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Optimization of Active 1, 5-Benzothiazepine Derivatives by Design of Experimental (DOE) Studies

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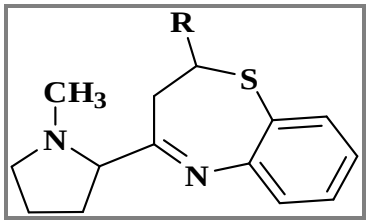
ABSTRACT

Optimised Synthesis of 1,5-Benzothiazepinederivatives (1a-1f) using numerous bases through a condensation reaction between 1-(1-methyl-1H-pyrrol-2-yl)-3-(substituted)-2-propen-1-one and 2-Aminothiophenol in various solvents have been studied. Favourable conditions for the preparation of derivatives of 1,5-Benzothiazepinewere established by Design of Experiments (DOE). These1,5-Benzothiazepinederivatives (1a-1f) were prepared with good-to-excellent yields and have been investigated in detail.

Graphical Abstract



Keywords: 1,5-Benzothiazepine, 2-Aminothiophenol, Design of experiment, Screening, Standard matrix array, Quality by Design.

INTRODUCTION

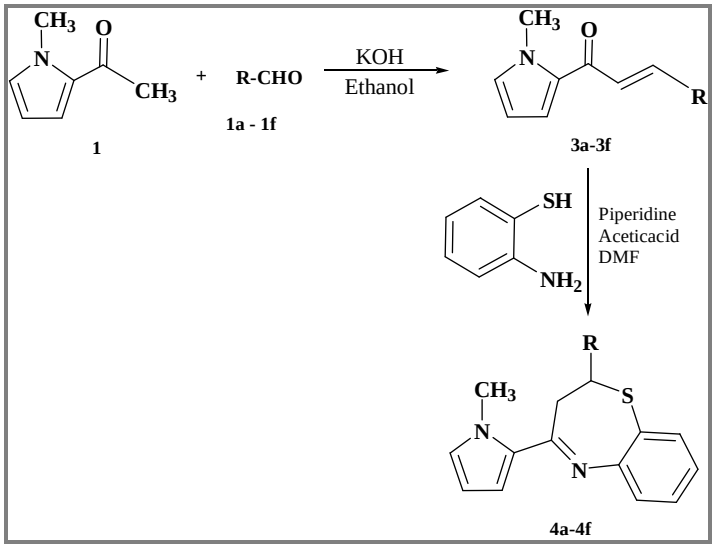
Benzothiazepines [1] belongs to class of seven-membered heterocyclic compounds, with a variety of potential biological activity. 1,5-Benzothiazepines are the most well-known representatives of benzologs of 1,4-thiazepine [2] and one of the three possible benzo-condensed derivatives, viz. 1,4 [3], 4,1 [4] and 1,5-benzothiazepines.

The importance of l,5-Benzothiazepine nucleus has been well established as illustrated by a large number of compounds which have been patented as chemotherapeutic agents [5]. A number of

biological activities have been associated with it, such as antifeedant [6], coronary vasodilatory [7], tranquilizer [8], antidepressant [9], CNS stimulant [10], antihypertensive [11], calcium channel blocker [12], antimicrobial [13] and cytotoxic [14]. l,5-Benzothiazepine molecules have been found to be useful in mucosal blood flow as antiulcer and gastric secretion inhibitor.

As 1,5-Benzothiazepine plays a major role in the pharmacological and medicinal field, various researchers are interested in its synthesis [15] and [16, 17] characterization. Recently, synthesis along with biological evaluation of thiazepine from chalcone and 2-aminoethanethiol has been investigated [18], Literature survey revealed that different synthetic routes of thiazepine have been reported [19, 20].

Various 1,5-Benzothiazepine derivatives were prepared in the earlier communication [21]. It was found that these derivatives have considerable potential to act as cytotoxicity and antimicrobial agents (Scheme 1). The novelty of this work is that none of the 1,5-Benzothiazepine derivatives synthesized were earlier not reported to possess there *in vitro* activity against cytotoxicity and antimicrobial agents.



Scheme 1. 1,5-Benzothiazepine derivatives.

In the present communication synthesis of these compounds was optimized by screening with various bases both organic and inorganic nature and other solvents to establish better conditions for improving yields by using Design of Experiments (DOE) [22].

