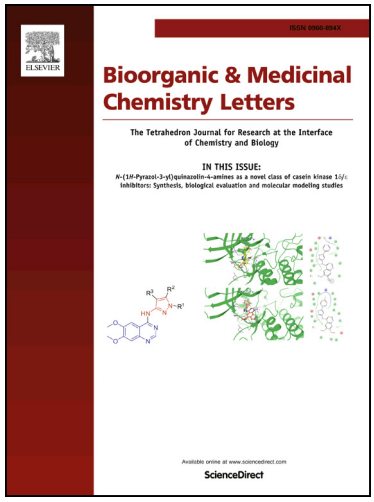
Accepted Manuscript



Design, synthesis, *in-silico* and *in-vitro* evaluation of thiophene derivatives: A potent tyrosine phosphatase 1B inhibitor and anticancer activity

Kali Charan Gulipalli, Srinu Bodige, Parameshwar Ravula, Srinivas Endoori, G.R. Vanaja, G. Sureshbabu, J.N. Narendra Sharath Chandra, Nareshvarma Seelam

PII: S0960-894X(17)30528-0
DOI: http://dx.doi.org/10.1016/j.bmcl.2017.05.047
Reference: BMCL 24992

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 8 March 2017
Revised Date: 6 May 2017
Accepted Date: 16 May 2017

Please cite this article as: Gulipalli, K.C., Bodige, S., Ravula, P., Endoori, S., Vanaja, G.R., Sureshbabu, G., Narendra Sharath Chandra, J.N., Seelam, N., Design, synthesis, *in-silico* and *in-vitro* evaluation of thiophene derivatives: A potent tyrosine phosphatase 1B inhibitor and anticancer activity, *Bioorganic & Medicinal Chemistry Letters* (2017), doi: http://dx.doi.org/10.1016/j.bmcl.2017.05.047

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

ACCEPTED MANUSCRIPT

Design, synthesis, *in-silico* and *in-vitro* evaluation of thiophene derivatives: A potent tyrosine phosphatase 1B inhibitor and anticancer activity

Kali Charan Gulipalli [a], Srinu Bodige [a], Parameshwar Ravula [b], Srinivas Endoori [a], Vanaja.GR[c], Sureshbabu G [c], JN. Narendra Sharath Chandra [d], Nareshvarma Seelam [a]*

[a] *Department of Chemistry, KL University, Green fields, Vaddeswaram, Guntur, 522502, India*

[b] *Department of Pharmaceutical Chemistry, Gurunanak Institutions Technical Campus, School of pharmacy, Hyderabad, India*

[c] *Department of Animal Biology, University of Hyderabad, Hyderabad, 500046, India*

[d] *Department of Pharmaceutical Chemistry, Bharath Institute of Technology- Pharmacy, Hyderabad, India*

***** Corresponding author: email: nareshvarma.klu@gmail.com
Tel: +91-7386591580

Abstract

A series of novel methyl 4-(4-amidoaryl)-3-methoxythiophene-2-carboxylate derivatives were designed against the active site of protein tyrosine phosphatise 1B (PTP1B) enzyme using MOE.2008.10. These molecules are also subjected for *in silico* toxicity prediction studies and considering their corresponding drug scores, it implied that, the molecules are promising as anticancer agents. The designed compounds were synthesized by using suitable methods and characterized. They were subjected to inhibitory activity against PTP1B and *in vitro* anticancer activity by MTT assay. Most of the tested compounds showed potent inhibitory activity against PTP1B, among the compounds tested, compound **5b** exhibited the highest activity (IC_{50} = 5.25 µM) and remarkable cytotoxic activity at 0.09 µM of IC_{50} against the MCF-7 cell line. In addition to this, compound **5c** also showed potential anticancer activity at 2.22 µM of IC_{50} against MCF-7 and 0.72 µM against HepG2 cell lines as well as PTP1B inhibitory activity at IC_{50} of 6.37 µM.

Keywords: synthesis, anticancer, molecular docking, protein tyrosine phosphatase inhibitor

ACCEPTED MANUSCRIPT

Protein tyrosine phosphatase 1B (PTP1B) is an intracellular phosphorylating enzyme, which controls both insulin and leptin signalling pathway and uses glucose for energy expenditure. PTP1B plays a prominent role in the regulation of metabolism. Hence, over expression of this enzyme can lead to various metabolic disorders, including diabetes, obesity, inflammation, cancer and Alzheimer's disease.[1-5] PTP1B regulates different growth factors such as epidermal and insulin, and it also controls receptor tyrosine kinase, which further regulates cell growth, cell proliferation, cell differentiation, cell to cell contact, cell glucose metabolism and cell insulin regulation.[6] Over expression of PTP1B, raises Src specific activity in colon cancer cell,[7, 8] and as such is mainly associated with P185c-erbB protein expression pathway and produces activation of stat5 induced phosphorylation in breast cancer patients.[9] The literature study, suggested the correlation between PTP1B depletion and breast cancer, inducing diminished oxygen supply to cells. Further, it can induce necrosis of breast cancer cells followed by hypoxia induced cell death. PTP1B promotes cell proliferation and metastasis through activating Src and Erk 1/2 in lung cancer cell. Moreover, PTP1B has recently been reported to function as an oncogene in breast cancer. Its inhibitors can be potentially used for the treatment of breast cancer. Therefore, PTP1B forms an important target for the treatment of cancer.[10]

