Bioorganic & Medicinal Chemistry Letters 21 (2011) 6433–6439

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

A Pd-mediated new strategy to functionalized 2-aminochromenes: Their in vitro evaluation as potential anti tuberculosis agents

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ARTICLE INFO

Article history:
Received 15 June 2011
Revised 16 August 2011
Accepted 18 August 2011
Available online 25 August 2011

Keywords:
Multi-component reactions (MCRs)
Palladium
2-Aminochromenes
Chorismate mutase

ABSTRACT

A multi component based synthesis involving palladium catalyzed C–C bond forming reaction has been developed as a new strategy to access systematically modified functionalized 2-aminochromenes. This MCR involves the use of bromobenzaldehyde as a key component and is highlighted by generating a new compound library. Many of these compounds showed *Mycobacterium tuberculosis* H37Rv chorismate mutase inhibiting properties in vitro representing the lead example of chorismate mutase inhibition by heteroarene based compounds.

Tuberculosis (TB) is one of the deadly diseases that kills more than two million people a year worldwide. The growing incidences of multi-drug-resistance TB and its synergism with HIV is a rising threat that needs immediate attention. Thus characterization of new enzyme targets and the identification of new anti tubercular agents are exceedingly desirable. Shikimate pathway for the biosynthesis of aromatic amino acids such as phenylalanine and tyrosine involve the Claisen rearrangement of chorismate to prephenate in the presence of chorismate mutase or CM (EC 5.4.99.5). Due to the absence of this pathway in animals but not in bacteria CM is considered as a valuable target for the identification of effective antibacterial agents.[1] However, to our knowledge only few small molecules[2] have been reported to possess inhibitory activity against CM and none based on heteroarene framework. In this Letter we wish to present our initial work on the discovery of novel small molecules as inhibitors of CM synthesis of which was carried out via a multi component reaction involving palladium catalyzed C–C bond forming reaction.

Multi-component reactions (MCRs)[3] that usually involve three or more different starting materials to afford the target compound in a one-pot operation have become a powerful tool[4] in modern drug discovery. While combination of MCRs with other reactions for example Ugi and Asinger[5] have been reported a similar example on combining MCRs with Suzuki/Heck/Sonogashira coupling reactions in tandem in a single-pot are not common in the literature.[6] In 2006, the Ugi/Heck combination has been demonstrated to work well for high-throughput combinatorial library production of indol-2-ones having four points of diversity.[6c] This prompted us to explore the combination of other MCRs with Pd-catalyzed reactions to develop a new strategy for the generation of a library based on small molecules of potential pharmacological interest. Herein we present the synthesis of 2-aminochromene based small molecules as potential inhibitors of *Mycobacterium tuberculosis* H37Rv chorismate mutase. 2-Aminochromenes (especially 2-amino benzochromenes) attracted our attention because of their occurrences in many natural products and wide range of pharmacological activities.[7,8] These include antibacterial activities of 2-amino benzo[*h*]chromene derivatives against standard strains of *Escherichia coli*, *Pseudomonas aeruginosa*, and *Staphylococcus aureus* in vitro.[7] Thus, generation of a small-molecule library **A** (Fig. 1) based on 2-amino benzo[*h*]chromene was undertaken (particularly

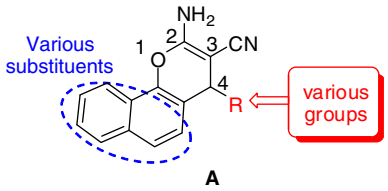

Figure 1. Diversity-based 2-aminochromene scaffold.

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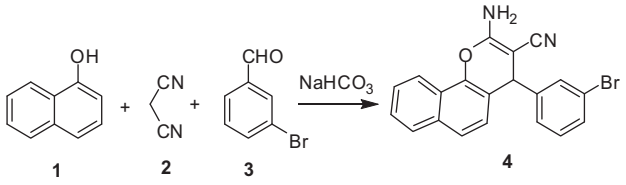
doi:10.1016/j.bmcl.2011.08.088

via functionalization of C-4 substituent) for their pharmacological evaluation against CM.

