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Synthesis and pharmaceutical importance of 2-azetidinone derivatives of phenothiazine

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Abstract. A new series of *N*-[3-(10*H*-phenothiazin-1-yl)propyl]-4-(substituted phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide **4**(**a**–**m**) have been synthesized from phenothiazine in four steps. Phenothiazine on reaction with $Cl(CH_2)_3Br$ at room temperature gave 1-(3-chlorophenyl)-10*H*-phenothiazine, **1**. The compound **1** yielded the condensation product with urea at room temperature, *N*-[3-(10*H*-phenothiazin-1-yl)propyl]urea **2**. The compound **2** on further reaction with several substituted aromatic aldehydes produced *N*-[3-(10*H*-phenothiazin-1-yl)propyl]-*N*′-[(substituted phenyl)methylidene]-urea **3**(**a**–**m**). The compounds **3**(**a**–**m**) on treatment with $ClCH_2COCl$ in the presence of Et_3N furnished final products **4**(**a**–**m**). The structures of all the newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR and FAB-Mass spectra and chemical methods. All the final synthesized compounds were evaluated for their antibacterial, antifungal and antitubercular activities which displayed acceptable activities.

Keywords. Synthesis; 2-azetidinone; phenothiazine; antimicrobial.

1. Introduction

The β-lactam ring is the main feature of the most of the penicillins and other antibiotics. The β-lactam ring shows various biological activities such as antifungal,[1,2] antibacterial,[3,4] antitubercular,[5,6] anticonvulsant,[7] analgesic, anti-inflammatory,[8] synthetic precursor for amino acids,[9] antiviral,[10] CNS,[11] cholesterol absorption,[12] etc. Phenothiazine is also bioactive heterocyclic compound and having pharmaceutical importance possesses different biological activities viz. antibacterial,[13] antifungal,[2] antitubercular,[14] antischizophrenic,[15] anti-inflammatory,[16] etc. Phenothiazine derivatives are major content of several antipsychotic drugs. Chemically phenothiazine has two active sites at 2 and 10 positions. In the present study our research group reporting substitution at 10th position of phenothiazine and introducing phenothiazine and 2-azitidinone ring in a single frame work. Phenothiazine and 2-azitidinone ring together display important biological activities. The titled compounds were synthesized in four different steps according to scheme 1.

Phenothiazine on reaction with $Cl(CH_2)_3Br$ at room temperature gave 1-(3-chlorophenyl)-10*H*-phenothiazine, compound **1**. The compound **1** react with urea at room temperature to yield condensation product, *N*-[3-(10*H*-phenothiazin-1-yl)propyl]urea, compound **2**. The compound **2** on further reaction with several substituted aromatic aldehydes produced *N*-[3-(10*H*-phenothiazin-1-yl)propyl]-*N*′-[(substituted phenyl)methylidene]-urea, compounds **3**(**a**–**m**). The compounds **3**(**a**–**m**) on treatment with $ClCH_2COCl$ in the presence of Et_3N furnished final products, *N*-[3-(10*H*-phenothiazin-1-yl)propyl]-4-(substituted phenyl)-3-chloro-2-oxo-1-azetidinecarboxamide, compounds **4**(**a**–**m**). The structures of all the newly synthesized compounds were confirmed by IR, ^{1}H NMR, ^{13}C NMR, FAB-Mass and chemical methods. All the final synthesized compounds were evaluated for their antibacterial, antifungal and antitubercular activities which displayed acceptable activity.

2. Experimental

Melting points were taken in open capillaries and are uncorrected. Progress of reaction was monitored by silica gel-G coated TLC plates using MeOH:$CHCl_3$ system (1:9). The spot was visualized by exposing

