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Original article

Design, synthesis and antitubercular evaluation of novel series of *N*-[4-(piperazin-1-yl)phenyl]cinnamamide derivatives

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ABSTRACT

The analogs of *N*-[4-(piperazin-1-yl)phenyl]cinnamamide were designed and synthesized by molecular hybridization approach in which part C of the designed molecule was linked through amide and carbamate functionality that improves the physicochemical properties and govern the pharmacokinetic and pharmacodynamic behavior. The systematic modification was done around the Part C to explore the structure activity relationship of antitubercular cinnamamide. All 52 compounds were evaluated for its antitubercular activity against *Mycobacterium tuberculosis* (*M. tb*) using Resazurin microtitre plate assay (REMA). Compound 11g with trifluoromethyl substitution exhibited good antitubercular activity of 3.125 μg/ml. The synthesized *N*-[4-(piperazin-1-yl)phenyl]cinnamamide derivatives showed promising activity against *M. tb*.

1. Introduction

Tuberculosis, or TB, the global epidemic caused by *Mycobacterium tuberculosis* (*M. tb*) is infectious disease that has infected about one-third of the world population. Around 19% cases were identified with MDR-TB that reached almost 60,000 in 2011. India and China together account for almost 40% of the world's TB cases, thus the global burden of TB remains enormous [1].

The current therapy, first-line and second-line drugs for anti-TB drugs are around 50 years old and nonetheless, it requires 6 months of treatment and 20 months in the case of MDR-TB. Hence, new drugs are required to shorten and simplify the treatment, to improve the efficacy and tolerability of treatment for MDR-TB. In the last four decades not a single molecule was introduced in the TB therapy except US-FDA approves bedaquiline in December-2012, a new antitubercular agent, as a part of combination therapy to treat adults with MDR-TB [2].

In recent years, *trans*-cinnamic acid derivatives have attracted much attention due to their antioxidative [3], antitumor [4], and antimicrobial properties [5]. Though some of the research papers on cinnamic acid derivatives were reported as antitubercular agents [6–9], still they were not much explored and yet their mechanism of action of antitubercular activity was not exactly identified. However Yoya et al. [7] and Kakwani et al. [8] has described the possible way of the mechanism of cinnamic acid derivatives that may act on the fatty acid synthase type II (FAS-II) pathway. The FAS-II pathway is unique in mycobacteria and is essential for mycobacterial cell survival. Hence, the FAS-II biosynthesis pathway represents a validated and promising target for drug discovery [10]. Additionally it was reported that diphenyl ethers, indols, benzofurans and recently cinnamic acid derivatives have been acting through FAS-II system [7,8].

It was interesting to note that trans-cinnamic acid was used for tubercular infection even before when the current therapy was not discovered. Warbasse et al. and Corper et al. have reported the use of ethyl cinnamate and sodium cinnamate in the treatment of patients with tuberculosis [11–13]. The synergistic activity of trans-cinnamic acid in drug combinations with isoniazid, rifamycin, have been reported against *M. tuberculosis* [14]. It was also observed that the rifamycin SV, a hybrid derivative of cinnamic acid and rifamycin has higher activity than its individual counterpart [15].

The importance of cinnamic acid moiety was also found from natural product constituents as depicted in Fig. 1. The organic extract of a native American plant *Ipomoea leptophylla* leaves contain a resin glycoside Leptophyllin A with a *trans*-cinnamic acid residue attached to one Rhamnose moiety which exhibited 13% inhibition at 6.25 μg/ml [16]. Additionally, the bioassay of these natural products revealed that Leptophyllin B, a glycoside from the same plant without cinnamic acid residue, was having no *in-vitro*

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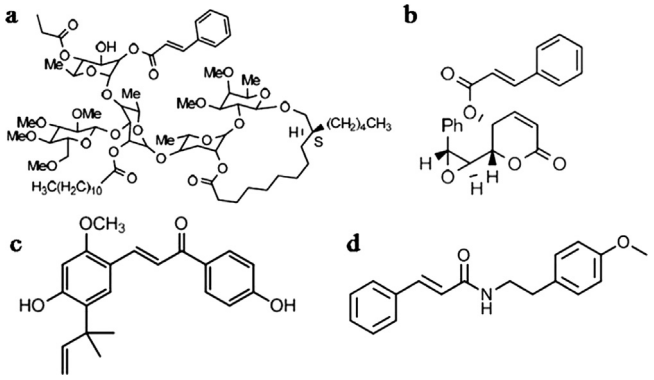


Fig. 1. Antitubercular natural products containing cinnamic acid moiety (a) Leptophyllin A, (b) Howiinin A, (c) Licochalcone A and (d) Pisoniamide.

activity. Recently, a styryllactone, Howiinin A, was isolated from flowers of *G. laoticus* which showed promising activity at 6.25 μg/ml against *M. tuberculosis* [17]. Licochalcone A, extracted from chinese licorice roots, exhibited promising antitubercular activity [18]. The cinnamamide natural products Pisoniamide and *N-trans*-(*p*-coumaroyl)tyramine isolated from *Pisonia aculeate* and *Piper sanctum* respectively were also having antitubercular activity [19,20].

Previously synthesized cinnamic acid derivatives were moderately active may be due to poor bioavailability as log *P* value was higher. Based on these findings, we decided to explore novel cinnamic acid derivatives which can be easily bioavailable and have promising antitubercular activity. Furthermore it was proved that the addition of the piperazine ring to the first-generation quinolones led to a significant improvement in bioavailability of the second-generation fluoroquinolones (norfloxacin and levofloxacin). Hence, the piperazine moiety might be helpful to adjust the physicochemical properties and to improve the pharmacokinetic and pharmacodynamic behavior. Moreover LL-3858, a pyrrole analog from Lupin Ltd., and SQ786 both were having piperazine moiety showed promising antitubercular activity [8]. Thus considering the above importance, we decided to hybridize cinnamic acid derivatives with a piperazine ring as a 4-substituted piperazinylaniline derivatives.

On the basis of these literature reports, we set out to explore our promising drug candidate by molecular hybridization of common pharmacophore of cinnamic acid derivatives with 4-substituted piperazinylaniline. Our designed molecule was divided into three parts: part A with cinnamic acid backbone having antitubercular activity, part B with 4-piperazinyl aniline moiety having a promising antitubercular activity and part C with substitution at piperazinyl nitrogen to govern physicochemical, pharmacokinetic and pharmacodynamic property (Fig. 2).

To explore the in depth physicochemical behavior of the cinnamic acid derivatives, we designed a variety of substitutions at part C with different type of functional groups like amide and

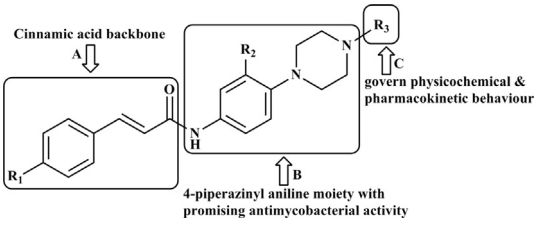


Fig. 2. Pictorial representation of designed cinnamic acid derivatives.

carbamate with varying degree of lipophilicity. Moreover FAS-II pathway was described as a possible way of mechanism for cinnamic acid like derivatives. Hence, secondary amide bond and carbamate linkage may help cinnamic acid derivatives to stabilize drug–receptor interaction through H-bond formation. Based on these preliminary reports, we have designed our cinnamic acid derivatives into following three scaffolds as shown in Fig. 3 (Fig. 3).

As a part of our research to explore novel antitubercular agents, we planned to synthesize the series of *N*-[4-(piperazin-1-yl) phenyl]cinnamamide, with the hope that these novel compounds would exhibit improved antitubercular activity. The all newly synthesized derivatives were further evaluated for its antitubercular activity against *M. tb* H37Rv strain.

2. Results and discussion

2.1. Chemistry

The novel series of *N*-[4-(piperazin-1-yl)phenyl]cinnamamide derivatives were synthesized according to Schemes 1–3. The intermediate amines, 4-(piperazine-1-yl)aniline, were synthesized as depicted in Scheme 1. The starting material 4-Chloronitrobenzene **1a** and 3,4-Difluoronitrobenzene **1b** was reacted with different 4-substituted piperazine derivatives **2a**–**d** in the presence of K_2CO_3 as a base and DMSO at 90 °C to get the condensed nitro product **3a**–**h** in good yield. The 1-(4-nitrophenyl)piperazine derivatives were further reduced to amines **4a**–**h** with the help of Pd/C catalyst at 100 psi in quantitative yields. As described in Scheme 2, the cinnamic acid derivatives **5a** and **5b** were converted to the acid chloride using thionyl chloride in DCM which was added dropwise to 0 °C cooled solution of 4-(piperazine-1-yl)aniline derivatives in dry pyridine to give product cinnamamide **7a**–**p**. (Table 1) The BOC protected amines **7d**, **7h**, **7l** and **7p** were further treated with trifluoroacetic acid to give deprotected piperazinyl amine **9a**–**d**.

The carbamate and amide derivatives were synthesized as depicted in Scheme 3 by using triethyl amine as a base in dry DCM at 0 °C to afford corresponding cinnamamide in moderate to good yields. Compounds **9a**–**d** were further reacted with alkyl/aryl chloroformate to give corresponding carbamate derivatives **10a**–**l** as shown in Table 2. For the synthesis of amide analogs, **9a**–**d** were reacted with different acyl chloride in the presence of triethyl amine as a base to give respective products **11a**–**p** as shown in Table 2. The isonicotinoyl analogs **12a**–**d** were also prepared using the same method as compound **11**.

The structure of all newly synthesized *N*-[4-(piperazin-1-yl) phenyl]cinnamamide derivatives were determined by IR, NMR and Mass spectroscopic analysis and the results were in agreement with the proposed structures. In ^{1}H NMR spectra, the aromatic protons resonated at δ 7.10–7.85 ppm. The piperazine ring proton resonated with two triplets around δ 3.1 and 3.9. The conjugated double bond of cinnamic acid showed two doublet of which C–H proton near to aromatic ring (Ph–C<u>H</u>=CHC–) resonated around δ 7.8 while C–H proton towards the carbonyl end (Ph–CH=C<u>H</u>–CO) resonated around δ 6.6. The presence of proton of CONH group was confirmed by one proton singlet between δ 9.10–10.85 ppm. However one proton peak of NH group of piperazine in compounds **9a**–**d** could not be able to resolve as a result they lack one proton peak. In ^{13}C NMR spectra aromatic carbon resonated between δ 115–145 with many overlaps in that region while the C=O carbon resonated around δ 160–165. In IR spectra, the C=O stretch of secondary amide of synthesized cinnamic acid derivatives was demonstrated by the appearance of the IR absorption band at 1690–1640 cm^{-1}. The presence of NO_2 group of compounds was indicated by the appearance of asymmetric and symmetric NO_2 stretching bands at 1560–1505 cm^{-1} and 1385–1330 cm^{-1} respectively. The

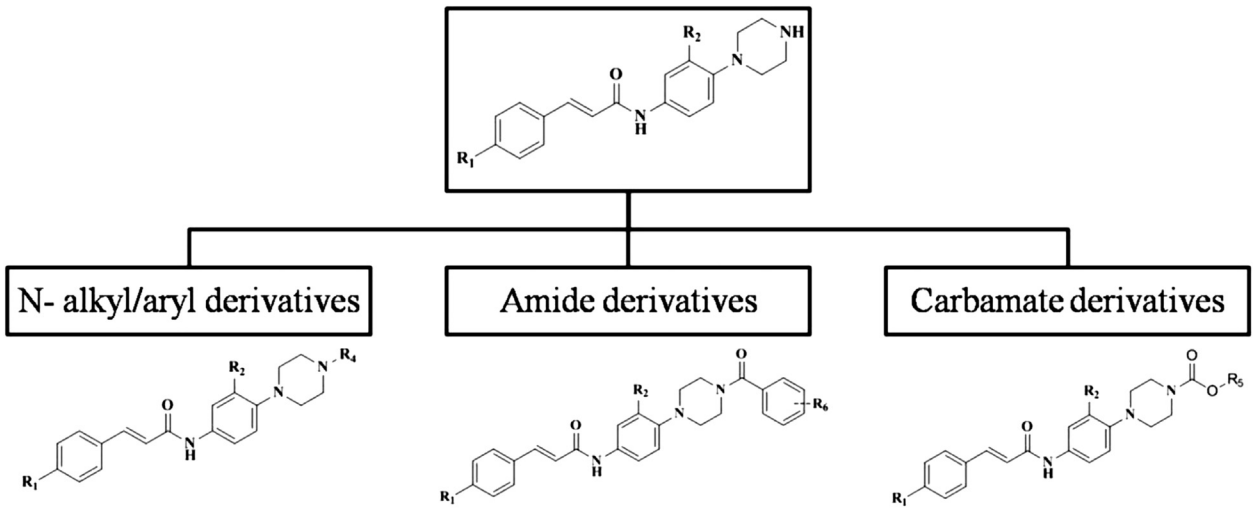


Fig. 3. Designed scaffold of cinnamic acid derivatives.

synthesized compounds exhibited characteristic peak of cinnamic acid double bond at 1680–1620 cm^{-1}.