In recent year, much attention has been paid by the researchers to the chemistry of the versatile heterocyclic rings bearing different functionalities to target PTP1B enzyme, namely; isoxazoles[11], tetrazoles[12], thiazolidinedione derivatives[13, 14], triaryl sulfonamide derivatives[15], pyrroloazepines[16], benzotriazoles[17] and thiophene derivatives[18, 19]. Compounds bearing thiophene nucleus are among the widely explored molecules to target against PTP1B active site to improve their binding affinity. Recently, Wyeth pharmaceuticals performed structure based optimization and identified a series of thiophenes that can be used as potent PTP1B inhibitors.[20, 21]

In present study, substituents were decided on the thiophene ring by virtual screening of thiophene analogous using chemexper software on java window, correlating physiochemical properties and bioavailability. It calculates molecular weight, lipophilicity, solubility, bioavailability, drug score, mutagenicity, tumorigenicity, irritancy and C Log P. The virtual substituted thiophene analogous with significant drug score computed values along with least predicted toxicity scores, have been the main variables, facilitating lead optimization. Furthermore, selected structures were subjected to molecular docking studies using MOE

ACCEPTED MANUSCRIPT

software version 2008.10.[22, 23] Docking studies assess the molecules, virtually in the exact conformation pose in the active site, using exact geometry of the active site structure of the enzyme. It predicts the binding mode and type of interaction between active site amino acids and ligand along with their distance and proximity of functional groups involved. Interaction pattern of ligands was compared to that of interaction pattern of the known drugs binding to the active site amino acids of the target in order to select the best one for further studies.

In recent years, numbers of report have been documented on thiophene derivatives with promising anticancer activity.[24-26] Inspired by above information; we herein designed a new series of thiophene analogues as guided by molecular docking studies against human PTP1B active site. They were synthesized, characterized and subjected to *in vitro* inhibitory PTP1B activity. The synthesized compounds were also evaluated for their *in vitro* cytotoxic activity against cancer cell lines, such as MCF-7, MDA-MB-231, K562, HepG2, HeLa and HEK293.

Osiris program was used for prediction of the overall toxicity of the initially designed structures against PTP1B. The prediction strategies rely on a sub-structure search process determining the frequency of any fragment (constructed and core fragments) within any of toxicity classes. Virtual structures selected for the study were found to be less toxic as predicted by Osiris online software. Osiris program also can be used for prediction of C Log P, in turn an established parameter to measure the hydrophilicity. Compounds show a reasonable probability of being well absorbed, when they have a C Log P value less than 5.0. It is well established that 80% of the drugs on the market have Log S value around -5.0. From **Table 1**, it was observed that all designed structures (**5a-o**) have showed C Log P near to 5.0 and Log S values near to -5.0 indicating that the selected structures could be tested as drug candidates. The drug score combination of C Log P, Log S, molecular weight and toxicity risks may be used to judge the virtual structures for their overall potential to qualify for a drug. A value around 0.2 makes this structure a promising lead for future development of safe and efficient drug. Predictions of C Log P, solubility, and drug score for virtual structures selected were given in **Table 1** and almost all the designed ligands showed good drug score values.

ACCEPTED MANUSCRIPT

Table 1. Computationally predicted lipophilicity, solubility, drug score, and toxicity risks of the synthesized compounds (www.chemexper.com)

Compound	C Log P	Log S	Drug score	Toxicity risks [a]
5a	5.22	-6.16	0.19	Negative
5b	5.64	-6.99	0.16	Negative
5c	5.29	-6.41	0.18	Negative
5d	5.46	-6.71	0.16	Negative
5e	3.49	-4.61	0.43	Negative
5f	4.30	-5.39	0.37	Negative
5g	5.68	-6.86	0.24	Negative
5h	4.69	-6.14	0.20	Negative
5i	2.90	-5.30	0.38	Negative
5j	4.25	-5.39	0.25	Negative
5k	5.92	-6.99	0.13	Negative
5l	5.39	-6.40	0.18	Negative
5m	4.80	-6.18	0.20	Negative
5n	4.24	-5.43	0.28	Negative
5o	5.22	-6.16	0.19	Negative

[a] mutagenicity, tumorigenicity, irritancy, reproductive effects

Methyl-4-(4-amidoaryl)-3-methoxythiophene-2-carboxylate derivatives selected from chemexper studies were docked on the active site of PTP1B. The docking experiments were performed to virtually screen selected derivatives from virtual toxicity studies and also to know their affinity level towards the key amino acids of PTP1B enzyme active site with their binding and interaction mode. In general, scaffold with the aryl ring system showed better interaction as compared to scaffold containing pyridyl derivatives. Some derivatives selected for this study interacted with amino acids such Asp 48, Arg 24 and Tyr 46. These amino acids were also found to interact with known inhibitors.[27] Ligand **5b** exhibited effective interaction fit with Arg 24 of 46.6 % binding at a distance of 2.70 Å and Tyr 46 of 65.6% binding at 2.62 Å distance through water, naphthyl ring of the **5b** formed stacking interaction with Arg 24 and also showed potent inhibitory activity against PTP1B (IC_{50} = 5.25 µM) in their series. Extent of binding of **5c** is also equally good, methoxy group of **5c** ligand predicted to form polar bond to Arg 24 of amino acid residues with 56.1% binding at a distance of 2.71 Å, thiophene carboxylate carbonyl group also interacted with Arg 24 of 75.3% binding at a distance of 2.48 Å. Data pertaining to the interaction of thiophene derivatives (**5a-o**) with amino acids on PTP1B active site was given in

ACCEPTED MANUSCRIPT

Table 2. The two-dimensional and three-dimensional representation of compound **5b** and **5c** were showed in **Fig. 1** and **Fig. 2**.

