Anna V. Gulevskaya*, Shee Van Dang, and Alexander F. Pozharskii

Faculty of Chemistry, Rostov-on-Don State University, Zorge str., 7, Rostov-on-Don, 344090 Russian Federation

Synthesis of some condensed pyrrolo-, thieno-, furo-, pyrido- and pyranopteridines as well as isomeric pyrrolo- and thienopyrimido[4,5-*c*]pyridazines from alkynyl derivatives of 6,8-dimethylpyrimido[4,5-*c*]pyridazine-5,7(6*H*,8*H*)-dione and 1,3-dimethyllumazine is represented.

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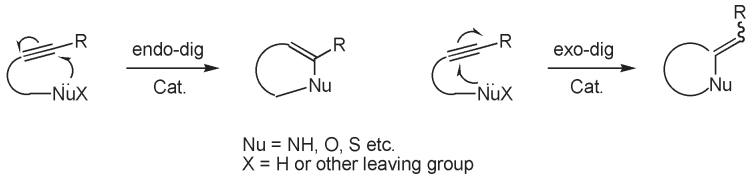
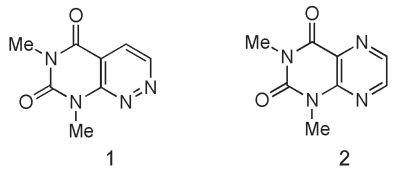
The cyclization of alkynes possessing a nucleophile in proximity to the triple bond has been shown to be extremely effective for synthesis of a wide variety of carbo- and heterocycles [1-4]. In general, such transformations proceed according to Scheme 1 and require a catalyst (a base, transition metal complex or electrophile).

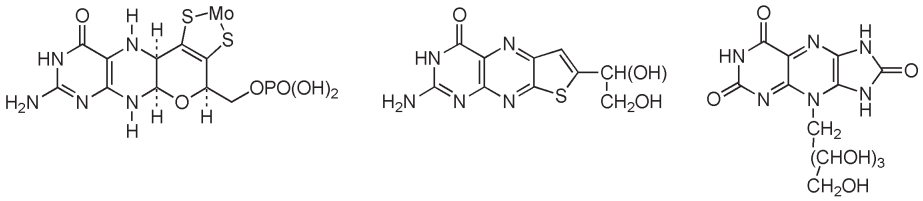
Scheme 1



Scheme 2



1 2



Molibdopterine Urothione Russupteridine yellow

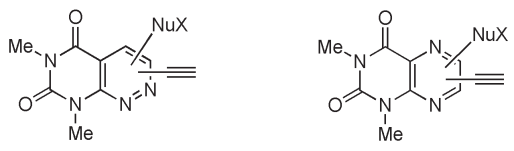
its metabolite urothione and pigment russupteridine yellow (Scheme 2).

Thus, our initial goal consisted in introducing of alkynyl and nucleophilic groups into diazine nucleus of compounds **1** and **2** (Scheme 3).

One of the best synthetic methods for arylacetylenes is palladium-catalyzed Sonogashira cross-coupling of aryl-

For some time we were interested in extending this methodology to pyrimidopyridazine **1** and lumazine **2** in hope to obtain analogues of some naturally occurring pteridines, such as molybdenum cofactor molibdopterine,

