, D. O'Hagan, J. Fluorine Chem. 127 (2006) 303–319;

(m) F.M.D. Ismail, J. Fluorine Chem. 118 (2002) 27–33;

(n) B.E. Smart, J. Fluorine Chem. 109 (2001) 3–11.

[17] (a) Organoselenium Chemistry: Between Synthesis and Biochemistry, C. Santi (Ed.), Bentham Science Publishers (2014);

(b) L. Flohe, Selenium and Tellurium Chemistry: From Small Molecules to Biomolecules and Materials, J.D. Woollins, R.S. Laitinen (Eds.), Springer (2011), 285–302;

(c) M. Ninomiya, D.R. Garud, M. Koketsu, Coord. Chem. Rev. 255 (2011) 2968–2990;

(d) T.G. Chasteen, R. Bentley, Handbook of Chalcogen Chemistry: New Perspectives in Sulfur, Selenium and Tellurium, F.A. Devillanova (Ed), The Royal Society of Chemistry (2007) 671–713;

(e) J. Mlochowski, K. Kloc, R. Lisiak, P. Potaczek, H. Wojtowicz, ARKIVOC (2007) 14–46;

(f) C.W. Nogueira, G. Zeni, J.T. Rocha, Chem. Rev. 104 (2004) 6255–6285.

[18] (a) A.V. Zibarev, I.V. Beregovaya, Rev. Heteroatom Chem. 7 (1992) 171–190;

(b) A.V. Zibarev, A.O. Miller, J. Fluorine Chem. 50 (1990) 359–363;

(c) A.V. Zibarev, O.M. Fugaeva, A.O. Miller, S.N. Konchenko, I.K. Korobeinicheva, G.G. Furin, Khim. Geterotsikl. Soed. (1990) 1124–1133 (in Russian).

[19] A.G. Makarov, I.Yu. Bagryanskaya, Yu.V. Gatilov, A.Yu. Makarov, K. Tersago, C. Van Alsenoy, F. Blockhuys, A.V. Zibarev, J. Mol. Struct. 978 (2010) 158–162.

[20] NMR, δ: 5-Dimethylamino-6,7,8-trifluoroquinoxaline (minor isomer of **6**): ^{1}H: 8.86, 8.84, 3.13; ^{19}F: –152.9 (m, 2F), –154.0 (t, 1F). 4-(Dimethylamino)-5,6,7-trifluoro-2,1,3-benzothiadiazole (minor isomer of **15**): ^{1}H: 3.21; ^{19}F: –147.8, –154.0, –156.1. 4-Dimethylamino-5,6,7-trifluoro-2,1,3-benzoselenadiazole (minor isomer of **24**): ^{1}H: 3.14; ^{19}F: –147.8, –154.3, –154.8. 4,5,7-Tris(dimethylamino)-6-fluoro-2,1,3-benzothiadiazole (isomer of **17**): ^{1}H: 3.03; ^{19}F: –129.2. For compounds **6**, **15**, **17** and **24**, see Table 5.

[21] Relative yields of products **2**, **11** and **20** in the reaction of an equimolar (0.5 mmol each) mixture of **1**, **10** and **19** with MeONa (0.5 mmol) in MeOH were 3.0 : 1.0 : 2.2 according to ^{19}F NMR, and 2.8 : 1.0 : 1.3 according to GC-MS, respectively. Some discrepancy between the data may be caused by different sensitivity of the GC-MS detector towards different types of the heterocycles.

[22] (a) Fluorine in Heterocyclic Chemistry, V. Nenajdenko (Ed.), Springer (2014);

(b) A. Gakh, K.L. Kirk, Fluorinated Heterocycles, Oxford University Press (2008).

[23] (a) E. Clot, O. Eisenstein, N. Jasim, S.A. Macgregor, J.E. McGrady, R.N. Perutz, Acc. Chem. Res. 44 (2011) 333–348;

(b) J. Burdeniuc, B. Jedicka, R.H. Crabtree, Chem. Ber. 130 (1997) 145–154;

(c) J.L. Kiplinger, T.G. Richmond, C.E. Osterberg, Chem. Rev. 94 (1994) 373–431.

[24] V.P. Fadeeva, D.O. Panin, O.N. Nikulicheva, V.D. Tikhova, J. Analyt. Chem. 69 (2014) 432–437.

[25] G.M. Sheldrick, Acta Crystallogr. A 64 (2008), 112–122.

[26] SADABS, Version 2008-1, Bruker AXS, Madison, WI, USA (2008).

[27] (a) A.L. Spek, PLATON, A Multipurpose Crystallographic Tool, Version 10M, Utrecht University, The Netherlands (2003);

(b) A.L. Spek, J. Appl. Crystallogr. 36 (2003) 7–13.

[28] Y. Zhao, N.E. Schultz, D.G. Truhlar, J. Chem. Theory Comput. 2 (2006) 364–382.

[29] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J.L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J.A. Montgomery, J.E. Peralta, F. Ogliaro, M. Bearpark, J.J. Heyd, E. Brothers, K.N. Kudin, V.N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J.C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J.M. Millam, M. Klene, J.E. Knox, J.B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R.E. Stratmann, O. Yazyev, A.J. Austin, R. Cammi, C. Pomelli, J.W. Ochterski, R.L. Martin, K. Morokuma, V.G. Zakrzewski, G.A. Voth, P. Salvador, J.J. Dannenberg, S. Dapprich, A.D. Daniels, Ö. Farkas, J.B. Foresman, J.V. Ortiz, J. Cioslowski, D.J. Fox, Gaussian 09, Revision D.01, Gaussian Inc., Wallingford CT (2009).

[30] (a) J. Tomasi, B. Mennucci, R. Cammi, Chem. Rev. 105 (2005) 2999–3093;

(b) V. Barone, A. Polimeno, Chem. Soc. Rev. 36 (2007) 1724–1731.

[31] A.V. Marenich, C.J. Cramer, D.G. Truhlar, J. Phys. Chem. B 113 (2009) 6378–6396.

[32] Compound **6** was isolated in the form of two polymorphs having identical elemental analysis but different melting points and powder X-ray diffraction patterns (Figure S2, ESI). Two polymorphs of compound **7** were characterized by XRD (Figure 2; Table 2; ESI, Table S4).

