Nat. Volatiles & Essent. Oils, 2021; 8(4): 16717-16727

NVEO
Natural Volatiles &
Essential Oils

Synthesis, Characterization And Anti Inflammatory Activity Of Some Novel 5-((6-(Methylthio)Benzo[D]Oxazol-2-Yl)Methyl)-3-(((4-Substituted Phenyl) Amino) Methyl) -1,3,4-Oxadiazole-2(3H)-Thione Derivatives

T.Prathima[1*] , T.Ramamohan Reddy[2]

1. Research Scholar, Mewar University, Gangrar, Rajasthan, India.
2. Research Supervisor, Mewar University, Gangrar, Rajasthan, India.

Abstract

The design, synthesis, spectral and biological activities of some new benzo[d]oxazolederivatives are studied in this work. The acid hydrazides 2-(6-(methylthio)-benzo[d]oxazol-2-yl) acetohydrazide (II) was subjected to cyclization with carbon disulphide under basic conditions to yield 5-((6-(methylthio)-benzo[d]oxazol-2-yl) methyl)-1,3,4-oxadiazole-2(3H)-thione (III) which on aminomethylation with formaldehyde and primary aromatic amines afforded a series of Mannich bases (P16-P30). Purity of the compounds has been confirmed by TLC. The structures of these newly synthesized compounds were established on the basis of their IR, ^{1}H-NMR, and Mass spectral data. All the title compounds have been screened for their anti-inflammatory activity. It's worth noting that title compounds (P16-P30) were shown to have anti-inflammatory efficacy as compared to the normal medication, diclofenac at 10 mg/kg p.o, in a carrageenan-induced paw oedema test in rats. The tested compounds showed anti-inflammatory activity ranging from 24.96 % (P21) to 78.62 % (P28) whereas standard drug diclofenac sodium showed 73.66 % inhibition after 3h. The highest activity (78.71 %) was found for the Mannich base, P28.

Keywords: benzo[d]oxazole, Anti-inflammatory, paw edema technique

1. Introduction

The pharmaceutical industry as a whole is currently facing the task of rising productivity and creativity. The main roadblocks are raising research and development prices, as well as a stagnant number of new chemical organizations (NCEs). The origin of this creativity gap is unquestionably not genetics. The human genome's decoding has resulted in a plethora of medication goals. With over 30,000 human genes, it's safe to assume that at least 1,000 are active in the onset and progression of illness. Furthermore, each of these genes is related to the action of between five and ten proteins, implying that there may be 5,000–10,000 potential drug targets [1-5].

Despite the popularity of protein therapeutics and the possibility of gene therapy, large pharmaceutical firms continue to concentrate their efforts on the research and production of low-molecular-weight compounds [6-9]. As a result, the challenge is to identify the most druggable targets and drug-like molecules that not only interact with

the target but also have unique pharmacokinetic and toxicological properties that enable them to be formulated as a drug [10-14]. Combinatorial chemistry, microwave-assisted organic synthesis (MAOS) [14-17], and high-throughput purification are only a handful of the latest methods that medicinal chemistry has developed in recent years to speed up the drug development method [18-29].

Despite this continuous growth in research and development, the amount of NCEs joining the industry has dropped sharply. Selecting suitable molecules to synthesize seems to be one of the most difficult tasks. The number of potential molecules with a molecular weight of less than 500 Da has been calculated to be 10200, with only 1060 having drug-like properties [30-34]. One part in 1057, or approximately the mass of one proton to the mass of the sum, has been calculated as the proportion of these drug-like molecules synthesized to date. The challenge is to find new molecules in this large world that have the ability to be biologically involved [35-37].

The aim of this research was to create several new benzo[d]oxazole derivatives in order to provide a limited library of "drug-like" substances. Since benzo[d]oxazole is a unique shape, compounds synthesized in this research are supposed to provide anti-inflammatory activity.

