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# Convenient synthesis of novel *N*-(5-allyl-7,7-difluoro)-4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-carboxymides

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ABSTRACT

5-Allyl-7,7-difluoro-2-(2,4-difluorophenyl)-6-(4-methoxyphenyl)-4,5,6,7-tetrahydro-2*H*-pyrazolo[4,3-*c*]pyridine-3-amine represents a fluorinated heterocyclic scaffold, potentially attractive. It was synthesized via Michael addition, Mannich reaction of the difluorinated ethyl bromoacetate with a benzotriazole derivative, followed by a Dieckmann condensation. Starting from simple materials, this efficient route which gives access to novel functionalized *N*-(5-allyl-7,7-dihalo)-4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-carboxymides, was explored and adapted for parallel synthesis, resulting in a compound library.



Indazole and its derivatives have gained considerable importance in medicinal chemistry in view of their promising pharmacological properties.[1,2] Several indazoles are found to exhibit significant levels of activity as HIV protease inhibitors,[3,4] serotonin 5-$HT_{1\alpha}$, 5-$HT_2$[5] and 5-$HT_3$ receptor antagonists,[6,7] and acetylholinesterase inhibitors,[8] whereas 1-[3-(dimethylamino)-propyl]-5-methyl-3-phenyl-1*H*-indazole (FS-32),[9a] MK-4827,[9b] and compound **3** have been shown to be potent antidepressant drug candidates and PARP-1 inhibitors.[9c]

Fipronil is a wide spectrum insecticide (Fig. 1).

Fused pyrazoles or tetrahydroindazoles have been reported to inhibit protoporphyrinogen oxidase (PPO), an enzyme which catalyzes the oxidation of protoporphyrinogen to protoporphyrin and is the site of action of membrane disrupting herbicides.[10] With the aim of finding a new class of potent PARP-1 inhibitors, we designed tetrahydroindazoles. The structure was designed bearing a functionalizable site to allow the introduction of various substituents. We were particularly interested in 5-allyl-7,7-difluoro tetrahydroindazole derivatives. Early PARP-1 inhibitors were analogs of 3-aminobenzamide. It was observed that amide functionality was crucial for specific binding to the enzymatic site, forming three key hydrogen bonds with the enzyme. Several methods for the synthesis of indazoles and their derivatives have been reported in the literature.[11–13] Most of them involve the construction of the pyrazole moiety starting from preconstructed benzene derivatives. On the other hand, methods based on pyrazole precursors, more easily accessible, are briefly described in the literature.[14] The introduction of fluorine atoms into organic molecules has proven to be a valuable tool for changing the physical and chemical properties of the compound without major steric implications.[15,16] In that respect, there is a growing demand for synthetic methods

