"DESIGN, SYNTHESIS AND EVALUATION OF SOME BIOLOGICAL IMPORTANT CINNAMIC ACID-AMIDE HYBRID MOLECULES"

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Abstract:
Most of the cinnamic acids, their esters, amides, aldehydes and alcohols, show significant growth inhibition against one or several bacterial and fungal species. A series of cinnamic acid-amide hybrids was rationally design and synthesized by reaction of (e)-3-(benzo d 1 3 dioxol-5-yl)acrylic acid with diversified biologycaly active fragments. The synthesis of multitargeted molecule is easy by coupling cinnamic acid derivatives with biologycally active piperidine derivatives by effiecient method with good to excellent yield. The identified and multitarget molecule serve as a lead for the future research in connection of potent targets for bilogically importantant applications such as anitmicrobial, antituberculasis and antifungal drug candidate. Synthesized molecules were characterized by using analytical techniques such as ^{1}H-NMR, melting point and Mass.

Keywords: Cinnamic acid amide hybrids, (e)-3-(benzo d 1 3 dioxol-5-yl)acrylic acid, biologycal active fragments, antifungal, antimicrobial, antituberculosis.

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Introduction:

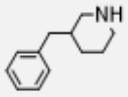
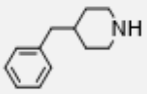
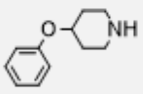
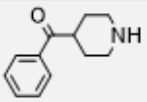
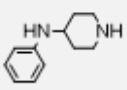
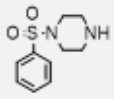
Hybrid molecules are the chemical entities with two or more than two structural areas having different biological purposes and dual activity indicates that a hybrid molecule acts as two distinct pharmacophores. Both entities of the hybrid molecule are not necessarily acting on the same biological target. These hybrid molecules should be disorganized with prodrugs. When a drug candidate has a weak bioavailability, the prodrug strategy is highly convenient to correct the pharmacokinetic and pharmacodynamic profiles of a valuable lead [1].

Cinnamic acid, a natural aromatic carboxylic acid is key chemical observed in plant like cinnamomum cassia and panax ginseng [2]. The presence of an acrylic acid group substituted on the phenyl ring gives cinnamic in the form of cis or a trans configuration[3,4]. Studies have reported that cinnamic acid derivatives exhibit antioxidant [5], anti-tuberculosis [6], antifungal [7], antimicrobial [8, 9], anticancer [10], neuroprotective [11], anti-inflammatory [12] and antidiabetic properties [13]. Cinnamic acid terminates the radical chain reactions forming stable products [14]. It is also used as a fragrant ingredient in toiletries, flavourings cosmetics and detergents [3].

Cinnamic acid contains benzene ring and acrylic acid group makes it possible to modify it resulting in synthetic cinnamic acid derivatives [12]. Cinnamic acid derivatives that have been reported by researchers include ferulic acid, curcumin [11], caffeic acid, p-hydroxycinnamic acid [15] coumaric and chlorogenic acids [16]. These cinnamic acid analogues are differentiated by the presence of hydroxyl groups on the phenyl ring that are either free or methoxylated [16].

Along with cinnamic acid derivative some hybrid multitargeted molecule can be synthesis using different linkers and spacers commonly used in bioactive molecules. The most common linkers are methylene, amine, acetoxy, oxy and sulphonamide. benzylpiperazine derivatives have received attention due to their significant anti-inflammatory agent, inhibitor and antifungal activities [17-18]. N-Phenyl-4-piperidinamine derivatives having benzoyl piperidyl alkyl and related compounds possessing tranquilizing, anti-hypertensive and analgesic properties and a process for the preparation thereof are described [19].

The most common linker connecting two rings present in bioactive molecules is a simple methylene group [20] was synthesis by various synthetic route [21-23] for example as a linker incorporated very successfully in kinase inhibitors. [24, 25]. A range of synthetic strategies are available for the preparation of derivatives incorporating alkene linkers [26].

