SYNTHESIS, CHARATERIZATION AND BIOLOGICAL ACTIVITIES OF UREAS AND THIOUREAS DERIVATIVES

Dr. Salem Edrah

Al-Mergeb University, Al-Khums, Libya

Department of Chemistry, Faculty of Arts & Sciences

Abstract: Urea, a naturally occurring compound, became the first organic compound which was synthesized in lab by Wohler in 1928, and played important physiological and biological roles in animal kingdom. Synthesis of urea became a revolutionary step in the history of synthetically organic chemistry. [1]. et al explained its use as topical drug; urea is absolutely none toxic, undesirable actions occur if skin state and concentration of urea are on a misbalance. It is most valuable substance for restoring hydration in skin and in eczemas due to skin dryness.

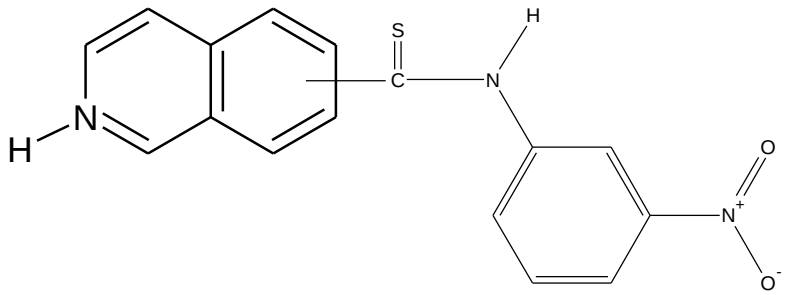
Key words: Urea, Thiourea Derivatives

Introduction

Replacement of oxygen atom in urea by sulphur atom produces Thiourea which has been successfully used in many diseases. Mitchell et al explained that 'Thiourea' the sulphur analogue of urea has been known for over a century and a quarter during which time it has found a variety of uses, some within the biological field. Most noted of these have been their employments as a plant growth stimulator to break bud dormancy and increase crop yield (1920-40) and more recently as a therapeutic agent to treat thyroid dysfunction (1940-50).

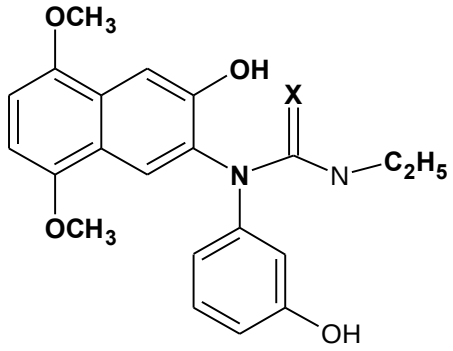
NH_2CONH_2 (UREA) I	NH_2CSNH_2 (THIOUREA) II

Physiological effects of Thiourea are closely related with those ureas which possess bioisosteric pharmacophore groups. Thus these groups are responsible for the origin of biological spectrum in the compound. But in many cases Thiourea containing same pharmacophore group like in urea diminishes the potential of drug e.g. N – 1,2,3,4 – tetrahydro-6-isoquinolyl- N'-3-nitrophenyl Thiourea, III, showed 35% less anticonvulsant activity to its resembling urea.



III

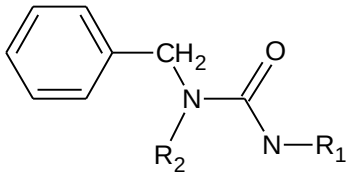
Synthesized N-(2-hydroxy-5, 8-di-methoxy-1,2,3,4-tetra hydronaphthalene-3-yl)-N'-(3-hydroxyphenyl) Thiourea IV., And N-ethyl –N'-(2-hydroxy-5,8-dimethoxy-1,2,3,4-tetrahydronaphthalene-3-yl)-N'-(3-hydroxyphenyl) urea V., and tested them for hypertensive and antirrhythmic activities in anesthetized rats. Compound V is found more potent than that of compound IV.[2]



IV, X = S

V, X = O

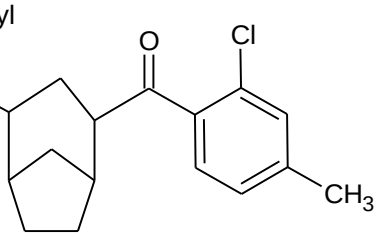
Certain urea and Thiourea have remarkable bioactivities in plant kingdom. Urea derivatives [3]. VI' were tested as synergistic herbicides for rice paddy. A small amount of the compound of series XVIII was found effective against monocotyledon and dicotyledonous for a long period.



