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Arbidol: a quarter-century after. Past, present and future of the original Russian antiviral

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The present review is concerned with the synthesis and structure – activity relationship studies of Arbidol and its structural analogues. The latter are roughly divided into several unequal parts: indole- and benzofuran-based compounds, benzimidazole and imidazopyridine bioisosteres and ring-expanded quinoline derivatives. Much attention is focused on various types of antiviral activity of the above-mentioned Arbidol congeners, as well as of the parent compound itself. Features of Arbidol synthesis and metabolic changes are also discussed.
The bibliography includes 166 references.

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1. Introduction

Arbidol is an original Russian antiviral drug widely used for etiotropic therapy of influenza and flu.[1] It can be considered as an outstanding medicine among other drugs developed in Russia due to a great commercial success in the domestic market. In 2011, the World Health Organization (WHO) rendered an international nonproprietary name Umifenovir to an active ingredient of Arbidol, but the original name given to this drug by its creators is still much more common and familiar both to patients and researchers. In 2013, WHO assigned an ATC code J05AX13 to Arbidol, as to an oral antiviral preparation with the maximum daily intake up to 800 mg.

The chemical structure of Arbidol is one of its most intriguing features. It is not so easy to find another substance so suitable for different structural modifications and optimization. Moreover, Arbidol is one of the most controversial medicines with regard to the mechanisms of pharmacological activity. Up to now, its primary therapeutic action has not yet been known for certain: whether it is a direct antiviral activity, stimulation of immune system or

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anti-inflammatory action [2] (due to 5-lypoxygenase inhibition). The present review covers the history and reasons for the emergence of this extraordinary substance characterized by a mosaic set of functional groups, as well as chemistry and structure – activity relationships of its close analogues and bioisosteres.

2. Synthesis, metabolism and biological activities of Arbidol

From the chemical point of view, Arbidol (**1**) is a hydrate form of 6-bromo-4-[(dimethylamino)methyl]-5-hydroxy-2-[(phenylsulfanyl)methyl]-1*H*-indole-3-carboxylic acid ethyl ester hydrochloride.[3,4]

A relatively simple indole derivative representing 1,2-dimethyl-5-hydroxy-1*H*-indole-3-carboxylic acid ethyl ester is known under the trade name 'Dimecarbine' (**2**) [5] (or 'Mecarbinate' [6]) and appeared to be an Arbidol predecessor, both historically and chemically.

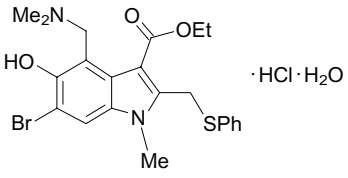
This compound, obtained for the first time by Grinev and co-workers [4] when studying the Nenitzescu reaction between 1,4-benzoquinone and ethyl 3-(methylamino)crotonate, became an active substance of the original Soviet hypotensive drug. It was successfully used in the treatment of first two stages of arterial hypertension and was then considered to be a privileged structure [7] in the design of subsequent analogues. Numerous attempts to modify the structure have been performed. One of them resulted in the synthesis of a debrominated Arbidol analogue, so-called 'Phercaptoline' (**3**).[8,9]

There are no published data on the hypotensive activity of this substance, but it is argued that neither Phercaptoline (**3**) nor its close analogues are more potent than Dimecarbine (**2**).[8]

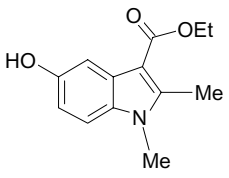
Extensive pharmacological trials demonstrated that Phercaptoline (**3**) alleviates pathological symptoms in experimental animals suffering from influenza. Phercaptoline (**3**) also shortened the reconvalescence period in the same trials. Surprisingly, these pharmacological properties disappear when testing this compound in humans. On the other hand, 6-bromophercaptoline appeared to be effective both in animal and human studies.[4] Hence, the old Soviet hypotensive drug Dimecarbine (**2**) was virtually reincarnated into an actual candidate for further clinical trials as a novel antiviral drug named later as 'Arbidol'.[4] The comprehensive data on pharmacological activity and clinical use of Arbidol (**1**) are summarized in several reviews.[10 – 13] At the same time, there is no systematic survey covering the synthesis and structure – activity relationships of Arbidol in comparison with its more or less close structural analogues, including metabolites.

In terms of medicinal chemistry, Arbidol has been developed as a result of structure-based design and structural optimization of a lead compound with an established and proven pharmacological profile. On the other hand, there has been a fortuitous combination of both an insight and advanced discovery technologies, such as high-throughput screening, in introducing Arbidol as an antiviral drug. It is worth noting, that at first, no exact biological target and mechanism of action were established for both Phercaptoline (**3**) and Arbidol (**1**). Moreover, we still do not know

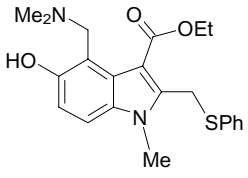
Structures 1 – 3



1 (Arbidol)



2 (Dimecarbine)



3 (Phercaptoline)

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why the expressed antiviral activity of Phercaptoline in animals cannot be translated into human trials, despite application of the same viral pathogen. On the contrary, Arbidol retains its activity both in animal and human trials. Meanwhile, it is to be noted that methanesulfonate salt of Arbidol [14, 15] has appeared to be more bioavailable compared to its hydrochloride monohydrate. These facts strongly indicate that Phercaptoline may be just a prodrug transforming into an active metabolite within the body of an animal.

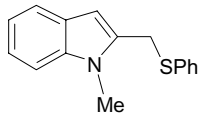
It is also possible that Phercaptoline (**3**) and Arbidol (**1**) display their pharmacological activities as interferon inducers (*e.g.* by analogy with Tilorone [16]) by stimulating immune-competent colon endothelium cells. This explanation is close to the truth, taking into consideration low oral bioavailability of Arbidol. This assumption can also be supported by a high structural similarity between the scaffolds of Arbidol (**4**) and Bendazol (**5**) (an immune stimulant and hypotensive agent developed in the USSR),[17, 18] in which the indole heterocycle serves as a bioisostere for the benzimidazole nucleus, and both heterocycles are bonded to the phenyl ring *via* short linkers.

It can also be assumed that both substructures, in some way, are variants of a pharmacophore responsible for the immune stimulating activity. Here it is worth citing that Arbidol was initially included into the list of the vital and important medicines as an immune-stimulant (2009), and only two years later (2011) — as a direct-acting antiviral drug.

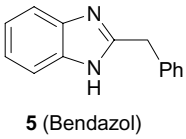
It is to be noted that no published data on Arbidol's metabolism were available at the time of the drug launch to the pharmaceutical market of the USSR (in 1988). The first data on metabolic transformations of Arbidol in mice were published by Chistyakov and co-workers [19, 20] in 1995. According to these data, Arbidol underwent intensive metabolic changes, including microsomal oxidation of sulfide to sulfone and sulfoxide, monodemethylation of the (dimethylamino)methyl group and complete dealkylation of the fourth position of the indole nucleus. The parent compound, as well as its metabolites, also underwent conjugation with sulfuric and glucuronic acids. The main metabolic transformation routes for Arbidol are shown in Scheme 1.

Further detailed investigation of Arbidol metabolism in humans was published in 2008, along with several articles related to HPLC-MS analysis of its intermediates [21, 22] and

Structures 4, 5

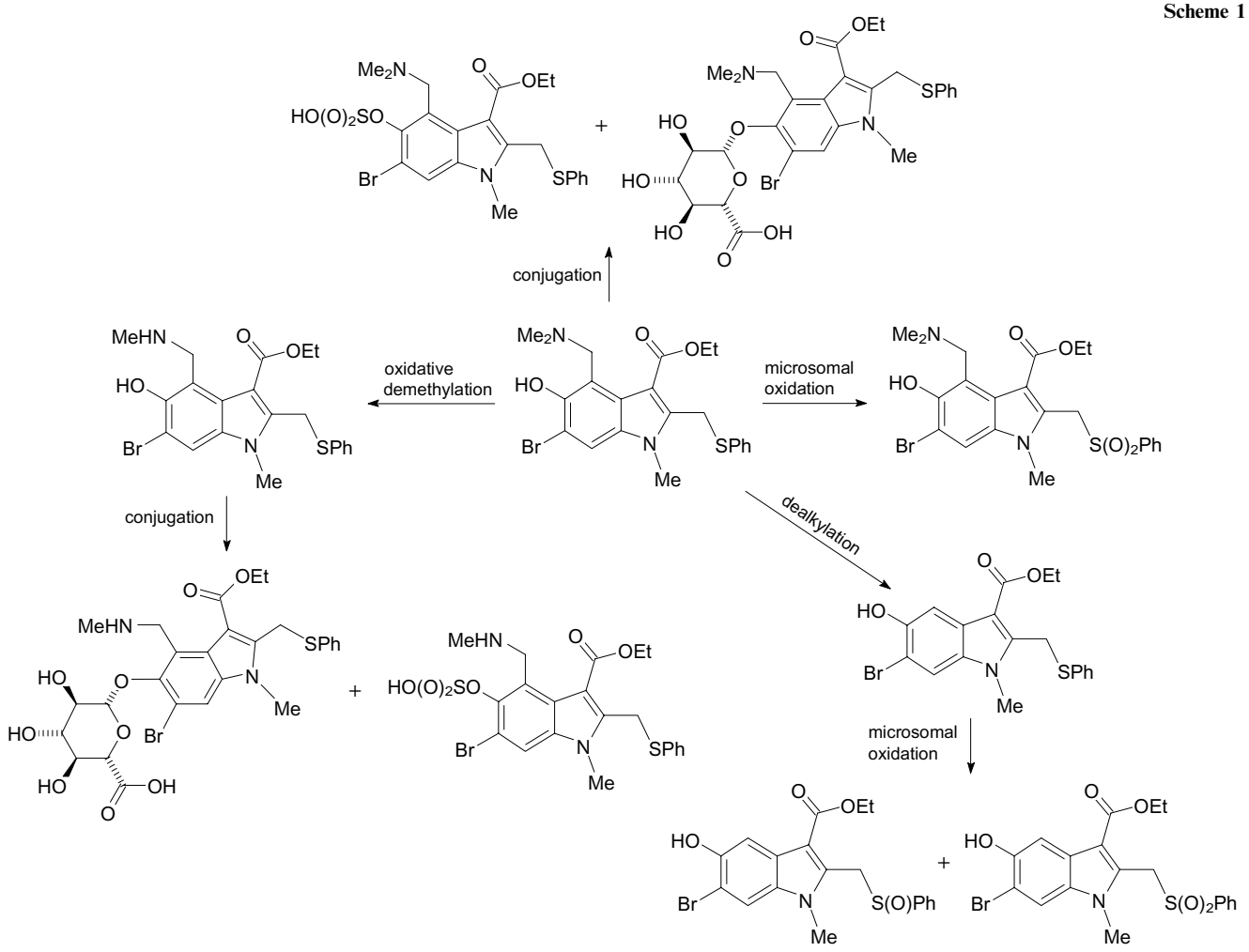


4 (Arbidol's 'core')

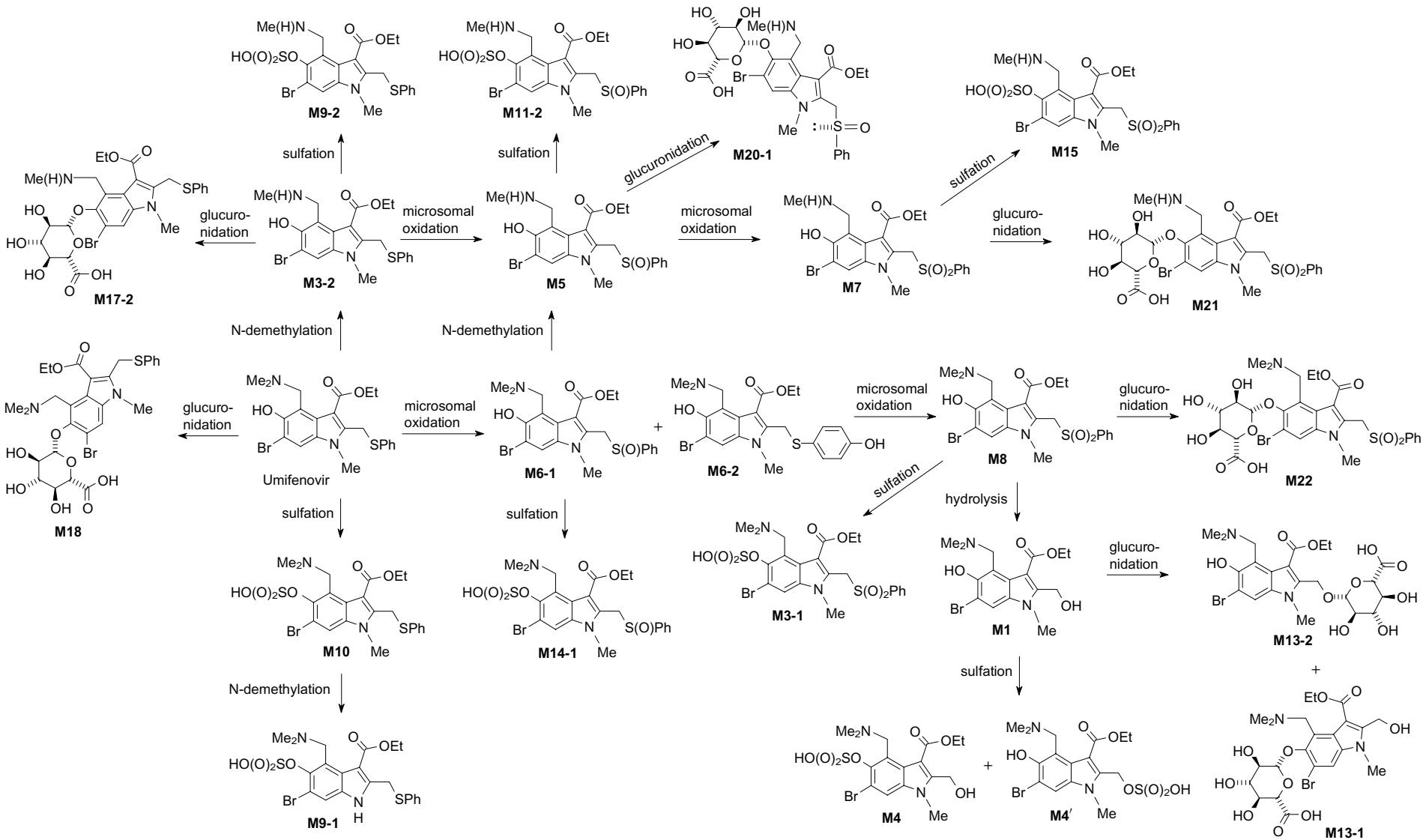


5 (Bendazol)

Scheme 1



Scheme 2


M9-2
M11-2
M20-1
M15
M17-2
M3-2
M5
M7
M21
M18
Umifenovir
M6-1
M6-2
M8
M22
M10
M14-1
M3-1
M1
M13-2
M9-1
M4
M4′
M13-1
sulfation
glucuronidation
microsomal oxidation
glucuro-nidation
N-demethylation
hydrolysis

metabolites.[23] Nevertheless, an exhaustive information on metabolism and excretion of Arbidol from a human body appeared only in 2013, as a result of extensive studies of Chinese researchers.[24] The complete metabolic conversion routes are depicted in Scheme 2.

The above-mentioned data enable to figure out some significant differences between the metabolic transformations of Arbidol in mice and humans. First of all, a total of 31 metabolites with a small amount of an unchanged material have been identified. The following main metabolic pathways were revealed:

1. Oxidation of the sulfide moiety into sulfone and sulfoxide ones.

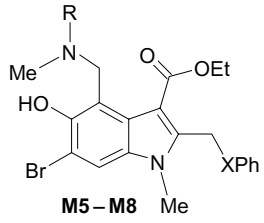
2. *Mono*- and *bis*-demethylation of the exocyclic nitrogen atom and demethylation of the endocyclic indole nitrogen atom.

3. 4-Hydroxylation of the benzene ring in the thiophenol residue.

4. Replacement of the phenylsulfanyl group by hydroxyl one (probably, *via* oxidation of the former to a better leaving phenylsulfonyl group).

The main non-conjugated metabolites of Umifenovir have the general formulae **M5** – **M8**.

Structures M5 – M8



M5 – M8

M5: R = H, X = S(O);
M6-1: R = Me, X = S(O);
M8: R = Me; X = $S(O)_2$

These data suggest that Arbidol undergoes an extensive first-pass metabolism involving microsomal oxidation of sulfide to sulfoxide, while the further oxidative demethylation and sulfoxide oxidation play a secondary role. The main difference between Arbidol metabolism in mice and in human lies in complete C(4) dealkylation of the indole nucleus in mice, which is not observed in humans.

Also, *S*-oxidation to sulfoxide in humans seems to be of poor stereoselectivity and affords a pair of enantiomeric sulfoxides. It was confirmed by separation of a pair of diastereomeric glucuronides of the resulting sulfoxides (designated as **M20-1** and **M20-2** in Scheme 2) on an achiral stationary phase using HPLC-MS technique.[24]

It is also necessary to point out that the only metabolically stable fragments in Umifenovir structure are the bromine atom and, surprisingly, the ethoxycarbonyl group (the ethyl group in the latter is not even hydroxylated). This fact plays a serious role in structural optimization of the Arbidol molecule by directed modification of these metabolically stable fragments and particularly the ester moiety. Thus, Arbidol is likely to be a molecule of choice for a plethora of different structural optimization routes aimed at decreasing cytotoxicity and increasing the therapeutic index of the title compounds. On the other hand, the success in chemical modification of Arbidol is strongly influenced by synthetic feasibility of the intended reaction schemes.

There are several synthetic approaches available at the moment, which are suitable for the scalable production of the active substance of Arbidol (**1**) (Scheme 3).

These reaction sequences represent two different types of synthetic strategies: the first one is based on the Nenitzescu reaction,[30] and the second one comprises the reductive indole ring closure.[28] Both strategies can use acetoacetic ester (**6**) as the starting material, which is then converted to ethyl 3-amino- (**7**) or 3-(methylamino)crotonate (**8**). The latter was introduced into the Nenitzescu indole synthesis, yielding *nor*-Dimecarbine (**9**)[30] or Dimecarbine (**2**),[6] respectively. Dimecarbine (**2**) should be acetylated prior to bromination, while *nor*-Dimecarbine requires subsequent methylation of the indole nucleus of *nor*-Dimecarbine *O*-acetate (**10**).

It should be noted that *nor*-Dimecarbine *O*-acetate (**10**) can also be prepared *via* non-Nenitzescu route[28] comprising C(2) arylation of acetoacetic ester (**6**) with 3-iodo-4-nitrophenyl acetate (**11**) in the presence of potassium *tert*-butoxide, followed by reductive indole ring closure of the resulting intermediate (**12**). The corresponding arylating agent is prepared by acetylation of 3-iodo-4-nitrophenol (**13**), the synthesis of which was described in the literature.[31 – 33] In our opinion, such a kind of orthogonal protection of phenolic hydroxyl in the corresponding arylating agent seems questionable. The reason is the ability of 3-iodo-4-nitrophenyl acetate to serve as an acetylating, rather than an arylating agent with respect to acetoacetate enolate. Thus, the current method may need to be revised.

The key step of classical Grinev's procedure is, undoubtedly, the Nenitzescu reaction leading to Dimecarbine (**2**), a key intermediate in the total synthetic scheme.

Of course, the most unfavourable elements of Arbidol structure, in terms of its synthesis technology, are the bromine atom and the thiophenol residue. It has been clearly shown that bromination of Dimecarbine *O*-acetate (**14**) is not regioselective and along with the target 6-bromo derivative (**15**) affords 6,7-dibrominated (**16**) and 4,6-dibrominated (**17**) side products (Scheme 4).[34]

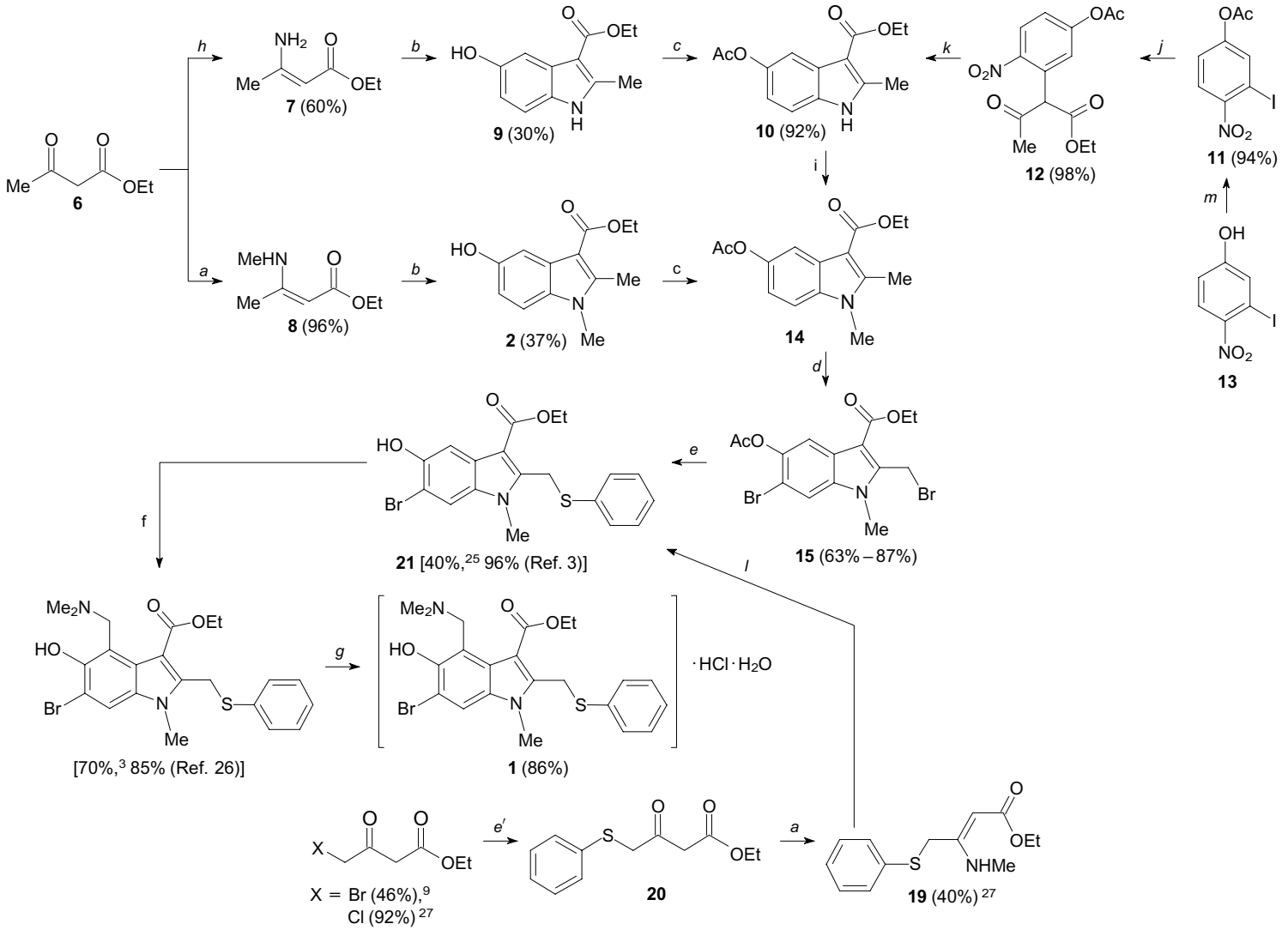
The main contaminating side product resulting from this stage of the synthesis is so-called 7-bromo-Arbidol (**18**) (up to 15% by mass in the resulting product).

Thiophenol residue is another disadvantageous part of the Arbidol molecule from the technological point of view. Its presence is associated with the appearance of trace amounts of thiophenol, a highly toxic and environmentally dangerous substance, in waste water from Arbidol manufacture.[35, 36] It should be noted that an alternative synthetic route based on the direct Nenitzescu reaction of ethyl 3-(methylamino)-4-(phenylsulfanyl)crotonate (**19**) with 2-bromo-1,4-benzoquinone[29, 37] does not lead to polybrominated side products (see Scheme 3), but also suffers from thiophenol-containing waste water. In this synthetic route thiophenol is used in the synthesis of ethyl 3-oxo-4-(phenylsulfanyl)butanoate (**20**). On the other hand, regioselectivity issues of the reaction between 2-bromo-1,4-benzoquinone and enamino ester have not yet been thoroughly studied, and it is not clear whether considerable amounts of a 4- and/or 7-bromo-1*H*-indole derivative are formed.

The third unfavourable part of the Arbidol molecule is the Mannich base moiety which enhances toxicity of the resulting compounds (*vide infra*). Of note, even the step of dimethylaminomethylation of the corresponding indole precursor (**21**) can yield different regioisomers (*vide infra*).

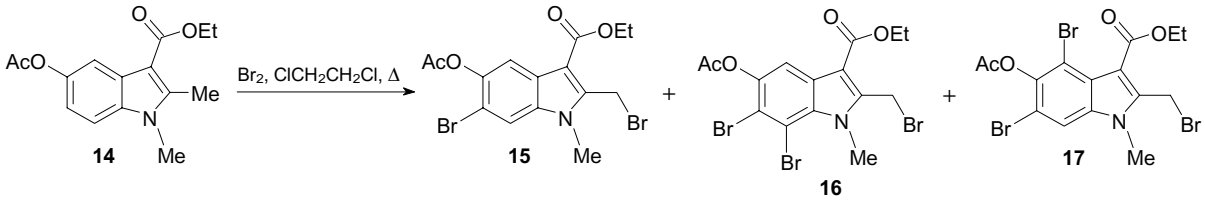
Chinese researchers also reported some optimizations in the Arbidol synthesis.[38]

Scheme 3

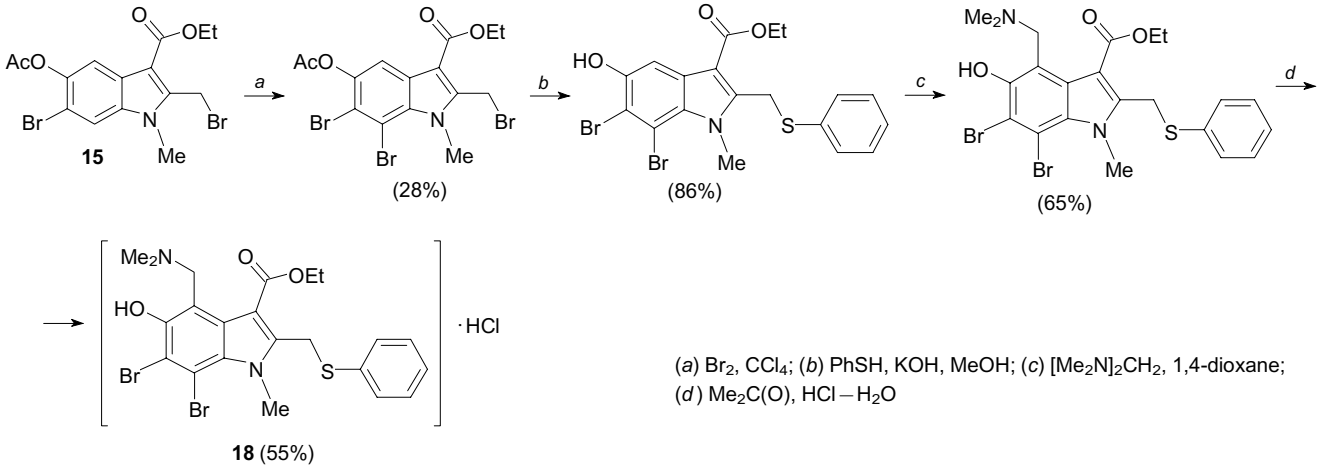


(*a*) $MeNH_2$;[15, 27] (*b*) 1,4-benzoquinone, $ClCH_2CH_2Cl$; (*c*) Ac_2O or AcCl, C_5H_5N, $Me_2C(O)$; (*d*) Br_2 or NBS, CCl_4;[26] (*e′*) X = Br: PhSH, NaOEt, EtOH;[9] X = Cl: 1) PhSH, $[OH]^-$, 2) $HCl-H_2O$, EtOH;[27]
(*e*) 1) PhSH, KOH, MeOH; 2) $HCl-H_2O$, EtOH or AcOH, H_2O;[3] (*f*) 1) CH_2O, H_2O, Me_2NH; AcOH; or $[Me_2N]_2CH_2$, 1,4-dioxane;[3, 26] 2) KOH, H_2O; (*g*) HCl, $Me_2C(O)$, H_2O;[3, 26]
(*h*) NH_3; (*i*) 1) DMF, $(MeO)_2SO_2$; 2) K_2CO_3, H_2O;[28] (*j*) $MeC(O)CH_2C(O)OEt$, THF, Bu^tOK;[28] (*k*) Fe, AcOH, H_2O; (*l*) 2-bromo-1,4-benzoquinone;[29] (*m*) AcCl, Et_3N, $Me_2C(O)$ [28]

Scheme 4



Reaction conditions		Product distribution (HPLC) **15** : **16** : **17** (%)
Br_2 /equiv.	time /h	
2.2	2	84 : 2 : 2
3.3	3	53 : 23 : 4
4.2	4	20 : 39 : 14



(*a*) Br_2, CCl_4; (*b*) PhSH, KOH, MeOH; (*c*) $[Me_2N]_2CH_2$, 1,4-dioxane; (*d*) $Me_2C(O)$, $HCl - H_2O$

As far as Arbidol appeared to be an attractive and valuable object for further structural modifications, a significant number of its analogues have been prepared and studied up to date. Vast majority of them belong to the indole family, but there is also a number of Arbidol derivatives based on other heterocycles. Some of them are indole bioisosteres, while the others are ring-expanded analogues or compounds with altered conformational flexibility.