2. Materials and Methods

2.a. Chemistry

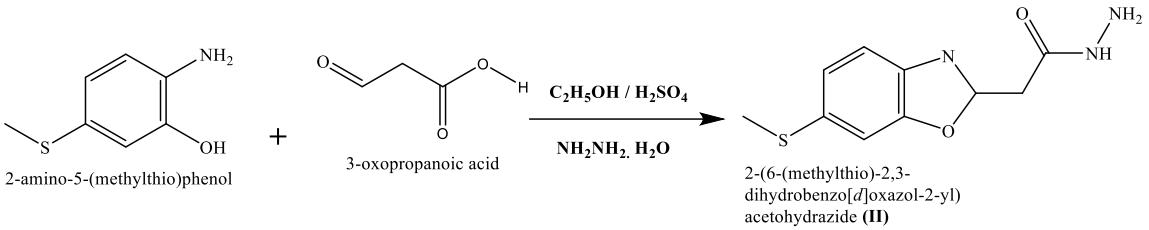
2.a.i. Materials

Commercially 2-amino (5-methylthio) phenol and 3-oxopropanoic acid were used without further purification. The melting points were determined by an open capillary method and are uncorrected. A Shimadzu FT-IR 157 spectrophotometer was used to capture the IR spectra (in KBr pellets). The ^1H spectra were recorded on a BRUKER AP14NCE II-300 (300 MHz) spectrometer using TMS as an internal standard ($CDCl_3$/DMSO-ds mixture). Mass spectra were recorded using argon/xenon in a JEOL SX 102/DA-6000 mass spectrometer (6kv, 10mA). Thin Layer Chromatography (TLC) on silica gel plates was used to monitor the reaction's development.

2.a. ii. Methodology

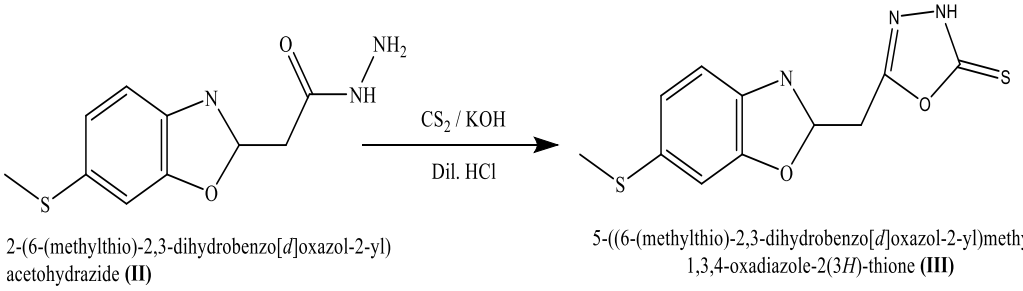
Step-I: Synthesis of 2-(6-(methylthio)-benzo[d]oxazol-2-yl) acetohydrazide (II)

The 2-(6-(methylthio)-benzo[d]oxazol-2-yl) acetohydrazide (II) was synthesized by refluxing 2-amino-5-(methylthio)phenol (I) with 3-oxopropanoic acid in excess absolute ethanol in the presence of a few drops of con. sulphuric acid, as described in the general method [38]. TLC had determined that the resulting 2-(6-(methylthio)-benzo[d]oxazol-2-yl) acetic acid was clean. For 8 hours, a mixture of 0.1 mole 2-(6-(methylthio)-benzo[d]oxazol-2-yl) acetic acid and 0.2 mole hydrazine hydrate was refluxed in absolute alcohol (50 ml). The residual solvent was then distilled off under reduced pressure before being quenched in freezing cold water. Filtered, cleaned, and dry solids are separated and recrystallized from ethanol.



Synthesis of 5-((6-(methylthio)-benzo[d]oxazol-2-yl) methyl)-1,3,4-oxadiazole-2(3H)-thione (III)

In a found bottom flask, a mixture of 2-(6-(methylthio)-benzo[d]oxazol-2-yl) acetohydrazide (II) (0.1 mole), potassium hydroxide (5.6 g, 0.1 mole) in absolute alcohol (50 ml), and carbon-di-sulphide (15.2 g, 0.2 mol) was refluxed for around 4 hours until no hydrogen sulphide was generated[39]. The reaction mixture was mixed with water after cooling to room temperature. After being acidified with dilute hydrochloric acid, the stock was purified, vigorously cleaned with cold water, and recrystallized from ethanol.



