Heterocyclic Letters
Vol. 12| No.3|507-514|May-July|2022
ISSN: (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

SYNTHESIS OF 3-CHLORO-8-(2-(1,3-DIOXOISOINDOLIN-2-YLOXY)ETHYL-1-PHENYL-5-THIA-1,8-DIAZASPIRO[3.4]OCTANE-2,7-DIONES AND THEIR PHARMACOLOGICAL SCREENING

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Abstract. In the present study, substituted anilines were converted to 2-chloro-N-phenyl acetamide **(1a-c)** by the reaction with chloroacetyl chloride. These were treated with ammonium thiocyanate to get corresponding thiazolidinones **(2a-c)** which were further reacted with chloroacetyl chloride in presence of base (TEA) in dioxane media to obtain 3-chloro-1-phenyl-5-thia-1,8diazaspiro[3,4]octane-2,7-dione **(3a-c)**. Reaction of **(3a-c)** with bromoethoxyphthalimide afforded the final spiro compounds **(4a-c)**. Structures of synthesized compounds were confirmed by the spectral studies (IR, ^{1}H-NMR and mass spectrometry), elemental analysis and chemical tests. Subsequently, compounds were subjected to their *in-vitro* antimicrobial activity against a panel of pathogenic strains of bacteria and fungi.

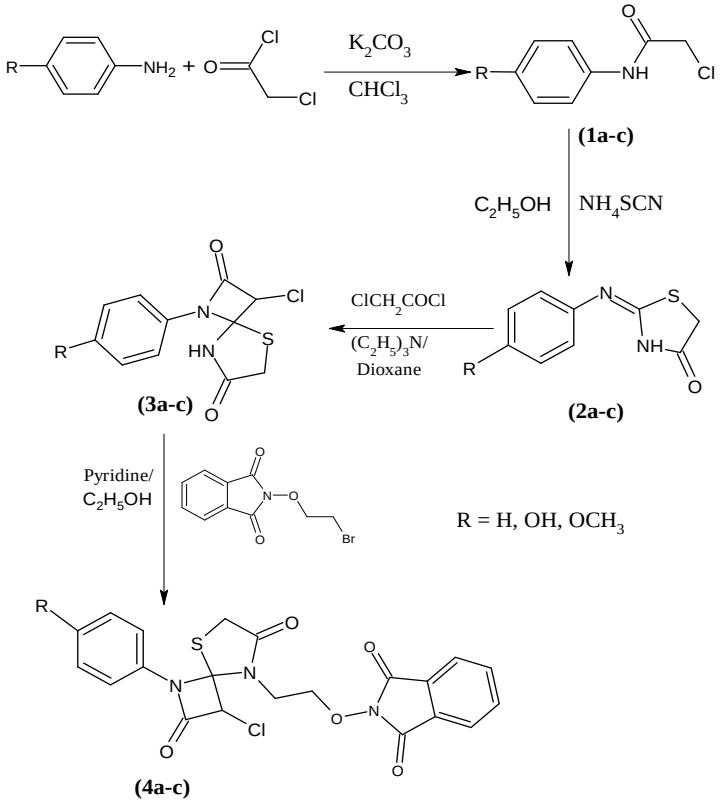
Keywords: Thiazolidinone, Azitidinone, Spiro-compounds, Anti-microbial activity

Introduction

Heterocyclic motifs bearing nitrogen, sulphur and thiazolidinone moieties constitute the core structure of a number of biologically interesting compounds. Spiro-compounds form a group of generally less investigated compounds. Spiro compounds having heterocyclic structures fused at a central carbon are of recent interest due to their interesting features and their structural implications on biological systems [1]. Many spiro-compounds possess very promising biological activities as anticancer agents [2, 3], antibacterial agents [4, 5], anticonvulsant agents [6, 7 8], anti-tuberculosis agents [9], anti-Alzheimer's agents [10], pain-relief agents [11,12], anti-dermatitis agents [13] and antimicrobial agents [14,15]. In addition to their medical uses, some spiro-compounds have found other uses in the agricultural and industrial fields. Spiro compounds have also been recently used as antioxidants [16,17]. Various combinations of heterocyclic rings attached to alkoxyphthalimide group have been synthesized and tested for different biological activities [18-22]. From all the above findings and in continuation of our interest in the synthesis of novel ethoxyphthalimide-linked spiro heterocyclic framework starting from 2-chloro-N-phenyl acetamide, our plan was to design and

