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V. Kameshwara Rao
Defence Research & Development Establishment

Bhupender S. Chhikara
University of Rhode Island

Rakesh Tiwari
Chapman University, tiwari@chapman.edu

Amir Nasrolahi Shirazi
Chapman University, shirazi@chapman.edu

Keykavous Parang
Chapman University, parang@chapman.edu

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

V. Kameshwara Rao,[a] Bhupender S. Chhikara,[b] Rakesh Tiwari,[b] Amir Nasrolahi Shirazi,[b] Keykavous Parang[b,*] Anil Kumar[a,*]

[a]*Department of Chemistry, Birla Institute of Technology and Science, Pilani 333031, Rajasthan, India*

[b]*Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island, Kingston, RI, 02881, USA*

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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 μM 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 (**a**, Fig. 1) 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 Fig. 1 is a potent inhibitor of *Mycobacterium tuberculosis* (MTB).[6a]

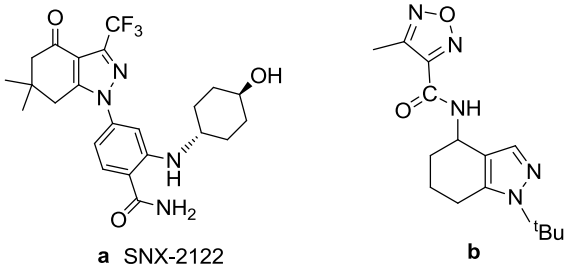


Figure 1. Chemical structures of lead compounds containing tetrahydroindazolone scaffolds (a) SNX-2122: HSP90 inhibitor; (b) MTB inhibitor.

Combretastatin A-4 (CA4) (Fig. 2) is a potent antiproliferative agent which acts through interaction with microtubules. Analogues 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 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.

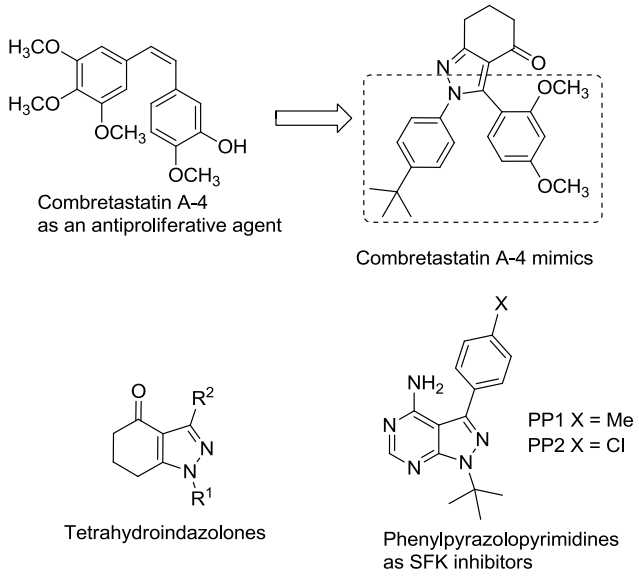
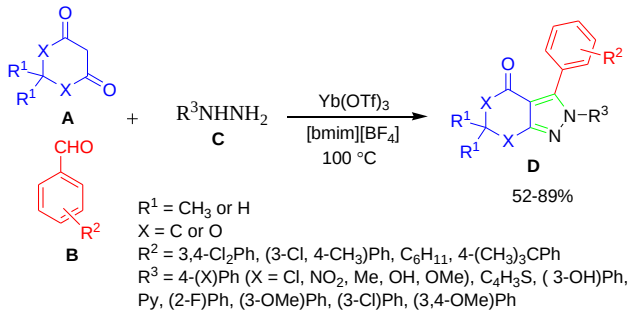


Figure 2. Structural relativity of THIs to Combrestatin A-4 mimics and phenylpyrazolopyrimidines as anticancer agents and Src kinase inhibitors, respectively.

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 mole %), 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, 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 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.



Scheme 1. Synthesis of substituted tetrahydroindazolones.