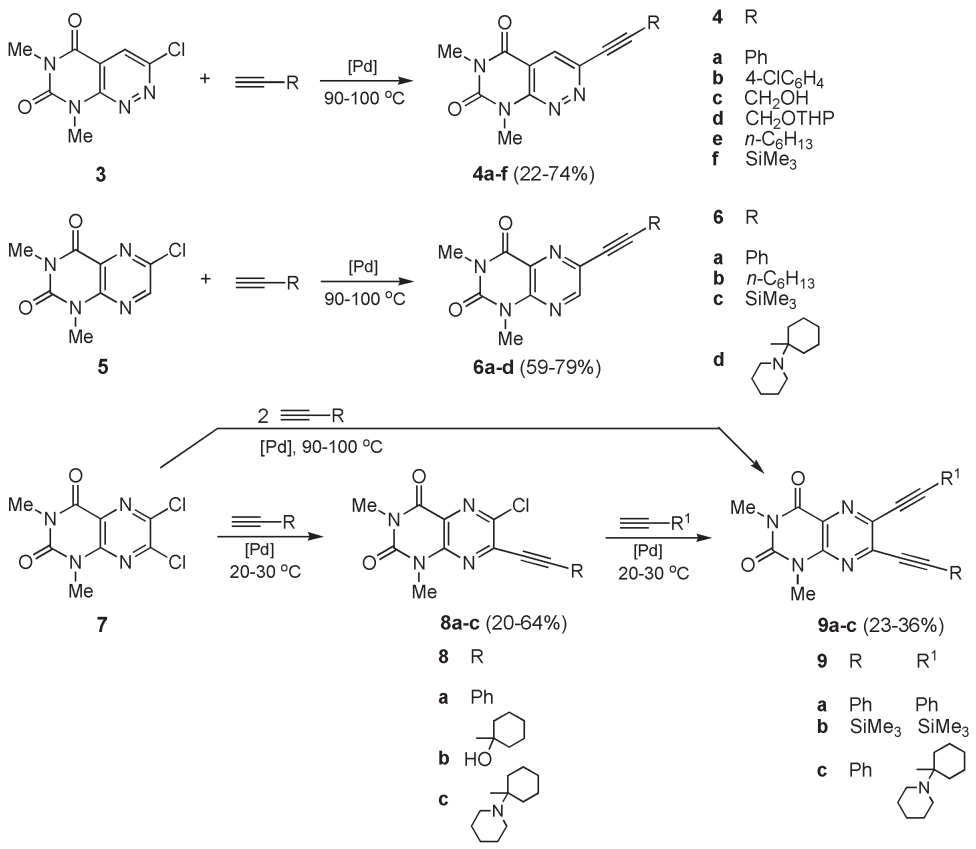
Scheme 3



halides with terminal alkynes [5]. We have applied similar procedure for pyrimidopyridazine and lumazine chlorides **3** and **5** (Scheme 4). As a result alkynyl derivatives **4** and **6** were obtained in good yields. In 6,7-dichlorolumazine **7** the chlorine atoms exhibit strongly different lability making it possible to replace them successively: thus at room

Based on these data we have assumed that oxidative amination of alkynes **4** and **6** could also provide aminoacetylenes **14** and **16** capable to cyclization into pyrroles **15** and **17** (Scheme 6). Indeed, we were pleased to find that the interaction of compounds **4** and **6** with primary alkylamines in the presence of an oxidant at 0-20 °C

Scheme 4

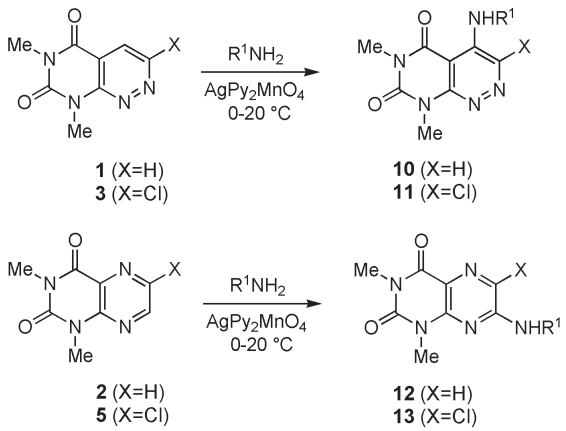


[Pd] = Pd_2dba_3, PPh_3, CuI, K_2CO_3, DMF, argon *or* Pd_2dba_3, PPh_3, CuI, Et_3N, argon

temperature monoacetylenes **8** are formed, whereas at a higher temperature diacetylenes **9** can be obtained. Compounds **8** are converted into **9** by the same way [6-8].

It is well known that common strategy for inserting of amino and other nucleophilic functions into an azine ring is replacement of good-leaving groups. However, in last years nucleophilic substitution of hydrogen finds ever-increasing use for this aim [9,10]. Recently [11,12], we have shown that pyrimidopyridazine **1** and its 3-chloride **3** undergo oxidative amination with ammonia and alkylamines at position 4 (Scheme 5). Under the same conditions the lumazines **2** and **5** affords 7-amino derivatives **12** and **13** [7,13,14].