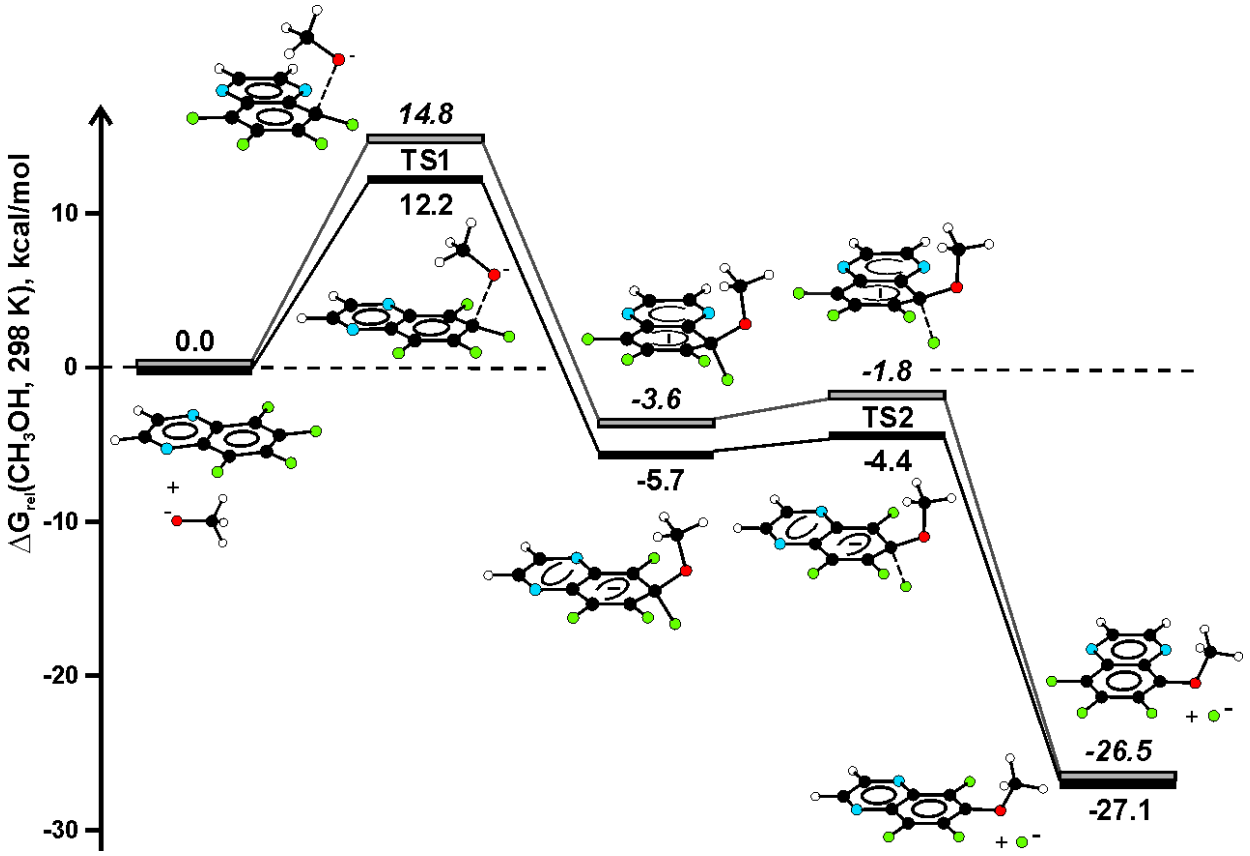
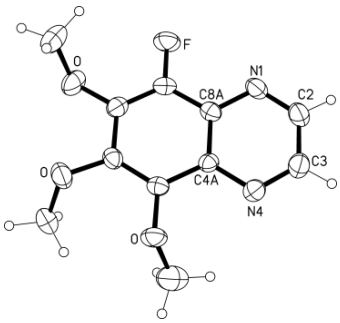
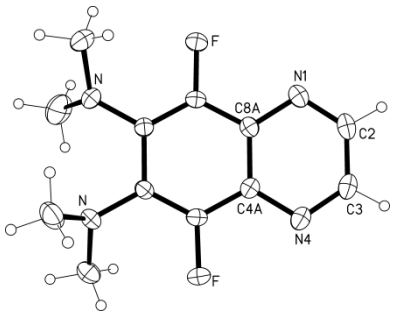


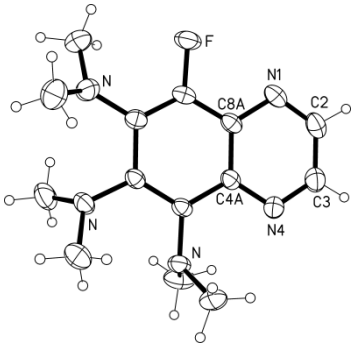
Figure 1. Relative Gibbs free energies (ΔG_{rel}, kcal.mol^{-1}) of the stationary points on the potential energy surface for the reaction of quinoxaline **1** with MeO^- in MeOH calculated by the M06-2X/6-31+G(d,p) method for T = 298 K, the solvent was taken into account using polarized continuum model. Color code: C – black, H – white, N – blue, O – red, F – green.