Table 1. Optimization of reaction conditions for the model reaction.

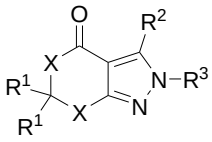
S. No	Catalyst	Moles (%)	Solvent	Time (h)	Yield (%)[a]
1	$Yb(OTf)_3$	0	[bmim][BF_4]	2.00	45
2	$Yb(OTf)_3$	10	-	2.00	NP[b]
3	$Yb(OTf)_3$	10	[bmim][BF_4]	2.00	51
4	$Yb(OTf)_3$	20	[bmim][BF_4]	2.00	88
5	$Yb(OTf)_3$	30	[bmim][BF_4]	2.00	90
6	$Yb(OTf)_3$	40	[bmim][BF_4]	2.00	89
7	$Zn(OTf)_2$	20	[bmim][BF_4]	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

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.

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

The chemical structures of all synthesized compounds were elucidated by ^{1}H NMR, ^{13}C NMR, and mass spectroscopy (Supporting information). 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] Furthemore, regioselective formation of 2-substituted THIs was confirmed by X-ray crystalographic 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.

(A) (B)

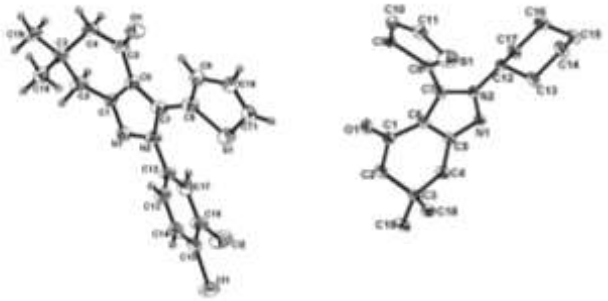
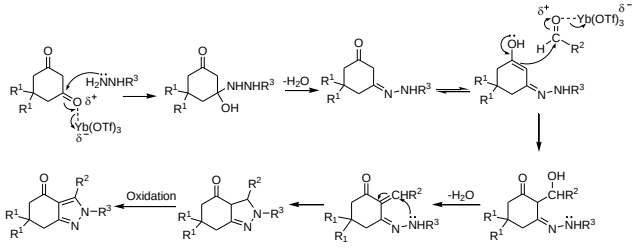


Figure 3. ORTEP view of molecular structure of compound (A) **6** and (B) **27**.

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.



Scheme 2: Plausible mechanism for synthesis of THIs.

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 compound **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 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 anti-proliferative activity as seen in compounds **15** and **16**.

