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One-pot regioselective synthesis of tetrahydroindazolones and evaluation of their antiproliferative and Src kinase inhibitory activities

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ABSTRACT

A number of 2-substituted tetrahydroindazolones were synthesized by three-component condensation reaction of 1,3-diketones, substituted hydrazines, benzaldehydes, and $Yb(OTf)_3$ as a catalyst in $[bmim][BF_4]$ ionic liquid using a simple, efficient, and economical one-pot method. The synthesized tetrahydroindazolones were evaluated for inhibition of cell proliferation of human colon carcinoma (HT-29), human ovarian adenocarcinoma (SK-OV-3), and c-Src kinase activity. 3,4-Dichlorophenyl tetrahydroindazolone derivative (**15**) inhibited the cell proliferation of HT-29 and SK-OV-3 cells by 62% and 58%, respectively. 2,3-Diphenylsubstituted tetrahydroindazolone derivatives, **19**, **25**, and **33**, inhibited the cell proliferation of HT-29 cells by 65–72% at a concentration of 50 μM. In general, the tetrahydroindazolones showed modest inhibition of c-Src kinase where 4-tertbutylphenyl- (**32**) and 3,4-dichlorophenyl- (**13**) derivatives showed the inhibition of c-Src kinase with IC_{50} values of 35.1 and 50.7 μM, respectively.

Multi-component reactions (MCRs) have emerged as a powerful synthetic strategy in organic and medicinal chemistry to generate structurally diverse libraries of drug-like molecules.[1] MCRs offer significant advantages over conventional linear-type syntheses, such as being rapid and one-pot reactions without the need to generate and purify intermediates.

Tetrahydroindazolones (THIs) have a broad spectrum of biological and pharmacological activities.[2] Compounds with indazoles and indazolones scaffolds have been reported to exhibit herbicidal,[3] anti-inflammatory,[4] anticancer,[5] and antituberculosis activities.[6] A tetrahydroindazolone scaffold containing SNX-2122 (Fig. 1(a)) is a heat-shock protein 90 (HSP-90) inhibitor,[5a] and it exhibits potent antiproliferative activities against HER2-dependent breast cancer cells.[5b] Tetrahydroindazole-based compound (b) in Figure 1 is a potent inhibitor of *Mycobacterium tuberculosis* (MTB).[6a]

Combretastatin A-4 (CA4) (Fig. 2) is a potent antiproliferative agent which acts through interaction with microtubules. Analogs of CA4 and several other derivatives where *cis*-double bond was replaced with a tetrazole, thiazole, imidazole, or oxazole rings have been synthesized and studied for evaluation of anticancer activities and establishing structure–activity relationships.[7,8] THIs have also been previously reported possessing antitumor activity.[9] The synthesized THIs have structural resemblance to the tetrazole, triazole, imidazole, or oxazole derivatives of CA4 that were shown to exhibit potent cytotoxicity and anti-tumor activity.[7,8] We hypothesized that incorporation of crucial structural features of CA4 and THIs may generate lead compounds with anticancer properties (Fig. 2).

Furthermore, phenylpyrazolopyrimidine derivatives, such as PP1 and PP2[10] have been reported as inhibitors of the Src family of tyrosine kinases (SFKs) that play prominent roles in multiple signal transduction pathways, which involve cell growth and differentiation. The nine members of non receptor SKFs (Src, Yes, Lck, Fyn, Lyn, Fgr, Hck, Blk, and Yrk) share a great deal of structural homology and are present in the cytoplasm.[11] The expression of Src tyrosine kinase, the prototype of SFKs, is frequently elevated in a number of epithelial tumors compared with the adjacent normal tissues. Src reduces cancer cell adhesions and facilitates their motility,[12] thus it is a key modulator of cancer cell invasion and

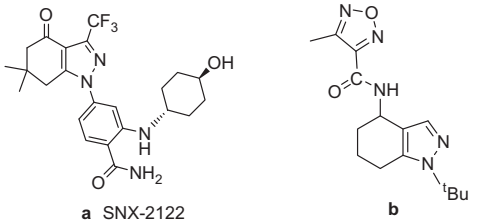

Figure 1. Chemical structures of lead compounds containing tetrahydroindazolone scaffolds (a) SNX-2122: HSP90 inhibitor; (b) MTB inhibitor.