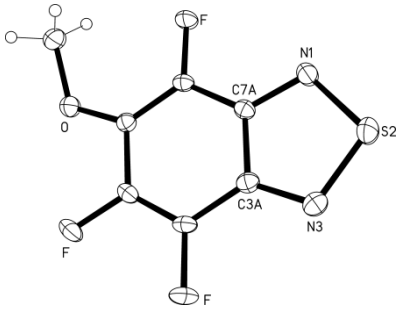
4



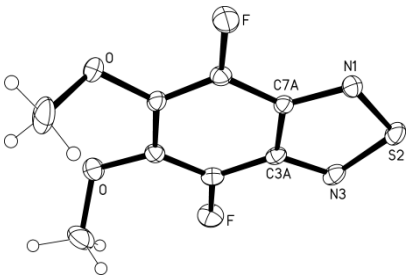
7



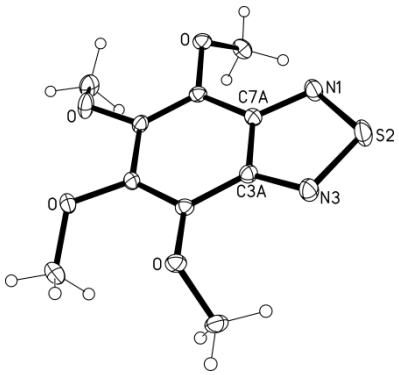
8



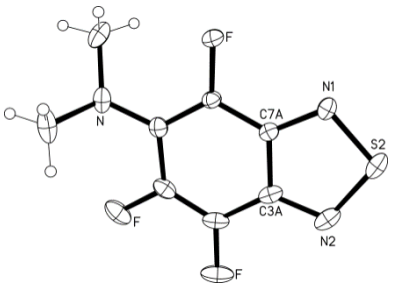
11



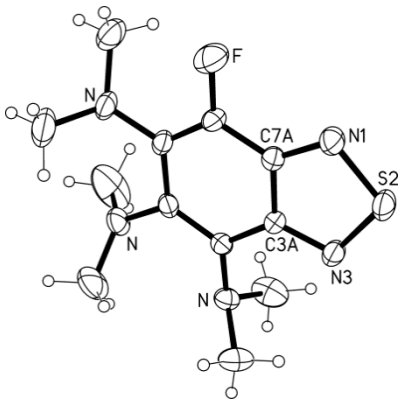
12



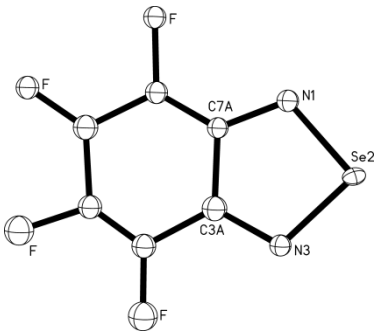
14



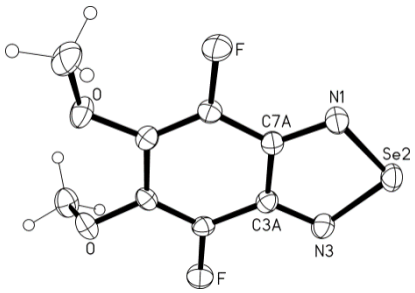
15



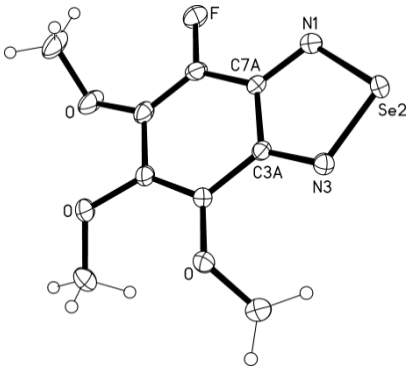
17



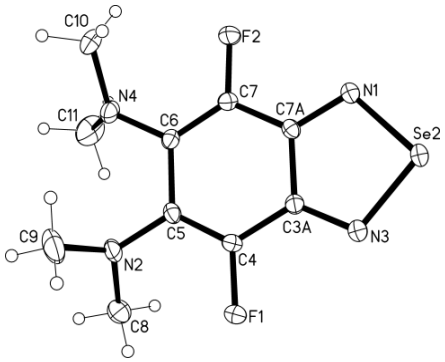
19



21



22



25

Figure 2. XRD molecular structures (displacement ellipsoids at 30%) of compounds (**22** from 3 : 1 co-crystal with **21**). For selected bond lengths and angles, see Table 2.

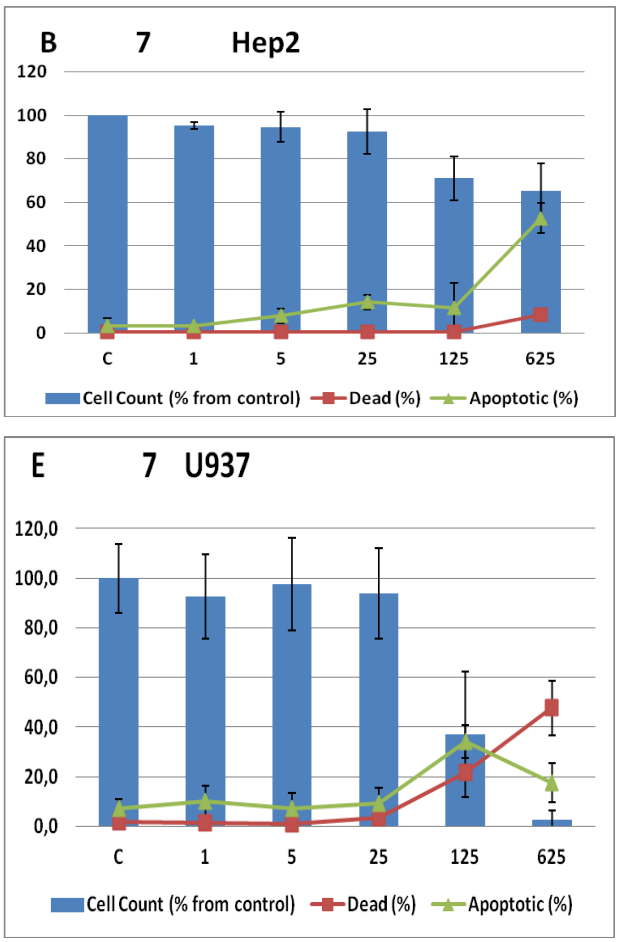
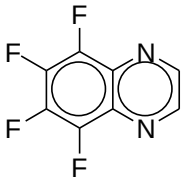
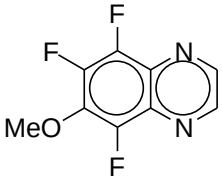


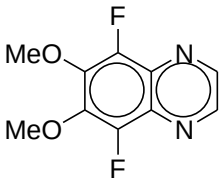
Figure 3. Treatment of Hep2 and U937 cells with different concentrations (from 1 to 625 µM) of compound **7** for 72 hours. The percentage of apoptotic cells was determined by staining with Hoechst 33342 and percentage of dead cells was determined by using propidium iodide. The data represent the mean ± S.D. of three independent experiments.