3. Indole- and benzofuran-based Arbidol derivatives

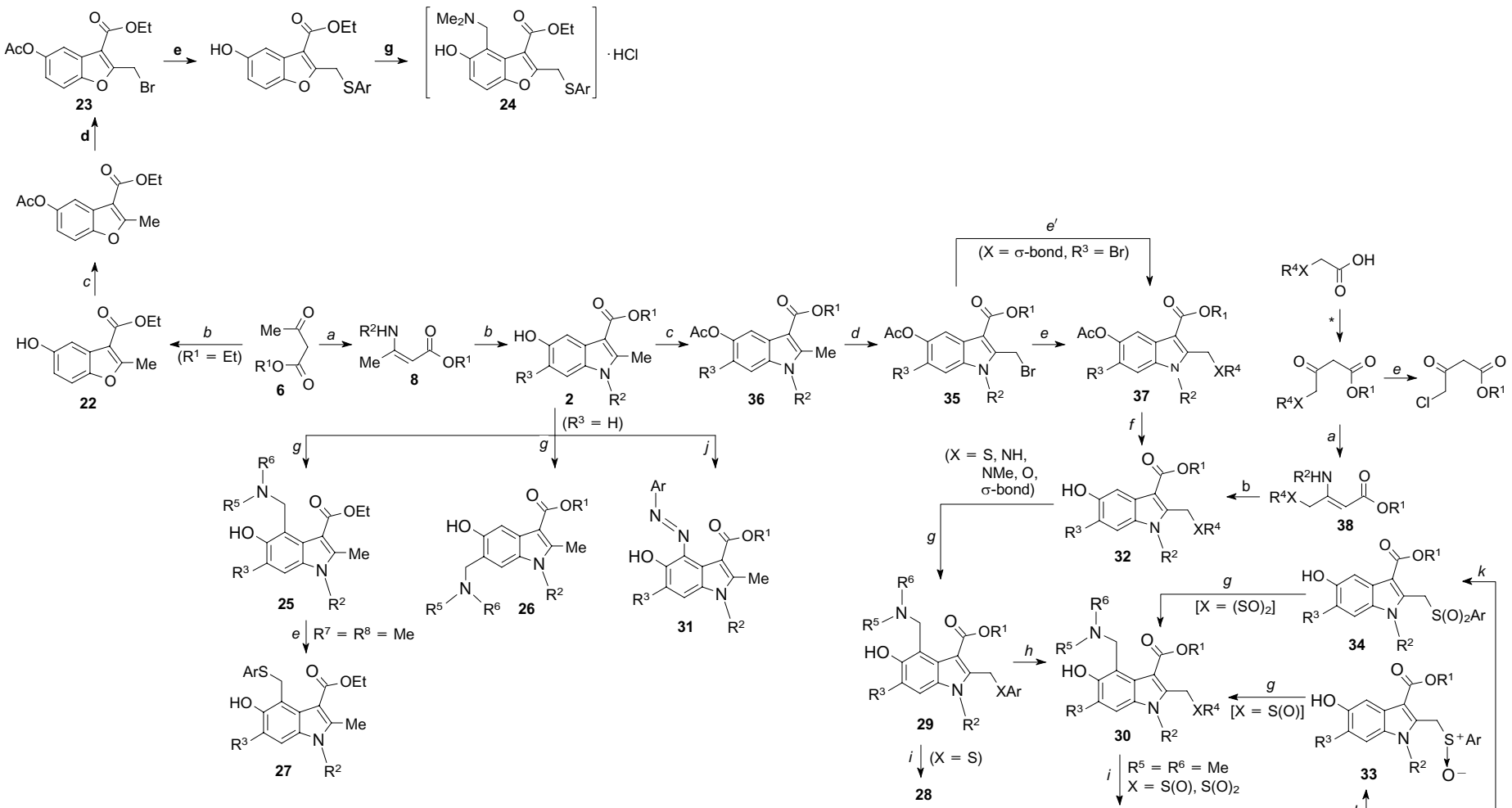
3.1. Synthesis of Arbidol structural analogues based on indole or benzofuran heterocyclic nucleus

Preparation of a number of indole- and benzofuran-based structural analogues and derivatives of Arbidol is a good example of the diversity-oriented synthesis[39,40] of exploratory libraries of new drug-like compounds. The developed 'synthetic trees' are shown in Scheme 5.

According to this scheme, the starting material in both indole and benzofuran series is the corresponding alkyl 3-oxobutanoate (**6**) (in most cases, acetoacetic ester[37,46,49,50,56,63]). In the case of benzofurans, it is directly introduced into the Nenitzescu reaction with 1,4-benzoquinone, leading to the formation of the desired heterocyclic system (**22**). The latter then undergoes an orthogonal protection followed by bromination of the side chain. The corresponding 2-(bromomethyl)benzofuran derivative is treated with the appropriate thiophenol in alkaline medium followed by deprotection and aminomethylation to obtain the benzofuran derivative **24**. It is to be noted that, in general, a synthetic route based on the Mannich reaction is reasonably suspected to be challenging, as the structures of the resulting compounds have not yet been unequivocally proved. For instance, the reasons for poor ability of the less sterically hindered unsubstituted C(6) position to undergo substitution are not clear. The same situation is observed for C(6) unsubstituted indoles. Moreover, C(6) aminomethylation of the similar compounds has been found to be a dominant direction of the Mannich reaction. For example, Grinev *et al.*[74] have synthesized a 4-(dimethylamino)methyl derivative (**25**) in the form of its hydrochloride salt (m.p. 193.5 – 194.5 °C) using dimethylaminomethylation of Dimecarbine (**2**). Previously, Steck obtained 6-substituted isomer **26** (m.p. 203 – 204 °C for the corresponding hydrochloride[75]) by the same reaction.

Most of indole-based structural analogues of Arbidol have been obtained in a similar way with several more or less significant differences. First of all, it is necessary to point out that in some cases the thiophenol moiety has been introduced *via* the substitution of dimethylamino group in the corresponding Mannich bases, *e.g.*, (**25**), thus leading to regioisomeric ethyl 4-[(arylsulfanyl)methyl]-5-hydroxy-1*H*-indole-3-carboxylates (**27**).[72] A similar approach was utilized for introduction of the 1*H*-imidazol-1-yl or (2-methyl-1*H*-imidazol-1-yl)methyl moiety into the C(4) position of the indole nucleus of different Arbidol analogues (**28**).[44,49–51] In this case, the Mannich bases (**29**, **30**) were

A general synthesis tree of Arbidol and its indole- and benzofuran-based structural analogues **Scheme 5**



(*a*) R^2NH_2;[8,9,15,25,27,28,41–44] (*b*) 1,4-benzoquinone, $ClCH_2CH_2Cl$ or 1,4-benzoquinone, CH_2Cl_2, ZnI_2 (Ref. 45) or 1,4-benzoquinone, AcOH[28,46–48] or 1,4-benzoquinone, EtOH;[45] (*c*) AcCl, C_5H_5N[49–52] or Ac_2O, Et_3N (Ref. 53) or AcCl, Et_3N[54–56] or Ac_2O, C_5H_5N[46,57–59] or Ac_2O, AcOH;[28,37,47,60] (*d*) R^3 = Br: Br_2, CCl_4;[4,15,26,28,34,47,49–53,58,60–63] or R^3 = H: NBS, CCl_4, Bz_2O_2;[3,4,26,37,57,58,62–66] or NBS, $ClCH_2CH_2Cl$;[55,63] (*e*) X = S: R^4SH, KOH, EtOH or MeOH, C_6H_6, 2) HCl, Et_2O;[3,4,15,26–28,34,37,41,44,46,47,49–53,57,59,60,63,66] X = O: 1) R^4OH, KOH, MeOH; 2) AcOH – H_2O;[67] or R^4OH, KOH, $Me_2C(O)$;[68] X = O, R^4 = 4-$MeOC_6H_4O$, K_2CO_3, 1,4-dioxane; X = NH or NHMe: R^4NH_2 or NH(Me)R^4, Et_3N, C_6H_6; (*e′*) $R^4B(OH)_2$, Na_2CO_3, $Pd[P(Ph)_3]_4$, PhMe – EtOH – H_2O, 35 °C, 3 h; (*f*) HCl – H_2O, EtOH, $Me_2C(O)$; (*g*) $[Me_2N]_2CH_2$, 1,4-dioxane;[3,4,8,26,34,46,67–69] or 1) CH_2O – H_2O, R^5R^6NH, AcOH; 2) KOH, H_2O or NH_4OH;[4,8,15,26–28,37,41,44,46,49–53,60,63,70,71] (*h*) H_2O_2, AcOH, 2) NaOH, H_2O [X = S → S(O)] or $NaBO_3 \cdot 4H_2O$, AcOH; 2) NH_4OH; (*i*) 1*H*-imidazole or 2-methyl-1*H*-imidazole, EtOH; (*j*) $[ArN_2]^+X^-$ (Ref. 72); (*k*) 1) H_2O_2, $Na_2WO_4 \cdot 2H_2O$, MeOH, $CHCl_3$; 2) $NaHSO_3$, H_2 or *m*-CPBA, CH_2Cl_2 or 1) $NaBO_3 \cdot 4H_2O$, AcOH; 2) NaOH, H_2O; (*l*) 1) $NaBO_3 \cdot 4H_2O$, AcOH; 2) NH_4OH or *m*-CPBA, CH_2Cl_2 (continued on the next page)

Scheme 5 (continued)

* Such kind of transformations have been systematically analyzed for this type of 3-oxoesters in a recent review.[73]
R^1 = Et, Bu^t;
R^2 = H; alkyl: Me, Et, Pr^i, Hex, Oct; Bn, $(CH_2)_2Ph$, $CH_2CH(Me)Ph$, $(CH_2)_4Ph$; cycloalkyl: Pr^c, Hex^c;
R^3 = H, Br, CN, 3-Py, pyrimidin-5-yl;
R^4 = 2-Py, 3-Py, 4-Py, 2-methylfuran-3-yl, furan-2-yl methyl, furan-3-yl methyl; aryl: Ph, naphtyl, 4-FC_6H_4, 4-$MeOC_6H_4$, 2-$MeOC_6H_4$, 3-FC_6H_4, 2-FC_6H_4, 4-F,2-ClC_6H_3, 3-$F_3CC_6H_4$, 2-$F_3CC_6H_4$, 4-$F_3CC_6H_4$, 4-NCC_6H_4, 1-$C_{10}H_7$, 3-HOC_6H_4, 3-$NH_2C_6H_4$, 3-Pr^iC_6H_4, 4-$FC_6H_4CH_2$, 3-MeC_6H_4, 4-MeC_6H_4, 3-$MeOC_6H_4$, 2,6-$Cl_2C_6H_3$, 3-ClC_6H_4, 4-$F_3COC_6H_4$, 2-$FC_6H_4CH_2$, 3-$ClC_6H_4CH_2$, 4-ClC_6H_4, 3,4-$F_2C_6H_3$ 3,4-$(MeO)_2C_6H_3$, 3-Cl,4-FC_6H_3, 4-BrC_6H_4, 4-$(AcNH)C_6H_4$, 2-MeC_6H_4, 3-$FC_6H_4CH_2$, 2-ClC_6H_4, 2,4-$Me_2C_6H_3$, 4-$NO_2C_6H_4$, 2-MeC_6H_4, $(CH_2)_2OPh$, $(CH_2)_2Ph$, 1,3,4-triazol-2-yl, 4-EtC_6H_4, 4-$EtOC_6H_4$, 2-$HOC_6H_4CH_2$, Bn; tricycloalkyl: 1-Ad; R^5 = alkyl: Me, Et, Pr, Pr^i, Bu, Hex;
R^6 = alkyl: Me, Et, Pr, Pr^i, Bu, Hex, Bu^i, n-C_9H_{19};
$N(R^5 + R^6)$ = 4-(hydroxymethyl)piperidin-1-yl, 4-(2-hydroxyethyl)piperazin-1-yl, pyrrolidin-1-yl, 4-methylpiperazin-1-yl, morpholin-4-yl, piperidin-1-yl, 3-ethylpyrrolidin-1-yl, 2,3-dimethylmorpholin-4-yl;
R^7 = H; Me;
X = S, S(O), $S(O)_2$, NH, NMe, O, σ-bond

treated with 1*H*-imidazole or 2-methyl-1*H*-imidazole, respectively.

During the search for antibacterial analogues of such kind, the arylazo group was also utilized to decorate the C(4) position of the indole ring (**31**).[72]

In the works of Chinese researchers, much attention has also been paid to oxidative modification of the (phenylsulfanyl)methyl group in various Arbidol analogues (**32**). Depending on the nature of the oxidizing agent, this group was converted into the corresponding sulfoxides (**33**)[41, 44, 49 – 51, 53, 57, 64] or sulfones (**34**)[41, 44, 51, 53] in good yields. It should be noted that a number of readily oxidizable groups in the starting compounds remained unchanged under these conditions, and this is a nontrivial fact taking into consideration the high sensitivity of the activated phenol moiety and the tertiary aliphatic amino group to peroxide-based oxidizing agents.

Moreover, in a recent paper on Arbidol analogues, it was reported that even in the reaction of the 2-(bromomethyl)-1*H*-indole derivative (**35**), obtained by bromination of the orthogonally protected derivative **36**, with 3-hydroxythiophenol, the latter was readily oxidized in alkaline or acidic media similarly to the target product **29**.[76] These observations prompted the authors to use alkali metal carbonate instead of the corresponding hydroxide, and dichloromethane instead of dioxane, in order to improve the yield of the desired compounds **29**.[76]

The major disadvantage of the Arbidol analogues **30** [X = S(O)] containing a sulfoxide moiety is the appearance of an additional chiral centre in the molecule. As it was shown for the structurally related pharmacologically active sulfoxides, the target type of activity is mostly shared by only one of two possible enantiomers. For example, an active metabolite of albendazole is only (+)-(*R*)-albendazole sulfoxide.[77] Also, only (*S*)-omeprazole is endowed with the desired antiulcerogenic properties.[78] Nevertheless, there is not even a single work providing a comparison of the antiviral activity of (*S*)- and (*R*)-enantiomers of Imidol[79] or Arbidol *S*-oxide, not to mention numerous structural analogues of these compounds.

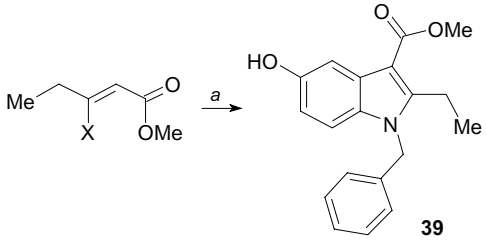
From the 'synthesis tree' presented above it is clearly seen that a number of Arbidol structural analogues (**29**, **30**) contain the ethyl 4-(aminomethyl)-6-bromo-5-hydroxy-2-[(phenylsulfanyl)methyl]-1*H*-indole-3-carboxylate motif in their molecules (Refs 3, 4, 8, 15, 26 – 28, 34, 37, 41, 44, 46, 49 – 53, 60, 63, 67 – 71). So, a general synthetic scheme for this plethora of substances, in most cases, appears to be an augmented variant of Grinev's preparation of Arbidol.

Thiophenol motif, or its oxidized bioisostere, were not the sole types of substituents at the C(2) methyl group in the indole core of Arbidol analogues **29**, **30**. In place of the arylsulfanyl moiety, the aniline or *N*-methylaniline residues,[69] as well as aryloxy groups,[68] were also used (compounds **29**). From the point of view of medicinal chemistry, such a leap can be regarded as a classical example of structural modification according to Sheridan's criterion.[80]

In studies[45, 81] as well as in the Chinese patent,[82] a heteroatom in a linkage between the indole ring and the aromatic nucleus was omitted (X is σ-bond in compound **29**). The main difference between these works lies in the way of introduction of the benzyl group at the second position of the indole heterocycle. The authors of the patent used palladium-catalyzed cross-coupling of 2-(bromomethyl)-1*H*-indole derivative **35** with a suitable arylboronic acid to obtain the corresponding arylmethyl derivatives **37** (path *e*′ in Scheme 5).[82] It should be noted that the same approach was used by Ivashchenko *et al.* to replace the C(6) bromine atom with a (het)aryl group in structurally similar indoles.[53, 58, 70]

The authors[45] synthesized the desired 2-benzyl-1*H*-indoles **32** *via* the direct Nenitzescu reaction of 1,4-benzoquinone with alkyl 3-(alkylamino)-4-crotonate **38**. In this case, the Nenitzescu reaction was conducted according to the method of Velezheva *et al.*,[83] using zinc halogenide as a catalyst. Other authors predominantly used Grinev's proce-

Scheme 6



39

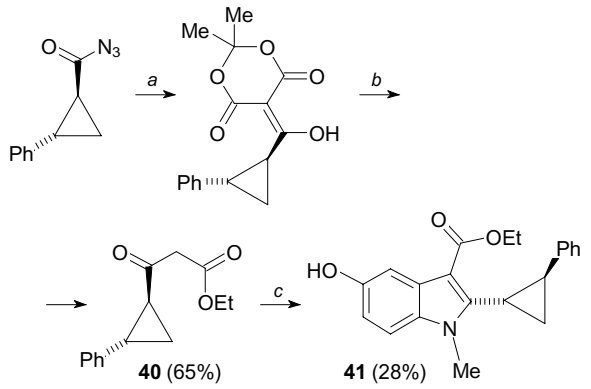
(*a*) X = OH: 1) $BnNH_2$; 2) 1,4-benzoquinone, $MeNO_2$;
X = NHBn: 1,4-benzoquinone, $MeNO_2$

Solvent	Dielectric constant (ε)	Yield (%)
PhMe	2.38	25
$CHCl_3$	4.70	49
PhMe : AcOH = 2 : 1	6.19	50
$ClCH_2CH_2Cl$	10.40	47
$Me_2C(O)$	20.70	22
MeOH	32.60	30
$MeNO_2$	38.60	83

dure based on refluxing the solution of the starting reagents in 1,2-dichloroethane with azeotropic removal of water.[8,9,25,27,37,41,44,46,49–52,56] At the same time, during the search for the optimal reaction medium for the synthesis of 1-benzyl derivatives **39**, Pawlak found that nitromethane is the solvent of choice for this reaction, allowing one to significantly improve the yield of the target compound even at room temperature (Scheme 6).[84]

The solvent effect in the Nenitzescu reaction, together with the influence of an excess of 1,4-benzoquinone, was also demonstrated in our works by the example of (*trans*-2-phenylcyclopropyl)-1-substituted Arbidol analogues. So, carrying out the reaction between *in situ* prepared ethyl 3-(methylamino)-3-(*trans*-2-phenylcyclopropyl)acrylate (**40**) and a slight excess of 1,4-benzoquinone and methylammonium acetate in absolute ethanol, only the target product **41** was isolated in moderate yield (Scheme 7).[85]

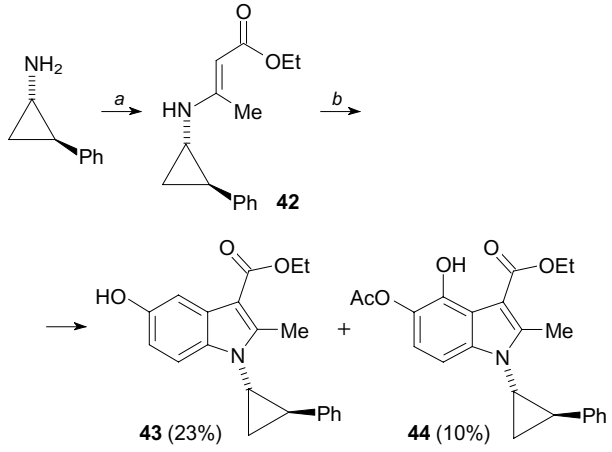
Scheme 7



(*a*) 2,2-dimethyl-1,3-dioxane-4,6-dione, $(Pr^i)_2NEt$, CH_2Cl_2;
(*b*) EtOH, Δ; (*c*) 1) 1,4-benzoquinone, $MeNH_2 \cdot AcOH$, EtOH, Δ;
2) EtOAc

However, the same reaction, but using ethyl 3-[(*trans*-2-phenylcyclopropyl-1)amino]crotonate **42** and two-fold molar excess of 1,4-benzoquinone in glacial acetic acid (conditions recommended by Bell[48]) resulted in a mixture of two different indoles. One of them was identified as the target compound **43**, while the other one, indole **44**,

Scheme 8



(*a*) $AcCH_2C(O)OEt$, $MgSO_4/Et_2O$;
(*b*) 1) 1,4-benzoquinone, Et_2O–AcOH; 2) K_2CO_3–H_2O

appeared to be a product of oxidative acetylation and intramolecular *trans*-esterification (Scheme 8).[86]

Nothing like this was observed by Bell. However, the same side reaction was also described by Allen[87] and Kucklander,[88–90] but the exact positions of acetoxy and hydroxy groups in the benzene portion of the indole heterocycle were not unambiguously established.

Close structural analogues of these substances **45**–**49** were also obtained by the Nenitzescu reaction using arylated or benzannulated 1,4-benzoquinones (Scheme 9).[45,91–93]

The same authors[81,94] also reported the synthesis of 2-amino-1*H*-indole derived bioisosteres **50**, **51** of the corresponding 2-benzyl-substituted analogues *via* the Nenitzescu reaction of ethyl 3-amino-3-(disubstituted amino)acrylate **52**, as well as by chlorination and subsequent amination of alkyl 1*H*-indole-3-carboxylates **53** (Scheme 10).

Various 5-hydroxy-1*H*-indole- and benzofuran-3-carboxylic acid ester derivatives have been prepared and evaluated in biological assays as more distant Arbidol analogues. Most of them resulted from the early works of Grinev's team, as well as from the late works of Ivashchenko *et al*. Synthesis of 2-[(dialkylamino)methyl]- **54**, **55** and 2,4-bis-[(dialkylamino)methyl]-5-hydroxy-1*H*-indole-3-carboxylates **56** was performed starting from tosylates of ethyl 2-(bromomethyl)-1*H*-indole-3-carboxylates **35** (Scheme 11).[95]

Similar approach has also been used to synthesize 3-cyanopyridin-2-yl ethers **57**, **58** of a series of structurally related compounds and ethyl 2-[(dialkylamino)methyl]-5-methoxybenzofuran-3-carboxylates **59**, **60** (Scheme 12, 13).[66,96]

Ivashchenko *et al*.[58,70] has developed a procedure to obtain 6-halogen- and pyridyl-substituted ethyl 2- and 2,5-bis[(dialkylamino)methyl]-1*H*-indole-3-carboxylates **61**–**63** (Scheme 14).

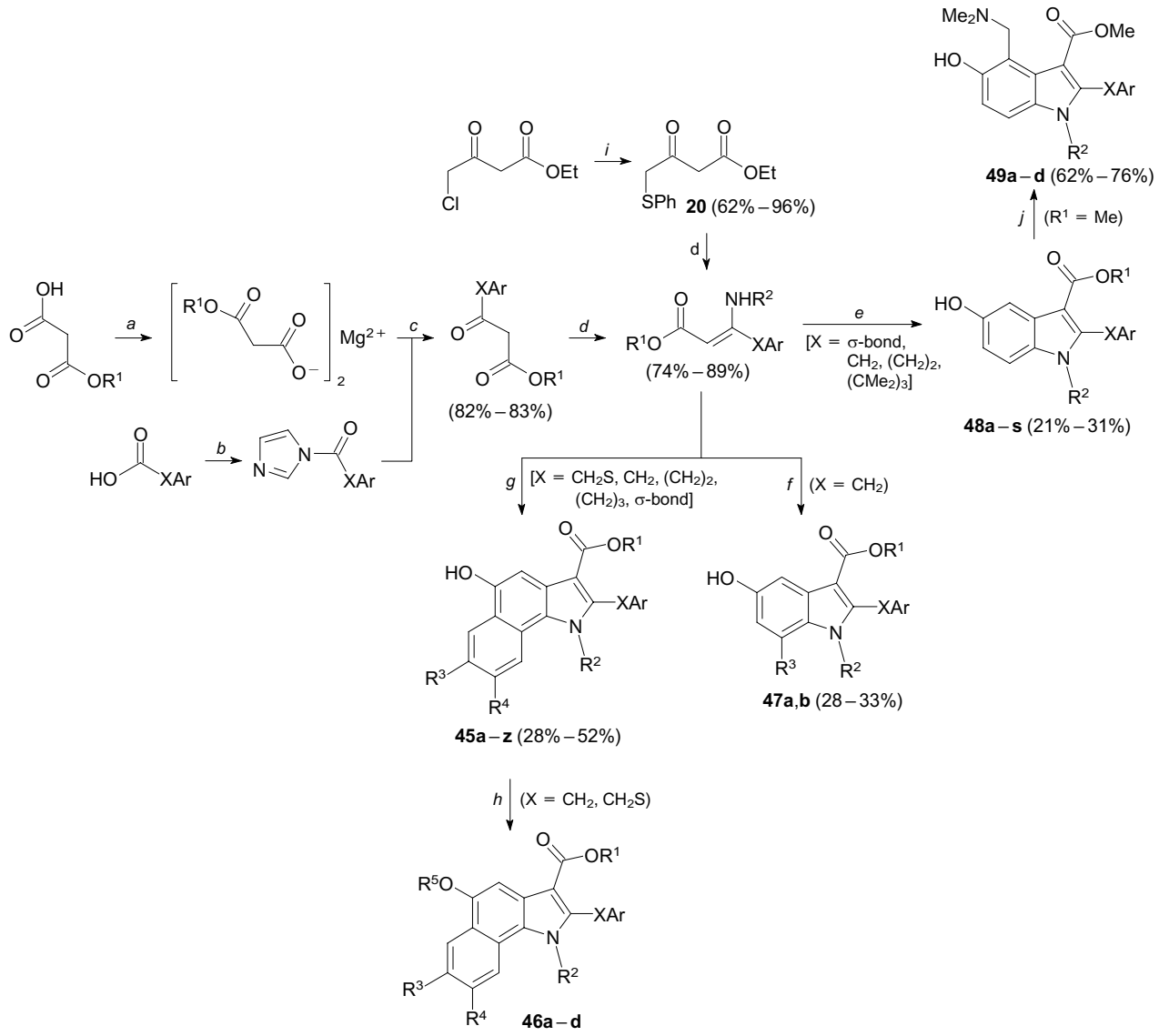
Thus, the joined efforts of Russian and Chinese research groups provided the significant enlargement of the scope of Arbidol analogues. However, these groups proposed different types of pharmacological activities of the obtained substances. While the Russian team performed the search for novel inhibitors of influenza virus (**64**–**76**),[53,58,95,97] the Chinese group was searching for novel Arbidol–Ranbezolid hybrids (**77**, **78**).[98] Chemical transformations underlying the formation of these compounds are depicted in Scheme 15.

It is necessary to point out that these works were focused mostly on the decoration of the C(6) position of the indole nucleus. The previous studies concerned predominantly C(6)-unsubstituted or C(6)-brominated compounds, whereas the more recent papers reported also 6-aryl-1*H*-indoles **66** (prepared using metal-complex catalysis),[58] 6-cyano-1*H*-indoles **69**, **70**,[58,70] and 6-nitro-1*H*-indoles **71**–**74**.[55] In the latter case, the nitro group in compounds **72**, **79** can be reduced followed by *N*-acetylation of resulting amines **75**, **80** to obtain indoles **76**, **81** as shown in Schemes 15 and 16.

The synthetic efforts in the above-mentioned works were focused on 2-[(dialkylamino)methyl]-1*H*-indoles **64**–**70**, **72**, **75**, **76** but the corresponding 2-[(phenylsulfanyl)methyl]-substituted analogues **73**, **74**, **82**, **83** have also been prepared for comparison.