2.2. Biological screening

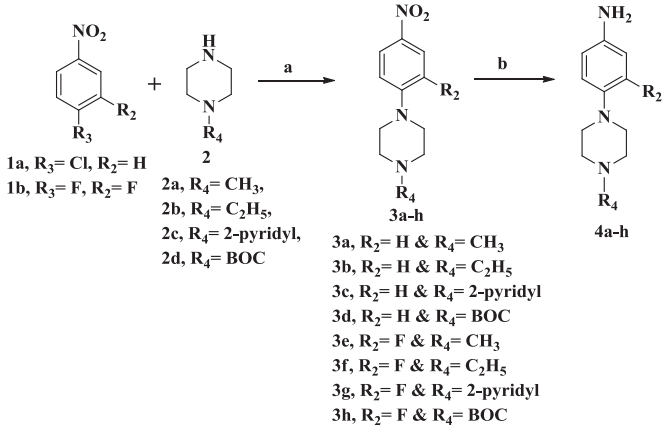
All 52 novel *N*-[4-(piperazin-1-yl)phenyl]cinnamamide derivatives were evaluated for its *in-vitro* antitubercular activity against *M. tb* H37Rv strain using Resazurin microtitre plate assay (REMA) [21]. All compounds were evaluated for its antitubercular activity at a concentration of 1.56–50 μg/ml. The serial dilution technique was used to find out the minimum inhibitory concentration (MIC) of the synthesized cinnamamide derivatives. Isoniazid was used as the standard drug.

The results of biological screening are summarized in Tables 1and 2. From the antitubercular screening, it was found that the highest active compounds **11g** and **7a** were having a MIC of 3.125 and 6.25 μg/ml respectively. The most active compound was amide derivatives **11g** with trifluoromethyl substitution at ortho position of the benzene ring. The other compounds like 7b, 7d, 7f, 7i, 7j, 9a, 9d, 11f, 11h, 11i, 11m, 11n and 12d were having good antitubercular activity of 12.5 μg/ml against *M. tb* H37Rv strain. The amide derivatives were also having promising antitubercular activity of 12.5–50 μg/ml. The alkyl/aryl derivatives of the cinnamamide **7c**, **7g**, **7k** and **7o** contains 2-pyridyl ring which were not active even at 50 μg/ml. This may be attributed to the bulky nature of the 2-pyridyl ring. The antitubercular activity of the carbamate derivatives 10a–l were not appreciable as none of the compounds were active at 50 μg/ml.

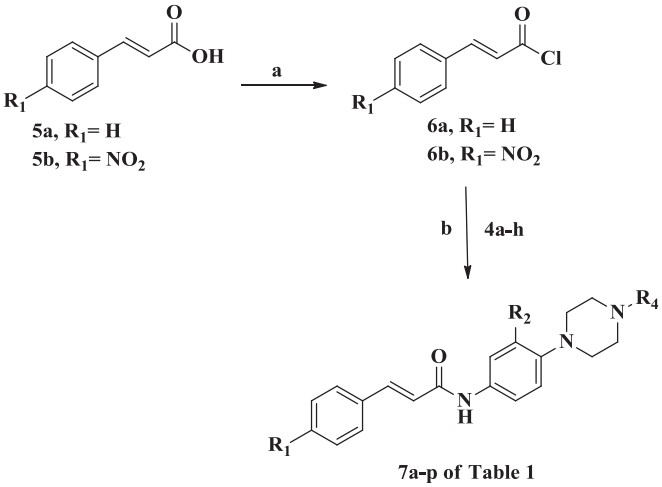
2.3. SAR of N-[4-(piperazin-1-yl)phenyl]cinnamamide derivatives

2.3.1. SAR of alkyl/aryl derivatives

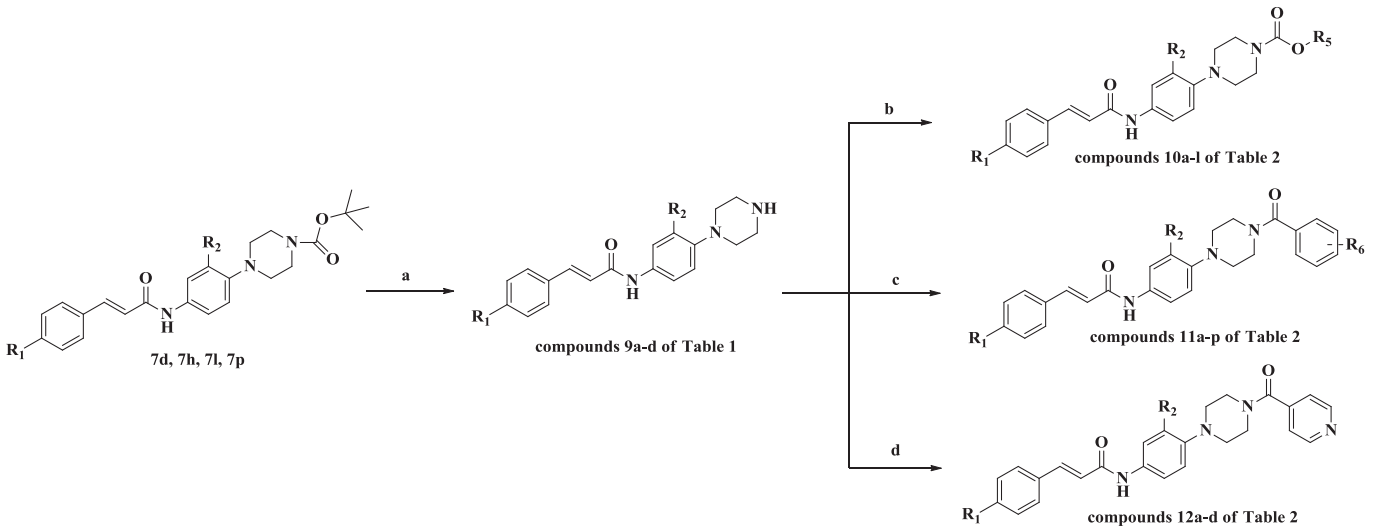
From the biological screening of alkyl or aryl derivatives of cinnamamide, it was found that cinnamamide derivative of *N*-methyl piperazine **7a** was active at 6.25 μg/ml. The other *N*-ethyl piperazine derivatives were also active at 12.5 μg/ml. SAR of part A showed that cinnamic acid and nitrocinnamic acid were equally active against *M. tb*. In the design of part B, fluoro substitution at aromatic ring has no effect on improvement of antitubercular activity. However part C showed that smaller molecular weight functional group substitutions were more active and exhibited significant improvement in the antitubercular activity. It was also found that compounds **7c**, **7g**, **7k** and **7o** with bulkier 2-pyridyl ring substitution at piperazinyl nitrogen leads to decrease in the antitubercular activity of cinnamic acid derivatives.



Scheme 1. [a]: Synthesis of 4-(piperazine-1-yl)aniline derivatives. [a] Reagents: (a) K_2CO_3, DMSO at 90 °C for 12 h; (b) H_2, 10% Pd/C, MeOH-EA at 100 PSI for 6 h.



Scheme 2. [a]: Synthesis of *N*-[4-(piperazin-1-yl)phenyl]cinnamamide derivatives. [a] Reagents: (a) $SOCl_2$, MDC, reflux, 4 h; (b) amines 4a–h, pyridine at 0 °C, 3 h.



Scheme 3. Synthesis of carbamate and amide derivatives of N-[4-(piperazin-1-yl)phenyl]cinnamamide. Reagents: (a) TFA, MDC, rt, 12 h then 1 N NaOH; (b) alkyl/aryl Chloroformate, TEA, MDC, 0 °C, 0.5 h; (c) acyl chloride, TEA, MDC, 0 °C, 0.5 h; (d) isonicotinoyl chloride, TEA, MDC, 0 °C, 0.5 h.

2.3.2. SAR of carbamate derivatives

We have postulated that carbamate derivatives may be active as it contains carbamate functional group that may help by hydrogen bonding with the receptor active site. But the SAR of part A and B explained that the substitution of nitro or fluoro derivatives have no effect on antitubercular activity. Furthermore it also explains that any carbamate substitution at part C have resulted in compounds that were not active at 50 μg/ml. The biological screening of carbamate derivatives 10a–l showed that carbamate moiety may not be crucial for antitubercular activity in case of cinnamamide derivatives.

2.3.3. SAR of amide derivatives

SAR of amide derivatives showed that nitrocinnamic acid derivatives were more active as compared to cinnamic acid as it was evidenced from the compound **11i**, **11m**, **11n** and **12d**.

But the most interesting thing found by SAR of part B was that the compounds containing fluoro substitution at aromatic ring were having higher activity than nonfluoro derivatives. It was evidenced that compounds **11f**, **11g**, **11h**, **11i**, **11m** and **11n** were containing fluoro substitution hence were active against *M. tb*. At the 2-position of the part C aromatic ring, introduction of the trifluoromethyl group leads to increase in the antitubercular activity. At the 4-position of the part C, fluoro derivative was found to be more active. The amide derivatives were also able to retain the antitubercular activity even with the introduction of the bulkier chloro atom at 3 and 5 position of the part C benzene ring.

Table 1
Antitubercular activity of *N*-(4-(piperazin-1-yl)phenyl)cinnamamide derivatives.

Compd	R_1	R_2	R_4	MIC (μg/ml)
7a	H	H	CH_3	6.25
7b	H	H	C_2H_5	12.5
7c	H	H	2-pyridyl	>50
7d	H	H	BOC	12.5
7e	H	F	CH_3	25
7f	H	F	C_2H_5	12.5
7g	H	F	2-pyridyl	>50
7h	H	F	BOC	50
7i	NO_2	H	CH_3	12.5
7j	NO_2	H	C_2H_5	12.5
7k	NO_2	H	2-pyridyl	>50
7l	NO_2	H	BOC	12.5
7m	NO_2	F	CH_3	25
7n	NO_2	F	C_2H_5	>50
7o	NO_2	F	2-pyridyl	>50
7p	NO_2	F	BOC	50
9a	H	H	H	12.5
9b	H	F	H	25
9c	NO_2	H	H	50
9d	NO_2	F	H	12.5

Table 2
Antitubercular activity of *N*-(4-(piperazin-1-yl)phenyl)cinnamamide derivatives.

Compd	R_1	R_2	R_5	R_6	MIC (μg/ml)
10a	H	H	CH_3	–	>50
10b	H	H	C_2H_5	–	>50
10c	H	H	C_6H_5	–	>50
10d	H	F	CH_3	–	>50
10e	H	F	C_2H_5	–	>50
10f	H	F	C_6H_5	–	>50
10g	NO_2	H	CH_3	–	>50
10h	NO_2	H	C_2H_5	–	>50
10i	NO_2	H	C_6H_5	–	>50
10j	NO_2	F	CH_3	–	>50
10k	NO_2	F	C_2H_5	–	>50
10l	NO_2	F	C_6H_5	–	>50
11a	H	H	–	4-F	25
11b	H	H	–	3-Cl, 5-Cl	>50
11c	H	H	–	2-CF_3	50
11d	H	H	–	4-NO_2	>50
11e	H	F	–	4-F	>50
11f	H	F	–	3-Cl, 5-Cl	12.5
11g	H	F	–	2-CF_3	3.125
11h	H	F	–	4-NO_2	12.5
11i	NO_2	H	–	4-F	12.5
11j	NO_2	H	–	3-Cl, 5-Cl	>50
11k	NO_2	H	–	2-CF_3	>50
11l	NO_2	H	–	4-NO_2	>50
11m	NO_2	F	–	4-F	12.5
11n	NO_2	F	–	3-Cl, 5-Cl	12.5
11o	NO_2	F	–	2-CF_3	>50
11p	NO_2	F	–	4-NO_2	>50
12a	H	H	–	–	50
12b	H	F	–	–	>50
12c	NO_2	H	–	–	>50
12d	NO_2	F	–	–	12.5
INH	–	–	–	–	0.39

2.4. In vitro cytotoxicity

The *in vitro* cytotoxicity study was carried out for five compounds (**7a**, **7f**, **11g**, **11i**, and **12d**) in a mammalian Vero cell line on three different concentrations. The tetrazolium salt, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), was used to measure cytotoxicity (IC50) in 96 well microtitre plate [22,23]. After 72 h of exposure, the cell viability was assessed based on conversion of yellow tetrazolium salt to its purple formazan product. It was found that all the five compounds were having IC50 values more than 125 μg/ml indicating that the compounds were nontoxic up to 125 μg/ml. The in vitro cytotoxicity assay gives IC50 value which is used to calculate SI (Selectivity Index). The selectivity index is defined as the ratio of the measured IC50 (mammalian cell toxicity) to the MIC (H37Rv *M. tuberculosis*). If the SI value is $\geq$ 10, then the compound may be considered for further screening. The SI value of compound **11g** was more than 40 indicating that 11g is safe for further screening. The SI value of other compounds like **7a**, **7f**, **11i**, and **12d** were also found to be more than **10**.

3. Conclusion

The present study revealed that N-[4-(piperazin-1-yl)phenyl] cinnamamide derivatives possess good to moderate activity against *M. tb*. Out of 52 synthesized cinnamamide derivatives, compound **11g** with trifluoromethyl substitution emerged with antitubercular activity of 3.125 μg/ml. In case of alkyl/aryl derivatives, the compounds with lower molecular weight with small functional group substitutions were more active and exhibited significant improvement in the antitubercular activity as compared to bulkier group. Moreover cinnamamide containing fluoro group were more active than nonfluoro derivatives. A further cytotoxicity study of five compounds also revealed that they are safe for further screening as the safety index was more than 10. The promising activity of the *N*-[4-(piperazin-1-yl)phenyl]cinnamamide derivatives established them as crucial pharmacophore which can be used as lead to design further novel derivatives of cinnamic acid with better antitubercular activity. Considering this pharmacophore, the further expansion of the cinnamamide series are underway to find a potent antitubercular agent.

4. Experimental protocols

4.1. General

Starting materials were purchased from commercial sources and were used without further purification. Solvents were dried according to standard procedure. The reaction progress was monitored by thin layer chromatography (TLC) on aluminum sheet obtained from Merck. Silica gel 60–120 mesh was used for column chromatography. Melting points were recorded on Thermomik Campbell Melting Point apparatus having an oil bath system and were uncorrected. IR spectrum was recorded on FTIR (Perkin Elmer Spectrum RX1) by preparing KBr pellets.