VI

R_1 = aryl, alkyl

R_2 = H_3CS



Thiourea, itself has been used as stimulator to break bud dormancy. Prepared sulphonyl urea derivatives and evaluated them as synergistic herbicides [4].

Corresponding author: Salem Edrah**,** Department of Chemistry, Faculty of Arts and Sciences, Al-Mergeb University, Al-Khums, Libya

Email: ragaada@yahoo.com

Experimental

The following compounds were synthesized according to the scheme as given before under plan of study. Elemental analysis was done by using carbon and nitrogen analyzers. Melting points were determined in open capillary and are uncorrected. The IR spectral study of the synthesized compounds was done by using JASCO infra-red spectrophotometer. K Br disc method was used. The UV spectral study was done by using UV/ VIS Spectrophotometer. Spectral grade ethanol is used as solvent... NMR spectral study was performed on JEOL, FX90Q, FOURIER, Transform NMR spectrometer.

Preparation of phenyl Thiourea:-

0.1mol (9.3g) of aniline was dissolved in 10 ml. of conc. HCl acid, diluted to 100 ml with water in a 250 ml. conical flask. To this added 0.1 mol (7.6g) of NH4SCN solution (in 50 ml. warm water) with constant stirring and mixture was refluxed for 30-45 minutes. It is allowed to cool in ice for 30 minutes and the obtained white crystals were filtered, washed with water and recystallised.

Preparation of 4- sulphonyl phenyl Thiourea, sodium salt:-

0.1mol () of sulphanilic acid was diluted to 100 ml with water in a 250 ml conical flask. To this added 0.1 mol (7.6g) of NH_4SCN solution (in 50ml warm water) with constant stirring. Reaction mixture was refluxed on water bath for 30-45 minutes. Sodium carbonate solution was added to adjust pH alkaline and mixture was again heated on water bath for 10 min. It is allowed to cool in ice for few minutes. The obtained white crystals were filtered, washed and recystallised from alcohol. .

Preparation of 4-carboxy-phenyl Thiourea:-

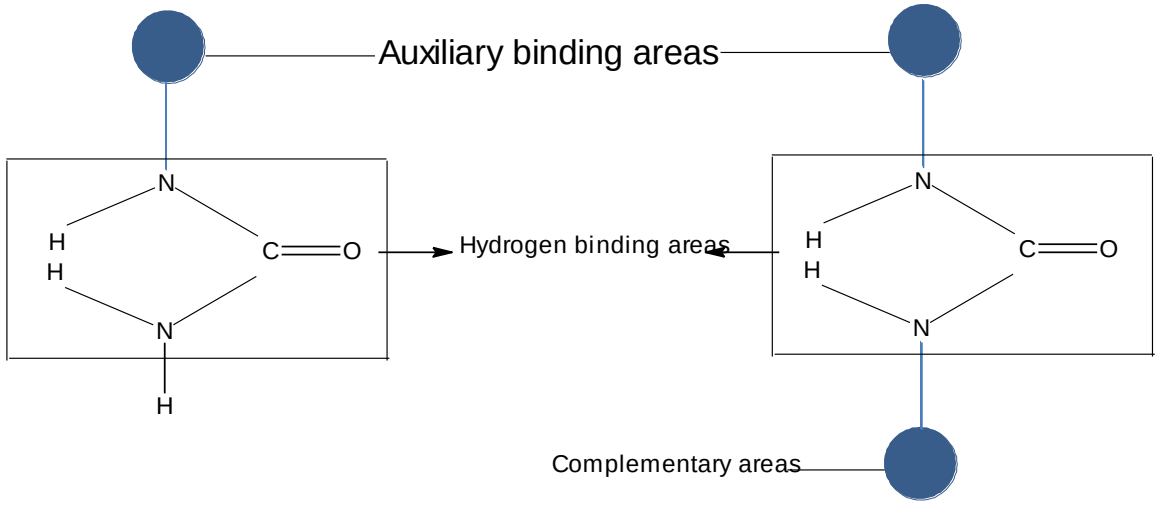
0.1mol () of 4-carboxy phenyl aniline was diluted to 100 ml with water in a 250 ml conical flask. To this added 0.1 mol (7.6) of NH_4SCN solution (in 50ml warm water) with constant stirring. Reaction mixture was refluxed on water bath for 30-45 minutes. Sodium carbonate solution was added to adjust proper alkaline pH to achieve maximum product formation .The mixture was again heated on water bath for about 10 minutes and was allowed to cool in ice for few minutes. The obtained yellowish- brown product was filtered, washed and recystallised.

