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.

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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
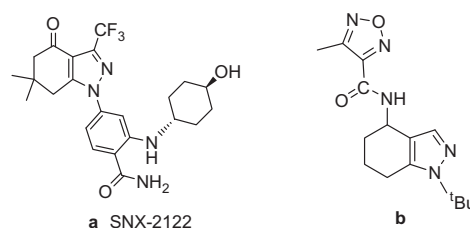

Figure 1. Chemical structures of lead compounds containing tetrahydroindazolone scaffolds (a) SNX-2122: HSP90 inhibitor; (b) MTB inhibitor.

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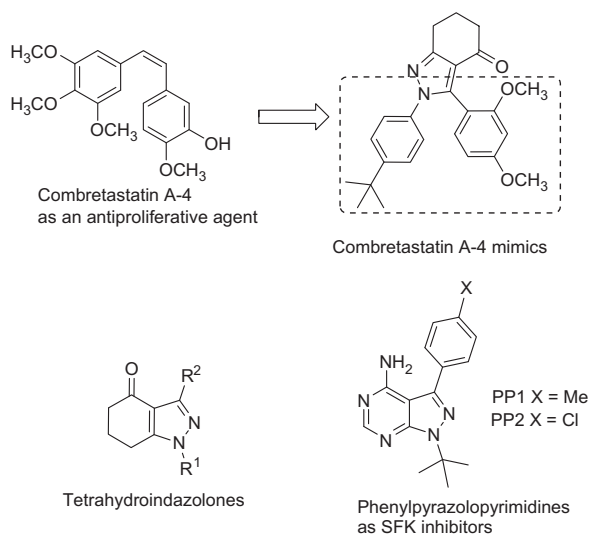 E-mail address: kparang@uri.edu (K. Parang).

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-dimethyl-cyclohexane-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$_2$Ph, 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,
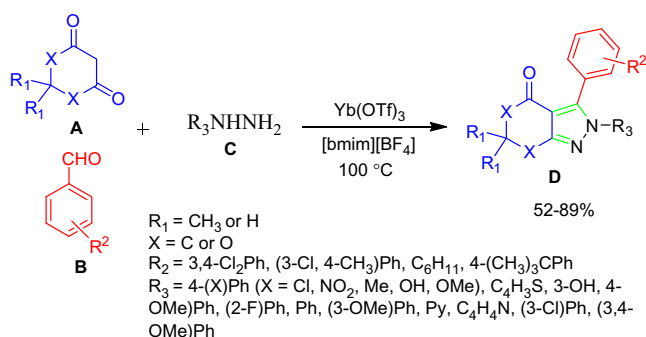
**Scheme 1.** Synthesis of substituted tetrahydroindazolones.