General procedure for the preparation of Mannich bases (P16- P30)

A mixture of formaldehyde (0.45 g, 15 mmole) and substituted aniline (10 mmol) in 10 ml ethanol was added with stirring to a solution of 5-((6-(methylthio)-benzo[d]oxazol-2-yl) methyl)-1,3,4-oxadiazole-2(3H)-thione (III) (10 mmol) in ethanol (15 mL). Once all of the ingredients had been added, the stirring was started at room temperature overnight. The solids that had precipitated were filtered, washed in water, and dried. Ethanol was used to recrystallize the crude product.

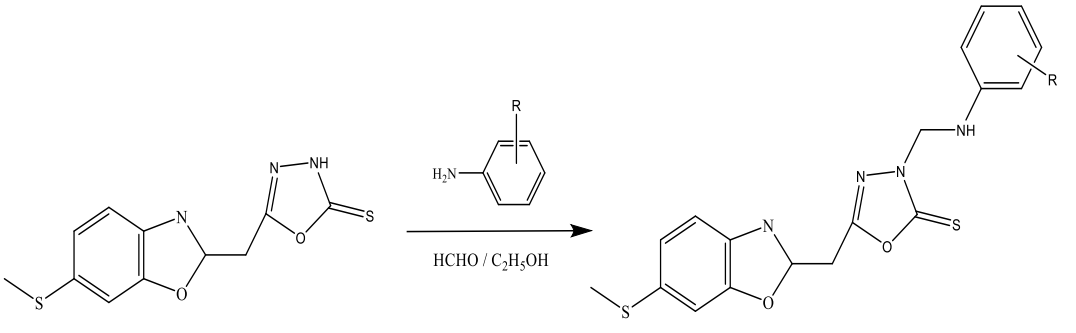
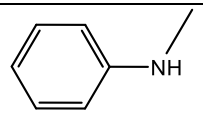
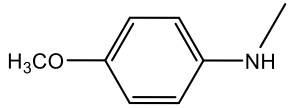
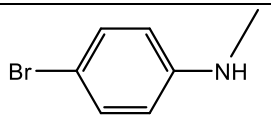
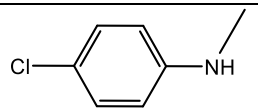
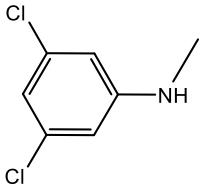
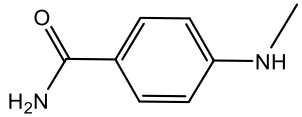
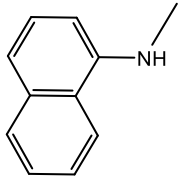
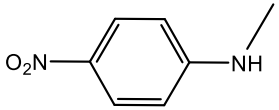
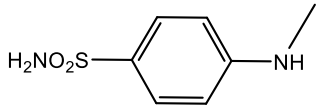
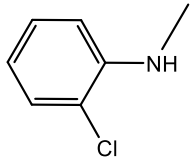
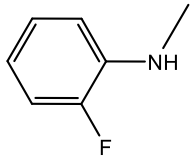
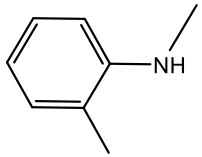
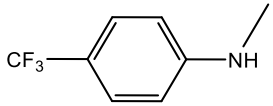
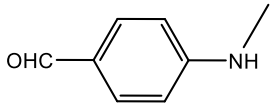
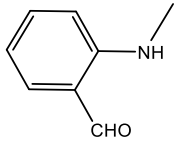


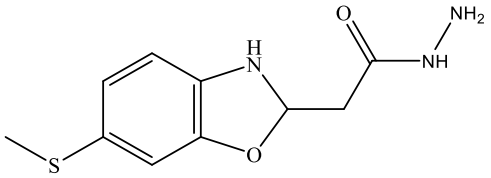
Table 2: Physical characterization data of Mannich bases (P16- P30)