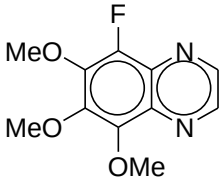
1



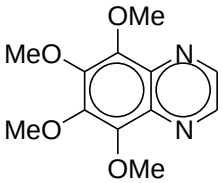
2



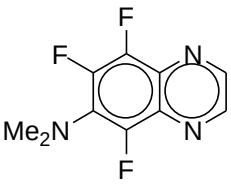
3



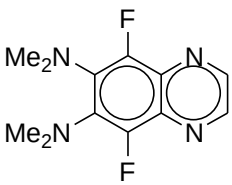
4



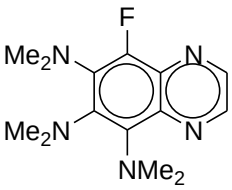
5



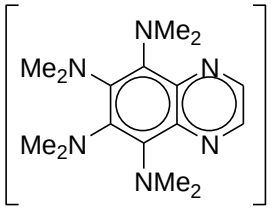
6



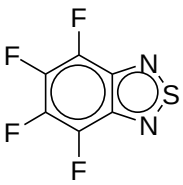
7



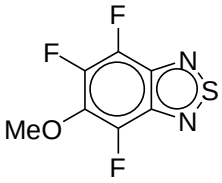
8



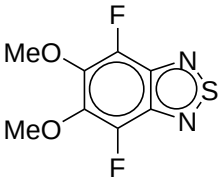
9



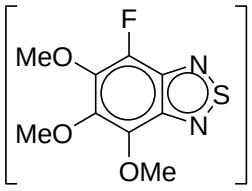
10



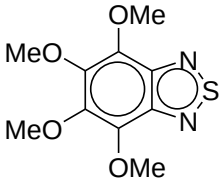
11



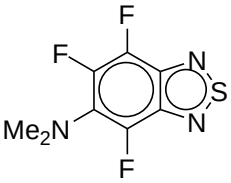
12



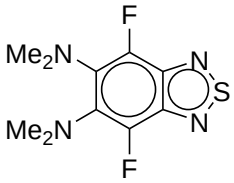
13



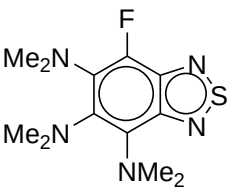
14



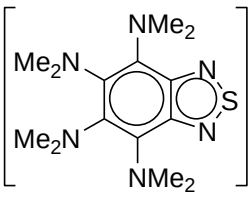
15



16



17



18

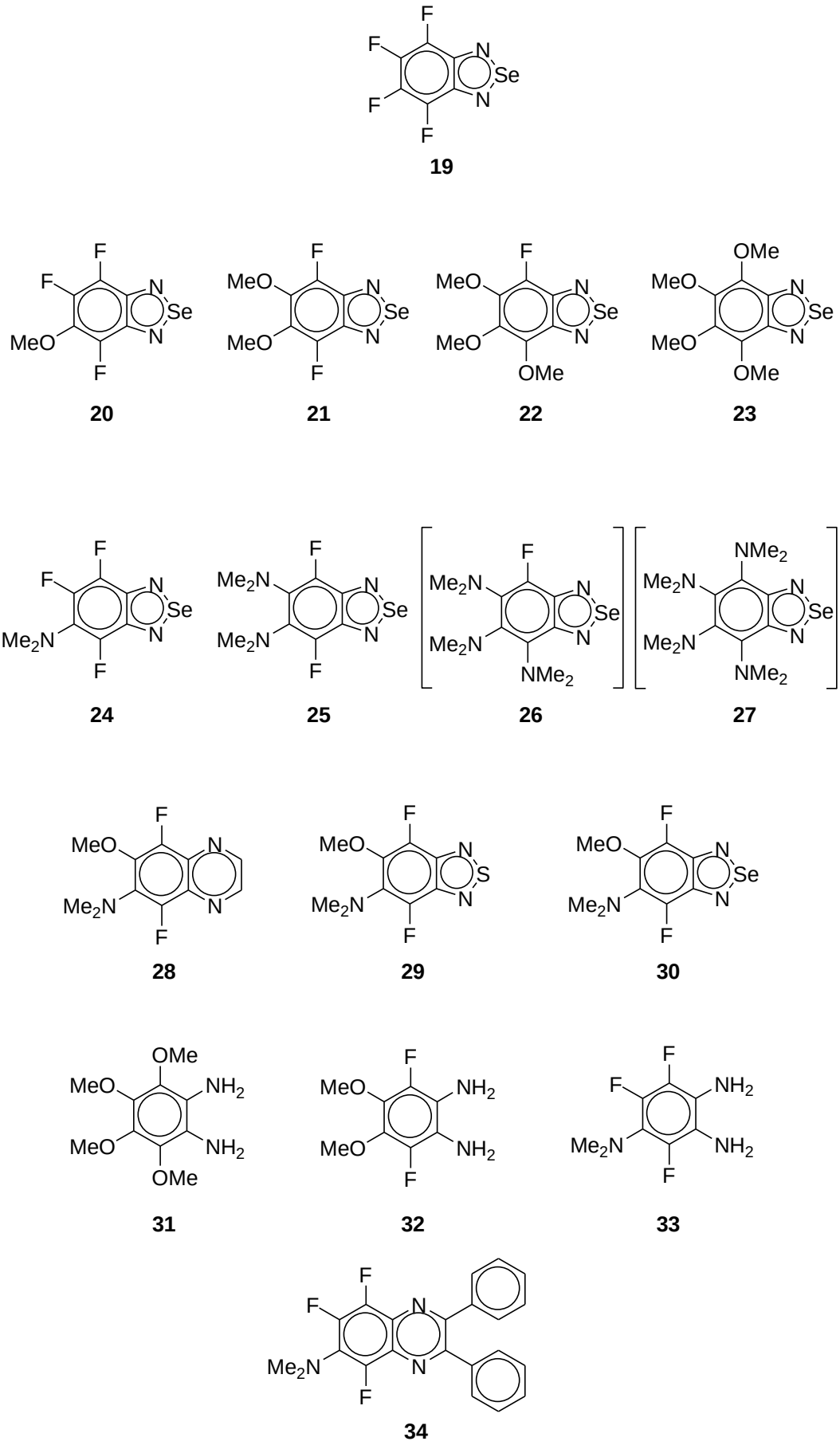
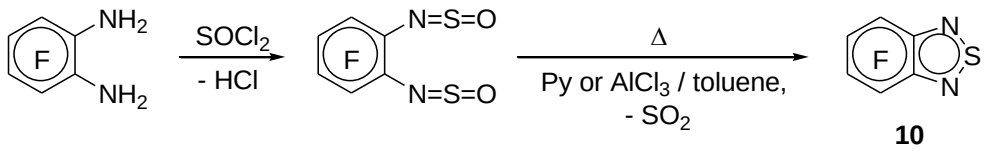


Chart 1. Compounds **1**-**34** (for chemical names, see ESI, Table S1).