Table 2. Interaction of thiophene derivatives (**5a-o**) with amino acids on PTP1B active site

Compound	Interaction with amino acids of PTP1B
5a	Asp 48, Arg 24 (surrounded by Gln 262, Phe 182, Tyr 46)
5b	Arg 24, Tyr 46 (surrounded by Asp 48, Phe 182, Gln 262)
5c	Arg 24 (surrounded by Asp 48, Phe 182, Gln 262, Asp 181)
5d	Tyr 46 (surrounded by Asp 181, Phe 182)
5e	Phe 182, Tyr 46, (surrounded by Asp 48, Gln 262)
5f	Tyr 46, (surrounded by Asp 181, Asp 48, Phe 182)
5g	Tyr 46, (surrounded by Arg 47, Asp 181, Phe 182,Asp 48)
5h	Asp 48, Arg 24 (surrounded by Gln 262, Phe 182, Tyr 46)
5i	Arg 24 (surrounded by Asp 48, Phe 182, Gln 262, Tyr 46)
5j	Arg 221, Gln 262 (surrounded by Asp 48, Phe 182)
5k	Asp 48 (surrounded by Phe 182, Tyr4 6, Gln 262)
5l	Asp 48, Arg 221, Tyr 46, Phe 182 (surrounded by Asp 181)
5m	Asp 48, Arg 47, Tyr 46, Arg 221 (surrounded by Phe 182)
5n	Asp 48, Tyr 46, Lys 120 (surrounded by Asp 181, Phe 182)
5o	Asp 48, Arg 221, Tyr 46, Phe 182

ACCEPTED MANUSCRIPT

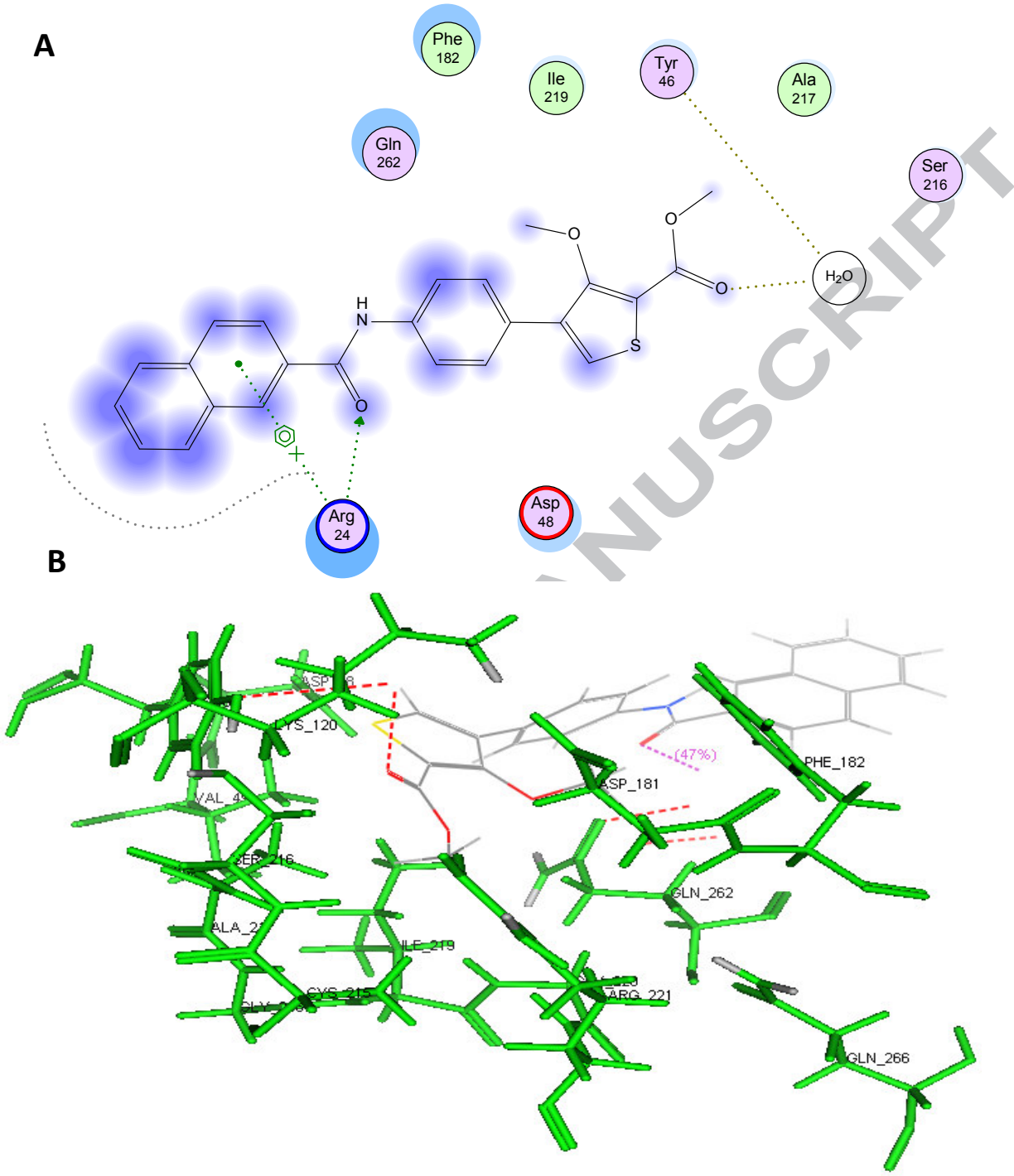


Fig. 1. (A) Two-dimensional representation of the interacting mode of **5b** on PTP1B enzyme. (B) Three-dimensional structural model of compound **5b** (purple) on PTP1B enzyme.