S. No	Compound Code	-R	Mol. Formula	Mol. Wt.	M.P (°C)	%Yield
1	P16		$C_{16}H_{15}N_3OS_2$	329.44	97-99	85
2	P17		$C_{17}H_{17}N_3O_2S_2$	359.46	101-103	90
3	P18		$C_{16}H_{14}BrN_3OS_2$	408.33	112-115	75
4	P19		$C_{16}H_{14}ClN_3OS_2$	363.08	126-128	82
5	P20		$C_{16}H_{13}Cl_2N_3OS_2$	398.32	117-119	68
6	P21		$C_{17}H_{16}N_4O_2S_2$	372.46	130-132	74
7	P22		$C_{20}H_{17}N_3OS_2$	379.50	123-125	69
8	P23		$C_{16}H_{14}N_4O_3S_2$	374.43	110-112	56

9	P24		$C_{16}H_{16}N_4O_3S_3$	408.51	99-101	66
10	P25		$C_{16}H_{14}ClN_3OS_2$	363.88	140-142	56
11	P26		$C_{16}H_{14}FN_3OS_2$	347.43	126-128	69
12	P27		$C_{17}H_{17}N_3OS_2$	343.46	115-117	68
13	P28		$C_{17}H_{14}F_3N_3OS_2$	397.43	114-116	85
14	P29		$C_{17}H_{15}N_3O_2S_2$	357.45	127-129	59
15	P30		$C_{17}H_{15}N_3O_2S_2$	357.45	118-120	82

5. a. iii. Spectral Data Analysis

Spectral Data of 2-(6-(Methylthio)-benzo[d]oxazol-2-yl) Acetohydrazide (II)

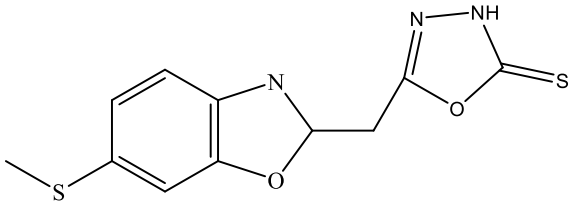


2-(6-(methylthio)-2,3-dihydrobenzo[*d*]oxazol-2-yl)acetohydrazide

IR (KBr) cm^{-1}:3356 (NH_{Str}), 3025 (Ar-CH_{Str}), 2946 (CH_3-CH_{Str}), 1741 (C=O_{Str}), 1627 (C=C_{Str}), 755 (C-S-C_{Str}): **^{1}H NMR ($CDCl_3$) δ (ppm):** 9.08 (s, 1H, CONH), 7.15-7.88 (m, 4H, Ar-H), 4.21 (s, 2H, CH_2 linkage), 3.40 (s, 3H, SCH_3), 2.26 (s, 2H, NH_2):**Mass (m/z):** $C_9H_{12}N_2OS$; 196 (M^+).

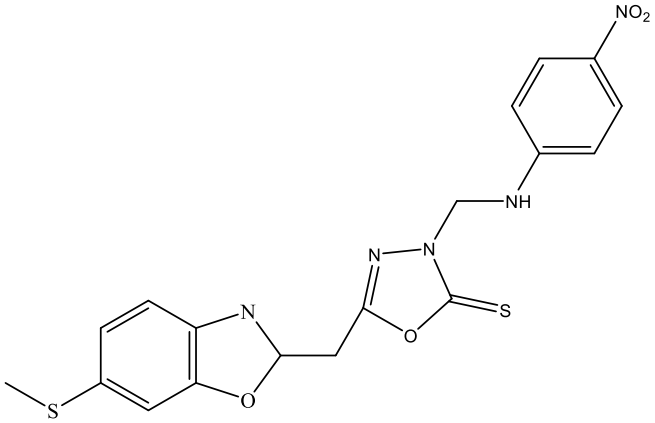
Spectral Data of 5-((6-(methylthio)-benzo[d]oxazol-2-yl) methyl)-

