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6,7-Dimethoxy-3,4-dihydroisoquinolin-1(2*H*)-ylidenoacetonitrile in Some Fusion Reactions

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Abstract—6,7-Dimethoxy-3,4-dihydroisoquinolin-1-ylacetonitrile in the enamine form readily reacts with acyl iso(thio)cyanates affording in high yields 1,2-fused oxo- and thioxodihydropyrimidoisoquinolines and thiouracyloisoquinolines. The reaction of the enamine with primary amines of diverse classes in the presence of 2 equiv of formaldehyde resulted in 1,2-fused N-substituted tetrahydropyrimidinoisoquinolines whose yields depended on the basicity and sterical accessibility of the reagent. Fused 5-hydroxyindolo-, dioxopyrrolo-, pyrroloisoquinolines formed in medium yields in the one-stage reactions of the enamine with *p*-benzoquinone, oxalyl chloride, and β-nitrostyrene respectively. The reaction of 1-cyanomethyl-6,7-dimethoxydihydroisoquinoline with acrylonitrile leads to the formation of 1,2-fused iminopyridinoisoquinoline easily hydrolysable to pyridine derivative and readily reacting by the amidine group with aroyl chlorides and arylsulfonyl chlorides.

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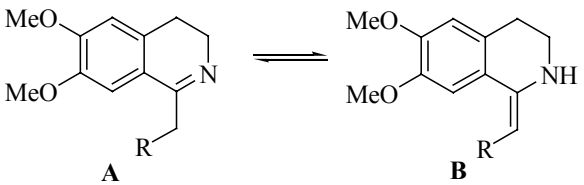
1-Alkyl-6,7-dimethoxy-3,4-dihydroisoquinolines as typical cyclic Schiff bases suffer the imine-enamine isomerization [1–4].

Each tautomeric form possesses a considerable synthetic potential in 1,2-cyclocondensation reactions leading to the formation of alkaloid- [5] and steroid-like [3, 5] compounds. Imine tautomer **A** being a dipole is prone to reactions with dipolarophiles, enamine tautomer **B** is a pronounced C,N-dinucleophile [3, 6, 7] ready to react with dielectrophiles of various nature. Both isomers can be involved into various modifications of Diels–Alder reaction as a dienophile [3], and sometimes also as diene [8].



A **B**

In the 1-alkyl-3,4-dihydroisoquinoline series the reactions involving imine and/or enamine forms have been thoroughly studied within the last 40 years; the results of this research has been summarized in a number of reviews and books [1–5, 9–12]. For instance, examples are known of reactions of enamines of **B** type with diverse representatives of α,β-unsaturated carbonyl compounds (nitriles, amides, esters and anhydrides of unsaturated acids, enones and enales, acetylenedicaboxylic acid esters), with β-di- and some β,β'-tricarbonyl compounds and their enol forms, with dielectrophiles of various character (1,3-dihaloalkanes) [3, 4], and also with haloalkanecarboxylic acids esters [13], bromoacetal [13], oxalyl chloride [14, 15], alkyl isocyanate haloderivatives [5], quinones [13], pyrilium salts [3], etc. Many among the above cited compounds are prone to react also with the imine form **A** forming sometimes the products of quite different structure [16, 17]. The range of dielectrophiles brought into the reactions of cycles formation is significantly wider for aliphatic enamines with the open chain, in particular, with the primary, secondary and especially with the tertiary amino function of enamine [9–12].

Therefore disregarding the huge amount of research performed on 1-alkyl-3,4-dihydroisoquinolines still the extension of the reagents series remains urgent with

respect to dielectrophiles (dipolarophiles) whose reactions with enamines (imines) of another structure would provide isoquinoline compounds previously unknown or difficultly available, with the selective involvement of one of the tautomeric forms **A**, **B** into fusion reactions.

This target can presumably be fulfilled by the use as substrates in the new fusion versions of such 1-alkyl-3,4-dihydroisoquinolines where the equilibrium is essentially shifted to the side of one of the isomers. The easiest case is the materially complete shift of the equilibrium to the side of enamine **B**. This is favored either by the N-acylation of 1-alkyl-3,4-dihydroisoquinolines with the formation of the corresponding enamides [1, 9], or by the introduction of an electron-withdrawing substituent R [3, 4].

6,7-Dimethoxy-3,4-dihydroisoquinolin-1-ylacetonitrile (**I**) exists mainly in the enamine form **B** [20]. This is confirmed by the presence of the absorption bands at 3332, 3335 (N–H) and 2185 cm^{-1} (conjugated C≡N bond) in the IR spectrum [18], by the presence of strong absorption maxima at 328 nm and weak absorbance at 280 nm (characteristic maximum for 1-methyl-3,4-dihydroisoquinoline existing mainly in the imine form) in the UV spectrum [18], the appearance of singlet signals at 5.65 (methylene CH) and 4.25 ppm (NH) in the ^{1}H NMR spectrum with an appropriate integral intensity. The assignment of the signals of the enamine fragment was performed taking into account the results of the study of various isomers of N-methylated structural analogs of compound **I** [19].

We brought compound **I** into reactions with versatile dielectrophiles and obtained as a result 1,2-heterofused 6,7-dimethoxytetrahydroisoquinolines, structural analogs of a series of natural alkaloids promising as biologically active substances.

Iso(thio)cyanates, highly reactive biselectrophiles, are widely applied as C,N,O(S)-containing α-synthons in designing heterocycles [20, 21]. They readily react with enamines of diverse structures [8, 10, 20–27]. The reaction as a rule is started by the attack of the carbon atom of the iso(thio)cyanate group on the C-nucleophilic site of the enamine (when it is inaccessible, the attack is directed on the N-nucleophilic site [25]) followed by the cyclization of the formed intermediate [25–27]. The cyclization character depends on the structure of the initial enamine and the type of isocyanate.

For instance, after the reaction with acyl iso(thio) cyanates the aliphatic and carbocyclic enamines with a tertiary amino group loose it in the stage of cyclization giving as a result fused oxazinethiones [8, 25–27], and in the presence of a source of ammonium group (ammonia, ammonium acetate), substituted and/or fused pyrimidones, pyrimidonethiones [26], pyrimidonethiols [10] of various degree of aromatization. Yet the primary and secondary amino groups as structural elements of aliphatic [10, 19, 25–27], carbocyclic [25–27] and some heterocyclic [20–27] enamines in analogous transformations remain intact in the course of the formation of similar cyclization products, pyrimidone(thione)s of various structures.

Unlike the acyl derivatives the alkyl isocyanates require severe conditions in the reactions with enamines and basic catalysis in the cyclization stage [25]. Therewith the intermediate products of the reaction between the aliphatic enamines and activated chloroalkyl isocyanates [25–27] can suffer more complex transformations loosing a number of functional groups and forming dihydropyridones of various structures.

We did not find any publications on the reactions of acyl iso(thio)cyanates with enamines[1] of type **B.**

We found that compound **I** readily reacted with acyl iso(thio)cyanates of various structures. In anhydrous acetonitrile after heating for 15 min at 50°C enamine **I** with 5% excess of benzoyl isothiocyanate or benzoyl isocyanate (at room temperature) we obtained in 88 and 85% yield two compounds whose presumable structures were 9,10-dimethoxy-4-phenyl-2-thioxo-6,7-dihydro-2*H*-pyrimido-[6,1-*a*]isoquinoline-1-carbonitrile (**II**) and its 2-oxo-analog **III** respectively (Scheme 1).

In the ^{1}H NMR spectra of arising compounds **II** and **III** the singlet signals 4.25 and 5.55 ppm of amino group and the hydrogen at sp^2-carbon atom of the initial enamine disappear, and a new group of signals of five aromatic protons of the phenyl group appears. The IR spectrum contains the characteristic absorption bands of the stretching vibrations of thion and carbonyl groups respectively.

Compound **II** at the treatment with methyl iodide in DMSO formed an orange precipitate of compound **IV** whose ^{1}H NMR spectrum contains a singlet signal at

[1] Similar in structure 6,7-dimethoxy-1-(cyanomethyl)tetrahydroisoquinoline reacted like a common secondary amine with β-chloroethyl isocyanate at the NH group, and further under the action of a base suffered tandem cyclizations involving the cyano group of the side chain and formed finally an imidazo[1',2',3,4]pyrimido[6,1-*a*]isoquinoline[15].

2.95 ppm from the protons of CH_3 group and the retained set of signals of the initial compound. This means that a methylsulfanyl group formed indicating the presence of a thione fragment in compound **II**. Also the argentometric titration showed the presence of a iodide anion in the composition of compound **IV**. The assumed conversions are also confirmed by significant changes in the IR spectrum in going from compound **II** to its methylation product **IV**: The absorption bands at 1203, 1155, 1107 cm^{-1} disappeared, and the intensity of absorption in the region 1560 and 1278 cm^{-1} essentially decreased.

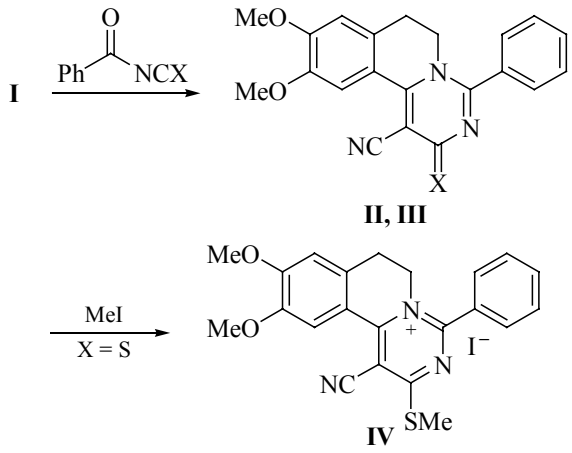
The result of the reaction of enamine **I** with acyl iso(thio)cyanates significantly depends on the reactivity and the structure of the latter. In the series of the investigated iso(thio)cyanates the benzoyl derivatives leading to the formation of fused pyrimidoisoquinoline derivatives possess moderate reactivity.