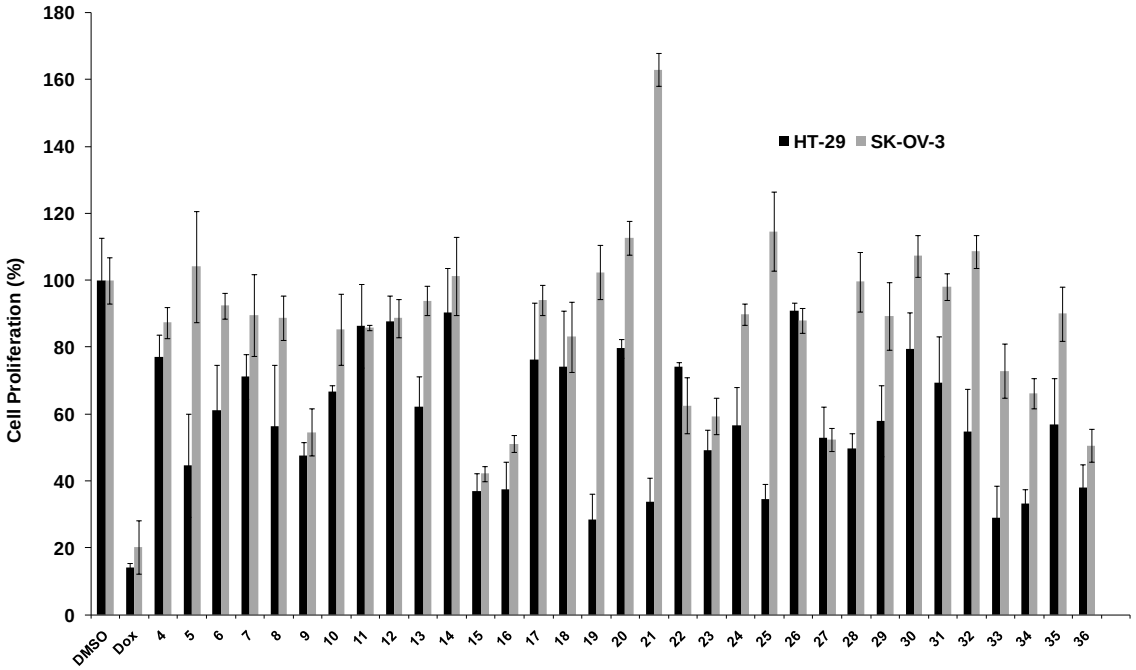


Figure 4. Inhibition of HT-29 and SK-OV-3 cell proliferation by compounds **4**–**33** (50 µM) after 72 h incubation. The results are shown as the percentage of the control DMSO that has no compound (set at 100%). All the experiments were performed in triplicate.

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.

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

Compd.	IC_{50} (µM)[a]	Compd.	IC_{50} (µM)[a]
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.

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 anti-proliferative activities of the compounds.

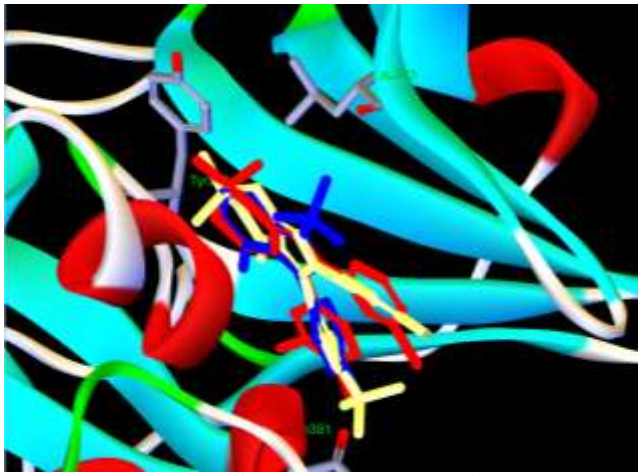


Figure 5. Comparison of structural complexes of Src kinase with different THIs derivatives. **32** (yellow), PP1 (blue), and **13** (red)) based on molecular modeling. The compounds and side chains of amino acids are rendered in stick styles. Compounds are in the lowest energy conformers predicted. The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

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 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 anti-proliferative activities of THIs.

Acknowledgments

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Supplementary data

Supplementary data containing experimental procedures for c-Src kinase assay and cell culture, and physical and spectral for compounds (**4–36**) can be found in the online version of this article.

