1. INTRODUCTION

Fused pyrimidines represent a very important and widely investigated class of nitrogen heterocycles. Since the discovery of uric acid (by Carl Wilhelm Scheele in 1776), a great interest in this heterocyclic system is because of fused pyrimidines are ubiquitous components of natural products and biologically active substances. Significant influence on the biological activity of these compounds exerts the nature of the pyrimidine moiety, contained in their structure. In particular, multiplicities of compounds that have been isolated from natural sources.
and synthesized by medical chemists in the last century contain as a common structural motif the pyrimidine skeleton in various oxidation states. According to R.F. Evans fundamental classification [1] formally, there are nine hydrogenated derivatives of pyrimidine: five dihydropyrimidines, three tetrahydropyrimidines, and one hexahydropyrimidine (Fig. 1), excluding tautomomerism or the possibility of existence of ring conformational isomers.

The enormous interest in these compounds, as evidenced by a growing number of publications, patents, and reviews, is founded in the multifunctional pyrimidine scaffold presenting a broad range of biological effects and pharmacological properties [1,2]. On the other hand, development of the new synthetic strategies for scaffold decorations of these compounds led, in particular, to the unique class of condensed heterocycles containing as a fragment partially saturated pyrimidine nuclei. A selection of representative annulated pyrimidines, either synthetic or isolated from natural sources and possessing significant biological and pharmaceutical activities, are given in Figs. 2 and 3, respectively.

Fenquizone, quimethazone, and metolazone containing the 2,3-dihydroquinazoline-4(1H)-one skeleton are thiazide diuretics and are used for the treatment of high blood pressure [3]. The lead compound in the series of spirocyclic amidines AR-C 102222 is a highly potent and selective inhibitor of inducible nitric synthase with good oral activity [4]. Discovered at Merck Research Laboratories, the non-nucleoside reverse transcriptase inhibitor (NNRTI) Efavirenz (Sustiva) is widely prescribed in the treatment of HIV-1 [5]. The structurally Efavirenz related 4-alkynyl- (DPC 961, DPC 963) and 4-alkenyl-3,4-dihydro-4-(trifluoromethyl)-quinazolin-2(1H)-ones (DPC 083, DPC 082) bearing a chiral trifluoromethyl group represent the second-generation NNRTIs, which exhibits increased efficacy against K103 N-containing human immunodeficiency virus as well as other NNRTI-resistant viruses [5].

RO4858542 is a 5-hydroxytryptamine (serotonin) receptor (5-HT₆) antagonist developed at Roche Palo Alto for central nervous system indications including Parkinson’s disease [6]. The 3,4-dihydroquinazoline-4-acetic acid derivative AIC 246 (Letermovir) has been recently described as a potent inhibitor of human cytomegalovirus replication [7] and is currently undergoing phase II evaluations. Corresponding amide derivatives have been known as novel and potent T-type calcium channel blockers. In particular, compound KYS05090 exhibits both a selective potent T-type calcium channel blocking effect and a strong anticancer effect on A549 cancer cell lines comparable with doxorubicin and paclitaxel in vivo [7].

The selective calcitonin gene-related peptide antagonist olcegepant (BBN 4096) developed at Boehringer Ingelheim Pharmaceuticals represents a new class of drugs in development for the treatment of acute migraine attacks [8] and undergoes phase II trials in Europe and in the USA. The Biginielli compounds have long been proven as a heterocyclic system of remarkable pharmacological efficiency [2]. Related fused compounds in this series, containing the 3,4-dihydropyrimidin-2(1H)-thione scaffold, have also attracted attention in medicinal chemistry. For example, (S)-enastron, (S)-dimethylenastron [9], and (±)-vasastrol VS-83 [9] – annulated across the C-5–C-6 bond monastrol analogs showed promising anticancer activity.

Some active compounds were also found in the series of tricyclic and tetracyclic derivatives. Imidazoquinazoline derivative anagrelide (Xagrid) is phosphodiesterase inhibitor and aroused great hope for the treatment of primary thrombocytosis [10]. Batracylin displays antitumor activity in vivo against murine leukemia P-388 and colon adenocarcinoma 38 cell lines that are resistant to Adriamycin, cisplatin, and methotrexate. However, because of the high toxicity of batracylin, it has never been approved for further clinical trials in humans [11]. The pyrimidobenzothiazine derivative PD 404,182 was recently discovered to be an antibiotic agent. This compound is considered to be an important lead in the development of structurally novel antibiotics effective against multidrug resistant bacteria and was identified as a potent anti-HIV agent [12].

The quinazolinone skeleton is found as a constituent for approximately 150 naturally occurring alkaloids with

![Figure 1. Structures of hydrogenated pyrimidines.](image-url)
interesting biological properties [13]. Tricyclic quinazoline alkaloids such as peganine and peganidine were isolated from the leaves of the Indian plants of *Adhatoda vasica* Nees. These 3,4-dihydro-9-hydroxyquinazoline derivatives exhibit high hypotensive and respiratory stimulant activity [14]. *Linaria vulgaris* Mill., distributed in the northeastern and Inner Mongolia regions of China, is known as a traditional Chinese medicine with various pharmacological properties [15]. (−)-Linarinic acid is a novel tricyclic quinazoline alkaloid. It was found that this compound protects against ischemia-induced cell injury in an *in vitro* oxygen glucose deprivation model of ischemic stroke in SH-SY5Y cells [15]. Evodiamine, naturally occurring indole alkaloid isolated from *Evodia rutaecarpa* – a very popular multipurpose herb traditionally used in China for the treatment of headaches, abdominal pain, postpartum hemorrhage, dysentery, and amenorrhea [16]. With respect to the pharmacological actions of evodiamine, more attention has been paid to beneficial effects against cancer, obesity, nociception, inflammation, cardiovascular diseases, Alzheimer’s disease, infectious diseases, and thermoregulative effects. Evodiamine has evolved a superior ability to bind various proteins, so we also argue that it is a good starting point for multitarget drugs [16].

