WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 9, 1641-1649. Research Article ISSN 2277– 7105

# MW ASSISTED SYNTHESIS AND BIOLOGICAL PREDICTION STUDY OF SOME NEW PYRAZOLE-4-CARBONITRILE DERIVATIVES USING MALONONITRILE

**Savita Dhongade-Desai*, Poonam K. Shetake, Vitthal A. Divate and Reshma P. Khot**

India.

Article Received on
19 March 2018,

Revised on 09 April 2018,
Accepted on 30 April 2018,

DOI: 10.20959/wjpr20189-12198

***Corresponding Author**
**Savita Dhongade-Desai**
India.

## ABSTRACT

The different pyrazole-4-carbonitrile derivatives were synthesised by the reaction between thiophene-2-aldehyde (1 mmol) and malononitrile (1 mmol) under microwave irradiations at low power (210 W) with a catalytic amount of alcoholic sodium ethoxide followed by addition of phenyl hydrazine (1 mmol). The synthesized compounds were characterized by $^{1}H$ NMR, $^{13}C$ NMR, IR, and Mass spectra. The biological activity of some new synthesized compounds was evaluated by PASS prediction and appeared to be significant.

**KEYWORDS:** Pyrazole-4-carbonitrile, Heterocyclic aldehyde, microwave irradiations.

## INTRODUCTION

Heterocyclic compounds with nitrogen atoms have received a great importance as bioremedial agents. Among the five membered heterocycles, the pyrazole and its carbonitrile derivatives have provided inormous functionality and stereochemical complexity. In the history, studies have reported a growing body of data on different pyrazole derivatives and their innumerable physiological and pharmacological activities. Such reports have exhibited the several biological medicinal properties of derivatives of pyrazole and established the relation between the structure and activities so that the full potential of the moieties can be exploited. Considering the recent advances in synthetic medicinal chemistry, with the aim of discovering new drug molecules, we have attempted to synthesis new pyrazole-4-carbonitrile derivatives in the present work. Most of the synthetic pyrazole-4-carbonitrile derivatives have been found to possess biological activities such as antimicrobial[1,2], P-38α MAP kinase

inhibitory[3], insecticidal[4,5], diuretic[6], anticancer[7], antibiotic[8], cardio–vascular[9,10], anti-infective[11], monoamine oxidase inhibitory[12], antioxidant[13] and anti-HIV[14].

## MATERIALS AND METHODS

All chemicals used were commercially available and purchased from Acros organics. All the melting points checked in an open capillary method and are uncorrected. The reactions were monitored by thin layer chromatography (TLC) using precoated chromatoplates. The spots are visualized under ultraviolet tube. Proton nuclear magnetic resonance ($^1$H NMR) and $^{13}$C NMR spectra were recorded on a Bruker DPX 300 MHz spectrophotometer using tetramethylsilane (TMS) as an internal standard in DMSO-$d_6$. Infrared spectra were recorded on a Perkin-Elmer, JASCO 4600 FTIR spectrophotometer and expressed in $cm^{-1}$.

### General procedure for the synthesis of pyrazole-4-carbonitriles [V(a-e)]

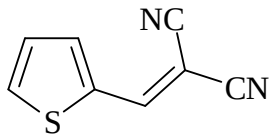
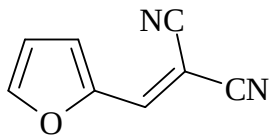
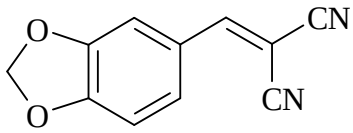
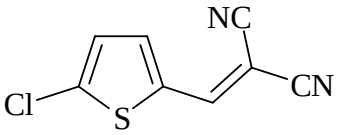
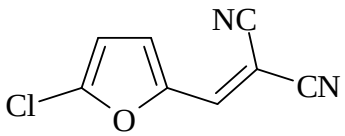
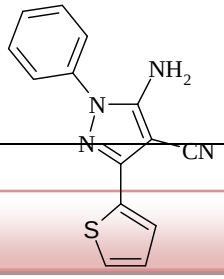
In a 50 ml clean round bottomed flask, heterocyclic aldehyde (1 mmol) and malononitrile (1 mmol) were irradiated with microwaves at 30 % power (210 W) with catalytic amount of alcoholic sodium ethoxide to form heteroarylidine malononitriles [III(a-e)] which on further condensation with phenyl hydrazine (1 mmol) produced pyrazole-4-carbonitrile derivatives under MWI at same power till the completion of reaction as monitored by TLC. The crude product was filtered off, washed with water. The solid was dried and recrystallized from absolute ethanol to obtain desired product in purest form.