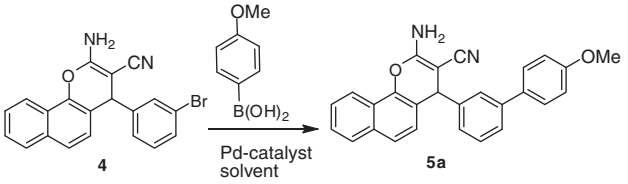
While a number of methods have been reported for the synthesis and modification of 2-amino chromenes[9] only few are known for 2-amino benzochromenes.[7,8,10] Moreover, none has been reported on the structural elaboration of 2-amino benzochromenes using Pd-mediated methods especially C–C bond forming reactions. One of the commonly used method for the preparation of 2-amino-chromenes generally involved refluxing malononitrile, aldehyde and activated phenol in the presence of organic bases like piperidine in an organic solvent such as ethanol or acetonitrile for several hours.[11] A number of modifications of this reaction conditions have been reported including the use of aqueous K_2CO_3 under a microwave irrediation[7] or Preyssler type heteropolyacid, $H_{14}[NaP_5W_{30}O_{110}]$, in water[8] or $NaHCO_3$ under a solvent-free condition[10a] or Et_3N in EtOH under refluxing condition.[10b] Nevertheless, in our approach we had to fulfill two major objectives for example, (i) identification of a suitable base or catalyst for MCR compatible for subsequent Pd-mediated transformation in the same pot, (ii) establishing appropriate reaction condition for efficient C–C coupling to complete the functionalization step. Accordingly, 2-amino-4-(3-bromophenyl)-4*H*-benzo[*h*]chromene-3-carbonitrile (**4**) was prepared in 52% yield following a standard method via reacting 1-naphthol (**1**) with malononitrile (**2**) and 3-bromobenzaldehyde (**3**) in the presence of $NaHCO_3$ under a solvent free condition (Scheme 1).[10a] We choose Suzuki coupling as the Pd-mediated step to be conducted with MCR in the same pot and the bromo derivative **4** was used for our initial study. Thus compound **4** was coupled with 4-methoxyphenyl boronic acid under various conditions including the conventional Suzuki condition (Table 1). Initially the reaction was carried out under a standard Suzuki condition that is, in a 2:1 mixture of toluene–H_2O in the presence of $NaHCO_3$ at 100 °C for 12 h (Table 1, entry 1). While the reaction proceeded well to give the desired product **5a** the product yield however was not impressive. Considering the poor solubility of the bromide **4** in an aqueous mixture we carried out the reaction in neat toluene (Table 1, entry 2). However, no improvement in yield was observed. The use of 1,4-dioxane in place of toluene increased the product yield perhaps due to the better solubility of $NaHCO_3$ in 1,4-dioxane (Table 1, entry 3). We then replaced $NaHCO_3$ with an organic base such as pyrrolidine which is miscible with 1,4-dioxane when the product **5a** was isolated in 85% yield (Table 1, entry 4). Notably, the reaction could be performed at 70 °C in this solvent. Changing the solvent from 1,4-dioxane to DMF decreased the yield (Table 1, entry 5). The use of other Pd-catalysts for example, $Pd(OAc)_2$ (Table 1, entry 6) and $(PPh_3)_4Pd$ (Table 1, entry 7) was examined when $(PPh_3)_4Pd$ was found to be equally effective in terms of product yield. The reaction did not proceed in the absence of a Pd catalyst (Table 1, entry 8).