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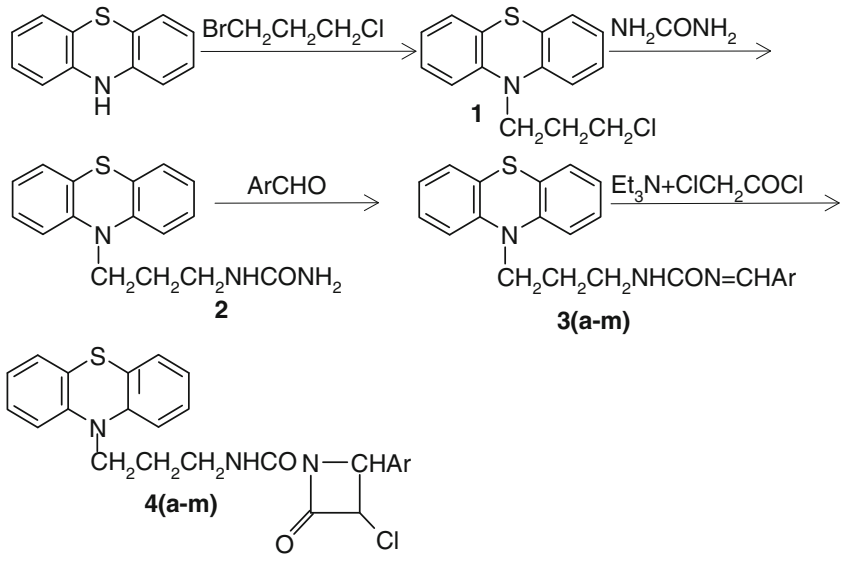


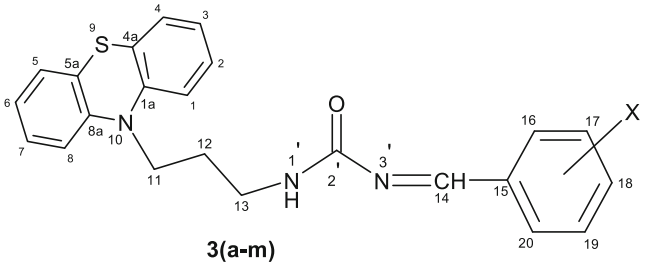
Scheme 1. Synthesis of compounds **1**, **2**, **3**(**a**–**m**) and **4**(**a**–**m**).

dry plate at iodine vapours chamber. IR spectra were recorded in KBr disc on a Schimadzu 8201 PC, FTIR spectrophotometer (ν_{max} in cm^{-1}) and ^1H NMR and ^{13}C NMR spectra were measured on a Brucker DRX-300 spectrometer in $CDCl_3$ at 300 and 75 MHz, respectively using TMS as an internal standard. All chemical shifts were reported on δ scale. The FAB-Mass spectra were recorded on a Jeol SX–102 mass spectrometer. Elemental analyses were performed on a Carlo Erba–1108 analyzer. The analytical data of all the compounds were highly satisfactory. For the column chromatographic purification of the products, Merck silica Gel 60 (230–400 Mesh) was used. The reagent grade chemicals were purchased from the commercial sources and further purified before use.

2.1 *Synthesis of 1-(3-chloropropyl)-10H-phenothiazinyl, compound **1**[17,18], synthesis of N-[3-(10H-phenothiazinyl)-propyl]- urea, compound **2**,[19] and synthesis of N-[3-(10H-phyenothiazinyl)-propyl]-N_{65}-[(phenyl)-methylidene] urea, compound **3a***

The compound **2** (7.77 g, 0.026 mol) and benzaldehyde (2.75 g, 0.026 mol) in ethanol (100 ml) in the presence of 2–4 drops glacial acetic acid were first stirred on a magnetic stirrer for about 2.00 h at room temperature followed by reflux on a steam bath for about 3.30 h. The completion of the reaction was monitored by silica gel-G coated TLC plates. The product was filtered, cooled and purified over a silica gel packed column chromatography using CH_3OH: $CHCl_3$ (7:3 v/v) system as eluant (90 ml). The purified product was dried under vacuo and recrystallized from acetone at room temperature to furnish compound **3a**.

Compounds **3(b–m)** have also been synthesized by using similar method as above.