ACCEPTED MANUSCRIPT

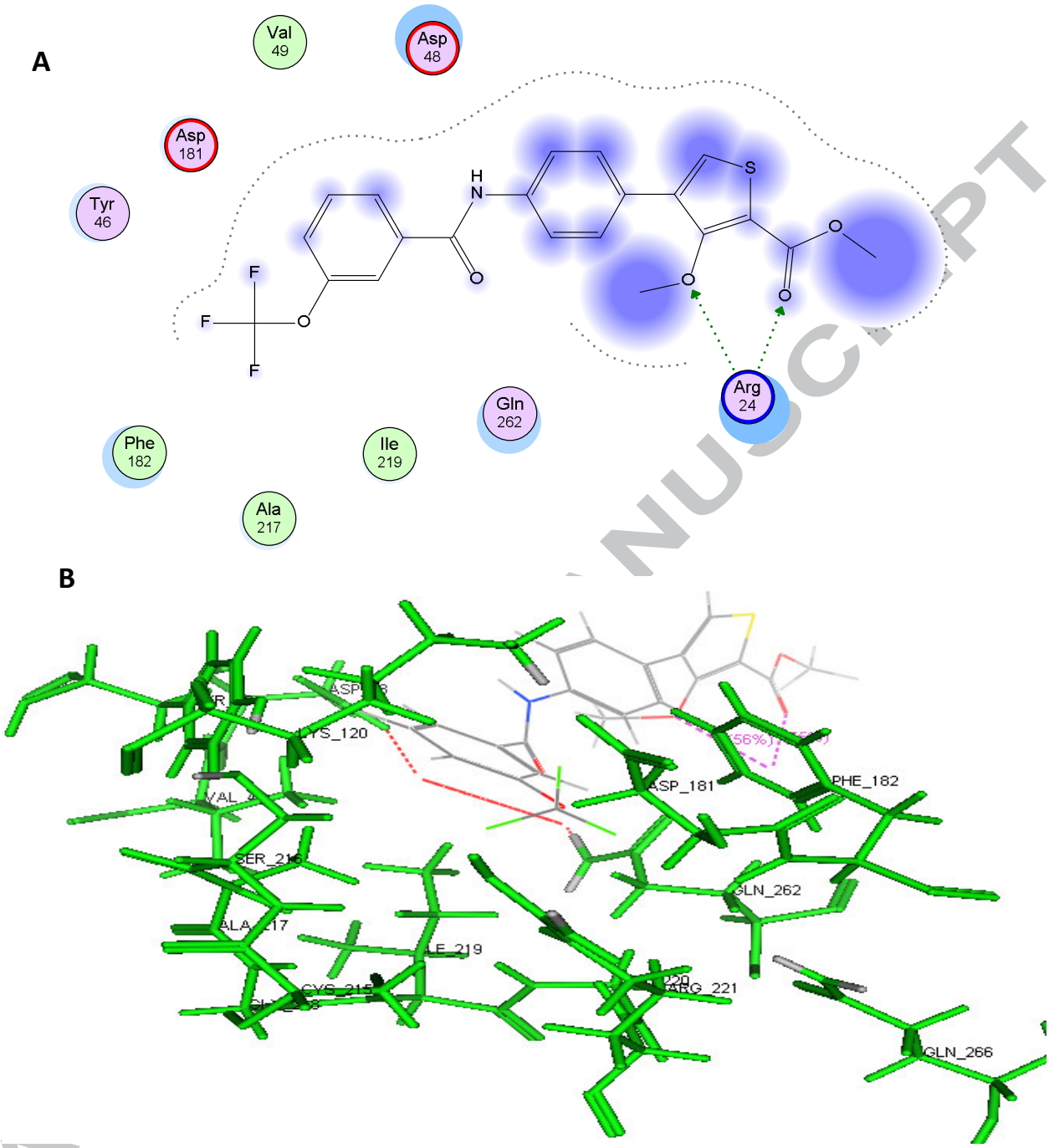
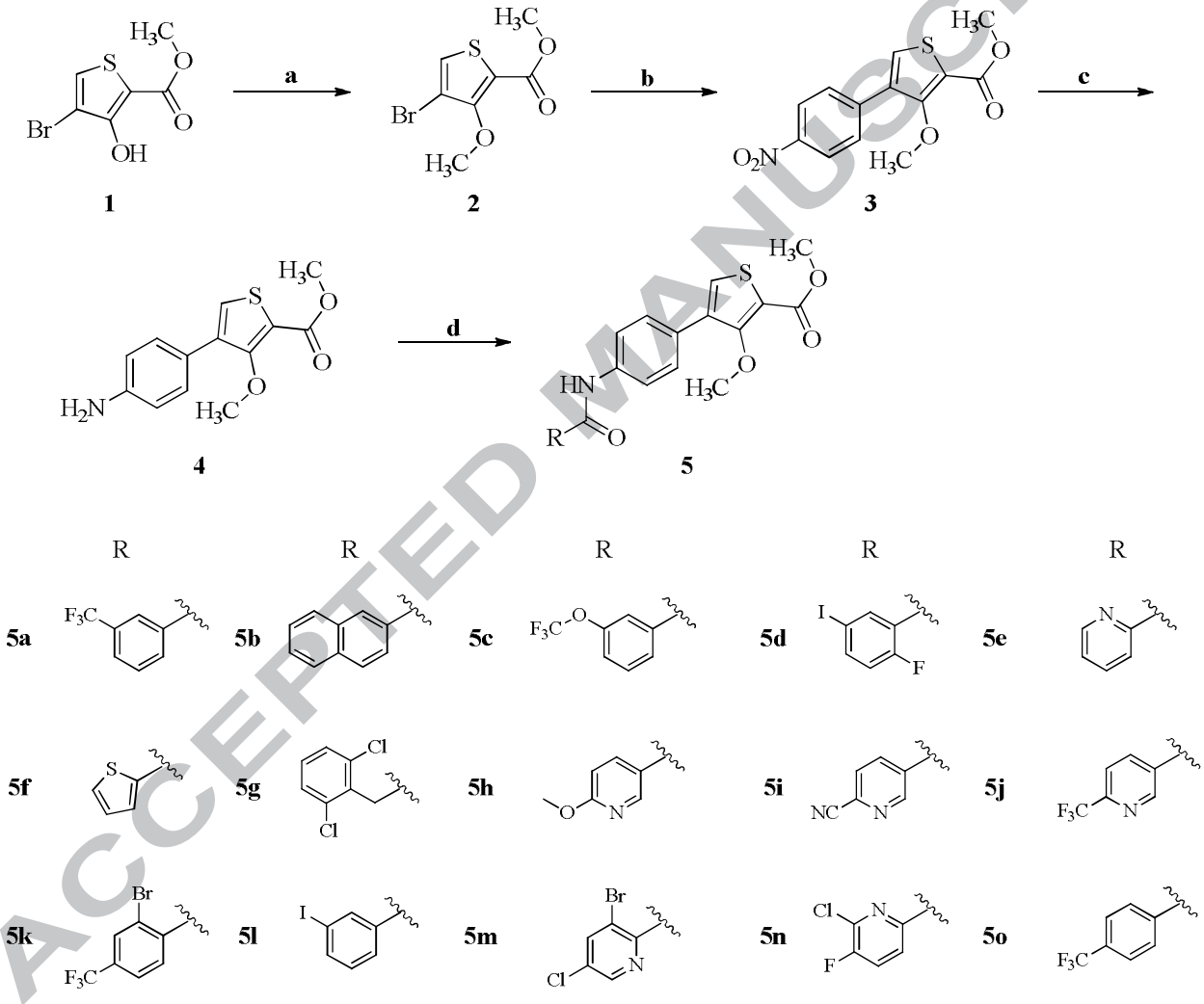


