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Bioorganic & Medicinal Chemistry Letters 17 (2007) 3445–3453
Bioorganic & Medicinal Chemistry Letters

Synthesis and structure–activity relationships of novel pyrimido[1,2-*b*]indazoles as potential anticancer agents against A-549 cell lines☆

T. Yakaiah,[a] B. P. V. Lingaiah,[a] B. Narsaiah,[a,*] B. Shireesha,[b] B. Ashok Kumar,[c] S. Gururaj,[d] T. Parthasarathy[c] and B. Sridhar[e]

[a]*Fluoroorganic Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India*
[b]*College of Pharmaceutical Sciences, Kakatiya University, Warangal 506 302, India*
[c]*Department of Chemistry, Nizam College, Basheer Bagh, Hyderabad 500 001, India*
[d]*Global Institute of Biotechnology, Himayatnagar, Hyderabad 500 001, India*
[e]*Laboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India*

Received 7 November 2006; revised 5 March 2007; accepted 27 March 2007
Available online 30 March 2007

Abstract—A series of novel pyrimido[1,2-*b*]indazoles **5**, **7** have been prepared from 3-trifluoromethyl-5-phenyl-2,6-dicyano anilines **1** via novel indazole regioisomers **3** and **4** through a facile strategy. Specific examples were evaluated for anticancer activity in vitro and found to exhibit promising activity against A-549 cell lines and are more effective than Etoposide. QSAR models were developed and validated by cross-validation method. The results of the best QSAR model were further compared with the crystal structure of tubulin protein. The binding energies estimated were found to have a good correlation with the experimental inhibitory potencies.
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The modern trend is directed towards discovery of new organic molecules as potential anticancer agents by adopting various synthetic approaches. In this process some of the molecules considered to interfere effectively with DNA either directly or inhibiting DNA–binding enzymes led to identification of new promising anticancer agents.[1] However, these molecules lack specificity towards cytotoxicity and damage cell lines in the tissue as a result no clear-cut drug is available. The principal driving force for stacking and charge transfer interactions is through hydrogen bonding and electrostatic forces.[2] In addition, strategically positioned suitable substituents promote interference with cellular detoxification pathways. Therefore, our attention was attracted towards synthesis of a series of novel pyrimido[1,2-*b*]indazoles with trifluoromethyl group at an appropriate position in order to identify suitable lead compounds as new pyrimido[1,2-*b*]indazoles as anticancer agents. Earlier findings have been on indazole derivatives specifically known to be active as protein kinase inhibitors, in cancer cell proliferative disorders, Alzheimer's disease, viral infections, auto-immune diseases and neuro degenerative disorders.[3–6] Further, pyrimidine ring in an organic molecule also shows prominent activity against several diseases.[7–9] Therefore interest is continuously increasing on fusion of pyrimidine ring over indazoles as a result pyrimido[1,2-*b*]indazoles are formed and are considered to have promising activity against many infections. Synthesis of pyrimido[1,2-*b*]indazoles is mainly starting from 3-amino indazoles and their reaction with 1,3-diketones,[10–12] β-ketoester,[13] propiolic acid ester,[14] DEEM[15] or DMAD.[16] In recent past, synthesis based on microwave irradiation conditions[17,18] is considered as a powerful synthetic tool due to its short reaction times, operational simplicity with improved yields and is of modern trend in organic synthesis. In continuation of our efforts[19–22] on the synthesis of novel ring systems of biological interest, we wish to report the synthesis of new indazole regioisomers **3**, **4** and each isomer is independently reacted with various substrates such as 1,3-diketones (symmetrical/unsymmetrical), diethyleth-

Keywords: Regioisomers; Indazoles; 1,3-Diketones; Pyrimido[1,2-*b*]indazoles; Cyclisation; A-549 cell lines; QSAR modelling studies; Tubuline.
☆ IICT Communication No. 041004.
* Corresponding author. Fax: +91 40 27160387x27193185; e-mail: narsaiah@iict.res.in

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doi:10.1016/j.bmcl.2007.03.087