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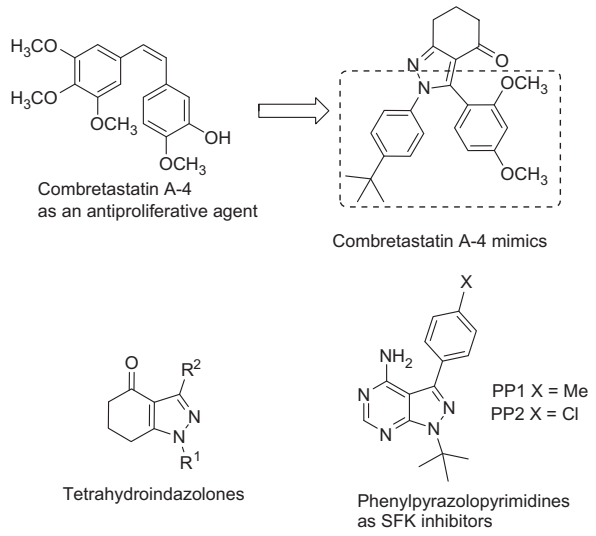


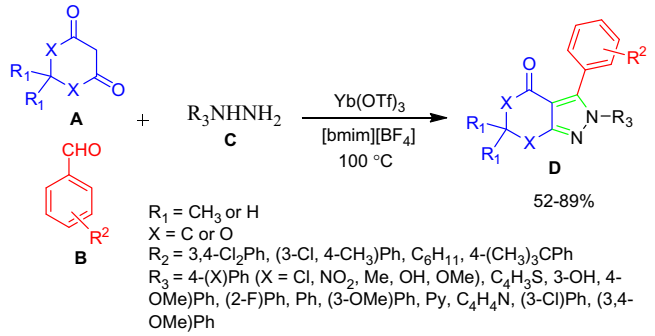
Figure 2. Structural relativity of THIs to combrestatin A-4 mimics and phenylpyrazolopyrimidines as anticancer agents and Src kinase inhibitors, respectively.

metastasis.[13] Heterocyclic THIs have some structural similarity with phenylpyrazolopyrimidine derivatives (Fig. 2), and were investigated to determine whether they can mimic PP1 or PP2.

In continuation of our efforts towards the synthesis of small molecules as anticancer agents and/or *c*-Src kinase inhibitors,[14] herein we report the synthesis and evaluation of an array of 33 synthesized diversely substituted THIs.

The most common method for the synthesis of THIs is simple condensation of arylhydrazines with 2-acylcyclohexane-1,3-diones.[15] However, this method results in regioisomeric mixtures of tetrahydroindazolone. There are only very a few methods for the synthesis of 2-substituted THIs. Separation of 2-substituted THIs from a mixture of isomers is challenging and, therefore, these compounds have not been much explored for biological activity. We have previously reported the synthesis of other heterocyclic compounds through MCRs catalyzed by metal triflates.[16] One-pot three component regioselective synthesis of substituted THIs catalyzed by ytterbium triflate [$Yb(OTf)_3$] in 1-butyl-3-methylimidazolium tetrafluoroborate ([bmim][BF_4]) ionic liquid is shown in Scheme 1.

In a protocol standardization experiment, when 5,5-dimethylcyclohexane-1,3-dione (**2**), 4-chloro-benzaldehyde (**2**), and 3,4-dichlorophenyl hydrazine (**3**) were reacted in ethanol at room temperature in presence of $Yb(OTf)_3$ (20 mol %), the product **4** (R_1 = Me, X = C, R_2 = 3,4-Cl_2Ph, R_3 = 4-ClPh) (see **A**–**D** for general synthesis in Scheme 1) was obtained in 20% yield. Further optimization of reaction condition was carried out by changing solvents,



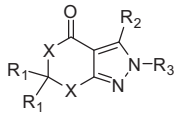
Scheme 1. Synthesis of substituted tetrahydroindazolones.

Table 1
Optimization of reaction conditions for the model reaction

S. No.	Catalyst	Moles (%)	Solvent	Time (h)	Yield[a] (%)
1	$Yb(OTf)_3$	0	[bmim][BF_4]	2.00	45
2	$Yb(OTf)_3$	10	—	2.00	NP[b]
3	$Yb(OTf)_3$	10	[bmim][BF_4]	2.00	51
4	$Yb(OTf)_3$	20	[bmim][BF_4]	2.00	88
5	$Yb(OTf)_3$	30	[bmim][BF_4]	2.00	90
6	$Yb(OTf)_3$	40	[bmim][BF_4]	2.00	89
7	$Zn(OTf)_2$	20	[bmim][BF_4]	2.00	70
8	Ag(OTf)	20	[bmim][BF_4]	2.00	50
9	$Sc(OTf)_3$	20	[bmim][BF_4]	2.00	60
10	$Cu(OTf)_2$	20	[bmim][BF_4]	2.00	56
11	$Yb(OTf)_3$	20	[bmim][PF_6]	2.00	65
12	Mont. K-10	20	Ethanol	2.00	20
13	*p*TSA	20	Ethanol	2.00	20
14	$Yb(OTf)_3$	20	Ethanol	2.00	20
15	$Yb(OTf)_3$	20	Toluene	2.00	NA
16	$Yb(OTf)_3$	20	THF	2.00	NA

[a] Isolated yield.
[b] No product formed.