With a mind to better understanding the structure–activity relationships in this series of compounds, a number of heteroauxins substituted with their homo-analogues **84**–**88** have been synthesized and studied by Ivashchenko's

Scheme 9



(*a*) $Mg(OEt)_2$, THF; (*b*) CDI, DMF; (*c*) HCl, H_2O; (*d*) R^2 = H: NH_4OAc, AcOH, PhMe; R^2 = Bn: $BnNH_2$, HC(O)OH, PhMe; (*e*) 1,4-benzoquinone, EtOH, Δ; (*f*) 2-Aryl-1,4-benzoquinone, ZnI_2, CH_2Cl_2; (*g*) 1,4-naphtoquinone, ZnI_2, CH_2Cl_2; (*h*) R^5 = Me: NaOH, MeI, THF; R^5 = Bz: BzCl, Et_3N, EtOAc; (*i*) PhSH, NEt_3, CH_2Cl_2; R^5 = Et: EtI, K_2CO_3, $Me_2C(O)$, MW, Δ; (*j*) $[Me_2N]_2CH_2$, 1,4-dioxane

Compound	R^1	R^2	R^3	R^4	R^5	Ar	X
45a	Et	H	H	H	H	3-ClC_6H_4	CH_2
45b	Et	H	H	H	H	2-ClC_6H_4	CH_2
45c	Et	H	H	H	H	4-ClC_6H_4	CH_2
45d	Et	H	H	H	H	3-FC_6H_4	CH_2
45e	Et	H	H	H	H	4-FC_6H_4	CH_2
45f	Et	H	H	H	H	3-BrC_6H_4	CH_2
45g	Et	H	H	H	H	3-$MeOC_6H_4$	CH_2
45h	Et	H	H	H	H	4-$MeOC_6H_4$	CH_2
45i	Et	H	H	H	H	4-$F_3CC_6H_4$	CH_2
45j	Et	H	H	H	H	3-ClC_6H_4	σ-bond
45k	Et	H	H	H	H	4-ClC_6H_4	σ-bond
45l	Et	H	H	H	H	3-ClC_6H_4	$(CH_2)_2$
45m	Et	H	H	H	H	4-ClC_6H_4	$(CH_2)_2$
45n	Bn	H	H	H	H	3-ClC_6H_4	CH_2

Scheme 9 (continued)

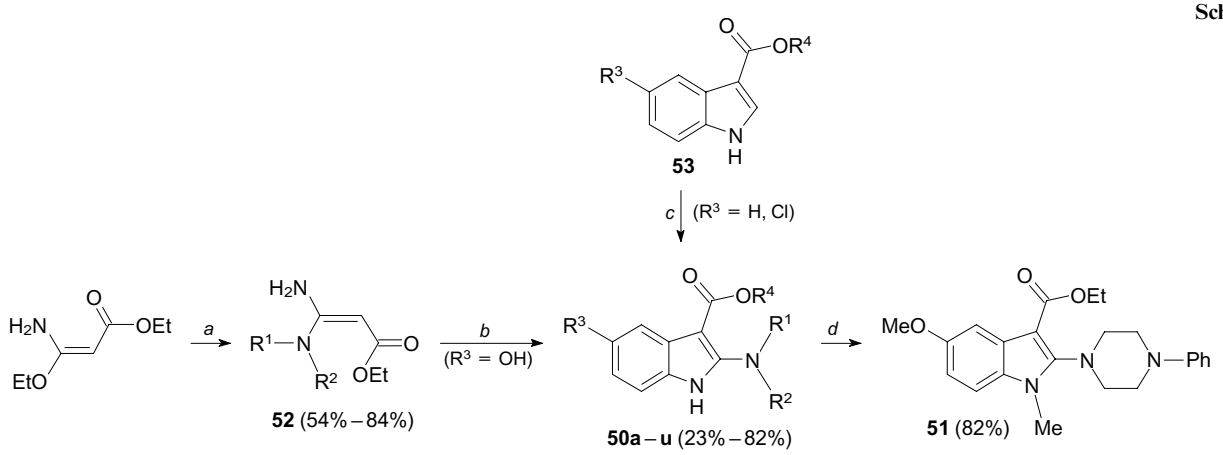
Compound	R^1	R^2	R^3	R^4	R^5	Ar	X
45o	Bn	H	H	H	H	4-ClC_6H_4	CH_2
45p	Et	H	H	H	H	Ph	$(CH_2)_3$
45q	Et	H	MeO	MeO	H	3-ClC_6H_4	CH_2
45r	Et	H	H	H	H	3-ClC_6H_4	CH_2S
45s	Et	H	H	H	H	2-ClC_6H_4	CH_2S
45t	Et	H	H	H	H	2-MeC_6H_4	CH_2S
45u	Et	H	H	H	H	2,3-$Cl_2C_6H_3$	CH_2S
45v	Et	H	H	H	H	3,4-$Cl_2C_6H_3$	CH_2S
45w	Et	H	H	H	H	2,6-$Cl_2C_6H_3$	CH_2S
45x	Et	H	H	H	H	2,6-$Me_2C_6H_3$	CH_2S
45y	Et	H	H	H	H	3,5-$Me_2C_6H_3$	CH_2S
45z	Et	H	H	H	H	2,4,6-$Me_3C_6H_2$	CH_2S
46a	Et	H	H	H	Bz	3-ClC_6H_4	CH_2
46b	Et	H	H	H	Me	3-ClC_6H_4	CH_2
46c	Et	H	H	H	Et	2-ClC_6H_4	CH_2S
46d	Et	Et	H	H	Et	2-ClC_6H_4	CH_2S
47a	Et	H	Ph	–	H	3-ClC_6H_4	CH_2
47b	Et	H	4-PhC_6H_4	–	H	3-ClC_6H_4	CH_2
48a	Et	H	–	–	H	3-ClC_6H_4	CH_2
48b	Et	H	–	–	H	2-ClC_6H_4	CH_2
48c	Et	H	–	–	H	4-ClC_6H_4	CH_2
48d	Et	H	–	–	H	3-FC_6H_4	CH_2
48e	Et	H	–	–	H	4-FC_6H_4	CH_2
48f	Et	H	–	–	H	3-BrC_6H_4	CH_2
48g	Et	H	–	–	H	4-BrC_6H_4	CH_2
48h	Et	H	–	–	H	3-$MeOC_6H_4$	CH_2
48i	Et	H	–	–	H	4-ClC_6H_4	CH_2
48j	Et	H	–	–	H	4-$F_3CC_6H_4$	CH_2
48k	Et	H	–	–	H	3-ClC_6H_4	σ-bond
48l	Et	H	–	–	H	4-ClC_6H_4	σ-bond
48m	Et	H	–	–	H	3-ClC_6H_4	$(CH_2)_2$
48n	Et	H	–	–	H	4-ClC_6H_4	$(CH_2)_2$
48o	Et	H	–	–	H	Ph	$(CH_2)_3$
48p	Et	Bn	–	–	H	4-ClC_6H_4	CH_2
48q	Bn	H	–	–	H	3-ClC_6H_4	CH_2
48r	Bn	H	–	–	H	4-ClC_6H_4	CH_2
48s	Et	H	–	–	H	Ph	$(CH_2)_2$
49a	Me	Me	–	–	H	Ph	CH_2
49b	Me	Bn	–	–	H	Ph	CH_2
49c	Me	Ph	–	–	H	Ph	CH_2
49d	Me	4-MeC_6H_4	–	–	H	Ph	CH_2

group.[65, 99] As a starting material for this study, the non-steroidal anti-inflammatory agent Indomethacine (**89**) was chosen which was subjected to saponification or bromination[65] prior to subsequent synthetic steps. These chemical transformations are presented in Scheme 17.

Finally, the most recent publications on the indole-based Arbidol analogues are related to the synthesis and different types of biological activity of compounds **97** devoid of hydroxy and bromo groups at the indole C(5) and C(6) positions and bearing an amino substituent in the C(5) rather than in the C(4) position. Another feature of such substances setting them apart from Arbidol is that the Nenitzescu reaction was not used for their preparation. Instead, the indole scaffold was built *via* the direct arylation of various acetoacetic esters with the proper 2-iodoanilines (4-bromo-2-iodoaniline (**98**)[100] or ethyl 4-amino-3-iodobenzoate[64]), and its subsequent functionalization comprised a multistep reaction sequence as shown in Scheme 18.

Another approach utilizing ethyl 4-aminobenzoate **101** is somewhat closer to the preparation of other Arbidol analogues, since it comprises the Wohl – Ziegler bromination of the indole **102** C(2) methyl group followed by the

Scheme 10



(*a*) NH(R^1)R^2, EtOH, Δ; (*b*) 1,4-benzoquinone, EtOH, Δ; (*c*) 1) *N*,*N*-dimethylpiperazine, NCS, CH_2Cl_2; 2) $Cl_3CC(O)OH$, amines; 3) $NaHCO_3$, H_2O; (*d*) NaH, $(MeO)_2SO_2$, DMF, Δ

Compound	R^1	R^2	R^3	R^4	Compound	R^1	R^2	R^3	R^4
50a	3-ClC$_6$H$_4$	H	H	Me	**50l$_1$**(*R*)-isomer	CH(Me)Ph	H	OH	Me
50b	4-ClC$_6$H$_4$	H	H	Me	**50l$_2$**(*S*)-isomer	CH(Me)Ph	H	OH	Me
50c	2-ClC$_6$H$_4$	H	H	Me	**50m**	(CH$_2$CH$_2$)$_2$NPh		OH	Et
50d	3-ClC$_6$H$_4$	H	OH	Me	**50n**	Me	Me	OH	Et
50e	3-ClC$_6$H$_4$	H	Cl	Me	**50o**	(CH$_2$)$_4$		OH	Et
50f	3-FC$_6$H$_4$	H	H	Me	**50p**	(CH$_2$)$_5$		OH	Et
50g	3-F$_3$CC$_6$H$_4$	H	H	Me	**50q**	(CH$_2$CH$_2$)$_2$O		OH	Et
50h	3,5-F$_2$C$_6$H$_3$	H	H	Me	**50r**	(CH$_2$CH$_2$)$_2$NMe		OH	Et
50i	3,4-FC$_6$H$_3$	H	H	Me	**50s**	(4-FC$_6$H$_4$)N(CH$_2$CH$_2$)$_2$		OH	Et
50j	2,6-F$_2$C$_6$H$_3$NH	H	H	Me	**50t**	(4-ClC$_6$H$_4$)N(CH$_2$CH$_2$)$_2$		OH	Et
50k	3-ClC$_6$H$_4$	Me	H	Me	**50u**	(CH$_2$CH$_2$)$_2$NBn		OH	Et

reaction with the corresponding thiophenoxide prepared *in situ* to obtain substituted thiophenols **103**, which were subsequently reduced to 5-(hydroxymethyl) derivatives **104** and then the sulfur atom was oxidized to produce sulfoxides **105** (Scheme 19).[64]

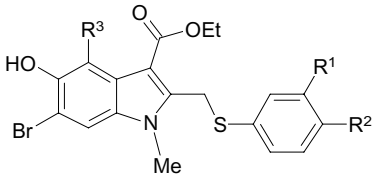
Several interesting conclusions can be drawn from analyzing the synthetic schemes described above. First of all, surprisingly, but it's true: Arbidol appears to be an extremely suitable object for targeted structural optimization, but there are only a few examples of research works of such kind. One of the primary purposes of such optimization is to decrease cytotoxicity of the parent compound. However, the absolute majority of the research works in this field continue to produce the endless libraries of compounds, which are synthesized mostly according to pioneering Grinev's scheme. And this is due to the simplicity of this approach; however, this simplicity correlates well with the questionable productivity of the further high-throughput screening of these myriads of compounds.

3.2. Indole- and benzofuran-based Arbidol analogues showing anti-influenza virus activity

Since Arbidol has been positioned as an anti-influenza drug, the first attempts to modify its structure were associated with a search for novel highly active inhibitors of influenza virus replication. The results of these works may be considered as quite encouraging, but it seems reasonable to start with the latest data from the Scripps Institute group. First of all, they have clearly demonstrated for the first time the binding mode of Arbidol with viral hemagglutinin.[101] Second, they have prepared a series of compounds **29**, **32** structurally very similar to Arbidol.[76]

Investigations of an affinity of these compounds to influenza hemagglutinin led to surprising conclusions. First of all, it was established that Arbidol analogue **32ae** unsubstituted at the C(4) position of the indole ring was

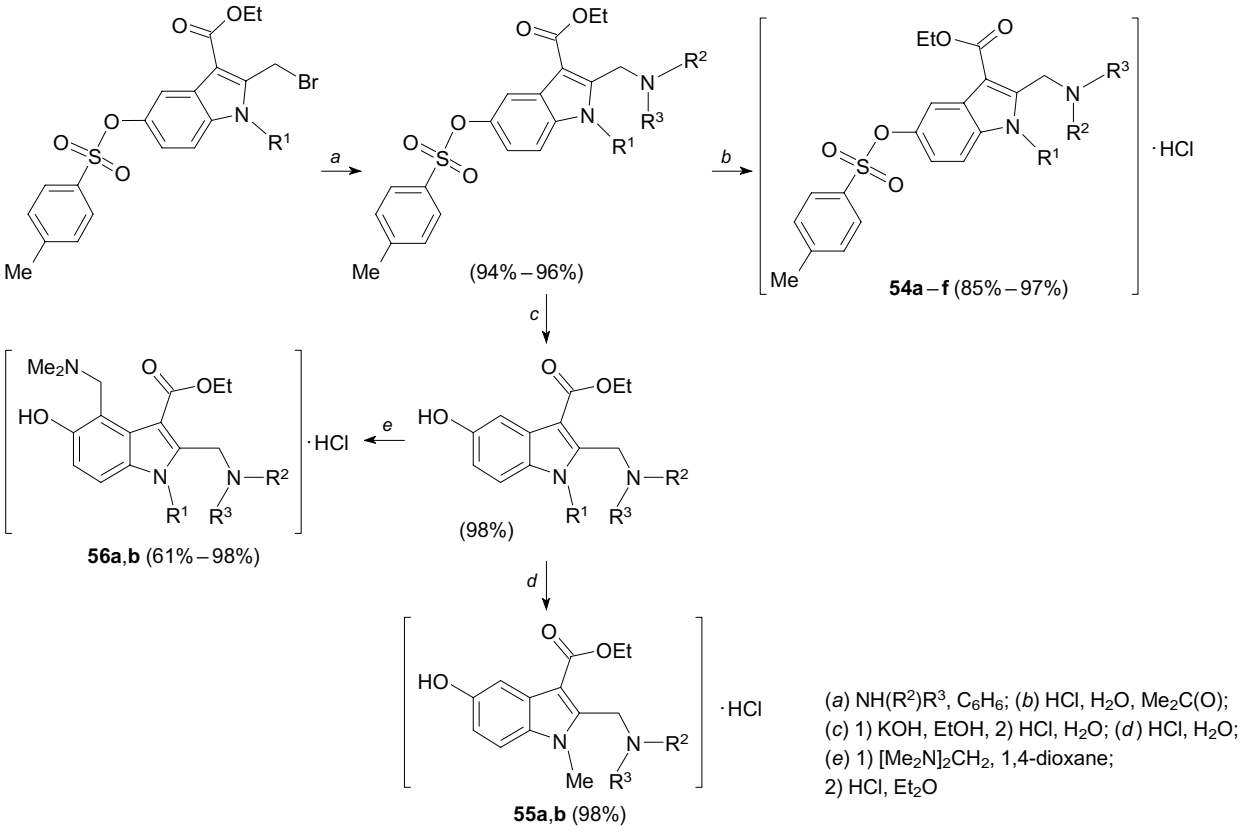
Structures 29, 32



29aa – af, **32aa – ad**

29aa: R^1 = R^2 = H, R^3 = CH_2NMe_2; **29ab**: R^1 = R^2 = H, R^3 = $CH_2N(CH_2CH_2)_2NC(O)OCMe_3$; **29ac**: R^1 = R^2 = H, R^3 = $CH_2N(CH_2CH_2)_2N(CH_2)_2OH$; **29ad**: R^1 = OH, R^2 = H, R^3 = CH_2NMe_2; **29ae**: R^1 = NH_2, R^2 = H, R^3 = CH_2NMe_2; **29af**: R^1 + R^2 = $(CH)_4$, R^3 = CH_2NMe_2; **32aa**: R^1 = R^2 = R^3 = H; **32ab**: R^1 = OH, R^2 = H, R^3 = H; **32ac**: R^1 = NH_2, R^2 = H, R^3 = H; **32ad**: R^1 + R^2 = $(CH)_4$, R^3 = H

Scheme 11

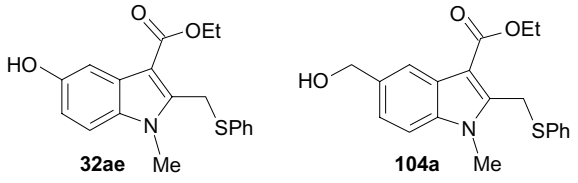


Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
54a	Ph	Me	Me	**54f**	4-BrC_6H_4	$(CH_2CH_2)_2O$	
54b	Me	Me	Me	**55a**	–	Et	Et
54c	Ph	H	Bn	**55b**	–	$(CH_2CH_2)_2O$	
54d	4-BrC_6H_4	H	Bn	**56a**	–	Et	Et
54e	4-BrC_6H_4	Me	Me	**56b**	–	$(CH_2CH_2)_2O$	

nearly equipotent to Arbidol when tested on PR8 (H1) hemagglutinin and about 9 times more potent when tested on HK68 (H3) hemagglutinin.[76] It should be noted that this compound had been previously identified by Chistyakov and co-workers[19] as one of Arbidol metabolites in rats. Looking back, it should be noted that Phercaptoline **3**, being active in rats, but not in humans, may display activity against influenza as a prodrug that undergoes metabolic *in vivo* (C4) dealkylation in rats affording more active compound **32ae**.

Screening of the above mentioned series of compounds led to identification of a hit compound **29ad** bearing the hydroxy group in the *meta*-position of the thiophenol residue. This compound was 98- and 1150-fold more potent than Arbidol when tested on PR8 (H1) and HK68 (H3) hemagglutinins, respectively. Unfortunately, this substance proved to be readily oxidizable when exposed to air. It should be noted that its (C4) dealkylated analogue **32b** was much less active in both tests.

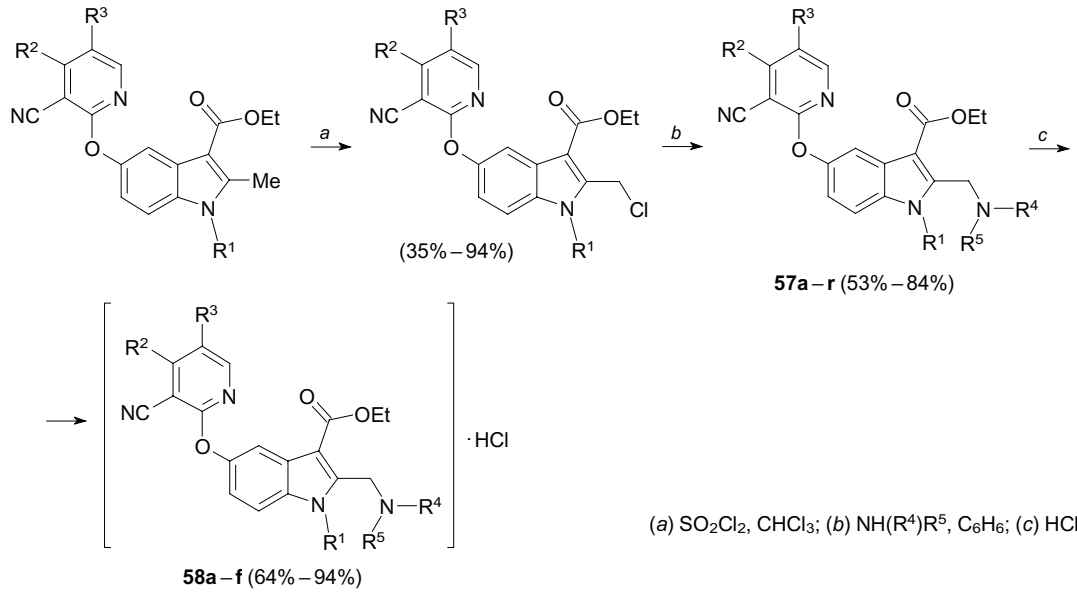
Structures 32ae, 104a



An Italian research group has also prepared a series of compounds **97**, **104** (see Schemes 18, 19) in which the (C4) position of the indole core remained unsubstituted,[102] whereas the (C5) position was substituted with hydroxy, hydroxymethyl and various aminomethyl moieties. The methyl group at the indole (C2) position was unsubstituted or contained the thiophenol group, as in the Arbidol molecule.

Analysis of the structure – activity relationships for this series of compounds showed that the hit compound **104a** lacking a bromine atom at the (C6) position of the indole heterocyclic system was almost equipotent to Arbidol but much less cytotoxic. At the same time, replacing the hydroxymethyl group for the aminomethyl one led to a complete loss of antiviral activity. On the contrary, introduction of the (dialkylamino)methyl group into the (C5) position of the indole nucleus yielded active, but highly cytotoxic derivatives. Furthermore, ethyl 6-bromo-1,2-dimethyl-5-(hydroxymethyl)-1*H*-indole-3-carboxylate, prepared and screened in this study, had approximately the same therapeutic index as the parent compound, exhibiting at the same time far more high antiviral activity. At the

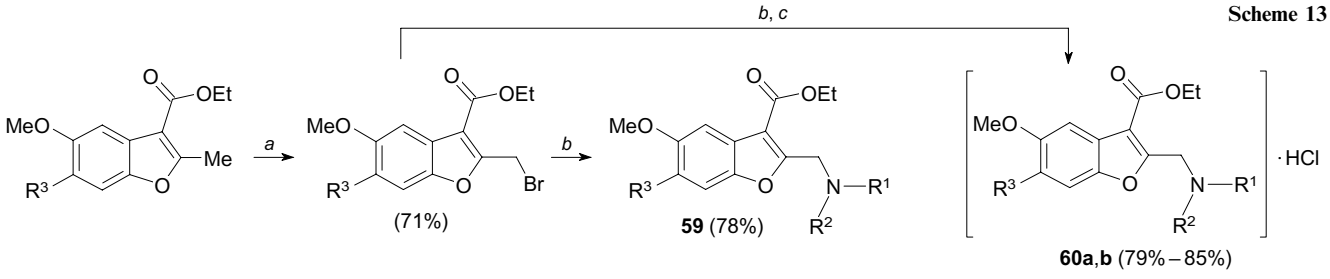
Scheme 12



(*a*) SO_2Cl_2, $CHCl_3$; (*b*) $NH(R^4)R^5$, C_6H_6; (*c*) HCl, $Me_2C(O)$

Compound	R^1	R^2	R^3	R^4	R^5	Compound	R^1	R^2	R^3	R^4	R^5
57a	4-MeC_6H_4	H	H	Et	Et	**57m**	4-BrC_6H_4	H	4-$MeOC_6H_4NH$	Et	Et
57b	4-$MeOC_6H_4$	H	H	Et	Et	**57n**	4-MeC_6H_4	H	4-$MeOC_6H_4NH$	Et	Et
57c	4-$MeOC_6H_4$	H	H	Me	Me	**57o**	4-$MeOC_6H_4$	H	4-$MeOC_6H_4NH$	Et	Et
57d	4-MeC_6H_4	H	NHPh	Me	Me	**57p**	4-BrC_6H_4	H	4-MeC_6H_4NH	Et	Et
57e	4-MeC_6H_4	H	NHPh	Et	Et	**57q**	4-$MeOC_6H_4$	H	4-MeC_6H_4NH	Me	Me
57f	4-MeC_6H_4	H	NHPh	$(CH_2)_2O(CH_2)_2$		**57r**	Ph	H	4-MeC_6H_4NH	Et	Et
57g	4-BrC_6H_4	H	NHPh	Et	Et	**58a**	4-MeC_6H_4	H	H	Et	Et
57h	4-$MeOC_6H_4$	H	NHPh	Et	Et	**58b**	4-$MeOC_6H_4$	H	H	Et	Et
57i	4-$MeOC_6H_4$	H	NHPh	Me	Me	**58c**	4-MeC_6H_4	H	NHPh	Me	Me
57j	4-$MeOC_6H_4$	CN	NHPh	Et	Et	**58d**	4-MeC_6H_4	H	NHPh	Et	Et
57k	Me	H	4-MeC_6H_4NH	Et	Et	**58e**	4-MeC_6H_4	H	NHPh	$(CH_2)_2O(CH_2)_2$	
57l	4-MeC_6H_4	H	4-MeC_6H_4NH	Et	Et	**58f**	4-BrC_6H_4	H	NHPh	Et	Et

Scheme 13



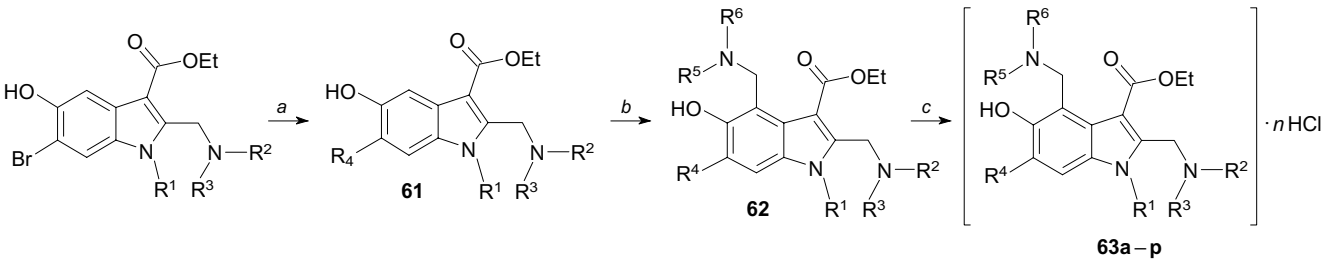
(*a*) NBS, Bz_2O_2, CCl_4; (*b*) $NH(R^1)R^2$, C_6H_6; (*c*) HCl, EtOH; **59**: $R^1 + R^2 = (CH_2CH_2)_2O$; **60a**: $R^1 = R^2 = Et$ (85% yield); **60b**: $R^1 + R^2 = (CH_2)_5$ (79%)

same time, the spectrum of antiviral activity for this compound was somewhat narrower compared to its predecessor.

These data suggest that modification of the ethyl 1*H*-indole-3-carboxylate scaffold significantly influences antiviral activity and cytotoxicity of the resulting compounds. On the other hand, it appears that the presence of the thiophenol residue, as well as the bromine atom and the Mannich base moiety, has no effect on antiviral properties of this structural chemotype. At the same time, the most part of such compounds retain a relatively high cytotoxicity.

Among a number of Arbidol congeners synthesized by the group of Ping Gong,[52, 63, 103, 104] some substances attract more attention than the others. For example, the results obtained during the screening of Arbidol and its close analogues against influenza virus A3, seem truely surprising.[52, 63] In this study, two series of compounds have been studied, namely, **29ag** – **am** and **70a**,**b**, and **29an** – **ay**.

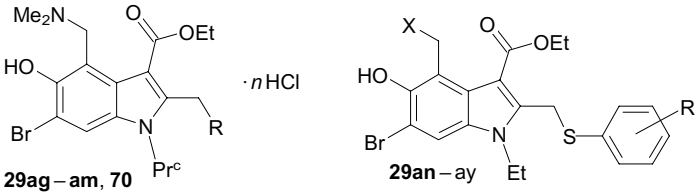
Scheme 14



(*a*) CuCN, NMP, Δ (R^4 = Br → CN) or $PyB(OH)_2$, $Pd(PPh_3)_2Cl_2$, Na_2CO_3, EtOH, H_2O (R^4 = Br → Py); (*b*) 1) $NH(R^5)R^6$, $CH_2O - H_2O$, 1,4-dioxane (R^4 = F, Br, CN); 2) THF, HCl, 1,4-dioxane; (*c*) HCl, H_2O; NMP is N-methylpyrrolidone

Compound	R^1	R^2	R^3	R^4	R^5	R^6	*n*
63a	Pr^c	$(CH_2)_5$		Br	Me	Me	–
63b	Pr^c	$(CH_2CH_2)_2O$		Br	Me	Me	–
63c	Me	Me	Me	F	Me	Me	2
63d	Me	Me	Me	Br	Me	Me	2
63e	Me	Me	Me	CN	Me	Me	2
63f	Me	Me	Me	3-Py	Me	Me	3
63g	Pr^i	Me	Me	3-Py	Me	Me	3
63h	Pr^c	Me	Me	3-Py	Me	Me	3
63i	Hex^c	3-Py	Me	Me	Me	Me	3
63j	Ph	3-Py	Me	Me	Me	Me	3
63k	Me	$(CH_2)_4$		3-Py	Me	Me	3
63l	Me	Me	Me	3-Py	$(CH_2)_4$		3
63m	Me	Me	Me	4-Py	Me	Me	3
63n	Me	$(CH_2)_4$		4-Py	Me	Me	3
63o	Me	$(CH_2)_4$		4-Py	$(CH_2)_4$		3
63p	Me	Me	Me	4-Py	$(CH_2)_4$		3

Structures 29, 70



29: R = S–(4-R^1-phenyl) [R^1 = H (**ag**), 4-F (**ah**), 2-F (**ai**), 3,4-F_2 (**aj**), 3-MeO (**ak**), 4-Pr^i (**al**), 4-Me (**am**)]; *n* = 1;

70: **R** = N(X), X = CH_2 (**a**), O (**b**), *n* = 2

Compound **29**	R	X
an	H	4-Methylpiperazin-1-yl
ao	H	Et_2N
ap	H	Pyrrolidin-1-yl
aq	H	Morpholin-4-yl
ar	3,4-F_2	4-Methylpiperazin-1-yl
as	3,4-F_2	Me_2N
at	3,4-F_2	Pyrrolidin-1-yl
au	3,4-F_2	Morpholin-4-yl
av	4-Pr^i	Me_2N
aw	4-Pr^i	Et_2N
ax	4-Pr^i	Morpholin-4-yl
ay	4-Pr^i	Pyrrolidin-1-yl

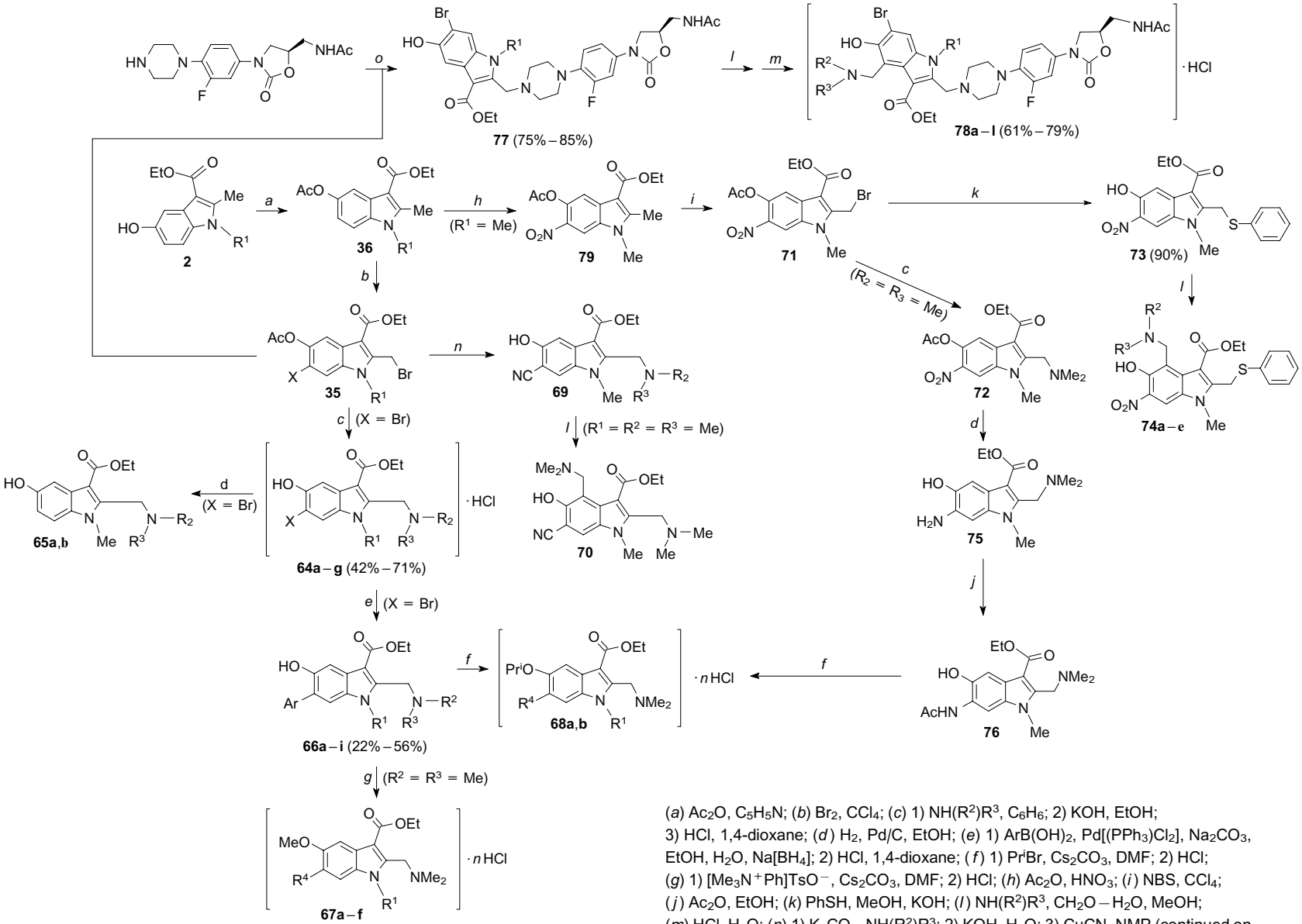
The results of biological screening are presented in Table 1 below. However, it should be noted that in all the described experiments, the relative error of measurements is zero, that seems questionable.