A very interesting group of polycyclic marine alkaloids containing both guanidine and di- or tetrahydropyrimidine functionalities was isolated from marine sponges. In this series, in a strikingly high percentage of pharmacologically active natural products as well as being an important feature of several clinical agents and numerous exploratory drug candidates are found [17].
Batzelladines A – I, along other known guanidine alkaloids such as crambescin A, (-)-ptilomicalin A and ptilocaulin were isolated by Patil and coworkers [18] from Caribbean sponge Batzella sp. It was found that batzelladines A and B inhibit protein–protein interactions, including the binding of HIV gp120 to CD4 receptors and are therefore of potential interest for the treatment of AIDS [18]. Ptilomycalin A displays significant activity against a series of cancer cell lines and DNA polymerase activity of the reverse transcriptase of human immunodeficiency virus type 1 [19]. The tricyclic guanidine ptilocaulin [20] and crambescin A [21] is reported to have a broad spectrum antimicrobial activity in vitro as well as in vivo activity against L1210 murine leukemia.

The selected examples of the fused saturated pyrimidines, which are presented in Figs. 2 and 3 showed a broad spectrum of pharmacological activity. Therefore, synthetic investigations in this area have received extensive attention. In general, methods for preparation of these compounds can be broadly divided into two groups: (a) cyclization from appropriate acyclic precursors and (b) modification of preexisting aromatic or partially saturated pyrimidine derivatives. The present review is devoted to the preparation of condensed heterocycles containing dihydropyrimidine and tetrahydropyrimidine nuclei through various transformations of preexisting aromatic pyrimidine derivatives. Special attention is given to structural and stereochemical features of these compounds. In the present review, we are considering the developments in this area over the past 15 years.

2. REDUCTION OF FUSED AROMATIC PYRIMIDINES

The reduction of fused pyrimidines is a facile way for the preparation of corresponding condensed heterocycles containing dihydropyrimidine and tetrahydropyrimidine skeletons. These transformations allow increasing the structural diversity and changing the overall geometry of those heterocycles.

2.1. Reduction of 5,6-fused pyrimidines. Catalytic reduction of the C2 substituent free quinazolin-4(3H)-ones 1 over palladium on charcoal [22] or platinum oxide [23] at ambient temperature afforded 2,3-dihydro-4(1H)-quinazolines 2 in 92–95% yields (Scheme 1).

Ohba and coworkers reported [24] the first total synthesis of the adenine-related bicyclic diterpenoid (+)-agelasimine B (5a), which was recently isolated from the orange sponge Agelas mauritiana [25]. The final stage of this synthesis is the reduction of N7-substituted purine 3a...
with sodium borohydride and the subsequent methylation of the formed 1,2-dihydroderivative 4a (Scheme 2). In a similar way, corresponding analogues of (+)-agelasimine B, containing at the N7 position β-cyclocitral- (5b) [26] and hexadecatetraenyl- (5c) substituents, were prepared in moderate yields [27].

A mild and efficient method for the regioselective reduction of inosines was described [28]. Treatment of substituted in sugar moiety inosines 6 with 5 eq of borane-tetrahydrofuran complex at room temperature leads to the regioselective reduction of the C2=N3 double bond in hypoxantine nucleus and afforded the corresponding 2,3-dihydroinosine derivatives 9 (Scheme 3). Moreover, the presence of a substituent at the C2 position of inosine derivatives strongly depressed this process. According to the authors, the initial formed borane complex 7 undergoes hydride attack on the electrophilic carbon atom at C2 position and followed by methanolic work-up the corresponding 2,3-dihydroinosine 8 was obtained. It should be noted that these reactions are very important for the synthesis of chemically modified nucleosides.

Sodium borohydride was used for the reduction of 2-substituted quinazolines alkaloids [29]. Reaction of \( \text{R}(+)-2-(\text{heptan-3-yl})\text{quinazolin-4(3H)}\)-one (10) with NaBH₄ in HOAc furnished 2,3-dihydroquinazoline 11 as a pair of nonisolable epimers in 50% yield (Scheme 4).

The attempts to reduce the condensed heterocycles 12a–c containing the \(N,N'\)-dimethylpyrimidin-2,4-dione moiety with lithium borohydride, lithium triethylborohydride and under hydrogen atmosphere in the presence of Adam’s catalyst were unsuccessful [30]. At the same time, reaction of these compounds with four equivalents of DIBAL-H in dry THF at \(-78^\circ\)C occurs completely regioselectively at the carbonyl group of the urea moiety and afforded fused 2,3-dihydropyrimidin-4(1H)-ones 13a–c in 79–93% yields [30] (Scheme 5).

Similarly, the reduction of fully protected purine-2,6-diones 14 occurs with 4 eq of lithium aluminum hydride [31]. However, in these cases, along with tetrahydropurin-6-ones 15, imidazoles 16 were isolated as pyrimidine ring-opened products (Scheme 6).

Pd-catalyzed asymmetric hydrogenation of imines [32] and α-fluorinated imines [33] is well documented. J.-A. Ma and coworkers have applied Pd[(S)-SynPhos] (OCOCF₃)₂ as a catalyst for the asymmetric hydrogenation of 4-tri- and 4-difluoromethylquinazolin-2(1H)-one derivatives [34]. The best results were obtained when the hydrogenation of the cyclic ketimine...
17 was carried out by using 4 mol% of the catalyst in 3,3,3-
trifluoroethanol at a pressure of 700 psi (Scheme 7). The
corresponding 3,4-dihydroquinazolinon-2(1H)-ones 18
were obtained with excellent yields (89–98%) and
enantioselectivities (94–97% ee).