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	pTSA	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**)
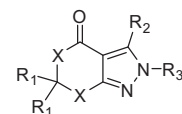
Compd	R^1	X	R^2	R^3	Yield[a] (%)
4	CH$_3$	C	3,4-Cl$_2$C$_6$H$_3$	4-ClC$_6$H$_4$	88
5	CH$_3$	C	3,4-Cl$_2$C$_6$H$_3$	4-NO$_2$C$_6$H$_4$	85
6	CH$_3$	C	3,4-Cl$_2$C$_6$H$_3$	C$_4$H$_3$S	73
7	CH$_3$	C	3,4-Cl$_2$C$_6$H$_3$	4-CH$_3$C$_6$H$_4$	83
8	CH$_3$	C	3,4-Cl$_2$C$_6$H$_3$	3-OH,4-OMeC$_6$H$_3$	65
9	CH$_3$	C	3,4-Cl$_2$C$_6$H$_3$	4-OHC$_6$H$_4$	70
10	CH$_3$	C	3,4-Cl$_2$C$_6$H$_3$	C$_4$H$_4$N	80
11	CH$_3$	C	3,4-Cl$_2$C$_6$H$_3$	4-OMeC$_6$H$_4$	74
12	CH$_3$	C	3,4-Cl$_2$C$_6$H$_3$	C$_6$H$_5$	75
13	CH$_3$	C	3,4-Cl$_2$C$_6$H$_3$	3-ClC$_6$H$_4$	82
14	H	C	3,4-Cl$_2$C$_6$H$_3$	4-ClC$_6$H$_4$	82
15	H	C	3,4-Cl$_2$C$_6$H$_3$	C$_4$H$_3$S	71
16	H	C	3,4-Cl$_2$C$_6$H$_3$	4-CH$_3$C$_6$H$_4$	78
17	H	C	3,4-Cl$_2$C$_6$H$_3$	2-FC$_6$H$_4$	77
18	H	C	3,4-Cl$_2$C$_6$H$_3$	4-OMeC$_6$H$_4$	70
19	H	C	3,4-Cl$_2$C$_6$H$_3$	C$_6$H$_5$	72
20	H	C	3,4-Cl$_2$C$_6$H$_3$	4-OHC$_6$H$_4$	65
21	H	C	3,4-Cl$_2$C$_6$H$_3$	3-OH,4-OMeC$_6$H$_3$	60
22	H	C	3,4-Cl$_2$C$_6$H$_3$	4-NO$_2$C$_6$H$_4$	84
23	H	C	3-Cl, 4-CH$_3$C$_6$H$_3$	3-OMeC$_6$H$_4$	77
24	CH$_3$	C	3-Cl, 4-CH$_3$C$_6$H$_3$	4-ClC$_6$H$_4$	81
25	CH$_3$	C	3-Cl, 4-CH$_3$C$_6$H$_3$	C$_5$H$_4$N	69
26	CH$_3$	C	3-Cl, 4-CH$_3$C$_6$H$_3$	C$_4$H$_4$N	54
27	CH$_3$	C	C$_6$H$_{11}$	C$_4$H$_3$S	78
28	CH$_3$	C	C$_6$H$_{11}$	4-NO$_2$C$_6$H$_4$	80
29	CH$_3$	O	C$_6$H$_{11}$	4-ClC$_6$H$_4$	50
30	H	C	C$_6$H$_{11}$	3-ClC$_6$H$_4$	76
31	H	C	C$_6$H$_{11}$	4-CH$_3$C$_6$H$_4$	76
32	CH$_3$	C	4-(CH$_3$)$_3$CC$_6$H$_4$	4-OMeC$_6$H$_4$	77
33	CH$_3$	C	4-(CH$_3$)$_3$CC$_6$H$_4$	3,4-(OMe)$_2$C$_6$H$_3$	81
34	CH$_3$	C	4-(CH$_3$)$_3$CC$_6$H$_4$	4-ClC$_6$H$_4$	77
35	CH$_3$	O	4-(CH$_3$)$_3$CC$_6$H$_4$	4-ClC$_6$H$_4$	48
36	CH$_3$	C	4-(CH$_3$)$_3$CC$_6$H$_4$	4-CH$_3$C$_6$H$_4$	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
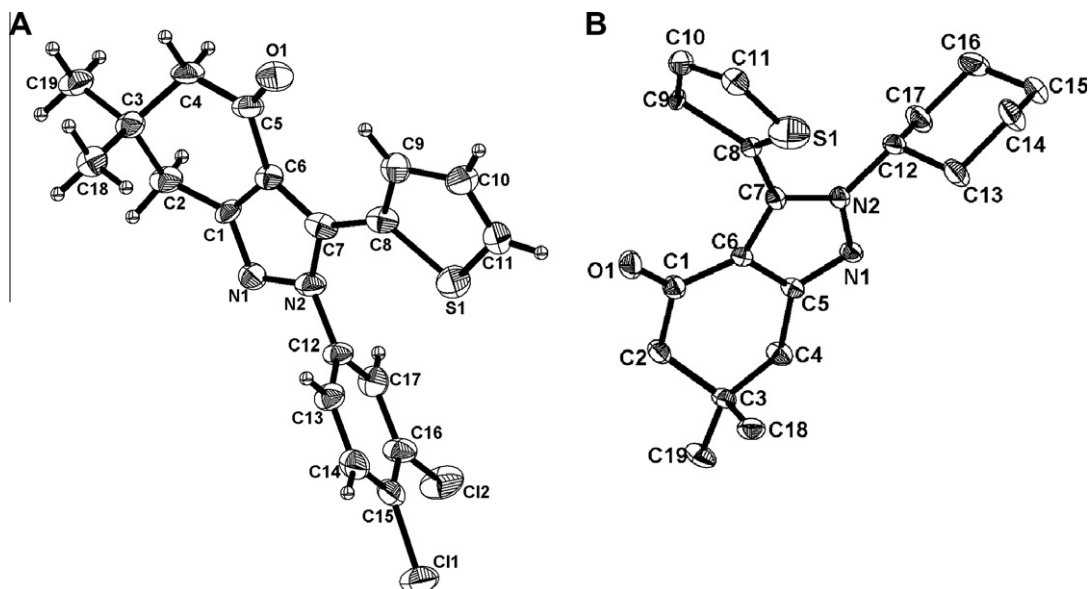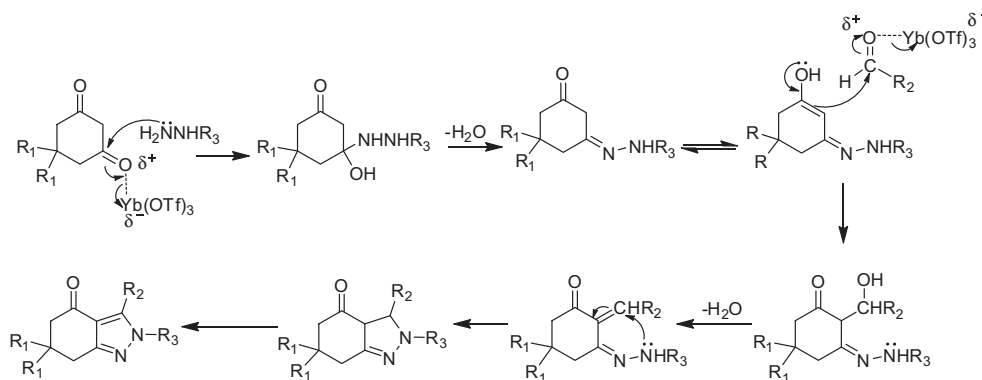
Figure 3. ORTEP view of molecular structure of compound **27**.