As can be seen in Table 1, IC_{50} values for a number of the tested compounds (such as **29ag** – **ak**, and **70a**) were identical to those for Arbidol, namely, 3.9 μg ml^{-1}.

Interestingly, when used as a reference drug, Ribavirin also showed IC_{50} = 3.9 μg ml^{-1}. These data look really doubtful since the latest studies,[76, 102] together with the previous reports of Grinev's team, clearly showed that such serious modification of the Arbidol molecule (in particular, the substitution of the thiophenol moiety) leads to severe changes in the compound activity. Moreover, cytotoxicity data for Arbidol (CC_{50} ~ 500 μg ml^{-1} for MDCK and HeLa cells)[52, 63] are absolutely different from those reported later (~20 μg ml^{-1} for both cell cultures).[85]

Meanwhile, the data on high cytotoxicity of Arbidol and a variety of its structural analogues are in good agreement with the results of both the early Russian[105] and the recent Italian reports.[56, 102]

Scheme 15



(*a*) Ac_2O, C_5H_5N; (*b*) Br_2, CCl_4; (*c*) 1) $NH(R^2)R^3$, C_6H_6; 2) KOH, EtOH; 3) HCl, 1,4-dioxane; (*d*) H_2, Pd/C, EtOH; (*e*) 1) $ArB(OH)_2$, $Pd[(PPh_3)Cl_2]$, Na_2CO_3, EtOH, H_2O, $Na[BH_4]$; 2) HCl, 1,4-dioxane; (*f*) 1) Pr^iBr, Cs_2CO_3, DMF; 2) HCl; (*g*) 1) $[Me_3N^+Ph]TsO^-$, Cs_2CO_3, DMF; 2) HCl; (*h*) Ac_2O, HNO_3; (*i*) NBS, CCl_4; (*j*) Ac_2O, EtOH; (*k*) PhSH, MeOH, KOH; (*l*) $NH(R^2)R^3$, CH_2O-H_2O, MeOH; (*m*) HCl, H_2O; (*n*) 1) K_2CO_3, $NH(R^2)R^3$; 2) KOH, H_2O; 3) CuCN, NMP (continued on the next page)

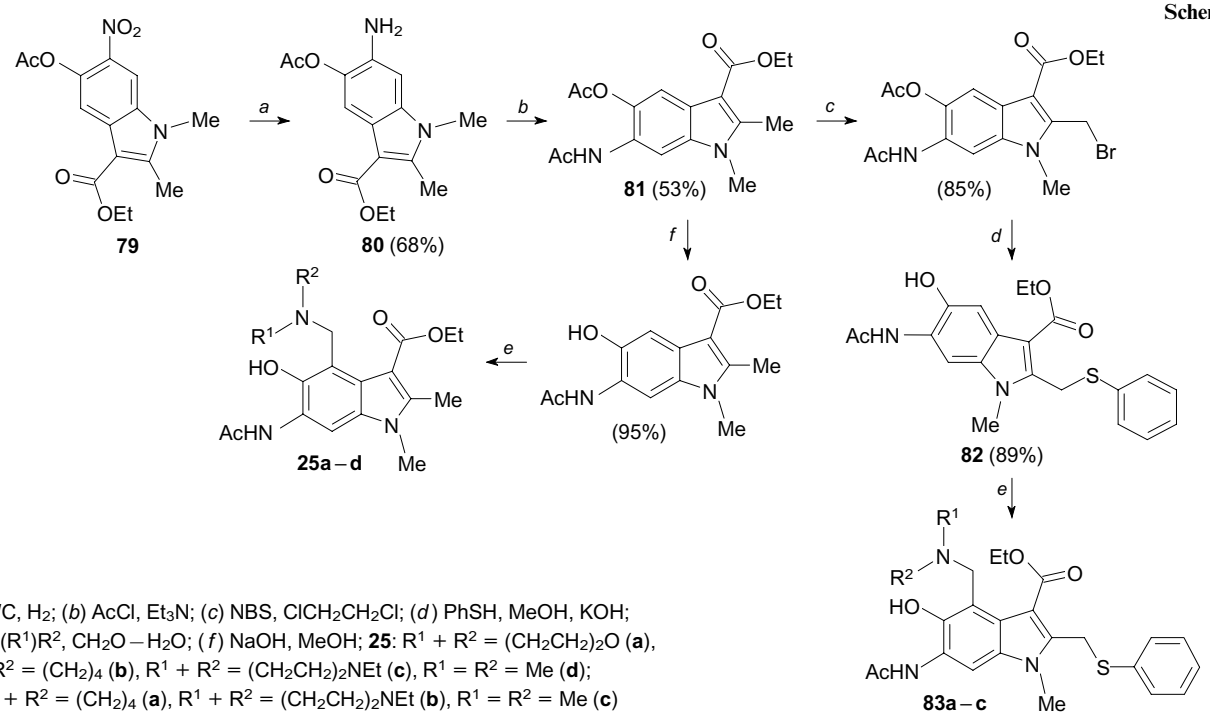
Scheme 15 (continued)

Compound	R^1	R^2	R^3	R^4/X	Ar	*n*
64a	Me	Me	Me	Br	–	–
64b	Me	$(CH_2)_4$		Br	–	–
64c	Me	$(CH_2CH_2)_2O$		Br	–	–
64d	Pr^i	Me	Me	Br	–	–
64e	Pr^c	Me	Me	Br	–	–
64f	Hex^c	Me	Me	Br	–	–
64g	Ph	Me	Me	Br	–	–
65a	–	$(CH_2)_4$		–	–	–
65b	–	$(CH_2CH_2)_2O$		–	–	–
66a	Me	Me	Me	–	3-Py	–
66b	Me	$(CH_2)_4$		–	3-Py	–
66c	Me	$(CH_2CH_2)_2O$		–	3-Py	–
66d	Me	Me	Me	–	4-Py	–
66e	Me	$(CH_2)_4$		–	4-Py	–
66f	Pr^i	Me	Me	–	3-Py	–
66g	Pr^c	Me	Me	–	3-Py	–
66h	Hex^c	Me	Me	–	3-Py	–
66i	Ph	Me	Me	–	3-Py	–
67a	Me	Me	Me	3-Py	–	2
67b	Pr^i	Me	Me	3-Py	–	2
67c	Pr^c	Me	Me	3-Py	–	2
67d	Hex^c	Me	Me	3-Py	–	2
67e	Ph	Me	Me	3-Py	–	2
67f	Me	Me	Me	F	–	1
68a	Me	Me	Me	3-Py	–	2
68b	Me	Me	Me	NHAc	–	1
76a	–	Bu	Bu	–	–	–
76b	–	$(CH_2CH_2)_2O$		–	–	–
76c	–	$(CH_2)_4$		–	–	–
76d	–	$(CH_2CH_2)_2NCH_2OH$		–	–	–
76e	–	$(CH_2CH_2)_2NEt$		–	–	–
78a	Me	$(CH_2)_4$		–	–	–
78b	Me	$(CH_2CH_2)_2O$		–	–	–
78c	Me	$(CH_2CH_2)_2NMe$		–	–	–
78d	Me	Me	Me	–	–	–
78e	Me	Me	$CH_2CH{=}CH_2$	–	–	–
78f	Me	Me	Bu^i	–	–	–
78g	Pr^c	$(CH_2)_4$		–	–	–
78h	Pr^c	$(CH_2CH_2)_2O$		–	–	–
78i	Pr^c	$(CH_2CH_2)_2NMe$		–	–	–
78j	Pr^c	Me	Me	–	–	–
78k	Pr^c	Me	$CH_2CH{=}CH_2$	–	–	–
78l	Pr^c	Me	Bu^i	–	–	–

Considering such heterogenous and, in some cases, not very reliable experimental data, it seems problematic to build a general SAR model for this series of compounds, and this appears to be an Achilles heel in the targeted design of derivatives of such kind. No docking studies have been presented, and the main molecular target remains unknown. In most cases, the researchers try to follow the principle of pharmacophore similarity, which is, in fact, a 'blackbox' strategy, equating a pharmacophore with the structure of a parent compound, *i.e.* Arbidol. So, the exploratory work again depends mostly on high-throughput screening of libraries of structurally similar compounds.

Several unusual Arbidol analogues bearing 5-ethoxycarbonyl-2-thiouracil (**106**) or thiourea (**107**) substituents at

Scheme 16



(*a*) Pd/C, H_2; (*b*) AcCl, Et_3N; (*c*) NBS, $ClCH_2CH_2Cl$; (*d*) PhSH, MeOH, KOH; (*e*) $NH(R^1)R^2$, $CH_2O - H_2O$; (*f*) NaOH, MeOH; **25**: $R^1 + R^2 = (CH_2CH_2)_2O$ (**a**), $R^1 + R^2 = (CH_2)_4$ (**b**), $R^1 + R^2 = (CH_2CH_2)_2NEt$ (**c**), $R^1 = R^2 = Me$ (**d**); **83**: $R^1 + R^2 = (CH_2)_4$ (**a**), $R^1 + R^2 = (CH_2CH_2)_2NEt$ (**b**), $R^1 = R^2 = Me$ (**c**)

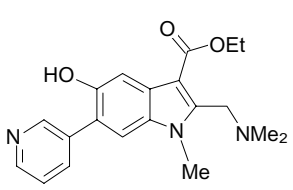
the C(2) methyl group of the indole nucleus have been prepared by Granik *et al.*[105] according to Scheme 20.

Among these compounds, thiuronium salts **107a**,**b** were almost equipotent to Arbidol as inhibitors of influenza virus A/PR/8/34 in MDCK cells.

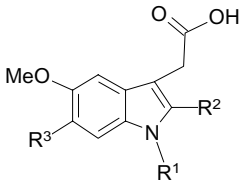
Interestingly, these compounds contain neither the Mannich-base moiety nor the phenyl ring in the C(2) side chain, while the C(5) hydroxy group is acetylated.

Ivashchenko *et al.* attempted a relatively deep and successful modification of Arbidol structure, which led to identification and preclinical evaluation of a new antiviral drug candidate AV0038 (**66a**).[106]

Structures 66a, 85b, 94a



66a (AV0038)



85b, **94a**

85b: R^1 = 4-$ClC_6H_4C(O)$, $R^2 = CH_2NHMe$, R^3 = Br;
94a: R^1 = Me, $R^2 = CH_2OH$, R^3 = Br

The structure of compound **66a** differs considerably from that of Arbidol. At the same time, it still contains the ethyl 5-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylate scaffold, whereas the bromine atom at the C(6) position is replaced by another deactivating group, namely, a planar pyridin-3-yl radical, and the thiophenol moiety is omitted. On the other hand, the position of the Mannich-base moiety is changed from the C(4) to C(2) atom of the indole ring.

A number of heteroauxin **84** – **96** derivatives structurally related to compound **66a** have also been investigated.[99]

Obviously, these compounds are even structurally less similar to Arbidol than AV0038. Two of them (**85b**, **94a**) showed moderate antiviral activity in infected cell lines, but were less potent than Remantadine **108** used as an external standard.

At the same time, they were equipotent to Remantadine **108** in mice infected with viral pneumonia. These observations suggest that metabolic activation or direct anti-inflammatory activity could be crucial for efficiency of these compounds as therapeutics.

It should be noted that before identification of the hit compound AV0038, a number of Arbidol analogues containing the ethyl 5-hydroxy-1,2-dimethyl-1*H*-indole-3-carboxylate motif have been prepared and studied. Their particular structural features are as follows:

1. The presence of various deactivating substituents (for example, fluorine, pyridin-3-yl, cyano group, *etc.*), different from the bromine atom, at the C(6) position of the indole core.[49]

2. The presence of phenylsulfanyl bioisosteres[107] or dialkylamino groups in the side chain at the C(2) atom.[53]

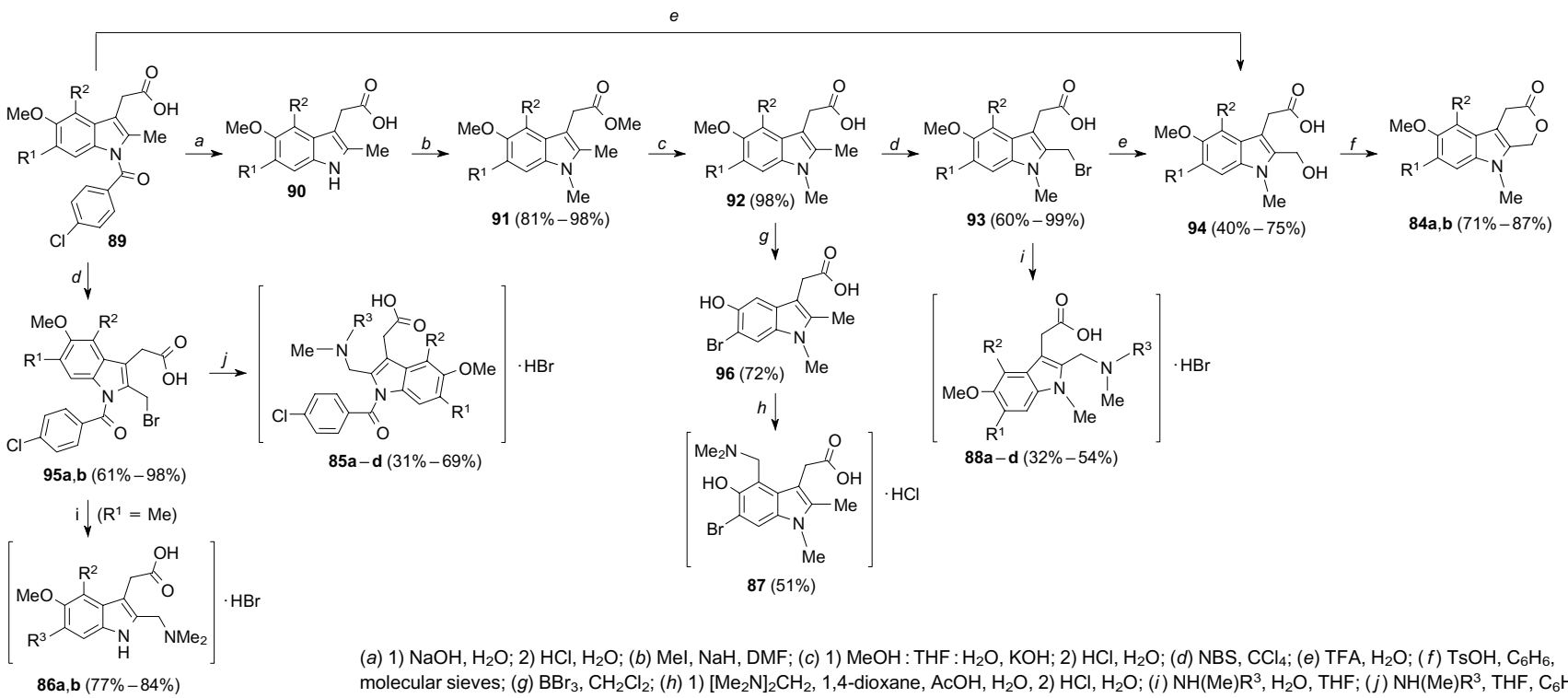
3. Ring closure between the C(5) hydroxy and C(4) aminomethyl groups by a methylene linker to form an oxazine annulated with the benzene ring of the indole moiety.[70]

4. Modification of the C(3) ethoxycarbonyl group and its transformation into the amide or nitrile moiety.[58]

Unfortunately, no information is available concerning the antiviral properties of these compounds, except for 3-ethoxycarbonyl-1*H*-indoles.

In summary, none of the above-mentioned heteroauxin derivatives showed antiviral activity at concentrations below the single-digit micromolar range. Some of them were more or less similar in their antiviral activity to Arbidol. Due to obvious structural discontinuity in the

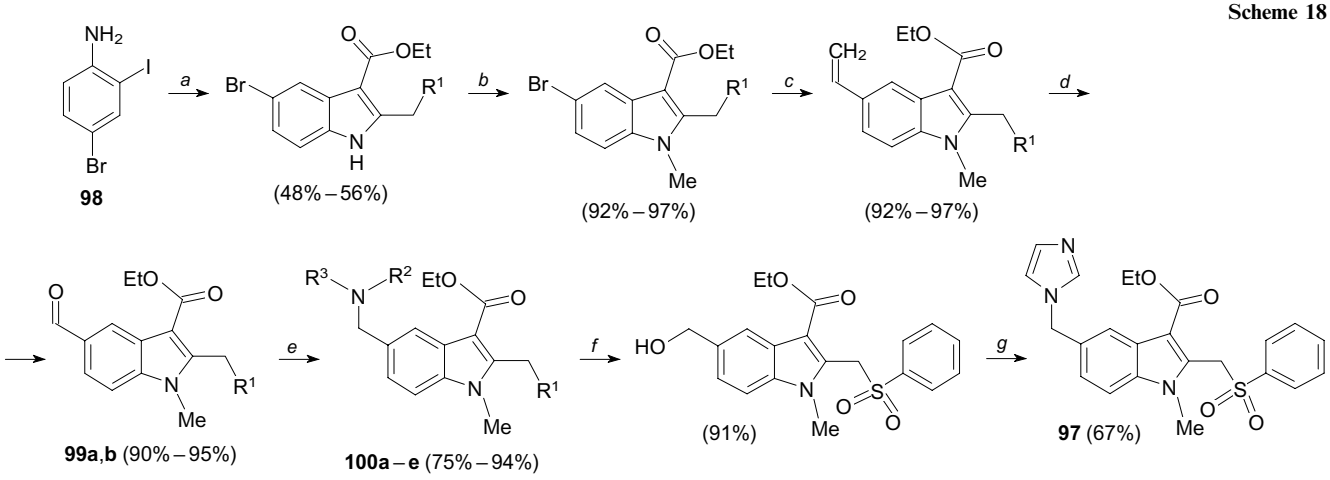
Scheme 17



(*a*) 1) NaOH, H_2O; 2) HCl, H_2O; (*b*) MeI, NaH, DMF; (*c*) 1) MeOH : THF : H_2O, KOH; 2) HCl, H_2O; (*d*) NBS, CCl_4; (*e*) TFA, H_2O; (*f*) TsOH, C_6H_6, molecular sieves; (*g*) BBr_3, CH_2Cl_2; (*h*) 1) $[Me_2N]_2CH_2$, 1,4-dioxane, AcOH, H_2O, 2) HCl, H_2O; (*i*) NH(Me)R^3, H_2O, THF; (*j*) NH(Me)R^3, THF, C_6H_6

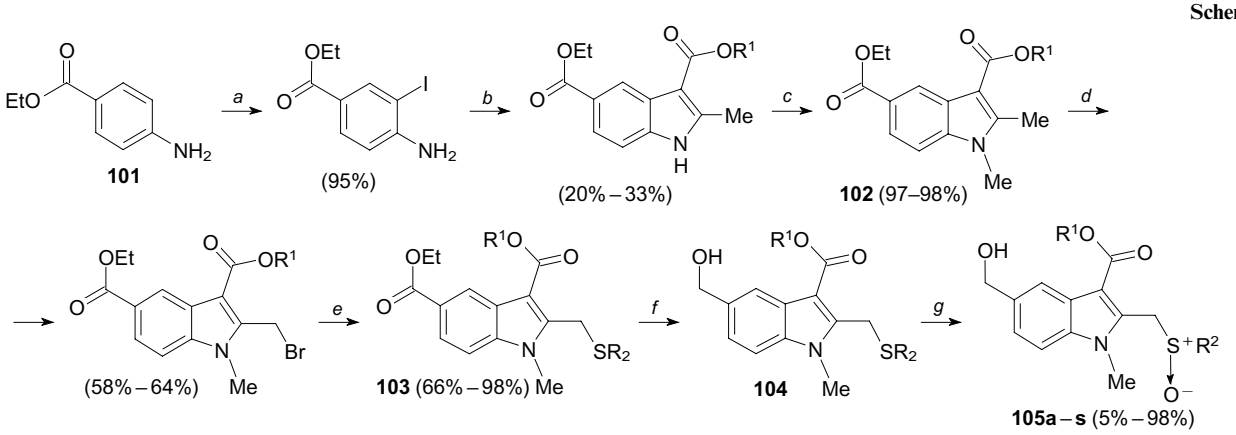
Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
84a	H	Br	–	**86a**	H	Br	–
84b	Br	H	–	**86b**	Br	H	–
85a	H	Br	H	**88a**	H	Br	H
85b	Br	H	H	**88b**	Br	H	H
85c	H	Br	Me	**88c**	H	Br	Me
85d	Br	H	Me	**88d**	Br	H	Me

Scheme 18



(*a*) $R^1CH_2C(O)CH_2C(O)OEt$, CuI, Cs_2CO_3, DMSO, BINOL; (*b*) MeI, KOH, DMF; (*c*) $KF \cdot F_2BCH{=}CH_2$, $PdCl_2$, PPh_3, Cs_2CO_3, THF/H_2O; (*d*) OsO_4, $NaIO_4 - H_2O$, 1,4-dioxane, 2,6-lutidine; (*e*) 1) $NH(R^2)R^3$, AcOH, THF, $Na[B(OAc)_3H]$, MW; 2) MeOH, HCl; 3) $K_2CO_3 - H_2O$; (*f*) $Na[BH_4]$ – MeOH, THF; (*g*) 1*H*-imidazole, CDI, MeCN; **99**: $R^1 = S(O)_2Ph$ (**a**), $R^1 = H$ (**b**); **100**: $R^1 = (SO)_2Ph$, $R^2 = R^3 = Me$ (**a**); $R^1 = (SO)_2Ph$, $R^2 + R^3 = (CH_2)_4$ (**b**); $R^1 = (SO)_2Ph$, $R^2 + R^3 = (CH_2CH_2)_2NMe$ (**c**); $R^1 = (SO)_2Ph$, $R^2 + R^3 = (CH_2CH_2)_2O$ (**d**); $R^1 = H$, $R^2 = R^3 = Me$ (**e**); $R^1 = H$, $R^2 + R^3 = (CH_2)_4$ (**f**)

Scheme 19



(*a*) KI, $NaIO_4$, NaCl, AcOH; (*b*) $MeC(O)CH_2C(O)OR^1$, CuI, BINOL, Cs_2CO_3, DMSO; (*c*) MeI, NaH, DMF; (*d*) NBS, CCl_4, Bz_2O_2; (*e*) R^2SH, NaH, THF; (*f*) 1) DIBAL – H, CH_2Cl_2, THF; 2) MeOH, $CHCl_3$, citric acid; (*g*) *m*-CPBA, CH_2Cl_2

Compounds **105**	R^1	R^2	Compounds **105**	R^1	R^2	Compounds **105**	R^1	R^2
a	Et	Ph	**g**	Et	$2,4\text{-}Cl_2C_6H_3$	**m**	Bu^t	$4\text{-}F_3COC_6H_4$
b	Et	$4\text{-}MeOC_6H_4$	**h**	Et	$2,6\text{-}Cl_2C_6H_3$	**n**	Bu^t	$2,4\text{-}F_2C_6H_3$
c	Et	$4\text{-}FC_6H_4$	**i**	Bu^t	Ph	**o**	Bu^t	$2,4\text{-}Cl_2C_6H_3$
d	Et	$4\text{-}F_3CC_6H_4$	**j**	Bu^t	$4\text{-}MeOC_6H_4$	**p**	Bu^t	$4\text{-}ClC_6H_4$
e	Et	$4\text{-}F_3COC_6H_4$	**k**	Bu^t	$4\text{-}FC_6H_4$	**q**	Bu^t	$2,4,6\text{-}Me_3C_6H_2$
f	Et	$2,4\text{-}F_2C_6H_3$	**l**	Bu^t	$4\text{-}F_3CC_6H_4$	**r**	Bu^t	$2\text{-}F_3CC_6H_4$
						s	Bu^t	$2,6\text{-}Cl_2C_6H_3$

arrays of the synthesized compounds, it seems problematic to figure out some meaningful SAR without using 3D QSAR methodologies.[108]

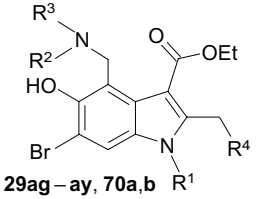
The last data from Chinese scientists also indicate that the presence of the sulfur atom in the C(2) linker is not mandatory for anti-influenza activity of Arbidol analogues. So, a number of Arbidol derivatives **29az** – **bg**, wherein the sulfur atom was 'omitted' have been prepared and evaluated for antiviral activity.[82]

The authors reported that these compounds possessed high anti-influenza activity without significant cytotoxicity. Unfortunately, no quantitative data were provided in this publication.