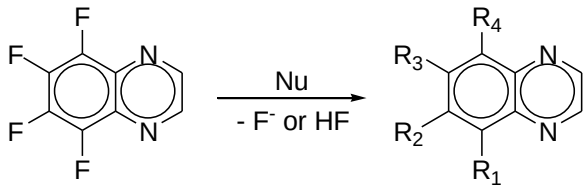


10

Conditions	Yield, % [a]
Pyridine, 100 °C, 4 h	53
$AlCl_3$ / toluene, reflux, 6 h	61

[a] Isolated yield of analytically pure product.

Scheme 1. Synthesis of compound **10**.



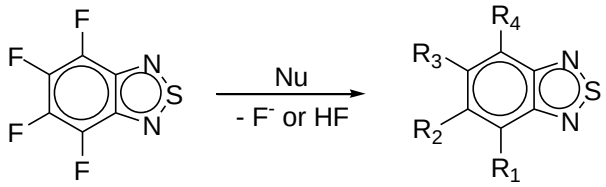
1 **2** - **9**

Compound	Nu	R_1	R_2	R_3	R_4	Yield, % [a,b]
2	MeO^-	F	MeO	F	F	67
3	MeO^-	F	MeO	MeO	F	78
4	MeO^-	MeO	MeO	MeO	F	44
5	MeO^-	MeO	MeO	MeO	MeO	39
6	Me_2NH	F	Me_2N	F	F	46
7	Me_2NH	F	Me_2N	Me_2N	F	76
8	Me_2NH	Me_2N	Me_2N	Me_2N	F	24
9	Me_2NH	Me_2N	Me_2N	Me_2N	Me_2N	not isolated

[a] Reaction conditions: **2**: MeOH, 20 °C, 24 h; **3**: MeOH, reflux, 8 h; **4**: MeOH / Me_2SO, reflux, 1 h; **5**: MeOH / Me_2SO, 100 °C, 3 h; **6**: dioxane, 60 °C, 7 h; **7**: DMF, 150 °C, 6h; **8**, **9**: N-methyl-2-pyrrolidone, 230 °C, 22 h.

[b] Isolated yield of analytically pure product.

Scheme 2. Synthesis of compounds **2**-**8** and attempted synthesis of compound **9**.



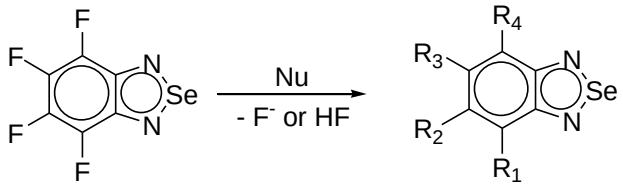
10 **11** - **18**

Compound	Nu	R_1	R_2	R_3	R_4	Yield, % [a,b]
11	MeO^-	F	MeO	F	F	69
12	MeO^-	F	MeO	MeO	F	63
13	MeO^-	MeO	MeO	MeO	F	not isolated
14	MeO^-	MeO	MeO	MeO	MeO	57
15	Me_2NH	F	Me_2N	F	F	90
16	Me_2NH	F	Me_2N	Me_2N	F	25
17	Me_2NH	Me_2N	Me_2N	Me_2N	F	8
18	Me_2NH	Me_2N	Me_2N	Me_2N	Me_2N	not isolated

[a] Reaction conditions: **11**: MeOH, 20 °C, 4 h; **12**: MeOH / THF, 20 °C, 60 h; **13**: MeOH / dioxane, 95 °C, 90 h; **14**: MeOH / dioxane, reflux, 9 h; **15**: THF, 20 °C, 3 h; **16**: DMF, 150 °C, 7 h; **17**, **18**: Me_2SO, 170 °C, 35 h.

[b] Isolated yield of analytically pure product.

Scheme 3. Synthesis of compounds **11**, **12**, **14-17** and attempted synthesis of compounds **13** and **18**.



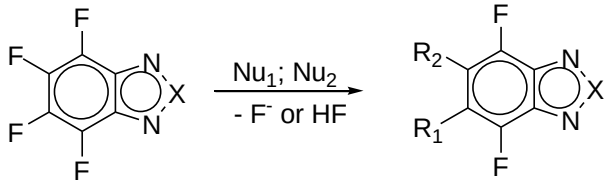
19 **20** - **27**

Compound	Nu	R_1	R_2	R_3	R_4	Yield, % [a,b]
20	MeO^-	F	MeO	F	F	68
21	MeO^-	F	MeO	MeO	F	58
22	MeO^-	MeO	MeO	MeO	F	14
23	MeO^-	MeO	MeO	MeO	MeO	57
24	Me_2NH	F	Me_2N	F	F	49
25	Me_2NH	F	Me_2N	Me_2N	F	48
26	Me_2NH	Me_2N	Me_2N	Me_2N	F	not isolated
27	Me_2NH	Me_2N	Me_2N	Me_2N	Me_2N	not isolated

[a] Reaction conditions: **20**: MeOH / THF, 50 °C, 5 h; **21**: MeOH / dioxane, 85 °C, 8 h; **22**: MeOH / dioxane, 85 °C, 16 h; **23**: MeOH / Me_2SO, reflux, 8 h; **24**: dioxane, 20 °C, 5 h; **25**-**27**: Me_2SO, 175 °C, 12 h.

[b] Isolated yield of analytically pure product.

Scheme 4. Synthesis of compounds **20**-**25** and attempted synthesis of compounds **26** and **27**.