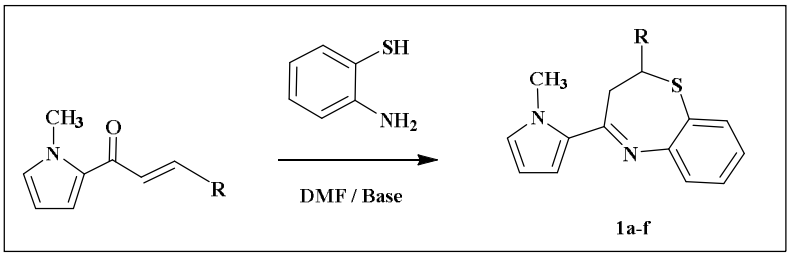
Quality by Design (QbD) [23] is defined as per the ICH Q8 guidelines as a systematic approach to development that begins with predefined objectives, emphasizes product and understanding with process control, based on sound science and quality risk management [23]. Quality by Design is an essential part of modern approach to pharmaceutical quality. QbD is emerging to enhance the assurance of safe, effective drug supply to the consumer, and also offers promise to significantly improve manufacturing quality performance. Implementing the QbD strategy it has been recommended recently by the drug regulatory agencies for the development of better quality product.

Design of Experiment (DOE) is extensively used for the implementation of Quality by Design (QbD) in product development, especially to screen and optimize chemical process. DOE provides valuable information about the interactions among the various reaction parameters, than traditional optimization testing (OFAT- one factor at a time). DOE study gives design space for each parameter in order to make the process robust and GMP complaint.

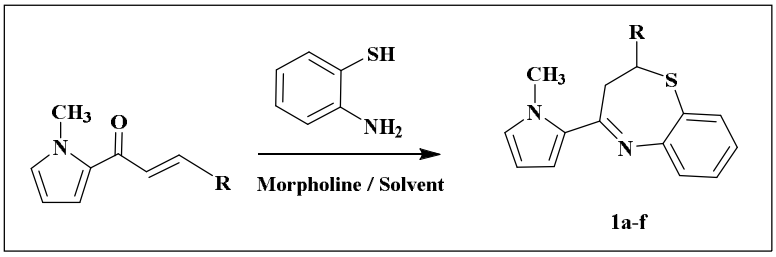
Present work also describes implementation of the DOE strategy as systematic approach to the optimization of1,5-Benzothiazepine derivatives in order to improve the product quality, by understanding and controlling the process parameter variables.

MATERIALS AND METHODS

Synthesis:1-(1-methyl-1H-pyrrol-2-yl)-3-(substituted)-2-propen-1-one was treated with 2-Aminothio-phenol in presence of various bases in different solvent medium yielded 1,5-Benzothiazepine derivatives. Preliminarily, the reaction was carried out in DMF solvent and screened for different bases (Scheme II).After the screening process, the synthesis was carried out by taking Morpholine as a base screened for different solvents (Scheme III).



Scheme-II. 1,5-Benzothiazepine derivatives.



Scheme-III. 1,5-Benzothiazepine derivatives.

General procedure for the preparation of 1,5-Benzothiazepine derivatives (1a–1f): Chalcone derivative [24] (1a-1f) was treated with 2-Aminothiophenol in the presence of Morpholine, Acetic acid and DMSO as solvents. The reaction mixture was stirred for 3-5 h at ambient temperature and monitored by thin layer chromatography (silica gel). This was then quenched by mild cold water and then filtered the precipitate (light yellow color) solid material. The same experiment was repeated with acetone and as well as acetonitrile.

Synthesis of 2,3-Dihydro-2-(4-hydroxyphenyl)-(1-methyl-1H-pyrrol-2-yl)-5-benzothiazepine (1a): 3-(4-Hydroxyphenyl)-1-(1-methyl-1H-pyrrol-2-yl)prop-2-en-1-one (2.0 gm, 0.0088 mol) was treated with 2-Aminothiophenol (1.10 gm, 0.0088 mol) in presence of Morpholine (0.76 g, 0.0088 mol), Acetic acid (1.03g, 0.0088 mol) and DMSO (5 volumes) as solvents. The reaction mixture was then stirred for 3-5 h at ambient temperature and monitored by Thin layer chromatography (silica gel) and quenching with cold water followed by filtered the precipitate as light yellow color solid material(91% yield).The same experiment was repeated with both the solvents Acetone and Acetonitrile as done earlier.

Other compounds (1b-1f) were prepared following the same procedure and hence are characterized under similar conditions.

Spectral data analysis of 1,5-Benzothiazepine derivatives (1a–1f):

Compound 1a: FT-IR (KBr, V_{max}, cm^{-1}):3411 (O-H), 1653 (C=N), 1528 (C-N), 1502 (C=C), 697 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.21b[t, $J_{3b,3a}$= J_{3b},2=12.9 Hz, 1H, C_3-H-3b], 2.34 (3H, s, N-CH_3), 3.24 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.0 Hz, 1H, C_3-H-3a), 3.82(dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.21 (1H, s, Ar-H), 7.37 (3H, m, Ar-H), 7.11-7.88 (7H, m, Ar-H), 7.99 (1H, s, Ar-OH). ESI-MS (m/z): 335 $[M+H]^+$.