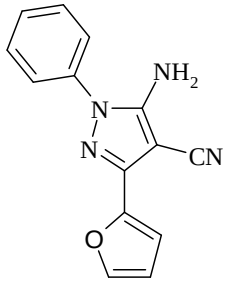
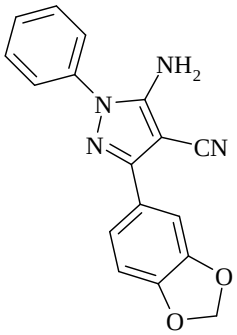
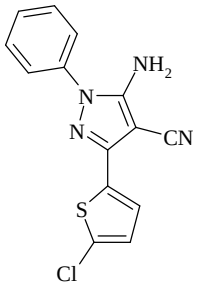
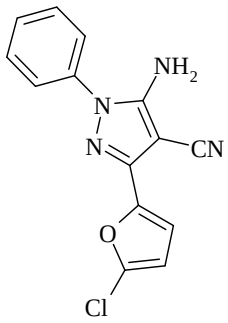
**Table 1: General characteristics and elemental analysis data of the compounds [III (a-e)-IV (a-e)].**

| Com | Time (sec) | Yield | MP$^0$C | Molecular Formula (M.F.) | Elemental Analysis | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | % of C | | % of H | | % of N | |
| | | | | | Found | Calcd | Found | Calcd | Found | Calcd |
| IIIa | 20 | 91 | 116 | $C_8H_4N_2S$ (160.20) | 59.96 % | 59.98 % | 2.59% | 2.52% | 17.52% | 17.49% |
| IIIb | 35 | 82 | 105 | $C_8H_4N_2O$ (144.13) | 66.58 % | 66.67 % | 2.82% | 2.80% | 19.52% | 19.44% |
| IIIc | 25 | 92 | 128 | $C_{11}H_6N_2O_2$ (198.18) | 66.62 % | 66.67 % | 3.02% | 3.05% | 14.24% | 14.14% |
| IIId | 30 | 84 | 122 | $C_8H_3ClN_2S$ (194.64) | 49.29 % | 49.37 % | 1.59% | 1.55% | 17.42% | 14.39% |
| IIIe | 45 | 80 | 118 | $C8H_3ClN_2O$ (178.58) | 53.76 % | 53.81 % | 1.59% | 1.69% | 15.82% | 15.69% |
| Va | 150 | 90 | 142 (140-141)[38] | $C_{14}H_{10}N_4S$ (266.33) | 63.11 % | 63.14 % | 3.79% | 3.78% | 21.10% | 21.04% |
| Vb | 170 | 85 | 135 | $C_{14}H_{10}N_4O$ | 67.16 | 67.19 | 4.10% | 4.03% | 22.37% | 22.39% |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | (250.26) | % | % | | | | |
| Vc | 155 | 91 | 148 | $C_{17}H_{12}N_4O_2$ (304.31) | 67.04 % | 67.10 % | 3.95% | 3.97% | 18.52% | 18.41% |
| Vd | 160 | 86 | 130 | $C_{14}H_9ClN_4S$ (300.77) | 55.86 % | 55.91 % | 3.09% | 3.02% | 18.65% | 18.63% |
| Ve | 185 | 82 | 138 | $C_{14}H_9ClN_4O$ (284.71) | 59.01 % | 59.06 % | 3.22% | 3.19% | 19.75% | 19.68% |