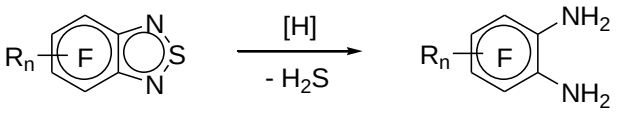
1, **10**, **19** **28** - **30**

Compound	X	Nu_1	Nu_2	R_1	R_2	Yield, % [a,b]
28	$H_2C=CH_2$	Me_2NH	NaOMe	Me_2N	MeO	44
29	S	Me_2NH	NaOMe	Me_2N	MeO	56
30	Se	Me_2NH	NaOMe	Me_2N	MeO	64

[a] Reaction conditions: **28**: dioxane, 60 °C, 7 h (Nu_1), MeOH, reflux, 8 h (Nu_2); **29**: THF, 20 °C, 3 h (Nu_1), MeOH / dioxane, 70 °C, 24 h (Nu_2); **30**: dioxane, 20 °C, 5 h (Nu_1), MeOH / dioxane, 65 °C, 7 h (Nu_2).

[b] Isolated yield of analytically pure product.

Scheme 5. Synthesis of compounds **28**-**30**.



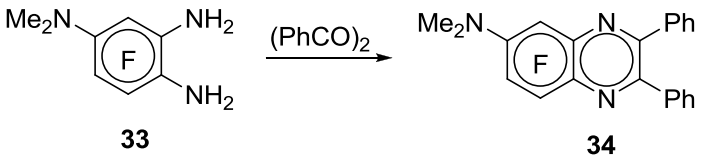
12, **14**, **15** **31** - **33**

Compound	Isolated as	Yield, % [a,b]
31	**31**·2HCl	34
32	**32**·2HCl	78
33	**33**·2HCl	76

[a] Reaction conditions: **31**, **32**: [H] = $LiAlH_4$, THF, 0 °C, 1 h; **33**: [H] = $SnCl_2 \cdot 2H_2O$, conc. HCl, reflux, 1 h.

[b] Isolated yield of analytically pure product.

Scheme 6. Synthesis of compounds **3**1-**33**.



33 **34**

Scheme 7. Synthesis of compound **34**.

Table 1: Relative Gibbs free energies (ΔG_{rel}) of the species involved in the reactions of heterocycles **1**, **10** and **19** with methoxide calculated by the M06-2X/6-31+G(d,p) method for T = 298 K with MeOH solvent accounted using PCM. Relative yields were estimated at 298 K from $\Delta G^{\#}_{rel}$ for the rate determining step.[a]

Compound	Position of substitution	ΔG_{rel}, kcal·mol^{-1}					Relative yield, %
		Starting materials	Transition state TS1	Key intermediate (σ-complex)	Transition state TS2	Final products	
1	6	0.0	12.2	–5.7	–4.4	–27.1	99
	5	0.0	14.8	–3.6	–1.8	–26.5	1
10	5	0.0	11.5	–7.1	–5.9	–27.2	82
	4	0.0	12.4	–7.5	–4.9	–27.5	18
19	5	0.0	11.9	–5.9	–5.2	–27.3	94
	4	0.0	13.6	–6.2	–4.0	–27.0	6

[a] For the full data of the calculations, see ESI, Tables S2-S4.

Table 2: Selected bond lengths (Å) and angles (°) for compounds **4**, **7**, **8**, **11**, **12**, **14**, **15**, **17**, **19**, **21**, **22** and **25**.[a,b]

Compound	Bond / Angle					
	Quinoxalines					
4	N1-C2	C2-C3	C3-N4	N4-C4a	C4a-C8a	C8a- N1
	1.301(4)	1.397(5)	1.308(4)	1.352(3)	1.416(4)	1.358(4)
	C8a-N1-C2	N1-C2-C3	C2-C3-N4	C3-N4-C4a	N4-C4a-C8a	C4a-C8a-N1
	115.7(3)	123.0(3)	122.9(3)	116.1(3)	120.8(2)	121.5(2)
7[c]	N1-C2	C2-C3	C3-N4	N4-C4a	C4a-C8a	
	1.320(4)	1.395(4)	1.318(3)	1.361(4)	1.412(4)	1.360(4)
	C8a-N1-C2	N1-C2-C3	C2-C3-N4	C3-N4-C4a	N4-C4a-C8a	C4a-C8a-N1
	115.3(3)	123.2(4)	123.1(2)	115.3(3)	121.7(6)	121.5(4)
7[d]	N1-C2	C2-C3	C3-N4	N4-C4a	C4a-C8a	N1-C8a
	1.334(8)	1.37(3)	1.305(3)	1.368(5)	1.396(4)	1.35(1)
	C8a-N1-C2	N1-C2-C3	C2-C3-N4	C3-N4-C4a	N4-C4a-C8a	C4a-C8a-N1
	115.3(1)	123.1(2)	123(1)	115.5(5)	121.7(3)	121.2(4)
8	N1-C2	C2-C3	C3-N4	N4-C4a	C4a-C8a	C8a-N1
	1.316(2)	1.393(2)	1.320(2)	1.356(2)	1.416(2)	1.360(2)
	C8a-N1-C2	N1-C2-C3	C2-C3-N4	C3-N4-C4a	N4-C4a-C8a	C4a-C8a-N1
	115.4(1)	123.1(2)	123.1(2)	116.5(1)	120.3(1)	122.1(1)
	Thiadiazoles					
11	N1-S2	S2-N3	N3-C3a	C3a-C7a	N1-C7a	
	1.620(2)	1.616(2)	1.339(3)	1.431(3)	1.342(3)	
	C7a-N1-S2	N1-S2-N3	S2-N3-C3a	N3-C3a-C7a	C3a-C7a-N1	
	106.5(1)	100.7(1)	106.2(1)	113.8(2)	112.9(2)	
12	N1-S2	S2-N3	N3-C3a	C3a-C7a	C7a-N1	
	1.619(2)	1.618(2)	1.347(2)	1.432(3)	1.339(3)	
	C7a-N1-S2	N1-S2-N3	S2-N3-C3a	N3-C3a-C7a	C3a-C7a-N1	
	106.1(1)	100.85(9)	106.4(1)	112.8(2)	113.8(2)	
14	N1-S2	S2-N3	N3-C3a	C3a-C7a	C7a-N1	
	1.619(1)	1.619(1)	1.343(2)	1.435(2)	1.343(2)	
	C7a-N1-S2	N1-S2-N3	S2-N3-C3a	N3-C3a-C7a	C3a-C7a-N1	
	106.52(9)	100.64(9)	106.52(9)	113.16(7)	113.16(7)	
15	N1-S2	S2-N3	N3-C3a	C3a-C7a	C7a-N1	
	1.620(2)	1.617(2)	1.343(2)	1.430(2)	1.338(3)	
	C7a-N1-S2	N1-S2-N3	S2-N3-C3a	N3-C3a-C7a	C3a-C7a-N1	
	106.5(1)	100.59(8)	106.4(1)	113.3(2)	113.3(2)	