The most active chlorosulfonyl and also trichloroacetyl iso(thio)cyanates with a labile acyl moiety even at low temperature and in solvents of low polarity afforded intractable mixtures containing both the products of the reaction of the iso(thio)cyanate group with each nucleophilic site of the enamine and a mixture of the decomposition products of the acylating agent itself and the intermediates of acylation.

The least reactive ethoxycarbonyl isothiocyanate reacted with enamine **I** loosing the ethoxy group and forming fused thiouracyl (**V**) (Scheme 2). This structure is confirmed by the lack of the amino group protons and of the sp^2-carbon atom of the initial enamine, of the ethoxy group of the reagent, by the appearance of a broad signal at 13.05 ppm in the ^{1}H NMR spectrum and of the characteristic bands of the stretching vibrations of S=O and C=O groups in the IR spectrum. In contrast to the reaction with benzoyl iso(thio)cyanates where the 1,2-cyclization results apparently from the intramolecular dehydration of the formed in the equilibrium the hydroxyimine and amine structural fragments of intermediates of **VI** type, the fusion involving the ethoxycarbonyl isothiocyanate (Scheme 2) alongside the above mentioned has another possibility of the intramolecular attack on the amino group of the enamine of the carbon atom of the ester group in intermediate **VI** giving reaction product **V**.

For the less active ethoxycarbonyl isothiocyanate we were able to establish the sequence of the reaction of the nucleophilic centers of enamine **I** with the thiocyanate group of the reagent reacting first of all. In acetonitrile, in keeping with the data of ^{1}H NMR spectra and HPLC,

Scheme 1.



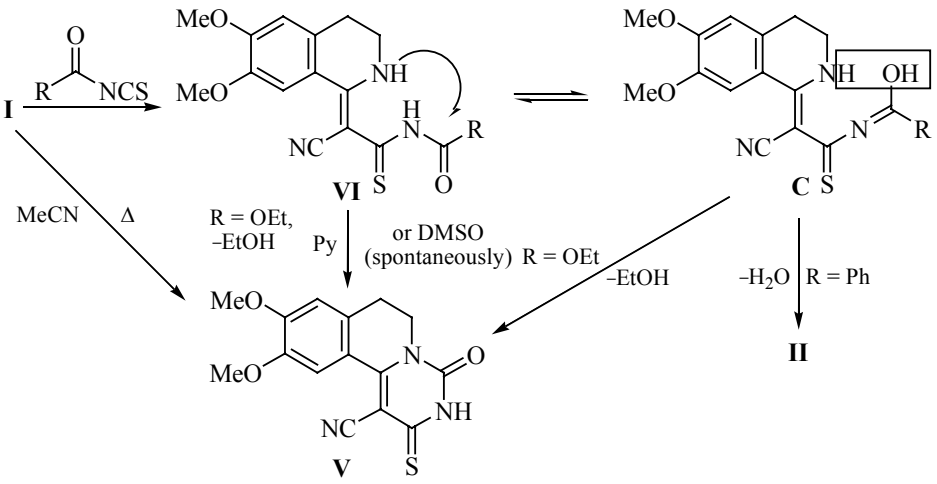
X = O (**II**), S (**III**).

formed a mixture of compounds **V** and **VI** (R = OEt), ~90:10, which in the conditions of recording the spectrum (DMSO, 25°C) spontaneously converted into the monosubstituted product **V**. In ether the intermediate compound (**VI**, R = OEt) prevailingly formed which was successfully isolated and characterized. Its ^{1}H NMR spectrum contained a signal at 10.45 ppm, and also a set of signals characteristic of the ethoxy and NH groups of enamine; the signal at 13.05 ppm characteristic of the final product was absent.

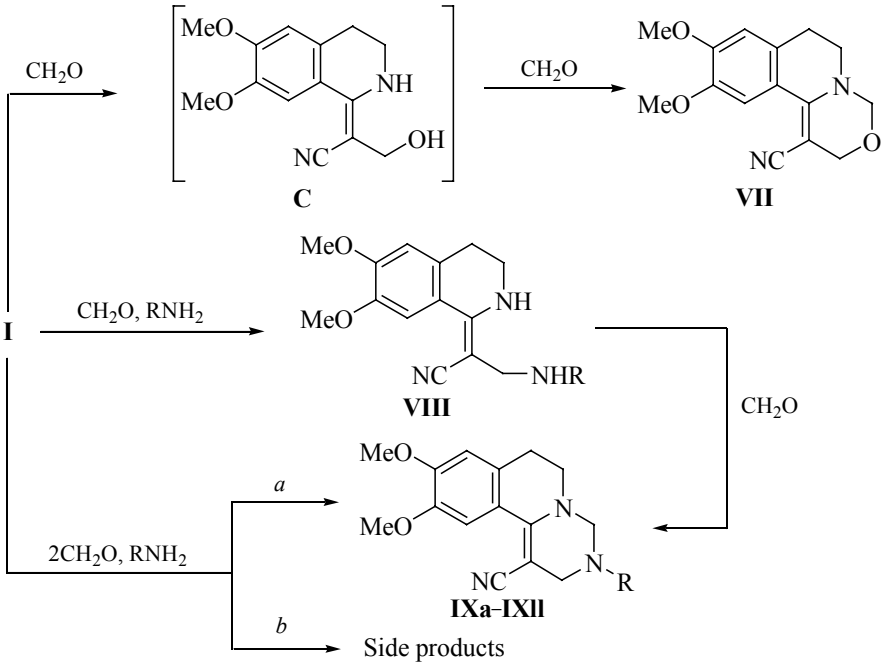
At heating in DMSO or at treating with pyridine compound (**VI**, R = OEt) gave cyclization product **V** identical to that obtained directly from compound **I** in acetonitrile.

Enamines, especially those containing a primary and a secondary amino groups, seldom are used [28] as substrates in the Mannich reaction for they include at least two reaction sites of aminomethylation capable of reacting as an independent amine component and thus compete with the target amine. The enamines of the **B** type are only occasionally used as substrates of amino(oxy)methylation [29]. For instance, at the action of the mixture formaldehyde–amine [29] or of single formaldehyde [30] compound **I** was converted respectively into C-monoaminomethylated derivatives of **VIII** kind (Scheme 3) (in the case of a series of secondary aliphatic amines) in low yield, or into 1,2-fusedый oxazine (at the use at least of 2 equiv of formaldehydea in the absence of amine) in a moderate yield. For a limited number of primary amines the fundamental possibility was shown [29] of the bisaminomethylation opening another path to the preparation of 1,2-fused hydropyrimidinoiso-

Scheme 2.



Scheme 3.



R = $PhCH_2CH_2$ (**a**), 3,4-$(MeO)_2C_6H_3CH_2CH_2$ (**b**), 4-$EtOC_6H_4CH_2CH_2$ (**c**), 2,4-$(MeO)_2C_6H_3CH_2CH_2$ (**d**), 2,5-$(MeO)_2C_6H_3CH_2CH_2$ (**e**), 4-$MeSC_6H_4CH_2CH_2$ (**f**), 2-(4-methylpiperidino)ethyl (**g**), 2-(cyclohex-1-en-1-yl)ethyl (**h**), 3-(2-oxopyrrolidin-1-yl)propyl (**i**), 3-[3,4-dihydro-2(1*H*)-isoquinolin-1-yl]propyl (**j**), $HOCH_2CH_2$ (**k**), $HOCH_2CH_2CH_2$ (**l**), $MeOCH_2CH_2$ (**m**), Ph (**n**), 3,4-$Me_2C_6H_3$ (**o**), 4-BrC_6H_4 (**p**), 3-$CF_3C_6H_4$ (**q**), 3-MeC_6H_4 (**r**), 4-$EtOC_6H_4$ (**s**), 4-$(Et_2NSO_2)C_6H_4$ (**t**), 4-$(EtOCO)C_6H_4$ (**u**), 3-pyridyl (**v**), Bn (**w**), $Me(Ph)CH_2$ (**x**), 1,3-dihydro-2-benzofuran-5-ylmethyl (**y**), 1-(2,3-dihydro-1,4-benzodioxan-6-yl)ethyl (**z**), $HOCH_2CHPh$ (**aa**), 4-$TolCH_2$ (**bb**), 4-$ClC_6H_4CH_2$ (**cc**), 3-$ClC_6H_4CH_2$ (**dd**), 3-$FuCH_2$ (**ee**), 3-tetrahydrofurfuryl (**ff**), cyclohexyl (**gg**), cyclopentyl (**hh**), $HOCOCH_2$ (**ii**), $HOCOCH_2CH_2$ (**jj**), $EtOCOCH_2$ (**kk**), 1-(ethoxycarbonyl)piperidino (**ll**).

quinolines, structural analogs of some antihelmintic and antihypertensive agents, hair growth stimulators [31, 32]. Enamine **I** reacts with various primary amines in the presence of 2 equiv of formaldehyde with the formation of N-R[3]-substituted 6,7-dihydro-2*H*-pyrimidoisoquinolines **IXa–IXll** (path *a,* Scheme 3). Thus after short boiling in ethanol compounds formed in 12–94% yield whose ^{1}H NMR spectrum lacked the signals of both protons CH and NH of the initial enamine moiety, and the spectra contained a set of singlet signals from two methylene groups (4.20–4.90 and 3.60–4.35 ppm), and also specific signals belonging to the variable N-R-substituent. These compounds may sometimes be isolated as free Mannich bases or in most cases as hydrochlorides or hydrooxalates. Hydrochlorides of some compounds **IX** readily absorb water and/or suffer tarring and require anhydrous conditions of isolation (first of all, at the filtration).