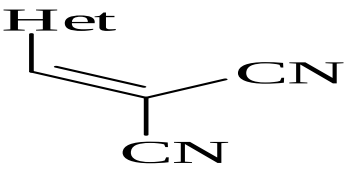
**Spectral data of the synthesised compounds**

| Comp. | Structure | Spectral data |
|---|---|---|
| IIIa |  | **IR (KBr) $\nu_{max}$:** 3100.97, 3022.87, 2221.59, 1670.11, 1570.74, 1404.89, 1318.11 $cm^{-1}$ |
| | | **$^1$H NMR ($CDCl_3$, 300 MHz):** δ 7.26-7.28 (t, 1H, Ar-H), 7.80-7.81(d, 1H, Ar-H), 7.87-7.89 (d, 2H, Ar-H) ppm |
| | | **$^{13}$C NMR ($CDCl_3$, 75 MHz):**δ 78.37, 112.96, 113.80, 129.05, 135.43, 136.92, 138.18, 151.12 ppm |
| IIIb |  | **IR (KBr) $\nu_{max}$:** 3123.15, 3038.3, 2224.49, 1748.16, 1604.48, 1455.99, 1230.36 $cm^{-1}$ |
| | | **$^1$H NMR ($CDCl_3$, 300 MHz):** δ 6.56 (s, 1H, -CH), 7.30-7.98 (d, 1H, Ar-H), 8.01 (m, 2H, Ar-H) ppm |
| | | **$^{13}$C NMR ($CDCl_3$, 75 MHz):** δ 74.58, 126.48, 129.15, 132.06, 138.58, 139.30, 156.74 ppm |
| IIIc |  | **IR (KBr) $\nu_{max}$:** 3697.84, 3595.63, 2392.26, 2216.7, 1606.41, 1494.56 $cm^{-1}$ |
| | | **$^1$H NMR ($CDCl_3$, 300 MHz):** δ 6.14 (s, 2H, $CH_2$), 6.93-6.96 (s, 1H, -CH), 7.32-7.35 (m, 2H, Ar-H), 7.61-7.62 (d, 2H, Ar-H) ppm |
| | | **$^{13}$C NMR ($CDCl_3$, 75 MHz):** δ 79.26, 102.67, 108.26, 109.15, 113.07, 114.23, 125.61, 130.01, 149.01, 153.45, 158.70 ppm |
| IIId |  | **IR (KBr) $\nu_{max}$:** 3697.84, 3595.63, 2392.26, 2216.7, 1606.41, 1494.56 $cm^{-1}$ |
| | | **$^1$H NMR ($CDCl_3$, 300 MHz):** δ 6.76-6.78 (s, 1H, -CH), 7.80-7.81 (d, 1H, Ar-H), 7.87-7.89 (d, 1H, Ar-H) ppm |
| | | **$^{13}$C NMR ($CDCl_3$, 75 MHz):** δ 78.77, 112.69, 113.74, 128.95, 135.44, 137.12, 138.08, 150.99 ppm |
| IIIe |  | **IR (KBr) $\nu_{max}$:** 3617.11, 3505.13, 2381.16, 2202.21, 1676.31, 1454.50 $cm^{-1}$ |
| | | **$^1$H NMR ($CDCl_3$, 300 MHz):** δ 6.48-6.55 (s ,1H, -CH), 6.72-6.86 (d, 1H, Ar-H), 7.86 (d, 1H, Ar-H) ppm |
| | | **$^{13}$C NMR ($CDCl_3$, 75 MHz):** δ 77.39, 108.76, 113.41, 114.12, 116.01, 125.08, 139.31, 151.59 ppm |
| IVa |  | **IR (KBr) $\nu_{max}$:** 3416.28, 3303.46, 2357.56, 2200.02, 1688.37, 1511.92, 1358.6 $cm^{-1}$ |
| | | **$^1$H NMR ($CDCl_3$, 300 MHz):** δ 6.27-6.91 (s, 2H, -$NH_2$), 7.01-7.02 (m, 1H, Ar-H), 7.03-7.11 (m, 4H, |