With the optimized reaction conditions for the Suzuki coupling of **4** with an arylboronic acid in hand we then examined the MCR to prepare **4** in situ under a similar reaction conditions. Thus the reaction of **1**, **2** and **3** was examined in 1,4-dioxane in the presence of pyrrolidine initially at room temperature. Since a vigorous exothermic reaction was observed with the sharp rise in reaction



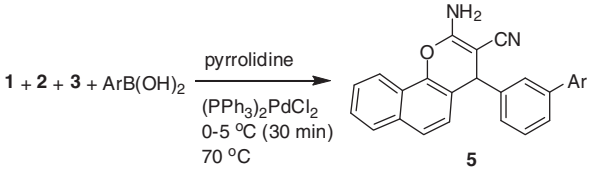
Scheme 1. Preparation of compound **4** according to a known method.[10]

Table 1
The effect of reaction conditions on the Suzuki coupling of **4** with 4-methoxyphenyl boronic acid[a]



Entry	Pd cat.	Solvent	Base	Time (h)/*T* (°C)	% Yield[b]
1	$(PPh_3)_2PdCl_2$	Toluene–H_2O (2:1)	$NaHCO_3$	12; 100	55
2	$(PPh_3)_2PdCl_2$	Toluene	$NaHCO_3$	12; 100	67
3	$(PPh_3)_2PdCl_2$	1,4-Dioxane	$NaHCO_3$	10; 80	75
4	$(PPh_3)_2PdCl_2$	1,4-Dioxane	Pyrrolidine	4; 70	85
5	$(PPh_3)_2PdCl_2$	DMF	Pyrrolidine	4; 70	55
6	$Pd(OAc)_2$	1,4-Dioxane	Pyrrolidine	4; 70	69
7	$(PPh_3)_4Pd$	1,4-Dioxane	Pyrrolidine	4; 70	80
8	No Pd cat.	1,4-Dioxane	Pyrrolidine	4; 70	0

[a] All the reactions were carried out using compound **4** (10 mmol), 4-methoxyphenyl boronic acid (12.0 mmol), a Pd-catalyst (0.002 mmol) and a base (5 mmol) in a solvent (5 mL).
[b] Isolated yield.



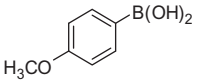
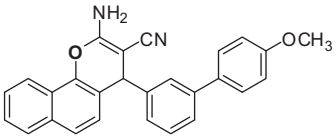
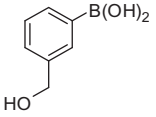
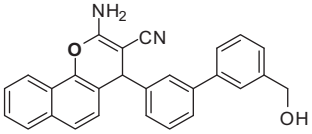
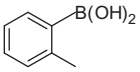
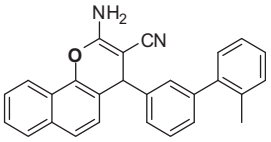
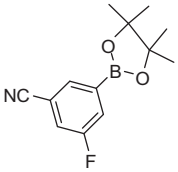
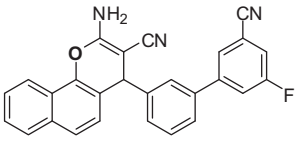
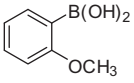
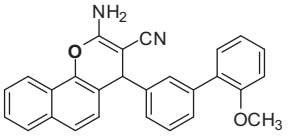
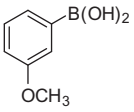
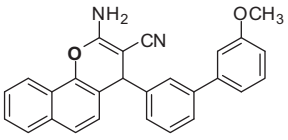
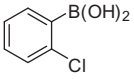
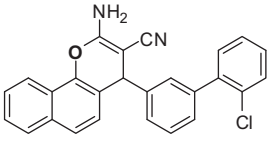
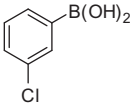
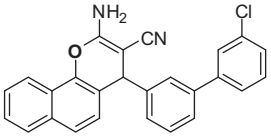
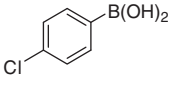
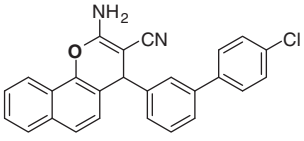
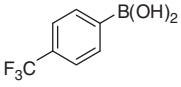
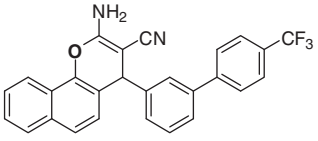
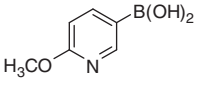
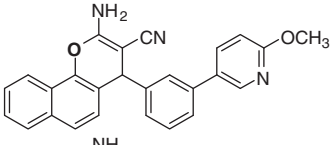
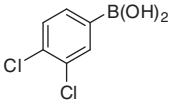
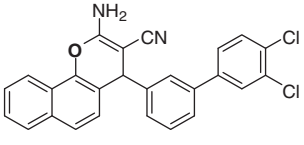
Scheme 2. Suzuki coupling based MCR strategy for the preparation of 4-biaryl substituted 2-amino benzochromenes (**5**).