Under alkaline conditions in the absence of the amine component the reaction actually results in the formation of fused oxazine **VII** (yield 76%) whose characteristics are identical to those described in [29]. Its formation is likely to result from the successive hydroxymethylation first of enamine **I** and then its C-hydroxymethyl derivative **C** with the second formaldehyde molecule [29]. A like sequence may also exist in the bisaminomethylation involving primary amines where as intermediates may serve either compound **C** or**,** more likely**,** its aminomethylene analog of type **VIII**, (R = H), where the free NH group is capable of the subsequent reaction with the second formaldehyde molecule with the closure of the dihydropyrimidine ring and the formation of compound **IX**.

The range of the primary amines capable to act as a donor of the N-R-function in the formation of the fused dihydropyrimidine ring (Scheme 3) is sufficiently wide and includes aliphatic amines, phenethylamine and its structural analogs, aminoalcohols and their derivatives, benzylamines of diverse structure, alicyclic amines and their heteroanalogs, aromatic amines, some amino acids and their esters.

As a rule the preparative yields of the fused hydropyrimidinoisoquinolines **IX** is 1.5–2 times higher with more basic aliphatic amines, but the yields decrease with the diminishing spatial accessibility of the primary amino group of the reagent and with its functionalization, impeding the isolation of the final product. For instance, the high sensitivity of the bisaminomethylation of enamine **I** toward the spatial accessibility of the primary amino group is clearly demonstrated by the decrease in the yield from 92 to 45% in going from benzylamine to α-methylbenzylamine.

At the use of weakly basic heteroaromatic exocyclic amines (thiazo-2-ylamines, 1-aminotriazole), aromatic amines with *ortho*-substituents (2,5-dimethoxyaniline, 2-chloroaniline), some functional amines (triptamine, a series of aminoalcohols) the Mannich bisaminomethylation finishes either by the formation of side products[2] (path *b*, Scheme 3) where alongside compound **VII** products are present of the intermolecular reaction of two molecules of initial enamine **I** and formaldehyde, or by the formation of unstable target products that easily suffer tarring and whose stabilization as tertiary ammonium salts is unsuccessful.

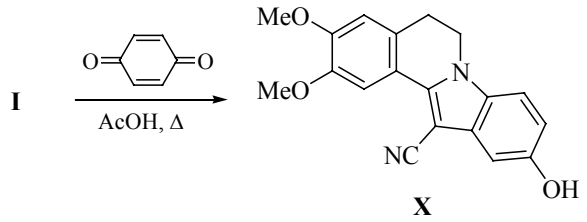
Among the free amino acids only with glycine and β-alanine plausible results of bisaminomethylation were obtained at the use of these amino acids as the source of the primary amino group. The reaction does not occur with α-alanine, tryptophan, methionine, and also with *ortho*-anilines mainly due to the steric shielding of the amino group. Since the esters of these amino acids also cannot be brought into the bisaminomethylation reaction, it confirms the dominant effect of the steric factors and lesser effect of low solubility of amino acids in ethanol, and of compound **I** in water (the medium for the reaction with amino acids is aqueous ethanol).

Enamine fragment of reagent I can potentially react with many α-functional components, in particular, with unsaturated compounds often used as synthons in cycle formation [4]. A special interest attracts the reaction of enamine **I** with *p*-benzoquinone under the conditions of Nenitzescu reaction as a route to fused 5-hydroxyindoloisoquinolines exhibiting anticancer [13, 33], antidepressant [34], and the other kinds of physiologic activity. A number of approaches to the synthesis of the like compounds was described that were developed for the preparation of dibenzopyrrocoline alkaloids and were based on the photocyclization of enamines [35], on the transformations of 1-(2-bromobenzyl)isoquinolines [36], on the cyclization by Bischler-Napieralski reaction [37] etc. The Nenitzescu reaction with enamine **I** was not described in the literature, but close in structure 1-ketoderivatives enamines of type **B** (R = COMe) in ni-

[2] In ^{1}H NMR spectra of side products (path *b*, Scheme 3) appear singlets of the methylene protons, a double set of proton signals of methoxy groups and the aromatic ring enamine, and one proton signal of CH or NH functions of enamine fragment is absent.

tromethane medium led to the formation of indolo[2,1-*a*] isoquinolines in up to 75% yields [13].

Under the conditions described in [13] (stirring for two days of the mixture of enamine **I** with 40% excess of *p*-benzoquinone at room temperature in nitromethane) the target compound **X** formed in small quantity and was contaminated with difficultly separable impurities. For practical purposes it proved to be more convenient to carry out the reaction in acetic acid which had been successfully used as solvent in a number of Nenitzescu reactions [38].



X

For instance, after stirring equimolar amounts of reagents at 40°C in acetic acid for 2 h a light-green precipitate formed in 38% yield, and its spectral characteristics and elemental analysis were consistent with the expected structure **X**. Its ^{1}H NMR spectrum contained a characteristic signal of the OH group (8.85 ppm), an adequate set of signals from both aromatic rings (7.9, 7.7, 7.45, 7.10, 6.95 ppm), triplet signals of the methylene protons of the tetrahydroisoquinoline ring (4.4 and 3.15 ppm), and singlets from methoxy groups (3.8 and 3.9 ppm); the proton signals of the fragments CH and NH of the initial enamine were absent. The IR spectrum characteristically contained strong bands of cyano and and hydroxy groups (2210 and 3350 cm^{-1}).

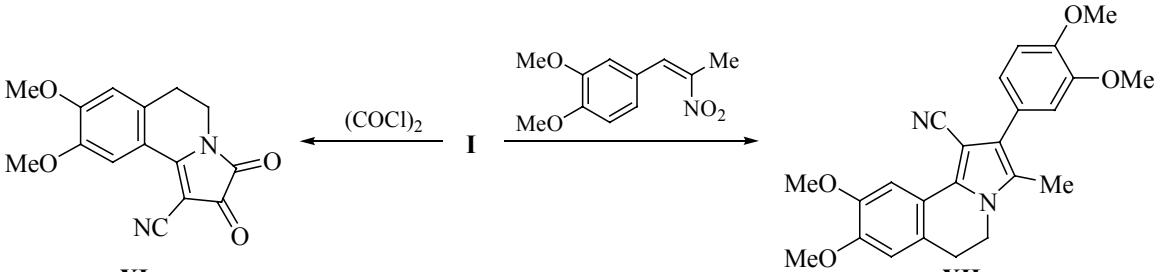
Fused pyrroloisoquinolines **XI** and **XII** of similar structure were obtained by the reaction of enamine **I** with oxalyl chloride in anhydrous chloroform in the presence of Et_3N and after 3 h of boiling with β-methyl-3,4-dimethoxy-β-nitrostyrene in ethanol respectively (Scheme 4).

Dioxo compound **XI** was obtained as bright red crystals characteristic of isatin-like derivatives. Yield of 64% was not optimized; evidently higher yield would be obtained at stronger cooling of the reaction mixture. Its ^{1}H NMR spectrum characteristically lacked the singlet signals of NH and CH of the initial enamine and possessed all groups of signals corresponding to the 3,4-dimethoxytetrahydroisoquinoline fragment.

Nitrile **XII** was obtained in 86% yield along the method described for the reaction of compound **B** (R = COOEt) with some nitroalkanes [39]. It was presumed that such Michael addition proceeded through the stage of attack of the CH group of enamine on the α-position of the activated double bond of the alkene followed by the attack of the NH group of the enamine now on the β-carbon atom with the loss of the nitro group and the closure of the pyrrole ring [39].

The Michael addition of enamine **I** to acrylonitrile widely used in fusion reactions finished by the formation of a product of fundamentally another structure, tetrahydropyridinoisoquinoline (**XIII**). Therewith the acrylonitrile in contrast to β-nitrostyrene acted as 1,3-carbon synthon, namely, in the formation of the hydropyridine ring the carbon atom of the cyano group was involved, and the nitrogen atom was converted into a part of the amidine group. It is known that acryl derivatives in the fusion reactions with some enamines are capable of multiple reactions, especially when they are present in excess [40]. Yet in ethanol in the presence of 1 equiv of sodium ethylate[3] the boiling of enamine **I** with 10% excess of acrylonitrile for 30 min led to the formation of monoproduct of the reaction **XIII** in 79% yield (Scheme 5).

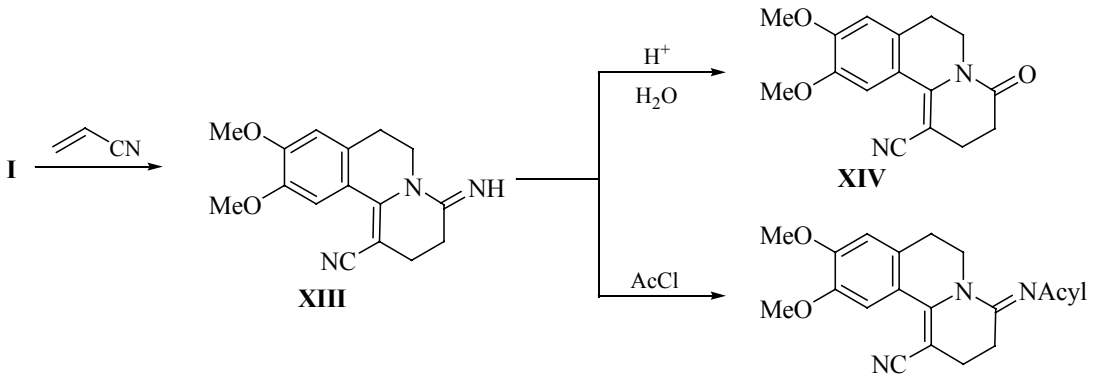
Scheme 4.



XI **XII**

[3] The reaction with acrylonitrile proceeds in the presence of bases in contrast to the reaction with β-nitrostyrene where the basic catalysis essentially complicates the course of the process.

Scheme 5.