Scheme 2. Plausible mechanism for synthesis of THIs.

was established for the synthesis of **4** based on isolated yield in [bmim][BF$_4$]. There was not much increase in yield of **4** on changing the amount of Yb(OTf)$_3$ from 20 mol % to 40 mol % (Table 1, entries 4–6). However, reducing the amount of Yb(OTf)$_3$ decreased yield of **4** to 51%. It should be noted that no product formation was observed in solvent free conditions; however 45% of **4** was formed in the absence of Yb(OTf)$_3$. The structure of the compound **4** was confirmed by ^{1}H NMR, ^{13}C NMR, and mass spectrometry. In ^{1}H NMR three singlet peaks were observed at δ 2.81, 2.42 and 1.16 ppm for C$_7$-CH$_2$, C$_5$-CH$_2$, and C$_6$-(CH$_3$)$_2$, respectively, along with other aromatic protons. It is worthy to mention that under these conditions only 2-substituted tetrahydroindazolones were obtained.

Under the optimized reaction conditions, various arylhydrazines, arylaldehydes, and 1,3-diones underwent one-pot reaction and afforded the corresponding 2-substituted THIs (**4**–**36**) (Table 2). Various benzaldehydes and arylhydrazines with electron withdrawing and donating substituents, such as nitro, halo, hydroxyl, methoxy, alkyl, and aryl, were used to establish the structure–activity relationships.

The chemical structures of all synthesized compounds were elucidated by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy (Supplementary data). A single peak for two protons of C$_7$-carbon at around 2.8 ppm confirmed formation of only a single isomer. These

values are in agreement with the literature report for regioselective formation of 2-substituted THIs.[15d] Furthermore, regioselective formation of 2-substituted THIs was confirmed by X-ray crystallographic data for compound **6** (CCDC 848784) and **27** (CCDC 850178). The ORTEP view for compound **6** (Fig. 3A) and **27** (Fig. 3B) clearly shows that 3,4-dichlorophenyl and cyclohexyl group are at N-2 position in **6** and **27**, respectively.

The regioselective formation of N-2-substituted THI indicates that hydrazine first attacks at carbonyl group of diketone. Based on the product formation the reaction is believed to proceed through the formation of hydrazone followed by attack of aldehyde to give aldol product, which undergoes nucleophilic addition as shown in Scheme 2. It appears that ionic liquid helps in stabilization of charged intermediate generated by coordination of Yb(OTf)$_3$ to aldehydes and diones. Furthermore, the acidic C-2 proton of imidazolium ionic liquid also facilitates the enolization of dione.