temperature (70–80 °C) hence we conducted the reaction at a lower temperature that is, at 0–5 °C. To our satisfaction the reaction was still found to be faster under this condition and was completed within 10 min to give the product **4** in quantitative yield. To assess the role of solvent and base in this one-pot reaction we conducted few more experiments and observed that the use of DMF as a solvent required longer reaction time whereas replacing pyrrolidine with NaOAc required elevated temperature for the initiation of reaction. Thus combination of pyrrolidine and 1,4-dioxane was not only identified as an appropriate medium for a faster MCR under mild conditions but also found to be favorable for subsequent Suzuki coupling in the same pot. Overall, this combination appeared to be a promising and significant for the realization of present approach leading to the library of 2-amino benzochromene. We then performed a reaction by combining all the reactants that is, **1**, **2**, **3** and **4** and catalysts/reagents for example, $(PPh_3)_2PdCl_2$ and pyrrolidine in 1,4-dioxane at 0–5 °C. The mixture was stirred for 30 min at 0–5 °C initially and then at 70 °C for 4 h. We were delighted to observe the formation of desired product **5a** without any significant side products. The initial step was not affected by the presence of a Pd-catalyst or boronic acid and **5a** was finally isolated in 82% yield.

To demonstrate the utility of our approach a variety of 4-biaryl substituted 2-amino benzochromenes (**5**) were synthesized (Scheme 2) and the results are presented in Table 2.

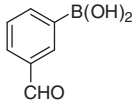
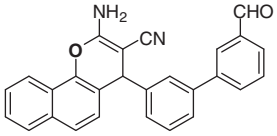
A range of aryl boronic acids were employed in this reaction separately and the reaction proceeded well to give the expected products in good to excellent yields.[12] Various functional groups such as alkoxy (Table 2, entries 1, 5 and 6), hydroxyalkyl (Table 2, entry 2), alkyl (Table 2, entry 3), cyano (Table 2, entry 4), halo (Table 2, entries 7, 8, 9 and 12), trifluoroalkyl (Table 2, entry 10)

Table 2
Synthesis of 4-biaryl substituted 2-amino benzochromenes (**5**) using Suzuki coupling based MCR[a]

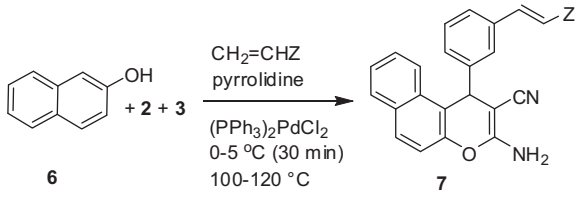
Entry	Aryl boronic acid	4-Biaryl substituted 2-amino benzochromenes (**5**)		Time[b] (h)	%Yield[c]
1			**5a**	4	82
2			**5b**	4	87
3			**5c**	5	79
4			**5d**	6	93
5			**5e**	4	83
6			**5f**	4	87
7			**5g**	6	78
8			**5h**	5	80
9			**5i**	5	91
10			**5j**	5	84
11			**5k**	4	95
12			**5l**	6	90

(*continued on next page*)