Results and Discussions

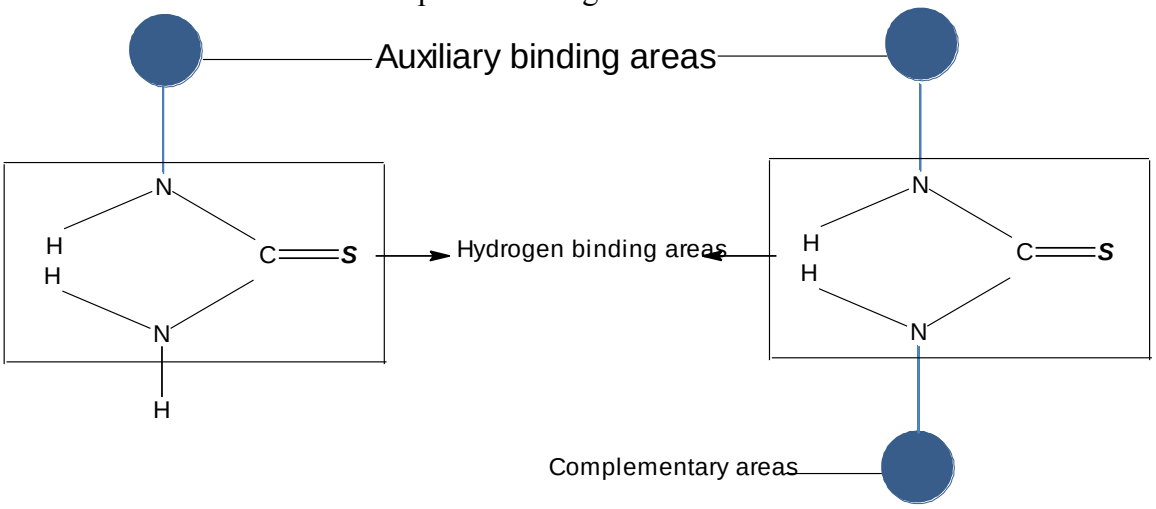
Chemical structure and biological activity:

It was observed that biological activity of a compound is associated with a particular structural unit or group and hence if this structural unit or group is present in other Compound, the latter also becomes biologically active. Such a part of drug, which is responsible for biological action, termed as pharmacophore group.

Urea and Thiourea displaying biological activities possess specific binding sites, known as hydrogen binding area, complementary area and auxiliary binding area shown in the given figures.



Proposed binding sites in urea's



Proposed binding sites in Thiourea

Size and shapes of various groups in these molecules co-related positively with the biological activity. The x-ray crystallographic data suggested that the distal aryl/ heterocyclic ring, present in complementary area, occupies different positions depending on bond angles and in the atomic distances, affects the potency of a drug.

The aim of investigation of new drug is based to investigate and optimize the auxiliary binding area for producing more potent biological activities.