All the synthesized compounds (**4**–**36**) were evaluated for their effect on proliferation of ovarian adenocarcinoma cells (SK-OV-3) and colon adenocarcinoma (HT-29), two human cancer cells lines that overexpress c-Src.[17] Doxorubicin (Dox) and DMSO were used as positive and negative controls, respectively. The results for cell proliferation at 50 μM after 72 h for compounds **4**–**30** are shown in Fig. 4. All the compounds were more active against HT-29 cells than SK-OV-3 cells. Compounds **19**, **25**, and **33** inhibited the cell
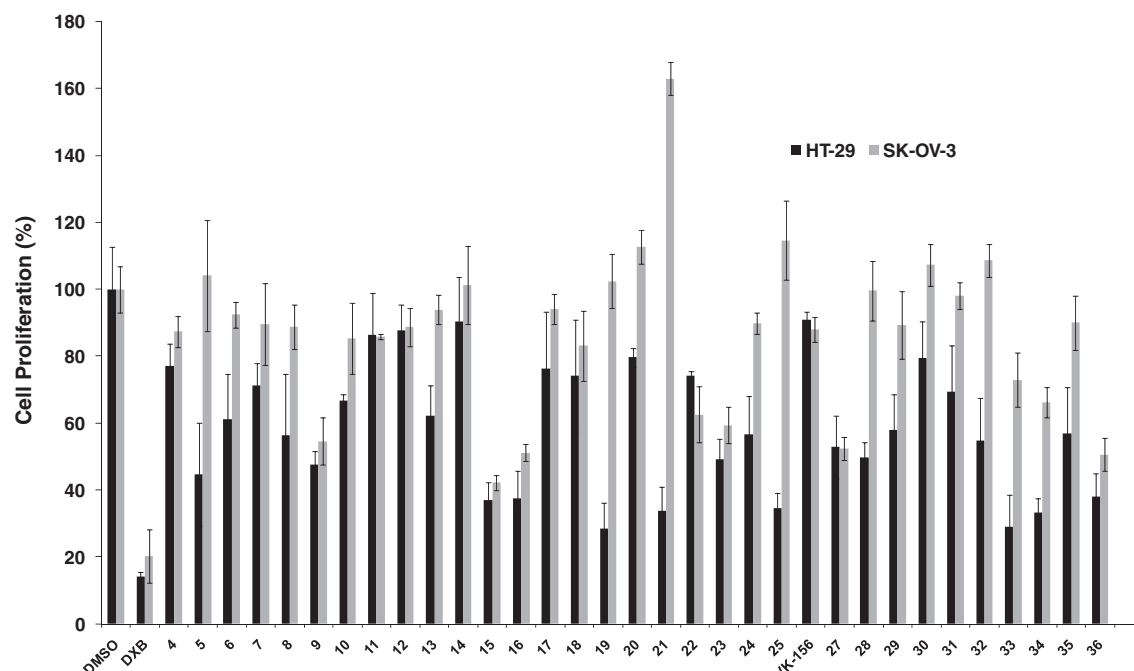
Figure 4. Inhibition of HT-29 and SK-OV-3 cell proliferation by compounds **4–33** (50 μM) after 72 h incubation. The results are shown as the percentage of the control DMSO that has no compound (set at 100%). All the experiments were performed in triplicate.

Table 3
Src kinase inhibitory activity of substituted THIs (**4–36**)

Compd	IC_{50}^a (μM)	Compd	IC_{50}^a (μM)
4	86.0	**22**	>150
5	>150	**23**	82.7
6	>150	**24**	131.8
7	>150	**25**	74.3
8	>150	**26**	>150
9	66.6	**27**	77.3
10	>150	**28**	>150
11	94.1	**29**	>150
12	62.1	**30**	58.4
13	50.7	**31**	57.7
14	81.0	**32**	35.1
15	>150	**33**	>150
16	>150	**34**	>150
17	>150	**35**	>150
18	>150	**36**	>150
19	65.8	Staurosporine	0.6
20	>150	**PP2**	0.5
21	>150		

^a The concentration at which 50% of enzyme activity is inhibited.

a The concentration at which 50% of enzyme activity is inhibited.