Electron-withdrawing, electron-donating, and electron-
neutral groups as well as substrates substituted at various
positions on the aromatic rings were all good partners for
the hydrogenation. It should be noted that the
hydrogenation of the N-deprotected quinazolinone could
also occur smoothly with 94% yield and 98% ee.

2.2. Reduction of 2,3-fused pyrimidines. Reduction of
pyrazolo[1,5-a]pyrimidines 19 with sodium borohydride
does not stop on the stage of the dihydropyrimidines
formation (Scheme 8). In these cases, the 4,5,6,7-
tetrahydropyrazolo[1,5-a]pyrimidine derivatives 20 were
solely yielded as cis-isomer [35,36]. Reduction of 19
containing chloro substituents over Pd-C (10%) under a
hydrogen atmosphere is accompanied by dehalogenation.

2.3. Reduction of 3,4-fused pyrimidines. The series of
bicyclic pyrrolo[1,2-c]pyrimidines 22 was obtained from
corresponding enaminnitrile 21 by reduction with
NaBH₄ in ethanol [37–39] (Scheme 9).

2.4. Reduction of 2,3- and 5,6-bis-fused pyrimidines.
There are numerous studies described in the literature
devoted to the reduction of the quinazoline fragment of
the nitrogen bridgehead in tri-, tetra- and pentacyclic
alkaloids [13]. For example, deoxypeganine (24, R=H,
n=1) and their derivatives were obtained from tricyclic
quinazolinones 23 under Clemmensen reduction
conditions [40,41] (Scheme 10).

Treatment of quinazoline alkaloid rutacearpine (25)
with LiAlH₄ at room temperature not only led to the
dihydroquinazoline derivative 26 as a result of an amide
group reduction but also to the tetrahydroquinazoline 27
through the saturation of C=N bond [42] (Scheme 11).

Both of these processes are observed simultaneously by
reduction of the N-methyl quaternary salt 28 with LiAlH₄
at 70°C [43] (Scheme 11). The desired tricyclic
quinazoline derivatives 29 were obtained in 74–78%
yields. Lithium aluminum hydride is also an ideal reagent
for the decarbonylation of evodiamine [43–45].

The chemical behavior of the fused quinazoline alkaloid
tryptanthrin (30 a), which has been isolated from numerous
natural sources and contains indolo[2,1-b]quinazoline core, was thoroughly studied [46,47]. In particular, reaction of tryptanthrin (30a) and its bromoderivative (30b) with NaBH₄ in acetic acid occur via a chemoselective reduction of imine bond of the quinazolinone fragment and yielded the secondary alcohols 31a and 31b, respectively [47,48] (Scheme 12). At the same time, the reduction of 30a with the more powerful lithium aluminum hydride was accompanied by decarbonylation and formation of the non-isolated tetrahydroquinazoline derivative 33. These both products of reduction were characterized as their mono-(32) and diacetyl esters (34) [47]. Moreover, partial oxidation of 33 with manganese dioxide led to dihydroquinazoline derivative 35 [46].

Tryptanthrin (30a) has also been chosen as a starting material in transition metal free diastereoselective total synthesis of (±)-cruciferane (38) [49,50]. This fused quinazoline alkaloid was recently isolated from Phaius mishmensis and Isatis tinctoria and represents the first natural products with an pyrrolo[2,3-b]indolo[5,5a,6-b, a]quinazoline skeleton [51,52]. The chemoselective aldol condensation of 30a with methyl acetate in the presence of LDA at −78°C provided the natural product phaitanthrin B (36) [49] (Scheme 13). The highly chemo- and diastereoselective reductive intramolecular cyclization of 36 is effected by NaBH₄ and afforded (±)-cruciferane 38 with 82% yield. The mechanism of this transformation suggests [49] that the initially developed boron-oxygen complex with the hydroxyl group delivers a hydride to the imine moiety and allows realize the cyclization to a γ-lactam via transition state 37.

Another approach to the (±)-cruciferane (38) synthesis is also based on the aldol condensation of tryptanthrin (30a) [50]. The first step of this method is a chiral auxiliary mediated diastereoselective acetate aldol reaction of the lithium enolate of N-acetyl-(S)-4-isopropyl-1-[(R)-1-phenylethyl]-imidazolidin-2-one with tryptanthrin
The resulting product 39 is a highly appreciable *syn* acetate aldol selectivity of 98:2 was observed (according to $^1$H NMR spectrum). The transformation of 39 into the desired final product 38 was achieved by two different methods. The chemoselective imine reduction of 39 using NaBH₄ in acetic acid stereoselectively afforded 41. Subsequent cyclization of 41 using lithium perchlorate as a catalyst and triethylamine as a base in acetonitrile led to the target (+)-cruciferane 38 throughout an electrophilic activation mechanism [51].

The other method allows to obtain 38 by reductive cyclization of the chiral auxiliary product 39 via transamidation using a combination of NiCl₂·6H₂O and NaBH₄ in methanol [50]. The key step of this transformation is a hydride transfer from the nickel–boron complex to the electrophilic imine carbon in a stereoselective fashion and the generation of the nitrogen nucleophile, stabilized by the Lewis acidic boron (transition state 40). This nucleophilic species attacks the carbonyl carbon atom with a solvent assisted auxiliary cleavage and afforded (+)-cruciferane 38 in good yield. Moreover, this reductive cyclization took place stereoselectively in a substrate controlled asymmetric induction. It should be noted that the given transformation is the first example of application of NiCl₂·6H₂O/NaBH₄ system for the reductive transamidation imines.

3. ADDITION OF REAGENTS OTHER THAN HYDROGEN TO FUSED AROMATIC PYRIMIDINES

Reactions based on the direct nucleophilic attack on the unsubstituted carbon atom C(sp²) – H of heteroaromatic compounds were actively developed in the past decades [53]. One of the necessary requirements for the success of such reactions in the fused pyrimidines series is the increase of electron deficiency of pyrimidine moiety in these compounds, which can be achieved, in particular, either by introducing of an electron-withdrawing group in the pyrimidine ring or its annulations. These reactions are usually completed by the substitution of hydrogen atom (SN₂ reactions) or are stopped at the stage of σ⁺H-adducts formation (ÅN reactions). Last opportunity, leading to the
formation of partially saturated fused pyrimidines, will be considered in this section.