References and notes

1. D. B. Rubinov, I. L. Rubinova, A. A. Akhrem, *Chem. Rev.* **1999**, 99, 1047.
2. (a) Rosati, O.; Curini, M.; Marcotullio, M. C.; Macchiarulo, A.; Perfumi, M.; Mattioli, L.; Rismondo, F.; Cravotto, G. *Bioorg. Med. Chem. Lett.* **2007**, 15, 3463; (b) Connolly, P. J.; Wetter, S. K.; Beers, K. N.; Hamel, S. C.; Johnson, D. H.; Kiddoe, M.; Kraft, P.; Lai, M. T.; Campen, C.; Palmer, S.; Phillips, A. *Bioorg. Med. Chem. Lett.* **1997**, 7, 2551.
3. Benson, G. M.; Bleicher, K.; Grether, U.; Kirchen, E.; Kuhn, B.; Richter, H.; Taylor, S. US2010/0076027 A1, **2010**.
4. Claramunt, O. M.; Lopez , C.; Medina, C. P.; Torralba, M. P.; Elguero, J.; Escames, G.; Castroviejo, D. A. *Bioorg. Med. Chem. Lett.* **2009**, *17*, 6180.
5. (a) Huang, K. H.; Veal, J. M.; Fadden, R. P.; Rice, J. W.; Eaves, J.; Strachan, J. P.; Barabasz, A. F.; Foley, B. E.; Barta, T. E.; WeiMa, M. A.; Hu, S. M.; Partridge, J. M.; Scott, A.; DuBois, L. G.; Freed, T.; Steed, P.; Ommen, A. J.; Smith, E. D.; Hughes, P. F.; Woodward, A. R.; Hanson, G. R.; StephenMcCall, W.; Markworth, C. J.; Hinkley, L.; Jenks, M.; Lewis, L. M.; Otto, J.; Pronk, B.; Verleysen, K.; Hal, S. E. *J. Med. Chem.* **2009**, *52*, 4288. (b) Chandarlapaty, S.; Sawai, A.; Ye, Q.; Scott, A.; Silinski, M.; Huang, K.; Fadden, P.; Partdrige, J.; Hall, S.; Steed, P.; Norton, L.; Rosen, N.; Solit, D. B. *Clin Cancer Res*, **2008**, *14*, 240.
6. (a) Guo, S.; Song, Y.; Huang, Q.; Yuan, H.; Wan, B.; Wang, Y.; He, R.; Beconi, M. G.; Franzblau, S. G.; Kozikowski, A. P. *J. Med. Chem.* **2010**, *53*, 649; (b) Strakova, I.; Turks, M.; Strakovs, A. *Tetrahedron Lett.* **2009,** *50*, 3046; (c) Guo, S.; Song, Y.; Huang, Q.; Yuan, H.; Wan, B.; Wang, Y.; He, R.; Beconi, M. G.; Franzblau, S. G.; Kozikowski, A. P. *J. Med. Chem.* **2010**, *53*, 649; (d) Nagakura, M.; Ota, T.; Shimidzu, N.; Kawamura, K.; Eto, Y.; Wada, Y. *J. Med. Chem.* **1979**, *22*, 48.
7. (a) Cirla, A.; Mann, J. *Nat. Prod. Rep.* **2003**, *20*, 558; (b) Ohsumi, K.; Nakagawa, R.; Fukuda, Y.; Hatanaka, T.; Morinaga, Y.; Nihei, Y.; Ohishi, K.; Suga, Y.; Akiyama, Y.; Tsuji, T. *J. Med. Chem.* **1998**, *41*, 3022.
8. (a) Ohsumi, K.; Hatanaka, T.; Fujita, K.; Nakagawa, R.; Fukuda, Y.; Niher, Y.; Suga, Y.; Morinaga, Y.; Akiyama, Y.; Tsuji, T. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3153; (b) Wang, L.; Woods, K. W.; Li, Q.; Kenneth, J. B.; McCroskey, R. W.; Hannick, S. M.; Gherke, L.; Credo, R. B.; Hui, Y. H.; Marsh, K.; Warner, R.; Lee, J. Y.; Zielinski-Mozng, N.; Frost, D.; Rosenberg, S. H.; Sham, H. L. *J. Med. Chem.* **2002**, *45*, 1697; (c) Kumar, D.;

Reddy, V. B.; Chang, K.-H.; Shah, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2320.