Sr. No.	A	B	C	D	E	F
Active Fragments						
Activities with other derivatives	Kinase inhibitor, Antimicrobial Anti-inflammatory	Kinase inhibitor, Antimicrobial, Anti-inflammatory	Anticonvulsant, Muscle relaxant, antitubercular, Analgesic.	Anticonvulsant, Antihypertensive, Muscle relaxant,	Analgesic, Antagonist, antimicrobial	Antibacterial, Anti-inflammatory, Antagonist, Antifungal,

The most common aliphatic ring linkers are cyclic amines - piperazine, piperidine, pyrrolidine and azetidine - usual medicinal chemistry building blocks [27]. This type of small aliphatic rings introduces three dimensionalities into the molecule, for their beneficial physicochemical properties and applications as functional group bio isosteres [28]. Piperamide derivatives were synthesized by treating different piperazine and piperidine compounds with (E)-3-(7-methoxybenzo [d] [1,3] dioxol-5-yl) acrylic acid. The compounds were evaluated for their antibacterial, antifungal, antidepressant, antioxidant activities and also for their mono amino oxidase A and B inhibitory activity [29].

4 & 3 benzyl piperidines (A, B), 4-benzoylpiperid -ines (D) [30] and 3-phenoxypyrrolidines (C) [31] are the biological active fragments possess anticonvulsant activities and muscle relaxant activities [33]

By considering all these facts and finding in the present invention we have synthesized a series of Cinnamic acid amide hybrid derivatives.

Results and discussion:

Cinnamic acid derivatives 3(a–j) were prepared by treating of 3-Benzo [1,3] dioxol-5-yl-acrylic acid with corresponding diversified biological active spacers/linkers such as piperidine and piperazine derivatives in the presence of activators and coupling reagents at ambient temperature. (figure 2). Products were isolated by simple solvent extraction and trituration to get pure targeted molecule with order of moderate to excellent molar yield. Isolated reaction condition was very favorable as compared with previous methods. especially those that need harsh reaction conditions, large amount of organic solvent, special reagents and column purifications. For process optimization, screened various coupling reagents and activators to get desired products and it is observed that HATU and DIPEA serve as excellent role. The current optimized process and stichometry of amine, HATU and DIPEA gives pure compound without column chromatography for purification. The reaction progress was monitored by TLC and isolated compound purity was tested by HPLC chromatography (agilent), product structure was confirmed by ^{1}H NMR and Mass spectra and Melting points. The isolated hybrid target molecules were tested for antimicrobial activities using E. Coli ATCC25922, Pseudomonas aeruginosa ATCC27853, Staphylococcus aureus ATCC25923 and Candida species against gentamycin and nystatin.