Fig. 2. (A) Two-dimensional representation of the interacting mode of **5c** on PTP1B enzyme. (B) Three-dimensional structural model of compound **5c** (purple) on PTP1B enzyme.

According to scheme **1,** hydroxyl group of methyl 4-bromo-3-hydroxythiophene-2-carboxylate (**1**) was methylated using methyl iodide and sodium hydride as a base to get methyl 4-bromo-3-methoxythiophene-2-carboxylate (**2**) [28], in 85% yield. The obtained product was further coupled with 4-nitro phenyl boronic acid under Suzuki coupling conditions[29], using

ACCEPTED MANUSCRIPT

tetrakis(triphenylphosphine)palladium and potassium carbonate to obtain methyl 3-methoxy-4-(4-nitrophenyl)thiophene-2-carboxylate (**3**). The nitro group of previous step product was reduced in the presence of zinc and ammonium chloride using ethanol as solvent to yield corresponding amine (**4**), the resultant product was made to react with different aryl/ heteroyl carboxylic acids to get the corresponding amide derivatives (**5a-o**) using HATU/DIPEA (**Table 3**). The obtained structures were confirmed by ^{1}H NMR, ^{13}C NMR, elemental and mass spectral analysis.



Scheme 1. Synthesis of title compounds. Reagents and conditions (a) NaH (1.2 equiv), MeI (3.0 equiv), THF, 0°C, 16 h (b) 4-nitrophenylboronic acid (1.2 equiv), K_2CO_3 (3.0 equiv),

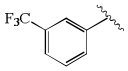
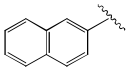
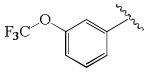
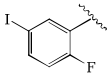
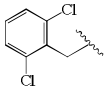
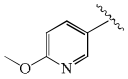
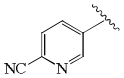
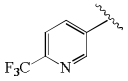
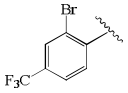
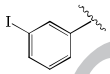
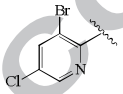
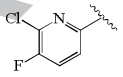
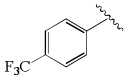
ACCEPTED MANUSCRIPT

$Pd(PPh_3)_4$ (0.05 equiv), DME, 85 °C (c) Zn (3.0 equiv), NH_4Cl (3.0 equiv), EtOH, 85°C, 16 h (d) R-COOH (1.2 equiv), HATU (1.5 equiv), DIPEA (3.0 equiv), CH_2Cl_2, R.T.,

Table 3. Protocol for the synthesis of the title compounds **(5a-o)**

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

Entry	R	Time	Yield (%)	m.p. (°C)
5a		3 h	75	135–140
5b		4 h	80	122–129
5c		3 h	70	132–138
5d		2 h	79	190–194
5e		4 h	68	190–194
5f		3 h	50	160–165
5g		3.5 h	74	215–220
5h		4 h	72	199–205
5i		5 h	76	192–197
5j		5 h	50	217–222
5k		3 h	70	190–194
5l		2 h	76	217–222
5m		3 h	74	184–189
5n		4 h	70	169–174
5o		3 h	75	140–145