Table 2 *(continued)*

Compound	Bond / Angle				
17	N1-S2	S2-N3	N3-C3a	C3a-C7a	C7a-N1
	1.626(2)	1.624(2)	1.344(3)	1.438(3)	1.341(3)
	C7a-N1-S2	N1-S2-N3	S2-N3-C3a	N3-C3a-C7a	C3a-C7a-N1
	105.8(1)	100.7(1)	106.9(1)	112.3(2)	114.4(2)
	Selenadiazoles				
19[e]	N1-Se2		Se-N3		
	1.80(4)		1.81(3)		
21	N1-Se2	Se2-N3	N3-C3a	C3a-C7a	C7a-N1
	1.798(4)	1.793(4)	1.328(5)	1.435(5)	1.325(5)
	C7a-N1-Se2	N1-Se2-N3	Se2-N3-C3a	N3-C3a-C7a	C3a-C7a-N1
	106.7(3)	93.6(2)	106.6(3)	116.6(3)	116.4(3)
22[f]	N1-Se2	Se2-N3	N3-C3a	C3a-C7a	C7a-N1
	1.790(4)	1.790(3)	1.323(4)	1.446(4)	1.326(4)
	C7a-N1-Se2	N1-Se2-N3	Se2-N3-C3a	N3-C3a-C7a	C3a-C7a-N1
	106.4(2)	93.5(5)	107.1(4)	115.8(5)	116.6(4)
25	N1-Se2	Se2-N3	N3-C3a	C3a-C7a	C7a-N1
	1.801(3)	1.800(1)	1.325(1)	1.444(6)	1.324(3)
	C7a-N1-Se2	N1-Se2-N3	Se2-N3-C3a	N3-C3a-C7a	C3a-C7a-N1
	106.8(4)	93.5(1)	106.7(1)	116.6(2)	116.4(2)

[a] For atom numbering, see Figure 2. [b] In thia/selenadiazoles the bond distances C3a-C4 and C7-C7a lie in the range of 1.408–1.423 Å, C4-C5 and C6-C7 in the range of 1.341–1.371 Å, and C5–C6 in the range of 1.447–1.463 Å, except **25** where this bond elongated to 1.478 Å. Bond distances C-C in quinoxalines are close to corresponding values in thia/selenadiazoles. Data span of the bond distances C-F for the all compounds is 1.338–1.361 Å. [c] Average data for 4 independent molecules of the polymorph (m. p. 113-114 °C). [d] Average data for 2 independent molecules of another polymorph (m. p. 115-116 °C). [e] Average data for 8 crystallographically independent molecules of racemic twin. [f] From 3 : 1 co-crystal with **21**.

Table 3: Melting points and MS data of compounds.

Compound	M. p., ºC	MS, m/z, found / calc. (formula)
2	62-63	214.0348 / 214.0349 ($C_9H_5F_3N_2O$)
3	126.5-127.5	226.0052 / 226.0548 ($C_{10}H_8F_2N_2O_2$)
4	66-67	238.0745 / 238.0748 ($C_{11}H_{11}FN_2O_3$)
5	54-55	250.0947 / 250.0948 ($C_{12}H_{14}N_2O_4$)
6	78-79; 86-87[a]	227.0661 / 227.0665 ($C_{10}H_8N_3F_3$)
7	113-114; 115-116[a]	252.1175 / 252.1181 ($C_{12}H_{14}F_2N_4$)
8	81-82	277.1695 / 277.1697 ($C_{14}H_{20}FN_5$)
11	35-36	219.9915 / 219.9913 ($C_7H_3F_3N_2OS$)
12	70-71	232.0115 / 232.0113 ($C_8H_6F_2N_2O_2S$)
14	43-44	256.0509 / 256.0512 ($C_{10}H_{12}N_2O_4S$)
15	42-43	233.0230 / 233.0229 ($C_8H_6F_3N_3S$)
16	59-60	258.0741 / 258.0745 ($C_{10}H_{12}F_2N_4O_3S$)
17	57-58	283.1264 / 283.1261 ($C_{12}H_{18}FN_5S$)
20	156-157	265.9361 / 265.9365 ($C_7H_3F_3N_2O^{78}Se$)
21	119-120	277.9569 / 277.9565 ($C_8H_6F_2N_2O_2{}^{78}Se$)
22	136-137	287.9781 / 287.9784 ($C_9H_9FN_2O_3{}^{76}Se$)
23	77-78	301.9970 / 301.9965 ($C_{10}H_{12}N_2O_4{}^{78}Se$)
24	124-125	280.9678 / 280.9673 ($C_8H_6F_3N_3{}^{80}Se$)
25	162-163	304.0194 / 304.0198 ($C_{10}H_{12}F_2N_4{}^{78}Se$)
28	49-50	239.0864 / 239.0865 ($C_{11}H_{11}F_2N_3O$)
29	78-79	245.0424 / 245.0429 ($C_9H_9F_2N_3OS$)
30	108-109	290.9878 / 290.9881 ($C_9H_9F_2N_3O^{78}Se$)
31·2HCl	180-184 (dec.)	–
32·2HCl	176-180 (dec.)	–
33·2HCl	100-103 (dec.)	–
34	149-150	379.1295 / 379.1291 ($C_{22}H_{16}F_3N_3$)

[a] Two polymorphs.[32]

Table 4: Analytical data for compounds.[a]