Acyl = ArCOCl (**XV**), $ArSO_2Cl$ (**XVI**); **XV**, Ar = Ph (**a**), 3-IC_6H_4 (**b**), 4-ClC_6H_4 (**c**), 2-FC_6H_4 (**d**), 4-$MeOC_6H_4$ (**e**), furfuryl (**f**); **XVI**, Ar = Ph (**a**), 3-ClC_6H_4 (**b**), 3-$NO_2C_6H_4$ (**c**).

After crystallization from ethanol its physicochemical characteristics were well consistent with published data [18]. Imine **XIII** is easily hydrolyzed in the presence of acids giving hydropyridonoisoquinoline **XIV** in 78% yield, and its amidine group due to sufficiently high basicity is able to react with aroyl chlorides and arylsulfonyl chlorides providing the corresponding N-acyl and N-sulfonyl derivatives **XVa–XVf, XVIa–XVIc**. Chlorides and anhydrides of aliphatic acids (in particular acetic and succinic anhydrides, phenylacetyl chloride, chloride of O-acetylmandelic acid) under similar conditions react more complex and provide intractable products.

In some known cyclization reactions enamine **I** among the other enamines, in particular, of **B** type (R ≠ CN) shows significant special features of the reactivity. For instance, attempts failed to prepare hydroxypyrrolo- and pyridonoisoquinolines respectively from enamine **I** and 1 equiv of glyoxal by analogy with [41, 42], or ethyl phenylpropiolate by procedure [43]; the reagent **I** was recovered from these attempts. We also failed to involve into reactions of 1,2-fusion with compound **I** the barbituric acid and its derivatives, which relatively easily reacted with 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline [44] less prone to the formation of enamine isomer **B**.

EXPERIMENTAL

^{1}H NMR spectra were registered on spectrometers Bruker AM-200 and Bruker AM-400 (200 and 400 MHz), internal reference TMS. IR spectra were recorded from pellets with KBr on a spectrophotometer Shimadzu FTIR-8400S. The completeness of the reactions was monitored and the chromatographic purity of the reaction products was tested by HPLC on an instrument Shimadzu equipped with UV detector (254 nm). Columns ProntoSIL 120-5-C18AQ 5.0 μm (150 × 4.6 mm), gradient elution, 0.1 N H_3PO_4–acetonitrile, and Hypersil-Silica 5.0 μm (150 × 4.6 mm), isocratic elution, hexane–ethyl acetate–acetonitrile, 72 : 17 : 11. Melting points were measured on the Boëtius heating block. The solvents were purified as described in [45], the moisture was determined by Fischer method on an instrument Metrohm 787 KF Titrino/703 Ti Stand.

Reagent **I** was obtained by cyclization of cyanoacetic acid homoveratrylamide in boiling toluene by the action of P_2O_5, yield 85%, mp 170–171°C (EtOH) [18 ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.85–2.90 t (2H, CH_2), 3.40–3.45 t (2H, CH_2), 3.85 s (3H, CH_3O), 3.95 s (3H, CH_3O), 4.25 s (1H, NH), 5.60 s (1H, CH), 6.65 s (1H, Ht), 6.95 s (1H, Ht). The initial homoveratrylamide was synthesized by procedure [46] reacting the homoveratrylamine with freshly distilled ethyl cyanoacetate at 100°C over 16 h, mp 113–115°C [46].

Ethoxycarbonyl isothiocyanate and trichloroacetyl isothiocyanate were obtained by procedure [47] from potassium thiocyanate and ethyl chloroformate or trichloroacetyl chloride respectively, their characteristics were consistent with the published data. Benzoyl isothiocyanate was used as a solution obtained as described above; the other acyl isocyanate were commercial products and were used without purification.

Reaction of enamine I with acyl iso(thio)cyanates.

To a solution of 4 mmol of enamine in 10 ml of acetonitrile was added 5 ml of solution of 4.2 mmol of acyl iso(thio)cyanate[4] in acetonitrile. The mixture was kept for 20 min at room temperature and 15 min at 50°C. On cooling the precipitate (compounds **II, III, V**) were filtered off and recrystallized. Reactions with trichloroacetyl iso(thio)cyanate, chlorosulfonyl isocyanate were carried out at 0°C for 10 h.

9,10-Dimethoxy-2-thioxo-4-phenyl-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (II). Yield 88%, mp 282–283°C (from acetonitrile). IR spectrum, ν, cm^{-1}: 2217, 1587 s, 1560 s, 1521, 1479 s, 1392 m, 1350 m, 1277 s, 1203 m, 1155 m, 1107 m, 1064 m. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.80–2.90 m (2H, CH_2), 3.90 s (3H, CH_3O), 3.95 s (3H, CH_3O), 3.95–4.0 m (2H, CH_2), 7.00 s (1H, Ht), 7.50–7.60 m (3H, Ar), 7.70–7.80 m (2H, Ar), 7.90 s (1H, Ht). Found, %: C 67.22, 67.31; H 4.58, 4.60; N 11.28, 11.23; S 8.55, 8.57. $C_{21}H_{17}N_3O_2S$. Calculated, %: C 67.18; H 4.56; N 11.19; S 8.54.

9,10-Dimethoxy-2-oxo-4-phenyl-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (III). Yield 85%, mp 222–223°C (from acetonitrile). IR spectrum, ν, cm^{-1}: 2183, 1716 s, 1647 m, 1597 s, 1560 m, 1473 s, 1434 m, 1274 m, 1215 s, 1120 m. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.80–2.9 m (2H, CH_2), 3.50–3.60 m (2H, CH_2), 3.80 s (3H, CH_3O), 3.90 s (3H, CH_3O), 7.00 s (1H, Ht), 7.45–7.50 m (2H, Ar), 7.55–7.60 m (1H, Ar), 7.75 s (1H, Ht), 7.85–7.90 d (2H, Ar). Found, %: C 70.20, 70.11; H 4.79, 4.71; N 11.62, 11.71. $C_{21}H_{17}N_3O_3$. Calculated, %: C 70.18; H 4.77; N 11.69.

9,10-Dimethoxy-4-oxo-2-thioxo-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (V). Yield 87%, mp 297–298°C (from acetonitrile). IR spectrum, ν, cm^{-1}: 2220, 1717 s, 1577 m, 1545 s, 1508 s, 1294 m, 1279 m, 1265 m, 1253 m, 1223 m, 1068 s. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.80–2.90 m (2H, CH_2), 3.80 s (3H, CH_3O), 3.90 s (3H, CH_3O), 3.95–4.05 m (2H, CH_2), 7.00 s (1H, Ht), 7.90 s (1H, Ht), 13.05 s (1H, NH). Found, %: C 57.18, 57.11; H 4.09, 4.11; N 13.38, 13.31; S 10.19, 10.26. $C_{15}H_{13}N_3O_3S$. Calculated, %: C 57.13; H 4.16; N 13.33; S 10.17.

2-(Methylsulfanyl)-9,10-dimethoxy-4-phenyl-1-cyano-6,7-dihydropyrimido[6,1-*a*]isoquinolin-5-ium iodide (IV). To a dispersion of 1.8 mmol of compound **II** in 5 ml of DMSO was added a 10% excess (0.12 ml) of methyl iodide. On adding the methyl iodide the initial dispersion of substrate **II** became a homogeneous solution, and after stirring for 15 min precipitated orange substance, it was washed with ether till complete removal of DMSO and dried in a vacuum. Yield 65%, mp 236–237°C (decomp., from DMSO). IR spectrum, ν, cm^{-1}: 2222, 1585 m, 1555 m, 1487 s, 1281 s, 1055 m. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.95 s (3H, CH_3S), 3.05–3.15 m (2H, CH_2), 3.90 C (3H, CH_3O), 4.00 C (3H, CH_3O), 4.40–4.50 m (2H, CH_2), 7.30 s (1H, Ht), 7.65–7.80 m (3H, Ar), 7.90 m (2H, Ar), 8.00 s (1H, Ht). Found, %: C 51.10, 51.15; H 3.85, 3.91; I 24.57, 24.62; N 8.15, 8.19; S 6.13, 6.25. $C_{22}H_{20}IN_3O_2S$. Calculated, %: C 51.07; H 3.90; I 24.53; N 8.12; S 6.20.

Ethyl [2-(6,7-dimethoxy-3,4-dihydro-2*H*-isoquinolin-1-ylidene)-2-cyanothioacetyl]carbaminate (VI, R = OEt). A solution of 4 mmol of enamine **I** in 5 ml of acetonitrile was added to a solution of 4 mmol of ethoxycarbonyl isothiocyanate in 20 ml at 25°C. In some time yellow precipitate formed, it was washed with ether on the filter and dried in a vacuum. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.20 t (3H, CH_2CH_3), 2.85–2.95 m (2H, CH_2), 3.50–3.60 m (2H, CH_2), 3.80 s (3H, CH_3O), 3.90 s (3H, CH_3O), 4.00 s (1H, NH), 4.05–4.15 q (2H, CH_2CH_3), 7.10 s (1H, Ht), 7.55 s (1H, Ht), 10.45 s (1H, NH imide). Found, %: C 56.42, 56.55; H 5.31, 5.25; N 11.65, 11.72; S 8.80, 8.92. $C_{16}H_{17}N_3O_4S$. Calculated, %: C 56.50; H 5.30; N 11.63; S 8.87.

A slight heating for 10 min of 0.7 g of ester **VI** (R = OEt) in 5 ml of anhydrous pyridine followed by adding to the cooled reaction mixture of ethyl ether led to precipitation of the product whose physicochemical and spectral characteristics were identical to those of compound **V**.