2.2 *Synthesis of N-[3-(10H-phenothiazinyl)-propyl]-4-(phenyl)-3-chloro-2-oxo-1-azetidine-carboxamide, compounds 4a*[20,21]

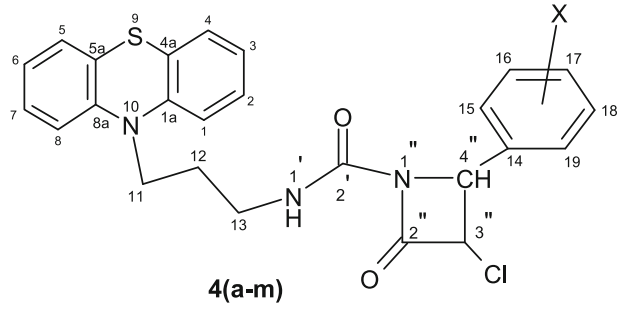
The compound **3a** (2.70 g, 0.007 mol), chloroacetyl chloride (0.791 g, 0.007 mol) and Et_3N (0.707 g, 0.007 mol) in methanol (50 ml) were first stirred on a magnetic stirrer for about 2.00 h at room temperature followed by reflux on a steam bath for about 4.00 h. The completion of the reaction was monitored by silica gel-G coated TLC plates. The product was filtered, cooled and purified over a silica gel packed column chromatography using CH_3OH: $CHCl_3$ (7:3 v/v) system as eluant (70 ml). The purified product was dried under vacuo and recrystallized from ethanol at room temperature to furnish compound **4a**.

Table 1. Antibacterial and antifungal activities of compounds **4**(**a**–**m**). Minimum Inhibition Concentration (MIC) given in μg/mL.

	Antibacterial activity				Antifungal activity			
Comp.	*B. subtilis*	*E. coli*	*S. aureus*	*K. pneumoniae*	*A. niger*	*A. flavus*	*F. oxisporium*	*C. albicans*
4a	12.5	9.25	12.5	6.25	27.25	27.75	28.25	29.75
4b	3.50	6.25	3.25	3.50	12.25	13.25	25.75	12.25
4c	6.25	3.50	6.25	3.25	13.50	25.00	15.50	19.50
4d	3.75	3.75	3.25	6.25	12.75	25.50	12.75	13.25
4e	6.25	3.50	3.25	3.75	132.5	15.00	12.50	15.75
4f	3.50	3.25	6.25	3.50	12.75	13.50	12.75	13.50
4g	5.75	6.25	7.25	6.25	15.25	17.50	16.75	18.25
4h	3.25	3.75	3.25	3.25	13.25	12.50	13.50	15.50
4i	3.25	3.25	3.75	3.25	12.50	13.50	12.25	14.50
4j	3.25	3.75	3.25	3.25	12.25	13.25	12.75	13.75
4k	12.75	8.25	13.50	8.25	25.75	27.25	26.25	28.75
4l	25.00	25.00	19.50	18.50	29.25	50.00	50.00	31.25
4m	7.25	4.25	6.25	10.25	18.25	20.50	12.50	14.50

The MIC values of standard streptomycin for all bacterial strain and griseofulvin for all fungi strain were in the range of 1.25–3.25 and 6.25–12.5 μg/ml, respectively

Compounds **4**(**b**–**m**) have also been synthesized by using similar method as above.



4(a-m)

Spectral and physical data of compounds **3**(**a**–**m**) and **4**(**a**–**m**) are submitted as supplementary data.

2.3 *Biological study*

2.3a *Antibacterial, antifungal and antitubercular activities*: The antibacterial, antifungal and antitubercular activity of compound **4**(**a**–**m**) has been assayed *in vitro* against selected bacteria, *B. subtilis, E. coli, S. aureus, K. pneumoniae* and fungi *A. niger, A. flavus, F. oxisporium, C. albicans* and *M. tuberculosis* (H37Rv strain), respectively. The MIC of compounds **4**(**a**–**m**) were determined using filter paper disc diffusion method (antibacterial and antifungal activity) and L.J. medium (Conventional) method (antitubercular activity). Streptomycin and Griseofulvin used as standard for antibacterial and antifungal activity, respectively and for antitubercular activity, Isoniazid and Rifampicin taken as standards. Concentration of the compounds was given in μg/mL. Results of all given activities of above compounds were given in tables 1 and 2.

