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SYNTHESIS AND BIOLOGICAL INVESTIGATION OF NOVEL *N*-(((2-(DIMETHYLAMINO)ETHYL) DISULFANYL)METHYL) SUBSTITUTED AMIDE DERIVATIVES

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ABSTRACT

Objectives: A novel method for synthesis of *N*-(2-(2-(2-(dimethyl amino) ethyl disulfonyl substituted amides is developed by using simple peptide coupling, *N*-methylation and displacement reaction in good yields. We have synthesized 26 molecules in gram scale. This method is extremely useful for the synthesis of disulfide compounds in excellent yields. All synthesized compounds were evaluated for antimicrobial activity *in vitro*. **Method:** Antimicrobial activity against two bacteria; *Staphylococcus aureus (NCIM-2901), Escherichia coli (NCIM-2256)* and two fungal strains; *Candida albicans* (NCIM-3471) and *Aspergillus Niger* (NCIM-1196). **Results:** We have synthesized 26 different N-(2-(2-(2-(dimethyl amino)ethyl)disulfonyl) substituted amides compounds (Scheme 1). We have synthesized target in simple three step procedure. We have optimized all the steps. There is no need for purification in first two steps and only silica gel column required in final stage. We have optimized condition for amide formations by varying different coupling reagents, varying bases, varying solvents, reaction time, different equivalents of coupling reagents and purifications. **Conclusion:** Amongst these, the compounds **7a**, **7b, 7c**, **7d**, **7e, 7f, 7m**, **7n** and **7v-7z** showed highest antibacterial and antifungal activity. The compound **7a-7f** exhibited significant antimicrobial activity; the *in vitro* antimicrobial studies revealed that **7f**, **7m**, **7n**, **7x** and **7z** are the most active compounds against tested strain, which can be regarded as the promising drug candidate for development of antimicrobial drugs.

KEYWORDS: Disulfides; Amide synthesis; 2-Chloro-*N*,*N*-dimethylethanamine; antimicrobial activity.

INTRODUCTION

Disulfides are class of organic compounds containing S-S bond. The structural and therapeutical diversity coupled with S-S bond has fascinates organic and medicinal chemists. There has been considerable interest in disulfide molecules. Literature reveals there is considerable role of disulfides in many biological processed. Organic compounds containing disulfide plays important role in medical chemistry and biology.[1-4] Disulfides are used for preparation of self-assembled monolayers and monolayers protected clusters with number of different properties.[5-8] Recently, many reports are there for the synthesis of disulfide by considering their significance in biological and industrial processes.[9-14]

Thiols are very labile at room temperature so they are easily converts into disulfides.[15-16] Disulfide linkage stabilize the tertiary structure of proteins and it enhances thiol-mediated protein retention in the endoplasmic reticulum.[17-20] Disulfides are important for maintaining the redox state within and without cells for latentiating thiols in prodrugs.[21-30] Disulfides are used for valcanizing agents and elastomers. Self-assembled monolayers of disulfide are mainly used for metal surface coatings.[31-33] Disulfides helped to identify novel allosteric site in therapeutical relevant targets such as caspases.[34-36]

There are many methods for synthesis of disulfides symmetrical or unsymmetrical disulfides. Mainly the reaction of an thiol with sulfenylating reagents,[37-40] by using aromatic sulfonyl chloride using samarium metal,[41] Triphenyl phosphin,[42] or neutral alumnina.[43] The oxidative coupling of the thiols, in the presence of iodine,[44] hydrogen peroxide,[45] organometallic magnese complexes.[46] The disulfide synthesized by oxidative coupling of thiols,[47-48] air oxidation of thiol gives disulfide.[49-50] Garcia and Ruano synthesized symmetrical disulfide by sonication of thiols in N,N-dimethylformamide (DMF) in Triethyl amine (TEA) in atmospheric oxygene.[51] The convenient one pot synthesis of symmetrical disulfide from thio acetate by nickel boride catalyzed methanolysis and dispropotination,[52] hydrolysis catalized by sodium azide,[53] treatment with alkoxy stannanes and ferric chloride,[54] have been reported. The Treatment of the thiobenzoate, with piperadione,[55] treatment of thiobenzoate with samarium diiodide.[56] Disulfides synthesized from Burgers reagent,[47] strong bases,[57] CAN,[58] Al_2O_3/KF,[59] CsF,[60] benzyl triethyl

ammoniumtrithiors,[61] silica/H_2SO_4/$NaNO_2$,[62] All these condition are used for synthesis of symmetrical disulfides.