| | | |
|---|---|---|
| | | ArH), 7.26-7.29 (m, 3H, Ar-H) ppm |
| | | **$^{13}$C NMR ($CDCl_3$, 75 MHz):** δ 72.15, 112.79, 115.5, 123.5, 125.89, 126.37, 127.17, 129.28, 132.15, 140.46, 144.41, 150.9 ppm |
| IVb |  | **IR (KBr) $\nu_{max}$:** 3397.78, 3311.26, 3112.58, 2357.57, 2231.24, 1668.27, 1519.42, 1342.56 $cm^{-1}$ |
| | | **$^{1}$H NMR ($CDCl_3$, 300 MHz):** δ 6.51-6.95 (s, 2H, -$NH_2$), 7.00-7.04 (m, 1H, Ar-H), 7.05-7.11 (m, 4H, Ar-H), 7.16-7.19 (m, 3H, Ar-H) ppm |
| | | **$^{13}$C NMR ($CDCl_3$, 75 MHz):** δ 72.51, 111.84, 112.05, 115.55, 123.53, 124.72, 129.20, 138.36, 144.67, 150.75,151.04, 153.86 ppm |
| IVc |  | **IR (KBr) $\nu_{max}$:** 3435.23, 3215.46, 3120.25, 2207.26, 1670.85, 1349.68 $cm^{-1}$ |
| | | **$^{1}$H NMR ($CDCl_3$, 300 MHz):** δ 6.14 (s, 2H, -$CH_2$), 6.93-6.96 (s, 2H, -$NH_2$), 7.32-7.36 (m, 3H, Ar-H), 7.61-7.62 (m, 5H, Ar-H) ppm |
| | | **$^{13}$C NMR ($CDCl_3$, 75 MHz):** δ 72.50, 100.14, 107.66, 108.27, 109.14, 123.51, 125.62, 129.98, 132.64, 138.33, 147.93, 149.01, 152.90, 158.68 ppm |
| IVd |  | **IR (KBr) $\nu_{max}$:** 3416.28, 3303.46, 2357.56, 2200.02, 1688.37, 1511.92, 1358.6 $cm^{-1}$ |
| | | **$^{1}$H NMR ($CDCl_3$, 300 MHz):** δ 6.80-7.01 (s, 2H, -$NH_2$), 7.02-7.03 (m, 1H, Ar-H), 7.08-7.11 (m, 4H, Ar-H), 7.26-7.30 (m, 2H, Ar-H) ppm |
| | | **$^{13}$C NMR ($CDCl_3$, 75 MHz):** δ 72.05, 112.46, 115.55, 123.05,125.37, 126.89, 127.09, 129.41, 137.15, 139.41, 145.60, 150.70 ppm |
| IVe |  | **IR (KBr) $\nu_{max}$:** 3411.68, 3296.21, 3114.48, 2413.47, 2232.45, 1668.31, 1542.19, 1356.41 $cm^{-1}$ |
| | | **$^{1}$H NMR ($CDCl_3$, 300 MHz):** δ 6.95 (s, 2H, -$NH_2$), 7.28-7.33 (m, 2H, Ar-H), 7.37-7.49 (m, 1H, Ar-H), 7.55-7.89 (m, 4H, Ar-H) ppm |
| | | **$^{13}$C NMR ($CDCl_3$, 75 MHz):** δ 74.51, 115.54, 123.52, 124.70, 127.74, 129.21, 129.82, 136.26, 137.12, 138.3, 145.66, 150.75 ppm |