All ^{1}H and ^{13}C NMR were recorded on 400 MHz Varian Mercury NMR instrument. All NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 solutions using TMS as an internal standard. Chemical shifts are reported in ppm (δ). Mass spectra were recorded on Agilent 7820A GC systems (SIS-Direct insertion probe) and LC-MS TOF 6520A.

4.2. General procedure for the synthesis of compounds *3a–h*

Compounds **3a–h** were synthesized as per literature [24].

4.3. General procedure for the synthesis of compounds *4a–h*

Compounds **4a–h** were synthesized as per literature [24].

4.4. General procedure for the synthesis of compounds *6a* and *6b*

1 equiv of cinnamic acid derivatives **5a** or **5b** was dissolved in DCM (20 ml/g) and a catalytic amount of DMF was added followed by the addition of 1.2 equiv is $SOCl_2$. The reaction mixture was refluxed for 3 h and then solvent was evaporated under vacuum to get the product **6a** or **6b** in the form of solid residue in quantitative yield. The solid residue was used directly for second step without further purification.

4.5. General procedure for the synthesis of compounds *7a–p*

1 equiv of piperazinyl amine was dissolved in pyridine (20 ml/g) and stirred at 0 °C under inert atmosphere. 1.2 equiv of cinnamoyl chloride derivative was dissolved in dry DCM (10 ml/g) and added dropwise to above stirred solution at 0 °C. The reaction mixture was stirred for 3 h and was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (20 ml/g) and ethyl acetate (30 ml/g) followed by 2 N HCl to make it acidic. The precipitate came out which was filtered as yellow solid and further washed with 2 N HCl and then water. The precipitate was suspended in saturated bicarbonate solution and stirred vigorously to remove acid impurities. The crude compound was purified either by column chromatography or by recrystallization from ethyl acetate and hexane.

4.5.1. N-[4-(4-Methylpiperazin-1-yl)phenyl]cinnamamide (*7a*)

4-(4-Methylpiperazin-1-yl)aniline **4a** (0.3 g, 1.57 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6a** (0.31 g, 1.88 mmol) was dissolved in 3 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.39 g of **7a**. Light yellow solid; Yield 78%; mp 223–225 °C; IR (KBr pellets, cm^{-1}): 3417, 3277, 3042, 2929, 2834, 1653, 1616, 1535, 1448, 1337, 1255, 967, 819, 755; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.39 (3H, s, C$\underline{H}_3$), 2.63 (4H, t, J = 3.51 Hz), 3.22 (4H, t, J = 3.51 Hz), 6.58 (1H, d, J = 15.1 Hz, Ph–CH=C$\underline{H}$–), 6.96 (2H, d, J = 7.4 Hz, Ar–$\underline{H}$), 7.30–7.75 (7H, m, Ar–$\underline{H}$), 7.78 (1H, d, J = 15.1 Hz, Ph–C$\underline{H}$=C$\underline{H}$–), 9.65 (1H, s, CON$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 46.11, 49.37, 55.06, 116.53, 121.07, 121.32, 127.89, 128.81, 129.77, 130.46, 134.78, 141.74, 148.32, 163.74; HR–MS m/z: 321.2086 (M^+).

4.5.2. N-[4-(4-Ethylpiperazin-1-yl)phenyl]cinnamamide (*7b*)

4-(4-Ethylpiperazin-1-yl)aniline **4b** (0.3 g, 1.46 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6a** (0.29 g, 1.76 mmol) was dissolved in 3 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.31 g of **7b**. Light yellow solid; Yield 65.96%; mp 224–226 °C; IR (KBr pellets, cm^{-1}): 3350, 3254, 2948, 2827, 1631, 1602, 1542, 1428, 1261, 1194, 985, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.15 (3H, t, J = 7.6 Hz, C$\underline{H}_3$), 2.43 (2H, q, J = 7.6 Hz, C$\underline{H}_2$), 2.61 (4H, t, J = 3.67 Hz), 3.21 (4H, t, J = 3.69 Hz), 6.56 (1H, d, J = 15.6 Hz, Ph–CH=C$\underline{H}$–), 6.94 (2H, d, J = 7.1 Hz Hz, Ar–$\underline{H}$), 7.20–7.59 (7H, m, Ar–$\underline{H}$), 7.75 (1H, d, J = 15.6 Hz, Ph–C$\underline{H}$=C$\underline{H}$–), 9.69 (1H, s, CON$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 12.43, 45.52, 49.81, 55.62, 112.27, 117.41, 119.54, 122.65, 125.73, 127.29, 128.73, 135.47, 141.82, 145.91, 165.11; HR–MS m/z: 335.3234 (M^+).

4.5.3. N-{4-[4-(Pyridin-2-yl)piperazin-1-yl]phenyl}cinnamamide (**7c**)

4-[4-(Pyridin-2-yl)piperazin-1-yl]aniline **4c** (0.3 g, 1.18 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6a** (0.24 g, 1.42 mmol) was dissolved in 3 ml dry DCM and added dropwise to above stirred solution at 0 °C. After completion of the reaction, the mixture was diluted with water and ethyl acetate. The precipitate was filtered and washed heavily with first cold water then tap water to remove pyridine. The precipitate was suspended in saturated bicarbonate solution and stirred vigorously to remove acid impurities. The crude compound was purified by column chromatography to afford 0.34 g of **7c**. Light yellow solid; Yield 75.56%; mp 218–220 °C; IR (KBr pellets, cm^{-1}): 3380, 3266, 1698, 1665, 1596, 1435, 1244, 987, 845, 789; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.17 (4H, t, $J = 3.82$ Hz), 3.59 (4H, t, $J = 3.85$ Hz), 6.57 (1H, d, $J = 15.3$ Hz, Ph–CH=CH–), 6.59–6.81 (4H, m, Ar–H), 7.21–7.58 (8H, m, Ar–H), 7.75 (1H, d, $J = 15.3$ Hz, Ph–CH=CH–), 8.05 (1H, s, Ar–H), 9.11 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 45.52, 51.10,110.52, 112.76, 118.93, 119.51,123.89, 127.10, 127.92, 128.31, 128. 34, 132.54, 139.41, 142.63, 144.21, 149.84, 156.20, 165.73; HR–MS *m/z*: 384.2532 (M^+).

4.5.4. tert-Butyl 4-(4-cinnamamidophenyl)piperazine-1-carboxylate (**7d**)

tert-Butyl 4-(4-aminophenyl)piperazine-1-carboxylate **4d** (3 g, 10.83 mmol) was dissolved in 40 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6a** (2.16 g, 13 mmol) was dissolved in 20 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was stirred for 3 h. After completion of the reaction, the reaction mixture was diluted with 40 ml water and 60 ml ethyl acetate followed by 2 N HCl to make it acidic. The organic layer was separated and again washed with 2 N HCl followed by saturated bicarbonate solution (2 × 50 ml) and brine solution. The organic layer was dried over anhydrous sodium sulfate and was evaporated under reduced pressure. The crude product was recrystallized from ethyl acetate and hexane to afford 3.25 g of **7d**. Off-white solid; Yield 73.86%; mp 186–188 °C; IR (KBr pellets, cm^{-1}): 3335, 3106, 2976, 2822, 1689, 1624, 1521, 1423, 1232, 1173, 971, 827, 763; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.41 (9H, s, CH_3), 3.12 (4H, t, $J = 4.15$ Hz), 3.71 (4H, t, $J = 4.12$ Hz), 6.75 (1H, d, $J = 14.8$ Hz, Ph–CH=CH–), 7.09–7.45 (9H, m, Ar–H), 7.71 (1H, d, $J = 14.8$ Hz, Ph–CH=CH–), 8.61 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 28.37, 51.48, 80.43, 118.47, 121.14, 121.38, 127.97, 128.83, 129.84, 134.74, 141.93, 154.43, 164.33; HR-MS *m/z*: 407.2267 (M^+).

4.5.5. N-[3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl]cinnamamide (**7e**)

3-Fluoro-4-(4-methylpiperazin-1-yl)aniline **4e** (0.3 g, 1.44 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6a** (0.29 g, 1.72 mmol) was dissolved in 3 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.34 g of **7e**. Light yellow solid; Yield 64.15%; mp 236–238 °C; IR (KBr pellets, cm^{-1}): 3445, 3294, 2935, 2845, 1686, 1636, 1516, 1342, 12611, 1191, 920, 858, 766; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.36 (3H, s, CH_3), 2.60 (4H, t, $J = 3.39$ Hz), 3.10 (4H, t, $J = 3.38$ Hz), 6.49 (1H, d, $J = 15.3$ Hz, Ph–CH=CH–), 6.90 (1H, d, $J = 7.1$ Hz, Ar–H), 7.16–7.55 (7H, m, Ar–H), 7.73 (1H, d, $J = 15.3$ Hz, Ph–CH=CH–), 9.85 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 48.16, 49.52, 53.26, 110.51, 116.20, 120.09, 121.95, 126.90, 128.32, 129.12, 131.46, 134.22, 141.04, 149.11, 151.71, 163.74; HR-MS *m/z*: 339.3642 (M^+).

4.5.6. N-[4-(4-Ethylpiperazin-1-yl)-3-fluorophenyl]cinnamamide (**7f**)

4-(4-Ethylpiperazin-1-yl)-3-fluoroaniline **4f** (0.3 g, 1.35 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6a** (0.27 g, 1.61 mmol) was dissolved in 3 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.31 g of **7f**. Light yellow solid; Yield 60.78%; mp 194–196 °C; IR (KBr pellets, cm^{-1}): 3366, 3266, 2952, 2857, 1630, 1602, 1510, 1339, 1258, 1191, 993, 876, 758; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.07 (3H, t, $J = 7.15$ Hz, CH_3), 2.49 (2H, q, $J = 7.15$ Hz, CH_2), 2.62 (4H, t, $J = 3.67$ Hz), 3.32 (4H, t, $J = 3.69$ Hz), 6.76 (1H, d, $J = 15.2$ Hz, Ph–CH=CH–), 6.99 (1H, d, $J = 8.2$ Hz, Ar–H), 7.29–7.63 (7H, m, Ar–H), 7.70 (1H, d, $J = 15.2$ Hz, Ph–CH=CH–), 10.29 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 12.89, 46.42, 49.24, 53.12, 111.78, 112.27, 118.29, 118.94, 121.15, 125.03, 127.90, 128.11, 134.41, 142.80, 145.22, 152.33, 165.11; HR-MS *m/z*: 353.3216 (M^+).

4.5.7. N-{3-Fluoro-4-[4-(pyridin-2-yl)piperazin-1-yl]phenyl} cinnamamide (**7g**)

3-Fluoro-4-[4-(pyridin-2-yl)piperazin-1-yl]aniline **4g** (0.3 g, 1.1 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6a** (0.22 g, 1.32 mmol) was dissolved in 3 ml dry DCM and added dropwise to above stirred solution at 0 °C. After completion of the reaction, the mixture was diluted with water and ethyl acetate. The precipitate was filtered and washed heavily with first cold water then tap water to remove pyridine. The precipitate was suspended in saturated bicarbonate solution and stirred vigorously to remove acid impurities. The crude compound was purified by column chromatography to afford 0.28 g of **7g**. Light yellow solid; Yield 59.57%; mp 217–219 °C; IR (KBr pellets, cm^{-1}): 3436, 3312, 1622, 1514, 1431, 1336, 1256, 1155, 1021, 842, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.45 (4H, t, $J = 4.71$ Hz), 3.27 (4H, t, $J = 4.68$ Hz), 6.79 (1H, d, $J = 15.9$ Hz, Ph–CH=CH–), 6.89–7.01 (3H, m, Ar–H), 7.26–7.78 (8H, m, Ar–H), 7.85 (1H, d, $J = 15.9$ Hz, Ph–CH=CH–), 8.11 (1H, s, Ar–H), 10.61 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 46.55, 50.18, 110.67, 111.06, 117.23, 118.31,122.19, 127.34, 128.22, 128.81, 129. 24, 131.14, 139.40, 143.73, 145.22, 149.34, 151.23, 156.21, 164.23; HR-MS *m/z*: 402.2125 (M^+).

4.5.8. tert-Butyl 4-(4-cinnamamido-2-fluorophenyl)piperazine-1-carboxylate (**7h**)

tert-Butyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate **4h** (4 g, 13.56 mmol) was dissolved in 40 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6a** (2.7 g, 16.27 mmol) was dissolved in 20 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was stirred for 3 h. After completion of the reaction, the reaction mixture was diluted with 40 ml water and 60 ml ethyl acetate followed by 2 N HCl to make it acidic. The organic layer was separated and again washed with 2 N HCl followed by saturated bicarbonate solution (2 × 50 ml) and brine solution. The organic layer was dried over anhydrous sodium sulfate and was evaporated under reduced pressure. The crude product was recrystallized from ethyl acetate and hexane to afford 4.3 g of **7h**. Light yellow solid; Yield 70.15%; mp 183–185 °C; IR (KBr pellets, cm^{-1}): 3305, 3059, 2911, 1621, 1527, 1333, 1285, 1201, 1027, 971, 812; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.42 (9H, s, CH_3), 2.99 (4H, t, $J = 3.46$ Hz), 3.59 (4H, t, $J = 3.46$ Hz), 6.45 (1H, d, $J = 15.5$ Hz, Ph–CH=CH–), 6.91 (1H, d, $J = 7.7$ Hz, Ar–H), 7.20–7.61 (7H, m, Ar–H), 7.79 (1H, d, $J = 15.5$ Hz, Ph–CH=CH–), 9.81 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 28.43, 50.69, 79.91, 115.74, 119.30, 120.51, 127.95, 128.89, 130.04, 134.54, 142.55, 154.11, 154.75, 163.94; HR–MS *m/z*: 425.3239 (M^+).