ACCEPTED MANUSCRIPT

ACCEPTED MANUSCRIPT

The synthesized thiophene derivatives (**5a-o**) were evaluated for inhibitory activity against PTP 1B[30] using *p*-nitrophenyl phosphate (*p*NPP) as a substrate and the results are shown in **Table 4**. The known PTP1B inhibitor, ursolic acid (IC_{50} = 4.12 µM), was used as positive control. Compounds **5b**, **5c** and **5j** were exhibited potent activity against PTP1B with IC_{50} values ranging from 5.25 to 7.29 µM, whereas compounds **5a**, **5d**, **5e**, **5i**, **5g**, **5k**, **5l**, **5m**, **5n** and **5o** displayed moderate activity with IC_{50} values varying from 11.29 to 20.56 µM. The aryl scaffolds bearing electron withdrawing functional groups, namely, trifluoro methoxy (**5c**), trifluoro methyl (**5a**) exhibited a better inhibition than scaffolds bearing electron withdrawing functional groups as disubstituents on aryl ring (**5d**, **5g**, and **5k**). On the other hand, pyridyl ring bearing scaffolds with disubstituents (**5m** and **5n**) elicited more inhibitory activity than pyridyl compounds with mono substitution (**5h** and **5i**). Moreover, trifluoro methyl (**5j**) showed significant inhibition than the rest of the pyridyl derivatives (**5e**, **5h**, **5i**, **5m** and **5n**).

Further, the synthesized compounds (**5a-o**) were tested for *in vitro* anticancer activity against MCF-7, MDA-MB-231, K562, HepG2, HeLa and HEK293 cell lines using the MTT colorimetric assay[31], doxorubicin was used as a reference standard. From percentage inhibition, IC_{50} values were calculated (µM) and provided in **Table 4**. The synthesized compounds displayed potent to moderate cancer growth inhibitory activity. Among the tested compounds, **5b** and **5c** showed more potent activity against different cell lines. Compound **5b** with naphthyl ring elicited exceptionally potent activity against MCF-7 cell lines with IC_{50} value of 0.096 µM. This activity is better than that obtained IC_{50} value of doxorubicin (0.41 µM). The naphthyl ring replaced with trifluoro methyl pyridyl (**5j**) led to a reduction in antiproliferative activity, but the potency was still essentially sustained. Compound **5c** with trifluoro methoxy group displayed excellent antiproliferative activity against MCF-7 and HepG2 with IC_{50} value of 2.22 µM and 0.72 µM respectively. The replacement of trifluoro methoxy (**5c**) with trifluoro methyl moiety (**5a**) led to decrease antiproliferative activity. Introduction of trifluoro methyl on pyridyl (**5j**) showed potent cellular activity as compared to pyridyl scaffold with nitrile and trifluoro methoxy groups (**5h and 5i**). Anticancer data from compounds (**5a-o**) showed that the presence of disubstitutions on aryl ring (**5d**, **5g** and **5k**) led to decrease of anticancer activity. The replacement of the naphthyl ring in **5b** to thiophene (**5f**) led to a decline in anticancer activity. The compound **5b** showed potency with more than fivefold anticancer activity than doxorubicin

ACCEPTED MANUSCRIPT

against the MCF-7 cell line. It also showed the highest inhibitory activity against PTP1B *in vitro* assay. Furthermore, trifluoro methoxy compound **5c** displayed a seven fold higher potency than doxorubicin against HepG2 cell line. All the synthesized compounds were tested against non-cancerous HEK293 cells. It is evident from **Table 4** that, none of the compounds exhibited significant toxic effect on HEK293 cells indicating their selective toxicity towards the cancer cell and possible safety against normal cells.

The comparison of PTP1B inhibitory and anticancer activities of investigated potent derivatives led to the interesting findings. The compounds (**5b, 5c** and **5j**) were found to be superior in both PTP1B inhibitory and anticancer activities. This might be due to the high degree of association between PTP1B and ErbB2 in their expression in cancer.

The compound 5b solubility and stability was also investigated in various solvents. The compound 5b was found to be stable, even for an extended period of time up to 96 h at the different temperature.

Table 4. *In vitro* anti proliferative activity and inhibitions of PTP1B of synthesized compounds

Compound	PTP1B IC_{50} (µM)	Anticancer activity, IC_{50} (µM)					
		MCF-7	K562	HepG2	MDA-MB 231	HeLa	HEK293
5a	12.28	26.24	6.13	32.54	24.56	19.26	ND
5b	5.25	0.09	10.25	19.52	5.25	18.24	ND
5c	6.37	2.22	18.25	0.72	7.54	16.56	ND
5d	20.56	22.52	35.56	ND	16.54	ND	45.25
5e	11.29	19.20	24.22	10.26	8.25	> 50	ND
5f	24.29	18.56	ND	15.28	> 50	> 50	> 50
5g	16.32	12.25	9.56	13.52	14.21	ND	ND
5h	22.25	5.25	18.25	> 50	15.28	24.42	> 50
5i	12.46	9.54	ND	22.52	28.52	ND	ND
5j	7.29	1.47	12.54	23.26	7.25	23.52	ND
5k	16.52	22.41	9.25	28.24	19.59	16.22	> 50
5l	14.53	12.25	14.69	16.52	8.24	12.65	42.68
5m	11.22	5.46	12.62	9.53	8.36	18.26	> 50
5n	12.34	10.26	8.25	10.26	10.28	16.23	ND
5o	14.79	24.61	9.26	24.62	18.26	14.36	48.29
Urasolic acid	4.12						
Doxorubicin		0.41	0.07	5.00	0.60	0.37	