Taking into consideration the principal findings presented in this part of the review, the following conclusions can be made:

1. An enormous experimental material on the structures of different Arbidol analogues has been accumulated; how-

Table 1. Anti-influenza and cytotoxic properties of a series of structurally diverse ethyl 1-(cyclo)alkyl-4-(aminomethyl)-6-bromo-5-hydroxy-1*H*-indole-3-carboxylates **29**, **70**.[52, 63]

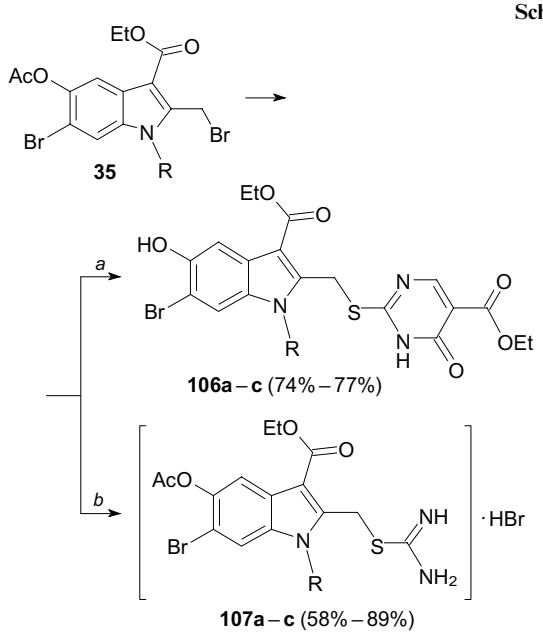


29ag – ay, **70a**,**b**

Compound	R^1	R^2	R^3	R^4	MDCK		HeLa		IC50 /μg ml^{-1}		MIC /μg ml^{-1}	
					TD_0 /μg ml^{-1}	TD_{50} /μg ml^{-1}	TD_0 /μg ml^{-1}	TD_{50} /μg ml^{-1}	influenza A3	RSV	influenza A3	RSV
29ag	Pr^c	Me	Me	SPh	2000 ± 0	3000 ± 0	2000 ± 0	3000 ± 0	3.9 ± 0	3.9 ± 0	7.8 ± 0	7.8 ± 0
29ah	Pr^c	Me	Me	4-FC_6H_4S	2000 ± 0	3000 ± 0	2000 ± 0	3000 ± 0	3.9 ± 0	3.9 ± 0	7.8 ± 0	7.8 ± 0
29ai	Pr^c	Me	Me	2-FC_6H_4S	500 ± 0	1000 ± 0	500 ± 0	1000 ± 0	3.9 ± 0	3.9 ± 0	7.8 ± 0	7.8 ± 0
29aj	Pr^c	Me	Me	3,4-$F_2C_6H_3S$	250 ± 0	500 ± 0	250 ± 0	500 ± 0	3.9 ± 0	3.9 ± 0	7.8 ± 0	7.8 ± 0
29ak	Pr^c	Me	Me	3-$MeOC_6H_4S$	2000 ± 0	4000 ± 0	2000 ± 0	4000 ± 0	3.9 ± 0	3.9 ± 0	7.8 ± 0	7.8 ± 0
29al	Pr^c	Me	Me	4-Pr^iC_6H_4S	1000 ± 0	1500 ± 0	500 ± 0	1000 ± 0	62.5 ± 0	62.5 ± 0	125 ± 0	250 ± 0
29am	Pr^c	Me	Me	4-MeC_6H_4S	1000 ± 0	2000 ± 0	2000 ± 0	4000 ± 0	62.5 ± 0	62.5 ± 0	125 ± 0	250 ± 0
29an	Et	$(CH_2CH_2)_2NMe$		SPh	1000 ± 0	2000 ± 0	1000 ± 0	2000 ± 0	< 3.9 ± 0	7.8 ± 0	3.9 ± 0	15.6 ± 0
29ao	Et	Et	Et	SPh	500 ± 0	1000 ± 0	500 ± 0	1000 ± 0	15.6 ± 0	31.3 ± 0	15.6 ± 0	31.3 ± 0
29ap	Et	$(CH_2)_4$		SPh	500 ± 0	1000 ± 0	500 ± 0	1000 ± 0	7.8 ± 0	31.3 ± 0	3.9 ± 0	15.6 ± 0
29aq	Et	$(CH_2CH_2)_2O$		SPh	1000 ± 0	2000 ± 0	500 ± 0	1000 ± 0	15.6 ± 0	31.3 ± 0	15.6 ± 0	62.5 ± 0
29ar	Et	$(CH_2CH_2)_2NMe$		3,4-$F_2C_6H_3S$	1000 ± 0	2000 ± 0	1000 ± 0	2000 ± 0	15.6 ± 0	31.3 ± 0	15.6 ± 0	62.5 ± 0
29as	Et	Me	Me	3,4-$F_2C_6H_3S$	1000 ± 0	2000 ± 0	1000 ± 0	2000 ± 0	7.8 ± 0	15.6 ± 0	< 3.9 ± 0	7.8 ± 0
29at	Et	$(CH_2)_4$		3,4-$F_2C_6H_3S$	125 ± 0	250 ± 0	125 ± 0	250 ± 0	7.8 ± 0	15.6 ± 0	3.9 ± 0	15.6 ± 0
29au	Et	$(CH_2CH_2)_2O$		3,4-$F_2C_6H_3S$	500 ± 0	1000 ± 0	500 ± 0	1000 ± 0	15.6 ± 0	31.3 ± 0	7.8 ± 0	15.6 ± 0
29av	Et	Me	Me	4-Pr^iC_6H_4S	250 ± 0	500 ± 0	250 ± 0	500 ± 0	< 3.9 ± 0	3.9 ± 0	< 3.9 ± 0	3.9 ± 0
29aw	Et	Et	Et	4-Pr^iC_6H_4S	2000 ± 0	3000 ± 0	2000 ± 0	3000 ± 0	7.8 ± 0	15.6 ± 0	3.9 ± 0	7.8 ± 0
29ax	Et	$(CH_2CH_2)_2O$		4-Pr^iC_6H_4S	1000 ± 0	2000 ± 0	1000 ± 0	2000 ± 0	15.6 ± 0	31.3 ± 0	7.8 ± 0	31.3 ± 0
29ay	Et	$(CH_2)_4$		4-Pr^iC_6H_4S	1000 ± 0	2000 ± 0	1000 ± 0	2000 ± 0	3.9 ± 0	7.8 ± 0	3.9 ± 0	15.6 ± 0
70a	Pr^c	Me	Me	Piperidin-1-yl	500 ± 0	1000 ± 0	250 ± 0	750 ± 0	3.9 ± 0	3.9 ± 0	15.6 ± 0	9.4 ± 0
70b	Pr^c	Me	Me	Morpholin-1-yl	250 ± 0	500 ± 0	250 ± 0	1000 ± 0	11.2 ± 0	5.6 ± 0	18.8 ± 0	19.2 ± 0
Ribavirin					2000 ± 0	4000 ± 0	2000 ± 0	4000 ± 0	3.9 ± 0	3.9 ± 0	7.8 ± 0	7.8 ± 0
Amantidine					500 ± 0	1000 ± 0	500 ± 0	1000 ± 0	0.97 ± 0	0.97 ± 0	1.95 ± 0	1.95 ± 0
Arbidol					250 ± 0	500 ± 0	250 ± 0	500 ± 0	3.9 ± 0	3.9 ± 0	7.8 ± 0	7.8 ± 0

Note. TD_0 is tolerance dose at which toxicity occurs in 0% of cases, TD_{50} is tolerance dose at which toxicity occurs in 50% of cases, MDCK is Madin – Darby canine kidney cells, MIC is minimum inhibitory concentration.

Scheme 20



(*a*) ethyl 4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate, C_6H_6, DMF, NaOEt; (*b*) thiourea, EtOH; **106**: R = Me (**a**), Ph (**b**), 4-BrC_6H_4 (**c**), **107**: R = Me (**a**), Ph (**b**), 4-BrC_6H_4 (**c**)

ever, highly heterogenous biological activity data render its comparative analysis difficult. Antiviral activity was measured using various viral strains, models and approaches. Cytotoxic properties have also been analyzed under dissimilar conditions. In this case, for further targeted design and synthesis of novel anti-influenza drugs, utilization of QSAR methodology, especially a one-class approach,[108] together with model building for virtual screening may be advisable.

2. With quite a few exceptions, such as the breakthrough study performed by the Scripps Research team,[101] the molecular modes of action of Arbidol and its analogues are very poorly studied. Arbidol *per se* may be considered as a clathrin-dependent fusion inhibitor[109,110] and as a drug with relatively high affinity for influenza hemagglutinin. Mowever, it is probably incorrect to attribute the same modes of action to its above-mentioned analogues. Obvious structural diversity of these compounds suggests the need for further detailed studies of the biomolecular mechanism of their antiviral activity.

3. Only moderate antiviral activity of the most part of Arbidol analogues, along with their cytotoxic properties, remains to be the unsolved problem as yet. Even the most promising compounds are characterized by one- or two-digit selectivity indices, being, in fact, no more safe than barbiturates in terms of acute toxicity.

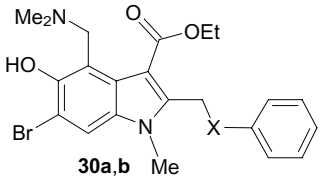
4. Despite the aforesaid problems, several promising candidates for further studies and structural optimization have been identified to date, such as 3′-hydroxy-Arbidol from the Scripps Institute and AV0038 from ChemDiv.[106]

3.3. Arbidol structural analogues as inhibitors of Chicungunya fever virus replication

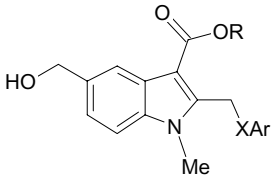
Characterization of Arbidol, its sulfoxide and sulfone derivatives (**30a**,**b**) as inhibitors of the corresponding Arbovirus[111–113] appeared to be a starting point for these works which have been conducted mostly by Italian scientists.

So, a number of 5-(hydroxymethyl)-1-methyl-2-[(phenylsulfanyl)methyl]-1*H*-indole-3-carboxylic acid derivatives (**104**, **105**) have been prepared and screened for their antiviral and cytotoxic properties.[64]

Structures 30, 104, 105



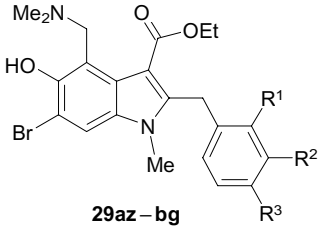
X = S(O) (**a**), $S(O)_2$ (**b**)



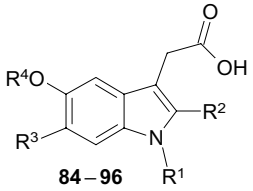
R = Et, Bu^t;
X = S, S(O); Ar = Ph,
4-$MeOC_6H_4$, 4-FC_6H_4,
4-$F_3CC_6H_4$, 4-$F_3OCC_6H_4$,
2,4-$F_2C_6H_3$, 2,6-$Cl_2C_6H_3$,
2,4-$Cl_2C_6H_3$, 2,4,6-$Me_3C_6H_2$,
4-ClC_6H_4, 2-$F_3CC_6H_4$

These compounds differ from each other by the benzene ring substituents, while the carboxylic group was esterified with ethyl or *tert*-butyl alcohols, the sulfide moiety, in some cases, was oxidized to sulfoxide, and C(5) hydroxyl was replaced by the hydroxymethyl group. Comparison of these compounds with Arbidol shows that the main structural modifications comprised elimination of the Mannich-base moiety (potential toxicophore) from the C(4) position of the indole nucleus and also the C(6) bromine atom. At the same time, the core scaffold of 1-methyl-2-[(phenylsulfanyl)methyl]-1*H*-indole-3-carboxylic acid remained

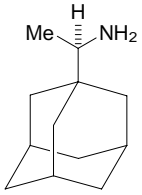
Structures 29, 84 – 96, 108



$R^1 = R^2 = R^3 = H$ (**az**); $R^1 = R^2 = H$, $R^3 = F$ (**ba**);
$R^1 = R^2 = H$, $R^3 = Me$ (**bb**); $R^1 = R^2 = H$, $R^3 = MeO$ (**bc**);
$R^1 = F$, $R^2 = R^3 = H$ (**bd**), $R^1 = Me$, $R^2 = R^3 = H$ (**be**),
$R^1 = MeO$, $R^2 = R^3 = H$ (**bf**), $R^1 = H$, $R^2 + R^3 = (CH_2)_4$ (**bg**)



R^1, R^5 = H, Me; R^2 = Me, CH_2NMe_2, $CH_2NH(Me)$, CH_2OH; R^3, R^4 = H, Br



108 (Remantadine)

Table 2. Anti-Chikungunya virus activity and cytotoxicity of several 5-(hydroxymethyl)-1-methyl-1*H*-indole-3-carboxylic acid derivatives.[64]

Compound	R	Ar	X	CC_{50} /μM	EC_{50} /μM	SI
104a	Et	Ph	S	563 ± 12	> 157	3.6
104b	Et	4-$MeOC_6H_4$	S	ND	> 674	–
104c	Et	4-FC_6H_4	S	ND	> 691	–
104d	Et	4-$F_3CC_6H_4$	S	ND	> 557	–
104e	Et	4-$F_3COC_6H_4$	S	464 ± 18	81.9 ± 12	5.7
104f	Et	2,4-$F_2C_6H_3$	S	ND	> 654	–
104g	Et	2,6-$Cl_2C_6H_3$	S	104 ± 12	35 ± 8	2.9
104h	Bu^t	Ph	S	NC	NA	–
104i	Bu^t	4-$MeOC_6H_4$	S	NC	NA	–
104j	Bu^t	4-FC_6H_4	S	35 ± 8	14.4 ± 1.3	2.4
104k	Bu^t	4-$F_3CC_6H_4$	S	102 ± 39	11.0 ± 1.3	9.0
104l	Bu^t	4-$F_3COC_6H_4$	S	47 ± 18	28 ± 7	1.7
104m	Bu^t	2,4-$F_2C_6H_3$	S	NC	NA	–
104n	Bu^t	2,6-$Cl_2C_6H_3$	S	33 ± 4	18.5 ± 3	1.8
104o	Bu^t	4-ClC_6H_4	S	48 ± 7	11.0 ± 3	4.4
104p	Bu^t	2,4,6-$Me_3C_6H_2$	S	NC	NA	–
104q	Bu^t	2-$F_3CC_6H_4$	S	ND	> 492	–
105a	Et	Ph	S(O)	172 ± 20	32 ± 3	5.4
105h	Et	2,6-$Cl_2C_6H_3$	S(O)	203 ± 8	85 ± 4	2.4
105i	Bu^t	Ph	S(O)	NC	NA	–
105k	Bu^t	4-FC_6H_4	S(O)	527 ± 28	80 ± 11	6.6
105l	Bu^t	4-$F_3CC_6H_4$	S(O)	> 685	115 ± 1.2	5.9
105m	Bu^t	4-$F_3OCC_6H_4$	S(O)	180 ± 17	37 ± 4	4.9
105r	Bu^t	2-$F_3CC_6H_4$	S(O)	> 468	32 ± 1.1	14.6
105s	Bu^t	2,6-$Cl_2C_6H_3$	S(O)	397 ± 24	30 ± 4	13.2
Arbidol				161 ± 18	35 ± 8	4.6

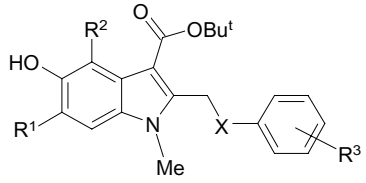
Note. ND is not determined, NA is not active, NC is not possible to calculate, SI is selectivity index, EC_{50} is cytotoxic concentration that cause 50% cell lethality.

unchanged, indicating that these compounds have been designed according to the concept of pharmacophore similarity. Data on antiviral activity and cytotoxicity of compounds **104**, **105** are summarized in Table 2.[64]

These studies led to identification of two hit compounds, racemic *tert*-butyl 2-[(arylsulfinyl)methyl]-5-(hydroxymethyl)-1-methyl-1*H*-indole-3-carboxylates **105r**,**s**.

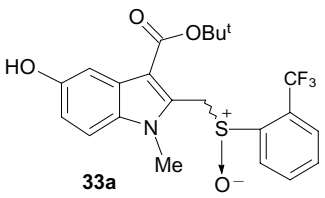
These two substances proved to be as active as Arbidol, but having a higher therapeutic index. However, the corresponding substances have their own peculiarities in biological activity. 2,6-Dichloro-substituted sulfide analogue **104n** is a little more active and 12-times more cytotoxic than the corresponding sulfoxide **105s**. On the other hand, 4-trifluoromethyl-substituted sulfide derivative **104k** was 10-times more active and 7-times more cytotoxic than the sulfoxide one (**105l**). Replacement of the *tert*-butyl residue by the ethyl group in the ester moiety of 2,6-dichloro-substituted sulfoxide resulted (**105s**) in a decrease in anti-

Structures 32, 33, 105

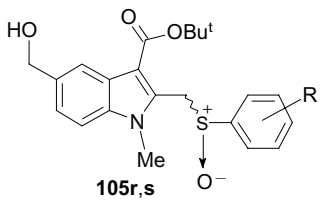


29bh – bk, **32f – k**

R^1 = H, Br; R^2 = H, CH_2NMe_2; R^3 = 4-F, 4-Cl, 4-CF_3, 2,6-Cl_2, 2-CF_3; X = S, S(O)



33a



105r,**s**

R = 2-CF_3 (**r**), 2,6-Cl_2 (**s**)

Table 3. Anti-Chikungunya virus activity and cytotoxicity of several *tetr*-butyl 5-(hydroxymethyl)-1-methyl-1*H*-indole-3-carboxylates.[57]

Compound	R^1	R^2	R^3	X	CC_{50} /μM	EC_{50} /μM	SI
29ac	Br	CH_2NMe_2	2,6-Cl_2	S	17	⩾17	—
29af	H	CH_2NMe_2	2,6-Cl_2	S(O)	9.2	4.1	2.2
29ag	H	CH_2NMe_2	2-CF_3	S(O)	66	22	3
29ah	Br	CH_2NMe_2	2-CF_3	S(O)	56	12	4.6
32af	H	H	4-CF_3	S	11	3.6	3.1
32ag	H	H	2,6-Cl_2	S	7.8	2.9	2.7
32ah	H	H	2-CF_3	S	19	3.4	4.1
32ai	Br	H	2-CF_3	S	26	9.6	2.7
32aj	H	H	4-F	S	11	4.5	3.2
32ak	H	H	4-Cl	S	15	4.8	3.2
32al	Br	H	2,6-Cl_2	S	13	5.7	2.3
32am	H	H	4-CF_3	S(O)	24	13	1.9
32an	H	H	2,6-Cl_2	S(O)	151	20	7.6
32ao	H	H	2-CF_3	S(O)	156	6.5 ± 1	22
32ap	Br	H	2-CF_3	S(O)	26	9.6	2.7
32aq	H	H	4-F	S(O)	> 100	17 ± 3	> 5.7
32ar	H	H	4-Cl	S(O)	93	8.2 ± 6	11
Arbidol					161 ± 18	35 ± 8	4.6

viral activity and increase in cytotoxicity of the resulting compound (**105h**).

These data indicate the importance of sulfide to sulfoxide oxidation (an interchange of functional groups according to Sheridan's criterion[80]), together with a crucial role of the alcohol residue in the ester moiety. The latter was mainly neglected in previous works on the design of biologically active Arbidol derivatives.

A recent work from the same team of researchers led to a series of more close Arbidol structural analogues **29ae** – **ah**, **32af** – **ak** which appeared to be highly active against Chickungunya virus.[57]

Data on antiviral activity and cytotoxicity of these compounds are summarized in Table 3.

It is remarkable that the most toxic and, in general, the least active compounds **29ag**,**ah** beared the [(dimethylamino)methyl] group at C(4) of the indole nucleus. On the contrary, the most active compounds were sulfides **32ag**,**ah**.

The high therapeutic index (22) was observed for sulfoxide **32ao**.

It is to be noted that bromination of the C(6) position of the indole heterocycle resulted in a decrease of antiviral activity. These data suggest once again that both the Mannich-base moiety and the bromine atom are controversial substituents in Arbidol analogues in regard to antiviral activity and cytotoxicity.

3.4. Search for novel anti-herpes and anti-hepatitis B and C drugs among Arbidol derivatives

The discovered ability of Arbidol to block replication of hepatitis B[114–116] and C[100] viruses initiated active works in this direction. They resulted in development of a novel drug candidate, called 'Imidol' (**28a**), undergoing currently preclinical trials in China.[79]

The first indole derivatives from this series were designed and synthesized by structural optimization of Arbidol.[41,44,50] The main changes in the structure of the parent compound comprised:

1. Structural variations of the amino group substitution in the Mannich-base moiety at the C(4) atom of the indole core.[117]

2. Oxidation of the bridged sulfur atom to sulfoxide or sulfone.

3. Variation of different substituents in the thiophenol moiety.

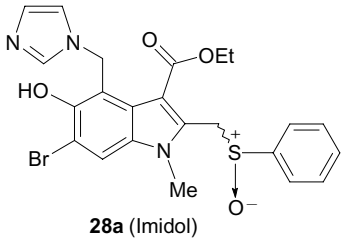
In other words, the authors perfomed the simplest and stereotypical transformations, without deep modification of the Arbidol structure. Interestingly, Lamivudine (**109**) was used as an external standard for comparison of antiviral activity and cytotoxic properties in these studies.[118]

This choice was surprising because Lamivudine is an anti-HIV drug used only as a supportive therapy in persons suffering from hepatitis. In this respect, it seemed to be much more reasonable to perform a direct comparison with the approved anti-hepatitis drugs such as Telbivudine (**110**),[118] Entecavir (**111**),[119,120] *etc*.

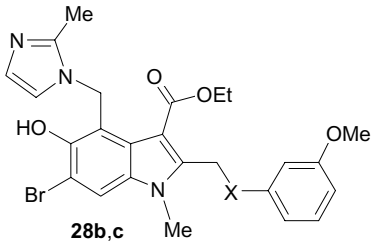
Anyhow, the vast majority of the tested compounds appeared to be inactive at all,[121] while their cytotoxic properties were well marked [3 – 200-fold more toxic than Lamivudine (**109**)]. Compounds **28b**,**c** and **112** turned out to be the most cytotoxic.[121]

For illustrative purposes, compounds **28d**,**e**, **30c**, **113a** being the most active, have CC_{50} (50% cytotoxic concentration) values in the range of 6.5 – 8.0 μmol, and EC_{50}

Structures 28, 30, 100, 109 – 113

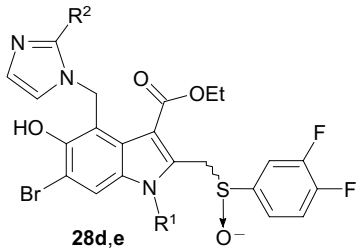


28a (Imidol)



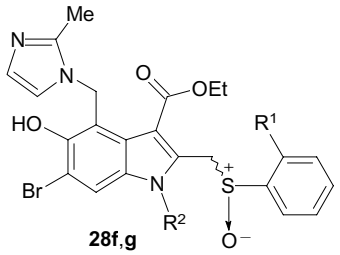
28b,**c**

X = S (**b**), S(O) (**c**)



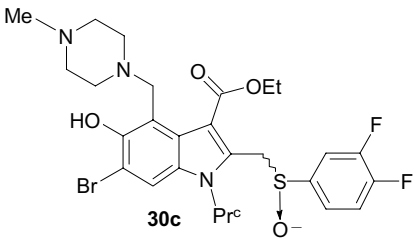
28d,**e**

28d: $R^1 = R^2 = Me$; **28e**: $R^1 = Pr^c$, $R^2 = H$

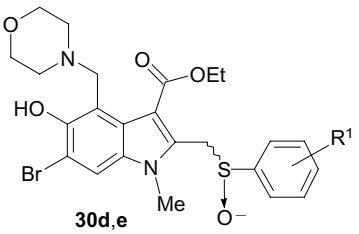


28f,**g**

28f: $R^1 = H$, $R^2 = Me$; **28g**: $R^1 = F$, $R^2 = Pr^c$

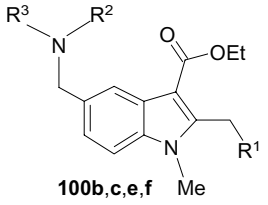


30c



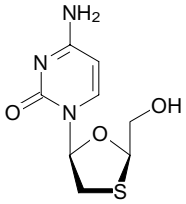
30d,**e**

R^1 = 4-F (**d**), 3-Cl (**e**)

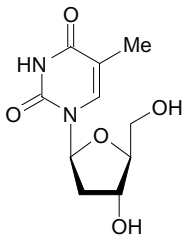


100b,**c**,**e**,**f**

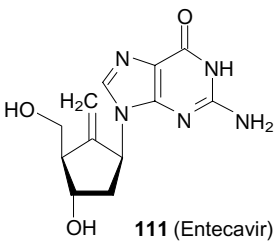
100b: $R^1 = S(O)_2Ph$, $R^2 + R^3 = (CH_2)_4$;
100c: $R^1 = S(O)_2Ph$, $R^2 + R^3 = (CH_2)_2N(Me)(CH_2)_2$;
100e: $R^1 = H$, $R^2 = R^3 = Me$; **100f**: $R^1 = H$, $R^2 + R^3 = (CH_2)_4$



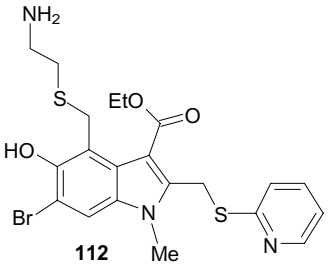
109 (Lamivudine)



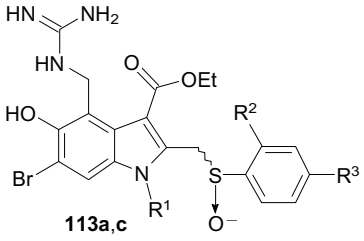
110 (Telbivudine)



111 (Entecavir)



112



113a,**c**

113a: $R^1 = Pr^c$, $R^2 = H$, $R^3 = F$;
113b: $R^1 = Me$, $R^2 = OMe$, $R^3 = H$

(50% effective concentration) values in the range of 3.6 – 3.7 μmol.

Interestingly, introduction of fluorine atoms into the benzene ring of the thiophenol moiety, together with cyclopropyl substitution at the indole nitrogen enhances antiviral activity. In these compounds, the imidazole and guanidine moieties can be considered as bioisosteric. Moreover, the nitrogen atoms of the piperazine ring in 4-[(4-methylpiperazin-1-yl)methyl]-substituted compounds can play the role of N(1) and N(3) atoms of imidazole/guanidine residues. The highest therapeutic indices have been observed for compounds **30d**,**e**.

On the other hand, these compounds showed rather moderate activity as antivirals.

Their novel analogues were designed using a 3D QSAR [49] approach that led to identification of equipotent, but less cytotoxic substances such as compounds **28f**,**g**.

Despite the promising results, these studies have not provide insight into the true configuration of the chiral sulfur atom in the sulfoxide moiety.

It is difficult to say why Imidol (**28a**) became a compound of choice for preclinical and clinical trials. In fact, it has quite moderate 50% inhibitory concentration of 5 μmol (Ref. 49) [another data, 0.75 μmol (Ref. 122)]. Probably, the relative availability or better synthetic feasibility of the starting compounds weighted in on, making Imidol more attractive in terms of scalable production.

In addition to hepatitis B virus inhibitory activity, Arbidol (**1**) also possesses pronounced antiviral properties against hepatitis C virus (IC_{50} 1 – 2 μmol).[100] Unfortunately, an Achilles heel of Arbidol is still its high cytotoxicity. Italian scientists reported several Arbidol analogues (**100**,**c**,**e**) with potent hepatitis C inhibitory activity.

Although these substances were 3 – 4-times less active than their prototype, they showed much lower cytotoxicity.

It should also be noted that structures **100b**,**c** bear the phenylsulfonyl moiety, while the third one (**100e**) is devoid of this substituent. Taking into consideration such a clear difference in the chemical structures together with virtually the same level of antiviral activity, it can be assumed that compounds **100b**,**c** may serve as prodrugs transforming metabolically into the active substances. The possible way of such activation may comprise, *e.g.*, the hydrolytic cleavage of the phenylsulfonyl group, by analogy with metabolic transformations of Arbidol. It is also notable that related compounds (**100b**,**f**,**e**, as well as Arbidol *per se*) have been reported as inhibitors of Herpes virus replication.[123]

Phenylsulfonyl substituted compound **110b** showed the most prolonged effect. All the tested compounds influenced the cytokin expression by host cells, thus activating a cellular response to the viral invasion. Recent data also supported an idea that these substances display immune-stimulating activity.

3.5. Arbidol derivatives as inhibitors of HIV replication

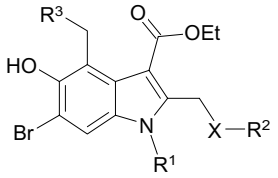
A number of structurally diverse indole derivatives are endowed with anti-HIV-1 activity.[124]

A limited series of close Arbidol analogues studied by Gong *et al*. have been characterized as non-nucleoside inhibitors of HIV protease.[121] This enzyme plays an important role in the whole HIV replication cycle, being responsible for the cleavage of Gag-Pol viral polypeptide into separate functional proteins. Inhibition of protease activity leads to the production of non-virulent HIV particles. The authors reported that the synthesized compounds displayed protease inhibitory activity in a micromolar range, but, surprisingly, no data for the reference compound Indinavir (**114**) have been presented in this work.[125]

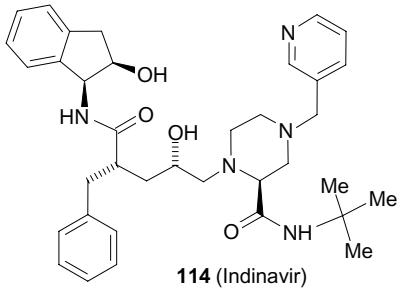
Data on protease inhibitory activity of these novel substances (as salts with muriatic acid) are presented in Table 4.

The activity data for the described compounds were obtained using the high-throughput screening technique. The compounds *per se* were designed using the strategy of

Structures 28 – 30, 133, 144



28a,**f**,**h**,**i**; **29bl**,**bm**; **30b**,**d** – **g**; **113a**,**c**



114 (Indinavir)

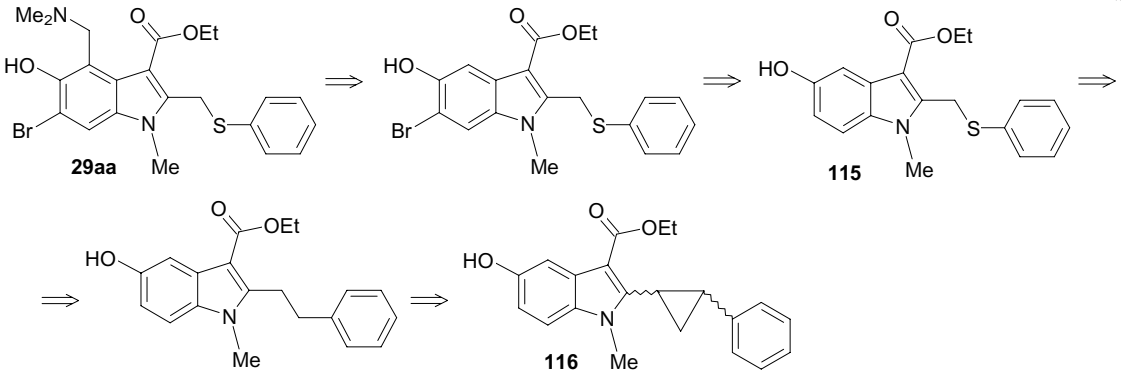
Arbidol modification according to Sheridan's criterion, along with the concept of pharmacophore similarity. Due to the obvious structural diversity of the tested compounds and discontinuity of this series, it is difficult to reveal the reliable structure – activity relationships. But, anyhow, introduction of the cyclopropyl group at the indole nitrogen seems to be more favourable than methylation in terms of activity. Also, 1*H*-imidazol-1-yl or guanidine moieties are likely to be the substituents of choice for the Mannich base portion. On the other hand, protease inhibitory activity can be increased by introduction of *ortho*/*para* directors into *meta*- and *para*-positions of the thiophenol residue, while substitution of its *ortho*-position gives a negative effect.