9,10-Dimethoxy-6,7-dihydro-2*H*-[1,3]oxazino-[4,3-*a*]isoquinoline-1-carbonitrile (VII) was obtained by treating enamine **I** with 2 equiv of formaldehyde by method [29]. Yield 76%, mp 152–153°C (from MeOH) {154°C (from anhydrous EtOH) [29]}. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.80–2.85 t (2H, CH_2), 3.30–3.35 t (2H, CH_2), 3.80 s (3H, CH_3O), 3.90 s (3H, CH_3O), 4.45 s (2H, CH_2 oxazine), 4.75 s (2H, CH_2 oxazine), 6.70 s (1H, Ht), 7.85 s (1H, Ht) {publ. ($CDCl_3$–DMSO-d_6): 4.48 s

[4] The solution of benzoyl isothiocyanate was prepared *in situ* by short heating of a mixture of 4.3 mmol of benzoyl chloride with the 10% molar excess of potassium thiocyanate in 7 ml of dried acetonitrile. On completing the reaction the suspension was separated on a centrifuge, the separated solution of isothiocyanate was mixed with a solution of 4 mmol of enamine. In other events the solutions of acyl iso(thio)cyanates were prepared by dissolving a weighed portion in dry solvent.

(2H, CH_2), 4.75 s (2H, CH_2) [29]}.

Reactions of enamine I with primary amines in the presence of formaldehyde. Into a solution of 4.35 mmol of enamine and 5.4 mmol of primary amine[5] in 20 ml of ethanol was added 0.87 ml (2.3 equiv) of formaldehyde water solution, the mixture was boiled for 10 min and evaporated on a rotary evaporator. The residue as a viscous mass was either crystallized from MeOH or was converted into hydrochloride. To this end the residue was dissolved in 20 ml of dried acetone, and a calculated amount of HCl solution in ether was added. The precipitate was filtered off at exclusion of the contact with air moisture, washed on the filter with ether, and dried over P_2O_5.

In the case of especially moisture-sensitive hydrochlorides the products of Mannich aminomethylation were transformed into hydrooxalates: The residue after evaporation of the reaction mixture was dissolved in 15–20 ml of MeOH, and 1 equiv of oxalic acid was added. On cooling the precipitated crystals were filtered off and recrystallized from methanol.

At the use of amino acids in Mannich reaction they were dissolved in 5 ml of water, a calculated amount of the formaldehyde solution in 15–20 ml of EtOH was added, the mixture was boiled for 10 min, then a weighed portion of enamine was added, and the mixture again was boiled for 10 min. Several days after from the solution cooled to 2–6°C a precipitate separated, it was filtered off and recrystallized from methanol.

9,10-Dimethoxy-3-phenethyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXa). Yield 86% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.85–2.90 m (2H, CH_2), 3.25–3.30 m (2H, CH_2), 3.35–3.40 m (2H, CH_2), 3.45–3.50 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 7.15–7.35 m (5H, Ar), 6.75 s (1H, Ht), 7.80 s (1H, Ht), 8.60 (HCl). Found, %: C 67.00, 67.09; H 6.28, 6.33; Cl 8.58, 8.70; N 10.18, 10.23. $C_{23}H_{26}ClN_3O_2$. Calculated, %: C 67.06; H 6.36; Cl 8.61; N 10.20.

3-[2-(3,4-Dimethoxyphenyl)ethyl]-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXb). Yield 77%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.70–2.85 m (6H, $2CH_2$), 3.20 m (2H, CH_2), 3.60 s (2H, CH_2), 3.75 s (3H, CH_3O), 3.78 s (3H, CH_3O), 3.82 s (3H, CH_3O), 3.85 s (3H, CH_3O), 4.25 s (2H, CH_2), 6.65 s (1H, Ht), 6.70–6.75 m (3H, Ar), 7.80 s (1H, Ht). Found, %: C 69.01, 69.03; H 6.69, 6.66; N 9.70, 9.74. $C_{25}H_{29}N_3O_4$. Calculated, %: C 68.95; H 6.71; N 9.65.

9,10-Dimethoxy-3-[2-(4-ethoxyphenyl)ethyl]-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*] isoquinoline-1-carbonitrile (IXc). Yield 77% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.40 m (3H, CH_3), 2.85–2.90 m (CH_2), 3.25–3.30 m (2H, CH_2), 3.35–3.40 m (2H, CH_2), 3.45–3.50 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 6.80–6.90 m (2H, Ar), 6.95–7.00 m (2H, Ar), 7.80 s (1H, Ht). Found, %: C 65.81, 65.85; H 6.60, 6.69; Cl 7.70, 7.72; N 9.22, 9.35. $C_{25}H_{30}ClN_3O_3$. Calculated, %: C 65.85; H 6.63; Cl 7.78; N 9.22.

3-[2-(2,4-Dimethoxyphenyl)ethyl]-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXd). Yield 45% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.85–2.90 m (2H, CH_2), 3.25–3.30 m (2H, CH_2), 3.35–3.40 m (2H, CH_2), 3.45–3.50 m (2H, CH_2), 3.70 s (6H, $2CH_3O$), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.35 s (1H, Ar), 6.65 s (1H, Ht), 6.75 d (1H, Ar), 7.00 d (1H, Ar), 7.80 s (1H, Ht). Found, %: C 63.57, 63.60; H 6.37, 6.34; Cl 7.45, 7.46; N 8.94, 8.83. $C_{25}H_{30}ClN_3O_4$. Calculated, %: C 63.62; H 6.41; Cl 7.51; N 8.90.

3-[2-(2,5-Dimethoxyphenyl)ethyl]-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXe). Yield 51% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.85–2.90 m (2H, CH_2), 3.25–3.30 m (2H, CH_2), 3.35–3.40 m (2H, CH_2), 3.45–3.50 m (2H, CH_2), 3.65 s (6H, $2CH_3O$), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 6.95–7.00 m (3H, Ar), 7.80 s (1H, Ht). Found, %: C 63.52, 63.65; H 6.38, 6.42; Cl 7.43, 7.54; N 8.93, 8.98. $C_{25}H_{30}ClN_3O_4$. Calculated, %: C 63.62; H 6.41; Cl 7.51; N 8.90.

3-{2-[4-(Methylsulfanyl)phenyl]ethyl}-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]-isoquinoline-1-carbonitrile (IXf) Yield 36% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.50 s (3H, CH_3), 2.85–2.90 m (2H, CH_2), 3.25–3.30 m (2H, CH_2), 3.35–3.40 m (2H, CH_2), 3.45–3.50 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 6.80 m (2H, Ar), 6.80–6.90 m (2H, Ar), 7.80 s (1H, Ht). Found, %: C 62.90, 62.85; H 6.10, 6.05; Cl 7.70, 7.65; N 9.12, 9.19; S 6.95, 6.90. $C_{24}H_{28}ClN_3O_2S$.

[5] The samples of primary amines were supplied by "Kontakt-Servis" Co. (Dolgoprudnyi, Russian Federation).

Calculated, %: C 62.94; H 6.16; Cl 7.74; N 9.17; S 7.00.

3-[2-(4-Methylpiperazin-1-yl)ethyl]-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]-isoquinoline-1-carbonitrile (IXg). Yield 26% (hydrooxalate). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.25–2.00 (group of multiplets), 2.30 s (3H, CH_3), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 7.80 s (1H, Ht). Found, %: C 59.10, 58.86; H 6.78, 6.78; N 14.34, 14.28. $C_{24}H_{33}N_5O_6$. Calculated, %: C 59.12; H 6.82; N 14.36.

9,10-Dimethoxy-3-[2-(cyclohex-1-en-1-yl)-ethyl]-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXh). Yield 26% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.25–2.50 (group of multiplets), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 7.80 s (1H, Ht). Found, %: C 66.38, 66.35; H 7.20, 7.16; Cl 8.45, 8.42; N 10.18, 10.25. $C_{23}H_{30}ClN_3O_2$. Calculated, %: C 66.41; H 7.27; Cl 8.52; N 10.10.

9,10-Dimethoxy-3-[3-(2-oxopyrrolidin-1-yl)-propyl]-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*] isoquinoline-1-carbonitrile (IXi). Yield 37% (hydrooxalate). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30–3.60 (group of multiplets), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 7.80 s (1H, Ht). Found, %: C 59.20, 59.18; H 6.12, 6.17; N 11.52, 11.61. $C_{24}H_{30}N_4O_7$. Calculated, %: C 59.25; H 6.22; N 11.52.

3-{3-[3,4-Dihydro-2(1*H*)-isoquinoline]propyl}-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido-[6,1-*a*]isoquinoline-1-carbonitrile (IXj). Yield 69% (hydrooxalate). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.30–2.70 (group of multiplets), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 7.00–7.20 m (4H, Ar), 7.80 s (1H, Ht). Found, %: C 65.11, 65.28; H 6.28, 6.34; N 10.40, 10.52. $C_{29}H_{34}N_4O_6$. Calculated, %: C 65.15; H 6.41; N 10.48.

3-(2-Hydroxyethyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXk). Yield 69% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.85–2.90 m (2H, CH_2), 3.25 m (2H, CH_2), 3.45 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 3.90 m (2H, CH_2), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.80 s (1H, Ht), 7.80 s (1H, Ht), 8.20–8.30 (HCl). Found, %: C 57.93, 58.00; H 6.25, 6.13; Cl 10.00, 9.84; N 11.90, 12.05. $C_{25}H_{34}ClN_6O_3$. Calculated, %: C 58.03; H 6.30; Cl 10.08; N 11.94.

3-(3-Hydroxypropyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXl). Yield 87% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.00–3.70 m ($5CH_2$), 3.80 s (6H, $2CH_3O$), 3.90 s (2H, CH_2), 4.60 s (2H, CH_2), 6.75 s (1H, Ht), 7.80 s (1H, Ht). Found, %: C 59.00, 58.86; H 6.55, 6.47; Cl 9.60, 9.68; N 11.47, 11.55. $C_{18}H_{24}ClN_3O_3$. Calculated, %: C 59.09; H 6.61; Cl 9.69; N 11.49.