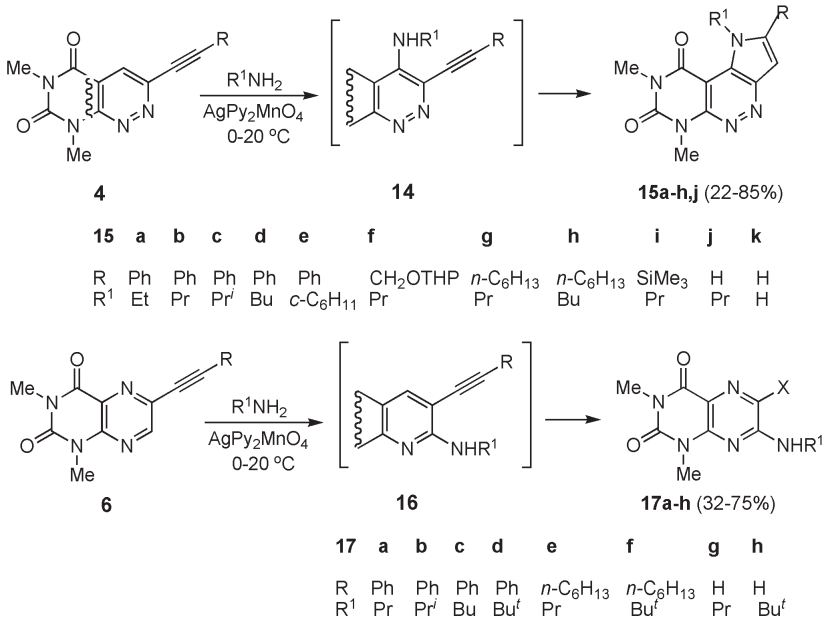
Scheme 5



produced right away pyrroles **15** and **17** [6,7]. Apparently, these transformations proceed through intermediate *ortho*-aminoacetylenes **14**,**16** and their cyclizations are likely promoted by coordination of silver ion with the carbon-carbon triple bond.

to a procedure recently reported by English chemists [15]. It involves the addition of bromine to the arylalkyne's triple bond and subsequent cyclization of the resulted dibromide at treatment with sodium trithiocarbonate. Using acetylenes **4**,**6** as starting material and

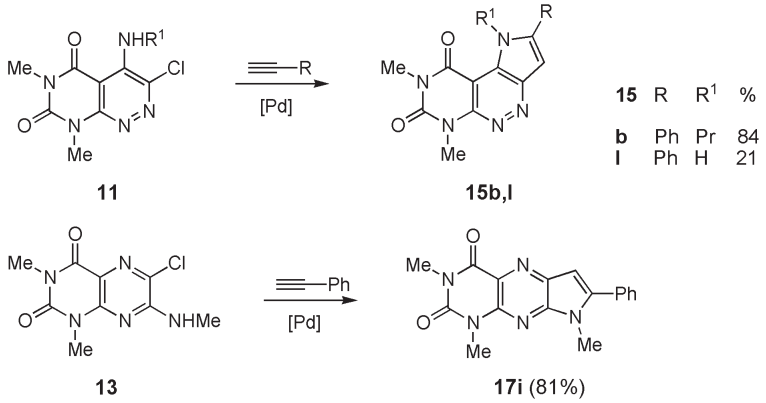
Scheme 6



Both pyrroles **15** and **17** were also obtained by Sonogashira cross-coupling of *ortho*-aminohalides **11**,**13** with terminal alkynes (Scheme 7) [7,12].

the pointed out conditions we have prepared desired thiophenes **19** and **21** in moderate to good yields (Scheme 8) [7,16].

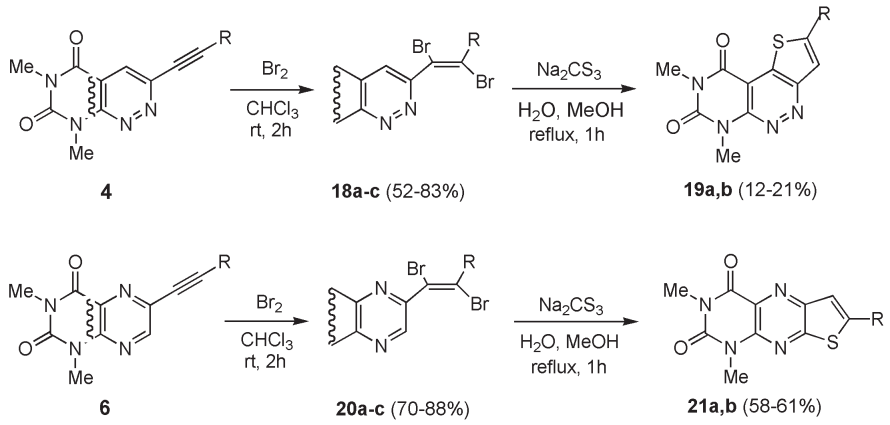
Scheme 7



Next, we attempted to annulate the thiophene ring to pyrimidopyridazine and lumazine systems according