3. Results and discussion

N-[3-(10*H*-phenothiazinyl)-propyl]-2-(substituted phenyl)-3-chloro-4-oxo-1-azetidine-carboxamide, compounds **4**(**a**–**m**) were synthesized in four different steps. Phenothiazine on reaction with $Cl(CH_2)_3Br$ at room temperature afforded 1-(3-chlorophenyl)-10*H*-phenothiazine, compound **1**. IR spectrum of compound **1** displayed

Table 2. Antitubercular activity of compounds **4**(**a**–**m**). MIC given in μg/mL.

Compound	Concentration	Compound	Concentration	Compound	Concentration
4a	13.50	**4f**	2.50	**4k**	12.75
4b	2.75	**4g**	6.25	**4l**	13.75
4c	3.25	**4h**	2.50	**4m**	6.25
4d	2.50	**4i**	2.50	–	–
4e	2.75	**4j**	2.75	–	–

Isoniazid and Rifampicin were used as standards, MIC values in the range of 1.25–2.50 μg/ml for *M. tuberculosis* (h37rv strain)

absorption at 1320 and 744 for (C-N) and (C-Cl), respectively, this clearly indicated the disappearance of NH absorption (3465) of Phenothiazine. The compound **1** on reaction with urea at room temperature yielded *N*-[3-(10*H*-phenothiazin-1-yl)propyl]urea, compound **2**. IR spectrum of compound **2** showed absorption for NH and NH_2 at 3290 and 3413 cm^{-1}, respectively, while absorption for (C-Cl) has been disappeared in IR spectrum of compound **1**. The ^1H NMR spectrum of **2** displayed a signal at δ 5.64 and 5.86 ppm for NH and NH_2, respectively. The compound **2** on further reaction with selected several substituted aromatic aldehydes produced *N*-[3-(10*H*-phenothiazin-1-yl)propyl]-*N′*-[(substituted phenyl) methylidene]-urea, compounds **3**(**a**–**m**). The characteristic absorption for Schiff base in IR spectra of compounds **3**(**a**–**m**) appeared in the range of 1539–1560 cm^{-1} and in the ^1H and ^{13}C NMR spectra, signal appeared at δ 7.85–8.05 and δ 152.1–157.6 ppm, respectively. In the ^1H NMR spectrum of compound **2** a broad signal of NH_2 has been disappeared. The compounds **3**(**a**–**m**) on treatment with $ClCH_2COCl$ in the presence of Et_3N furnished final products compounds **4**(**a**–**m**). In the IR spectra of compounds **4**(**a**–**m**) carbonyl group of β-lactam ring showed characteristic absorption in the range of 1725–1746 cm^{-1} and ^1H NMR spectra of compounds **4**(**a**–**m**) showed two doublet for (N-CH) and (CH-Cl) in the range δ 5.09–5.23 and 4.40–4.61 ppm, respectively. In ^{13}C NMR spectra of compounds **4**(**a**–**m**) three characteristic signals appeared for (N-CH), (CH-Cl) and (CO cyclic) in the range of (δ) 60.2–65.7, 51.6–56.7 and 165.7–170.7 ppm, respectively. The IR absorption, ^1H and ^{13}C NMR signals of N=CH have been disappeared. The compounds **4**(**a**–**m**) shows stereoisomerism, spectral data as well as literature support the synthesis of diastereomer of azetidine in good yield.[22] These all fact collectively suggested for the synthesis of all above compounds. Spectral and physical data of compounds **3**(**a**–**m**) and **4**(**a**–**m**) are given as supplementary data (table S1).