*4.5.9. N-[4-(4-Methylpiperazin-1-yl)phenyl]-3-(4-nitrophenyl) acrylamide (**7i**)*

4-(4-Methylpiperazin-1-yl)aniline **4a** (0.3 g, 1.57 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6b** (0.5 g, 1.88 mmol) was dissolved in 4 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.22 g of **7i**. Light yellow solid; Yield 38.6%; mp 265–267 °C (charred); IR (KBr pellets, cm^{-1}): 3400, 3238, 2957, 2683, 1597, 1516, 1415, 1339, 1250, 981, 827; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.31 (3H, s, CH_3), 3.05 (4H, t, J = 3.34 Hz), 3.86 (4H, t, J = 3.33 Hz), 6.50 (1H, d, J = 16.3 Hz, Ph–CH=CH–), 6.88 (2H, d, J = 7.4 Hz, Ar–H), 7.20–7.56 (4H, m, Ar–H), 7.73 (1H, d, J = 16.3 Hz, Ph–CH=CH–), 8.18 (2H, d, J = 6.8 Hz, Ar–H), 9.95 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 46.90, 48.24, 54.36, 117.51, 121.15, 122.92, 127.34, 129.57, 131.49, 133.28, 141.10, 147.81, 148.25, 163.20; HR-MS m/z: 366.2082 (M^+).

*4.5.10. N-[4-(4-Ethylpiperazin-1-yl)phenyl]-3-(4-nitrophenyl) acrylamide (**7j**)*

4-(4-Ethylpiperazin-1-yl)aniline **4b** (0.3 g, 1.46 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6b** (0.46 g, 1.76 mmol) was dissolved in 4 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.32 g of **7j**. Light yellow solid; Yield 58.18%; mp 228–230 °C; IR (KBr pellets, cm^{-1}): 3428, 3100, 2945, 2828, 1664, 1604, 1544, 1515, 1427, 1342, 1221, 1140, 990, 846, 756; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.19 (3H, t, J = 6.8 Hz, CH_3), 2.49 (2H, q, J = 6.8 Hz, CH_2), 2.59 (4H, t, J = 3.87 Hz), 3.10 (4H, t, J = 3.89 Hz), 6.49 (1H, d, J = 15.6 Hz, Ph–CH=CH–), 6.84 (2H, d, J = 7.9 Hz, Ar–H), 7.31–7.80 (4H, m, Ar–H), 7.75 (1H, d, J = 15.6 Hz, Ph–CH=CH–), 8.10 (2H, d, J = 6.4 Hz, Ar–H), 9.71 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 48.96, 51.90, 52.36, 115.92, 120.76, 123.70, 126.42, 127.98, 130.85, 137.08, 141.40, 147.46, 147.71, 162.56; HR-MS m/z: 380.3129 (M^+).

*4.5.11. 3-(4-Nitrophenyl)-N-{4-[4-(pyridin-2-yl)piperazin-1-yl] phenyl}acrylamide (**7k**)*

4-[4-(Pyridin-2-yl)piperazin-1-yl]aniline **4c** (0.3 g, 1.18 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6b** (0.37 g, 1.42 mmol) was dissolved in 4 ml dry DCM and added dropwise to above stirred solution at 0 °C. After completion of the reaction, the mixture was diluted with water and ethyl acetate. The precipitate was filtered and washed heavily with first cold water then tap water to remove pyridine. The precipitate was suspended in saturated bicarbonate solution and stirred vigorously to remove acid impurities. The crude compound was purified by column chromatography to afford 0.25 g of **7k**. Light yellow solid; Yield 50%; mp 270–272 °C (charred); IR (KBr pellets, cm^{-1}): 3462, 3327, 2834, 1653, 1600, 1510, 1434, 1339, 1227, 1174, 951, 783; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.11 (4H, t, J = 3.37 Hz), 3.62 (4H, t, J = 3.39 Hz), 6.65 (1H, d, J = 15.1 Hz, Ph–CH=CH–), 6.81–6.98 (4H, m, Ar–H), 7.23–7.71 (5H, m, Ar–H), 7.79 (1H, d, J = 15.1 Hz, Ph–CH=CH–), 8.12 (3H, m, Ar–H), 9.41 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 44.12, 46.01,111.42, 112.23, 118.13, 119.50,122.29, 127.11, 127.98, 128.24, 131.64, 138.30, 141.94, 143.57, 147.56, 148.04, 155.93, 164.38; HR-MS m/z: 429.2185 (M^+).

*4.5.12. tert-Butyl 4-{4-[3-(4-nitrophenyl)acrylamido]phenyl} piperazine-1-carboxylate (**7l**)*

tert-Butyl 4-(4-aminophenyl)piperazine-1-carboxylate **4d** (4 g, 14.44 mmol) was dissolved in 40 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6b** (4.45 g, 17.33 mmol) was dissolved in 20 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was stirred for 3 h. After completion of the reaction, the reaction mixture was diluted with 40 ml water and 60 ml ethyl acetate followed by 2 N HCl to make it acidic. The organic layer was separated and again washed with 2 N HCl followed by saturated bicarbonate solution (2 × 50 ml) and brine solution. The organic layer was dried over anhydrous sodium sulfate and was evaporated under reduced pressure. The crude product was recrystallized from ethyl acetate and hexane to afford 4.52 g of **7l**. Light yellow solid; Yield 69.33%; 216–218 °C (charred); IR (KBr pellets, cm^{-1}): 3425, 3105, 1666, 1604, 1544, 1514, 1427, 1342, 1220, 1141, 991, 844; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.43 (9H, s, CH_3), 3.10 (4H, t, J = 3.79 Hz), 3.62 (4H, t, J = 3.76 Hz), 6.71 (1H, d, J = 16.5 Hz, Ph–CH=CH–), 6.98 (2H, d, J = 7.2 Hz, Ar–H), 7.29–7.87 (4H, m, Ar–H), 7.89 (1H, d, J = 16.5 Hz, Ph–CH=CH–), 8.23 (2H, d, J = 7.0 Hz, Ar–H), 9.24 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 28.76, 49.41, 51.48, 78.50, 112.10, 118.03, 121.31, 123.72, 126.08, 129.45, 141.79, 142.11, 145.21, 147.29, 157.22, 167.52; HR–MS m/z: 453.2067 (M + 1).

*4.5.13. N-[3-Fluoro-4-(4-methylpiperazin-1-yl)phenyl]-3-(4-nitrophenyl)acrylamide (**7m**)*

3-Fluoro-4-(4-methylpiperazin-1-yl)aniline **4e** (0.3 g, 1.44 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6b** (0.45 g, 1.72 mmol) was dissolved in 4 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.3 g of **7m**. Light yellow solid; Yield 50%; mp 221–223 °C; IR (KBr pellets, cm^{-1}): 3448, 2925, 2830, 1606, 1542, 1508, 1426, 1341, 1217, 1139, 988, 845; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.41 (3H, s, CH_3), 3.25 (4H, t, J = 3.35 Hz), 3.81 (4H, t, J = 3.36 Hz), 6.75 (1H, d, J = 15.9 Hz, Ph–CH=CH–), 7.02 (1H, d, J = 7.7 Hz, Ar–H), 7.26–7.45 (4H, m, Ar–H), 7.58 (1H, d, J = 15.9 Hz, Ph–CH=CH–), 8.01 (2H, d, J = 6.8 Hz Hz, Ar–H), 10.85 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 46.11, 48.42, 52.50, 111.14, 117.22, 121.03, 122.15, 128.12, 130.11, 131.06, 135.72, 142.01, 147.89, 148.45, 152.81, 165.28; HR-MS m/z: 384.3025 (M^+).

*4.5.14. N-[4-(4-Ethylpiperazin-1-yl)-3-fluorophenyl]-3-(4-nitrophenyl)acrylamide (**7n**)*

4-(4-Ethylpiperazin-1-yl)-3-fluoroaniline **4f** (0.3 g, 1.35 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6b** (0.43 g, 1.61 mmol) was dissolved in 4 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.25 g of **7n**. Light yellow solid; Yield 43.1%; mp 217–219 °C; IR (KBr pellets, cm^{-1}): 3421, 3100, 2945, 2832, 1664, 1602, 1542, 1514, 1421, 1341, 1225, 995, 847; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.14 (3H, t, J = 7.31 Hz, CH_3), 2.32 (2H, q, J = 7.31 Hz, CH_2), 3.44 (4H, t, J = 3.68 Hz), 3.98 (4H, t, J = 3.69 Hz), 6.37 (1H, d, J = 14.6 Hz, Ph–CH=CH–), 7.23–7.66 (5H, m, Ar–H), 7.68 (1H, d, J = 14.6 Hz, Ph–CH=CH–), 8.22 (2H, d, J = 7.2 Hz, Ar–H), 9.62 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.12, 46.40, 48.25, 52.19, 110.08, 113.21, 117.19, 118.55, 120.19, 125.82, 128.92, 134.20, 141.32, 145.67, 147.23, 152.12, 167.08; HR-MS m/z: 398.3010(M^+).

*4.5.15. N-{3-Fluoro-4-[4-(pyridin-2-yl)piperazin-1-yl]phenyl}-3-(4-nitrophenyl)acrylamide (**7o**)*

3-Fluoro-4-[4-(pyridin-2-yl)piperazin-1-yl]aniline **4g** (0.3 g, 1.1 mmol) was dissolved in 5 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6b** (0.35 g, 1.32 mmol) was dissolved in 4 ml dry DCM and added dropwise to above stirred solution at 0 °C. After completion of the reaction, the mixture was diluted with water and ethyl acetate. The precipitate was filtered and washed heavily with first cold water then tap water to remove

pyridine. The precipitate was suspended in saturated bicarbonate solution and stirred vigorously to remove acid impurities. The crude compound was purified by column chromatography to afford 0.21 g of **7o**. Light yellow solid; Yield 40.38%; mp 242–244 °C (charred); IR (KBr pellets, cm^{-1}): 3386, 3102, 2848, 1664, 1596, 1514, 1435, 1342, 1243, 986, 845, 789; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.97 (4H, t, J = 3.45 Hz), 3.59 (4H, t, J = 3.45 Hz), 6.58 (1H, d, J = 15.3 Hz, Ph–CH=CH–), 6.83–6.96 (3H, m, Ar–H), 7.21–7.57 (5H, m, Ar–H), 7.61 (1H, d, J = 15.3 Hz, Ph–CH=CH–), 8.19 (3H, m, Ar–H), 9.97 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 47.15, 49.01, 110.17, 111.23, 117.11, 118.56,122.30, 127.12, 128.11, 128.89, 129. 45, 131.22, 139.23, 143.12, 145.72, 149.68, 151.59, 156.90, 165.54; HR–MS m/z: 447.2128 (M^+).

4.5.16. tert-Butyl 4-{2-fluoro-4-[3-(4-nitrophenyl)acrylamido] phenyl}piperazine-1-carboxylate (**7p**)

tert-Butyl 4-(4-amino-2-fluorophenyl)piperazine-1-carboxylate **4h** (4 g, 13.56 mmol) was dissolved in 40 ml of dry pyridine and stirred at 0 °C under inert atmosphere. Cinnamoyl chloride **6b** (4.29 g, 16.27 mmol) was dissolved in 20 ml dry DCM and added dropwise to above stirred solution at 0 °C. The reaction mixture was stirred for 3 h. After completion of the reaction, the reaction mixture was diluted with 40 ml water and 60 ml ethyl acetate followed by 2 N HCl to make it acidic. The organic layer was separated and again washed with 2 N HCl followed by saturated bicarbonate solution (2 × 50 ml) and brine solution. The organic layer was dried over anhydrous sodium sulfate and was evaporated under reduced pressure. The crude product was recrystallized from ethyl acetate and hexane to afford 4.42 g of **7p**. Light orange solid; Yield 65.19%; 205–207 °C; IR (KBr pellets, cm^{-1}): 3452, 3273, 3065, 2863, 1720, 1656, 1594, 1514, 1342, 1215, 1165, 975, 914, 838, 754; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.39 (9H, s, CH_3), 3.14 (4H, t, J = 3.50 Hz), 3.74 (4H, t, J = 3.51 Hz), 6.82 (1H, d, J = 15.9 Hz, Ph–CH=CH–), 7.01–7.68 (5H, m, Ar–H), 7.75 (1H, d, J = 15.9 Hz, Ph–CH=CH–), 8.18 (2H, d, J = 7.1 Hz, Ar–H), 9.92 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 26.22, 49.67, 50.12, 80.41, 116.44, 118.50, 119.31, 127.33, 131.21, 135.32, 141.95, 147.90, 154.56, 155.09, 166.23; HR-MS m/z: 470.3026 (M^+).

4.6. General procedure for the synthesis of compounds **9a–d**

The BOC protected amines were stirred at room temperature in a mixture of TFA/DCM (1:1) for 12 h. The volatiles were removed in vacuo, and the residue was scratched with little water to get yellow solid. The solid was filtered and washed with water and ethyl acetate to get product in the form of TFA salt. The TFA salt was suspended in the 1 N NaOH solution and stirred for 10 min to get salt free base form which was recrystallized from chloroform-Hexane to get pure product.