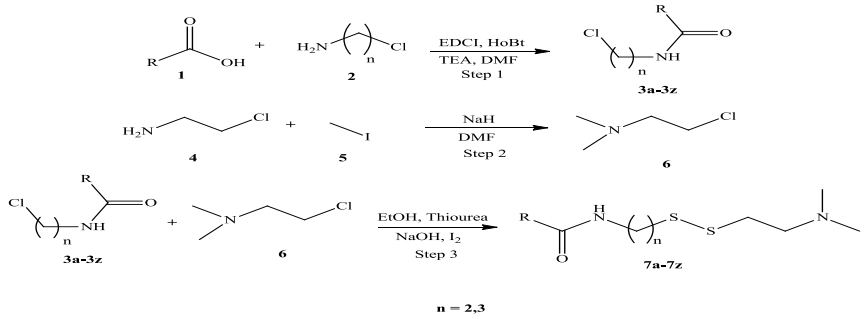
In one paper unstable nitroso thiols used as sunstrate to form unsymmetrical dithio compounds by sulfonamide intermediate.[63] Many unsymmetrical disulfides synthesized from dialkoxy thio phosphrane sulfenyl halides.[64] Many unsymmetrical disulfides are synthesized from different dialkyl azodicarboxylate.[65] Recently disulfide was synthesized by using thiol protected with TBDMS group.[66] The earlier study for the synthesis of disulfide requires toxic reagents, toxic solvents and need for high temperature, unstable intermediates, costly reagents and tedious purification techniques. We have developed a simple and convenient method for synthesis of disulfides in gram scale.

In view of the above considerations, in continuation of our previous work on triazoles, pyrimidine, thiazoles and thiazolidinones of pharmaceutical interest[67,68] we report here on the synthesis, characterization and antimicrobial evaluation of new synthesis of disulfides derivatives.

RESULTS AND DISCUSSION

Chemistry

We have synthesized 26 different N-(2-(2-(2-(dimethyl amino)ethyl)disulfonyl) substituted amides compounds (Scheme 1). We have synthesized target in simple three step procedure. We have optimized all the steps. There is no need for purification in first two steps and only silica gel column required in final stage. We have optimized condition for amide formations by varying different coupling reagents, varying bases, varying solvents, reaction time, different equivalents of coupling reagents and purifications. We presented optimization conditions in Table 1.



Scheme 1 Synthesis of novel disulfide compounds.

We have optimized reaction condition of amide formation because we are using aromatic, aliphatic and heterocyclic acids. We need to develop a condition all formed amides need not

to be purified and crude compound used as such for further reaction. With different coupling reagents we got varying results as given in Table 1. With benzotriazol-1-yl-oxytripyrrolidinophosphonium hexafluorophosphte (PyBOP) the amide formation of plane aromatic amides done well with good yields (**3a, 3b, 3c, 3d, 3g, 3h, 3k, 3l, 3e, 3f, 3g, 3i, 3j, 3r, 3s, 3t**), but low yields obtained with (**3m, 3n, 3o, 3p, 3u**) and no any amide formation was seen with (**3v, 3w 3x, 3y, 3z**). With HATU the amide formation done well with (**3g, 3h, 3q, 3i, 3j, 3r, 3s**) less product with (**3a, 3b, 3c, 3d, 3o, 3p, 3k, 3l, 3e, 3f, 3t, 3u**) and no reaction with (**3m, 3n, 3v, 3w 3x, 3y, 3z**). With T3P amide formation done well with (**3a, 3b, 3c,3d, 3g, 3h,3o, 3p, 3k, 3l, 3e, 3f, 3q, 3i, 3j, 3r, 3s, 3t, 3u**) and less products with (**3m, 3n, 3v**, **3w 3x, 3y, 3z**) all reactions shows product formation in T3P. With EDCI (1.5 eq), HoBt (1.5 eq), TEA (2.5 eq) in DMF for 16 h all amide formations has been achieved with good yields. By changing base some.

Table 1 Optimization of reaction condition for amide 3a.

Coupling Reagent	Base	Solvent	Time (h)	Yield (%)
HATU (1.1 eq.)	TEA (1,2 eq.)	DMF	16	25
	DIPEA (1.2 eq.)			35
PyBOP (1.1 eq.)	TEA (1,2 eq.)	THF	16	27
	DIPEA (1.2 eq.)			40
EDCI (1.5 eq.) HOBt (1.5 eq.)	TEA (2.5 eq.)	DMF	16	80
EDCI (1.5 eq.) HOBt (1.5 eq.)	DIPEA (2.5 eq.)	DMF	12	30
EDCI (1.5 eq.) HOBt (1.5 eq.)	TEA (4 eq.)	DMF	16	46
	DIPEA (4 eq.)			55
T3P (1.2 eq.)	TEA (2.5 eq.)	DCM	12	50
	DIPEA (2.5eq)			60

Acid (1eq.) and amine (1 eq).

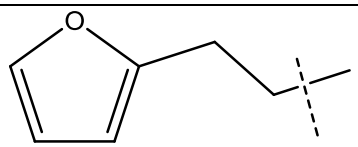
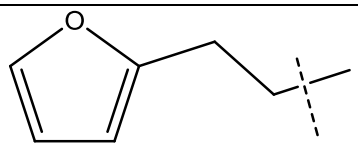
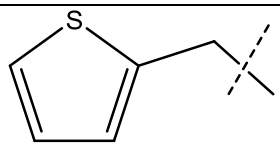
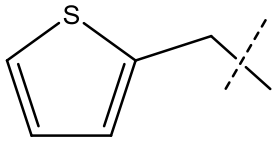
Table 2 Optimization of reaction condition for synthesis of 2-chloro-N,N-dimethylethanamine 6