synthesize a new class of heterocyclic spiro hybrid in which all of the above moieties are present with the hope to achieve enhanced biological activities.

Reaction Scheme



Synthesis of ethoxyphthalimide-linked spiro heterocycles

Results and Discussion

Bromoethoxyphthalimide was prepared by reported method [23]. Compounds **(2a-c)** have been prepared by cyclization of **(1a-c)** with ammonium thiocynate. An intense band at 1612 (C=N), 695 (C-S-C linkage) cm^{-1} in IR and singlet at δ = 4.58 (S-CH_2) in ^{1}H-NMR confirmed the formation of the compound **(2a)**. Treatment of compounds **(2a-c)** with triethylammine and chloroacetyl chloride in dioxane media furnished **(3a-c)**. Structure of **(3a)** was confirmed on the basis of 752 cm^{-1} (C-Cl str.) band in IR spectrum. Compounds **(3a-c)** were converted to corresponding ethoxyphthalimide derivatives **(4a-c)** by the reaction with bromoethoxyphthalimide. Structure of these was confirmed by spectral data. IR and ^{1}H-NMR spectra revealed absorption band at 1359 of N-O group, C-O str. band at 1173 cm^{-1} and two triplets respectively at δ = 4.10 and 4.41 for N-CH_2 and O-CH_2 group of ethoxyphthalimde moiety in **(4a)**. Additional confirmation of ethoxyphthalimide group attachment was done by usual fluorescence test. All these reactions have been shown in Reaction Scheme.

Experimental Section

General. All the melting points were determined by electro thermal method in open capillary tubes and are therefore uncorrected. The IR spectra of the compounds were recorded on a 4000-450 cm^{-1} ranges using KBr discs on FTIR IR RX1Perkin Elmer spectrophotometer and ^{1}H-NMR spectra were recorded on a Bruker DRX-200 MHz spectrometer in ($CDCl_3$) solvent using TMS as an internal standard. The mass spectra were recorded on a Jeol SX-102 (FAB) mass spectrometer. Purity of the synthesized

compounds was checked on silica gel G TLC plates of 2 mm thickness using suitable solvent. The visualization of spot was carried out in UV chamber. Structures of all the synthesized compounds were assigned on basis of their chemical tests as well as analytical and spectral data. The observed physical properties are presented in Table 1.

Synthesis of 2-chloro-N-phenyl acetamide(1a) **[24]**

A solution of the appropriate amines (10 mmol) and chloroacetyl chloride (1.12 g, 10 mmol) in chloroform (50 mL) was refluxed in the presence of K_2CO_3 (15 mmol) for about 10 hrs. Then the solution was concentrated and the residue was stirred with water (100 mL) and filtered. The solid product is then washed with 5% $NaHCO_3$ solution and subsequently with water. The crude product is dried and crystallized from appropriate solvent to furnish pure solid product. Similarly, all the compounds **(2b-c)** were synthesized by the above method with minor change in reaction conditions.

Synthesis of 2(phenylimino)-1,3-thiazolidin-4-one(2a)

A solution of **1a** (10mmol) and ammonium thiocyanate (15mmol) in absolute alcohol (30 mL) was refluxed for 4 hrs and allowed to stand overnight. The formed precipitated was filtered off, washed with water and then recrystallized from the ethanol solvent. Similarly, all the compounds **(2b-c)** were synthesized by the above method with minor change in reaction conditions.