Reaction of quinazoline \textbf{42} with 1,3-dimethylbarbituric acid under heating in butanol afforded the quantitative formation of $\sigma$-adduct \textbf{43} [54] (Scheme 14). In this case, the addition of dimethylbarbituric acid is a consequence of protonation of the quinazoline system by the nucleophile itself.

G. Oliviero and coworkers reported a method for functionalization of C6 position of purine derivatives by reaction of sugar protected purine $N$-oxides with both $N$-methylmaleimide (as dipolarophile) and with Grignard reagents [55] (Scheme 15). Treatment of 2',3',5'-tri-$O$-acetylnebularine $N$1-oxide (\textbf{44}) with $N$-methylmaleimide in dioxane/toluene (1:1) at reflux afforded 5,6-dihydropurine derivative \textbf{47} in a 60% yield as a 1:1 mixture of diastereomers. It is assumed that the formation of this $\sigma$-adduct is the result of an isoxazoline ring opening in cycloadduct \textbf{46}. At the same time, the reaction of \textbf{45} with some Grignard reagents (2 eq) in THF afforded the six-substituted $N$-hydroxy adducts \textbf{48a–d} (as diastereomers mixture) [55] (Scheme 15). These compounds are not stable and aromatized on standing to 6-substituted nebularine derivatives. In the described cases, the formation of 6-substituted purine derivatives obviously explained by the increased electrophilic nature of the C-6 atom of the nucleobase compared with the C-2 atom.

Furoxanopyrimidine includes in its structure a 1,2,5-oxadiazolo moiety, which can be considered as a “masked” nitro group. Presence of this five-membered heterocycle significantly increased the electron deficiency of pyrimidine ring. Earlier, we reported [56] that 5-methoxy[1,2,5]-oxadiazolo[3,4-$d$]pyrimidine 1-oxide (\textbf{49}) reacts with carbanions derived from different CH-acids to yield the corresponding $\sigma$-adducts \textbf{50} (Scheme 16). By dissolving of furoxanopyrimidine \textbf{49} in primary, secondary or tertiary alcohols as well as in water are formed 6,7-dihydropyrimidine derivatives \textbf{51} even without base [57].

Furthermore, \textbf{49} reacts with electron-rich aromatic systems and enolizable carbonyl derivatives in DMSO or CH$_2$Cl$_2$ at room temperature also without base to give the 7-substituted 5-methoxylfuroxano[3,4-$d$]-6,7-dihydropyrimidines \textbf{52}, respectively [58]. Kinetic investigations of these reactions [58] showed that the rate constants can be described by the correlation equation log $k$ (20°C) = $s$ ($N$ + $E$). The electrophilicity parameter $E$ (\textbf{49}) = –8.37 derived from the second-order rate constants indicates that \textbf{49} reacts with nucleophiles of $N$ > 3 [59]. Such an $E$ value remains considerably higher than that of 1,3,5-trinitrobenzene ($E$ = –13.19 [60]), leaving no doubt that the 5-methoxy[1,2,5]-oxadiazolo [3,4-$d$]pyrimidine 1-oxide (\textbf{49}) has to be classified as a strongly electron-deficient heteroaromatic compound [60].

The aforementioned examples describe the condensed heterocycles where the pyrimidine ring is fused via C5–C6 linked centers. A pyrimidine, which is incorporated in 1,2,4-triazolo- and 1,2,3,4-tetrazolo-6-nitropyrimidine
derivatives, is activated as via annulations of C2–N3 linked centers as well as the availability of an electron withdrawing group. Highly electron-deficient 6-nitro[1,2,4]triazolo[1,5-a]pyrimidine 53 reacts with substituted methyl ketones in the presence of triethylamine to give Meisenheimer σ-complexes, which are transformed into 4,7-dihydropyrimidine derivatives 55 under acidic conditions [61] (Scheme 17).

The reaction of 53 and 54 with some π-excessive aromatic and heterocyclic compounds to proceed smoothly at reflux temperature giving the corresponding σ-adducts 56 and 57 [62,63]. These fused dihydropyrimidine derivatives 55–57 are formed in high yields as stable crystalline substances.

Among biologically active dihydroquinazolinone drug candidates DPC 961 and DPC 083, bearing a chiral trifluoromethyl moiety in quaternary center (Fig. 1), take a special place. Many synthetic methodologies have been developed to access to these compounds [64]. Previously, tremendous efforts mainly focused on the synthesis of this class of compounds via 1,2-enantioselective addition of a lithium acetylide to cyclic N-acylketimines using lithium cinchona alkaloids as the chiral moderator [65], diastereoselective 1,4-addition of a magnesium acetylide to 2-(3H)-quinazolinones containing a chiral auxiliary N-substituent [66,67], and a highly enantioselective addition of in situ generated zinc acetylide [68] and varying terminal 1,3-diynes [69] to a cyclic N-acylimine in the presence of the chiral chloramphenicol ligand. This chemistry is amenable to a multiple kilogram scale and proves to be a versatile way to prepare enantiopure dihydroquinazolinones. In the last decade, research in this area has shifted focus to the further functionalization of a quaternary stereogenic centers in dihydroquinazolone scaffolds. In this sense, much attention has been given to the investigation of organocatalyzed carbon–carbon forming aza-Henry, Mannich, Strecker, aza-Friedel–Crafts and aza-Morita–Baylis–Hillman reactions of 4-(trifluoromethyl)quinazolin-2(1H)-one derivatives. Furthermore, it was suggested that the generated trifluoromethyl dihydroquinazoline derivatives could lead to the formation of new druglike substances.