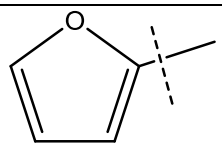
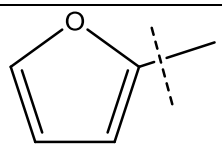
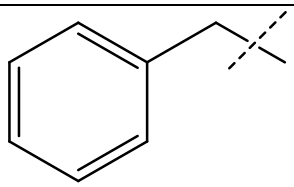
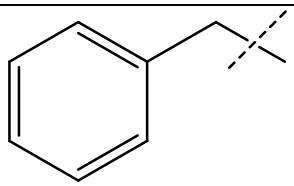
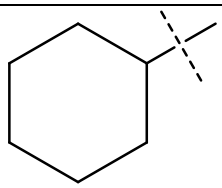
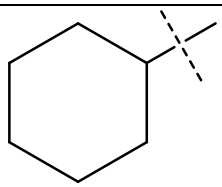
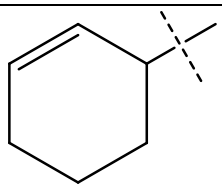
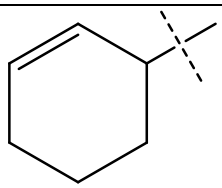
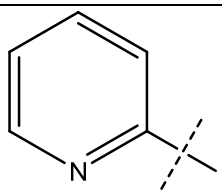
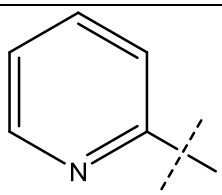
heterocyclic amides not formed in good yields. Almost in all cases there is problem in synthesis of nitrogenous acids and heterocyclic acids. Amide formed but in low yields in

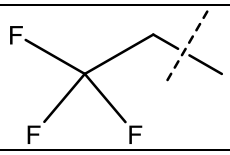
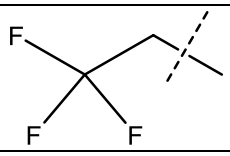
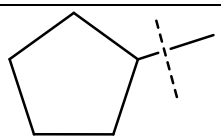
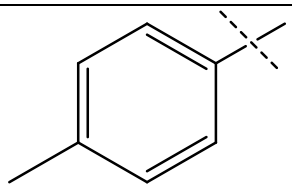
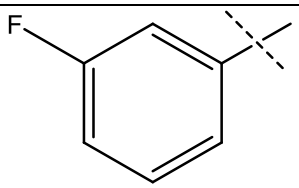
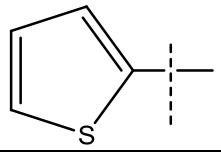
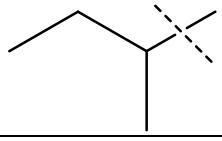
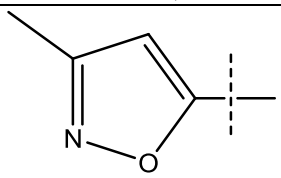
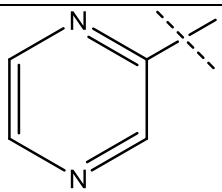
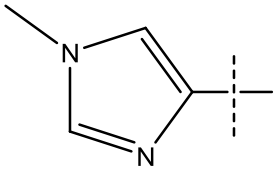
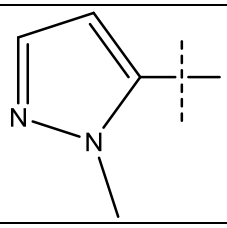
MeI	Reagent	Base	Solvent	Time (h)	Temp.	Yield
2.5eq	NaH (3 eq)	TEA (1,2 eq)	DMF	8	0^0C-RT	80 %
2.5eq	NaH (1.5 eq)	DIPEA(1.2 eq)	DMF	12	0^0C-RT	30 %
2.5eq	Cs_2CO_3 (2.5 eq)	TEA(1,2 eq)	DMF	16	0^0C-RT	50 %
2.5 eq	KOtBu (2.5 eq)	DIPEA(1.2 eq)	DMF	8	0^0C-RT	27 %
	HCHO (5 eq)	PtSA (catalyst)	Toluene	16	RT-120^{0}C	20 %
2-Chloroethylamine (1 eq.) used in all reactions						

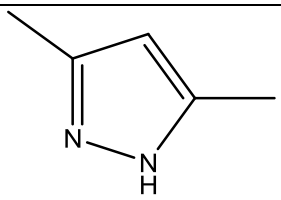
PyBOP condition compounds formed but they need purification crude showing only 40-50% pure compounds. Same results obtained with HATU condition also the RM shows on 45-55% of product formation. T3P reaction gives good results 60-65% product formation obtained in crude but it is costly reagent. With 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) (1.5 eq), HoBt (1.5 eq), TEA (2.5 eq) in DMF for 16 h all amide formations has been achieved with good yields. Crude itself is showing 75-85% amide formation so we don't need any purification. For step 2 we have used again different conditions and finally optimized one condition that gives good yield without purification and crude used further for next reactions. 2-chloroethanamine reacted with HCHO and catalyst (Table 2). The Pra-Toluenesulfonic acid (PtSA) in toluene, with azeotropic distillation of water using dean stark. This required longer reaction time and harsh condition like heating at 120^0C. Amine reacted with bases like Cesium Carbonate (Cs_2CO_3), Potassium tert-Butoxide (KOtBu) and K_2CO_3 with excess of methyl iodide (5 eq). All these reactions are failing to give good yields and not able to isolate in pure compound. We treated 2-chloroethanamine (1 eq) with NaH (3 eq) in DMF at 0°C to RT for 30 min. then MeI (2.5 eq) for 8 h to give desired product. Aqueous work up gives crude product compound isolated by treating it with 6N aq. HCl by adjusting pH to 4 and extracting it with diethyl ether to obtain colorless oily compound in good yields. We have optimized condition for step 3 we used amide.