9. Pevarello, P.; Villa, M.; Varasi, M.; Isacchi, A. *Int. Pat. Appl.* WO0069846, 2000; *Chem. Abstr*. 2000, 133, 362767.
10. (a) Schindler, T.; Sicheri, F.; Pico, A.; Gazit, A.; Levitzki, A.; Kuriyan, J. *Mol Cell* **1999**, *3*, 639. Zhao, H.; Morgenstern, K. A. *Structure Fold Des.* **1999**, *7*, 651; (b) Zhu, X.; Kim, J. L.; Newcomb, J. R.; Rose, P. E.; Stover, D. R.; Toledo, L. M.; Zhao, H.; Morgenstern, K. A. *Structure* **1999**, *7*, 651.
11. (a) Bamborough, P.; Drewry, D.; Harper, G.; Gary G. K.; Smith, K.; Schneider, K. J. *J. Med. Chem.* **2008**, *51*, 7898; (b) Roskoski, J. R. *Biol. Chem. **2004**. 324.* 1155; (c) Thomas, S. M.; Brugge, J. S. *Annu. Rev. Cell Dev. Biol.* **1997**, *13*, 513.
12. (a) Summy, J. M.; Gallick, G. E. *Cancer Metastasis Rev.* **2003**, *22*, 337. (b)Yeatman, T. J. *Nat. Rev. Cancer* **2004**, *4*, 470.
13. (a) Frame, M. C. *Biochim. Biophys. Acta* **2002**, 1602, 114; (b) Irby, R. B.; Yeatman, T. J. *Oncogene* **2000**, *19*, 5636; (c) Summy, J. M.; Gallick, G. E. *Clin. Cancer Res.* **2006**, *12*, 1398; (d) Biscardi, J. S.; Ishizawar, R. C.; Silva, C. M.; Parsons, S. J. *Breast Cancer Res.* **2000**, 2, 203; (e) Fizazi, K. *Ann. Oncol.* **2007**, *18*, 1765.
14. (a) Parang, K.; Sun, G. *Expert Opin. Ther. Patents*, **2005**, *15*, 1183; (b) Kumar, A.; Wang Y.; Lin X.; Sun G.; Parang K. *ChemMedChem*, **2007**, *2*, 1346; (c) Kumar, D.; Reddy, V. B.; Kumar, A.; Mandal, D.; Tiwari, R.; Parang, K. *Bioorg. Med. Chem. Lett.* **2011**, *12*, 449; (d) Kumar, A.; Ahmad, I.; Chhikara, B. S.; Tiwari, R.; Mandal, D.; Parang, K. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1342; (e) Rao, V. K.; Chhikara, B. S.; Shirazi, A. N.; Tiwari, R.; Parang, K.; Kumar, A. *Bioorg. Med. Chem. Lett.* **2011**, 21, 3511; (f) Chhikara, B. S.; Mandal, D.D.; Parang, K. *Eur. J. Med. Chem.*, **2010**, 45, 4601; (g) Chhikara, B. S.; Parang, K. *Expert Opin. Drug Del.* **2010**, *7*, 1399; (h) Chhikara, B. S.; Jeans, N.S.; Mandal, D.; Kumar, A.; Parang, K. *Eur. J. Med. Chem.* **2011**, *46*, 2037.
15. (a) Strakova, I.; Strakovs, A.; Petrova, M. *Chem. Heterocycl. Compd.* **2005**, *41*, 1398; (b) Strakova, I.; Strakovs, A.; Petrova, M. *Chem. Heterocycl. Compd.* **2005**, *41*, 1405; (c) Kennedy, L. J. *Synlett* **2008**, 600; d) Kim, J.; Song, H.; Park, S. B. *Eur. J. Org. Chem*. **2010**, *10*, 3815.
16. (a) Rao, M. S.; Ahmad, I.; Khungar, B.; Kumar, A. *Can. J. Chem.* **2009**, *87*, 714. b) Kumar, A.; Rao, M. S.; Ahmad, I.; Khungar, B. *Aus. J. Chem.* **2009**, *62*, 322; (c) Kumar, A.; Rao, M. S.; Rao, V. K. *Aust. J. Chem.* **2010**, *63*, 1538; (d) Kumar, A.; Rao, M. S.; Rao, V. K. *Aust. J. Chem*. **2010**, *63*, 135.
17. (a) Budde, R. J.; Ke, S.; Levin, V. A. *Cancer Biochem. Biophys*. **1994**, *14*, 171; (b) Belches-Jablonski, A. P.; Biscardi, J. S.; Peavy, D. R.; Tice, D. A.; Romney, D. A.; Parsons, S. J. *Oncogene*, **2001**, *20*, 1465.