ND: Not determined

ACCEPTED MANUSCRIPT

In conclusion, the novel derivatives of methyl 4-(4-amidophenyl)-3-methoxythiophene-2-carboxylates (**5a-o**) were designed against PTP1B enzyme active site using MOE.2008.10. They were further synthesized and characterized by ^{1}H NMR, ^{13}C NMR, elemental and mass spectral analysis. The synthesized compounds were subjected to inhibitory action against PTP1B and *in vitro* antiproliferative activity against selected cancer cell lines, such as MCF-7, MDA-MB-231, K562, HepG2, HeLa, and HEK293 by MTT assay. Most of the tested compounds showed potent inhibitory activity for PTP1B with compound **5b** exhibited the highest activity (IC_{50} = 5.25 µM). Compound **5b** also showed potent cytotoxic activity with IC_{50} value of 0.096 µM against MCF-7 cell line with positive control Doxorubicin.

Acknowledgments

The authors would like to thank the management of AMRI Hyderabad research centre for giving an opportunity to carry out this research. The authors are also thankful to Dr. A. Sunil Kumar Reddy for his valuable guidance.

References and notes

1. Wiener, J. R.; Kerns, B. J.; Harvey, E. L.; Conaway, M. R.; Iglehart, J. D.; Berchuck, A.; Bast Jr., R. C. *J Natl Cancer Inst* **1994**, *86*, 372.

2. Dubé, N.; Tremblay, M. L. *Biochim. Biophys. Acta - Proteins Proteomics* **2005**, *1754*, 108.

3. Zabolotny, J. M.; Kim, Y. B.; Welsh, L. A.; Kershaw, E. E.; Neel, B. G.; Kahn, B. B. *J. Biol. Chem.* **2008**, *283*, 14230.

4. Verma, M.; Gupta, S. J.; Chaudhary, A.; Garg, V. K. *Bioorg. Chem.* **2017,** 70, 267.

5. Thiebaut, P. A.; Besnier, M.; Gomez, E.; Richard, V. *J. Mol. Cell. Cardiol.* **2016**, 101, 50.

6. Ahmad, F.; Azevedo, J. L.; Cortright, R.; Dohm, G. L.; Goldstein, B. J. *J. Clin. Invest.* **1997**, *100*, 449.

7. Bentires-Alj, M.; Neel, B. G. *Cancer Res.* **2007**, *67*, 2420.

8. Irby, R. B.; Yeatman, T. J. *Oncogene* **2000**, *19*, 5636.

9. Zhu, S.; Bjorge, J. D.; Fujita, D. J. *Cancer Res.* **2007**, *67*, 10129.

10. Julien, S. G.; Dubé, N.; Read, M.; Penney, J.; Paquet, M.; Han, Y.; Kennedy, B. P.; Muller, W. J.; Tremblay, M. L. *Nat. Genet.* **2007**, *39*, 338.

ACCEPTED MANUSCRIPT

11. Basu, S.; Prasad, U. V.; Barawkar, D. A.; De, S.; Palle, V. P.; Menon, S.; Patel, M.; Thorat, S.; Singh, U. P.; Das Sarma, K.; Waman, Y.; Niranjan, S.; Pathade, V.; Gaur, A.; Reddy, S.; Ansari, S. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2843.

12. Liljebris, C.; Larsen, S. D.; Ogg, D.; Palazuk, B. J.; Bleasdale, J. E. *J. Med. Chem.* **2002**, *45*, 1785.

13. Wang, Z.; Liu, Z.; Lee, W.; Kim, S.-N.; Yoon, G.; Cheon, S. H. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 3337.

14. Ge, M.; Meilin, Z,; Mei, Wang,; Jing, T,; Weijuan, G,; Jiehe, Z,; Aqun, Z,; Jingya, L,; Lixin, G,; Jia, L. *Eur. J. Med. Chem.* **2016**, 122, 756.

15. Patel, D.; Jain, M.; Shah, S. R.; Bahekar, R.; Jadav, P.; Joharapurkar, A.; Dhanesha, N.; Shaikh, M.; Sairam, K. V. V. M.; Kapadnis, P. *Bioorganic Med. Chem. Lett.* **2012**, *22*, 1111.

16. Xie, J.; Tian, J.; Su, L.; Huang, M.; Zhu, X.; Ye, F.; Wan, Y. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4306.

17. Patel, D.; Jain, M.; Shah, S. R.; Bahekar, R.; Jadav, P.; Darji, B.; Siriki, Y.; Bandyopadhyay, D.; Joharapurkar, A.; Kshirsagar, S.; Patel, H.; Shaikh, M.; Sairam, K. V. V. M.; Patel, P. *ChemMedChem* **2011**, *6*, 1011.

18. Wan, Z. K.; Follows, B.; Kirincich, S.; Wilson, D.; Binnun, E.; Xu, W.; Joseph-McCarthy, D.; Wu, J.; Smith, M.; Zhang, Y. L.; Tam, M.; Erbe, D.; Tam, S.; Saiah, E.; Lee, J. *Bioorganic Med. Chem. Lett.* **2007**, *17*, 2913.

19. Malamas, M. S.; Sredy, J.; Moxham, C.; Katz, A.; Xu, W.; McDevitt, R.; Adebayo, F. O.; Sawicki, D. R.; Seestaller, L.; Sullivan, D.; Taylor, J. R. *J. Med. Chem.* **2000**, *43*, 1293.