**Biological prediction study of heteroarylidine malononitriles [III(a-e)] and pyrazole-4-carbonitrile derivatives [V(a-e)]**

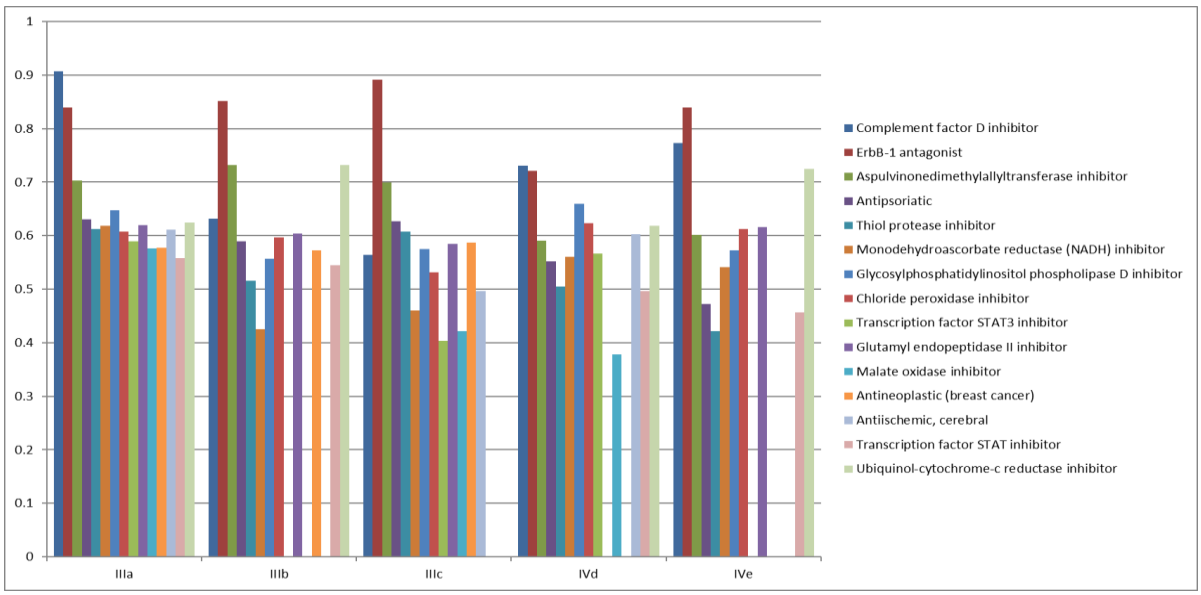
The confirmed structures were subjected to computer programme PASS for the prediction of their biological activities.

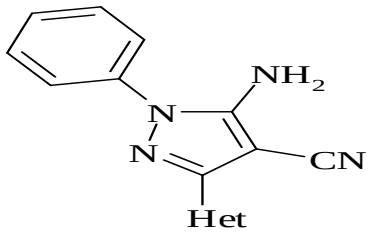



[III(a–e)]