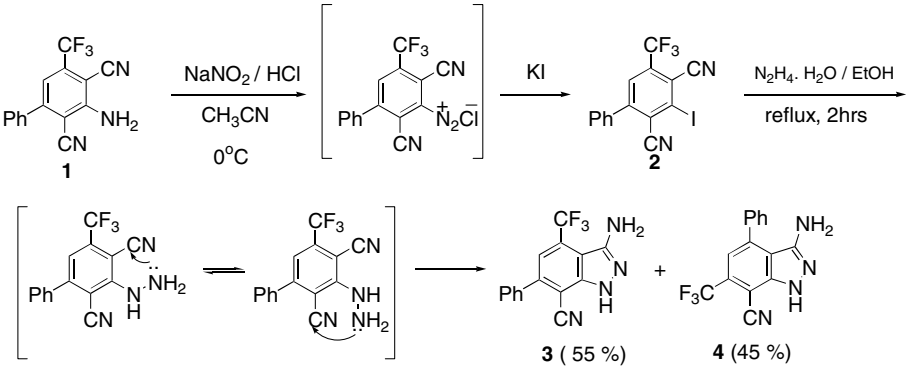
oxymethylene malonoate (DEEM), ethoxymethylene malononitrile (MMN), ethyl ethoxymethylene cyanoacetate (EMCA), diethyl *N*,*N*-dimethylaminomethylene malonate (DAMM), β-ketoesters and dimethyl acetylenedicarboxylate (DMAD) under microwave irradiation conditions obtaining pyrimido[1,2-*b*]indazoles **5**, **7** in high yields. Representative examples were screened for anticancer activity against A-549 cell lines and found to have more activity than Etoposide, a standard drug. Molecular modelling studies further confirmed the activity.

The 3-trifluoromethyl-5-phenyl-2,6-dicyano aniline **1** has three active functional groups ortho to each and is subjected to diazotisation using $NaNO_2$/HCl at 0 °C followed by potassium iodide obtaining corresponding iodobenzene **2**.[21] It is further reacted with hydrazine hydrate in refluxing ethanol resulting in two 3-amino-4/6-trifluoromethyl-6/4-phenyl indazole regioisomers **3**, **4** in definite proportions. The reaction is mainly nucleophilic substitution of iodine by hydrazine on benzene ring due to presence of powerful electron-withdrawing groups followed by selective attack on one of the nitrile carbons at a time to result in products **3**, **4**. The reaction is schematically drawn below in Scheme 1.

Each of indazole regioisomers **3** and **4** is separated due to their small difference in polarity and characterised based on IR, ^{1}H NMR, ^{13}C NMR, ^{19}F NMR (Table 1), mass spectral data and X-ray analysis. Compound **3** is less polar than compound **4** based on TLC and characteristic difference in chemical shifts of NH_2 group and proton on C-5 carbon is clearly observed in ^{1}H NMR. In compound **3**, NH_2 and C-5 proton signals appeared in upfield compared to compound **4** and it is assumed to be the influence of CF_3 and CN groups. If CF_3 and CN are para to each other, the electron-withdrawing effect in ring nullifies as a result the signals appeared in upfield as seen in compound **3**. In case CF_3 and CN are ortho to each, the cumulative electron-withdrawing effect enhances and with that, the signals for NH_2 and C-5 proton in ^{1}H NMR appeared in downfield in compound **4**. Further, phenyl protons appeared as singlet due to magnetic equivalence when CF_3 and CN are para to each other and multiplet if ortho to each other.

The ^{13}C NMR data of compounds **3** and **4** further support that the CF_3 carbon in compounds **3** appeared as quartet at δ 121.31 and in compound **4** as quartet at δ 122.76 with the same coupling constant 274 Hz. However, a characteristic difference of absorption of *C*-CF_3 is observed. In compound **3** the *C*-CF_3 appeared as quartet at δ 123.29 with coupling constant 31 Hz, whereas in compound **4** the *C*-CF_3 appeared as quartet at δ 130.16 with coupling constant 31 Hz. In addition nitrile carbon (CN) appeared at 126.99 for compound **3** and 113.16 for compound **4**. Thus, the structure of each isomer is determined. It is further confirmed by single crystal X-ray analysis of compound **3** and presented in Figure 1. CCDC 270847 contains supplementary crystallographic data for the structure **3** (see Figs. 2 and 3).

Reaction of compounds **3** *and* **4** *with 1,3-diketones.* The regioisomers **3** and **4** are independently reacted with 1,3-diketones (symmetrical and unsymmetrical) in a sealed tube under microwave irradiation conditions obtaining pyrimido[1,2-*b*]indazoles **5** in single step. The sequence of reaction is initially nucleophilic attack



Scheme 1.

Table 1. ^{19}F NMR ($CDCl_3$) in ppm data for compounds **5d**, **5f** and **5k**, **5m**, **5n**

	3	4	5d	5f	5k	5m	5n
3-CF_3	—	—	58.78	58.46	—	—	—
4-CF_3	55.04	—	—	—	—	—	—
5-CF_3	—	—	—	—	60.90	61.10	58.07
6-CF_3	—	55.37	—	—	—	—	—
8-CF_3	—	—	66.43	66.95	—	—	—
10-CF_3	—	—	—	—	67.09	67.52	66.42

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