Compound 1b: FT-IR (KBr, V_{max}, cm^{-1}):1536 (C=N), 1515 (N=O), 1506 (C=C), 1380 (C-N), 1338 (N=O), 713 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.58 (3H, s, N-CH_3), 3.10 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.47 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.7 Hz, 1H, C_3-H-3a), 5.42 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.18 (1H, s, Ar-H), 7.25 (3H, m, Ar-H), 7.65-8.20 (7H, m, Ar-H). ESI-MS (m/z): 364 $[M+H]^+$.

Compound 1c: FT-IR (KBr, V_{max}, cm^{-1}):1592 (C=N), 1502 (C=C), 1370 (C-N), 1232 (O-CH_2), 689 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.46 (3H, s, N-CH_3), 3.14 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.25 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.1 Hz, 1H, C_3-H-3a), 4.13 (2H, s, -CH_2), 4.94 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 5.10 (2H, s, O-CH2), 7.15 (1H, s, -CH), 7.25-7.85 (11H, m, Ar-H). ESI-MS (m/z): 375 $[M+H]^+$.

Compound 1d: FT-IR (KBr, V_{max}, cm^{-1}):1603 (C=N), 1514 (C=C), 1377 (C-N), 689 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.43 (3H, s, N-CH_3), 3.38 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.42 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.6 Hz, 1H, C_3-H-3a), 4.83 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 6.78 (1H, d, J = 15.2 Hz, -CH),7.22 (1H, d, J = 15.2 Hz, -CH), 7.37 (4H, m, Ar-H), 7.69 (1H, d, J= 8Hz, Ar-H), 7.71-7.98 (6H,m, Ar-H), 8.05 (1H, d, J = 8 Hz, Ar-H). ESI-MS (m/z): 345 $[M+H]^+$.

Compound 1e: FT-IR (KBr, V_{max}, cm^{-1}):1599 (C=N), 1506 (C=C), 1382 (C-N), 698 (C-S).^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.07 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 2.40 (3H,s, N-CH_3), 3.37 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.6 Hz, 1H, C_3-H-3a), 4.38 (dd, $J_{2,3a}$ = 5.3 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 7.25 (2H, s, Ar-H), 7.30 (4H, m, Ar-H), 7.75-8.10 (5H, m, Ar-H). ESI-MS (m/z): 320 $[M+H]^+$.

Compound 1f: FT-IR (KBr, V_{max}, cm^{-1}):1592 (C=N), 1502 (C=C), 1370 (C-N), 2912 (Ar-CH), 689 (C-S). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.46 (3H, s, N-CH_3), 3.14 (t, $J_{3b,3a}$ = $J_{3b,2}$ = 12.9 Hz, 1H, C_3-H-3b), 3.25 (dd, $J_{3a,3b}$ = 14.4 Hz, $J_{3a,2}$ = 9.1 Hz, 1H, C_3-H-3a), 4.94 (dd, $J_{2,3a}$ = 5.1 Hz, $J_{2,3b}$ = 12 Hz, 1H, C_2-H), 6.10 (3H, m, Ar-H), 7.25 (2H, s, Ar-H), 7.40 (6H, m, Ar-H), 7.91-7.85 (5H, m, Ar-H). ESI-MS (m/z): 419 $[M+H]^+$.

Design of Experiments (DOE): Finally the optimization is done by DOE (Design of experiments) using Fusion pro software which is completely aligned with Quality by Design principles [**25**], the better reaction conditions were established to improve yields.

Table 1. Study variable settings

Name	Units	Range/Levels
Morpholine	(g)	0.90 <= Morpholine<=1.1
DMSO	(v)	4.0 <= DMSO<= 6.0
Temperature	(degrees)	30<= Temperature<= 45.0

Global ordering settings: Ordering strategy; Standard matrix array, Renumber rows, -.

Design wizard settings: Design type; 2-level-full factorial, Design model; Quadratic, Generate design option; New, Number of design runs; 11.

Replication/Degrees of Freedom settings: Number of center points; 3, Number of non-center points to be repeated; 0.