A highly efficient hydrogen bond-mediated enantioselective addition of nitroalkanes to 4-trifluoromethylquinazolin-2(1H)-ones 58 (aza-Henry reaction) has been achieved in toluene at room temperature in the presence of 1 mol% thiourea-containing quinine derivative as a catalyst [70] (Scheme 18). Dihydroquinazolin-2(1H)-ones 59 were obtained in 72–97% yields with good to excellent enantioselectivity (82–98% ee) unaffected by the electronic nature of the substituents on the aromatic rings of the cyclic ketimine. It should be noted that the absence of an
N-protection at the ketimine substrate and the replacement of the trifluoromethyl group with methyl or phenyl substituents do not lead to condensation products.

B. Jiang and coworkers developed a highly enantioselective construction of a quaternary carbon center of 3,4-dihydroquinazolin-2(1H)-one by Mannich reaction of N-protected 6-chloro-4-trifluoromethylquinazolin-2-ones 60 with various methyl ketones [71] (Scheme 19).

The best results were obtained by using a combination of (R)-1-(2-pyrrolidinylmethyl)-pyrrolidine as diamine and dibenzoyl L-tartaric acid (L-DBT) as a Brønsted acid (in a ratio 1:1.1) catalyst in this reaction. These reactions proceeded smoothly and gave the desired products 60 in high yields (91–95%) except for the bulky isobutyl methyl ketone (51–75%). Recrystallization of dihydroquinazolines 60 from ethanol afforded enantiopure compounds 61, which remained in mother liquor. At the same time, the collected crystals represented hydrogen-bonding dimers of two enantiomers with opposite absolute configurations (for example 62), that is, unusual phenomenon of self-discrimination of enantiomers.

In continuation of the study the possibility of organocatalyzed carbon–carbon-forming reactions in 4-trifluoromethylquinazolin-2(1H)-one series, J.-A. Ma and coworkers reported the enantioselective decarboxylative Mannich reaction of β-ketoacids [72] and malonic acid half oxyesters [73] with these electrophilic acceptors.

It was shown that the hydrogen-bond-directed enantioselective decarboxylative Mannich reaction was promoted by saccharide-derived amino thioureas bifunctional organocatalysts [73]. For example, the condensation of ketimine 58 with 3-oxo-3-phenylpropanoic acid (2 eq) in THF at −20°C in the presence of 10 mol% 63 as catalyst afforded 64 in 99% yield and 99% ee enantioselectivity (Scheme 20). In these optimized conditions, the reaction proceeded smoothly with a variety of substituted both cyclic N-protected trifluoromethyl ketimines and β-ketoacids, generating the desired products 71 in excellent (92–99%) yield and enantioselectivity (90–99% ee). A high yield (99%) but poor enantioselectivity (38% ee) was observed for the
derivative where the protective group was absent. At the same time, the application of the L-glucose-derived catalyst 65 enabled in synthesis of compound 66 exhibited an asymmetric induction in the opposite sense.

Similar regularities were also observed in the asymmetric organocatalytic Mannich reaction of cyclic 4-trifluoromethylketimines with less reactive malonic acid half esters [73].

Reaction of 58 with 3-oxo-3-phenyloxypropanoic acid in the presence of catalyst 67 afforded the adduct 68 in 99% yield and 99% ee enantioselectivities (Scheme 20). Reaction of various aryl substituted N-protected cyclic trifluoromethylketimines with 3-oxo-3-arylxypropanoic acid in similar conditions afforded the corresponding β-amino esters 72 in 90–99% yield and 90–99% ee enantioselectivities. It should be noted that a dramatic decrease in enantioselectivity was observed by carrying out of this reaction in the absence of an N-protection at the ketimine substrate. At the same time, replacing the trifluoromethyl group by a methyl or phenyl group was ineffective in the decarboxylative Mannich reaction. When catalyst 69 was employed, the reaction afforded corresponding compound 70 with the opposite sense of asymmetric induction in 97% yield and 97% ee enantioselectivity.

$^{19}$F NMR and ESI/MS experiments were used to study of this decarboxylative Mannich reaction, suggesting that the nucleophilic addition to the ketimine occurs prior to the decarboxylation of the adduct. Based on these results as well as computationally analyses, the nucleophile can only be delivered from the $Si$ face of the C=N group, thus giving predominantly the $R$ enantiomer of the Mannich products after decarboxylation of the initial adduct (Fig. 4).

J.-A. Ma and coworkers developed a highly efficient organocatalytic enantioselective Strecker reaction of
cyclic N-acyl ketimines [74]. Trifluoromethylsubstituted quinazolinones 58 was treated with trimethylsilylcyanide in toluene at 0°C in the presence of various cinchona alkaloid-based thioureas (Scheme 21). The best results were obtained by employing catalysts 73a,b in these reactions. Using even 1 mol % of catalyst 73a afforded R enantiomer 74 in 93–99% yields and 92–96% ee enantioselectivity regardless of the electronic properties of the substituents on the aromatic ring. Under similar reaction conditions, the use of aminothiourea 73b as the chiral catalyst gave the S-configured adducts 75 with comparable yields and ee values.

Similar results about the course of Strecker reaction were reported by W. Wang and coworkers [75]. The authors suggest (Fig. 5) that the nucleophilic attack of the cyanide at the C=N double bond of trifluoromethylquinazolin-2(1H)-ones occurs from the Re face due to coordination with the thiourea moiety by hydrogen bonding and leads to the formation of the adduct with R-configuration.