Synthesis of 3-chloro-1-phenyl-5-thia-1,8diazaspiro[3.4]octane-2,7-dione(3a)

A mixture of compound **2a** (1 mmol) and chloroacetyl chloride (1 mmol) in dioxane and triethylamine were stirred at 0–5^{0}C for 3 hrs. The solvent was evaporated under reduced pressure and the residue was recrystallized from ethanol.Similarly, all the compounds **(3 b-c)** were synthesized by the above method with minor change in reaction conditions.

Synthesis of 3-chloro-8-(2-(1,3-dioxoisoindolin-2-yloxy)ethyl-1-phenyl-5-thia-1,8-diazaspiro[3.4]octane-2,7-dione (4a)

A mixture of **3a** (0.01mol) and bromoethoxyphthalimide (0.01 mol) in absolute ethanol (15 mL) was refluxed for 16-20 hrs using Pyridine (0.02 mol) as a base. It was concentrated by removing the solvent under reduced pressure and the resultant filtrate was poured into crushed ice to obtain solid product. Similarly, all the compounds **(4b-c)** were synthesized by the above method with minor change in reaction conditions. The spectral data are mentioned in Table 2 & 3.

Table 1: Physical and analytical data of synthesized compounds

Compd. No.	Mol. Formula	Mol. Weight	R	m.p. (ºC)	Yield (%)	Found (Calcd.)%N
1a	C_8H_8ClNO	169	H	120-122	94	7.98(8.26)
1b	$C_8H_8ClNO_2$	185	OH	127-129	86	7.32(7.55)
1c	$C_9H_{10}ClNO_2$	199	OCH_3	131-134	89	6.67(7.02)
2a	$C_9H_8N_2OS$	192	H	180-183	64	12.69(14.57)
2b	$C_9H_8N_2O_2S$	208	OH	186-189	71	12.18(13.45)
2c	$C_{10}H_{10}N_2O_2S$	222	OCH_3	178-181	68	10.79(12.60)
3a	$C_{11}H_9ClN_2O_2S$	268	H	90-95	91	9.27(10.42)
3b	$C_{11}H_9ClN_2O_3S$	284	OH	86-88	83	8.21(9.84)
3c	$C_{12}H_{11}ClN_2O_3S$	298	OCH_3	81-84	76	8.32(9.38)
4a	$C_{21}H_{16}ClN_3O_5S$	457	H	130-135	58	5.90(6.13)
4b	$C_{21}H_{16}ClN_3O_6S$	473	OH	128-132	62	5.01(5.92)
4c	$C_{22}H_{18}ClN_3O_6S$	487	OCH_3	122-125	53	4.24(5.75)

Table 2: IR and ^{1}H-NMR Spectral data of compounds (2a-c), (3a-c)

Compd. No.	IR (cm^{-1})	^{1}H-NMR (δ)
2a	3129 (Ar C-H str.),1612 (C=N str.), 1678 (-C=O str.), 3428 (N-H str.), 695 (C-S-C str.)	7.22-6.89 (m, 5H, Ar-H), 8.32 (s, 1H, -NH), 4.58 (s, 2H, $-CH_2$)
2b	3064 (Ar C-H str.),1537 (C=N str.), 1657 (-C=O str.), 3378 (N-H str.), 631 (C-S-C str.),1143 (C-O str.)	7.01-6.37 (m, 4H, Ar-H), 8.25 (s, 1H, -NH), 4.29 (s, 2H, $-CH_2$)5.76 (s, 1H, -OH)
2c	3023 (Ar C-H str.),1518 (C=N str.), 1639 (-C=O str.), 3347 (N-H str.), 616 (C-S-C str.),1121 (C-O str.)	7.09-6.57 (m, 4H, Ar-H), 8.03 (s, 1H, -NH), 4.10 (s, 2H, $-CH_2$), 3.97 (s, 3H, $-OCH_3$)
3a	3047 (Ar C-H str.),1247 (C-N str.), 1719 (-C=O str.), 752 (C-Cl)	7.19-7.89 (m, 5H, Ar-H), 8.76 (s, 1H, -NH), 4.49 (s, 2H, $-CH_2$)
3b	3028 (Ar C-H str.),1226 (C-N str.), 1708 (-C=O str.), 724 (C-Cl), 1176 (C-O str.)	6.89-7.37 (m, 4H, Ar-H), 8.42 (s, 1H, -NH), 4.26 (s, 2H, $-CH_2$), 5.27 (s, 1H, -OH)
3c	3015 (Ar C-H str.), 1215 (C-N str.), 1695(-C=O str.), 713 (C-Cl), 1151 (C-O str.)	7.05-7.67 (m, 4H, Ar-H), 8.19 (s, 1H, -NH), 4.03 (s, 2H, $-CH_2$), 3.68 (s, 3H, $-OCH_3$)