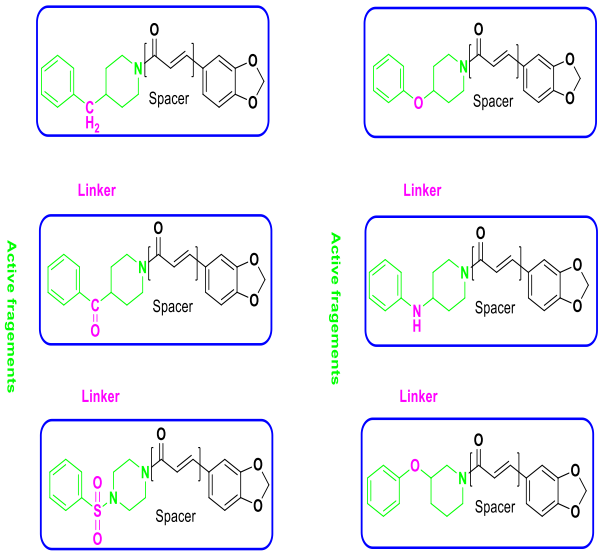


Figure-1: The attractive targeted hybrid molecule

1. Reaction scheme to synthesis of new target molecules:

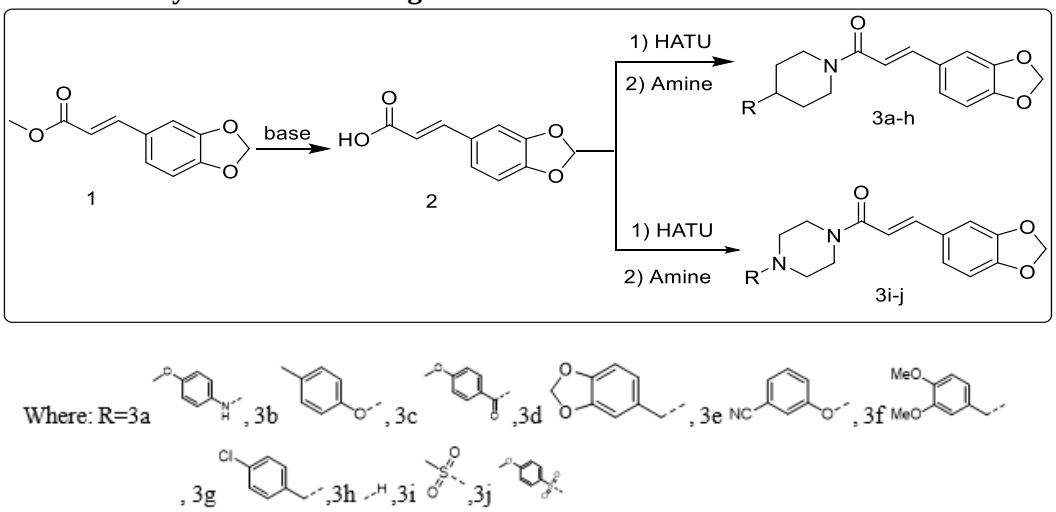
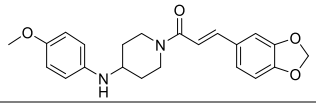
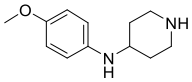
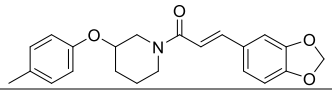
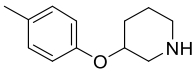
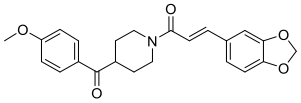
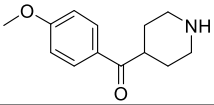
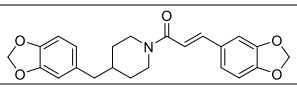
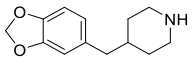
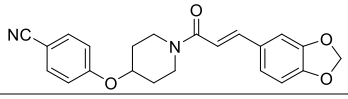
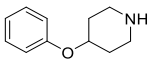
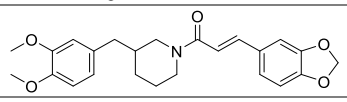
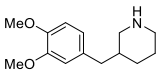
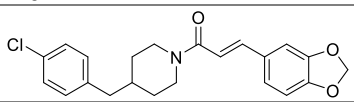
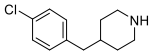
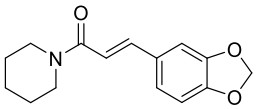
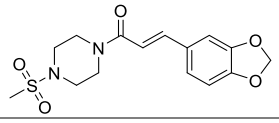
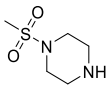
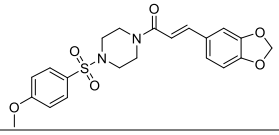
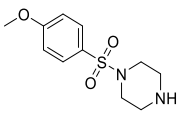


Figure-2: *Synthetic route for intermediate and target molecules*

2. Synthesized targeted hybrid molecules, active fragments, appearance and melting points:

Code	Structure 3 (a-j)	Active fragments	Appearance	Meting range
3a			Pale yellow solid	122-124 °C
3b			Off white solid	120-123 °C
3c			Off white solid	119-123 °C

3d			Light brown solid	124-127 °C
3e			Off white solid	122-124 °C
3f			Brown color solid	95-98 °C
3g			Off white solid	*125-129 °C
3h			Off white solid	*88-90 °C
3i			Off white solid	187-189 °C
3j			Off white solid	168-169 °C

Where * Literature known melting range.