It must be emphasized that all previously presented 4-substituted 4-trifluoromethyl-3,4-dihydroquinazolin-2(1H)-
ones, which were obtained as a result of corresponding catalytic highly enantioselective Mannich-, aza-Henry- and Strecker reactions, could be considered as attractive starting materials for the synthesis of numerous derivatives, and they are in particular representatives for the second-generation non-nucleoside HIV reverse transcriptase inhibitors DCP 083 (Fig. 1) [71–74]. Moreover, as already mentioned above, N1-protected 4-arylquinazolin-2(1H)-ones are inert in aza-Henry [70], Mannich [71] and decarboxylative Mannich [72] reactions. At the same time the investigations on the behavior of 4-arylsubstituted quinazolin-2(1H)-ones under Strecker reaction conditions [75] showed that upon carrying out this reaction in CH₂Cl₂ in the presence of 73a (10 mol %) as a catalyst the corresponding adducts were obtained with good yields and moderate ee values. In this context, in situ generated N3-protected 4-arylquinazolin-2(3H)-ones 77, which contain another conjugated π-system than N1-protected analogue, react with a large excess of Grignard reagents and afford the 4,4-disubstituted 3,4-dihydroquinazolin-2(1H)-ones 78 [76,77] (Scheme 22).

J.-A. Ma and coworkers reported the construction of chiral tetrasubstituted carbon stereocenters by aza-Friedel–Crafts reaction of indoles with cyclic trifluoromethyl ketimines [78]. It was found that the reaction of N-protected 4-trifluoromethylquinazolin-2(1H)-ones 58, containing electron-withdrawing, electron-donating and electron-neutral substituents with indoles 79 afforded in the presence of (S)-BINOL-derived phosphoric acid (5 mol%) as catalyst in dichloroethane at −35°C in all cases σ-adducts 80 (Scheme 23) in respectable yields and enantioselectivities (except 5-cyanoindole derivative).

The proposed transition state for this reaction (Fig. 6) indicates that the phosphoric acid could simultaneously activate both the indole and the cyclic ketimine by hydrogen bonding, which leads to the preferred attack of the indole from the Re face of C==N fragment. Analogously, the same reaction with an electron-enriched pyrrole or 3-(dimethylamino)phenol gave the corresponding products with good yield (92% and 93%) albeit low enantioselectivities (80% ee and 63% ee).

The bifunctional thiourea catalyst 73 a (Soós catalyst), which was used by carrying out the Strecker reaction with the cyclic ketimine series [74], has been successfully applied by the hydrophosphonylation of N-protected 6-substituted 4-trifluoromethylquinazolin-2(1H)-ones 58 [79]. Reaction of 58 with methyl- or phenylphosphonates 81 in chloroform (or dichloromethane) in the presence of 10% of 73 a afforded dihydroquinazolinones 82 with 75–91% yield and 87–93% ee enantioselectivity, independent of the electronic nature of the substituent on the aryl ring (Scheme 24).

The proposed transition state model of this asymmetric hydrophosphonylation reaction [79] is similar to the one.
that has been observed by carrying out of the Strecker reaction (Fig. 5) and ensuring the formation of the absolute R configuration of σ-adducts 82. Analogously, ethylphosphonates or benzylphosphonates were obtained with satisfactory results.

From the aforementioned examples of the construction of quaternary stereogenic centers in dihydroquinazolinone scaffolds, it can be seen that the nature of the Lewis base catalysts and various reaction conditions has a decisive influence on the nucleophilic activation. Excellent investigations of this different reactivity patterns were reported in series of publications by J.-A. Ma’s group. First of all, the use of pyridine as a Lewis base catalyst in the aza-Morita–Baylis–Hillman reaction of ethyl 2,3-butadienoate with cyclic ketimines 58 was studied [80] (Scheme 25).

The reaction was performed with a catalyst loading of 10% in toluene and afforded aza-Morita–Baylis–Hillman adducts 83 with good to high yields. This reaction also tolerated an N-deprotected ketimine. The driving force of this reaction pathway is the formation of the enolate intermediate 84, which can undergo α-addition with ketimine 85. Proton transfer of the most acidic proton of the newly generated intermediate 86 followed by a catalyst regeneration step yields the desired products 83. The use of other Lewis base catalysts in this reaction leads to a cardinal change of its direction. These transformations will be considered in the next section.

4. CYCLOADDITION WITH FUSED AROMATIC PYRIMIDINES

In continuation of the investigations on the reaction of 2,3-butadienoate with di- and trifluoromethylquinazolin-2(1H)-ones 58, J.-A. Ma and coworkers studied the
influence of several other commonly used nitrogen-containing Lewis bases (TEA, DBU, DMAP, and DABCO) on their ability to catalyze this reaction [80]. It has been shown that carrying out this reaction in 1,4-dioxane in the presence 20 mol% of DABCO as a catalyst (Scheme 26) afforded the corresponding 4,5-dihydro-1H-azeto[1,2-c]quinazolin-4(2H)-ones 87 as the E isomers (the structure was determined by single crystal X-ray structural analysis) in 53–87% yields.

The presence of a trifluoromethyl group in the substrates 58 was necessary for carrying out this reaction. Replacement of this group by a difluoromethyl group and the absence of N-protection lead to a dramatic decrease in the yield (13% and 18%, respectively). Thus, in this case, the reaction does not stop at the stage of the nucleophilic addition but leads to the formation of tricyclic heterocycles containing an azetidine ring, which was formed as result of [2 + 2] annihilations of ethyl 2,3-butanedioate with cyclic ketimines. It should be noted that the application of DMAP in this reaction leads to a significantly lower yield whereas neither DBU nor triethylamine provided any reactivity in this reaction. The formation of allylic carbanion 88 as a zwitterionic intermediate upon conjugate addition of DABCO to 2,3-butanedioate is the driving force of this [2 + 2] annulations reaction. γ-Addition of 88 to cyclic ketimine 58 and subsequent intramolecular nucleophilic attack furnishes the zwitterionic intermediate 90. Catalyst elimination along with double bond formation produced the desired derivatives 87.