9,10-Dimethoxy-3-(2-methoxyethyl)-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXm). Yield 25% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.85–2.90 m (2H, CH_2), 3.20 s (3H, CH_3), 3.30 m (2H, CH_2), 3.45 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 3.90 m (2H, CH_2), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 7.80 s (1H, Ht). Found, %: C 59.16, 58.93; H 6.55, 6.47; Cl 9.60, 9.53; N 11.54, 11.58. $C_{18}H_{24}ClN_3O_3$. Calculated, %: C 59.09; H 6.61; Cl 9.69; N 11.49.

9,10-Dimethoxy-3-phenyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXn). Yield 33%, mp 135–136°C (and3 MeOH) {136°C (from EtOH) [29]}. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.75–2.80 m (2H, CH_2), 3.30–3.40 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.20 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 6.85 t (1H, Ar), 7.0 d (2H, Ar), 7.20–7.25 t (2H, Ar), 7.80 s (1H, Ht) {publ. in DMSO-d_6–$CDCl_3$: 4.25 s (2H, CH_2), 4.72 s (2H, CH_2) [29]}.

3-(3,4-Dimethylphenyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXo). Yield 41%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.15 s (3H, CH_3, Ar), 2.25 s (3H, CH_3, Ar), 2.75 m (2H, CH_2), 3.30 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.15 s (2H, CH_2), 4.70 s (2H, CH_2), 6.65 s (1H, Ht), 6.70 d (1H, Ar), 6.80 s (1H, Ar), 6.95 d (1H, Ar), 7.80 s (1H, Ht). Found, %: C 73.45, 73.58; H 6.68, 6.55; N 11.10, 11.23. $C_{23}H_{25}N_3O_2$. Calculated, %: C 73.57; H 6.71; N 11.19.

3-(4-Bromophenyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXp). Yield 30%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.70–2.80 m (2H, CH_2), 3.30–3.40 m (2H, CH_2), 3.75 s (3H, CH_3O), 3.85 s (3H, CH_3O), 4.25 s (2H, CH_2), 4.90 s (2H, CH_2), 6.90 s (1H, Ht), 7.10–7.15 d (2H, Ar), 7.40–7.50 d (2H, Ar), 7.70 s (1H, Ht). Found, %: C 59.21, 59.12; H 4.67, 4.65; Br 18.78, 18.67; N 9.88, 9.96. $C_{21}H_{20}BrN_3O_2$. Calculated, %: C 59.17; H 4.73; Br 18.74; N 9.86.

9,10-Dimethoxy-3-[3-(trifluoromethyl)phenyl]-3,4,6,7-tetrahydro-2-pyrimido[6,1-*a*]isoquinoline-

1-carbonitrile (IXq). Yield 44%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.70–2.80 m (2H, CH_2), 3.30–3.40 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.40–6.60 m (4H, Ar), 6.65 s (1H, Ht), 7.80 s (1H, Ht). Found, %: C 63.57, 63.55; H 4.80, 4.68; N 10.21, 10.15. $C_{26}H_{25}F_3N_3O_2$. Calculated, %: C 63.61; H 4.85; N 10.12.

3-(3-Methylphenyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXr). Yield 35% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.30 s (3H, CH_3), 2.70–2.80 m (2H, CH_2), 3.30–3.40 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.40 m (2H, Ar), 6.50 s (1H, Ar), 6.65 s (1H, Ht), 6.80 m (1H, Ar), 7.80 s (1H, Ht). Found, %: C 66.38, 66.35; H 6.03, 6.00; Cl 8.88, 8.95; N 10.65, 10.55. $C_{22}H_{24}ClN_3O_2$. Calculated, %: C 66.41; H 6.08; Cl 8.91; N 10.56.

9,10-Dimethoxy-3-(4-ethoxyphenyl)-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXs) Yield 65%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.40 m (3H, CH_3), 2.75 m (2H, CH_2), 3.25–3.30 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 3.95 m (2H, CH_2), 4.10 s (2H, CH_2), 4.65 s (2H, CH_2), 6.70 s (1H, Ht), 6.75 m (2H, Ar), 6.90 m (2H, Ar), 7.75 s (1H, Ht). Found, %: C 70.55, 70.45; H 6.47, 6.38; N 10.77, 10.68. $C_{23}H_{25}N_3O_3$. Calculated, %: C 70.57; H 6.44; N 10.73.

4-{9,10-Dimethoxy-1-cyano-6,7-dihydro-2*H*-pyrimidino[6,1-*a*]isoquinolin-3(4*H*)-yl}-N,N-diethylbenzenesulfamide (IXt). Yield 32%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.10 m (6H, $2CH_3$), 2.75 m (2H, CH_2), 2.80–2.90 m (4H, $2CH_2$), 3.25–3.30 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 6.75 m (2H, Ar), 6.90 m (2H, Ar), 7.80 s (1H, Ht). Found, %: C 62.18, 62.16; H 6.20, 6.12; N 11.68, 11.76; S 6.60, 6.58. $C_{25}H_{30}N_4O_4S$. Calculated, %: C 62.22; H 6.27; N 11.61; S 6.64.

4-{9,10-Dimethoxy-1-cyano-6,7-dihydro-2*H*-pyrimidino[6,1-*a*]isoquinolin-3(4*H*)-yl}ethyl benzoate (IXu). Yield 30%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.20 m (3H, CH_3), 2.75 m (2H, CH_2), 3.25–3.30 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 m (2H, CH_2), 4.20 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 6.75 m (2H, Ar), 6.90 m (2H, Ar), 7.80 s (1H, Ht). Found, %: C 68.68, 68.66; H 6.08, 5.99; N 10.08, 10.16. $C_{24}H_{25}N_3O_4$. Calculated, %: C 68.72; H 6.01; N 10.02.

9,10-Dimethoxy-3-(3-pyridyl)-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXv). Yield 40%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.40 m (2H, CH_2), 3.80 s (3H, CH_3O), 3.90 s (3H, CH_3O), 3.95 m (2H, CH_2), 4.35 s (2H, CH_2), 4.65 s (2H, CH_2), 6.80 s (1H, Ht), 7.30 d (1H, Ar), 7.40 m (1H, Ar), 7.80 s (1H, Ht), 8.20 d (1H, Ar), 8.50 s (1H, Ar). Found, %: C 68.90, 68.88; H 5.75, 5.63; N 16.20, 16.12. $C_{20}H_{20}N_4O_2$. Calculated, %: C 68.95; H 5.79; N 16.08.

3-Benzyl-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXw). Yield 92% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.90 m (2H, CH_2), 3.40 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 3.95 m (2H, CH_2), 4.35 s (2H, CH_2), 4.65 s (2H, CH_2), 6.75 s (1H, Ht), 7.40–7.65 m (5H, Ar), 7.80 s (1H, Ht), 8.90 (HCl). Found, %: C 66.38, 66.35; H 6.06, 6.04; Cl 8.88, 8.87; N 10.58, 10.52. $C_{22}H_{24}ClN_3O_2$. Calculated, %: C 66.41; H 6.08; Cl 8.91; N 10.56.

9,10-Dimethoxy-3-(1-phenylethyl)-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXx). Yield 45% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.90 m (2H, CH_2), 3.40 m (2H, CH_2), 4.30 m, 4.40 m, 3.30 m, 1.75–1.85 m (3H, CH_3), 3.80 s (3H, CH_3O), 3.90 s (3H, CH_3O), 4.60 s (2H, CH_2), 6.75 s (1H, Ht), 7.35–7.45 m (3H, Ar), 7.65 m (2H, Ar), 7.80 s (1H, Ht). Found, %: C 67.01, 66.95; H 6.34, 6.23; Cl 8.67, 8.64; N 10.25, 10.29. $C_{23}H_{26}ClN_3O_2$. Calculated, %: C 67.06; H 6.36; Cl 8.61; N 10.20.

3-(1,3-Dihydro-2-benzofuran-5-ylmethyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido-[6,1-*a*]isoquinoline-1-carbonitrile (IXy). Yield 49% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.70 s (2H, CH_2), 2.90 m (2H, CH_2), 3.40 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 3.90 s (4H, $2CH_2$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 6.70–6.85 m (3H, Ar), 7.80 s (1H, Ht). Found, %: C 65.48, 65.46; H 5.91, 5.88; Cl 7.98, 8.03; N 9.65, 9.52. $C_{24}H_{26}ClN_3O_3$. Calculated, %: C 65.52; H 5.96; Cl 8.06; N 9.55.

3-[1-(2,3-Dihydro-1,4-benzodioxin-6-yl)-ethyl]-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXz). Yield 34% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.90 m (2H, CH_2), 1.75–1.85 m (3H, CH_3), 4.30 m, 4.40 m, 3.30 m, 3.40 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 6.70–6.90 m (3H, Ar), 7.80 s (1H, Ht). Found, %: C 63.85, 63.82; H 6.01, 5.95; Cl 7.57, 7.49; N 8.98, 9.04. $C_{25}H_{28}ClN_3O_4$. Calculated, %: C 63.89; H 6.01;

Cl 7.54; N 8.94.

3-(2-Hydroxy-1-phenylethyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXaa). Yield 12% (hydrooxalate). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.50–2.70 (group of multiplets), 3.40 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 2.90 m (2H, CH_2), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 7.15–7.35 m (5H, Ar), 7.80 s (1H, Ht). Found, %: C 62.31, 62.28; H 5.60, 5.62; N 8.77, 8.85. $C_{32}H_{33}N_5O_7$. Calculated, %: C 62.36; H 5.65; N 8.73.

3-(4-Methylbenzyl)-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXbb). Yield 55%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.40 s (3H, CH_3), 2.70 s (2H, CH_2), 2.90 m (2H, CH_2), 3.40 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 6.95–7.00 m (4H, Ar), 7.80 s (1H, Ht). Found, %: C 73.57, 73.48; H 6.67, 6.75; N 11.15, 11.22. $C_{23}H_{25}N_3O_2$. Calculated, %: C 73.57; H 6.71; N 11.19.