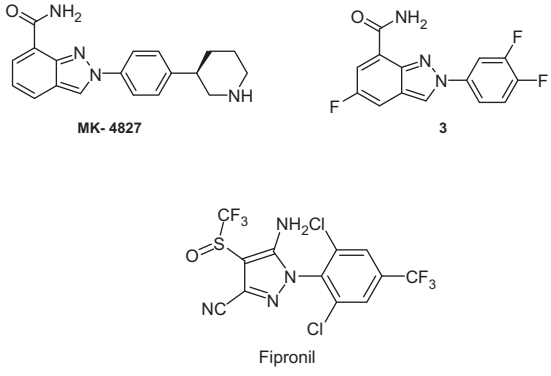


**Figure 1.** Bioactive indazoles (PARP inhibtors and insectiside).

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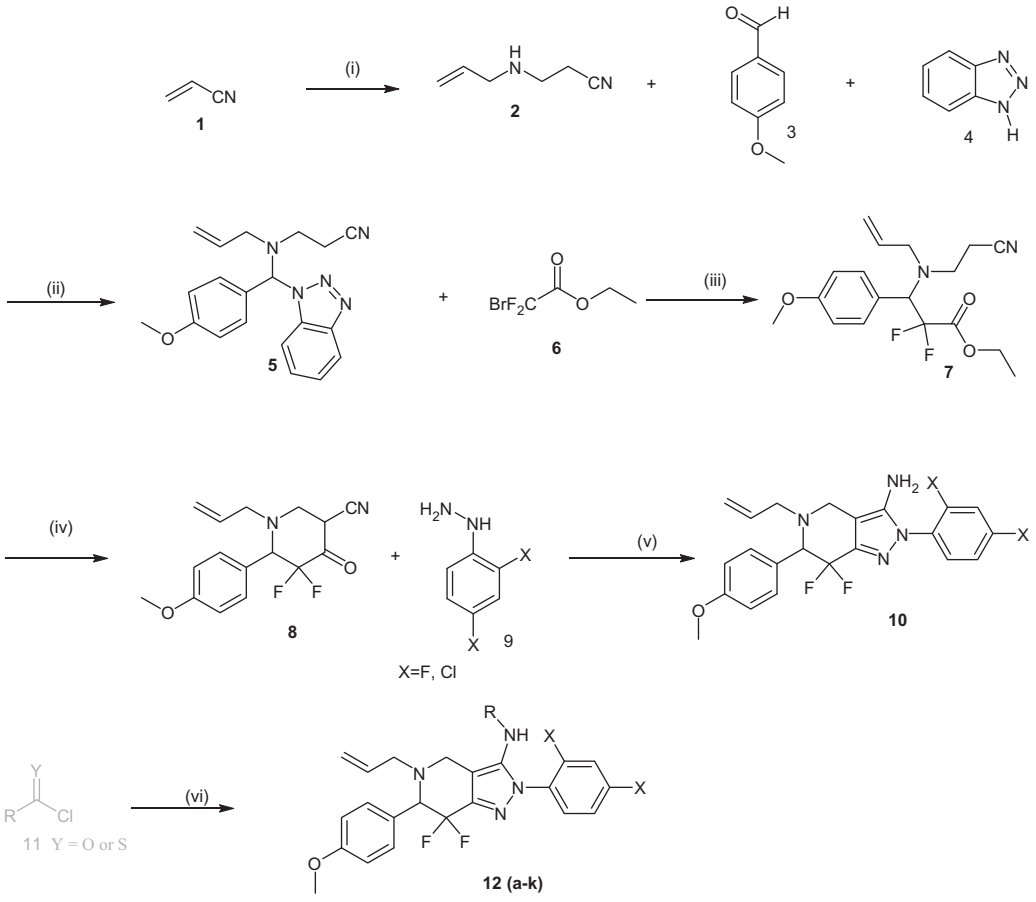
for the preparation of selectively fluorinated heterocyclic compounds used in pharmaceutical and agrochemical industries.[17] Consequently, fluorinated pyrazoles are of specific interest because the introduction of a fluorine atom can drastically affect the biological properties of this class of heterocyclic compounds.[18,19] In continuation of our work on the development of bioactive synthetic molecules[20,21] and synthetic methodology,[22–25] we were interested in synthesizing tetrahydroindazoles which are analogs of MK-4827 and compound **3**, both PARP-1 inhibitors. We now report an efficient synthesis of *N*-(5-allyl-7,7-difluoro-2-(2,4-difluorophenyl) tetrahydroindazole analogs involving, the Mannich reaction, Dieckmann cyclization, followed by cyclocondensation of (2-fluoro-4-halogeno-phenyl)-hydrazine with the cyanoketone intermediate (Scheme 1).