Table 1*: Name, Structure of target hybrid molecules, Active fragments and molecular formula*.

3. Screening of reagents and optimization of reaction to develop synthesis process for 3a:

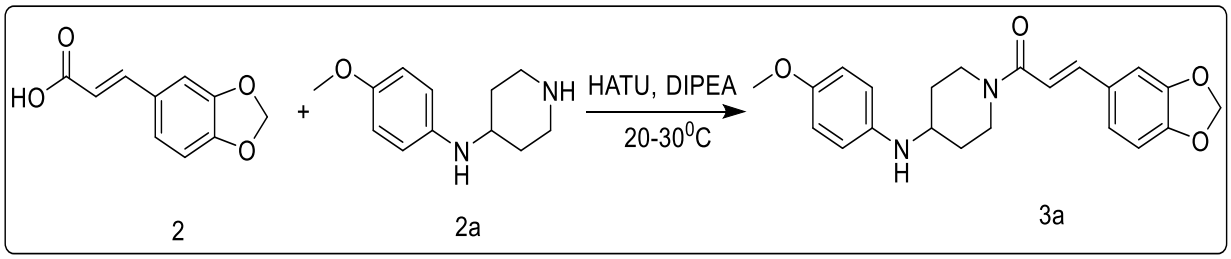


Figure-3: Reaction scheme to synthesis 3a.

Screening the coupling reagent/ activators:

Sr. No	Coupling reagents/activators	Yield % mol
1	$SOCl_2$, TEA	39%
2	T3P	44%
3	EDC, HCl	50%
4	HATU, DIPEA	65%
5	HOBT, DIPEA	60%
6	CDI, DIPEA	56%

Table 2: *Screening of the various activators and coupling reagents*

All above reagent screening experiments showed, that all reagents work effective for acid -amine coupling and obtained product with moderate to good yields. The coupling using activator HATU and DIPEA base showed good yield.

4. Stichometry optimization of reagent in synthesis of 3a:

Sr. No.	Stichometry (eq.)				Temp (°C)	Yield (% mol)
	2	2a	HATU	Amine		
1.	1.0	**0.95**	2.0	2.5	25±5	63
2.	1.0	**1.00**	2.0	2.5	25±5	75
3.	1.0	**1.05**	2.0	2.5	25±5	70
4.	**1.0**	**1.10**	**2.0**	**2.5**	**25±5**	**80**
5.	1.0	1.10	**1.0**	2.5	25±5	60
6.	1.0	1.10	**1.2**	2.5	25±5	70
7.	**1.0**	**1.10**	**1.5**	**2.5**	**25±5**	**82**
8.	1.0	1.10	1.5	**1.0**	25±5	**60**
9.	1.0	1.10	1.5	**1.5**	25±5	80
10.	1.0	1.10	1.5	**2.0**	25±5	**82**
11.	**1.0**	**1.10**	**1.5**	**2.2**	**25±5**	**83**
12.	1.0	1.10	1.5	**2.5**	25±5	83

Table 3: *Optimization of reaction stichometry of the reagents.*

Experimental:
All chemicals and reagent purchased from commercial vendors like Spectrochem, Avra, and Sigma Aldrich. Chemicals and reagents were used without further purification. Melting points were measured on an electrothermal digital melting point apparatus and are uncorrected. ^{1}H NMR and ^{13}C-NMR spectra were recorded using Brucker 300-MHz instrument in $CDCl_3$/DMSO solutions with a tetramethyl silane (TMS) as the internal standard. Reaction progress was routinely monitored by Thin layer chromatography (TLC) was carried out on silica gel 60 F254 pre-coated plates (0.25 mm, Merck). TLC plates were visualised under UV illumination at 254 nm. and the solvent for the development of the plate was ethyl acetate: hexane (1:1). The purity of synthesized target molecule was checked by HPLC (Agilent). mass spectrometry data were obtained from With the SCIEX Triple Quad™ 3500 LC-MS/MS system.