9,10-Dimethoxy-3-(4-chlorobenzyl)-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXcc). Yield 69% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.70 s (2H, CH_2), 2.90 m (2H, CH_2), 3.40 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 6.95–7.00 m (2H, Ar), 7.20 m (2H, Ar), 7.80 s (1H, Ht). Found, %: C 61.21, 61.18; H 5.22, 5.34; Cl 16.34, 16.45; N 9.77, 9.84. $C_{22}H_{23}Cl_2N_3O_2$. Calculated, %: C 61.12; H 5.36; Cl 16.40; N 9.72.

9,10-Dimethoxy-3-(3-chlorobenzyl)-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXdd). Yield 72% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.70 s (2H, CH_2), 2.90 m (2H, CH_2), 3.40 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 7.10–7.30 m (3H, Ar), 7.30 s (1H, Ar), 7.80 s (1H, Ht). Found, %: C 61.16, 61.20; H 5.32, 5.37; Cl 16.38, 16.35; N 9.70, 9.65. $C_{22}H_{23}Cl_2N_3O_2$. Calculated, %: C 61.12; H 5.36; Cl 16.40; N 9.72.

9,10-Dimethoxy-3-furfuryl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXee). Yield 91% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.90 m (2H, CH_2), 3.30–3.40 m (2H, CH_2), 3.75 s (3H, CH_3O), 3.80 s (3H, CH_3O), 3.90 s (2H, CH_2), 4.35 s (2H, CH_2), 4.60 s (2H, CH_2), 6.55 m (1H, Ar), 6.70 m (1H, Ar), 6.95 s (1H, Ht), 7.75 s (1H, Ar), 7.80 s (1H, Ht). Found, %: C 61.88, 61.86; H 5.75, 5.68; Cl 9.11, 9.08; N 10.84, 10.76. $C_{20}H_{22}ClN_3O_3$. Calculated, %: C 61.93; H 5.72; Cl 9.14; N 10.83.

9,10-Dimethoxy-3-tetrahydrofurfuryl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXff). Yield 91% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.60–2.30 m (6H, CH_2), 3.10–3.30 m (2H, CH_2), 3.40 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.10 s (2H, CH_2), 4.65 s (2H, CH_2), 6.75 s (1H, Ht), 7.80 s (1H, Ht). Found, %: C 61.24, 61.27; H 6.60, 6.56; Cl 9.08, 9.13; N 10.79, 10.76. $C_{20}H_{26}ClN_3O_3$. Calculated, %: C 61.30; H 6.69; Cl 9.05; N 10.72.

3-Cyclohexyl-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXgg). Yield 65%, mp 139–140°C (from MeOH) {140°C (from MeOH) [29]}. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.25–2.00 m (10H, $5CH_2$), 2.60 m (1H, CH), 2.80–2.85 m (2H, CH_2), 3.20–3.30 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 3.65 s (2H, CH_2), 4.20 s (2H, CH_2), 6.65 s (1H, Ht), 7.80 s (1H, Ht).

9,10-Dimethoxy-3-cyclopentyl-3,4,6,7-tetrahydro-2*H*-pyrimido[6,1-*a*]isoquinoline-1-carbonitrile (IXhh). Yield 94% (HCl). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.60–2.25 m (9H, CH_2), 2.90 m (2H, CH_2), 3.45–3.60 m (4H, $2CH_2$), 3.80 s (6H, $2CH_3O$), 4.65 s (2H, CH_2), 6.75 s (1H, Ht), 7.80 s (1H, Ht), 8.40 (hydrochloride). Found, %: C 63.88, 63.86; H 6.94, 6.96; Cl 9.40, 9.38; N 11.14, 11.22. $C_{20}H_{26}ClN_3O_2$. Calculated, %: C 63.91; H 6.97; Cl 9.43; N 11.18.

2-{9,10-Dimethoxy-1-cyano-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolin-3(4*H*)-yl}acetic acid (IXii). Yield 73%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.85 m (2H, CH_2), 3.20 m (2H, CH_2), 3.40 s (2H, CH_2 of glycine), 3.60 s (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.25 s (2H, CH_2), 6.90 s (1H, Ht), 7.80 s (1H, Ht), 12.50 (1H, COOH). Found, %: C 61.96, 61.89; H 5.8, 5.86; N 12.78, 12.72. $C_{17}H_{19}N_3O_4$. Calculated, %: C 62.00; H 5.81; N 12.76.

3-{9,10-Dimethoxy-1-cyano-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolin-3(4*H*)-yl}propanoic acid (IXjj). Yield 74%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.40 m (2H, CH_2 of β-alanine), 2.75–2.95 m (4H, CH_2, CH_2 of β-alanine), 3.20–3.30 m (2H, CH_2), 3.60 s (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.20 s (2H, CH_2), 6.70 s (1H, Ht), 7.80 s (1H, Ht). Found, %: C 62.92, 62.98; H 6.12, 6.01; N 12.20, 12.34. $C_{18}H_{21}N_3O_4$. Calculated, %: C 62.96; H 6.16; N 12.24.

Ethyl 2-{9,10-dimethoxy-1-cyano-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolin-3(4*H*)-yl}acetate (IXkk).

Yield 23% (hydrochloride). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.20 m (3H, CH_3), 2.75–2.85 m (2H, CH_2), 3.25 m (2H, CH_2), 3.40 s (2H, CH_2 of glycine), 3.65 s (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.00 m (2H, CH_2), 4.25 s (2H, CH_2), 6.65 s (1H, Ht), 7.80 s (1H, Ht). Found, %: C 57.89, 57.98; H 6.10, 6.01; Cl 9.03, 9.09; N 10.62, 10.69. $C_{19}H_{24}ClN_3O_4$. Calculated, %: C 57.94; H 6.14; Cl 9.00; N 10.67.

Ethyl 4-{9,10-dimethoxy-1-cyano-6,7-dihydro-2*H*-pyrimido[6,1-*a*]isoquinolin-3(4*H*)-yl}-piperidine-1-carboxylate (IXll). Yield 43%. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.40–2.90 m, 1.20 m (3H, CH_3), 3.25 m (2H, CH_2), 3.80 s (6H, $2CH_3O$), 4.00 m (2H, CH_2), 4.10 s (2H, CH_2), 4.75 s (2H, CH_2), 6.65 s (1H, Ht), 7.80 s (1H, Ht). Found, %: C 64.67, 64.78; H 6.95, 7.02; N 13.21, 13.24. $C_{23}H_{30}N_4O_4$. Calculated, %: C 64.77; H 7.09; N 13.14.

10-Hydroxy-2,3-dimethoxy-5,6-dihydroindolo[2,1-*a*]isoquinoline-12-carbonitrile (X). To a solution of 4.3 mmol of enamine **I** in 20 ml of glacial acetic acid heated to 40°C was added within 1 h by small portions at stirring 4.3 mmol of freshly sublimed *p*-benzoquinone, and the mixture was stirred under the same conditions till complete separation of the precipitate. The precipitate was filtered off, washed with a fresh portion of acetic acid and a large volume of methanol and dried in a deep vacuum. Yield 38%. IR spectrum (KBr), ν, cm^{-1}: 3350, 2210 s, 1540 m, 1490 m, 1480 s, 1430 m, 1350 m, 1300 m, 1260 s, 1230 s, 1160 m, 1020 m. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.15–3.20 t (2H, CH_2), 3.80 s (3H, CH_3O), 3.90 s (3H, CH_3O), 4.40–4.45 t (2H, CH_2), 6.95 d (1H, Ar), 7.10 s (1H, Ar), 7.45 d (1H, Ar), 7.70 s (1H, Ar), 7.90 s (1H, Ht), 8.85 s (1H, OH). Found, %: C 70.46; H 5.42; N 8.80. $C_{19}H_{16}N_2O_3$. Calculated, %: C 71.24; H 5.03; N 8.74.

8,9-Dimethoxy-2,3-dioxo-2,3,5,6-tetrahydropyrrolo[2,1-*a*]isoquinoline-1-carbonitrile (XI). To a solution of 12 mmol of oxalyl chloride in 50 ml of dry chloroform cooled to 0°C was added at stirring within 30 min a mixture of 10 mmol of enamine **I** and 20 mmol of Et_3N in 25 ml of dry chloroform, and the obtained mixture was left standing for 10 h at 25°C. The separated red precipitate was filtered off, washed with chloroform, water, and ether, dried, and crystallized. Yield 64%, mp 241°C (decomp., from *i*-PrOH–acetone). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 3.15–3.20 t (2H, CH_2, overlapped with H_2O signal), 3.75–3.80 t (2H, CH_2), 3.85 s (3H, CH_3O), 3.95 s (3H, CH_3O), 7.15 s (1H, Ar), 7.85 s (1H, Ht). Found, %: C 63.36, 63.32; H 4.21, 4.12; N 9.88, 9.93. $C_{15}H_{12}N_2O_4$. Calculated, %: C 63.38; H 4.25; N 9.85.

2-(3,4-Dimethoxyphenyl)-3-methyl-8,9-dimethoxy-5,6-dihydro-2*H*-pyrrolo[2,1-*a*]isoquinoline-1-carbonitrile (XII). A solution of 8.5 mmol of enamine **I** and 8.5 mmol of β-nitro-β-methyl-3,4-dimethoxystyrene in 20 ml of EtOH was boiled for 3 h. The light-yellow precipitate was filtered off, washed with 30–50 ml of MeOH, and recrystallized. Yield 86%, mp 193–194°C (EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.25 s (3H, CH_3), 3.00–3.10 t (2H, CH_2), 3.75 s (3H, CH_3O), 3.78 (3H, CH_3O), 3.82 s (3H, CH_3O), 3.90 s (3H, CH_3O), 4.00–4.10 t (2H, CH_2), 6.90–6.95 d (1H, Ar), 6.98 s (1H, Ar), 7.00 s (1H, Ht), 7.05–7.10 d (1H, Ar), 7.60 s (1H, Ht). Found, %: C 71.28, 71.22; H 5.92, 5.94; N 6.99, 6.88. $C_{24}H_{24}N_2O_4$. Calculated, %: C 71.27; H 5.98; N 6.93.