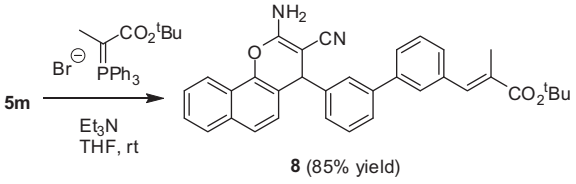
Table 2 (*continued*)

Entry	Aryl boronic acid	4-Biaryl substituted 2-amino benzochromenes (**5**)		Time[b] (h)	%Yield[c]
13			**5m**	4	89

[a] All the reactions were carried out using 1-naphthol **1** (10 mmol), malononitrile **2** (10 mmol), bromo aldehyde **3** (10 mmol), aryl boronic acid (12.0 mmol), $(PPh_3)_2PdCl_2$ (0.002 mmol) and pyrrolidine (5 mmol) in dioxane (5 mL) at 0–5 °C for 30 min and then at 70 °C.
[b] After stirring the mixture at 0–5 °C for 30 min.
[c] Isolated yield.



Scheme 3. Heck reaction based MCR strategy for the preparation of 4-alkenylaryl substituted 2-amino benzochromenes (**7**).

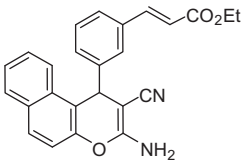
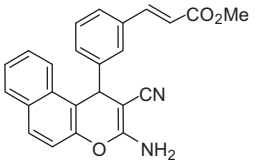
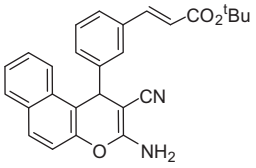
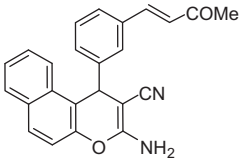


Scheme 4. Fictionalization of compound **5m**.

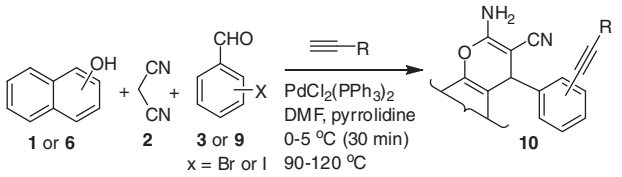
and aldehyde (Table 2, entry 13) present in the aryl boronic acid was well tolerated. Notably, the use of a heteroaryl boronic acid (Table 2, entry 11) was also successful in the present reaction.

Encouraged by these results we then examined the feasibility of MCR based on Heck reaction (Scheme 3 and Table 3). Initially, a reaction was carried out using 2-naphthol **6**, malononitrile **2**, bromo aldehyde **3** and ethyl acrylate (15.0 mmol) in the presence of $(PPh_3)_2PdCl_2$ and pyrrolidine in 1,4-dioxane (5 mL) at 0–5 °C for 30 min and then at 70 °C for 24 h (Table 3, entry 1). While the desired product **7a** was obtained in this case but the yield of isolated product was not satisfactory. However, replacing 1,4-dioxane by DMF and conducting the reaction at higher temperature that is, 100–120 °C afforded the better yield of **7a** (Table 3, entry 2). The reaction time was also reduced to 7 h under this condition. The use of other alkenes provided the corresponding products in good yields (Table 3, entries 3–5).

Table 3
Synthesis of 4-alkenylaryl substituted 2-amino benzochromenes (**7**) using Heck reaction based MCR[a]

Entry	Aryl boronic acid	4-Alkenylaryl substituted 2-amino benzochromenes (**7**)		Time[b] (h)	%Yield[c]
1	CH_2=$CHCO_2Et$		**7a**	24	40[d]
2	CH_2=$CHCO_2Et$		**7a**	6	85
3	CH_2=$CHCO_2Me$		**7b**	6	85
4	CH_2=$CHCO_2{}^tBu$		**7c**	6	89
5	CH_2=CHCOMe		**7d**	5	79

[a] All the reactions were carried out using 2-naphthol **6** (10 mmol), malononitrile **2** (10 mmol), bromo aldehyde **3** (10 mmol), alkene (15.0 mmol), $(PPh_3)_2PdCl_2$ (0.002 mmol) and pyrrolidine (5 mmol) in DMF (5 mL) at 0–5 °C for 30 min and then at 100–120 °C.
[b] After stirring the mixture at 0–5 °C for 30 min.
[c] Isolated yield.
[d] The reaction was carried out in 1,4-dioxane.