To obtain pyrroles **23** and **24** isomeric to **17** (Scheme 9) we have studied the interaction of alkynyllumazines **8** and

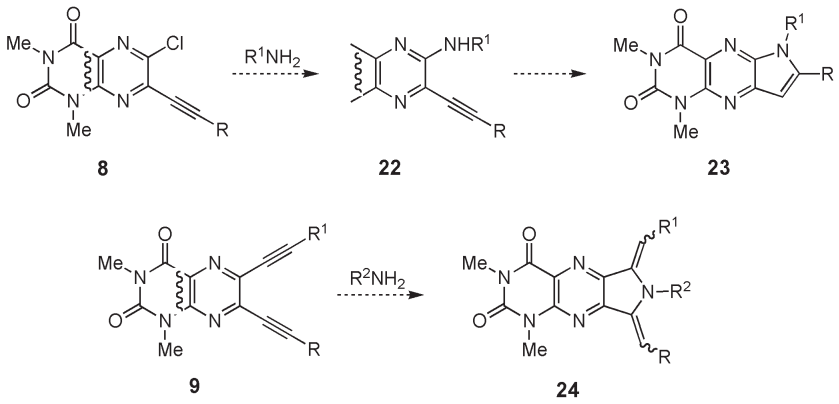
Scheme 8



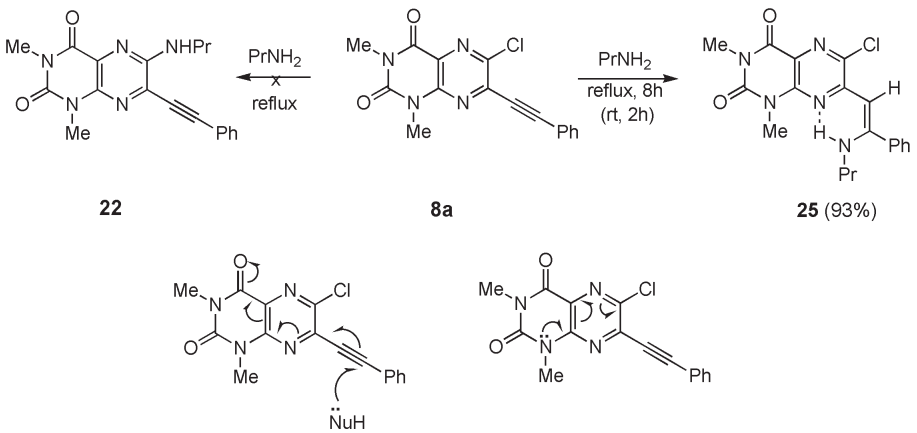
18-21: R=Ph (**a**), *n*-C_6H_{13} (**b**), $SiMe_3$ (**c**)

9 with alkylamines. However, we have found that treatment of alkynylchoride **8a** with propylamine at room temperature or under reflux afforded almost quantitative yield of enamine **25** instead of expected compound **22** or its cyclization product (Scheme 10) [8]. Perhaps the simplest explanation for this behaviour of molecule **8a** is activation of the triple bond to nucleophilic attack due to its conjugation with carbonyl group. On the contrary, the 6-chlorine atom is deactivated by electron donating influence of the uracil nitrogen atom.