Figure 5. Comparison of structural complexes of Src kinase with different THIs derivatives. **32** (yellow), PP1 (blue), and **13** (red) based on molecular modeling. The compounds and side chains of amino acids are rendered in stick styles. Compounds are in the lowest energy conformers predicted. The Figure is drawn using the Accelrys visualization system.

proliferation of HT-29 cells by 65–72% while they were not effective against SK-OV-3. Compounds **15**, **16**, and **27** showed 48–62% and 49–58% inhibition in the cell proliferation of HT-29 and SK-OV-3 cells, respectively. The presence of $C_4H_3S–$ substituent as R_3 or 3,4-dichlorophenyl or tolyl as R_2 is critical for maximum antiproliferative activity as seen in compounds **15** and **16**.

Synthesized substituted THIs were evaluated for c-Src kinase inhibitory activity. The results of Src kinase inhibitory activity of compounds (**4–33**) are shown in Table 3. Among all the compounds, **12**, **13**, **19**, **30**, **31**, and **32** showed modest inhibition of Src kinase with IC_{50} values in the range of 35–69 μM.

Compounds **32** and **13** were found to show the highest Src kinase inhibitory activities with IC_{50} values of 35.1 and 50.7 μM, respectively, among all the compounds. Molecular modeling and minimization of compounds **32** and **13** was used to explore and
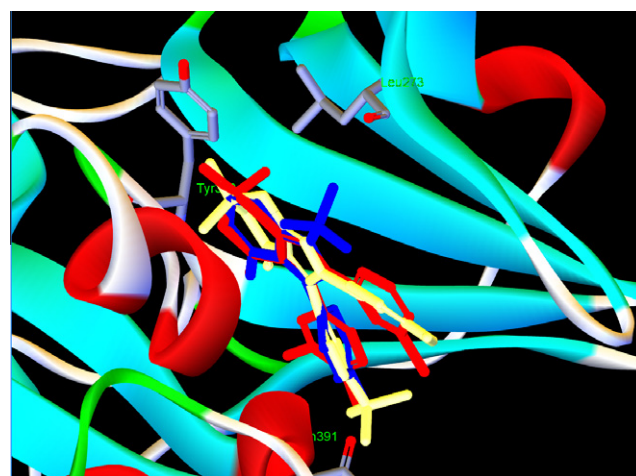
compare with the binding mode of these compounds when compared with PP1 within the ATP-binding site of the enzyme (Fig. 5). The backbone tetrahydroindazolone in **32** and **13** and pyrazolopyrimidine in PP1 occupied a similar pocket in ATP-binding site of Src. The modeling studies indicated that 3,4-dichlorophenyl and 4-(*tert*)butylphenyl at R_2 position in **13** and **32**, respectively, occupy and fit the hydrophobic binding pocket similar to tolyl group of PP1 with slightly different orientations of phenyl groups (Fig. 5). The 4-methoxyphenyl and 3-chlorophenyl at R_3 position of **32** and **13**, respectively, are oriented far from the large cavity that is formed from side chains of helix αC and helix αD, where the triphosphate group of ATP usually binds similar to that of *t*-butyl group of PP1, thus suggesting that substitution at R_3 position of THIs does not generate any advantageous in Src kinase inhibition

through interactions with adjacent amino acids in the ATP binding site.

These data suggest that further structural modifications in tetrahydroindazolone scaffold is required to convert them to more potent Src kinase inhibitors such as phenylpyrazolopyrimidine derivatives PP1 and PP2. Poor correlation between inhibition of Src kinase and the cell proliferation could be due to the differential cellular uptake and alternative mechanisms in antiproliferative activities of the compounds.

In conclusion, an ecofriendly and regioselective method was developed for the synthesis of 2-substituted THIs by one-pot three-component coupling reaction of benzaldehydes, arylhydrazines, and 1,3-diones using Yb(OTf)$_3$ as a catalyst in ionic liquid. To the best of our knowledge, this is the first report of one-pot synthesis and evaluation of THIs as Src kinase inhibitors and anticancer agents. The synthesized compounds were evaluated for c-Src kinase inhibitory activity and compound **32** showed moderate inhibition of Src kinase with an IC$_{50}$ value of 35.1 μM. Compounds **15** and **16** consistently inhibited the cell proliferation of SK-OV-3 and HT-29 cells by 49–62% at a concentration of 50 μM. Further structure–activity relationship studies are required for optimizing the Src kinase inhibition and antiproliferative activities of THIs.

Acknowledgments

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.10.124.

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