An alternative approach to structural design and optimization of Arbidol analogues has been proposed by our group (Scheme 21).[85,86] First of all, we excluded the (dimethylamino)methyl group as a potential toxicophore from the parent structure. Then, the bromine substituent was

Table 4. *In vitro* HIV-1-protease inhibitory activity of a series of ethyl 1-(cyclo)alkyl-4-(aminomethyl)-6-bromo-5-hydroxy-1H-indole-3-carboxylates **28** – **30**, **113**.[121]

Compound	R^1	R^2	R^3	X	IC_{50} /μg ml^{-1}	Inhibition (%) (concentration 250 μg ml^{-1})
28a	Me	Ph	1*H*-Imidazol-1-yl	S(O)	–	37.5
28f	Me	Ph	2-Methyl-1*H*-imidazol-1-yl	S(O)	156.07	55.1
28h	Pr[c]	3,4-$F_2C_6H_3$	1*H*-Imidazol-1-yl	$S(O)_2$	12.69	97.8
28i	Pr[c]	4-FC_6H_4	2-Methyl-1*H*-imidazol-1-yl	S(O)	63.5	75.7
29ai	Me	4-FC_6H_4	4-Methylpiperazin-1-yl	S	–	27.6
29aj	Pr[c]	4-FC_6H_4	4-Methylpiperazin-1-yl	S	133.7	63.9
30d	Me	4-FC_6H_4	Morpholin-4-yl	S(O)	–	37.4
30f	Me	2-MeC_6H_4	Morpholin-4-yl	S(O)	–	41.0
30g	Me	3,4-$F_2C_6H_3$	4-Methylpiperazin-1-yl	S(O)	–	19.3
30h	Me	3-$MeOC_6H_4$	Me_2N	$S(O)_2$	26.43	98.0
30i	Me	2-Py	2-Aminoethyl	S(O)	–	30.1
113a	Pr[c]	4-FC_6H_4	Guanidin-1-yl	S(O)	23.96	99.3
113c	Me	4-FC_6H_4	Guanidin-1-yl	S(O)	70.11	75.3

Scheme 21



eliminated (compound **115**) since the selectivity of bromination was questionable. And, what is the most important, the (phenylsulfanyl)methyl moiety has been totally reconstructed in order to get rid of toxic thiophenol in the synthetic scheme and also to remove the alkyl(aryl)sulfide motif as a potential toxicophore. The latter has been transformed into the 1,2-cyclopropylidene moiety during two sequential replacements to give indole **116**.

Introduction of the 1,2-cyclopropylidene moiety was based upon an idea to reconstruct the 3D pharmacophore model which still remained unknown for us. An attempt was made to use a certain conformational restriction to switch the binding mode of the ligand with a potential target from Koshland's induced-fit model [126] to 'lock and key' Fischer model.[127] The aim of conformational restrictions was to answer the question whether *cis*- or *trans*-mutual orientation of indole and benzene rings is more favourable in terms of antiviral activity. On the other hand, conformationally constrained derivatives had to diminish the entropy losses of energy during the interaction of a ligand with its molecular target.

A similar approach to another type of indole derivatives has been successfully utilized by different authors [128-133] for a targeted design of conformationally constrained analogues of a variety of medicines and experimental drug-like molecules.

The possibility to replace a SCH_2-linker with the 1,2-vinylidene group looked problematic from the pharmacological point of view. Specifically, it could result in a decreased solubility, potential *cis*,*trans*-isomerization under UV irradiation and enhanced hidden toxicity due to ability to act as a Michael acceptor. Thus, Lovering *et al.* have demonstrated that increasing the number of unsaturated bonds and planar moieties in a molecule decreases its chances for success as a drug candidate.[134]

So, we have prepared a number of compounds **41**, **43** bearing the *trans*-2-phenylcyclopropyl group at the C(2)/N(1) (regioisomer) positions of the ethyl 1- or 5-hydroxy-2-methyl-1*H*-indole-3-carboxylate core, together with a byproduct (**44**).

Despite the relative simplicity of the 2-(2-phenylcyclopropyl-1)-1*H*-indole scaffold of these substances, it appeared to be a new molecular construction which has been previously described only as a hidden substructure in cytotoxic polycyclic indole-quinones.[135] While testing compounds **41**, **43**, **44** for their anti-HIV-1/2 activity and cytotoxicity, HIV-1 inhibitory properties of Arbidol (**1**) have been discovered for the first time. These data are summarized in Table 5.[86]

The shown data clearly demonstrate much lower cytotoxicity together with higher activity of compounds **41**, **43**, **44** in comparison with Arbidol. Two of them (**41**, **44**) are able to inhibit both HIV-1 and HIV-2, what is a unique feature for non-nucleoside derivatives. Moreover, they exhibit antiviral activity against both viruses in a similar range of low micromolar concentrations. These findings suggest that these compounds are promising candidates for further development as broad-spectrum antiretroviral agents. Of note, the clockwise rotation of both C(5) hydroxyl and C(2) *trans*-2-phenylcyclopropyl to C(4) and

Structures 41, 43, 44

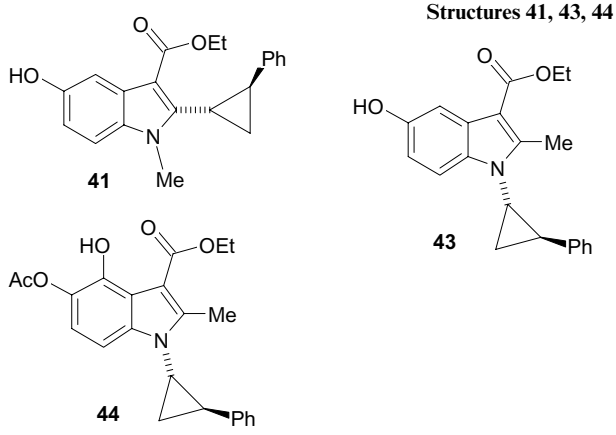


Table 5. Anti-HIV-1 and HIV-2 activity of Arbidol and compounds **41**, **43**, **44** in infected MT-4 lymphoid tissue cell culure.

Compound	EC_{50} [a] μmol HIV-1	EC_{50} [a] μmol HIV-2	CC_{50} [b] μmol	SI [c] HIV-1	SI [c] HIV-2
Arbidol	20.32	> 8.4	23	1.1	< 2.7
41	3.58	5.4	> 298	> 83.3	> 55.2
43	5.91	> 250	> 250	> 42.3	–
44	6.37	11.09	50	~ 7.8	~ 4.5

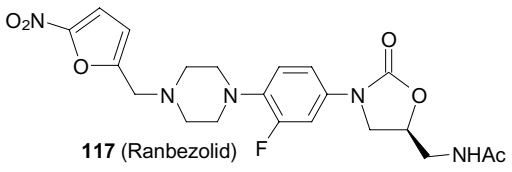
[a] The effective concentration of compound leading to 50% inhibition of HIV cytopathic effects.
[b] The cytotoxic concentration of compound, at which only 50% of cells survive.
[c] The ratio of CC_{50} to EC_{50}.

N(1) positions of the indole ring, respectively, preserves anti-HIV-2 activity, which is lost in the opposite case C(5) and N(1) substitutions, respectively.

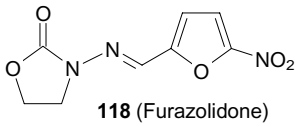
3.6. Arbidol – Ranbezolid hybrids as novel antibacterials

The underlying idea for preparation of hybrid antimicrobial agents is based on the established efficiency of Arbidol in combinational therapy of pneumonia.[136] As the antibacterial, Ranbezolid (**117**)[137,138] was used, being an effective antibacterial agent with minimum of adverse side effects, and a MAO inhibitor, like a number of other nitrofuran-derived antibacterials, for example, Furazolidone **118**.[139]

Structures 117, 118



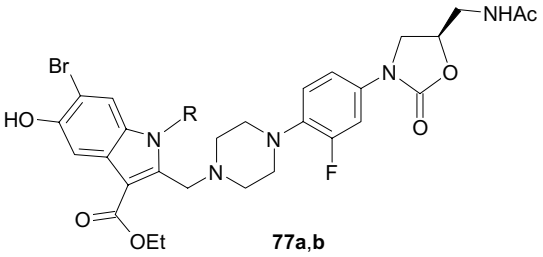
117 (Ranbezolid)



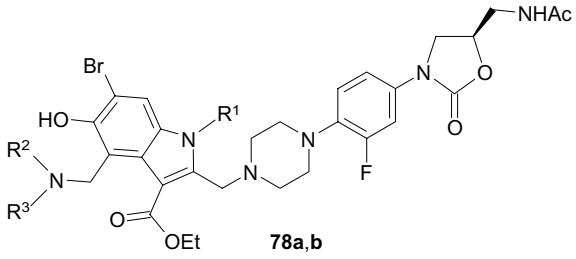
118 (Furazolidone)

Guided by this idea, Chinese scientists attempted to develop a novel class of effective antibacterial agents as a continuation of their studies of the oxazolidinone family of antibacterials[140,141] possessing the positive effects of both Arbidol (**1**) and Ranbezolid (**117**) but devoid of unwanted MAO-inhibitory activity of the latter. A number of Arbidol – Ranbezolid hybrids **77**, **78** have been prepared and tested for antibacterial activity.[98]

Structures 77, 78, 119

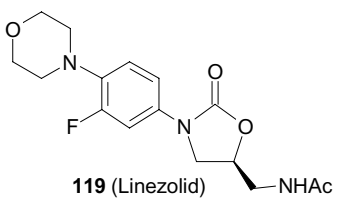


77a,**b**



78a,**b**

77: R^1 = Me (**a**), Pr^c (**b**); **78**: R^1 = Me, NR^2R^3 = morpholin-4-yl (**b**); R^1 = $CH_2-CH{=}CH_2$, $CH_2CH(Me)_2$, NR^2R^3 = pyrrolidin-1-yl, 4-methylpiperazin-1-yl



119 (Linezolid)

Compounds **77**, **78** and Linezolid were tested in the form of muriatic acid salts. It was observed that three novel compounds are about as active as Linezolid (**119**) against *Staphylococcus epidermidis*. At the same time, only compounds **77a** and **78a** proved to be half as active as Linezolid (**119**) against *Staphylococcus aureus* and can be considered as hit compounds.

It was found that the presence of a Mannich-base residue at the indole C(4) position is not crucial for the activity. On the other hand, replacing the N(1) methyl group with cyclopropyl one in compounds **77a**,**b** led to a substance twice less active than Linezolid (**119**) against *S. epidermidis* and as active as the reference drug against *S. aureus*. It would be interesting to assess antiviral and anti-inflammatory properties of the obtained hybrids, but these data are not available yet.

3.7. Arbidol structural analogues as lypoxygenase-5 inhibitors

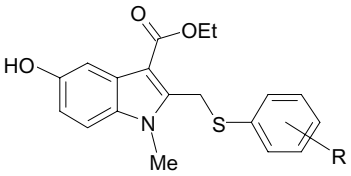
One of the major features of the pharmacological profile of Arbidol is its anti-inflammatory activity. And it is no a little wonder that Arbidol has been patented as a topical drug for the treatment of skin inflammatory reactions.[143] Probably, this feature of Arbidol is due to its ability to inhibit lypoxygenase-5 activity.[144–146] This enzyme belongs to a group of iron-containing proteins catalyzing the oxidation of *cis,cis*-1,4-pentadiene moiety in polyunsaturated fatty acids.[147]

Namely, 5-LOX is a key enzyme in the conversion of arachidonic acid (AA) to leukotriene A4 (LTA4) in two succesive steps: oxygenation of AA affords (5S)-hydroperoxy-6,8,11,14(*E,Z,Z,Z*)-eicosatetraenoic acid (5-HPETE), and subsequent dehydration of 5-HPETE yields the unstable epoxide LTA4 which is then converted to either LTB4 by LTA4 hydrolase or cysteinyl-leukotrienes (LTC4, D4 and E4) through conjugation with glutathione catalyzed by LTC4 synthases. In fact, they primarily mediate inflammatory and allergic reactions and are involved in the onset of inflammatory diseases as well as cardiovascular disorders. The only inhibitor of 5-LOX, being currently in clinical use, is Zileuton (**120**),[148] a benzothiophene derivative produced and marketed by Abbott.

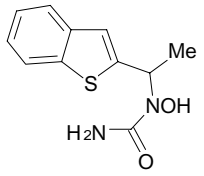
Zileuton (**120**) differs significantly in its structure from Arbidol (**1**), but both compounds seem to have the same biological target. Peduto *et al.*[59] studied lypoxygenase-5 inhibitory activity of a series of indoles **32** structurally similar to Arbidol, using Zileuton (**120**) as a reference compound.

Compounds **32** represent ethyl 5-hydroxy-1-methyl-2-[(phenylsulfanyl)methyl]-1*H*-indole-3-carboxylate derivatives. It was shown that their 50% inhibitory concentration against recombinant lypoxygenase-5 ranged 0.7 – 5.7 μmol. The least active compounds **32ae**,**aj**,**af** beared an unsubstituted, *para*-fluorinated or *para*-trifluoromethyl-substituted thiophenol moiety. At the same time, introduction of activating groups into *ortho*-positions of the phenyl ring significantly improved activity of the resulting compounds, especially in the case of 2,4,6-trimethyl- and 2,6-dimethylphenyl-substituted analogues.

Structures 32, 120



32ae,**aj**,**at**,**ah**,**av**,**as** – **ac**



120 (Zileuton)

R^1 = Ph (**ae**), 4-FC_6H_4 (**aj**), 4-$F_3CC_6H_4$ (**af**), 2-$F_3CC_6H_4$ (**ah**), 2,6-$Cl_2C_6H_3$ (**an**), 4-$F_3COC_6H_4$ (**as**), 2,4-$F_2C_6H_3$ (**at**), 2,4,6-$Me_3C_6H_2$ (**au**), 3,5-$Me_2C_6H_4$ (**av**), 4-$MeOC_6H_4$ (**aw**), 3-ClC_6H_4 (**ay**), 2,6-$Me_2C_6H_3$ (**az**)

The similar situation was observed for the intact enzyme, but in these tests 4-(trifluoromethyl)phenyl- (**32t**) and 3-chlorophenyl-substituted compounds **32ab** appeared to be almost inactive. Hit compound **32av** showed IC_{50} values against the intact and recombinant enzymes of 0.23 and 0.7 μmol, respectively. In the same tests, IC_{50} values of Zileuton **120** were 0.7 and 0.6 μmol. Comparison of the prescribed daily doses of Zileuton **120** (up to 2.4 grams) and Arbidol (**1**) (up to 0.8 grams) brings up to a conclusion, that a complex pharmacological profile of the latter may be also based upon its lypoxygenase-5 inhibitory properties.

Structural modification of Zileuton (**120**) performed by Karg *et al.* provided novel structural analogues **50** of Arbidol showing potent lypoxygenase-5 inhibitory activity.[94]

Among ethyl 2-anilino-5-hydroxy-1*H*-indole-3-carboxylate derivatives **50**, 2-(3-chlorophenylamino)-substituted compound **50v** has been identified as a lead one. It showed IC_{50} values of 2.4 and 0.3 μmol (*cf.* 0.7 and 0.6 μmol for Zileuton), against the intact and recombinant lypoxygenase-5, respectively.

A deeper structural modification of the Arbidol molecular scaffold resulted in a series of 2-benzylindoles (**45**, **46**).[45]

Compound **45a** proved to be a highly active lypoxygenase-5 inhibitor with IC_{50} values of 0.23 and 0.686 μmol against the intact and recombinant enzymes, respectively.

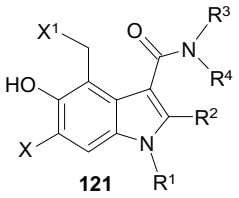
Replacement of the 3-chlorophenyl moiety with different thiophenol residues in lead compound **45a** performed by an Italian group of scientists led to a series of active compounds **45r** – **z**.

Among them, the hit compound **45w** bearing 2,6-dichlorothiophenol moiety, demonstrated IC_{50} values of 0.17 and 0.19 μmol against the recombinant and intact enzyme, respectively.

The obtained compounds **45r** – **z** showed a remarkable anti-inflammatory activity *in vivo*, together with the ability to inhibit PGE synthase *in vitro*. It appears that in this case, as well as in the case of antiviral Arbidol congeners, the benzylic residue at the C(2) position is more preferable than the (phenylsulfanyl)methyl group.

Earlier, Tahara *et al.*[149] have prepared a series of 5-hydroxy-1*H*-indole-3-carboxamides **121** and screened them for lypoxygenase-5 inhibitory properties (intact enzyme).

Structures 121



121

R^1 = H, Bu, $(CH_2)_2$Ph, Ph, Hex, Bn, Pent, 4-MeC_6H_4; R^2 = Me; R^3 = H, Me, Et, Bu; R^4 = Bu, n-C_8H_{17}, 4-Py, Hex, Ph, $(CH_2)_2$Ph, Pent, Bn, Oct, Et; X = H, Br, acetyl, propionyl; X^1 = piperidin-1-yl

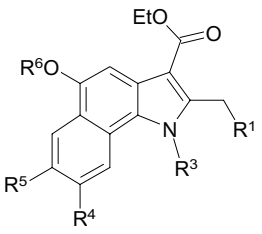
Compounds **121** simulated the 'indole' part of the Arbidol molecule. Their synthesis was performed according to Scheme 22.

Among the screened compounds, two hit compounds **121a**,**b** have been identified.

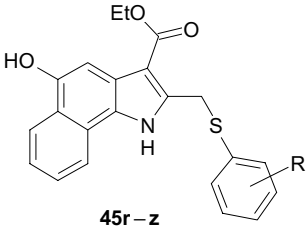
Their structures demonstrate that an 'improper' location of the phenyl ring leads to decreased activity as compared to 2-benzylindoles (*vide supra*).

In general, the presented data undoubtedly suggest that further search for new lypoxygenase-5 inhibitors among the structural analogues of Arbidol is a promising strategy for identification of novel anti-inflammatory drugs for both topical and systemic therapy.

Structures 45 – 47, 50

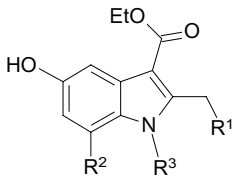


45a – **i**,**l**,**m**; **46a**,**b**



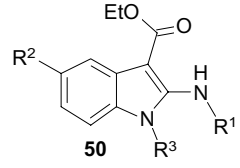
45r – **z**

45a: R^1 = 3-ClC_6H_4, R^3 = R^4 = R^5 = R^6 = H;
45b: R^1 = 2-ClC_6H_4, R^3 = R^4 = R^5 = R^6 = H;
45c: R^1 = 4-ClC_6H_4, R^3 = R^4 = R^5 = R^6 = H;
45d: R^1 = 3-FC_6H_4, R^3 = R^4 = R^5 = R^6 = H;
45e: R^1 = 4-FC_6H_4, R^3 = R^4 = R^5 = R^6 = H;
45f: R^1 = 3-BrC_6H_4, R^3 = R^4 = R^5 = R^6 = H;
45g: R^1 = 3-$MeOC_6H_4$, R^3 = R^4 = R^5 = R^6 = H;
45h: R^1 = 4-$MeOC_6H_4$, R^3 = R^4 = R^5 = R^6 = H;
45i: R^1 = 4-$F_3CC_6H_4$, R^3 = R^4 = R^5 = R^6 = H;
45l: R^1 = 3-$ClC_6H_4CH_2$, R^3 = R^4 = R^5 = R^6 = H;
45m: R^1 = 4-$ClC_6H_4CH_2$, R^3 = R^4 = R^5 = R^6 = H;
45r: R = 3-Cl; **45s**: R = 2-Cl;
45t: R = 2-Me; **45u**: R = 2,3-Cl_2,
45v: R = 3,4-Cl_2; **45w**: R = 2,6-Cl_2;
45x: R = 2,6-Me_2, **45y**: R = 3,5-Me_2,
45z: R = 2,4,6-Me_3
46a: R^1 = 3-ClC_6H_4, R^3 = R^4 = R^5 = H, R^6 = Bz;
46b: R^1 = 3-ClC_6H_4, R^3 = R^4 = R^5 = H, R^6 = Me



47a,**b**

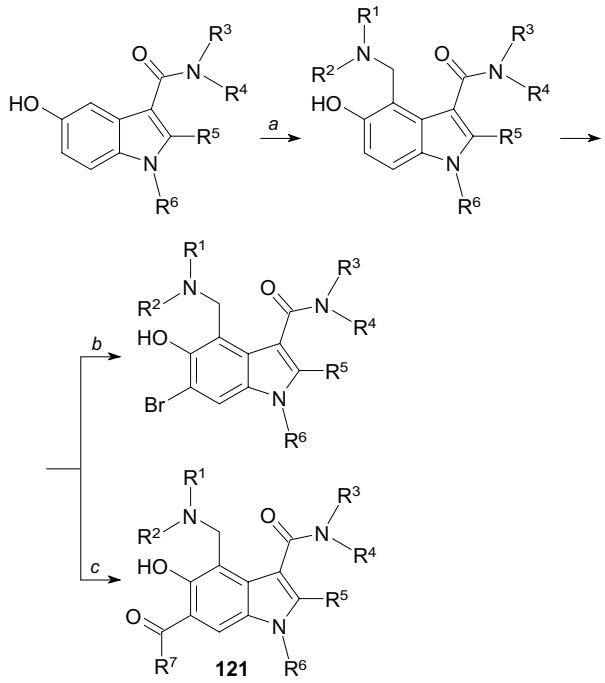
47a: R^1 = 3-ClC_6H_4, R^2 = Ph, R^3 = H;
47b: R^1 = 3-ClC_6H_4, R^2 = 4-PhC_6H_4, R^3 = H



50

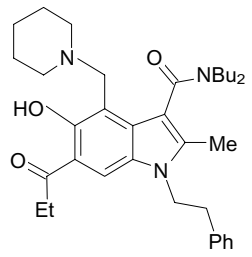
R^1 = 3-ClC_6H_4, 2-ClC_6H_4, 4-ClC_6H_4, 3-FC_6H_4, 3-BrC_6H_4, Bn; R^2 = H, OH; R^3 = H, Me

Scheme 22

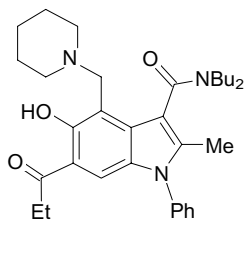


(**a**) 1) amines, CH_2O-H_2O, AcOH, Δ; 2) K_2CO_3, H_2O;
(*b*) 1) Br_2, AcOH; 2) K_2CO_3, H_2O;
(*c*) 1) $R^7C(O)Cl$, $AlCl_3$, $ClCH_2CH_2Cl$, Δ; 2) K_2CO_3, H_2O

Structures 121



121a (IC_{50} = 20 μM)

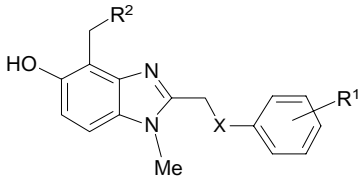


121b (IC_{50} = 19 μM)

4. Benzimidazole and imidazo[1,2-a]pyridine-based Arbidol analogues

During the investigations of the antiviral activity profile of Arbidol (**1**) and its structural analogues, it was established that this chemotype possesses promising hepatitis B virus inhibitory properties. So, one of Arbidol's close structural analogues, Imidol (**28a**)[79] (see part 3, 4 of this review), is under evaluation as a promising candidate for clinical use. The latter also belongs to the indole family, but the above-mentioned findings prompted the search for novel anti-HBV agents among the substances based on bioisosterically transformed heterocyclic cores. It is well known that the benzimidazole moiety can be considered as a privileged structure in targeted drug design and discovery.[150–152] Three series of benzimidazole-based bioisosteres of Arbidol have been prepared and studied. In the first series, 6-bromo-3-ethoxycarbonyl-1*H*-indole was replaced by the benzimidazole nucleus affording compounds **122** – **124**.[153]

Structures 122 – 124



122a – n, **123a – c**, **124a – c**

Compound	R^1	R^2	X
122a	H	NMe_2	S
122b	H	Pyrrolidin-1-yl	S
122c	H	Morpholin-4-yl	S
122d	H	4-Methylpiperazine-1-yl	S
122e	4-F	Pyrrolidin-1-yl	S
122f	4-F	4-Methylpiperazine-1-yl	S
122g	H	1*H*-Imidazol-1-yl	S
122h	H	2-Methyl-1*H*-imidazol-1-yl	S
122i	4-F	1*H*-Imidazol-1-yl	S
122j	4-Me	1*H*-Imidazol-1-yl	S
122k	4-Me	2-Methyl-1*H*-imidazol-1-yl	S
122l	4-MeO	1*H*-Imidazol-1-yl	S
122m	4-MeO	2-Methyl-1*H*-imidazol-1-yl	S
122n	3-MeO	2-Methyl-1*H* -imidazol-1-yl	S
123a	H	Morpholin-4-yl	S(O)
123b	H	1*H*-Imidazol-1-yl	S(O)
123c	4-Me	1*H*-Imidazol-1-yl	S(O)
124a	H	Morpholin-4-yl	$S(O)_2$
124b	H	1*H*-Imidazol-1-yl	$S(O)_2$
124c	4-Me	1*H*-Imidazol-1-yl	$S(O)_2$

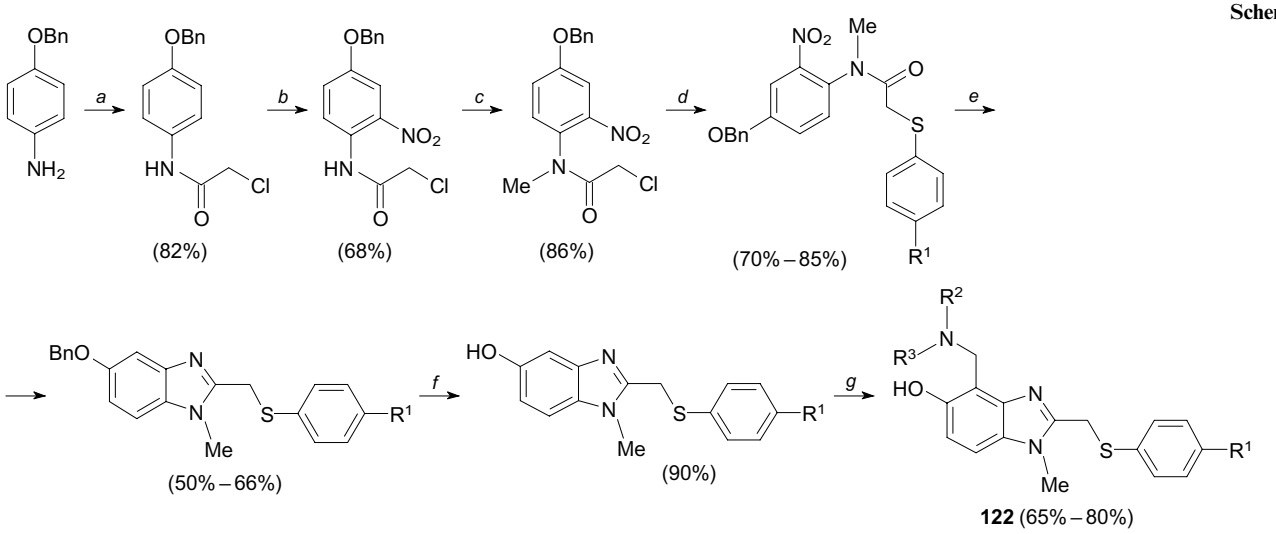
The target compounds were obtained using 4-(benzyloxy)aniline as a starting material, and a reductive benzimidazole ring closure as a key step in the total synthetic sequence (Scheme 23).[153]

Treatment of the corresponding 4-[(dimethylamino)-methyl]-1*H*-benzimidazoles **122** with hydrochlorides of either 1*H*-imidazole or 2-methyl-1*H*-imidazole led to substitution of the dimethylamino group with the desired heterocyclic moiety (Scheme 24).[153]

Oxidation of substituted 4-(aminomethyl)-5-hydroxy-1-methyl-2-[(phenylsulfanyl)methyl]-1*H*-benzimidazoles **122** with sodium peroxoborate in acidic medium or with hydrogen peroxide and sodium tungstate yielded the desired sulfoxides **123** and sulfones **124**, respectively, in good yields (Scheme 25).[153]

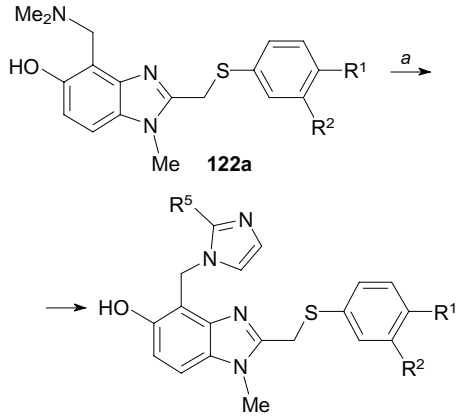
It should be mentioned that the direction of the Mannich reaction has not been established for a certainty, since no X-ray diffraction or correlation spectroscopy data were provided in the article. Also, it is not clear whether racemic sulfoxides or individual enantiomers were used in biological screening. The last two facts are very important in view of the SAR and are critical for the success of this methodology. Moreover, conversion of sulfides to sulfoxides and sulfones under the action of peroxides may also be of poor selectivity due to formation of *N*-oxides and *ortho*-quinones. Unfortunately, no information is given in the article about such chemical features. Biological data for the tested compounds indicate that the most active inhibitors of

Scheme 23



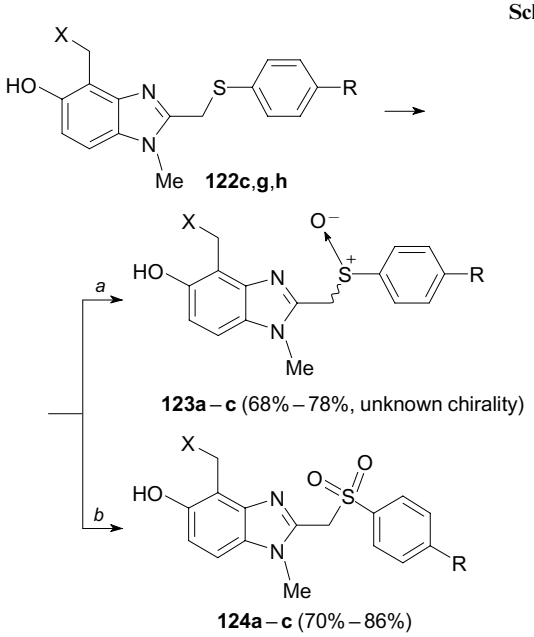
(*a*) $ClCH_2C(O)Cl$, C_5H_5N, CH_2Cl_2; (*b*) HNO_3, H_2SO_4, $CHCl_3$; (*c*) $(MeO)_2SO_2$, NaH, DMFA; (*d*) thiophenols, KOH, MeOH; (*e*) Fe, NH_4Cl, AcOH, MeOH; (*f*) 1) HCl, AcOH; 2) NH_4OH; (*g*) amines, $CH_2O - H_2O$, MeOH; **122a**: R^1 = H, R^2 = R^3 = Me; **122b**: R^1 = H, $R^2 + R^3 = (CH_2)_4$; **122c**: R^1 = H, $R^2 + R^3 = (CH_2CH_2)_2O$; **122d**: R^1 = H, $R^2 + R^3 = (CH_2CH_2)_2NMe$; **122e**: R^1 = F, $R^2 + R^3 = (CH_2)_4$; **122f**: R^1 = F, $R^2 + R^3 = (CH_2CH_2)_2NMe$

Scheme 24



(*a*) 1*H*-imidazole or 2-methyl-1*H*-imidazole hydrochloride, 1,4-dioxane; **122g**: R^1 = R^2 = R^5 = H; **122h**: R^1 = R^2 = H, R^5 = Me; **122i**: R^1 = F, R^2 = R^5 = H; **122j**: R^1 = Me, R^2 = R^5 = H; **122k**: R^1 = R^5 = Me, R^2 = H; **122l**: R^1 = MeO, R^2 = R^5 = H; **122m**: R^1 = MeO, R^2 = H, R^5 = Me; **122n**: R^1 = H, R^2 = MeO, R^5 = Me

Scheme 25



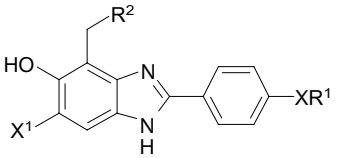
(*a*) 1) $NaBO_3 \cdot 4\,H_2O$, AcOH; 2) NH_4OH; (*b*) H_2O_2, Na_2WO_4, MeOH; **123a**: R^1 = H, X = $N(CH_2CH_2)_2O$; **123b**: R^1 = H, X = 1*H*-imidazol-1-yl; **123c**: R^1 = Me, X = 1*H*-imidazol-1-yl; **124a**: R^1 = H, X = $N(CH_2CH_2)_2O$; **124b**: R^1 = H, X = 1*H*-imidazol-1-yl; **124c**: R^1 = Me, X = 1*H*-imidazol-1-yl

HBsAg were sulfides **122d**,**f** bearing a 4-methylpiperazin-4-yl residue (IC_{50} = 27.0 and 10.7 μmol, respectively). At the same time, the most active HBV DNA replication inhibitors were 1*H*-imidazol-1-yl- and 2-methyl-1*H*-imidazol-1-yl-substituted derivatives (**122g** – **i**). The influence of *para*-fluorine substitution of the thiophenol moiety appeared to be negligible.