Phosphorus-containing Lewis base catalyst has also been used successfully for annulation of ethyl 2,3-butanedioate with cyclic ketimines. Furthermore, different phosphanes showed markedly different behaviors on providing various cycloadducts. The reaction of ethyl 2,3-butanedioate (2 eq) with N-protected di- and trifluoromethylquinazolin-2(1H)-ones 58 in the presence of triphenylphosphine in dichloromethane at 0°C afforded dihydropyrrolo[1,2-c]quinazolin-5(3H)-one 91 as result of [3 + 2] annihilations in nearly quantitative yields [80] (Scheme 27).

At the same time, cyclic ketimine without a protecting group on the nitrogen atom reacts in moderate yield (52%). Surprisingly, the difluoromethyl derivative underwent in the [3 + 2] annulation smoothly, and corresponding cycloadduct was obtained in 97% yield. The tentative mechanism (Scheme 27) involves a cycloaddition of the initially formed 1,3-dipole 92 with the ketimine upon formation of ylide 93. Subsequent proton transfer and elimination of PPh3 afforded the cycloadducts 91.

The solvent plays an essential role in these reactions. A similar reaction of the N-protected 6-chloro-4-trifluoromethylquinazolin-2(1H)-one 58 with ethyl 2,3-butanedioate (2 eq) in the presence PPh3 proceeded in toluene smoothly to give the [3 + 2] cycloadduct 95 along with a sequential [3 + 2]/[3 + 2] cycloadduct 96 [80] (Scheme 28), (Table 1, Entry 1). Obviously, the product of the first [3 + 2] annulation is simultaneously the electron-deficient substrate for a subsequent [3 + 2] annulation reaction. Similar products were isolated in the presence of 1,3-bis(diphenylphosphano)propane (DPPP) as bisphosphane Lewis base catalyst [81] (Table 1, Entry 2). The use of an excess of ethyl 2,3-butanedioate was found to significantly increase the yield of sequential annihilations. And by using of 2.5 eq of ethyl 2,3-butanedioate, the yields of 95 and 96 were 3% and 96%, respectively (Table 1, entry 3), whereas the increase of this excess to 3.0 eq exclusively leads to 95 (Table 1, Entry 4) in 97% yield. Additional proof of this reaction
pathway is the formation of 96 in 97% yield by [3 + 2] annulation of 95 with ethyl 2,3-butadienoate in the presence of DPPP as a catalyst. A variety of di- and trifluoromethyl substituted as well as cyclic ketimines also enter these bisphosphane-triggered sequential [3 + 2]/[3 + 2] annulations reaction [81] (Scheme 28). As a result, tri-(95) and tetracyclic (96) N-fused heterocycles containing dihydroquinazoline skeleton were obtained in excellent regio- and diastereoselectivities. J.-A. Ma and coworkers reported a highly regio- and diastereoselective intermolecular [3 + 2] annulation of Morita-Baylis-Hillman carbonates 97 with 4-di- and trifluoromethyl-quinazolin-2(1H)-ones 58 [82]. Several phosphanes were studied as catalyst in this reaction. The best results were obtained in toluene in the presence of 10 mol % tri-n-butylphosphane as a catalyst (Scheme 29).

The desired tricyclic N-fused compounds 98 were obtained in high yields and excellent diastereoselectivities (greater than 99:1 dr) irrespective of the nature and position of the substituents in both aryl rings. Absence of the N-protecting group in the cyclic ketimine leads to a significant decrease in yield of the corresponding product (18%).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Experimental conditions and resulting yields for the production of 95 and 96.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entry</td>
<td>Ethyl 2,3-butadienoate</td>
</tr>
<tr>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
</tr>
<tr>
<td>3</td>
<td>2.5</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
</tr>
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95/96 R = PMB; R² = CF₃; R³ = 8-F (4%/96%), 8-Br (2%/98%), 8-CF₃ (3%/95%), 5,6-F₂ 26%/66%; 5,6-F₂ (20%/85%), H (1%/99%), 6-Me (20%/84%), 6-Pr (21%/75%), 6-OMe (19%/89%); R¹ = 6-C₆H₄; R² = CF₃; R¹ = PMB (2%/98%), 1-naphthylmethyl (2%/96%); 8-anthracenylmethyl (2%/88%), 1-naphthylmethyl (2%/95%), H (10%/82%); R¹ = 6-C₆H₄; R = PMB; R² = CF₃ (7%/91%).

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attempts to carry out the aforementioned transformations with 4-methyl- or 4-phenylquinazolin-2(1H)-ones were unsuccessful. These permits asserting that the strong electron-withdrawing di- and trifluoromethyl groups at position 4 of heterocycles and N1-protective group are critical for this formal [3 + 2] annulation process. The study of the possibility of catalytic enantioselective annulations using chiral phosphanes (for example (R,R)-DIPAMP, (S,S)-Ph-BPE) leads to asymmetric [3 + 2] annulations products in 71–90% yields and low enantioselectivity (42–54% ee). Plausible reaction mechanisms (Scheme 32) suggest a cycloaddition of the initially formed ylide $99$ to ketimine $58$ with the formation of intermediate $100$. The latter undergoes an intramolecular Michael addition to generate the zwitterionic intermediate $101$. Subsequent elimination of $\text{PBu}_3$ produces the desired products $98$.

Efficient approach to the synthesis of a variety bridged N-fused heterocycles was proposed by P. Langer and coworkers [83–86]. The reaction of quinazoline derivatives $102$ with 1,3-bis(trimethylsiloxy)-1,3-butadienes $103$ in the presence of chloroformate (4.0 eq) afforded 3,4-benzo-7-hydroxy-2,9-diazabicyclo[3.3.1]non-7-enes $104$ (Scheme 30).