The bioactivity of compounds depends on 'Bioisosteric'. Isosteric modifications involve the replacement of an atom, or group of atoms in a molecule by another atom or group of atoms with similar electronic and steric configurations. Thus 'Burger' explained, the isosteric pairs have similar peripheral electronic arrangements with similar shapes and similar volumes, and which exhibits similar chemical & physical properties. Since the biological properties of classically related isosteric compounds, often turned out to be more similar than their chemical and physical properties.

The synthesized compounds were characterized by elemental analysis, IR, UV and NMR spectral studies. Elemental analysis data were found within ± 0.4% of the theoretical values. Melting point of phenyl Thiourea was compared with the literature value and was in agreement with the observed value. All the physical and analytical data are given in Table-1

TABLE-1

Compound	R	Yield	Molecular Formula	Melting point °C	ELEMENTAL ANALYSIS %C		%N	
					Found	Calcd.	Found	Calcd.
Phenyl Thiourea	H	14.3g	$C_7H_8N_2S$	154	52.31	52.26	18.43	18.42
4-Sulphonyl-phenyl-Thiourea	SO3Na	12.0g	C7H7N2S2Na	197.5	40.69	40.77	13.56	13.5
4-Carboxy-Thiourea	COOH	11.7g	$C_8H_8N_2S$	177.5	58.48	58.53	17.11	17.07

The IR, UV and NMR spectral methods are the important tools for the structural elucidation of the synthesized compounds. All the spectral data of the synthesized compounds are given below-

Infrared Spectral Studies of Synthesized Thioureas:

Infrared radiation refers broadly to that part of the electromagnetic radiation spectrum between the visible and microwave regions. Of greatest practical use to organic chemistry is the limited portion between 4000 and 400 cm^{-1}.

Even a very simple molecule can give an extremely complex spectrum. Although the IR spectrum is characteristic of entire molecule, it is true that certain groups of atom give rise to bonds at or near the same frequency regardless of the rest of the molecule.

The persistence of these characteristic bonds permits to obtain useful information about the compounds synthesized.

The infrared spectral study was done on JASCO infrared spectrophotometer IR report100. KBR disc method was used. The spectra data are given below in cm^{-1}

Phenyl Thiourea:-

3430	asymmetric NH stretching
3320	symmetric NH stretching
3040	aromatic C-H stretching
1500	C=C stretching
1260	N-CS-N stretching
1200	C=S stretching

4-Sulphonyl phenyl Thiourea, sodium salt:-

3410	asymmetric NH stretch
3300	symmetric NH stretch
3020	aromatic C-H stretch
1480	C=C stretching
1250	N-CS-N stretching
1180	C=S stretching

4-Carboxy-phenyl Thiourea, sodium salt:-

3420	asymmetric NH stretch
3310	symmetric NH stretch
3030	aromatic C-H stretch
1490	C=C stretching
1250	N-CS-N stretching
1190	C=S stretching

Ultra-violet Spectral Studies of Synthesized Thioureas:

Molecular absorption in the ultra-violet (UV) and visible region of the spectrum is dependent on the electronic structure of the molecule. Absorption of energy is quantized; resulting in the elevation of electrons from orbital in the ground state to higher energy orbital's in the excited state. In practice, UV spectroscopy is limited to conjugated systems.

Characteristic groups with diverse electronic environment absorb at selective wavelengths, and this helps in recognizing characteristic groups in molecules of widely varying complexity.

UV spectra were taken on Jasco model 7800, UV/VIS Spectrophotometer. Spectral grade methanol and ethanol were used as solvents.

UV spectral data for synthesized Thiourea are given below. The value of λ max is given below-

Phenyl Thiourea	263.5 nm , 204.5 nm
Sulphonyl phenyl Thiourea	323.3 nm , 205.5 nm
Carboxyl phenyl Thiourea	316.5 nm , 205 nm

Nuclear Magnetic Resonance Spectral Studies of Synthesized Thioureas :(NMR)

Nuclear Magnetic Spectrometry is an important tool for determining the structure of a molecule. An NMR spectrum can give almost unbelievably detailed information about molecular structure.