1. Procedure A: to synthesis of 3-Benzo [1,3] dioxol-5-yl-acrylic acid (2)
A solution of 3-Benzo [1,3] dioxol-5-yl-acrylic acid methyl ester (19.4 mmol, 1.0 eq.) in 25% methanol in THF (5.0 rel. volume) was treated with Lithium hydroxide (38.80 mmol, 2.0 eq.) and water at 25±5°C and stirred until the reaction deemed complete after 4h by TLC. The reaction mass was concentrated and diluted with water (6 rel. volumes). The mass was cooled to 2±3°C, and acidified with concentrated 2N hydrochloric acid (1.25 rel. volumes) until the pH was 4±1. The resulting mixture was stirred for 30±20 min, filtered, with the filter cake washed with water (2 x 2.0 rel. volumes) before the solid was dried under vacuum to get dried as a light of white solid 3.72 g, 86% molar yield with HPLC purity of 99.4% area., Melting range-135-138°C, Mass m/z (M+H) 193.75, ^{1}H NMR (300 MHz, DMSO-d6): δ ppm 12.23 (s, 1H), 7.54-7.48 (d, 1H), 7.38-7.37 (d, 1H), 7.18-7.15 (dd, 1H), 6.96-6.94 (d, 1H), 6.42-6.37 (d, 1H), 6.08 (d, 2H).

3. Procedure Synthesis of Cinnamic acid-amide hybrids molecules 3(a-j).
General procedure: B
A solution of 3-Benzo [1,3] dioxol-5-yl-acrylic acid (15.61 mmol, 1.0 eq.) in dimethyl formamide (5 rel. volumes) was treated with HATU (23.42 mmol, 1.5 eq.) and DIPEA (34.34 mmol, 2.2 eq.) dropwise at 0°C and stirred for 10 minutes. Followed by addition of substituted amine R (17.17 mmol, 1.1 eq.) and stirred at room temperature until reaction deemed complete after 6h by TLC. After completion of the reaction, the reaction mass was poured on cold water (25 rel. volumes), the solid crushed out was filtered through Buckner funnel. The obtained solid was slurred in sodium bicarbonate solution, filter and wash with water and Solid was dried under vacuum at 45±5°C. The obtained crude triturated with hexane and dried under reduced pressure to afford dried and pure yellow solid.

Synthesis of (E)-3-(benzo[d] [1,3] dioxol-5-yl)-1-(4-((4-methoxyphenyl) amino) piperidin-1-yl) prop-2-en-1-one (3a): Synthesis of this molecule according to general procedure B, N-(4-methoxyphenyl) piperidin-4-amine used as a substituted amine R and obtained pale yellow color solid with HPLC purity 99.6% purity. Melting range 122-124 °C, Mass m/z (M+H) 381.48, ^{1}H NMR (300 MHz, DMSO-d6): δ ppm 7.36-7.46 (m, 2H), 7.09-7.19 (m, 4H), 6.84-6.97 (m, 3H), 6.06 (s, 2H), 4.23-4.44 (m, 2H), 3.78 (s, 3H), 3.15 (m, 1H), 2.90-2.98 (m, 1H), 2.70-2.74 (m, 1H), 1.57-1.61 (m, 1H), 1.24-1.37 (m, 2H), 1.08-1.12 (m, 2H).