**Table 2. Biological Activities predicted for the compounds III (a-e).**

| Activity | IIIa | IIIb | IIIc | IIId | IIIe |
|---|---|---|---|---|---|
| Complement factor D inhibitor | 0.907 | 0.632 | 0.564 | 0.731 | 0.773 |
| ErbB-1 antagonist | 0.839 | 0.851 | 0.892 | 0.721 | 0.84 |
| Aspulvinonedimethylallyltransferase inhibitor | 0.703 | 0.732 | 0.699 | 0.591 | 0.602 |
| Antipsoriatic | 0.631 | 0.59 | 0.627 | 0.552 | 0.472 |
| Thiol protease inhibitor | 0.612 | 0.516 | 0.607 | 0.505 | 0.421 |
| Monodehydroascorbate reductase (NADH) inhibitor | 0.619 | 0.425 | 0.460 | 0.561 | 0.541 |
| Glycosylphosphatidylinositol phospholipase D inhibitor | 0.647 | 0.557 | 0.575 | 0.66 | 0.572 |
| Chloride peroxidase inhibitor | 0.608 | 0.597 | 0.532 | 0.623 | 0.612 |
| Transcription factor STAT3 inhibitor | 0.589 | - | 0.403 | 0.566 | - |
| Glutamyl endopeptidase II inhibitor | 0.620 | 0.604 | 0.584 | - | 0.616 |
| Malate oxidase inhibitor | 0.576 | - | 0.422 | 0.378 | - |
| Antineoplastic (breast cancer) | 0.577 | 0.573 | 0.587 | - | - |
| Antiischemic, cerebral | 0.611 | - | 0.497 | 0.603 | - |
| Transcription factor STAT inhibitor | 0.558 | 0.545 | - | 0.497 | 0.457 |
| Ubiquinol-cytochrome-c reductase inhibitor | 0.625 | 0.732 | - | 0.619 | 0.725 |

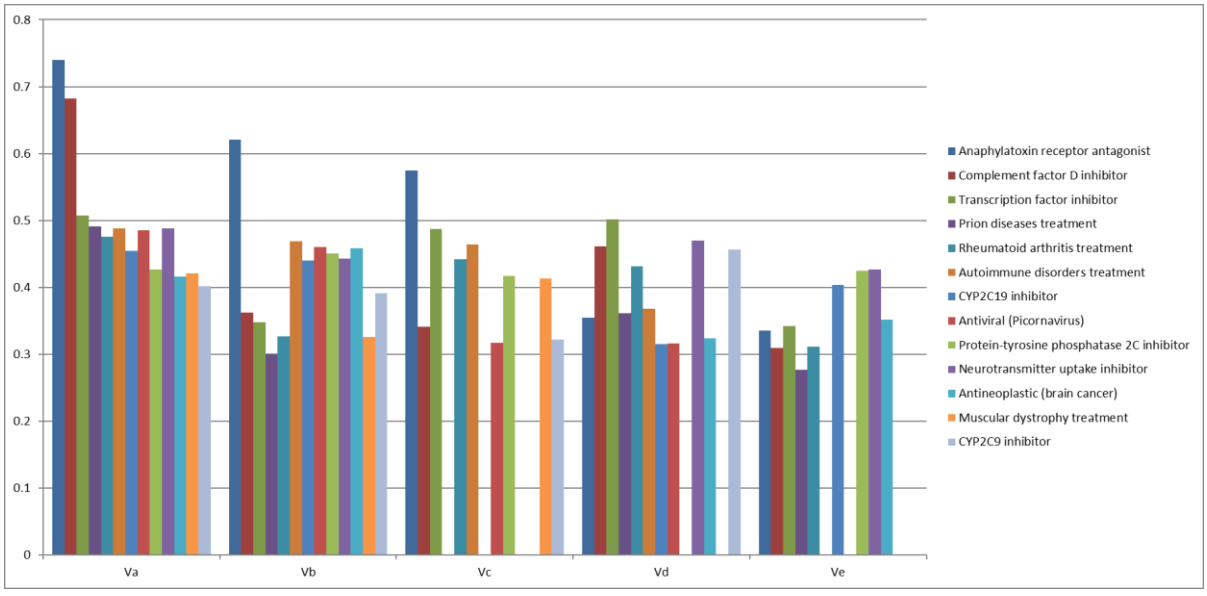





[V(a-e)]