(a) The number of signals, which tells us how many different kinds of protons there are in molecule.

(b) The positions of the signals, which tells us something about the electronic environment of each kind of proton.

(c) The intensities of the signals, which tells us how many protons of each kind there are, and

(d) The splitting of a signal into several peaks, which tells us about the environment of a proton with respect to other, nearby protons...

NMR spectral study was done on JEOL, FX90Q, Fourier, and Transform NMR Spectrometer. NMR ($CDCl_3$) signal values on $ scale are given below-

Phenyl Thiourea	9.7	(bs, 1H, NH)
	6.7	(bs, 2H, $CSNH_2$)
	7.4	(d, 2H, ortho to aromatic amino group)
	7.32	(d, 2H, Meta to aromatic amino group)
	7.12	(d, 1H, Para to aromatic amino group)
Sulphonyl phenyl Thiourea	9.74	(bs, 1H, NH)
	6.72	(bs, 2H, $CSNH_2$)
	7.46	(d, 2H, ortho to aromatic amino group)
	7.34	(d, 2H, Meta to aromatic amino group)
	7.15	(d, 1H, Para to aromatic amino group)
Carboxyl phenyl Thiourea	9.72	(bs, 1H, NH)
	6.71	(bs, 2H, $CSNH_2$)
	7.43	(d, 2H, ortho to aromatic amino group)
	7.32	(d, 2H, Meta to aromatic amino group)

All the above compounds were synthesized according to the scheme as mentioned under plan of study. The methods of preparation are described in experimental part .was proved by the elemental analysis and spectral data of the synthesized compounds. The data reveal and confirm the proposed planned structure of synthesized compounds with satisfactory elemental data within ± 0.4 limit to the theoretical values, satisfactory UV λ max values,

-NCON- and N-CS-N absorption peaks in IR spectra and satisfactory aromatic and NH proton signals in NMR spectra.

C O N C L U S I O N S

Biological importance of Thiourea is well known as mentioned earlier under the review of literature. This prompted us to synthesize Thiourea derivatives. The synthesis of the proposed Thiourea was done according to the plan successfully as evident from the relevant elemental data, melting points and spectral data.

The observed elemental data for C and N are almost compatible with the calculated values. Melting point of phenyl Thiourea is found to be similar to the reported value given in literature. The λ max values as apparent in UV spectra are well agreed to the structure of the compounds. IR spectral absorption frequencies are appeared in similar pattern to the structures of the compounds. NMR proton signals data are consistent with the protons environment as found in the corresponding compound.

The above study thus concludes that the synthesized compounds are aryl/ 4-substituted Thiourea as evident by elemental and UV, IR and NMR spectral data.

ACKNOWLEDGEMENTS

Thanks to Al-Mergeb University and to Faculty of Arts and Sciences, for kindly support and research facilities.

R E F E R E N C E S

1. Rabb, W. : J. Appl. Cosmetol. 1997, 15(4), 115-123 .

2. Chalina, E.G.; Chakarova, L. : Eur. J. Med. Chem. 1998, 33(12) 975-983.

3. Yamada, J. ; Koyanagi, H. ; Torii, H.F. A. ; Sato, T. Sekino, K. : Jpn. kokai Tokkyo koho JP 08,268,815 (96,268,815) (Cl.A01N43/90).15Oct 1996 Appl.95/73,635 30 Mar. 1995; 41pp (Japan).

4. Eda S.; Oohata, T.; Fukai, S.; Arai, S.; Koizumi, F. : Jpn. Kokai Tokkyo koho JP 08,268,815 (96,268,815) (Cl.A01N43/90). 15Oct 1996 Appl. 95/73,635 30 Mar.1995; 41pp (Japan).