Scheme 9



Scheme 10

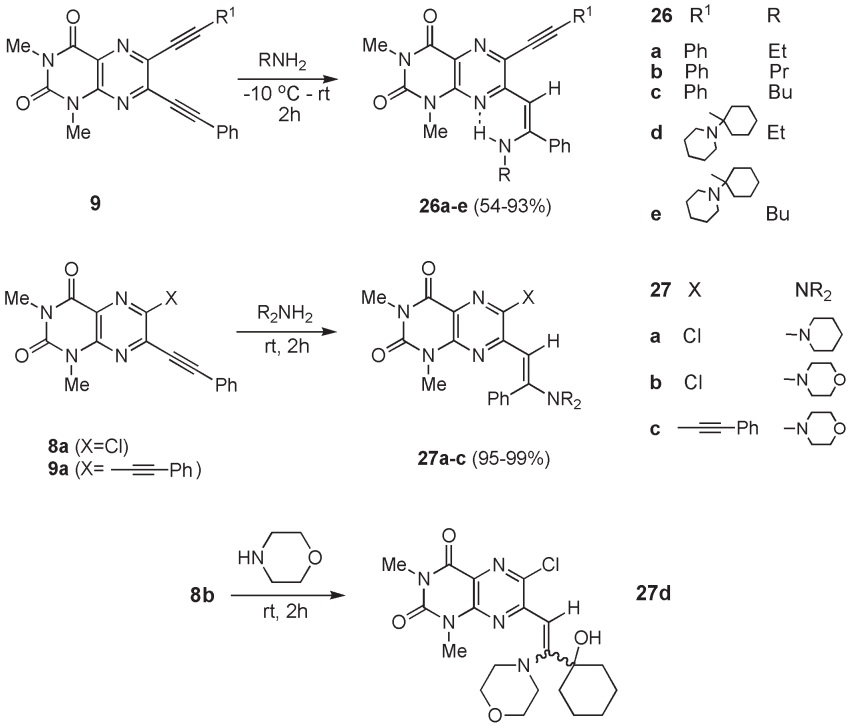


Dialkynyllumazines react with primary amines by the same way to yield adducts **26** (Scheme 11) [8]. As it follows from spectral data compounds both compounds **25** and **26** are stabilizing by intramolecular hydrogen bonding shown on Schemes 10,11. But it seems to be not sole reason for their stability, because of enamines **27** derived from secondary amines are also stable. Evidently, the conjugation of amino group with azine π-system should be also taken into account.

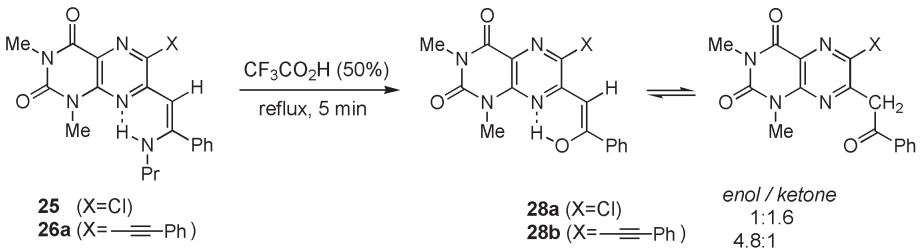
Enamines **25** and **26a** are hydrolyzed under reflux in aqueous trifluoroacetic acid to furnish compounds **28** existing as a mixture of enol and the corresponding ketone (Scheme 12) [8].

Enamines **25** and **27d** as well as enols **28a** were successfully employed in annulation reactions [8]. Thus, heating of enamine **25** with potash in DMF solution leads to formation of pyrrole **29a** (Scheme 13). Prolonged reflux of alkynylchloride **8a** with butylamine