1,3,4-oxadiazole-2(3H)-thione (III)



IR (KBr) cm^{-1}: 3358 (NH_{Str}), 3024 (Ar-CH_{Str}), 2946 (CH_3-CH_{Str}), 1647 (C=N_{Str}), 1601 (C=C_{Str}), 1213 (C=S_{Str}), 1029 (C-O-C_{Str}), 756 (C-S-C_{Str}): **^{1}H NMR ($CDCl_3$) δ (ppm):** 8.13 (s, 1H, CSNH), 6.95-7.55 (m, 4H, Ar-H), 2.88 (s, 2H, CH_2 linkage), 1.92 (s, 3H, SCH_3):**Mass (m/z):** $C_{10}H_{10}N_2OS_2$; 238 (M^+).

Spectral Data of 5-((6-(methylthio)-benzo[d]oxazol-2-yl) methyl)-3-(((4-nitrophenyl) amino) methyl)-1,3,4-oxadiazole-2(3H)-thione (P30)



IR (KBr) cm^{-1}:3326 (NH_{Str}), 3075 (Ar-CH_{Str}), 2916 (CH_3-CH_{Str}), 1644 (C=N_{Str}), 1608 (C=C_{Str}), 1494 & 1390 (NO_{2Str}), 1221 (C=S_{Str}), 1085 (C-O-C_{Str}), 785 (C-S-C_{Str}): **^{1}H NMR ($CDCl_3$) δ (ppm):** 6.79-7.90 (m, 8H, Ar-

H), 4.61 (s, 2H, CH_2 linkage), 3.78 (s, 1H, NH_2), 2.89 (s, 2H, CH_2 linkage), 2.53 (s, 3H, SCH_3):**Mass (m/z):** $C_{17}H_{16}N_4O_3S_2$; 388 (M^+).

2.b. Biological Activity

2.b.i. Anti-Inflammatory Activity

Procedure

The animals were divided into 8 groups with each group containing 6 animals. A mark was made on the hind paw (left) just below the tibiatarsal junction, so that every time the paw was dipped in the mercury column up to fixed mark to ensure constant paw volume. The initial paw volume of each rat was noted by plethysmometrically[40-45].

Group I received 0.6 % Na CMC (sodium carboxy methyl cellulose) and the Group II received diclofenac sodium at a dose of 10 mg/kg body weight p. o. The Group III to Group VIII groups were administered with the test compounds at a dose 10 mg/kg (suspended in 0.6 % CMC given p. o.). Thirty minutes after the treatment of test compounds, 0.1 ml of 1 % (w/v) carrageenan was injected in the subplantar region of the left hind paw. The right paw served as a reference to non-inflamed paw for comparison. The initial paw volume was measured within 30s of the injection. The relative increase in paw volume was measured in control, standard and test compounds at 3 h after the carregeenan injection. The difference between the two readings was taken as the volume of oedema & the percentage inhibition by the drugs was calculated using the formula,

$$\text{Percentage inhibition} = 100\text{-} \left[\frac{\text{Vtest}}{\text{Control}} \right] * 100$$

Where,

V control = volume of paw oedema in control group;

V test = volume of paw oedema in the test compounds in treated group.

The results were expressed as % inhibition of oedema over the untreated control group. The results of anti-inflammatory studies are given in **Table 2**.

The tested compounds showed anti-inflammatory activity ranging from 33.68 % to 76.63 %, whereas standard drug diclofenac sodium showed 73.66 % inhibition after 3h.