Replicate Group	Run No.
1	2
	8
	9

Table 2. Experimental Design matrix

Run No	Morpholine (eq.)	DMSO (v)	Temperature (degrees)
1	1.10	6.0	45.0
2	1.00	5.0	37.5
3	0.90	4.0	45.0
4	1.10	6.0	30.0
5	1.10	4.0	45.0
6	0.90	4.0	30.0
7	0.90	6.0	45.0
8	1.00	5.0	37.5
9	1.00	5.0	37.5
10	1.10	4.0	30.0
11	0.90	6.0	30.0

RESULTS AND DISCUSSION

1,5-Benzothiazepine derivatives (1a-1f) were synthesized by choosing DMF as solvent and screened with bases Triethylamine, Morpholine and Potassium carbonate and the corresponding yields were tabulated. These results show that by using Morpholine as base was advantageous than other bases employed in the study. So the same base Morpholine was selected for screening for different solvents (Table 3).

Table 3. Yield data with respect to base used

Compound	R	Solvent	Base	Yield (%)
1a	4-OHC_6H_4	DMF	Piperidine	75.0
			Triethylamine	80.0
			Morpholine	85.0
			Potassium carbonate	78.0
1b	4-$NO_2C_6H_4$	DMF	Piperidine	71.0
			Triethylamine	80.0
			Morpholine	83.0
			Potassium carbonate	72.0
1c	4-Allyl-OC_6H_4	DMF	Piperidine	66.0
			Triethylamine	75.0
			Morpholine	81.0
			Potassium carbonate	76.0
1d	Stren-yl	DMF	Piperidine	74.0
			Triethylamine	76.0
			Morpholine	83.0
			Potassium carbonate	78.0
1e	Pyridin-3-yl	DMF	Piperidine	73.0
			Triethylamine	74.0
			Morpholine	83.0
			Potassium carbonate	79.0
1f	Anthracen-9-yl	DMF	Piperidine	66.0
			Triethylamine	71.0
			Morpholine	81.0
			Potassium carbonate	77.0

1,5-Benzothiazepine derivatives (1a-1f) were synthesized by choosing Morpholine as base and screened for the solvents like DMSO, acetone and acetonitrile. The results show that the use of DMSO as solvent was advantageous than other solvents as described previously. Table 4 shows that the combination of DMSO, Morpholine resulted in better yield. So the combinations of these two were selected for Design of experiments (DOE).

Table 4. Yield data with respect to solvent used

Compound	R	Base used	Solvent	Yield (%)
1a	4-OHC_6H_4	Morpholine	DMF	85.0
			DMSO	91.0
			Acetone	72.0
			Acetonitrile	79.0
1b	4-$NO_2C_6H_4$	Morpholine	DMF	83.0
			DMSO	92.0
			Acetone	72.0
			Acetonitrile	76.0
1c	4-Allyl-OC_6H_4	Morpholine	DMF	81.0
			DMSO	93.0
			Acetone	77.0
			Acetonitrile	79.0
1d	Stren-yl	Morpholine	DMF	83.0
			DMSO	92.0
			Acetone	77.0
			Acetonitrile	79.0
1e	Pyridin-3-yl	Morpholine	DMF	83.0
			DMSO	91.0
			Acetone	79.0
			Acetonitrile	76.0
1f	Anthracen-9-yl	Morpholine	DMF	81.0
			DMSO	90.0
			Acetone	76.0
			Acetonitrile	80.0

Experiments were designed by taking equivalent amounts of Morpholine, Volumes of DMSO and temperature of reaction by 2 level-full factorial design. Table 5 shows that the DOE results of the experiments by using DMSO as solvent and Morpholine as base for preparing the compound 1c which is the better active substrate among all other synthesized compounds. The yield was better by performing the reaction with 1.1 equivalents of Morpholine, 6 volumes of DMSO and maintaining the reaction at 30°C temperature.

Table 5. DOE Results

Run No	Morpholine (eq.)	DMSO (v)	Temperature (degrees)	Yield (%)
1	1.10	6.0	45.0	91.0
2	1.00	5.0	37.5	90.0
3	0.90	4.0	45.0	89.0
4	1.10	6.0	30.0	95.0
5	1.10	4.0	45.0	93.0
6	0.90	4.0	30.0	88.0
7	0.90	6.0	45.0	87.0
8	1.00	5.0	37.5	92.0
9	1.00	5.0	37.5	93.0
10	1.10	4.0	30.0	84.0
11	0.90	6.0	30.0	88.0

APPLICATION

The 1,5-Benzothiazepines are of great interest due to their pharmacological properties. The synthesized compounds are active substrates against cytotoxicity and antimicrobial agents. The present work describes the optimization of active 1,5-Benzothiazepines derivatives by Design of Experiments (DOE) in order to get better conditions for the synthesis of these active substrates. This is a simple and convenient synthetic method which gives better yields of target molecule.

CONCLUSION

An efficient and simple method was developed for the preparation of 1,5-Benzothiazepine derivatives(1a-1f) by using Morpholine as base in presence of DMSO at 25-35°C which resulted better yields for desired compounds.

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