5. Pandeya, S.N. In : Text Book of Medicinal Chemistry,pp 586-600 ,edn. 2002, SGP, Varanasi.

6. Pandeya, S.N. In :Text Book of Medicinal Chemistry ,pp 664-704 , edn. 2002, SGP, Varanasi.

7. Pandeya, S.N. In: Text Book of Medicinal Chemistry , pp 705-734 , edn. 2002 , SGP, Varanasi.

8. Dumas, J. ; Khire, U. ; Lowinger, T.B. Paulsen, H.;Riedl,B. ; Scott, W.J. ; Smith ,R.A. ; Wood, J.E. ; Hatoum-Mokdad, H. ; Johnson, J. ; Lee, W. ; Redman, A. PCT Int.Appl. WO 99 32,106 (Cl. A61K31/34), 1 July 1999, US Appl. 996,343, 22Dec 1997, 163pp.

9/10. Miller, S.; Osterhaut, M; Dumas, J.; Khire, U.; Lowinger, T.B.; Riedl, B.; Scott, W.J.; Smith, R.A. ; Wood, J.E.; Gunn D; Rodriquez, M. ; Wang, Ming : PCT Int. Appl. WO 99 32,436 (Cl. C07C275/24, 1 July.1999, US Appl. 996,344 22Dec. 1997; 89pp (Eng.).
11. Brozozowski, Z.: Acta Pol.Pharm. 1998, 53, 233-238.
12. Petersen ,S., Gauss, W. ; Urbacht, E: Angew Chem. 67, 217, 1955.
13. Jadhav,P.K.; Ko Soo Sung U.S. US 5,683,999 (Cl. 514-218;C07D243/04),4 Nov. 1997 U.S. Appl. 406,240. 17 Mar. 1995; 68pp. Cont.-in-port of U.S. Ser. No. 406-240 abandoned(Eng.).
14. Sahlberg, C.; Noreen, R. ; Engelhardt,P.; Hogberg, M. ; Kangasmetsa, Jussi; Vrang, Lotta; Zhang, H. : Bioory. Med. Chem. Lett. 1998, 8(12). 1511-1556 (Eng.), Elsevier Science Ltd.
15. Vig, Rakesh; Mao, C.; Uckun, F.M. :PCT Int.Appl. WO 99 47 501 (Cl. C07D213/00), 23Sept. 1999 US Appl. 40,538, 17 March 1998; 146pp.(Eng.).
16. Toribia, H. : Arch. Sci. 16,405,1963.
17. Georgiev, V. : Izv. Inst. Fiziol. Bulg. Acad. Nauk. 9,115,1965.
18. Georgiev, V. : Compt. Rend. Acad. Bulgare Sci. 18,883,1965.
19. Georgiev, V.: Eksp. Med. Morfol 6, 205, 1967.
20. Georgiev, V.; Vasilieva, O. : Izv Inst Fiziol Blg. Akad Nauk. 9, 105, 1965.
21. Georgiev, V.; Rousinov K. ; Vasileva, O. ; Izv Inst. Fiziol. Bulg. Akad Nauk., 7,233,1964.
22. Echague, E.S.; Linn. R.K.S., J. Pharmacol. Exp. Ther. 138, 224, 1962.
23. Mercier, J. Int. Encyl. Pharmacol. Ther.1, 203 , 1973.
24. Bakibaev A.A.; Gorshkova, K.K. : Russ. Rv. From Izobreteniya 154, 1995.
25. Harrington, F.P.; Thompson, M. : PCT Int. Appl. WO99 15, 526 (Cl. CO7D471/00) 1 April 1999, GB Appl. 97/20,052, 19 Sept. 1997; 24pp. (Eng.).
26. Heiniseh , G.; Matuszczak, B.; Rakowitz, D. ; Tantisira, B. : Arch. Pharm. 1997, 330, 207-210.
27 Chalina, E.G.;Chakarova, L.; Staneva, D.T. : Eur. J. Med. Chem. 1998, 33, 985-990.
29. Akita, H.; Imamura, Y.; Sanui, K.; Kurashima, K.; Seri, K. : PCT Int. Appl. WO 99 48, 864 (Cl. C07C311/58), 30 Sep 1999, JP Appl.1998/77,736 25 Mar 1998,82pp.(Japan).
30. Crooks, S.L.; Merrill, B.A.; Wightman,P.D.: PCT Int. Appl. WO 96 03,983 (CI.A61K31/17), 15 Feb 1996, US Appl.28,6017, 4 Aug 1994, 80pp. (Eng.).
31. Pandeya, S.N. In : A Text Book of Med. Chem., Vol.1 , 265-291, edn.2002 , SGP, Varanasi, India.
32.Saundane,A.R.; Prayagraj, G.; Rangnath, S.H.; Rudresh, K.: Asian J. Chem. 1998,10(4) 856-860.
33. Zhong, M.; Wen, X., Zhong, L.; Chen, J.; Xin, Y.; Guo, D.: Hecheng Huaxue 1997, 5(3), 305-308.
34. Pang,H.;Zhang, J.; Liu, X.; Ran, X.;Mei, L.: Jingxi Huagong 1996, 13(6),21-22.
35. Rutala,W.A.: J. Infect Control. 17 Feb,1989.
36. Block, S.S. In : Disinfection, Sterlization and Preservation, third ed. Lea and Fabiger, Philadelphia, 1983.
37. Brater,D. In: Clinical Pharmacology of Loop Diuretica. Drugs, 41 , 14-22, 1991.
38. Ankersen, M.; Stidsen, C.E.; Andersen, H.S. : PCT Int. Appl. WO97 43,278(Cl.CO7D401/12),20Nov 1997, DK Appl.96/576, 14 May 1996,102pp(Eng.).
39. Prayagraj, G.; Rangnath, S.H.: Asian J. Chem. 1998, 10(4),856-860 .
40. Gotoda, S.; Yoshioka,K.; Izumi, S.; Murai, K.: Jpn. Kokai Tokkyo, Koho JP08 41,018 (96 20 ,571) (Cl. C07C337/06), 13 Feb 1996 JP Appl. 94/108, 304 , 23 May 1994, 7pp (Japan).