Synthesis of (E)-3-(benzo[d] [1,3] dioxol-5-yl)-1-(3-(p-tolyloxy) piperidin-1-yl) prop-2-en-1-one (3b): Synthesis of this molecule according to general procedure B, 3-(p-tolyloxy) piperidine used as a substituted amine R and obtained off white color solid with HPLC purity 99.8% purity. Melting range 120-123 °C, Mass m/z (M+H) 366.33, ^{1}H NMR (300 MHz, DMSO-d6): δ ppm 7.34-7.47 (m, 2H), 7.10-7.14 (m, 2H), 6.84-6.94 (m, 4H), 6.69-6.80 (d, 1H), 6.07 (s, 2H), 4.27-4.30 (m, 1H), 4.13-4.17 (m,1H), 2.90-3.08 (m, 2H), 2.38 (s, 3H), 1.68-1.71 (m, 2H), 1.19-1.33 (m, 2H).

Synthesis of (E)-3-(benzo[d][1,3] dioxol-5-yl)-1-(4-(4-methoxybenzoyl)piperidin-1-yl)prop-2-en-1-one (3c): Synthesis of this molecule according to general procedure B, (4-methoxyphenyl)(piperidin-4-yl) methanone used substituted amine and obtained off white color solid with HPLC purity 98.8% purity and Melting range 119-123 °C. Mass m/z (M+H) 393.39, ^{1}H NMR (300 MHz, DMSO-d6): δ ppm 8.00-8.03 (d, 2H), 7.39-7.48 (m, 2H), 7.06-7.17 (m, 4H), 6.92-6.95 (d, 1H), 6.07 (s, 2H), 4.33-4.47 (m, 2H), 3.86 (s,3H), 3.72 (m, 1H), 3.27 (m, 1H), 2.89-2.94 (m, 1H), 1.45-1.49 (m, 2H), 1.20-1.25 (m, 2H).

Synthesis of (E)-3-(benzo[d][1,3] dioxol-5-yl)-1-(4-(benzo[d][1,3]dioxol-5-ylmethyl)piperidin-1-yl)prop-2-en-1-one (3d): Synthesis of this molecule according to general procedure B, 4-(benzo[d][1,3]dioxol-5-ylmethyl)piperidine used as a substituted amine R and obtained yellow color solid with HPLC purity 99.6% purity. Melting range 124-127 °C, Mass m/z (M+H) 378.51, ^{1}H NMR (300 MHz, CDCl3-d1): δ ppm 7.61-7.56 (d, 1H), 7.28-7.00 (m, 2H), 6.83-6.59 (m, 5H), 6.61 (s, 2H), 6.01 (s, 2H), 4.71 (m, 1H), 4.11-4.07 (d, 1H), 3.06 (m, 1H), 2.63 (m, 1H), 2.51-2.49 (d, 2H), 1.77-1.74 (m, 3H), 1.28-1.16 (m, 2H).

Synthesis of (E)-4-((1-(3-(benzo[d][1,3] dioxol-5-yl)acryloyl)piperidin-4-yl)oxy)benzonitrile (3e): Synthesis of molecule according to general procedure B, obtained yellow color solid with HPLC purity 98.4% purity. Melting range 122-124 °C, Mass m/z (M+H) 411.49, ^{1}H NMR (300 MHz, DMSO-d6): δ ppm 7.34-7.54 (m, 6H), 7.14-7.19 (m, 2H), 6.93-6.95 (d, 1H), 6.07 (s, 2H), 4.76 (m, 2H), 4.01 (m, 1H), 3.53 (m, 1H), 2.00 (m, 1H), 1.59 (m, 2H).

Synthesis of (E)-3-(benzo[d][1,3] dioxol-5-yl)-1-(3-(3,4-dimethoxybenzyl)piperidin-1-yl)prop-2-en-1-one (3f): Synthesis of molecule according to general procedure B, obtained yellow color solid with HPLC purity 98.4% purity. Melting range 95-98 °C, Mass m/z (M+H) 411.49, ^{1}H NMR (300 MHz, DMSO-d6): δ ppm 7.36-7.46 (m, 2H), 7.09-7.19 (m, 2H), 6.84-6.97 (m, 3H), 6.06 (s, 2H), 4.23-4.44 (m, 2H), 3.78 (s, 3H), 3.60 (s, 1H), 2.90-2.98 (m, 1H), 2.70-2.74 (m, 1H), 1.57 (m, 1H),1.88-1.94 (m, 1H), 1.24-1.31 (m, 2H), 1.08-1.12 (m, 2H).