20. Wilson, D. P.; Wan, Z. K.; Xu, W. X.; Kirincich, S. J.; Follows, B. C.; Joseph-McCarthy, D.; Foreman, K.; Moretto, A.; Wu, J.; Zhu, M.; Binnun, E.; Zhang, Y. L.; Tam, M.; Erbe, D. V.; Tobin, J.; Xu, X.; Leung, L.; Shilling, A.; Tam, S. Y.; Mansour, T. S.; Lee, J. *J. Med. Chem.* **2007**, *50*, 4681.

21. Moretto, A. F.; Kirincich, S. J.; Xu, W. X.; Smith, M. J.; Wan, Z. K.; Wilson, D. P.; Follows, B. C.; Binnun, E.; Joseph-McCarthy, D.; Foreman, K.; Erbe, D. V.; Zhang, Y. L.; Tam, S. K.; Tam, S. Y.; Lee, J. *Bioorganic Med. Chem.* **2006**, *14*, 2162.

22. Parameshwar, R.; Harinadha Babu, V.; Manichandrika, P.; Narendra Sharath Chandra, J. N.; Swetha, K. *EXCLI J.* **2016**, *15*, 187.

23. Verma, M.; Luxami, V.; Paul, K. *Eur. J. Med. Chem.* **2013**, *68*, 352.

ACCEPTED MANUSCRIPT

24. Buduma, K.; Chinde, S.; Dommati, A. K.; Sharma, P.; Shukla, A.; Srinivas, K. V. N. S.; Arigari, N. K.; Khan, F.; Tiwari, A. K.; Grover, P.; Jonnala, K. K. *Bioorganic Med. Chem. Lett.* **2016**, *26*, 1633.

25. Romagnoli, R.; Baraldi, P. G.; Lopez-Cara, C.; Salvador, M. K.; Preti, D.; Tabrizi, M. A.; Balzarini, J.; Nussbaumer, P.; Bassetto, M.; Brancale, A.; Fu, X.-H.; Yang-Gao; Li, J.; Zhang, S.-Z.; Hamel, E.; Bortolozzi, R.; Basso, G.; Viola, G. *Bioorg. Med. Chem.* **2014**, *22*, 5097.

26. Sztanke, M.; Rzymowska, J.; Sztanke, K. **2015**, *23*, 3448.

27. Wan, Z. K.; Lee, J.; Xu, W.; Erbe, D. V.; Joseph-McCarthy, D.; Follows, B. C.; Zhang, Y. L. *Bioorganic Med. Chem. Lett.* **2006**, *16*, 4941.

28. Chao, J.; Taveras, A. G.; Aki, C. J. *Tetrahedron Lett.* **2009**, *50*, 5005.

29. Frizler, M.; Schmitz, J.; Schulz-Fincke, A. C.; Gütschow, M. *J. Med. Chem.* **2012**, *55*, 5982.

30. Ye, D.; Zhang, Y.; Wang, F.; Zheng, M.; Zhang, X.; Luo, X.; Shen, X.; Jiang, H.; Liu, H. *Bioorganic Med. Chem.* **2010**, *18*, 1773.

31. Varache-Lembege, M.; Moreau, S.; Larrouture, S.; Montaudon, D.; Robert, J.; Nuhrich, A. *Eur. J. Med. Chem.* **2008**, *43*, 1336.

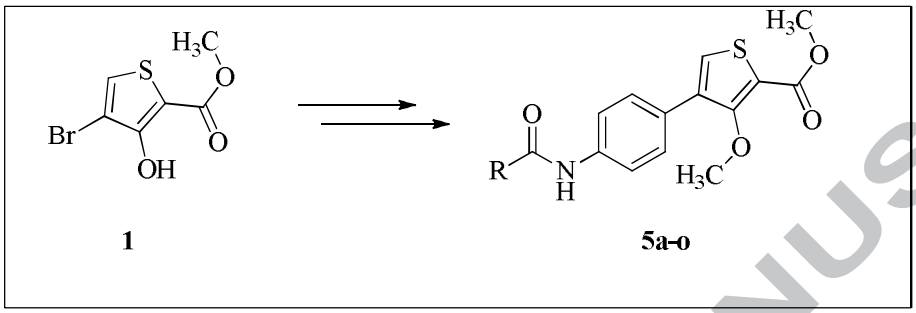
ACCEPTED MANUSCRIPT

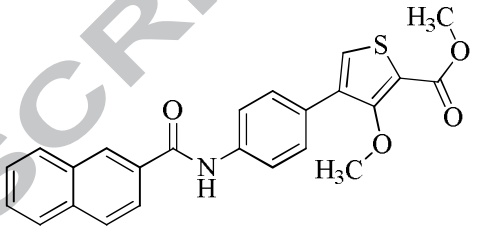
ACCEPTED MANUSCRIPT

Graphical Abstract

Design, synthesis, *in-silico* and *in-vitro* evaluation of thiophene derivatives: A potent tyrosine phosphatase 1B inhibitor and anticancer activity

Kali Charan Gulipalli [a], Srinu Bodige [a], Parameshwar Ravula [b], Srinivas Endoori [a], Vanaja.GR [c], Sureshbabu G [c], JN. Narendra Sharath Chandra [d], Nareshvarma Seelam [a]*





MCF-7 cell line: IC50 = 0.09 μM

PTP1B: IC50= 5.25 μM

ACCEPTED MANUSCRIPT

Highlights:

- A novel series of 3-methoxythiophene-2-carboxylate derivatives have been synthesized.
- The series of compounds were evaluated for their anticancer activity.
- Couple of compounds exhibited significant inhibitory activity against cancer cells.
- Compound **5b** showed highest cytotoxic activity against MCF-7 cell line.

ACCEPTED MANUSCRIPT