Table 3 Physical data of synthesis novel disulfide derivatives (3a-z and 7a-z).

Entry	Comp.	Comp.	R	n	Time (h)		Yield (%)	
					3a-z	7a-z	3a-z	7a-z
1	3a	7a		2	16	6	80	50
2	3b	7b		3	16	6	78	55
3	3c	7c		2	16	6	80	60
4	3d	7d		3	16	6	85	60

5	3e	7e		2	16	6	80	60
6	3f	7f		3	16	6	80	55
7	3g	7g		2	16	6	75	55
8	3h	7h		3	16	6	80	50
9	3i	7i		2	16	6	80	55
10	3j	7j		3	16	6	80	60
11	3k	7k		2	16	6	70	60
12	3l	7l		3	16	6	70	60
13	3m	7m		2	16	6	80	55
14	3n	7n		3	16	6	75	50

15	3o	7o		2	16	6	80	50
16	3p	7p		3	16	6	70	60
17	3q	7q		2	16	6	80	60
18	3r	7r		3	16	6	85	60
19	3s	7s		3	16	6	80	65
20	3t	7t		3	16	6	85	60
21	3u	7u		3	16	6	70	65
22	3v	7v		3	16	6	60	60
23	3w	7w		3	16	6	80	50
24	3x	7x		2	16	6	70	50
25	3y	7y		2	16	6	70	50

26	3z	7z		2	16	6	72	50

compound (1 eq) is treated with dimethyl amine compound (1.1 eq) in EtOH and thiourea (1.5 eq) reaction refluxed for 2 h (Table 3). Cooled RM and added 2N aq. NaOH (2 ml) then added Iodine (1.5 eq) and again stirred RM for 2 h at room temperature. Diluted RM with 2N aq. HCl and stirred for 10 min filter the solid formed in RM. Extracted filtrate twice with 5% MeOH: DCM and obtain crude RM. The purification of all derivatives done by silica gel column chromatography by using gradient 40-90 Ethyl acetate: Hexane to obtain all compounds 1 as colorless oily compounds. By using this methodology many symmetric and unsymmetrical disulfide compounds are synthesized in gram scale. All compounds are purified by using column chromatography by using different proportions and ethyl acetate hexane and all compounds and colorless semisolids.

In view of the facts mentioned above, disulfide derivatives were synthesized (**7a-z**), characterized by different spectral analytical techniques and screened for their antimicrobial.

Table 4 Antimicrobial activity of the synthesized compounds (7a -7z).

Compounds	**MIC values (µg/ml) [a]**			
	E. coli	***S. aureus***	***C. Albicans***	***A. Niger***
7a	20	58	72	73
7b	18	68	69	74
7c	50	54	73	15
7d	42	44	48	16
7e	21	64	74	54
7f	14	54	64	87
7g	61	67	63	61
7h	59	54	75	62
7i	66	56	75	56
7j	56	88	100	100
7k	78	77	56	66
7l	55	54	75	75
7m	22	15	17	25
7n	24	24	25	12.5
7o	64	54	33	64
7p	69	54	75	67
7q	62	46	55	56
7r	61	67	61	62
7s	88	100	96	94

7t	67	24	78	55
7u	34	75	75	78
7v	21	22	23	14
7w	24	19	25	13
7x	16	18	33	57
7y	17	15	50	25
7z	24	12	25	12.5
Ciprofloxacin	14.50	13.50	-	-
Ampicillin	10.50	9.50	-	-
Fluconazole	-	-	4.70	6.58
Miconazole	-	-	6.69	12.5
[a] Values are the average of three readings.				
Escherichia coli (NCIM-2256), *Staphylococcus aureus* (NCIM-2901), *Candida albicans* (NCIM-3471), *Aspergillus Niger* (NCIM-1196)				

activity against two bacteria; *Staphylococcus aureus (NCIM-2901), Escherichia coli (NCIM-2256)* and two fungal strains; *Candida albicans* (NCIM-3471) and *Aspergillus Niger* (NCIM-1196).

Antimicrobial activity

The antimicrobial activity of compounds was monitored by observing their Minimum Inhibitory Concentration (MIC, µg/ml) as previously mentioned[69] by broth dilution methods with Ciprofloxacin and Ampicillin as control drugs. While the antifungal study was carried by the standard agar dilution method, Fluconazole and Miconazole used as control drugs.

