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Fluorine-containing indoles: Synthesis and biological activity

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ABSTRACT

In the frames of this review article the recently obtained data on new synthetic approaches to fluorinated indoles, as well as their biological properties are considered.

1. Introduction

The indole moiety represents certainly an important structural subunit for a large number of natural products and pharmaceuticals [1]. Thus, **reserpine** is a well known drug for the treatment of central nervous and cardiovascular systems diseases; **vincristine** and **tryprostatins A, B** are used as antimitotic agents for cancer chemotherapy [2,3]. Iindole is reported to be a novel signaling molecular fragment in diverse bacterial genes [4]. A number of indole derivatives have been found to exhibit anti-inflammatory, antidepressive, antihypertensive and other types of activity. For instance, **vilazodone** represents a new antidepressant drug acting as dual ligand, serotonin transporter (SERT) inhibitor and partial agonist of 5HT receptor (Fig. 1) [5]. **Indomethacin** has been used as a nonsteroidal anti-inflammatory drug [6]; **arbidol** and **methisazone** are indole-derived compounds, which have been marketed as drugs for treatment of viral diseases (Fig. 1) [7].

Nowadays much attention is paid to the development of synthetic methods leading to indole derivatives, and heterocyclizations based on using suitable "building-blocks" appear to be the most wide-spread approach. In a number of publications synthetic ways to indoles are classified on the basis of the starting materials [8–10].

It is well known that the incorporation of fluorine atoms into heterocyclic compounds can impact their solubility, lipophilicity or affect biological potency with either increases or decreases dependent on context [11–17]. Another rather established effect of fluorination is a modulation of metabolic stability; in particular, replacing hydrogen with fluorine on aromatic rings is a very effective strategy to slow down significantly the oxidative metabolic step by cytochrome monooxygenases [18].

Taking into account the importance of both indoles and fluorinated compounds in medicinal chemistry, the synthesis of fluorine-containing indole derivatives is gaining a great interest. 2-Trifluoromethyl- and 3-trifluoromethylindoles were mentioned in the review [19]. The recently published book [11] contains a special chapter [20], dedicated to the chemistry of indoles and their aza-analogues, bearing fluorine atoms or trifluoromethyl groups in the pyrrole ring; also derivatives with perfluorinated benzene ring are observed. Unfortunately, a little attention has been paid to biological activity of fluorine-containing indoles; nevertheless, authors have noted that fluorinated indoles possess a broad scope of physiological activity, thus being considered to be promising candidates for application as drugs. In particular, compound **A (sunitinib)**, an oral multi-targeted receptor tyrosine kinase (RTK) inhibitor, was approved by the FDA (US Food and Drug Administration) in 2006 for the treatment of renal cell carcinoma (RCC) and imatinib-resistant gastrointestinal stromal tumor (GIST) [21–25]. Compound **B** is an inhibitor of HIV-1 attachment [26], compound **C** is a factor Xa inhibitor [27], compound **D** is a potassium channel opener, known as Flindokalner (MaxiPost, BMS 204352) [28] (Fig. 2).

In the current review article synthetic approaches to a variety of fluorinated indoles are considered, including chemical transformations and heterocyclizations of the key intermediates. Also the data on biological activity of these compounds will be discussed. In the section 2.1 of the manuscript new data on the chemistry of fluoroindoles are presented for the period 2013–2017 and data collected in the Sections 2.2–6.6 cover the literature for the period 2000-2017.

2. Synthesis of fluoroindoles

In order to incorporate fluorine atoms into the indole bicylcic system, various types of cyclocondensations based on using fluorinated

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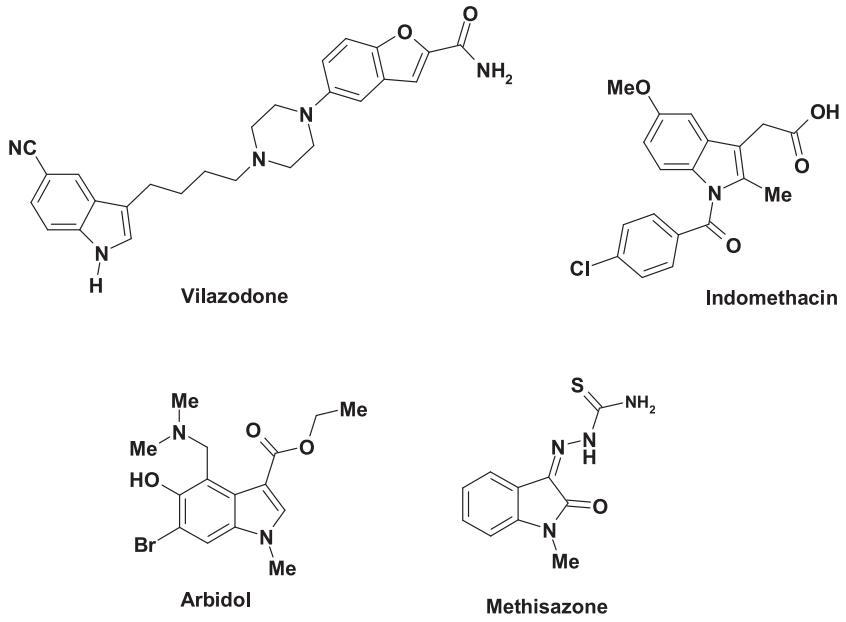

Fig. 1. Structures of vilazodone, indomethacin, arbidol and methisazone.