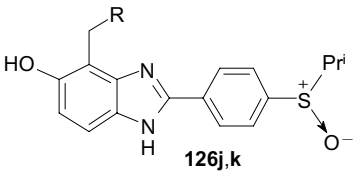
Another series of 5-hydroxy-1*H*-benzimidazoles **125**, **126** contained a phenyl ring directly attached to the second position of the heterocyclic nucleus while the sulfur functionality was attached to the *para*-position of the phenyl ring.[154]

In other words, these compounds possessed an upturned molecular moiety in the second position of the benzimidazole nucleus compared to the above mentioned chemotype. Also, in some cases the benzimidazole ring was fluorinated in the 6-position. The only compounds displaying the comparable activity against inhibition of HBsAg secretion were sulfoxides **126de** (IC_{50} = 16.5 and 32.1 μmol, respectively). On the other hand, the most potent inhibitors of HBeAg secretion were found to be sulfoxides **122j**,**k**

Structures 125, 126



125a – l, **126a – l**



126j,k

R = 1*H*-imidazol-1-yl (**j**), 2-methylimidazol-1-yl (**k**)

Compound	R^1	R^2	X	X^1	Compound	R^1	R^2	X	X^1
125a	Me	NMe_2	S	H	**126a**	Me	NMe_2	S(O)	H
125b	Me	Pyrrolidin-1-yl	S	H	**126b**	Me	Pyrrolidin-1-yl	S(O)	H
125c	Me	Morpholin-4-yl	S	H	**126c**	Me	Morpholin-4-yl	S(O)	H
125d	Et	Pyrrolidin-1-yl	S	H	**126d**	Et	Pyrrolidin-1-yl	S(O)	H
125e	Pr^i	Morpholin-4-yl	S	H	**126e**	Pr^i	Morpholin-4-yl	S(O)	H
125f	Me	NMe_2	S	F	**126f**	Me	NMe_2	S(O)	F
125g	Me	Pyrrolidin-1-yl	S	F	**126g**	Me	Pyrrolidin-1-yl	S(O)	F
125h	Me	Morpholin-4-yl	S	F	**126h**	Me	Morpholin-4-yl	S(O)	F
125i	Et	2-Methylimidazol-1-yl	S	H	**126i**	Et	2-Methylimidazol-1-yl	S(O)	H
125j	Pr^i	1*H*-Imidazol-1-yl	S	H	**126j**	Pr^i	1*H*-Imidazol-1-yl	S(O)	H
125k	Pr^i	2-Methylimidazol-1-yl	S	H	**126k**	Pr^i	2-Methylimidazol-1-yl	S(O)	H
125l	Pr^i	1*H*-Imidazol-1-yl	S	F	**126l**	Pr^i	1*H*-Imidazol-1-yl	S(O)	F

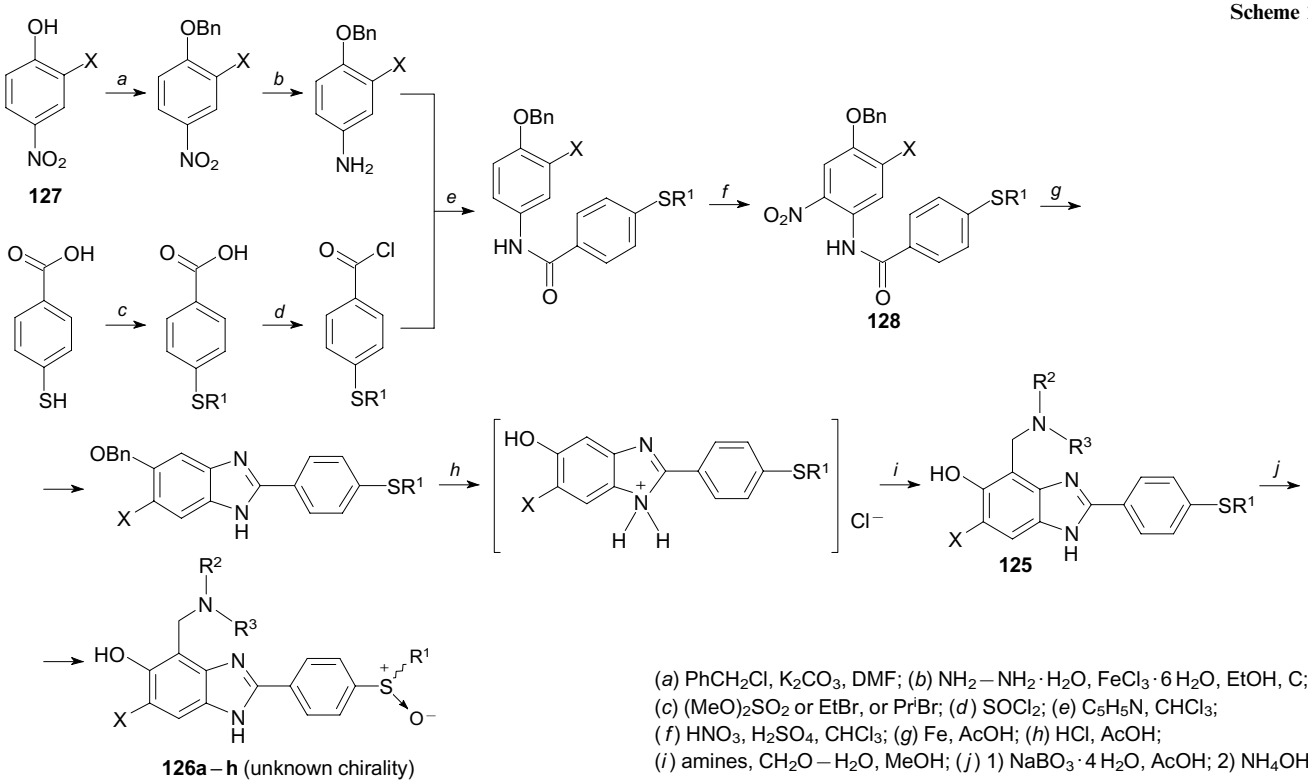
(IC_{50} = 6.8 and 5.2 μmol, respectively) bearing the [(1*H*-imidazol-1-yl)methyl] or [(2-methyl-1*H*-imidazol-1-yl)methyl] group at the benzimidazole C(4) atom.

Compounds **126** were synthesized using 4-nitrophenol **127** or its 2-fluorinated derivative as starting materials. Analogously to the above-mentioned series of benzimidazoles, the key synthetic step was a reductive heterocyclization of corresponding *N*-(2-nitrophenyl)benzamides **128** (Scheme 26).

In the case of fluorine-substituted compounds, the direction of nitration was questionable. The authors gave no reliable proofs for the selective formation of *N*-(2-nitrophenyl)benzamides *versus* their 6-nitrophenyl isomers. Moreover, the direction of aminomethylation was not elucidated. Steric configuration of the sulfoxide moiety in compounds **126d**,**e** remained unknown (Scheme 27).

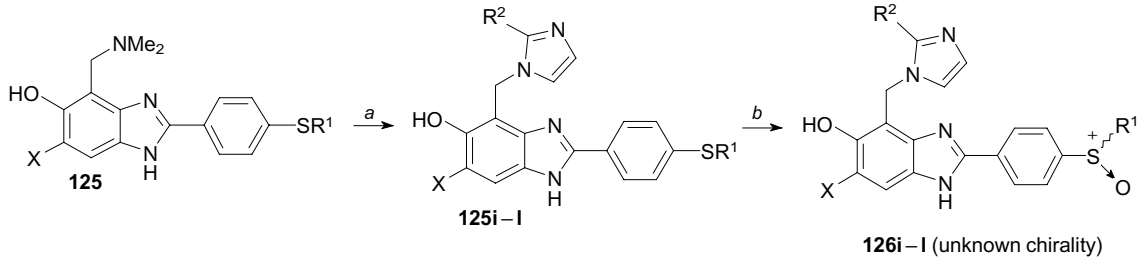
Another structurally relevant class of HBV inhibitors has been studied by Luo *et al.*[155] These compounds, similar

Scheme 26



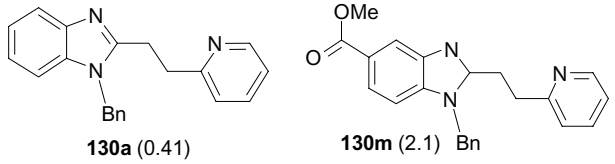
(*a*) $PhCH_2Cl$, K_2CO_3, DMF; (*b*) $NH_2-NH_2\cdot H_2O$, $FeCl_3\cdot 6H_2O$, EtOH, C; (*c*) $(MeO)_2SO_2$ or EtBr, or Pr^iBr; (*d*) $SOCl_2$; (*e*) C_5H_5N, $CHCl_3$; (*f*) HNO_3, H_2SO_4, $CHCl_3$; (*g*) Fe, AcOH; (*h*) HCl, AcOH; (*i*) amines, CH_2O-H_2O, MeOH; (*j*) 1) $NaBO_3\cdot 4H_2O$, AcOH; 2) NH_4OH

Scheme 27



(*a*) 1*H*-imidazole or 2-methyl-1*H*-imidazole hydrochloride, 1,4-dioxane, H_2O; (*b*) 1) $NaBO_3 \cdot 4\,H_2O$, AcOH; 2) NH_4OH;
126i: R^1 = Et, R^2 = Me, X = H; **126j:** R^1 = Pr^i, R^2 = H, X = H; **126k:** R^1 = Pr^i, R^2 = Me; X = H; **126l:** R^1 = Pr^i, R^2 = Me, X = F

Structures 130

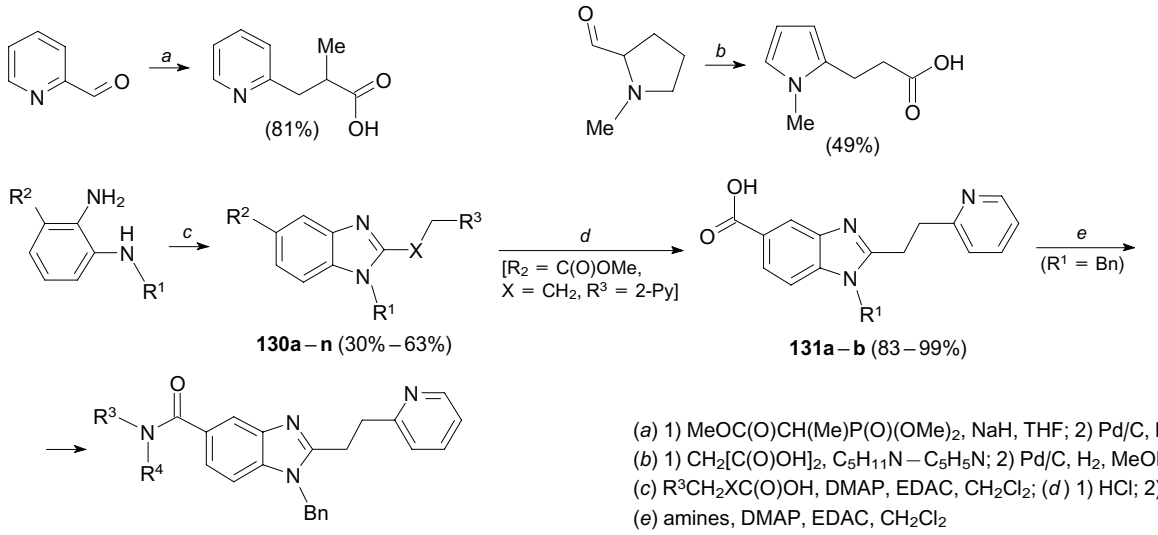


to those described by Zhao *et al.*,[153] comprised a dimethylene linker, instead of CH_2S [or $CH_2S(O)$ or $CH_2S(O)_2$], between two heteroaromatic systems (the phenyl residue was replaced with the pyridine ring — compounds **129** – **131**). The synthesis of compounds **129** is illustrated in Scheme 28.

The hit compounds **130a**,**m** showed $IC_{50} < 0.41$ and 2.1 μmol, respectively, in inhibition of HBV DNA synthesis (*cf.* Lamivudine (**109**) $IC_{50} = 0.16$ μmol).[155]

Another structural modification of the core heterocyclic scaffold was based on introduction of the imidazo[1,2-*a*]-pyridine moiety instead of the indole one. A series of 6-bromo-8-hydroxyimidazo[1,2-a]pyridine-3-carboxylates **132** was prepared and screened for HBV DNA replication inhibitory properties.[156] Hit compounds, **132o**,**s**, containing morpholin-4-yl and 4-methylpiperazin-1-yl substituents showed $IC_{50} = 1.3$ and 2.6 μmol, respectively.

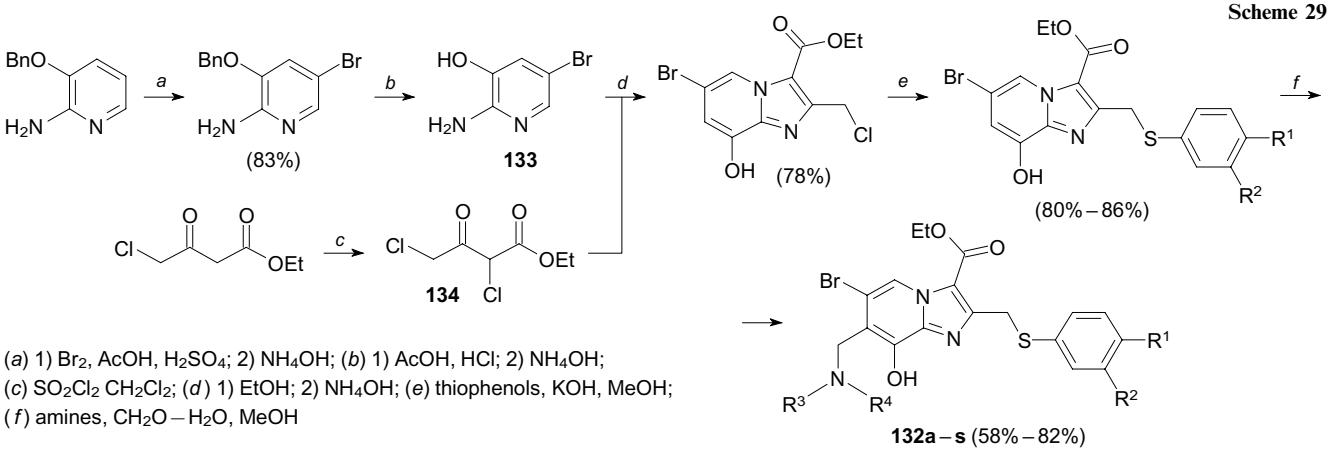
Scheme 28



(*a*) 1) $MeOC(O)CH(Me)P(O)(OMe)_2$, NaH, THF; 2) Pd/C, H_2; 3) HCl;
(*b*) 1) $CH_2[C(O)OH]_2$, $C_5H_{11}N - C_5H_5N$; 2) Pd/C, H_2, MeOH;
(*c*) $R^3CH_2XC(O)OH$, DMAP, EDAC, CH_2Cl_2; (*d*) 1) HCl; 2) NaOH, H_2O;
(*e*) amines, DMAP, EDAC, CH_2Cl_2

Compound	R^1	R^2	R^3	R^4	X	Compound	R^1	R^2	R^3	R^4	X
129a	–	–	Me	H	–	**130h**	Hex[c]	H	2-Py	–	σ-bond
129b	–	–	Me	Me	–	**130i**	Pr^i	H	2-Py	–	σ-bond
130a	Bn	H	2-Py	–	CH_2	**130j**	Bn	H	2-Py	–	CHMe
130b	Hex[c]	H	2-Py	–	CH_2	**130k**	Hex[c]	H	2-Py	–	CHMe
130c	Pr^i	H	2-Py	–	CH_2	**130l**	Pr^i	H	2-Py	–	CHMe
130d	Bn	H	1-methyl-1*H*-pyrrol-2-yl	–	CH_2	**130m**	Bn	C(O)OMe	2-Py	–	CH_2
130e	Hex[c]	H	1-methyl-1*H*-pyrrol-2-yl	–	CH_2	**130n**	Me	C(O)OMe	2-Py	–	CH_2
130f	Pr^i	H	1-methyl-1*H*-pyrrol-2-yl	–	CH_2	**131a**	Bn	–	–	–	–
130g	Bn	H	2-Py	–	σ-bond	**131b**	Me	–	–	–	–

Scheme 29



(*a*) 1) Br_2, AcOH, H_2SO_4; 2) NH_4OH; (*b*) 1) AcOH, HCl; 2) NH_4OH; (*c*) SO_2Cl_2 CH_2Cl_2; (*d*) 1) EtOH; 2) NH_4OH; (*e*) thiophenols, KOH, MeOH; (*f*) amines, $CH_2O - H_2O$, MeOH

Compound	R^1	R^2	R^3	Compound	R^1	R^2	R^3
132a	H	H	pyrrolidin-1-yl	**132j**	4-Br	H	NMe_2
132b	H	H	piperidin-1-yl	**132k**	4-Br	H	morpholin-4-yl
132c	H	H	4-methylpiperazin-1-yl	**132l**	4-Br	H	4-methylpiperazin-1-yl
132d	4-F	H	NMe_2	**132m**	4-Me	Me	NMe_2
132e	4-F	H	pyrrolidin-1-yl	**132n**	4-Me	Me	pyrrolidin-1-yl
132f	4-F	H	piperidin-1-yl	**132o**	4-Me	H	morpholin-4-yl
132g	4-F	H	morpholin-4-yl	**132p**	3-MeO	H	pyrrolidin-1-yl
132h	4-Cl	H	pyrrolidin-1-yl	**132q**	3-MeO	H	piperidin-1-yl
132i	4-Cl	H	4-methylpiperazin-1-yl	**132r**	3-MeO	H	morpholin-4-yl
				132s	3-MeO	H	4-methylpiperazin-1-yl

The target compounds **132** have been prepared from 2-aminopyridin-3-ol **133** and 4-chloroacetoacetic ester **134** according to Scheme 29.[156]

Like in all the previous examples, the direction of the Mannich reaction was not evident. So, the introduction of the substituted aminomethyl group at the C(7) versus C(5) position was questionable.

In biological tests Lamivudine (**109**), a nucleoside anti-HIV agent, was typically used as a reference drug. However, in one of the above mentioned papers, IC_{50} of Lamivudine (**109**) (HBV DNA replication inhibition) was 0.16 μmol,[155] while in two others it was 240.0 μmol,[153, 156] that is not just the same.

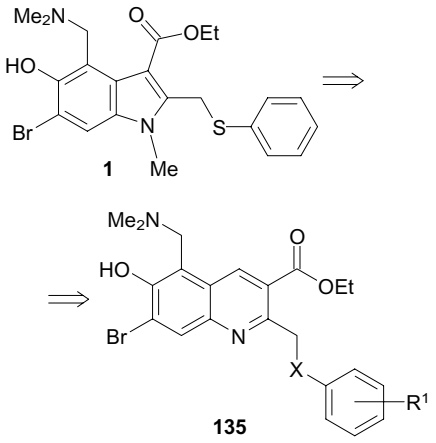
5. Ring-expanded Arbidol derivatives based on the quinoline nucleus

An idea to expand the indole ring in the Arbidol molecule has driven a Chinese research group to the synthesis and biological studies of a series of substituted quinolines **135**. This change from the Arbidol structure to compounds is illustrated in Scheme 30.

In addition to the transformation of the heterocyclic scaffold, the bromine atom in compounds **135** was replaced by another *ortho*-/*para*-director, namely, the methoxy group. Another serious difference is that the endocyclic nitrogen atom in quinolines **135** is much more basic than in its indole analogue **1** and unsubstituted.

The synthesis of the title compounds **136** using isovanillin **137** and 4-chloroacetoacetic ester as starting materials, has been carried out according to Scheme 31.[157 – 159]

Scheme 30

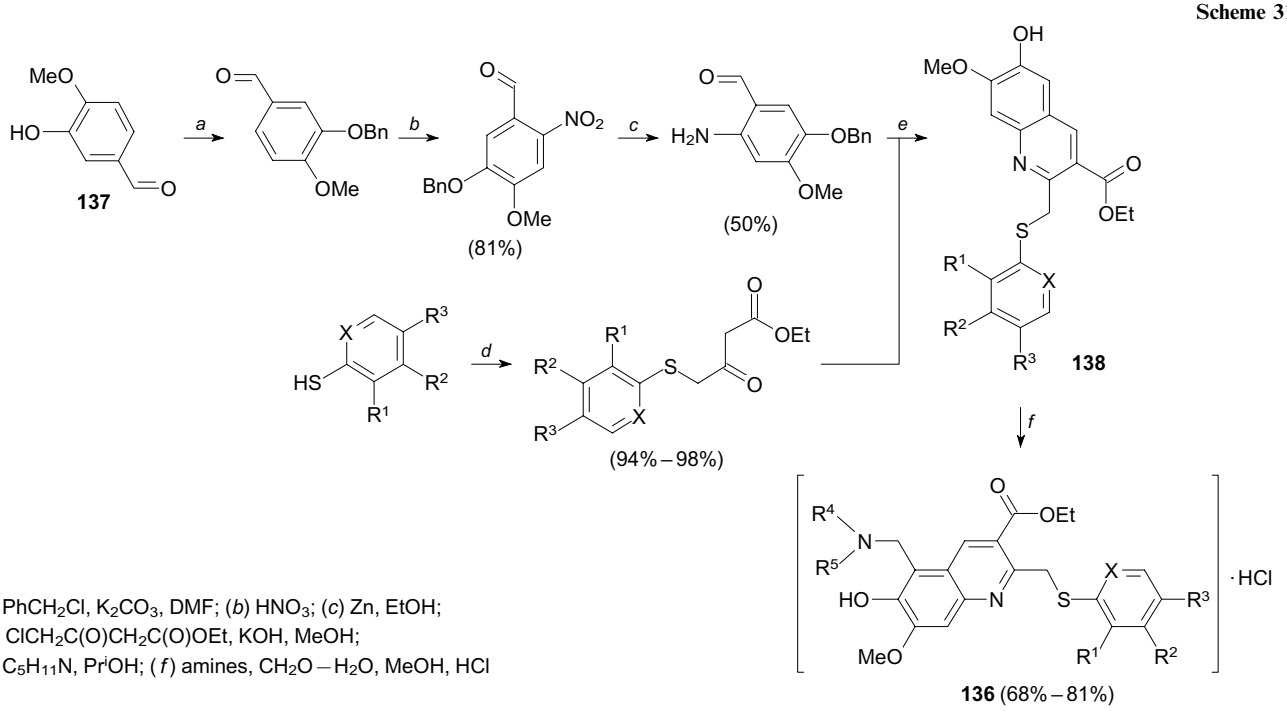


When studing the Mannich reaction in this synthetic sequence, it was found that in the case of piperidine, a competitive *bis*-aminomethylation occurred in compound **138** resulting in the substitution of the methylene group in the quinoline C(2) position (**139**) (Scheme 32).

In (dimethylamino)methyl-substituted compounds **136b**,**f**,**g**,**l**, the Mannich base fragment was replaced by treatment with 2-methyl-substituted or unsubstituted 1*H*-imidazole hydrochloride to obtain quinolines **136m – q** (Scheme 33).

Upon oxidation of the sulfur atom in compounds **136**, the corresponding racemic sulfoxides **140** were obtained (Scheme 34). Surprisingly, neither the dimethylamino

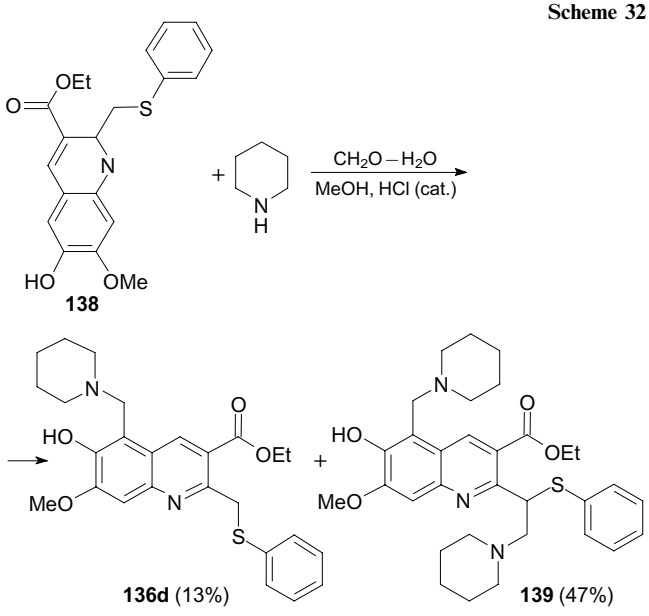
Scheme 31



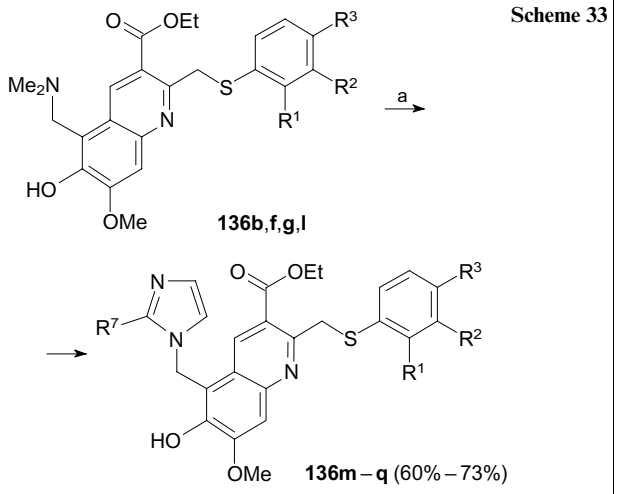
(*a*) $PhCH_2Cl$, K_2CO_3, DMF; (*b*) HNO_3; (*c*) Zn, EtOH;
(*d*) $ClCH_2C(O)CH_2C(O)OEt$, KOH, MeOH;
(*e*) $C_5H_{11}N$, Pr^iOH; (*f*) amines, CH_2O-H_2O, MeOH, HCl

Compound	R^1	R^2	R^3	R^4	R^5	X	Compound	R^1	R^2	R^3	R^4	R^5	X
136a	H	H	H	$(CH_2)_5$		CH	**136g**	H	F	F	Me	Me	CH
136b	H	H	F	Me	Me	CH	**136h**	H	F	F	$(CH_2)_4$		CH
136c	H	H	F	$(CH_2)_4$		CH	**136i**	H	F	F	$(CH_2)_5$		CH
136d	H	H	H	$(CH_2)_4$		N	**136j**	H	F	F	$(CH_2CH_2)_2O$	CH	
136e	MeO	H	H	Me	Me	CH	**136k**	H	F	F	$(CH_2CH_2)_2NMe$		CH
136f	H	MeO	H	Me	Me	CH	**136l**	H	MeO	MeO	Me	Me	CH

Scheme 32



Scheme 33

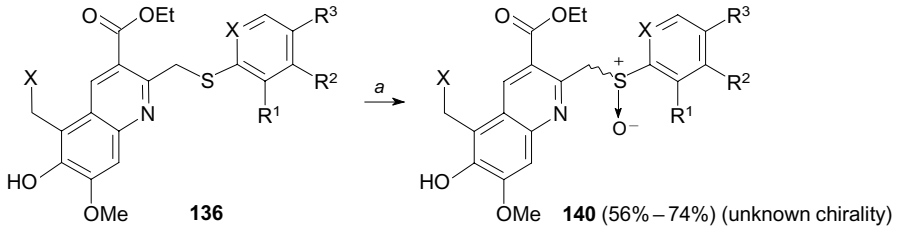


(*a*) 1*H*-imidazole or 2-methyl-1*H*-imidazole hydrochloride, H_2O, 1,4-dioxane; **134m:** $R^1 = R^2 = H$, $R^3 = F$, $R^7 = H$; **134n:** $R^1 = R^2 = H$, $R^3 = F$, $R^7 = Me$; **134o:** $R^1 = R^3 = H$, $R^2 = MeO$, $R^7 = H$; **134p:** $R^1 = H$, $R^2 = R^3 = F$, $R^7 = H$; **134q:** $R^1 = H$, $R^2 = R^3 = MeO$, $R^7 = H$

group nor the quinoline nitrogen atom were oxidized to *N*-oxide under these conditions.