4.6.1. N-[4-(Piperazin-1-yl)phenyl]cinnamamide (**9a**)

tert-Butyl 4-(4-cinnamamidophenyl)piperazine-1-carboxylate **7d** (3 g, 9.77 mmol) was stirred at room temperature in a 20 ml mixture of TFA/DCM (1:1) for 12 h. The reaction mixture was worked up as per the general procedure to afford 2.1 g of **9a**. Light yellow solid; Yield 92.92%; mp 205–207 °C; IR (KBr pellets, cm^{-1}): 3317, 3254, 2945, 2826, 1665, 1599, 1316, 1448, 1338, 1244, 1177, 977, 820, 761; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.01–3.12 (8H, t, J = 3.89 Hz Hz), 6.59 (1H, d, J = 15.2 Hz, Ph–CH=CH–), 6.91 (2H, d, J = 7.5 Hz, Ar–H), 7.21–7.59 (7H, m, Ar–H), 7.79 (1H, d, J = 15.2 Hz, Ph–CH=CH–), 9.84 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 45.98, 52.38, 112.82, 117.37,121.40, 127.85, 128.11, 128.78, 131.33, 135.32, 141.36, 146.28, 165.93; HR-MS m/z: 307.2045 (M^+).

4.6.2. N-[3-Fluoro-4-(piperazin-1-yl)phenyl]cinnamamide (**9b**)

tert-Butyl 4-(4-cinnamamido-2-fluorophenyl)piperazine-1-carboxylate **7h** (4 g, 12.31 mmol) was stirred at room temperature in a 20 ml mixture of TFA/DCM (1:1) for 12 h. The reaction mixture was worked up as per the general procedure to afford 2.85 g of **9b**. Light yellow solid; Yield 93.44%; mp 210–212 °C; IR (KBr pellets, cm^{-1}): 3400, 3327, 2834, 1667,1630, 1544, 1513, 1426, 1261, 1208, 1130, 869; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.51 (4H, t, J = 3.69 Hz), 3.34 (4H, t, J = 3.70 Hz Hz), 6.71 (1H, d, J = 14.1 Hz, Ph–CH=CH–), 6.93 (1H, d, J = 7.2 Hz, Ar–H), 7.23–7.64 (7H, m, Ar–H), 7.69 (1H, d, J = 14.1 Hz, Ph–CH=CH–), 9.78 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 44.29, 53.94, 112.12, 113.84, 117.92,122.32, 127.13, 128.09, 129.18, 130.12, 135.38, 142.36, 147.78, 153.37, 167.14; HR-MS m/z: 325.3367 (M^+).

4.6.3. 3-(4-Nitrophenyl)-N-[4-(piperazin-1-yl)phenyl]acrylamide (**9c**)

tert-Butyl 4-{4-[3-(4-nitrophenyl)acrylamido]phenyl}piperazine-1-carboxylate **7l** (4 g, 11.36 mmol) was stirred at room temperature in a 20 ml mixture of TFA/DCM (1:1) for 12 h. The reaction mixture was worked up as per the general procedure to afford 2.7 g of **9c**. Light yellow solid; Yield 86.82%; mp 227–229 °C (charred); IR (KBr pellets, cm^{-1}): 3433, 3322, 2957, 2835, 1675, 1594, 1512, 1335, 1239, 1171, 901, 818; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.43 (4H, t, J = 3.24 Hz), 3.37 (4H, t, J = 3.24 Hz), 6.79 (1H, d, J = 15.4 Hz, Ph–CH=CH–), 7.41–7.80 (6H, m, Ar–H), 7.92 (1H, d, J = 15.4 Hz, Ph–CH=CH–), 8.09 (2H, d, J = 6.9 Hz, Ar–H), 9.95 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 47.18, 53.25, 114.52, 118.17, 122.12, 126.10, 128.90, 131.17, 136.10, 141.11, 145.21, 147.01, 165.04; HR-MS m/z: 352.2725 (M^+).

4.6.4. N-[3-Fluoro-4-(piperazin-1-yl)phenyl]-3-(4-nitrophenyl) acrylamide (**9d**)

tert-Butyl 4-{2-fluoro-4-[3-(4-nitrophenyl)acrylamido]phenyl} piperazine-1-carboxylate **7p** (4 g, 10.81 mmol) was stirred at room temperature in a 20 ml mixture of TFA/DCM (1:1) for 12 h. The reaction mixture was worked up as per the general procedure to afford 2.9 g of **9d**. Light yellow solid; Yield 92.36%; mp 212–214 °C (charred); IR (KBr pellets, cm^{-1}): 3448, 3326, 2952, 1667, 1607, 1511, 1340, 1217, 1128, 910, 866; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.62 (4H, t, J = 3.47 Hz), 3.45 (4H, t, J = 3.47 Hz), 6.66 (1H, d, J = 14.8 Hz Hz, Ph–CH=CH–), 6.91 (1H, d, J = 7.4 Hz, Ar–H), 7.27 (4H, m, Ar–H), 7.71 (1H, d, J = 14.8 Hz Hz, Ph–CH=CH–), 8.24 (2H, d, J = 7.8 Hz, Ar–H), 9.88 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 46.19, 54.04, 111.78, 113.11, 117.73,121.28, 128.17, 129.75, 131.12, 135.68, 141.30, 147.10, 147.67, 154.37, 164.89; HR–MS m/z: 370.2189 (M^+).

4.7. General procedure for the synthesis of compounds **10a–l**

1 equiv of cinnamamide was dissolved in dry DCM followed by addition of 3 equiv of Et_3N and stirred at 0 °C under inert atmosphere. 1.5 equiv of alkyl/aryl chloroformate derivative was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was stirred for 0.5 h. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (30 ml) and extracted with DCM twice. The organic layer was washed successively with 2 N HCl (2 × 20 ml), saturated bicarbonate solution (2 × 20 ml) and brine solution (20 ml). The organic layer was dried over anhydrous sodium sulfate and was evaporated under reduced pressure. The crude product was recrystallized from ethyl acetate and hexane to afford the desired product.

*4.7.1. Methyl 4-(4-cinnamamidophenyl)piperazine-1-carboxylate (**10a**)*

N-[4-(Piperazin-1-yl)phenyl]cinnamamide **9a** (0.12 g, 0.39 mmol) was dissolved in 10 ml dry atmosphere. Methyl chloroformate (0.04 g, 0.47 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to DCM followed by addition of Et_3N (0.16 ml, 1.17 mmol) and stirred at 0 °C under inert afford 0.089 g of **10a**. Light yellow solid; Yield 63.57%; mp 215–217 °C; IR (KBr pellets, cm^{-1}): 3229, 3105, 2919, 2821, 1695, 1612, 1532, 1449, 1341, 1248, 1126, 995, 819, 757; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.49 (4H, t, $J = 4.31$ Hz), 3.34 (4H, t, $J = 4.32$ Hz), 3.65 (3H, s, C$\underline{H}_3$), 6.76 (1H, d, $J = 15.6$ Hz, Ph–CH=C$\underline{H}$–), 6.92 (2H, d, $J = 7.4$ Hz, Ar–$\underline{H}$), 7.36–7.62 (7H, m, Ar–$\underline{H}$), 7.77 (1H, d, $J = 15.6$ Hz Hz, Ph–C$\underline{H}$=C$\underline{H}$–), 10.03 (1H, s, CON$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 50.65, 52.02, 52.77, 112.56, 118.72, 121.86, 127.44, 127.92, 128.01, 128.78, 134.11, 142.02, 146.10, 154.30, 165.24; HR–MS *m*/*z*: 365.2384 (M^+).

*4.7.2. Ethyl 4-{2-fluoro-4-[3-(4-nitrophenyl)acrylamido]phenyl} piperazine-1-carboxylate (**10b**)*

N-[4-(Piperazin-1-yl)phenyl]cinnamamide **9a** (0.12 g, 0.39 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.16 ml, 1.17 mmol) and stirred at 0 °C under inert atmosphere. Ethyl chloroformate (0.05 g, 0.47 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.094 g of **10b**. Light yellow solid; Yield 67.14%; mp 206–208 °C; IR (KBr pellets, cm^{-1}): 3260, 3116, 2976, 2826, 1702, 1653, 1535, 1439, 1336, 1250, 1121, 990, 816; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.22 (3H, t, $J = 7.3$ Hz, O–CH_2–C$\underline{H}_3$), 3.05 (4H, t, $J = 4.78$ Hz), 3.42 (4H, t, $J = 4.78$ Hz), 4.07 (2H, q, $J = 7.3$ Hz, O–C$\underline{H}_2$–CH_3), 6.66 (1H, d, $J = 15.1$ Hz, Ph–CH=C$\underline{H}$–), 6.85 (2H, d, $J = 7.5$ Hz, Ar–$\underline{H}$), 7.40–7.59 (8H, m, Ar–$\underline{H}$), 10.23 (1H, s, CON$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 12.30, 50.35, 52.28, 63.37, 113.52, 118.26, 121.47, 127.19, 127.48, 128.71, 128.90, 135.10, 142.72, 145.16, 155.36, 165.20; HR-MS *m*/*z*: 379.3461 (M^+).

*4.7.3. Phenyl 4-(4-cinnamamidophenyl)piperazine-1-carboxylate (**10c**)*

N-[4-(Piperazin-1-yl)phenyl]cinnamamide **9a** (0.12 g, 0.39 mmol) was dissolved in10 ml dry DCM followed by addition of Et_3N (0.16 ml, 1.17 mmol) and stirred at 0 °C under inert atmosphere. Phenyl chloroformate (0.07 g, 0.47 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.1 g of **10c**. Light yellow solid; Yield 62.5%; mp 219–220 °C; IR (KBr pellets, cm^{-1}): 3240, 3038, 2919, 2857, 1723, 1651, 1540, 1418, 1343, 1248, 1072, 922, 822, 744; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.17–3.73 (8H, m), 6.82 (1H, d, $J = 16.9$ Hz, Ph–CH=C$\underline{H}$–), 6.99 (2H, d, $J = 7.7$ Hz, Ar–$\underline{H}$), 7.13–7.51 (12H, m, Ar–$\underline{H}$), 7.60 (1H, d, $J = 16.9$ Hz, Ph–C$\underline{H}$=C$\underline{H}$–),10.06 (1H, s, CON$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 49.10, 52.73, 112.29, 118.27, 121.18, 121.86, 126.04, 127.48, 127.86, 128.07, 128.78, 129.89, 134.11, 142.02, 146.10, 151.84, 154.04, 165.50; HR-MS *m*/*z*: 427.2161 (M^+).

*4.7.4. Methyl 4-(4-cinnamamido-2-fluorophenyl)piperazine-1-carboxylate (**10d**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]cinnamamide **9b** (0.12 g, 0.37 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.15 ml, 1.11 mmol) and stirred at 0 °C under inert atmosphere. Methyl chloroformate (0.04 g, 0.44 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.08 g of **10d**. Off-white solid; Yield 57.14%; mp 210–212 °C; IR (KBr pellets, cm^{-1}): 3254, 2857, 1686, 1622, 1518, 1440, 1348, 1241,1124, 995, 758; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.13 (4H, t, $J = 4.28$ Hz), 3.39 (4H, t, $J = 4.30$ Hz Hz), 3.68 (3H, s, C$\underline{H}_3$), 6.79 (1H, d, $J = 14.8$ Hz, Ph–CH=C$\underline{H}$–), 6.85 (1H, d, $J = 7.2$ Hz, Ar–$\underline{H}$), 7.12–7.56 (7H, m, Ar–$\underline{H}$), 7.81 (1H, d, $J = 14.8$ Hz, Ph–C$\underline{H}$=C$\underline{H}$–), 9.85 (1H, s, CON$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 50.21, 52.78, 111.75, 112.55, 119.72, 121.06, 127.82, 127.98, 128.36, 128.24, 134.11, 142.23, 146.17, 152.09, 154.27, 165.10; HR-MS *m*/*z*: 383.2011 (M^+).

*4.7.5. Ethyl 4-(4-cinnamamido-2-fluorophenyl)piperazine-1-carboxylate (**10e**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]cinnamamide **9b** (0.12 g, 0.37 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.15 ml, 1.11 mmol) and stirred at 0 °C under inert atmosphere. Ethyl chloroformate (0.05 g, 0.44 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.11 g of **10e**. Off-white solid; Yield 78.57%; mp 226–228 °C; IR (KBr pellets, cm^{-1}): 3335, 2975, 2822, 1689, 1512, 1422, 1233, 1123, 972, 826, 761; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.59 (3H, t, $J = 7.14$ Hz, O–CH_2–C$\underline{H}_3$), 2.99 (4H, t, $J = 3.30$ Hz), 3.61 (4H, t, $J = 3.29$ Hz), 3.84 (2H, q, $J = 7.14$ Hz, O–C$\underline{H}_2$–CH_3), 6.49 (1H, d, $J = 14.2$ Hz, Ph–CH=C$\underline{H}$–), 6.84 (1H, d, $J = 7.7$ Hz, Ar–$\underline{H}$), 7.18–7.59 (7H, m, Ar–$\underline{H}$), 7.79 (1H, d, $J = 14.2$ Hz Hz, Ph–C$\underline{H}$=C$\underline{H}$–), 9.43 (1H, s, CON$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 28.53, 43.89, 50.63, 52.69, 119.37, 122.18, 122.47, 127.96, 128.91, 130.08, 134.53, 142.66, 156.12, 167.63; HR-MS *m*/*z*: 397.3012 (M^+).

*4.7.6. Phenyl 4-(4-cinnamamido-2-fluorophenyl)piperazine-1-carboxylate (**10f**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]cinnamamide **9b** (0.12 g, 0.37 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.15 ml, 1.11 mmol) and stirred at 0 °C under inert atmosphere. Phenyl chloroformate (0.07 g, 0.44 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.15 g of **10f**. Light yellow solid; Yield 93.75%; mp 194–196 °C; IR (KBr pellets, cm^{-1}): 3258, 2918, 2855, 1692, 1516, 1428, 1222, 1197, 993, 748; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.10 (4H, t, $J = 3.90$ Hz), 3.81 (4H, t, $J = 3.92$ Hz), 6.51 (1H, d, $J = 15.5$ Hz, Ph–CH=C$\underline{H}$–), 6.92 (1H, d, $J = 8.2$ Hz, Ar–$\underline{H}$), 7.11–7.60 (12H, m, Ar–$\underline{H}$), 7.78 (1H, d, $J = 15.5$ Hz, Ph–C$\underline{H}$=C$\underline{H}$–),10.11 (1H, s, CON$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 52.11, 52.75, 111.45, 112.10, 118.73, 121.29, 121.49, 126.05, 127.37, 127.77, 128.16, 128.80, 129.90, 135.14, 141.22, 145.15, 151.05, 153.10, 155.26, 168.14; HR-MS *m*/*z*: 445.2251 (M^+).