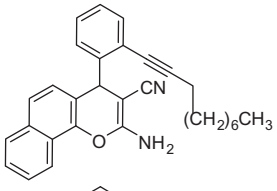
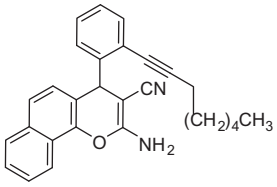
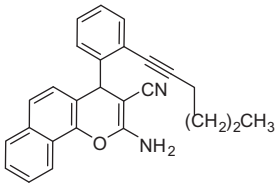
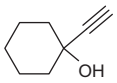
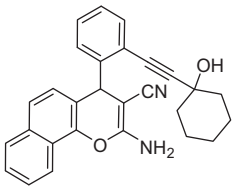
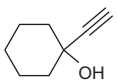
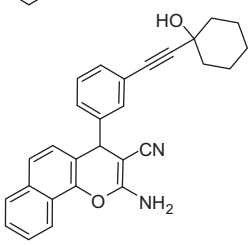
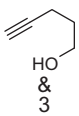
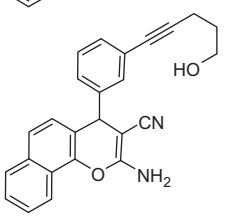
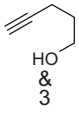
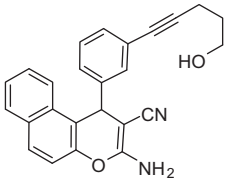


Scheme 5. Sonogashira reaction based MCR strategy for the preparation of 4-alkynylaryl substituted 2-amino benzochromenes (**10**).

To demonstrate the further potential of the present strategy for the introduction of additional diversity functionalization of compound **5m** was carried out under Wittig condition (Scheme 4).

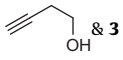
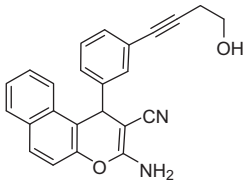
We also examined the feasibility of MCR based on Sonogashira reaction (Scheme 5) the results of which are summarized in Table 4. A number of 4-alkynylaryl substituted 2-amino benzochromenenes (**10**) were prepared using this strategy in good yields. Notably, the Sonogashira step does not require the use of copper cocatalyst and therefore avoids the generation of side products

Table 4
Synthesis of 4-alkynylaryl substituted 2-amino benzochromenes (**10**) using Sonogashira reaction based MCR[a]

Entry	Naphthol	Alkynes & araldehyde	4-Alkynylaryl substituted 2-amino benzochromenes (**10**)		Time[b] (h)	%Yield[c]
1	**1**	$CH{\equiv}CCH_2(CH_2)_6CH_3$ & 2-iodobenzadehyde (**9**)		**10a**	4.5	92
2	**1**	$CH{\equiv}CCH_2(CH_2)_4CH_3$ & **9**		**10b**	5	87
3	**1**	$CH{\equiv}CCH_2(CH_2)_2CH_3$ & **9**		**10c**	3	85
4	**1**	 & 9		**10d**	4	75
5	**1**	 & 3		**10e**	3	80
6	**1**	 & 3		**10f**	2	85
7	**6**	 & 3		**10g**	3	84

(*continued on next page*)

Table 4 (*continued*)

Entry	Naphthol	Alkynes & araldehyde	4-Alkynylaryl substituted 2-amino benzochromenes (**10**)	Time[b] (h)	%Yield[c]
8	**6**	 & **3**	 **10h**	2	95

[a] All the reactions were carried out using naphthol **1** or **6** (10 mmol), malononitrile **2** (10 mmol), halo aldehyde **3** or **9** (10 mmol), alkyne (15.7 mmol), $(PPh_3)_2PdCl_2$ (0.002 mmol) and pyrrolidine (5 mmol) in DMF (5 mL) at 0–5 °C for 30 min and then at 100–120 °C.
[b] After stirring the mixture at 0–5 °C for 30 min.
[c] Isolated yield.