The antimicrobial activities of the synthesized compounds against selected Gram-positive and Gram-negative bacteria and multidrug-resistant bacteria are illustrated in tables 4. The synthesized compounds of present novel series shows variety of antibacterial and antifungal activity, ranging from broad spectrum molecule active against the majority of bacterial and fungal strains tested to the narrow spectrum compounds, active only against only one strains. Amongst these, the compounds **7a**, **7b, 7c**, **7d**, **7e, 7f, 7m**, **7n** and **7v-7z** showed highest antibacterial and antifungal activity and they are specific towards the gram positive bacterial, *S. aureus* and *E. coli*. The compound **7a, 7b, 7e** and **7f** is specific active (MIC of 20, 18, 21 and 14 µg/mL) respectively against *E. coli* and compound **7c** and **7d** (MIC of 15 and 16 µg/mL) are fungal specific molecule specifically active towards the *A.niger*, while the compound (**7m** and **7n**) (MIC of 12.5-25 µg/mL against all tested strains. Interestingly the compound **7n** (MIC of 12.5 µg/mL) against *A. Nigar* and its same value compared to standard drugs of miconazole. The compound **7f** (MIC of 14 µg/mL) have more activity than Ciprofloxacin. Although compounds (**7v-7z**) have somewhat better activity both the standard

drugs, more important is that, they are broad spectrum in nature and shows the activity against majority of bacterial and fungal strains, against bacteria *S. aureus* and *E. coli* and fungus *A.niger* and *C. albicans.* Remaining compounds of the series (**7g-7l** and **7o-7u**) have high MIC values and therefore they are inactive as antimicrobial agents.

EXPERIMENTAL SECTION

General remarks

All acids, HATU, PyBOP, EDCI, HOBt, DIPEA, TEA, DMF, MeI, 2-chloroethaneamine and 3-chloropropane amine are available from Sigma Aldrich and Avra labs. Various solvents were commercially available. Progress of reaction was monitored by TLC on silica gel precoated F254 Merck plates. Developed plated were examined with ultraviolet lamps (254 nm) and visualization done by ninhydrine and $KMnO_4$. Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100MHz, respectively by using $CDCl_3$ as a solvent. The ^1H NMR chemical shifts are referenced to TMS or residual chloroform in $CDCl_3$ (7.26 ppm). ^{13}C NMR was referenced to residual chloroform in $CDCl_3$ (77.0 ppm).

General procedure for the synthesis of target compounds

General procedure for the synthesis of amide derivatives 3

The acid (1 eq.) was treated with EDCI (1.5 eq), HoBt (1.5 eq), TEA (2.5 eq) in DMF. Then added amine (1 eq) and stirred RM at room temperature for 16 h. The reaction was monitored by TLC. Added 25 ml of cold water and stirred for 20 min. (For aromatic acids) Filtered the formed solid and filter, wash it with water and dry it properly to obtain respectively amide. Purification done by washing with 5% ethylacetate: hexane and diethyl ether. For isolation of some heterocyclic amide extraction of ethyl acetate is used.

Synthesis of 2-chloro-N,N-dimethylethanamine 6

The 2-chloroethanamine (1 eq), NaH (3 eq) in DMF at 0^0C to RT for 30 min, MeI (2.5 eq) for 8 h. to give desired product. Aqueous work up gives crude product compound isolated by treating it with 6N aq HCl by adjusting pH to 4 and extracting it with diethyl ether to obtain colorless oily compound in good yields.

General procedure for the synthesis of disulfide compounds 7

The substituted amide compounds (**3a-3z**) (1 eq) are treated with 2-chloro-N,N-dimethylethanamine (**6**) (1.1 eq) in EtOH and thiourea (1.5 eq) reaction refluxed for 2h. Cooled RM and added 2N aq. NaOH (2 ml) then added Iodine (1.5 eq) and again stirred RM

for 2 h. at room temperature. Diluted RM with 2N aq. HCl and stirred for 10 min fileted the solid formed in RM. Extracted filtrate twice with 5% MeOH: DCM and obtain Crude RM. Purification of all derivatives done by silica gel column chromatography by using gradient 40-90 Ethyl acetate: Hexane to obtain all compounds (**7a-7z**) as colorless oily compounds.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)-3-(furan-2-yl)propanamide* (7a)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 7.29 (d, J=2 H_Z, 1 H); 6.82 (br, NH, 1 H); 6.27 (d, J=2.1 H_Z 1 H); 6.03 (s, 1 H); 3.53 (q, 2 H); 3.37 (m, 2 H); 2.95-3.14 (m, 4 H); 2.92 (t, J=7.2 H_Z, 2 H); 2.86 (s, 6 H); 2.53 (t, J=8.1 H_Z, 2 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 25, 33, 37, 38, 40, 45, 57, 105, 110, 140, 155, 173; LCMS (m/z) 302 (M^+). $C_{13}H_{22}N_2O_2S_2$.