Compound	Found / calculated %			
	C	H	F	N
2	50.60 / 50.48	2.50 / 2.35	26.60 / 26.62	13.01 / 13.08
3	52.96 / 53.10	3.42 / 3.57	16.76 / 16.81	12.26 / 12.39
4	55.60 / 55.46	4.37 / 4.65	8.15 / 7.98	11.97 / 11.76
5	57.55 / 57.58	5.37 / 5.59	–	11.21 / 11.19
6	52.91 / 52.87	3.22 / 3.55	25.03 / 25.09	18.53 / 18.50
7	57.26 / 57.13	5.83 / 5.59	15.24 / 15.06	22.60 / 22.22
8	60.62 / 60.63	7.21 / 7.27	6.90 / 6.85	25.17 / 25.25
11	38.37 / 38.19	1.47 / 1.37	25.56 / 25.89	12.51 / 12.72
12	41.50 / 41.38	2.70 / 2.60	16.50 / 16.36	12.08 / 12.06
14	46.84 / 46.87	4.73 / 4.72	–	10.97 / 10.93
15	41.19 / 41.20	2.81 / 2.59	24.78 / 24.44	18.26 / 18.02
16	46.40 / 46.50	4.63 / 4.68	14.63 / 14.71	21.56 / 21.69
17	51.10 / 50.86	6.36 / 6.40	6.86 / 6.70	24.80 / 24.71
20	31.25 / 31.48	1.02 / 1.13	21.33 / 21.34	10.70 / 10.49
21	34.10 / 34.43	2.04 / 2.17	13.47 / 13.61	9.98 / 10.04
22	37.56 / 37.13	3.23 / 3.12	6.10 / 6.53	9.44 / 9.62
23	39.26 / 39.62	3.99 / 3.99	–	9.38 / 9.24
24	34.52 / 34.30	2.21 / 2.26	20.20 / 20.35	15.14 / 15.00
25	38.88 / 39.36	H 4.11 / 3.96	12.53 / 12.45	18.09 / 18.36
28	55.25 / 55.23	4.48 / 4.63	15.94 / 15.88	17.41 / 17.57
29	44.03 / 44.08	3.62 / 3.70	15.62 / 15.49	17.26 / 17.13
30	37.25 / 37.00	3.29 / 3.11	13.35 / 13.01	14.5 / 14.38
31·2HCl	39.94 / 39.88	5.94 / 6.02	–	9.28 / 9.30
32·2HCl	34.36 / 34.68	3.99 / 4.37	14.12 / 13.71	9.83 / 10.11
34	69.43 / 69.65	4.37 / 4.25	14.73 / 15.02	11.35 / 11.08

[a] S: **11**: 14.52 / 14.56; **12**: 14.08 / 13.81; **15**: 13.87 / 13.75; **16**: 12.34 / 12.41; **17**: 11.16 / 11.32. Se: **20**: 29.45 / 29.57; **21**: 28.10 / 28.29; **22**: 26.98 / 27.12; **23**: 26.42 / 26.04; **24**: 28.05 / 28.19; **25**: 25.74 / 25.87; **30**: 27.12 / 27.03. Cl: **31**·2HCl: 23.78 / 23.54; **32**·2HCl: 25.40 / 25.59. O: **5**: 25.49 / 25.59.

Table 5: NMR, UV-Vis and FL data for compounds.[a,b]

Compound	NMR, δ		UV-Vis, λ_{max}, nm (log ε)	FL, λ_{max} (λ_{exc}), nm
	^{1}H	^{19}F [c]		
2	8.87, 4.26	–148.0, –150.3, –155.3	320 (3.70)	396 (320)
3	8.86, 4.24	–151.4	327 (3.73)	408 (329)
4	8.75, 4.16, 4.09, 4.06	–151.8	330 (3.68)	474 (332)
5	8.72, 4.07, 4.05	–	334 (3.70)	514 (344)
6	8.79, 8.72, 3.10	–140.7, –144.9, –156.8	373 (3.70)	438 (369)
7	8.63, 2.99	–144.8	385 (3.86)	461 (386)
8	8.60, 8.55, 2.96, 2.93, 2.92	–142.6	390 (3.96)	579 (390)
11	4.28	–146.4, –147.8, –151.1	312 (4.06), 343 (sh., 3.49)	423 (313)
12	4.19	–147.5	319 (4.14)	433 (319)
13	4.18, 4.14, 4.00	–149.4	–	–
14	4.16, 4.01	–	323 (4.07), 372 (3.45)	551 (324)
15	3.08	–139.6, –140.8, –152.1	388 (3.76)	464 (3.87)
16	2.99	–140.7	378 (3.97)	490 (378)
17	2.92	–139.3	384 (3.96)	601 (379)
20	4.27	–147.8, –149.0, –151.2	333 (4.10)	404 (361)
21	4.17	–148.5	334 (4.15), 337 (4.15)	539 (341)
22	4.14, 4.12, 4.03	–149.2	342 (3.79)	553 (342)
23	4.11, 4.04	–	397 (3.24)	607 (397)
24	3.06	–142.1, –142.2, –152.4	417 (3.69)	499 (424)
25	2.96	–141.0	394 (4.07)	532 (394)
28	8.72, 8.68, 4.11, 3.05	–145.1, –151.8	371 (3.70)	445 (363)
29	4.11, 3.02	–141.4, –148.1	389 (3.66)	472 (388)
30	4.13, 3.02	–142.0, –148.5	417 (3.61)	581 (435)
31·2HCl [d]	3.96, 3.94	–	–	–
32·2HCl [d]	3.93	–149.9	–	–
33	3.38, 2.84	–148.6, –159.2, –164.6	–	–
34	7.55, 7.37, 3.15	–141.8, –144.1, –156.7	386 (3.94)	455 (385)

[a] ^{13}C: **5**: 147.9, 143.2, 142.9, 135.5, 62.4, 61.6.

[b] ^{77}Se: **20**: 1555; **21**: 1546; **22**: 1530; **23**: 1514; **24**: 1548; **25**: 1533; **30**: 1550.

[c] Standard $CFCl_3$; for standard C_6F_6, $\delta^{19}F$ = –162.9 ppm with respect to $CFCl_3$.

[d] In methanol-d_4.