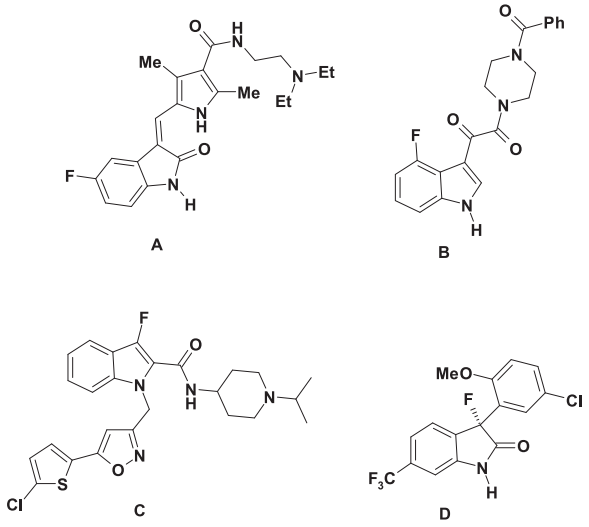

Fig. 2. Structures of some bioactive fluorinated indole derivatives.

"building blocks", functionalization of the pyrrole ring and modification of substituents have been applied for the synthesis of fluorinated indoles.

2.1. Synthesis of 2- and 3-fluoroindoles

2.1.1. Heterocyclizations

New data on heterocyclization reactions to prepare 2- and 3-fluoroindoles have been published [29–32]. For instance, 2,2-difluoro-3-methyleneindolines **5** were synthesized by using the *gem*-difluoroallylic electrophiles, as fluorine-containing three-carbons building blocks and a palladium catalyst (Scheme 1) [29]. The authors have demonstrated that *α*-selective substitution of 3-bromo-3,3-difluoropropene **1** with 2-bromoanilines **2a-h** proceeds via the Tsuji-Trost reaction with the formation of *N*-(1,1-difluoroallyl) compounds **3a-h** as the main products. Optimum conditions have been found to be as follows: tris(dibenzylideneacetone)dipalladium $Pd_2(dba)_3$, 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene (Xantphos), hexamethyldisilazane lithium salt (LiHMDS), ether. The ratio of products **3** and **4** under these reaction conditions proved to be varied from 91:9 to 95:5. The intramolecular Heck reaction of compounds **3a-h** gave *N*-sulfonyl-2,2-difluoro-3-methylene-indolines **5a-h** in good yields. Separation of **3** and **4** proved to be troublesome, and the Heck cyclization has been carried out by using mixtures of **3** and **4**, taken immediately after aqueous workup.

Indoline derivative **5a** was transformed into *N*-tosylated 2-fluoroindole **6** in 95% yield through the reaction with benzylmethylamine (Scheme 1). The nickel-catalyzed defluorinative coupling of **5a** with 3-hexyne led to 3-allylated 2-fluoroindole **7** in 87% yield.

3-Substituted 2-fluoroindoles **9** were obtained through the intramolecular cyclization of *β,β*-difluoro-*o*-sulfonamidostyrenes **8** [30] (Scheme 2). Heating of difluorostyrene **8** in 1,1,1,3,3,3-hexafluoropropan-2-ol (HFIP) in the presence of Ag(I), as catalyst, and N,O-bis(trimethylsilyl)acetamide (BSA), as a fluoride captor, led to 2-fluoroindoles **9** in 32 – 99% yields. This Ag-catalyzed reaction proceeds as 5-*endo-trig* addition, followed by *β*-elimination of silver fluoride.

Gem-difluorostyrenes **10** have also been used as building blocks for the synthesis of a variety of *N*-substituted-2-fluoroindoles **12** (Scheme 3) [31]. It has been found that the Pd-catalyzed Buchwald-Hartwig reaction of 1-X-2-(2,2-difluoroethenyl)benzenes **10** with anilines **11**, followed by base-promoted intramolecular nucleophilic displacement of a fluorine atom leads to the targeted products **12** in moderate to good yields. It is worth noting that this method is a mild one, easy to carry out, and it has a wide scope of substrates.

Diethyl 2-fluoromalonate ester **13** proved to be another building block useful for the synthesis of fluorooxindole derivatives [32]. The nucleophilic substitution reaction of 2-fluoronitrobenzenes **14** with the C-N ucleophile, generated from compound **13** in DMF in the presence of NaH, followed by the reaction with potassium hydroxide in MeOH gave the corresponding 2-fluoro-2-arylacetic acids **15** in good yields (Scheme 4). Reductive cyclization of methyl esters **16** in the presence of sodium dithionite afforded fluorooxindoles **17** in reasonable yields. Fluorinated 3,3'-linked disoxindoles **18** were prepared from **17** by a highly diastereoselective method under the action of isatine or N-Boc-imine (Scheme 4) [33]. Synthesis of C3-fluorinated oxindoles **20** through cross-dehydrogenative coupling from malonate amides **19** under mild electrochemical conditions (Scheme 4) was reported [34].

3-Fluoroindoles **22** were obtained from N-arylamines **21** bearing CF_2I group (Scheme 5). The reaction is mediated by ruthenium photocatalyst in the presence of substoichiometric amount of triphenylphosphine upon irradiation with blue light [35].