Synthesis of (E)-3-(benzo[d][1,3]dioxol-5-yl)-1-(4-(4-chlorobenzyl)piperidin-1-yl)prop-2-en-1-one (3g): Synthesis of molecule according to general procedure B, N-(4-chlorophenyl)piperidin-4-amine used as a substituted amine R and obtained off white color solid with HPLC purity 98.4% purity, Melting range 125-129 °C.

Synthesis of (E)-3-(benzo[d][1,3]dioxol-5-yl)-1-(4-methyl piperidin-1-yl)prop-2-en-1-one (3h): Synthesis of molecule according to general procedure A, piperidine used a substituted amine R and obtained off white solid with 98.3% a purity by HPLC, melting range 88-90 °C.

Synthesis of (E)-3-(benzo[d][1,3] dioxol-5-yl)-1-(4-(methylsulfonyl)piperazin-1-yl)prop-2-en-1-one (3i):
Synthesis of molecule according to general procedure B, 1-(methylsulfonyl)piperazine used as a substituted amine R and obtained off white solid with 99.8% a purity by HPLC, melting range 187-189 °C. Mass m/z (M+H) 362.10, ^{1}H NMR (300 MHz, DMSO-d6): δ ppm 7.43-7.50 (m, 2H), 7.13-7.18 (m, 2H), 6.93-6.96 (m, 3H), 6.08 (s, 2H), 3.68-3.83 (m, 2H), 3.14 (m, 4H), 2.91 (s, 3H).

Synthesis of (E)-3-(benzo[d] [1,3] dioxol-5-yl)-1-(4-((4-methoxyphenyl) sulfonyl) piperazin-1-yl) prop-2-en-1-one (3j):
Synthesis of molecule according to general procedure B, 1- ((4-methoxyphenyl) sulfonyl) piperazine used as a substituted amine R and obtained off white solid with 100% a purity by HPLC, melting range 168-169°C. Mass m/z (M+H) 432.13, ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 7.82-7.85 (t, 2H), 7.38-7.45 (t, 2H), 7.24-7.26 (m,1H), 7.06-7.15 (m, 2H), 6.92-6.95 (m, 3H), 6.08 (s, 2H), 3.90 (s, 3H), 3.61-3.74 (m, 4H), 3.16 (m, 4H).

Biological Evaluation:
Synthesized Cinnamic acid hybrid molecules were evaluated at Metropolis laboratory Nasik against gentamycin and nystatin for E. Coli ATCC25922, Pseudomonas aeruginosa ATCC27853, Staphylococcus aureus ATCC25923 and Candida species and result showed synthesized molecule were

unfavorable for antimicrobial activities for these bacteria except 3i and 3j which shows moderate activity against Pseudomonas aeruginosa ATCC27853.

Conclusions:

The present synthesis gives screened and optimised reaction condition will help chemist to synthesis of cinnamic acid-amide hybrid molecules using different biological active fragments. The synthesized hybrid molecule unfavourable for antibacterial activity on tested bacteria except 3i and 3j which shows moderate activity against Pseudomonas aeruginosa ATCC27853. Molecules like 3i and 3j will help researcher to study other activities like antimicrobial, antifungal, anticancer activities and designing newer targets. We hope that this will help to all researcher for the synthesis of multi bioactive cinnamic acid-amide hybrid molecules using different bioactive molecules. This synthesis also helps chemists to better understand the relationship between linkers and make rational decisions in selecting spacers in their project and ultimately make the quest for novel bioactive molecules slightly more efficient.

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