4-Imino-9,10-dimethoxy-3,4,6,7-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinoline-1-carbonitrile (XIII) was obtained by procedure [18] heating the mixture of 44 mmol of enamine **I** and 47 mmol of acrylonitrile (Merck) in 60 ml of anhydrous EtOH in the presence of 44 mmol of sodium ethylate for 30 min. On cooling the separated precipitate was filtered off, washed with 10 ml of alcohol, and recrystallized. Yield 79%, mp 158–159°C (EtOH) [18]. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.50–2.55 m (2H, CH_2), 2.65–2.70 m (2H, CH_2), 2.80–2.90 m (2H, CH_2), 3.80 s (3H, CH_3O), 3.85 s (3H, CH_3O), 3.90–3.95 t (2H, CH_2), 6.75 s (1H, Ht), 7.60–7.65 br.s (1H, =NH), 7.65–7.70 s (1H, Ht).

9,10-Dimethoxy-4-oxo-3,4,6,7-tetrahydro-2*H*-pyrido[2,1-*a*]isoquinoline-1-carbonitrile (XIV) was obtained by boiling a solution of 2 mmol of imine **XIII** in a mixture of 12 ml of water and 1.5 ml of acetic acid over 2 h. In the course of the reaction the initial dispersion of amidine dissolved, and to the end of hydrolysis precipitate formed again. The precipitate was filtered off, washed with water, and dried. Yield 78%, mp 147°C (from petroleum ether) [18]. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.60–2.70 m (4H, $2CH_2$), 2.80–2.90 m (2H, CH_2), 3.75–3.80 t (2H, CH_2), 3.85 s (3H, CH_3O), 3.90 s (3H, CH_3O), 6.75 s (1H, Ht), 7.65 s (1H, Ht).

General procedure of acylation (sulfonylation) of amidine XIII. To a solution of 2.65 mmol of amidine and 7.9 mmol of Et_3N in 7 ml of dioxane was added at 25°C while stirring 3.0 mmol of carboxylic or arenesulfonic acid chloride prepared by common method and dissolved in 3 ml of dioxane. After 2 h the solution was slightly heated for 10 min, on cooling it was diluted with

methanol and water and was kept in a refrigerator till the formation of a precipitate. The precipitate was filtered off, washed with water and minimal quantity of methanol and recrystallized.

***N*-{(4*E*)-9,10-Dimethoxy-1-cyano-2,3,6,7-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-ylidene}-benzamide (XVa).** Yield 48%, mp 188–190°C (EtOH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 2.60 m (2H, CH_2), 2.80–2.90 m (4H, $2CH_2$), 3.95 s (6H, $2CH_3O$), 4.10 m (2H, CH_2), 6.75 s (1H, Ht), 7.40–7.60 m (3H, Ar), 7.70 s (1H, Ht), 8.05 d (2H, Ar). Found, %: C 71.25, 71.23; H 5.54, 5.42; N 10.80, 10.82. $C_{23}H_{21}N_3O_3$. Calculated, %: C 71.30; H 5.46; N 10.85.

***N*-{(4*E*)-9,10-Dimethoxy-1-cyano-2,3,6,7-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-ylidene}-3-iodobenzamide (XVb).** Yield 96%, mp 134–135°C (methanol–toluene, 2:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.55 m (2H, CH_2), 2.80 m (2H, CH_2), 2.95 m (2H, CH_2), 3.75 s (3H, CH_3O), 3.85 s (3H, CH_3O), 3.95 m (2H, CH_2), 7.05 s (1H, Ht), 7.30 t (1H, Ar), 7.60 s (1H, Ht), 7.95 d (1H, Ar), 8.05 d (1H, Ar), 8.30 s (1H, Ar). Found, %: C 53.76, 53.78; H 3.89, 3.83; I 24.76, 24.68; N 8.15, 8.23. $C_{23}H_{20}IN_3O_3$. Calculated, %: C 53.81; H 3.93; I 24.72; N 8.19.

***N*-{(4*E*)-9,10-Dimethoxy-1-cyano-2,3,6,7-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-ylidene}-4-chlorobenzamide (XVc).** Yield 84%, mp 156–157°C (MeOH–toluene, 2:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.55 m (2H, CH_2), 2.80–2.85 m (2H, CH_2), 2.95 m (2H, CH_2), 3.85. Found, %: C 65.42, 65.48; H 4.72, 4.63; Cl 8.42, 8.35; N 10.09, 9.99. $C_{23}H_{20}ClN_3O_3$. Calculated, %: C 65.48; H 4.78; Cl 8.40; N 9.96.

***N*-{(4*E*)-9,10-Dimethoxy-1-cyano-2,3,6,7-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-ylidene}-2-fluorobenzamide (XVd).** Yield 83%, mp 164–165°C (from MeOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.60 m (2H, CH_2), 2.80–2.95 m (4H, $2CH_2$), 3.85 s (3H, CH_3O), 3.90 s (3H, CH_3O), 4.05 m (2H, CH_2), 6.80 s (1H, Ht), 7.15 m (1H, Ar), 7.20 m (1H, Ar), 7.50 m (1H, Ar), 7.60 s (1H, Ht), 7.90 m (1H, Ar). Found, %: C 68.11, 68.08; H 4.82, 4.85; N 10.38, 10.42. $C_{23}H_{20}FN_3O_3$. Calculated, %: C 68.14; H 4.97; N 10.36.

***N*-{(4*E*)-9,10-Dimethoxy-1-cyano-2,3,6,7-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-ylidene}-4-methoxybenzamide (XVe).** Yield 76%, mp 170–171°C (MeOH–toluene, 3:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.55 m (2H, CH_2), 2.80–2.85 m (2H, CH_2), 2.95 m (2H, CH_2), 3.85 s (3H, CH_3O), 3.90 s (6H, $2CH_3O$), 4.05 m (2H, CH_2), 6.85 s (1H, Ht), 6.90 d (2H, Ar), 7.60 s (1H, Ht), 7.95 d (2H, Ar). Found, %: C 69.08, 69.03; H 5.45, 5.51; N 10.13, 10.18. $C_{24}H_{23}N_3O_4$. Calculated, %: C 69.05; H 5.55; N 10.07.

***N*-{(4*E*)-9,10-Dimethoxy-1-cyano-2,3,6,7-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-ylidene}-2-furamide (XVf).** Yield 82%, mp 162–163°C (from MeOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.60 m (2H, CH_2), 2.80–2.95 m (4H, $2CH_2$), 3.85 s (3H, CH_3O), 3.90 s (3H, CH_3O), 4.05 m (2H, CH_2), 6.55 m (1H, Ar), 6.80 s (1H, Ht), 7.10 d (1H, Ar), 7.65 s (1H, Ht), 7.70 m (1H, Ar). Found, %: C 66.78, 66.77; H 5.01, 4.98; N 11.16, 11.19. $C_{21}H_{19}N_3O_4$. Calculated, %: C 66.83; H 5.07; N 11.13.

***N*-{(4*E*)-9,10-Dimethoxy-1-cyano-2,3,6,7-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-ylidene}-benzenesulfamide (XVIa).** Yield 58%, mp 179–180°C (from EtOH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.65 m (2H, CH_2), 2.80–2.90 m (2H, CH_2), 3.30 m (2H, CH_2), 3.75 m (2H, CH_2), 3.80 s (3H, CH_3O), 3.90 s (3H, CH_3O), 6.80 s (1H, Ht), 7.50–7.60 s+m (4H, Ar, Ar), 7.85 d (2H, Ar). Found, %: C 62.42, 62.49; H 4.94, 5.03; N 9.95, 9.86; S 7.66, 7.59. $C_{22}H_{21}N_3O_4S$. Calculated, %: C 62.40; H 5.00; N 9.92; S 7.57.

***N*-{(4*E*)-9,10-Dimethoxy-1-cyano-2,3,6,7-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-ylidene}-3-chlorobenzenesulfamide (XVIb).** Yield 41%, mp 174°C (from toluene). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.65 m (2H, CH_2), 2.80 m (2H, CH_2), 3.30 m (2H, CH_2), 3.75 m (2H, CH_2), 3.80 s (3H, CH_3O), 3.90 s (3H, CH_3O), 6.80 s (1H, Ht), 7.50–7.60 s+m (3H, Ar), 7.80–7.90 m (2H, Ar). Found, %: C 57.75, 57.79; H 4.37, 4.41; Cl 7.72, 7.66; N 9.26, 9.20; S 7.02, 7.08. $C_{22}H_{20}ClN_3O_4S$. Calculated, %: C 57.70; H 4.40; Cl 7.74; N 9.18; S 7.00.

***N*-{(4*E*)-9,10-Dimethoxy-1-cyano-2,3,6,7-tetrahydro-4*H*-pyrido[2,1-*a*]isoquinolin-4-ylidene}-3-nitrobenzenesulfamide (XVIc).** Yield 33%, mp 219–220°C (EtOH–C_6H_6, 2:1). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.65 m (2H, CH_2), 2.80 m (2H, CH_2), 3.30 m (2H, CH_2), 3.75 m (2H, CH_2), 3.80 s (3H, CH_3O), 3.90 s (3H, CH_3O), 6.80 s (1H, Ht), 7.50 s (1H, Ht), 8.25 d (1H, Ar), 8.40 d (1H, Ar), 8.65 s (1H, Ar). Found, %: C 56.42, 56.45; H 4.29, 4.33; N 11.90, 11.97; S 6.78, 6.82. $C_{22}H_{20}N_4O_6S$. Calculated, %: C 56.40; H 4.30; N 11.96; S 6.84.

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