Table 5
Inhibition of chorismate mutase by functionalized 2-amino benzochromenenes

Entry	Compounds	% Inhibition[a] at 50 μM	SD[a]
1	**7a**	30	0.049
2	**7b**	33	0.016
3	**7c**	64	0.057
4	**7d**	10	0.153
5	**10a**	50	0.049
6	**10b**	55	0.090
7	**10c**	57	0.122
8	**10d**	24	0.060
9	**10e**	28	0.130
10	**10f**	32	0.119
11	**10g**	70	0.055
12	**10h**	69	0.025

[a] SD = standard deviation.

caused by homocoupling of terminal alkynes used. Nevertheless, the present MCR based strategy appeared to be a general for the synthesis of diversity based benzochromene derivatives via involving

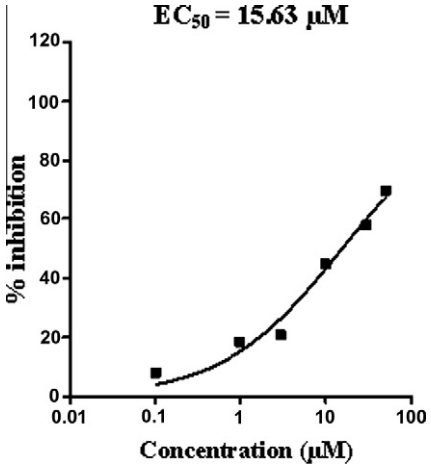


Figure 2. Dose dependent inhibition of CM by compound **10g**.

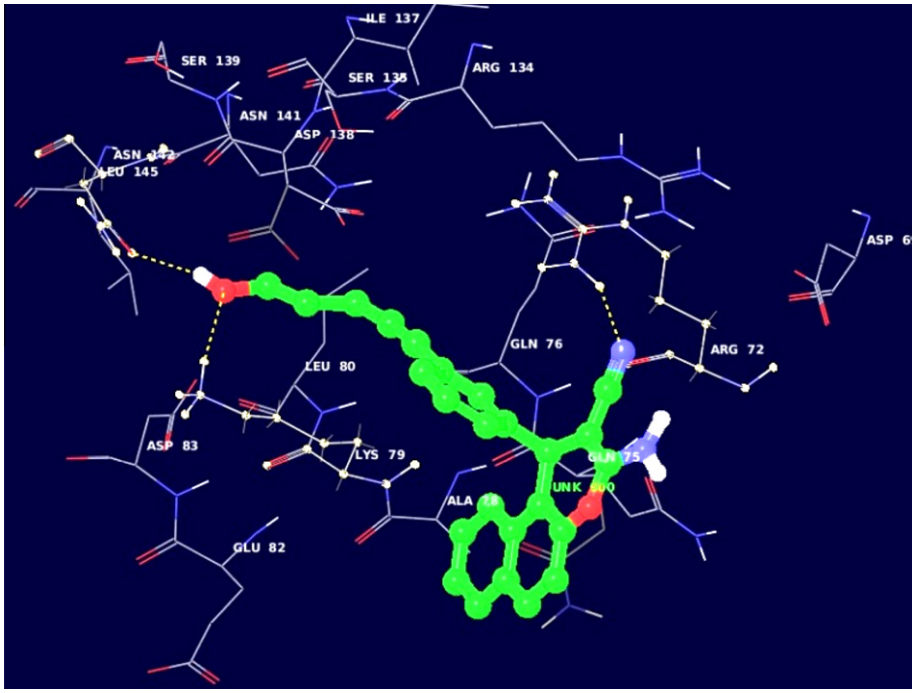


Figure 3. Docking of compound **10g** at the active site of chorismate mutase.

various Pd-mediated C–C bond forming reactions as demonstrated above.