*4.7.7. Methyl 4-{4-[3-(4-nitrophenyl)acrylamido]phenyl} piperazine-1-carboxylate (**10g**)*

3-(4-Nitrophenyl)-*N*-[4-(piperazin-1-yl)phenyl]acrylamide **9c** (0.12 g, 0.34 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 1.02 mmol) and stirred at 0 °C under inert atmosphere. Methyl chloroformate (0.05 g, 0.41 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.11 g of **10g**. Light yellow solid; Yield 84.62%; mp 267–269 °C (charred); IR (KBr pellets, cm^{-1}): 3262, 2954, 2834, 1705, 1652, 1622, 1514, 1446, 1339, 1232, 1119, 973, 819; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.19 (4H, t, $J = 4.11$ Hz), 3.44 (4H, t, $J = 4.12$ Hz), 3.95 (3H, s, C$\underline{H}_3$), 6.69 (1H, d, $J = 15.4$ Hz, Ph–CH=C$\underline{H}$–), 6.88 (2H, d, $J = 7.8$ Hz, Ar–$\underline{H}$), 7.33–7.51 (4H, m, Ar–$\underline{H}$), 7.71 (1H, d, $J = 15.4$ Hz, Ph–C$\underline{H}$=C$\underline{H}$–), 8.05 (2H, d, $J = 6.8$ Hz, Ar–$\underline{H}$), 9.43 (1H, s, CON$\underline{H}$); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 50.65, 52.80, 112.13, 118.43, 121.16, 127.23, 128.92, 128.71, 134.90, 142.22, 146.84, 147.43, 154.38, 165.64; HR-MS *m*/*z*: 410.2195 (M^+).

*4.7.8. Ethyl 4-{4-[3-(4-nitrophenyl)acrylamido]phenyl}piperazine-1-carboxylate (**10h**)*

3-(4-Nitrophenyl)-*N*-[4-(piperazin-1-yl)phenyl]acrylamide **9c** (0.12 g, 0.34 mmol) was dissolved in10 ml dry DCM followed by addition of Et_3N (0.14 ml, 1.02 mmol) and stirred at 0 °C under inert atmosphere. Ethyl chloroformate (0.06 g, 0.41 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.08 g of **10h**. Light yellow solid; Yield 57.14%; mp 254–256 °C; IR (KBr pellets, cm^{-1}): 3447, 3290, 2820, 1699, 1621, 1517, 1342, 1248, 1125, 991, 822; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.21 (3H, t, J = 7.2 Hz, O–CH_2–CH_3), 3.11 (4H, t, J = 4.65 Hz), 3.61 (4H, t, J = 4.65 Hz), 4.19 (2H, q, J = 7.2 Hz, O–CH_2–CH_3), 6.61 (1H, d, J = 15.8 Hz, Ph–CH=CH–), 6.92 (2H, d, J = 7.8 Hz, Ar–H), 7.51 (2H, d, J = 7.1 Hz, Ar–H), 7.62 (2H, d, J = 7.9 Hz, Ar–H), 7.79 (1H, d, J = 15.8 Hz, Ph–CH=CH–), 8.21 (2H, d, J = 7.1 Hz, Ar–H), 10.11 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 13.30, 51.25, 51.32, 62.37, 112.52, 118.51, 121.09, 127.13, 128.21, 128.87, 134.89, 141.72, 146.36, 147.68, 154.36, 167.19; HR-MS *m*/*z*: 424.3048 (M^+).

*4.7.9. Phenyl 4-{4-[3-(4-nitrophenyl)acrylamido]phenyl} piperazine-1-carboxylate (**10i**)*

3-(4-Nitrophenyl)-*N*-[4-(piperazin-1-yl)phenyl]acrylamide **9c** (0.12 g, 0.34 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 1.02 mmol) and stirred at 0 °C under inert atmosphere. Phenyl chloroformate (0.08 g, 0.41 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.09 g of **10i**. Light yellow solid; Yield 56.25%; mp 263–265 °C; IR (KBr pellets, cm^{-1}): 3447, 3269, 2833, 1719, 1621, 1515, 1414, 1340, 1203, 1046, 918, 751; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.32 (8H, m), 6.88 (1H, d, J = 15.1 Hz, Ph–CH=CH–), 6.95 (2H, d, J = 7.5 Hz, Ar–H), 7.22–7.63 (9H, m, Ar–H), 7.72 (1H, d, J = 15.1 Hz, Ph–CH=CH–), 8.03 (2H, d, J = 6.7 Hz, Ar–H), 9.23 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 51.19, 52.12, 112.30, 117.21, 120.19, 121.66, 127.68, 127.97, 128.27, 128.59, 130.19, 135.14, 141.02, 146.50, 147.28, 150.32, 155.04, 166.17; HR-MS *m*/*z*: 472.3141 (M^+).

*4.7.10. Methyl 4-{2-fluoro-4-[3-(4-nitrophenyl)acrylamido]phenyl} piperazine-1-carboxylate (**10j**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]-3-(4-nitrophenyl)acrylamide **9d** (0.12 g, 0.32 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 0.94 mmol) and stirred at 0 °C under inert atmosphere. Methyl chloroformate (0.05 g, 0.39 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.07 g of **10j**. Light yellow solid; Yield 53.85%; mp 238–240 °C (charred); IR (KBr pellets, cm^{-1}): 3380, 3266, 2848, 1698, 1665, 1596, 1514, 1435, 1342, 1244, 987, 845; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.01 (4H, t, J = 4.09 Hz), 3.65 (4H, t, J = 4.07 Hz), 3.72 (3H, s, CH_3), 6.61 (1H, d, J = 14.6 Hz, Ph–CH=CH–), 6.91 (1H, d, J = 7.5 Hz, Ar–H), 7.15 (2H, d, J = 7.7 Hz, Ar–H), 7.59 (2H, d, J = 7.1 Hz, Ar–H), 7.80 (1H, d, J = 14.6 Hz, Ph–CH=CH–), 8.25 (2H, d, J = 7.0 Hz, Ar–H), 9.87 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 49.21, 51.42, 111.05, 112.12, 119.74, 121.86, 127.32, 127.92, 128.23, 128.84, 134.51, 142.13, 146.10, 152.39, 154.07, 167.56; HR-MS *m*/*z*: 428.2002 (M^+).

*4.7.11. Ethyl 4-{2-fluoro-4-[3-(4-nitrophenyl)acrylamido]phenyl} piperazine-1-carboxylate (**10k**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]-3-(4-nitrophenyl)acrylamide **9d** (0.12 g, 0.32 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 0.94 mmol) and stirred at 0 °C under inert atmosphere. Ethyl chloroformate (0.05 g, 0.39 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.08 g of **10k**. Light yellow solid; Yield 57.14%; mp 237–239 °C; IR (KBr pellets, cm^{-1}): 3448, 3266, 2861, 1699, 1597, 1515, 1342, 1246, 1147, 865; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.28 (3H, t, J = 7.5 Hz, O–CH_2–CH_3), 3.09 (4H, t, J = 4.45 Hz), 3.62 (4H, t, J = 4.47 Hz), 4.18 (2H, q, J = 7.5 Hz, O–CH_2–CH_3), 6.54 (1H, d, J = 15.4 Hz, Ph–CH=CH–), 6.89 (1H, d, J = 7.4 Hz, Ar–H), 7.35 (2H, d, J = 7.1 Hz, Ar–H), 7.50–7.54 (2H, m, Ar–H), 7.71 (1H, d, J = 15.4 Hz, Ph–CH=CH–), 8.21 (2H, d, J = 6.8 Hz, Ar–H), 10.11 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 12.67, 50.15, 52.43, 62.27, 111.41, 112.02, 118.24, 121.27, 127.23, 128.84, 128.99, 135.89, 141.70, 145.06, 147.28, 154.36, 155.30, 165.10; HR-MS *m*/*z*: 442.2183 (M^+).

*4.7.12. Phenyl 4-{2-fluoro-4-[3-(4-nitrophenyl)acrylamido]phenyl} piperazine-1-carboxylate (**10l**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]-3-(4-nitrophenyl)acrylamide **9d** (0.12 g, 0.32 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 0.94 mmol) and stirred at 0 °C under inert atmosphere. Phenyl chloroformate (0.08 g, 0.39 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.08 g of **10l**. Light yellow solid; Yield 53.33%; mp 269–271 °C; IR (KBr pellets, cm^{-1}): 3422, 3272, 2863, 1720, 1655, 1593, 1514, 1432, 1345, 1215, 1070, 914, 853, 754; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.13 (4H, t, J = 4.56 Hz), 3.74 (4H, t, J = 4.55 Hz), 6.69 (1H, d, J = 15.9 Hz, Ph–CH=CH–), 6.91 (1H, d, J = 7.2 Hz, Ar–H), 7.32–7.67 (9H, m, Ar–H), 7.81 (1H, d, J = 15.9 Hz, Ph–CH=CH–), 8.11 (2H, d, J = 7.1 Hz, Ar–H), 10.18 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 51.47, 52.01, 110.27, 112.19, 118.03, 121.20, 121.43, 126.25, 127.10, 128.37, 128.48, 129.87, 134.29, 141.15, 145.29, 147.07, 151.36, 154.29, 154.19, 164.28; HR-MS *m*/*z*: 490.3634 (M^+).

*4.8. General procedure for the synthesis of compounds **11a–p***

1 equiv of cinnamamide was dissolved in dry DCM followed by addition of 3 equiv of Et_3N and stirred at 0 °C under inert atmosphere. 1.5 equiv of acyl chloride derivative was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was stirred for 0.5 h. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (30 ml) and extracted with DCM twice. The organic layer was washed successively with 2 N HCl (2 × 20 ml), saturated bicarbonate solution (2 × 20 ml) and brine solution (20 ml). The organic layer was dried over anhydrous sodium sulfate and was evaporated under reduced pressure. The crude product was recrystallized from ethyl acetate and hexane to afford the desired product.

*4.8.1. N-{4-[4-(4-Fluorobenzoyl)piperazin-1-yl]phenyl} cinnamamide (**11a**)*

N-[4-(Piperazin-1-yl)phenyl]cinnamamide **9a** (0.12 g, 0.39 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.16 ml, 1.17 mmol) and stirred at 0 °C under inert atmosphere. 4-fluoro benzoylchloride (0.07 g, 0.47 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.13 g of **11a**. Off-white solid; Yield 81.25%; mp 227–229 °C; IR (KBr pellets, cm^{-1}): 3443, 3273, 2835, 1674, 1633, 1589, 1519, 1442, 1343, 1240, 1020, 848; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.12–3.33 (8H, m), 6.76 (1H, d, J = 15.8 Hz, Ph–CH=CH–), 6.93 (2H, d, J = 7.5 Hz, Ar–H), 7.26–7.61 (12H, m, Ar–H), 10.03 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 51.05, 53.20, 112.56, 115.72, 118.22, 122.97, 127.13, 127.71, 128.10, 128.52, 128.87, 130.67, 135.28, 141.63, 145.29, 159.60, 165.35, 169.30; HR-MS *m*/*z*: 429.2375 (M^+).

*4.8.2. N-{4-[4-(3,5-Dichlorobenzoyl)piperazin-1-yl]phenyl} cinnamamide (**11b**)*

N-[4-(Piperazin-1-yl)phenyl]cinnamamide **9a** (0.12 g, 0.39 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.16 ml, 1.17 mmol) and stirred at 0 °C under inert atmosphere. 3,5-dichloro benzoylchloride (0.1 g, 0.47 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.15 g of **11b**. Off-white solid; Yield 83.33%; mp 194–196 °C; IR (KBr pellets, cm^{-1}): 3449, 3311, 2804, 1659, 1630, 1515, 1415, 1285, 1176, 1018, 976, 769; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.42 (4H, t, J = 4.12 Hz), 3.57 (4H, t, J = 4.10 Hz), 6.56 (1H, d, J = 15.3 Hz, Ph–CH=CH–), 6.89 (2H, d, J = 7.7 Hz, Ar–H), 7.31–7.65 (10H, m, Ar–H), 7.78 (1H, d, J = 15.3 Hz, Ph–CH=CH–), 9.83 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 50.45, 54.25, 113.06, 118.74, 121.67, 125.13, 127.83, 128.45, 128.96, 130.60, 130.93, 135.17, 135.70, 138.21, 141.03, 145.58, 165.10, 169.97; HR-MS m/z: 479.2278 (M^+).

*4.8.3. N-{4-[4-(2-(Trifluoromethyl)benzoyl]piperazin-1-yl} phenylcinnamamide (**11c**)*

N-[4-(Piperazin-1-yl)phenyl]cinnamamide **9a** (0.12 g, 0.39 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.16 ml, 1.17 mmol) and stirred at 0 °C under inert atmosphere. 2-(trifluoromethyl)benzoylchloride (0.1 g, 0.47 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.16 g of **11c**. Light yellow solid; Yield 88.89%; mp 201–203 °C; IR (KBr pellets, cm^{-1}): 3448, 2922, 1627, 1518, 1438, 1317, 1181, 1016, 768; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.04–3.45 (8H, m), 6.76 (1H, d, J = 16.1 Hz, Ph–CH=CH–), 6.92 (2H, d, J = 7.9 Hz, Ar–H), 7.39–7.80 (11H, m, Ar–H), 7.85 (1H, d, J = 16.1 Hz, Ph–CH=CH–), 10.04 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 50.62, 54.81, 113.16, 118.45, 121.47, 123.34, 127.37, 127.88, 127.97, 128.35, 128.17, 128.45, 130.28, 134.24, 135.22, 135.57, 141.03, 145.30, 164.32, 169.78; HR-MS m/z: 479.2183 (M^+).