3. Results and Discussion

3.a. Chemistry

The structures of 2-(6-(methylthio)-benzo[d]oxazol-2-yl) acetohydrazide (II), 5-((6-(methylthio)-benzo[d]oxazol-2-yl) methyl)-1,3,4-oxadiazole-2(3H)-thione (III) and their mannich derivatives (P1-P15) were established on the basis of IR, ^{1}H NMR, Mass spectral data. Characterization data of all the newly synthesized compounds are presented in Table 1. The IR spectrum of Mannich base P2 showed the absence of absorption bands corresponding to the NH group of the parent benzo[d]oxazole. It showed absorption bands at 3014 for aromatic C-H, 1670 cm^{-1} for C=N, 1206 cm^{-}

^{1} for C=S and 1013 cm^{-1} for C-O stretching vibrations. The 300 MHz ^{1}H NMR spectrum P2 showed the signals corresponding to the NH/SH tautomeric proton was absent and a new singlet for N-CH_2-N was observed at δ 4.25, thus confirming the aminomethylation. It also showed prominent singlets at δ 2.21 and δ 2.57 for its SCH_3 and CH_2 protons, respectively. Multiplet at δ 3.01-3.78 for eight protons were due to the methylene protons of the morpholine ring. The four protons of 4-methylthiophenyl moiety appeared as multiplet in the range δ 7.69-8.22. The FAB mass spectrum of P30 showed a protonated molecular ion ($M^{+|}$) peak at m/z 388 consistent with its molecular formula $C_{17}H_{15}N_3O_2S_2$.

3.b. Biological Activity

3.b.i. Anti-Inflammatory Activity

Table 2: Anti-inflammatory activity data of Mannich bases (P16-P30)

Compound	Dose (mg/kg body weight, p.o)	Increase in paw volume in ml (MEAN ± SEM)	% Inhibition of paw oedema
P16	10	0.386 ± 0.0025	29.36
P17	10	0.371 ±0.0021	33.68
P18	10	0.271 ± 0.0025	52.25
P19	10	0.236 ± 0.0025	57.26
P20	10	0.403 ± 0.0025	25.36
P21	10	0.412 ± 0.0025	24.96
P22	10	0.379 ± 0.0025	32.36
P23	10	0.281 ± 0.0025	51.17
P24	10	0.385 ± 0.0025	30.87
P25	10	0.289 ± 0.0034	50.71
P26	10	0.262 ± 0.0025	55.17
P27	10	0.362 ± 0.0025	35.17
P28	10	0.014 ± 0.0027	78.62
P29	10	0.215 ± 0.0025	60.37
P30	10	0.210 ±0.0019	61.63

Result was Mean ± SD, n = 6

The tested compounds showed anti-inflammatory activity ranging from 24.96 % (P21) to 78.62 % (P28), whereas standard drug diclofenac sodium showed 73.66 % inhibition after 3h (Table 2). The highest activity (78.62 %) was found for the Mannich base, P28.

4. Summary & Conclusion

The design, synthesis, spectral and biological activities of some new benzo[d]oxazole derivatives are studied in this work. The acid hydrazides 2-(6-(methylthio)-benzo[d]oxazol-2-yl) acetohydrazide (II) was subjected to cyclization with carbon disulphide under basic conditions to yield 5-((6-(methylthio)-benzo[d]oxazol-2-yl) methyl)-1,3,4-oxadiazole-2(3H)-thione (III) which on

aminomethylation with formaldehyde and primary aromatic amines afforded a series of Mannich bases (P16-P30). Purity of the compounds has been confirmed by TLC. The structures of these newly synthesized compounds were established on the basis of their IR, ^{1}H-NMR, and Mass spectral data. All the title compounds have been screened for their antimicrobial and anti-inflammatory activities.
With the aim of developing stronger anti-inflammatory agents, a total of 15 numbers of benzo[d]oxazolemannich bases were obtained from 2-amino-5-(methylthio) phenol with 3-oxopropanoic acid. It's worth noting that title compounds (P16-P30) were shown to have anti-inflammatory efficacy as compared to the normal medication, diclofenac at 10 mg/kg p.o, in a carrageenin-induced paw oedema test in rats. The tested compounds showed anti-inflammatory activity ranging from 24.96 % (P21) to 78.62 % (P28), whereas standard drug diclofenac sodium showed 73.66 % inhibition after 3h (Table 1). The highest activity (78.62 %) was found for the Mannich base, P28. Hence, these analogs may serve as a lead molecule to obtain more effective and safer anti-inflammatory. Further studies are planned for lead optimization to increase the anti-inflammatory activity.