Table 3:IR, ^{1}H-NMR and Mass Spectral data of compounds (4a-c)

Compd. No.	IR (cm^{-1})	^{1}H-NMR (δ)	Mass (m/z)
4a	3165 (Ar C-H str.), 1236 (C-N Str.), 695 (C-S-C str.), 1173 (C-O str.), 1359 (N-O str.), 764 (C-Cl str.)	6.60-7.82 (m, 9H, Ar-H), 5.13 (t, 2H, $-OCH_2$), 4.41 (s, 2H, $-CH_2$), 4.10 (t, 2H, N-CH_2),	457[M] +· 459[M+2]+· 421[M-Cl]+· 379[M-C_6H_6]+· 310[M-$C_8H_5NO_2$]+· 294[M-$C_8H_5NO_3$]+· 266[M-$C_{10}H_9NO_3$]+· 192[M-$C_{12}H_{11}NO_4S$]+· 177[M-$C_{12}H_9N_2O_2SCl$]+· 147[M-$C_{13}H_{11}N_2O_3SCl$]+·
4b	3116 (Ar C-H str.), 1219 (C-N Str.), 647 (C-S-C str.), 1154 (C-O str.), 1328 (N-O str.), 720 (C-Cl str.)	7.06-6.98 (m, 8H, Ar-H), 5.03 (t, 2H, $-OCH_2$), 4.21 (s, 2H, $-CH_2$), 4.01 (t, 2H, N-CH_2), 5.64 (s, 1H, -OH)	473[M]+· 475[M+2]+· 379[M-C_6H_6O]+· 326[M-$C_8H_5NO_2$]+· 310[M-$C_8H_5NO_3$]+· 296[M-$C_9H_7NO_3$]+·

			282[M-$C_{10}H_9NO_3$]+· 208[M-$C_{12}H_{11}NO_4S$]+· 163[M-$C_{13}H_{11}N_2O_3SCl$]+· 94[M-$C_{15}H_{10}N_3O_5SCl$]+·
4c	3068 (Ar C-H str.), 1201 (C-N Str.), 611 (C-S-C str.), 1123 (C-O str.), 1310 (N-O str.), 705 (C-Cl str.)	7.27-8.02 (m, 8H, Ar-H), 5.13 (t, 2H, -OCH_2), 4.41 (s, 2H, -CH_2), 3.97 (t, 2H, N-CH_2), 3.73 (s, 3H, -OCH_3)	487[M] +· 489[M+2] +· 451[M-Cl]+· 340[M-$C_8H_5NO_2$]+· 310[M-$C_9H_7NO_3$]+· 296[M-$C_{10}H_9NO_3$]+· 222[M-$C_{12}H_{11}NO_4S$]+· 191[M-$C_{12}H_9N_2O_3SCl$]+· 163[M-$C_{14}H_{13}N_2O_3SCl$]+· 108[M-$C_{15}H_{10}N_3O_5SCl$]+·

PHARMACOLOGICAL SCREENING [25-27]

MATERIAL AND METHODS

Selection of bacterial strains for present investigation:

Pathogenic bacteria used for antibacterial activity were subculture and characterized by standard methods of identification. Following strains of various bacteria were used for antibacterial screening:

(i) ***Escherichia coli*** (Gram -ve): Causes cholecystitis, urinary tract infections, bacteremia, gastroenteritis, pneumonia, gastroenteritis and neonatal meningitis

(ii) ***Straphylococcus aureus*** (Gram +ve): Causes skin infections such as abscesses, respiratory infections such as sinusitis, food poisoning.