Table 2
Synthesized 2-substituted THIs (**4**–**36**)



Compd	R^1	X	R^2	R^3	Yield[a] (%)
4	CH_3	C	3,4-$Cl_2C_6H_3$	4-ClC_6H_4	88
5	CH_3	C	3,4-$Cl_2C_6H_3$	4-$NO_2C_6H_4$	85
6	CH_3	C	3,4-$Cl_2C_6H_3$	C_4H_3S	73
7	CH_3	C	3,4-$Cl_2C_6H_3$	4-$CH_3C_6H_4$	83
8	CH_3	C	3,4-$Cl_2C_6H_3$	3-OH,4-$OMeC_6H_3$	65
9	CH_3	C	3,4-$Cl_2C_6H_3$	4-OHC_6H_4	70
10	CH_3	C	3,4-$Cl_2C_6H_3$	C_4H_4N	80
11	CH_3	C	3,4-$Cl_2C_6H_3$	4-$OMeC_6H_4$	74
12	CH_3	C	3,4-$Cl_2C_6H_3$	C_6H_5	75
13	CH_3	C	3,4-$Cl_2C_6H_3$	3-ClC_6H_4	82
14	H	C	3,4-$Cl_2C_6H_3$	4-ClC_6H_4	82
15	H	C	3,4-$Cl_2C_6H_3$	C_4H_3S	71
16	H	C	3,4-$Cl_2C_6H_3$	4-$CH_3C_6H_4$	78
17	H	C	3,4-$Cl_2C_6H_3$	2-FC_6H_4	77
18	H	C	3,4-$Cl_2C_6H_3$	4-$OMeC_6H_4$	70
19	H	C	3,4-$Cl_2C_6H_3$	C_6H_5	72
20	H	C	3,4-$Cl_2C_6H_3$	4-OHC_6H_4	65
21	H	C	3,4-$Cl_2C_6H_3$	3-OH,4-$OMeC_6H_3$	60
22	H	C	3,4-$Cl_2C_6H_3$	4-$NO_2C_6H_4$	84
23	H	C	3-Cl, 4-$CH_3C_6H_3$	3-$OMeC_6H_4$	77
24	CH_3	C	3-Cl, 4-$CH_3C_6H_3$	4-ClC_6H_4	81
25	CH_3	C	3-Cl, 4-$CH_3C_6H_3$	C_5H_4N	69
26	CH_3	C	3-Cl, 4-$CH_3C_6H_3$	C_4H_4N	54
27	CH_3	C	C_6H_{11}	C_4H_3S	78
28	CH_3	C	C_6H_{11}	4-$NO_2C_6H_4$	80
29	CH_3	O	C_6H_{11}	4-ClC_6H_4	50
30	H	C	C_6H_{11}	3-ClC_6H_4	76
31	H	C	C_6H_{11}	4-$CH_3C_6H_4$	76
32	CH_3	C	4-$(CH_3)_3CC_6H_4$	4-$OMeC_6H_4$	77
33	CH_3	C	4-$(CH_3)_3CC_6H_4$	3,4-$(OMe)_2C_6H_3$	81
34	CH_3	C	4-$(CH_3)_3CC_6H_4$	4-ClC_6H_4	77
35	CH_3	O	4-$(CH_3)_3CC_6H_4$	4-ClC_6H_4	48
36	CH_3	C	4-$(CH_3)_3CC_6H_4$	4-$CH_3C_6H_4$	79

[a] Isolated yield.

catalysts, and catalyst loading. As shown in Table 1, the use of 20 mol % $Yb(OTf)_3$ in [bmim][BF_4] gave the desired product **4** in high yield (88%) (entry 4). When $Yb(OTf)_3$ was changed with other metal triflates such as $Sc(OTf)_3$, $Zn(OTf)_2$, $Cu(OTf)_2$ or AgOTf the yield of **4** was moderate to good (Table 1, entries 7–10). The catalytic order $Yb(OTf)_3$ > $Zn(OTf)_2$ > $Sc(OTf)_3$ > $Cu(OTf)_2$ > AgOTf