Some of the compounds synthesized were tested for CM inhibiting properties in vitro and the results are summarized in Table 5. The assay[13] involved determination of activity of enzyme CM which catalyzes the conversion of chorismate to prephenate. Thus determination of activity of CM is based on the direct observation of conversion of chorismic acid to prephenate spectrophotometrically at OD_{274}. This reaction is performed in the presence of test compounds to determine their CM inhibiting activities. A known inhibitor of CM that is, 4-(3,5-dimethoxyphenethylamino)-3-nitro-5-sulfamoylbenzoic acid[2a] was prepared and used as a reference compound the IC_{50} value of which was found to be less than 10 μM. While none of the compound **5** showed significant inhibition[14] of CM at 50 μM compounds 7 and **10** however showed moderate to good inhibition at the same concentration depending on the nature of substituents present. In general, alkyne substituted compounds for example, 10 was found to be superior than alkenyl derivatives **7**. Among the alkyne derivatives a linear side chain attached to the triple bond usually showed good inhibitory activities and presence of a hydroxy group at the end of the side chain was found to be beneficial. Nevertheless, compound **10g** and **10h** was identified as best inhibitors in this series. Compound **10g** showed dose dependent inhibition of CM with an IC_{50} value 15.63 μM (Fig. 2).

To understand the nature of interactions between **10g** and CM docking studies were performed (Fig. 3) which showed H-bonding interactions between (i) the –CN group of **10g** and the ARG72 residue of CM, (ii) the –OH group of **10g** and ASN142 and LYS79 residues of the CM. The overall binding energy was found to be -5.5 kcal mol^{-1} indicating significant interactions of **10g** with CM.

In conclusion, systematically modified functionalized 2-aminochromenes has been prepared via a new strategy involving a MCR and palladium catalyzed C–C bond forming reaction. This strategy involves the use of bromobenzaldehyde as a key component and afforded a new compound library based on 2-aminochromene framework. Many of these compounds showed *M. tuberculosis* H37Rv chorismate mutase inhibiting properties in vitro and the IC_{50} value of one compound was found to be 15.63 μM. Overall, 2-aminochromene framework has been identified as a new template for the design and discovery of small-molecule based inhibitors of CM for the potential treatment of tuberculosis.

Acknowledgments

The authors (T.R.R., L.S.R., N.V.S. and G.R.R.) thank Dr. Vilas Dahanukar and Dr. Amrendra Kumar Roy for support and the analytical group of DRL for spectral data. M.P., S.S. and P.M. thank Professor Seyed E. Hasnain and Professor J. Iqbal for encouragement and DBT, New Delhi, India for financial support (Grant No. BT/01/COE/07/02). Technical help in pharmacology from Dr. K. Chatti is acknowledged.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.08.088.

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12. The one-pot transformation was typically carried out as follows: a mixture of 1-naphthol **1** (10 mmol), malononitrile **2** (10 mmol) and bromo aldehyde **3** (10 mmol) in dioxane (5 mL) was cooled to 0–5 °C and then aryl boronic acid (12.0 mmol), $(PPh_3)_2PdCl_2$ (0.002 mmol) and pyrrolidine (5 mmol) was added at 0–5 °C. The resulting mixture was stirred at 0–5 °C for 30 min and then at 70 °C for the duration as indicated in Table 2. The desired product **5** was isolated after usual work-up (see the Supplementary data).
13. (a) Kim, S. K.; Reddy, S. K.; Nelson, B. C.; Vasquez, G. B.; Davis, A.; Howard, A. J.; Patterson, S.; Gilliland, G. L.; Ladner, J. E.; Reddy, P. T. *J. Bacteriol.* **2006**, *188*, 8638; (b) Sasso, S.; Ramakrishnan, C.; Gamper, M.; Hilvert, D.; Kast, P. *FEBS J.* **2005**, *272*, 375.
14. Precipitation of the compound **5** observed in most of the cases in assay medium.