During biological studies, three hit compounds **136c**,**j**,**k** with IC_{50} = 8.5, 5.8 and 11.2 μmol, respectively (inhibition of HBsAg secretion) have been identified. Two of them (**136c**,**j**) also effectively inhibited HBeAg secretion (IC_{50} = 9.3 and 10.5 μmol, respectively). As for the inhibition of HBV DNA replication [using Lamivudine (**109**) as an external standard, IC_{50} = 311.2 μmol] compounds **140c** (IC_{50} = 4.7 μmol) and **140f** (IC_{50} = 5.3 μmol) proved to be

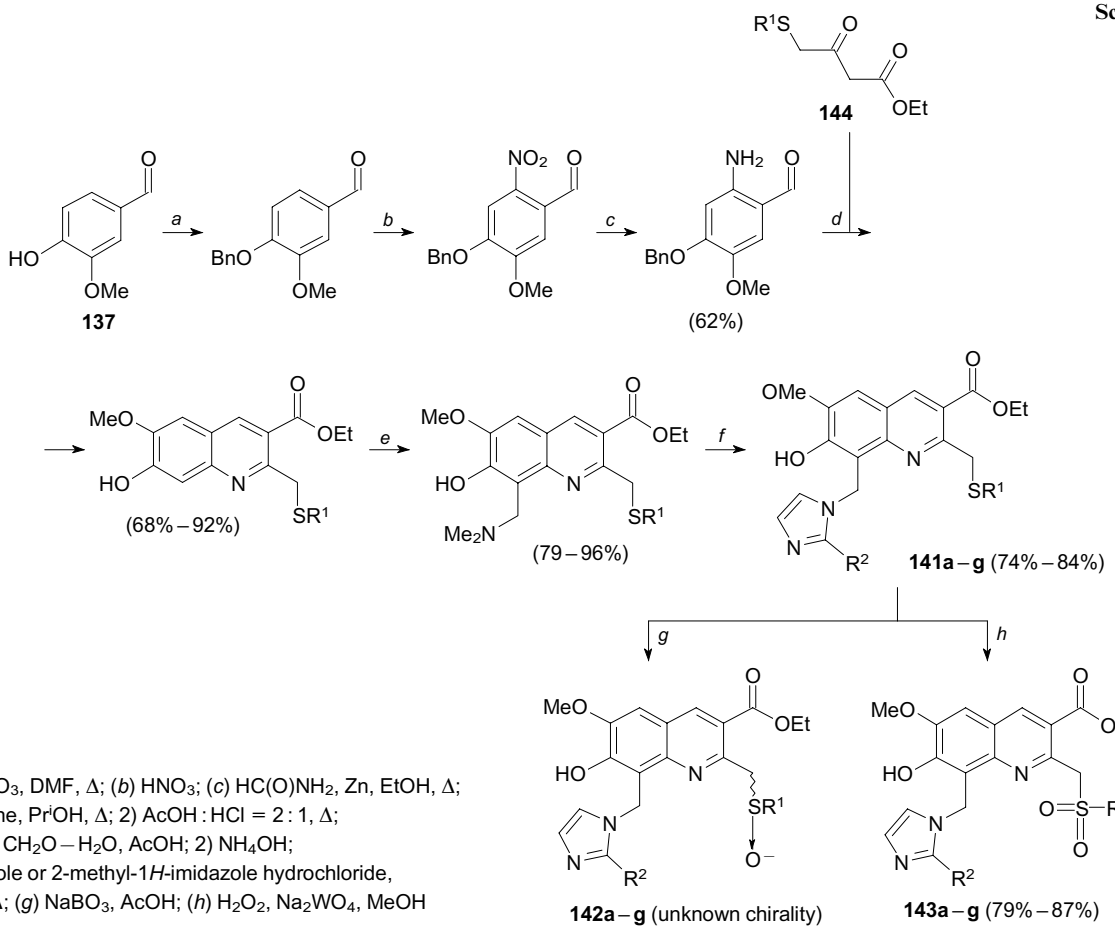
Scheme 34



(*a*) 1) $NaBO_3 \cdot 4\,H_2O$, Na_2WO_4, AcOH; 2) NaOH, H_2O

Compound	R^1	R^2	R^3	X	X^1	Compound	R^1	R^2	R^3	X	X^1
140a	H	H	F	CH	NMe_2	**140d**	H	H	H	N	$(CH_2)_4N$
140b	H	H	F	CH	$(CH_2)_4N$	**140e**	H	MeO	H	CH	1*H*-imidazol-1-yl
140c	H	H	F	CH	1*H*-imidazol-1-yl	**140f**	H	F	F	CH	$(CH_2)_4N$
						140g	H	MeO	MeO	CH	1*H*-imidazol-1-yl

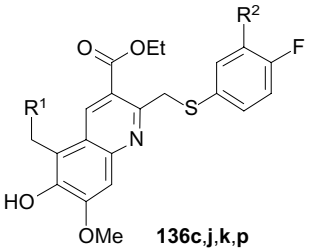
Scheme 35



(*a*) BnCl, K_2CO_3, DMF, Δ; (*b*) HNO_3; (*c*) $HC(O)NH_2$, Zn, EtOH, Δ;
(*d*) 1) piperidine, Pr^iOH, Δ; 2) AcOH : HCl = 2 : 1, Δ;
(*e*) 1) Me_2NH, $CH_2O - H_2O$, AcOH; 2) NH_4OH;
(*f*) 1*H*-imidazole or 2-methyl-1*H*-imidazole hydrochloride, 1,4-dioxane, Δ; (*g*) $NaBO_3$, AcOH; (*h*) H_2O_2, Na_2WO_4, MeOH

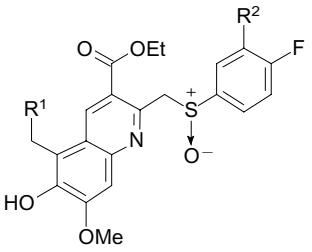
Compound	R^1	R^2	Compound	R^1	R^2	Compound	R^1	R^2
141a	Ph	H	**142a**	Ph	H	**143a**	Ph	H
141b	Ph	Me	**142b**	Ph	Me	**143b**	Ph	Me
141c	4-FC_6H_4	H	**142c**	4-FC_6H_4	H	**143c**	4-FC_6H_4	H
141d	4-$MeOC_6H_4$	Me	**142d**	4-$MeOC_6H_4$	Me	**143d**	4-$MeOC_6H_4$	Me
141e	4-$ClC_6H_4CH_2$	Me	**142e**	4-$ClC_6H_4CH_2$	Me	**143e**	4-$ClC_6H_4CH_2$	Me
141f	3-MeC_6H_4	H	**142f**	3-MeC_6H_4	H	**143f**	3-MeC_6H_4	H
141g	3,4-$F_2C_6H_3$	H	**142g**	3,4-$F_2C_6H_3$	H	**143g**	3,4-$F_2C_6H_3$	H

Structures 136, 140



136c,**j**,**k**,**p**

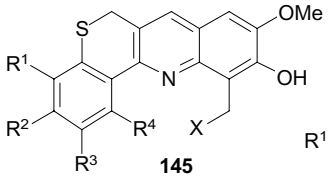
136c: R^1 = pyrrolidin-1-yl, R^2 = H;
136j: R^1 = morpholin-4-yl, R^2 = F;
136k: R^1 = 4-methylpiperazin-1-yl, R^2 = F;
136p: R^1 = 1*H*-imidazol-1-yl, R^2 = F



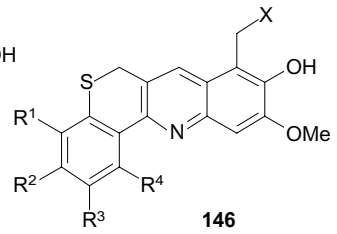
140b,**c**,**f** (unknown chirality)

140b: R^1 = pyrrolidin-1-yl, R^2 = H;
140c: R^1 = 1*H*-imidazol-1-yl, R^2 = H (**180c**);
140f: R^1 = pyrrolidin-1-yl, R^2 = F.

Structures 143, 144



145



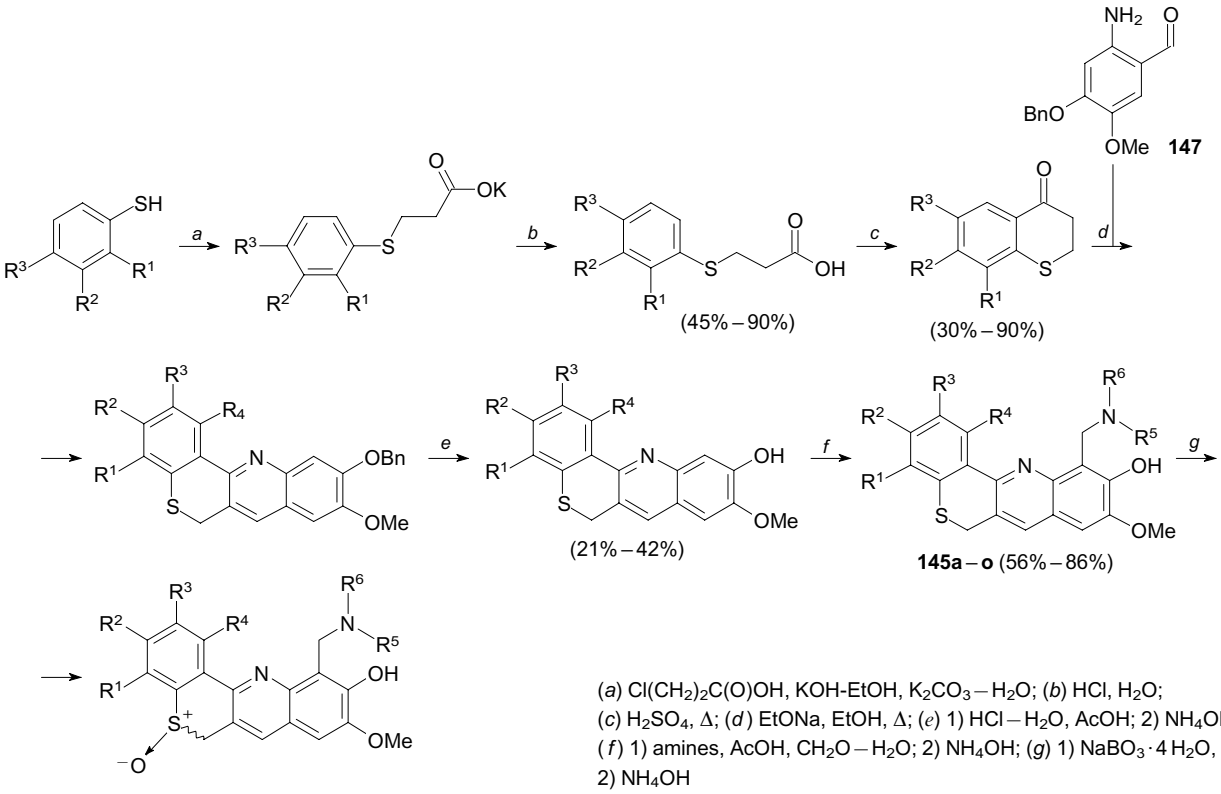
146

R^1 = H; R^2 = H, F, Me, MeO; R^3 = H, F, Me, MeO; R^4 = H, Me;
X^1 = NMe_2, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl

the lead ones, being practically twice as potent as **136c**,**p** and **140b**.[157]

Inspired by the results described above, Gong *et al.* have prepared regioisomeric quinolines **141** differing from their regioisomeric analogues **136** in the interchanged positions

Scheme 36



147

148a – **d** (60% – 83%) (unknown chirality)

(*a*) $Cl(CH_2)_2C(O)OH$, KOH-EtOH, $K_2CO_3 - H_2O$; (*b*) HCl, H_2O; (*c*) H_2SO_4, Δ; (*d*) EtONa, EtOH, Δ; (*e*) 1) HCl – H_2O, AcOH; 2) NH_4OH; (*f*) 1) amines, AcOH, $CH_2O - H_2O$; 2) NH_4OH; (*g*) 1) $NaBO_3 \cdot 4\,H_2O$, AcOH; 2) NH_4OH

Compound	R^1	R^2	R^3	R^4	R^5	R^6	Compound	R^1	R^2	R^3	R^4	R^5	R^6
145a	H	F	H	H	$(CH_2CH_2)_2O$		**145j**	H	Me	H	H	$(CH_2)_5$	
145b	H	F	H	H	$(CH_2)_5$		**145k**	H	MeO	H	H	$(CH_2)_5$	
145c	H	H	Me	H	$(CH_2)_5$		**145l**	H	MeO	MeO	H	$(CH_2CH_2)_2O$	
145d	H	H	Me	H	$(CH_2)_4$		**145m**	H	Me	H	Me	$(CH_2)_5$	
145e	H	H	Me	H	$(CH_2CH_2)_2O$		**145n**	Me	H	Me	H	$(CH_2)_5$	
145f	H	H	F	H	Me	Me	**145o**	H	H	MeO	H	$(CH_2)_5$	
145g	H	H	F	H	$(CH_2CH_2)_2O$		**148a**	H	H	F	H	$(CH_2CH_2)_2O$	
145h	H	H	F	H	$(CH_2)_5$		**148b**	H	H	F	H	$(CH_2)_5$	
145i	H	H	F	H	$(CH_2)_4$		**148c**	H	Me	H	H	$(CH_2)_5$	
							148d	H	Me	H	H	$(CH_2)_4$	

of the hydroxy and methoxy substituents in the quinoline nucleus.[160] Also, the corresponding sulfoxides **142** and sulfones **143** were obtained (Scheme 35). According to the already established structure – activity relationships, the title compounds contained 1*H*-imidazol-1-yl or 2-methyl-1*H*-imidazol-1-yl residues at C(8) of the quinoline nucleus. The reason of changing the direction of the Mannich reaction in respect to the previously described analogues remained unknown. Similar to the preceding examples, it has not been elucidated for certainty.

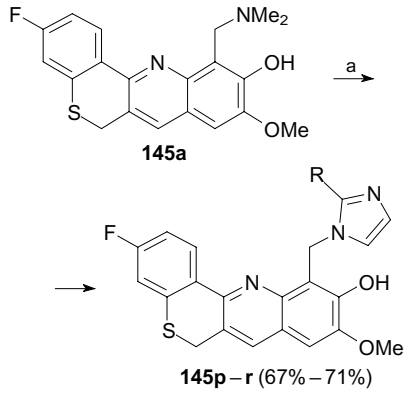
As the starting materials for the synthesis of quinolines **141**, vanilline **137** and various ethyl 4-(arysulfanyl)- or 4-[(arylmethyl)sulfanyl]-3-oxobutyrates **144** were used (see Scheme 35).[160]

Compounds **141** – **143** were tested for their ability to suppress the expression of the viral surface antigens HBsAg and HBeAg and, also, to inhibit the HBV DNA replication (using Lamivudine (**109**) as a reference compound, characterized by IC_{50} = 343.2 μmol). The hit compounds were found to be sulfoxides **142c**,**g** having IC_{50} = 3.5 μmol and IC_{50} = 2.6 μmol, respectively.

A yet deeper modification of the Arbidol structure, comprising elimination of the ester group together with conformational restrictions, resulted in two novel series of regioisomeric quinoline derivatives.[161,162] These tetracyclic compounds **145**, **146** are structurally quite different from the parent compound **1**.

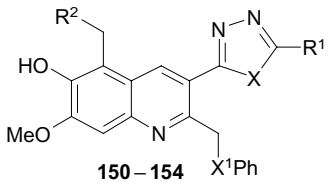
Being regioisomers of each other, these two general structures do not seem very promising for purposes of medicinal chemistry. The accumulation of a large number of aromatic rings in a molecule decreases the chances of a compound to become a drug candidate.

Scheme 37



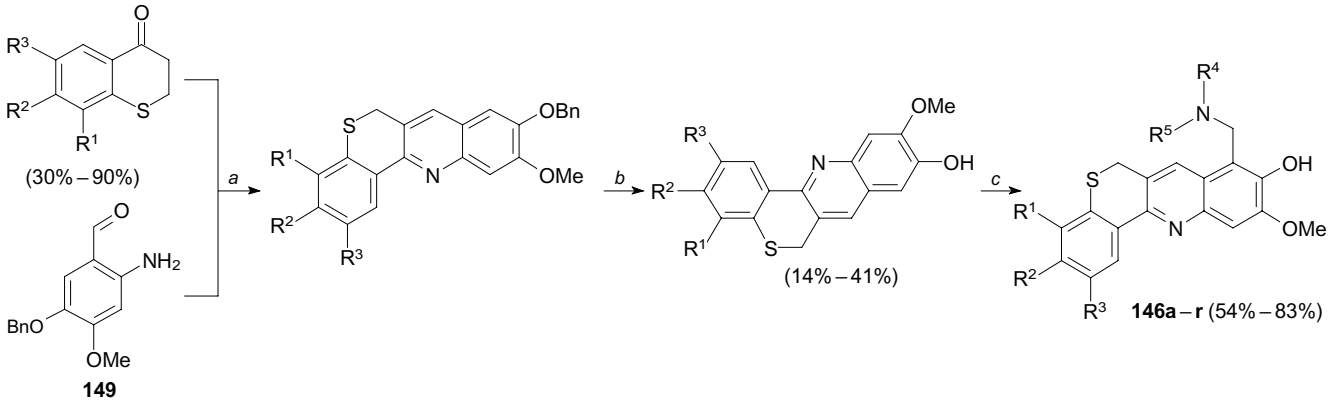
(*a*) 1*H*-imidazole or 2-methyl-1*H*-imidazole hydrochloride, H_2O, 1,4-dioxane; **145**: R = H (**p**, 71%), Me (**r**, 67%)

Structures 150 – 154



150: X = O, X^1 = S; R^1 = H, Me, Ph; R^2 = NMe_2, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, 4-methylpiperazin-1-yl;
151: X = X^1 = S; **152**: X = S, O; X^1 = S, R^1 = H, Me, Ph, R^2 = 1*H*-imidazol-1-yl, 2-methyl-1*H*-imidazol-1-yl;
153: X = S, X^1 = S(O), R^1 = Me, R^2 = 1*H*-imidazol-1-yl;
154: X = S, O; X^1 = S(O) R^1 = H, Me, Ph; R^2 = NMe_2, pyrrolidin-1-yl, piperidin-1-yl, morpholin-4-yl, 4-methylpiperazin-1-yl

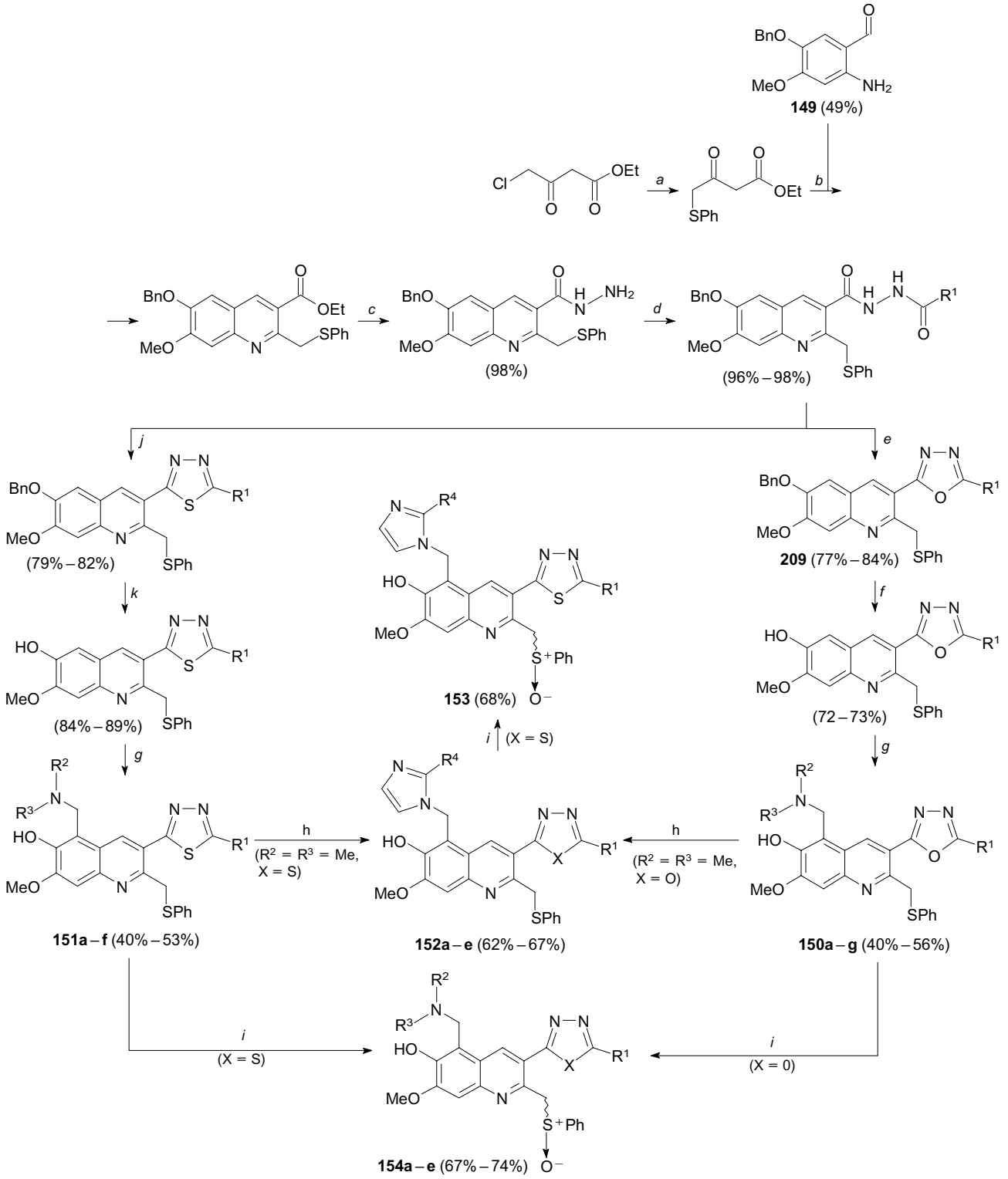
Scheme 38



(*a*) NaOEt; (*b*) 1) HCl – H_2O, AcOH; 2) NH_4OH, H_2O; (*c*) 1) amines, AcOH, CH_2O – H_2O; 2) NH_4OH

Compound	R^1	R^2	R^3	R^4	R^5	Compound	R^1	R^2	R^3	R^4	R^5
146a	H	H	H	$(CH_2CH_2)_2NMe$		**146j**	H	H	Me	Et	Et
146b	H	H	H	Et	Et	**146k**	H	H	Me	Me	Me
146c	H	H	H	Me	Me	**146l**	H	H	Me	$(CH_2CH_2)_2O$	
146d	H	H	H	$(CH_2CH_2)_2O$		**146m**	H	H	Me	$(CH_2)_4$	
146e	Me	H	Me	Me	Me	**146n**	H	F	H	$(CH_2CH_2)_2N(Me)$	
146f	Me	H	Me	$(CH_2CH_2)_2O$		**146o**	H	F	H	Et	Et
146g	Me	H	Me	$(CH_2)_5$		**146p**	H	F	H	$(CH_2CH_2)_2O$	
146h	H	H	F	$(CH_2)_4$		**146q**	H	Me	H	$(CH_2CH_2)_2O$	
146i	H	H	Me	$(CH_2CH_2)_2NMe$		**146r**	H	Me	H	$(CH_2)_4$	

Scheme 39



(*a*) PhSH, K_2CO_3, DMF; (*b*) piperidine, Pr^iOH, Δ; (*c*) $[H_2N-NH_2]\cdot H_2O$, Δ; (*d*) HC(O)OH or AcCl; (*e*) $P(O)Cl_3$, Δ; (*f*) BBr_3, TFA, CH_2Cl_2; (*g*) amines, CH_2O-H_2O, MeOH; (*h*) 1) 1*H*-imidazole or 2-methyl-1*H*-imidazole, HCl, 1,4-dioxane, Δ; 2) NH_4OH; (*i*) 1) $NaBO_3\cdot 4\,H_2O$, AcOH; 2) NH_4OH; (*j*) Lawesson's reagent, THF, Δ; (*k*) AcOH/HCl, Δ (continued on the next page)

Scheme 39 (continued)

Compound	R^1	R^2	R^3	R^4	X	Compound	R^1	R^2	R^3	R^4	X
150a	H	Me	Me	–	–	**151f**	Ph	$(CH_2)_4$	–	–	
150b	H	$(CH_2)_4$		–	–	**152a**	H	–	–	H	O
150c	Me	Me	Me	–	–	**152b**	Me	–	–	H	O
150d	Me	$(CH_2)_4$		–	–	**152c**	Me	–	–	H	S
150e	Me	$(CH_2)_5$		–	–	**152d**	Ph	–	–	H	S
150f	Me	$(CH_2CH_2)_2O$		–	–	**152e**	Me	–	–	Me	S
150g	Me	$(CH_2CH_2)_2NMe$		–	–	**153**	Me	–	–	H	S
151a	Me	Me	Me	–	–	**154a**	Me	Me	Me	–	O
151b	Me	$(CH_2)_4$		–	–	**154b**	Me	Me	Me	–	S
151c	Me	$(CH_2)_5$		–	–	**154c**	Ph	Me	Me	–	S
151d	Me	$(CH_2CH_2)_2O$		–	–	**154d**	Me	$(CH_2)_4$	–	S	
151e	Ph	Me	Me	–	–	**154e**	Ph	$(CH_2)_4$	–	S	

Anyhow, compounds **146** showed high biological activity. All of them were obtained from amino-substituded vanillin **147** according to general Schemes 36 and 37.[161]

Among compounds **145**, only sulfides **145h**,**j**,**n**,**o** appeared to be active in a single-digit micromolar range as HBV DNA replication inhibitors [IC_{50} = 240 μmol for Lamivudine (**109**)].[161]

On the other hand, compounds **148b**–**d** of unknown chirality of the sulfone series proved to be the only active HBeAg and HBsAg secretion inhibitors.[161]

Regioisomers of the above-described series of quinoline derivatives have been prepared starting from isovanillin **149** according to the synthetic sequence as illustrated in Scheme 38.[162]

As in the series of regioisomers described above (**145a**–**o**, **146a**–**r**), most of the compounds synthesized proved to be inactive. Only one of them (**146c**) inhibited HBsAg secretion with IC_{50} = 9.3 μmol, while compounds **146j**,**o** showed IC_{50} = 4.2, 2.0 and 2.4 μmol, respectively, as HBV DNA replication inhibitors [IC_{50} for Lamivudine (**109**) in the latter test was 240 μmol].

In a recent study, the same authors have described the novel analogues of quinolines **148** (**150**–**154**).[163] The main feature of their chemical structure is a switch from the ethoxycarbonyl substituent to heteroaryl one.

In these examples a five-membered heterocyclic moiety (1,3,4-oxadiazole or 1,3,4-thiadiazole) can be recognized as a planar bioisostere of the ethoxycarbonyl group. At the same time, the authors did classify this replacement as bioisosteric. They assumed that such heterocyclic moieties are widely met in the structures of representative antivirals.

The synthesis of compounds **150**–**154** was quite similar to that of their ethoxycarbonyl analogues, but it also comprised additional steps to construct an additional heteroaromatic ring (Scheme 39).[163]

Lead compounds **152c** and **153** had the IC_{50} values in the range of 1.01 – 1.38 μmol [*c.f.*, IC_{50} 0.75 μmol for Imidol (**28a**) in the same study].

Among them, (1*H*-imidazol-1-yl)methyl-substituted compounds were the least cytotoxic.

6. Conclusions

Stahl and Baier [164] wondered how much compounds does it take to tell a story in terms of medicinal chemistry? It's difficult to give an unambiguous answer to this question, but, in our opinion, the discovery of Arbidol, giving rise to a whole synthesis tree for numerous compounds, does deserve an individual story.

The data presented in this review clearly demonstrate an extraordinary potential for design of novel drugs on the basis of Arbidol and its congeners. It is worth to mention only some of them, which have already found their clinical use or entered clinical and preclinical trials:

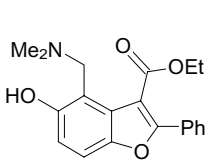
1. Arbidol (**1**) *per se*, widely used in the Commonwealth of Independent States and China as antiviral and immune-stimulating agent possessing also anti-inflammatory properties.

2. Dimecarbine [Mecarbinate (**2**)], which has been used as a hypotensive drug in the Soviet Union.

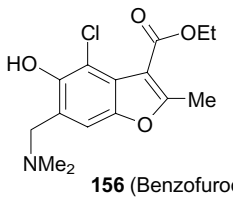
3. Phenicaberan (**155**) — a spasmolytic agent.[165]

4. Benzofurocaine (**156**) — an analgesic with local anaesthetic properties.[166]

Structures 155, 156



155 (Phenicaberan)



156 (Benzofurocaine)

5. Imidol (**28a**) — an experimental preparation against hepatitis B (*vide supra*), undergoing clinical trials in China.

6. AV0038 (**66a**) — an experimental drug candidate with anti-influenza activity (*vide supra*), now undergoing preclinical trials in Russia.

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