(iii) ***Streptococcus pyogenes*** (Gram +ve): Causes pharyngitis (strep throat) and localized skin infection (impetigo) *etc*.

(iv) ***Pseudomonas aeruginosa*** (Gram -ve): Causes infections in the pulmonary tract, urinary tract, burns, wounds, and also causes other blood infections.

Cefixime was used as a standard drug for the present study.

Growth Medium:

Nutrient agar medium was used for culture of the bacteria. The composition of nutrient agar medium is as follows:

i)	Beef extract	:	3 gm.
ii)	Peptone	:	5 gm.
iii)	Sodium chloride	:	5 gm.
iv)	Agar agar	:	15 gm.
v)	Distilled water	:	1000 mL.

For the present investigation Disc diffusion method was used.

Disc diffusion method: The bacterial microorganisms were cultured on nutrient agar/YEPD (yeast extract peptone dextrose) by using spread plate technique. The bacterial strains were grown in Mueller-Hinton agar (MHA) plates at 37°C (the bacteria were grown in the nutrient broth at 37°C and maintained on nutrient agar slants at 4°C). Each sample were dissolved in dimethyl sulfoxide, sterilized by filtration using sintered glass filter, and stored at 4°C. The dilutions of sample and standard drugs (50µg/mL) were prepared in double-distilled water using nutrient agar tubes. Mueller-Hinton sterile agar plates were seeded with indicator bacterial strains (10^8 cfu) and allowed to stay at 37°C for 3 hours. Control experiments were carried out under similar condition by using a standard drug. The zones of growth inhibition around the disks were measured after 18 to 24 hours of incubation at 37°C. The measurement

obtained has compared with standard to determine activity index and to predict whether the bacterial species tested is resistant or sensitive to the antibiotic. The results of this investigation are presented in Table 4. Results of antibacterial activity are presented on the basis of zone of inhibition and activity index (Table 5.1). Out of screened compounds **4a, 4b** and **2.b** have shown strong activity against all bacterial strains. Compound **2c** and **4c** have shown remarkable activity against *E. coli*. Compound **3c** is found to show considerable activity against *pseudomonas pyogenes*. All the rest compounds have shown good to moderate activity against all bacterial strains.

Table 4: ***Antibacterial activity of Compounds zone of inhibition in mm (Activity Index)***

Compd No.	**Code**	***Staphylococcus aureus***	***Streptococcus pyogenes***	***Escherichia coli***	***Pseudomonas aeruginosa***
2a	1	15(0.71)	16(0.69)	18(0.72)	16(0.66)
2b	2	17(0.80)	18(0.78)	20(0.80)	21(0.87)
2c	3	13(0.61)	15(0.65)	21(0.84)	13(0.54)
3a	4	16(0.76)	17(0.73)	19(0.76)	17(0.70)
3b	5	19(0.90)	20(0.86)	22(0.88)	20(0.83)
3c	6	17(0.80)	19(0.82)	17(0.68)	15(0.62)
4a	7	19(0.90)	21(0.91)	23(0.92)	22(0.91)
4b	8	17(0.80)	19(0.82)	21(0.84)	18(0.75)
4c	9	16(0.76)	15(0.65)	20(0.80)	17(0.70)
Cefixime	**C_1**	21	23	25	24

Activity index = Inhibition area of the sample / inhibition area of the standard.

ANTIFUNGAL ACTIVITY

MATERIAL AND METHOD

Selection of fungal strains for investigation:

Pathogenic fungi were sub cultured on potato dextrose agar (PDA) and characterized by standard methods of identification. Following strains of various fungai were used for antifungal screening:

(i) ***Candida albicans***: Causal agent of opportunistic oral andgenital infections in humans and candidal onychomycosis, an infection of the nail plate.