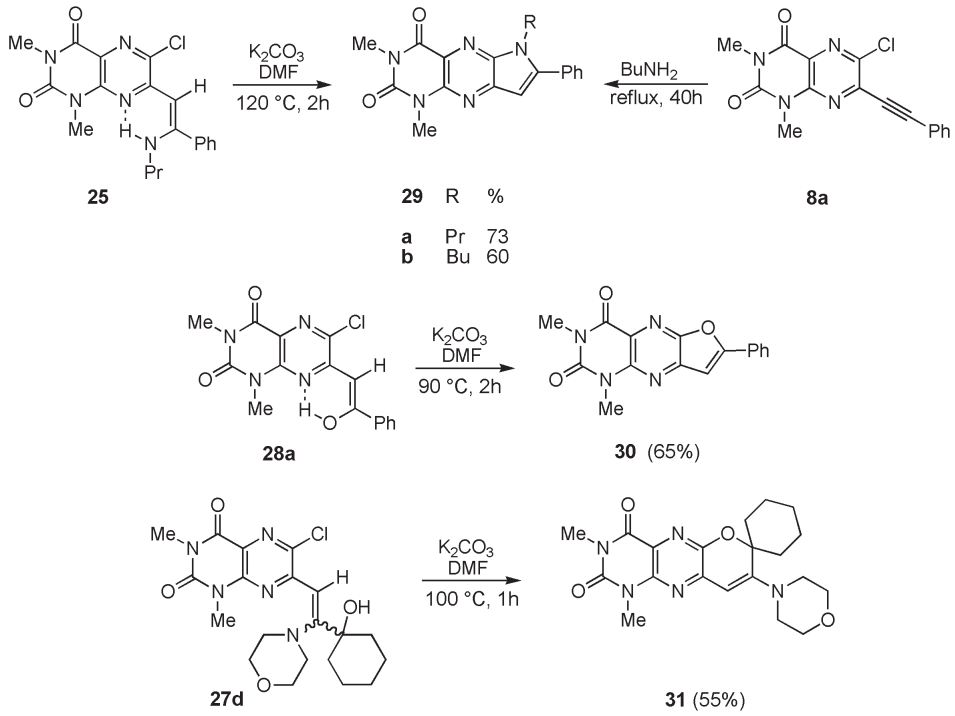
Scheme 11



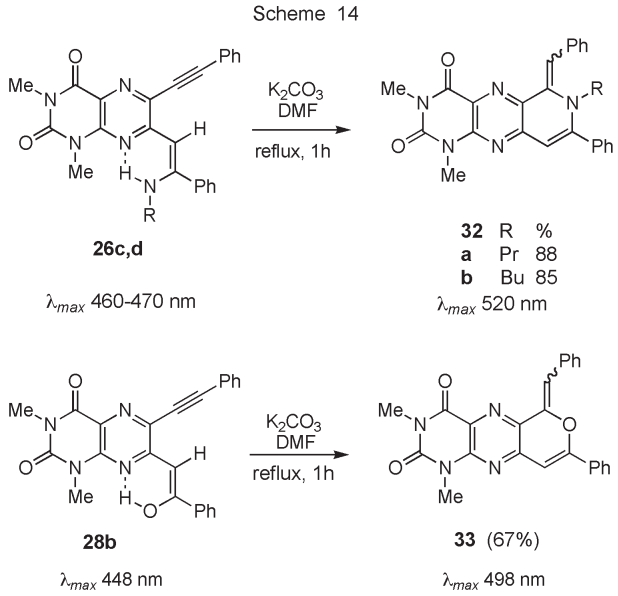
Scheme 12



Scheme 13



Scheme 14



is also resulted in pyrrole-ring annulation, undoubtedtly proceeding via enamine intermediate of a type **29**. Using potash as a catalyst we performed cyclizations of compounds **28a** and **27d** into furopteridine **30** and pyranopteridine **31** respectively.

Interestingly, that enamines and enols derived from dialkynyllumazines are also able to cyclization. Thus, when compounds **26c,d** were heated with potassium carbonate cyclomerization products **32** were isolated (Scheme 14) [8]. Under similar conditions enol **28b** produced pyrane **33**. It should be noted, that the above transformations represent new routes for [*c*]-condensed pyridines and pyranes.

In summary, we have elaborated the synthesis of the following nine types of heterocyclic systems, closely related to naturally occurring pteridines (Scheme 15).

Acknowledgement.

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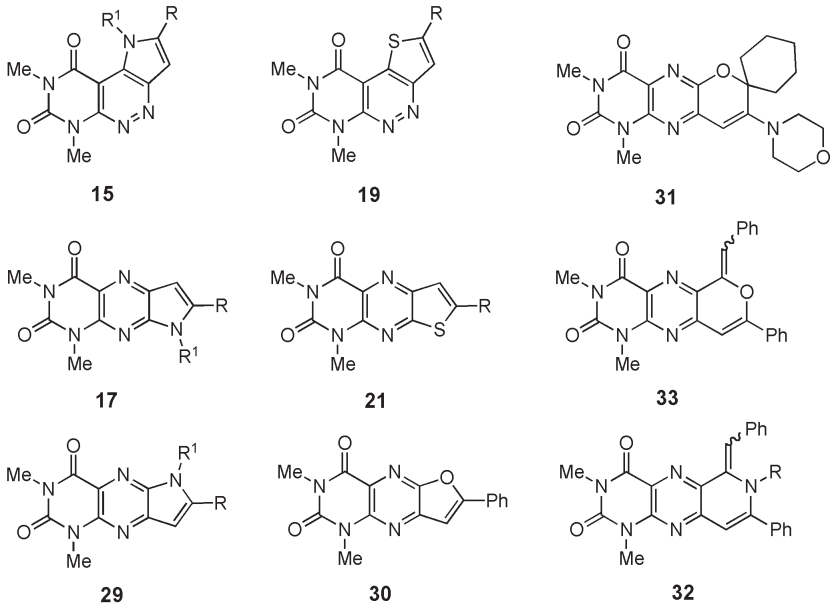
Scheme 15



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* Corresponding authors. E-mail: agulevskaya@chim-fak.rsu.ru

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