5. Consent for Publication

The text has been approved by all of the writers and they have given them for it to be published.

6. Conflict of Interest

There are no conflicts of interest declared by the authors.

7. References

1. MS. Mohamed, MM. Kamel, EM. Kassem, N. Abotaleb, SM. Nofal and MF. Ahmed; Acta. Pol. Pharm., 66 (5), 487-500 (2009).
2. V. Alagarsamy, D. Shankar, VR. Solomon, RV. Sheorey and P. Parthiban; Acta.Pharm. 59 (1), 75-88 (2009).
3. V. Alagarsamy, V. Raja Solomon, RV. Sheorey and R. Jayakumar; Chem. Biol. Drug Des., 73 (4), 471-9 (2009).
4. RS. Giri, HM. Thaker, T. Giordano, J. Williams, D. Rogers, V. Sudersanam and KK. VAsu; Eur. J. Med. Chem., 44 (5), 2184-9 (2009).
5. AB. El-Gazzar, MM. Youssef, AM. Youssef, AA. Abu-Hashem and FA. BadriaFA; Eur. J. Med. Chem., 44 (2), 609-24 (2009).
6. RS. Giri, HM. Thaker, T. Giordano, J. Williams, D. Rogers, KK. VAsu and V. Sudarsanam, Bioorg. Med. Chem. 18 (7), 2796-808 (2009).
7. S. Boyapati, U. Kulandaivelu, S. Sangu and MR. VAnga; Arch. Pharm., 343 (10), 570-6 (2010).
8. AM. Alafeefy, AA. Kadi, OA. Al-Deeb, KE. El-Tahir and NA. Al-Jaber; Eur. J. Med. Chem., 45 (11), 4947-52 (2010).
9. T. PanneerselVAm and P. Vijayaraj; Bulletin of the Korean Chemical Society, 31 (11), 3265-3271 (2010).
10. RS Hunoor, BR. Patil, DS. Badiger, RS. VAdavi, KB. Gudasi, CV. MagannaVAr and IS. Muchandi; Chem. Pharm. Bull (Tokyo). 58 (5), 712-6 (2010).