(ii) ***Aspergillus clavatus***: Toxin patulin.

Griseofulvin was used as a standard drug for present study.

Growth Medium:

Potato agar medium was used for culture of the fungi. The composition is as follows:

i) Dextrose : 20 gm.
ii) Potatoes : 200 gm.
iv) Agar powder : 20 gm.
v) Distilled water : 1000 mL.

Disc diffusion method: Each sample were dissolved in dimethyl sulfoxide, sterilized by filtration using sintered glass filter, and stored at 4°C. For the determination of zone of inhibition, fungal strains were taken as *Candida albicans*, and *Aspergillus clavatus*. The

dilutions of sample and standard drug (50μg/mL) were prepared in double-distilled water using nutrient agar tubes. Mueller-Hinton sterile agar plates were seeded with indicator bacterial strains (10^8 cfu) and allowed to stay at 37°C for 3 hours. Control experiments were carried out under similar condition by using a griseofulvin as standard drug. The zones of growth inhibition around the disks were measured after 48 to 96 hrs incubation at 28°C. The measurement obtained has compared with standard to determine activity index and to predict wheather the fungal species tested is resistant or sensitive to the antibiotic. The results of this investigation are presented in Table 5. Out of synthesized compounds nine compounds are evaluated for antifungal activity against two fungal strains. Compound **2b, 3a** and **4c** showed good activity against *Candida albicans* and *Aspergillus clavatus* respectively. Compound **3b** and **4a** has been shown strong activity against both fungal strains. Compound **4b** having azitidinone nucleus attached to thiazolidinone, ethoxyphthalimide functionality are found to show considerable activity against both fungal strains. Rest of the compounds possesses good to moderate activity against both fungal strains.

Table 5: Antifungal Activity of compound Zone of inhibition in mm (Activity Index)

Compd No.	**Code**	***Candida albicans***	***Aspergillus clavatus***
2a	1	14 (0.63)	17(0.60)
2b	2	17 (0.77)	20 (0.71)
2c	3	12(0.54)	15(0.53)
3a	4	16(0.72)	19 (0.67)
3b	5	18(0.81)	23(0.82)
3c	6	13(0.59)	17 (0.60)
4a	7	20(0.90)	26(0.92)
4b	8	18(0.81)	23(0.82)
4c	9	15(0.68)	22(0.78)
Amphotericin	C_2	22	28

Activity index = Inhibition area of the sample / inhibition area of the standard.

Conclusion

In this paper, a series of ethoxyphthalimide-plugged spiro-heterocycles were synthesized and characterized by IR, ^{1}H-NMR, mass, and analytical studies. The compounds were evaluated for its antibacterial and antifungal activity against a panel of pathogenic strains of bacteria and fungi. Some of the spiro-heterocycles were found to be equipotent or more potent than the standard drugs.

Acknowledgments

The authors are thankful to the Head, Department of Chemistry, MLSU, Udaipur (Rajasthan) for providing laboratory facilities. I thankful to B. N Pharmacy college, Udaipur for pharmacological screening of compounds. I also thankful to chemistry staff members of the Shree KV Parekh College, Mahuva and MUIS, Ganpat University, Gujarat for their kind support.

References

I. D. Bhambi, C. Sharma, S. Sharma, V. K. Salvi, G.L. Talesara, *IJCB,* 48B, **2009**, 1006-1012.

II. W. C. Young, S. Angela, N. S. Bao M. Qiuwen, B. C. Hee, R. Soedarsono, K. Leonardus, R. Agus, F. Norman, S. Steven, K. Douglas, *J. Nat. Prod.* **2008**, *3*, 390–395.

III. L. W. Wen, J. Z. Tian, W. T. Hong, Y. L. Zhen, C. F. Yu, Q. G. Qian, M. Z. Wei, *Chem. Biodivers.* **2007**, *4*, 2913–2919.