The results of the all described activities (antibacterial, antifungal and antitubercular) were summarized in tables 1 and 2. The results of the antimicrobial screening data revealed that all the compound **4**(**a**–**m**) showed considerable and varied activity against the selected microorganism. A new series of *N*-[3-(10*H*-phenothiazinyl)-propyl]-2-(substituted phenyl)-3-chloro-4-oxo-1-azetidine-carboxamide, compound **4**(**a**–**m**) were prepared and screened for their antimicrobial and antitubercular activities data (as shown in tables 1 and 2) revealed that all the synthesized compound **4**(**a**–**m**) have a structure activity relationship (SAR) because activity of compounds varies with substitution. Nitro group containing compounds (**4h**, **4i** and **4j**) showed higher activity than chloro (**4c**, **4d**), or bromo group containing compounds (**4e**, **4f**). Chloro and bromo derivatives also have higher activity than other rested compounds. On the basis of SAR, concluded that the activity of compounds depends on electron withdrawing nature of the substituted groups. The sequence of the activity is following

$$NO_2 > Cl > Br > OH > OCH_3 > H > CH_3.$$

The investigation of antimicrobial (antibacterial, antifungal and antitubercular) data revealed that the compounds (**4c**), (**4d**), (**4e**), (**4f**), (**4h**), (**4i**) and (**4j**) displayed high activity in the series, the compounds (**4b**), (**4g**) and (**4m**) showed moderate activity and rested compounds showed less activity against all the strains compared with standard drugs.

4. Conclusions

In conclusion, a new series of compound **4**(**a**–**m**) were synthesized, Synthesized compounds screened for their biological study. The investigation of antimicrobial (antibacterial, antifungal and antitubercular) activities data revealed that the compounds **(4b), (4d), (4e), (4f), (4h), (4i)** and **(4j)** displayed excellent activity, the compounds **(4c), (4g)** and **(4m)** showed moderate activity and rested compounds showed less activity compared with standard drugs.

Supplementary information

Table S1 as supplementary information can be seen in www.ias.ac.in/chemsci.

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References

1. Shukla D K and Srivastava S D 2008 *Indian J. Chem.* **47B** 463

2. Rawat T R and Srivastava S D 1998 *Indian J. Chem*. **37B** 91
3. Nema A and Srivastava S K 2007 *J. Indian Chem. Soc*. **84** 1037
4. Mulwad V V and Mir A A 2008 *J. Korean Chem. Soc*. **52(6)** 649
5. Parikh A K, Oza P S and Bhatt S B 2005 *Indian J. Chem*. **44B** 585
6. Patel R B, Desai P S and Chikhalia K H 2006 *Indian J. Chem*. **45B** 773
7. Srivastava S K, Srivastava S and Srivastava S D 2000 *Indian J. Chem*. **38B** 464
8. Srivastava S K, Srivastava S L and Srivastava S D 1999 *Indian J. Chem*. **39B** 183
9. Alonsodel E, Pozo C and Gonzalez J 2002 *Synlett* **1** 69
10. Skiles J W and McNeil D 1990 *Tetrahedron Lett*. **31** 7277
11. Vashi B S, Mehta D S and Shah V H 1995 *Indian J. Chem*. **34B** 802
12. Wu G and Tormos W 1997 *J. Org. Chem*. **62** 6412
13. Srivastava S D and Kohli P 2007 *Proc. Natl. Acad. Sci. India* **77** 199
14. Trivedi A R, Siddiqui A B and Shah V H 2008 *Arkivoc* **2** 210
15. Fang W and Jie T 2003 *Acta Pharm. Sin*. **24(10)** 1001
16. Rajasekaran A and Tripathi P P 2003 *Acta pharm. Turc*. **45** 235
17. Sarmiento G P, Vitale R G, Afeltra J, Moltrasio G Y and Moglioni A G 2010 *Eur. J. Med. Chem*. **46** 101
18. Komine Y, Ueda I, Goto T and Fujihara H 2006 *Chem. Commun*. **42(3)** 302
19. Cerbai G and Di Paco G F 1963 *Boll. Chim. Farmac*. **102** 709
20. Samadhiya P S, Sharma R, Srivastava S K and Srivastava S D 2011 *J. Chem. Sci*. **123(5)** 631
21. Sharma R, Samadhiya P S, Srivastava S D and Srivastava S K 2011 *Acta Chim. Slov*. **58** 110
22. Upadhyay A, Srivastava S K and Srivastava S D 2011 *Synth. Commun*. **41** 2544