*4.8.4. N-{4-[4-(4-Nitrobenzoyl)piperazin-1-yl]phenyl} cinnamamide (**11d**)*

N-[4-(Piperazin-1-yl)phenyl]cinnamamide **9a** (0.12 g, 0.39 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.16 ml, 1.17 mmol) and stirred at 0 °C under inert atmosphere. 4-nitrobenzoylchloride (0.09 g, 0.47 mmol) was directly added portionwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.14 g of **11d**. Light orange solid; Yield 82.35%; mp 218–220 °C; IR (KBr pellets, cm^{-1}): 3449, 3273, 2922, 2852, 1677, 1622, 1522, 1447, 1350, 1172, 1014, 849, 719; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.29 (4H, t, J = 4.22 Hz), 3.44 (4H, t, J = 4.25 Hz), 6.83 (1H, d, J = 16.7 Hz, Ph–CH=CH–), 6.87 (2H, d, J = 8.4 Hz, Ar–H), 7.28–7.84 (11H, m, Ar–H), 7.88 (1H, d, J = 16.7 Hz, Ph–CH=CH–), 10.12 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 47.05, 51.29, 111.56, 115.02, 117.21, 121.90, 127.14, 127.79, 128.23, 128.55, 128.93, 131.67, 133.20, 141.03, 145.59, 147.60, 166.30, 168.34; HR-MS m/z: 456.2213 (M^+).

*4.8.5. N-{3-Fluoro-4-[4-(4-fluorobenzoyl)piperazin-1-yl]phenyl} cinnamamide (**11e**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]cinnamamide **9b** (0.12 g, 0.37 mmol) was dissolved in10 ml dry DCM followed by addition of Et_3N (0.15 ml, 1.11 mmol) and stirred at 0 °C under inert atmosphere. 4-fluoro benzoylchloride (0.07 g, 0.44 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.12 g of **11e**. Light yellow solid; Yield 75%; mp 212–214 °C; IR (KBr pellets, cm^{-1}): 3417, 3256, 2834, 1674, 1613, 1520, 1444, 1343, 1238, 1017, 821, 765; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.13 (4H, t, J = 4.69 Hz), 3.56 (4H, t, J = 4.66 Hz), 6.52 (1H, d, J = 15.5 Hz, Ph–CH=CH–), 6.81 (1H, d, J = 8.1 Hz, Ar–H), 7.21–7.60 (11H, m, Ar–H), 7.80 (1H, d, J = 15.5 Hz, Ph–CH=CH–), 9.11 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 50.14, 54.29,111.78, 113.56, 115.32, 117.21, 121.90, 127.10, 127.83, 128.38, 128.62, 128.98, 130.31, 132.37, 134.28, 142.63, 155.78, 159.98, 165.01, 168.90; HR-MS m/z: 447.3197 (M^+).

*4.8.6. N-{4-[4-(3,5-Dichlorobenzoyl)piperazin-1-yl]-3-fluorophenyl}cinnamamide (**11f**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]cinnamamide **9b** (0.12 g, 0.37 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.15 ml, 1.11 mmol) and stirred at 0 °C under inert atmosphere. 3,5-dichloro benzoylchloride (0.09 g, 0.44 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.1 g of **11f**. Light yellow solid; Yield 55.56%; mp 189–190 °C; IR (KBr pellets, cm^{-1}): 3366, 3058, 2817, 1622, 1527, 1446, 1334, 1258, 1029, 875, 604; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.56 (4H, t, J = 4.27 Hz), 3.72 (4H, t, J = 4.29 Hz), 6.69 (1H, d, J = 15.4 Hz, Ph–CH=CH–), 6.83 (1H, d, J = 7.9 Hz, Ar–H), 7.28–7.62 (10H, m, Ar–H), 7.75 (1H, d, J = 15.4 Hz, Ph–CH=CH–), 9.92 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 47.15, 51.53, 111.26, 113.06, 118.84, 121.60, 124.24, 126.53, 127.44, 128.26, 129.60, 130.25, 135.10, 135.82, 138.31, 141.43, 145.10, 155.27, 165.69, 168.34; HR-MS m/z: 497.2092 (M^+).

*4.8.7. N-{3-Fluoro-4-[4-(2-(trifluoromethyl)benzoyl)piperazin-1-yl]phenyl}cinnamamide (**11g**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]cinnamamide **9b** (0.12 g, 0.37 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.15 ml, 1.11 mmol) and stirred at 0 °C under inert atmosphere. 2-(trifluoromethyl)benzoylchloride (0.09 g, 0.44 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.13 g of **11g**. Light yellow solid; Yield 72.22%; mp 192–194 °C; IR (KBr pellets, cm^{-1}): 3368, 2922, 1676, 1531, 1438, 1315, 1181, 1016, 767; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.11 (4H, t, J = 4.67 Hz), 3.38 (4H, t, J = 4.69 Hz), 6.51 (1H, d, J = 14.9 Hz, Ph–CH=CH–), 6.88 (1H, d, J = 7.8 Hz, Ar–H), 7.19–7.69 (11H, m, Ar–H), 7.79 (1H, d, J = 14.9 Hz, Ph–CH=CH–), 9.37 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 47.28, 50.32, 108.86, 109.14, 115.73, 119.42, 120.63, 125.00, 126.74, 126.78, 127.07, 127.25, 127.93, 128.84, 129.30, 129.98, 132.25, 134.01, 134.58, 135.77, 142.39, 154.25, 156.69, 164.08, 167.53; HR-MS m/z: 497.3178 (M^+).

*4.8.8. N-{3-Fluoro-4-[4-(4-nitrobenzoyl)piperazin-1-yl]phenyl} cinnamamide (**11h**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]cinnamamide **9b** (0.12 g, 0.37 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.15 ml, 1.11 mmol) and stirred at 0 °C under inert atmosphere. 4-nitrobenzoylchloride (0.08 g, 0.44 mmol) was directly added portionwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.11 g of **11h**. Light yellow solid; Yield 64.71%; mp 217–219 °C; IR (KBr pellets, cm^{-1}): 3323, 3058, 1648, 1556, 1417, 1316, 1020, 962, 748, 604; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.53 (4H, t, J = 4.02 Hz), 3.92 (4H, t, J = 4.04 Hz), 6.43 (1H, d, J = 15.5 Hz, Ph–CH=CH–), 6.85 (1H, d, J = 8.2 Hz, Ar–H), 7.21–7.61 (9H, m, Ar–H), 7.77 (1H, d, J = 15.5 Hz, Ph–CH=CH–), 8.23 (2H, d, J = 6.9 Hz, Ar–H), 9.45 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 49.25, 53.22, 112.52, 113.18, 115.71, 118.21, 122.91, 126.14, 127.25, 127.98, 128.45, 128.67, 131.60, 135.20, 142.03, 145.39, 146.61, 154.23, 165.11, 168.74; HR-MS m/z: 474.2052 (M^+).

*4.8.9. N-{4-[4-(4-Fluorobenzoyl)piperazin-1-yl]phenyl}-3-(4-nitrophenyl)acrylamide (**11i**)*

3-(4-Nitrophenyl)-*N*-[4-(piperazin-1-yl)phenyl]acrylamide **9c** (0.12 g, 0.34 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 1.02 mmol) and stirred at 0 °C under inert atmosphere. 4-fluoro benzoylchloride (0.08 g, 0.41 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.11 g of **11i**. Light orange solid; Yield 68.75%; mp 267–269 °C; IR (KBr pellets, cm^{-1}): 3216, 2926, 1640, 1569, 1508, 1387, 1233, 1054, 801, 718; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.17 (4H, t, $J = 4.38$ Hz), 3.81 (4H, t, $J = 4.39$ Hz), 6.69 (1H, d, $J = 16.7$ Hz, Ph–CH=CH–), 6.86 (2H, d, $J = 7.6$ Hz, Ar–H), 7.23–7.57 (8H, m, Ar–H), 7.82 (1H, d, $J = 16.7$ Hz, Ph–CH=CH–), 8.12 (2H, d, $J = 7.1$ Hz, Ar–H),10.12 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 44.35, 47.38, 111.06, 116.70, 117.12, 121.46, 127.93, 128.37, 128.71, 128.90, 129.67, 134.27, 140.63, 145.29, 145.93, 158.20, 164.35, 168.83; HR-MS *m/z*: 474.2149 (M^+).

*4.8.10. N-{4-[4-(3,5-Dichlorobenzoyl)piperazin-1-yl]phenyl}-3-(4-nitrophenyl)acrylamide (**11j**)*

3-(4-Nitrophenyl)-*N*-[4-(piperazin-1-yl)phenyl]acrylamide **9c** (0.12 g, 0.34 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 1.02 mmol) and stirred at 0 °C under inert atmosphere. 3,5-dichloro benzoylchloride (0.11 g, 0.41 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.11 g of **11j**. Light brown solid; Yield 64.71%; mp > 270 °C; IR (KBr pellets, cm^{-1}): 3414, 2832, 1635, 1522, 1332, 1238, 1169, 1024, 830; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.22 (4H, t, $J = 4.24$ Hz), 3.78 (4H, t, $J = 4.22$ Hz), 6.73 (1H, d, $J = 15.8$ Hz, Ph–CH=CH–), 6.82 (2H, d, $J = 7.9$ Hz, Ar–H), 7.27–7.59 (7H, m, Ar–H), 7.88 (1H, d, $J = 15.8$ Hz, Ph–CH=CH–), 8.21 (2H, d, $J = 8.1$ Hz, Ar–H),10.09 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 50.90, 53.89, 112.26, 117.88, 121.07, 125.31, 127.45, 128.35, 130.48, 131.63, 135.87, 135.97, 138.51, 142.13, 145.28, 147.28, 165.35, 168.32; HR-MS *m/z*: 524.1016 (M^+).

*4.8.11. 3-(4-Nitrophenyl)-N-{4-[4-(2-(trifluoromethyl)benzoyl) piperazin-1-yl]phenyl}acrylamide (**11k**)*

3-(4-Nitrophenyl)-*N*-[4-(piperazin-1-yl)phenyl]acrylamide **9c** (0.12 g, 0.34 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 1.02 mmol) and stirred at 0 °C under inert atmosphere. 2-(trifluoromethyl)benzoylchloride (0.11 g, 0.41 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.12 g of **11k**. Light orange solid; Yield 70.59%; mp 249–251 °C; IR (KBr pellets, cm^{-1}): 3352, 2923, 1648, 1613, 1517, 1488, 1390, 1268, 1133, 938, 755; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.46 (4H, t, $J = 4.11$ Hz), 3.82 (4H, t, $J = 4.13$ Hz), 6.78 (1H, d, $J = 15.5$ Hz, Ph–CH=CH–), 6.80 (2H, d, $J = 7.4$ Hz, Ar–H), 7.29–7.60 (8H, m, Ar–H), 7.71 (1H, d, $J = 15.5$ Hz, Ph–CH=CH–), 8.19 (2H, d, $J = 7.7$ Hz, Ar–H),10.14 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 47.29, 51.19, 113.52, 116.71, 118.24, 121.47, 123.64, 127.46, 128.45, 128.59, 128.99, 130.14, 135.47, 142.60, 145.24, 146.32, 147.89, 164.30, 168.88; HR-MS *m/z*: 525.1191 (M + 1).

*4.8.12. N-{4-[4-(4-Nitrobenzoyl)piperazin-1-yl]phenyl}-3-(4-nitrophenyl)acrylamide (**11l**)*

3-(4-Nitrophenyl)-*N*-[4-(piperazin-1-yl)phenyl]acrylamide **9c** (0.12 g, 0.34 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 1.02 mmol) and stirred at 0 °C under inert atmosphere. 4-nitrobenzoylchloride (0.09 g, 0.41 mmol) was directly added portionwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.13 g of **11l**. Light orange solid; Yield 76.47%; mp > 270 °C; IR (KBr pellets, cm^{-1}): 3270, 2923, 1667, 1635, 1521, 1444, 1367, 1283, 1013, 767; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.13 (4H, t, $J = 4.21$ Hz), 3.67 (4H, t, $J = 4.19$ Hz), 6.82 (1H, d, $J = 15.2$ Hz, Ph–CH=CH–), 6.96 (2H, d, $J = 8.2$ Hz, Ar–H), 7.22–7.54 (7H, m, Ar–H), 7.83 (1H, d, $J = 15.2$ Hz, Ph–CH=CH–), 8.09 (2H, d, $J = 7.3$ Hz, Ar–H), 9.35 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 48.45, 52.53, 112.56, 114.92, 117.01, 121.55, 127.30, 128.23, 128.55, 128.86, 131.60, 132.20, 141.13, 144.50, 147.61, 148.41, 165.38, 169.80; HR-MS *m/z*: 501.2182 (M^+).