Our synthetic approach (Scheme 1) begins with the addition of allylamine to acrylonitrile which gave compound **2**. This one was converted to benzotriazole derivative **5** by reaction with 4-methoxy benzaldehyde and benzotriazole.[26] Compound **7** was prepared starting from 2-bromo-2,2-difluoroacetate via benzotriazole derivative **5** using the Mannich reaction in THF under nitrogen. The Dieckmann condensation of **7** was optimized in the presence of various bases (NaH, *t*-BuO-K, *n*-BuLi) and solvents. The best yield in cyanoketone **8** was obtained by the in situ generation of LDA at −78 °C. The reactivity of the ester carbonyl toward the nucleophiles has increased due to the presence of the geminal-difluoro group. 5-allyl-3-amino-7,7-difluoro-2-(2,4-dihalophenyl)-6-(4-methoxyphenyl)-4,5,6,7-tetrahydro-2*H*-pyrazolo[4,3-*c*]pyridine **10** was synthesized by the condensation of 2,4-diflurophenylhydrazine with cyanoketone **8**. Several syntheses of isomeric 4,5-fused bicyclicpyrazoles or tetrahydroindazoles have been reported.[27,28] However, to the best of our knowledge, there is no report for the synthesis of *N*-(5-allyl-7,7-difluoro-1-(2,4-difluorophenyl) tetrahydroindazol analogs. Here,[29] we report an efficient, versatile, and convenient synthetic route, which provides rapid access to 4,5,6,7-tetrahydro-2*H*-indazoles.[30] The cyclocondensation of hydrazines with the cyclic β-cyanoketone **10** under neutral conditions generally leads to *N*-(5-allyl-difluorophenyl)-4,5,6,7-tetrahydro-2*H*-indazole analogs. The more reactive ketone and terminal $NH_2$ group of the arylhydrazine react first, leading to the formation of the corresponding intermediate imine which is then cyclized to afford compound **10**. In order to attain the regioselectivity of these reactions, we attempted many conditions like the reaction of binucleophile phenylhydrazine with cyanoketone in the presence of NaH. This was unsuccessful as we observed the decomposition product. We also explored a strategy by using Boc protected phenylhydrazine but we were unsuccessful. The primary amine of 4,5,6,7-tetrahydraindazole **10** was derivatized to give the corresponding *N*-(4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-carboxamides **12**(**a**–**k**) by treatment of compound **10** with acyl chlorides. These molecules are being evaluated as selective PARP-1 inhibitors (Table 1).

In conclusion, we have developed an efficient strategy for the synthesis of 5-allyl-3-amino-7,7-difluoro-2-(2,4-dihalophenyl)-6-(4-methoxyphenyl)-4,5,6,7-tetrahydro-2*H*-pyrazolo[4,3-c]pyridine **10** as an important scaffold in the synthesis of PARP-1 inhibitors. Our synthesis is a six-step strategy via 1,4-addition, Mannich reaction, Dieckmann cyclization, and cyclocondensation of 2,4-dihalophenylhydrazine with an intermediate cyanoketone. The method is based on industrially accessible chemicals.




**Scheme 1.** Synthesis of *N*-(5-allyl-7,7-difluoro)-4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-carboxymides. Reagents and conditions: (i) allyl amine, EtOH, rt; (ii) MeOH, rt; (iii) zinc dust, trimethylsilyl chloride, THF, rt; (iv) diisopropyl amine, *N*-butyl lithium, THF; (v) EtOH, reflux; (vi) pyridine, rt.

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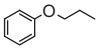
**Table 1**
*N*-(5-Allyl-7,7-difluoro)-4,5,6,7-tetrahydro-2*H*-indazol-3-yl)-carboxymides

| Product | R | X |
|---|---|---|
| **12a** |  | F |
| **12b** |  | F |
| **12c** |  | F |
| **12d** |  | F |
| **12e** |  | F |
| **12f** |  | F |
| **12g** |  | Cl |
| **12h** |  | Cl |
| **12i** |  | F |
| **12j** |  | F |
| **12k** |  | F |

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## Supplementary data

Supplementary data (relevant spectra ($^1$H NMR, $^{13}$C NMR spectra) for all compounds and $^{19}$F NMR spectra for key intermediates **7**, **8**, **10a**, **10b** and **12a**–**k**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.07.076.

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