Activation of quinazoline ring in these cases via generating of the iminium salts $105$ is achieved in situ by using methyl and benzyl chloroformate. At the same time, substituted 1,3-bis-silyl enol ethers can be regarded as electroneutral equivalents of dianions (“masked” dianions). Regioselective attack of the terminal C-atom of corresponding silyl enol ethers onto the C4 position of the iminium salts of quinazolines give the $\sigma$-adduct $106$. The formation of the second iminium ion and subsequent attack by the central C-atom of 1,3-dicarbonyl unit provides the formation of meta-bridged tetrahydroquinazolines $104$.

Optimal yields were obtained when the reaction was carried out with 4.0 eq of chloroformate, and direct chromatographic purification was performed without aqueous work-up [85]. The cyclization of quinazoline with 1,3-bis(silyl enol ethers) containing methyl and ethyl groups attached to carbon atom C-4 ($R^3 = \text{Me, Et}$) afforded products as mixtures of not separable diastereomers with moderate to good diastereoselectivity [85]. Attempts to remove of protecting groups from tetrahydroquinazoline derivatives $104$ (hydrogenation under Pd/C conditions) lead to complete decomposition of the tetrahydropyrimidine fragments of these compounds [83].

### 5. INTRAMOLECULAR CYCLOADDITION OF PYRIMIDINONE DERIVATIVES

With respect to novel photophysical properties of nucleosides, the condensation of 5-aminocytidine and 5-amino-2′-deoxycytidine with 1,2-dicarbonyl compounds was studied [87,88]. It turned out that the reactions of 5-aminocytidine $107$ with isatins $108$ at reflux does not stop at the stage of condensation product $109$ but forms a fused dihydropyrimidin-2(1H)-one derivatives $110$ as a result of the intramolecular nucleophilic attack of the

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**Scheme 29**

![Scheme 29](image-url)
5'-hydroxy group on the C6 position of the pyrimidine ring (Scheme 31).

The S configuration of the new chiral center has been proven by using a combination of Nuclear Overhauser Effect (NOE) techniques and molecular modeling studies [88]. Moreover, the generality of this synthetic approach was demonstrated by preparing a wide range of 5'-6'-locked nucleosides by reaction of 5-amino-2'-deoxycytidine with a variety of 1,2-diketones [89,90].

Synthesis of modified cyclonucleosides containing a methylene group between the glycone moiety and the nucleobase is well documented [91]. Among these compounds, 5',6'-cyclonucleosides having saturated pyrimidine as nucleobase moiety occupies a special place [91–95]. These compounds were obtained as a result of an intramolecular radical cyclization of 5'-formyl or 5'-halogeno nucleoside derivatives promoted either with Bu3SnH or (TMS)3SiH in the presence of azobisisobutyronitrile (AIBN) [91]. For example, cyclization of 5'-carbaldehyde 111 occurs in the presence of (TMS)3SiH as the mediator and AIBN as a radical initiator in benzene at reflux and afforded two diastereoisomers of cyclonucleoside 112a and 112b in the 30:70 ratio [93] (Scheme 32). The (5'S,6S,5S) configuration to the isomer 112a and the (5'R6S5S) configuration to the isomer 112b were determined by NMR spectroscopic analysis. Subsequent UV irradiation of these compounds at room temperature furnished the quantitative formation of the monosilylated products 113a and 113b. The driving force of this intramolecular cyclization is the generation of Cs radicals by addition of the (TMS)3Si radical to the 5'-carbaldehyde 111. This key intermediate transforms into the cyclonucleosides 113a and 113b as a result of 6-exo-trig cyclization. At the same time, the use of Bu3SnH as the reducing reagent in this reaction leads to the formation of tricycle 114 as a (5'S)/(5'R) diastereomeric mixture in a 80:20 ratio. Based on these data, the authors concluded
[93] that spatial shapes of the (TMS)₃Si and Bu₃Sn groups were responsible for the inverted diastereoselectivity in these both reactions.

Conformationally, rigid modified nucleosides can be also prepared from N1-substituted uracil derivatives containing 3-bromo(iodo)propyl group under free radical cyclization conditions. Reaction of alkyl iodide 115 with $n$-Bu₃SnH in the presence of a catalytic amount of AIBN (Scheme 33) afforded the azabicycle 116 in 85% yield and excellent diastereoselectivity ($ds > 19: 1$). Hydrogenolysis of 116 and elimination of protecting group completed the synthesis of the conformationally rigid nucleoside 117 [94]. Analogously, the treatment of 5-(hydroxymethyl)-uracil derivative 118 with TTMS and
triethylborane, in the presence of air, furnished a mixture of azabicycle 119 and 120, in which 119 is the major diastereoisomer [95] (Scheme 33).

Novel evodiamine analogues, bearing an amide group at position 5 of the pentacyclic skeleton, were obtained as a result of the synthetic sequence presented in Scheme 34 [96]. Intramolecular cyclization of N-methyl-4-oxo-3,4-dihydroquinazolinium salt 121 in pyridine furnishes the indolopyrido[2,1-b]quinazoline 122 in 3:5 configuration and its epimer at quaternary carbon center in a 8:2 ratio. Finally, hydrolysis of ester 122 and subsequent treatment of the corresponding acid with various amines afforded diverse amidoderivatives of evodiamine 123.

6. CONCLUSIONS

Fused pyrimidines occupy a distinct and unique place in our life, because this heterocyclic moiety has great biological and medicinal significance. Myriads of compounds that have been isolated from natural sources and synthesized by medical chemists in the last century contain as a common structural motif the pyrimidine skeleton in its various oxidation states. This synthetic review has summarized current developments in the preparation of condensed heterocycles containing di- and tetrahydropyrimidine nuclei by various transformations of preexisting aromatic pyrimidine derivatives. The review presents a variety of concepts and strategies for the construction of these highly functional heterocyclic systems. Moreover, the expansion of the structural diversity of these compounds will contribute to medicinal chemistry.

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REFERENCES AND NOTES

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