*4.8.13. N-{3-Fluoro-4-[4-(4-fluorobenzoyl)piperazin-1-yl]phenyl}-3-(4-nitrophenyl)acrylamide (**11m**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]-3-(4-nitrophenyl)acrylamide **9d** (0.12 g, 0.32 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 0.94 mmol) and stirred at 0 °C under inert atmosphere. 4-fluoro benzoylchloride (0.08 g, 0.39 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.1 g of **11m**. Light yellow solid; Yield 66.67%; mp 245–247 °C; IR (KBr pellets, cm^{-1}): 3448, 3323, 3110, 2921, 1678, 1604, 1515, 1429, 1342, 1226, 1155, 840, 756; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.49 (4H, t, $J = 4.32$ Hz), 3.87 (4H, t, $J = 4.31$ Hz), 6.56 (1H, d, $J = 15.5$ Hz, Ph–CH=CH–), 6.89 (1H, d, $J = 7.7$ Hz, Ar–H), 7.24–7.73 (8H, m, Ar–H), 7.82 (1H, d, $J = 15.5$ Hz, Ph–CH=CH–), 8.07 (2H, d, $J = 7.6$ Hz, Ar–H), 9.62 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 49.10, 53.26,112.78, 113.02, 116.32, 118.23, 122.91, 127.86, 128.08, 128.77, 128.94, 130.50, 131.37, 135.28, 141.63, 146.64, 154.70, 158.98, 166.47, 169.92; HR-MS *m/z*: 492.2296 (M^+).

*4.8.14. N-{4-[4-(3,5-dichlorobenzoyl)piperazin-1-yl]-3-fluorophenyl}-3-(4-nitrophenyl)acrylamide (**11n**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]-3-(4-nitrophenyl)acrylamide **9d** (0.12 g, 0.32 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 0.94 mmol) and stirred at 0 °C under inert atmosphere. 3,5-dichloro benzoylchloride (0.1 g, 0.39 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.12 g of **11n**. Light orange solid; Yield 70.59%; mp 269–271 °C; IR (KBr pellets, cm^{-1}): 3467, 3320, 2922, 1677, 1608, 1515, 1339, 1226, 1021, 840, 742; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.59 (4H, t, $J = 4.17$ Hz), 3.91 (4H, t, $J = 4.19$ Hz), 6.81 (1H, d, $J = 14.2$ Hz, Ph–CH=CH–), 6.85 (1H, d, $J = 8.1$ Hz, Ar–H), 7.27–7.78 (7H, m, Ar–H), 7.79 (1H, d, $J = 14.2$ Hz, Ph–CH=CH–), 8.21 (2H, d, $J = 6.7$ Hz, Ar–H), 9.59 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 46.45, 50.23, 111.67, 112.16, 118.26, 121.15, 125.22, 127.53, 128.19, 129.27, 130.14, 134.11, 135.16, 138.28, 141.23, 145.89, 147.29, 155.11, 166.21, 169.84; HR-MS *m/z*: 542.1288 (M^+).

*4.8.15. N-{3-Fluoro-4-[4-(2-(trifluoromethyl)benzoyl)piperazin-1-yl]phenyl}-3-(4-nitrophenyl)acrylamide (**11o**)*

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]-3-(4-nitrophenyl)acrylamide **9d** (0.12 g, 0.32 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 0.94 mmol) and stirred at 0 °C under inert atmosphere. 2-(trifluoromethyl)benzoylchloride (0.1 g, 0.39 mmol) was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.11 g of **11o**. Light yellow solid; Yield 64.71%; mp 252–254 °C; IR (KBr pellets, cm^{-1}): 3447, 3335, 2926, 1635, 1605, 1510, 1336, 1284, 1177, 1015, 838, 776; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.62–3.78 (8H, m), 6.69 (1H, d, $J = 14.1$ Hz, Ph–CH=CH–), 6.93 (1H, d, $J = 7.8$ Hz, Ar–H), 7.31–7.84 (8H, m, Ar–H), 7.88 (1H, d, $J = 14.1$ Hz, Ph–CH=CH–), 8.24 (2H, d, $J = 7.1$ Hz, Ar–H), 9.78 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 49.32,

53.27, 111.46, 115.73, 118.42, 121.63, 123.63, 125.10, 126.14, 127.17, 127.32, 128.43, 128.84, 129.21, 130.65, 131.27, 134.20, 135.71, 141.18, 147.61, 165.19, 169.33; HR-MS *m/z*: 542.2273 (M^+).

4.8.16. *N*-{3-Fluoro-4-[4-(4-nitrobenzoyl)piperazin-1-yl]phenyl}-3-(4-nitrophenyl)acrylamide (**11p**)

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]-3-(4-nitrophenyl)acrylamide **9d** (0.12 g, 0.32 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 0.94 mmol) and stirred at 0 °C under inert atmosphere. 4-nitrobenzoylchloride (0.09 g, 0.39 mmol) was directly added portionwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.13 g of **11p**. Light yellow solid; Yield 81.25%; mp 245–247 °C; IR (KBr pellets, cm^{-1}): 3481, 3335, 3101, 2966, 1670, 1597, 1508, 1334, 1282, 1012, 844, 775; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.44–3.57 (8H, m), 6.72 (1H, d, J = 15.8 Hz, Ph–CH=CH–), 6.85 (1H, d, J = 7.9 Hz, Ar–H), 7.27–7.78 (8H, m, Ar–H), 7.81 (1H, d, J = 15.8 Hz, Ph–CH=CH–), 8.19 (2H, d, J = 7.1 Hz, Ar–H), 10.12 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 50.25, 54.12, 111.12, 112.18, 115.74, 118.83, 121.45, 125.14, 127.58, 128.40, 128.77, 132.61, 134.20, 141.03, 145.09, 146.21, 147.81, 154.27, 165.87, 169.34; HR-MS *m/z*: 519.2072 (M^+).

4.9. General procedure for the synthesis of compounds **12a–d**

1 equiv of cinnamamide was dissolved in dry DCM followed by addition of 3 equiv of Et_3N and stirred at 0 °C under inert atmosphere. 1.5 equiv of isonicotinoyl chloride dissolved in DCM was directly added dropwise to above stirred solution at 0 °C. The reaction mixture was stirred for 0.5 h. The reaction progress was monitored by TLC. After completion of the reaction, the reaction mixture was diluted with water (30 ml) and extracted with DCM twice. The organic layer was washed successively with saturated bicarbonate solution (2 × 20 ml) and brine solution (20 ml). The organic layer was dried over anhydrous sodium sulfate and was evaporated under reduced pressure. The crude product was recrystallized from ethyl acetate and hexane to afford the desired product.

4.9.1. *N*-[4-(4-Isonicotinoylpiperazin-1-yl)phenyl]cinnamamide (**12a**)

N-[4-(Piperazin-1-yl)phenyl]cinnamamide **9a** (0.12 g, 0.39 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.16 ml, 1.17 mmol) and stirred at 0 °C under inert atmosphere. Isonicotinoyl chloride (0.07 g, 0.47 mmol) was directly added portionwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.12 g of **12a**. Light yellow solid; Yield 75%; mp 216–218 °C; IR (KBr pellets, cm^{-1}): 3452, 3281, 3049, 2914, 1674, 1617, 1522, 1447, 1289, 1165, 1015, 930, 829, 773; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.11 (4H, t, J = 4.10 Hz), 3.59 (4H, t, J = 4.12 Hz), 6.58 (1H, d, J = 15.2 Hz, Ph–CH=CH–), 6.91 (2H, d, J = 7.4 Hz, Ar–H), 7.21–7.59 (9H, m, Ar–H), 7.79 (1H, d, J = 15.2 Hz, Ph–CH=CH–), 8.74 (2H, d, J = 6.8 Hz, Ar–H), 10.15 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 50.14, 54.39, 113.51, 117.12, 121.50, 121.47, 127.14, 127.34, 128.28, 128.92, 134.28, 141.12, 144.60, 145.39, 149.42, 165.09, 169.11; HR-MS *m/z*: 413.1490 (M + 1).

4.9.2. *N*-[3-Fluoro-4-(4-isonicotinoylpiperazin-1-yl)phenyl]cinnamamide (**12b**)

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]cinnamamide **9b** (0.12 g, 0.37 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.15 ml, 1.11 mmol) and stirred at 0 °C under inert atmosphere. Isonicotinoyl chloride (0.06 g, 0.44 mmol) was directly added portionwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.1 g of **12b**. Off-white solid; Yield 66.67%; mp 252–254 °C; IR (KBr pellets, cm^{-1}): 3401, 3110, 2947, 1664, 1631, 1602, 1542, 1512, 1428, 1357, 1212, 1011, 997, 874, 761; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.31 (4H, t, J = 3.32 Hz), 3.57 (4H, t, J = 3.30 Hz), 6.68 (1H, d, J = 16.9 Hz, Ph–CH=CH–), 6.93 (1H, d, J = 7.9 Hz, Ar–H), 7.24–7.67 (9H, m, Ar–H), 7.73 (1H, d, J = 16.9 Hz, Ph–CH=CH–), 8.56 (2H, d, J = 6.9 Hz, Ar–H), 10.08 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 47.32, 51.22,111.26, 113.24, 117.09, 118.12, 121.19, 127.01, 127.29, 128.16, 128.34, 135.78, 142.10, 144.14, 145.52, 149.27, 155.24, 166.72, 168.10; HR-MS *m/z*: 430.2050 (M^+).

4.9.3. *N*-[4-(4-Isonicotinoylpiperazin-1-yl)phenyl]-3-(4-nitrophenyl)acrylamide (**12c**)

3-(4-Nitrophenyl)-*N*-[4-(piperazin-1-yl)phenyl]acrylamide **9c** (0.12 g, 0.34 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 1.02 mmol) and stirred at 0 °C under inert atmosphere. Isonicotinoyl chloride (0.07 g, 0.41 mmol) was directly added portionwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.09 g of **12c**. Reddish solid; Yield 60%; mp 262–264 °C (charred); IR (KBr pellets, cm^{-1}): 3394, 3239, 1637, 1562, 1542, 1449, 1261, 1185, 1038, 802, 739; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.24 (4H, t, J = 4.56 Hz), 3.48 (4H, t, J = 4.53 Hz), 6.62 (1H, d, J = 15.5 Hz, Ph–CH=CH–), 6.83 (2H, d, J = 7.8 Hz, Ar–H), 7.32–7.74 (8H, m, Ar–H), 7.76 (1H, d, J = 15.5 Hz, Ph–CH=CH–), 8.89 (2H, d, J = 7.1 Hz, Ar–H), 9.85 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 50.35, 54.11, 113.89, 117.23, 121.38, 122.31, 127.30, 128.08, 128.18, 135.23, 141.41, 144.89, 145.19, 147.20, 148.32, 166.01, 168.48; HR-MS *m/z*: 458.1320 (M+1).

4.9.4. *N*-[3-Fluoro-4-(4-isonicotinoylpiperazin-1-yl)phenyl]-3-(4-nitrophenyl)acrylamide (**12d**)

N-[3-Fluoro-4-(piperazin-1-yl)phenyl]-3-(4-nitrophenyl)acrylamide **9d** (0.12 g, 0.32 mmol) was dissolved in 10 ml dry DCM followed by addition of Et_3N (0.14 ml, 0.97 mmol) and stirred at 0 °C under inert atmosphere. Isonicotinoyl chloride (0.07 g, 0.39 mmol) was directly added portionwise to above stirred solution at 0 °C. The reaction mixture was worked up as per the general procedure to afford 0.11 g of **12d**. Light brown solid; Yield 73.33%; mp 266–268 °C (charred); IR (KBr pellets, cm^{-1}): 3445, 3322, 1623, 1512, 1430, 1340, 1254, 1020, 992, 843; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm): 3.12 (4H, t, J = 4.15 Hz), 3.53 (4H, t, J = 4.16 Hz), 6.61 (1H, d, J = 15.9 Hz, Ph–CH=CH–), 6.92 (1H, d, J = 7.3 Hz, Ar–H), 7.21–7.68 (6H, m, Ar–H), 7.75 (1H, d, J = 15.9 Hz, Ph–CH=CH–), 8.22 (2H, d, J = 7.1 Hz, Ar–H), 8.78 (2H, d, J = 6.8 Hz, Ar–H), 10.14 (1H, s, CONH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 51.32, 54.67, 112.30, 113.02, 117.15, 121.87, 122.54, 127.19, 128.28, 128.43, 135.78, 141.80, 144.33, 145.65, 147.29, 148.87, 155.90, 165.45, 169.12; HR-MS *m/z*: 475.2190 (M^+).

4.10. Antitubercular assay

Resazurin Microtiter Assay (REMA) protocol was used to determine the minimum inhibitory concentration (MIC) of all the synthesized *N*-[4-(piperazin-1-yl)phenyl]cinnamamide derivatives [21]. The synthesized compounds were screened against *M. tb.* H37Rv using serial dilution technique in middlebrook 7H9 broth medium. Each compound (2 mg) was dissolved in 1 ml of DMSO. The serial dilution of each compounds were prepared using 96-well microtitre plate and 100 µl of *M. tb.* H37Rv cell suspension in nutrient media was added to each well. After 7 days of incubation, resazurin dye solution (0.02% w/v dissolved in distilled water) was added to each well and again incubated for 1 day. The MIC was determined by minimum concentration of compound that inhibits the growth of *M. tb.* that is indicated by color change from non-fluorescent blue to fluorescent pink color. The MIC values were

calculated by visual inspection for each well showing more than 90% inhibition. Isoniazid (INH) was used as the reference drug.

4.11. Cytotoxicity assay

The MTT assay was used for the determination of the cytotoxicity of the synthesized compounds using mammalian VERO cell line in 96-well microtitre plates [22,23]. The mammalian VERO cells were subcultured and the three serial dilutions (125, 62.5, 31.25 μg/ml) of compounds were made in 96-well microtitre plates. After 72 h of incubation, 50 μl MTT reagent was added to each well and again incubated for 4 h. 150 μl of DMSO was added to solubalize the formazan precipitate. The cell viability was assessed on the basis of cellular conversion of yellow MTT into a purple formazan product.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2014.01.024.

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