**Table 5.4 Biological Activities predicted for the compounds V (a-e).**

| **Activity** | Va | Vb | Vc | Vd | Ve |
|---|---|---|---|---|---|
| Anaphylatoxin receptor antagonist | 0.740 | 0.621 | 0.575 | 0.355 | 0.335 |
| Complement factor D inhibitor | 0.682 | 0.362 | 0.341 | 0.461 | 0.309 |
| Transcription factor inhibitor | 0.507 | 0.348 | 0.487 | 0.502 | 0.342 |
| Prion diseases treatment | 0.491 | 0.301 | - | 0.361 | 0.277 |
| Rheumatoid arthritis treatment | 0.476 | 0.327 | 0.442 | 0.431 | 0.311 |
| Autoimmune disorders treatment | 0.488 | 0.469 | 0.464 | 0.368 | - |
| CYP2C19 inhibitor | 0.454 | 0.44 | - | 0.315 | 0.404 |
| Antiviral (Picornavirus) | 0.485 | 0.46 | 0.317 | 0.316 | - |
| Protein-tyrosine phosphatase 2C inhibitor | 0.427 | 0.451 | 0.417 | - | 0.425 |
| Neurotransmitter uptake inhibitor | 0.488 | 0.443 | - | 0.47 | 0.427 |
| Antineoplastic (brain cancer) | 0.416 | 0.458 | - | 0.324 | 0.352 |
| Muscular dystrophy treatment | 0.421 | 0.326 | 0.413 | - | - |
| CYP2C9 inhibitor | 0.402 | 0.391 | 0.322 | 0.456 | - |




The following conclusions have been made when the compounds from this scheme were subjected to PASS programme,

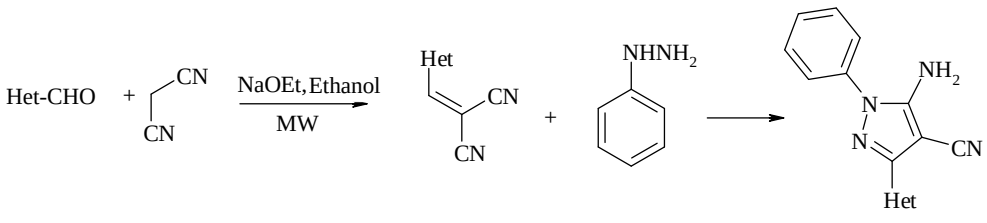
1) All the compounds [III(a-e)] and [V(a-e)] show a variety of possible biological activities.
2) Maximum compounds have highest Pa values from 0.8 to 0.4.

3) The highest Pa value (0.907) for complement factor D inhibitor is being shown by 2-thiophen-2-ylmethylene-malononitrile (IIIa) while anaphylatoxin receptor antagonist activity (Pa=0.740) is being shown by 5-amino-1-phenyl-3-thiophen-2-yl-1H-pyrazole-4-carbonitrile (Va).
4) All the compounds [III(a-e)] and [V(a-e)] are expected to be active for all the activities from Complement Factor D inhibitor to Ubiquinol-cytochrome-c reductase inhibitor with more or less probability.
5) All the compounds [V(a-e)] are active for all the activities from Anaphylatoxin receptor antagonist to CYP2C9 inhibitor with comparable probabilities of being active.

In summary, we have developed a quick, clean, novel, practically efficient and diversity oriented simple method for the synthesis of heteroarylidene malononitriles and pyrazole-4-carbonitriles. The basic catalyst NaOEt efficiently promotes the reaction in a comparatively lesser reaction time. The operational simplicity, easy work up, short reaction time, excellent yield and easy purification of products simply by recrystallization are the captivating features of this method.

## RESULT AND DISCUSSION

Initially, 0.112 g of thiophene-2-aldehyde (1 mmol) was added with 0.066 g of malononitrile (1 mmol) and irradiated under microwave irradiations at low power (210 W) in a catalytic amount of alcoholic sodium ethoxide. While the reaction intermediate [IIIa] was formed, 0.108 g of phenyl hydrazine (1 mmol) was added and irradiated in microwave oven. To our surprise the reaction gives the desired product in an excellent yield of 91% within 2.5 minutes. The completion of reaction was confirmed by TLC on precoated silica gel plates and visualized under UV light.