***N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)-3-(furan-2-yl)propanamide* (7b)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MHz) δ 7.29 (d, J=2.8 H_Z, 1 H); 6.27 (s, 2 H); 6.02 (d, J=2.6 H_Z, 1 H); 3.35 (m, 4 H); 3.02 (m, 4 H); 2.83 (m, 2 H); 2.80 (s, 6 H); 2.78 (t, J=8.1 H_Z, 2 H); 2.58 (t, J=8.2 H_Z, 2 H); 1.83 (t, J=8 H_Z, 2 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 24, 29, 34, 36, 37, 38, 45, 57, 105, 110, 140, 155, 173; LCMS (m/z) 316 (M^+). $C_{14}H_{24}N_2O_2S_2$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)-2-(thiophen-2-yl)acetamide* (7c)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 7.31 (d, J=3.5 H_Z, 1 H); 7.15 (s, 1 H); 7.03(d, J=5.5 H_Z, 1 H); 6.67 (br, NH, 1 H); 3.48 (q, 4 H); 3.31 (m, 2 H); 2.93 (m, 2 H); 2.87 (m, 2 H); 2.81 (s, 6 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 35, 37, 39, 40, 45, 57, 122, 125, 126, 135, 170; LCMS (m/z) 304 (M^+). $C_{12}H_{20}N_2OS_3$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)propyl)-2-(thiophen-2-yl)acetamide* (7d)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MHz) δ 7.32 (d, J=3.2 H_Z, 1 H); 7.19 (S, 1 H); 7.01 (s, 1 H); 6.12 (br, NH, 1H); 3.60 (s, 2 H); 3.40 (d, J=8.1 H_Z, 4H); 2.98 (m, 2 H); 2.80 (s, 6 H); 2.69 (d, J=8.5 H_Z, 2 H); 1.87 (t, J=8.6 H_Z, 2H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 29, 30, 32, 38, 40, 45, 57, 122, 127, 128, 135, 173; LCMS (m/z) 318 (M^+) $C_{13}H_{22}N_2OS_3$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)furan-2-carboxamide* (7e)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 7.45 (s, 1 H); 7.18 (s, 1 H); 6.49 (d, J=2.1 H_Z, 1 H); 3.78 (q, 2 H); 3,38(m, 2 H); 3.12(m, 2 H); 3.03 (m, 2 H); 2.89(s, 6 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 35, 37, 40, 45, 57, 110, 112, 148, 149, 158; LCMS (m/z) 274 (M^+) $C_{11}H_{18}N_2O_2S_2$.

***N-(3-(2-(2-(dimethylamino)ethyl)disulfanyl)propyl)furan-2-carboxamide* (7f)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 7.45(s, 1 H); 7.12(d, J=4 H_Z, 1 H); 6.65 (d, J=2 H_Z, 1 H); 6.50(d, J=2.5 H_Z, 1 H); 3.57(q, 2 H); 3.35(m, 2 H); 3.01(m, 2 H); 2.82(s, 6 H); 2.80 (m, 2 H); 2.01(m, 2 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 30, 34, 36, 40, 45, 57, 110, 112, 145, 157; LCMS (m/z) 288 (M^+) $C_{12}H_{20}N_2O_2S_2$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)-2-phenylacetamide* (7g)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 7.35(m, 4 H); 6.61(s, 1 H); 3.61 (s, 2 H); 3,59(m, 2 H); 3.31(m, 2 H); 2.95 (m, 2 H); 2.88 (m, 2 H); 2.79 (s, 6 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 33, 35, 37, 41, 45, 57, 128, 130, 132, 138, 162; LCMS (m/z) 298 (M^+) $C_{14}H_{22}N_2OS_2$.

***3.2.11 N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)-2-phenylacetamide* (7h)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 7.40 (m, 4 H); 6.01 (br, NH, 1 H); 3,60(m, 2 H); 3.35 (m, 4 H); 2.89(m, 2 H); 2.80(s, 6 H); 2.75(m, 2 H); 1.80(t, J=8.1 H_Z, 2 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 28, 33, 35, 36, 39, 45, 57, 128, 130, 137, 163; LCMS (m/z) 312 (M^+) $C_{15}H_{24}N_2OS_2$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)cyclohexanecarboxamidede* (7i)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 6.45(Br, NH, 1 H); 3.48(q, 2 H); 3.38(m, 2 H); 3.11(m, 2 H); 2.85(m, 2 H); 2.81(s, 6 H); 2.13 (q, 1 H); 1.85 (m, 4 H); 1.61 (m, 1 H); 1.41.(m, 2 H); 1.28(m, 3H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 25, 27, 30, 33, 35, 37, 43, 45, 57, 173; LCMS (m/z) 290 (M^+) $C_{13}H_{26}N_2OS_2$.

***N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)cyclohexanecarboxamide* (7j)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 9.12(br, NH, 1 H); 3.82 (m, 2 H); 3.30 (m, 2 H); 3.10 (m, 2 H); 2.80 (s, 6 H); 2.65 (t, J=8.1 H_Z, 1 H); 2.12 (q, 2 H); 1.85 (m, 4 H); 1.42-1.20 (m, 6 H); ^{13}C NMR ($CDCL_3$, 1080 MH_Z): 25, 27, 30, 34, 36, 39, 43, 45, 57, 175; LCMS (m/z) 304 (M^+) $C_{14}H_2N_2OS_2$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)cyclohex-2-enecarboxamide* (7k)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 6.61 (Br, NH, 1 H); 5 71(m, 2 H); 3.55 (q, 2 H); 3.39 (m, 2 H); 3.11 (m, 2 H); 2.85 (m, 2 H); 2.83 (s, 6 H); 2.42 (m, 1 H); 2.21 (m, 2 H); 2.15 (m, 2 H); 1.85 (m, 1 H); 1 65 (m, 1 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 22, 24, 28, 28.2, 35, 37, 40, 42, 45, 57, 127, 132, 176; LCMS (m/z) 288 (M^+) $C_{13}H_{24}N_2OS_2$.