41. Klayman, D.L.; Scovill, J.P.; Mason, C.J.; Bartosevich, J.F., Bruce,J.; Lin, A.J. : Arzeneim. Forsch. 33, 909,1983.
42. Klayman, D.L.; Scovill,J.P.; Mason, C.J.; Bartosevich, J.F. , Bruce , J.; Lin, A.J.: Arzeneim. Forsch. 22,1367,1979.
43. Klayman, D.L.; Scovill, J.P.; Mason, C.J.; Bartosevich,J.F., Bruce, J.M.; Grant, S. D.; Gonzalez, A. : Eur. J. Med. Chem.,19,49,1984.
44. Wright, J.B. and Willette, R.E. : J.Med.Pharm.Chem., 5, 815, 1962.
45. Chaubey, M. and Pandeya, S.N.: Farmaco, Ed. Sci., 44,987,1989.
46. Guo,Z.R.;Zhang,S.R.;Yang, G.Z.; Yu, Y.W.. DE 3710254; ref.CA 110,94991p,1989.
47. While,J.R. and Ward, I.J.,: UK 202158A Int. C.A.,93, 715711, 1980.
48. Chapman,J.M. Jr.; Cocolas,G.H. ; Hall, I.H., J. Pharm.Sci.,72,1344,1983.
49. Andree, Ronald; Drewes, M.W.; Dollinger, M. : Ger.Offen. DE 18,728,125 (Cl. C07D239/545), 7Jan 1999, Appl. 19,728,125, 2Jul 1997,28pp.(Ger).
50.Dixit,P.P.;Patil,V.J.;Nair,P.S.;Jain,S.;Sinha,S. and Arora,S.K. : Eur. J. Med. Chem. 41,423,2006.
51.Mahajan,A.; Yeh,S.; Hell,M.; Renburg,C.E. and Chibale,K. : Bioorg.Med.Chem.Lett. 17, 5683, 2007.
52. Arslan, H.; Duran,N.;Borekai,G.; Ozer, C.K. and Akbay, C. : Molecules, 14,519,2009.