[I(a-e)] [II] III(a-e)] [IV] [V(a-e)]

Encouraged by this initial success in order to compile a diverse library of these biologically significant pyrazole-4-carbonitrile derivatives, we accessed this protocol for further study

using different hetero aldehydes. The reagent phenyl hydrazine requires a strong basic agent for being activated as a nucleophile. Thus, to attain a rapid formation of desired product the use of weaker bases was avoided. The catalytic efficiency of sodium ethoxide was compared with the other relevant bases.

## CONCLUSION

Here, we have presented an overview of the many efficient, mild, operationally simple and non-conventional synthetic methods to access a library of highly functionalized pyrazole-4-carbonitrile derivatives and a broad range of biological activities displayed by these scaffolds that can optimally present a way to capture their intrinsic value.

## ACKNOWLEDGMENT

We are thankful to University Grants Commission (UGC) for financial support and Department of Chemistry, CFC, Shivaji University, Kolhapur, Vellore University, Vellore for spectral analysis and Elemental analysis for providing facilities for carrying out biological activities for instrumental support.

## REFERENCES

1. J. Panda, S. V. Srinivas and M. E. Rao, *J. Indian Chem. Soc.*, 2002; 79: 770.
2. K. N. Sarma, M. C. Subha and K. C. Rao, *Eur. J. Med. Chem.*, 2010; 7: 745.
3. A. L. Gill, M. Frederickson, A. Cleasby, S. J. Woodhead, M. G. Carr, A. J. Woodhead, M. T. Walker, M. S. Congreve, L. A. Devine, D. Tisi, M. O'Reilly, L. C. A. Seavers, D. J. Davis, J. Curry, R. Anthony, A. Padova, C. W. Murray, R. A. E. Carr and H. J. Jhoti, *Med. Chem.*, 2005; 48: 414.
4. T. Singh, S. Sharma, V. K. Srivastava and A. Kumar, *Arch. Pharm.*, 2006; 339: 24.
5. Y. Kando, T. Kiji, M. Noguchi and Y. Manade, *Jpn. Kokai Tokkyo Koho*, 2008; 311: 36.
6. P. T. Chovatia, J. D. Akabari, P. K. Kachhadia, P. D. Zaalavadia and H. S. Joshi., *J. Serb. Chem. Soc.*, 2007; 71: 713.
7. I. Bouabdallah, L. A. M'Barek, A. Zyad, A. Ramdani, I. Zidane and A. Melhaoui, *Nat. Prod. Rep.*, 2006; 20: 1024.
8. A. Kirschining, C. Guang-Wu, G. Drager, I. Schuberth and L. F. Tietz, *Bioorg. Chem.*, 2000; 8: 2347-2354.
9. S. Naoa and K. Yoshimi, *PCT Int. Appl. WO 03*, 066, 051, A1**2003**, *Chem. Abstr.*, 2003; 139: 180058.

10. M. M. Mohy El-Din, A. M. Senbel, A. A. Bistawroos, A. El-Mallah, N. A. Nour El- Din, A. A. Bekhit and H. A. Abd ElRazik., *Basic Clin. Pharmaco. lToxicol*., 2011; 108: 26.
11. C. Joukhadar, H. Derendrorf and M. Muller, *Eur. J. Clin. Pharmacol.*, 2001; 57: 211-219.
12. F. Chimenti, A. Bolasco, F. Manna, D. Secci, P. Chimenti, O. Befani, P. Turini, V. Giovannini, B. Mondovi, R. Cirilli and F. La Torre, *J. Med Chem.*, 2004; 47: 2071.
13. J. Lertvorachon, J. P. Kim, D. V. Soldatov, J. Boyd, G. Roman, S. J. Cho, T. Popek, Y. S. Jung, P. C. K. Lau and Y. Konishi, *Bioorg. Med. Chem.*, 2005; 13: 4627.
14. J. J. Vora, D. R. Patel, A. R. Patel and Y. S. Patel, *Asian J. Biochem. Pharm. Res.*, 2011; 1: 108.