***N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)cyclohex-2-enecarboxamide* (7l)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 6.23 (Br, NH, 1 H); 5.68 (s, 2 H); 3.40 (m, 4 H); 3.01 (m, 2 H); 2.85 (s, 6 H); 1.98 (t, J=8 H_Z, 2 H); 2.40 (m, 1 H); 2.33 (m, 3 H); 2.15 (m, 1 H); 1.88 (m, 2 H); 1.65 (m, 1 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 22, 26, 28, 28.2, 35, 37, 40, 42, 45, 57, 127, 132, 176; LCMS (m/z) 302 (M^+) $C_{14}H_{26}N_2OS_2$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)-2-(pyridin-2-yl)acetamide* (7m)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 8.57 (d, J=5.5 H_Z, 1 H); 8.41 (Br, NH, 1 H); 8.18 (d, J=10.5 H_Z, 1 H); 7.87 (t, J=7.5 H_Z, 1 H); 7.43 (m, 1 H); 3.81 (q, 2 H); 3.39 (m, 2 H); 3.15 (m, 2 H); 3.03 (m, 2 H); 2.84 (s, 6 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 35, 37, 40, 45, 57, 123, 127, 137, 148, 152, 162; LCMS (m/z) 285 (M^+) $C_{12}H_{19}N_3OS_2$.

***N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)-2-(pyridin-2-yl)acetamide* (7n)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 8.59 (d, J=5.6 H_Z, 1 H); 8.20 (d, J=9.2 H_Z, 1 H); 7.85 (t, J=7.1 H_Z, 1 H); 7.43 (d, J=7.6 H_Z, 1 H); 7.38 (Br, NH, 1 H); 3.60 (q, 2 H); 3.38 (m, 2 H); 3.03 (m, 2 H); 2.83 (s, 6 H); 2.80 (t, J=8.5 H_Z, 2 H); 2.10 (t, J=8.1 H_Z, 2 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 30, 35, 37, 38, 45, 57, 123, 127, 127, 138, 148, 152, 162; LCMS (m/z) 299 (M^+) $C_{13}H_{21}N_3OS_2$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)-3,3,3-trifluoropropanamide* (7o)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 7.83 (Br, NH, 1 H); 3.54 (m, 2 H); 3.39 (m, 2 H); 3.15 (t, J=8.1 H_Z, 2 H); 3.03 (m, 4 H); 2.83 (s, 6 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 34, 36, 38, 43, 45, 57, 109, 173; LCMS (m/z) 290 (M^+) $C_9H_{17}F_3N_2OS_2$.

***N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)-3,3,3-trifluoropropanamide* (7p)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 7.30 (Br, NH, 1 H); 3.40 (m, 4 H); 3.20-3.12 (m, 4 H); 2.83 (s, 6 H); 2.80 (m, 2 H); 1.85 (t, J=8.1 H_Z, 2 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 30, 34, 36, 38, 43, 45, 57, 109, 173; LCMS (m/z) 304 (M^+) $C_{10}H_{19}F_3N_2OS_2$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)cyclopentanecarboxamide* (7q)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 6.58 (Br, NH, 1 H); 3.51 (q, 2 H); 3.38 (m, 2 H); 3.12 (m, 2 H); 2.89 (m, 2 H); 2.81 (s, 6 H); 2.58 (q, 1 H); 1.85-1.49 (m, 8 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 24, 32, 34, 36, 38, 45, 50, 57, 173; LCMS (m/z) 276 (M^+) $C_{12}H_{24}N_2OS_2$.

***N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)-4-methylbenzamide* (7r)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 7.71 (d, J=10 H_Z, 2 H); 7,23 (d, J=10.4 H_Z, 2 H); 6.81 (Br, NH, 1 H); 3.61 (d, J=8.8 H_Z, 2 H); 3,35 (d, J=8.4 H_Z, 2 H); 3.01 (m, 2 H); 2.83 (m,2 H); 2.80 (s, 6 H); 2.38 (s, 3 H); 2.03 (t, J=8.2 H_Z, 2 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 24, 30, 34, 36, 38, 45, 57, 124, 126, 128, 142, 167; LCMS (m/z) 312 (M^+) $C_{15}H_{24}N_2OS_2$.

***N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)-3-fluorobenzamide* (7s)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 7.61 (m, 2 H); 7.40 (q, 1 H); 7.19 (q, 2 H); 3.58 (q, 2 H); 3.36 (m, 2 H); 3.15 (m, 2 H); 2.85 (m, 2 H); 2.81 (s, 6 H); 2.10 (m, 2 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 28, 34, 36, 38, 45, 57, 112, 118, 124, 131, 138, 163, 167; LCMS (m/z) 316 (M^+) $C_{14}H_{21}FN_2OS_2$.