IV. V. D. Sar, J. Blunt, M. Munro, *Org. Lett.* **2006**, *8*, 2059–2069.

V. B. P. Hyeong, H. J. Nam, H. H. Joon, H. C. Jung, H. C. Jung; H. Y. Kyung, H. O. Chang, *Arch. Pharm.* **2007**, *340*, 530–537.

VI. O. Jolanta, K. Krzysztof, *Acta Pol. Pharm.* **2006**, *63*, 101–108.

VII. K. Krzysztof, O. Jolanta, D. Malgorzata, *Eur. J. Med. Chem.* **2008**, *43*, 53–61.

VIII. O. Jolanta, K. Krzysztof, T. Ewa, *Pharmacol. Rep.* **2006**, *58*, 207–214.

IX. M. S. Chande, R. S. Verma, P.A. Barve, R. R. Khanwelkar, R.B. Vaidya, K. B. Ajaikumar, *Eur. J. Med. Chem.* **2005**, *40*, 1143–1148.

X. F. Masakazu, H. Kenji, K. Jiro, *Int. Pat.* WO/2001/066546 (App. PCT/JP2001/001793), **2001**.

XI. R. Frank, M. Reich, R. Jostock, G. Bahrenberg, H. Schick, B. Henkel, H. Sonnenschein, *US Pat.* 20080269271 (App. USPTO: 514278), **2008**.

XII. S. Hans, F. Robert, M. Reich, O. Ruth, B. Gregor, T. Fritz, B. Henkel, *Int. Pat.* WO/2006/122769 (App. No.: PCT/EP2006/004651), **2006**.

XIII. K. Nakao, K. Ikeda, T. Kurokawa, Y. Togashi, H. Umeuchi, T. Honda, K. Okano, H. Mochizuki, *Nihon Shinkei Seishin Yakurigaku Zasshi* **2008**, *28*, 75–83.

XIV. M. J. Pawar, A. B. Burungale, B. K. Karale, *ARKIVOC* **2009**, *(XIII)*, 97–107.

XV. B. Thadhaney, D. Sain, G. Pemawat, G. L. Talesara, *Indian J. Chem.* **2010**, *49B*, 368–373.

XVI. B. K. Sharma, D. Manna, M. Minoura, G. Mugesh, *J. Am. Chem. Soc.* **2010**, *132*, 5364–5374.

XVII. S. Shimakawa, Y. Yoshida, E. Niki, *Lipids,* **2003**, *38*, 225–231.

XVIII. P. Prajapat, M. Kumawat, B. Kherodiya, G. L. Talesara, J. Indian Chem. Soc.**2016**, 93, 539.

XIX. M. Kumawat, B. Kherodiya, P. Prajapat, G. L. Talesara, Indian J. Chem.**2015**,54B, 117.

XX. P Prajapat, G. L. Talesara, J. Heterocyclic Chem.**2016**, 53, 1603.

XXI. J. L.Jat, S.Ojha,D.B. N.Dhakar, G. L. Talesara, J. Enzyme Inhib. Med. Chem.**2008**, 23, 882.

XXII. N. Hussain, M. Ahmed, S. Khan,A. Joshi, P. Yogi, P. Prajapat, J. Heterocyclic. Chem.**2017**, 54, 993.

XXIII. L. Bauer, K. S. Suresh, *J. Org. Chem.***1963**, 28, 1604.

XXIV. H. Behbehani, H. M. Ibrahim, *Molecules*, **2012**, 17, 6362-6385.

XXV. W. A. McCracken, R. A. Cowsan, New York: Hemispher Publishing Corporation; *Clinical and Oral Microbiology*, 512, 1983.

XXVI. N. S. Alzoreky, K. Nakahara, *Int Journal of Food Microbiol.* **2003,** 80, 223–230.

XXVII. J. L. Rios, M. C. Recio, A. Villar, *Journal of Ethnopharmacol*, **1988**, 23, 127-149.

Received on June 24, 202