11. C. Rajveer, B. Stephenrathinaraj, D. Kumaraswamy, S. Sudharshini, C. Swarnalatha and V. Rajamanickam; Int. J. of Pharma. resear., 2 (3), 50-56 (2010).
12. OI. El-Sabbagh, SM. Ibrahim, MM. Baraka and H. Kothayer; Arch. Pharm., 343 (5), 274-81 (2010).
13. RS. Hoonur, BR. Patil, DS. Badiger, RS. VAdavi, KB. Gudasi, PR. Dandawate, MM. Ghaisas, SB. Padhye and M. Nethaji; Eur. J. Med. Chem., 45 (6), 2277- 82 (2010)
14. KM. Amin, MM. Kamel, MM. Anwar, M. Khedr and YM. Syam; Eur. J. Med. Chem. 45 (6), 2117-31(2010).
15. BA. Rather, T. Raj, A. Reddy, MP. Ishar, S. SIVAkumar and P. PaneerselVAm; Arch. Pharm. (Weinheim), 343 (2), 108-13 (2010).
16. RS. Hunoor, BR. Patil, DS. Badiger, RS. VAdavi, KB. Gudasi, CV. MagannaVAr and IS. Muchandi; Chem. Pharm. Bull (Tokyo)., 58 (5), 712-6 (2010).
17. MS. Mohamed, MM. Kamel, EM. Kassem, N. Abotaleb, M. Khedr and MF. Ahmed; Acta. Pol. Pharm., 68 (5), 665-75 (2011).
18. KS. Kumar, PM. Kumar, KA. Kumar, M. SreenIVAsulu, AA. Jafar, D. Rambabu, GR. Krishna, CM. Reddy, R. KapaVArapu, K. ShIVAkumar, KK. Priya, KV. Parsa and M. Pal; Chem. Commun., 47 (17), 5010-2 (2011).
19. J. M. Patnaik, M. Patnaik and D. Bhatta; Indian J. Chem., 37(B), 451-457 (1998).
20. S. Kumar, A. K. ShrIVAstaVA and P. C. Sankar; J. Inst. Chem., (India) 70(4), 135-139 (1998).
21. A. O. Farghaly and A. M. Moharram; Bull. Chim. Farm., 138(6), 280 (1999).
22. L. Xin, H. R. Li, H. Yang and S. Zhao; Chim. Tunis, 7(2), 23 (1999).
23. M. M. Ghorab, S.M. Abdel Gawad and M.S.A. Gaby; Farmaco, 55(4), 249 (2000).
24. C. Qi Deng, L. Khih, H. Leoni, L. Genini, D. Carson, A. Dennis Lottam and B. Howard; J. Med. Chem., 42(19), 3860-3865 (1999).
25. G. V. S. Rama Sharma, T. John, V. Murugan and K. Elango; Indian J. Heterocycl. Chem., 9(2), 151-155 (1999).
26. M. Giedrute, U. Emilija, G. Povilas, S. VAinilavicius and R. Povilas; Chemija, 10(3), 214 (1999).
27. S. Pramilla and S. P. Garg; J. Indian Comm. Chem., 16(2), 17-20 (1999).
28. A. Mateo, M. Pedro, V. Angel and T. Fulgencio; Conf. Synth. Org. Chem., 33, 335 (1999).
29. K. Mohammadsadegh, S. Hosseini, S. Saheh and M. Nasser; Iran J. Chem., 18(1), 30-34 (1999).
30. H. Feng and S. Berry; J. Org. Chem., 64(4), 1397-1403 (1999).
31. A. Santagati, M. Modica, L. Scolaro, M. Monsu and M. Santagati; J. Chem. Res. Synop., 86(2), 460-465 (1999).
32. D. Xuedong and V. Scott; Tetrahedron Asymmetry, 10(1), 25 (1999).
33. R. K. Kawadkar and B. J. Ghiya; Asian J. Chem., 11(2), 388-395 (1999).
34. S. Keith, E. L. Hiti, A. Gamal, A. F. Mohamed and A. A. Mohamed; Collect. Czech. Chem. Commun., 64(3), 515 (1999).
35. H. F. Laurent, B. Sylvie and K. PIVA Le ; Tetrahedron Lett. 40(20), 3881 (1999).
36. P. S. N. Reddy, T. VAsantha and S. Raju; Indian J. Chem., 38(B), 40-45 (1999).
37. V. Bhardwaj, V. N. Gupta and O. P. Suri; Indian J. Heterocycl. Chem., 8(3), 173-178 (1999).

38. Trost B M, Fleming I, Comprehensive Organic Synthesis, Heathcock C H, Pergamon Press, New York, 2, 1991.

39. Reser A, Leyshon L J, Saunolers D, Mijovic M V, Bright A, Bogie J, J Am Chem Soc., 94, 1972, 2414.

40. E. L. Hiti and A. Gamal; J. Pharm. Sci., 14(1), 37-41 (2000).

41. D. M. Purohit and V. H. Shah; Indian J. Heterocycl. Chem., 8(3), 13-17 (1999).

42. S. JantoVA, K. SpirkoVA, S. Stankovsky and P. DuchonoVA; Folia Microbiol., (Prague), 44(2), 187 (1999).

43. K. Pei-pei, C. D. Martin, C. L. Kimberley, W. Lingardo, L. Risen, M. Lisa, V. A. Timethy, R. Ray, B. B. Lawrence, W. R. Jacqueline, C. P. Dan, and E. J. David; J. Med. Chem., 42(22), 4705-4712 (1999).

44. V. K. Ahluwalia, S. Ranjanadas and V. Uma shankar; Indian J. Chem., 38(B), 1136-1140 (1999).

45. S. N. Pandeya, D. Sriram, G. Nath and E. De Clercq; Pharm. Acta. Helv. 74(1), 11 (1999).