***N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)thiophene-2-carboxamide* (7t)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 3.58 (d, J=2.1 H_Z, 1 H); 7.43 (d, J=2 H_Z, 1 H); 7.15 (d, J=10.2 H_Z, 1 H); 6.81 (Br, MH, 1 H); 3.58 (q, 2 H); 3.35 (m, 2 H); 3.15 (m, 2 H); 2.81 (s, 6 H); 2.80 (m, 2 H); 2.03 (q, 2 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z):28, 34, 36, 38, 45, 57, 128, 137, 139, 140, 163; LCMS (m/z) 304 (M^+) $C_{12}H_{20}N_2OS_3$.

***N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)-2-methylbutanamide* (7u)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 6.18 (Br, NH, 1 H); 3.38 (m, 4 H); 3.12 (m,2 H); 2.83 (s, 6 H); 2.80 (t, J=8.1 H_Z, 2 H); 2.15 (q, 1 H); 1.85 (t, J=8.4 H_Z, 2 H); 1.65 (q, 2 H); 1.15 (d, J=8.8 H_Z, 3 H); 0,91 (t, J=9.2 H_Z, 3 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 10, 17, 28, 30, 34, 36, 38, 42, 45, 57, 173; LCMS (m/z) 278 (M^+) $C_{12}H_{26}N_2OS_2$.

***N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)-3-methylisoxazole-5-carboxamide* (7v)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 7.17 (Br, NH, 1 H); 6.09 (s, 1 H); 3.70 (s, 2 H); 3.39 (m, 4 H); 3.12 (m, 2 H); 2.83 (s, 6 H); 2.80 (m, 2 H); 2.28 (s, 3 H); 1.89 (m, 2 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 18, 30, 34, 36, 38, 45, 57, 101, 157, 161, 163; LCMS (m/z) 318 (M^+) $C_{12}H_{21}N_3O_2S_2$.

***N-(3-((2-(dimethylamino)ethyl)disulfanyl)propyl)pyrazine-2-carboxamide* (7w)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 9.40 (S, 1 H); 8.76 (s, 1 H); 8.53 (s, 1 H); 8.01 (Br, NH,1 H); 3.61 (q, 2 H); 3.37 (m, 2 H); 3.15 (m, 2 H); 3.83 (s, 6 H); 3.79 (m,2 H); 2.18 (t, J=8.4 H_Z, 2 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 28, 34, 36, 38, 45, 57, 142, 145, 147, 163; LCMS (m/z) 300 (M^+) $C_{12}H_{20}N_4OS_2$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)-1-methyl-1H-imidazole-4-carboxamide* (7x)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 7.55 (m, 2 H); 7.45 (s, 1 H); 3.76 (s, 3 H); 3.75 (m, 2 H); 3.39 (m, 2 H); 3.11 (m, 2 H); 2.99 (m, 2 H); 2.83 (s,6 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 34, 36, 37, 38, 45, 57, 137, 138, 145, 162; LCMS (m/z) 288 (M^+) $C_{11}H_{20}N_4OS_2$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)-1-methyl-1H-pyrazole-5-carboxamide* (7y)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z)δ 7.72 (m, 2 H); 7.61 (Br, NH,1 H); 3.89 (s, 3 H); 3.63 (m, 2 H); 3.39 (m, 2 H); 3.15-3.01 (m, 4 H); 2.83 (s, 6 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 34, 36, 37, 38, 45, 57, 108, 131, 140, 162; LCMS (m/z) 288 (M^+) $C_{11}H_{20}N_4OS_2$.

***N-(2-((2-(dimethylamino)ethyl)disulfanyl)ethyl)-3-methyl-1H-pyrazole-5-carboxamide* (7z)**

Colorless Oil; ^{1}H NMR ($CDCL_3$, 400MH_z) δ 7.31 (Br, NH, 1 H); 6.54 (s, 1 H); 3.74 (q, 2 H); 3.41 (m, 2 H); 3.15 (m, 2 H); 3.07 (m, 2 H); 2.80 (s, 6 H); 2.34 (s, 3 H); ^{13}C NMR ($CDCL_3$, 100 MH_Z): 18, 34, 36, 38, 45, 57, 106, 142, 150, 162; LCMS (m/z) 288 (M^+) $C_{11}H_{20}N_4OS_2$.

CONCLUSIONS

We have developed simple and convenient method for synthesis of disulfide by simple reaction steps. No costly reagents used any pre-purification and all compounds synthesized in good yields. We developed methodologies for synthesis of disulfides in laboratory scale. All reactions are carried out in minimum time, absent of toxic organic solvents, getting better product yield, easy of product isolation and avoids laborious column purification steps and good prospects for synthetic chemistry, medicinal chemistry and chemical science. All synthesized compounds were evaluated for antimicrobial activity *in vitro*. Amongst these, the compounds **7a**, **7b, 7c**, **7d**, **7e, 7f, 7m**, **7n** and **7v-7z** showed highest antibacterial and antifungal activity. The compound **7a-7f** exhibited significant antimicrobial activity; the *in vitro* antimicrobial studies revealed that **7f**, **7m**, **7n**, **7x** and **7z** are the most active compounds against tested strain, which can be regarded as the promising drug candidate for development of antimicrobial drugs.

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